Insoluble drug delivery technologies: review of health benefits and business potentials

B Siddalingappa, V Nekkanti, GV Betageri*

Abstract

Introduction
An estimated 40% of approved drugs in the market and nearly 90% of molecules in the developmental pipeline are poorly water-soluble. The challenge to formulate insoluble drugs has met with advent of various insoluble drug formulation technologies. This review discusses the different insoluble drug formulation technologies, clinical benefits and business potentials are elaborated.

Conclusion
The large number of insoluble drugs in the market and in the development pipeline provides challenges and opportunities for formulation scientists to optimise the formulation to meet the clinical needs and create the intellectual assets.

Introduction
The search of innovative medicine for safe and effective treatment and management of various disease conditions is a never ending process. Advances in chemistry and biology have hastened the drug discovery process. As a result, the significant number of drugs getting approval have poor biopharmaceutical properties. An estimated 40% of approved drugs are poorly water soluble and nearly 90% of developmental pipeline consist of poorly water soluble molecules. In the year 2012, Food & Drug Administration (FDA) approved overwhelming 47 NDA’s under section 505(b)(2)². The majority of those NDA’s under this section are new formulations. New dosage form, change of forms of drugs (Ester/salt), prodrug/active metabolite of drug and different route of administration are the few changes that the pharmaceutical companies are exploring for 505(b)(2) fillings³. The insoluble drugs are being reformulated. Hence this review summarises various solubilisation technologies and their commercial and health benefits. This review discusses drug formulations approved exploring different solubilisation technologies with insight to health benefits and commercial profits.

Discussion
Listed below are the solubilisation and insoluble drug formulation technologies.

**pH modification and salt forms**
A reported nearly 70% of drugs are ionisable and the majority of them are weakly basic. Acidic drugs are soluble in alkaline pH and basic drugs are soluble in acidic pH. Salt formation and pH adjustments have been used for formulating insoluble drugs. Ciprofloxacin is a classic drug which is weakly basic and practically insoluble in water at neutral pH and most intravenous formulations contain lactic acid as pH modifiers to improve solubility. Intravenous ciprofloxacin infusions are essential for treating different kinds of severe bacterial infections. Telmisartan is another drug, which is practically insoluble in water at pH 3–9. The current formulation in the market, include alkalis such as sodium hydroxide and meglumine for pH modification.

The product reported to have a pH independent dissolution profile. Because of the insoluble nature of the free acid form of Telmisartan and critical process of making formulation, the alternative formulations are hard to come by, thus providing additional market capitalisation to the inventor. Similarly, Repaglinide is also water insoluble and formulated with alkali Meglumine.

Aspirin is a century old NSAID, yet currently explored by various companies for commercial benefits. The Aspro Clear, the soluble tablet formulation of aspirin was found to be superior over plain tablets in terms of pain relief action.

Identification of the bisulphate salt form of Atazanavir is an interesting example of how salt screening could help molecules to progress from being dropped at preclinical development to clinical studies and finally to marketing approval. Atazanavir as a free base is practically insoluble in water (<1 µg/mL). The selection of bisulphate salt resulted in significant improvement in bioavailability and enabled the molecule to reach the market. The patented salt form provided additional market exclusivity. Similarly, Imatinib as mesylate salt form improved solubility and also provided patent exclusivity because of polymorphs.

Development of the choline salt of fenofibric acid leads to a blockbuster drug product in the market. This is a nice example of an old drug being reformulated for both health and commercial benefits. Aspirin lysine (injection) and calcium salts have proven clinically beneficial in terms of migraine and dental pain relief actions respectively. The new salt formulation of aspirin was found to be superior over plain tablets in terms of pain relief action.

*Corresponding author
Email: gbetageri@westernu.edu

Graduate College of Biomedical Sciences, Western University of Health Sciences, Pomona, CA, USA

forms of Clopidogrel, besilate and hydrochloride are marketed in Europe for commercial reasons. The Ibuprofen sodium salt has been recently approved by FDA for faster pain relief action than plain Ibuprofen.

Co-solvency and surfactant solubilisation

Formulation of insoluble drugs using co-solvents is also one of the oldest and widely used technologies for formulation of insoluble drugs, especially for liquid formulation intended for oral and intravenous administration. Often co-solvent solubilisation is used in conjunction with surfactants and pH modifiers in order to maximise solubility and prevents precipitation upon dilution. Most debated formulation in this approach is Paclitaxel intravenous injection, original formulation (Taxol) with Cremophore EL and ethanol. The formulation has problems in terms of safety and tolerability. The new formulations such as Abraxane and Genexol have been developed without Cremophore EL for better tolerability. Similarly, Docetaxel was initially formulated using ethanol and Tween 80. However modified formulations contain less Tween 80 and were reported to be less tolerated than original formulation.

A list of pharmaceutical formulations containing highest amount of co-solvents and surfactants is provided in Table 1.

Table 1 List of parenteral drug formulations containing co-solvents and surfactants

<table>
<thead>
<tr>
<th>Name of co-solvent</th>
<th>% in the formulation</th>
<th>Drug, Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>80</td>
<td>Tacrolimus, IV infusion</td>
</tr>
<tr>
<td>Glycerine</td>
<td>32.5</td>
<td>Epinephrine, Subcutaneous</td>
</tr>
<tr>
<td>PEG 300</td>
<td>50</td>
<td>Methacarbamil IM, IV</td>
</tr>
<tr>
<td>PEG 400</td>
<td>65</td>
<td>Etoposide, IV</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>74</td>
<td>Oxytetracycline, IM</td>
</tr>
<tr>
<td>Tween 80</td>
<td>54</td>
<td>Docetaxel, IV</td>
</tr>
<tr>
<td>Cremophore EL</td>
<td>65</td>
<td>Cyclosporin, IV</td>
</tr>
</tbody>
</table>

Solid state modification including, amorphous forms, solid dispersions and co-crystals

Amorphous forms

Various approaches have been reported to change solid state characteristics of active pharmaceutical ingredients in order to render molecules more soluble. Higher lattice energy of stable crystal forms of drugs pose problems in solubilisation. Hence disordered amorphous forms provide a distinct advantage over crystal forms with regards to solubility and dissolution rate. Cefuroxime axetil, Quinapril hydrochloride, Nelfinavir mesylate and Rosuvastatin calcium are a few of the drugs in the market as amorphous form.

Solid dispersion is one of the technologies explored extensively in the recent decade for the delivery of insoluble drugs. Solid dispersions consist of drug dispersed in a carrier. Physically the dispersions are either eutectic mixtures or solid solutions. Drugs exist either as amorphous form dispersed in the carrier or molecular dispersion in the carrier. The amorphous forms have increased solubility and dissolution. A list of currently marketed solid dispersion products is presented in Table 2. These products are beneficial clinically and commercially.

Co-crystals

Pharmaceutical co-crystal technology is another evolving approach for the delivery of insoluble drugs which has received greater attention in the last decade. Co-crystals are stoichiometric solids of drug and the second component called conformer, which exist as crystals in ambient temperature. The conformers can be generally recognised as safe listed excipients such as succinic acid, malic acid and saccharine. The drug and conformer are held in the crystal by bonds such as acid–acid, acid–amide and amide–amide. Itraconazole, Carbamazepine, Piroxicam, Caffeine, Gabapentin and Modafinil are examples of a few drugs explored for co-crystal technology for the enhancement of solubility. However, till date, there is no approved product with drug co-crystals, with enormous potential for delivery of insoluble drugs; the future of co-crystals seems to be bright.

Polymeric micelles

The polymers with both hydrophilic and hydrophobic moiety in the chain can assemble into nano-sized micelles in water, if the favourable process is followed. These polymeric micelles can entrap hydrophobic drugs and can be used for intravenous delivery. Unlike hydrophilic surfactants, the polymers have low critical micelle concentration

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and micelles are stable even after dilution with biological fluids\(^{18}\). Diblock polymers such as PLA–PEG, triblock polymers such as PLA–PEG–PLA are used for polymeric micelle-based drug delivery. The Genexol–PM, PEG–D(1, L-lactide) micelles containing Paclitaxel has been approved by FDA, and Gsplatrin micelles are in clinical trial\(^{18}\).

### Inclusion complexation

Cyclodextrins (CDs) are the versatile excipients studied extensively for pharmaceutical applications\(^{1,2,20}\). CD are chemically cyclic oligosaccharides consisting of glucopyranose units connected via \(\alpha\), \(\beta\), and \(\gamma\) with six, seven and eight glucopyranose units. Central cavity of CD is hydrophobic due to skeletal carbon atoms and ethereal oxygen.

Semisynthetic hydroxy propyl-\(\beta\)-CD and hydroxy propyl-\(\gamma\)-CD are more soluble and safer than natural CDs\(^{26}\).

The first US FDA approval for drug product containing is for Itraconazole (Sporanox® oral and intravenous solution) containing Itraconazole with 40% of hydroxy propyl-\(\beta\)-CD in the year 1999\(^{31}\). The Zericonazole and Ziprasidone formulations in the USA are with hydroxy propyl-\(\gamma\)-CD. Drugs such as Aripiprazole, Mitomycine, Diclofenac sodium, Chlrodizepoxide, Meloxicam, Alfalexalone, Cisapride, Indomethacine, Insulin (nasal spray), Omeprazole and many other drugs have been reformulated using CDs for both commercial and health benefits\(^3\).

### Size reduction and nanonisation

Nanotechnology-enabled drug delivery has substantial development and application history. Nanoparticles offered the formulation scientists a potential opportunity to overcome the challenges associated with insoluble drug compounds.

The technologies used to produce drug nanoparticles can be broadly categorised into ‘bottom-up’ and the ‘top-down’ technologies. In bottom-up technologies, controlled precipitation of the drug is done by adding a suitable non-solvent. The example for the precipitation technique is hydrosol developed by Sucker (Sandoz, presently Novartis)\(^{27}\).

The top-down technologies are milling or homogenisation methods. The two top-down technologies are employed for producing drug nanoparticles include high pressure homogenisation and milling. Danazol nanosuspension with a median diameter 169 nm showed enhanced oral bioavailability (82.3 ± 10.1%) as compared to ‘as-is’ drug suspension (5.1 ± 1.9%) in preclinical studies\(^{29}\).

The homogenisation (micro fluidisation) process has been successfully used to produce fine particles of Atovaquone in the 100–300 nm range. The nanoparticle formulation in comparison to micronised Wellvone\(^6\), at equivalent doses enhanced the drug concentration in plasma from 15% to 40% following oral administration\(^{29}\).

The first United States approval of a product produced incorporating the NanoCrystal\(^{5}\) technology was in August 2000. The product, Wyeth’s first solid-dose formulation of the immunosuppressant Rapamune\(^5\) (sirolimus) received marketing approval from the U.S. FDA. The NanoCrystal\(^{5}\) dispersion of sirolimus provided a drug product with enhanced bioavailability and improved stability.

Another drug product that was approved and introduced into the market in April 2003 was the Antiemetic drug, Emend\(^{5}\) (aprepitant, MK 869). Emend is a capsule dosage form containing 80 or 125 mg of aprepitant formulated as NanoCrystal\(^{5}\) drug particles, the nanosuspension was able to overcome the significant food effect (~3.2X) observed with the microsuspension formulation.

For parenteral applications, the nanoparticle technology is selected when the drug is a low potency compound with high dose, requires excess co-solvent and extreme pH conditions. The nanoparticle-based product Abraxane\(^{5}\) (a reformulation of Paclitaxel) was approved by FDA in 2006 for intravenous administration.

The nanoparticle approach has potential application in developing viable formulations for poorly soluble drugs and has opened the stage gates for reviving the current products with suboptimal drug delivery in the market which can lead to better therapeutic applications and commercial benefits as well.

### Solid lipid nanoparticles

Application of solid lipid particles for enhancing the dissolution rate and bioavailability for poorly soluble compounds has been reported from a long time. Solid lipid nanoparticles (SLNs) are coloidal carriers with a mean particle size between 50 nm and 1 \(\mu\)m. The lipid excipients used in the SLN formulations are biocompatible and biodegradable and most of them are physiological components that are generally recognised as safe. SLN technology has been explored in developing site-specific drug delivery particularly for poorly soluble proteins and peptide drugs\(^{30}\).

The poorly soluble compound Ofloxacin formulated in SLN showed a significant increase in the bioavailability. The enhancement in the drug’s bioavailability is attributed to increase in the surface area of the particles, improved dissolution rate and concentration of Ofloxacin in gastrointestinal tract (GIT) fluids\(^{31}\).

The potential therapeutic benefits of SLNs include protection of drug degradation in GIT and reduced toxicity. However the product with SLN is yet to hit the market.
Liposomes including proliposomes

Liposomes are micro-particulate or colloidal carriers, which form 0.05–5.0 µ in diameter spontaneously when lipids are hydrated in aqueous media. Liposomes are biocompatible and biodegradable materials, and constitute an aqueous volume entrapped by bilayers of lipids. Poorly soluble lipophilic drugs can be encapsulated in liposomes, either in the phospholipid bilayer, in the entrapped aqueous volume or at the bilayer interface. Due to recent developments in liposome technology, more effective strategies are available for improving the stability of liposomes after systemic administration.

Liposomal drug delivery offers significant therapeutic benefits to poorly soluble compounds. The examples are Cyclosporine and Paclitaxel, which were formulated initially with surfactants and organic cosolvents for systemic administration in humans. These solubilisers may cause toxicity at the administered doses. In comparison, liposomes are relatively non-toxic, non-immunogenic, biocompatible and biodegradable. Paclitaxel liposomes were able to deliver the drug systemically and increase the therapeutic index of paclitaxel in human ovarian tumour models.

Proliposomes

Proliposomes are dry, free-flowing granular products composed of drugs and phospholipids which, upon addition of water, redisperse to form a multi-lamellar liposomal suspension. It provides a novel solution to product stability problems associated with the storage of aqueous liposome dispersions, wherein it produces a dry product that can be stored for long durations and hydrated immediately before use. Liposomes can either be formed in the physiological fluids or can be formed using a suitable hydrating fluid prior to administration. The liposomes formed on reconstitution are similar to conventional liposomes and are more uniformed in size.

Katare et al., reported Indomethacin proliposomes for oral administration, the efficacy of the oral formulation was studied by measuring ulcerogenic index and anti-inflammatory activity using carrageenan-induced paw oedema tests in rats. The liposomal formulation showed an enhanced performance in vivo with reference to their cytoprotective and anti-inflammatory properties.

Vinpocetine in proliposomes was reported to have greater efficacy and less toxicity. The study showed that the oral bioavailability of proliposomes was enhanced in New Zealand rabbits and thereby provided a new delivery platform to enhance the absorption of poorly soluble drugs in the GIT.

Proliposomes have shown a potential application in developing formulations for small molecules as well as protein and peptides. Therapeutic benefits of proliposomes include enhanced bioavailability, protection of drugs from degradation in the GIT, reduced toxicity and taste masking. The proliposomes can also provide targeted drug delivery and controlled drug release.

Emulsions, micro-emulsions and self-emulsifying drug delivery systems

Micro-emulsions are thermodynamically stable, isotropic mixtures of oil, water, surfactant and a co-surfactant. In comparison to conventional emulsions, micro-emulsions produce a clear emulsion on mild agitation. The advantage of micro-emulsions over conventional and solution formulations is that the former produces a stable heterogeneous system. Micro-emulsion technology is widely used to address the challenges associated with poorly soluble compounds.

Insoluble drugs can be formulated into micro-emulsions for parenteral drug delivery. The micro-emulsions for parenteral delivery comprise lipid droplets (10%–20%), an osmotic agent and an emulsifier. If the emulsion is packed in multi-dose containers then an antimicrobial agent shall be incorporated.

Self-emulsifying drug delivery systems gained a lot of interest because of their ability to enhance the solubility and bioavailability of insoluble drugs. The self-emulsifying systems forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous environment in the GIT and is used for improving lipophilic drug dissolution and absorption. Vinpocetin and Atorvastatin in self-emulsifying systems showed a significant improvement in bioavailability as compared to conventional tablet formulation, indicating the concentration of surfactants in formulations is critical for yielding the smaller particles for enhanced drug permeation and absorption.

Conclusion

The large number of insoluble drugs on the market and in the development pipeline provides challenges and opportunity for formulation scientists to optimise the formulation to meet the clinical needs and create the intellectual assets. The formulation of insoluble drugs would enable many more new drug application filings in the near future.

References

Review


