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Conceptualization of cross-linking polymers and lipids for better bio adhesion and oral bioavailability

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ABSTRACT

Over the last decades, approaches in designing several lipid carriers have been evolved to deliver the poorly soluble drugs. Lipid based systems can play a vital role in improving the efficacy and safety, thus finally enhancing the therapeutic efficiency. LBDS can be modified in several ways to meet the wide range of product necessities as per the disease condition, product stability and route of administration. Crosslinking of polymers or lipids using modern techniques have greatly helped to modulate the specific release of drugs and as well safe guard the drug from various enzymes produced in the body thereby increasing the bioavailability greatly. The cross-linking will greatly enable to swell and even allow these varieties of polymers to adhere to the natural human tissues, mucosal membranes allowing them to be used for site specific release. The review emphasis on different approaches of crosslinking employed for complementing to prepare novel drug delivery systems like Emulsions, vesicular system and lipid particulate systems.

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INTRODUCTION

Till today, oral route is the most preferred route of administration, owing to highest patient compliance, greater convenience, reduced cross-infections/contaminations and economy [1]. Conversely, this route is continuously looking into newer advances due to the drawbacks associated with solubility, poor gastrointestinal absorption, larger fluctuations in plasma drug levels and rapid metabolism. All these factors may cause for unsatisfactory in vivo performance, leading to failure of conventional drug delivery systems [2-4]. Many significant efforts have been tried for the potential application of lipid-based drug delivery systems (LBDS), to provide the required site specific controlled release of wide range of drugs and bioactive agents by improving their solubility. Especially, Class II drugs are challenging the formulator in view of their bioavailability. LBDS, have shown their efficient size dependent properties to attract a lot of consideration. There are important few points to be considered while formulating LBDS as follows, (a) solubility, (b) digestion, (c) dispersion, (d) absorption, (e) miscibility, (f) solvent capacity etc and also includes morphology at room temperature, regulatory issue, purity and chemical stability [5]. Several advantages of LBDS are depicted in Figure 1.

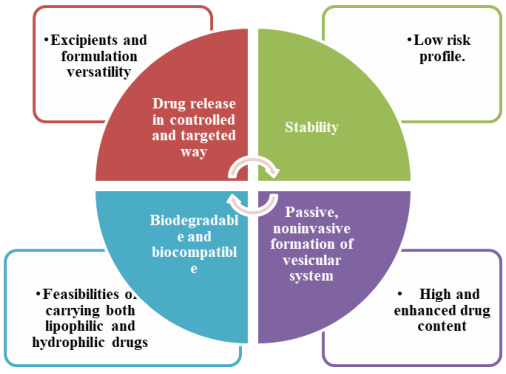

Figure 1: Advantages of LBDS

These systems are commercially feasible to formulate the dosage forms for oral, topical, pulmonary, or parenteral delivery. Carrier for LBDS are proved as safe and efficient and hence applied to formulate several vaccines, nutraceuticals and diagnostics. Hence, present review emphasis on design and application of LBDS.

Trends and drawbacks in design and formulation of LBDS

LBDS can be modified in several ways to meet the wide range of product necessities as per the disease condition, product stability and route of administration. But, at a very early stage of development,formulation strategies based on a rational and systematicapproach need to be developed to avoid erratic and poor invitro/in vivo correlations and thus increase the chances of successin formulation development. Several useful strategies have been published by several authors [6-10]. LBDS can be classified majorly into Emulsions, Vesicular system and Lipid particulate systems.

Emulsions

Emulsions are heterogeneous systems of dispersed liquid throughout another continuous liquid in the form of droplets (droplets size usually exceeding 0.1µ diameter). Emulsions are again classified in to microemulsion, emulsifying drug delivery systems (SEDDS), nano-emulsions and Pickering Emulsions. Microemulsion concept was first introduced by Hoar and Schulman in 1940 and size was varied from 10-200 nm. These were evolve between various structures in range of swollen micelles to droplets. Thermodynamic stability, ease in formulation and optical clarity are the few advantages associated with microemulsions. SEDDS are mixtures of oil and surfactants and sometimes co-solvents, which emulsify immediately to produce a fine O/W type of emulsion when added to an aqueous phase with gentle agitation [11].

Recently, SEDDS were formulated using triglyceride oils and non ionic surfactants were proved to be less toxic. Potential benefits of these systems includes, improved bioavailability, more reliable temporal profiles of absorption and site specific. Nanoemulsions having the size of droplets in range of 50-1000 nm and formulated with surfactants that are approved by GRAS (Generally Recognized as Safe) [12].Nanoemulsion can reduce the frequency of administration and can guarantee the drug release in controlled manner.

Lipid based emulsions which were stabilized by solid particles such as silica, clays, titanium dioxide etc are known as Pickering emulsions. The added sold particles will bind to the surface of the interface and prevents the droplets from coalescing, which make the formulation more stable. In addition, stability of Pickering emulsions can be improved by adding amphiphilic particles, owing to their high adsorption energy.

Vesicular drug delivery systems

Several novel vesicular systems were evolved every day [13-26]. Drug delivery systems as well as biomedical applications of these systems along with other microstructures are currently enjoying the enormous recognition among the researchers of several disciplines. These systems includes liposomes, proliposomes, ethosome, phytosome, transfersome and niosome etc [27-59].

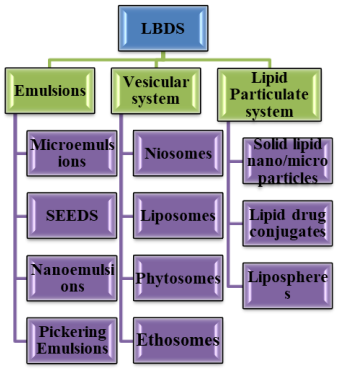

Figure 2: Approaches for LBDS.

Lipid particulate systems:

Since few decades, lipids of nanoparticle and microparticle were evolved as potential polymeric carriers due to their size dependant properties. Few advantageous characters of these systems includes,

- Higher levels of drug targeting,
- Controlled drug release,
- Physiologically compatible and stable,
- Ease of technology transfer to large scale,
- Protection of active ingredient,
- Matrix is composed of well tolerable lipids.
- High stability.

These systems comprises of lipospheres, lipid drug conjugates, solid lipid nanoparticles and microparticles. Despite of all these merits, LBDS have few limitations with respect to gastric retention especially for the drug which are having the absorption window in the upper GIT. Thus, can encounter with the less bioavailability and absorption. Hence to overcome this several cross linking techniques were incorporated to enhance the gastric retention either gastric retention approaches.

Application of mucoadhesion technologies

Application of mucoadhesive systems or cross linking with other related polymers can also improve the residence of dosage form in the absorption site [60] Mucoadhesive polymers have to enhance the contact with mucus membrane by forming strong covalent bonds. Thiolation is one of the approach to improve mucoadhesion property of several natural and synthetic polymer [61,62]. Thiolated LBDS are proved as efficient in improving the bioavailability of several

insoluble drugs, which are having the absorption window in the stomach [63-67]. Response surface methodology can be applied successfully to study the interaction of independent factors [68].

Future prospective and conclusion

There is a need to consider more about the characteristics of various lipid formulations, so that experimental conditions and guidelines can be established. More technologies to be applied for the identification of suitable candidates at early stages. Attention to several physical and chemical stability issues of drug in the lipid systems. There a need to seek the tracking of solubilization of drug in in-vivo conditions. Despite the fact that these present challenges, there is a great potential in the use of lipid formulations. The safety of the different nano-delivery carriers following uptake needs to be explored further. Studies focused on the nanotoxicology of these delivery systems in human skin have been limited, especially with the newer classes, and is likely to vary according to the composition and size of the vesicles. Finally, LBDS are physiologically well tolerated class of systmes, which provides a vast array of possibilities to formulate and potentially increase the bioavailability of poorly soluble drugs.

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