Chapter II

Poorly Aqueous Soluble Drugs
2. Poorly Aqueous Soluble Drugs

The BCS classifies a drug substance based on two factors: its aqueous solubility and intestinal permeability\(^1\). It was introduced in the year 1995\(^2,3\), and since then it has had a tremendous influence on the pharmaceutical market and research worldwide. It has been a very handy yardstick in the discovery, development, and regulatory validation of drugs and new chemical entities. The BCS has also been commendably incorporated by drug regulatory agencies globally as bioavailability/bioequivalence (BA/BE) standards for the approval of immediate-release (IR) orally administered drug products\(^4,5\). When combined with the \textit{in vitro} dissolution characteristics of the drug product, the BCS takes into account three major factors:

- a) solubility,
- b) intestinal permeability, and
- c) dissolution rate,

all of which govern the rate and extent of oral drug absorption from solid oral-dosage forms\(^1\).

2.1 Solubility and Dissolution rate

Poorly water-soluble drug candidates often emerge from contemporary drug discovery programs, and present formulators with considerable technical challenges\(^2\). The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability. Especially for class II substances according to the Biopharmaceutics Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids\(^3\). Consideration of the modified Noyes-Whitney equation\(^4\) provides some hints as to how the dissolution rate of Even very poorly soluble compounds might be improved to minimize the limitations to oral availability:

\[
\frac{dC}{dt} = \frac{AD. (Cs - C)}{h}
\]

Where, \(dC/dt\) is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, Cs is the solubility of the compound in the dissolution
medium, C is the concentration of drug in the medium at time t, h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions. Often ‘AD/h’ in the Noyes Whitney equation is defined as the ‘dissolution constant’ (k). The surface area (‘A’ in the equation) is directly related to k. The rate of the solvent that freshly comes in contact with surface area of the solid depends on factors like particle size and shape of the solid, and density of the medium. A common observation consistent with experiments with many pharmaceutical preparations is that as the particle size of the solid decreases the dissolution increases. By encapsulating the drug particles in hydrophilic polymeric nanoparticles, apart from preventing the particles from agglomeration, we would also be increasing the surface area of interphase between the dissolving surface and the medium (A in the equation), and Solubility (Cs) since drug is incorporated in the hydrophilic polymer.

Larger the surface area, higher will be the dissolution rate. Since the surface area increases with decreasing particle size, which can be accomplished by conventional methods like trituration, grinding, ball milling, fluid energy micronization, salt formation and controlled precipitation. Although these conventional methods have been used commonly to increase dissolution rate of drug, there are practical limitation with these techniques as the desired bioavailability enhancement may not always be achieved. Therefore, formulation approaches are being explored to enhance bioavailability of poorly soluble drugs. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate solid nanofromulations.

2.2 Memberane Permeability

The second aspect of bioavailability, according to the BCS, is membrane permeability. The drugs are classified as poorly permeable (Class III and IV, BCS) based on permeability data across
human jejunal experiments, or distinct mass balance studies when compared to an intravenous dose as reference. But such data is often tedious to obtain and is available for only a limited number of drugs. Hence, provisionally, permeability classification could be based on correlation of the assessed $n$-octanol/water partition coefficient using Log $P$ of the uncharged form of the drug molecule$^{6,7}$. Drugs exhibiting $n$-octanol/water partition coefficient value greater than metoprolol (Log $P \approx 1.72$) were categorized as high-permeability since metoprolol is known to be 95% absorbed from the GI and hence may be used as a reference standard for the low/high class boundary$^8$. One noticeable short coming regarding the permeability prediction by lipophilicity correlations is that drugs whose intestinal absorption is carrier-mediated, either in the absorptive direction or exsorptive direction, will have their permeabilities underestimated or overestimated, respectively.

2.3 The Poor Water-Solubility Challenge

Researchers and product development scientists frequently run into substantial challenges in solving the problem of poor water solubility of drug candidates in the development pharmaceutical dosage forms$^{9,10}$. A couple of decades ago, it was reported that more than 41% of such NCEs coming from new drug development have failed as pharmaceutically active agents due to poor biopharmaceutical properties, including water insolubility$^{11,12}$, while it was still indicated still recently that about 50% failure of drug candidates was due to poor “drug-like” properties$^{13}$.

The past two decades have seen far more drug candidates than before due to the advancement in genomics, robotics, high-throughput screening, computational and combinatorial chemistry, informatics, and miniaturization and simulations and their applications to drug discovery$^{14}$. However, biopharmaceutical or “drug-like” properties of new drug candidates with very low water solubility tend to suffer during the screening process$^{10,13}$. A compound having a remarkable receptor affinity/selectivity, but poor “drug-like” characteristics and thus is difficult formulate or deliver. Most compounds coming out of such screening processes are usually hydrophobic or water insoluble. Hence, the early formulation development of such drugs has become a challenge to the pharmaceutical$^{9,13,15}$. For such NCEs aqueous insolubility could delay or totally terminate the development. Thus poor aqueous solubility of lipophilic emerging molecules throws challenging complications to be dealt with, to pharmacists and formulation scientists.
Not just NCEs, even existing and marketed drugs with very low aqueous solubility usually suffer from considerable problems such as inter- and/or intra-subject variability in their pharmacokinetics which makes the assessment of dose–response and exposure–response relationships more difficult, and makes the dose recommendation and optimization less feasible for New Drug Applications (NDA) and product labeling. Water-insoluble drugs usually have high tendency for drug interactions at absorption level, such as food interaction, interactions with GI prokinetic agents, especially if these drugs also have narrow therapeutic windows. Such hurdles and risks should be taken into consideration when a clinical drug development plan is put together. Risk/benefit reality check should be done at each critical stage gates, and if the risks are deemed too large, then a tough call for termination of the program should be made. Owing to the inherent limitations of such drugs, more caution needs to be exercised and more resources may be warranted to make a sound assessment of their safety and efficacy profiles.

Similarly, testing may also pose significantly higher hurdles for bioanalytical sensitivity and reproducibility, as well as pharmacokinetic evaluations of these drugs. To date, not many pharmacokinetic strategies are available to address such problems and eventually to assist in the dose regimen selection and optimization. For example, the growing popularity of the pharmacostatistical modeling approach (such as population exposure–response analyses in late-stage clinical development) may mitigate the negative impact arising from the low water solubility and associated disadvantages. Moreover, the introduction of more and more validated and predictive surrogate markers or biomarkers early in the drug development stage may certainly help to overcome some (if not all) limitations of the current pharmacokinetic assessment of these water-insoluble drugs.

Also, such water insoluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.

The improvement of drug solubility thereby its oral bio-availability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly
water-soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. As for BCS class II drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs.

2.4 Non-Steroidal Anti-Inflammatory Drugs

NSAIDs are a widely used class of drugs with common analgesic, anti-inflammatory, and anti-pyretic therapeutic properties. They reduce pain and inflammation by blocking cyclo-oxygenases (COX), enzymes which are necessary for the production of prostaglandins. NSAIDs may block different cyclo-oxygenases, COX-1 and COX-2. COX-2, found in joints and muscle, contributes to pain and inflammation.

The global pain management market for pharmaceuticals and medical devices was worth $36.6bn in 2014. The market for NSAIDs drugs was worth $11.4bn in 2014\(^\text{12}\). Growth in this segment is driven by an ageing global population, the increased incidence of obesity and changing attitudes towards pain management\(^\text{13}\).

NSAIDs are amongst the most popularly consumed drugs worldwide, estimated to used by more than 30 million people every day\(^\text{16,17}\). About 111 million medical prescriptions are written for NSAIDs in the USA every year, and they account for approximately 60% of the USA over-the-counter (OTC) analgesic market\(^\text{18}\). Among the NSAIDs, diclofenac and ibuprofen account for almost 40% of global NSAID sales for oral administration. Excluding OTC use, ibuprofen and naproxen are the most commonly prescribed NSAIDs in the USA, while diclofenac prescription is more common in the UK\(^\text{18}\). The introduction of COX-2-selective agents with improved gastrointestinal safety led to an overall increase in the use of NSAIDs. Current treatments for pain mainly include non-steroidal anti-inflammatory drugs ("NSAIDs") for mild to moderate pain, and
opioids, such as morphine, for moderate to severe and chronic pain. The opioids are notoriously associated with tolerance and dependence, while safety issues with Cox-2 inhibitors, an important class of NSAIDs, have limited their use.

These trends, combined with the increased incidence of osteoarthritis, the need for patients to manage contra-indications and their pain relief medication, means that topical formats of pain relief have become increasingly favoured by consumers, patients and healthcare professionals. Moreover the National Institute for Health and Care Excellence (NICE) gives clear guidance to healthcare professionals to prescribe topical NSAIDs in the first instance for joint pain associated with osteoarthritis, in preference to oral NSAIDs, owing to concerns over systemic side effects caused by the long term use of oral NSAIDs.

Non-steroidal anti-inflammatory drugs (NSAIDs) like, ibuprofen, ketoprofen, flurbiprofen, naproxen, diclofenac, aceclofenac, indometacin, flufenamin, piroxicam, meloxicam, celecoxib, parecoxib, etoricoxib etc… are very commonly used as painkillers. In India a large number of the generic products of these drugs are available over the counter, even without a prescription. Although very effective as pain killers and anti-inflammatory agents, these belong to the type II category of the biopharmaceutical classification system\(^1\), indicating that, though these drugs have a relatively high membrane permeability, their bioavailability remains limited due to their poor (or rather sparing) solubility in aqueous media. In fact, currently about 40% or more of drugs in development and about 60% of molecules obtained directly from synthesis are poorly soluble in aqueous media.\(^2\) For example, it takes more than two hours for the drug piroxicam (an NSAID) to attain the maximum concentration after being administered orally.

NSAIDs have similar absorption characteristics and are considerably lipophilic molecules.\(^10\) Although absorption of these molecules occurs throughout the gastrointestinal tract, an acidic environment better promotes the absorption of NSAIDs which as weak acids, are less ionized in gastric juice and therefore absorbed by the mechanism of ionic or diffusion trapping.

The three popular classes of NSAIDs are:

- Enolic derivatives
- Propionic acid derivatives and
Acetic acid derivatives

For our study, the model drugs identified from each of the categories based on their widespread usage in India are:

piroxicam (enolic derivative), and naproxen and ibuprofen (propionic acid derivative), aceclofenac.

Figure 2-1: Chemical Structure of the NSAIDs used in the study.

Piroxicam

Piroxicam, one of the most potent NSAID prescribed very often for various joint ailments, belongs to the BCS class II category. Hence, faster dissolution in the GI tract is the rate limiting step for its absorption and thus bioavailability. It belongs to the oxicam class of NSAIDs and reduces pain
by inhibiting prostaglandin synthesis and reducing the sensitivity of the pain receptors. It also reduces fever by modulating the center of the hypothalamus responsible for heat-regulation. It inhibits thromboxane A2, the platelet-aggregating substance. Other mechanisms proposed for its anti-inflammatory properties include stabilisation of lysosomes, synthesis of kinin and leukotriene, alteration of chemotactic factors and inhibition of neutrophil activation.

It, however, belongs to the BCS class II category. Hence, its dissolution rate in the gastro intestinal track (GIT) is the limiting step for its absorption. For poorly soluble, highly permeable drugs like piroxicam, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal (GI) tract. Hence, along with permeability, the solubility and dissolution characteristics of a drug are prime determinants of its overall oral bioavailability. This undesirable property of poor aqueous solubility could also lead to increased damage of the intestinal layers, due to long duration contact of drug with the mucosal layer of the GI tract. Many multi-component systems have been considered in efforts to improve the bioavailability of piroxicam. Some promising ones include dispersions of piroxicam in several amorphous polymers and lipids, and crystalline systems like nicotinamide, maltodextrin, and urea. The various polymeric carriers explored include PVP, eudragit, labrasol, etc. Nanoparticles of piroxicam, dispersed in Eudragit RS100 by emulsion method, were evaluated for improved ocular drug delivery. Using a variation of the single emulsion method, piroxicam was nanodispersed in an external phase of palm oil esters and the formulated ‘nanocream’ was shown to have superior membrane transport properties in rats.

**Naproxen**

Naproxen, a propionic acid derivative, is a member of the profen (2-arylpropionic acid) family of the NSAIDs. The API is pale white in color and is an odorless, crystalline substance. Naproxen is widely administered against fever, inflammation, and pain related to a variety of diseases including osteoarthritis, bursitis, rheumatoid arthritis, kidney stones, ankylosing spondylitis, psoriatic arthritis, gout, menstrual cramps, tendinitis, and migraine. Though a very old drug, it is highly lipophillic and practically insoluble in aqueous media. The drug, when orally administered, has quite some undesirable side effects like hemorrhage and ulceration of the stomach. And owing to its negligible aqueous solubility, the dosing amount in the formulations needs to be quite high to achieve the desired therapeutic effect. However, raising the dosage amount also increases the risk.
of side effects. These adverse factors have limited the usage of naproxen in most therapeutic prescriptions. Since the use of nanocarriers for dissolution enhancement has been established as effective dosage form for solid systems with reduced dosing amount, the bioavailability of naproxen can be effectively improved by polymeric nanostructures. The use of amphiphilic polymers can be used for controlled, yet quick release of the drug at low, as well as, high pH media.

Aceclofenac

Aceclofenac belongs to the same class as that of diclofenac (acetic acid derivative) and is essentially the glycolic ester of diclofenac. It is a new generational NSAID, showing effective anti-inflammatory and analgesic properties and a better tolerability profile in a variety of painful conditions like ankylosing spondylitis, rheumatoid arthritis and osteoarthritis and overcomes many of the side effects of diclofenac. However, it is only slightly soluble in water and hence increasing its aqueous solubility remains a major challenge to its formulations. Aceclofenac is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after an oral dose. The drug is also highly protein bound. The presence of food does not alter the extent of absorption of aceclofenac but the absorption rate is, however, reduced. This drug shows lower solubility at acidic pH but considerably higher solubility at higher pH. Though improving its aqueous solubility for higher pH (intestinal medium) has been explored its enhancement for lower pH (stomach/ gastric medium) has seldom been achieved. Several crystalline (urea, mannitol\textsuperscript{31–33}) as well as amorphous carriers\textsuperscript{34–38} (PVP, PEG 6000, etc..) have been reported to act as solubilizing matrices for aceclofenac. Dispersions in biopolymers like have been reported to enhance not only the in vitro dissolution rate but also the anti-inflammatory activity when tested in male wistar rats\textsuperscript{39}.

Ibuprofen

Ibuprofen or 2-(4-Isobutylphenyl)propionic acid, is a Nonsteroidal Anti-Inflammatory Drug that functions by inhibiting the cyclooxygenase activity. It is generally used as an analgesic and antipyretic agent for several inflammatory pathologies. Ibuprofen is a weak acid with a pKa value of 4.4. It has sparing solubility in water or acidic media thus, has relatively long residence duration in the acid environment of the stomach and slowing of absorption of the substance could be expected. As the pH of the buffer medium increases, solubility increases and the drug can be better
absorbed during dissolution in the intestine. Dissolution of ibuprofen is thus the rate-limiting step for its absorption, and the quick release of ibuprofen in the gastrointestinal tract after oral administration is desirable. Rapid ibuprofen absorption is a prerequisite for the quick onset of its action and dissolution and in vitro dissolution rates of ibuprofen should be enhanced to improve its bioavailability and reduce drug dosages and occurrence of adverse reactions.

Since more than one third of the existing drugs are poorly water and the gastro-intestinal tract is primarily an aqueous environment, solubilization of water-insoluble drugs is of great concern in pharmaceutical research. The dissolution of a solid into a liquid has been widely studied and that the process is energy driven has been established. When administered as a crystalline entity, a higher energy is required to break down the crystal lattice and thus dissolve the drug. To lower the energy required to dissolve the drug forms the major aim of the pharmaceutical formulations used to administer these drugs. It is obvious that reduction in particle size of the drug to nanoscale becomes an effective way to increase the dissolution rates of drugs. However, in this phase the particles are highly unstable (rather metastable) and tend to spontaneously recrystallize. Thus, it becomes crucial that these metastable states must be stabilized in suitable stable matrices used to dose the drug. Thus, the use of polymeric nanoparticles containing active pharma ingredients (APIs) have gained much interest in scientific and pharmaceutical areas as these are potential prospects for site-specific drug delivery, and thus optimization of drug therapy.

2.5 References


18. Conaghan, P. G. A turbulent decade for NSAIDs: Update on current concepts of


