REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

A Comprehensive Overview of Lipid-Based Drug Delivery Approach

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Abstract

The majority of the pharmaceutically active chemical moieties represent a challenge in their formulation. Most of these drugs have intricate bioavailability issues either related to their low solubility or permeability. Many problems may arise during formulations such as pH dependent ionization, poor drug solubility, limited absorption, unpredicted bioavailability, degradation, metabolism, and cellular efflux. Poor aqueous solubility is a determinate criterion, during formulation and Biopharmaceutical Classification System (BCS) categorization. Among the most important approaches to enhance solubility, the Lipid-Based Drug Delivery Systems (LBDDS). The strategies involving lipid incorporation was a revolutionary step and included: vesicular systems, lipid particulate systems and emulsions.

Keywords: BCS, LBDDS, Vesicular systems, Lipid particulate, emulsions.

1. Drug solubility

Solubility is one of the most important molecular parameters that affect the bioavailability of orally administered drugs. Hence, the determination of solubility and its detailed knowledge display immense importance in the drug research area (Völgyi et al. 2010). Accordingly, optimized formulations of conventional drugs are still of interest. Drug solubility is expressed as the maximum drug amount dissolved in a given volume of solvent at a certain temperature, pressure and pH (Pobudkowska and DomańSka 2014). Active pharmaceutical ingredients with insufficient solubility have a higher risk of experiencing indetermined alteration during formulation approaches, consequently, might have undesirable therapeutic efficacy associated with higher costs in drug development (Gadade et al. 2018). Solubility studies has been mainly used as a screening parameter with other physicochemical properties for lead selection and optimization during the discovery phase of new chemical entities. Besides, in the developmental phase of the API, solubility is required for the Biopharmaceutical Classification System (BCS) categorization of the drug. Also, required during formulation optimization and salt selection (Völgyi et al. 2010).

2. Biopharmaceutical Classification System (BCS)

Based on the aqueous solubility and the intestinal permeability of the drug, Amidon et al in 1995, developed the BCS as a well-established framework, which is composed of four classes

representing four distinctive manners of the in vitro-in vivo correlation (IVIVC) (Amidon et al. 1995). The BCS is summarized in Error! Reference source not found.. Studies reported that 75% of the drug candidates possess low solubility and showed poor bioavailability. The aqueous solubility of the drug and its dissolution rate have a profound effect on its bioavailability. As most of the drugs, whether those available in the market or those under investigation, are considered PWSDs. Thus, their dissolution rate is considered to be the rate-limiting step in the absorption process. Any modification in the dissolution rate has a great implication on bioavailability.

Hence, the augmentation of PWSDs dissolution rate with subsequent improvement in the bioavailability has occupied much of the formulators' attention (Amidon et al. 1995; Fahr and Liu 2007; Hauss 2007; Williams et al. 2013). The poor bioavailability limits the drug performance leading to an increase in the drug dose. This might induce some undesirable side effects related to increased dose as well as pharmacoeconomic problems due to increased cost. In some cases, the formulator might even be obliged to change the route of administration instead of the oral route (Gadade et al. 2018). For acceptable oral bioavailability, the drug must be sufficiently soluble in the gastro-intestinal fluids and also has good membrane permeability in order to diffuse to the bloodstream (Gadade et al. 2018).

Although massive advances have been occurred in drug delivery systems, oral route remains the most preferred route of administration in terms of cost and patient acceptance.

3. Strategies for delivery of poorly water-soluble drugs

The drug delivery research field is continuously updated with novel approaches to adapt and overcome delivery hinders. The approaches to address the delivery hurdles may be chemical or physical including pH adjustment (Stephenson, Aburub, and Woods 2011), prodrug (Stella 2010), micronization (Liu et al. 2006; Mosharraf and Nyström 1995), complex formation (Loftsson and Brewster 1996; Brewster and Loftsson 2007), lipid-based drug delivery systems (LBDDS) (Porter, Trevaskis, and Charman 2007) mixed micelles and nanotechnological approaches (Chen et al. 2011; Rodriguez-Aller et al. 2015; Douroumis and Fahr 2013; Rasenack and Müller 2002; Kipp 2004). Nanotechnology is regarded as a promising strategy that leads to reduction of dose size and frequency and yet enhances drug delivery (Sharma, Sharma, and Jain 2016). The different nanotechnology strategies include dendrimers, polymeric micelles, polymeric nanoparticles, carbon nanotubes, nano-emulsions, and nanosuspensions.

A schematic representation of various strategies of drug delivery is presented in **Figure 2.** Schematic representation of various strategies of drug delivery adopted from (Rodriguez-Aller et al. 2015).

4. Lipid-Based Drug Delivery Systems (LBDDS)

Incorporating lipids in drug delivery systems has been considered a revolutionary step in the past decades. LBDDS offered a lot of comprehensive solutions and appropriate vehicles for the delivery of poorly water-soluble drugs (PWSDs), particularly very lipophilic drugs (grease balls) (Mehanna and Mneimneh 2021; Rawat et al. 2008). LBDDS are considered one of the most important and popular strategies used to increase bioavailability of PWSDs.

Several lipid carriers (LC) were used in the development of LBDDS. Examples are phospholipids, cholesterol, cholesterol esters and triglycerides. The physiochemical diversity of LC their biocompatibility, owing to their biological origin, are beneficial in manipulating such vehicles to become suitable for most routes of drug administration. LBDDS can be used for controlled and targeted drug release offering high stability, ease of manufacturing and scale-up. Besides, some lipid matrices are not susceptible to erosion phenomena and offer pronounced increments in drug loading (Mehanna and Mneimneh 2021; Pouton 2006; Rawat et al. 2008).

Nevertheless, LC may also exhibit certain limitations such as polymorphism induced by lipid crystallization leading to different melting points, different drug loading capacities and various kinetic processes. Moreover, the common manufacturing technique is high-pressure homogenization which may cause prominent degradation to drug molecules (Rawat et al. 2008).

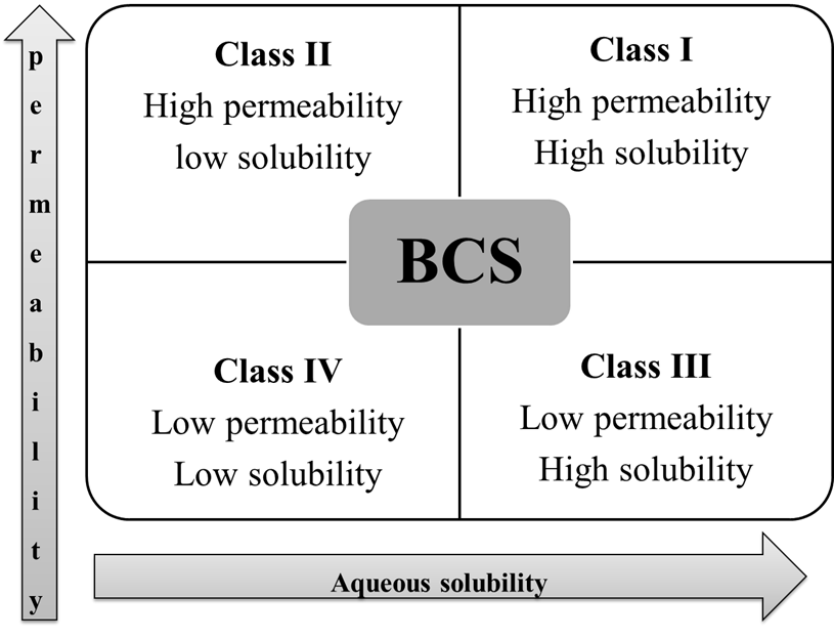

Figure 1. Biopharmaceutical classification system as described by Amidon adapted from(Pouton 2006).

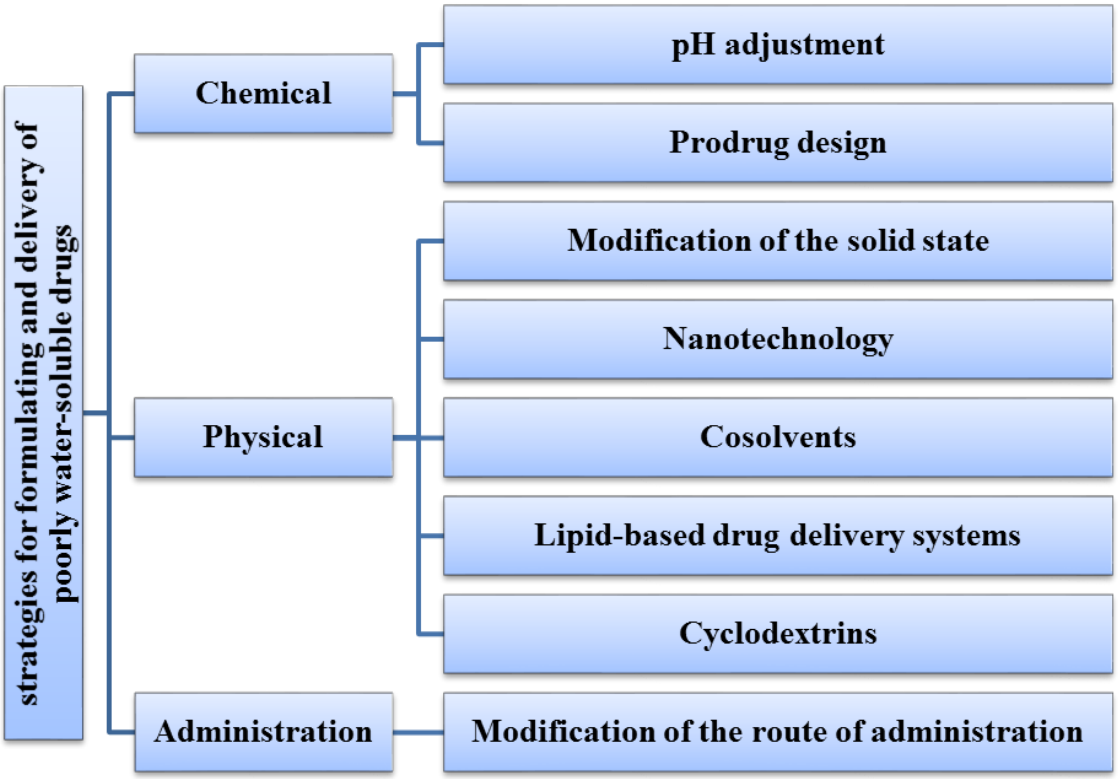

Figure 2. Schematic representation of various strategies of drug delivery adopted from (Rodriguez-Aller et al. 2015).

Drugs of class II can be manipulated by LBDDS to circumvent its poor aqueous solubility and mimic the absorption profile of class I drugs. However, these strategies do not influence the absorption of drugs belonging to classes III and IV which is limited by the membrane permeation ability. Those can be modified by going back to the lead optimization phase and chemical structure modification (Pouton 2006).

LBDDS are classified into vesicular systems, lipid particulate systems, and emulsion systems (Mehanna and Mneimneh 2021).

4.1. Vesicular systems

4.1.1. Liposomes

Liposomes are microscopic, colloidal, concentric spherical bilayered vesicles **Error! Reference source not found.** with a diameter ranging from 0.02 to 10 μm. They are composed of amphiphilic phospholipids, either natural or synthetic. Upon contact with an aqueous medium, they assemble as vesicles to shield their hydrophobic tails (Huang 2008). Liposomes can be classified regarding lipid layers into uni-lamellar and multilamellar vesicles. They are considered to be important carriers for a wide range of hydrophobic and hydrophilic drugs. Furthermore, they are biocompatible and biodegradable (Lu et al. 2016). Hence, they are under intensive investigation for their multiple applications in the food, cosmetics and drug industry (Mehannaet al. 2012).

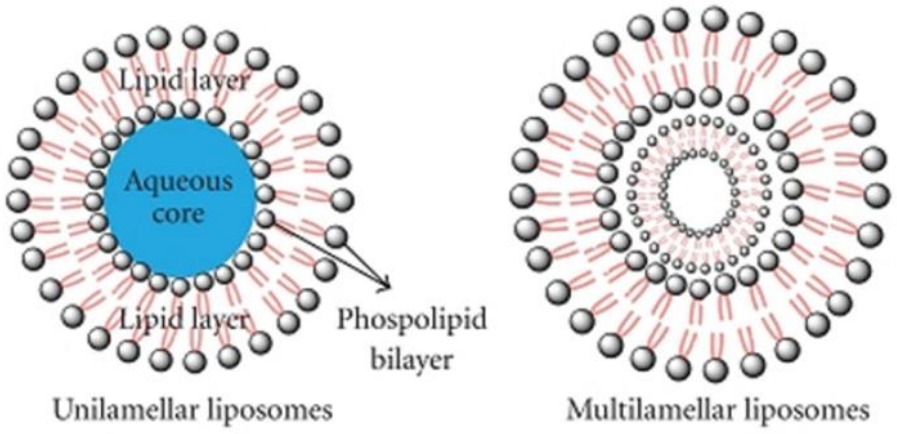

Figure 3. Schematic representation of liposomes structure (adapted from (Mishra et al. 2011)).

4.1.2. Niosomes

They resemble liposomes in function with only a small modification in the structure (**Figure 2**). Phospholipids are replaced with non-ionic surfactants. Such a change enabled niosomes to outweigh some of the liposomes' drawbacks, for example, chemical instability. Also, niosomes have higher penetration ability (Hua 2015).

4.1.3. Transferosomes

Liquid vesicles consisting of phospholipids and an edge activator, a single chain surfactant, which might be Spans or Tweens (**Figure 2**). The surfactant increases the deformability of the transferosomes by destabilizing the lipid bilayer structure of the vesicles and reducing the interfacial tension (Cevc and Blume 1992; Gregor Cevc and Blume 2001).

Ethanol is well known for its permeation enhancement through skin lipids (Touitou et al. 2000; Elsayed et al. 2006). Hence, whenever deep penetration is desired, these vesicles have shown an improved therapeutic potency in comparison with the conventional liposomes.

4.1.4 Ethosomes

Soft, flexible and highly liquid vesicles, composed of phospholipids accompanied with a high concentration of ethanol (20-50%) (**Figure 4**).

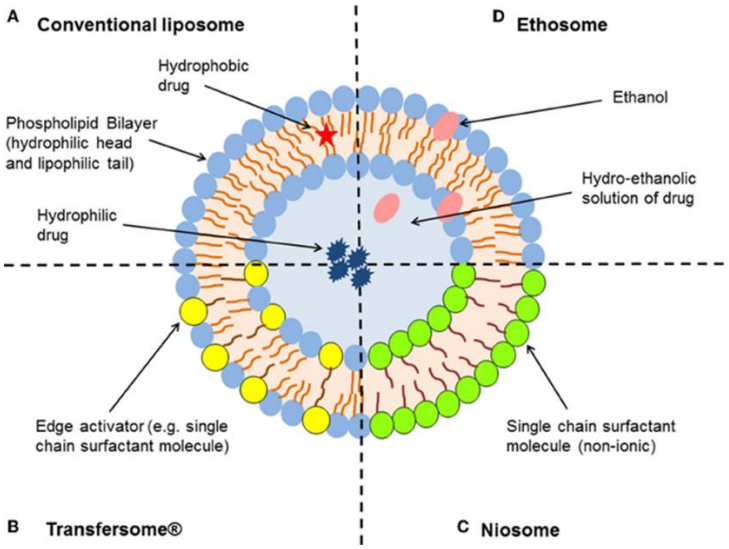

Figure 1. Illustration of different types of vesicular systems (adapted from (Hua 2015)).

4.2. Lipid Particulate Systems

4.2.1. Solid Lipid Nanoparticles (SLNs)

SLNs were developed in the 1990s and were reported as the first lipid nanoparticles used for drug delivery. They are colloidal systems having a size of 50 to 1000 nm that are composed primarily of solid lipid nucleus stabilized by an amphiphilic surfactant shell. Drugs are incorporated in these colloidal systems either by cold or hot homogenization (Patidar et al. 2010; Zur Mühlen, Schwarz, and Mehnert 1998). The nano-size range offered the benefit of site-targeted delivery, also helped to protect the drug from chemical degradation (**Figure 5**). Moreover, these organic solvent-free systems can be scaled up easily (Zur Mühlen, Schwarz, and Mehnert 1998).

However, the SLNs crystalline core led to low drug loading capacity. They also face particle size growing and even drug expulsion might occur during storage (Tran, Rades, and Müllertz 2018).

4.2.2. Nanostructured Lipid Carriers (NLCs)

NLCs are unstructured matrices formulated by mixing solid and liquid lipids with an aqueous phase along with surfactant. Recognized as the second generation of lipid particulate carriers. NLCs are considered to be attractive drug delivery systems due to the high scalability of production and improved drug safety (**Figure 5**). The imperfect core of the NLCs allows higher drug incorporation, besides drug expulsion from such core is not a common probability (Salvi and Pawar 2019).

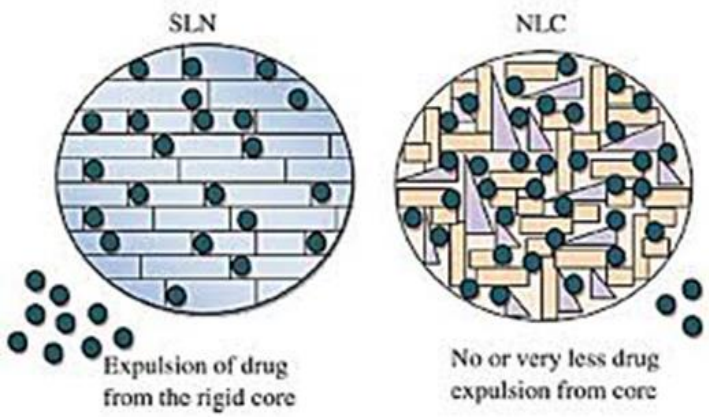

Figure 2. Representation of the SLNs and NLCs structures adapted from (Salvi and Pawar 2019).

4.3. Emulsions

Emulsions are composed of at least two immiscible liquids, for example, oil and water, in which one is finely dispersed through the other by the aid of mechanical force. They are considered to be thermodynamically unstable, yet surfactants can stabilize the system and act as emulsifying agents. Depending on the continuous phase, emulsions can be classified into (O/W) or (W/O). Other factors, like the droplet size of the dispersed phase, can serve as the basis of classification.

Formulators usually give great attention to whether the droplet size falls in the micro or nano range (Lu and Gao 2010).

In the 1940s, Hoar and Schulman introduced microemulsions for the first time (Hoar and Schulman 1943). They are systems of oil, water, surfactant and co-surfactant.Microemulsions are thermodynamically stable mixtures that enhance drug solubility and have high drug loading capacity.

Nanoemulsions (NE) are characterized by droplet size in the nanometric range (20-200 nm). Due to this nano-size, they appear transparent or slightly turbid and have remarkable stability against flocculation and phase separation (McClements 2011).

SNEDDS have been discussed. The enhancement of dissolution process, presenting the drug in the solubilized state, lymphatic transport via the intestinal lymphatic system induced by the lipid content and even the belief that some SNEDDS excipients may inhibit P-gp efflux are considered to be the most substantial postulates (Pouton 2006; Patel, Shelat, and Lalwani 2015; Aswathanarayan and Vittal 2019; Gursoy and Benita 2004). The resultant nanoemulsions are O/W with a droplet size range from few nanometers to 200 nm, the drug is dissolved in the internal phase while water constitutes the external hydrophilic phase (Siqueira Jørgensen et al. 2018).

SNEDDS can typically be encapsulated in its liquid form, however many drawbacks are accompanied by such liquid formulations. For instance, instability during storage, leakage and interaction with capsule shell, possible drug precipitation and special manufacturing requirements (Kim et al. 2017). Hence, alternative approaches are desirable e.g., solidification of the liquid SNEDDS. The solid SNEDDS (S-SNEDDS) surpasses the limitations and introduces the merits of both SNEDDS and solid dosage forms (Kim et al. 2017). The solidification techniques included adsorption, spray drying, melt granulation, extrusion-spheronization and eutectic mixing (Beg et al. 2012; B et al. 2008).

Numerous advantages of these systems appealed to the scientists for further investigations and development. Various mechanisms and assumptions of bioavailability enhancement PWSDs by Self-nano emulsifying drug delivery systems (SNEDDS) is one of the promising drug formulations, which have gained much attention because several drugs oral absorption and bioavailability have been improved when formulated as SNEDDS (Imada et al. 2015).

SNEDDS are anhydrous isotropic blends of drug, oil, and surfactant usually with one or more hydrophilic co-solvents/co-surfactants. Compared to self-emulsifying drug delivery systems (SEDDS) and self-micro-emulsifying drug delivery systems (SMEDDS), SNEDDS tend to form transparent nanoemulsion upon dilution and mild agitation. Accordingly, inside the body, the peristaltic movement inherent in the gastrointestinal tract and the GIT fluids act as the proper media for nanoemulsion formation.

The absence of water in the formulation offered a long-term stability advantage compared to the conventional nanoemulsions (Patravale and Mandawgade 2008).

Beside overcoming the disadvantages of liquid form, potential advantages may be introduced by the solidification including: Ease of handling, dose precision and diversity in solid dosage formulation options (Verma et al. 2016).

The behavior of the LBDDS in the body and the fate of the drug in the GIT predominantly depends on the physical changes that might take place upon dispersion and dilution, and the effect of the digestion process on drug solubilization.

The most important advantage of LBDDS is the maintenance of the drug in the solubilized state throughout its retention time in the GIT. LBDDS containing higher percentage of hydrophilic excipients may lose such merit and possible drug precipitation is prevalent (Pouton 2006).

In 2000, a classification system was introduced to identify the characteristic behavior of LBDDS. This system has been developed several times to finally offer what could be described as the lipid formulations classification system (LFCS) (Pouton and Porter 2008). LFCS helps in predicting and analyzing the behavior of the different LBDDS and in consequence, serves as a guide for the choice of the most suitable lipid formulation. The LFCS introduced by Pouton (Pouton and Porter 2008) is summarized in **Table** .

Table 1. The Lipid Formulations Classification System introduced by Pouton (Pouton and Porter 2008).

Formulation type	Composition	Characteristics	Advantages	Disadvantages
Type I	Oils without surfactants	Non-dispersing requires digestion	GRAS*; simple; excellent capsule compatibility	The formulation has poor solvent capacity unless drug is highly lipophilic
Type II	Oils and water-insoluble surfactants	SEDDS formed without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersions (particle size 0.25–2 μm)
Type III	Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)	SEDDS/SMEDDS /SNEDDS formed with water-soluble components	Clear or almost clear dispersions; drug absorption without digestion	Possible loss of solvent capacity on dispersion; less easily digested
Type IV	Water-soluble surfactants and cosolvents (no oils)	The formulation disperses typically to form a micellar solution	The formulation has good solvent capacity for many drugs	Likely loss of solvent capacity on dispersion; may not be digestible

* GRAS is generally regarded as safe.

Conclusion

This review article demonstartes the LBDDS as one of the various approaches utilized in the delivery of PWSDs. The LBDDS include several techniques for instance,vesicular systems, particulate systems and emulsions. These techniques are under continous investigation and developing. The details regarding some LBDDS have been elucidated in the context.

Conflict of interest

There is no conflict of interest.

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