Improving the Tablet Characteristics and Dissolution Profile of Ibuprofen by Using a Novel Coprocessed Superdisintegrant: A Technical Note

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INTRODUCTION

The gastrointestinal tract provides sufficient fluid to facilitate disintegration of the dosage form and dissolution of the drug. The large surface area of gastric mucosa favors the drug absorption. Therefore, the oral route has continued to be the most appealing route for drug delivery despite the advancements made in the new drug delivery systems. Banker and Anderson stated that at least 90% of all drugs used to produce systemic effect are administered orally.[1] Rapidly disintegrating tablets have received much attention in recent years, as they are preferred by pediatric and geriatric patients. Moreover, the drug dissolution is facilitated by the tablets' quick disintegration.

The simplest way to achieve quick disintegration is to use a superdisintegrant in concert with suitable diluents. Superdisintegrants such as croscarmellose sodium, crospovidone, and sodium starch glycolate are frequently used in tablet formulations to improve the rate and extent of tablet disintegration and thereby increase the rate of drug dissolution.[2] It has been reported that the rate and extent of liquid uptake and the swelling capacity of crospovidone are not reduced in 0.1N HCl when compared with aqueous medium.[3] The tablets of crospovidone exhibit significantly higher hardness than do those of croscarmellose sodium.[4] Croscarmellose sodium aids in the disintegration and dissolution of pharmaceutical tablets, capsules, and granules.[5] Coprocessing has been extensively examined for diluents. However, it has not been explored for the development of more functional disintegrants.

The purpose of the present investigation was to explore the feasibility of preparing a coprocessed superdisintegrant and to evaluate its functionality. Croscarmellose sodium and crospovidone were selected in the present investigation since crospovidone acts by wicking action and croscarmellose sodium acts mainly by swelling action. Therefore, the superdisintegrants complement each other, accelerating the disintegration process when used together. The water uptake by the tablet is facilitated by the wicking action of crospovidone, while the tablet disintegration is facilitated by the swelling force exhibited by croscarmellose sodium.

The drug selected for this study needed to have a medium dose, low solubility, and high permeability (Class II). Based on these criteria, ibuprofen was selected as a model drug. The dose of ibuprofen is 200 to 600 mg.

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MATERIALS AND METHODS

Materials

Croscarmellose sodium, crospovidone, and hydroxypropyl cellulose (HPC) were a gift from Intas Pharma (Ahmedabad, India). Directly compressible dicalcium phosphate anhydrous (DCPA) and ibuprofen were a gift from Zydus Cadila Health Care Ltd (Ahmedabad, India). Magnesium stearate was purchased from Apex Chemicals (Ahmedabad, India). Cab-O-Sil was a gift from Cabot Sanmar Ltd (Channai, India).

Methods

Evaluation of Croscarmellose Sodium, Crospovidone, and 1:1 Physical Blend of Crospovidone and Croscarmellose Sodium

Measurement of angle of repose. A glass funnel was secured with its tip positioned at a fixed height (H) above a graph paper placed on a horizontal surface. The sample was poured through the funnel until the apex of the conical pile touched the tip of the funnel. The angle of repose was calculated using the formula $\tan \alpha = H/R$, where α is the angle of repose and R is the radius of the conical pile.

Measurement of particle size. The method of sieving was adopted. The powder was passed through 30# (500 μm) and 100# (150 μm). The amount of sample retained on each sieve was weighed. Microscopic pictures were taken using a scanning electron microscope (Quanta 200 3D, FEI, Eindhoven, The Netherlands).

Preparation of tablets using direct compression. The tablets of croscarmellose sodium, crospovidone, and the physical blend (1:1) of both the superdisintegrants were prepared on a single-punch tablet machine (Cadmach Machinery

Table 1. Results of Pure Croscarmellose Sodium, Crospovidone, and 1:1 Physical Blend and Agglomerated Blend of Both the Disintegrants

Disintegrant	Angle of Repose (°)	Flow Type*	Crushing Strength (N)	Tablet Thickness (mm)	Particle Size Range
Croscarmellose sodium	43	P	92	5.0	Below 100#
Crospovidone	40	F	184	3.5	74% below 100# and 26% retained on 100#
Physical fine mixture of both disintegrants	41	P	132	3.1	90% below 100# and 10% retained on 100#
Agglomerated blend of both disintegrants	37	F	70	3.7	Below 30#

*As per *USP29–NF24*. P indicates passable; F, fair.

Ltd, Ahmedabad). The die cavity was kept the same for all 3 samples.

Measurement of crushing strength and thickness. Crushing strength and thickness of the tablets were measured using a Dr Schleuniger Pharmatron Tablet Tester 8M (Solothurn, Switzerland). The results are shown in Table 1.

Preparation and Evaluation of Coprocessed Superdisintegrants

A powder blend consisting of equal proportions of croscarmellose sodium and crospovidone was compressed on the single-punch tablet machine to obtain slugs. The slugs were lightly crushed in a mortar to obtain an agglomerated blend of the superdisintegrants. Finally, the agglomerates were tapped on 30#. The granules and the tablets were characterized as described above.

Preparation and Evaluation of DCPA Tablets

Directly compressible DCPA was mixed with either the powder blend of the superdisintegrants (4% wt/wt, batch A) or the agglomerated superdisintegrants (4% wt/wt, batch B). Magnesium stearate (1% wt/wt) was used as a lubricant. The blending time of the lubricant was either 2 minutes or 5 minutes. Tablets with an average weight of 260 mg were prepared on the single-punch tablet machine. The results are shown in Table 2.

The time required for disintegration of 6 tablets placed in the tubes of a US Pharmacopeia (USP) disintegration test apparatus (Electrolab, model ED2, Mumbai, India) was measured at 37 ± 2°C using 900 mL of distilled water.[6]

Preparation and Evaluation of Various Formulations of Ibuprofen Tablets

Ibuprofen tablets were prepared by the direct compression method (Table 3). The angle of repose of the powder blend and the tablet properties (eg, disintegration time, crushing strength, friability, water uptake rate) were evaluated (Table 4). To optimize the concentration of superdisintegrant, dissolution data were also generated for selected batches.

Measurement of friability.[1] Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a friabilator (USP XXIII, Electrolab, model EF2, Mumbai) at 25 rpm for 4 minutes. The tablets were dedusted, and the loss in weight caused by fracture or abrasion was recorded as the percentage weight loss. A friability below 1% is considered acceptable.

Measurement of liquid uptake. The method of Gohel et al was used.[7] A glass petri dish was partially filled with water, and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from the lower surface of the tablet. The time required for water to reach the center of the upper surface of the tablet was the wetting time.

Evaluation of Dissolution Profile of Ibuprofen in Tablet Formulation

The drug dissolution study was performed in a USP XXIII paddle apparatus (Electrolab, TDT-06T, Mumbai). The dissolution medium was phosphate buffer (900 mL, pH 7.2, 37°C). A vacuum was used to deaerate the medium. The rate of agitation of the paddle was 50 rpm. Ibuprofen was analyzed at 221 nm by UV spectrophotometry (UV-1700

Table 2. Results of Dicalcium Phosphate Anhydrous Tablet Using Physical Blend or Granulated Disintegrant Blend

Batch	Batch A	Batch B
Angle of repose (°)	35	33
Flow type*	G	G
	Lubricant mixing time = 2 minutes	
Crushing strength (N)	55	63
Disintegration time (sec)	14.0	8.5
	Lubricant mixing time = 5 minutes	
Crushing strength (N)	72	68
Disintegration time (sec)	17.0	9.0

*As per *USP29–NF24*. G indicates good.

Table 3. Formulations of Ibuprofen Tablets*

Batch	1	2	3	4	5A	5B	5C	6	7	8	9
Ibuprofen (mg)	200	200	200	200	200	200	200	200	200	200	200
DCPA-DC (mg)	—	200	50	100	—	—	—	—	—	—	—
Croscarmellose sodium (mg)	—	—	150	150	200	150	100	—	50	—	—
Crospovidone (mg)	—	—	—	—	—	—	—	—	—	50	—
Coprocessed superdisintegrant (mg)	—	—	—	—	—	—	—	100	—	—	50
Cab-O-Sil (%)	—	—	—	—	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPC (%)	—	—	—	—	—	—	—		6	6	6

*DCPA-DC indicates dicalcium phosphate anhydrous-directly compressible; HPC, hydroxypropyl cellulose.

Shimadzu Corporation, Kyoto, Japan) after suitable dilution with the phosphate buffer.

Evaluation of Dissolution Profile of Drug Without Excipients

Ibuprofen (200 mg) was filled in empty hard-gelatin-capsule shells without any excipients. A USP XXIII basket apparatus (Electrolab, model TDT-06T, Mumbai) was used for the dissolution study. The dissolution conditions and evaluation methods are described above.

Results and Discussion

The most common method for preparing coprocessed diluents is spray-drying. This method is unsuitable for preparing coprocessed superdisintegrants since wetting and subsequent drying of superdisintegrant can change the characteristics of croscarmellose sodium.[8] Therefore, the slugging method was adopted in the present study. Table 1 displays the angle of repose, crushing strength, and thickness of the pure superdisintegrant tablets. The 2 most important attributes for the direct compression formula are good flow and good compressibility. The angle of repose gives important information about the flow characteristics of the powder mixture. *USP 29–NF24,* effective from January 2006, is the first USP edition to include chapter <1174> on powder flow. Grading of powder flow was done as per USP. The lower acceptable value of crushing strength was set at 40 N.[9] Compressibility is the ability of a powder bed to be compressed (be reduced in volume) as a result of the application of a given stress.[10] Coprocessing resulted in improvement in flow from "passable" to "fair" because of size enlargement. The lowest angle of repose was exhibited by the coprocessed superdisintegrant, which justifies the need for coprocessing. The results of crushing strength and thickness reveal that crospovidone exhibited higher crushing strength and better compressibility compared with croscarmellose sodium. The tablets prepared using the agglomerated blend of both the superdisintegrants exhibited acceptable crushing strength (> 40 N). In the granular superdisintegrant, particle-particle bond formation may not be as intense as that in powdered disintegrant because of decreased surface area. This may be one reason why the granular mixture had a lower crushing strength than the fine physical mixture did.

Directly compressible DCPA was selected as a diluent over microcrystalline cellulose (MCC), as MCC works as an auxiliary tablet disintegrant because of its high water-absorbing

Table 4. Results of Ibuprofen Formulations

Batch	1	2	3	4	5A	5B	5C	6	7	8	9	Market Formulation
Angle of repose (°)	46	42	42	40	40	39	39	36	42	39	42	—
Flow type*	P	P	P	F	F	F	F	F	P	F	P	—
Crushing strength (N)	Tablet showed capping	47	53	76	65	50	45	60	104	100	84	65
Friability (%)		2.20	1.20	0.70	0.76	0.80	0.88	0.96	0.63	0.83	0.62	†
Disintegration time (min.sec)		‡	1.45	1.50	4.00	2.35	2.24	0.45	6.00	2.00	2.30	3.30
Time required for complete drug release (min)		—	—	—	6	6	6	6	10	10	6	40
Water uptake time (min.sec)		—	—	—	—	—	—	—	4.32	2.19	1.34	—

*As per *USP29-NF24.* P indicates poor; F, fair.

†The friability of the coated tablet was <0.10%.

‡The disintegration time was >2 hours.

capacity.[11] The purpose of the present study was to evaluate the superdisintegrant, and hence DCPA was selected rather than MCC. Moreover, MCC is more lubricant-sensitive as it undergoes plastic deformation on compression, while DCPA has a low fragmentation propensity, dicalcium phosphate dihydrate also exhibited low lubricant sensitivity due to fragmentation on compression.[12] Table 2 displays the characteristics of batch A (4% powdered blend of the superdisintegrants) and batch B (4% agglomerated blend of the superdisintegrants). Both the batches exhibited "good" flow (angle of repose $\leq 35°$). The good flow is mainly attributed to the presence of a higher concentration of free-flowing directly compressible DCPA. The tablets of batches A and B showed acceptable crushing strength (>40 N) after 2 or 5 minutes of mixing with magnesium stearate. The marginally lower crushing strength of the tablets of batch A (55 N) may be attributed to higher surface coverage of DCPA agglomerates by the finer superdisintegrant particles as compared with the granular disintegrant used in batch B. The results shown in Table 2 reveal that coprocessing resulted in the formation of quickly disintegrating tablets. The probable reason for the faster disintegration could be the development of a higher disintegration force. Marshall et al[13] stated that the force generated by disintegrant particles is more critical than the actual swelling because this force is responsible for the breaking up of the tablet.

Longer blending time with magnesium stearate resulted in the formation of stronger tablets in both batch A and batch B. The probable reason for this unexpected result could be the breakage of DCPA agglomerates on mixing for 5 minutes. The hypothesis was tested by separately exposing DCPA to 2 minutes and 5 minutes of tumbling. Microscopic analysis (Figure 1) revealed that the average particle size of DCPA was initially 147 μm, and this reduced to 102 μm and 78 μm on 2 minutes and 5 minutes of mixing, respectively. Better particle-particle bond formation may have resulted in the formation of stronger tablets during extended tumbling times. Another possible reason for the higher crushing strength is the disruption of the magnesium stearate layer on prolonged tumbling.

Ibuprofen powder (Table 4, batch 1) showed poor flow and tableting characteristics (capping and lamination). The result justifies the need for incorporation of other excipients to prepare an acceptable tablet. To reduce capping and improve the flow property, a mixture containing an equal proportion of ibuprofen and directly compressible DCPA was tableted (batch 2). The blend showed passable flow, and the tablets exhibited acceptable crushing strength. However, the tablet failed to disintegrate in 2 hours. The friability of the tablets was unacceptable (>1%). The problem of disintegration was resolved when croscarmellose sodium was used as the superdisintegrant (batch 3). However, the tablets of batch 3 failed in the friability test. The problem was rectified by increasing the amount of DCPA (batch 4). In another combination, DCPA was omitted and Cab-O-Sil was used to enhance the flow property (batch 5A). This batch also showed acceptable tablet characteristics. Batch 5A was selected for further evaluation, as DCPA is water-insoluble and may retard drug release.

The dissolution study was performed in phosphate buffer (pH 7.2) since this approach is recommended in the *USP*. The

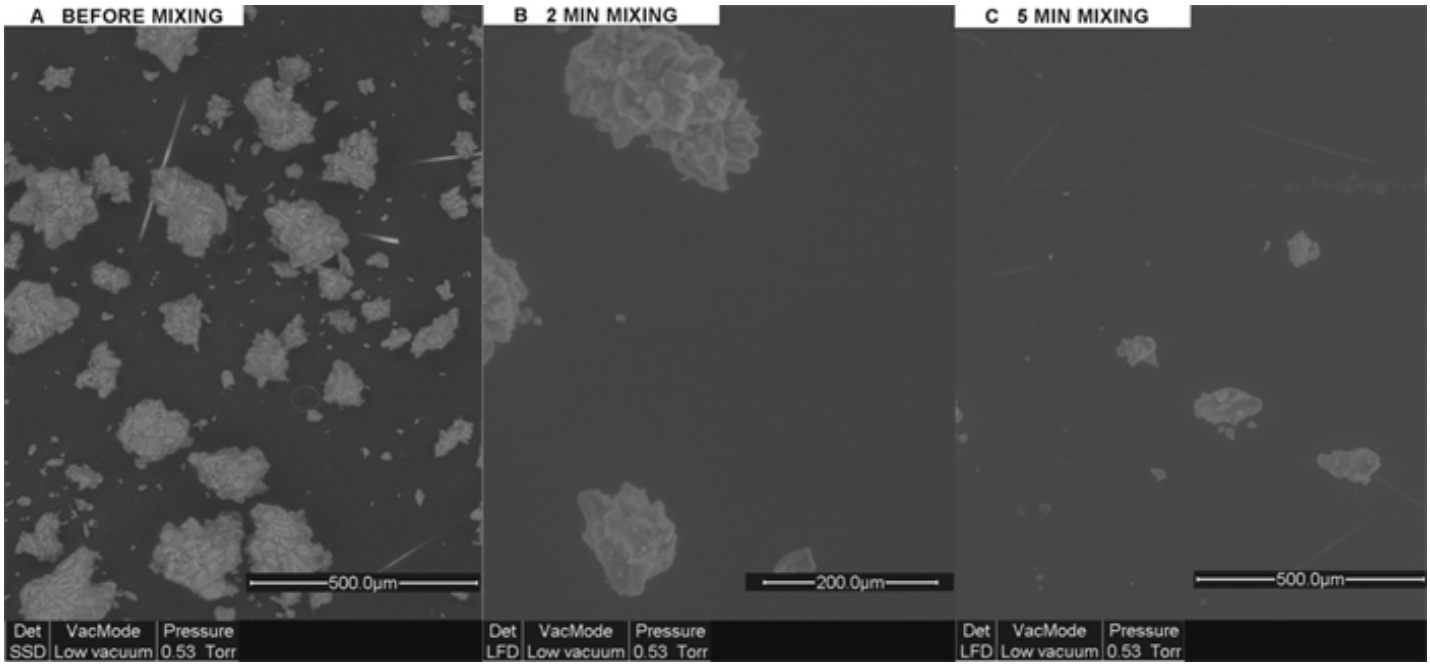

Figure 1. Scanning electron microscopy photomicrographs of dicalcium phosphate anhydrous samples: (A) before mixing—bar length 500 μm; (B) 2-minute mixing—bar length 200 μm; and (C) 5-minute mixing—bar length 500 μm.

dissolution study of the market formulation of ibuprofen tablets (200 mg) showed complete drug release within 40 minutes. Gordon et al[14] reported that croscarmellose sodium produce faster drug dissolution than sodium starch glycolate or crospovidone. The basic purpose of preparing batches 5B and 5C was to minimize the concentration of croscarmellose with maximum improvement in dissolution while maintaining the tablet characteristics in terms of crushing strength and friability. Batches 5A, 5B, and 5C showed complete drug release in 6 minutes. When the concentration of croscarmellose sodium was further reduced to 80 mg per tablet, the tablet failed in friability and hardness tests. Therefore, batch 5C was considered to be the optimum batch among batches 1 to 5.

Batch 6, prepared using coprocessed superdisintegrant, showed a noticeable improvement in crushing strength and disintegration time compared with batch 5C while maintaining a similar dissolution profile. The results show the benefits of using coprocessed superdisintegrant rather than croscarmellose sodium. In batch 6, the coprocessed superdisintegrant was used at 50% of ibuprofen concentration. The use of dry binder was explored to further reduce the amount of coprocessed superdisintegrant.

To prove the superiority of coprocessed superdisintegrant, 3 batches of ibuprofen tablets, batches 7 (croscarmellose sodium), 8 (crospovidone), and 9 (coprocessed superdisintegrant), were prepared along with HPC as a dry binder. The tablets were evaluated for in vitro drug dissolution in the USP XXIII paddle apparatus. The formulation and dissolution data are shown in Table 3 and Figure 2, respectively. Batch 9, prepared using coprocessed superdisintegrant, showed the fastest drug dissolution while maintaining the other tablet characteristics. The tablet containing croscarmellose sodium showed the longest time for wetting, as the major mechanism of disintegration for croscarmellose sodium is swelling. Crospovidone showed a quicker water uptake rate, as the major mechanism of disintegration for crospovidone is wicking. The tablet prepared using coprocessed superdisintegrant showed the quickest water uptake (Table 4). Mishra et al[15] reported that tablets with the shortest wetting time also had the shortest disintegration time, showing a strong correlation between disintegration time and wetting time ($r^2 = 0.9773$). The results of our study show the superiority of coprocessed material in enhancing the disintegration and dissolution of ibuprofen tablets. The probable reason for the quick disintegration of batch 9 tablets appears to be faster water uptake (Table 4).

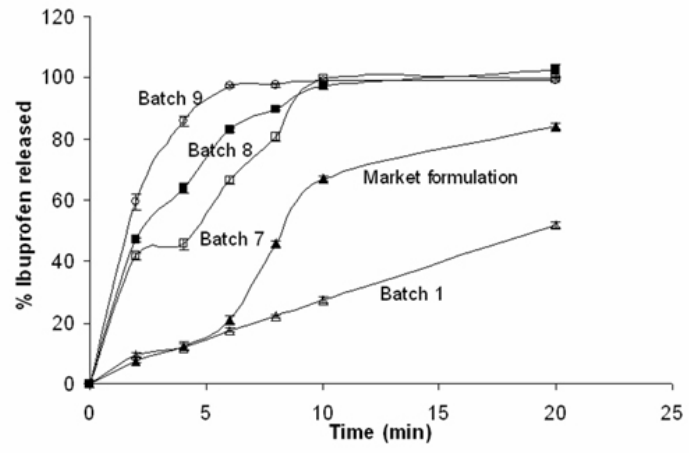

Figure 2. Dissolution profile of ibuprofen tablets.

Coprocessed superdisintegrants offer new avenues and opportunities for formulation scientists as an additional option for improving the solubility of sparingly soluble drugs. The superdisintegrants in this study were kept away from aqueous fluid, which might have changed their characteristics.

Summary and Conclusion

The coprocessed superdisintegrant proved to be superior to the physical blend in terms of flow due to size enlargement. Furthermore, the coprocessed superdisintegrant displayed superiority in terms of crushing strength, disintegration time, and drug dissolution. The advantages of the proposed method are easy adaptability in industry and the possibility of bypassing the existing patents in the areas of quick disintegration and dissolution.

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