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Review Article

LIPIDS - THE INSTRUMENTAL EXCIPIENT IN PHARMACEUTICAL DOSAGES FORM

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INTRODUCTION

Lipids are a broad group of naturally occurring and semisynthetic molecules, soluble in non polar solvent and insoluble in polar solvent. A clear advantage of the lipid is their structure resembles to that of biological lipids which decreases the danger of acute and chronic toxicity.[1]

Lipids used in pharmaceutical industries exhibit unique physical and chemical properties. Their composition, crystalline structure, melting properties and ability to associate with water and other non-lipid molecules are especially important to their functional properties.

Classification of Lipids[2]

1. Biological lipids.
2. Fatty acid .
3. Fatty alcohol.
4. Glycero lipids.
5. Wax and oils.
6. Fat-soluble vitamins (such as vitamins A, D, E and K).

1) Biological lipid[3]

a) **Phospholipid**

Phospholipids is a biological lipid and are a major component of all cell membranes as they can form lipid bi layers. Most phospholipids contain a di glyceride, a phosphate group and a simple organic molecule such as choline.

b) Glycolipids

Glycolipid is also biological lipid, carbohydrate attached to phospholipid. The role of phospholipid is to provide the energy and also serve as marker for cellular recognition.

c) Cholesestrol

Cholesterol, waxy steroid of fat generated in liver and intestine is an essential structural component of mammalian cell membrane responsible to establish proper membrane permeability and fluidity and also use to produce hormones.

The Biological lipids are amphiphilic in nature, the amphiphilic nature of these lipids allows them to form structures such as vesicles, liposomes etc in an aqueous environment.

2) Fatty acid[4]

A Fatty acid is a carboxylic acid with a long unbranched aliphatic chain, which is either saturated or unsaturated. Most naturally occurring fatty acids have a chain of an even number of carbon atoms, from 4 to 28.

***a)* Saturated Fatty acid**

Saturated fatty acids are long-chain carboxylic acids that usually have carbon atom between 4 and 28 having no double bonds.

i) Very long chain fatty acid: Fatty acid having more than 22 carbon atom.

ii) Long chain fatty acid: Fatty acid having 12 to 22 carbon atom.

iii) Medium chain Fatty acid: Fatty acid having 6 to 12 carbon atom.

iv) Short chain Fatty acid: Fatty acid having less than 6 carbon atom.

Trivial Name	Systematic Name	Chemical structure	C: D	MP(^{0}c)
Butyric acid	Butanoic acid	$CH_3(CH_2)_2COOH$	4:0	-7.9
Caproic acid	Hexanoic acid	$CH_3(CH_2)_4COOH$	6:0	-3.4
Caprylic acid	Octanoic acid	$CH_3(CH_2)_6COOH$	8:0	16
Capric acid	Decanoic acid	$CH_3(CH_2)_8COOH$	10:0	31.6
Lauric acid	Dodecanoic acid	$CH_3(CH_2)_{10}COOH$	12:0	44
Myristic acid	Tetradecanoic acid	$CH_3(CH_2)_{12}COOH$	14:0	54.4
Palmitic acid	Hexadecanoic acid	$CH_3(CH_2)_{14}COOH$	16:0	63
Stearic acid	Octadecanoic acid	$CH_3(CH_2)_{16}COOH$	18:0	70
Arachidic acid	Eicosanoic acid	$CH_3(CH_2)_{18}COOH$	18:0	75.5
Behenic acid	Docosanoic acid	$CH_3(CH_2)_{20}COOH$	22:0	80
C = No of carbon atom D= No of Double bond				

b)Unsaturated fatty acid

Unsaturated fatty acids having one or more double-bonds between carbon atoms. The two carbon atoms in the chain that are bound next to either side of the double bond can occur in a cis or trans configuration. omega-3 fatty acids are essential unsaturated fatty acids with a double bond (C=C) starting after the third carbon atom from the end of the carbon chain. The carbon chain has two ends -- the acid (COOH) end and the methyl (CH_3) end. The location of the first double bond is counted from the methyl end, which is also known as the omega (ω) end or the n end.

Trivial Name	Systematic Name	Chemical structure	C:D
α-Linolenic acid	cis-9,12,15-Octadecatrienoic acid	CH3(CH2CH=CH)$_3$(CH2)$_7$COOH	18:3
Myristoleic acid	9-Tetradecenoic acid	$CH_3(CH_2)_3CH=CH(CH_2)_7COOH$	14:1
Palmitoleic acid	9-Hexadecenoic Acid	$CH_3(CH_2)_5CH=CH(CH_2)_7COOH$	16:1
Oleic acid	cis-9-Octadecenoic acid	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	18:1
Linoleic acid	cis,cis -9- 12 Octadecadienoic acid	$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$	18:2
C = No of carbon atom D= No of Double bond			

C)Fatty alcohols [5]

Fatty alcohol are aliphatic alcohols consisting of a chain of 8 to 22 carbon atoms. Fatty alcohols usually have even number of carbon atoms and a single alcohol group (-OH) attached to the terminal carbon**.** Some are unsaturated and some are branched.

Trivial Name	Chemical structure	C:D	MP(^{0}c)	Saturated/unsaturated
Capryl alcohol	$CH_3(CH_2)_7OH$	8:0	-17	Saturated
Capric alcohol	$CH_3(CH_2)_9OH$	10:0	6.4	Saturated
Lauryl alcohol	$CH_3(CH_2)_{11}OH$	12:0	24	Saturated
Myristyl alcohol	$CH_3(CH_2)_{13}OH$	14:0	37 to 39	Saturated
Palmityl alcohol	$CH_3(CH_2)_{15}OH$	16:0	49 to 52	Saturated
Stearyl alcohol	$CH_3(CH_2)_{17}OH$	18:0	60	Saturated
Arachidiyl alcohol	$CH_3(CH_2)_{19}OH$	20:0	64 - 66	Saturated
Behenyl alcohol	$CH_3(CH_2)_{21}OH$	22:0	65 - 73	Saturated
Oleyl alcohol	C18H36O	18:1	13-19	Un Saturated
Cetostearyl alcohol	Mixture of Palmityl alcohol and stearyl alcohol having MP 49-56^{0}c			
C = No of carbon atom D=No of Double bond				

Myristyl alcohol serves as emulsifying agent, skin penetrant, tablet and capsule lubricant, Stearyl alcohol is used in cosmetics and topical pharmaceutical creams and ointments as a stiffening agent. Cetyl alcohol is widely used in cosmetics and pharmaceutical formulations such as suppositories, modified-release solid dosage forms, emulsions, lotions, creams and ointments.

a)Glycero lipids [6]

Glycero lipids are glycerol ester of the fatty acid and fabricating by incorporating the functional moiety to modify physicochemical properties. Depending upon substitution of

the hydroxyl group of the glycerol and Propylene glycol by fatty acid they are as monoglycerides, diglycerides and triglycerides.
i) Liquid glycerides
ii) Solid triglycerides
ii) Partial glycerides

i) Liquid glycerides
Liquid glycerides are short chain fatty acid and alcohol (C-8 to C-10) esters. As they have high polarity hence act as good solvent, solubalizer and penetration enhancer. Some of the liquid glycerides are as

Common Name	Physical State	Trade Name	HLB Value
Propylene glycol monocaprylate	Oily Liquid	Capryol™ 90	6
Propylene glycol caprylate	Oily Liquid	CAPRYOL™ PGM	5
Propylene glycol Monolaurate	Liquid	CAPRYOL™ PGM	5
Oleoyl macrogolglycerides	Liquid	Labrafil®M 1944CS	4
Linoleoyl macrogolglycerides	Liquid	Labrafil® M 2125CS	4
Polyoxyl 35 castor oil	Pale yellow, oily liquid	Cremophor EL	12 to14
Polyoxyl 40 hydrogenated castor oil	white to yellowish, semisolid	Cremophor RH40	14 to 16
Polyoxyl 60 hydrogenated castor oil	white paste	Cremophor RH60	15–17

ii) Solid triglycerides
Solid triglycerides are esterified glycerol with defined fatty acid blends and have therefore precise properties like melting point, polarity (Hydroxyl Value) and consistency. Mainly used in cosmetic preparation .They also act as surface treatment and binder in tablets.
Eg Hydrogenated Coco-Glycerides + Glyceryl Ricinoleate , Hydrogenated Coco-Glycerides + Ceteareth-25 + Bees Wax , Cetyl Palmitate and Trimyristin etc

iii) Partial Triglycerides
Partial glycerides are esters of glycerol with fatty acids, whereby only a part of the existing hydroxyl groups are esterified. Some hydroxyl groups within the glycerol ester are free contributing to the polaric properties of the material. Short chain partial glycerides are more polaric and have excellent solvent properties for many hard-to-solubilise drugs.

Common Name	Physical State	Trade Name	HLB Value
Glyceryl Monostearate	Solid	Capmul GMS-50	3.8
Glycerol Mono-oleate	Liquid	Imwitor 948	3.3
Medium-Chain Triglycerides	Liquid	Captex 300	2.0
Sorbitan MonoStearate	Cream solid	Span 60	4.7
Sorbitan MonoPalmitate	Cream solid	Span 40	6.7
Sorbitan MonoLaurate	Yellow viscous liquid	Span 20	8.6
Sorbitan Monooleate	Yellow viscous liquid	Span 80	4.3
Sorbitan Trioleate	Amber viscous liquid	Span 85	1.8
Polyoxethylene 20 Sorbitan mono stearate	Yellow oily liquid	Polysorbate 60	9.6
Polyoxethylene 20 Sorbitan mono palmitate	Yellow oily liquid	Polysorbate 40	15.6
Polyoxethylene 20 Sorbitan Mono Laurate	Yellow oily liquid	Polysorbate 20	16.7
Polyoxethylene 20 Sorbitan Mono Oleate	Yellow oily liquid	Polysorbate 80	15.0

a) Waxes and Oils [7]
The term wax generally refers to a substance that is a plastic solid at room temperature and liquid of low viscosity above its melting point. Wax is chemically defined as an ester of a monohydric long chain fatty alcohol and a long chain fatty acid. They usually contain a wide variety of materials including glycerides, fatty alcohols and fatty acids and their esters. The difference between lipophilic fats and waxes is that fats may be saponified by either aqueous or alcoholic alkali but waxes are saponified only by alcoholic alkali. This is so because esters in waxes are usually much more resistant to saponification than glycerides of fats and fixed oils.
Classification of Waxes
Waxes are generally classified according to their source as
Animal waxes – e.g. spermaceti wax, wool fat, etc.
Insect waxes – e.g. beeswax

Vegetable waxes – e.g. carnauba wax, Japan wax, castor wax, candelila wax
Mineral waxes – e.g. microcrystalline wax
Synthetic waxes – e.g. PEGs/carbowaxes (above MW 700), ross wax and, polyoxyethylene alkyl ethers etc.

Characterisation of Lipids [8,9 10 &11]
To characterise Lipids various chemical and Instrumental (G.C.) method are available to measure the constant of lipids they are

Sr.No	Constant of lipids	Significance
1	Acid value	Free fatty acid content
2	Saponification value	Average molecular weight
3	Iodine value	Average degree of unsaturation
4	Peroxide value	Progress of lipid oxidation
5	Thin layer chromatography	Concentration of different lipid fraction
6	Gas chromatographic method	Fatty acid methyl esters
7	Gravimetric and Soxhlet method	To determine lipid content
8	Viscosity	High pressure capillary viscometer

Physicochemical Properties
Solid fat content (SFC**)** The solid fat content of lipid influences such as spreadability, firmness, mouth feel and stability The density of solid fat is higher than the density of liquid and so there is an increase in density when a fat crystallizes and a decrease when it melts. By measuring the density over a range of temperatures it is possible to determine the solid fat content .[12 &13]

Melting point[14]
In case of pure triacylglycerol has a single melting point that occurs at a specific temperature. The following points are very significant during processing

Clear point
The temperature at which the fat completely melts and becomes transparent is called the clear point.

Slip point
The temperature at which the fat just starts to move downwards due to its weight is called the slip point.

Wiley melting point
The temperature at which the disc changes shape to a sphere is called the Wiley melting point

Cloud point
This gives a measure of the temperature at which crystallization begins in a liquid oil. It is often of practical importance to have an oil which does not crystallize when stored at 0^{o}C for prolonged periods. A simple test to determine the ability of lipids to withstand cold temperatures without forming crystals.

Smoke, Flash and Fire Points
These tests give a measure of the effect of heating on the physicochemical properties of lipids. They are particularly important for selecting lipids that are going to be used at high temperatures.
The smoke point is the temperature at which the sample begins to smoke when tested under specified conditions. Temperature at which a thin continuous stream of bluish smoke is first observed**.**
The flash point is the temperature at which a flash appears at any point on the surface of the sample due to the ignition of volatile gaseous products.
The fire point is the temperature at which evolution of volatiles due to the thermal decomposition of the lipids proceeds so quickly that continuous combustion occur

Rheology of lipids[15]
It is an important in monitoring characteristics like creaminess, juiciness, smoothness, brittleness, tenderness, hardness etc. The stability and appearance of pharmaceutical dosages form also often depends on the rheological characteristics of their components.

Pharmaceutical Application of Lipids
Oral bioavailability enhancement with lipid [16,17.]
Solid lipid Nanoparticles are made up of solid lipid, emulsifier and water/solvent . The lipids used may be triglycerides (tri-stearin), partial glycerides (Imwitor), fatty acids (stearic acid, palmitic acid), and steroids (cholesterol) and waxes (cetyl palmitate). Various emulsifiers and their combination (Pluronic F 68, F 127) have been used.

Selfmicroemulsifying drug delivery system (SMEDDS) used to improves the oral bioavailability of the lipophilic drug. SMEDDS comprises of mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. [18 &19]

Lipid as cushioning agent for MUPS [20& 21]

The beads of the lipid are used as cushioning agent to protect the modified release coat as particle deformation is essential during compression to ensure consolidation of the material, functional coat must withstand the compression process without being damaged to maintain its function as a protective barrier or as a controlled release membrane. Diltiazem hydrochloride film-coated MUPS can be prepared by incorporating soft cushioning of paraffin beads.

Taste masking with Lipids

One of the physical approaches to mask the drug taste is encapsulating it in a waxy material. Recent method developed byYajima, using a spray-congealing technique to mask the bitter taste of clarithromycin. Glyceryl monostearate and aminoalkyl methacrylate copolymer E (AMCE) were selected as ingredients. The palatability and taste of optimized formulation (CAM: GM: AMCE, 3:6:1) were significantly improved, compared with conventionally coated granules.In yet another invention, triglycerides in combination with polymethacrylate has been used to mask the bitter Taste of metronidazole [22.]

Lipid matrix tablets and beads

Lipid matrix tablet are fabricated by hot melt granulation in which solubilise or suspended the drug in molten lipid along with tableting excipient. Sustained-release diclofenac tablets based in cetyl alcohol and a combination of ethyl cellulose and paraffin wax or hydrogenated castor oil as carrier material in sustained-release aminophylline tablets,[23] were developed. The modified release drug beads are also prepared by spray congealing.

Lipids as emulsifying agent

Lipid used as emulsifier or solubalizer consist primarily of two basic component hydroxyl group i.e of glycerol, polyethylen glycol, polyglycerol and propylene glycol and fatty acids of varying length and degree of saturation. The combination of these two group makes its amphiphilic in nature which allows them to used as emulsifying agent to prepare both types of emulsions – oil-in-water (i.e. o/w) and water-in-oil (i.e. w/o). Synthetic emulsifying lipid includes anionic emulsifying lipid, cationic emulsifying lipid and nonionic surfactants such as glyceryl monostearate. These emulsifying lipid produce stable emulsions, creams, lotions, etc.[24, 25 &26.]

Lipid as ointment bases

Lipids are widely used as ointment bases or as ingredient(s) of ointment bases that serve as carrier or vehicle for the medicament(s). Examples of ointment bases that include waxes are - hydrocarbon bases (hard paraffin, petrolatum), absorption bases (anhydrous lanolin, bees wax), emulsion bases (cetyl alcohol, glyceryl monostearate) and water soluble bases (carbowaxes).[27]

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