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Improving the Precision of Ibuprofen Free Acid and Its Salts in Vitro Dissolution Assays

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ABSTRACT
Researchers have questioned the predictive potential of in vitro dissolving tests for BCS class 2 weak acids utilizing the Bio pharmaceutics Classification System (BCS) as an experimental design to predict in vivo bioequivalence results. As a potential strategy for guaranteeing the discriminative capability of the in vitro dissolving techniques, this study examined the influence of buffer concentration media. Various salt forms of ibuprofen, as well as the free acid, were used to evaluate this method. In order to improve the discriminative power of the in vitro dissolution tests, the concentration of buffers used to prepare media that mimic intestinal conditions was adjusted to match that of bicarbonate buffer, the most common species of buffer in living organisms, so that both sets of samples reached the same surface pH (pH0). In order to enhance the resemblance to the in vivo findings, a two-stage test was combined with a pretreatment at an acidic pH to mimic the circumstances in the stomach. In order to more accurately represent the in vivo performance of the different formulations, the 2-stage test allowed for a more physiologically realistic accounting for variations in disintegration.

Introduction

Numerous drug regulatory agencies' legislative frameworks have included the scientific concepts of the Bio pharmaceutics Classification System (BCS) since 1995.1- 4 The opportunity to offer regulatory relief for the registration of oral solid immediate-release formulations containing BCS classes 1 and 3 drugs has been widely agreed upon, but it does not appear to be easy to extend the BCS-based bio waiver to certain BCS class 2 drugs. Despite the fact that from 2006 to 2015, the World Health Organization (WHO) advised against conducting in vivo bioequivalence (BE) studies on certain weakly acidic compounds that are poorly soluble but highly permeable. These compounds must meet the "rapid dissolution" criteria at pH 6.8, have a dose number of ≦1, and achieve similar dissolution to the comparator product at pH 1.2, 4.5, and 6.8.2 Due to a lack of evidence, this idea was not adopted by many other regulatory bodies, and the World Health Organization (WHO) has recently recanted its stance in its most recent BE guidelines.5

To clarify how scientists generate hypothesis in his seminal 1959 work, Popper6 built on Sir Francis Bacon's inductive empiricism approach. A 2006 conjectural hypothesis in the BCS-based bio waiver area at the WHO postulated that weak acids with a high permeability and limited solubility may dissolve quickly in the intestines, leading to complete absorption. From then, the BCS-based bio waiver for these drugs was constructed. Like the "all swans are white" paradigm, the World Health Organization (WHO) idea cannot be conclusively supported by any number of favorable correlations between in vitro disintegration data and in vivo BE studies. But one bad example, the "black swan," shows that the idea can't be true.6,7 Ibuprofen is a classic example of a BCS class 2 weak acid. The World Health Organization (WHO) proposed doing BE studies in vitro instead of in vivo, using the experimental dissolution conditions suggested by the regulatory BCS guidelines. These conditions include 50 mm phosphate buffer at pH 6.8, stirred at 75 rpm with a paddle apparatus. However, this theory is now in question.8,9 Using pharmacopoeia experimental conditions for in vitro dissolution tests of oral solid immediate-release formulations containing BCS class 2 drugs has not been found to aid in the diagnosis of a BE or non-BE. These tests are intended for quality control and to release the entire dosage form's worth of drug.10

Continuing with the 2006 theory of poorly soluble but highly permeable weak acids, the small intestine is the primary site of absorption. Therefore, it stands to reason that a drug product should dissolve quickly and identically to the reference formulation under intravenous conditions if the acid in question is a highly permeable BCS class 2 weak acid that is highly soluble at pH 6.8. This remark makes it clear that the hypothesis relies on two things: first that the substance must have high solubility at pH 6.8, which would rule out the possibility of solubility-limited absorption, and second, that in vitro dissolution conditions must be used to simulate the luminal milieu in vivo. The solubility definition in BCS guidelines is quite conservative because it is measured using plain buffers. On the other hand, for poorly soluble ionizable drugs, the current concentration of total phosphate buffer (e.g., 50 mm) used in BCS-based dissolution media is not considered bio relevant enough.12-16 The experimental condition that would correspond to the surface pH (pH0) of dissolving ibuprofen particles in bicarbonate buffer, which is at pH 6.7 and the most common buffer species in the body, would be 50 mm phosphate buffer, and the projected ibuprofen flow would be 6.5 times quicker than 5 mm phosphate buffer. The number of Considering the bio relevance issue with the current BCS-based dissolution media, it is unclear if Alvarez et al.8 and Shohin et al.9 saw actual "black swans" or just "black swans in monochrome negative pictures" when applied to BCS class 2 weakly acidic compounds whose dissolution process is better described by a simultaneous dissolution and chemical reaction model. To rephrase, is the proposed in vitro dissolving technique flawed or is the conjectural hypothesis for BCS class 2 weak acids incorrect? The findings reported by Krieg, who conducted dissolving experiments in bicarbonate buffer with the identical batches of ibuprofen pills used by Alvarez et al.8,15, lend credence to the second idea. In addition to noting that the T formulations had a noticeably slower dissolving rate compared to the R formulations, the f2 values were less than 50, which confirmed a good agreement between the in vitro and in vivo findings, as predicted by the 90% confidence interval for Cmax.15

Here, we sought to determine if, by replacing 50 mM of phosphate buffer with 5 mM, the in vitro BCS-based dissolution methods would be more discriminating, able to predict the luminal fate of BCS class 2 weak compounds, and, ultimately, lead to a revised theory based on more bio relevant dissolution conditions. Since ibuprofen free acid (IBU-H) and its salts are known to have significantly different absorption rates, the purpose of this study was to determine if the present or revised in vitro dissolving conditions would be more effective in differentiating between the two formulations.19-22

MaterialsandMethods

DrugSubstances

The German company Caesar & Lorentz GmbH (Hilden) was the source of the IBU-H (lot 13105125). The medication Ibuprofen sodium dehydrate salt (IBU-Na; lot BCBM8701V) was acquired from SigmaeAldrich in Schlndorf, Germany. Molecule GmbH of Munich, Germany, was contacted in order to get ibuprofen lysinate (IBU-Lys; lot 210741). We were unable to locate ibuprofen alginate in its crystalline form (IBU-Arg) for sale. It was not feasible to replicate the current patented method for synthesizing IBU-Arg, as previously described by another research group23.24 As mentioned before, the outcome was a solution that looked like yellow oil, which made it impossible to conduct research on the solubility and dissolution of the active pharmaceutical ingredient (API) IBU-Arg.

DrugProducts

Dolormin 342-mg or dispersible tablets (lot EDL2E00; McNeil GmbH & Co. oHG, Neuss, Germany), Nurofen Express 256-mg coated tab-lets (lot BH731; Reckitt Benckiser Healthcare Limited, Hull, UK), and Spidufen 770-mg granulate (lot 332821; Zambon Switzerland Ltd, Cadempino, Switzerland) were among the pharmaceutical items that were examined.

ChemicalsandReagents

The following components were acquired from Merck KGaA in Darmstadt, Germany: triethylamin (lot 51316991), citric acid monohydrate (lot K91366644), di-potassium monohydrate phosphate (lot A368601), and high-performance liquid chromatography grade acetonitrile (lot 38994280). Merck Schuchardt OHG of Hohenbrunn, Germany, supplied the maleic acid (lot 036) and monosodium dihydrogen phosphate (lot 746). We bought the following from VWR Chemicals in Darmstadt, Germany: 100% acetic acid (lot 13B150522), sodium hydroxide (number 09D090020), 85% orthophosphor acid (lot 13K220514), 37% hydrochloric acid (lot 13L100505), and sodium acetate (lot 14B240013).

How Soluble Substances Dissolve Composition of Media

You may find a summary of the media compositions used in this work in Table 1.

Ibuprofen pHmax Estimation

The equation for calculating the maximum pH at which both ionized and unionized species coexist at saturation, which is pK is derived from the equations that describe the total solubility of weak acids in regions 1 and 2 of pH-solubility profiles. This equation was also reported by Bogardus and Blackwood for weak bases.

Equation (pKa + log S0) for pHmax

where S0 is the intrinsic solubility and Ksp is the salt's solubility product, which is considered to equal the square of the salt's solubility without extra counter ions.

Checking the Solubility of an Equilibrium

To create saturated solutions at pH 1.2, 4.5, and 6.8, 3 mL of 0.063 N HCl, acetate buffer, or phosphate buffer (McIlvaine) was added to the amounts of solid IBU-H that were determined to provide a 30% excess over the reported equilibrium solubility27 in each of the evaluated media. The vials were made by What man GmbH, Dassel, Germany, and used for this purpose. Triplicate or quintuplicate preparation was used for samples where considerable variability necessitated it. The vials were kept in an incubator set at 37 ± 1◦C, gently shook to eliminate air bubbles, and then sealed with the Uniprep lid. The Uniprep vials' built-in plunger was used to filter the dispersions over a 0.45 mm polytetra- flour ethylene membrane after 12, 16, and 24 hours. Mobile phase was added to filtered samples with a pH of 6.8 until they were diluted to a concentration within the calibration range of 0.025-2 mg/mL.

Quantifying the Rate of Solubility

It is possible that the salts' typically increased dissolving rate may cause them to seem more soluble on physiologically

Table1 MediaComposition

Composition(mM)	HCl	AcetateBuffer	McIlvaineBuffer	PhosphateBuffer			MaleateBuffer
Hydrochloricacid	63/10	e	e	e	e	e	e
Aceticacid	e	28	e	e	e	e	e
Sodium acetate	e	22	e	e	e	e	e
Citricacid	e	e	23.5	e	e	e	e
Monohydratephosphate	e	e	153	e	e	e	e
Dihydrogenphosphate	e	e	e	50	13.5	5.0	e
Sodium hydroxide	e	e	e	12	3.2	1.2	12.3
Maleicacid	e	e	e	e	e	e	7.0
Sodiumchloride	e	e	e	45.5	90.8	101.3	97.6
pH	1.2/2.0	4.5	6.8	6.8	6.7	6.7	6.7

Relevant timescales,[28] we also investigated the ibuprofen salt soul-abilities up to 4 h. All experiments were also carried out using thepreviouslydescribedUniprepmethod.Asithasbeenreportedthatapparentsolubilityseemstodependont heexcessofanalyteaddedto the medium,[29,30]we investigated different nominal concentrate-ionsranging from thatusedforIBU-Hexperiments up to amountsofthe saltsequivalentto40 mgofibuprofenper milliliterofthesolubilitymedium.Foreachapparentsolubilityexperiment,asetof$n$=3vials was used. Filtered samples at pH 6.8 were further diluted inmobilephase,to fall withinthecalibrationrange(0.025-2 mg/mL).

SurfaceActivityProfiling

The tests and calibration for surface activity profiling (SAP) were conducted in accordance with the methods previously detailed by Petereit et al.31 at a nutshell, 3. mL of McIlvaine buffer pH 6.8 was added to the Uniprep vials containing IBU-H, IBU-Na, and IBU-Lys at a ratio of 40 mg/mL of ibuprofen (zz195 mM). After a day of sitting at room temperature, the vials were placed on an orbital shaker. After 4 hours, the pH of the whole solution was adjusted to 6.8 if needed. Use disposable 96-well plates (lot 300148; Kibron Inc., Helsinki, Finland) to construct a dilution series of 10 analyte concentrations in McIlvaine buffer. A multichannel microtensiometer, namely the Delta 8 from Kibron Inc., was used to measure the surface pressure. The technology is built upon an adaptation of the traditional Du Nuoy ring method that measures the maximum draw force of the surface tension using microbalances and tiny needles.31,32 years Finding out whether a critical micelle concentration (CMC), represented by a plateau in the surface pressure profile, has been attained was the primary goal of a simplified analysis of the ensuing Gibbs adsorption isotherms.

Analysis of Dissolution

Using a calibrated USP 2 dissolution test equipment (Erweka DT 80, Heusenstamm, Germany) with 500 mL of each medium, all dissolution experiments were conducted at 37 ± 0.5◦C and 75 rpm. At5,10,15,20,30, and 45 minutes, samples were taken for each dissolution test. In tests of the dissolution of the pure APIs of IBU-Na and IBU-Lys, earlier sample periods ranging from 2 to 5 minutes were also used. In order to simulate the environment of the upper small intestine, IBU-H and its salts were dissolved in phosphate and maleate buffers utilizing reduced total buffer concentrations at pH 6.7.33 in an in vitro experiment. By titrating with NaOH 2N (for IBU-H) or HCl 2N (for IBU-Arg), the pHbulk was maintained at 6.70 ± 0.05. A 5-milliliter glass syringe was used to manually draw samples. It was attached to a 10-millimeter polyethylene cannula filter (Erweka GmbH) and a stainless steel sampling cannula. Using a glass syringe, 5 mL of medium was withdrawn and filtered through a 0.45-mm polythene filter (Rezist 30; GE Healthcare UK Ltd., Buckinghamshire, UK) at each sample interval. 5 mL of new, prewarmed medium was then added.
such that the capacity remains 500 mL. Triplicates of each dissolution test were performed.

"Dumping" Analyze

The search for a more discriminative in vitro experimental condition may be skewed if only dissolution at intestinal pH is used, as traditional 1-stage dissolution testing does not take into consideration the gastric compartment, where dosage form disintegration typically occurs before reaching the proximal small intestine. To further simulate the in vivo process, we used a simplified 2-compartment technique, namely an in vitro "dumping" test. To mimic the stomach compartment, tablets with IBU-H, IBU-Na, or IBU-Lys were pre-dissolved in 20 mL of 0.01 N HCl and kept on an orbital shaker at 37◦C for 20 minutes. Next, the USP paddle device was used to stir 500 mL of 5 mM phosphate buffer at 75 rpm after the suspensions were "dumped" into it. Titration with NaOH 2N was used to neutralize the acid load and get a final pH of 6.7. Every trial included sampling at5, 10,15,20,30, and 45 minutes. Methods for preparing the samples are detailed in the section on dissolution tests. Triplicate runs of each dumping experiment were carried out.

Evaluation of Ibuprofen Samples using Quantitative Methods

A high-performance liquid chromatography approach that had been previously established and confirmed by Cristofoletti and Dressman was used to quantitatively assess ibuprofen samples that had been collected from solubility, dissolution, and dumping studies.16

Final Product

Solubility at Rest and in Motion

Table 2 displays the results of the solubility studies, including the equilibrium solubility for IBU-H and the kinetic solubility for IBU-Na and IBU-Lys after 4 hours at 37◦C. There was no difference of more than 0.05 U between the original pH values and the final bulk. Due to ibuprofen's low acidity, its pH-solubility profile shows two areas: (1) at pH < pHmax, where the ionized form is the equilibrium species, and (2) at pH > pHmax, when the surplus solid phase is in equilibrium with saturated solution. Since neither free acid nor any salt is required as a starting material, the pH-solubility profiles at equilibrium should be the same until supersaturating or self-association of solute molecules occurs.25 However, salt forms may have greater apparent solubility’s over physiologically relevant timeframes due to the often observed accelerated dissolving rate. For instance, after 1 hour of incubation at pH 4.5, the solubility of IBU-Na dropped from 0.30 mg/mL to 0.21 mg/mL.

Table2
IbuprofenSolubilityDataat37°C

pH	EquilibriumSolubility(mg/mL)	KineticSolubility(mg/mL)	
	IBU-H	IBU-Na	IBU-Lys
1.2	0.07(0.7%)	0.14(0.7%)	0.13(0.6%)
4.5	0.19(0.4%)	0.21(12.0%)	0.36(3.0%)
6.8	3.91(6.0%)	8.70(9.4%)[a]	9.90(7.3%)[a]

[a] Maximum tested nominal concentrations of IBU-Na, 8.7 mg/mL, and IBU-Lys, 10mg/mL, that did not affect the final pH of bulk solution. The numbers between pa-rentheses are the respective CV% values. Kinetic and equilibrium solubility resultswere obtained at 4 and 24 h, respectively.

Thekineticgastricsolubilityof IBU-NaandIBU-Lys,butnot theequilibrium solubility of IBU-H, was affected by the amount ofexcess solid. Upon incubation for 1 hour under stomach circumstances, the apparent solubility rose to 0.8 mg/mL with an increased variability of 40% and salt concentrations equal to 30 mg of ibuprofen added to 3 mL of solubility medium. The final pHbulk also changed from 1.2 to 3-5 because to the overabundance of salts.

After adding salt levels comparable to 20 or 40 mg/mL of IBU-H, the apparent solubility of the salts and pHbulk were compared under intestinal circumstances. Even though the medium had a large buffer capacity, the pHbulk was still impacted by the quantity of extra material that was added (Table 3).

Consistent with the experimental value determined for ibuprofen, which ranges from 6.9 to 7.2, the projected pHmax for the drug, based on S0 and Ksp from the pH-solubility profile published by Potthast et al.,27, is around 6.6.34 That the observed higher kinetic solubility of the salts is not attributable to a pH shift is supported by the fact that even the beginning condition of the McIlvaine buffer, pH 6.8, is quite near to the plateau phase of the pH-solubility profile (Fig. 1). The stated equilibrium solubility of IBU-H at pH 6.8 and 7.4, 3.37 and 3.44 mg/mL, respectively, does not alter, lending credence to this notion.27 Furthermore, we explored the possibility that ibuprofen, a chemical with a short hydrophobic moiety and an amphiphilic nature, may cluster in water and act as a hydrotrope. All chemicals tested were surface active, but only the salts achieved the CMC. This was shown by the surface pressure profile of successive dilutions of solutions containing IBU-H, IBU-Na, and IBU-Lys at pH 6.8 after 24 hours of incubation at ambient temperature. Approximately 40 mM yielded the salts' minimal surface tension value (z30 mN/m) (Fig. 2). The SAP experiment's sample equilibrium solubility values are shown in Table 4.

Analyses of Dissolution

The APIs and dosage forms that included IBU-H or its salts were subjected to in vitro dissolving tests (Fig. 3). The IBU-Lys and IBU-Na APIs dissolved at pH 1.2 and 4.5, respectively, caused short-lived supersaturated states that lasted for 15 or 30 minutes. Following this, the concentrations of the dissolving agents declined until the free acid attained its equilibrium solubility in both mediums. The dissolution findings were more variable due to precipitation, which led to broader error bars.

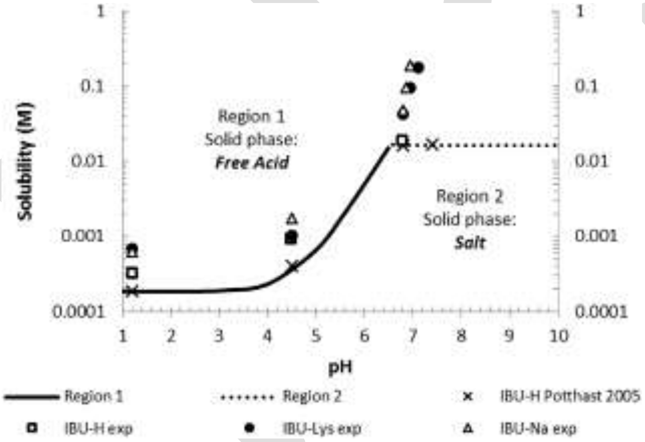


Figure1.pHsolubilityprofileofIBU-H,IBU-Na,andIBU-Lysasthestartingmaterials.

(Figs. 3aand 3c). A similar trend can be seen in the dissolution ofthedosageforms.Thefasterthemaximumsupersaturatinglevelisreached(e.g.,around70%-80%drugdissolvedatpH4.5),thefasterthe precipitation rate seems to be (Figs. 3cand 3d). Interestingly,there seems to be a mismatch between the dissolution results oftheAPIsanddosageformscontainingIBU-Handitssaltsin50mMphosphate buffer at pH 6.8. For instance, although dissolution ofIBU-NaAPIisvirtuallyinstantaneous,thatis,100%dissolvedin 2 min, 85% dissolution was reached only after 30 min whenreleased from the dosage form. More intriguing, the dissolutionrateofIBU-Htabletswasfasterthanof IBU-NaandIBU-Lystablets,although the opposite behavior was observed with the pure APIs(Figs. 3eand 3f).

Dissolution profiles of dosage forms containing IBU-Arg, IBU-Lys,andIBU-Nawerenotaffected bychanges in the dissolution medium.On the other hand, decreasing the total phosphate buffer concen-trationfrom50to5mMmarkedlydecreasedthedissolutionrateofIBU-H. As expected, dissolution results obtained in 13.5 mMphos-phate buffer were similar tothat in 7 mM maleate buffer (Fig. 4).[16]

Based on the dissolution results obtained for the salt APIs andIBU-Arg granulate, it seems highly likely that dissolution of tabletscontaining IBU-Na or IBU-Lys in intestinal conditions was delayedbyslowdisintegration,especiallyincaseofIBU-Na(e.g.,practicallyno dissolution before 10 min). In fact, dissolution of the dosageforms containing ibuprofen salts in the simulated intestinalcompartment after being "dumped" from the donor compartmentwasimmediate,similartodissolutionofthepureAPIsalts,whereasdissolution of IBU-H was not affected because it

At this point, the pH-solubility profile has been attained, and the salt form is the equilibrium species. It is the first time that apparent solubility results for ibuprofen salts within the pH range of 1.2-6.8 have been reported over a physiologically relevant timescale (Table 2) that we are aware of, with the exception of a report by Terebetski et al.38 that noted a rather transient and slight super saturation of IBU-Na in simulated gastric fluid.

With the exception of the pHmax area, where super saturation may be seen, the pH-solubility profiles employing the unionized drug or its salts are shown to be superimposable. A tendency toward super saturation at pHmax has been seen in drug-salt systems, which may lead to the formation of aggregates.39,40 Ibuprofen seems to be no different; at its salt perceived solubility in the pHmax area, micelle-like aggregates are generated (Table 2 and Fig. 2). In contrast to other examples where super saturation was accomplished with free drugs (such as CEL50, theophylline, phenazopyridine, and papaverine), ibuprofen could only be supersaturated when utilized in salt form. This could be because, as previously reported, only the salts of IBU-H reached the CMC, even though both the compound and its salts exhibited considerable surface activity.36,42 dollars Since the salts' greater apparent solubility at pH 6.8 is due to a dissolution-precipitation imbalance, it is extremely probable that this state will persist long enough to initiate the aggregation process.

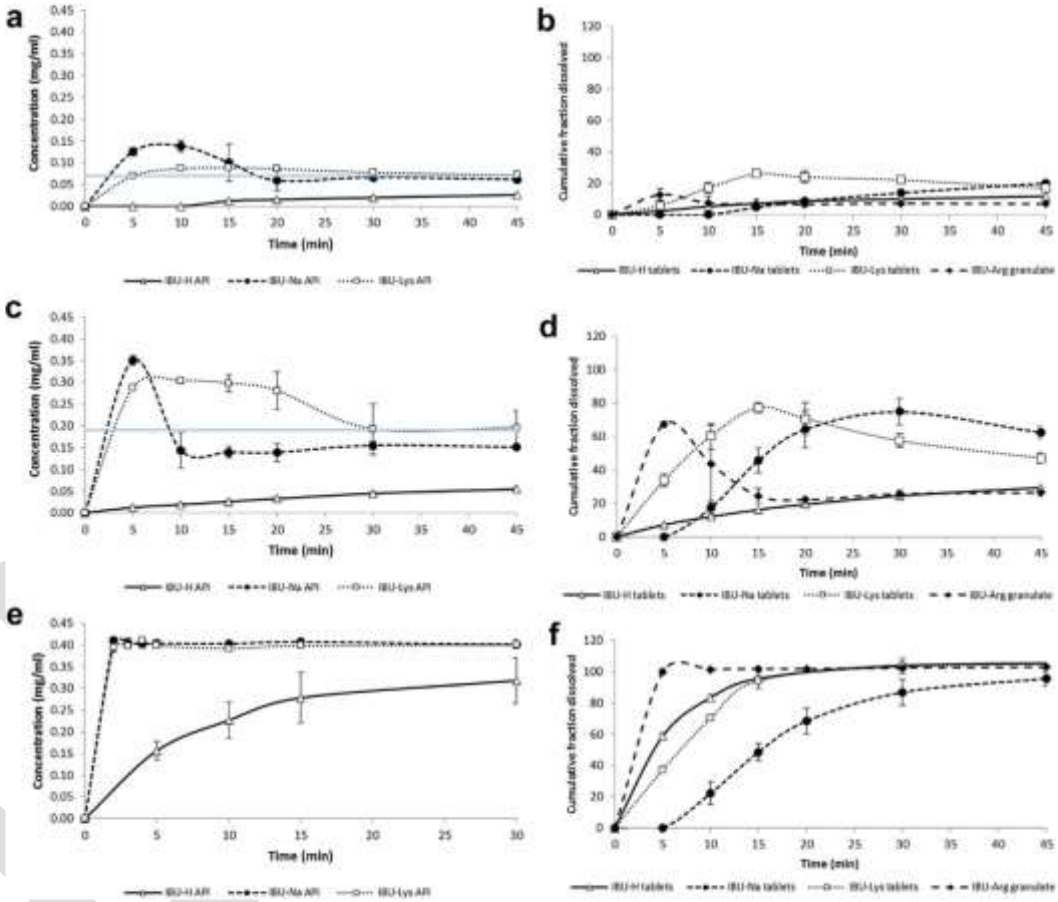
Taking into account the uncertainty linked to the measurements of

When studying the intestinal conditions for the kinetic solubility of IBU-Na and IBU-Lys, it seems that the whole solid dose injected to the phosphate buffer at 37◦C was dissolved, indicating that the apparent intestinal solubility could be considerably greater. Yet, no more studies were conducted since IBU-H is known to be very soluble at pH 6.8 and because it is exceedingly improbable that such a high luminal concentration would be achieved in vivo after standard dosages. Regarding the salts' stomach solubility, it's interesting to note that even at the lowest dose strength of 200 mg, there is still not enough solubility due to the transitory increased apparent solubility, which is only two times higher than the already very low equilibrium solubility of IBU-H (Table 1).

Is the Difference in Absorption Rate Between IBU-H and Its Salts Caused by Dissimilarities in Gastric Dissolving?

We previously discovered that ibuprofen salts have a greater gastric solubility, leading to quicker and more thorough stomach dissolution, which may explain their faster absorption rate.43 It was postulated that, employing IBU-Na as the starting material, the solubility at pH 2.0 would be about 310 mg/mL, in accordance with the known pH-solubility curve of IBU-Na.23 We have revisited their approaches and found a few problems: First, the final pHbulk was not measured. Second, the aqueous solubility of IBU-Na at a given pH was determined by dividing the weight of the salt (10 mg) by the total volume of the stock solution (32 mL) added to the vial. This could mean that only 32 mL of solution was added, leading to a solubility of approximately 310 mg/mL. Ibuprofen self-aggregation happens at concentrations >8.5 mg/mL, and our previous work shows that the amount of excess solid added to the simulated gastric medium significantly affects the final pHbulk. Therefore, the solubility measured by Lee and Wang23 probably represents an experimental condition closer to the pHmax, not at pH 2.0. This means that the evidence we used to support our prior premise was dubious.

The IBU-Na and IBU-Lys APIs showed a small and short-lived supersaturation when dissolved in a pH 1.2 solution (e.g., IBU-Na reached a maximum supersaturation degree of 2.1 and remained in a supersaturated condition for just 20 minutes). Very same outcomes when



Picture 3. Mean ± SD in vitro dissolution of active pharmaceutical ingredients (a, c, e) and dose forms (b, d, f). A and b Hydrochloric acid solution, pH 1.2, (c, d) Solubility in a USP acetate buffer with a pH of 4.5 (e, f) As a solution in 50 millimolar USP phosphate buffer at a pH of 6.8. All investigations used a USP paddle device operating at 75 rpm. The equilibrium solubility of IBU-H in each media is shown by the horizontal solid blue line. The symbols include the majority of the standard deviation

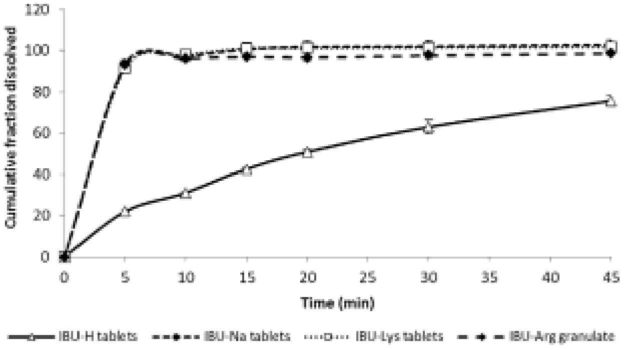
Another group published IBU-Na and shown that up to 60 minutes of stomach supersaturation could only be sustained in formulations with precipitation inhibitors, or "parachutes," such as hydroxypropylmethylcellulose (HPMC).38 Despite the presence of HPMC in Nurofen 200-mg and Dolormin 342-mg or dispersible tablets, Figures 3a and 3b indicate that the dissolving of the API alone and its dosage form exhibited identical behavior at pH 1.2. Therefore, it may be inferred that the quantity of excipient used in these formulations was insufficient to serve as an adequate parachute.

The results of the in vitro dissolution testing at pH 1.2 for IBU-Lys and IBU-H or dispersible formulations did not match the observed Tmax because the profiles for IBU-Na and IBU-H were low and superimposable up to 30 minutes, even though they seemed to differ at first glance.22 Curiously, when ibuprofen was combined with methylcellulose, the largest peak and amount of exposure were seen in rats. However, the stomach dissolution profile of this drug polymer formulation was identical to that of IBU-Na API alone. However, the ensuing PK profile was identical to that of IBU-Na alone, even though the combination of HPMC:IBU-Na consistently caused gastric supersaturation.38 The rapid stomach disintegration or dissolution of sparingly soluble weak acids may cause over- or under-discriminating situations, in contrast to highly soluble medications whose absorption is connected with their rate of gastric disintegration or dissolution.

Does Surface pH matchingbetween Bicarbonate Buffer and Simulated Intestinal Buffers Enhance the Discriminatory Power of in Vitro Dissolution Testing without Causing a Decrease in Bio relevance?

Despite the experimental setup's sink environment, IBU-H API exhibited wettability concerns; in contrast, IBU-Na and IBU-Lys APIs dissolved very instantly in 50 mm phosphate buffer (Fig. 3e). The problem was obviously remedied during development using pharmacological technology, as the IBU-H dosage form dissolved very quickly under the same experimental conditions—even quicker than the IBU-Na and IBU-Lys tablets (Fig. 3f). Naturally, this contradicts the claims of a quicker absorption rate for the salts. The years 19–22 Some publications have previously found that in vitro dissolution tests for BCS class 2 weak acids do not adequately predict in vivo BE results when employing experimental conditions or quality-control approaches based on BCS.8-10 Furthermore, the PK profiles acquired by giving various formulations comprising IBU-Na and IBU-H to rats were not anticipated by 2-stage dissolving tests using simulated stomach fluid and a high phosphate buffer content of 115 mM.38

We measured the bulk values of the saturated solutions of IBU-H, IBU-Na, and IBU-Lys in water. Actually, Serajuddin and Jarowski39 came up with this method to determine pH0 in a realistic way. A saturated solution with a pH of 4.2 was produced using IBU-H as the starting material, while pH values of 7.6 and 8.9 were achieved using IBU-Lys.



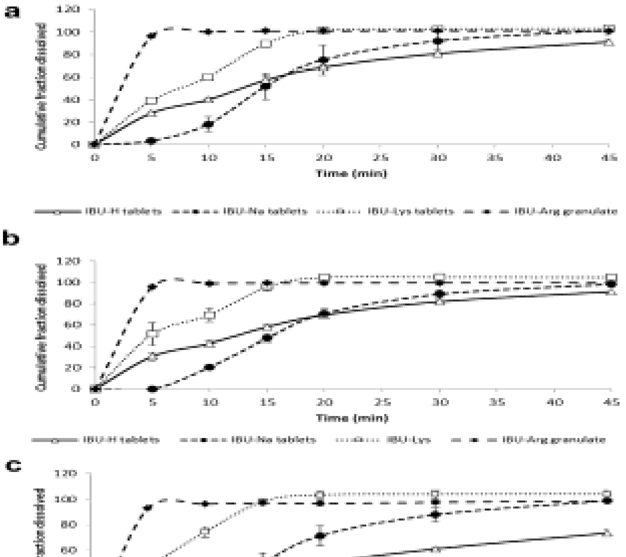


Figure 4.*In vitro* dissolution (mean ±SD) of dosage forms containing ibuprofen freeacidor itssalts in(a)13.5 mmphosphatebuffer,(b)7.0mmmaleatebuffer,and (c)5mm phosphate buffer. USP paddle apparatus at 75 rpm was used in all experiments.Most standard deviation bars lie within the symbols.

1. Correspondingly, IBU-Na were used. Therefore, the dissolving salts had a pH0 greater than the pHmax in a nonreactive media, which was favorable for the drug's solubility. Conversely, IBU-H has a poorer solubility at the solid-liquid interface and a slower dissolution rate in water because its experimental pH0 is less than its pKa. A drug's solubility in reactive medium may be affected by changes to pH0 caused by buffer-related characteristics.18 If we take a solution of IBU-H in 50 mm phosphate buffer at bulk 6.7, we get an estimated pH0 of 6.04,16, which is closer to the pHmax of ibuprofen. In contrast, IBU-H would dissolve more slowly in vivo than in 50 mM phosphate buffer due to the predicted pH0 of dissolving ibuprofen particles at bio relevant quantities of bicarbonate buffer, which is 5.13,15. When dissolving in 5 mm phosphate buffer, the expected pH0 of IBU-H is comparable to that predicted for bicarbonate buffer. The number of changing the buffer capacity of the dissolution medium had no effect on the dissolution of the dosage forms containing IBU-Arg, IBU-Lys, and IBU-Na, but lowering the total phosphate buffer concentration from 50 to 5 mm significantly reduced the dissolution rate of IBU-H (Figs. 3f, 4a and 4c). Even in inert medium, their pH0 values exceed ibuprofen's pHmax, therefore this result was not surprising.
2. Figure 5: Dumping test results. The dosage forms containing ibuprofen free acid or its salts were disintegrated in 0.01 N HCl for 20 minutes before being incubated at 37◦C. Then, they were dissolved in 5 mm phosphate buffer in an in vitro setting. The results were shown as the mean ± SD. All investigations used a USP paddle device operating at 75 rpm. The symbols include the majority of the standard deviation bars.
3. Lastly, and most critically, it seems that the disintegration time affects the dissolution of ibuprofen salts from their dosage forms. Solubility of IBU-Arg granulate is quite similar to that of the other salt APIs; however, IBU-Na tablets dissolved much more slowly than their equivalent API; in fact, almost no dissolution took place prior to 10 minutes (Fig. 4). Also, across the board with phosphate buffers, the dissolved IBU-Na quantity coefficient of variation was greater than the acceptability regulatory criterion.3 The variation in exposure peak and extent after IBU-H and its salt administration is very similar.22 There may be an artefact in the in vitro evaluation due to variations in the disintegration time of the formulations under intestinal conditions. This is because conventional 1-stage dissolution testing does not consider the gastric compartment, where the disintegration of dosage forms typically occurs or starts. A workaround for this is the "dump-ing" test, which compared the

solubility of ibuprofen salt dosage forms in intestinal circumstances to that of the APIs after predisintegration under stomach conditions. In contrast, the experimental dissolution setup did not impact the dissolution of IBU-H (Fig. 5). The dissolving profiles that come out of the dumping test seem to represent the quicker absorption rate of the ibuprofen salts, according to a comparison of in vivo data with findings from in vitro tests.

4. Because ibuprofen is able to pass through almost any kind of skin
5. intestine,45,46 the mean residence time seems to be sufficient to guarantee full drug absorption, leading to equivalent exposure whether IBU-H or its salts are given orally,19-22 despite the slower dissolving of IBU-H.
6. Last thoughts
7. The observed differences in absorption rates cannot be explained by the fact that gastric dissolution of IBU-H and its salts is not significantly different. The present intestinal dissolving medium based on BCS did not account for the fact that ibuprofen, when given as sodium or lysine salts, is absorbed more quickly than when given as free acid. Although results from the classical 1-stage dissolution method could be skewed due to slow disintegration, it appears that in vitro dissolution testing becomes more discriminatory when simulated intestinal buffers and bicarbonate buffer are surface pH-matched. By including a decreased buffer concentration into the intestinal medium and integrating the "dumping" test, a biorelevant in vitro test was successfully conducted. To determine whether modifying phosphate levels is effective, more research with additional weak acids that are poorly soluble but very permeable is required.
8. If the buffer concentration is adjusted to match the pH0 of the weak acids being dissolved in the bicarbonate buffer, then it should be possible to identify variations in the exposure length and peak between the reference and test formats.
9. Notes of Thanks
10. The views expressed in this article are those of the writers, who are scientists, and not ANVISA, the Brazilian health surveillance agency.

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