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RESEARCH ARTICLE

DISSOLUTION CHARACTERIZATION OF COMPOUNDED IBUPROFEN-CONTAINING TABLET FORMULATIONS FOR POTENTIALLY FASTER PAIN RELIEF: THE EFFECTS OF DISINTEGRANTS

[1,*]Yousif Rojeab, [1]Cal VonStein, [1]Elaina Gollmar, [1]Jessica Fernandez, [1]Alexandria Dingess, [1]Elaine Chiu, [1]Taylor Hoffman, [2]Deirdre Myers

[1]Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, Ohio Northern University, USA
[2]Deptartment of Pharmacy Practice, College of Pharmacy, Ohio Northern University, Ada, OH 45810

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ABSTRACT

Ibuprofen is one of the most commonly used nonsteroidal anti-inflammatory drugs (NSAIDs) to alleviate pain and inflammation. Faster disintegration and consequently dissolution of an ibuprofen-containing oral tablet is expected to speed up relief from pain and/or inflammation. The purpose of this study was to 1) compound series of ibuprofen-containing tablet formulations for oral administration with varied types and amounts of disintegrants and 2) thoroughly evaluate ibuprofen's dissolution rates and extents from those formulations compared to a commercially available tablet. United States Pharmacopeia (USP) type II dissolution apparatus was implemented in the dissolution studies where samples were collected at predetermined time points and analyzed for ibuprofen content using a validated High Performance Liquid Chromatography (HPLC) method. Statistical analyses of dissolution results were performed based on single-factor ANOVA. Three of the six compounded formulations; ones with starch 5%, starch 20% and microcrystalline cellulose (MCC) 10% as the disintegrants, demonstrated higher rates of dissolution compared to the commercial product ($p< 0.0003$, 0.0032 and 0.0043, respectively). For dissolution extents, two formulations; ones with MCC 20% and hypromellose 2910 USP (E4M) 5% as the disintegrants, showed enhancement over commercial tablet ($p< 0.001$ and 0.0103, respectively). These results demonstrate the feasibility of compounding ibuprofen-containing tablets for oral administration with enhanced dissolution characteristics over a commercially available tablet, thereby potentially reducing time to pharmacologic effect. More importantly, our results demonstrate that sound formulation optimization of a compounded tablet formula can be directly guided by *in vitro* dissolution evaluations.

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INTRODUCTION

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that is weakly acidic, and soluble in most organic solvent, and very soluble in alcohol (Davies, 1998; O'Neil, 2001; Osol, 1980). Ibuprofen was originally developed for use in the treatment of rheumatoid arthritis in the 1960s. This drug became available for prescription use only in the United States in 1974, and in 1984 became available for over-the-counter (OTC) use (Adams *et al*., 1967). There are several labeled indications for orally administered ibuprofen, including inflammatory disease, mild to moderate pain, fever, dysmenorrhea, and osteoarthritis. OTC uses include headache, sore throat, muscle sprains, dental pain, and backache (Lexicomp, 2017).

Corresponding author: **Yousif Rojeab,**
Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, Ohio Northern University, USA.

Ibuprofen has also been studied as a novel treatment of high altitude headaches as well as patent ductus arteriosus in premature infants (Xiong *et al*., 2017; Lu *et al*., 2017). The plethora of indications and potential indications for ibuprofen demonstrate the significance of studying this molecule, its pharmacokinetics and how manipulation of the excipients in a tablet formulation may significantly enhance its disintegration, dissolution, oral absorption and eventually pharmacological effect(s). Ibuprofen is rapidly absorbed into the bloodstream, and blood levels peak approximately 90 to 120 minutes following oral administration (Laska *et al*., 1986). In a study comparing the blood levels and clinical response following administration of various doses of ibuprofen in patients undergoing dental procedures, it was shown that increased serum ibuprofen is correlated with increased pain relief (Laska *et al*., 1986). While this is not surprising for a molecule whose main purpose is pain relief in this case, it certainly underscores the need for rapid disintegration, followed by rapid dissolution resulting in faster absorption from the GI tract. Dissolution

studies are conducted to determine the conditions under which a compound will dissolve, its rate of dissolution, and its absorption (Phillips *et al*., 2012). The dissolution mechanism can be separated into two distinct phases. The first is disintegration, in which the drug is broken down into small/fine particles. The second is dissolution, which is the process by which drug particles are solubilized, or enter solution phase. One purpose of dissolution studies is to determine whether the rate-limiting step in the dissolution process for a solid dosage form is disintegration or dissolution, the latter being highly dependent on the physicochemical nature of the drug under investigation. Inherent to the dissolution process is the fact that lipophilic drugs, such as ibuprofen, tend to have longer dissolution times than their more water-soluble counterparts.

Accordingly, the type/amount of disintegrant (s) in an oral tablet formulation can have a significant impact on disintegration time and subsequently dissolution rate. Common excipients tested in ibuprofen tablet formulations included mixtures of galactomannan and crospovidone (Schiermeier, 2002). Another common disintegrant in compounded ibuprofen tablets is microcrystalline cellulose (MCC) which is often co-milled with a lubricant to improve the compressibility, and therefore pharmacokinetics, of the ibuprofen tablet (Mallick *et al*., 2013). More recently tested disintegrants have included different kinds of polymers that play a role in the timing of release of ibuprofen (Gaikwad *et al*., 2015). A better understanding of the importance and role of disintegrants may allow for application of ibuprofen in unique and innovative ways. Therefore, a careful and thorough evaluation of the impact of disintegrants on ibuprofen's dissolution characteristics may provide strategies for delivering ibuprofen in a safer and more efficient ways to patients. For several decades, compounded pharmaceutical preparations, as opposed to manufactured, offered flexibility in dosing, addressed individual patient needs and allowed compounding pharmacists/pharmaceutical scientists to utilize science-based principles to develop and compound formulations with potentially enhanced and/or customized characteristics over their commercially available counterparts.

Therefore, the goals of this research were to 1) compound series of ibuprofen-containing tablet formulations for oral administration with varied types and amounts of disintegrants and 2) thoroughly evaluate ibuprofen's dissolution rates and extents from those formulations compared to commercially available tablet. The working hypothesis for the first goal was that ibuprofen-containing tablet formulations with sufficiently high mechanical strength to withstand handling and storage will be successfully compounded using tablet press. The working hypothesis for the second goal was that at least one compounded tablet formulation will demonstrate significantly enhanced dissolution characteristics over commercially available ibuprofen in terms of rate and/or extent of dissolution. This work bears the unique aspect of linking a fundamental pharmacy practice component; the art and science of compounding, to basic pharmaceutics; in terms of *in vitro* dissolution evaluations, in a fashion that is not typically pursued in the practice of pharmaceutical compounding whether in the United States or globally since it is not common practice for compounding decisions or formulation optimizations efforts to be guided by sound dissolution results which is what this project proposes.

MATERIALS AND METHODS

Materials

Ibuprofen, USP grade was purchased from Medisca Inc., Plattsburgh, NY and was utilized in tablet compounding. Immediate-release ibuprofen 200 mg tablet formulation, reference commercial product, was obtained from Meijer Distribution, Inc., Grand Rapids, MI. All three disintegrants employed in this study; corn starch, MCC and hypromellose 2910 USP (also referred to as Methocel E4M or simply E4M for the purpose of this article) were obtained Medisca Inc., Plattsburgh, NY. Stearic acid and lactose, necessary for tablet formulations, were purchased from Letco Medical, Decatur, AL and Fagron, St. Paul, MN, respectively. Dyes for color-coding of the various tablet formulations were obtained from Lor Ann Oils, Lansing, MI. Hydrochloric acid, HCl, 6 N and sodium lauryl sulfate (SLS) required for preparation of dissolution media were purchased from VWR International, West Chester, PA and Chemistry Connections, Conway, AR, respectively. HPLC-grade water and acetonitrile (Avantor Performance Materials, Inc., Center Valley, PA) were purchased from Fisher Scientific, USA and were used in preparation of the mobile phase for HPLC analyses. Glacial acetic acid used for adjustment of mobile phase pH was obtained from EMD Chemicals Inc., Gibbstown, NJ.

Tablet Compounding Procedure: Ibuprofen tablets were initially compounded based on the formula described in The Art, Science, and Technology of Pharmaceutical Compounding (Allen Jr., 2012) This formula was designed to make 225 mg ibuprofen tablets but also included 75 mg of caffeine, 140 mg of microcrystalline cellulose, and 2 mg of stearic acid for a total tablet weigh of 442 mg. For this study, the formula was modified by reducing ibuprofen to 200 mg per tablet to better mimic the standard OTC ibuprofen formulation strength. Caffeine was eliminated while the amount of stearic acid in each tablet remained the same. The new formulations included lactose as diluent to maintain final tablet weights consistent (Table 1). Lactose was chosen as diluent because it is a highly water-soluble tablet filler, so it would not be expected to impact tablet dissolution pattern or create an artifact. A negligible amount of food coloring was added to each compounded tablet formulation for color-coding of the different formulations. This amount ranged from two drops for the formulations with high amount of disintegrant, to one drop for the mid-range amount of disintegrant, to one-half of a drop for the ones with low disintegrant amount (we tested a high- and a low amount for each disintegrant evaluated; selection of such amounts was based on percentages commonly employed in commercially available products – more details under Discussion). For the tablet compounding procedure, all ingredients were pre-weighed and added to a size 8 ceramic mortar and pestle. Corresponding amount of food coloring was added and the powdered tablet ingredients were triturated until uniform color/particle size was visibly achieved. The powdered mixture was then weighed into 442 mg portions and contents were poured in a ½" Parr Instrument Company pellet press (Moline, IL) and each tablet was pressed into a cylindrical disk after three separate presses of the plunger. Each compounded tablet was weighed to ensure uniformity and then each batch of uniform tablets was placed in a pre-labeled plastic bag and stored until used within no longer than two months from preparation time.

***In Vitro* Dissolution Studies:** United States Pharmacopeia (USP) Dissolution apparatus type II (VK 7000, VanKel Technology Group, Cary, NC) was employed in the *in vitro* dissolution studies. Each tablet formulation (n = 3 - 9) was placed in 500 mL of 0.1 N HCl as the dissolution medium to which 2% SLS was added to maintain sink conditions while not interfering with the dissolution process since rate of ibuprofen dissolution from tablets in HCl solutions is not affected by the nature of surfactant, i.e., cationic vs. anionic vs. nonionic (Park, 2006). Temperature was maintained at 37±1°C with a circulating water-bath. Dissolution medium was continuously stirred with paddles at 50 rpm. One milliliter sample aliquots were withdrawn at predetermined time points up to 120 min, filtered through 0.45 µm syringe filters, adequately diluted and analyzed by HPLC for ibuprofen concentration. Each withdrawn sample was replaced by an equal volume of temperature-equilibrated fresh dissolution medium.

HPLC Method and Analysis: One milliliter samples were collected during the dissolution process at 3, 5, 10, 15, 30, 45, 60, 90, and 120 minutes from the start of experiment and stored at -20°C until analysis was performed (within 7 days of collection). A reverse-phase HPLC assay for quantification of ibuprofen in collected samples was employed and validated based on the method of Farrar H. *et al* (15), with slight modification. The method consisted of ultraviolet detection at 220 nm (Waters, Milford, MA, USA) and Waters Symmetry® C_{18} column (4.6 X 150 mm). Mobile phase consisted of 40% water (pH adjusted to 2.6 with acetic acid) and 60% acetonitrile in isocratic mode at a flow rate of 1.0 mL/min. Assay linearity was established over full range of ibuprofen concentrations encountered.

Statistical Analysis: Statistical analyses of dissolution results (dissolution rate and dissolution extent) from all compounded formulations as well as commercial product were performed based on single-factor ANOVA using R statistical software(version 3.3.2; copyrighted by The R Foundation for Statistical Computing). Mean and standard deviation for rate of dissolution (expressed as %/min) and extent of dissolution (expressed as %) for each compounded tablet formulation was plotted and compared to the commercially available product as the positive control. *p*-values < 0.05 were considered statistically significant.

RESULTS

ANOVA Model Assumptions: Single-factor ANOVA was used to analyze data. Two assumptions need to be satisfied in order for an ANOVA model to be valid. The first is that observations are adequately described by the model. This can be evaluated through the Shapiro-Wilk normality test. For this test, a high *p*-value is preferred because the null hypothesis here states that data comes from normal distribution (bell-shaped curve). Since *p*-values for both dissolution rate extent were > 0.05 (0.8489 and 0.2222, respectively), it is safe to assume that data followed normal distribution. The second assumption is that standard errors are normally and independently distributed with a mean of zero and constant but unknown variance. This is an important assumption because the ANOVA model can be sensitive to the violation of the constant variance assumption. This especially holds true for unbalanced designs in terms of the number of subjects per group. If the constant variance assumption cannot be confirmed, the ANOVA model is invalid. This can be evaluated through Levene's test for homogeneity of variance. For this test, a high *p*-value is also preferred because the null hypothesis states that the variance is the same for all treatment groups (in our case, "tablet formulations"). Since *p*-values for both dissolution rate and extent were > 0.05 (0.9042 and 0.4169, respectively), it is safe to assume that the variance is the same across all formulations tested. A total of nine compounded tablet formulations were developed (Table 1, Figure 1) of which six were evaluated for their disintegration/dissolution characteristics. Analyses of dissolution results revealed that three of the six compounded formulations; ones with starch 5%, starch 20% and MCC 10% as the disintegrant, demonstrated higher rates of dissolution compared to the commercial product ($p< 0.0003$, 0.0032 and 0.0043, respectively – Figure 2 and Table 2). As for dissolution extent, two formulations; ones with MCC 20% and E4M 5% as the disintegrant, showed enhancement over commercial tablet ($p< 0.001$ and 0.0103, respectively – Figure 2 & Table 2).

DISCUSSION

As stated previously, this work attempts to link the art and science of pharmaceutical compounding to basic pharmaceutical sciences, in terms of *in vitro* dissolution evaluations, in a novel fashion that is not typically pursued in the practice of pharmaceutical compounding. The purpose of this study was to develop series of ibuprofen-containing tablet formulations and examine and characterize the effects of common disintegrants, used in varied concentrations, on the rate and extent of ibuprofen's dissolution in comparison to a commercial product. More precisely, we attempted to introduce drug dissolution as a tool to guide further formulation optimization in pharmaceutical compounding. A variety of disintegrants have been proposed in ibuprofen tablet formulation (Schiermeier, 2002; Mallick *et al*., 2013). In our study, we evaluated the impact on dissolution of three disintegrants; corn starch, a conventional disintegrant, MCC, a super disintegrant and E4M, which could be viewed as a novel disintegrant of a different class. All three excipients have been used in direct compression tablet manufacturing. Rationale for selection of disintegrant amounts (%) in the different formulations was based on commonly reported and acceptable ranges (Rowe, 2009) as well as our intent to detect statistically significance difference in dissolution characteristics, if any, based on amount of disintegrant. Accordingly and for each disintegrant evaluated, we selected an amount representing the lower and the upper end of the normal usage range (Table 1). Dissolution data demonstrated variability in both rate and extent, with more variability detected in rate for the various formulations tested. Four compounded tablet formulations demonstrated mean rates of dissolution superior to that of the commercial product, with three formulations bearing statistical significance; starch 5%, starch 20%, and MCC 10% (Table 2). It was interesting to observe that starch % as low as 5% was sufficient to enhance rate of ibuprofen's dissolution over that of the commercial tablet formulation. Further increased in % to 20% did not show any additional improvement. One plausible explanation for the enhancement in dissolution rates with multiple compounded formulations over commercial product is the fact that those tablets were developed with the aid of a manual tablet press which would typically provide a force of compression that is significantly lower than the 3,000-40,000 lb of force exerted by a commercial tablet press (Allen, 2014),

Table 1. Composition of ibuprofen-containing compounded tablet formulations for which dissolution has been evaluated.

[a]MCC"High" Formulation	Weight (g)	Weight (%)
Ibuprofen	0.2	45.25%
Microcrystalline Cellulose 20%	0.09	20.36%
Stearic Acid	0.002	0.45%
Lactose	0.15	33.94%
Total Weight	0.442	100.00%
MCC "Low" Formulation		
Ibuprofen	0.2	45.25%
Microcrystalline Cellulose 10%	0.045	10.18%
Stearic Acid	0.002	0.45%
Lactose	0.195	44.12%
Total Weight	0.442	100.00%
Starch "High" Formulation		
Ibuprofen	0.2	45.25%
Starch (Corn) 20%	0.09	20.36%
Stearic Acid	0.002	0.45%
Lactose	0.15	33.94%
Total Weight	0.442	100.00%
Starch "Low" Formulation		
Ibuprofen	0.2	45.25%
Starch (Corn) 5%	0.022	4.98%
Stearic Acid	0.002	0.45%
Lactose	0.218	49.32%
Total Weight	0.442	100.00%
[b]E4M "High" Formulation		
Ibuprofen	0.2	45.25%
E4M 10%	0.044	10.01%
Stearic Acid	0.002	0.45%
Lactose	0.196	44.29%
Total Weight	0.442	100.00%
E4M "Low" Formulation		
Ibuprofen	0.2	45.25%
E4M 5%	0.022	5.01%
Stearic Acid	0.002	0.45%
Lactose	0.218	49.29%
Total Weight	0.442	100.00%

[a]MCC = microcrystalline cellulose
[b]E4M = hypromellose 2910 USP

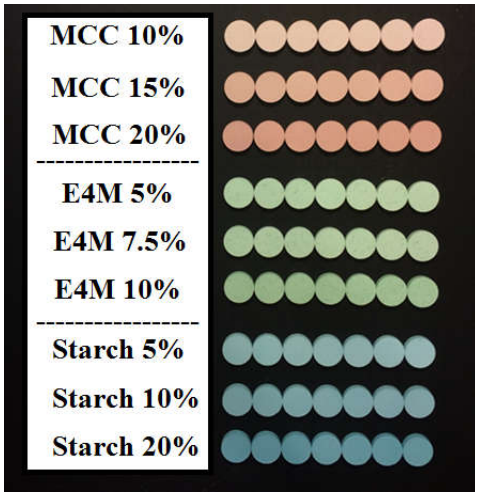
Table 2. Summary of ibuprofen dissolution rates and extents from ibuprofen-containing compounded tablets compared to commercial product (n = 3 - 6)

Dosage Form	Dissolution Rate (%/min)[a]	*p* value	Extent of Dissolution (%)[a]	*p* value
Commercial	2.51 ± 0.54	N/A	91.76 ± 9.87	N/A
Starch 5%	4.93 ± 0.66	0.0003*	104.78 ± 2.39	0.2728
Starch 20%	4.44 ± 0.70	0.0032*	106.67 ± 2.91	0.1623
[b]MCC 10%	4.01 ± 1.58	0.0043*	102.07 ± 1.18	0.5091
MCC 20%	2.97 ± 0.99	0.7540	115.3 ± 8.73	<0.001*
[c]E4M 5%	2.43 ± 0.17	1.0000	114.95 ± 6.02	0.0103*
E4M 10%	1.80 ± 0.67	0.5802	103.5 ± 22.11	0.3737

[a]Data presented as mean ± standard deviation
[b]MCC = microcrystalline cellulose
[c]E4M = hypromellose 2910 USP
*Denotes statistical significance, $p < 0.05$.

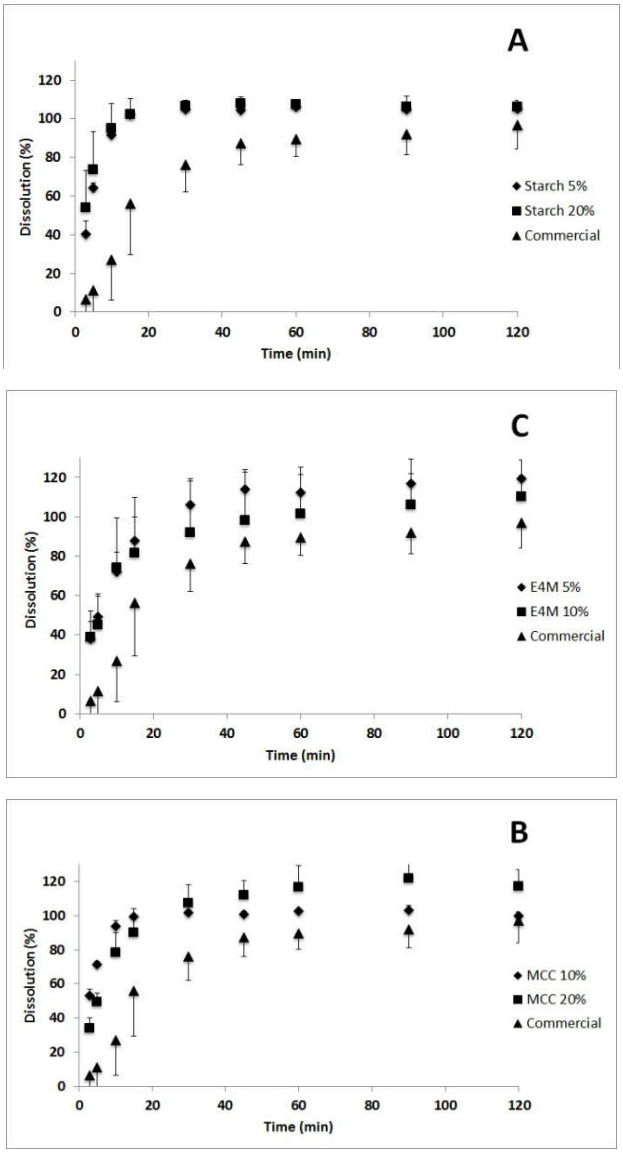
presumably leading to faster disintegration and subsequent dissolution. It is worth noting that while force of compression was not formally evaluated during the compounding process, tablets produced demonstrated high degree of consistency (minimum variability) in their dissolution profiles (Figure 2 and Table 2) which provided confidence in the compounding procedure and its reproducibility. Study results demonstrated less variability in extent of dissolution, with only two formulations, E4M 5% and MCC 20%, demonstrating statistically significant enhancement in dissolution extent when compared to commercial product. In a parallel trend to the impact of starch on dissolution rate, data suggests that when E4M was employed as the disintegrant, it did enhance extent of dissolution at a % as low as 5%. Further increase in amount to 20% not did not provide further enhancement. This finding warrants examining the feasibility of further reduction in disintegrant's %, possibly to 3 or even 2%, and evaluating such impact on dissolution.

Such low disintegrant's % in tablet formulations is not unusual and is actually common with excipients like carboxymethylcellulose (Rowe, 2009) and other disintegrants (https://www. lfatabletpresses.com/ articles/ overview-of-disintegrants. Accessed September 15, 2018). In summary, these results unambiguously demonstrate the feasibility of compounding ibuprofen-containing tablets for oral administration with enhanced disintegration/dissolution characteristics over commercially available product. There is still, however, room for formulation optimization for optimum disintegrant, disintegrant % and potentially using a combination or mixture of disintegrants, as with some commercially available tablet formulations, for maximum enhancement in rate and/or extent of dissolution. Work of this nature is certainly not devoid of shortcomings. We realize that while some factors pertinent to tablet dissolution (e.g., tablet thickness, hardness, force of compression and friability) have not been comparatively evaluated, which could very well be an



Nine total tablet formulations have been developed with low, intermediate and high strength of disintegrant for all three disintegrants employed. *In vitro* dissolution has been evaluated for the low and high, but not intermediate, disintegrant strengths.
[a]MCC = microcrystalline cellulose
[b]E4M = hypromellose 2910 USP

Figure 1. Compounded ibuprofen-containing tablet formulations.



X-axis: Time (in minutes). Y-axis: Amount dissolved, expressed as a % of ibuprofen content in tablet,200 mg. Error bars represent standard deviation. Each panel, A, B & C, compares dissolution for a given disintegrant in two strengths, high and low, to that from commercial tablet. MCC = microcrystalline cellulose; E4M = hypromellose 2910 USP

Figure 2. Dissolution profiles, i*n vitro*, of ibuprofen from the different ibuprofen-containing tablet formulations

extension of this project, our purpose at this time was a "proof-of-concept" that it is feasible to compound ibuprofen-containing tablets with at least non-inferior dissolution characteristics compared to a commercial tablet formulation which was clearly accomplished. Lastly and while commercial production is not a major focal point at this time for this research project, it is potentially feasible that successful results and further enhancements in dissolution rate and/or extent may encourage such consideration.

Conclusion

Ibuprofen-containing tablet formulation for oral administration were compounded and their dissolution profiles were generated and characterized for rate and extent of ibuprofen's dissolution. On more than one occasion, compounded formulations demonstrated significant enhancement in dissolution rate or extent over a commercially available tablet formulation. Data suggests that such enhancement may lead to better therapeutic outcome for a pain/inflammation relieving medication such as ibuprofen. Further enhancement in dissolution behavior of compounded tablets is likely upon optimizing the amount of disintegrant in the formulation which would be guided by sound dissolution data. Finally, use of disintegrant mixture is feasible which, again, would be guided and optimized, in terms of disintegrants amounts and ratios, by tablet disintegration/dissolution studies.

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