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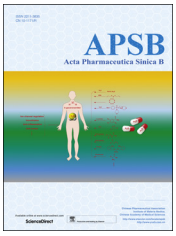

REVIEW

Insoluble drug delivery strategies: review of recent advances and business prospects

Sandeep Kalepu[a,*], **Vijaykumar Nekkanti**[b]

[a]*Department of Pharmaceutical Technology, Shri Vishnu College of Pharmacy, Bhimavaram 534202, Andhra Pradesh, India*
[b]*College of Pharmaceutical Sciences, Western University of Health Sciences, Pomona, California 91766, USA*

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Abstract The emerging trends in the combinatorial chemistry and drug design have led to the development of drug candidates with greater lipophilicity, high molecular weight and poor water solubility. Majority of the failures in new drug development have been attributed to poor water solubility of the drug. Issues associated with poor solubility can lead to low bioavailability resulting in suboptimal drug delivery. About 40% of drugs with market approval and nearly 90% of molecules in the discovery pipeline are poorly water-soluble. With the advent of various insoluble drug delivery technologies, the challenge to formulate poorly water soluble drugs could be achieved. Numerous drugs associated with poor solubility and low bioavailabilities have been formulated into successful drug products. Several marketed drugs were reformulated to improve efficacy, safety and patient compliance. In order to gain marketing exclusivity and patent protection for such products, revitalization of poorly soluble drugs using insoluble drug delivery technologies have been successfully adopted by many pharmaceutical companies. This review covers the recent advances in the field of insoluble drug delivery and business prospects.

*Corresponding author. Tel.: +91 9948444546; fax: +91 8816 250863.
E-mail address: sandeepk@svcp.edu.in (Sandeep Kalepu).

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1. Introduction

The search for innovative medicines in disease management without compromising on safety and efficacy is a challenge. In spite of significant success in the discovery of new drugs, there are still unmet medical conditions which need effective therapy. Market potential, competition among companies, dry pipeline of developmental candidates of various companies have hastened the drug discovery and development process. As a result, a significant number of drugs getting approvals have poor biopharmaceutical properties. An estimated 40% of approved drugs and nearly 90% of the developmental pipeline drugs consist of poorly soluble molecules[1]. Several marketed drugs suffer from poor solubility, low permeability, rapid metabolism and elimination from the body along with poor safety and tolerability[2].

Recent studies have revealed that discovery and development of new drugs alone are not sufficient to achieve therapeutic excellence and capture market economies[3]. Therefore, modified formulations of existing drugs are gaining more importance. The improved formulation of existing drugs is turning out to be lucrative business for pharmaceutical industry which is facing innovation deficit these days for new molecules[4]. New dosage form, change of forms of drugs (ester/salt), prodrug/active metabolite of drug, different routes of administration are few changes that pharmaceutical companies are exploring for 505(b)(2) fillings[5]. Significant number of insoluble drugs in the market provides profitable strategies for pharmaceutical companies to file NDA under 505(b)(2) with improved formulations providing faster dissolution and enhanced bioavailability. Hence this review summarizes various solubilization technologies. The recent advances, clinical benefits and business potentials of these technologies are discussed in detail. The potential benefits of insoluble drug delivery technologies are depicted in Fig. 1.

2. Insoluble drug delivery technologies

2.1. *pH modification and salt forms*

Nearly 70% of drugs are reported to be ionizable, of which a majority are weakly basic. A pH-dependent solubility is exhibited by ionizable drugs, wherein weakly acidic drugs are more soluble at pH > p*K*a (ionization constant) and weakly basic drugs are soluble at pH < p*K*a[6]. This pH dependent solubility was explored extensively to formulate insoluble drugs. On the other hand, salt formation of weakly acidic or basic drugs provided alternate strategies for formulation of drugs which have pH dependent solubility. Pharmaceutically acceptable counter ions in the salt can provide favorable pH conditions upon dissolution in water, and thus the pH of resulting solution would be close to maximum pH of drugs. Hence salt forms may sometimes avoid pH adjustments necessary for solubilization of drugs. In addition, salt formation has been reported to improve crystallinity, stability and pharmaceutical processibility of drugs[6].

Figure 1 Benefits of insoluble drug delivery strategies.

There are many insoluble drugs on the market which are formulated with pH modification technology. Ciprofloxacin is a classic drug which is weakly basic and practically insoluble in water at neutral pH. However it exhibits pH-dependent solubility with higher solubility at acidic condition. Most of the intravenous formulations contain lactic acid as pH modifier to improve solubility[7]. Intravenous ciprofloxacin infusions are essential for treating different kinds of severe bacterial infections. Telmisartan is another drug which exhibits pH-dependent solubility. The currently marketed oral formulation of telmisartan contain alkalis, such as sodium hydroxide and meglumine for pH modification[7–10]. Telmisartan formulation marketed under brand name Micardis® is manufactured using a expensive spray-drying process, wherein drug and alkalis along with other excipients are dissolved in water and spray-dried to produce granules[11]. The spray-dried granules obtained were reported to have a pH-independent dissolution profile. However, generic versions of the telmisartan formulation are hard to come by, owing to the insoluble nature of the drug's free-acid-form and the critical steps involved in its manufacturing process that provided an additional market capitalization to the innovator[12].

Repaglinide is an example of Zwitterion drug with poor water solubility of 37 μg/mL[13]. Currently repaglinide, marketed as Prandin® in USA, is formulated with meglumine as pH modifier. Various patents disclose the use of meglumine in the formulation and spray-drying as the process for preparing the granules[14–17]. Tricky process and critical formulation sometimes prove to be hard to make generic copies. In case of both telmisartan and repaglinide, actual salt forms of drugs are not used in the formulation, instead the bases such as meglumine and sodium hydroxide were added to the formulation. This could be due to technical reasons, such as lack of crystallinity, poor stability and deliquescent nature of resulting salts. On other hand, including bases in the formulation could be due to commercial reasons, in order to build complexity in the process and product, such that it is hard to make generic versions. These are a few examples of how a clinically and commercially beneficial drug product could be launched in the market by altering the formulation strategies.

Aspirin is century old non-steroidal anti-inflammatory drug (NSAID), yet currently explored by various companies for commercial benefits. Soluble formulations of aspirin are currently available on the market. Aspro Clear, is soluble, effervescent tablet containing aspirin. The effervescence and favorable pH condition required for solubility of aspirin are facilitated by incorporating sodium bicarbonate and citric acid in the formulation. Aspro Clear reported to provide faster relief of pain than plain aspirin tablets[18]. This is another example, how insoluble drug formulation technology can be explored for commercial and clinical benefits.

Insoluble drugs are mostly formulated using the salt forms of weakly acid and basic drugs. Various salt forms of drugs have