Design and Evaluation of Deformable Talc Agglomerates Prepared by Crystallo-Co-Agglomeration Technique for Generating Heterogeneous Matrix

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ABSTRACT

The crystallo-co-agglomeration technique was used to design directly compressible and deformable agglomerates of talc containing the low-dose drug bromhexine hydrochloride (BXH). The process of agglomeration involved the use of dichloromethane as a good solvent and bridging liquid for BXH, water as a poor solvent, talc as diluent, and Tween 80 to aid dispersion of BXH and diluent into the poor solvent. Hydroxypropyl methylcellulose (50 cps) 4% wt/wt was used to impart the desired mechanical strength and polyethylene glycol 6000 5% wt/wt was used to impart the desired sphericity to the agglomerates. Clarity of the supernatant was considered an endpoint for completion of the agglomeration process. The drug-to-talc ratio in optimized batch 1 (BT1) and batch 2 (BT2) was kept at 1:15.66 and 1:24, respectively. The spherical agglomerates obtained were evaluated for topographic, micromeritic, mechanical, deformation, compressional, and drug release properties. The agglomeration yield and drug entrapment for both batches were above 94% wt/wt. Crushing strength and friability studies showed good handling qualities of agglomerates. Heckel plot studies showed low mean yield pressure and high tensile strength, indicating excellent compressibility and compactibility of agglomerates. Diametral and axial fracture of compacts showed deformation of agglomerates revealing formation of a heterogeneous compact. Drug release was sustained for 9 hours and 5 hours from BT1 and BT2, respectively, in 0.1N HCl. Hence, the crystallo-co-agglomeration technique can be successfully used for obtaining spherical, deformable, and directly compressible agglomerates, generating a heterogeneous matrix system and providing sustained drug release.

KEYWORDS: Crystallo-co-agglomeration, deformable agglomerates, heterogeneous compact, sustained release.

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INTRODUCTION

Particle size enlargement has become an important tool in modifying the primary and secondary properties of pharmaceuticals. Various novel methods have been reported to improve the efficiency of the manufacturing process and to offer a high degree of functionality to the particles. Recently, Kadam et al used crystallo-co-agglomeration (CCA)[1,2] as a novel particle size enlargement technique for modifying the micromeritic, mechanical, compressional, and drug release properties of ibuprofen-talc[3] and ibuprofen-paracetamol.[4]

The agglomerates of ibuprofen-talc prepared by CCA had very good mechanical strength. Crushing strength studies on agglomerates revealed that the deformation force for agglomerates containing 33.3% wt/wt of talc was more than that for agglomerates containing 25% wt/wt of talc. These deformed agglomerates remain as such in the green compact-generating heterogeneous matrix. Jarosz and Parrot[5] have used a mercury load cell method to study the crushing strength of agglomerates. Studies on the effect of agglomerate surface morphology on granule breakage and a method involving observation of thin compact under an optical microscope to study granule deformation have been reported.[6] A free fall impact test employing high-velocity impact has been used to study the fracture of weaker granules.[7] The use of laser light reflection to identify contact areas and the extent of deformation in the compact has also been reported.[8]

To prevent fracture of pellets, Lundqvist et al[9] and Pinto et al[10] suggested addition of soft pellets as a cushion agent to promote compact disintegration. Use of 50% wt/wt paraffin wax beads as a cushion agent is reported to prevent fracture of enteric-coated diltiazem pellets during compaction.[11] Studies performed by Beckert et al on rapidly disintegrating enteric-coated bisacodyl pellets showed that plastically deformable fillers, high crushing strength of the agglomerate, a greater amount of polymer coating, and higher elongation at the break of film coating prevents fracture of pellets.[12] Dashevsky et al[13] have observed that a coating mixture of 10% triethyl citrate and Kollicoat SR30D on sucrose pellets remains intact during compression, whereas a brittle coat of Aquacoat ECD30 and Kollicoat SR30D gets ruptured. But seldom are reports available on preparation of drug-loaded deformable agglomerates without the need for a cushion or

polymer coat. Hence, the objective of this research was to prepare deformable agglomerates of talc loaded with a drug and to prepare its compact to generate a heterogeneous matrix system.

The present work reports on preparation of deformable agglomerates of talc with poorly compressible bromhexine hydrochloride (BXH) and comparatively lower quantities of polymer. The agglomerates obtained were subjected to micromeritic, mechanical, compressional, and drug release kinetic studies. The crushing strength of the agglomerates and the diametral and axial crushing of the compact were used to study the deformation phenomenon. Deformed agglomerates for newly generated surfaces of the fractured compact were photographed to study deformation.

Materials and Methods

Materials

BXH was a gift from IPCA Laboratories Ltd (Mumbai, India). Hydroxypropyl methylcellulose (HPMC 50 cps) was a gift from Colorcon Asia Pvt Ltd (Mumbai). Talc (Indian Pharmacopoeia grade) was supplied by Get-Rid Pharma (Pune, India). Polyethylene glycol (PEG 6000, BDH Chemicals, Mumbai), dichloromethane (DCM, Merck Ltd, Mumbai), and all other chemicals were of analytical grade.

Methods

Process Design

The CCA technique was followed as per a previous report using a Morishima vessel (1000-mL capacity)[14] with walled baffles and a stirrer with modified blades (Remi Udyog Ltd, Mumbai) designed for the agitation.

Process Development

A homogeneous powder mixture of talc, HPMC 50 cps, Tween 80, and BXH was wetted by DCM (30 mL) in a vessel and stirred for 1 minute. The walled baffle was placed in the vessel, and an aqueous solution of PEG (100 mL) was poured into the vessel with continuous stirring. The proportion of BXH to talc—1:15.66 (94% wt/wt talc) in batch 1 (BT1) and 1:24 (96% wt/wt talc) in batch 2 (BT2)—was optimized. Polymers PEG 6000, HPMC 50 cps, and Tween 80 were used as 5% wt/wt, 4% wt/wt, and 1.5% wt/wt, respectively, of the total weight of BXH and talc. The stirring was continued until spherical agglomerates were obtained and the supernatant was clear. At the completion of agglomeration, the whole mass was filtered. The same filtrate was used for subsequent washings of agglomerates. Then agglomerates were dried at 37°C for 24 hours in a hot air oven. The composition of optimized batches of agglomerates is shown in Table 1.

Yield and Drug Entrapment

The percent yield of the agglomerate was determined by applying the mass balance equation to the process. A drug entrapment study was performed for BT1 and BT2 separately in triplicate. Exactly 200 mg of agglomerates from each batch were weighed, powdered, and added to 50 mL of 0.1 M methanolic hydrochloride solution. The volume was adjusted to 100 mL by 0.1 M methanolic hydrochloride and filtered through Whatman filter paper no 42. The filtrate was analyzed spectrophotometrically at 317 nm (Shimadzu 160, Kyoto, Japan). BXH content was determined from a standard curve. The values of the slope, Y intercept (constant), and coefficient of correlation obtained from the standard curve were 119.658, 0.051, and 0.9999, respectively.

Drug Loss in Supernatant

At the completion of the agglomeration process, 1 mL of supernatant was pipetted out from BT1 and BT2, diluted to 10 mL with 0.1 M methanolic hydrochloride, and analyzed spectrophotometrically, as above, at 317 nm for appearance of BXH in the supernatant.[15]

HPMC Loss in Supernatant

During the agglomeration process, 2.5 mL of continuous phase was removed at time intervals of 15 minutes up to the completion of the process; the whole mass was filtered and kept at 38°C to 40°C for 30 minutes for complete evaporation of DCM.[16] Withdrawn samples were immediately replaced by the same volume of distilled water. The content of HPMC in each sample was determined spectrophotometrically at 635 nm against a standard blank. Study was performed on BT1 and BT2 in triplicate. The data on time and log HPMC concentration were subjected to regression analysis.

Table 1. Composition and Condition of Agglomeration Process*

Batches	Talc (g)	BXH (g)	HPMC (g)	PEG (g)	Tween (g)	Speed (rpm)	Time (min)
BT1	18.8	1.2	0.80	1.0	0.3	950 ± 50	150 ± 20
BT2	19.2	0.8	0.80	1.0	0.3	800 ± 50	90 ± 10

*BXH indicates bromhexine hydrochloride; HPMC, hydroxypropyl methylcellulose; PEG, polyethylene glycol.

Topography

Photomicrographs of agglomerates were taken using a Nikon HFX-DX camera (Mumbai, Maharashtra, India) (magnification x40) and were observed for surface morphology.

Micromeritic Properties

The fixed-funnel free-standing cone method was used to assess the flowability of agglomerates. Particle size distribution of BT1 and BT2 was studied by sieve analysis (Ro-Tap sieve shaker, Labtronicas, Haryana, India). The agglomerates retained on sieves were weighed, and the resulting data were used to obtain the mean geometric diameter by plotting the cumulative percentage undersize versus the average particle size on log probability paper.[17]

Sphericity Determination

The tracings obtained from photomicrographs were used to calculate the area (A) and perimeter (P') of agglomerates.[18] The particle shape of both batches was measured by computing the shape factor, the circularity factor, and the length-to-width ratio.

$$\text{Shape Factor (P)} = P''/P' \quad (1)$$

where $P'' = 2\pi\,(A/\pi)^{1/2}$.

$$\text{Circularity Factor(S)} = (P')^2/(12.56 \times A) \quad (2)$$

Mechanical Properties

The crushing strength of agglomerates of BT1 and BT2 was determined by the mercury load cell method.[5] Agglomerates were randomly sampled and subjected to crushing strength determination. For friability studies, 20 g of agglomerates

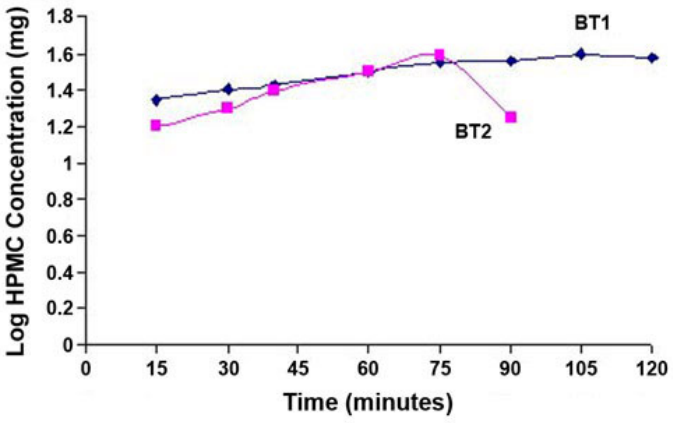

Figure 1. Loss of HPMC in supernatant: BT1 and BT2. HPMC indicates hydroxypropyl methylcellulose.

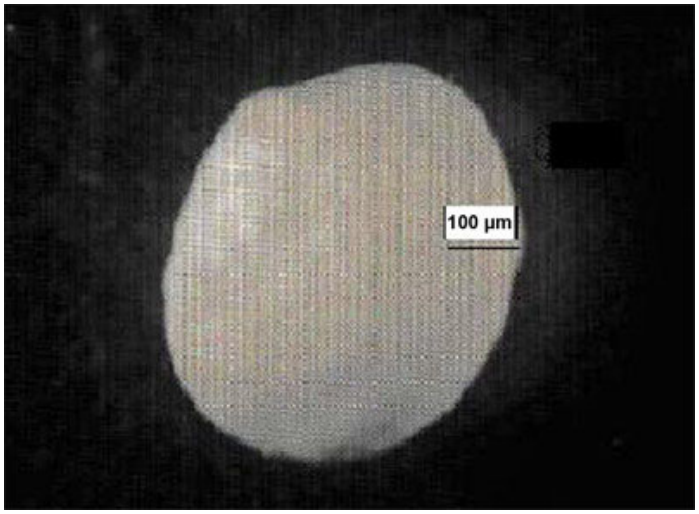

Figure 2. Photomicrograph of agglomerate (magnification x40).

from BT1 and BT2 were subjected separately to attrition in a ball mill with polyethylene balls weighing 40 mg and having a diameter of 0.915 cm. Every time agglomerates were subjected to a sieve nest of mesh (ASTM) numbers 5, 10, 16, 22, 30, 36, 44, 60, and 72 for 1 minute of shaking using a Ro-Tap sieve shaker.[19]

The fraction retained on each mesh was weighed, and the mean geometric diameter was obtained from extrapolation of the log probability plot of cumulative percentage undersize versus the particle size in microns. The percent friability index (FI) was calculated at each time using the following formula:

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

where $(dg)_0$ and $(dg)_t$ are mean geometric diameters at the initial time and at time t.

Pressure–Relative Density Relationship

Intact agglomerates (800 ± 10 mg) of BT1 and BT2 were compressed separately by using a hydraulic press (Spectra Lab) (Mumbai, Maharashtra, India) having a 13-mm flat-faced punch and die set at pressures of 0.5, 1.0, 1.5, 3.0, and 7.0 tons for 1 minute of dwell time. Lubrication of the die and punches was performed by a 1% wt/vol dispersion of magnesium stearate in acetone. Compacts were allowed to relax for 24 hours at ambient conditions and then subject to compressional studies by the following equation[20,21]:

$$Ln(1 - p_f) = \text{KP} + \text{A} \quad (4)$$

where P_f is the packing fraction of the tablet, P is the applied pressure in tons, and K is a Heckel constant equal to $1/3\sigma_{0.}$, where σ_0 is yield strength and $3\sigma_0$ is mean yield pressure (MyP). A is a constant.

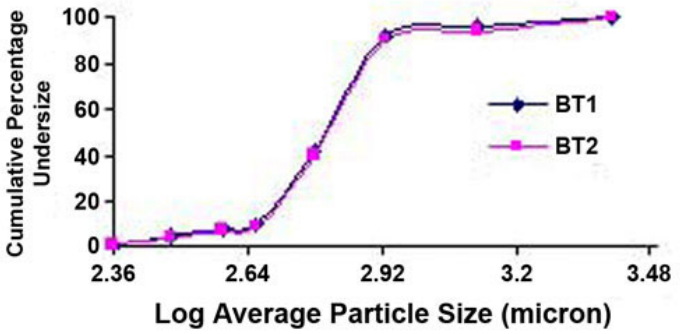

Figure 3. Particle size distribution for BT1 and BT2.

Pressure–Tensile Strength (σt) Relationship

The same data used for compressional studies were used to study the pressure–tensile strength relationship. The hardness value of compacts was determined by a Monsanto-type hardness tester and used for σ_t determination by the following equation[22]:

$$\sigma_t = 2F / \pi Dt \qquad (5)$$

where F is the crushing force in g, D is the diameter of the compact, and t is the thickness of the compact.

Fracture Studies

Compacts crushed diametrically and axially were observed for newly generated surfaces and the deformation of agglomerates during compression.

Contact Angle Determination

Agglomerates were compacted at 7 tons by using a hydraulic press for 1 minute of dwell time. A drop of water (50 μL) was placed on the compact by using a micropipette. A photograph of the placed drop was taken to measure the contact angle.

In Vitro Dissolution

Disintegration of Agglomerates. Exactly 300 mg and 400 mg of intact agglomerates from BT1 and BT2, respectively, were taken and subjected to dissolution in a US Pharmacopeia dissolution test apparatus (DA-6D Veego Scientific, Mumbai) in triplicate. The study was performed in 900 mL of 0.1 N HCl maintained at 37 ± 2°C and stirred by paddles at 100 rpm, until 100% of the drug was released.

BXH Release Rate From Compact. Exactly 300 mg and 400 mg of intact agglomerates from BT1 and BT2, respectively, were weighed and compressed by a hydraulic press having a 13-mm flat-faced punch and die set at 2 tons of pressure for 1 minute of dwell time. The compacts obtained were subjected to dissolution in triplicate, similar to that of agglomerates. Each time, 5 mL of sample was withdrawn and analyzed spectrophotometrically at 317 nm. The same amount of fresh 0.1 N HCl was used to replace the amount withdrawn.

Results and Discussion

The performance of the CCA process was evaluated on the basis of ease of processing, clarity of supernatant, agglomeration yield, and agglomerate handling qualities. All these process performance characteristics were observed in BT1 and BT2.

For BT1 and BT2, the yield of agglomeration was 94% to 98.5% wt/wt and 94% to 98% wt/wt, respectively. The amount of BXH entrapped in agglomerates was 93% to 96% wt/wt and 94% to 97% wt/wt for BT1 and BT2, respectively. The percentage of fines generated in both batches was 2% to 6% wt/wt. Fines might have been generated because of sticking of the wet powder mass to the vessel, baffle, and stirrer during agglomeration. The loss of BXH to supernatant was statistically significant between BT1 and BT2 (at $P < .05$). This may have been due to miscibility of DCM with water (1.30% vol/vol), resulting in migration of BXH from DCM into water.[23] Since BT1 had more drug and less talc (Table 1), the surface area available for the deposition of BXH might have been smaller, leading to statistically significant drug loss.[24] Loss of HPMC to the supernatant followed a logarithmic relationship with time for both batches, as shown in Figure 1. It was greater in the initial stages but later got reduced because of entrapment of HPMC during the progress of agglomeration. A greater amount of BXH increased the loss of HPMC to supernatant in BT1. Although the loss of HPMC was greater in BT1 than in BT2, the difference was statistically insignificant.

Table 2. Regression Analysis Data for Loss of HPMC, Sphericity Determination*

				Regression Analysis for Log HPMC Concentration vs Time		
Batch	S	C	L/W Ratio	m	c	r
BT1	1.052 ± 0.012	1.003 ± 0.001	1.135 ± 0.001	0.0046 ± 0.0002	1.191 ± 0.003	0.981 ± 0.089
BT2	1.040 ± 0.010	1.004 ± 0.001	1.130 ± 0.001	0.0040 ± 0.0003	1.187 ± 0.002	0.849 ± 0.045

*HPMC indicates hydroxypropyl methylcellulose; S, shape factor; C, circularity factor; L, length; W, width. Values in all columns are mean ± SD for 3 readings.

Table 3. Tabletting Properties of Agglomerates*

	Regression Analysis										
	Log CS vs PS			Log P_f vs Log P			Log TS vs P_f			P and RD Relationship	
Batch	q	n	r	q	n	r	q	n	r	MyP	σ_t at 0.9 P_f
BT1	11.376 ± 0.021	0.350 ± 0.005	0.973 ± 0.023	–0.034 ± 0.003	0.096 ± 0.001	0.974 ± 0.009	–1.927 ± 0.012	3.07 ± 0.03	0.952 ± 0.002	0.957 ± 0.004	6.958 ± 0.103
BT2	11.015 ± 0.004	0.947 ± 0.003	0.960 ± 0.012	–0.036 ± 0.001	0.097 ± 0.001	0.982 ± 0.002	–4.557 ± 0.022	4.23 ± 0.04	0.949 ± 0.003	0.724 ± 0.013	3.312 ± 0.098

*CS indicates crushing strength, PS, particle size, q, n, and r are the constant, slope, and coefficient of correlation for regression analysis, MyP and TS are the mean yield pressure and the tensile strength in the pressure (P) and relative density (RD) relationship. Values are mean ± SD for 3 readings.

Topographic studies on the agglomerates showed small pits at the surface (Figure 2). This was because of evaporation of DCM during drying. The mean geometric diameter for BT1 ranged from 770 to 795 μm and for BT2 it was 780 to 800 μm (Figure 3). The presence of DCM at the surface of the growing agglomerate, the agitation force, interparticulate attraction, and polymers (PEG and HPMC) influenced the size of agglomerates, as reported in earlier studies.[25] More BXH loading in BT1 decreased the cohesive attraction, reducing the size of agglomerates, and the presence of HPMC increased the size of agglomerates because of increased viscosity of DCM. Here, increased viscosity reduced the destructive forces acting on the agglomerates. PEG, because of its tendency to reduce interfacial tension, is reported to generate smaller agglomerates.[25,26] More processing time required for BT1 also reduced the size of agglomerates because of destructive forces like agitation acting for a long time (Table 1). And more loss of HPMC was seen because of processing of agglomerates at higher speed, causing less deposition of HPMC at the surface of the talc.

Lalla and Bhat have reported an angle of repose of 25° to 30° for a spheronized product.[27] Hence, the observed angle of repose for both batches in the range of 29° to 30° indicated good flowability of agglomerates. Moreover, the shape factor, the circularity factor, and the length-to-width ratio close to unity confirmed the sphericity of the agglomerates (Table 2).

The crushing strength of BT1 agglomerates was 104 to 138 g, and that of BT2 agglomerates was 83 to 161 g. The logarithmic relationship was established between the crushing strength and the size of the agglomerates as shown by Equation 6:

$$\log CS = \log q + n\log D \qquad (6)$$

where CS is crushing strength, D is average diameter of agglomerates, and n and q indicate the slope and constant for linear regression, respectively.

Since bromhexine has low inherent cohesiveness, its presence in agglomerates had a pronounced effect on the crushing strength of agglomerates. This resulted in n being smaller for BT1 than for BT2 (Table 3). Simultaneously, reducing the amount of HPMC in the agglomerate also reduced its crushing strength. The studies on friability of agglomerates showed a linear relationship between friability index and time, as seen in Figure 4. A greater reduction in the friability index indicates uneven distribution of HPMC in BT1 and reduced cohesive interaction with talc. The consolidation ability of agglomerates is indicated by MyP. In the case of BT2, MyP was less than BT1, indicating good compressibility of BT2 because of a lower amount of badly compressible BXH (Table 3). The drug loading increased the tensile strength (TS) of the compact because of more crystal bridges formed by the drug-drug molecules (Table 3). In addition to that, positive polymer-polymer, polymer-drug, drug-drug, and drug-talc interaction increased the TS of the compact. The effect of PEG and HPMC on the TS of BT1 and BT2 seemed to be the same.

The release of drug from agglomerates of batch BT1 required 13 to 30 minutes, whereas BT2 released all drug in 10 minutes. Compacts prepared from agglomerates of BT1

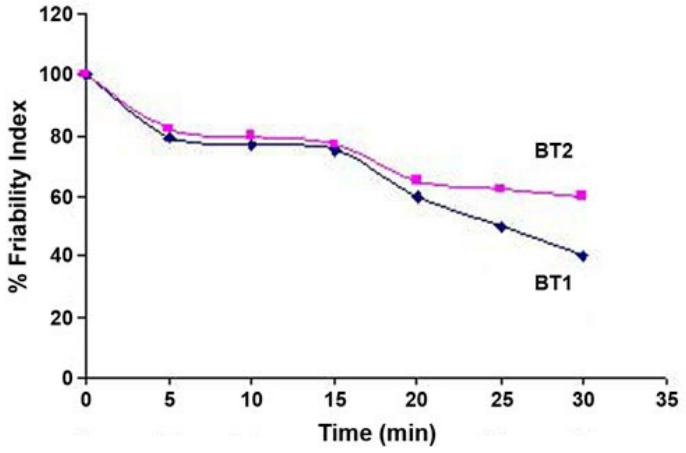

Figure 4. Friability studies for BT1 and BT2.

showed drug release over a period of 9 hours, and compacts of BT2 agglomerates sustained the drug release up to 5 hours only (Figure 5). The value of $t_{50\%}$ for BT1 was 6 hours, whereas for BT2 it was 2.5 hours. In this case it was clearly evident that talc was not the sole factor retarding drug release. Predominantly, the extent of drug-diluent bonding in the compact (TS) determined the release of drug. This finding supported the fast release of drug from agglomerates of BT2. A higher value of $t_{50\%}$ for BT1 indicated that there was a strong drug-diluent interaction and a reduced amount of HPMC in the compact. Use of talc in the system retarded the release of drug because of talc's hydrophobic nature.

Very few researchers have prepared miniscular dosage forms by using excipients with a large surface area.[28,29] Pawar et al designed a miniscular dosage form for ibuprofen-talc by CCA. Mainly, recrystallization of drug during agglomeration generates the miniscular dosage form. The miniscular dosage form of BXH-talc in this new study showed sustained drug release fitting the Higuchi matrix model, whereas sustained zero-order drug release was reported for ibuprofen-talc.[3]

Compression studies on agglomerates of both BT1 and BT2 showed deformation of agglomerates instead of fracture, because the agglomerates had lower voids (porosity) showing interparticular slippage during compression. The high value of Young's modulus and the high yield strength of HPMC contributed to deformation of the agglomerates. Along with HPMC adsorbed at the surface of talc, high talc content also imparted deformability to agglomerates. The BT2 agglomerates required more deformation force than did the BT1 agglomerates, in agreement with the study performed by Pawar et al.[3] An increase in the talc percentage increased the deformation force. Agglomerate deformation was observed in the form of convexities appearing at newly generated surfaces in the fractured compact. The diametral fracture (Figure 6B)

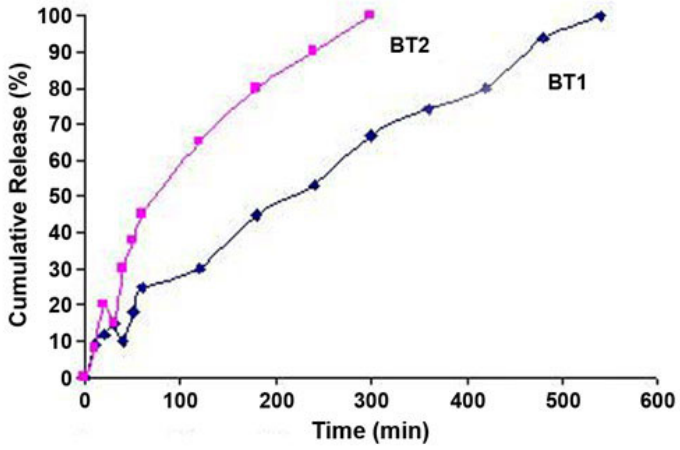

Figure 5. Dissolution profile of compacted bromhexine hydrochloride–talc agglomerates obtained by crystallo-co-agglomeration: BT1 and BT2.

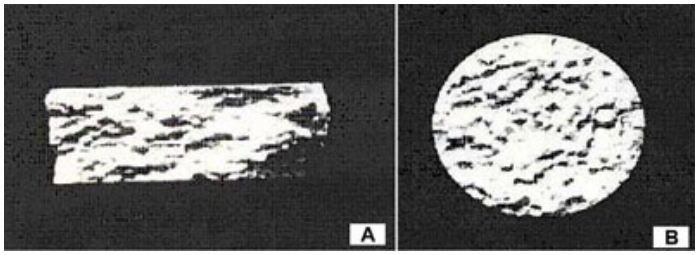

Figure 6. Fracture of compact (magnification x40): (A) axial and (B) diametral.

of compacted agglomerates showed convexities, and the axial fracture (Figure 6A) showed the newly generated surfaces caused by breaking of deformed agglomerates in the form of uneven protrusions.

Conclusion

The CCA technique can be successfully used for generation of deformable and directly compressible agglomerates forming a heterogeneous matrix system. As the amount of talc in the agglomerates increases, the deformation force required also increases. But to some extent the TS gets decreased because of the reduced number of crystal bridges at low drug loading. The release of drug from such compacts can be sustained and modeled to the matrix type.

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