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Agglomeration of Ibuprofen With Talc by Novel Crystallo-Co-Agglomeration Technique

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ABSTRACT

The purpose of this research work was to obtain directly compressible agglomerates of ibuprofen with talc by a novel crystallo-co-agglomeration (CCA) technique, which is an extension of spherical crystallization. Ibuprofen-talc agglomerates were prepared using dichloromethane (DCM)-water as the crystallization system. DCM acted as a good solvent for ibuprofen as well as a bridging liquid for agglomeration of crystallized drug with talc. The agglomerates were characterized by differential scanning calorimetry, powder X-ray diffraction, and scanning electron microscopy and were evaluated for tableting properties and for drug release. The process yielded spherical agglomerates containing ~95% to 96% wt/wt of ibuprofen. Agglomerates containing talc showed uniform distribution of hydroxypropylmethylcellulose and decreased crystallinity, and deformed under pressure. The miniscular form of ibuprofen and the hydrophobicity of talc governed the drug release rate. The batch containing a higher proportion of talc showed zero-order kinetics and drug release was extended up to 13 hours. The CCA technique developed in this study is suitable for obtaining agglomerates of drug with talc as an excipient.

KEYWORDS: ibuprofen, talc, crystallo-co-agglomeration, miniscular drug form, drug release retardation.

INTRODUCTION

Nonconventional particle size enlargement techniques employed in pharmacy include extrusion-spheronization,[1,2] melt solidification,[3-5] melt granulation,[6,7] melt extrusion,[8,9] and spherical crystallization.[10-12] Apart from modifications in the primary and secondary properties of the particles, these techniques offer advantages in terms of reduction in the number of unit operations and, in turn, processing cost. The suitability of these techniques depends on the desired properties of the enlarged particle and the physico-chemical properties of the drug and excipients.

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Recently, Pawar et al[13] reported a crystallo-co-agglomeration (CCA) technique, which is a modification of spherical crystallization.[10-12] CCA has been designed to overcome the limitations of spherical crystallization to obtain directly compressible agglomerates of low-dose and poorly compressible drugs and combination of drugs. The application of CCA to obtain directly compressible agglomerates of ibuprofen-paracetamol has been reported previously.[13]

An excipient to be incorporated in the agglomerates should have affinity toward the bridging liquid. Talc, due to its hydrophobicity, undergoes preferential wetting with bridging liquid and is a suitable excipient for incorporation in the CCA. Lin and Peck[14,15] have developed talc agglomerates by fluidized bed granulation for incorporation in tablets. Ibuprofen is a water insoluble, tube-shaped crystalline powder. It has low bulk density and poor compressibility. Many attempts have been reported for particle size enlargement for improvement of the micromeritic properties of ibuprofen. The microspheres and microsponges of ibuprofen were developed by a spherical crystallization technique to produce controlled drug release.[16,17] The combination of talc and magnesium stearate was also used to achieve zero-order release of ibuprofen from extended release tablets.[18]

The present work reports a CCA technique,[13,19,20] in which ibuprofen was crystallized in the presence of talc, and the agglomerates obtained were evaluated using differential scanning calorimetry (DSC), scanning electron microscopy (SEM), powder X-ray diffraction (XRPD), and tableting and drug-release properties.

MATERIALS AND METHODS

Materials

Ibuprofen was a kind gift from Seksaria Chemicals (Mumbai, India). Get-Rid Pharma Pvt Ltd (Pune, India) supplied purified Talc IP as a gift sample. Hydroxypropylmethylcellulose (HPMC, 50 cps, Dow Chemical, Mumbai, India), polyethylene glycol (PEG 6000, BDH Chemicals, Mumbai, India), and polyvinyl alcohol (PVA, Research Labs, Mumbai, India) were purchased. Dichloromethane (DCM) and all other chemicals were of analytical grade (Merck Ltd, Mumbai, India).

Table 1. Composition for Ibuprofen Agglomerates*

Composition	IB-1	IB-2	IT-1	IT-2
Talc (g)	-	-	2.0	3.0
HPMC (% wt/wt of solids)	12.5	16.16	12.5	11.11
PEG (% wt/wt of solids)	6.25	8.33	6.25	5.55

*HPMC indicates hydroxypropylmethylcellulose; and PEG, polyethylene glycol. Agglomerates contain 6 g ibuprofen and 6 mg polyvinyl alcohol.

Crystallo-Co-Agglomeration Technique

The agglomerates were prepared using composition as shown in Table 1. In a crystallization vessel described by Morishima et al,[21] ibuprofen (6 g) and HPMC were dissolved in DCM (6 mL), and talc was uniformly dispersed in it. An aqueous phase (45 mL) containing PEG and PVA was added, and contents were stirred at 900 ± 25 rpm using a constant speed stirrer (Eurostar power control-visc, IKA labortecnik, Staufen, Germany). The stirring was continued to obtain agglomerates, which were then filtered and dried overnight at room temperature.

Drug Content

Agglomerates (800 mg) were powdered, from which powder equivalent to 100 mg of ibuprofen was weighed and extracted using 3 portions of 25 mL each of methanol. After sufficient dilution with methanol, the samples were analyzed spectrophotometrically at 263.8 nm (Shimadzu 160, Kyoto, Japan). Drug content was calculated by comparison with standard solution.[22]

HPMC Content in the Supernatant

The supernatant aqueous phase of each agglomeration batch was kept open for 30 minutes and filtered to get a clear solution. Absorbance of standard and sample solution was determined at 635 nm against water as blank.[23] HPMC content of the agglomerates was calculated by material balance.

Surface Topography

Photomicrographs of primary drug particles suspended in liquid paraffin were taken using a polarized microscope (Nikon Lab, Phot-Pol, Japan) fitted with a camera The agglomerates were photographed using an optical microscope with camera (Nikon FX-35 X) at original magnification ×22.5. Area (A) and Perimeter (P) obtained from tracings of enlarged photomicrographs of agglomerates were used to calculate the shape factor (S). Twenty granules per batch were evaluated.

$$S = P_{actual}^2 / (4 \pi A_{actual}) \quad (1)$$

After gold-coating in a Polaron SC 7640 sputter coater (Polaron, Hertfordshire, UK), the agglomerates were observed at original magnification ×700 using SEM (SEM. Lieca Stereoscan 440, Wetzlar, Germany).

Differential Scanning Calorimetry

Thermal studies of ibuprofen, HPMC, and agglomerates were performed using a DSC (model 821 star^e, Mettler Toledo, Greifensee, Switzerland). Indium standard was used to calibrate the DSC temperature and enthalpy scale. Accurately weighed samples were hermetically sealed in an aluminum crucible. The system was purged with nitrogen gas at a flow rate of 60 mL/min. Heating was done from 30°C to 120°C at rate of 10°C/min.

Powder X-ray Diffraction

XRPD patterns of ibuprofen and agglomerates were obtained (Philips X-ray diffractometer, PW-1729, Netherlands), using Cu K_α radiation ($\lambda = 1.542$ Å) at 30 kV voltage, and current of 30 mA. The data were recorded over a range of 2° to 100° at a scanning rate of 5×10^3 cps using a chart speed of 5 mm/2°.

Micromeritic Properties

Agglomerates were evaluated for flowability by the angle of repose using the fixed funnel method. Particle size distribution was studied by sieve analysis (Ro-Tap sieve shaker, Labtronics, Haryana, India). The retained weight of agglomerates was subjected to analysis by Rosin-Rammler distribution[24] as follows:

$$\text{Ln (2-log } R) = \text{Ln (a log e)} + b \text{ Ln } d \text{ ,} \quad (2)$$

where R is the cumulative residual percentage by weight, d is the particle size (μm), and a and b are constants.

Mechanical Properties

Crushing strength of agglomerates of 3 different size fractions (855, 567, and 390 μm) were determined by mercury load cell method.[25] Friability of agglomerates was performed after subjecting to attrition, in which samples (10 g) with size of no 14/85 and 20 plastic balls (each of 0.95 cm diameter and 530 ± 10 mg weight) were placed on no 85 and shaken for 5 minutes using a Ro-Tap sieve shaker.[26] After sieve analysis, every time mean geometric diameter was obtained fitting the data in Rosin-Rammler distribution. Percentage friability index (FI) was calculated at each time using as the following equation:

$$FI = [(dg)_t / (dg)_0] \times 100 \text{ ,} \quad (3)$$

where $(dg)_t$ and $(dg)_0$ are mean geometric diameters after time t and initial time, respectively.

Table 2. HPMC Content and Micromeritic Properties of Agglomerates*

Batch	HPMC content (%)	Shape factor	RRD (μm)	Angle of Repose (°)	Fines (%)
IB-1	8.71 ± 0.594	1.052 ± 0.0112	929.356 ± 194.27	22.624 ± 0.948	10.737 ± 2.483
IB-2	11.95 ± 0.845	0.9209 ± 0.011	986.105 ± 64.695	29.237 ± 1.523	4.150 ± 0.586
IT-1	9.39 ± 0.640	1.003 ± 0.0118	940.45 ± 98.239	23.118 ± 4.115	5.635 ± 0.740
IT-2	8.89 ± 0.679	0.9756 ± 0.098	1034.241 ± 75.996	24.640 ± 0.698	9.970 ± 2.250

*HPMC indicates hydroxypropylmethylcellulose; and RRD, Rosin-Rammler diameter.

Pressure-Tensile Strength Relationship

Agglomerates (500 ± 10 mg) were compressed using a 13-mm flat punch at a compaction pressure of 0.52, 1.57, 3.15, 4.20, 5.25, 6.30, and 14.70 mPa for 1 minute, using a hydraulic press. Lubrication of the die and punch was performed using 1% wt/vol dispersion of magnesium stearate in acetone. The compacts were allowed to relax for 24 hours and subjected to tensile strength (σ_t) determination.[27]

$$\sigma_t = 2\ F / \pi\ Dt\ , \qquad (4)$$

where D is the diameter and t is the thickness of compacts, and F is the force required to break the compacts.

Pressure-tensile strength data were subjected to nonlinear regression analysis to fit into the Leuenberger equation[28] to calculate compression susceptibility (γ) and compactibility ($\sigma_{t\ max}$).

$$\sigma_t = \sigma_{t\ max}\ [1 - e^{(\gamma P \rho_r)}], \qquad (5)$$

where P is pressure and ρ_r is the relative density calculated from tablet dimensions.

In Vitro Dissolution

The agglomerates (800 ± 10 mg) were compacted using a 13-mm flat punch at a pressure of 1 ton for a dwell time of 1 minute. Ten percent wt/wt of sodium starch glycolate was added as a disintegrating agent. The dissolution was performed in *United States Pharmacopeia (USP)* dissolution test apparatus (DA-6, Veego Scientific, Mumbai, India). The dissolution medium used was 900 mL of phosphate buffer IP, pH 7.2 at 37°C ± 2°C. The paddle speed was 100 rpm. Samples were collected and analyzed spectrophotometrically at 221 nm.

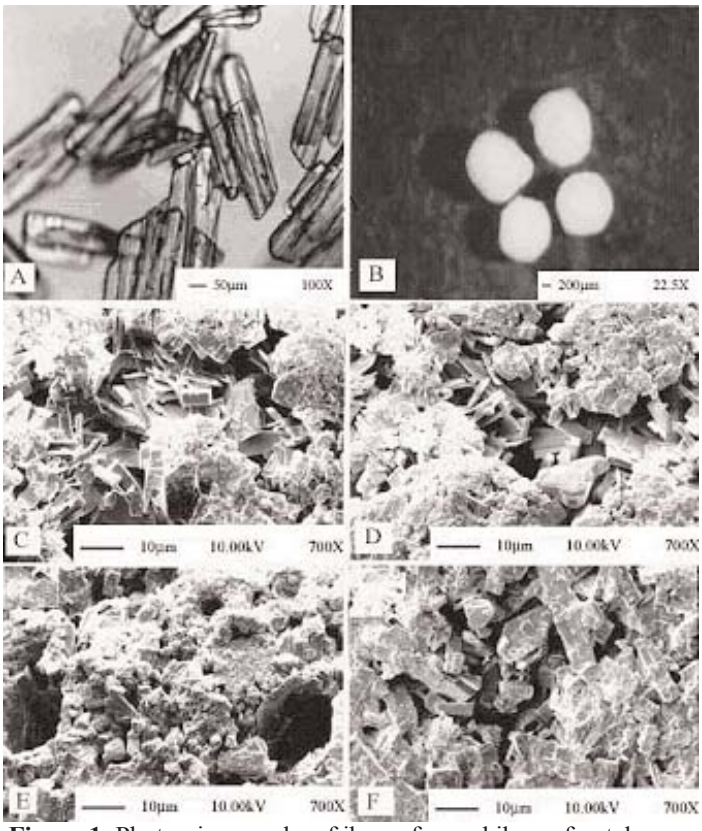

Figure 1. Photomicrographs of ibuprofen and ibuprofen-talc agglomerates by CCA: (A) ibuprofen crystals at original magnification ×100; (B) agglomerates of batch IB-2 at ×22.5; (C) SEM of IB-1 at ×700; (D) SEM of IB-2 at ×700; (E) SEM of IT-1 at ×700; and (F) SEM of IT-2 at ×700.

Results and Discussion

The average yields and drug entrapment of the agglomerates were 94% and 96% wt/wt, respectively. HPMC content of agglomerates was from 8.7% to 12% wt/wt, and the batches may be ranked as IB-2 > IT-1 > IB-1 > IT-2 (Table 2). Photomicrographs of ibuprofen powder and agglomerates (Figure 1) showed needle-shaped ibuprofen crystals with narrow crystal size distribution. The agglomerates were spherical with shape factor values near to unity (Table 2). SEM revealed that agglomerates contain uniformly packed needles with some plates of ibuprofen having well-developed edges. Clumps of polymers embedded with fine crystals were observed on the surface of agglomerates and these clumps were thicker in the agglomerates that contained higher amounts of HPMC (Figure 1D). Presence of talc in the batches caused an increase in the agglomerate size with reduced surface deposits. Due to the thin and uniform polymer coating, more holes were observed on the surface of talc containing agglomerates (Figures 1E and 1F).

DSC thermograms of ibuprofen and agglomerates showed sharp melting endotherms (Figure 2). The enthalpy of melting was reduced significantly for batches containing talc and was lowest for batch IT-2 (Table 3). Surface topography showed significant reduction in crystal size and indicated

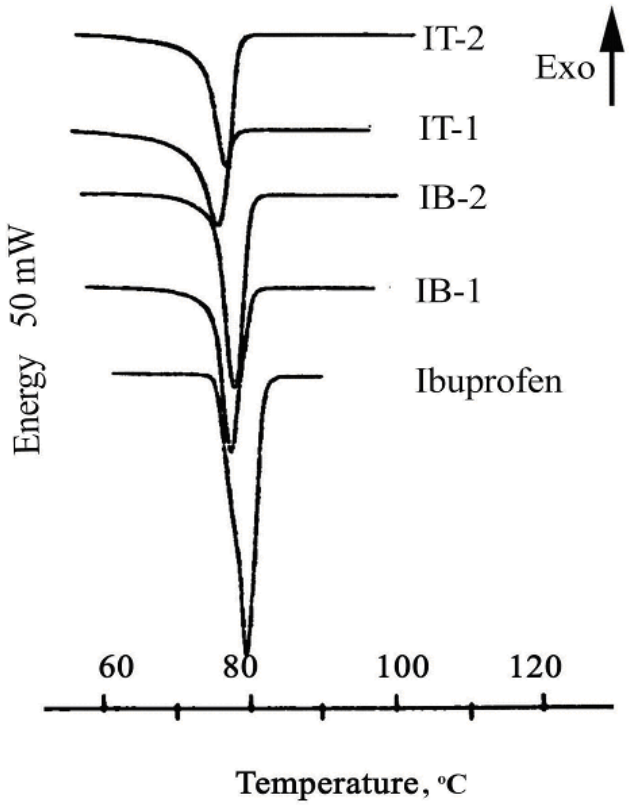

Figure 2. DSC thermograms of ibuprofen and ibuprofen-talc agglomerates obtained by CCA.

Table 3. Thermal Properties of Ibuprofen Agglomerates

Parameter	IB-1	IB-2	IT-1	IT-2
Endotherm (°C)	76.48	76.32	74.69	75.83
Enthalpy (J/g)	136.81	122.13	73.79	68.42
Crystallinity (%)	98.78	88.18	53.28	49.40

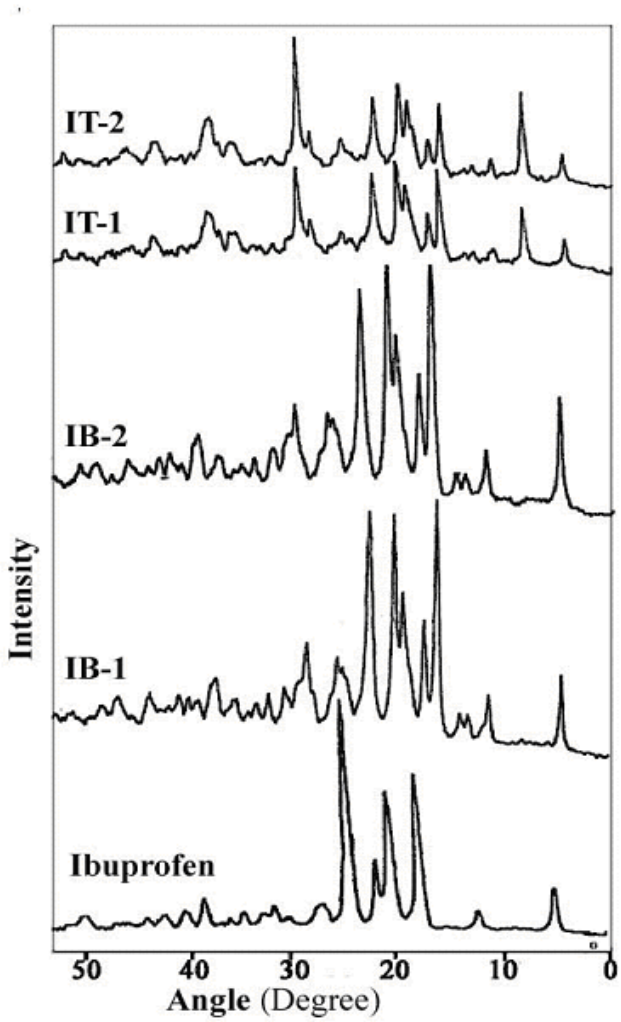

Figure 3. X-ray powder diffraction patterns of ibuprofen and ibuprofen-talc agglomerates obtained by CCA.

formation of miniscular drug form. Many workers have designed a miniscular drug form using excipients with high surface area.[29,30] The reduction in peak intensity of XRPD spectra of agglomerates of batches IT-1 and IT-2 supported the observation (Figure 3). Decrease in peak intensities was due to dilution and formation of some plate-type crystals. Though enthalpy of fusion and intensity of peaks in XRPD is reduced, there is no change in d-spacing values suggesting no change in the crystal form of ibuprofen.

The Rosin-Rammler diameter of agglomerates was in the range of 930 to 1035 µm. Agglomerates of the IT-2 batch were larger (Table 2). The batch containing the lower amount of HPMC per solid content (ie, batch IT-2) showed a higher particle size, which is in contrast to a previous report by Morishima et al.[21] Particle size of the agglomerates was determined by the presence of a cohesive layer of bridging liquid on the surface of growing agglomerates. Wetting of particles by bridging liquid, viscosity of bridging liquid, and interparticulate attraction are the major factors that influence squeezing of bridging liquid to the agglomerate surface. PEG reduces interfacial tension and favors wetting of the particles.[31,32] Fine particles of talc, having higher attraction, reduce the capillary diameter and drive of bridging liquid to surface and favor growth of agglomerate. In correlation with these results, uniform distribution of HPMC in the form of thin coat may have occurred in the presence of talc. On the basis of percentage fines produced, the batches were ranked as IB-1 > IT-2 > IT-1, and IB-2. Although batches IB-1 and IT-1 have the same percentage of HPMC per solid content, stronger interaction of HPMC and talc as compared with ibuprofen causes decrease in the production of fines. The agglomerates showed better flow properties with angle of repose in the range of 22° to 24° (Table 2).

The agglomerates containing talc did not break but deformed under applied force. Agglomerates of batch IT-2 required maximum deformation force (Table 4). Although agglomerates of batch IB-2 contained higher HPMC, mechanical strength of these agglomerates was less than talc containing agglomerates. Deformation and fracture of the agglomerate depends on the particle size, granule porosity,

Table 4. Tableting Properties of Ibuprofen Agglomerates*

Batch	CS (g) No. 10/16	Friability Constants			P-σ_t Relationship			$t_{90\%}$ (hours)
		β_0	β_1	r*	$\sigma_{t\,max}$	γ	*r*	
IB-1	73.912 ± 8.081	47.97	-1.06	0.97	0.783 ± 0.02	0.015 ± 0.001	0.804	7.109 ± 0.164
IB-2	87.205 ± 26.58	103.3	-2.59	0.95	1.257 ± 0.13	0.0107 ± 0.002	0.836	7.858 ± 0.197
IT-1	99.580 ± 24.93	80.68	-2.23	0.96	0.788 ± 0.03	0.0179 ± 0.004	0.867	7.241 ± 0.665
IT-2	115.05 ± 14.36	84.46	-1.84	0.95	0.812 ± 0.01	0.0192 ± 0.001	0.837	13.556 ± 1.602

*CS indicates crushing strength; and r, correlation coefficient.

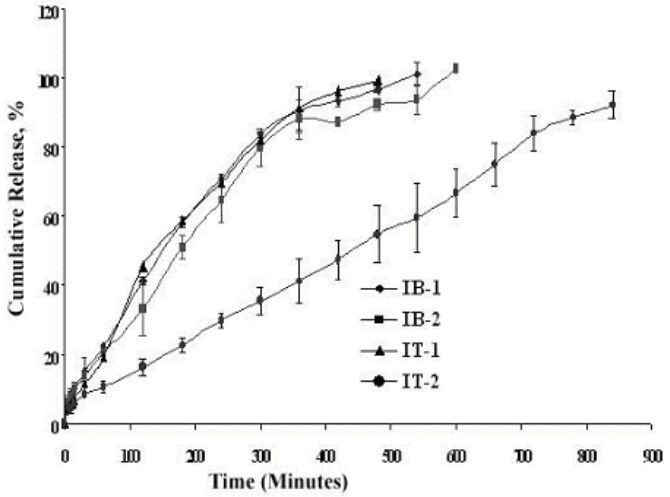

Figure 4. Dissolution Profile of compacted ibuprofen-talc agglomerates obtained by CCA: IB-1 (◆); IB-2 (■); IT-1 (▲); and IT-2 (●).

interparticulate bond strength, and properties of particles forming agglomerates. Agglomerates formed in the presence of talc have lower voids and larger size causing deformation rather than breaking.

Friability constants revealed lower and higher surface strength, respectively, of agglomerates of batch IB-1 and batch IB-2. Further abrasion at a faster rate indicated nonuniform distribution of HPMC. Agglomerates of batch IT-2 showed slower breakdown as compared with IT-1 due to higher talc content. Agglomerates of batch IB-1 showed poor surface strength as compared with IB-2. Nonuniform distribution of HPMC was responsible for faster rates of weight loss due to abrasion.

Agglomerates containing talc showed inferior compression susceptibility due to their deformation under applied pressure. Highest $\sigma_{t\,max}$ values of compacts of IB-2 agglomerates might be associated with asperity melting of ibuprofen in the presence of PEG. The cold welding in addition to the large area of contact produced by the fracture of agglomerates of IB-1 and IB-2 batches imparted high tensile strength to the compacts (Table 4). The low tensile strength of talc containing agglomerates may be due to the lower area of contact, as the agglomerates do not fracture.

The drug release profiles indicated the initial lower drug release from compacts of IT-1 and IT-2 agglomerates due to hydrophobicity of talc (Figure 4). The time required for 90% drug release ($t_{90\%}$), in the case of IT-1 was less compared with IT-2 (Table 4). After initial slow release, IT-1 compacts also showed faster drug release when compared with IB-1. IT-2 batches significantly retarded release with zero-order kinetics.

The precipitation of drug on the surface of talc in the form of very fine crystals with low crystallinity resulted in the formation of miniscular drug form. However, the hydrophobic effect of increased content of talc in IT-2 batches completely blanketed the effect of miniscular drug form. The retarded rate of water penetration and the reduced rate of disentanglement of polymer in the presence of embedded talc might have contributed to drug release retardation.

CONCLUSION

In conclusion, the CCA technique developed in the present study can be used for the design of sustained release ibuprofen-talc agglomerates containing lower amounts of polymers. The agglomerates have shown zero-order release due to the combined effect of the generation of miniscular drug form and the hydrophobicity of talc.

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