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Novel Formulatory Approaches with Cubic, Lipid and Microdispersion Systems

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ABSTRACT

Drugs now a day either synthesized or identified, though showing desired pharmacological activity, tend with formulatory difficulties. Scientists having a big deal to optimize these pharmacologically active moieties into pharmaceutical active dosage form with patient compliance and commercial viability. The drugs developed were grouped under BCS into 4 classes, which have their own limitations in designing a dosage form. Many novel and traditional methods had been identified to limit these limitations and to develop a dosage form. Present review post a brief out look over different dispersions system developed in recent past for solving both hydrophilic and lipophyllic drug delivery challenges. The coarse dispersions are microemulsions, a novel technique, present drug in solubilized form improve permeation and absorption owing to their less size suitable for ease passage through GI membranes where the colloidal are liquid crystals, a carrier systems employ encapsulation the drugs for developing a dosage form of inventor choice. The method of preparation and applications in related fields were given along with their mode through which they provide suitability for their roles in dosage form development.

Keywords: Microemulsions, Dispersions, Lipospheres, Cubosomes, Carrier systems, Solubility, Stability.

INTRODUCTION

The active moieties which are pharmacodynamically active are prone to either solubility or permeation problems for their better systemic profiles when given *in vivo* through varied routes. All these drugs are grouped chemically under two categories, hydrophilic and lipophillic i.e. water loving and oil loving respectively. The hydrophilic drugs will have permeation as the major limitation step for the absorption into systemic circulation when taken pre systemically. To enhance their permeation the drugs are designed as liquid crystals from the recent past due to their multiple advantages. Being small sized and by encapsulation these liquid crystals enhance the permeation of the drugs. The liquid crystals are colloidal dispersions and the -somes come under this categories i.e. liposome and Cubosomes. These -somes ensure site specificity when attached with markers on to their type of lipid. These also provide advent of formulating lipophillic drug.

The lipophyllic drug poses a disadvantage of solubility in GI medium which is a rate limiting event for its high bioavailability. The administration of such drugs via parentral route may avoid this problem but regarding the compliance this route of administration is limited. So for the development of oral dosage form the solubility of the drug has to be enhanced to meet the criterions for the formation of a dosage form. Researches had developed many tools to fix the problem of solubility like salt formation, solid dispersion and microemulsion. Among these the micro emulsion is such a tool which can help in this regard by marinating the drug in solubilized form. Like colloidal dispersion both kind of drugs can be formulated in microemulsions. Hydrophilic were formulate as w/o preferably and the other in other kind of emulsion.

Lipospheres as Liquid Crystals

The liquid crystals combine both properties of both liquid and solid states. The liquid state has the ability to flow, whereas solids have an ordered structure. Their i.e. liquid crystals, formation start with the crystalline state, A prerequisite for the formation of liquid crystalline phases is an anisometric molecular shape, the agents which have a anisotropic stretcher are called

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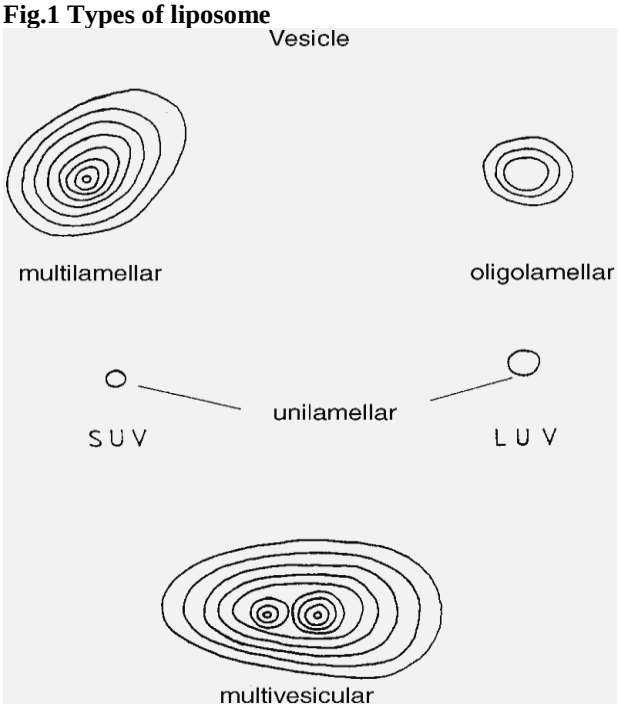
mesogens. The mesophase an intermediate phase before formation of liquid crystals is formed by raising the temperature or by adding a solvent leading to formation of thermotropic and lyotropic liquid crystals, respectively. As with thermotropic liquid crystals, a variation of the temperature can also cause transformation between different mesophases with lyotropic liquid crystals. A high concentration of mesogens results in a lamellar phase such lamellar phase when dispersed in the form of concentric layered particles in excess water or aqueous solution results in a vesicular dispersion.

Liposomes

If the mesogen is phospholipid, the vesicular dispersion formed is called a liposomal dispersion. The liposomes dispersed in oil phase, are of minimal interest in drug formulation. Liposomes consist of many phospholipid bilayers or just one bilayer (Fig. 1). Therefore multilamellar vesicles (MLV), oligolamellar vesicles (OLV), small unilamellar (SUV), and large unilamellar vesicles (LUV) have to be further distinguished. Furthermore, multivesicular liposomes (MVL) may also form.

Fig.1 Types of liposome



The mechanism of liposomes acting as carriers for polar drugs with its polar character of core makes the encapsulation of polar drug molecules possible due to which the drug is protected from the GI hostile environment and also these provide essential permeation required for absorption for BCS class III and IV drugs. Amphiphilic and lipophili drugs are solubilized within the phospholipid bilayer based on their solubilization in phospholipids. A most followed and standard procedure for manufacturing liposomes is the film-forming method in which phospholipids are dissolved in an organic solvent. A thin and multilayered film of phospholipids formed at the inner wall of the rotational flask by evaporation of the solvent. Redispersion of this film in water or aqueous buffer results in the formation of vesicles. Being a conventional method the size of these vesicles and the number of bilayers vary. Hence further steps of manufacture have to follow to obtain defined vesicular dispersions with a long shelf life.

To get optimized vesicle size and the number of bilayers from large sized vesicals, high pressure filtration via polycarbonate membranes as well as high pressure homogenization in a French press or in a microfluidizer are appropriate manufacturing procedures. Sonication may also be applied, though the resulting dispersion does not have the same vesicular sizes. The injection method and reverse phase dialysis are additional procedures for the formation of SUV and LUV. Freeze–thaw procedures allow drug loading of the liposomes and offer an evaluation of the stability of the vesicular dispersion (Lill and Krempel, 1996).

Both macroscopic and microscopic methods appropriate for the investigation and characterization of liquid crystals are frequently used by formulators in drug development like struchter of liquid crystals by Polarized Light Microscopy, morphology of liposomes in Transmission Electron Microscopy (TEM), X-Ray Scattering, Differential Scanning Calorimetry (DSC), Rheology and Laser Light Scattering to determination of Vesicle Size.

Applications

Parenteral Administration

Depending on their size and surface charge, passive drug targeting of parenterally administered liposomes occur by interacting with the reticuloendothelial system (RES) and provoking an immune response. The antimykotic amphotericine is encapsulated in liposomes and marketed as Am-Bisomeä against severe systemic mycosis. The liposomal encapsulation reduces the toxicity of amphotericine while increasing the half-life of the drug and plasma level peaks (Schubert, 1998).

Daunorubicin a cytostatic, which is administered in the later state of Kaposi sarcoma of AIDS patients, is encapsulated in liposomes of about 45 nm size (Schubert, 1998). The liposome dispersion is administered as an infusion. Although daunorubicine itself is cardiotoxic, the liposomal formulation acts selectively on tumor cells and insignificantly on cardiac tissue. It is postulated that small unilamellar vesicles (SUV) may pass endothelial gaps in newly formed capillaries of the tumor.

Instillation into the Lung

A liposomal formulation containing a surfactant, has been developed for patients who suffer from infant respiratory distress syndrome (IRDS) or adult-acquired respiratory distress syndrome (ARDS), which usually coats the mucosa of the bronchi and prevents a collapse of the alveolar vesicles of the lung Premature babies often suffer IRDS before the development of a functional lung surfactant and pulmonary gas exchange. ARDS is also a life-threatening failure and loss of the lung

function and is usually acquired by illness or accident. Clinical trials with liposomal surfactant have proved to be effective in prophylactic treatment of IRDS and ARDS.

Sustained Drug Release

The therapy of a chronic disease requires repeated drug dosing. In the case of a short biological half-life, the drug has to be administered up to several times daily within short intervals. To reduce the application frequency, sustained formulations have been developed. For this purpose liquid crystalline excipients are appropriate candidates, because in a liquid crystalline vehicle the drug diffusion is reduced by a factor of 10 to 1000 in comparison with a liquid vehicle such as a solution (Wahlgren, 1984; Mueller-Goymann and Frank, 1986; Mueller-Goymann and Hamann, 1993). The factor depends on liquid crystal.

Cubosomes

These are self-assembled from aqueous surfactant systems where the mesogens forms a bicontinuous cubic phases. Bicontinuous cubic phase liquid crystals are newly discovered exotic materials originally found in the most unexpected places (Lindstrom *et al*., 1981; Andersson *et al*., 1998). Bicontinuous cubic liquid crystalline materials are an active research topic because of their unique structure lends itself well to controlled release applications. Cubosomes are typically discrete, submicron, nano particles of bicontinuous cubic liquid crystalline phase. These nanostructured particles (Hyde *et al*., 1997) are liquids instead of solid. The controlled release application of these nanoparticles is of a great significance in cosmeceutical and pharmaceutical fields. Low cost of the raw materials, versatility and the potential for controlled release make them an optional vehicle for several *in vivo* drug delivery routes (Engstrom *et al*., 1992; Sadhale and Shah, 1998).

The factors through which the cubosomes are used in the intent of controlled release are its cubic phase, unique and desirable as a result of its mesoscale structure: a contorted lipid bilayer separating two continuous but nonintersecting water regions (Spicer, 2003; Norlen and Amoudi, 2004). The tortuous structure of bulk cubic phase provides controlled release of solubilized active ingredients (Efrat *et al*., 2005), while cubosomes exhibit burst release because of their sub-micron length scales (Boyd, 2003). Cubosomes are typically produced by high-energy dispersion of bulk cubic phase, followed by colloidal stabilization using polymeric surfactants. After formation of the cubosomes, the dispersion is formulated into a product and then applied to a substrate of interest, usually bodily tissue (Spicer, 2003).

Precursor forms of cubosome

Since high-energy processes being expensive and difficult to scale-up. To avoid such high-energy processing and to protect the thermosensitive moieties it is planned to produce them in situ resulting in developments of precursors.

Liquid Precursors

The liquid dilution process is found to produce smaller and more stable cubosomes. In this process the cubosomes are formed by nucleation and growth, as in crystallization and precipitation processes. These were seen used in hand washes and mouth washes where cubosomes are formed when hand washed and by mouth rinsing. The liquid precursor allows easier scale up and avoids bulk solids handling.

Powdered Precursors

Powdered Cubosomes are composed of dehydrated surfactant coated with polymer. Cubosomes formed with a mean particle size of 600 nm after reconstitution with water, as confirmed by light scattering and TEM (Spicer *et al*., 2002). These were prepared by using spray drying technique, an excellent process. These powders render some process and performance advantages than the other types of precursors.

Applications

Monoglyceride based cubosomes dispersion can be prepared for topical use, such as for percutaneous or mucosal applications. Being microbial in nature it can be used for treatment for intravaginally transmitted sexual diseases caused by HSV and HIV viruses or by Chlamydia trachomatis and Neisseria genorrticae bacteria. As they are structurally similar cubic phase structure of the stratum corneum, it is assumed that the formation of mixture of cubosomal monolein with stratum corneum lipids. This structural interaction might lead to the formation of a cubosome depot in this layer, from which drug can be released in a controlled fashion (Larsson, 2000; Hansen *et al*., 1995).

Coarse Dispersions: Microemulsion

Microemulsions are the clear coarse dispersions, an isotropic mixture of oil, surfactant mixture which contains both surfactant and co-surfactant and water. These microemulsions contain a lobule size of 10 – 100 nm by which they can allow the light to pass through them giving them their characteristic transparency devoiding it from the normal emulsion (Holmberg, 2002). These are thermodynamically stable than macroemulsions and kinetically instable than nano emulsions. They have low viscosities following Newtonian rheological properties (Moulik and Paul, 1998). The microemulsions acts as coslovents in enhancing the solubility of water loving drugs they provide the drug in solubilized form to the GIT. With low particle size they have high surface area allowing enhanced window for absorption. These micro globules can easily permeate enhancing the drugs bioavailability. The hydrophilic drugs were formulated as w/o. The rate and extant of absorption will be fast from these delivery forms than others (Jadhav, 2006). The microemulsions are formed by taking appropriate compositions of oil: surfactant mixture: water from pseudo ternary plot drawn with critical points obtained from water titration techniques these are vortex mixed to obtain those (Mladen *et al*., 2012).

Table.1 Drugs and their liposome structures

Drug	Liposome structure
Arsphenamine	Nematic
Disodiumcromoglycinate	Nematic, hexagonal
Nafoxidin HCl	Lamellar and cubic
Diethylammon ium	Lamellar

Table.2 Drugs incorporated in Cubosomes

Drug	Category	Disease
2-amino-1-phenylpropanol HCl	Antidepressant	Mania, depression
Nitroglycerin	Anti-anginal	Angina pectoris
Oestriol	Hormonal therapy	Atrophic vaginitis, pruritus
Clomethiazole	Psychotropic	Insomnia
Quetiapine fumarate	Antipsychotic	Psychotic disorder

Applications

Oral delivery

Oral delivery offers the opportunity to deliver peptide and protein drugs (Kovarik, 1994). Usually when peptides and proteins are delivered orally, they are degraded in the GI and are not therapeutically active. Delivery of these molecules using microemulsions increases their bioavailability (Jadhav, 2006).

Oral cyclosporine formulation called neoral® is available in market as a soft capsule which contains an oil solution of drug and surfactant, which is converted to an o/w microemulsion when it comes in contact with the aqueous stomach environment. The main issue that limits with cyclosporine absorption orally is its poor intestinal absorption due to high molecular weight and lipophilicity (Kovarik, 1994). Microemulsions have given this drug more rapid and reproducible absorption with less inter- and intra-patient variability (Jadhav, 2006; Kovarik, 1994).

Transdermal Drug Delivery

Microemulsions have the ability to enhance transdermal drug delivery by favoring drug partitioning into skin by modifying the thermodynamic activity of the drug. This, along with altering the stratum corneum, allows for better drug delivery (Junyaprasert, 2008). There is a possibility for irritation with microemulsions used transdermally.

Ocular delivery

Ocular delivery of microemulsions had shown great promise and many properties inherent to microemulsions of less viscous, transparent and thermally stable, prove to be very advantageous. Microemulsions increase the water solubility of drugs and enhance absorption into the eye (Jadhav, 2006). This could ultimately lead to decreased number of applications.

Nasal delivery

Delivery of a microemulsion nasally increase bioavailability as in other forms and also the fine particles of microemulsions are cleared slowly from the body, increasing its residence time of the drug at the target site (Park and Kim, 1999).

Other uses of microemulsion

Microemulsions show its nature even outside the pharmaceutical industry. The cosmetic industry is one such an example. The clear look of these makes them suitable for the manufacturing of cosmetic gels lotions and creams. They possess low viscosity by which they are easily absorbed by the skin and easily washed away when applied (Sonneville-Aubrum *et al*., 2004). In other industries microemulsions are in use as cleaners, hair products, perfumes, gels, and skin care products. In short, microemulsions possess many characteristics that are ideal for multiple and versatile applications.

CONCLUSION

The solubility and permeation of the drugs can be enhanced, had enhanced and will be enhancing through these dispersions successfully. Varied particle size has its own identity in the field of pharmacy for their role in enhancing the absorption rate limiting steps. The drugs can be formulated to the choice of formulator with these dispersions.

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