Improvement in Flowability and Compressibility of Ampicillin Trihydrate by Spherical Crystallization

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Spherical crystallization was carried out by ammonia diffusion method to achieve agglomerates of primary crystals of the drug. Both agglomerated and primary crystals were subjected to measurement of micromeritic properties, compressibility, powder compaction properties and effect of crystal shape on tablet strength. Dispersible tablets of agglomerated ampicillin trihydrate were prepared using suitable excipients in formula and were evaluated for various physical parameters. The tablets gave comparable drug release with that obtained from a market product.

In production of tablets, it is both quicker and less expensive to avoid the wet granulation and drying steps and instead use materials, which are directly compressible. However depending on the morphology, drug may have extremely poor flow characteristics thereby eliminating the possibility of direct compression process. Significant difference in flow properties can be made by alteration of crystal morphology. In present work attempts were made to get ampicillin trihydrate powder with uniform particle size and spherical shape since spherical shape possesses several advantages such as free flowability, uniform packability and can be easily compounded with other pharmaceutical powders due to spherical form. The preparation of spherical agglomerates can be approached by several techniques[1]. In the present work a novel spherical crystallization technique, ammonia diffusion system proposed by Kawakita *et al.*[2], was used to achieve agglomeration of primary crystals.

Ampicillin trihydrate I.P., sodium starch glycolate (SSG) and microcrystalline cellulose (MCC) were received as gift samples from Intas Pharmaceuticals (Ahmedabad), Helios Pharmaceuticals (Ahmedabad) and Maruti Chemicals (Ahmedabad), respectively. All other ingredients and solvents were of analytical grade and were used as such.

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Ampicillin trihydrate was dissolved in ammonia water (25%) to produce 50%w/v solution. Four ml of this solution was poured into acetone (10 ml) and dichloromethane (3.5 ml) under agitation at 500 rpm using magnetic stirrer in a cylindrical vessel of 100 ml capacity. The system was thermally controlled at 20° during the process. After 45 min the agglomerated crystals were separated, washed with dichloromethane and dried at room temperature.

The particle shape and size of primary and agglomerated crystals were measured by optical microscope (Model 1669, Getner, India). Both, primary and agglomerated crystals were subjected to measurement of angle of repose[3], type of flow[4], flow rate[5], Hausner's ratio[6], percentage compressibility[7], Kawakita Parameter(a)[8] and Parameter(b)[8], Kuno parameter(k)[8] and Carr's index[9] using the methods as described in literature.

Five hundred milligram of the primary crystals and agglomerated crystals were blended separately with 5 mg magnesium stearate, and were compressed at a pressure of 200 kg/cm^2 using hydraulic press. Three samples of each of the primary and the agglomerated crystals were subjected to the process using different blending time (min) and dwell time (s) as shown in the Table 2. Compressibility of the tablets was evaluated by determining the tensile strength required for crushing the tablets using following equation[10]:tensile strength (kg/cm^2)=$2p/\pi.d.t$, where, 'p' represents breaking force, 'd' is diameter (cm) and 't' is the thickness of tablet (cm).

The compression process represented by the relationship between compression pressure and porosity of the powder bed was analyzed by means of the Heckel equation[11,12]. Dispersible tablets were prepared using agglomerated ampicillin trihydrate (250 mg), MCC (238 mg), SSG (10 mg) and magnesium stearate (2 mg) to get tablets of final weight of 500 mg. The tablets were subjected to dissolution test[14] and the concentration of the drug released was determined by UV spectrophotometry . Results were compared with a selected market product of dispersible tablet of the drug.

The micromeritic properties of the agglomerated crystals and primary crystals are compared as depicted in Table 1. As evident, the flow rate of agglomerated crystals has much improved as compared to that of the primary crystals. The agglomerates were easily packed by tapping. The smaller value of parameter (a) in Kawakita equation for the agglomerates indicated their higher packabilities than the primary crystals. The larger value of parameter (k) in Kuno's equation for the agglomerates indicated that the rate of their packing process was much higher than that of the primary crystals. The excellent flowability and packability of the agglomerated crystals may be attributed to an increase in particle size. Further the spherical shape was also a factor for improvement in the micromeritic properties. Value of Carr's index was found to be 22 and 09 for primary crystals and agglomerated crystals, respectively suggesting that flow pattern improved from poor in case of primary crystals to excellent in case of agglomerated crystals[9].

Table 2 shows the compressibility of tablets prepared using primary and agglomerated crystals. Crushing strength was same in case of primary crystals showing that new surface generated and primary crystals behaved like a fragmented material whereas agglomerated crystals have not generated new surface during compression. This material seems to undergo plastic deformation. This is time dependent and hence increasing the dwell time (sample B) increases bonding and crushing strength.

Tablet hardness-compression profile has been shown in Table 3. The compressibility of the agglomerated crystals was evaluated by the tensile strength. It is apparent from Table 3 that the higher tensile strength for the primary crystals of Ampicillin Trihydrate indicated their high compressibility due to their small particle size. On the other hand agglomerates retained the excellent compressibility of the original powder irrespective of pressure applied during compression.

Fig. 1 showed pressure porosity relationship. It can be seen that there is nonlinearity in the early stage of the compression, which may be due to the effect of rearrangement and the general behaviour of the powder as individual particles rather than as a coherent mass as suggested by Heckel[13]. The actual intercept was found to be 0.342 for primary crystals and 0.656 for agglomerated crystals.

TABLE 1: MICROMERITIC PROPERTIES OF PRIMARY AND AGGLOMERATED CRYSTALS.

Micromeritic properties	Primary crystals	Agglomerated crystals
Particle size	25 μ	200 μ
Angle of repose	55.00	33.20
Type of flow	doming	non-mass
Flow rate	-	150 gm/min
Hausner's ratio	1.4616	1.1096
Percentage Compressibility	31.5825	8.8300
Kawakita parameter (a)	0.3157	0.1093
Kawakita parameter (b)	0.0644	0.2670
Kuno parameter (k)	0.0703	0.1570
Carr's index	22	09

Micromeritic properties of primary crystals and agglomerated crystals were determined separately as per the methods cited in literature. Flow rate of primary crystals could not be determined due to 'doming' during flow through funnel.

TABLE 2: COMPRESSIBLITY OF PRIMARY AND AGGLOMERATED CRYSTALS.

Sample	Blending time (min)	Dwell time (s)	Crushing strength (kg)	Comments
Primary Crystals				
A	5	2	4.65	A=B=C
B	5	30	4.60	hence fragmenting material
C	30	2	4.63	
Agglomerated crystal				
A	5	2	8.79	C<A<B
B	5	30	10.32	
C	30	2	7.35	hence plastic material

Three samples of each of the primary and secondary crystals were blended separately with magnesium stearate for different time (shown in table as blending time) and the blend was compressed at a pressure of 200 kg/cm^2 with different dwell time during compression.

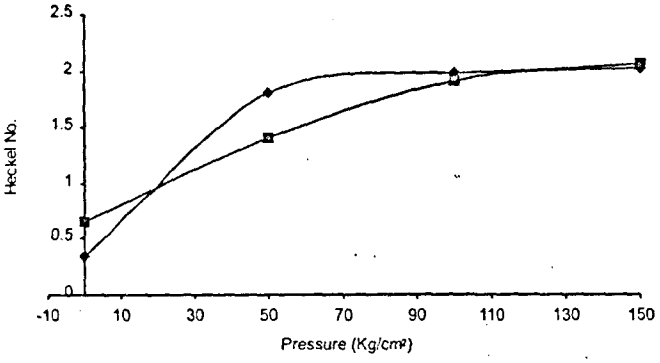

Fig.1: Pressure-porosity relationship.

Porosity of the tablets prepared by compressing the primary crystals (-♦-) and agglomerated crystals (-□-) at different compression pressure was measured by Heckel equation.

Extrapolated intercept was found to be 1.7 for primary crystals and 1.15 for agglomerated crystals. Thus both the actual intercept and the intercept extrapolated from the linear portion of the plot truly reflect the densification of the powders in the early stage of compaction. The linear portion of the plot was obtained from a straight line, which fitted most data points mostly in the range of compression pressure of 50-150 kg/cm^2. Agglomerated crystals showed very low fragmentation tendency due to the fact that the difference between extrapolated and actual densification of its Heckel plot was low. Having aggregated spherical shape, its densification could be initiated by segregation and tight packing without requiring high pressure. So further arrangement may not be due to fragmentation but deaggregation. Due to increasing pressure, agglomerates undergo plastic deformation. Pure crystals, on the other hand, might have increased the contact among particles, which resulted in higher tensile strength of the tablet compared with that of agglomerates. This fact was also supported by the shape of the Heckel plot. A linear Heckel plot is believed to indicate essentially ductile behaviour of the particle during compaction, while a curvilinear plot is believed to indicate brittle behaviour.

Therefore, the agglomerated crystals behaved like assembled secondary particle without compression and pri-

TABLE 3: TABLET HARDNESS-COMPRESSION PROFILE.

Pressure (kg)	Tensile Strength (kg/cm^2)	
	Primary crystal	Agglomerated crystal
50	12.23	7.349
100	13.18	9.982
150	5.415	11.31
200	*	8.793

* indicated capping

Tensile strength of tablets of primary crystals and agglomerated crystals, prepared by compressing at different compression pressure on a hydraulic press, was determined as per the given formula.

TABLE 4: COMPARISON OF CHARACTERISTICS OF MARKET PRODUCT AND FORMULATED PRODUCT.

Parameter	Market product	Formulated product
Hardness (kg/cm^2)	2.4	3.9
Friability (%)	0.2	0.61
Disintegration time (s)	24	28

A market product (tablet) of ampicillin trihydrate and tablet prepared from agglomerated crystals of drug were compared on the basis of chosen parameters.

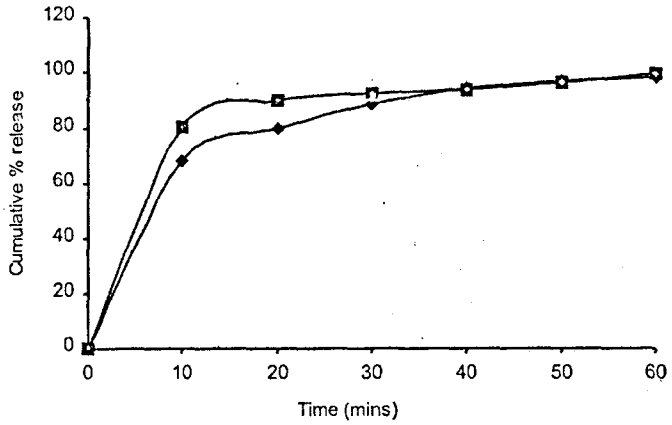

Fig.2: Comparative dissolution profile of market product and formulated tablet.

A market product (tablet) of the drug (-♦-) and the tablet prepared with agglomerated crystals (-□-) of the drug were separately subjected to dissolution study as per the pharmacopoeial method (I.P.).

mary particles after compression resulting in their excellent flowability, packability and compressibility.

Spherically agglomerated crystals were successfully formulated in the dispersible tablets. Results of comparison of formulated tablet with market product are shown in Table 4. Fig. 2 shows dissolution profile of a marketed product of the drug and that of the tablet prepared by using spherically agglomerated crystals. Prepared dispersible tablet gave sufficient results to prove its competitiveness to the one of the market product.

It can be concluded that the agglomerated crystals of ampicillin trihydrate have better tabletting properties as compared to primary crystals of the drug using the agglomerated crystals. The tablets prepared showed acceptable drug release profile and other physical attributes. This is promising method to be tried on for other challengeable materials.

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