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Immunity boosters' herbs and foodstuffs: Need of the hour to prevent COVID-19

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Abstract

Any foodstuffs, Ayurvedic concoctions (mixtures of various plant-based elements) and supplements which strengthen or enhance body's natural defense mechanism are known as immunity boosters. The current global public health crisis, a novel Coronavirus disease (COVID-19) also called as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) is rapidly spreading among human population. Foodstuffs and herbs/plants which strengthen immunity have been reported for their potential antiviral capability against SARS-COV-1 and can be further exploited to prevent COVID-19. In this present review, various medicinal herbs/plants like amla, garlic, ginger, eucalyptus, turmeric, tulsi, chhota gokhru, ashwagandha and giloy are listed and their usage in promoting health, improving immunity and prevention from COVID-19 is justified. Herbs/ plants have reported to possess low toxicity compared to synthetic drugs and have a potential to build and maintain immune system of an individual which can be an effective solution for this contagion. Various plants and its constituents are reported to be active against respiratory diseases such as SARS-CoV-1 and can provide basis for the research work and development of new bioactive drugs or even vaccines.

I. INTRODUCTION

Coronavirus (COVID-19) was announced as a 'pandemic' by World Health Organization (WHO) on 11th March 2020 causing 1,039,406 deaths and 35,347,404 confirmed cases globally as reported till 6th October 2020. Out of which, the most affected population is elderly patients in the age group of 61-70 years and least affected age group is 21-30 years.[1] The name coronavirus was coined by June Almeida and David Tyrrell in 1968 as the virus exhibited crown like appearance. The taxonomical classification of coronavirus consists of Coronaviridae family in the Nidovirates order.[2] SARS-CoV was first seen in Southern China in 2003, which again showed its existence in December 2019 in Wuhan City, Hubei province, China.[3] Nearly about 27 cases were hospitalized with a primary diagnosis of pneumonia of unknown etiology. Wuhan's Huanan seafood wholesale market which trades in fish and variety of live animals like bats, snakes, marmots, etc. are said to be associated with these hospitalized cases. A team of scientists were sent to gather information on the outbreak, by the Chinese Centre for Disease Control and Prevention (CCDC). After collection of nose and throat swab samples from patients, the causative agent was identified as Novel Coronavirus by CCDC on 7th February 2020 and WHO named it as COVID-19.[4] Since then many research scientists of all over the world are working in their laboratories to study in detail the pathogenesis and transmission of the virus, discover full proof diagnostic method to identify presence of the virus and develop best curative treatment against the virus.

Patients with COVID-19 infection experience a wide range of symptoms varying from mild signs, reported among 20% of infected patients which advanced to severe conditions like pneumonia, respiratory failure and even death in some cases. The most common symptoms include fever (98%),

cough (82%), shortness of breath (55%), fatigue (70%), myalgia (44%) and sputum production (33%) while the less common symptoms include headache (13%), diarrhea (10%), nausea and vomiting (10%) and haemoptysis (5%).[5]

Currently, the health crisis due to COVID-19 outbreak is affecting the mankind of entire globe where people with feeble immune system are at highest risk. So, improving body's immune system is of utmost importance to survive in this contagion. As there is no vaccine available in the market yet, boosting the immunity with self-care manifests the key to be safe and healthy.[6] This review article encompasses various medicinal plants, herbs and nutraceuticals which can are beneficial in fighting with COVID-19.

I. Amla

Indian goose berry fruits- *Emblica officinalis* Gaerth (*Phyllanthus emblica* Linn.) generally known as Amla belongs to the family of Euphorbiaceae. Amla is a rich source of Vitamin C which is recommended for boosting immunity during this pandemic.[7]

Constituents: Fruits are abundant nutritive reservoir of vitamin C, along with minerals and amino acids. Tannins- gallic acid, sugars, gums, albumin and crude cellulose are present in the pulpy portion of the fruit. An immature fruit may also contain phyllantidine, phyllantine, R1 and R2 growth inhibitors, four other auxins- A1, A3, A4, and A5 and indoleacetic acid.[7]

Pharmacological activities: Amla has been used as a remedy for symptoms of cold and cough since ancient times. It is rich in vitamin C which plays a major role in boosting immunity. Antioxidants present in amla help in reducing free radical activity which eventually avoids oxidative stress. This lowers the risk of diseases and also helps in repairing the body functions. Chromium present in amla helps in lowering the risk of diabetes which is a major cause of death in COVID-19.[7] 100g of amla contains 600mg of vitamin C, so it is recommended to consume it on a daily basis along with other supplements to meet daily requirement. Vitamin C boosts immunity by encouraging the production of white blood cells like lymphocytes and phagocytes which help to protect the body against cough and flu like infections. Being an antioxidant, it protects the body from free radical damage as growth and survival of the cells is affected due to the oxidative stress produced during free radical damage. Also, it reduces the severity of allergic reactions and helps to fight off infections.[8]

Marketed formulations: Chirayu Pharma (Jeevani malt), Zandu (Triphala churna 200mg), and Dabur (Chyavanprash).

II. Food stuffs rich in Vitamin D

Vitamin D is a group of fat-soluble secosteroid hormone normally produced on exposure of the skin to the sunrays emitting UVB rays. It is reported to contribute in decreasing lung injury and maintaining a balance in renin- angiotensin system. It also decreased the risk of acute respiratory tract infections and inflammatory responses along with improving immunity.[9] A connecting link is shown between the rising numbers of COVID-19 cases, mortality and lower levels of vitamin D. A majority of death cases were recorded in a retrospective cohort study conducted on 780 COVID-19 patients was carried out in Indonesia with the individuals having below normal vitamin D levels.[10] Foodstuffs rich in vitamin D should be consumed to meet the daily requirement, which includes fatty fish, cheese, egg yolks along with supplementation. It contributes in improving immune system and lowering COVID-19 induced cytokine storm by regulating white blood cells and controlling the release of higher number of inflammatory cytokines.[11]

Marketed formulations: Dvion (Cholecalciferol granules), D Drop Injection (Vitamin D3), Nano D3 (Vitamin D3 Supplement).

III. Garlic

Garlic- *Allium sativum* Linn. commonly called as Lasan belongs to the family Liliaceae.[12] It is the popular ingredient in cooking, due to its strong and delicious taste complementing most savory dishes like dals, soups and sauces.

Constituents: It contains Vitamin B6, Vitamin C, manganese, selenium and traces of fibre, Vitamin B1, iron, calcium, copper, potassium and phosphorous. Compounds like sulphur, allicin and

diallyl disulfide and s-allyl cysteine are present in garlic cloves.[12]

Pharmacological activities: Garlic and its bioactive molecules and formulations have been widely used for its anti- inflammatory and immunomodulatory properties. It is reported as a promising treatment for preventing colds and flu. It is extensively used as carminative, aphrodisiac, expectorant, stimulant and in intermittent fevers, respiratory diseases such as chronic bronchitis, bronchial asthma, whooping cough and tuberculosis. Along with this, it is reported to have antiviral, antibacterial, antifungal, antitumor and antidiabetic effects.[13] A research work was performed by Shojai et. al, in which specific pathogen free embryonic egg was used to determine the effect of *Allium sativum* extract on two strains (4/91-Intervet and M41) of infectious bronchitis virus (IBV). IBV is a single-stranded RNA virus, positive sense that belongs to the coronavirus. The outcomes of the study stated that a mixture of garlic extract had better inhibitory effects on non-acute strain as compared to acute strain of IBV. WHO has stated that- Garlic is a healthy food that may have some antimicrobial properties, however, there is no evidence from the current outbreak that eating garlic has protected people from the new coronavirus.[14]

Marketed formulations: Garlic plus, Garlic pearls, Organic garlic in honey, Garlic capsules.

IV. Ginger

Ginger- *Zingiber officinale Roscoe*, dried rhizomes popularly called as Adrak belongs to the family Zingiberaceae.[15] It is a perennial herb growing up to 1m and used regularly in Indian cooking items.

Constituents: A ginger rhizome is reported to contain terpenes such as zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, α-curcumene and phenolic compounds include gingerol, paradols, shogaol.[15]

Pharmacological activities: Ginger can relieve sore throat, hoarseness and loss in voice caused due to contagious infection laryngitis. It is used as an adjunct treatment in cold, cough, asthma and in painful stomach problems. It exhibits anti-inflammatory potential relieving the pain while suffering from sore throat. Being a spicy and pungent herb, it provides heat that body requires during this pandemic. Also, it is used as an antiemetic, positive inotropic, spasmolytic, aromatic stimulant, carminative, condiment and flavoring agent.[15] Wasim Raja et.al, highlighted the antibacterial and anti-cough forming activity of *Zingiber officinale* extract. The disc diffusion assay was performed to monitor the antibacterial activity of different concentrations of plant extract. Antibacterial activity was determined for three microorganisms *Proteus mirabilis, Klebsiella pneumoniae and Streptococcus aureus*. The results obtained after 12 hours showed sensitizing effect of extract against mentioned microorganisms at 250 and 500mg/kg concentration. *In vitro* Fenton reaction, *Z. officinale* and other plant constituents have shown the potent antioxidant property. Also, the anti-cough forming activity was exhibited by *Z. officinale* as compared to standard (Benadryl) using SGOT and SGPT enzymes.[16]

Marketed formulations: Immune boosting ginger tea, Herbalife Afresh, Amul milk including tulsi and ginger for boosting the immunity, Pain kill oil, J.P. Liver syrup (Jamuna Pharma), Abana, Gasex (Himalaya Drug Company), Hajmola (Dabur), Strepsils (Boots Piramal Healthcare), and Sage Massaj oil (Sage Herbals).

It is suggested to consume ginger on daily basis in order to fight cough and cold like symptoms which is a major concern in COVID-19. Now a days, to boost immunity against COVID-19 ginger-tulsi tea, lemon- ginger drink, raw ginger root, ginger-honey drink, ginger powder etc are recommended.[6]

V. Eucalyptus

Eucalyptus globulus and other subspecies of family Myrtaceae, consists of essential oil commonly known as Nilgiri obtained by the distillation of fresh leaves. Mostly, it is used with steam inhalation for cold and cough since ancient times.[17]

Constituents: The plant contains volatile oils such as 1, 8 cineole-eucalyptol; p-cymene, alpha-pinene, sesquiterpenes like aromadendrene; aldehydes and ketones and alcohols. [17]

Pharmacological activities: The leaf preparations are used as a tonic, stimulant, stomachic (dyspepsia), in typhoid fever, asthma, whooping cough etc. Various respiratory related ailments,

bronchitis, asthma, sore throat, cold, can be treated by taking a vapor bath with eucalyptus. Also it has allied properties such as stimulant, antiseptic, flavoring agent, aromatic, deodorant, expectorant etc. Eucalyptus is found to stimulate immune system response according to findings published in BMC immunology journal. It enhances immune system's phagocytic response to pathogens in a rat model. Another review article has also discussed its antiviral and antimicrobial properties. [18] Maryam Sadat Sadatrasul et. al., carried out a study in which emulsions of hydroalcoholic leaf extract of eucalyptus were formulated and its antiviral activity was determined. Further, the emulsion was tested against Madin-Darbey Canine Kidney (MDCK) cells infected with A/H1N1 virus (Swine flu). The hemagglutination (HA) and cell culture infectious dose 50% ($CCID_{50}$) assays were carried out to measure viral titers. This viral binding study showed that the oil-in-water emulsions containing 2% extract inhibited virus replication. Therefore, this formulation can be suggested to prevent transmission of influenza virus.[19]

Marketed formulations: USFDA approved Soulflower Eucalyptus Essential oil, Organic eucalyptus oil, Deva Eucalyptus Essential oil.

VI. Turmeric

Turmeric- *Curcuma longa* consists of the dried rhizomes generally called as Haldi or Kurkum belonging to the family Zingiberaceae.[20] It is safe, effective, easily available and regularly used in cooking of Indian food.

Constituents: The main active constituents of *Curcuma longa* are demethoxycurcumin, curcumin and diacetylcurcumin. Some essential oils such as tumerone, germacrone, atlantone, and zingiberene are also present. These oils are known to boost immunity related functions, blood circulation advancement, accelerate elimination of toxins from the body and improve digestion. [20]

Pharmacological activities: *Curcuma longa* exhibits anti-inflammatory and immunomodulatory activity. It is briefly used as a tonic, stomachic (aid in digestion and stimulate appetite), carminative, exhibits anthelmintic activity and acts as laxative. It is also commonly used for treating fever, gastritis, dysentery, cough (chest congestion), increased cholesterol, hypertension, rheumatoid arthritis, jaundice, problems related to liver and gall bladder, wounds (diabetes), urinary tract infections, menstrual discomfort and skin disorders.[20] Avasarala et. al., performed an experimental work on mouse infected with virus induced acute respiratory distress syndrome, wherein curcumin inhibited fibrosis by modulating the inflammatory response. Curcumin also modified chemokines/ cytokines including IL-6, IL-10, IFNγ and MCP-1 from both the inflammatory infiltrate and lung tissue through a reduction in the modulation of phosphorylated NFKβ65. Curcumin also significantly reduced TGFβR11 which is required for TGFβ signaling.[21]

Marketed formulations: Turmeric juice (Basic Ayurveda), Amul Turmeric milk for immunity boosting, Turmeric 60 capsules/ 36g (Maharishi Ayurveda).

VII. Tulsi

Sacred basil- *Ocimum sanctum* Linn. (Family - Labiatae) traditionally called as Tulsi.[22] All parts of tulsi are utilized for medicinal purpose, especially leaves. The plant is considered to be sacred in our Indian culture and so planted outside of many houses which make it readily available for use.

Constituents: The leaves of *Ocimum sanctum* contain volatile oils comprising of eugenol and methyl eugenol. The aqueous leaf extract of *Ocimum sanctum* reported to contain two flavonoids orientin and vicenin and phenolic compounds such as cirisilineol, circimaritin, rosameric acid, apigenin and isothymusin exhibiting antioxidant activity.[22]

Pharmacological activities: Tulsi is recommended to be used as a home remedy for prevention and treatment of wide range of illnesses such as common cold, cough, sore throat, fever (malarial), fatigue, earache, headache (migraine), digestive disorders (flatulence, colic pain, diarrhea), bronchitis, asthma, hepatic diseases, influenza, skin diseases, wound, insomnia, arthritis and as an antidote for snake bite and scorpion sting. In traditional medicine, the leaves are consumed daily to improve memory. The consumption of tulsi leaves cures mouth ulcer and infections; drinking water containing leaves can

kill germs present in it.[22] *Ocimum sanctum* is used in the management of pain, diarrhea, cough and fever which are the common symptoms of COVID-19. It has been used in the management of fever ranging from normal fever to malarial fever.[23] Also, it is good for boosting up the immune system of the body and aid to protect from threatening virus and bacteria.[24] Vinaya M et. al., conducted a single-blind cross-over study on *Ocimum sanctum* Linn. to evaluate its bronchodilation potential in asthmatic patients. The results depicted that *Ocimum sanctum* 200mg taken twice daily produced progress in both, FEV1 (Forced Expiratory Volume) and PEFR (Peak Expiratory Flow Rate) values on 4th and 7th day similar to Salbutamol 2mg when consumed twice daily.[26]

Marketed formulations: Adulsa cough syrup (Manbro), Amul Tulsi milk for immunity boosting, Tulsi Ghanvati (Patanjali), Dabur Honitus (Herbal cough remedy).

VIII. Chhota Gokhru

Chhota Gokhru- *Tribulus terrestris* Linn., the dried ripe seed belonging to family Zygophyllaceae. It is a saponin rich plant with other known components being flavonoids, alkaloids, lignanamides and cinnamic acids.[27]

Constituents: *Tribulus terrestris* contain numerous bioactive phytochemicals, such as steroidal saponins, flavonoids, glycosides, phytosterols, tannins, terpenoids, amide derivatives, amino acids and proteins.[26] Fruits contain major bioactive compounds like six cinnamic amides and ferulic acid which shows inhibition of Papain-like proteinase (PLpro) which is considered as major protein target of COVID-19. Papain-like protease (PLpro) shows an essential proteolytic enzyme for protection to pathogenic virus and bacteria. The methanol extract of fruits are reported as potent inhibitor of papain-like protease (PLpro).[27]

Pharmacological activities: It is mostly used for cough, chest pain, eczema, enlarged prostate and cancer. *Tribulus terrestris* are renowned for its use in pharmaceutical preparations and food supplements. It is popular as a general health supplement and as an ingredient in testosterone booster supplements.[27] Mallaiah et. al., performed a research work on evaluation of immunomodulatory activity of *Tribulus terrestris* in animal model. In this study, immunomodulatory activity of *Tribulus terrestris* was evaluated by using immunological studies like phagocytic test, carbon clearance test, humeral antibody titer (hat) and delayed type hypersensitivity (dth) response, t- cell population (rosette and e-rosette form) test and drug induced myelosuppression test. It was observed that *Tribulus terrestris* exhibited significant immunostimulatory effect.[28] M. Qiu et. al., examined the activity of Terrestrosin D, a constituent isolated from *Tribulus terrestris* for inflammation and fibrosis in murine pulmonary tissues. The inflammatory response was suppressed from the initial stage (reduction of IL-8 levels), with no “by passing” effects to initiate downstream process of inflammation. The co-administration of Terrestrosin D with Bleomycin in the pulmonary tissues of mice significantly reduced the inflammatory and fibrotic changes were observed in the classic bleomycin models.[29]

Marketed formulations: Healthy Hey Nutrition (extra strength 60% saponins) 700mg /serving 120 capsules.

IX. Ashwagandha

Indian Ginseng- *Withania somnifera* commonly called Ashwagandha belonging to Solanaceae family consists of roots and stems. It is present in Patanjali's Coronil tablets along with giloy and tulsi, which is marketed as an immunity supplement. It also possesses antioxidant properties and reduces the level of stress hormone Cortisol which increases when suffering from the deadly disease like COVID-19.[30]

Constituents: It contains phytoconstituents like withanolide A and B, withaferin A, withanone and withanosides. The main constituent present is an alkaloid withanine. Other compounds include pseudowithanine, hygrine, anahygrine somniferine, pseudotropine, tropine, isopellederine, anaferine, and steroid lactones. The leaves contain steroid lactone, commonly known as withanolides.[31]

Pharmacological activities: *Withania somnifera* would be a useful in the management of COVID-19 through modulation of host (Type 1 helper T lymphocytes) Th-1/Th-2 (Type 2 helper T

lymphocytes) immunity. The potential mechanism of action is beneficial in inducing antiviral immunity, which includes increased IFN-gamma responses with optimal anti-inflammatory activity and down regulation of IL-1, IL-6, TNF-alpha and other inflammatory mediators which are related to the clinical targets of COVID-19.[32] As reported in literature, several withanolides isolated from *Withania somnifera* possess both immunosuppressive and immunostimulatory properties.[32] It has proved its rejuvenating and life-prolonging property. *Withania somnifera* is mostly used as a tonic to calm the mind, reduce lethargy, increase stamina and improve sleep.[31] Oberholzer et. al., conducted a study on BALB/C mice induced asthma to investigate the effects of *Withania somnifera*, selenium and hydrocortisone on their blood count and bronchial lavage. *Withania somnifera* alone and in combination with selenium exhibited reduced cell number in blood compared to selenium alone. The study concluded that *Withania somnifera* considerably reduced white blood cells in both blood smear and bronchial lavage, signifying its anti-inflammatory potential and prove its effectiveness in the treatment of asthma.[34]

Marketed formulations: Ashwagandha spiced green herbal tea (Ban Labs), Coronil tablet (Patanjali), Ashwagandha capsules (Organic India).

X. Giloy

Giloy- *Tinospora cordifolia* is a herbaceous vine widely called as Guduchi, belonging to the family Menispermaceae and indigenous to tropical regions of the Indian subcontinent.[35]

Constituents: The chemical constituents present in *Tinospora cordifolia* are alkaloids, glycosides, hormones, phenolics, aliphatic compound, polysaccharides, protein-rich leaves, calcium and phosphorus [35]. The reported alkaloids are bitter gilonin, non- glycoside gilonin gilosterol and berberine. Also, tinosporaside, tinosporide, cordifol, cordifolide, columbin, b-sitosterol are present in it.[36]

Pharmacological activities: *Tinospora cordifolia* stem is one of the major part of Ayurvedic medicinal preparations used in general debility, dyspepsia, cough and urinary diseases. It has shown immunomodulatory activity, macrophage activation and immunostimulation effect against viral infections.[35] The extracts have multiple medicinal properties such as antibacterial, antiallergic, antidiabetic, analgesic, diuretic and anticancer. This Ayurvedic herb is a powerhouse of antioxidants that neutralize free radicals and prevent inflammation. Also, it purifies blood, boosts immunity, flushes out toxins from the body and fights against bacteria and virus effectively. Consuming giloy juice is helpful in reducing fever which is one of the indicative sign of COVID-19. It also helps in tackling another symptoms of COVID-19 like cough, cold and breathing problems.[37] Sagar and his coworkers have performed a study on evaluating the effectiveness of compounds isolated from *Tinospora* against SARS- COV-2 targets. The binding efficacy of isolated compounds such as berberine, tinocordiside, cordifoliside A, jatrorrhizine, magnoflorine, isocolumbin, sinapic acid, syringin and palmatine were tested against surface glycoprotein (6VSB) and receptor binding domain (6M0J), which are responsible for virus attachment to the host cell and RNA polymerase (6M71) and main protease (6Y84) responsible for virus replication in the host cell using *in-silico* tools. The results proved that compounds isolated from *Tinospora cordifolia* showed high binding efficacy against mentioned targets involved in virus attachment to host receptor and replication of the virus.[38]

Marketed formulations: Giloy juice (Baidyanath), Giloy juice (Patanjali), Giloy ki ghanvati (Dabur).

2. CONCLUSIONS

As the global pandemic of COVID-19 still persists, it is a very crucial time to investigate an active drug for therapeutic treatment. Herbs/ plants have reported low toxicity compare to synthetic drugs and have a potential to build and maintain immune system of an individual, which can be an effective solution for this contagion. Various plants *Toona sinensis Roem*[39], *Glycyrrhiza radix*[40], *Lycoris radiata*[41], *Rhizoma cibotii*[42] are reported to inhibit SARS-CoV-1 replication when tested against infected Vero cells and can provide basis for the research work and development of medicine or

even vaccines. The Ministry of AYUSH has also published following guidelines for enhancing the immunity which includes spices like haldi, jeera, dhaniya and garlic to be consumed in daily diet, amla based Chyavanprash, herbal tea/ decoction (kadha) prepared from tulsi, dalchini, kalimirch, shunthi and manuka and golden milk containing haldi powder in hot milk is recommended. Along with this, vitamins, nutrients, herbs, nutraceuticals and probiotics are also useful in boosting the immunity and fighting cold- flu like symptoms.[6]

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NDDS: Carving a Niche in the Treatment and Management of Diabetes

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Abstract

Diabetes is an incessant metabolic disorder that is defined by an increment in the level of glucose. Type 1 diabetes, which results from insufficient endogenous production of insulin by pancreatic beta cells, as well as abnormalities in the secretion and/or action of insulin, are the causes of this (type 2 diabetes). The worldwide human population seems to be the canter of a diabetic epidemic. Despite significant advancements in the treatment of diabetes, the number of problems associated with the condition is rising. Parallel to this, novel methods have been developed that have been found to reduce the risk of difficulty and are more advantageous. This article emphasizes the development of the modernistic method of synthetic drugs and their therapeutic usefulness in treatment and Management of Diabetes

1. INTRODUCTION

In diabetic conditions, blood glucose level increases more than the normal level. Hyperglycemia, sluggish fat and protein metabolism, and reduced insulin secretion are all symptoms of the metabolic condition of diabetes mellitus.[1]

In California more than 2.3 million adults and in United State 25.8 million children and adults have diabetes. California has increased the percentage of diabetes that is about 35 percent in the last 10 years.[2] Type 1 type of diabetes is found in about 5% of diabetes cases and type 2 is in about 95% of all diabetes cases Type 2 diabetes is more common.[3]

2. CAUSES

A significant risk factor for developing diabetes is obesity.

A growing body of research shows that sugary beverages –because they contain a high proportion of sugar level cause diabetes. These high sugar contents lead to the converted sugar into fat in the liver, which contributes directly to the development of diabetes.

Another cause of developing type-2 diabetes is drinking soda.

Diabetes Mellitus and its related complications are associated with resulting from the imbalance in the production of free radicals that Reactive Oxygen Species (ROS).[1]

3. TYPES OF DIABETES

There are mainly two types of Diabetes:

1. Diabetes Mellitus
2. Diabetes Insipidus

As shown in Fig. 1 Diabetes mellitus can be further classified into four types.[4]

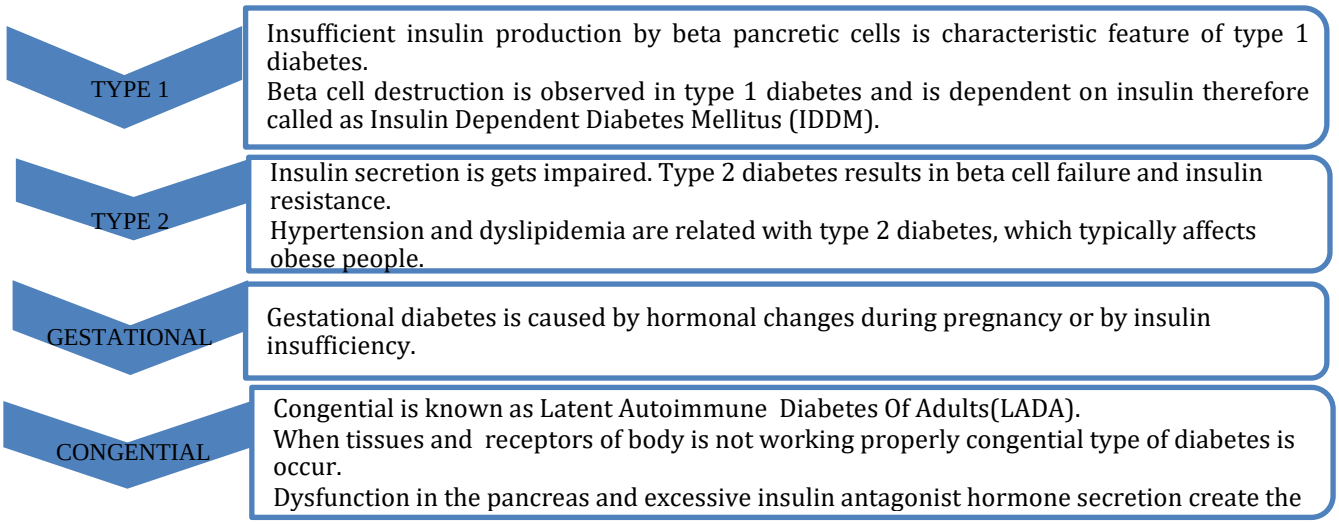

Fig 1: Types of Diabetes mellitus.

4. VARIOUS MEDICINES AND THERAPIES USED IN DIABETES

4.1 CONVENTIONAL MEDICINES

The oral hypoglycemic agents can be classified as shown in Table. 1.

Table 1: Classification of oral hypoglycaemic drugs

Chemical Classes	**Generation and example**	
Sulphonyl Urea	1st Generation	Tolbutamide, Chlorpropamide
	2nd Generation	Glibenclamde (Glyburide) Glipizide, Gliclazide
Biguanides	Metformin	
Meglitinides Phenyl Alanine Analogue	Repaglinide Nateglinide	
Thiazolidiones	Rosiglitazone Pioglitazone	
***α*-Glucosidase Inhibitors**	Acarbose Miglitol	

i. Sulphonyl Urea:-

Mechanism of Action: They act by blocking the conductance of ATP-sensitive K+ channels on the pancreatic B cell membrane, depolarizing the cell, and calcium influx promotes degranulation.[5]

It works by increasing pancreatic insulin release and decreasing post-absorptive rates of endogenous glucose generation.[6]

ii. Biguanides :

Mechanism of Action- It lowers hepatic glucose synthesis while raising peripheral glucose uptake and insulin sensitivity.[6]

They do not stimulate pancreatic β-cells.

1. The main activity is to inhibit the liver's production of glucose and hepatic gluconeogenesis.
2. Muscles and lipids have increased glucose disposal. They improve GLUT 1 transport from the intracellular site to the plasma membrane but do not affect the translocation of GLUT4, the main glucose transporter in skeletal muscle. Thus, the impact is distinct from that of insulin.
3. Slows down the absorption of vitamin B_{12}, amino acids, and other substances through the gut.
4. By enhancing the anaerobic glycolysis mitochondrial respiratory chain promotes peripheral glucose utilization. To the mitochondrial membrane, metformin binds less fervently, though.[5]

iii. Meglitinide or o-Phenylalanine Analogues:

Mechanism of action: -An oral hypoglycemic with a meglitinide analog that is intended to normalize mealtime glucose fluctuations. Although it is not a sulfonylurea, it behaves analogously by attaching to sulfonylurea receptors as well as to other

specific receptors, causing the closure of ATP-dependent K+ channels, which results in depolarization and insulin release.[5]

iv. Thiazolidinediones:

Reduces insulin resistance in peripheral tissue by stimulating PPAR-γ selective agonists for the nuclear peroxisome proliferator-activated receptor (PPAR-γ), which causes the transcription of numerous insulin-responsive genes.[6]By promoting GLUT4 expression and translocation, insulin resistance is overcome, improving glucose entry into muscle and fat. Additionally inhibited is hepatic gluconeogenesis. Activating genes that control fatty acid metabolism and lipogenesis in adipose tissue aids in insulin sensitization.[5]

v. α Glucosidase Inhibitors:

The final enzymes for digesting carbohydrates at the brush border of the small intestinal mucosa, -glucosidases, are inhibited by it. Polysaccharide and sucrose digestion and absorption are slowed and reduced as a result.[5]

4.2 NEWER APPROACHES IN THE MANAGEMENT OF DIABETES

GLP 1

GLP-1 (glucagon-like peptide-1) and GIP (glucagon-dependent insulinotropic peptide) are two major incretins. GLP-1 and GIP stimulate the release of insulin from beta pancreatic cells. GLP-1 inhibits gastric emptying by decreasing pancreatic beta cell glucagon secretion. It has an immediate suppressive effect on the appetite centers.

For the treatment of type 2 diabetes, Exenatideis the first glucagon-like peptide 1 (GLP-1) agonist used.GLP-1 is a gut-derived incretin hormone. Incretin hormones are released in response to nutrient intake, increasing insulin release even before blood glucose levels rise. GLP-1 is an incretin hormone that enhances the production of insulin in response to a meal, inhibits the release of glucagon, delays the emptying of the stomach, curbs hunger, and encourages the growth and regeneration of pancreatic beta cells.[7]

DPP-IV inhibitors

Due to its rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-IV), it is difficult to use in clinical settings. Exenatide is a synthetic GLP-1 analog with similar actions to those of DPP-IV but is resistant to it. It accelerates the release of insulin, suppresses glucagon, and slows down gastric emptying.[5]

Sodium-glucose transporter-2 inhibitors

A novel class of drugs called sodium-glucose transporter-2 (SGLT2) inhibitors is used to treat diabetes.

The other SGLT isoform, SGLT1, has much less involvement in the kidney than it does in the gastrointestinal tract as the primary transporter for glucose absorption. Sodium-glucose transporter-2, which reabsorbs filtered glucose, is present on the proximal convoluted tubule and plays a major role in glucose homeostasis. In diabetic patients, there was increased expression of SGLT2 and other renal glucose transporters. Due to their ability to reduce plasma glucose levels without increasing excessive insulin secretion and their higher selectivity for SGLT2 over SGLT1, SGLT2 inhibitors have a significant advantage over SGLT1 inhibitors as potential anti-diabetic medications.

Canagliflozin, an SGLT2 inhibitor taken orally, improves T2DM glycemic management by reducing the renal threshold for glucose reabsorption and increasing urine glucose excretion, resulting in weight loss.[6]

Insulin

Insulin plays an important role in the control of hyperglycemia in type 1 diabetes patients, whereas it is required later or in certain individuals in type 2 diabetes patients.[8]In the pancreatic islets' beta cells, insulin is produced. In a human pancreas, the exocrine parenchyma of the gland is home to nearly 1 million pancreatic islets.[9]Almost 1,000 endocrine cells, 75% of which are insulin-producing beta cells, are found in each pancreatic islet. In the secretary granules, insulin is converted from its pro-insulin state in the endoplasmic reticulum to its biologically active form. Diabetes patients can significantly lower their blood glucose levels with the help of insulin therapy.

Recombinant technology was used to create human insulin analogs, which is a significant advance.[10]Currently, accessible insulin delivery methods include pens, jet injectors, insulin infusion pumps, and syringes. Subcutaneous injections are the method used to administer insulin. The ultimate objective is to restore patients' ability to generate and use insulin, hence obviating the need for an exogenous insulin supply. Glycemic control in type 1 diabetes typically requires three or more insulin injections per day.[11]

4.3 NOVEL ASPECTS

The performance of an existing drug molecule can be improved in terms of patient compliance, safety, and efficacy by converting it from its conventional form to a novel delivery system. Novel Drug Delivery System an existing drug molecule may gain new life.[12]A significant improvement in drug release at specific locations and rates is the Novel Drug Delivery System. Pharmaceutical companies have been motivated to work on the development of new drug delivery systems by the need to deliver medications to patients effectively and with the fewest side effects.[13]

New concepts for regulating the pharmacokinetics, pharmacodynamics, non-specific toxicity, and efficacy of pharmaceuticals have emerged from interdisciplinary approaches that integrate polymer science, revolutionary pharmaceutical technology, and molecular biology. There are numerous medication delivery and targeting systems being developed right now to decrease drug degradation and loss, avoid negative side effects, boost drug bioavailability, and raise the amount drugs stored in the necessary zone.[14]

To meet the demands of the healthcare industry, new drug delivery systems are being created to get around the drawbacks of existing ones. These systems fall under the categories of targeted drug delivery systems and controlled drug release systems.

The therapeutic benefits of these new systems include[12]

- Increasing the drug's effectiveness
- Targeted delivery system
- Reduced toxicity and adverse effects
- Increased patient convenience
- Successful treatments for diseases that were once incurable
- Potential for prophylactic applications
- Improved patient compliance

According to the literature, the field of drug delivery has advanced tremendously over the past ten years, and several carrier systems have gained prominence.

Classification of NDDS:-

Various Novel Drug Delivery Systems are deduced as follows:

1. Carrier-based Drug Delivery System:
   a) Microparticulates
   b) Liposomes
   c) Nanoparticles
   d) Niosomes
2. Transdermal Drug Delivery Systems

1. Carrier-based Drug Delivery System

a) Microparticulates

Drug release to the targeted treatment site and the formulation of different drug-polymer combinations are two topics covered by microparticle-based therapy. By regulating their release, this aids in preserving the therapeutic concentration of drugs in plasma for a longer period.

Because they are small, microparticles have higher surface-to-volume ratios and can be created to increase the rate at which practically insoluble drugs dissolve.[15]By using microencapsulation techniques, adjusting the drug-polymer ratio, etc., variables like dose and release kinetic are occasionally changed as needed to achieve an optimal therapeutic concentration of the drug in the systemic circulation.[16]Systems with microparticulate content formulated for parenteral, nasal, topical, and oral administration. The concept of microencapsulation has been used to enhance in vivo hypoglycemic effect and modify drug release patterns of drugs.[17]

b) Liposomes

One or more phospholipid bilayers make up the vesicles known as liposomes. The polar aspect of the liposomal core enables the encapsulation of polar medicinal compounds. According to their affinity for the phospholipids, amphiphilic and

lipophilic compounds are solubilized within the phospholipid bilayer. Vesicle membranes can act as a size-selective filter that only enables the passive diffusion of tiny solutes like ions, nutrients, and antibiotics by incorporating channel proteins into the hydrophobic part of the membrane. Drugs that are capsuled successfully protect channel proteins from early proteolytic enzyme breakdown.[16]

c) Nanoparticulate

There are crystalline, amorphous, and solid types of nanoparticles. They can adsorb or encapsulate a medicine to protect it from enzymatic and chemical deterioration.[18]Biodegradable polymeric nanoparticles have drawn a lot of interest because they could be used to deliver drugs to specific organs and tissues, carry DNA for gene therapy, and deliver proteins, peptides, and genes orally.[19]

d) Niosomes:-

Niosomes are being studied as an alternative to liposomes, which have several drawbacks, including the following: due to their susceptibility to oxidative deterioration, phospholipids, one of its constituents, are chemically unstable and require particular treatment and storage. Additionally, the quality of naturally occurring phospholipids varies. Niosomes are made from a single-chain uncharged surfactant and cholesterol. Niosomes functions like liposomes, thus increasing the circulation of entice drugs and developing organ distribution and metabolic stability. Such vesicular drug carrier systems modify the drug's metabolism, tissue distribution, plasma clearance kinetics, and cellular interaction. They should direct the medication to the intended site of action and/or regulate its release. Niosomes can be used for a variety of drug delivery methods, including targeted, ophthalmic, topical, and parenteral.

2. Transdermal Drug Delivery System:

Transdermal drug delivery is the application of self-contained, discrete dosage forms to intact skin to deliver drugs to the bloodstream at a controlled rate. The transdermal drug delivery system (TDDS) became a crucial component of cutting-edge drug delivery systems.[20] Transdermal route is more convenient and safe thus it is the most preferred route for administration and most accepted by patients. The advantages of delivering drugs through the skin to achieve systemic effects are as follows [16]

- First-pass metabolism is avoided
- Avoiding gastrointestinal incompatibility
- Activity duration is predictable and improving physiological and pharmacological response
- Therapy can be stopped at any time with ease
- Higher patient adherence as a result of the removal of multiple dosing profiles
- Suitability for self-management
- Enhance therapeutic efficacy

Table 2 discusses various examples with their advantages with new formulations of known drugs.

Table 2: Novel drug delivery of a few drugs with their advantages

NDDS	Anti-diabetic drug	Advantages
Microparticles	Insulin	1.Preserved bioactivity 2.Improved proteolytic stability 3.Oral/nasal delivery 4.Protection against the stomach's acidic pH 5.Enhancing biodistribution
	Glipizide	Reduced dosage frequency, obtained sustained release, and reduced dose-related side effects
	Glimepiride	Improved dissolution rate
Liposomes	Insulin and peptide surrogate	1.Increased pulmonary retention time and as a result, extrapulmonary side effects were reduced 2.Proteolytic stability has been improved in oral administration, as it has chemically responsive release 3.Sustained release and transmucosaldelivery[21]

Nanoparticles	Insulin	1.Provided a non-invasive method of delivery 2.Encourage patient self-administration 3.Improved effectiveness even for 22 days 4.Compared to the insulin solution, there is a bioavailability improvement of up to 350%, 5.Nasal administration improves systemic absorption 6.Improved hypoglycaemic effect and permeability, 7.Retained bioactivity, 8.Targeted to the colon for better absorption[22]
	Metformin	1.Reduced dosing frequency[23]
	Glibenclamide	1.Improved dissolution rate[24]
	Repaglinide	Provided a delayed release and prevented a [25]
Niosomes	Insulin and peptide drugs	1.Protected from enzymatic deterioration in oral, 2.Prolonged bioactivity for 6 hrs.[26]
Transdermal systems	Glipizide	Avoid adverse effects like anorexia and fatal hypoglycemia, as well as gastrointestinal disturbances like nausea, vomiting, heartburn, and heartburn i.e. in connection with oral delivery [27]
	Insulin	1.Served as a perfect substitute for injectables 2.Controlled release for at least 8hrs

The field of drug delivery is continually inventing and developing to increase the effectiveness of intelligent drug delivery systems in order to maximize therapeutic efficacy and minimize unfavourable side effects. Because every delivery system has different pharmaceutical and physiological properties, careful consideration of independent variables is essential when designing the final product.

5. CURRENT STATUS AND FUTURE PROSPECTS

Despite the recent avalanche of new medications to treat and prevent the condition, diabetes is spreading widely and its popularity is increasing. Perhaps the most pessimistic ascent of all is that the rise is even emulated in children. Nanotechnology is a rudimentto change the spectrum and methods of visual imaging and drug delivery.[28]Nanomedicine initiatives visualize the Nanoscale technologies; will acquiescent more medical benefits within the next 10 years. Instead of pushing applications for some materials, the future of nanomedicine depends on the cognitive design of nanotechnology tools and materials based on a thorough understanding of biological processes. Synthetic medicine preparations should not be considered just as a collection of therapies. They are formulated and prepared to keep in mind the conditions of sickness and the mending properties of individual ingredients.[29] It is important, therefore, that the medicines and preparations should be taken into forethought of their integrated analeptic approach. Table 3, illustrates a few examples of some approved products already in the market.

Table: 3 Some Marketed product[31]

Therapeutic name	Trade name
New-generation insulins	Tresiba Ryzodeg®70/30 Xultophy®*
Glucagon-Like Peptide-1	Victoza®
Modern insulins	Novo Rapid® ** Novo Rapid® Pump Cart® Levemir® Novo Mix® 30 Novo Mix® 50 Novo Mix® 70
Human insulins	Insulatard® Actrapid® Mixtard® 30 Mixtard® 40 Mixtard® 50
Oral antidiabetic agents	Novo Norm®
Diabetes devices	FlexTouch® Flex Pen® Novo Pen® 4 Novo Pen® 5 Novo Pen Echo® Inno Let®

6. CONCLUSION

Synthetic therapy for diabetes has been widely accepted all over the World successfully. Synthetic medicines are always more effective and frequently used to treat Type 1 and Type II diabetes and its complications. The medicines mentioned in this paper have been considered for their possible hypoglycaemic actions. Utilizing a multifaceted approach, new chemical entities will focus on treating metabolic disorders.[30]Future antidiabetic treatment approaches may not only manage diabetes symptoms and alter the disease's course, but also possibly prevent or cure it. T2DM can currently be managed with a variety of medications, however practically all of them come with limitations and don't treat all of the problems that diabetic individuals have. In patients who have failed conventional oral therapies, insulin therapy is always an option. However, some concern has been raised by preliminary studies indicating an increase in mortality in HF patients treated with this, the most effective glucose-lowering agent.[7]

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8. CONFLICT OF INTEREST

Authors have no conflict of interest with anyone.

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Mesoporous Silica Nanoparticles: A promising carrier in various drug delivery systems

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Abstract

Mesoporous silica nanoparticles are at the frontier of the quickly evolving field of nanotechnology and have a number of potential uses in clinical medicine, research, medication delivery, and a wide range of other sciences. A promising possibility that can deliver a range of therapeutic compounds in a manageable and long-lasting way is mesoporous materials. Mesoporous silica nanoparticles in particular are frequently utilised as a agent of delivery because silica has excellent chemical property, biocompatibility and stability. For mesoporous silica nanoparticles (MSNs) to be used in therapeutics, catalyst, adsorption, polymer filler, and optical devices, bio-imaging, drug delivery, and biomedical applications, it is becoming more and more crucial to have good control over its morphology, uniformity, dispersity and particle size. Fictionalization can alter surface qualities and connect medicinal compounds thanks to active surfaces. This paper discusses the different varieties, synthesis processes, and uses of mesoporous silica nanoparticles. Silica nanoparticles which are Mesoporous in nature can be developed and used on a huge scale using a numerous synthesis techniques that are detailed. The release processes and drug loading of mesoporous silica nanoparticles are highlighted.

1. Introduction

Nanoparticles, particularly those used for delivery of drug, have dimensions below 0.1µm or 100 nm. A nanoparticulate matrix is used to dissolve, trap, encapsulate, or attach the drug. The size range of nanoparticles is crucial since it directly influences the bioavailability and biodistribution of particles. Various kind of nanoparticles used in drug delivery systems are Polymeric nanoparticles, Lipid based systems such as Solid-lipid nanoparticles, Polymeric micelles Nanostructured lipid carriers, Niosomes, Liposomes and Mesoporous silica nanoparticles (MSN). Research scientists have recently given MSNs a lot of attention among these various types of nanoparticulate systems.[1]

The Mobile Oil Corporation made the initial discovery of mesoporous silica nanoparticles (MSNs) in 1992.[2]. Meso refers to a certain pore size range of 2 to 50 nm. Amorphous silica is used to create these mesostructured materials. MSNs are Mesoporous forms of silica containing pores with diameters between 2nm and 50nm. MSNs have well-defined and controlled shape and porosity, as well as chemical and thermal stability.

They have developed into a promising and innovative drug delivery system thanks to their distinctive mesoporous structure, which maintains a level of chemical stability, surface functionality and biocompatibility. They also make certain that several drug molecules are delivered to the intended site with controlled release.[3]

MSNs have a number of qualities that make them interesting as prospective drug carriers, including homogeneous porosity, high inertness, uniform and tunable particle size, large specified area of surface (up to 1200 m^2/g), great loading capacity, and simplicity of functionalization. MSNs with active surfaces can be functionalized to change

surface characteristics and link medicinal compounds.[5]

MSNs possess certain advantages which give the flexibility to control the drug release. A wide variety of compounds, including polymers, biomolecules, and antibodies, can be functionalized because the surface has a lot of silanol groups.[6] The surface properties can also be modified by end-capping the surface silanol groups with polyethylene glycol (PEG) which will help in retention of nanoparticles in systemic circulation for longer period of time.

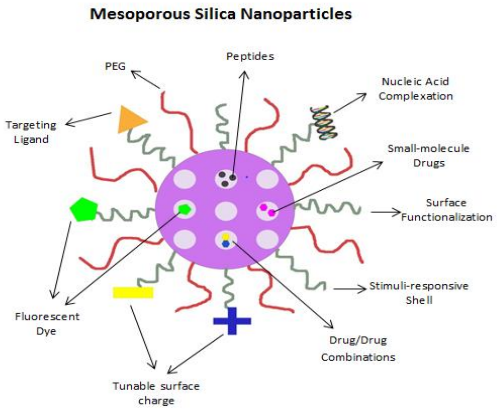

Fig 1: Functionalization of MSN

Small-molecule drugs can be linked to functional groups on the pore walls in addition to adsorbing from solutions and loading into MSNs. Proteins and nucleic acids, for example, can either be adsorbed onto the surface of the particle or connected there. By affixing MRI-active or fluorescent dyes to the exterior or pore walls of the particle, The MSNs can be made bio-imageable so that the drug delivery location or flow can be imaged simultaneously. [7]

MSNs can be passively targeted into tumours due to their optimal size. Increased Permeability and Retention of the nanoparticles is a common symptom of tumours, which typically have leaky vasculature with gaps between 100 nm and 2 m in size and inappropriate lymphatic drainage.[4]

MSN is associated with the major disadvantage of hemolysis due to the damage caused by silanol groups. Hemolysis is the result of reaction between the silanol groups present on the surface with the phospholipid of red blood cells. Another drawback is linked to metabolic alterations brought on by MSNs that promote melanoma.[1]

MSNs have been researched for their use in, gene expression, imaging agent, detecting agent, gene transport biosignal probing, controllable drug delivery, drug delivery and biomarking MSNs have been investigated for their potential use in significant biological applications such as , gene transport ,drug delivery, , biosignal probing, gene expression, imaging and detection and biomarking [1]

2. SYNTHESIS

Mesoporous Silica Nanoparticles can be of following 2 types: [8]

2.1. Mesoporous Silica Nanoparticles- Ordered

2.2 Mesoporous Silica Nanoparticles- Hollow

2.1 Ordered Mesoporous Silica (OMS)

Silica Mesoporous Surfactants can be used as structure-directing agents to create nanoparticles with consistent pore size and highly organized pore composition. One can regulate the pore size. and the synthesis method can be defined based on knowledge of the sol-gel chemistry of the surfactant, which determines the size and structure of the pores. Although the surfactants are abundantly available, the non-ionic block copolymers are being widely used in the synthesis of MSNs. Block copolymers have the benefit of being stable enough to change the molecular weight, copolymer composition or solvent content and yet control the ordering. Different temperatures are used during synthesis to control the size of the pores; higher temperatures result in larger pores.[9]

There is a commonality among all techniques of synthesis. By dissolving a surfactant (such as Cetyl Trimethyl Ammonium Bromide, Pluronic® P123), a template for the mesostructure can be made with one hand. On the other hand, a silica solution is created; it may be made from an inorganic origin, such as solution of sodium silicate, or from an organic origin, like tetraethyl ortho-silicate (TEOS). Low pH levels are attained in both situations. The TEOS can protonate when it is hydrolyzed in acidic environments. Because water is more apt to attack silicon atoms when they are protonated, silicon is

more electrophilic. Compared to media with a more basic pH, the rate of hydrolysis is significantly higher in acidic media. Getting to more organised materials also helps with low pH values.

As soon as all of the prerequisites for the synthesis are met, both solutions are vigorously stirred together for the required amount of time. The mixture is then aged in autoclaves following that. This method enables pore diameter control. The collecting of the particles and their subsequent calcinations are the final steps in the basic synthesis. This removes the surfactant template and results in the creation of the mesoporous material.[9]

The MCM-41 variety of MSNs for biomedical purposes has received the most investigation.

Method of Synthesis of MCM-41

MSNs with consistent 2D hexagonal pm arranged in an organised manner mesopores (MCM-41) can be created using the liquid crystal templating surfactant, tetraethyl orthosilicate (TEOS), sodium metasilicate (Na2SiO3)or cetyl trimethyl ammonium bromide (CTAB) as the silica precursor. The surfactant CTAB would self-aggregate into micelles any time the concentration exceeded the critical micelle level (CMC). In the polar head region of the micelles, the silica antecedents coalesce, where they create a silica wall that surrounds the micelles' surface. When the surfactant is removed, MSNs of the MCM-41 type can develop. The area of the surface exceeds 700m^2/g, and the size of the pore can be customized between 1.6 and 10 nm. It's crucial to have exact influence over pore geometry, shape, pore size, particle size and for biological applications. The design of the template of the surfactant mostly decides the size of the pore as well its alignment. The MCM-41 that is created when Na2SiO3 is utilised as a precursor has wider pores and a higher specific surface area than that created when TEOS is used as a precursor. [8]

2.2 Rattle-Type/Hollow Mesoporous Silica (HMS)

Low weight, huge specific area, rattle-type/ hollow MSNs with an internal void cavity and a porous coating make for the best succeeding drug delivery devices with exceptionally high loading capabilities.[8]One of the key areas of nanotechnology has been the development of novel techniques for manufacturing hollow/rattle-type MSNs.

In the past, hollow-type MSNs have been made utilising a dual template technique that uses a soft template or hard template to create the hollow core and a smooth template as a agent which forms pores to create mesopores in the core. The templates are eliminated by hot calcination or/and extraction of solvent after the sol-gel procedure produces a coating of the silica matrix on the core around the pore framework. A layered coating process on the particles of rattle-type core particles is necessary to create a detachable centre layer. A number of hollow/rattle-type NPs have been synthesized using a range of techniques, including soft and hard templating, Kirkendall effect, layer-by-layer approach, galvanic replacement and Ostwald ripening.[8]

The following are a number of Important Methods of HMS Synthesis:[8]

1. Endo Template/ Soft Template Method
2. Exo Template/ Hard Template Method

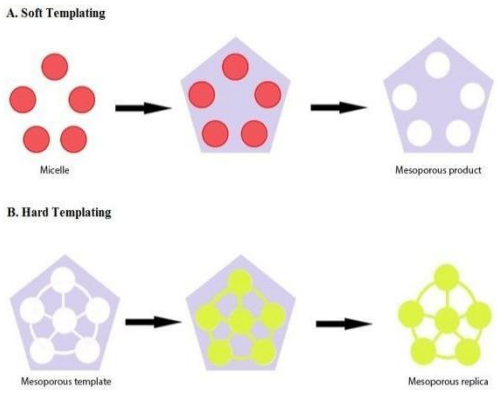

Fig 2: Methods of Synthesis of MSNs

2.2.1. Soft-Template Method

An easy formation approach to create MSNs which are hollow is being developed in an effort to expand the pore volume and enhance loading capacity. The hollow spheres can be filled with various substances that have magnetic, photoactive catalytic capabilities for a variety of possible uses.

Hollow silica particles have been produced using a variety of flexible templates, including micelles.[11] microemulsion droplets[12] or vesicular structures.[13] HMS using soft templating can be synthesized by:

2.2.1.1 Single micelle-templating

Small HSNs are formed via single micelle templating. Here, it appears that the cross-linking of the silica/ micelle spheres doesn't quite take place, contrary to the typical periodic silica which is templated by micelles. By utilising a copolymer of Pluronic Triblock with a varied poor aqueous solubility (PO/ EO ratio) and including the right quantity of an organosilica precursor, nanotubes and small hollow organosilica nanospheres and can be made. It appears that decreasing the proportion of surfactant to framework-precursor encourages creation of hollow nanoparticles that are modelled after single micelles. Under ambient settings,.[15] Micelles of cationic block copolymers also can serve as nanoscale framework of which the deposit of silicate can be created in aqueous solution (pH 7.2 and 20 1C).[16] 20 nm in size due to the small size of micelles.[17]

2.2.1.2 Vesicle-templating

Vesicle-templating would be ideal for further expanding HMSs' size. As meso structural templates, cationic surfactants and anionic co-surfactants can both be utilised to reduce curvature. Furthermore, silica can be obtained from a mixture of silicates and silanes. These synthesis concepts allow for the preparation of hollow spheres of mesoporous silica with mesostructural core via the S-N+...- reactions, which is beneficial for the immediate addition of -functional groups of amino into the structure of the silica after straightforward acid-extraction of the anionicsurfactant.[18]. Organo trimethoxy silanes and Tetraethylorthosilicate were co-condensed in an alkaline solution that contained triethanolamine and the cationic surfactant cetyltrimethylammonium chloride to produce uniform MSNs with dimensions spanning from 25 to 105 nm (CTACl). Even at high dilution, the mixture of anionic and single-tailed cationic surfactants with opposing charges results in a wide range of combined microstructures, including, cylindrical, vesicles, lamellar phases and rod-like micelles These aggregate microstructures can act as innovative organic structures for mesostructured silica with a variety of stunning forms. There is a process change from circular micelles to conical micelles to vesicles when the ratio steadily rises to 1.0. The desired form of mesoporous silica can be produced using these mesostructural surfactants as a co-template or template**.** A silica cast of the organic structures is then created by condensation and deposition over and surrounding the twisted exterior surfaces of the soft templates at a appropriate pH where and silica species and soft templates interact appropriately. For example, mesoporous silica nanorods, hollow spheres and individual silica nanofoams can be produced using the corresponding , rod-like micelles, vesicles and spherical micelles as templates. A ternary surfactant system can be used to introduce the mesostructure to the hollow MSNs' shell, where the neutral tri-block copolymers bind on the cationic surfactant vesicles.[13]A simple and reliable vesicle template can be created using a combination of cationic fluorocarbon surfactant and Pluronic F127 tri-block copolymer thanks to the better hydrophobic characteristics of fluorocarbons-.[20] Additionally, the flexible vesicles can encapsulate nanoparticles to create templates for the yolk-vesicle or core-vesicle.[21] The silica resources then undergo hydrolysis and condensation on the core-vesicle and vesicle framework as a result of attractive interactions, resulting in hollow spheres and composites of the core and shell.

2.2.1.3 Microemulsion-templating

The hollow MSNs can be created by making a consistent oil-in-water (o/w) microemulsion system from a combination of oil , surfactant ,water , and a tiny amount of alkaline solution which is aqueous. Hollow silica nanospheres have been effectively created by careful regulation of the silica silica shell thickness and framework condensation. In a one-pot procedure an organic silica source (such as tetraethylorthosilicate, TEOS) and hydrophobic silane are combined to create hollow MSNs that contain silane. The undergo a long hydrolysis reaction, turning hydrophilic as they

progressively disperse and co-condense on the top of the microemulsions to hardenand produce the vacant MSNs. The benefit of the water-in-oil (w/o) microemulsions is the simplicity with which additional forms (such as nanoparticles) can be encapsulated in the vacant MSNs or created as core-shell type MSNs. HSNs have also been produced using an oil-in-water (o/w) type microemulsion, on the other hand. Vacant silica nanospheres with huge mesopores can be created on the shell using 1, 3, 5-trimethylbenzene (TMB) as a swelling agent and triblock copolymer Pluronic F127 as a template and in the influence of a salt which is inorganic in nature like KCl. [23]

2.2.2. Hard template method

Highly stable colloid in a biological context and of an adequate size to permit prolonged the flow of bloods is also required for discrete, monodispersed MSNs. As was already said, the soft-templating approach is frequently used to create MSNs, however because mesostructures and low stiffness can coexist, the finished MSNs typically include a wide range of particle sizes as well as mixed mesostructures and morphologies. It is still difficult to create morphology-tunable discrete, mesostructured, monodisperse, MSNs for use in biological uses. The development of uniformly sized metal oxides, silica colloids, and polymer lattices has allowed these substances to be employed as hard framework for monodispersed MSN formulations. The creation of a dependable a clone of inorganic silica hard framework must satisfy three fundamental requirements.

The silicification of the organic template's surface occurs more quickly than the particles of silica in whole mixture self-condense. For the silicates to be recognized at the interface under the necessary reaction conditions, the surface must have the proper functional groups.

During the condensation and silicate deposition processes, the organic-template must remain stable. If one of the organic material in the organic templates that are surface-activated interacts with the silicates relatively more strongly than the others, it tends to prefer to elute in place of the initial organic design and gather with the silicates dissolved instead of relying on the surface of the biological template. This leads to failed silica casting.

It must be simple to remove the template without breaking the inorganic silica casting. Because of this, sacrificial design method is frequently employed. In this method, interiors of the combustible or dissolvable materials could be easily removed following moderate calcinations, liquid extractions, as well as acid dissolutions without damaging the mesoporous silica casting**.**

Some of the materials utilised in colloidal hard template processes include silver, gold, zinc, CdS and polymer beads.[24] Among these, polymer latex particles (e.g. polymethylmethacrylate, polystyrene,) in the dimension spectrum of a few micrometres to a few tens of nanometers the most suitable to fill open MSN positions because they are easily accessible ,cheap ,have uniform size , and can be simply eliminated with calcination in order to remove the organic material[2526] Contrarily, the expensive inorganic colloids must be eliminated in a caustic acid solution, which makes the technique risky as well as complicated. Surface activation must take place by mediating the necessary functional groups in order to enable silicification of the polymeric latexes interface. These groups have been added to the surface using a number of surface activation techniques, including as chemical modification proceeded by a deposition in layers procedure using electrostatic forces that are favorable.[27]The leaking of capping agents during the silica deposition can be stopped by the potent contacts between the functional groups and the polymer latexes and Although the widespread application of the polymer latex drafting technique to create homogenous hollowed silica spheres is expected to be hampered by such intricate surface-modification procedures. Therefore, a more practical method of silicifying the polymer latex surface activation is still needed. In order to stabilize the hydrophobic latexes with polymers and ensure effective hydrophobic interactions that cause dispersion within a hydrophilic solution both block polymers and surfactants have been used extensively. Additionally, the edge polymeric latexes effectively serve as a model for the empty MSNs by coating the polymers or surfactants by means of functional groups enabling gelation on

silica physically. The silica species would prefer to precipitate on the latex surfaces under ideal reaction circumstances (with regard to the, pH, water content and temperature), preserving the original structures. However, it was discovered such that MSNs may be also made under neutral pH settings in which the rate determinants self-condensation of silica is the largest, even though very acidic and alkaline conditions are typically needed to synthesis mesoporous silicas. The self-condensation speed of silicate needs to be reduced in a highly diluted solution, and heterogeneous condensation upon this advantageous surface should take precedence. It is expected that the rate of the face of the processed hard templates has a layer of silica will be higher than the rate of self-condensation of the silica species. Silicate itself is somewhat negatively charged in the same pH range of neutral solutions, which results in weaker interactions with the surfactant which is positively charged as well as over acidic and alkaline mixtures. The surfactant driven polymer latexes can then own integrated casting using mesoporous silica without surfactants leaching. The final objective in this case is to pre-program materials with mesopores to create a specified design with a defined performance in addition to simulating silicification in natural at neutral ph. The pH level has a direct impact on the density, kind and condensation rate constant of silica species. The pH value must therefore be well-controlled if high fidelity mesoporous silica replicas are to be obtained. It must be simple to remove the template without breaking the inorganic silica casting. Because of this, the sacrificial template method has been widely used. In this method, the interiors of the dissolvable or combustible materials can be easily removed following moderate calcinations, solvent extractions, and acid dissolutions without damaging the mesoporous silica casting. At a relevant polymer/latexes or surfactant ratio, replicas of continuous mesoporous silica will be created likewise the meso-structure. The surfactants utilised affect the pores of the highly porous shell. These cracked silica replicas, also known as mesoporous silica particles, would be produced at both lower and greater ratios along with the empty MSNs. Hollow MSNs are particularly well suited for bio-medical applications as they have a bigger room to load more medications, pharmaceuticals, enzymes, or nanoparticles because to their hollow interiors.[28]

Table 1: Differences in Methods of Synthesis of MSNs

Differences	**Soft templating**	**Hard templating**
Procedure	Few steps	Multi steps
Template	Surfactants	Silica, Alumina
Pore size	Highly uniform and narrowly distributed	Relatively wider than Silica templates
Prospect	Cheap Convenient, Large-scale production possible	Expensive, Time-consuming, large-scale production-impossible

By adjusting the reaction conditions, such as silica sources, reaction temperature, surfactants concentration, pH value, etc., mesoporous silicas can be made to produce a variety of mesostructures (for example, cubic, disordered, wormhole-like, hexagonal, and lamellar mesophases), morphologies (for example, fibres ,spheres, tubules, hollow spheres, crystals and gyroids.

Greener Approach for Synthesis of MSNs

Replacing organic templates by recyclable or environmentally acceptable amphiphilic chemicals that may be removed using solvent extraction rather than thermal treatment to conserve energy[29]

3. TYPES OF MSN[30]

3.1 Mobil crystalline materials No 41- MCM-41
3.2 - Mobil crystalline materials No 48- MCM-48
3.3 Mobil crystalline materials No 50 - MCM-50
3.4 Santa Barbara amorphous type material- SBA-15
3.5 Rod-like SBA-15- RL-SBA-15
3.6 - Michigan State University- MSU-F
3.7 Wormhole Hexagonal mesoporous silica

4. DRUG LOADING AND DRUG RELEASE MECHANISMS

4.1 Drug Loading

The final stage usually involves loading the medicines into MSNs. Huge amounts of medicament could be integrated and enters the pore-filled matrix via adsorption on the walls of the pore since MSNs have high particular areas and pore volumes. The distribution of poorly water soluble medicines, which can be challenging with numerous different kinds of carrier particles, is particularly well suited for MSNs. Since organic solvents preserve MSN's structural integrity, the process of drug loading is carried out in non-aqueous fluids. Additionally, the best fluid can be selected according to the solubility of the medication to be able to favor reactions between drugs as well as the pore wall over drug- solvent associations.

Increased loading levels than that are feasible with organic media can be achieved with more hydrophilic medicines by using pH-matching in an aqueous solvent.

Covalently attaching the medication by means of groups on the walls of the pore is another option for drug integration into MSNs. The drug activity should still be present in this situation after decoupling from the pore wall; hence it is preferable that the functional group that was originally employed to connect the drug molecule be reformed after detachment to protect the original drug molecular structure.[7]

Drug Loading is usually done as follows-

Drug loading is typically carried out as follows: The drug is loaded using an appropriate organic solvent. 0.1M HCl is one of the several solvents used for drug loading.[31, 32, 33], Acetic acid, Ethanol, Acetonitrile: dichloromethane34 DimethylSulfoxide(DMSO) etc. In the preliminary drug loading technique, a predetermined amount of medication is dissolved in a predetermined amount of solvent, and MSNs are then added. The mixture must be kept for magnetic stirring for a period of 24 hours at room temperature, additionally 2 hours of settling to permit for the settling of the fine residue that is extracted using sifting. The retrieved solid needs to be vacuum dried for 24 hours at room temperature before being stored.

4.2 Drug Release Mechanisms-

Mesoporous silica nanoparticles benefit from being functionalized with a variety of ligands since they have several silanol groups on their surface. Having a high amount of surface silanol groups enables end capping of MSN pores with various compounds that can regulate how much medication is released from the MSN in response to various external and intrinsic conditions. pH, light, magnetic fields, or redox potential are examples of stimuli that cause the drug release from MSN.

4.2.1 pH-Responsive MSN:

Various organic macromolecules and other biomolecules have been investigated as ligands as capping agents in the development of pH responsive MSN. With only a minor change in the pH of the environment, a suitable pH responsive MSN delivery system should offer the benefits of accurate drug release and simple production.

For example, it was reported that the formulation of controlled release pH responsive MSN end capped with cyclodextrin (CD) molecules. CD caps surrounded P-anisidine stalks capping the pores tightly. In acidic conditions, protonation takes place on-anisidine stalks which ultimately leads to dethreading and unblocking of pores on MSN.[35] Biomolecules have also been used as pH responsive end capping agents. In a study, Mengjun Xue group used Lysozymes as capping agents. Conformational changes in the capping enzyme are brought about by change in pH of the surrounding which leads to the drug release. In another example, Liu R, explored the potential of nanoparticles as capping agents. MSN pores were capped with Gold nanoparticles using acid-cleavable acetal linker. They came to the conclusion that these devices will be useful for delivering medications to tissues with low pH, like inflammatory tissues and tumours[36]

Chunlin Hu et al. explored the use of tannins S end capping agents by using Rhodamine as a model cargo. By forming boronate ester linkages, tannins were fixed to the exterior silanol groups of MSN. Under acidic conditions, ester bonds cleave, opening the pores and expelling the payload..[37]

4.2.2 Redox-Responsive MSN:

Endogenous reducing agents, such as glutathione, can be used as a trigger for medication release in redox responsive systems, negating the requirement for exogenous compounds. Several scientists have demonstrated the strategy of using redox responsive biomolecules as end capping agents for controlled drug release from MSNs.[38] In an extensive research, Dong Xiao et al elaborated the use of peptide shells as redox responsive end capping agent. The peptide sequences ((RGDWWW) 2KC) were connected to the MSN surface with the help of disulphide linkages. The peptide sequence served the dual purpose of gatekeeping agent as well as tumour targeting therapeutic agent. The uptake mechanism for anticancer drug loaded MSN was found to be integrin mediated endocytosis. Because of the high level of GSH in cancerous cells, disulphide bonds are broken, allowing drugs to be released. The peptide sequence reacts with and disturbs the DNA structure thud providing synergistic action for cancer cell death.[39]

In another study, Liangliang Dai et al hypothesized the efficiency of Heparin end capped MSN in the treatment of tumor tumors. Heparin which is a sulfated glycosaminoglycan serves as an ideal capping agent as it shows good hemocompatibility. Heparin was also hypothesized to be an inhibitor of angiogenesis and metastasis. Heparin was sealed on the surfaces of MSN through disulphide linkages to avoid any potential leakage of the drug. Lactobionic acid which was further attached to heparin served as a tumour targeting agent. Lactobionic acid will thus direct the drug delivery system towards the tumour cells. The disulphide bond will break because of the high levels of GSH in cancerous cells, allowing the drug to diffuse into the cancer cells.[40]

4.2.3 Light-Responsive MSN:

The mechanism of drug release from light responsive MSN relies on the photosensitivity of the gatekeeper molecule. The photosensitive end capping agent changes its conformation after irradiation with light and causes the drug release. Several such molecules have been explored for their potential in formulation of stimuli responsive drug delivery systems, for example Azobenzene, Coumarine and several other biomolecules. Use of Light as a triggering agent provides advantages of special and temporal control of the triggering agent and low toxicity. Also, use of these external stimuli avoids the need of complex procedures of coupling targeting moieties to nanocarriers. In an extensive study, by simultaneously employing peptide shell as a targeting and triggering agent, a unique photosensitive drug delivery system was created. The protein shell which is composed of streptavidin, biotinylated transferrin and Avidin was attached to MSN surface by covalent bond formation between Avidin/ Streptavidin and photosensitive Biotin linker. The nanocarrier system is internalized due to the presence of Transferrin as a targeting agent. After light irradiation, a cytotoxic agent is released in the tumour cells. Despite much research in this field, light-sensitive delivery devices have the disadvantage of having a low UV radiation's penetrating power. Thus, these systems have limited applications in treatment of surface tumours.

4.2.4 Glucose-Responsive MSN:

For the purpose of loading various guest molecules, MSN provides both internal pore and external particle surfaces. Limiting the order of release for various cargos, which is essential for the effectiveness of many codelivery features, is a special benefit of this. These codelivery systems that determines the release order may be crucial in helping therapy overcome some of its current difficulties. The insulin release decreases over time in typical glucose-responsive insulin delivery devices. This issue can be resolved if sequential delivery of cAMP, that also stimulates Ca2+channels of pancreatic beta cells and subsequently increases insulin production, can also induce the release of insulin from living cells. Researchers have created a glucose-responsive MSN-based dual delivery method with accurate limit on the release order.[41]

5. CHARACTERIZATION AND EVALUATION[42]

MSNs can be characterized by following methods:

5.1 Electron Microscopy

5.1.1 TEM Imaging
5.1.2 SEM Imaging

5.2 Surface analysis
5.2.1 BET(Brunauer-Emmett-Teller theory)
5.2.2 BJH (Barrett, Joyner and Halenda) method
5.2.3 Calculated surface characteristics

5.3 Differential Scanning calorimetry
5.4 Fourier transform infrared spectroscopy (FTIR analysis)
5.5 Powder X-ray diffraction

6. APPLICATIONS OF MSN

Due to flexibility of surface modification and functionalization, MSN are being explored in broad areas of applications. Some of the proven applications of MSNs in various areas are as follows:

6.1 MSN like a Platform for the distribution of water insoluble Anticancer Drugs Camptothecin (CPT), a hydrophobic anticancer medication, was incorporated into fluorescent MSNs' pores to assist deliver the drug towards a range of human tumour cells which causes them to die. As a result, MSNs can be employed to get around the low solubility issue that many antitumour treatments have.[43]

6.2 Highly Effective MRI Contrast Agents: MSN Gadolinium chelates now in use lack sensitivity and don't offer a good image in the early stages of disease. Due to the increased relaxivity brought on by lower tumble speeds and greater weights of active magnetic cores, nanoparticulate MR contrast elements are significantly more delicate. Because Gd chelates can hold a huge weight of Gd centres and have improved water proximity, they can be grafted onto MSNs to provide an perfect setting for producing extremely effective MR agents which are contrasting.[444528]

6.3 Use as Biosensors: MSNs are capped with a chemical that is friendly to the target cells and loaded with a fluorescent dye. These MSNs transport the dye across cell membrane when introduced to a cell culture. The dye may be seen through the walls of the silica because the particles are optically transparent.[46]

6.4 MSNs for the eradication of chemotherapy-resistant tumours through synergistic therapy, which involves the use of two or more medicines with various methods. To create a tightly regulated DDS for a combined cancer treatment, MSNs can be used as a nanoplatform to encase the antitumour treatment doxorubicin, TPP (mitochondria-targeting therapeutic peptide) and TCPP (tumor-targeting cellular membrane-penetrating peptide), and [47]

6.5 Application in Stimuli-responsive DDS- It is practical to attain the objective of drug retention in the pores by enclosing the top with gatekeepers until gatekeepers are dislodged by external influences such as pH, enzyme and temperature. By including tumor-targeting ligands in the gatekeepers, such as folic acid and peptide, one can create a DDS that responds to stimuli and allows for highly controlled drug release that is targeted specifically at the target tumour.[47]

6.6 Due to their high bioactivity, chemical stability, high payloads and biodegradability nanostructured materials, particularly MSN, have gained a lot of interest as a vaccine adjuvant for Schistosoma mansoni. This makes them a viable choice. MANs have a higher capacity for triggering an immune response than traditional adjuvants.[48]

6.7 MSN to improve nutraceutical delivery Resveratrol poor solubility and irregular pharmacokinetic profile, which result in low bioavailability) potential as a nutraceutical is constrained. Potential carriers for RES as well as other hydrophobic nutraceuticals include MSNs (MCM-48). In comparison to pure RES, MSN-RES dramatically improved both the solubility and in-vitro release kinetics.[49]

6.8 The penetration of substances into the skin is increased by MSN in cosmetics-MSNs. They have hydrophilic surfaces and are simple to functionalize on the surface. They work by regulating or maintaining the skin's absorption of medications or cosmetic

substances while also promoting the penetration of encapsulated compounds.

6.9 Applications of mesoporous silica materials in food-

i. To control the release of molecules with biological activity.

ii. In the synthesis of vital nutrients as catalysts.

iii. Creation of films and foods and and food and industrial packaging [30]

6.10 Nanomaterials are included into TFC membranes to improve the filtration efficiency of the membranes in water purification systems. The performance of desalination is improved by TFN membrane hybridised with Hollow MSN. Relatively speaking of the TFC membrane, the HMSN-TFN membrane has a greater compression resistance. High-pressure filtration processes require membranes with good strength and durability, such as HMSN-TFN membranes.[50]

7. CHALLENGES

As we have seen in this review, MSNs have a variety of benefits and uses, but their synthesis and production present a number of difficulties, including their non-reproducible production and difficulty in managing different surface features. For intracellular routing, a complete knowledge of the reactions at the nano-bio boundary and pickup processes is required. There are no standardised protocols or ways to measure drug release, cell function, or uptake. Additionally, it is essential to carefully plan animal studies for pharmacokinetics, biocompatibility and in vivo biodistribution studies. Another difficulty is maintaining the distinct morphology of nanoparticles across all processing stages.

8. FUTURE PROSPECTIVE

Realization of nanotechnology's in vivo promise for precise imaging and medicine delivery.

MSNs need to have more intelligent effects on a variety of diseases' treatments.

If nanoparticles of iron oxide can be placed inside the highly porous particles for MRI and magnetic modification, it will function as a good diagnostic tool.

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Recent Advancements in Cancer Therapies

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Abstract

Cancer is a disease where cells undergo abnormal division and can extend adjoining organs. In recent years cancer is regarded as the leading cause of death in many underdeveloped and developing countries. Hence, there is a constant need of developing newer approaches to cure cancer. Many industries and institutes are striving hard to overcome the resistance to many therapies and prevent the cancer relapse. This mini review consists of the global statistics and potential causes of cancer along with the recent developments in the field of cancer treatment.

1. Introduction:

Malignancy is a group of diseases which can initiate in any part within the body. It occurs when anomalous cells multiply uncontrollably, traverse their physical limits and extend to adjacent organs. Metastasis is a crucial contributor to mortalities due to cancer. The phrases "neoplasm" and "malignant tumors" are frequently employed to represent cancer.

Approximately 9.6 million casualties were due to malignancy in 2018, making it one of the most fatal diseases across the globe. The most prevalent tumors in males include pulmonary, prostate, colorectal, stomach, and hepatic cancer while those in females include breast, colorectal, pulmonary, cervical, and thyroid cancer [1].

The physical, psychological, and economic effect that cancer has on patients, family members, societies, and healthcare systems in the world keeps advancing. Numerous under-developed and developing country's healthcare systems are not well equipped to withstand this impact, and several patients have deficient access to instantaneous, efficacious prognosis and therapies. Due to readily accessible and timely diagnosis, sophisticated therapy, and survivorship caring, the mortality status of various types of cancer are decreasing in countries having robust medical services.

Whenever malignancy is detected in the initial phase, the patient is more responsive to appropriate therapies, increasing the likelihood of survival as well as reducing chances of mortality and treatment costs.

Early diagnosis is facilitated by two different techniques:

1. Rapid disease detection discovers symptoms of malignancy at the initial stage.
2. The goal of monitoring is to locate people who have deformity indicating a particular disease or pre-cancer but do not yet have any symptoms so that they can be quickly diagnosed and treated.

Surgical procedures, cancer medications, and/or radiation, either alone or in combination, are available as alternative treatments. Based on tumor kind, malignancy stage, clinical, and other characteristics, an interdisciplinary team of cancer experts suggests the ideal treatment strategy.

Patients' preferences should be taken into account, as well as the capabilities of the healthcare system. A crucial part of cancer treatment is palliative care, that aims to enhance the life experiences of patients and associated relatives. A comprehensive objective of keeping tabs on cancer relapse and identifying developing cancers, evaluating and treating the long-term adverse reactions of malignancy and/or accompanying therapy, and assistance to suffice the requirements of cancer survivors are all included in survivorship care.

2. GLOBAL STATISTICS OF CANCER [2,3]:

Cancer is the prevalent reason of casualties across the globe, comprising 10 million fatalities in 2020. Figure 1 and 2 gives the statistics of incidence and mortality rates of various cancers.

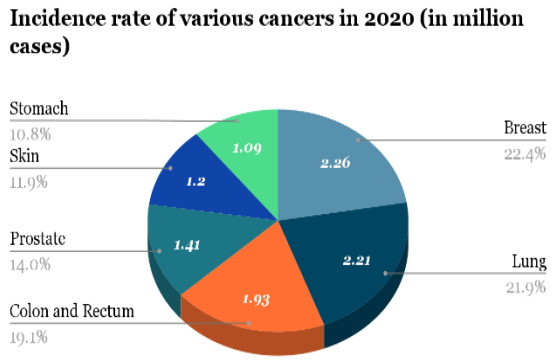

Fig 1: Incidence rate of cancers in 2020.

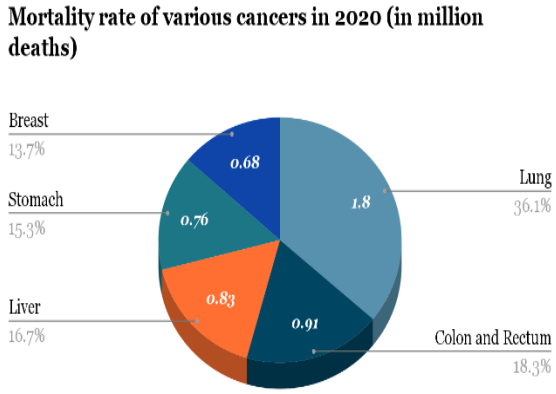

Fig 2: Mortality rate of cancers in 2020.

3. POTENTIAL CAUSES OF CANCER:

In a multilevel pathway that generally moves from a pre-malignant wound to a malignant tumor, the tumor progresses as the normal cells undergo a change to cancerous cells. The interaction of subject's genetics and predisposing factors of external agents which causes alterations include:

- Physical carcinogenic substances, like UV radiation and ionizing irradiation;
- Chemical carcinogenic substances, like alcohol, asbestos, smoke, and aflatoxin; and
- Biological carcinogenic substances, viral, bacterial, or parasitic infections.

The International Agency for Research on Cancer (IARC), a WHO division, monitors a taxonomy of cancer-causing substances.

Risk for many cancers increases with age due to inefficient cellular repair systems. This is the root-cause of the steep rise in incidence rates. Tobacco use, alcohol usage, poor diet, lifestyle factors, and pollution are the leading cause for malignancy and other related diseases.

Risk factors for cancer may comprise some chronic infectious diseases; underdeveloped and developing countries are majorly influenced by this. Internationally, malignant infections such as *H. pylori, human papillomavirus (HPV),* hepatitis B, hepatitis C, and *Epstein-Barr virus* were the cause of more than 13% of total cancer prognosis in 2018 [4].

Some types of HPV, hepatitis B and C viruses, increase the probability of hepatic and cervical cancer development, respectively. HIV infection remarkably elevates the chances of getting some cancers, including Kaposi sarcoma, and elevates the likelihood of developing cervical tumor.

Recently the medical industry has seen various developments in the field of cancer therapy. Here are some of the major developments in the past few years.

4. MAJOR DEVELOPMENTS IN THE FIELD OF CANCER THERAPY

4.1 Strategy to improve the success rate of immunotherapy [5]:

Researchers from University of Southampton discovered the justification of failure of immunotherapy treatment in some cancers. This breakthrough brings a ray of hope that many patients can survive cancer. Researchers along with Cancer Research UK, have identified a key cellular protein that prevents the treatment from working and crucially, have found a drug that can overcome it.

Immunotherapy acts by activating the immune system to identify and mitigate cancer cells and has great success in curing various cancers. Although, for many patients, the immunotherapy is unsuccessful due to a defensive barrier called cancer-associated fibroblasts (CAFs) present on the tumor into which the T-cells cannot penetrate.

4.2 Engineering immune cells to hunt down cancer [6]:

Adoptive cell treatment is a cancer treatment that uses immune system cells to get rid of tumor cells. This cutting-edge technique to treatment has shown to be, at least briefly, helpful for select cancers, such melanoma, however it is ineffective for the majority of tumors.

This research focuses on the immune cell subtype known as invariant natural killer T cells (iNKT cells). The cells are a regular component of the immunity system of the human body; they fight cancer cells by eliminating other immune cells which would promote the growth of the disease.

The application of nanotechnology to accurately transport the medicine to the tumor tissue increased the efficacy of this strategy by strengthening the anti-tumor effects of the therapy and enhancing the ability of iNKT cells to eradicate cancer cells.

4.3 Killing cells while they sleep to stop the spread of breast cancer [7]:

The researchers discovered that normal cells in the soft tissues produce more antioxidants, which are substances the body releases to shield the body from harm. Surprisingly, scientists discovered that the rise in antioxidants fosters the arrival of tumor cells and makes it challenging to eradicate them with chemotherapeutic agents.

In-depth study discovered that according to the flexibility of the tissue, molecules termed DRP1 and NRF2 were in charge of causing antioxidant production. According to the study's findings, inhibiting DRP1 and NRF2 may be a strategy for chemotherapeutically treating malignant cells that have migrated to unaffected areas of the body. Such Breast cancer discoveries are tremendously encouraging because they usher in a new era of therapies that may prevent the spread of metastatic or secondary breast cancer.

4.4 Promising results of Dostarlimab clinical trial [8]:

A small clinical trial conducted for Dostarlimab showed remarkable results in all the 18 patients suffering from rectal cancer. It was predicted that post- trial these patients will need to undergo surgery or radiation. But in physical examination through endoscopy, positron emission tomography scans, or MRI scans, the tumor growth was not detected. Also, all the did not show the common side effects like bowel, urinary, and sexual dysfunction which are more prevalent in conventional treatment such as chemotherapy, surgeries, and radiation. The researchers also stated that chemoradiotherapy or surgery was not applied to patients, and progression or recurrence had not been reported during follow-up post-trials.

4.5 Novel strategy for cancer patients offers a ray of hope [9]:

When other therapeutic options, like surgery, radiotherapy, or chemotherapy are unsuccessful, immunotherapy focuses on the immunity to locate and eradicate malignant cells and may save life. However, all patients are not benefited by it, and some tumors may become resistant to it. In the UK, oncologists have studied immunotherapy in conjunction with the ingenious investigational medicine guadecitabine that can prevent tolerance by malignant cells to immunotherapy. The patients who were not responding to any therapy sustained substantially better. More than 1/3rd of the enrolled patients in the preliminary phase I trial, the combined effect of the immunological drug pembrolizumab and the next-generation DNA

hypomethylating agent guadecitabine prevented the proliferation of the tumor. The two together might prove to be a potent new tool in the fight against various cancer types.

5. CONCLUSION:

This article provides a clear view of the global cancer statistics with respect to their incidence rates and mortality rates of various prominent cancers. This helps us to understand the severity of cancer progression across the globe. The article also put some light on the potential causes of cancer which can help us to take preventive measures at early stages. Further some of the research advancements in the field of cancer mitigation are also explored.

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Formulation and Evaluation of Enteric-Coated Lansoprazole Pellets

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Abstract

The objective of the research work was to develop an effective formulation for enteric-coated pellets of lansoprazole. The active ingredients and fillers in bulk pharmaceuticals were compressed into pellets. They are typically intended for oral delivery and have a unit size ranging from around 0.5mm to 1.5mm with a spherical or semi-spherical shape. There are a variety of ways to make pellets, but the most common include compression and drug stacking. The purpose of this research was to create a delayed-release pellet dosage form of lansoprazole, a Benz-imidazole anti-ulcer agent that is one of the most commonly prescribed medications for both mild and severe ulcers. In this investigation, polymers such as Hypermellose and Eudragit L30 D55 were used to create enteric-coated pellets. Suspension layering was used to create the pellets. USP II equipment was used to examine the release of the drug from the enteric-coated pellets in 0.1 N HCL and phosphate buffer at pH 6.8. The cumulative percentage of drug release was calculated.

1. INTRODUCTION:

Acid and secretion from the stomach can be tempered with proton pump inhibitors (PPIs). A proton pump inhibitor (PPI) works by inhibiting the activity of the hydrogen/potassium adenosine triphosphatase (H^+K^+ATPase) of the stomach parietal cell, also known as the "proton pump"[1]. Peptic ulcers are sores in the stomach, duodenum, or oesophagus that allow digestive juices to leak out. Gastric ulcers are those that form in the stomach, duodenal ulcers in the duodenum, and esophageal ulcers in the oesophagus. The stomach's acidic digesting acids can damage the lining of these organs, leading to an ulcer. Millions of people suffer from peptic ulcer disease yearly. The principal effect of proton pump inhibitors (or "PPIs"), as a class of medications, is a significant and long-lasting reduction in gastric acid output. Dyspepsia, Peptic Ulcer Disease (PUD), and Gastroesophageal Reflux Disease (GERD) are just few of the many disorders that these medications are used to treat. Disease of the Larynx (LPR), Esophagus (Breslow's), and Stomach (Stress Gastritis) Prevention. Hypersecretory diseases, such as gastrinomas and various tumours of the stomach lining, are also included. The syndrome of Zollinger-Ellison[5].

The H^+/K^+ATPase, or more commonly the gastric proton pump, is an enzyme system found in the gastric parietal cell that is irreversibly blocked by proton pump inhibitors. Since the proton pump is directly responsible for the secretion of H^+ ions into the gastric lumen, it is a prime target for suppressing acid production from the stomach.

In order to repair acid-related illnesses like gastric ulcers, duodenal ulcers, and reflux oesophagitis, lansoprazole may be used. It's an adjunct in the elimination of Helicobacter pylori and is used to treat acid-related dyspepsia, ulcers, and GERD. The pharmaceutical sector is extremely interested in pellets for many different reasons. Pelletized products are used to increase the safety and effectiveness of bioactive agents, and they also provide greater freedom in dosage form design and development. The primary goal of the current research work was to create a micro pellet

formulation of Lansoprazole that is stable, effective, robust, and has a delayed onset of action [2, 3].

The primary goal of enteric polymers is to delay the release of drugs that are inactivated by stomach contents or that may cause bleeding or nausea due to the irritation of gastric mucosa; because they remain intact in the stomach but dissolve and release the contents once it reaches the small intestine, they are gaining in popularity[4].

2. EXPERIMENTATION:

2.1 Materials:

Lansoprazole API was procured from Cipla Pvt. Ltd., Mumbai. Colloidal silicon dioxide, sugar spheres, light Magnesium carbonate, talc, titanium dioxide polyethylene glycol, and talc were obtained from Molychem Lab., Mumbai. Eudragit L30D55 copolymer methacrylic acid was procured from Evonik, Mumbai.

2.2 Methods:

2.2.1 Preparation of Lansoprazole pellets: Using The first generation of Lansoprazole pellets was created with the help of a Wruster coater and a suspension layering process,. Lansoprazole, sugar spheres, Hypermellose, Magnesium carbonate, Talc, and sterile water were mixed together to make the medication slurry. The pellets' center of gravity was measured. Following this, the pellets were sprayed with a sub-coating. The components of the sub-coating solution were Hypermellose, Magnesium carbonate, and distilled water. There was a record of both the undercoat and overall weight. The pellets containing the necessary amount of medication were removed and coated with a barrier. The pellets were filled with a barrier coat solution including Hypermellose, Talc, Titanium dioxide, and distilled water. The Wruster coater was used to apply an enteric coating to a measured amount of pellets. Pellets were loaded with a compound made of methacrylic acid copolymer (Eudragit L30D55), polyethylene glycol, talc, titanium dioxide, and distilled water. Both the total pellet weight and the enteric coat weight were recorded. Talc and colloidal silicon dioxide were used as lubricants on these drug-loaded and coated pellets.

2.2.2 Physical Appearance:

Visual inspection of pellets was performed during daytime hours.

2.2.3 Loss on drying (LOD):

The procedure recommended by U.S. Pharmacopeial Convention (U.S.P) was followed. About 1 g of the pellet was dried in a vacuum over phosphorus pentoxide at 60ºC for one hour. The formula used for calculation of LOD was:

$$\frac{W_1 - W_2}{W_1 - W_T} \times 100 = \%LOD$$

Where -

W_T = weight of empty bottle and stopper

W_2 = weight of bottle and dried sample

W_1 = weight of bottle and undried sample

2.2.4 Content in Drug loaded, sub - coated and barrier coated pellets:

Pellets were weighed, then transferred to a 250 ml volumetric flask (300 mg Lansoprazole). The pellets were sonicated in 60 ml of 0.1 M NaOH. The solution was diluted up to 100 ml with acetonitrile and mixed thoroughly. 25 ml of the resulting solution was further diluted up to 100 ml. To prepare the test solution, 5 ml of the stock solution to be tested was taken in a 50 ml volumetric flask and volume was made up to 50 ml. Remove the initial 2 ml of the solution and centrifuge the rest for at least 20 minutes at 2500 rpm before filtering the supernatant through a 0.45 nylon filter. (About 30 parts per million concentration)

% content of Lansoprazole for 30 mg drug was calculated using the following formula:

$$\text{\% Content of Lansoprazole for 30 mg strength} = \frac{At \times W\,ref \times 5 \times 250 \times 50 \times M \times P \times 100}{As \times 100 \times 50 \times W\,test \times 5 \times 100 \times 30}$$

A_t: Absorbance of the Lansoprazole from test solution;

A_s: Mean Absorbance of the Lansoprazole from the reference solution;

W_{ref}:: Mass (mg) of standard taken;

W_{test}: Mass (mg) of test substance;

M: Theoretical mass, in mg equivalent to unit dose;

P: Purity of standard on dry basis

2.2.5 Blend uniformity of pellet:

With the use of a funnel, the contents of the filled vial were carefully transferred to a "y" ml volumetric flask. Pellets were sonicated in 24% of the flask's capacity of 0.1M sodium hydroxide until they were entirely destroyed. After cooling the solution, 16% acetonitrile was added to the flask's capacity, the solution was shaken, and about 40% of diluent was added to fill the flask. The solution was stirred on a magnetic stirrer for 15 mins and volume was made up with the diluent. The test solution was prepared again and applied it to 9 more samples. The empty vial was dried for 10 minutes at 105°C, after rinsing it with acetone (around 5 ml to 10 ml). The vial was kept in a desiccator, and weighed after complete drying. Test solution was prepared by diluting 5 ml of the stock up to 50 ml with diluent. A part of solution was centrifuged for at least 20 minutes at 2500 rpm and a portion of the supernatant solution was filtered through 0.45µ nylon filter discarding the first 2 ml.

2.2.6 Dissolution of pellets:

Acid Stage:

For composite sample – Pellets were added into each of the six glass beakers which would amount to around 1 unit of dosage. Pellets were placed into the dissolution apparatus and the test was run under the specified parameters.

For unit dose sample - Full unit dose sample pellets were accurately weighed and transferred to the dissolving vessel. The dissolution profile was executed under the specified circumstances.

Using a pipette covered in nylon fabric, 5 ml of each test solution was removed at the end of the allotted time. The first 2 ml of the filtered solution was discarded.

Buffer Stage:

425 ml of preheated buffer was added to the remaining 475 ml of solution in each jar from the acid stage as soon as possible (within no more than 3 minutes). Temperature was maintained at 37 °C ± 0.5°C Appropriate amount of sodium hydroxide or phosphoric acid was added at the same time, following the instructions for making a blank solution.

Using a pipette whose tip is wrapped in nylon fabric, 10 ml of each test solution was removed at the end of the time period prescribed. The first 2 ml of the filtered solution was thrown away.

3. RESULTS AND DISCUCSSION

3.1 Physical parameters of drug loaded pellets:

Appearance was found to be white to off-white pellets, loss on drying at 60^0C for 30 minutes, and sieve analysis were done. It was found that the lansoprazole pellets met all the ideal characteristics and the acceptance criteria.

3.2 Uniformity of content for drug-loaded pellets:

Acceptance criteria: 90.0 – 110.0 % of the labelled amount with RSD of NMT 5.0%.

The Lansoprazole pellets formulated met the acceptance criteria.

The graphical representation of Uniformity of content results at the Drug loading stage of sugar pellets is described in **Figure 1.**

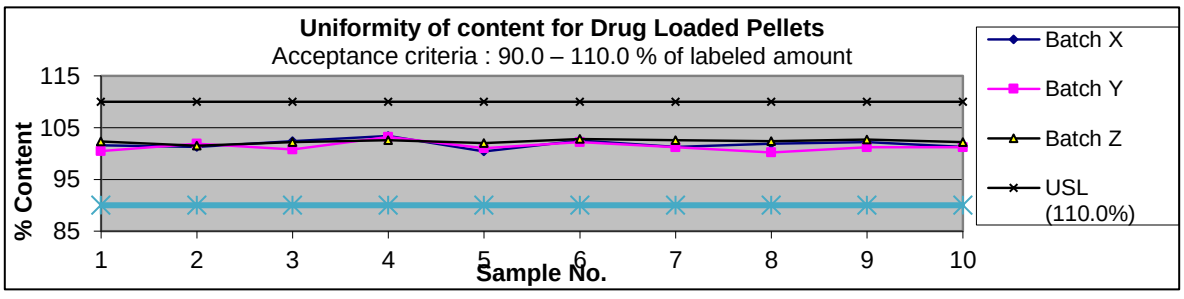

Fig 1: Graphical representation of results of Uniformity of content of Drug loaded pellets

3.3 Physical parameters of Sub-coated and barrier-coated pellets:

Three batches were formulated. The physical parameters like appearance, sieve analysis, loss on drying were tested. It was found that the pellets met the acceptance criteria.

3.4 Evaluation parameters of Enteric-coated pellets:

3.4.1 Physical parameters, Sieve analysis, and content uniformity of Enteric-coated pellets:

The appearance, sieve analysis, and content of lansoprazole results of enteric-coated pellets are described in **Table 1**.

Table 1: Appearance, Sieve analysis, and Content of Lansoprazole of Enteric-coated pellets

Test	Acceptance Criteria	Validation batches results		
		Batch X	Batch Y	Batch Z
Appearance	White to off white pellets	White to off white pellets	White to off white pellets	White to off white pellets
Content of Lansoprazole	95% to 105% of labeled amount	101.6%	101.4%	102.6%
Sieve analysis			---	
% retained on 18 # (1000 µ)	10% to 40% w/w	21.03%	24.4%	26.5%
% retained on 20 # (850 µ)	60% to 90% w/w	77.77%	74.5%	70.5%
Collector	NA	1.20%	1.1%	3.0%

3.4.2 Blend uniformity of Enteric-coated pellets:

Acceptance criteria: 90.0 – 110.0 % of labelled claim (mean of individual results) with RSD of NMT 5.0%. The blend uniformity results for three batches are described in **Table 2**.

The graphical representation of Blend Uniformity results of Enteric-coated pellets stage is given in **Figure 2**.

Table 2: Blend uniformity of Enteric-coated pellets

Sr. No.	% Content		
	Batch X	Batch Y	Batch Z
1	102.2	102.4	102.2
2	102.0	99.8	102.3
3	101.2	102.0	102.0
4	102.6	99.6	103.8
5	100.7	100.5	101.8
6	100.1	101.4	103.0
7	101.9	101.3	101.5
8	100.5	99.6	103.6
9	100.7	100.1	103.1
10	101.3	101.2	102.4
Min	**100.1**	**99.6**	**101.5**
Max	**102.6**	**102.4**	**103.8**
Mean	**101.3**	**100.7**	**102.6**
% RSD	**0.81**	**1.00**	**0.75**

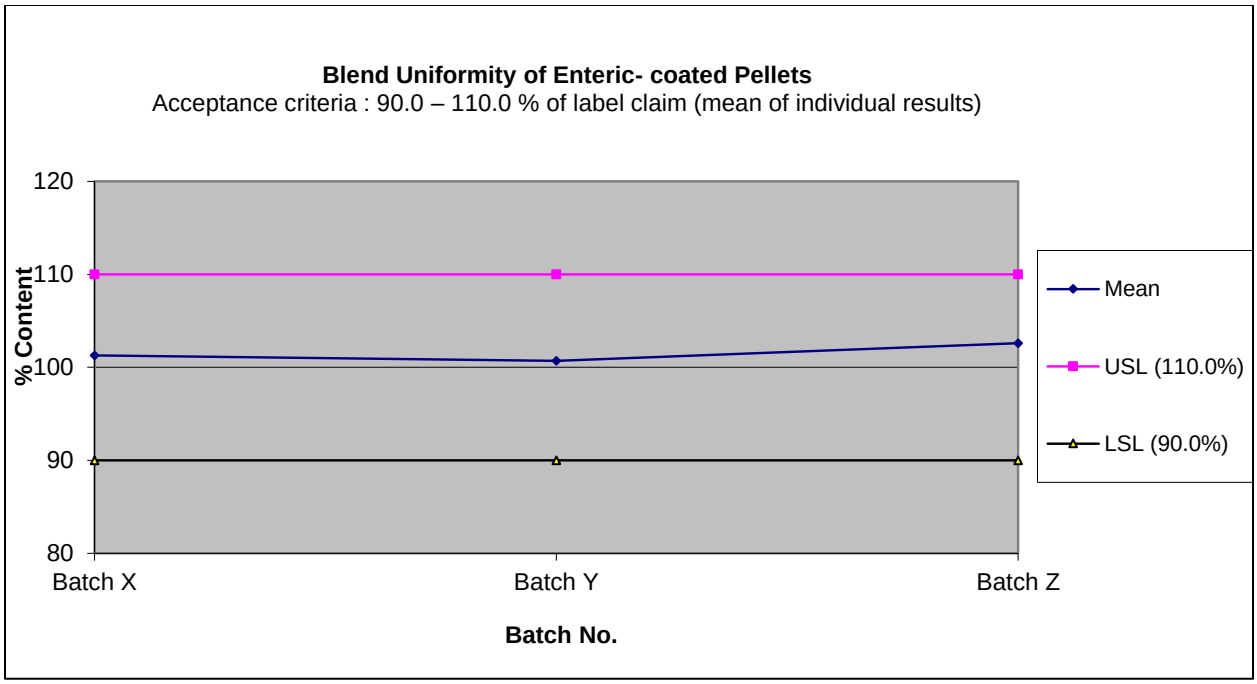

Figure 2: Graphical representation of results of Blend Uniformity of Enteric-coated pellets

3.4.3 Dissolution of Enteric-coated pellets:

Acceptance criteria for dissolution:

A) Acid Stage: NMT 10% of the labelled amount of Lansoprazole is released.

B) Buffer stage (After 60 minutes): NLT 80% (Q) of the labeled amount of Lansoprazole.

The dissolution data of Enteric-coated pellets is given in **Table 3**.

The graphical representation of Dissolution results of Enteric-coated pellets is shown in **Figure 3** for Acid stage and in **Figure 4** for Buffer stage.

Table 3: Dissolution data of Enteric-coated pellets

Sample No.	(%) release of Lansoprazole					
	Batch X		Batch Y		Batch Z	
	Acid Stage	Buffer stage	Acid Stage	Buffer stage	Acid Stage	Buffer stage
1	0	104	0	102	0	99
2	0	105	0	104	0	105
3	0	103	0	103	0	104
4	0	104	0	102	0	105
5	0	103	0	102	0	106
6	0	103	0	103	0	105
Min	**0**	103	**0**	102	**0**	99
Max	**0**	105	**0**	104	**0**	106
Mean	**0**	104	**0**	103	**0**	104

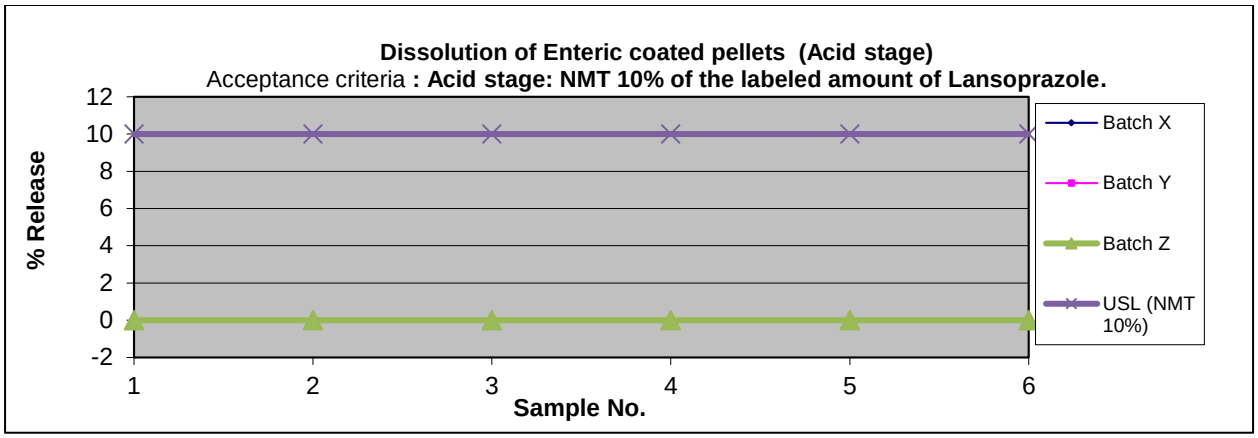

Figure 3: Graphical representation of Dissolution (Acid stage) results of Enteric-coated pellets

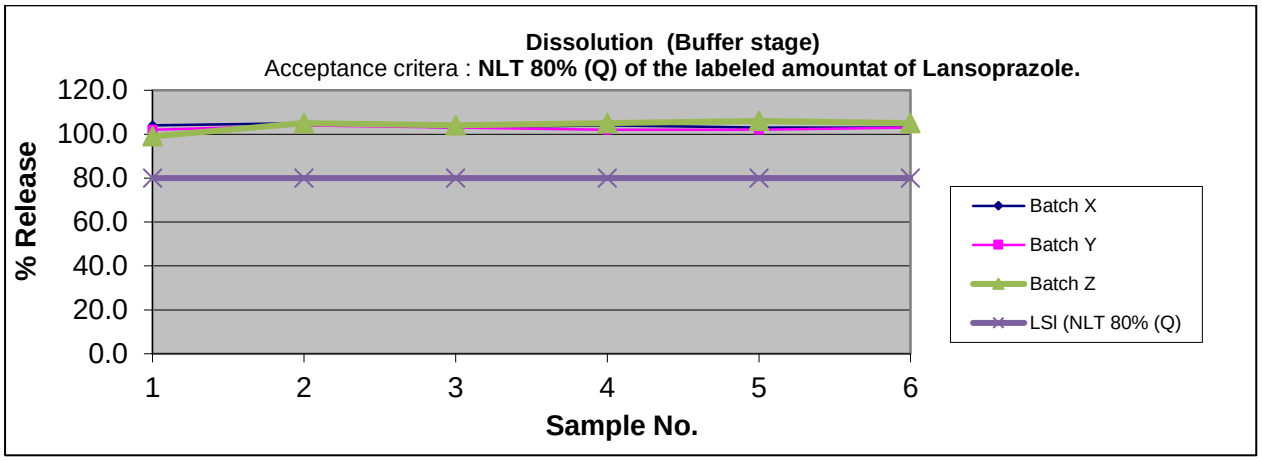

Figure 4: Graphical representation of Dissolution (Buffer stage) results of Enteric-coated pellets

4. CONCLUSION:

Lansoprazole was chosen as the active pharmaceutical ingredient and was developed into an Enteric Coated Pellet form. The developed formulation was found to deliver the appropriate drug release pattern. The technology used for pellet formulation exhibited the best way to incorporate the retarding agents Eudragit L-30D-55 and Hypermellose into a Lansoprazole Enteric Coated Pellet. However further work needs to be done to evaluate the preclinical and clinical efficacy of the formulation.

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A Review on lipid excipient for lipid based drug delivery system

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Abstract

Lipid based drug delivery systems provide an effective way to deliver drugs with different molecular weights (small and large Molecular weight) and bioactive ingredients at specific locations and times. Poorly water-soluble drugs present a challenge to formulation scientists in terms of solubility and bioavailability. Simple oil solutions and complicated blends of oils, co-surfactants, surfactants, and cosolvents are both examples of lipid-based delivery systems. Nevertheless, lipid excipients have the ability to solubilize hydrophobic drugs in the matrix of the dosage form. A decrease in the barriers of poor aqueous solubility and a slow drug dissolution rate in the gastrointestinal (GI) fluids leads to enhanced drug absorption, which is predominantly mediated by these factors. The quantity of potential excipients available to the formulator to select from when creating lipid-based formulations can appear daunting. Several currently available kinds of lipid excipients will be discussed in this review article regarding their pharmaceutically useful properties: Natural oils, fats, fatty acids, and fatty acids Semi-synthetic mono-, di-, and triglycerides, as well as derivatives of glycerides, fatty acids, and cholesterol, as well as Polyglyceryl and phospholipids, as well as Polyglyceryl fatty acid esters.

1. INTRODUCTION

As lipid-based drug delivery systems offer the suitable means of site-specific as well as time-controlled delivery of drugs with different molecular weights, either small or large, and the bioactive agents, significant efforts have been made in recent years to utilize their potentials.[1]

Most recently discovered medications exhibit low bioavailability when taken orally because they are hydrophobic. Additionally, because the newly identified chemical entities have high molecular weights and rising lipophilicity, the recent discovered drugs are not suitable for oral administration[1,2]. As a result, lipophilic drug discovery, formulation, and development are now complicated by the poor aqueous solubility of these drugs. It was clear that up to 70% of recently developed compounds and about 40% of drugs that are currently on the market may have poor water solubility. Due to poor bioavailability and lack of pharmacological action at the site of action, low water solubility causes insufficient amounts of drugs to enter the systemic circulation. [1] The oral bioavailability is constrained by the poor aqueous solubility and slow dissolution rate. Because of this, creating these therapeutic agents that have the highest oral bioavailability possible is a difficult task. The rate and degree of drug absorption through the GI membrane which is only possible when the maximum percentage of drugs is solubilized in GI contents is another sign of a drug's effectiveness. According to their aqueous solubility and GI membrane permeability, drugs are divided into four classes in the Biopharmaceutics Classification System (BCS). The formulation to increase bioavailability is thought to be challenging for class II drugs (high permeability and low

solubility) and class IV drugs (low permeability and low solubility).[3–5]

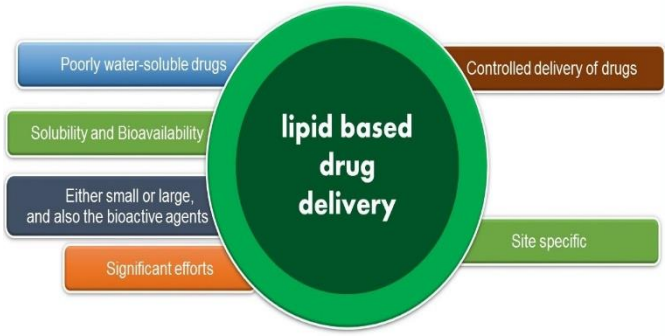

Fig 1: Rational behind lipid-based drug delivery system

2. GENERAL ROUTES OF LBDDS:

A significant risk factor for developing diabetes is obesity. There are several ways to provide lipid-based drug delivery systems, including oral, parenteral, ophthalmic, intranasal, dermal /transdermal, and vaginal methods (LBDDS). The least costly, least intrusive, and least likely to result in adverse effects, such as responses at the injection site, is the oral route, which is why it is the most often used. It is also seen to be the simplest and most useful method of giving patients long-term therapy. Formulation strategies based on a logical and systematic approach must be devised at an incredibly early stage of development in order to avoid irregular and poor in vitro/in vivo correlations and so boost the odds of formulation development success.[6]

3. LIPID FORMULATION CLASSIFICATION SYSTEM

There A new "type" of formulation was added to the lipid formulation classification system (LFC) in 2006 after it had already been introduced as a working model in 2000. In recent years, the pharmaceutical industry has discussed the LFCs more extensively to reach an agreement that can be used as a framework for comparing the performance of lipid-based formulations. [6] The main goal of the LFCs is to make it easier to interpret in vivo studies, which will then make it easier to identify the best formulations for drugs based on their physiochemical properties, which are shown in Table 1.[6,7]

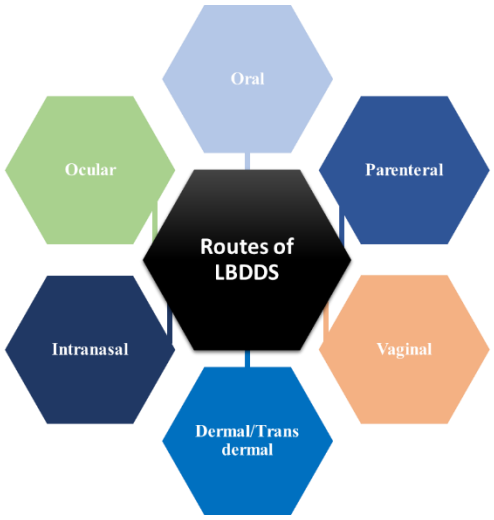

Fig 2: Routes of administration of lipid base drug delivery system.

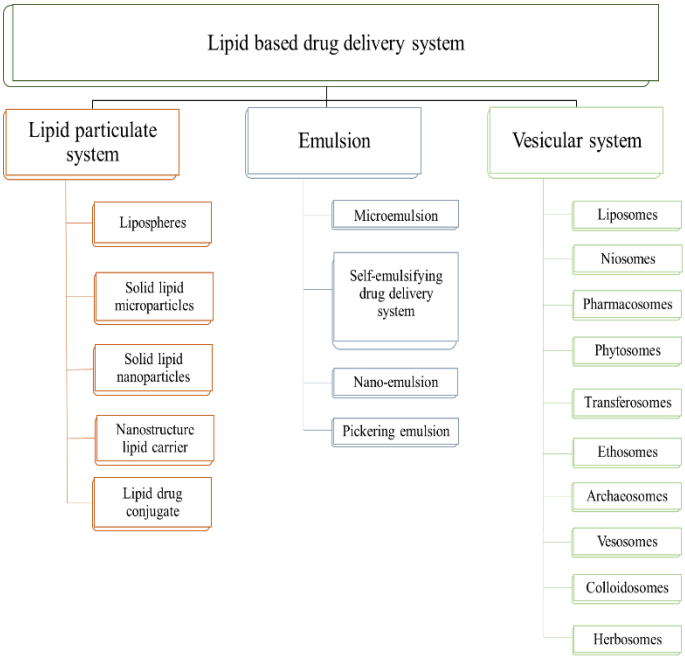

Fig 3: Types of lipid-based drug delivery systems

4. LIPID-BASED EXCIPIENTS FOR ORAL DRUG DELIVERY

An oral lipid-based formulation increases the bioavailability of a weakly water-soluble drug more than an oral solid dose form. Although

Table1.Lipid formulation classification system

Formulation type	Material	Characteristics	Advantages	Disadvantages
Type I	Oils without surfactants (e.g.,tri-, di-, and monoglycerides)	Non-dispersing requires digestion	Generally recognized as safe (GRAS) status; simple; and excellent capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	Oils and water insoluble surfactants	SEDDS formed without water soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (Particle size 0.25–2 μm)
Type III	Oils, surfactants, and cosolvents (both water-insoluble and water-soluble excipients)	SEDDS/SMEDDS formed with water soluble components	Clear or almost clear dispersion, drug absorption without digestion	Possible loss of solvent capacity on dispersion, less easily digested
Type IV	Water-soluble surfactants and cosolvents	Formulation disperses typically to form a micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity on dispersion may not be digestible

additional methods for improving absorption have also been put up, solubilizing the drug is the primary way that lipid-based formulations enhance bioavailability[8,9]. These additional methods include slowing down P-glycoprotein-mediated efflux, improving lymphatic transport to mitigate hepatic first pass metabolism, lengthening gastrointestinal (GI) transit time, or guarding against GI tract degradation. The formulator has access to hundreds of possible excipients for lipid-based formulations, and the variety of choices could appear daunting. In order to further confuse customers, it is fairly uncommon for a single excipient to be offered by a number of distinct vendors, each of whom uses a different trade name. Just a limited proportion of lipids have found use in clinical formulation development due to a scant or non-existent history of pharmaceutical application or, more commonly, a lack of regulatory permission. This will review describe the features of the following kinds of lipid excipients that are currently on the market from a pharmacological perspective[9,10]

I. Fatty acids, first
II. Pure fats and oils
III. Mono-, di-, and triglycerides that are semi-synthetic.
IV. Semi-synthetic glyceride and fatty acid derivatives in polyethylene glycol (PEG)
V. Esters of Polyglyceryl fatty acids
VI. Phospholipids and cholesterol

4.1 FATTY ACIDS

Aliphatic hydrocarbons, whether saturated or unsaturated, can be transformed into monocarboxylic acids, which are fatty acids. The individual fatty acid molecules can be more tightly aligned and interact more favourably because trans fatty acids are more linear in form than their comparable cis counterparts. Because of this, the fatty acids trans form has a greater melting point than its cis counterpart[10,11]. Naturally occurring cis fatty acids are partly transformed to trans fatty acids during the cleaning up of natural product sources and following hydrogenation procedures. Trans fatty acids are therefore common in the normal western diet. While semi-synthetic PEG fatty acid esters are used as solubilizers, surfactants, and emulsifiers, fatty acids are principally used in pharmaceuticals as solubilizing carriers for drugs that are poorly water-soluble (Table 2). Excipients from either class can be used to create both soft and hard gelatin capsules[10,12,13].

Table 2. Fatty Acids

Excipient	Chemical name composition	Trade name	Physical state at 25°Cor melting point	Uses
Oleic acid	c-9-Octadecenoic acid	Crodamol EO/Croda Estol ETO3660	Liquid	Vehicle, solubilizer, surfactant
Propylene glycol monolaurate	Monolauric acid ester of propylene glycol	Priolene 6929/Uniqema Crossential O94	Liquid	Vehicle, solubilizer,co-surfactant in microemulsions
Isopropyl palmitate	Isopropyl ester of palmitic acid	Estol 1517IPP/Uniqema Stepan IPP/Stepan CrossentialL99	Liquid	Vehicle, solubilizer lubricant, emulsifier
Linoleic acid	c-9, c-12-Octadecadienoic acid	Crossential L99	Liquid	Vehicle, solubilizer
Propylene glycol monocaprylate	Caprylic acid monoester of propylene glycol	Capryol 90/Gattefosse Capmul PG8	Liquid	Vehicle, solubilizer absorption enhancer co-emulsifier

4.2 NATURAL OILS AND FATS

In naturally occurring oils and fats, triglycerides (TG), which are fatty acid tri-esters of glycerol, are known more accurately (though less commonly) as triacylglycerols. Table 3 includes a list of many well-known natural oils along with their trade names and sources. Triglycerides are naturally occurring fatty acids with different chain lengths and degrees of unsaturation. Short chain triglycerides (less than five carbons), medium chain triglycerides (between six and twelve carbons), and long chain triglycerides (greater than twelve carbons) are the three groups (more than 12 carbons).[10]

Table 3. Lists trade names and suppliers of several common natural oils.

Excipient	**Trade name**	**Physical state at 25°Cor melting point**
Canola oil	Pureco Canola	Liquid
Coconut oil	Pureco 76 and Coconut Oil EP	Liquid
Corn oil	Super Refined Corn Oil NF and Super Refined Corn Oil NFNP Corn oil	Liquid
Cottonseed oil	Super Refined Cottonseed Oil NF Super Refined Cottonseed Oil NF-NP	Liquid
Palm oil	Palm oil	Liquid
Rapeseed oil	Rapeseed oil and Rapeseed Oil Refined EP	Liquid
Safflower oil	Super Refined Safflower Oil USP and Super Refined Safflower Oil USP-NP	Liquid
Soybean oil	Pureco Soybean and Super Refined Soybean Oil USP	Liquid

4.3 SEMI-SYNTHETIC MONO-, DI-, AND TRIGLYCERIDES

Many commercially available semi-synthetic glycerides provide compositions that are more uniform in addition to naturally occurring triglycerides (Table 4). These excipients are employed in a variety of controlled release dosage forms and as solubilizing, emulsifying, suspending, and wetting agents. They are compatible with both soft and hard gelatin capsules.[10,14]

Table 4. Semisynthetic Mono-, Di-, and Triglycerides

Excipient	Chemical name or composition	Trade name	Uses
Glyceryl triacetate (Triacetin)	Triacetic acid esters of glycerol	Captex 500 P and Triacetin	Solubilizer, vehicle
Glyceryl mono-, di-,tribehenate	Mono-, di-, and tri-docosanoic acid esters of glycerol	Compritol 888	Controlled release, tablet lubricant, and binder
Glyceryl monooleate	Monooleic acid ester of glycerol	Capmul GMO	Emulsifier, solubilizer, wetting agent, vehicle for capsule
Glyceryl tributyrate (Tributyric)	Tributyric acid esters of glycerol	Tributyrin	Solubilizer, vehicle

4.4 SEMI-SYNTHETIC POLYETHYLENE GLYC-OL (PEG) DERIVATIVES OF GLYCERIDES AND FATTY ACIDS

These excipients are utilised in self-emulsifying drug delivery systems (SEDDS) and self-micro emulsifying drugs as fluid or thermo-softening semi-solid solubilizing carriers, detergents and wetting agents, and emulsifiers and coemulsifier. delivery systems (SEDDS) (SMEDDS). These excipients range in HLB value from extremely lipophilic (PEG-6 glyceryl oleate, HLB 3-4) to water soluble, and they can be used with both soft and firm gelatin capsules (PEG-40 hydrogenated castor oil, HLB 14–16). Excipients that are mixes of mono-, di-, and triglycerides with fatty acid esters of PEG are included in Table 5 along with their brand names, suppliers, significant physical features, and typical pharmaceutical applications.[10,15]

Table 5. Lists several excipients that are mixtures of mono-, di-, and triglycerides with fatty acid esters of PEG.

Excipient	Chemical name composition	Trade name	Uses
PEG-4 glyceryl caprylate/caprate	Caprylic acid (C8:0) and capric acid (C10:0) esters of glycerol and PEG 200	Labrafac Hydro WL 1219	Vehicle, surfactant, solubilizer
PEG-6 glyceryl caprylate/caprate	Caprylic acid (C8:0) and capric acid (C10:0) esters of glycerol and PEG 300	Softigen 767 and Sasol Acconon CC-6	Vehicle, water soluble surfactant, solubilizer, coemulsifier
PEG-6 glyceryl linoleate	Mono-, di-, and trilinoleic acid (C18:2) esters of glycerol and mono and diesters of PEG 300	Labrafil M 2125 CS	Vehicle, solubilizer, vehicle for softgels,
PEG-35 castor oil (PEG-35 castor oil castor oil, USP/NF)	Mixture of glyceryl PEG ricinoleate (35 moles of ethylene oxide per mole of castor oil) with fatty acid esters of PEG, free PEGs and ethoxylated glycerol.	Cremophor EL/BASF Etocas 35 NF	Water soluble nonionic, surfactant, vehicle, solubilizer, emulsifier coemulsifier, lipid phase or cosurfactant in microemulsions.

4.5 POLYGLYCERYL FATTY ACID ESTERS

Polyglyceryl fatty acid esters are made up of a sequence of glycerol molecules linked together by ether bonds. After that, the esters are esterified with one or more fatty acid molecules. various example of Polyglyceryl fatty acid are given in table,(Table 6). Polyglyceryl-6 dioleate is formed when a chain of six glycerol molecules is esterified with two molecules of oleic acid.[10]

Table 6. Polyglyceryl fatty acid

Excipient	Chemical name or composition	Trade name	Physical state at 25°Cor melting point	Uses
Polyglyceryl-3 oleate	Monooleic acid ester of a 3-glycerol solubilizer, unit chain	Caprol 3GO	Liquid	Surfactant, solubilizer, vehicle, emulsifier
Polyglyceryl-3 dioleate	Dioleic acid [18:1 (9)] esterof a 3 glycerol unit chain	Plurol Oleique CC497	Liquid	Surfactant, solubilizer, vehicle, emulsifier, vehicle for capsules Surfactant, solubilizer, emulsifier
Polyglyceryl-3 stearate	Monostearic acid (18:0) ester of a 3 glycerol unit chain	Caprol 3GS	Liquid	Surfactant, solubilizer, emulsifier
Polyglyceryl-6 dioleate	Dioleic acid [18:1 (9)] ester of a 6 glycerol unit chain	Caprol MPGO and Plurol Oleique	Liquid	Surfactant, solubilizer, vehicle, emulsifier, lubricant, crystallization inhibitor

4.6 CHOLESTEROL AND THE PHOSPHOLIPIDS

Phospholipids and cholesterol are used as solubilizers, detergents, and emulsifiers in mixed micelles and emulsions (Table 7). Furthermore, phospholipids have been used as triglyceride antioxidants and are the primary component of liposomes, which have limited use in the delivery of oral medicines due to their instability in the GI system. In vitro testing, however, showed that liposomes having a 7:2 molar ratio of cholesterol to distearoylphosphatidylcholine were resistant to pancreatic lipase and bile salts, suggesting that these formulations could be used in oral drug administration. [16]

Table 7. Polyglyceryl fatty acid

Excipient	Chemical name or composition	Trade name	Uses
Cholesterol	Cholest-5-en-3_-ol	Avanti Polar Lipids	Neutral
Sodium cholesteryl sulfate	Cholest-5-en-3_-ol	Sigma-Aldrich	Negative
Phosphatidic acid	Mixture of fatty acid diesters of glycerophosphoric acid	Avanti Polar Lipids	Negative
Dioleoylphosphatidic acid	1,2-Dioleoyl-snglycero-3-phosphate (DOPA)	Avanti Polar Lipids	Negative
Phosphatidylserine	A mixture of 1,2diacyl-sn glycero- 3-phospho-Lserines with the composition varying with the source.	Avanti Polar Lipids Alcolec PS 90P/ American Lecithin	Zwitterion
Dioleoylphosphatidylserine	1,2-Dioleoyl-snglycero-3- phospho-L-serine (DOPS)	Avanti Polar Lipids	Zwitterion
Hydrogenated egg phosphatidylcholine	A mixture of 1,2hydrogenated diacyl-sn-glycero- 3-phosphocholines from eggs.	Avanti Polar Lipids	Zwitterion

5. LIPID EXCIPIENTS IN PHARMACEUTICAL TECHNOLOGIES

The growing demand for "Novel Drug Delivery Systems" to deal with novel chemical entities that may have weak solubility or permeability, to enhance the delivery of existing drugs, and even to extend product lines is fuelling interest in lipid excipients (generics or super generics).

More intriguingly, natural lipid excipients of "Vegetable Origin" are now playing a larger role in pharmaceutical development in general, and specifically in final pharmaceutical formulations for nearly all routes of administration, including injectable, parenteral IV and IM, as well as oral, topical, rectal, and vaginal. Vegetable oils are derived from seeds, grains, or berries**.**

Each of these species has its own unique makeup and distribution of fatty structures based on the length of the hydrocarbon chain and the number of unsaturated bonds in the chain. These structural differences influence the physical properties of veggie oils (glycerides). For example, the freezing point of glycerides grows with the length of the hydrocarbon chain but falls with the number of double bonds. Natural vegetable oils are unquestionably important excipients for use in pharmacies, but they frequently fall short of the standards established by the pharmaceutical industry and the drug development process in terms of stability, pharmacopoeia specifications, and, most importantly, the functionality of these excipients in pharmaceutical dosage forms**.**

For all these reasons, we prefer to focus on "Vegetable Oil Derivatives," lipid-based excipients created through "catalytic hydrogenation" of unsaturated bonds or "esterification or glycolysis" using a range of alcohols such as glycerol, polyglycerol, propylene glycol, or polyethylene glycol. These processes allow us to manufacture "Functional Excipients," which are distinguished mainly by their melting point and HLB value (Hydrophilic Lipophilic Balance). Lipid esters (or fatty acid esters) are created from organic oils by carefully choosing, extracting, purifying, and treating them with alcohol. As a consequence, an ester with exactly specified properties and characteristics is produced.

Because lipid esters are regulated at all phases of production and the finished product is methodically evaluated for purity, physical characteristics, and chemical characteristics, the customer is assured an excipient supply with carefully specified and consistent characteristics.

The most common "Vegetable Oil Derivatives" are polyalcohol esters of digestible fatty acids and various alcohols, partial glycerides, poloxylglycerides (also known as macrogol glycerides by the European Pharmacopoeia), ethoxylated glycerides, and hydrogenated vegetable oils.[10]

5.1 Chemical Analysis and characterization of lipid excipients:

A comprehensive collection of analytical techniques is accessible from USP/NF, EP, and the excipient manufacturer.

The precise makeup of lipid excipients in terms of esters, ethers, and fatty acid distribution can be determined using HPLC and GC techniques. Quick assays for excipient characterization, such as,

- Saponification Value linked to the ester function amount, are also accessible as chemical indices.
- Iodine Content as an indicator of hydrocarbon chain concentration.
- The amount of unbound hydroxyl groups is calculated using the Hydroxyl Value.
- Acid Value is a measurement of the quantity of natural (un-esterified) fatty acids.
- Peroxide Value is a metric that is used to measure and monitor oxidative changes. [8,10]

5.2 Physiological effects of lipid-based excipients

The lipid-based formulation was developed especially for medicines with minimal GI solubility, permeability, and bioavailability. The use of lipid-based excipients is intended to enhance drug pseudo-solubility in Gastrointestinal medium, drug absorption, and bioavailability. [17]

5.2.1 In-Vivo pseudo-solubility/micellar solution:

The first goal of an optimum lipid-based formulation is to prevent medication precipitation or interaction with other elements. The ideal lipid-based recipe must provide "Spontaneous

Formation" of an O/W emulsion or a microemulsion (or Nano emulsion) once in touch with the GI medium at 37°C, without the effect of enzymes and bile salt.

5.2.2 Permeability:

A complicated collection of barriers specific to each drug influences permeability. There is significant proof that lipids play a part in the fluidization of intestinal cell membranes, the opening of tight junctions, and the inhibition of efflux processes in most lipid-based surfactants. [17,18]

5.2.3 Lymphatic absorption:

Lipid networks have been shown to improve medication bioavailability by promoting lymphatic uptake. In general, the lymphatic pathway of absorption offers a fantastic window and chance to enhance the bioavailability of extremely lipophilic drugs with high glycerol solubility and affinity (log P>5). [18,19]

5.3 Formulation with lipids and lipid derivatives:

The first major use of lipid based excipients is to enhance the bioavailability of weakly soluble medications by boosting solubility or pseudo-solubility, targeting lymphatic transport, and/or modifying enterocyte-based drug transport and disposition.

Drug sustained release in solid dose forms as a lipidic matrix using direct compression or moist granulation is the second most frequent application, followed by drug coating for flavour concealing (chewable tablet) or drug protection (hydrolyses, oxidation...). Dermal, rectal, or vaginal semisolid dosage forms were also used, where lipid-based excipients enhanced drug diffusion /permeability while keeping good skin/mucosal tolerance. [8,12,19]

5.3.1 Formulation with lipids and lipid derivatives for oral bioavailability

In general, lipids or lipid derivatives could be used in oral bioavailability pharmaceutical formulations with a single excipient or a combination of several excipients to optimise the final formula, resulting in a variety of systems such as solid dispersions, physical mixtures, liquid/solid solutions, and Self-Micro or Self-Nano Emulsifying Drug Delivery Systems (SMEDDS, SNEDDS), with excipients such as glycerol. [19,20]

Table 8. Lipid excipient for oral drug delivery

Oral drug delivery Lipid excipients for oral drug delivery include solubility and bioavailability enhancers, lubricants, modified release, taste-masking, API protection and suspending agents. Excipients are used in a variety of processes enabling the formulation of different dosage forms, mainly tablets, granules, hard and soft capsules.	
Name of lipid Excipient	**Description**
Compritol® 888 ATO (GLYCEROL ESTER)	• It is the lubricant for challenging pharmaceutical tablets when used at 1 to 3%. • Its inertness eliminates drug excipient incompatibility issues. As mixing time and speed do not affect its efficiency nor tablet hardness, it offers flexibility in formulation development and production. • It is the 'troubleshooting' lubricant for tableting.
Precirol® ATO 5 (GLYCEROL ESTER)	• It is ideal for taste masking and API protection when used in a high shear or fluid bed coating process due to the formation of a film coating around the drug particle.
Compritol® 888 ATO (GLYCEROL ESTER)	• It is a smart solution to sustain drug release when used at 10 to 25%. It forms an inert matrix from which the drug diffuses slowly over time. Used alone or in combination with HPMC it enables the production of sustained release tablet using a direct compression process and with higher drug load achievable.

A simple "one-excipient" formulation: A simple lipid formulation in which the active component is entirely dissolved in the lipid phase. This mixture is exposed to the action of enzymes and bile salts when consumed orally, resulting in In-Vivo "mixed" micelles; in this instance, the oily phase used must be digestible.

In this instance, the oily phase is linked with other surfactants, enabling emulsification and In-Vivo micelle formation to be independent of biological effects. This formulation is known as SELF (Self Emulsifying Lipid Formulation).

To shield delicate actives from oxidation and hydrolysis, glycerides, and glycerol esters (based on C18-C22 fatty acids) with a high melting point and a low HLB value (1-2) are currently extensively used in hot coating methods without solvent. These coated actives can be taken directly or through direct pressing. These same excipients are also used in tablet lipid matrices, and they are well adapted to all compression methods, including direct compression, dry granulation, and wet granulation with water. Because long-chain lipids are not digested and there is no matrix erosion as in polymeric matrices, the process of active ingredient release from these lipid matrices is entirely regulated by diffusion (Fick's law). As a consequence, the In-Vitro-In-Vivo correlation is outstanding. Table 8 contains samples and explanations of lipid excipients used in oral medication administration. [19–21]

5.3.2 Formulation with lipids and lipid derivatives for dermal application

Lipid excipients offer numerous advantages to dermal tissues on multiple levels. PEG esters as an emulsifier give a simpler manufacturing method when compared to the conventional procedure (the One Pot Process). Solubilizers such as liquid esters, glycerol esters, polyglycerol esters, and propylene glycol esters offer a wide variety of

solubilizers while also increasing active component skin penetration. The majority of skin actives are chemically compatible. Esters are skin-friendly and have no detrimental adverse effects. Table 9 provides instances and explanations of lipid excipients used in topical medication administration. [22–24]

Table 9. Lipid excipient for Topical drug delivery.

Topical drug delivery Solubilizers, emulsifiers, and viscosity modifying agents are lipid excipients used in topical drug delivery. Emulsifiers provide excellent textural and sensory characteristics. Viscosity agents stabilize formulations while solubilizers improve skin penetration. Excipients are used in creams, emulgels, lotions, foams, microemulsions and gels.	
Name of lipid Excipient	**Description**
Tefosev® 63	• It is a multi-functional emulsifier, enabling one-pot process and offering excellent mucosal and skin tolerance. It is used worldwide with a broad range of APIs, including the 'azole' antifungals to treat vaginal infections and mycosis. In combination with Labrafil® M 1944 CS, it delivers exceptional heat stability to topical emulsions
Other emulsifiers like Gelot 64, Apifil, Sedefos75	• It's in combination with Plurol® Oleique CC 497, Lauroglycol™90 or Capryol®90 offer interesting synergies for transdermal drug delivery.

5.3.3 Formulation with lipids and lipid derivatives for rectal and vaginal applications

For a long time, cocoa butter was the only excipient used as a natural lipid in injections. Many factors have contributed to the preference for Hard Fat (glycerol esters) over the last 70 years, including the variability of its composition,

Table 10. Lipid excipient for Rectal and vaginal drug delivery

Rectal and vaginal drug delivery Lipid excipients for suppository and pessary formulation include hard fat and hard fat with additives. These bases provide excellent physico-chemical stability and optimize drug delivery for a wide range of active pharmaceutical ingredients and manufacturing equipment.	
Name of lipid Excipient	**Description**
Suppocire® N and M types	• These are versatile suppository bases used with numerous APIs, including
(GLYCEROL ESTER)	• paracetamol, guaranteeing excellent drug release properties for a fast-acting antipyretic effect.
Ovucire® family (GLYCEROL ESTER& ETHOXYLATED FATTY ALCOHOLS)	• It is a hard-fat pessary base delivering enhanced spread ability within the vaginal cavity and good mechanical resistance. As it is non-irritant and provides excellent mucosal tolerance, it is widely used in antifungal treatments.

The instability during storage, the polymorphism phenomenon, chemical incompatibility, tricky manipulation in industry, and commercial availability, which was subject to economic fluctuations. The Hard Fat is well positioned to be an excellent excipient for suppositories and ovule formation, as well as to ease any problems that may emerge with other excipients [24,25]. Table 10 contains samples and explanations of lipid excipients used in rectal and vaginal drug administration.

6. LIPIDIC EXCIPIENTS IN DRUG DELIVERY FOR SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT

Recent breakthroughs in drug finding and development have led in the creation of highly powerful but weakly water-soluble medications with limited systemic exposure. Drug intake requires drug breakdown in the gastrointestinal system. Prodrug creation, salt formation, and the use of metastable polymorphic forms, co-crystals, and particle size reduction, amorphization of the drug, and the use of natural or synthesised lipids are all used to increase bioavailability. Since the effective commercialization of Cyclosporine lipidic products as Sandimmune in 1981, followed by its reformulation as Neoral, the lipid-based drug delivery method has gotten a lot of focus over the last two decades. Sandimmune created a polydisperse oil-in-water emulsion in GI fluids and showed limited cyclosporine oral bioavailability while keeping effective exposure after oral administration. In comparison, Neoral emulsified in the Gastrointestinal fluids as microemulsions, increasing oral bioavailability while reducing dietary impact. To assist in processing during product creation and increase the oral bioavailability of weakly water-soluble medicines, a varied variety of lipid excipients with flexible utility is available. [20,24] Lipidic excipients include solubilizers, triglycerides, mixed glycerides, water-soluble surfactants, water insoluble surfactants, emulsifiers, and solubility boosters. They solubilize and retain the drug solubilized in the gastrointestinal tract, shield it from digestive enzymes, enable the creation of a self-emulsifying system, and eventually enhance the oral bioavailability of weakly water-soluble medications. A lipid-based drug delivery device is an efficient way to transport weakly water-soluble drugs with high lipophilicity (logP). Their advantages include dosage reduction, removal of the food impact, decrease in first-pass metabolism by enabling lymphatic route transfer, and improved physical and chemical stability of the drug product. A lipid-based medication delivery system can be as basic as an oil mixture or as complicated as a self-emulsifying system that

autonomously emulsifies in the presence of an aqueous environment.

These systems can be turned into basic liquid solutions for oral administration or soft or firm gelatin pills. In lipid-based drug delivery systems, the overall daily drug dosage varies from less than 0.25 g/mL to higher than 2000 mg, and the drug dose per capsule ranges from 0.25 g to 500 mg, and for oral solutions from 1 g/mL to 100 mg/mL. A single capsule and oral solution dosage of lipid excipient varies from 0.5 to 5 gm and 0.1 mL to 20 mL, respectively. [19,20,24,26]

6.1 Role of lipid-based excipients in drug delivery

Because of the availability of lipid excipients with adequate safety profiles and regulatory approval, lipid can be helpful as a carrier for weakly water-soluble medicines. Lipid excipients include long- or medium-chain triglycerides, mixed mono- and di-glyceride and polar oils, cosolvents, water-insoluble detergents, and water-soluble surfactants. Oil, surfactant, and co-solvent can be combined to make a lipid-based drug delivery system, which can then be converted to a solid intermediate and given orally in solid dosage form. The lipid composition of food influences lipophilic medication intake, resulting in greater absorption and thus improved bioavailability. Lipidic contents inhibit presystematic metabolism and efflux activity, improve solubility and permeability through gastrointestinal tract walls, and extend GI residence time and lymphatic transfer via various mechanisms. The inclusion of lipid excipients in the formulation can enhance the drug candidate's solubility and dissolution profile, enabling it to be absorbed in a more solubilized state and lowering the impacts of food dependent bioavailability. After ingestion of up to 100 gm per day, dietary lipids and lipophilic nutrients are well taken, and it is known that lipids in food can assist in the uptake of medicines with poor water solubility. As a consequence of combining a weakly water-soluble drug with lipids in a lipid-based drug delivery system, drug solubilization and absorption are enhanced. However, food consumption varies due to factors such as health, age, leisure, and society. While co-administration of a weakly water-soluble medication with formulated lipids can reduce the variability associated with food as a lipid supply. Because of the lipid itself, as well as by activating physiological processes that result in greater bile salt and phospholipid secretion, lipids can enhance solubilization capacity. Long-chain lipids are helpful for drug solubilization even at low quantities, whereas medium-chain lipids are most effective at high concentrations. Lipidic excipients (primarily surfactants) can suppress gut efflux transporter to enhance drug uptake via a variety of mechanisms, including changes in membrane fluidity, efflux transporter expression variations, and direct interaction with the transporter. By postponing gastric transit time, lipid excipients can expand the time available for dissolution and thus uptake of weakly water-soluble medicines. [20,26,27]

6.2 Formulation development of lipid-based drug delivery system

If the formulation objectives are carefully examined, lipid-based drug delivery methods can be created successfully. Excipients are chosen based on,

i. freezing point, fatty acid composition, hydrophilic lipophilic balance (HLB) value, solubility, and disposability.
ii. Excipient solubility, dissolution/dispers-Ion characteristics, durability, and compatibility testing.
iii. Choosing a suitable formulation technique for the planned dosage type.
iv. Creating appropriate animal models to forecast the in vivo performance of the chosen formulation; and
v. optimising the **formulation while keeping** drug loading and breakdown profile in mind. Lipid-based drug delivery systems include oily liquids, blended micelles, self-emulsifying systems, liposomes, and solid lipid nanoparticles. [10,13,28]

7. SELECTION CRITERIA OF DRUG AND LIPID EXCIPIENT

a) Drug

Drug prospects with poor uptake owing to dissolution or permeation are good candidates for lipid-based drug delivery methods. Drugs from BCS classes II and IV that are poorly water-soluble are ideal prospects for lipid-based drug delivery methods.

Poorly water-soluble medications are frequently referred to as "brick dust" or "greaseballs" in nature. "Brick dust" medicines have poor water solubility due to strong intermolecular interactions within the crystal lattice structure. As a consequence, developing brick dust drug formulation as a lipid-based drug delivery method is difficult. Drugs with a low freezing point and a high lipophilicity are incapable of creating links with water molecules. The lipid-based drug delivery method could be useful for "grease-ball" medicines that have not exhibited adequate bioavailability using traditional formulation approaches.

The drug's solubility and miscibility with an appropriate lipid excipient should be sufficient to integrate the entire amount into the finished dosage form.

BCS classification can be used to evaluate applicants for eligibility. The solubilization technology guide map, as shown in Figure 2, (10) shows which technique is best suitable for a drug or how much drug loading can be used for a drug based on melting point (Tm), logP, and dosage. This guidance map, however, may not always provide an exact indication of bioavailability because it is dependent on solubility rather than permeability. 20,29,30

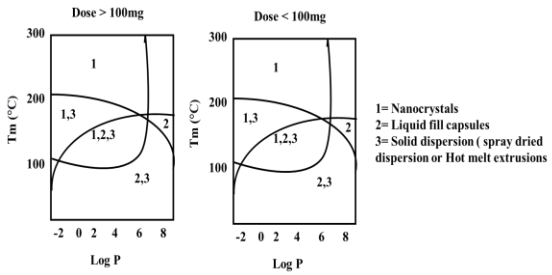

Fig. 4: Solubilization guidance map.

b) Lipid excipient

It is necessary to have a thorough understanding of fatty excipients and their in vivo behaviour, as well as their safety profile and regulatory approval. When selecting a lipid excipient for a lipid-based drug delivery system, miscibility, self-dispersibility and ability to promote self-dispersibility of the formulation, melting point, solvent capacity, fatty acid composition, HLB value, morphology at room temperature, digestibility and fate of digested products, chemical stability, purity, capsule compatibility, and regulatory issues such as irritancy and toxicity are all factors to consider. To effectively create a lipid-based dosage form, it is necessary to observe a favourable dietary influence when the medication is given with a lipid-rich dinner. A comprehensive study of possible incompatibilities between drug and lipid excipient is needed, as is the vulnerability of lipids to oxidation, which can reduce formulation durability. The excipient used in a lipid-based drug delivery system must be generally recognised as safe (GRAS) and lie within the inactive component database limits (IID). Excipients and lipid-based drug delivery methods There are several lipidic excipients available for drug distribution methods, including triglycerides, partial glycerides, semi-synthetic surfactant esters, and semi-synthetic oily esters. The part by Gibson et albook. contains a complete catalogue of lipidic excipients for oral drug delivery. Lipidic excipients with high to low

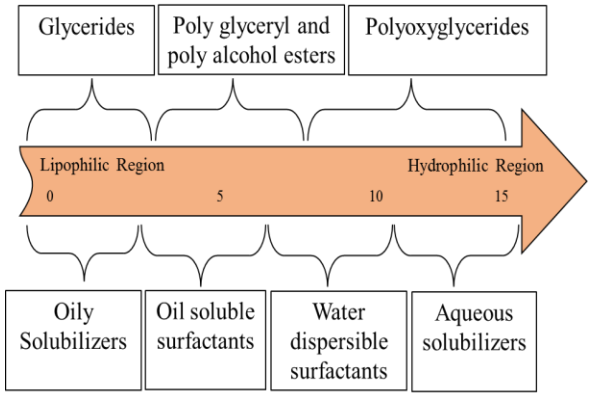

Fig. 5: HLB scale for selection of lipid excipients

HLB are used as a solubility and bioavailability booster, lubricant, drug release modulator, flavour

concealing agent, and drug degradation inhibitor in oral drug administration. Lipid excipients improve drug wettability and solubility, maintain the drug super saturated until it reaches the absorption location in the gastrointestinal system, and allow for selective lymphatic uptake. Drugs that are poorly soluble in water, whether lipophilic or hydrophobic in nature, are more soluble in fatty excipients. The HLB number can be used to calculate an excipient's preference for the watery phase. Generally, lipid excipient or mixture of lipid excipients with maximal solubilization capability can be selected for creation of formulation. [31,32]

8. CASE STUDIES OF LIPID-BASED DRUG DELIVERY SYSTEM.

Table 11 displays various lipid-based formulations of lipid base drug delivery systems together with summaries of their lipid excipient, characteristics, and PK (pharmacokinetics) investigations from various research articles. [33–37]

Table 11. Case studies of lipid-based drug delivery system.

Drug	Properties	Type of formulation	Lipid excipient	Description
Phenytoin	BCS Class II, solubility: 0.032 mg/mL, log P: 2.47, erratic absorption after oral administration, poor aqueous solubility	Emulsion, oily suspension, and aqueous suspension	Corn oil, Polysorbate 80	PK study of corn oil emulsion in adult male albino rats showed. 1.79-folds and 1.29-fold higher AUC in comparison to corn oil suspension and aqueous suspension respectively
Atorvastatin	BCS class II, solubility: 0.02 mg/mL (pH 2.1) and at PH6.0 solubility is 1.23mg/mL, logP: 5.7, pKa: 4.5, High presystolic clearance and first pass metabolism	SMEDDS	Labrafil M19CS, Cremophor RH40, propylene glycol	Pharmacokinetic (PK) study of SMEDDS in beagle dogs showed1.5 times higher. AUC in comparison to tablet formulation
Simvastatin	BCS class II, solubility: 0.8 µg/mL logP: 4.7, pKa: 14.91	SMEDDS, conventional tablet (Zocor)	Capryol 90, and Carbitol Cremophor EL	PK study was performed in fasted state beagle dogs showed 1.5-fold higher. bioavailability from SMEDDS in comparison to conventional tablet
Itraconazole	BCS II, solubility: less than 10 µg/mL, logP is 6.5, pKa: 3.7	SEDDS and Standard 'Sporanox' formulation	Pluronic L64, Transcutol & tocopherol acetate	PK evaluation in fed state (Lipidic diet) rats showed 3.7-fold increase in AUC of SEEDS in comparison to Sporanoxformuation
Danazol	BCS Class II, solubility:0.0176 mg/mL, logP: 4.6	Long chain (LC) SMEDDS and Medium chain (MC) SMEDDS	Long chain SMEDDS: 30% of soybean oil,30% of Maisine, Cremophor EL; Medium chain SMEEDS: 36% of MCT, 18% Capmul MCM, CremophorEL	PK study of LC-SMEDDS was carried out in dogs showed 5-folds greater oral bioavailability in comparison to MC-SMEEDS in fasted state

9. CONCLUSION

Lipids are one of the most adaptable excipient groups available today, providing formulators with an abundance of options for improving and regulating the absorption of poorly water-soluble medicines. The use of lipid-based drug delivery methods can enhance medicine absorption and oral bioavailability of medications that are poorly water soluble. Triglyceride digestion, solubilization, lymphatic absorption, and intestinal permeability are the main processes for increasing the oral bioavailability of weakly water-soluble medications using a lipid-based drug delivery system. A range of lipidic excipients are available for use as solubilizers, surfactants, and wetting agents in lipid-based drug delivery systems, and they can enhance the oral bioavailability of weakly soluble pharmaceuticals by integrating them into different lipid-based drug delivery systems. Lipid-based drug delivery system-based products are also available on the market, suggesting that lipidic excipients have a bright future for lipid-based drug delivery systems.

Consider the following to summarise the importance of these "Vegetable Oil Derivatives" as useful medicinal lipid excipients: The creation of novel excipients (lipidic esters) with appropriate regulation and safety characteristics. Toxin-free or near-toxic conditions. Long-term application modification (drugs intended for chronic diseases). The ability to resist decomposition (especially lipid esters excipients). In terms of medicine durability, high chemical inertness (compatibility). Versatile Material: Available in liquid, solid, atomized particle, and granule shapes. The capacity to adapt to all pharmaceutical kinds, including solid, semi-solid, and liquid. Adaptability to all techniques (pharmaceutical processes). A fluid containing a high concentration of lipidic or hydrophobic active substances (increase solubility). Lipidic excipients may play several functions in increasing sublingual bioavailability. Improving the capillary route to avoid first-pass metabolism. Adapted for drug coating using a heated process with no solvent, for either flavour masking or drug preservation. It has, however, been used as a matrix in continuous release dosage formulations.

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A review on Chemistry and Analytical challenges of Methamphetamine

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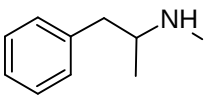
Abstract

Analytical chemistry not only helps to control drug abuse through identification, but it also helps in the field of sports by detecting drug traces in athletes. Methamphetamine is one such drug that has been widely used by athletes, and its detection in the blood has been a real challenge for analytical scientists. This article examines the chemical aspects and strategies used to analyse this compound over time. Many times, the harmful effects of drug of abuse are exacerbated by its impurities. This is precisely the case with the drug under consideration here. Scientists have been interested in Methamphetamine impurity profiling for a long time, and a chronicle of it has been presented here.

1. Introduction

Methamphetamine is a stimulant and extremely addictive substance. It is an N-methylated derivative of amphetamine with similar characteristics and a similar mode of action. Dopamine is a neurotransmitter that is produced in large quantities in the brain as a result of methamphetamine use. Dopamine has a role in pleasure, motivation, reward, and motor function. Methamphetamine rapidly triggers the release of dopamine in activating sections of the brain leading to a euphoric "rush" or "flash". Frequent use may lead to severe addiction.[1].



Methamphetamine

United Nations Office on Drugs and Crime (UNODC) has affirmed that amphetamine-like substances (ATS) on the illicit drug market, have overtaken cocaine and heroin combined.[2] Similarly, Cannabis and ATS are two major illicit drugs in Australia, trailing only [3]. Consumption of ATS, particularly methamphetamine, is rising in a major part of the Asian subcontinent.

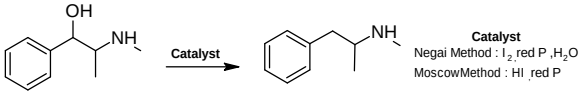
The following are some common methods for producing Methamphetamine from precursors such as phenyl-2-propanone (P-2-P), pseudoephedrine and ephedrine, 3,4-Methylenedioxyphenyl-2-propanone, and 4-methoxyphenyl-2-propanone. For the synthesis of Methamphetamine and 3,4-MethylenedioxyMethamphetamine (MDMA), a variety of methods such as the Nagai, "Moscow," and "Hypo" schemes, Emde method, The Leuckart method, Birch reduction, and Reductive amination are often used.[4].

Impurities formed during the synthesis of methamphetamine. This review examines the various types of impurities found in Methamphetamine, along with methods for profiling impurities such as gas chromatography, thermal desorption, liquid-liquid extraction by gas GCMS, capillary electrophoresis mass spectrometry, H1 NMR spectroscopy, and other techniques [5]

2. Synthetic Route for Manufacture Methamphetamine

A. The Nagai, "Moscow" and "Hypo" methods

The hydroxyl group of starting material is nucleophilically replaced by iodide in this technique, producing either iodoephedrine or iodopseudoephedrine. The Internal nucleophilic may cause the formation of cis- and trans-1,2-dimethyl-3-phenyl aziridines. These aziridine derivatives can undergo either reduction producing methamphetamine, or hydrolysis leading to P-2-P. P-2-P can condense in acidic conditions to form 1,3-dimethyl-2-phenyl naphthalene and 1-benzyl-3-methylnaphthalene. As a result, the possibility of two naphthalene by-products is route dependent. Importantly, one should understand that naphthalene is formed simply by heating P-2-P in the presence of acid for an extended period. Even reports of other naphthalene derivatives have been reported in other conditions. [8-11]

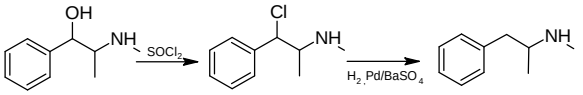


Scheme 1: Nagai and Moscow methods

Interestingly carbon at the 2-position of the propyl side chain is safe from nucleophilic attack hence the (S)-configuration of its centre is retained. [12]

B. The Emde method

In Southeast Asia, the Emde process has emerged as a well-known technique for large-scale synthesis. The Emde process, such as the Nagai process, includes halogenating ephedrine or pseudoephedrine and then hydrogenating it while preserving the chirality of the carbon-containing nitrogen. With the Emde process, the -OH group in starting material can be exchanged with chloride through the use of intramolecular nucleophilic substitution (also referred to as SNi substitution) or intermolecular substitution (SN_2 substitution).

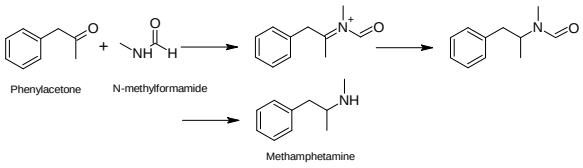


Scheme 2 : Emde method

While using thionyl chloride as the reagent, Lekskulchai et al. and Allen and Kiser proposed two routes. The latter group demonstrate that (-)-ephedrine produces a 99:1 mixture of (+)-chloropseudoephedrine and (-)-chlorefedrine, and (+)-pseudoephedrine produces a 6:4 mixture, while there is no difference between the chlorination products (+)-pseudoephedrine and (-) (approximately 1:1 chloride mixtures). The SNi substitution reaction was found to be more prominent in (+)-norpseudoephedrine, (-)-methyl ephedrine, and (+)-methyl pseudoephedrine as the extent of N-methylation enhanced.[13, 14] Both Allen and Kiser [14] and Barker and Antia [15] used nuclear magnetic resonance spectroscopy (NMR) and gas chromatography-mass spectrometry (GC-MS) for the characterization of reaction products.

C. The Leuckart method

The Leuckart reaction or Leuckart Wallach reaction is an important reaction for the synthesis of ATS because it can be employed to synthesise a variety of amphetamines derivatives using easily available reagents. Leuckart first described the reaction in 1885[6] using ammonium formate or formamide and Wallach expanded on it in 1893 using ammonium formate or formamide, and later in the presence of excess formic acid.[7]



Scheme 3 : Leuckart methods

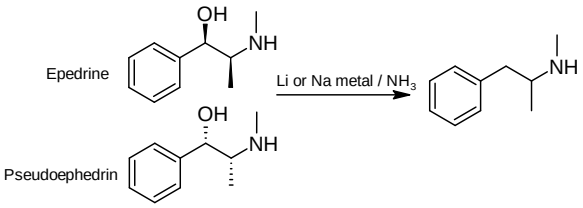
The key intermediate in the Leuckart approach to creating methamphetamine is N-formyl methylamphetamine. According to Kram and Kruegel[16], illegal Methamphetamine prepared by the Leuckart synthesis may contain N, N-di-(b-phenyl isopropyl)methylamine and N-formyl methylamphetamine. The latter among the two compounds might be route-specific. According to Sanger et al. [17], N-formyl methylamphetamine is route-specific for the Leuckart reaction. However, Qi et al. [18] and other groups[19, 20] have found N-formyl methylamphetamine, in very low

concentrations, in Methamphetamine produced by methods other than the Leuckart. Qi et al. noticed that the appearance of N-formyl methylamphetamine has been associated with the presence of N-acetyl methamphetamine, which was said to have resulted from a reaction between Methamphetamine and ethyl acetate. Conn et al. [21] were the first to report the coexisting N-acetyl methamphetamine in illicit Methamphetamine probably due to the use of propyl acetate to azeotropically desiccate Methamphetamine that had been precipitated out using aqueous HCl. Sasaki and Makino[22] demonstrate that the abundance of both N-formyl and N-acetyl-Methamphetamine rises with the temperature of the injection port increases, and they theorise that this phenomenon is caused by the thermal decomposition of an unknown compound(s) that decreases as you raise the temperature. Anyway, the presence of N-formyl methylamphetamine in minute amounts in seized Methamphetamine could be confusing and hence might require cautious interpretation.

Impurities in Methamphetamine[16, 23] can be detected if impure P-2-P, methylamine, or N-methyl formamide (probably containing dibenzyl ketone, ammonia, or formamide, respectively) are used in the Leuckart reaction. In addition to the earlier mentioned impurities, Kunulan[19] discovered dibenzyl, 3,4-diphenyl-3-butenone, benzyl methamphetamine, N-b-(phenyl isopropyl)benzyl methyl ketimine, N-benzoyl methamphetamine, benzylamphetamine, N-benzoyl methamphetamine, N-benzoyl methamphetamine (the latter demethylated by-products might have appeared from formamide in the N-methyl formamide employed).

D. The Birch reduction

Barker and Antia[15] discuss the consequences of starting with plant extracts from the genus Ephedra. It was envisaged that the methyl and desmethyl analogues of ephedrine and pseudoephedrine (e.g., methyl ephedrine and norephedrine) are reduced to amphetamine and dimethyl amphetamine, along with by-products 1,4-cyclohexadienyl-2-methylamino propane desmethyl and methyl analogues.

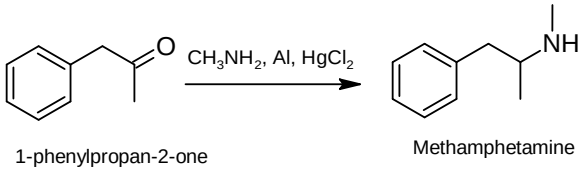


Scheme 4: Birch reduction

Per expectations, the 1,4-cyclohexadienyl moiety in 1-(1,4-cyclohexadienyl)-2-methylamino propane aromatises to form Methamphetamine. According to Pal et al, [24, 25] rapid aromatisation occurs in the soil, primarily through abiotic processes. Consequently, residues in soil samples from covert laboratories are devoid of 1-(1,4-cyclohexadienyl)-2-methylamino propane, even if it was previously detectable. Likewise, the oxidation of this diene may lead to the formation of Methamphetamine though it was not present from the beginning.

E. Reductive amination

Verweij[23] surveyed the reductive aminations of 1-phenylpropanoid-2-one in the presence of ammonia and methylamine. A common by-product of both was 1-phenyl-2-propanol, which results from the reduction of the starting material and hence was described as a route-specific by-product.



Scheme 5: Reductive amination

Salouros et al. [26] identified N-cyanoethyl-N-methyl-1-phenyl-2-propylamine as a route-specific impurity formed on reductive amination of 1-phenylpropanoid-2-one and methylamine.

Kunulan et al. [19] studied the impurities in Leuckart and reductive amination methamphetamines affirming Verweij's[23] discovery of 1-phenyl-2-propanol being a route-specific by-product.

3. Analytical methods for assay of Methamphetamine

A. Individual Analysis

For quantitative estimation of amphetamine and methamphetamine in different samples, a variety of analytical techniques such as titrimetric, spectroscopy, capillary electrophoresis, liquid chromatography, and gas chromatography have been employed. Without a doubt, the most viable tool for confirmation and identification is GC coupled online to an MS detection system. [27] The quest for non-destructive, simple, less analysis time, cost-effective, non-simple instruments, and less skilled technicians led to the development of the FTIR technique for in-situ detection and traces of methamphetamine. Riyanto et al utilised FTIR to identify wavenumber 698.83 cm-1, yielding an R2 value of 0.9998.[28] Hughes et al. curated a new quick and low-cost method using ATR-FTIR and PLS. The Root Mean Square Error of Prediction for this method was 3.8, R2 0.9779, and the lower LOQ was 0.7% of Methamphetamine. [29]

B. Trace Analysis

As a drug of abuse, it is essential to detect trace amounts of drugs in crime scenes, suspects, and biological samples. McKenzie et al invented a dynamic solid phase microextraction (SPME) attached with a field sampler capable of collecting enough samples in two hours and was followed by GC-MS. [30]

Though a successive review of biological sample analysis is expected, mention of analysis involving dried urine spot (DUS) analytical method based on spotting urine samples (10 µL) onto dried spot collection cards are made. The samples were analysed using extraction followed by the LC-MS-MS method with an r value greater than 0.995.[31]

C. Chiral separation

Another concern with methamphetamine is that it has a stereogenic centre and thus exists as an enantiomer. Both enantiomers have distinct pharmacological activities. As a result, developing enantioselective analysis was critical. Jirovska et al. reviewed several chiral separation methods.[32] They discussed different methods such as gas chromatography, high-performance liquid chromatography, high-performance capillary electrophoresis, as well as immunoassay in this review. Later that year, Li demonstrated super critical chromatography-single quadrupole mass spectrometry (SFC-SQD) for determining methamphetamine enantiomers. For optimal separation, a Trefoil AMY1 (150 x 2.1 mm, 2.5 m) column with a supercritical CO_2 mobile phase containing ethanol as the co-solvent and 1% cyclohexylamine as the amine additive was found to be ideal.[33]

D. Pharmacokinetics and Metabolism studies

Methamphetamine primarily metabolizes to amphetamine and 4-hydroxy methamphetamine[34] by human CYP2D6 and, to a lesser extent, CYP3A4 [35]. Amphetamine further metabolizes to 4-hydroxy methamphetamine and norephedrine by CYP2D6 [34, 36]. In most cases, GC-MS was used in these studies. Earla and co-workers while working with the same studies on Rhesus Macaque, developed and validated a very sensitive analytical method with liquid chromatography with tandem mass spectrometry (LC-MS/MS) method with sample preparation involving solid phase extraction of rhesus plasma. The method had a LOQ of 1.09 ng/ml for Methamphetamine and its metabolites, 4-hydroxy Methamphetamine, amphetamine, 4-OH amphetamine, and norephedrine.[37]

E. Bioanalysis

This discussion is in continuation of the earlier section**.** Campíns-Falcó et al [38] reviewed the analysis of amphetamine and Methamphetamine by HPLC. A comparison of the Fluorescence polarization immunoassay (FPIA) method, Radioimmunoassay (RIA) and GC–MS for blood samples has been reported.[39] Moellera et al, have presented an excellent review on the determination of Methamphetamine in blood. A tabular comparison of various chromatographic methods for the analysis of Methamphetamine can be found in this review. [40] In this regard, it is necessary to mention a US patent issued in 1992 by Heiman et al. It primarily makes use of the Fluorescence Polarization Immunoassay.[41]

There are many citations of analysis of urine samples for methamphetamine. [42, 43]. This includes a method involving derivatization for better detection in HLPC. [42 44-46]. Few are highly sensitive to trace concentration in a hair sample. [42, 47]

F. Simultaneous determinations

Another challenge for analytical scientists was developing and validating methods for various drug combinations. Methamphetamine has been marketed in numerous combinations with other drugs. Shabir et al. developed an RP-HPLC Method for the Determination of Methamphetamine and Propranolol in Tablet Dosage as an example.[48]

Illicit drug combinations pose an additional challenge to analysts; for example, an amphetamine, methamphetamine, caffeine, paracetamol, and theophylline combination was discovered in detained drugs in Riyadh, where Sultan et al. developed an analytical method.[49]

The problem multiplies when analysing the concentration of Methamphetamine in samples from drug addicts because they frequently use multiple substances in combination. One earlier referred article by Kim *et. al* [47], is representative of such a case where the group had successfully developed a method for the simultaneous analysis of 13 different drugs. Another instance is Chan et al's method for estimation of Methamphetamine in a beverage intoxicated with Methamphetamine, 3,4-methylenedioxyMethamphetamine and Ketamine.[50].

4. Impurity Profiling of Methamphetamine

Methamphetamine involves impurities which made the drug intolerable. Ira S. Lurie et al [51] performed impurity profiling of Methamphetamine using High-performance liquid chromatography (HPLC) with photodiode array (PDA) UV and fluorescence (FL) detection, and capillary electrochromatography (CEC) with laser-induced fluorescence (LIF) detection for analysis of acidic extracts derived from Methamphetamine. HPLC with conventional FL detection provided at least a 600 times increase in sensitivity over UV detection for certain of these solutes. The use of a fast scanning FL detector (with "on the fly" excitation or emission acquisition) provided structural information as well as "optimal" excitation and emission detection wavelengths. CEC with LIF detection via UV laser excitation provided significantly enhanced accuracy chromatographic technique over HPLC, with ng/ml detection limits.

Hiroyuki Inoue et al [52] went on to classify seized Methamphetamine through impurity profiling and established that it can furnish valuable information in criminal investigations of drug traffic routes, sources of supply and relationships between confiscations. They investigated a sample size of 50 mg sample of Methamphetamine HCl dissolved in phosphate buffer. Extraction using ethyl acetate with four internal standards (ISs) (n-decane, n-pentadecane, n-nonadecane, and n-hexacosane) was followed by gas chromatography (GC). Efficient separation was observed with the middle bore size column. The four internal standards helped for correcting impurity peak retention. The correction of impurity peak retention times with four ISs resulted in precise peak identification for subsequent data processing. After performing a logarithmic transformation, the statistical analysis was done using the Euclidean distance of the relative peak areas, and twenty-four characterizing peaks were chosen to enable comparison and the assessment of sample similarity and/or dissimilarity. According to the findings, it is possible to profile methamphetamine impurities using the current methodology.

Y. Marumo et al. [53] employed atomic absorption spectrometry(AAS) and inductively coupled plasma mass spectrometry (ICP-MS) to evaluate the effectiveness of inorganic impurity analysis in detecting samples of methamphetamine that had been confiscated in Japan. Triplicate aliquots from the 17 methamphetamine samples were used for qualitative analysis, employing water as solvent. Inorganic entities like Ba, Br, Cu, Pd, Sb, Sr, and Zn were determined using the ICP-MS, while Na was determined using the AAS. The contents of both Na and Br presented relatively lesser intra-sample variance despite being abundant in methamphetamine samples. ICP-MS qualitatively

identified trace elements as Au, Cs, Hg, and Tl. The fact that these components were consistent throughout all the confiscated samples, impurity profiling was made possible. One can conduct highly sensitive analyses due to ICP-MS and AAS. By employing these methods for the study of inorganic impurities, methamphetamine that has been seized can be profiled for impurities using organic impurity analysis.

By contrasting the impurity patterns of methamphetamine samples made using various synthesis techniques, Jae Sin Lee et al.[54], discovered the impurities reflecting the conditions of synthesis. Ephedrine and pseudoephedrine were converted into sixteen samples of methamphetamine using the three different production processes used in Emde, Nagai, and Moscow. After synthesising the sample, they extracted it using ethyl acetate that contained four internal standards and then used GC-MS and GC-FID to look into the patterns in the organic impurities. The final 10 peaks from the GC chromatogram relate to the synthetic methods employed. The regions of the chosen peaks were transformed into variables appropriate for statistical analysis, and the resulting cluster analysis allowed the synthesised samples to be divided into four groups. The appearance of the impurities was influenced by reaction conditions including pH, catalyst, and intermediates. The impurities were dimers derived from aziridine compounds, 1-phenyl-2-propanone, or other very reactive impurities.

Kenji Kuwayama et al[55] used thermal desorption (TD) and gas chromatography-mass spectrometry for impurity profiling of methamphetamine using GC–MS. Impurities from nine different batches were removed and separated using TD/GC-MS under diverse circumstances. The best chromatograms were recorded when a 20 mg sample of methamphetamine was extracted using a TD instrument at 120°C for 3 minutes. The extracts then were separated using a non-polar capillary column covered by (5%phenyl)-methylpolysiloxane. Without the need for a time-consuming extraction technique, methamphetamine-related substances such as amphetamine, benzaldehyde, benzyl alcohol, cis- and trans-1,2-dimethyl-3-phenyl aziridine, dimethylamphetamine, and N-acetyl ephedrine were detected in the chromatograms. Without the need for a time-consuming extraction technique, methamphetamine-related substances such as benzaldehyde, benzyl alcohol, amphetamine, cis- and trans-1,2-dimethyl-3-phenyl aziridine, dimethylamphetamine, and N-acetyl ephedrine were found in the chromatograms. Sample intensities varied from sample to sample. The impurity profile of methamphetamine via TD and liquid-liquid extraction (LLE) were studied. Higher intensities & numbers of peaks were found with TD, however, LLE provided greater resolution. They noticed that TD allowed for more effective solvent extraction.

The revolutionary step in methamphetamine profiling by Ying Qi et al. [56] involves the identification of the primary, route-specific flag impurity compounds. Fresh crystalline methamphetamine, also referred to as "ice," was seized by the Australian Federal Police in 2003 and 2004 at the Australian border. The impurity analysis of this sample produced markers for two different synthesis routes in the form of chemicals. Impurities typical of the Leuckart method and/or reductive amination were also present, along with 1,2-dimethyl-3-phenyl aziridine, 1,3-dimethyl-2-phenyl naphthalene & 1-benzyl-3-methylnaphthalene, alongside N-formyl methamphetamine, N, N-di-(β-phenyl isopropyl)amine and N, N-di-(β-phenyl isopropyl) methylamine, N-benzoyl amphetamine and N, N-di-(β-phenyl isopropyl)formamide commonly associated with the Leuckart route and/or reductive amination.

According to, Vanitha Kunalan[57] and the group's studies, impurity profiling of methamphetamine seizures can offer a wealth of information for forensic investigations, notably regarding drug trafficking routes, sources of supply, and connections between confiscations. It is particularly crucial to identify "route specific" contaminants or those that reveal the synthetic procedure utilised in illegal laboratories. They compared the contaminants in methamphetamine

produced internally using the Leuckart and reductive amination processes from the same starting material (P2P). With extraction using a basic buffer of pH 10.5, R, R-dimethyl diphenethylamine and N-R, R-trimethyldiphenethylamine we identified while. In the acidic media, at pH 6, 1-phenyl-2-propanol, was identified as a route-specific impurity.

Jaesin Lee et al.[58] used liquid-liquid extraction (LLE) and headspace solid-phase microextraction (HS-SPME) techniques to analyse 48 impurities in Methamphetamine samples. They used an MPS-2 autosampler and internal standard nonadecane (C19) diluted with potassium bromide (KBr) to improve the reproducibility. The SPME method identified impurities in a different pattern than the LLE method. The SPME method did not identify non-volatile impurities such as methamphetamine dimer, but it did reveal some volatile impurities such as diphenylketone, caprolactam, and many unknown factors. They discovered that the peaks of 1-phenyl-2-propanone (P2P), 1-phenyl-2-propanol, and benzyl cyanide could be differentiated by the SPME method with the least noise from amphetamine and methamphetamine degradants. They conclude that automation and the use of IS enabled them to perform multisampling analysis by the SPME method with high reproducibility, and cross-examination of the LLE and SPME methods improved the reliability of profiling results. The improved reliability of profiling results aided in the efficient investigation and regulation of methamphetamine and related chemicals, resulting in a lowering in methamphetamine abuse.

T. Mikuma et al[59] developed chiral capillary electrophoresis/tandem mass spectrometry (CE/MS/MS) using a chemically modified capillary containing sulfonated groups for amphetamine-type stimulants (ATS) viz; amphetamine, methamphetamine, norephedrine, or pseudoephedrine, ephedrine, pseudoephedrine, dimethylamphetamine and methyl ephedrine. A buffer system of 10 mM formic acid was used, along with a chiral selector of 20 mM highly sulphated—cyclodextrin (pH 2.5). They were able to resolve all 16 enantiomers in 60 minutes and correctly determine them due to their distinct mass spectra. Furthermore, the RSDs of the analytes' migration periods were less than 0.3% in the absence of any standardisation. They prepared a highly concentrated solution of methamphetamine (1 mg/mL) and added (1R,2S)-(-)-EP and (1S,2S)-(+)-Pseudoephedrine, which are considerable ATS impurities originating in the precursors, to it. They finally evaluated the mixture as mock samples for methamphetamine impurity analysis, and they noted acceptable repeatability of the migration times of (-)-E The limits of detection (LOD) for (-)-Ephedrine and (+)-Pseudoephedrine were estimated to be approximately 0.2% because their LOD as impurity values were around 2 g/mL. These techniques were used to analyse samples of methamphetamine that had been confiscated and had been highly concentrated (1 mg/mL) in water. Both (-)-Ephedrine and (+)-Pseudoephedrine might be detected, and they had equivalent migration periods and mass spectral patterns. The advantage of higher reproducibility and simplicity are two important aspects of this work.

In a work by Hun Joo Lee et al. [59], they described a visual peak selection system (VPSS) in conjugation with impurity profiling and used a newly developed normalising method for multi-Internal Standards (ISs) to improve the resolution of impurity peaks. They used relative retention time (RRT) as a criterion for classifying numerous chromatographic peaks for drug impurity profiling. Unfortunately, it was found that the classification of each chromatographic peak was challenging because RRT values ranged from 0 to 1, and tended to converge to 1 as the number of impurities in the sample increased, and accuracy was also low. A new visual peak selection method with a normalisation algorithm was developed to address the issue. By extending the range of the chromatogram, it successfully separated each chromatographic peak.

It might be a helpful tool for analytical samples with high impurity and IS concentrations. They found that impurity profiling had significantly

improved in terms of resolution, accuracy, speed, and user-friendliness.

Sanggil Choe et al [60] analysed 126 detained samples of Methamphetamine with GC-MS. All chromatogram peaks were analysed resulting in the identification of 61 impurities, including n-octacosane. Flunarizine and desloratadine, two pharmaceutical medicines, were found in crystalline Methamphetamine in different cases. The ORI, LOQ, and SQRT for data sets were reported in support.

5. Conclusion

The case of methamphetamine posed a significant challenge not only to synthetic chemists, druggists, and pharmacologists but also to analytical chemists. It was an ideal case with a variety of issues, but analytical scientists played a role in the identification, characterization, and forensic findings. Because there had been so much good work done, this review could only provide a brief overview.

6. Acknowledgments

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7. Conflict of interest

The authors declare there is no conflict of interest.

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