DESIGNING & DEVELOPMENT OF SPHERICAL AGGLOMERATES OF IBUPROFEN-PARACETAMOL BLEND FOR IMPROVED TABLETING AND DISSOLUTION

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ABSTRACT

Blends of paracetamol and ibuprofen (5:2) incorporating sodium starch glycolate as disintegrants was spherically agglomerated (SAPI) in benzene-water system. SAPI were agglomerated using aqueous hydroxypropylmethylcellulose (HPMC) solution as bridging liquid. Agglomeration process was optimized for several parameters like speed and duration of agitation, volume of bridging liquid added. The developed SAPI were evaluated for yield and micromeritics properties viz. bulk density, tapped density, compressibility index, angle of repose and mean agglomerate size measurement. The effect bridging liquid concentration on mean agglomerate size and other micromeritics properties were determined. SAPI was characterized for FTIR and differential scanning calorimetry analysis and its results revealed that there is no physical or chemical interaction existed in agglomerates. SAPIs were successfully compressed into directly compressible tablet. Results of in vitro drug release studies conducted on SAPI tablet showed that the dissolution rate is increased due to presence of HPMC as well as SSG in intra agglomerates. Results of this studies showed that HPMC bound SAPI produces improved micromeritics and excellent tabletting with higher dissolution rate and spherical agglomeration could be employed as an alternative method of tabletting.

Keywords: Spherical agglomeration, particle designing, paracetamol-ibuprofen blend, HPMC

INTRODUCTION

Spherical agglomeration is the latest technique of enlarging smaller particles of solid into large size by inter-particle agglomeration. [1] This process combines crystallization as well as granulation steps altogether and yields crystals with distinguished spherical shape and enlarged size equivalent to size of granules employed in tabletting compression.[2] This process improves flow ability, packability and compression properties of the pharmaceutical solids.[3] Hence, it is emerging as potential area of research in particle designing employed in development of capsules and tablet dosage forms. Briefly, agglomeration process consists of dispersed solvent phase distributed in bulk liquid where drug acquire spherical shape during crystallization of dispersed phase. [4]

Paracetamol and ibuprofen are the important drugs belonged to NSAIDS category and indicated for antipyretic and anti-inflammatory effects in therapeutics. Both candidates enjoyed a good market share and mostly prescribed in drug combinations. Manufacturing of drug combination tablets usually consists of wet granulation method, consisting of several steps of processing.

The objective of this study is to develop agglomerates of paracetamol-ibuprofen blend for direct compression and improved micromeritics features using spherical agglomeration technique.

MATERIAL AND METHODS

Pharmacopoeial grade paracetamol and ibuprofen was obtained from August Pharmaceutical, Mumbai, India. HPMC 15 cps was generously supplied as gift sample from Colorcon India Pvt. Ltd Mumbai, India. Sodium starch glycolate was kindly received from Ranbaxy Research Lab, Gurgaon Haryana, India. All solvents employed in this study were of analytical grade and used as it was received. Tablet tooling was employed in this study of 16 station press Cadmach, Ahmadabad, India with

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10 mm die punch tooling.

Preparation of Agglomerates

Powder blend of paracetamol and ibuprofen with specified amount of sodium starch glycolate were transferred to 250 ml beaker containing 100ml of benzene. The whole system was agitated for 20mins at 200 rpm using top mounted stirrer attached with digital rpm controller at ambient temperature. To this system, specified amount of 0.1% HPMC solution as given in the table 1 was added. This process was undergone in continuous stirring for half an hour to produce drug agglomerates. In the next stage, agglomerates were separated by decanting benzene, followed by drying in oven for one hour and stored in the air and light resistant container.

Table 1: Composition of paracetamol-ibuprofen agglomerates, processing parameters and their yield

Code	Pcm/Ibu ratio	Stirring rate (rpm)	Stirring time (min)	Bridging liquid (ml)	Bridging liquid vol (%)	Yield (%)
SAPI-1	5:2	250	15	0.1	0.1	91
SAPI-2	5:2	250	20	0.2	0.2	67
SAPI-3	5:2	250	15	0.1	0.4	97
SAPI-4	5:2	250	20	0.2	0.1	55
SAPI-5	5:2	350	15	0.1	0.2	93
SAPI-6	5:2	350	20	0.2	0.4	52
SAPI-7	5:2	350	15	0.1	0.1	95
SAPI-8	5:2	350	20	0.2	0.2	33
SAPI-9	5:2	450	15	0.1	0.4	87
SAPI-10	5:2	450	20	0.2	0.1	-
SAPI-11	5:2	450	15	0.1	0.2	93
SAPI-12	5:2	450	20	0.2	0.4	12

Micromeritics evaluation of Agglomerates

Drug agglomerates were evaluated for bulk density, tapped density, static angle of repose measurement and agglomerate size distribution by sieving method.

Characterization of Agglomerates

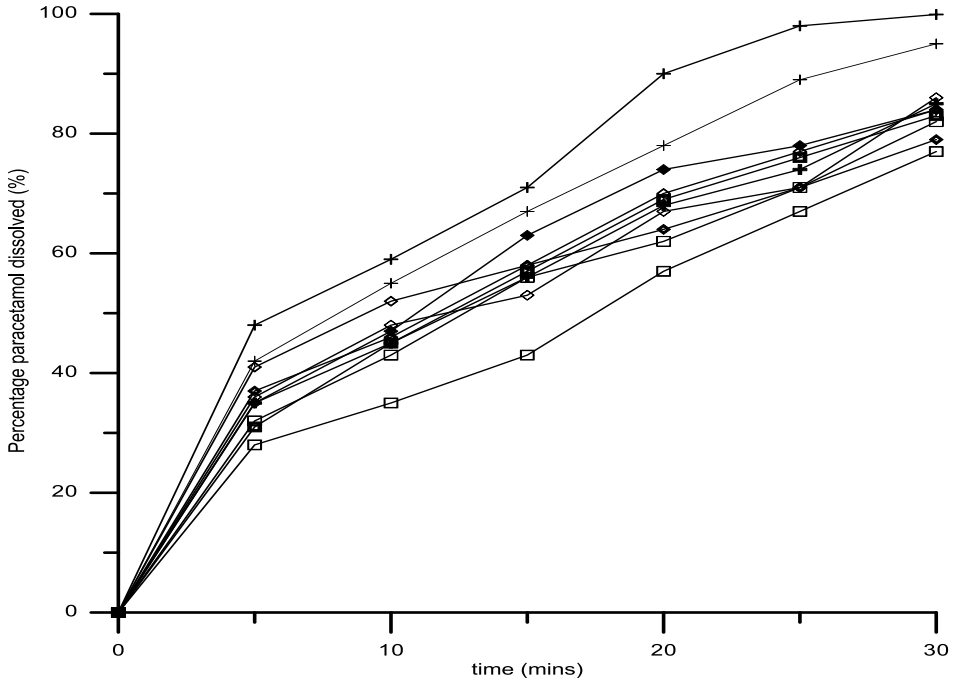

Fig1: In vitro dissolution testing of paracetamol from SAPI-2 formulation

Table-2 Micromeritics evaluation of paracetamol-ibuprofen agglomerates

Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose	CI	Mean size
SAPI-1	0.318	0.583	25.4		1267
SAPI-2	0.318	0.583	22.7		678
SAPI-3	0.318	0.583	28.6		1230
SAPI-4	0.318	0.583	24.3		708
SAPI-5	0.318	0.583	25.6		1138
SAPI-6	0.318	0.583	28.5		870
SAPI-7	0.318	0.583	22.6		1176
SAPI-8	0.318	0.583	29.1		456
SAPI-9	0.318	0.583	23.5		1074
SAPI-10	0.318	0.583	-		-
SAPI-11	0.318	0.583	23.6		905
SAPI-12	0.318	0.583	-		-

Drug agglomerates were characterized for FTIR, DSC and SEM studies.

Tabletability of Agglomerates

Drug agglomerates were compressed into tablets using extra-granular additives as given in the table 2. The tablets were evaluated for hardness, weight variation, friability and disintegration testing as per I.P.

In vitro dissolution testing of tablet made from agglomerates

Tablets prepared from agglomerates were subject to in vitro dissolution testing of paracetamol as well as ibuprofen as per the method given in Indian pharmacopoeia.

Table 3 Evaluation of tablets compressed from SAPI formulations

Code	Disinteg-ration time (sec)	Weight variation (%)	Friability (%)	Hardness kg/cm2
SAPI-1	180	4.5	0.21	4.3
SAPI-2	123	3.2	0.18	4.6
SAPI-3	121	5.6	0.25	4.7
SAPI-4	153	7.8	0.21	4.8
SAPI-5	190	4.5	0.23	5.2
SAPI-6	145	5.7	0.24	4.5
SAPI-7	137	8.7	0.24	4.6
SAPI-8	146	4.6	0.19	4.9
SAPI-9	177	6.8	0.17	5.7
SAPI-10	-	-	-	-
SAPI-11	204	9.5	0.15	6.8
SAPI-12	-	-	-	-

RESULTS

Paracetamol-ibuprofen blend (5:2) was successfully agglomerated at 0.1% w/v HPMC solution in benzene. Concentration above 0.1%, bridging liquid was relatively more viscous and resulted in complete wetting of powder blend to take place. Below this concentration, the binding strength of HPMC in SAPI was not sufficient enough to retain drug particles in spherically agglomerated shape. The rate of stirring at 350rpm was found to be effectively agglomerate powder blend of drugs. Agglomerate showed complete wetting of drug mass above 350 rpm of stirring and produced breakage of larger agglomerates whereas at lower agitation speed agglomerates produced had smaller size. [5] There has been a good correlation existed between the rate and extend of stirring, as rapid stirring for less time produce similar agglomerate size which can be obtained by slow stirring rate for longer duration.

The volume of bridging liquid used in agglomerate formation was found to be 0.4ml. This volume of 0.1% HPMC solution was sufficient enough to form capillary network within agglomerate mass formed during shearing of powder blend. Since HPMC solution is viscous, it exerts binding of crystals entrapped within agglomerates. [6]

Bulk density and tapped densities of SAPI were $0.654gm/cm^3$ and $0.765g/cm^3$ respectively when compared with untreated blend of drugs (0.457 and 0.722 gm/cm^3). This showed that agglomerated

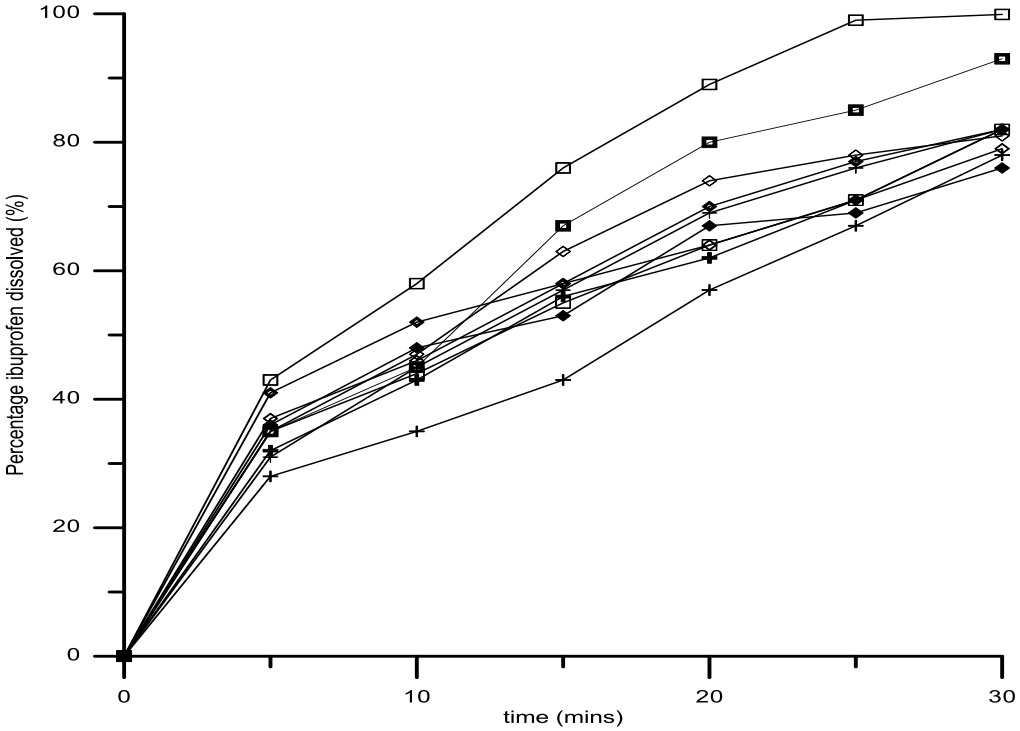

Fig2: In vitro dissolution testing of ibuprofen from SAPI-2 formulation

powder blend were more compact than untreated one. Angle of repose measurement of all SAPI formulations had in the range of 20 to 25° whereas 36° angle of repose of untreated blend. This decrease in angle of repose was ascribed to spherical shape of SAPI after agglomeration. The result of micromeritics studies showed that the SAPI was denser, compact, discrete and free flowing than untreated blend of drugs. [7]

FTIR studies on SAPI formulations showed

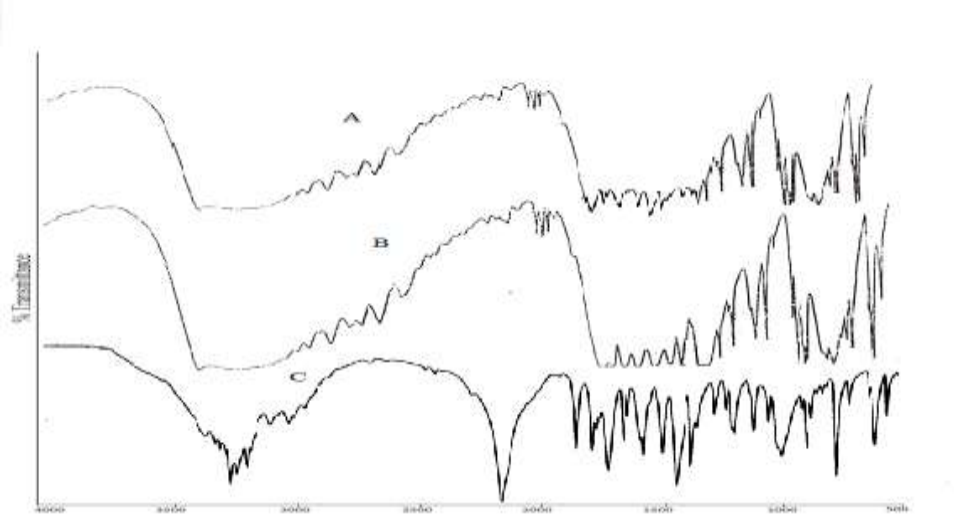

Fig3: FTIR spectra of A) spherical agglomerate formulation SAPI-2 B) pure paracetamol C) pure ibuprofen.

characteristics group frequencies at 3600, 3050 cm^{-1} confirming the –OH and $–NH_2$ groups in paracetamol. A characteristics frequency at 2670 cm^{-1} in SAPI confirmed the presence of –COOH group

Fig. 4 Scanning Electron Microscopy.

frequency of ibuprofen. Differential scanning calorimetry studies confirmed two melting endotherms at 168°C and 153°C which corresponds to the melting point of paracetamol and ibuprofen respectively. Both studies ruled out any possibility of drug-excipients interaction might be existed in SAPI.

Surface morphology of SAPI appeared to be perfectly spherical symmetry as observed through scanning electron microscopic images. The average agglomerate size was found to be 1150µm as appeared from SAPI image. It was also appeared from the SEM image that how packing of smaller particles in the available space existed in larger size of particles. Some areas in images showed existence of void spaces and very small particles occupying interstitial space of agglomerates.

SAPI along with other extra-granular portion consisted of sodium starch glycolate and dry binder (poly vinyl pyrrolidone k_{14}) was successfully compressed into tablet with no sign of lamination or capping. Tablet prepared from SAPI was shown to have permissible limit of weight variation, friability.[8] The average disintegration time of SAPI tablet was two minutes.

In vitro dissolution studies showed that the tablet prepared from SAPI took less than ten minute to dissolve 90% of drugs and whereas tablet made by conventional wet granulation method showed twenty minutes to dissolve the same amount of drugs. [9] This could be explained by the fact the HPMC at 0.1% concentration level also acts as tablet disintegrants and therefore SAPI released faster due to double disintegrants at inter –agglomerate level.

CONCLUSIONS

Spherical agglomeration technique was successfully applied to paracetamol- ibuprofen blend. Agglomeration was optimized for speed and extent of agitation, volume of bridging liquid required to bind the drug particles within agglomerates. Agglomerates showed no sign of drug excipients interaction during processing of agglomerates. SAPI were compact, free flowing and

discrete units. Agglomerates were directly compressed into tablet with quick disintegration time and produced higher dissolution rate.

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