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Review Article

SOME MULTIFUNCTIONAL LIPID EXCIPIENTS AND THEIR PHARMACEUTICAL APPLICATIONS

RAJNI DEVI*, SHWETA AGARWAL

Department of Pharmaceutics, LR Institute of Pharmacy, Solan, Himachal Pradesh, India
Email: pharma.rajni06@gmail.com

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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 devicing efficient drug delivery models and thereby have used in cosmetic and pharmaceutical industries.

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

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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 Bloor'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].

Table 1: Types of Lipids

S. No.	Clases of lipids	Nature of lipids	Types of lipids		Sources of lipids
1.	Simple lipids	Triglycerides	Oils	Vegetable oils	Almond, apricot, avocado, borage, canola, castor, coffee, corn, evening primrose, macadamia, olive, safflower, sesame etc.
				Animal oils	Black Sea dogfish, emu, sardine, shark liver
			Fats	Cocoa, coconut, palm, shea butter	
		Waxes			Beeswax, jojoba, lanolin, spermaceti
2.	Compound lipids	Phospholipids	Phosphatidic acids	1,2-Dimyristoyl-sn-glycero-3-phosphate (DMPA)1,2-Dipalmitoyl-sn-glycero-3-phosphate (DPPA) 1,2-Distearoyl-sn-glycero-3-phosphate (DSPA)	
			Phosphatidyl glycerols	1,2-Dimyristoyl-sn-glycero-3-phosphoglycerol (DMPG) 1,2-Dipalmitoyl-sn-glycero-3-phosphoglycerol (DPPG) 1,2-Distearoyl-sn-glycero-3-phosphoglycerol (DSPG) etc.	
			Phosphatidyl ethanolamines	1,2-Dimyristoyl-sn-glycero-3-phosphoethanolamine (DMPE) 1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE) 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine (DSPE)1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine(DOPE)	
			Phosphatidyl cholines	1,2-Dilauroyl-sn-glycero-3-phosphocholine (DLPC) 1,2-Dimyristoyl-sn-glycero-3-phosphocholine (DMPC) 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC) 1,2-Dioleoyl-sn-glycero-3-phosphocholine (DOPC)1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC)	
			Phosphatidyl serines		
			Phosphatidyl inositols		
			Phosphone analogs		
		Sphingolipids	Sphingophospholipids	Sphingomyelin	Egg sphingomyelin (ESM)N-palmitoyl sphingomyelin (C16SM) N-stearoyl sphingomielin (C18SM)
			Sphingoglycolipids	Cerebrosides Gangliosides	
		Glycolipids			
		Sulfolipids	Sulfogalactolipids		
3.	Derived lipids	Steroids	Sterols and sterol esters	Cholesterol, cholesterolstearate	
			Sterylglycosides and acylsterylglycosides		

Novel Lipids

Novel lipids are the new chemical entities, are designed using increasingly available receptor structural information. Such chemical entities formed 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 $C_{25}H_{50}O_4$ 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 microparticles (SLMs), 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 pre-emulsion 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

surfactant may immobilize lipid molecules by interfacial contact and, consequently, avoid reorientation of less-ordered configurations into the more organized structural lattice. It is important to understand 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 (GC) [56, 57].

Compritols family, manufactured by Gattefosse and Ferromet corp. include Compritol HD5 ATO (behenoyl polyoxyl-8 glycerides NF) and Compritol E ATO (glyceryl behenate E471) [58].

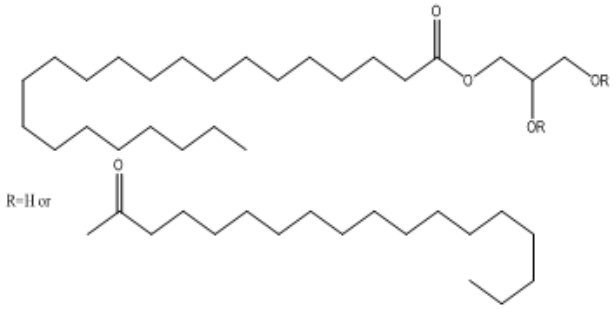

Fig. 1: Structure of Compritol ATO 888

Properties of Compritol ATO 888

Compritol 888 ATO is a novel lipid and it is used for retardant release, the binding agent also etc. Properties of Compritol 888 ATO is shown in table 2. [59, 60].

Table 2: Property of Compritol ATO 888

Melting point	65-77 °C
HLB Value	2
Molecular Weight	414.671g/mol
Water Content (%)	NMT 0.5%
Acid Value	≤4
Iodine Value	≤3
Saponification Value	145-165
Residue on Ignition	≤0.1%
Heavy Metals	≤0.001%
Free Glycerin	≤1%
Soluble	Chloroform and Dichloromethane
Insoluble	Ethanol, Hexane, Mineral Oil and Water

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 silico*n 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 $C_{37}H_{76}O_7$. Its Non-proprietary Name (EP) is Glycerol distearate, United States Food and Drug Administration (USFDA) Glyceryl 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 Glyceryl palmitostearate is a combination of mono-, di-, and triglycerides of C16 and C18 fatty acids, Glyceryl 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 (glyceryl 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].

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

Precirol ATO 5 is manufactured by Gattefosse corp. of France, Ferromet corp [76].

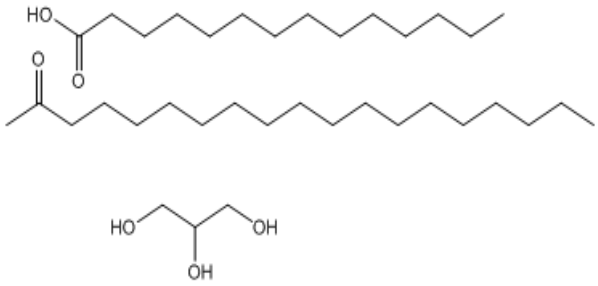

Fig. 2: Structure of Precirol ATO 5

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

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

Applications of Precirol ATO 5

Glyceryl palmitostearate is widely used in oral solid-dosage pharmaceutical formulations as a lubricant. Tablet disintegration and time strengths depends on mixing time of glyceryl 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 glyceryl palmitostearate content. Glyceryl palmitostearate is used to form microspheres, 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, diluents 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 C45H86O6. Its chemical names are Trimyristin; 555-45-3; Propane-1, 2, 3-triyl tritetradecanoate; Glycerol trimyristate; Myristin; Glyceryl trimyristate and its Synonyms are Tetradecanoic Acid 1, 1', 1''-(1, 2, 3-propanetriyl) Ester, Dynasan 114-Glycerin Trimyristate, Glycerol Trimyristate, Glyceryl Trimyristate, Glyceryl Tritetradecanoate, Myristic Acid Triglyceride, Myristic Triglyceride, NSC 4062, Triglyceride MMM, Trimyristin, Trimyristoylglycerol, Tritetradecanoin, VP 114, Dynasan microcrystalline triglycerides are glycerine esters of selected saturated, even-numbered and unbranched fatty acids of plant origin. They are free from antioxidants and other Stabilizers [85, 86].

Composition and name of manufactures of Dynasan 114

Trimyristin is an ester with the chemical formula $C_{45}H_{86}O_6$. It is saturated fat, which is the triglyceride of myristic acid (C-14). Trimyristin is a white to yellowish-gray solid that is insoluble in water, but soluble in ethanol, benzene, chloroform, dichloromethane, and ether [84].

Dynasan 114 is manufactured by some of these limited private corporations: IOI Oleo limited, Toronto research chemical, Sasol Germany GmbH, Cremer care [87, 88].

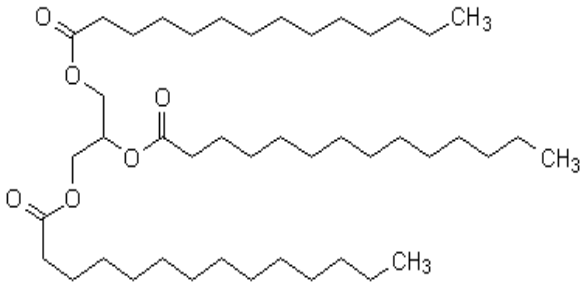

Fig. 3: Structure of Dynasan 114 have been myristic acid (C-14)

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]

Table 4: Property of Dynasan 114

Melting Point	55-58 °C
HLB Value	3
Molecular Weight	723.177g/mol
Hydroxyl Value	Max. 10 mg KOH/g
Acid Value	Max. 3
Iodine Value	Max. 1
Saponification Value	229-238
Unsaponifiable Matter	Max. 0.5
Soluble	N-Hexane and Diethyl ether
Insoluble	Ethanol and water

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 crystallisation 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), NLC (Nano-Structured lipid carriers), SLM (Solid Lipid Microparticles), SLN (Solid Lipid Nanoparticles), USFDA (United States Food and Drug Administration), 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 author have contributed equally

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Chapman KD, Dyer JM, Mullen RT. Biogenesis and functions of lipid droplets in plants, thematic review series lipid droplet synthesis and metabolism from yeast to man. J Lipid Res 2012;53:215–26.
2. A Report by Buddhist Chi Hong Chi Memorial College A. L. Bio Notes (by Denise Wong) The Cell. Enzymes; 2013. p. 49-50.
3. Sinha V, Rachna K. Polysaccharides in colon-specific drug delivery. Int J Pharm 2001;224:19-38.
4. Venkata R. Chemical and biological aspects of selected polysaccharides. Indian J Pharm Sci 1992;54:90-7.
5. Schwartz JB, Simonelli AP, Higuchi WI. Drug release from wax matrices I. Analysis of data with first-order kinetics and with the diffusion-controlled model. J Pharm Sci 1968;57 Suppl 2:274–7.
6. Lantz RJ, Robinson MJ. Method of preparing sustained release pellets and products thereof; 1964.
7. Porter CJ, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discovery 2007;6 Suppl 3:231–48.
8. Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: recent developments and approaches. Drug Dev Ind Pharm 2004;30 Suppl 5:429–48.
9. Dubey R, Shami TC, Bhasker Rao KU. Microencapsulation technology and applications. Def Sci J 2009;59 Suppl 1:82–95.
10. Singh MN, Hemant KSY, Ram M, Shivakumar HG. Microencapsulation: a promising technique for controlled drug delivery. Res Pharm Sci 2010;5 Suppl 2:65–77.
11. https://www.rose-hulman.edu/brandt/Chem330/lipid properties. [Last accessed on 05 Apr 2019]
12. Jannin V, Musakhanian J, Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. Adv Drug Delivery Rev 2008;60 Suppl 6:734–46.
13. Ako H, Okuda D, Gray D. Healthful new oil from macadamia nuts. Nutrition 1995;11:286-8.
14. Andersen KE, Nielsen R. Lipstick dermatitis related to castor oil. Contact Dermatitis 1984;11:253-4.
15. Bleck O, Abeck D, Ring J. Two ceramide subfractions detectable in Cer (AS) position by HPLTC in skin surface lipids of non-lesional skin of atopic eczema. J Invest Derm 1999;113 Suppl 6:894–900.
16. Bohlinder K, Olsson B. Use and characteristics of a novel lipid particle forming matrix as a drug-carrier system. Eur J Pharma Sci 1994;2 Suppl 4:271–9.
17. Bonte F, Pinguet P. Thermotropic phase behavior of *in vivo* extracted human stratum corneum lipids. Lipids 1997;3 Suppl 6:653–60.
18. Akoh CC, Yee LN. Enzymatic synthesis of position-specific low-calorie structured lipids. J Am Oil Chem Sci 1997;74 Suppl 11:1409-13.
19. Bell SJ, Bradley D, Forse RA, Bistrain BR. The new dietary fats in health and disease. J Am Diet Assoc 1997;97 Suppl 3:280-6.
20. Chambrier C, Guiraud M, Gibault JP, Labrosse H, Bouletreau P. Medium and long-chain triacylglycerols in postoperative patients: structured lipids versus a physical mixture. Nutr 1999;15 Suppl 4:274-7.
21. Pahlsson P. Characterization of galactosyl glycerolipids in the HT29 human colon carcinoma cell line. Arch Biochem Biophys 1998;396:187–98.
22. Koga Y, Nishihara M, Morii H, Matsushita MA. Other polar lipids of methanogenic bacteria: structures, comparative aspects and biosyntheses. Microbiol Rev 1983;57:164–82.
23. Pereto J, Garcia PL, Moreira D. Ancestral lipid biosynthesis an early membrane evolution. Tre Bio Chem Sci 2004;29:469–77.
24. Cronan JE. Bacterial membrane lipids: where do we stand? Annu Rev Microbiol 2003;57:203–24.
25. Merrill AH, Sandhoff K. In new comprehensive biochemistry: biochemistry of lipids, lipoproteins and membranes. Else Sci New York; 2002. p. 373–407.
26. Amidon GL, Lennernas H, Shah VP. A theoretical basis for a biopharmaceutical drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharma Res 1995;12:413–9.
27. http://www.gattefosse.com/node.php?Articleid=172. [Last accessed on 24 Jun 2009].
28. Barthelemy P, Laforet JP, Farah N, Joachim J. Compritol 888 ATO: an innovative hot-melt coating agent for prolonged-release drug formulations. Eur J Pharm Biopharm 1999;47:87-90.

29. Faham A, Prinderre P, Farah N, Eichler KD, Kalantzis G, Joachim J. Hot-melt coating technology. I. influence of compritol 888 ATO and granule size on theophylline release. Drug Dev Ind Pharm 2000;26:167-76.
30. Faham A, Prinderre P, Piccerelle P, Farah N, Joachim J. Hot melt coating technology: influence of compritol 888 ATO and granule size on chloroquine release. Pharmazie 2000;55:444-8.
31. Hamdani J, Moes AJ, Amighi K. Development and *in vitro* evaluation of a novel floating multiple unit dosage forms obtained by melt pelletization. Int J Pharm 2006;322:96-103.
32. Zhang YE, Schwartz JB. Melt granulation and heat treatment for wax matrix-controlled drug release. Drug Dev Ind Pharm 2003;29:131-8.
33. Freitas C, Muller RH. Correlation between long-term stability of solid lipid nanoparticles (SLN) and crystallinity of the lipid phase. Eur J Pharm Biopharm 1999;47:125-32.
34. Koo OMY, Varia SA. Case studies with new excipients: development, implementation and regulatory approval. Ther Delivery 2011;2:949-56.
35. Food and Drug Administration. Guidance for industry: Nonclinical studies for the safety evaluation of pharmaceutical excipients; 2005.
36. Maniruzzaman M, Slipper IJ, Vithani K, Douroumis D. Sustained release solid lipid matrices processed by hot-melt extrusion (HME). Colloids Surf B Biointerfaces 2013;110:403-10.
37. Jannin V, Erard BV, Diaye NA. Comparative study of the lubricant performance of Compritol 888 ATO either used by blending or by hot melt coating. Int J Pharm 2003;262:39-45.
38. Diaye NA, Jannin V, Erard BV. Comparative study of the lubricant performance of compritol HD5 ATO and compritol 888 ATO: effect of polyethylene glycol behenate on lubricant capacity. Int J Pharm 2003;254:263-9.
39. Jannin V, Cuppok Y. Hot-melt coating with lipid excipients. Int J Pharm 2013;457:480-7.
40. Hamdani J, Moes AJ, Amighi K. Development and evaluation of prolonged-release pellets obtained by the melt pelletization process. Int J Pharm 2002;45:167-77.
41. Hamdani J, Moes AJ, Amighi K. Development and *in vitro* evaluation of a novel floating multiple unit dosage forms obtained by melt pelletization. Int J Pharm 2006;322:96-103.
42. Nastruzzi C. Lipospheres in drug targets and delivery: approaches, methods and applications. CRC Press: New York; 2005.
43. Gan L, Gao YP, Zhu CL. Novel pH-sensitive lipid-polymer composite microspheres of 10-hydroxycamptothecin exhibiting colon-specific biodistribution and reduced systemic absorption. J Pharm Sci 2013;102:1752-9.
44. Cai S, Yang Q, Bagby TR, Forrest ML. Lymphatic drug delivery using engineered liposomes and solid lipid nanoparticles. Adv Drug Delivery Rev 2011;10:901-8.
45. Saettone MF, Torracca MT, Pagano A. Controlled release of pilocarpine from coated polymeric ophthalmic inserts prepared by hot. Int J Pharm 1992;86:159-66.
46. Aburahma MH, Badr eldin SM. Compritol 888 ATO: a multifunctional lipid excipient in drug delivery systems and nanopharmaceuticals. Expert Opin Drug Delivery 2015;11 Suppl 12:1865-83.
47. Jannin V, Rodier JD, Musakhanian J. Polyoxylglycerides and glycerides: effects of manufacturing parameters on API stability, excipient functionality and processing. Int J Pharm 2014;466(1, Suppl 2):109-21.
48. Pople P, Singh KK. Glyceryl behenate. In: Rowe RC, Sheskey PJ, Owen SC. editors. Handbook of pharmaceutical excipients. American Pharma Assoc 2009;6:286-8.
49. Small DM. Lateral chain packing in lipids and membranes. J lipid Res 1984;25:1490-500.
50. Freitas C, Muller RH. Correlation between long-term stability of solid lipid nanoparticles (SLN) and crystallinity of the lipid phase. Eur J Pharm Biopharm 1999;47:125-32.
51. Souto SB, Mehnert W, Muller RH. Polymorphic behavior of compritol 888 ATO as a bulk lipid and as SLN and NLC. J Microbiol 2006;234:417-33.
52. Negi LM, Jaggi M, Talegaonkar S. Development of protocol for screening the formulation components and the assessment of common quality problems of nanostructured lipid carriers. Int J Pharm 2014;461:403-10.
53. Bose S, Du Y, Takhistov P. Formulation optimization and topical delivery of quercetin from solid lipid-based nanosystems. Int J Pharm 2013;441:56-66.
54. Rosenblatt KM, Bunjes H. Poly (vinyl alcohol) as emulsifier stabilizes solid triglyceride drug carrier nanoparticles in the alpha-modification. Mol Pharm 2008;6:105-20.
55. Maniruzzaman M, Slipper IJ, Vithani K, Douroumis D. Sustained release solid lipid matrices processed by hot-melt extrusion (HME). Colloids Surf B 2013;110:403-10.
56. Jannin V, Cuppok Y. Hot-melt coating with lipid excipients. Int J Pharm 2013;457:480-7.
57. European Pharmacopoeia. 6th edition. Council of Europe: Strasbourg; 2007.
58. United States Pharmacopeia 32 and National Formulary 27. United States Pharmacopeial Convention: Rockville, MD; 2009.
59. Food Chemicals Codex. edited by Institute of Medicine (U. S.). Committee on food chemicals codex. National Academies Press; 2003.
60. Bunjes H, Westesen K, Koch MHJ. Crystallization tendencies and polymorphic transitions in triglyceride nanoparticles. Int J Pharm 1996;129:159-73.
61. Jenning V, Thunemann AF, Gohla SH. Characterization of a novel solid lipid nanoparticle carrier system based on binary mixtures of liquid and solid lipids. Int J Pharm 2000;199:167-77.
62. Vivek K, Reddy H, Murthy RS. Investigations of the effect of the lipid matrix on drug entrapment, *in vitro* release, and physical stability of olanzapine-loaded solid lipid nanoparticles. AAPS PharmSciTech 2007;8:83.
63. Passerini N, Albertini B. Solid lipid microparticles produced by spray congealing: influence of the atomizer on microparticle characteristics and mathematical modeling of the drug release. J Pharm Sci 2010;99:916-31.
64. Kalasz H, Antal I. Drug excipients. Curr Med Chem 2006;13:2535-63.
65. Brossard C, Ratsimbazafy V, Des Ylouses DL. Modeling of theophylline compound release from hard gelatin capsules containing gelucire matrix granules. Drug Dev Ind Pharm 1991;17:1267-77.
66. Volkhard Jenning SHG. Encapsulation of retinoids in solid lipid nanoparticles (SLN). J Microbiol 2001;18:149-58.
67. Achanta AS, Adusumilli PS, James KW, Rhodes CT. Hot-melt coating: water sorption behavior of excipient films. Drug Dev Ind Pharm 2001;27:241-50.
68. Negi LM, Jaggi M, Talegaonkar S. Development of protocol for screening the formulation components and the assessment of common quality problems of nanostructured lipid carriers. Int J Pharm 2014;461:403-10.
69. Rosenblatt KM, Bunjes H. Poly (vinyl alcohol) as emulsifier stabilizes solid triglyceride drug carrier nanoparticles in the alpha-modification. Mol Pharm 2008;6:105-20.
70. Achanta AS, Adusumilli PS, James KW, Rhodes CT. Thermodynamic analysis of water interaction with excipient films. Drug Dev Ind Pharm 2001;27:227-40.
71. Hariharan M, Wowchuk C, Nkansah P, Gupta VK. Effect of formulation composition on the properties of controlled-release tablets prepared by roller compaction. Drug Dev Ind Pharm 2004;30:565-72.
72. Obaidat AA, Obaidat RM. Controlled release of tramadol hydrochloride from matrices prepared using glyceryl behenate. Eur J Pharm Biopharm 2001;52:231-5.
73. Jannin V, Berard V, Diaye NA, Andres C, Pourcelot Y. Comparative study of the lubricant performance of compritol 888 ATO either used by blending or by hot melt coating. Int J Pharm 2003;262:39-45.
74. Muller RH, Mader K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery a review of state of the art. Eur J Pharm Biopharm 2000;50:161-77.
75. Gohla SH, Dingler A. Scaling up the feasibility of the production of solid lipid nanoparticles (SLN). Pharmazie 2001;56:61-3.
76. Manjunath K, Reddy JS, Venkateswarlu V. Solid lipid nanoparticles as drug delivery systems. Methods Find Exp Clin Pharmacol 2005;27:127-44.

77. Abdelbary G, Fahmy RH. Diazepam-loaded solid lipid nanoparticles: design and characterization. AAPS PharmSciTech 2009;10:211-9.
78. Gokce EH, Sandri G, Bonferoni MC. Cyclosporine loaded SLNs: evaluation of cellular uptake and corneal cytotoxicity. Int J Pharm 2008;364:76-86.
79. Report by Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, Mumbai. Narsee Monjee Institute of Management Studies, Mumbai; 2006.
80. Bodmeier RA, Swarbrick J, Boylan JC. Eds. Encyclopedia of pharmaceutical technology. 2nd ed. Vol. III. New York Marcel Dekkerlnc 1998;3 Suppl 2:2988-3000.
81. Hamdani J, Moes AJ, Amighi K. Physical and thermal characterization of precirol and compritol as lipophilic glycerides used for the preparation of controlled release matrix pellets. Int J Pharm 2003;260:47–57.
82. Zang YE, Schwartz JB. Melt granulation and heat treatment for wax matrix-controlled drug release. Drug Dev Ind Pharm 2003;29:131-8.
83. Zangenberg NH, Mullertz A, Kristensen HG, Hovgaard L. A dynamic *in vitro* lipolysis model. II. Evaluation of the model. Eur J Pharm Sci 2001;14:237-44.
84. PubChem. Available from: https://pubchem.ncbi.nlm.nih.gov. [Last accessed on 05 Apr 2019].
85. http: //www.americanpharmaceuticalreview.com. [Last accessed on 05 Apr 2019].
86. http://www.ferromet.com.arindex. [Last accessed on 05 Apr 2019].
87. Report by Shanghai Thanch Pharmaceuticals Technology Co., Ltd; 2011.
88. Martins A. Applying nanotechnology to human health: a revolution in biomedical sciences. J Biomed Nanotech 2009;5 Suppl 1:76.
89. https://www.trc-canada.com/structure-search/). [Last accessed on 05 Apr 2019].
90. Lide, David R. CRC Handbook of Chemistry and Physics. CRC Press; 2009.
91. Van Langevelde A, Peschar R, Schenk H. Structure of β-Trimyristin and β-tristearin from high-resolution X-ray powder diffraction data. Acta Crystallogr Sect B 2001;57 Suppl 3:372.
92. https://www.Cremercare.De. [Last accessed on 05 Apr 2019]
93. Bindu NHS, Kumar SR. *In vitro* assimilation of trimyristin in the seeds of myristica fragrans and in the polyherbal ayurvedic formulation by UFLC method. Asian J Pharm Clin Res 2013;6 Suppl 4:140-5.
94. Report by Institute of R and D, G. F. S. U. Gandhinagar, GUJARAT; 2011-2012.