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*Research Article*

# Combined Use of Crystalline Sodium Salt and Polymeric Precipitation Inhibitors to Improve Pharmacokinetic Profile of Ibuprofen through Supersaturation

**Jenna L. Terebetski,[1,2] John J. Cummings,[3] Scott E. Fauty,[4] and Bozena Michniak-Kohn[1,5,6]**

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***Abstract.*** To maximize the pharmacological effect of a pain reliever such as ibuprofen, early onset of action is critical. Unfortunately, the acidic nature of ibuprofen minimizes the amount of drug that can be solubilized under gastric conditions and would be available for immediate absorption upon entry into the intestine. Although the sodium salt of ibuprofen has higher solubility, rapid conversion from the salt to the poorly soluble free acid phase occurs under gastric conditions. Therefore, the combination of the highly soluble sodium salt form of ibuprofen with polymers was evaluated as an approach to prolong supersaturation of ibuprofen during the disproportionation of the salt. Binary combinations of ibuprofen sodium with polymers resulted in the identification of several formulations that demonstrated high degrees and extended durations of supersaturation during *in vitro* dissolution experiments. These formulations included HPMC, polyvinyl pyrrolidone-vinyl acetate copolymer (PVP-VA64), methylcellulose (MC), and hydroxypropyl cellulose (HPC). The *in vitro* supersaturation observed with these ibuprofen-polymer formulations translated to an increase in $C_{max}$ and an earlier $T_{max}$ for the PVP-VA64, MC, and HPC formulations relative to ibuprofen only controls when administered orally to rats under fasted conditions. Based on these observations, combining ibuprofen sodium with polymers such as PVP-VA64, MC, or HPC is a viable formulation approach to prolong supersaturation in the stomach and enable an optimized pharmacokinetic profile *in vivo* where rapid onset of action is desired.

**KEY WORDS:** dissolution; ibuprofen; precipitation inhibitor; pharmacokinetic profile; supersaturation.

## INTRODUCTION

There are many phase and formulation approaches that can be taken to optimize the oral absorption of drugs. One commonly used technique includes the use of a highly soluble salt form of a drug. Since salts are typically thermodynamically stable phases, they can carry minimal risk from a processing and storage perspective [1, 2]. In addition, the higher intrinsic aqueous solubility of the ionized form of the drug may enable more rapid and extensive dissolution compared to the free form of the drug. Unfortunately, the pH gradient of the GI tract may limit the solubility enhancement that is offered by salts. This is especially the case for salts of acidic drugs since initial dissolution of the formulation will occur under the acidic conditions of the stomach. Under these conditions, the salt form of an acidic drug can undergo rapid disproportionation, resulting in a phase change to the neutral free acid and subsequent loss of solubilization [3]. Therefore, the initial boost in solubility associated with the properties of an acidic salt can be lost prior to initiation of absorption.

Despite this risk of disproportionation, there may be opportunities to prolong the supersaturation that is initially achieved by the rapid dissolution of the salt in the stomach by leveraging the use of polymeric precipitation inhibitors to maintain enhanced solubilization above the intrinsic solubility of the neutral free acid drug. Polymeric precipitation inhibitors have a broad use in the maintenance of supersaturation for amorphous dispersions and emulsion systems [4]. The identification of suitable polymers that can inhibit crystallization and extend the dissolution profile of a supersaturated formulation *in vitro* has also led to the identification of formulations that have improved oral bioavailability based on *in vivo* testing [5, 6]. Other research demonstrates that the combination of a salt form of celecoxib can have enhanced supersaturation and increased exposure when combined with polymers and surfactants [7]. In this previous work, the addition of surfactant at concentrations above its critical micelle concentration was required for the maintenance of supersaturation *in vitro*. Therefore, it is hypothesized that a drug with

[1] Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey, USA.
[2] Discovery Pharmaceutical Sciences, Merck Research Laboratories, Kenilworth, New Jersey, USA.
[3] Pharmacokinetics, Pharmacodynamics and Drug Metabolism–Discovery Bioanalytical, Merck Research Laboratories, Rahway, New Jersey, USA.
[4] Safety Assessment and Laboratory Animal Resources–General Toxicology, Merck Research Laboratories, West Point, Pennsylvania, USA.
[5] NJ Center for Biomaterials, Rutgers, The State University of New Jersey, 145 Bevier Road, Life Sciences Bldg. Room 109, Piscataway, New Jersey 08854, USA.
[6] To whom correspondence should be addressed. (e-mail: michniak@biology.rutgers.edu )

surfactant-like properties in its salt form may be able to maintain a prolonged state of supersaturation with the presence of polymer, but without the need for additional surfactant.

For this work, we evaluated the feasibility of prolonging the supersaturation of ibuprofen under simulated gastric conditions by combining the highly soluble sodium salt with various polymers that are pharmaceutically acceptable as per the Handbook of Pharmaceutical Excipients [8]. In order to circumvent the need for a surfactant component in the formulation, ibuprofen sodium was selected based on its known surfactant-like properties [9]. It was hypothesized that formulations that prolonged supersaturation under acidic conditions may increase the $C_{max}$ and provide an earlier $T_{max}$ due to rapid absorption when administered *in vivo*. Therefore, in addition to identifying formulations that enabled supersaturation *in vitro*, the impacts of these formulations on pharmacokinetic parameters were also evaluated *in vivo*. The desired outcome of this work was to identify simple formulations comprised of crystalline drug and polymer blends that could afford rapid onset of action through prolonged supersaturation in the stomach and rapid absorption observed with an increased $C_{max}$ and earlier $T_{max}$, which is of particular interest for a pain reliever such as ibuprofen [10, 11].

## MATERIALS AND METHODS

### Materials

(R/S)-(±)-ibuprofen (free acid) was purchased from Sigma (Sigma-Aldrich, St. Louis, MO, USA) and the (R/S)-ibuprofen sodium dihydrate was purchased from Fluka (Sigma-Aldrich, St. Louis, MO, USA). Pharmacout 603 (hydroxypropyl methylcellulose, HPMC, Shin-Etsu, Tokyo, Japan), Kollidon VA64 (polyvinyl pyrrolidone-vinyl acetate copolymer, PVP-VA, BASF, Florham Park, NJ, USA), Carbopol 974P (Carbomer, polyacrylic acid, Lubrizol, Wickliffe, OH, USA), Plasdone K12 (polyvinyl pyrrolidone, Ashland, Covington, KY, USA), hydroxypropyl methylcellulose acetate succinate (HPMCAS, HF grade, Shin-Etsu, Tokyo, Japan), carboxymethylcellulose sodium salt (CMC Na, Sigma-Aldrich, St. Louis, MO, USA), hydroxypropyl cellulose (HPC, SL grade, Nisso America, Inc. (New York, NY, USA)), methylcellulose (MC, 400 cPs, Sigma-Aldrich, St. Louis, MO, USA), Kollidon 25 (polyvinyl pyrrolidone, Sigma-Aldrich, St. Louis, MO, USA), Soluplus (BASF, Florham Park, NJ, USA), HPMCP 50 (hydroxypropyl methylcellulose phthalate, Acros Organics, Fisher Scientific, Pittsburg, PA, USA), and Klucel EXF (hydroxypropyl cellulose, HPC, Ashland, Covington, KY, USA) were used as polymeric excipients.

Sodium chloride, hydrochloric acid, sodium phosphate monobasic, and sodium phosphate dibasic were purchased from Fisher Scientific (Pittsburg, PA, USA) for use in the preparation of the dissolution buffers. High performance liquid chromatography (HPLC) grade acetonitrile and 85% phosphoric acid were purchased from Sigma-Aldrich (St. Louis, MO, USA) and were used as received. Deionized water was used for all aqueous solutions which were prepared as needed for each experiment.

### 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 12 N 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 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 min, aliquots of the slurries were centrifuge-filtered through a MultiScreenHTS-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 h 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 h 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 h in the system of interest. The duration of supersaturation was the amount of time 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.

### Two-Stage Dissolution of Drug-Polymer Formulations

Based on the supersaturation screening results, polymers that significantly prolonged supersaturation of ibuprofen sodium following addition into SGF were selected for more detailed, larger-scale two-stage biorelevant dissolution experiments. These two-stage dissolution experiments were conducted in triplicate with a USP Apparatus II (paddle) method in a Distek dissolution system 2100C (Distek, Inc., North Brunswick, NJ, USA). In order to differentiate among formulations that may exhibit supersaturation in acidic media, formulations were first subjected to acid stage testing (1 h in 250 mL of SGF at pH 1.8, prepared as described above). During the transition to the buffer stage of testing, 250 mL of 0.115 M sodium dihydrogen phosphate buffer was added to each vessel for a final volume of 500 mL and final pH of 6.8 ± 0.5. The use of buffer rather than fasted-state simulated intestinal media was selected since immediate release formulations of ibuprofen have been previously demonstrated to have rapid dissolution (85% within 30 min or less) in pH 6.8 buffer [12]. The media was

controlled at a temperature of 37.0±0.5°C for the duration of the experiment and the rotational speed of the paddles was 50 rpm. To each dissolution vessel, 550 mg of 1:1 ibuprofen sodium:polymer blends was added (250 mg of ibuprofen, free acid equivalence). This amount of ibuprofen corresponds to a theoretical 1 mg/mL concentration of ibuprofen in the acid phase which represents a 20-fold level of supersaturation assuming an equilibrium solubility of 0.047 mg/mL in SGF (see Table II). At predetermined intervals (5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120, and 180 min), samples were withdrawn, filtered using a 0.45-μm PTFE membrane syringe filter (Thermo Fisher Scientific, Waltham, MA, USA), appropriately diluted, and analyzed for drug concentration using HPLC.

### High Performance Liquid Chromatography (HPLC) Analysis

Sample concentrations for the dissolution test and equilibrium solubility studies were determined using an Agilent 1100 Series HPLC instrument. The HPLC method used an Ascentis Express C18 column (2.7 μm fused-core particle size, 4.6 mm i.d.×100 mm length) at 40°C with a 3-min linear gradient from 10 to 95% mobile phase A (acetonitrile) and 90 to 5% of mobile phase B (0.1% phosphoric acid) followed by a 1-min hold at 95% A. The flow rate was 1.8 mL/min and the injection volume was 5 μL. The samples were analyzed by UV detection at 210 nm. Calibration curves were constructed from peak area measurements using standard solutions of ibuprofen free acid at known concentrations. The retention time of ibuprofen was approximately 3.1 min. Linearity was demonstrated from 0.01 to 0.27 mg/mL ($r^2 \geq 0.999$) and the relative standard deviation of six injections was less than 0.5%. All solubility values will be reported in free acid equivalents.

### *In Vivo* Studies

Pharmacokinetic studies were performed by Merck (West Point, PA, USA). All studies were conducted under a protocol approved by a Merck Institutional Animal Care and Use Committee. Six male Wistar Han rats were assigned to each arm of the study. Oral dosage formulations were dispensed into size 9 hard gelatin capsules (Harvard Apparatus, Holliston, MA, USA). The ibuprofen content in each dose was based on the animal weight range of 280–300 g with a target dose of 25 mg per kilogram (mpk). Rats were fasted overnight prior to each dosing session. Administration of capsule formulations was conducted by placing a filled capsule in the dosing syringe, inserting the delivery tube of the dosing syringe into the animal's esophagus, and then pressing the syringe plunger for placement of the capsule to be complete. Regardless of the location of the capsule in the esophagus, normal peristaltic action enabled the capsule to reach the stomach and then discharge its contents within 10 min. Plasma samples were collected at 0, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h post-dosing. EDTA was added to the samples as an anticoagulant and samples were then stored at −20°C pending analysis of parent drug (ibuprofen) by LC-MS/MS.

### Plasma Extraction and Chromatographic Analysis

Concentrations of ibuprofen in rat plasma were determined by protein precipitation followed by LC-MS/MS analysis. Calibration curves were generated and verified using standard and quality control (QC) samples prepared from an initial weighing of high purity compound. For the analysis of the plasma samples, standard samples were prepared by adding to 50 μL aliquots of control plasma, 10 μL of standard solutions containing 2.5, 5, 10, 25, 50, 250, 500, 1,000, 2,500, 5,000, 10,000, 25,000, 50,000, 75,000, and 125,000 ng/mL target compound in 1:1 acetonitrile:water (*v*:*v*). This yielded standard samples effectively containing 0.5, 1, 2, 5, 10, 50, 100, 200, 500, 1,000, 2,000, 5,000, 10,000, 15,000, and 25,000 ng/mL of target compounds.

For all unknown samples, 50 μL were used from each sample vial for analysis. To all aliquots of standards and QC samples, 10 μL of 1:1 acetonitrile:water were then added. This was followed by protein precipitation with 300 μL of acetonitrile containing 100–200 ng/mL of internal standards (IS) mixture, containing diclofenac-HCl, labetolol-HCl, and alprazolam (Cerillant, Round Rock, TX, USA), with diclofenac used as the IS for analysis. Sample mixtures were then lightly vortex-mixed. After spinning in a centrifuge for 5 min at 4,000 rpm, the supernatants were transferred to clean 96-well plates. The sample mixtures were analyzed by LC-MS/MS.

The LC-MS/MS system consisted of a Thermo Scientific LX2 autosampler equipped with two Transcend System pumps and an Applied Biosystems/MSD Sciex API 5000 mass spectrometer. Chromatographic separation of the analytes was achieved on a Waters Acquity HSS T3 column (2.1× 50 mm, 1.8 μm particle size) in conjunction with gradient conditions and mobile phases A (0.1% formic acid in water) and B (0.1% formic acid in acetonitrile). Total run time was 3.5 min. Mass spectrometric detection of the analytes was accomplished using the Turbo Spray interface operated in the negative ion mode. Analyte response was measured by multiple reaction monitoring (MRM) of transitions unique to each compound.

### Pharmacokinetic Analysis

Data were acquired and integrated by Sciex Analyst 1.5.1 software. Data were processed using Thermo Electron Corporation Watson v7.3. Peak area ratios of analyte to IS were plotted as a function of the nominal concentrations of the analyte. A line of best fit was generated from the curve points using linear regression type. The equation of this line was used to calculate the concentrations in all samples.

The area under the plasma concentration *versus* time curve (AUC) was determined using the Watson software (version 7.3). Toxicokinetic calculation method was performed and $C_{max}$, $T_{max}$, and AUC were reported. Statistical comparisons were performed by independent Student's *t* test ($\alpha = 0.05$). All statistical analysis was performed using SigmaPlot Statistics for Windows version 10.0.

## RESULTS AND DISCUSSION

### Supersaturation Screening

In order to monitor the degree and duration of supersaturation of ibuprofen in the presence of polymers without the variable of polymer dissolution kinetics, the kinetic solubility profile of ibuprofen sodium was evaluated in the presence of pre-dissolved polymers at a 1:1 weight ratio of drug: polymer.

The high polymer loading was selected in order to maximize the potential polymer effect on supersaturation and potentially differentiate among drug:polymer combinations at a fixed ratio. The dissolution profile of the active pharmaceutical ingredient (API) in the absence of polymer was also evaluated under the same conditions in order to differentiate the behavior of ibuprofen sodium disproportionation in SGF from supersaturation influenced by polymer. In the presence of pre-dissolved polymers in SGF (Fig. 1), prolonged supersaturation was observed for 20 min with MC, 60 min with HPMC and HPC-SL, and >120 min with PVP-VA64 and HPC. In addition, an increase in solubility was observed and maintained for 120 min with HPMCAS-HF and Soluplus.

Table I summarizes the degree of ibuprofen supersaturation achieved with pre-dissolved polymers in SGF relative to equilibrium solubility of the same system as well as the duration of supersaturation. 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 h in the system of interest [13]. The duration of supersaturation was the amount of time that the measured concentration of drug in solution remained above the equilibrium solubility of that system.

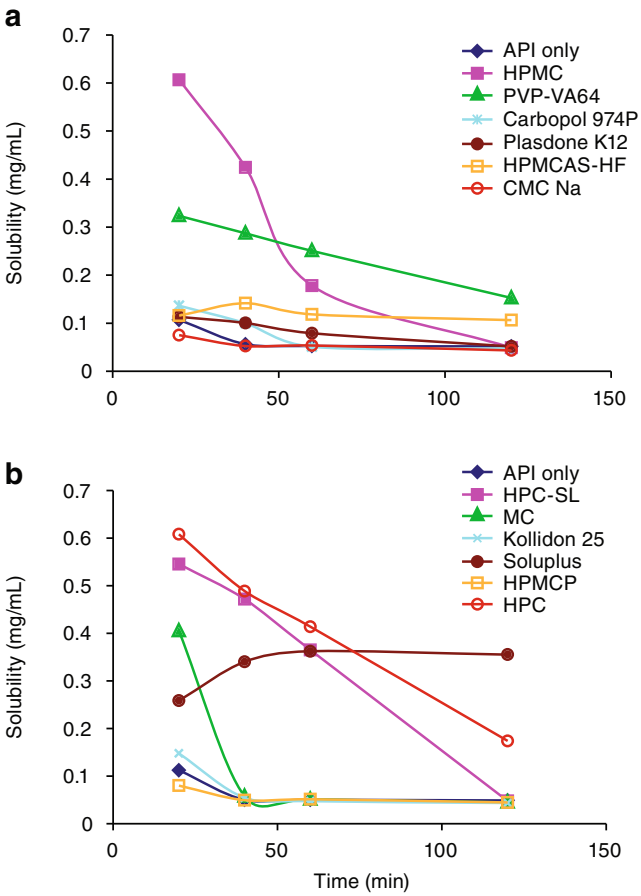


**Fig. 1.** Dissolution profiles of 1:1 ibuprofen sodium: pre-dissolved polymer in SGF at 37°C during supersaturation screen; **a** illustrates dissolution profiles in the presence and absence of HPMC, PVP-VA64, Carbopol 974P, Plasdone K12, HPMCAS-HF, or CMC Na while **b** illustrates dissolution profiles in the presence and absence of HPC-SL, MC, Kollidon 25, Soluplus, HPMCP, or HPC

**Table I.** Influence of Various Polymers on Maximum Degree of Supersaturation of Ibuprofen Following Dissolution of Ibuprofen Sodium in the Presence of pre-Dissolved Polymer in SGF at 37°C

| Polymer | Degree of supersaturation | Duration of supersaturation (minutes) |
|---|---|---|
| API-only | 2.4 | 20 |
| HPMC | 18.5 | 60 |
| PVP-VA64 | 8.0 | >120 |
| Carbopol 974P | 5.0 | 20 |
| Plasdone K12 | 2.2 | 20 |
| HPMCAS-HF | 1.7 | >120 |
| CMC Na | 1.5 | – |
| HPC-SL | 12.6 | 60 |
| MC | 11.2 | 20 |
| Kollidon 25 | 3.0 | 20 |
| Soluplus | 1.4 | >120 |
| HPMCP | 1.4 | – |
| HPC | 12.7 | >120 |

*API* active pharmaceutical ingredient, *HPMC* hydroxypropyl methylcellulose, *PVP-VA64* polyvinyl pyrrolidone-vinyl acetate copolymer, *HPMCAS-HF* hydroxypropyl methylcellulose acetate succinate, *CMC Na* carboxymethylcellulose sodium salt, *HPC-SL* hydroxypropyl cellulose, *MC* methylcellulose, *HPMCP* hydroxypropyl methylcellulose phthalate, *HPC* hydroxypropyl cellulose

In SGF, the highest degrees of supersaturation were observed in the presence of the polymers with the rank order: HPMC>HPC>MC>PVP-VA64. In general, higher degrees of supersaturation were associated with shorter durations of supersaturation. This was expected based on the greater thermodynamic drive toward precipitation at higher supersaturation values. Since equilibration to the crystalline free acid required nucleation and crystal growth, loss of supersaturation could be related to classical nucleation theory. In general, the difference in chemical potential of a supersaturated solution *versus* a saturated solution is the driver for crystallization of the thermodynamically stable crystalline phase. In other words, the driving force for nucleation is dependent on the maximum feasible degree of supersaturation that can be achieved in a system [14–18]. Alternatively, the PVP-VA64 copolymer system that enabled a more moderate degree of supersaturation was also associated with a prolonged duration of supersaturation compared to the other systems, suggesting an extended delay in nucleation and/or crystal growth.

Although supersaturation was observed with the PVP-VA64 copolymer, the two evaluated grades of PVP (Plasdone K12 and Kollidon 25) did not enable any supersaturation of ibuprofen. The average molecular weights of PVP-VA64, Kollidon 25, and Plasdone K12 varied from 45,000–70,000, 28,000–34,000, and 4,000 g/mol, respectively. Although the molecular weight of PVP-VA64 was significantly greater than Kollidon 25, the vinyl pyrrolidone portion of PVP-VA64 accounted for approximately 64% of the mass. Therefore, the average molecular weight attributed to PVP did not differ significantly between PVP-VA64 and Kollidon 25. Likewise, no significant increase in media viscosity was observed when these vinyl pyrrolidone-containing polymers were solubilized in SGF at the 1 mg/mL polymer concentration used in the supersaturation screen. Therefore, the primary difference between PVP-VA64 and PVP was the inclusion of vinyl acetate to the copolymer chain of PVP-VA64, suggesting that the vinyl

acetate moiety was contributing to the mechanism of ibuprofen supersaturation in the presence of PVP-VA64. In addition, PVP-VA64 has previously been reported to be a stronger binder to ibuprofen than PVP based on binding constant determination by affinity capillary electrophoreses (ACE) [19].

There were also several polymers that did not have sufficient solubility for complete dissolution at the target polymer concentration of 1 mg/mL and remained as suspensions, including the carbomer polymer (Carbopol 974) and the enteric polymers (HPMCAS-HF and HPMCP). Due to the lack of gastric solubility of these polymers, they were suboptimal candidates to enable large degrees of supersaturation under acidic conditions as exemplified by the lack of supersaturation observed with Carbopol 974 and HPMCP. In the presence of HPMCAS-HF, a modest two-fold increase in degree of supersaturation was achieved and maintained for the duration of the 120 min dissolution experiment. The ability of HPMCAS to delay crystal growth was hypothesized as the mechanism of supersaturation for this drug-polymer system. Following loss of supersaturation, observations of irregular particle morphology of ibuprofen crystals and amorphous HPMCAS polymer clustered around the crystals were made by optical microscopy (Fig. 2). The different ibuprofen free acid crystal morphologies and reduction in particle size following precipitation in the presence of HPMCAS suggested that adsorption of polymer to the free acid crystal surfaces during precipitation could be modifying the crystal habit and playing a role in delayed crystal growth. Similar observations of crystal habit modification due to varying adsorption of HPMC onto the crystalline faces of hydrocortisone acetate during loss of supersaturation have been reported [20]. Inhibition of crystal growth during nanosuspension stabilization has also been reported by Ghosh *et al.* and attributed to adsorption of HPMC on the surface of the drug due to drug-polymer interactions and steric stabilization [21].

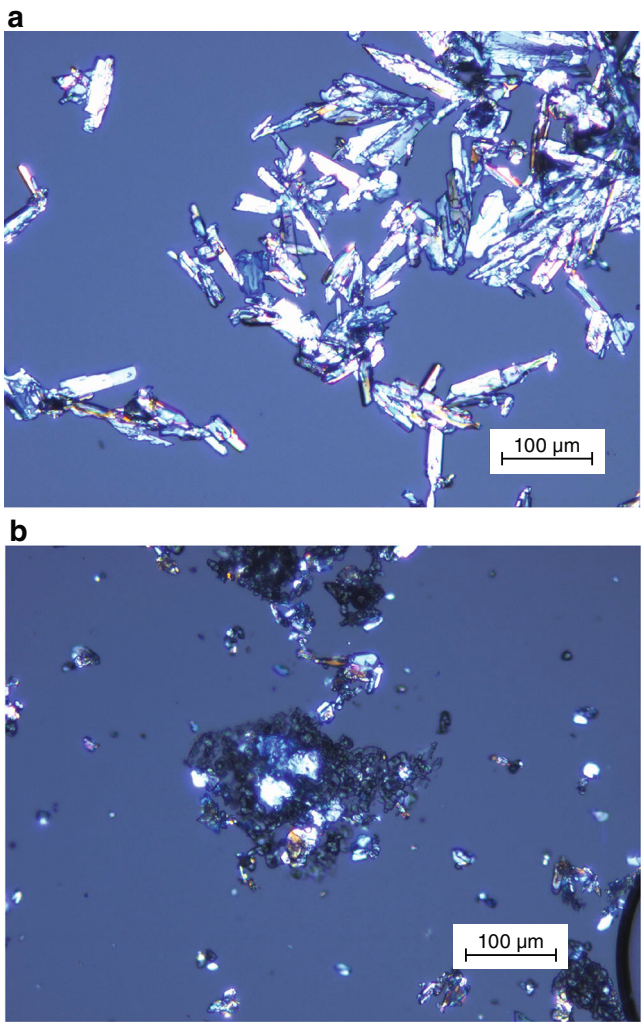


**Fig. 2.** Microscopy following dissolution of ibuprofen sodium in SGF **a** without polymer or **b** with HPMCAS-HF at ×100 magnification

The final polymer system that exhibited solubility enhancement in the supersaturation screen relative to the API-only control was Soluplus. However, it was noteworthy that the solubility of drug in solution increased over time rather than decreased to indicate a loss of supersaturation (Fig. 1b) and no significant degree of supersaturation was observed relative to the equilibrium solubility of the system at 24 h (Table I). In the case of Soluplus, the increased solubilization of ibuprofen is likely associated with an increase in equilibrium solubility of ibuprofen free acid rather than an actual increase in supersaturation (Table II). The solubilizing properties associated with Soluplus have previously been reported [22].

Table II summarizes the 24 h solubility data for ibuprofen with and without polymers in SGF. Since the SGF solubility of ibuprofen in the presence of a specific polymer was measured at ~0.04–0.05 mg/mL for both the free acid and the sodium salt, it was concluded that the ibuprofen sodium salt reached equilibrium as the free acid within the 24-h time period that was evaluated. Conversion of ibuprofen sodium salt to the free acid in SGF was also confirmed by XRPD (data not shown). Therefore, the solubility of ibuprofen slurried with the various polymers was compared to the control samples without polymer to determine whether any polymers significantly increased the equilibrium solubility of the free acid at the 24-h time point.

No appreciable increase in solubility was observed in SGF after 24 h in the presence of any polymer, except Soluplus. Since the solubility of ibuprofen free acid in the presence of Soluplus was in the same region as the ibuprofen sodium salt slurry with Soluplus, it was not believed that ibuprofen sodium was stabilized in this Soluplus system. Therefore, the prolonged dissolution profile of ibuprofen in the presence of Soluplus (Fig. 1b) was associated with ibuprofen free acid reaching a thermodynamically more soluble state rather than maintaining prolonged supersaturation. This increase in equilibrium solubility is likely due to the polyethylene glycol moiety incorporated into the Soluplus copolymer graft.

### Two-Stage Dissolution

Based on the supersaturation screen, polymers that were shown to increase degree and duration of ibuprofen supersaturation following the addition of the ibuprofen sodium salt to SGF were further evaluated by running a biorelevant two-stage dissolution experiment. The polymers evaluated in this experiment included HPMC, PVP-VA64, MC, and HPC. Although HPC-SL also demonstrated an increase in degree and duration of supersaturation, this polymer grade only differed from the other HPC polymer in terms of viscosity. Since increased viscosity can be a contributing factor to enable

**Table II.** Influence of Various Polymers on Solubility of Ibuprofen Following Equilibration in SGF Containing 1 mg/mL Polymer at 37°C

| | Ibuprofen sodium salt | | Ibuprofen free acid | |
|---|---|---|---|---|
| Polymer | Solubility at 24 h (mg/mL±SD) | Final pH of Media | Solubility at 24 h (mg/mL±SD) | Final pH of media |
| API-only | 0.046±0.002 | 2.02 | 0.047±0.000 | 1.82 |
| HPMC | 0.033±0.001 | 1.86 | 0.043±0.005 | 1.80 |
| PVP-VA64 | 0.040±0.002 | 2.10 | 0.043±0.005 | 1.76 |
| Carbopol 974P | 0.027±0.006 | 1.89 | 0.036±0.004 | 1.76 |
| Plasdone K12 | 0.051±0.004 | 2.13 | 0.049±0.001 | 1.72 |
| HPMCAS-HF | 0.069±0.039 | 1.78 | 0.045±0.001 | 1.75 |
| CMC Na | 0.049±0.002 | 2.14 | 0.042±0.012 | 1.81 |
| HPC-SL | 0.043±0.001 | 2.20 | 0.048±0.001 | 1.85 |
| MC | 0.036±0.001 | 2.10 | 0.047±0.001 | 1.82 |
| Kollidon 25 | 0.050±0.005 | 2.13 | 0.049±0.002 | 1.85 |
| Soluplus | 0.185±0.048 | 2.17 | 0.206±0.139 | 1.81 |
| HPMCP | 0.057±0.006 | 2.13 | 0.054±0.003 | 1.83 |
| HPC | 0.048±0.004 | 2.19 | 0.051±0.003 | 1.84 |

*API* active pharmaceutical ingredient, *HPMC* hydroxypropyl methylcellulose, *PVP-VA64* polyvinyl pyrrolidone-vinyl acetate copolymer, *HPMCAS-HF* hydroxypropyl methylcellulose acetate succinate, *CMC Na* carboxymethylcellulose sodium salt, *HPC-SL* hydroxypropyl cellulose, *MC* methylcellulose, *HPMCP* hydroxypropyl methylcellulose phthalate, *HPC* hydroxypropyl cellulose

supersaturation [4], only the higher viscosity grade of HPC was included in the two-stage dissolution studies. In addition, the Soluplus polymer that enhanced intrinsic solubility of ibuprofen was also included in the two-stage dissolution screen. Although an increase in solubilization of ibuprofen was observed in the presence of HPMCAS-HF during the 2-h supersaturation screen, the enteric properties of this polymer make it an undesirable candidate to study supersaturation for an immediate release formulation.

During the two-stage dissolution experiment, dissolution of solid blends of ibuprofen sodium with polymer at a one-to-one weight ratio were compared to the dissolution profiles of ibuprofen sodium or ibuprofen free acid alone. Solid blends were selected for this experiment in order to factor in the need for polymer dissolution under biorelevant conditions using formulation compositions that would be similar to those used in *in vivo* studies. The first stage of the dissolution experiment included the addition of solid blends or API-only to SGF. The addition of 250 mg ibuprofen (free acid equivalents) to 250 mL of SGF corresponded to a theoretical 1 mg/mL concentration of ibuprofen in the acid phase, which represented a 20-fold level of supersaturation assuming an equilibrium solubility of 0.047 mg/mL in SGF (Table II). These conditions were intended to differentiate formulations in terms of supersaturation performance. Following 1 h under acidic conditions, the media was adjusted to pH 6.8 with the addition of 250 mL of phosphate buffer to emulate transition to the intestine where complete dissolution of the drug was anticipated based on previously published solubility data for ibuprofen [12].

Dissolution of ibuprofen in the presence and absence of polymers during the acid stage is illustrated in Fig. 3. When comparing the dissolution of free acid to sodium salt, a more rapid rate of dissolution was associated with the higher solubility sodium salt form. The initial solubility at the 5-min time point was 0.16 mg/mL, which is 3.2-fold higher than the equilibrium solubility of ibuprofen. The solubility of the sodium salt slowly decreased toward equilibrium over the 1-h time-course for SGF dissolution likely due to disproportionation and precipitation of the free acid. Alternatively, the free acid exhibited significantly slower initial dissolution kinetics and did not approach the equilibrium solubility of 0.047 mg/mL until the 60-min time point.

In the presence of the various polymers, the dissolution of the sodium salt exhibited varying behaviors. The dissolution of ibuprofen sodium in the presence of Soluplus was similar to the dissolution profile of the sodium salt without polymer. Although an increase in equilibrium solubility of ibuprofen was observed in the presence of Soluplus (Table II) and solubility enhancement was initially observed at the 20-min

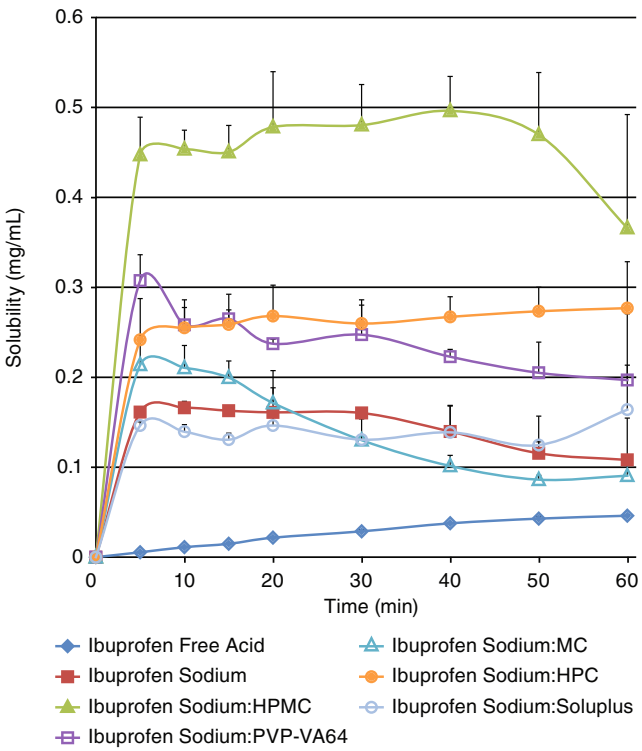


**Fig. 3.** Dissolution of ibuprofen free acid and ibuprofen sodium salt with the presence or absence of polymer in SGF at 37°C

time point during the supersaturation screen with pre-dissolved polymer (Fig. 1b), the slow rate of dissolution associated with the large granules of Soluplus prevented the polymer from providing significant solubility enhancement during this 1 h SGF dissolution experiment since full dissolution of Soluplus had not occurred within that period of time. Likewise, the slow dissolution kinetics observed with MC was believed to limit the degree of supersaturation of ibuprofen observed during this acid stage of the two-stage dissolution experiment. In other words, not enough polymers dissolved to provide maximum supersaturation behavior prior to ibuprofen free acid crystallization. Although a 4-fold increase in degree of supersaturation was observed with ibuprofen sodium in the presence of MC at the 5-min time point, loss of supersaturation relative to the sodium salt alone was observed within 20 min. This short duration of supersaturation also trended with data obtained from the high-throughput supersaturation screen (Fig. 1b); however, a significantly higher degree of supersaturation was observed with MC during the initial supersaturation screen where polymer was pre-dissolved.

A 4- to 6-fold increase in degree of supersaturation was observed and maintained for the duration of the 1-h dissolution experiment in SGF when ibuprofen sodium was in the presence of HPC or PVP-VA64. A 9-fold increase in degree of supersaturation was observed when ibuprofen sodium was in the presence of HPMC with loss of supersaturation beginning at 60 min. Overall, there was good correlation observed between the acid stage of the dissolution experiment, where blends of ibuprofen sodium with polymer were used, and the supersaturation screening results, where pre-dissolved polymers were evaluated.

Within 30 min following pH adjustment to pH 6.8, >85% of ibuprofen dissolution was observed for all formulations, except for the formulation containing MC (Fig. 4).

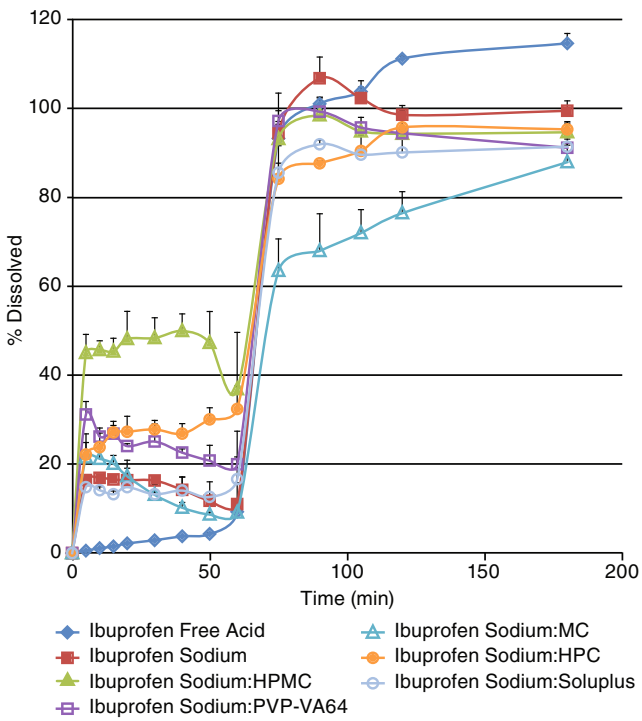


**Fig. 4.** Two-stage dissolution profile of ibuprofen with the presence or absence of polymer in SGF for 60 min followed by pH adjustment to pH 6.8 at 37°C

Therefore, formulations containing ibuprofen alone or with HPMC, HPC, PVP-VA64, or Soluplus met the criteria for an immediate release formulation containing ibuprofen [12]. For the ibuprofen sodium:MC formulation, 2 h of stirring at 50 rpm was required for 85% dissolution of ibuprofen. During the 2-h dissolution experiment, visual observations of slow MC wetting and lack of uniform dispersion within the vessel was noted. This suggested that the delayed dissolution of ibuprofen from the MC blends was related to slow MC dissolution. The delayed dissolution of ibuprofen was likely attributed to the low solubility and high viscosity associated with the selected grade of 400 cPs MC. Any ibuprofen from the drug:polymer blend that did not disperse and dissolve prior to initial swelling of the MC polymer was likely trapped in the MC agglomerates. This drug entrapment and the associated slow wetting of MC can explain why ibuprofen exhibited a delayed release profile during this dissolution experiment. Modified drug release due to slow erosion of cellulosic polymers has been previously described [23, 24]. In order to more rapidly dissolve the polymer, a lower viscosity grade of MC or an increase in the paddle speed should be considered.

## *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. The use of capsules also eliminated the potential for suspension inhomogeneity and provided a direct translation to the previously conducted two-stage biorelevant dissolution experiments where solid blends were evaluated. In addition to the drug and polymer formulations, ibuprofen sodium and ibuprofen free acid alone were also dosed for comparison. 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 [25].

The average plasma concentrations of various formulations of ibuprofen following oral administration to rats were compared in Fig. 5 below, with more details found in Fig. 6. 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-min 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

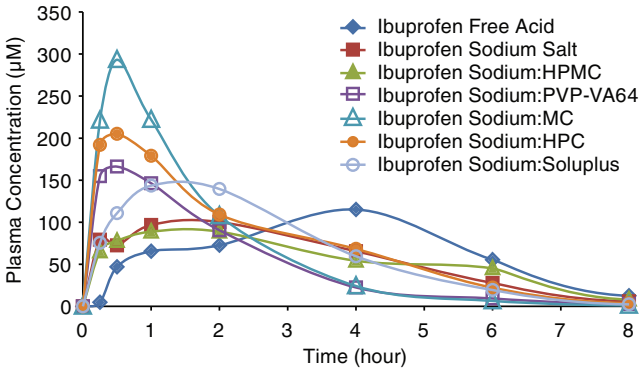


**Fig. 5.** Mean plasma concentration of ibuprofen following oral administration in Wistar Han rats ($n$=6) under fasted conditions at a dose of 25 mpk

$T_{max}$ 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 (Fig. 3).

A head-to-head comparison of ibuprofen sodium to free acid (Fig. 6a) showed that the higher solubility salt form had an initially faster rate of absorption when compared to the free acid, with a statistically significant increase in plasma concentration observed for the ibuprofen sodium formulation at 15 min. However, the ibuprofen sodium profile exhibited a trend toward a decrease in plasma concentration with the 30-min time point in comparison to the 15-min time point. Since complete gastric emptying from the stomach of a fasted rat takes 1 h [26, 27], this decrease in plasma concentration corresponded to an anticipated phase change of the sodium salt to the free acid during transit through the stomach. The need for re-dissolution of the free acid may explain why the $T_{max}$ of ibuprofen sodium did not differ significantly from the $T_{max}$ of the free acid formulation (Table III).

When comparing the pharmacokinetic parameters of ibuprofen in various polymer-containing formulations to the control ibuprofen sodium and ibuprofen free acid formulations, significant differences in $C_{max}$ and $T_{max}$ were observed (Table III). In general, statistically significant increases in $C_{max}$ were observed with the PVP-VA64, MC, HPC, and Soluplus formulations along with significant decreases in $T_{max}$ when compared to the sodium salt control formulation. Alternatively, no significant changes in AUC were observed with any systems, except when comparing the AUC of ibuprofen free acid to the formulation of ibuprofen sodium:PVP-VA64. Due to the absence of intravenous pharmacokinetics (PK) data, it is difficult to determine whether maximum bioavailability was

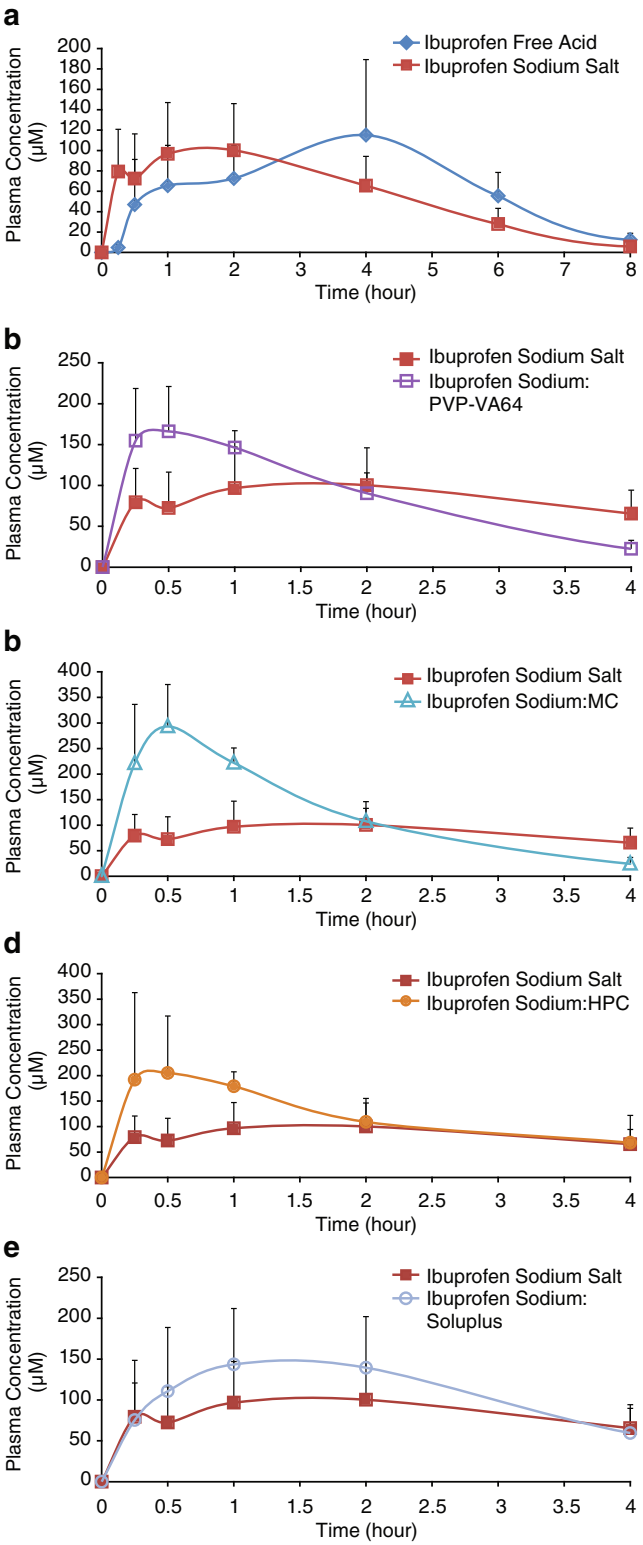


**Fig. 6.** Mean (±SD) plasma concentration of ibuprofen following oral administration in Wistar Han rats ($n$=6) under fasted conditions at a dose of 25 mpk. Figures compare the ibuprofen sodium salt profile to **a** ibuprofen free acid, **b** 1:1 ibuprofen sodium:PVP-VA64, **c** 1:1 ibuprofen sodium:MC, **d** 1:1 ibuprofen sodium:HPC, and **e** 1:1 ibuprofen sodium:Soluplus

**Table III.** Ibuprofen Pharmacokinetic Parameters Following Oral Administration to Wistar Han Rats at a Dose of 25 mpk

| Formulation | $AUC_{0-24\ h}$ (μM×h) | $C_{max}$ (μM) | $T_{max}$ (h) |
|---|---|---|---|
| Ibuprofen free acid | 541±132 | 136.2±61.1 | 2.6±1.6 |
| Ibuprofen sodium | 450±76 | 130.6±25.2 | 1.6±1.4 |
| 1:1 Ibuprofen sodium:HPMC | 434±91 | 115.3±36.4 | 2.6±2.1 |
| 1:1 Ibuprofen sodium:PVP-VA64 | 377±31[a] | 197.3±50.5[b] | 0.50±0.27[a] |
| 1:1 Ibuprofen sodium:MC | 491±88 | 301.0±79.0[a, b] | 0.63±0.31[a] |
| 1:1 Ibuprofen sodium:HPC | 556±117 | 252.9±115.2[b] | 0.58±0.34[a] |
| 1:1 Ibuprofen sodium:Soluplus | 497±94 | 199.8±43.1[b] | 1.4±0.7[a] |

*AUC* area under the curve, *HPMC* hydroxypropyl methylcellulose, *PVP-VA64* polyvinyl pyrrolidone-vinyl acetate copolymer, *MC* methylcellulose, *HPC* hydroxypropyl cellulose
[a] significant difference ($P<0.05$) compared to free acid
[b] significant difference ($P<0.05$) compared to sodium salt

already attained with the ibuprofen free acid formulation which could explain the lack of changes in AUC among formulations. Comparisons of the plasma concentration profiles for the ibuprofen sodium formulations with polymer *versus* ibuprofen sodium control demonstrated statistically significant increases in exposure at the 0.25-h time point with PVP-VA64 or MC (Fig. 6b, c) and at the 0.5- and 1-h time points with PVP-VA64, MC, or HPC (Fig. 6b, c, d, respectively). These differences in plasma concentrations also correlated with statistically significant differences in $C_{max}$ and $T_{max}$ of these formulations that were described in Table III. Significant reductions in plasma concentrations were also observed with later time points for the polymer-containing formulations *versus* the ibuprofen controls which explain the lack of an AUC increase with formulations that enabled earlier $T_{max}$ and higher $C_{max}$ profiles.

The inclusion of polymers in the ibuprofen sodium formulations contributed to changes in the PK profiles relative to the sodium salt alone for several systems. Increases in the $C_{max}$ were observed in the presence of PVP-VA64 (Fig. 6b), MC (Fig. 6c), and HPC (Fig. 6d) when compared to ibuprofen sodium alone. In addition, these formulations also had an average $T_{max}$ of 0.5–0.6 h which is significantly shorter than the ibuprofen free acid formulation (Table III). The early boost in ibuprofen plasma exposure following oral administration was believed to be directly linked to the ability of the polymer to prolong supersaturation under gastric conditions following rapid dissolution of ibuprofen sodium, as demonstrated in the *in vitro* dissolution studies. This *in vivo* profile also correlated with the *in vitro* dissolution profiles previously described in Fig. 3. A comparison of degree of supersaturation achieved during SGF dissolution of ibuprofen sodium-polymer blends to *in vivo* $T_{max}$ values in Table IV highlights the correlation between supersaturation and faster oral absorption in the presence of PVP-VA64, MC, and HPC. Similar correlations between *in vitro* supersaturation and improved exposure *in vivo* have been previously reported for amorphous solid dispersions [28–31].

The Soluplus formulation had a significantly higher $C_{max}$ compared to ibuprofen sodium (Table III); however, the broad range for the $T_{max}$ of this formulation made this difference more difficult to observe in Fig. 6e. The increase in $C_{max}$ and earlier $T_{max}$ relative to the ibuprofen free acid formulation was driven by the ability of Soluplus to increase the intrinsic solubility of ibuprofen; however, the slow rate of polymer dissolution minimized the ability of Soluplus to have a significant impact on the AUC of this formulation in comparison to the ibuprofen control arms during the time-course for absorption. This observation correlated with the two-stage *in vitro* dissolution profile where no significant differentiation between ibuprofen sodium with and without Soluplus was noted (Fig. 3).

Although a correlation between supersaturation in SGF and early absorption *in vivo* was noted for the PVP-VA64, MC, and HPC formulations, this was not the case for the ibuprofen sodium:HPMC formulation (Table IV). No significant difference in the ibuprofen PK profile with the inclusion of HPMC was noted in comparison to ibuprofen sodium alone. This suggested that the presence of the polymer was not affording any supersaturation in the stomach following oral administration to rats. This was contrary to the *in vitro* dissolution screen in which the presence of HPMC afforded the highest degree of

**Table IV.** Comparison of Degree of Ibuprofen Supersaturation Achieved during SGF Dissolution of Solid Drug-Polymer Blends to Pharmacokinetic Parameters Following Oral Administration to Wistar Han Rats at a Dose of 25 mpk

| Formulation | Degree of supersaturation | $T_{max}$ (h) |
|---|---|---|
| Ibuprofen free acid | – | 2.6±1.6 |
| Ibuprofen sodium | 3.5 | 1.6±1.4 |
| 1:1 Ibuprofen sodium:HPMC | 13.5 | 2.6±2.1 |
| 1:1 Ibuprofen sodium:PVP-VA64 | 7.7 | 0.50±0.27[a] |
| 1:1 Ibuprofen sodium:MC | 5.9 | 0.63±0.31[a] |
| 1:1 Ibuprofen sodium:HPC | 5.4 | 0.58±0.34[a] |
| 1:1 Ibuprofen sodium:Soluplus | 0.8 | 1.4±0.7[a] |

*AUC* area under the curve, *HPMC* hydroxypropyl methylcellulose, *PVP-VA64* polyvinyl pyrrolidone-vinyl acetate copolymer, *MC* methylcellulose, *HPC* hydroxypropyl cellulose
[a] significant difference ($P<0.05$) compared to free acid

supersaturation for the 1-h acid stage of the experiment relative to the other polymers evaluated in this experiment (Fig. 3). A possible explanation may be that HPMC was enabling supersaturation *via* a mechanism that was different than the mechanism(s) that were driving supersaturation of ibuprofen in the presence of PVP-VA64, HPC, or MC, which may explain the deviation between the *in vitro* and *in vivo* data with this specific formulation. Efforts are ongoing to elucidate the mechanism by which each of these polymers is prolonging supersaturation during *in vitro* dissolution.

## CONCLUSIONS

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 [7]. 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. Since the most substantial increase in $C_{max}$ was achieved in the presence of MC, this polymer would be prioritized for additional evaluation. This was also the only formulation that exhibited a statistically significant increase in $C_{max}$ compared to ibuprofen free acid control, as well as the ibuprofen sodium control. The optimized PK achieved with the MC formulations *versus* the ibuprofen free acid control, which has been used historically, provides an opportunity to conduct additional studies to probe the impact of PK profile on pharmacology *in vivo*. 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 the pharmacokinetic profile of a drug.

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