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Polymeric precipitation Inhibitors to improve the dissolution and absorption of poorly water-soluble drugs

Yashashwini M., P. K. Kulkarni and Sharon Fredric

Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Mysore -570015, India

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ABSTRACT

BCS class II drugs offer challenging problems in their pharmaceutical product development process because of their low solubility and dissolution rates. The basic drug will precipitate upon a shift from gastric pH (pH 1.5) to intestinal pH (pH 6.5-7.0). With the increasing number of poorly water-soluble compounds in present day drug discovery pipelines, the concept of supersaturation as an effective formulation approach for enhancing bioavailability is gaining steam. This is intended to design the formulation which yields significantly high intraluminal concentrations of the drug than the thermodynamic equilibrium solubility through achieving supersaturation and therefore to enhance the intestinal absorption. The major challenges faced by scientists in developing supersaturatable formulations include controlling the rate and degree of supersaturation with the application of polymeric precipitation inhibitor and maintenance of post-administration supersaturation. The extent of precipitation can be measured using various techniques. The precipitation of a poorly water-soluble weakly basic drugs were investigated under different concentration. It has been shown that the drug precipitates rapidly under supersaturation. Solid dispersion techniques and self-micro-emulsifying drug delivery systems (SMEDDS) with the inclusion of certain polymers can prevent recrystallization, stabilize amorphous APIs, enhance solubility and process ability and facilitate dissolution. Different polymers have been evaluated as precipitation inhibitors. HPMC was shown to be the most potent polymeric precipitation inhibitor.

Key words: supersaturation, polymeric precipitation inhibitors, intraluminal concentrations, solid dispersion, SMEDDS.

INTRODUCTION

Around 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system. A rate limiting step for the absorption of these drugs is often their solubilization in the GIT. These drugs are classified as class II drugs by Biopharmaceutical classification system (BCS), high permeability with poor aqueous solubility. Hence, a greater understanding of dissolution and absorption behavior of drugs with low aqueous solubility is expected to successfully formulate them into bioavailable product. The properties of drug that affect the drug dissolution includes solubility, particle size, polymorphism, salt form, complexation, wettability, etc. and it can be targeted to enhance the dissolution of poorly water soluble drugs[1-20]. Use of water soluble excipients is most common and simplest way to enhance the dissolution rate of hydrophobic drugs. These excipients includes polymers, superdisintegrants, carbohydrates, surfactants,etc. which works in different ways to enhance the water solubility of drugs. The role of technique of preparation of formulation is as important as the choice of the carriers to enhance dissolution of drugs due to difference in the reduction of crystallinity of the product and surface characteristics of the particles[19].

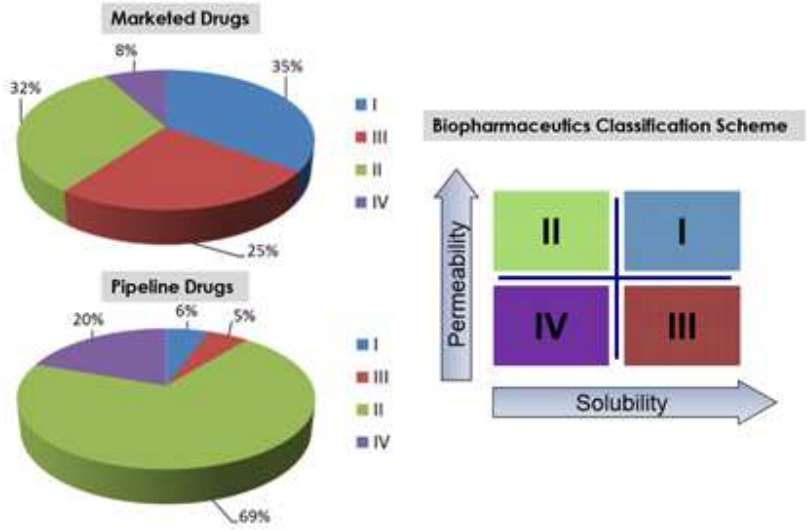


Fig.1 Prevalence of poorly soluble drugs in todays climate[6]

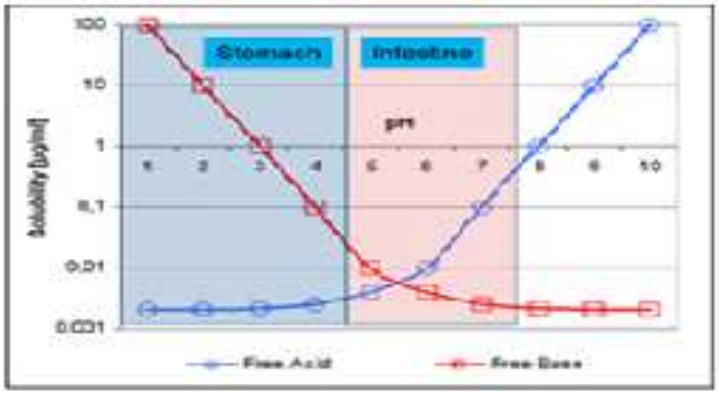


Fig.2 pH/solubility profile of weak acids and bases[6]

BCS class II weak basic drugs such as ketoconazole, dipyridamole, and carvedilol, easily dissolve in gastric pH and then may occur the precipitation or reach the supersaturation entering the duodenum due to higher environmental pH. *In vivo* drug precipitation has been a major issue facing poorly soluble drugs, especially weak bases. For this enhanced intestinal absorption to take place, supersaturation must be obtained and maintained in the gastrointestinal environment[7]. In vivo induction of supersaturation can be achieved through various formulation approaches. There are different approaches to induce supersaturation. The metastable state of supersaturation has to be sustained for a time period sufficiently long in order to improve intestinal absorption. It has been demonstrated that application of functional excipients (polymers, surfactants, etc.) can effectively minimize and/or delay drug precipitation in a highly supersaturated state and this stabilizes supersaturation as evidenced by appropriate in vitro tests. As it can be expected that the gastrointestinal environment induces drug precipitation in vivo, in vitro evaluation of supersaturation requires careful consideration of bio relevant test methods mimicking physiological environments[14].

Sirius has developed a novel titrimetric method for measuring solubility. The CheqSol1,2 method provides a fast method of obtaining both the equilibrium and kinetic solubility of ionizable compounds. The CheqSol method is a valuable tool for investigating the supersaturation and precipitation behavior of drugs. Compounds are described as

Chasers or Non-Chasers according to the way they behave in CheqSol assays. The differences between Chasers and Non-Chasers are indicated in Figure 3. In order to crystallize, a compound must first attain a supersaturated state, and differences between the kinetic (KS) and equilibrium (ES) solubility show how the compound will crystallize and how supersaturation may be maintained[13.]

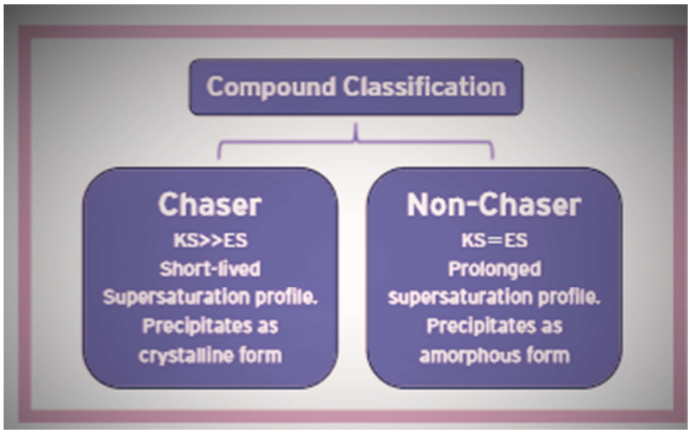


Fig.3 Difference between Chasers and Non-Chasers

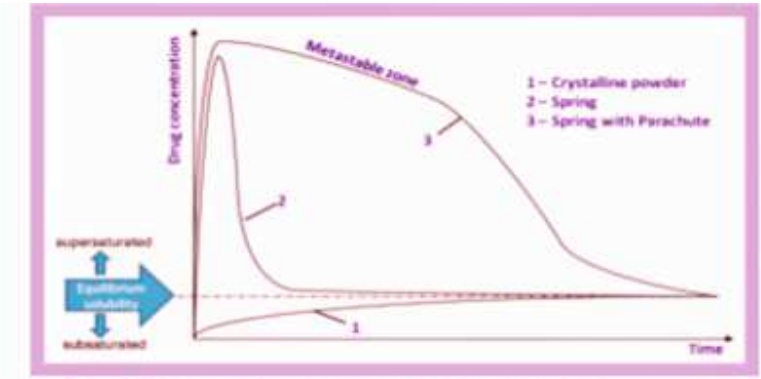


Fig. 4 The spring and parachute model of supersaturation

Strategies to enhance absorption by creating supersaturation:

A number of different formulating approaches have been used in order to create supersaturation of drug in the gastrointestinal tract and thereby increase absorption of low solubility compounds. Perhaps the most commonly used is salt formation of the base or acid, with a prevalence of approximately 40% reported for commonly used marketed drugs. Salts with different counter ions generally have different apparent solubility, and the choice of counter ion in pharmaceutical development is governed by a combination of physicochemical/formulation issues such as solubility, chemical stability, rate of dissolution and melting point, and the in vivo appropriateness of the salt[7]. Apparent solubility increase of the solid phase can also be utilized in vivo using other solid phases such as solvates and metastable polymorphs, prodrug, cocrystals and amorphous form of the drug. The latter is normally stabilized by making a molecular dispersion between a carrier, typically a polymer, and the drug. This locks the solid drug in an amorphous solid state with an apparent higher solubility than the crystalline solubility, if the carrier is carefully chosen[5-16].

Other formulation strategies involve finding some kind of solvent that the drug molecule prefers to the environment in the gastrointestinal tract, giving the drug a possibility to be diluted and absorbed without precipitation. This includes co-solvents, lipids and complex forming agents such as cyclodextrins or combinations thereof such as self - emulsifying drug delivery systems containing both lipids and co-solvents[3].

Factors which influence drug polymer interactions are:

a) **Temperature**: when temperature increases the binding between drug and polymer decreases[24].

b) **Molecular weight**: polymer with high molecular weight interact more strongly with drug molecule due to increases viscosity or availability of more functional groups[25-26].

c) **Viscosity**: as the viscosity increases it decreases the rate of drug diffusion from bulk solution, resulting in crystallization inhibition[22-27].

d) **Dielectric constant**: decreased dielectric constant can increase drug solubility, which in turn results in decreased degree of interaction between the drug and polymer[25].

e) **Hydrogen bonding**: as the number of hydrogen bonding sites increases drug-polymer interactions also get increase. This would lead to delayed nucleation or crystal growth inhibition[21-28-29].

INFLUENCE OF POLYMERS ON SUPERSATURATION OF IBUPROFEN SODIUM IN VITRO AND IN VIVO:

Ibuprofen is well-known NSAID which is widely used as analgesic, antipyretic, and anti-inflammatory effects[30]. The commercial form of ibuprofen is the racemic free acid. However, this drug is practically insoluble.

The salt form of a drug can be provided to circumvent the dissolution limited absorption of the free acid by selecting a highly soluble salt. But since compound ionization is driven by pH, if $pH_{max\ of}$ the compound is above the pH in that region of the GI, the dissolution enhancement afforded by the salt is quickly lost as the drug disproportionates and precipitates as the less soluble free acid[31-34].

Some excipients used have been shown to delay the disproportionation of salts by serving as pH modifiers during dissolution. But this has limited success. Alternatively, if disproportionation cannot be avoided, then it is desirable to prolong the solubility enhancement afforded by the salt over the equilibrium solubility of the thermodynamically stable free acid in the stomach by maintaining supersaturation of ibuprofen[35-37]. In order to prolong supersaturation achieved by higher energy phases, precipitation inhibitors have been shown to interfere in the nucleation and/or crystal growth stages of the more thermodynamically stable phase[38].

Guzmán et al. have demonstrated that specific combinations of crystalline salt forms of celecoxib with polymers and surfactants can provide both enhanced dissolution and high oral bioavailability; however a mechanistic understanding into how these excipients are interacting with celecoxib is not pursued[39]. Since a combination of drug, polymer, and the surfactant is required to maintain supersaturation in the case of celecoxib, it is advisable to evaluate an alternative drug substance to determine whether the simple combinations of salts with polymers could prolong supersaturation during in vitro dissolution testing. It is proposed that a variety of mechanisms could contribute to prolonged supersaturation depending on the drug-excipient combinations. Therefore, the primary objective of this study was to identify polymers that effectively prolonged the supersaturation of ibuprofen. And the second objective was to begin a mechanistic evaluation into how ibuprofen interacted with the specific polymers that maintained supersaturation for an extended period of time.

EXPERIMENTAL SECTION

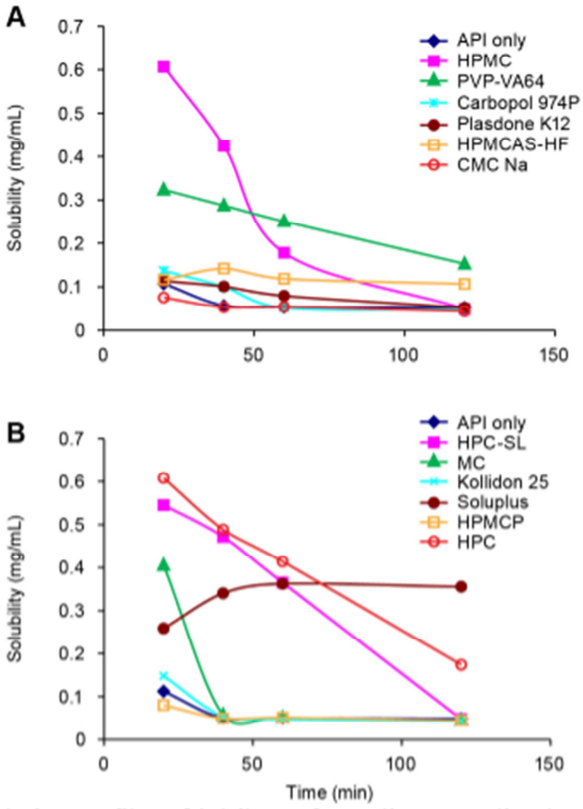
Materials:

Ibuprofen(free acid) was purchased from Sigma (Sigma-Aldrich, St. Louis, MO, USA) and the (R/S)-ibuprofen sodium dihydrate was prepared from the free acid and 1.006 molar equivalents of sodium hydroxide. The crystallization for ibuprofen sodium dihydrate was based on the procedures outlined by Lee and Wang [40], but without the need for cosolvent to facilitate precipitation. The final form of ibuprofen sodium dihydrate was confirmed to be the racemic conglomerate [41]. Pharmacoat 603 (hydroxypropyl methylcellulose, HPMC, Shin-Etsu, JAPAN), Kollidon VA64 (polyvinyl pyrrolidone-vinyl acetate copolymer, PVP-VA, BASF), Poly(acrylic acid) (PAA, Aldrich), Carbopol 974P (Lubrizol), Plasdone K12 (polyvinyl pyrrolidone, Ashland), hydroxypropyl methylcellulose acetate succinate (HPMCAS, HF grade, Shin-Etsu), carboxymethylcellulose sodium salt (CMC Na, Sigma), hydroxypropyl cellulose (HPC, SL grade), methylcellulose (MC, 400 cPs, Sigma-Aldrich), Kollidon 25 (polyvinyl pyrrolidone, Sigma), Carbopol 934P (Lubrizol), Soluplus (BASF), HPMCP 50 (hydroxypropyl methylcellulose phthalate, Acros), and Klucel EXF (hydroxypropyl cellulose, HPC, Ashland) were used as polymeric excipients. Sodium chloride, hydrochloric acid, and sodium acetate purchased from Fisher, USA and glacial acetic acid (Mallinckrodt, USA) were used in the preparation of the dissolution buffers. HPLC grade

acetonitrile and 85% phosphoric acid were purchased from Sigma-Aldrich (St. Louis, MO, USA). Deionized water from the house line was used for all aqueous solutions and these were prepared as needed for each experiment[42].

Characterization of Blends by X-ray Powder Diffraction (XRPD)

X-ray powder diffractograms of 1:1 ibuprofen sodium polymer blends were Measured on a D8 Discover X-ray diffractometer (Bruker AXS, Madison, WI, USA). Samples were prepared on a 20 mg scale and mixed at an intensity of 30% for 120 minutes prior to being analyzed in transmission scan mode with a 600 second acquisition time and oscillation amplitude of 0.5. Data were collected using Symyx Epoch and viewed using Spectra Studio (Accelrys, Inc., San Diego, CA, USA)[42].



Dissolution profiles of 1:1 ibuprofen sodium: pre-dissolved polymer in SGF at 37 °C during supersaturation screen.

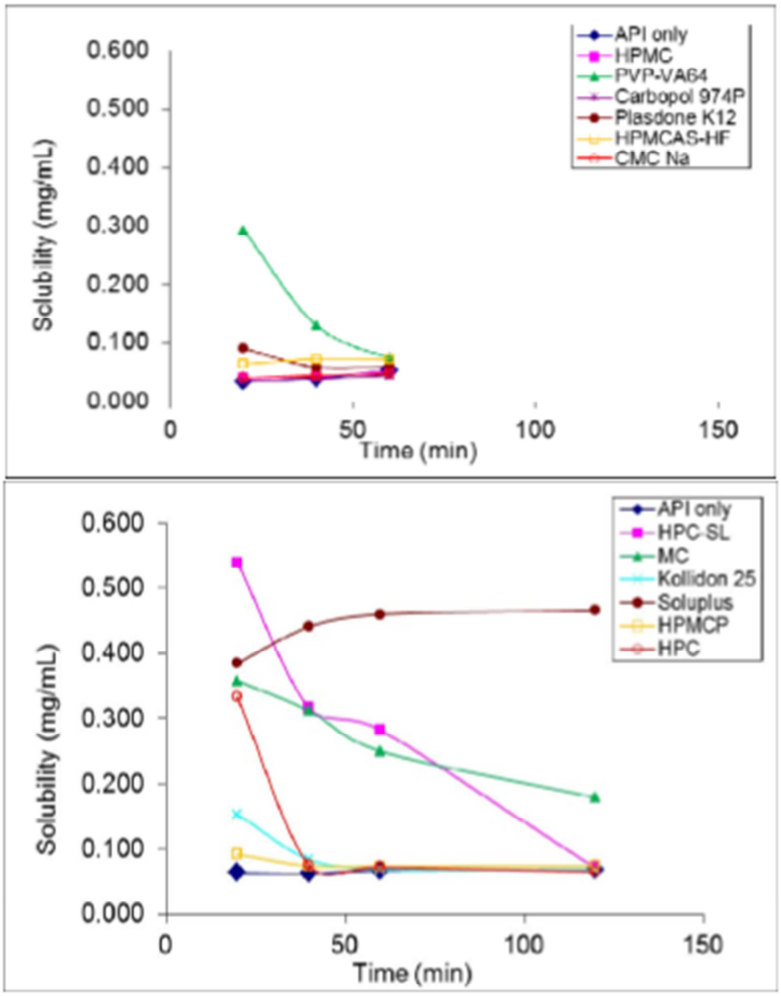
Supersaturation Screening of Ibuprofen in the Presence of Polymers

Preliminary supersaturation screening of ibuprofen sodium salt in pre-dissolved polymer solutions was conducted using a high-throughput screen to determine potential degree of supersaturation that could be achieved. Dissolution experiments with ibuprofen sodium were performed at 37 °C in simulated gastric fluid (SGF). The formula for SGF was 2 g/L sodium chloride and 1.4 mL/L of 12N hydrochloric acid in deionized water at a final pH of 1.8. For screening studies, polymer was pre-dissolved at a concentration of 1 mg/mL in SGF. Supersaturation screening was conducted in round bottom high performance liquid chromatography (HPLC) vials on a 1 mL scale, with solid ibuprofen sodium added to each vial at a target concentration of 1 mg/mL. Samples were shaken at 500 rpm on a temperature controlled shaker programmed at 37 °C to enable uniform mixing without the addition of a stir bar that could interfere with particle growth during equilibration. At 20, 40, 60, and 120 minutes, aliquots of the slurries were centrifuge filtered through a Multi Screen HTS-PCF filter plate (Millipore, Billerica, MA, USA) and the filtrate was diluted and assayed using HPLC to determine ibuprofen concentration. Since excess solid remained in the media, dissolution samples were allowed to equilibrate for 24 hours in order to determine equilibrium solubility of ibuprofen in the presence and absence of polymer. In order to confirm that equilibrium was achieved within that time, slurries starting from ibuprofen free acid were also evaluated with the same amount of polymer present following 24 hours for comparison. The degree of supersaturation was calculated by dividing the maximum

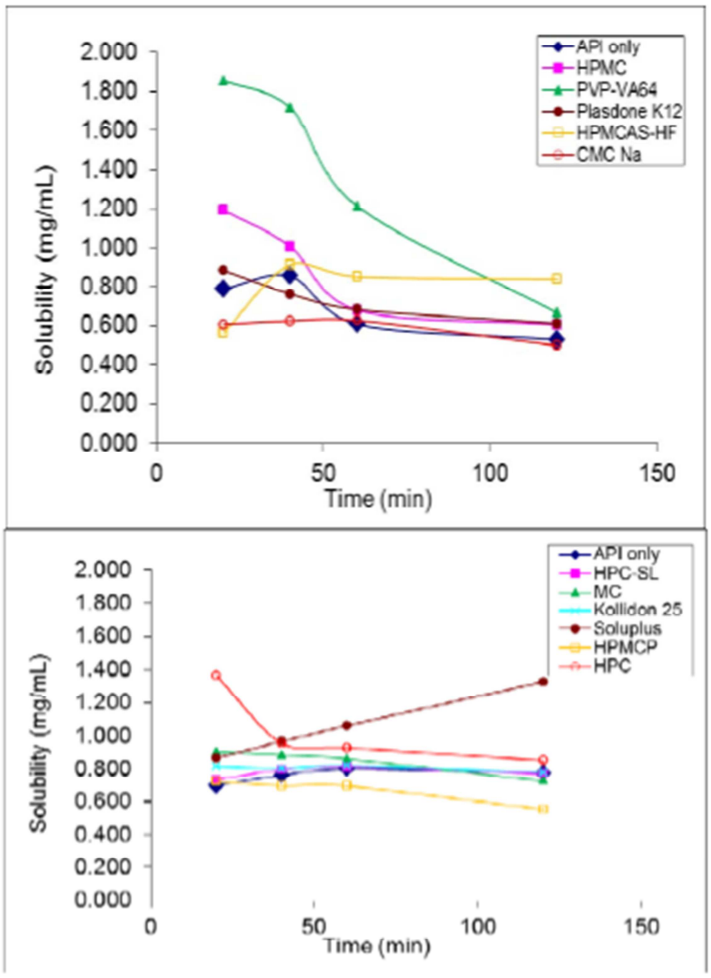
measured concentration of drug in solution during dissolution by its equilibrium solubility determined following 24 hours in the system of interest. The duration of supersaturation was the amount of time that that the measured concentration of drug in solution remained above the equilibrium solubility of that system. Measurements of pH of the samples were made using an Accumet pH meter. All dissolution experiments were conducted in triplicate and data is reported as average concentration of free acid in solution ± standard deviation[42].

In Vitro Dissolution Testing and Equilibrium Solubility Assessment

Dissolution experiments were performed at 37 °C in simulated gastric fluid (SGF) and 50 mM acetate buffer at pH 5.0. The recipe for SGF was 2 g/L sodium chloride and 1.4 mL/L of 12N hydrochloric acid in deionized water for a final pH of 1.8. In order to fully evaluate potential mechanisms of supersaturation, 50 mM acetate buffer at a pH of 5.0 was also used as dissolution media since it falls between the pKa of ibuprofen and the pH_{max} of the ibuprofen sodium salt. The intent was to avoid immediate neutralization of the ibuprofen sodium in the media by selecting a condition that could have slower kinetics of disproportionation and would have a lower degree of supersaturation from the starting concentration to the equilibrium solubility of ibuprofen in the selected media. For experiments where polymer was pre-dissolved in media, polymer solutions were prepared at 1 mg/mL in SGF and 2 mg/mL in pH 5 buffer[42].



Dissolution profiles of 1:1 ibuprofen sodium:polymer in SGF at 37 °C.



Dissolution profiles of 1:1 ibuprofen sodium:polymer in pH 5 buffer at 37 °C.

Dissolution screening was conducted in round bottom HPLC vials on a 1 mL scale, with an ibuprofen sodium concentration of 1 mg/mL for SGF studies and 2 mg/mL for dissolution in pH 5 buffer. Samples were shaken at 500 rpm on a temperature controlled shaker programmed at 37 °C to enable uniform mixing. At various time points, aliquots of slurries were centrifuge filtered through a Multi-Screen HTS-PCF filter plate (Millipore, Billerica, MA, USA) and the filtrate was diluted and assayed using high performance liquid chromatography (HPLC) to determine ibuprofen concentration. Since excess solid remained in the media, dissolution samples were allowed to equilibrate for 24 hours in order to determine equilibrium solubility of ibuprofen in the presence and absence of polymer. In order to confirm that equilibrium was achieved, slurries of ibuprofen free acid were also evaluated with the same amount of polymer present following 24 hours. The degree of supersaturation was calculated by dividing the actual concentration of the drug in the solution by its equilibrium solubility determined following 24 hours in the system of interest. Measurements of pH were also made using an Accumet pH meter. All dissolution experiments were conducted in triplicate and data is reported as average concentration of free acid in solution ± standard deviation[42].

In vivo Studies:

In vivo studies were conducted in Wistar Han rats to evaluate the influence of various polymers on the pharmacokinetic parameters of ibuprofen. Each of the polymers evaluated in the two-stage dissolution experiments, including HPMC, PVP-VA64, HPC, MC, and Soluplus, were blended in a 1:1 ratio with ibuprofen sodium and filled into gelatin capsules for oral administration. Size 9 hard gelatin capsules were selected because of their suitability for oral gavage to rats and their rapid disintegration profile, as per the manufacturer's specifications, which would

enable drug and polymer to quickly initiate their dissolution in the stomach so that the impact of formulation on C_{max} and T_{max} could be observed[42].

A dose of 25 mpk (ibuprofen free acid equivalent) was selected based on previous work by Newa et al. which suggested that there are opportunities to detect changes to the pharmacokinetic profile of ibuprofen at this dose since absorption did not seem to be maximized at this dose with a conventional ibuprofen free acid formulation. The average plasma concentrations of various formulations of ibuprofen following oral administration to rats were compared. Overall, a delay in the initial onset of absorption was observed with the ibuprofen free acid profile in comparison to all formulations containing ibuprofen sodium. Minimal plasma exposure was observed with the 15 minute time point for the free acid formulation while all other formulations containing the sodium salt of ibuprofen have significantly higher ibuprofen plasma concentrations at the same time point. In addition, the T_{max} for ibuprofen free acid was significantly delayed relative to the ibuprofen sodium-containing formulations. Upon initial assessment, a higher C_{max} was also achieved with some polymer-containing formulations which suggested that these polymers were successfully prolonging supersaturation in vivo when compared to the ibuprofen sodium formulation alone. These observations also correlated with the two stage dissolution experiments, where a significant delay in dissolution of neat ibuprofen free acid is observed relative to the ibuprofen sodium-containing formulations under SGF conditions[42].

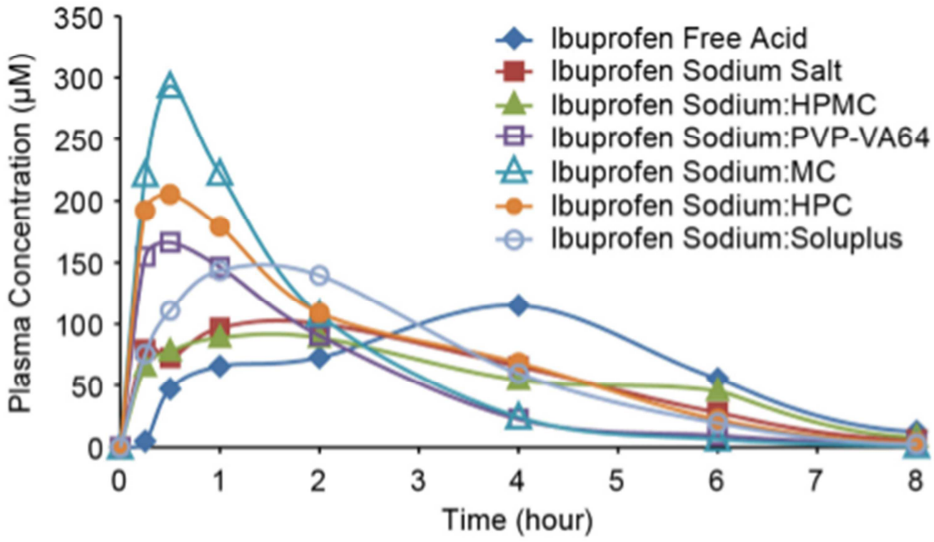


Figure 4.5. Mean plasma concentration of ibuprofen following oral administration in Wistar Han rats (n=6) under fasted conditions at a dose of 25 mpk. Ibuprofen free acid (◆),ibuprofen sodium salt (■),1:1 ibuprofen sodium:HPMC (▲),1:1 ibuprofen sodium:PVP-VA64 (□), 1:1 ibuprofen sodium:MC (△), 1:1 ibuprofen sodium:HPC (●), and 1:1 ibuprofen sodium:Soluplus (○).

CONCLUSION

Combining ibuprofen sodium with various pharmaceutically acceptable polymers alone resulted in the identification of several drug-polymer combinations that demonstrated high degrees and extended durations of supersaturation during in vitro dissolution experiments under conditions where the highly soluble ibuprofen sodium salt converted to a poorly soluble free acid phase. These formulations included HPMC, PVP VA64, MC, and HPC. These observations differ significantly from previous work that required the inclusion of surfactant to the salt-polymer formulation to enable supersaturation. It is likely that the surfactant-like properties of ibuprofen sodium eliminate the need for addition of surfactant to the formulation to enable supersaturation. This finding results in the feasibility of developing of a more simplistic formulation to achieve desirable supersaturation profiles. The in vitro supersaturation observed with these polymer-ibuprofen formulations translated to an increase in C_{max} of ibuprofen plasma concentrations relative to ibuprofen sodium without polymer and a decrease in T_{max} relative to ibuprofen free

acid without polymer for the PVP-VA64, MC, and HPC formulations. Based on these observations, a combination of an appropriate polymer with a salt form of an acidic drug may be a viable formulation approach to prolong supersaturation in the stomach and enable increased C_{max} and earlier T_{max} in vivo where rapid onset of action is desired for pharmacokinetic profile of a drug[42].

Examples of applications of polymeric precipitation inhibitors in the GI-tract:
Polymeric precipitation inhibitors have broad potential application in the inhibition of drug precipitation in the GIT. A number of formulation methods have been reported for overcoming or mitigating low aqueous solubility of oral drugs. One proven approach is to maintain an intraluminal concentration that is above the intrinsic solubility of the API. This strategy is also known as a supersaturating drug delivery system.

Which prevents the drug precipitation after dissolution of SDF and also after dispersion of lipid-based formulations[5].

Polymeric Precipitation Inhibitors and Solid Dispersion:
The inclusion of certain polymers within the solid dispersion or lipid based formulations can maintain drug supersaturation after dispersion of the vehicle, leading to enhancement in the bioavailability and variability in exposure. Polymeric precipitation inhibitors aim to maintain drug in a supersaturated, thermodynamically unstable state (metastable) over a period of time that is sufficient to allow absorption of drug from GIT. Polymeric precipitation inhibitor mode of action is not through co-solvency and they do not typically increase equilibrium drug solubility. Polymers like HPMC, PVP,PVA,PEG are used as polymeric precipitation inhibitors[10.]

Research materialized in Polymeric Precipitation Inhibitors:

- Liu,2008 reported that polymeric precipitation inhibitors can act as crystallization inhibitors at both nucleation and growth (kinetics and crystal habit) stages. Several potential sites of action were identified[10].
- Raghavan et al. 2001 revealed that changing the adsorption layer at the crystal solution interface, including the properties of the hydrodynamic boundary layer surrounding the crystal, potentially decreasing the rate of diffusion of drug molecules to the crystal nuclei[10].

Polymeric Precipitation Inhibitors and SEDDS:
The supersaturatable self-emulsifying drug delivery system comprises a new thermodynamically stable formulation approach where it is designed to turn back a reduced amount of surfactant and a water-soluble polymer (precipitation inhibitor or supersaturated promoter) in order to prevent the precipitation of the drug by generating and maintaining a supersaturated state in-vivo. Zhang N. et al. prepared supersaturatable self-microemulsifying drug delivery system (S-SMEDDS) of Carbamazepine (CBZ).The results showed the presence of small amount of polymeric precipitation inhibitor (PVP-polymer used in the study) effectively kept up supersaturated state by delaying precipitation kinetics[8]. S-SMEDDS formulation with precipitation inhibitor decreased impairment of cells due to a lower surfactant level compared to SMEDDS. The absorption of S- SMEDDS in-vivo results showed about 5-fold increase in bioavailability when compared to commercial tablet and the reproducibility of plasma concentration profiles intra-individual was improved remarkably[11].

The cellulosic polymers are excellent crystal growth inhibitors and are effective in sustaining the supersaturated state of the drugs in GIT. The ability generate a supersaturated state with HPMC along with the S-SEDDS formulations may be due to the formation of the widely spaced cellulosic polymer network that is formed due to the HPMC chains in water. HPMC chain inhibit nucleation as well as crystal growth by adsorption of the HPMC molecules onto the surface of the nuclei or onto the surface of crystals[12].

Precipitation/crystallization
Precipitation is influencing the bioavailability by affecting the rate and extent of drug absorption. When a molecule is precipitated from a supersaturated solution, it is transformed to its crystalline form, removed from the solution and hence does not contribute to the supersaturation effect on the concentration gradient. This in turn leads to decreased absorption and thus decreased bioavailability. Further it can be imagined that when molecules are absorbed over the membrane, the absorption rate decreases since the saturation decreases. This due to the decreased influence on the concentration gradient by the decreasing number of drug molecules in the small intestine[7]. The precipitation from a supersaturated solution is depending on the processes of nucleation and crystal growth. As previously stated, an increasing degree of supersaturation increases the risk of nucleation and crystallization, which leads to faster precipitation. Nucleation can be described as the formation of a solid phase in the supersaturated solution in an

attempt to separate the solute from the solution and thereby reducing the total Gibbs free energy, which is very high in supersaturated solutions. Crystallization is described as the further growth of the nuclei, resulting in precipitation. It is important to point out that these processes occur simultaneously[16-17].

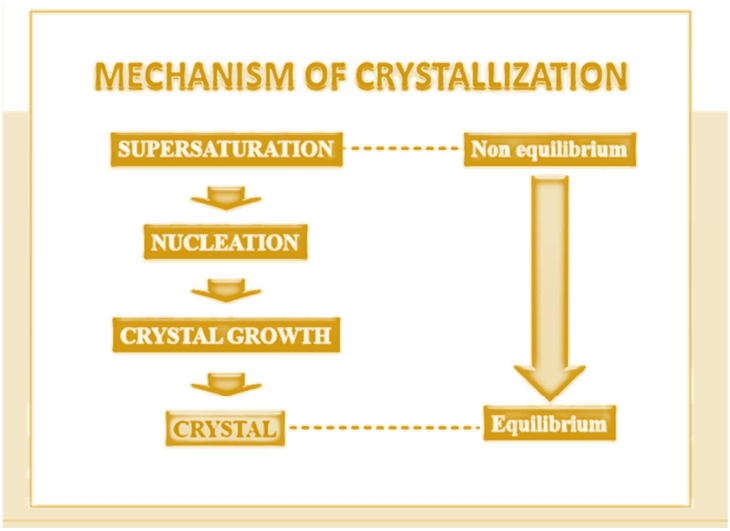


Fig.5 Mechanism of crystallization

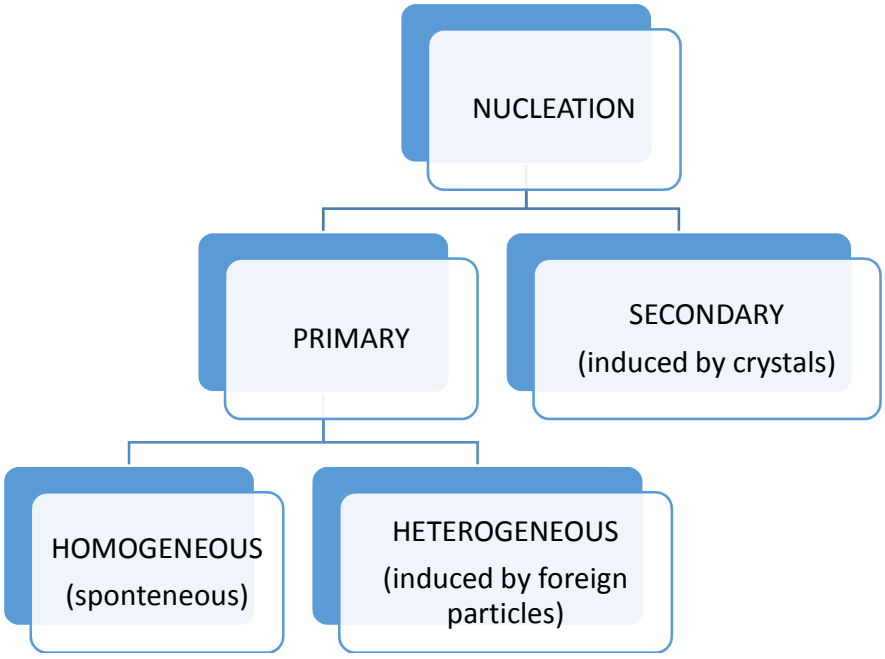


Fig.6 Schematic representation of classification of nucleation[15]

NUCLEATION:

The state of supersaturation is a crucial requirement for crystallization operations however, supersaturated solutions are not at equilibrium. Since every system tend to reach equilibrium, supersaturated solutions finally crystallize. Crystallization in the solution can be sub-divided into two kinetic steps, the first step is a phase separation, which is called nucleation, and the second step is the subsequent growth of nuclei to crystals. The relation between the degree of nucleation to crystal growth helps to determine the important product properties, such as product size distribution

and crystal size. Nucleation is strongly interrelated to the width of the metastable zone or the meta-stability of a system[15].

The condition of supersaturation (super -cooling)alone is not sufficient cause for a system to begin to crystallize. Before crystals can develop there must exists in the solution a number of minute solid bodies, embryos, nuclei or seeds that act as centers of crystallization. Nucleation process may occur spontaneously or it may be induced artificially[17].

Crystal growth

Is a diffusion process where solute molecules reach the growing surface by diffusion via liquid phase and are organized into space lattice. Growth rate of the most crystals is linear with super saturation. The rate of deposition is proportional to the driving force between the bulk of the liquid phase and that wetting the surface of the crystal which is approximately saturated with respect to crystals of that size. The driving force will vary because of increasing solubility for crystals with lower size range. Crystal growth takes place in meta-stable zone which lies between saturation and nucleation limits. In this region the solution is supersaturated and no nucleation occurs when crystals are growing[17].

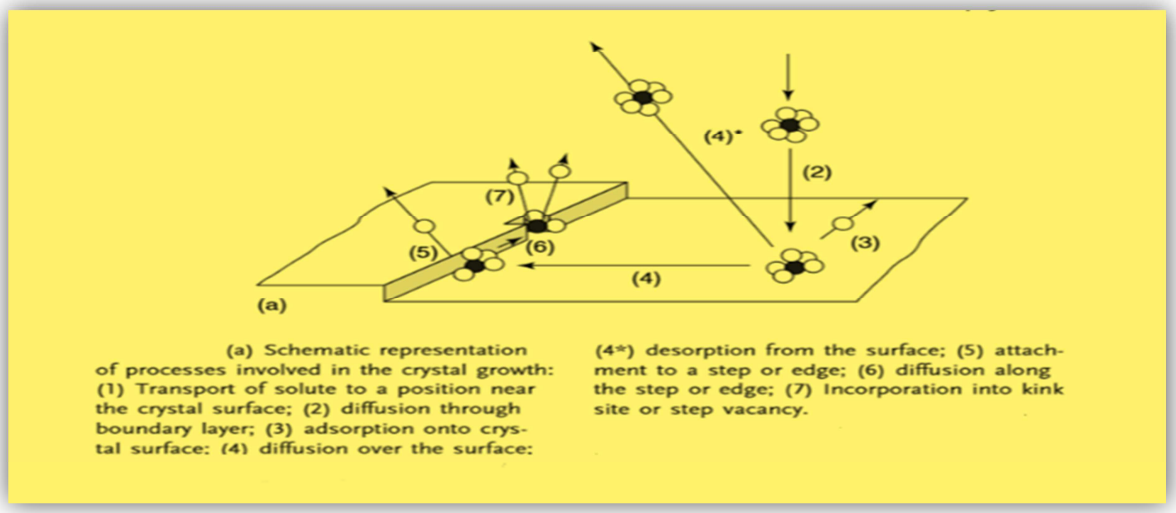


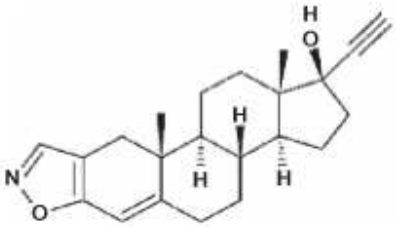
Fig.7 Schematic representation of processes involved in the crystal growth[17]

Interactions between polymers and drugs[5]

Sl. No.	Polymer	Drug	Stabilized Supersaturation	Increased Solubility
1	Poly(acrylic acid) (PAA)	Caffeine(Gift et al., 2008)	Yes	-
2	Polyethylene oxide(PEO)	Griseofulvin (Chiou, 1977)	-	Yes
3	PEO- PPO- PEO	Celecoxib (Guzman et al., 2007)	Yes	-
4	Polyvinyl alcohol (PVA)	Estradiol (Megrab et al., 1995)	Yes	-
5	Polyvinyl acetate phthalate (PVAP)	Itraconazole (DiNunzio et al., 2008)	Yes	-
6	Polyvinyl pyrrolidone (PVP)	Carbamazepine (Gift et al., 2008)	Yes	-
7	Cellulose acetate phthalate (CAP)	Itraconazole (DiNunzio et al., 2008)	Yes	-
8	Methyl cellulose (MC)	Hydrocortisone acetate (Raghavan et al., 2000)	Yes	-
9	Hydroxy propyl cellulose (HPC)	Celecoxib (Guzman et al., 2007)	-	Yes
10	Hydroxy propyl methyl cellulose (HPMC)	Acetazolamide (Loftsson et al., 1996)	-	Yes
11	Hydroxy propyl methyl cellulose phthalate (HPMCP)	Albendazole (Kohri et al., 1992)	Yes	-
12	Hydroxy propyl methyl cellulose acetate succinate (HPMCAS)	Felodipine (Kono et al., 2008, Alonzo et al., 2010)	Yes	-

Recent data on the interaction between polymeric precipitation inhibitors and Danazol[5].

Tab.1 Structure and physical properties of danazol

Molecular structure	
Molecular weight	337.5 g/mol
Solubility (25°C)	
Water	0.58 μg/mL (Erlich et al., 1999) 1 μg/mL (Alsenz et al., 2007)
Propylene glycol	9.05 mg/mL (Alsenz et al., 2007) 10.8 mg/mL (Erlich et al., 1999)
Log*P*	3.927 (Alsenz et al., 2007) 4.2 (Clarysse et al., 2009) 4.53 (Bakatselou et al., 1991)

EXPERIMENTAL SECTION

The following polymers were obtained from Sigma Aldrich Pty Ltd., Australia: HPMCAS HF, HPMC K4M, cellulose acetate phthalate, Eudragit. Danazol was supplied by Sterling Pharmaceuticals (Sydney, Australia). Analytical grade sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium chloride were used for the aqueous phase buffer. Propylene glycol was obtained from Merck Pty Ltd., Australia[5].

Turbidity Measurement:

The aqueous phase was buffered to pH 6.5, using 18 mM NaH2PO4 and 12 mM Na2HPO4 as the pH buffer, and adjusted to an ionic strength of 0.152 M using 98 mM NaCl. These were same buffer conditions used previously for simulated endogenous intestinal fluid (Kossena et al., 2004). The co-solvent phase was propylene glycol containing 1 mg/cm3 of danazol. Three hundred microliters of the co-solvent containing drug were thoroughly mixed in 3000 μL of aqueous phase (producing a degree of supersaturation of ~150). Four 300 μL samples of this dispersion were pipetted into individual wells of a 96-well microplate, which was introduced into nephelometer. The delay between mixing of the solution and the first nephelometer measurement was recorded (within the region of 30–60 s). Blanks were also run in parallel, consisting of propylene glycol, without the dissolved danazol, mixed with the aqueous phase. All measurements were performed at 20°C. The polymer concentrations within the aqueous phase tested were 0.001% and 0.1% w/v. This range was selected based on the approximate physiological concentration of 0.02% w/v obtained when a 1 g tablet/liquid capsule containing 5% w/w polymer is dispersed within 250 mL aqueous phase in the stomach. The drug precipitation was monitored using a NEPHELOstar Galaxy (BMG Labtechnologies) microplate nephelometer by measuring the turbidity of the solutions, with a λ = 635 nm laser. The nephelometer program settings used were: gain = 70, cycle time = 30 s, measurement time per well = 0.30 s, positioning delay 0.5 s; orbital shaking was employed with a width of 2 mm for 5 s at the end of each cycle. The 96-microwell plates made from polystyrene with flat-bottomed wells (NUNC) were used[5].

Precipitation data:

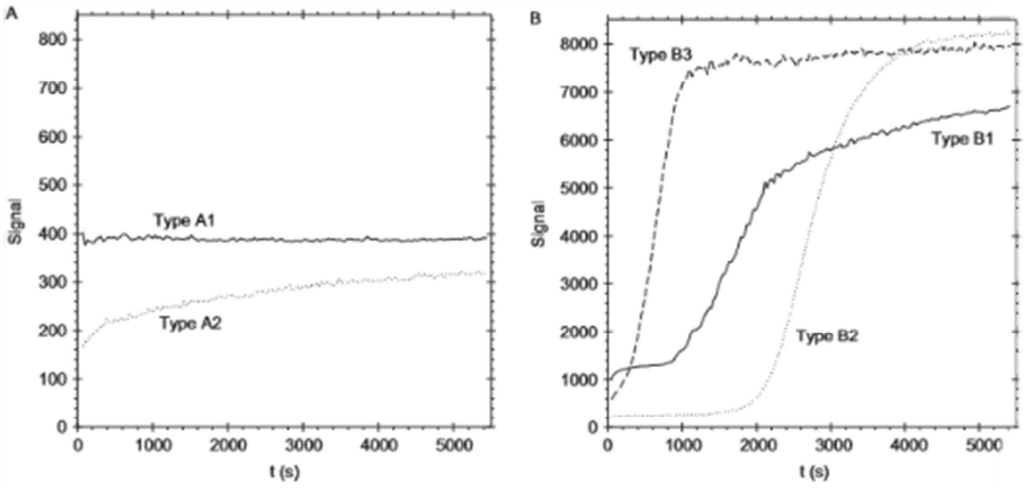


Fig. A) A1 - 0.1 % w/v HPMCAS HF and A2-0.01% w/v HPMC K4M B) B1 - 0.001% w/v,B2 - 0.001% w/v cellulose acetate phthalate and B3 - 0.001% w/v Eudragit L 100-55

RESULTS

All polymers exhibited a log phase in the precipitation process at 0.00 % w/v and a significant decrease of the precipitation rate at all stages. When the concentration of polymer was increased to 0.1% w/v the precipitation was slowed down significantly[5].

CONCLUSION

Drug candidate with low aqueous solubility pose a common product of drug discovery programs. As such drug delivery technologies that can be utilized to support the confident development and marketing of poorly water soluble molecules. In the current review, we have attempted to pull together the known literature describing the interaction of drug molecule with polymers that lead to a stabilization of supersaturation and a reduction in drug precipitation from supersaturated solution[1-3].

The current working hypothesis that support the use of polymeric precipitation inhibitors is that drug supersaturation is stabilized by the presence of drug-polymer interactions and a decrease in the relative capacities of a series of polymeric materials to impede the progress of danazol precipitation from a supersaturated solution. Using this data we propose a number of different modes of drug precipitation and the potential impact of polymeric precipitation inhibitors and identify a group of superiorpolymeric precipitation inhibitors, which are predominately cellulose based. However lack of data and the complexity of the GI environment have preclude definition of these attributes beyond a limited number of specific examples. More detailed studies are required to elucidate these mechanisms in detail, in an effort to define the relationships between drugs and polymers that control stabilization[5].

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