Middle-East Journal of Scientific Research 23 (12): 2811-2816, 2015
ISSN 1990-9233

DOI: 10.5829/idosi.mejsr.2015.23.12.10117

Lipid Material for the Preparation of Microsphere Challenges and Recent Advancement A Review

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Abstract: Lipid is a water insoluble biomolecule. It is soluble in nonpolar organic solvent. These are made up of fatty acids. Lipids are group of natural molecules such as vitamins etc. Fatty acids are the part of lipid and fatty acid are synthesized by chain elongation acetylacetyl-CoA primer with malonyl-CoA or methylmalonyl-CoA groups in a process called fatty acid synthesis. Glycerolipids are composed of mono-, di- and tri-substituted glycerols. Glycerophospholipids involved in metabolism and cell signaling. Sphingolipids base backbone that is synthesized *de novo* from the amino acid serine and a long-chain fatty acyl CoA. Polyketides are synthesized by polymerization of acetyl and propionyl subunits by classic enzymes as well as iterative and multimodular enzymes that share mechanistic features with the fatty acid synthesis. This paper deals with study about the role of different lipid material and their used in pharmaceutical formulations. Manuscript also emphasize on recent patents based on lipid material based pharmaceutical preparations.

Key words: Lipid · Fatty Acid · Cholesterol · Triacylglycerols · Glycerophospholipids

INTRODUCTION

A lipid is defined as a water-insoluble biomolecule which has a high solubility in nonpolar organic solvents such as chloroform. The simplest lipids are the fats, which are triesters made up of one glycerol and other three fatty acids. The term fats is also used as a general synonym for lipids, so the more precise terms triacylglycerols or triglycerides are preferable for the simplest lipids. Triacylglycerols are used primarily for energy storage in animals. More complex lipids, the phospholipids, glycolipids and cholesterol, are the major constituents of biological cell membranes [1, 2].

Lipids are a group of naturally occurring molecules that include fats, waxes, sterols, fat-soluble vitamins (Such as vitamins A, D, E and K), monoglycerides, diglycerides, triglycerides, phospholipids and others. The main biological functions of lipids include storing energy. Lipids have applications in the cosmetic and food industries as well as in nanotechnology [3].

Simple Lipids: Triacylglycerols: In mammals, the major reservoir of triacylglycerols is in the cytoplasm of adipose cells (Fat cells). A mammalian fat cell consists of a small droplet of condensed triacylglycerols surrounded by a thin cell membrane with the cell nucleus bulging out to one side. Most of the energy reserve of animals is stored in fat cells. The total energy reserve of a standard 70 kg man consists of about 0.17 MJ in glucose, 2.5 MJ in glycogen, 105 MJ in protein (Mostly in the muscles) and 420 MJ in triacylglycerols. The triacylglycerols constitute about 11 kg of his total body mass of 70 kg. The proportion of protein is lower and that of triacylglycerols higher, on average, in women [4].

The processing of glucose to triacylglycerols rather than glycogen and its reverse, require metabolic energy and one would expect, since energy storage as triacylglycerols is clearly preferred, that there is a major advantage to this form of energy storage. There is such an advantage; one gram of fatty acids yields on complete oxidation almost double the energy of one gram of anhydrous carbohydrate (Such as glycogen) or protein. Moreover, the triacylglycerols are hydrophobic and are stored in nearly anhydrous form by living organisms, while glycogen is hydrophilic; one gram of dry glycogen binds, under physiological conditions, about two grams of water. As a consequence, a gram of fat stores more than six times as much energy as does a gram of glycogen

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under physiological conditions. If most of the energy of the 70 kg standard man were not stored as triacylglycerols, his mass would have to be nearly doubled to 125 kg [5].

Fatty Acids: Fatty acids or fatty acid residues when they form part of a lipid, are a diverse group of molecules synthesized by chain-elongation of an acetyl-CoA primer with malonyl-CoA or methylmalonyl-CoA groups in a process called fatty acid synthesis They are made of a hydrocarbon chain that terminates with a carboxylic acid group; this arrangement confers the molecule with a polar, hydrophilic end and a nonpolar, hydrophobic end that is insoluble in water. The fatty acid structure is one of the most fundamental categories of biological lipids and is commonly used as a building-block of more structurally complex lipids. The carbon chain, typically between four and 24 carbons long may be saturated or unsaturated and may be attached to functional groups containing oxygen, halogens, nitrogen and sulfur. If a fatty acid contains a double bond, there is the possibility of either a *cis* or *trans* geometric isomerism, which significantly affects the molecule's configuration. *Cis*-double bonds cause the fatty acid chain to bend, an effect that is compounded with more double bonds in the chain. Three double bonds in 18-carbon *linolenic acid*, the most abundant fatty-acyl chains of plant *thylakoid membranes*, render these membranes highly *fluid* despite environmental low-temperatures and also makes linolenic acid give dominating sharp peaks in high resolution 13-C NMR spectra of chloroplasts. This in turn plays an important role in the structure and function of cell membranes Most naturally occurring fatty acids are of the *cis* configuration, although the *trans* form does exist in some natural and partially hydrogenated fats and oils [6-8].

Examples of biologically important fatty acids include the eicosanoids, derived primarily from arachidonic acid and eicosapentaenoic acid, that include prostaglandins, leukotrienes and thromboxanes. Docosahexaenoic acid is also important in biological systems, particularly with respect to sight. Other major lipid classes in the fatty acid category are the fatty esters and fatty amides. Fatty esters include important biochemical intermediates such as wax esters, fatty acid thioester coenzyme A derivatives, fatty acid thioester ACP derivatives and fatty acid carnitines. The fatty amides include N-acyl ethanolamines, such as the cannabinoid neurotransmitter anandamide [9, 10].

Glycerolipids: Glycerolipids are composed of mono-, di- and tri-substituted glycerols, the best-known being the fatty acid triesters of glycerol, called triglycerides. The word "Triacylglycerol" is sometimes used synonymously with "triglyceride". In these compounds, the three hydroxyl groups of glycerol are each esterified, typically by different fatty acids. Because they function as an energy store, these lipids comprise the bulk of storage fat in animal tissues. The hydrolysis of the ester bonds of triglycerides and the release of glycerol and fatty acids from adipose tissue are the initial steps in metabolizing fat [11, 12]. Additional subclasses of glycerolipids are represented by glycosylglycerols, which are characterized by the presence of one or more sugar residues attached to glycerol via a glycosidic linkage. Examples of structures in this category are the digalactosyldiacyl glycerols found in plant membranes and seminolipid from mammalian sperm cells [13].

Glycerophospholipids: Glycerophospholipids, usually referred to as phospholipids, are ubiquitous in nature and are key components of the lipid bilayer of cells, as well as being involved in metabolism and cell signaling. Neural tissue (Including the brain) contains relatively high amounts of glycerophospholipids and alterations in their composition has been implicated in various neurological disorders. Glycerophospholipids may be subdivided into distinct classes, based on the nature of the polar headgroup at the *sn*-3 position of the glycerol backbone in eukaryotes and eubacteria, or the *sn*-1 position in the case of archaebacteria [14-16].

Examples of glycerophospholipids found in biological membranes are phosphatidylcholine (Also known as PC, GPCho or lecithin), phosphatidylethanolamine (PE or GPEtn) and phosphatidylserine (PS or GPSer). In addition to serving as a primary component of cellular membranes and binding sites for intra- and intercellular proteins, some glycerophospholipids in eukaryotic cells, such as phosphatidylinositols and phosphatidic acids are either precursors of or, themselves, membrane-derived second messengers. Typically, one or both of these hydroxyl groups are acylated with long-chain fatty acids, but there are also alkyl-linked and 1Z-alkenyl-linked (Plasmalogen) glycerophospholipids, as well as dialkylether variants in archaebacteria [17, 18].

Sphingomyelin: The major phosphosphingolipids of mammals are sphingomyelins (Ceramide phosphocholines), whereas insects contain mainly ceramide phosphoethanolamines and fungi have phytoceramide phosphoinositols and mannose-containing headgroups. The glycosphingolipids are a diverse family of molecules composed of one or more

sugar residues linked via a glycosidic bond to the sphingoid base. Examples of these are the simple and complex glycosphingolipids such as cerebrosides and gangliosides [19-21].

Sterol Lipids: Sterol lipids, such as cholesterol and its derivatives, are an important component of membrane lipids, along with the glycerophospholipids and sphingomyelins. The steroids, all derived from the same fused four-ring core structure, have different biological roles as hormones and signaling molecules. The eighteen-carbon (C18) steroids include the estrogen family whereas the C19 steroids comprise the androgens such as testosterone and androsterone. The C21 subclass includes the progestogens as well as the glucocorticoids and mineralocorticoids. The secosteroids, comprising various forms of vitamin D, are characterized by cleavage of the B ring of the core structure. Other examples of sterols are the bile acids and their conjugates, which in mammals are oxidized derivatives of cholesterol and are synthesized in the liver. The plant equivalents are the phytosterols, such as β-sitosterol, stigmasterol and brassicasterol; the latter compound is also used as a biomarker for algal growth. The predominant sterol in fungal cell membranes is ergosterol [22-25].

Prenol Lipids: Prenol lipids are synthesized from the five-carbon-unit precursors isopentenyl diphosphate and dimethylallyl diphosphate that are produced mainly via the mevalonic acid (MVA) pathway. The simple isoprenoids (Linear alcohols, diphosphates, etc.) are formed by the successive addition of C5 units and are classified according to number of these terpene units. Structures containing greater than 40 carbons are known as polyterpenes. Carotenoids are important simple isoprenoids that function as antioxidants and as precursors of vitamin A. Another biologically important class of molecules is exemplified by the quinones and hydroquinones, which contain an isoprenoid tail attached to a quinonoid core of non-isoprenoid origin. Vitamin E and vitamin K, as well as the ubiquinones, are examples of this class. Prokaryotes synthesize polyprenols (Called bactoprenols) in which the terminal isoprenoid unit attached to oxygen remains unsaturated, whereas in animal polyprenols (Dolichols) the terminal isoprenoid is reduced [26-28].

Saccharolipids: Saccharolipids describe compounds in which fatty acids are linked directly to a sugar backbone, forming structures that are compatible with membrane bilayers. In the saccharolipids, a monosaccharide substitutes for the glycerol backbone present in glycerolipids and glycerophospholipids. The most familiar saccharolipids are the acylated glucosamine precursors of the Lipid A component of the lipopolysaccharides in Gram-negative bacteria. Typical lipid A molecules are disaccharides of glucosamine, which are derivatized with as many as seven fatty-acyl chains. The minimal lipopolysaccharide required for growth in *E. coli* is Kdo_2-Lipid A, a hexa-acylated disaccharide of glucosamine that is glycosylated with two 3-deoxy-D-manno-octulosonic acid (Kdo) residues [29].

Polyketides: Polyketides are synthesized by polymerization of acetyl and propionyl subunits by classic enzymes as well as iterative and multimodular enzymes that share mechanistic features with the fatty acid synthesis. They comprise a large number of secondary metabolites and natural products from animal, plant, bacterial, fungal and marine sources and have great structural diversity Many polyketides are cyclic molecules whose backbones are often further modified by glycosylation, methylation, hydroxylation, oxidation and/or other processes. Many commonly used anti-microbial, anti-parasitic and anti-cancer agents are polyketides or polyketide derivatives, such as erythromycins, tetracyclines, avermectins and antitumor epothilones [30].

Advantages of lipid includes.

- A healthy body needs fats, getting the sufficient amount of dietary at.
- Making the right dietary fat choice helps promotes long term health and well being.
- Carbohydrate and proteins, fats are nutrient that supply energy to our body.
- Lipids are the provide body's internal process working at their optimal level.
- Lipids are the important part of cell membranes and influences how our body muscle respond to insulin.
- Lipids are the help of production of certain hormones.
- Low risk profile [31].

Some of the Disadvantages of lipid are as:

- You eat too much amount of the wrong kind of fat so risk for health problems.
- The cholesterol lipid increases so risk for heart disease.
- Consuming saturated fats and Trans lipids is harmful for our body [31].

S.no	Drug	Polymer	Work done	References
1	Ketoprofen	Bees wax, ceresin wax	Developed and evaluated ketrofen lipid microsphere. The objective of this study was to minimise unwanted side effects. This formulation congeable disperse encapsulation method was used. with the various concentration of bees wax and ceresin wax and free flowing microsphere were obtained. The yield of microsphere was upto 92%. Microsphere prepared have smooth surface. The result was found this study was to be stable and compatible with waxes as confirmed by FTIR studies. Release followed by constant release upto 24 hour.	32
2	Lithium carbonate	Carnauba wax	In one study was prepared encapsulated carnauba wax microspheres. The main objective that study was minimise the unwanted side effects of lithium carbonate. Formulated this preparation by meltable emulsified dispersion cooling induced solidification technique utilizing a wetting agent. It was obtained free flowing microspheres. The yield of the microsphere was upto 92% having smooth surfaces with the good packing properties. The drug loaded microspheres was stable and compatible, as confirmed by DSC and FTIR studies. Release of drug was controlled more than 8 hours.	33
3	Olanzapine, Ranolazine, clonzapine	Bees wax	In three study main objective was to minimise unwanted side effects of different drug by kinetic control of drug release. Different ingredient in different concentration was used. Microsphere was prepared meltable emulsified dispersion cooling induced solidification method. The yield was obtained upto 94%. Microspheres had smooth surfaces with free flowing good packing properties. The result was found drug loaded microspheres to be stable and compatible.	34
4	Indomethacin	Sugarcane wax	Prepared indomethacin microspheres with sugarcane wax. Microspheres were prepared by melt emulsified dispersion and cooling induced solidification method. The result was found microspheres were spherical in shape and the yield was 98%.	35
5	Aceclofenac	Carnauba wax	The main objective in one study was minimize unwanted side effects of aceclofenac by kinetic control of drug release. Formulated by meltable emulsified dispersion cooling induced solidification method. Free flowing microsphere was obtained. The yield of the microsphere upto 90% having smooth surfaces and good packing properties. The result was found drug loaded microspheres was stable and compatible, as confirmed by DSC and FTIR studies. The drug release of drug was controlled for more than 8 hours.	36
6	Propafenone hydrochloride	Bees wax	Prepared and evaluated bees wax microspheres loaded with propafenone hydrochloride. It was entrapped into gastro resistant, biodegradable such as bees wax. Prepared by cooling induced solidification technique utilizing a wetting agent. The yield of the microsphere was upto 92.5%. The microspheres had smooth surface. The Result was found microsphere was stable and compatible, as confirmed by DSC and FTIR studies.	37

Patent Papers: Some of the patents based on lipid material for pharmaceutical applications are as:

S. no	Patent no.	Workdone	References
1	US 8765182B2	The invention relates to the production of microspheres having radial pores using thermally induced phase separation, especially	38
2	IND244381	The inventor was invented a controlled release microsphere preparation. microsphere for containing temozolomide and	39
3	CA2061124A1	The inventor invent microsphere by casting method. The inventor was found microsphere while heated so thermally collapsible expended microsphere.	40
4	US4331654A	The inventor invent a microsphere as a drug carrier. That formulation consisting of magnetically localizable, lipid microsphere. Finally result was found prepared novel biodegradable microsphere.	41
5	EP0350913	In one study make a lipid microsphere (Very small in size) just like a emulsion. Containing ibudilast drug. This microsphere can be used parentrally administered and it was used for intravenous injection.	42
6	US3822138	It has been discovered that hollow carbon microsphere. Main object was invention to provide a wax investment composition having a high melting point, ability form a stable suspension while wax melted.	43
7	US5185108	Formulated wax microsphere from molten wax comprising, flowing confined stream of hot motive liquid. In which molten wax is immiscible. The solidification liquid being maintained at a controlled temperature below the melting point of wax. Result was found free flowing wax microsphere.	44

CONCLUSION

It can be concluded from the literature survey that lipid material can be used as a drug delivery carrier for different pharmaceutical preparation. They are easily available can has been successfully used to prepare controlled and sustained release dosage form.

ACKNOWLEDGEMENT

Authors are highly thankful to Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University for providing library facilities to carry out literature survey.

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