**ABSTRACT**

This review is generally focussed on lipid-based excipients in solid oral formulations which increase its bioavailability. Several approaches have been used to deliver the drug efficiently in the body, and lipid excipients are one of the promising drug delivery systems which address challenges like solubility and bioavailability of water-soluble drugs. Lipids excipients can be tailored to meet a wide range of product requirements like disease indication, route of administration, stability, toxicity, and efficacy. This review discusses novel lipids like Compritol 888 ATO, Dynasan 114, and Precirol ATO 5 and how these can be employed for devising efficient drug delivery models and thereby have used in cosmetic and pharmaceutical industries.

**Keywords**: Bioavailability, Lipid-Based Drug Delivery System, Excipients

**INTRODUCTION**

Lipids are essential for life, and the existence of cells specialized in fat storage has been conserved from flies and worms to humans. However, almost all cells maintain the capability to retain and accumulate lipids. Cellular mechanisms of lipid storage are relatively conserved from unicellular organisms, such as yeast, to complex organisms such as plants and mammals [1, 2]. An excipient (derived from words excipere to take out, receive) may be defined as any substances mixed with the active pharmaceutical ingredient to give it consistency or used as a vehicle for its administration. It is impossible for any active pharmaceutical ingredient to have properties that allow incorporation in a therapeutic product that meets all the mentioned requirements. Therefore, every therapeutic product is a combination of drug and excipients [3-5].

The importance of lipid-based excipients in solid oral formulations has increased during the last decades, due to their outstanding benefits, such as providing modified release profiles or taste masking using solvent-free processing techniques [6]. Lipid-based excipients were first used in the 1960s for embedding drugs in a wax matrix in order to sustain drug release. In the more recent years, these excipients were successfully used in oral drug delivery systems to enhance the bioavailability of poorly aqueous soluble drugs and the novel lipids to control the release of easily soluble drug in the systemic circulation [7, 8]. Furthermore, taste masking and the improvement of swallow ability have been achieved with these excipients. Further reasons for the application of lipids in a formulation may be shelf life extension by protecting the drug from other ingredients or from environmental influences, the reduction of gastric irritation and the improvement of general attributes like flowability, lubrication performance, compressibility or mechanical resistance [9, 10].

**Lipids**

Lipids are biological molecules characterized by limited solubility in water and solubility in non-polar organic solvents. Their intermolecular interactions are dominated by the hydrophobic effect and van der Waals interactions. Many lipids are, however, amphipathic molecules, which interact with other molecules and with aqueous solvents via hydrogen bonding and electrostatic interactions [11, 12]. Lipids are a diverse group of organic compounds found in plants, animal and micro-organisms. Lipids are non-polar compound and in-soluble in water but sometimes soluble in organic solvents. They comprise one of the three large classes of foods and, with proteins and carbohydrates, are components of all living cells [13-15].

One of the most important functions of lipids is the role they play in cell membrane structure and metabolic processes, especially as cell membrane transport agents and precursors of signaling eicosanoids. These roles are becoming increasingly better understood and have allowed for the developments of a diverse number of applications of bioactive lipids both in the pharmaceutical and cosmetic fields.

The major types of lipids that are present in the human body which plays major roles in metabolic processes are: triacylglycerols, free fatty acids, phospholipids, sphingolipids, bile salts, steroids and sterols, cholesterol, eicosanoids, and fat-soluble vitamins. Lipid modification strategies for the production of functional fats and oils include chemically or lipase-catalyzed interesterification or acidolysis reactions and genetic engineering of oilseed crops [16-19].

**Classification of Lipids**

Lipids can be classified in many ways, due to their different composition, nature and origin. According to with Broo's classification, lipids can be divided into simple lipids, compound lipids, and derived lipids. Individual characteristics are not discussed in this section because they are well known.

**Simple Lipids**

These are those compounds which belong to heterogeneous class of predominantly nonpolar compounds such as Lecithin and Cephalins.

**Compound Lipids**

These are esters of fatty acids with alcohols. Compounds molecules also contain additional functional groups such as a phosphate ion, simple sugar, amino acid, sulphate ion and oligopeptides. Examples are fatty acids, alcohols, monoglycerides and diglycerides, steroids, terpenes, carotenoids.

**Derived Lipids**

These are those substances which are derived from simple and compound lipids by hydrolysis. Derived lipids include fatty acids, alcohols, monoglycerides and diglycerides, steroids, terpenes, carotenoids. Steroids, terpenes and carotenoids are the most common derived lipids. Some of the most important lipids are shown in table 1. [20-25]
A table is provided with the following columns: S. No., Classes of lipids, Nature of lipids, Types of lipids, and Sources of lipids. The table outlines various types of lipids, including triglycerides, waxes, phospholipids, steroids, and sterols. The sources of these lipids include almond, apricot, avocado, canal, castor, coffee, corn, elm, olive, safflower, sesame, and others.

Novel Lipids

Novel lipids are the new chemical entities, designed using increasingly available receptor structural information. Such chemical entities are polycyclic and very hydrophobic. Novel lipids are poorly soluble and hence poor bioavailability; in this review, we will be discussing three novel lipids: Compritol 888 ATO, Dynasan 114, and Precirol ATO 5 [26].

Compritol 888 ATO

Chemical Formula of Compritol 888 ATO is C_{56}H_{101}O_{14} and its Non-proprietary Name is Glycerol Dibehenate. Its chemical name is 2,3-dihydroxypropyl docosanoate: docosanoic acid or 2,3-dihydroxypropyl ester: glyceryl monobehenate [27].

Description

Glyceryl behenate occurs as a fine white to off-white, free-flowing powder or hard waxy mass with a faint odor it is tasteless, non-reactive with other formulation ingredients. The United States Pharmacopeia national formulary (USP NF) describes glyceryl behenate as a mixture of glycerides of fatty acid, mainly behenic acid. Glyceryl behenate is a hydrophobic, non-swelling, wax material commonly used as a lubricant [28, 29]. Over the past decade, glyceryl behenate has been used for controlled release applications by direct compression and more recently by hot melt coating, melt granulation or pelletization or the formation of solid lipid nanoparticles. Due to its low density and controlled release nature, it is used for the development of gastric floating matrix tablets [30, 31]. Compritol 888 ATO is a lipid excipient that is generally used in the cosmetic and pharmaceutical industry as a surfactant, emulsifying agent and viscosity-inducing agent in emulsions, creams and pharmaceutical product. Based on its chemical composition, Compritol 888 ATO is a blend of different esters of behenic acid with glycerol [32-34].

Rationale for the use of compritol 888 ATO in novel drug delivery system

Compritol 888 ATO has been extensively employed as a matrix-forming agent in the preparation of different sustained-release tablets. It has also been investigated as a hot-melt coating agent for powders or granules for controlled release purposes [35, 36]. It has provided several noteworthy advantages over polymers as it is generally required in lesser amounts to achieve the desired effect and it does not crack during tablets compression. Moreover, Compritol 888 ATO has been examined for the preparation of pellets and orally disintegrating tablets. In addition, it has been used as a taste-masking agent to improve drugs palatability by concealing the bitter or unpleasant taste. Different researches have highlighted the applicability of Compritol 888 ATO in the preparation of aqueous colloidal dispersions such as solid lipid nanoparticles (SLNs), solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) for entrapment of lipophilic drugs [37-41]. Compared to homogenous glycerides, Compritol 888 ATO is superior in terms of drug entrapment ability due to its complex nature and less perfect orientation thus leaving more space for the drug to be loaded. Also, the long-chain length of behenic acid in Compritol 888 ATO enhances the intermolecular entrapment of the drug by interchain intercalation. Generally, lipid polymorphism occurs due to the difference in lateral packing possibilities of fatty acid chains in a particular organization of hydrocarbon chains. Lipids exist in different three-dimensional structures: unstable, metastable and the most stable modification [42-46]. Additional intermediate form exists between the most stable and metastable. Studying the polymorphic behavior of Compritol 888 ATO alone and within the SLNs and NLCs, it was found that the lattice arrangement of Compritol 888 ATO crystals generally comprises small amounts of the unstable polymorphic form that disappears after thermal stress [47]. In preparing SLNs, the stresses that might affect lipid stability are the initial melting procedure of the lipid to produce the hot premulsion and the subsequent high temperature and high pressure during the hot homogenization process. Partial formation of lower-energy lipid modifications and reduction in crystallinity take place due to the transformation of Compritol 888 ATO into lipid nanoparticles. Also, the added surfactant during lipid nanoparticles preparation contributes to the lowering of the melting enthalpy of Compritol 888 ATO by distributing the melted lipid phase and distorting its crystallization [48-50]. It is postulated that the
Several studies have been conducted to examine the thermal behavior of Compritol 888 ATO when used for hot-melt coating process since it undergoes melting and exposure to high temperatures [51, 52]. The thermal history, glycerides are exposed to, determines its crystal structure’s composition in terms of including hexagonal, orthorhombic and triclinic, each with different polymorphic transition temperatures and melting points. The polymorphic transitions affect drug release as better drug sustained release is related to the metastable polymorph [53, 54].

### Composition and types of Compritol

Compritol 888 ATO (glyceryl dibehenate or glyceryl behenate) is a hydrophobic mixture of mono-(12-18% w/w), di-(45-54% w/w) and tri-(28-32% w/w) behenate of glycerol with melting point in range of 65-77 °C and with hydrophilic-lipophilic balance (HLB) of 2. Compritol 888 ATO is prepared by the esterification of glycerin by behenic acid without the use of catalysts. The raw materials used in preparing are of vegetable origin and the esterified material is atomized by spray cooling [55].

According to the European pharmacopeia (EP), glyceryl dibehenate is a mixture of diacylglycerols (40-60%), together with monoacylglycerols (13-21%) and triacylglycerols (21-35%). However, the USP 32-NF 27 describes glyceryl behenate as a blend of glycerides of fatty acids, predominantly behenic acid and specifies that the content of 1-monoglycerides should range between 12 and 18%. Glyceryl behenate can be identified using thin-layer chromatography and gas chromatography [56, 57].

**Table 2: Property of Compritol ATO 888**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>65-77 °C</td>
</tr>
<tr>
<td>HLB Value</td>
<td>2</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>414.67 g/mol</td>
</tr>
<tr>
<td>Water Content (%)</td>
<td>≤0.1%</td>
</tr>
<tr>
<td>Acid Value</td>
<td>≤3</td>
</tr>
<tr>
<td>Iodine Value</td>
<td>≤0.001%</td>
</tr>
<tr>
<td>Saponification Value</td>
<td>145-165</td>
</tr>
<tr>
<td>Residue on Ignition</td>
<td>≤0.1%</td>
</tr>
<tr>
<td>Heavy Metals</td>
<td>≤0.001%</td>
</tr>
<tr>
<td>Free Glycerin</td>
<td>≤1%</td>
</tr>
<tr>
<td>Soluble</td>
<td>Chloroform and Dichloromethane</td>
</tr>
<tr>
<td>Insoluble</td>
<td>Ethanol, Hexane, Mineral Oil and Water</td>
</tr>
</tbody>
</table>

Several studies have been conducted to examine the thermal behavior, crystallinity and possible interactions of the Compritol 888 ATO and the drug that may impact its release. Compritol 888 ATO has been mainly characterized using differential scanning calorimetry (DSC), X-ray powder diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR) [61]. Generally, lipid polymorphism occurs due to the difference in lateral packing possibilities of fatty acid chains in a particular organization of hydrocarbon chains. The polymorphic form of Compritol 888 ATO either depends on parameters such as crystallization rate and temperature during production or storage. In slow crystallization rates, each glyceride crystallizes separately, producing a complex matrix containing different lamellar phases. On the contrary, a fast crystallization rate, or more produces a single lamellar phase [62, 63].

**Applications of Compritol 888 ATO**

Glyceryl behenate is used in cosmetics, foods and oral pharmaceutical formulations. In cosmetics, it is mainly used as a viscosity-increasing agent lipophilic matrix or coating for sustained released tablets and capsules. Viscosity-increasing agent in silicone gels (cosmetics). Viscosity-increasing agent in w/o or o/w emulsions (cosmetics). Glyceryl behenate is mainly used as a tablet and capsule lubricant and as a lipidic coating excipient. Used in the preparation of sustained-release tablets, as a matrix-forming agent for the controlled release of water-soluble drugs and as a lubricant in oral solid dosage formulations and can also be used as a hot-melt coating agent sprayed onto a powder [64-66].

- **Modified-release dosage forms:** Lipid nanoparticles have gained great interest during the past decade as they are more biocompatible and more stable compared to polymeric nanoparticles. Also, they offer high drug entrapment along with the feasibility of delivering both lipophilic and hydrophilic drugs. Compritol 888 ATO is considered one of the most applied and cited excipients in preparing SLNs and NLCs. Compritol 888 ATO-based nano-lipid carriers have been successfully utilized for ocular, oral, pulmonary, topical, transdermal and rectal delivery routes. Authors have selected it because of its favorable characteristics exemplified by its nonpolarity and lower cytotoxicity than other lipids [67].

- **Microparticles or spheres:** Compritol 888 ATO used as core forming agent in preparing lipid-based porous microspheres. It has been shown that drug release from microspheres was dependent on Compritol 888 ATO and the increase in their concentration caused a reduction of drug release from the microspheres [68].

- **Compritol 888 ATO** has been used in pellet lipophilic binders to prolong the release of drug from matrix pellets. Pellets exhibited excellent floating ability combined with sustained-release property due to the lipophilic nature of Compritol 888 ATO [69].

- **Compritol 888 ATO** has been successfully used by different research groups as a sustained-release matrix for tablets, to reduce the frequency of administration of drug [70].
- In the hot-melt extrusion (HME) process, Compritol 888 ATO has been utilized for preparing extrudates with the immediate or sustained release [71].

**Precirol ato 5**

Molecular Formula of precious ATO 5 is C_45_ H_86_ O_6_. Its Non-proprietary Name (EP) is Glycerol distearate, United States Food and Drug Administration (USFDA) Glycerol palmitostearate and its Chemical Name is precirol ATO 5 is Glycerin palmitostearate, glycerol palmitostearate, 2-[(1-oxohexadecyl) oxy]-1, 3-propanediyl dioctadecanoate and 1, 2, 3 propane triol Glycerol palmitostearate is a combination of mono-, di-, and triglycerides of C16 and C18 fatty acids, Glycerol palmitostearate is available as a fine white powder with a faint odor [71, 72].

**Composition and name of manufactures of Precirol ATO 5**

Glycerides are a family of excipients which have generated considerable interest in the preparation of oral dosage forms. Some glycerides such as Precirol ATO 5 (glycerol palmitostearate) can be used for the preparation of sustained-release dosage forms. The esterification of glycerol by long-chain fatty acid gives them a pronounced hydrophobic character with a low HLB value of 2 [73, 74].

Glycerol palmitostearate (Precirol ATO 5) is a mixture of mono-, di-, and triglycerides of C16 and C18 fatty acids. Glycerol palmitostearate is used in oral solid-dosage pharmaceutical formulations as a lubricant [75].

**Properties of Precirol ATO 5**

Precirol ATO 5 is a novel lipid and its property is shown in table 3 [77].

**Table 3: Property of Precirol ATO 5**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>52-55 °C</td>
</tr>
<tr>
<td>HLB Value</td>
<td>2</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>633.008g/mol</td>
</tr>
<tr>
<td>Storage Condition</td>
<td>51-58 °C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>200 °C</td>
</tr>
<tr>
<td>Physical Appearance</td>
<td>White in Colour</td>
</tr>
<tr>
<td>Soluble</td>
<td>Chloroform and Dichloromethane</td>
</tr>
<tr>
<td>Insoluble</td>
<td>Ethanol, Mineral Oil, and Water</td>
</tr>
</tbody>
</table>

**Applications of Precirol ATO 5**

Glycerol palmitostearate is widely used in oral solid-dosage pharmaceutical formulations as a lubricant. Tablet disintegration and time strength depends on mixing time of glycerol palmitostearate, as an increase in the blending time, increases disintegration time of tablets and also decreases the strength of tablet. It is used as a lipophilic matrix for the preparation of sustained-release product [78-80].

Tablet formulations may be developed by granulation or any hot-melt technique, the former producing tablets that have a faster release profile. Release rate decreases with increased glycerol palmitostearate content. Glycerol palmitostearate is used to form micro spheres, which may be used in capsules or compressed to form tablets, pellets, coated beads and biodegradable gels. It is also used for taste-masking. It is used as a lipid in Solid Lipid Nanoparticles and other lipids nano and microparticulate colloidal delivery system [81, 82].

**Function of Precirol ATO 5**

Biodegradable material is well used as a coating agent, gelling agent, release modifying agent, sustained-release agent, dents in tablet capsule formulation, Lubricant, taste-masking agent. Lipid Matrix for Sustained Release, Coating for Protection and Taste Masking of Oral Solid Dosage forms in direct compression, Dry Granulation, Film Coating, Hot Melt Extrusion, Roller Compaction, Spheronization, Supercritical Fluid Extraction, Viscosity modification, Wet Granulation, Solid Lipid Nanoparticles, and Nano Lipid Carriers [83, 84].

**Dynasan 114**

Molecular formula of dynasan 114 is C_{45}H_{86}O_{6}. Its chemical names are Trimyristin, 555-45-3; Propa-1, 2, 3-triytetradecanone. Glycerol trimyristate; Myristin; Glycerol trimyristate and its Synonyms are Tetradecanoic Acid 1, 1', 1''-(1, 2, 3-propanetriyl) Ester, Dynasan 114-Glycerin Trimyristate, Glycerol Trimyristate, Glycerol Tritytetradecanoate, Myristic Acid Triglyceride, Myristic Triglyceride, NSC 4062, Triglyceride MMM, Trimmystrin, Trimmystrylglycerol, Tritytetradecanoin, VP 114, Dynasan palmitostearate is used in oral solid-dosage pharmaceutical formulations as a lubricant [75].

Dynasan 114 is manufactured by Gattefosse corp. of France, Ferromet corp [76].

**Properties of Dynasan 114**

Dynasan 114 is novel lipid and it is used for control release, pore form also and its property is shown on table 4 [89-92].

**Fig. 2: Structure of Precirol ATO 5**

**Fig. 3: Structure of Dynasan 114 have been myristic acid (C-14)**

**Table 4: Property of Dynasan 114**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
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<td>2</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>633.008g/mol</td>
</tr>
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</tr>
<tr>
<td>Insoluble</td>
<td>Ethanol, Mineral Oil, and Water</td>
</tr>
</tbody>
</table>
Applications of Dynasan 114

Trimyristin is the triglyceride of myristic acid, which is found naturally in many vegetable fats and oils. Dynasan 114 microcrystalline triglycerides are used in the cosmetic and pharmaceutical industries as adjuvants in the preparation of, in tablets as lubricants having a very low influence on disintegration, in suppositories, vaginal ovula and pharmaceutical/cosmetic sticks as crystalisation accelerators and seeding agents to improve the solidification process, in ointments, creams and lotions as body-imparting and structure-forming components.

Further, they can be used in cream and lotions as body imparting and structure forming. It is used in the pharmaceutical industry as a Biodegradable material, coating agent, gelling agent, release modifying agent, sustained-release agent, diluents in tablet and capsule formulation, lubricant, taste-masking agent [93, 94].

ABBREVIATION

DSC (Differential scanning calorimetry), EP (European pharmacopoeia), FTIR (Fourier Transform Infra-Red), GC (Gas Chromatography), HLB (Hydrophilic Lipophilic Balance), TLC (Thin-Layer Chromatography), USP (United States Pharmacopeia), FTIR (Fourier Transform Infra-Red), GC (Gas Chromatography), DSC (Differential scanning calorimetry), EP (European Pharmacopeia), USP-NF (United States Pharmacopoeia-National Formulary), XRD (X-Ray Diffraction).

CONCLUSION

By increasing the bioavailability of numerous poorly soluble drugs along with formulations for physiologically well-tolerated class, the lipid excipients provide vast possibilities in this emerging technology. Understanding the physicochemical nature of the compound, alimentary canal and target receptor mechanisms, better and proficient drug delivery systems can be designed. Characterization, proper evaluation, and classification of these drug delivery systems are prerequisites to developing formulations and thereby boosting the pharmaceutical industry.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

Declared none

REFERENCES


90. Lide, David R. CRC Handbook of Chemistry and Physics. CRC Press; 2009.