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Research Article

Enhancement of Flow Property of Poorly Flowable Aceclofenac Drug Powder by Preparation of Spherical Crystals using Solvent Change Method and Making Drug Powder Suitable for Direct Compression

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ABSTRACT

Aceclofenac spherical crystals were prepared by using a three solvent system comprising ethanol, dichloromethane (DCM), and water (good solvent, bridging liquid and bad solvent, respectively). Polyvinyl Pyrollidone (PVP-K-30) in different concentrations was used as hydrophilic polymer. The effect of speed of rotation, agitation time, temperature, mode of addition of bridging liquid, amount of bridging liquid as well as effect of different amounts of non-solvent (water) on spherical crystals were studied. The crystals were subjected to various evaluations such as %yield, drug content, particle size and particle size distribution, % fines, crushing strength, friability, packability and compression behaviour of spherical crystals(agglomerate) The agglomerates showed improved micromeritic properties as well as dissolution behaviour in comparison to conventional drug crystals. The optimized agglomerates showed good sphericity as well as high drug release, and hence they were compressed into tablets by direct compression.

Key Words: Spherical crystals, bridging liquid, particle size, non solvent

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1. Introduction

The production of spherical crystals agglomerates which is one possibility of crystal size growth has recently gained great attention and importance due to the fact that the crystal habit (form, surface, size and particle size distribution) can be modified during the crystallization process. In consequence of such modification in the crystal habit, certain parameters can also be changed; flow property, bulk density, compactibility, cohesiveness, dissolution rate, stability etc. [1-3].

In the pharmaceutical industry, the formation of spherical crystals due to crystal growth is very important for preparing the solid dosage form (e.g. capsules, tablets etc.). The particle size of the agglomerate produced by spherical crystallization techniques is approximate 300-500 μm in diameter and their form is more or less spherical. The agglomerate has very good flow property, high bulk density and compressibility values. They can be used directly for capsule-filling (without excipients) and direct tablet-making (without granulation, drying etc.). The drug material produced by spherical crystallization techniques result in the economical process in the development of the solid dosage form.

In the pharmaceutical field, kawashima et al [4] have given impulse to the research of the spherical crystallization process. The typical spherical crystallization technique employs three solvents: one is the substance dissolution medium, another is a medium, which is partially dissolves the substance, and the third is the wetting solvent for the substance. The traditional crystallization process (salting out precipitation, cooling crystallization, crystallization from melting. etc.) can also be used to produce spherical crystal agglomerates [5]. It may be called a non-typical spherical crystallization process. The flow property and compactibility of Aceclofenac are poor due to crystal habit. Since the drug is used for making tablet and the spherical form is very important because of their processibility.

In this work, spherical crystals of Aceclofenac were developed by solvent change method by using a three solvent system comprising ethanol, dichloromethane (DCM), and water (good solvent, bridging liquid and bad solvent, respectively).

2. Experimental

2.1Materials

Aceclofenac BP received as kind gift sample from Cadila Pharma, India, Polyvinylpyrrolidone (PVP-K 30) as gift sample. Diclromethane, Ethanol and all other chemicals used, were of analytical grade.

2.2 Method

In this study the solvent change method was used for the preparation of spherical crystals of Aceclofenac. The drug Aceclofenac and polymer Polyvinylpyrrolidone (PVP-K30) were dissolved in ethanol (a good solvent) and then heating at 75^0C at water bath and cooled to 65^0C .The talc (co-agglomerating agent to improve micromeritic properties) powder was uniformly dispersed in it. The drug polymer solution was added to an aqueous phase (water) which was maintained at temperature 5± 1^0C with continuous stirring at speed of 700± 25 RPM. The bridging liquid dicloromethane was added drop wise with mechanical stirring for 15 minutes. The spherical crystals were collected by filtration and dried at room temperature for 12 hours.

2.3. Process development and optimization

Designing the spherical crystallization process require optimization of various process variables, which could affect the preparation and properties of the spherical crystals were identified and studied. The method of crystallization was optimized and validated according to the study of variables.

2.3.1 Selection of bridging liquid

The effect of different bridging liquids was observed during preparation of spherical crystallization of Aceclofenac.

Table 1- Effect of different bridging liquids on preparation of spherical crystals (agglomerate) of Aceclofenac

S. No.	Bridging liquids	Observation
1.	Hexane	Clump formation
2.	Toluene	Clump formation
3.	Dichloromethane	Spherical agglomerates
4.	Benzene	Clump formation
5.	Chloroform	Clump formation
6.	Isopropyl alcohol	Disappearance of crystals

2.3.2 Amount of bridging liquid (Dichloromethane)

The effect of different amount of bridging liquid (i.e. Dichloromethane) was seen during preparation of spherical crystals of Aceclofenac.

Table 2: Effect of different amounts of bridging liquid on preparation of spherical crystals (agglomerate) of Aceclofenac.

S. No.	Amount of bridging liquid (ml)	Observation
1.	<5	No agglomeration
2.	5	Spherical agglomerates
3.	>5	Irregular shaped agglomerates

2.3.3 Agitation speed

The effect of different agitation speed on the preparation of spherical agglomerates of Aceclofenac was seen by performing agglomeration at different stirring rates.

2.3.4 Agitation time

The effect of different agitation time was also seen on preparation of spherical agglomerates of aceclofenac.

2.3.6 Mode of addition of bridging liquid

The effect of mode of addition of bridging liquid to reaction mixture was observed on the preparation of spherical agglomerates of Aceclofenac. The dichloromethane was added drop-wise or whole amount.

Table 3: Effect of agitation speed on preparation of spherical crystals (agglomerate) of Aceclofenac.

S. No.	Amount of bridging liquid (ml)	Observation
1.	300	Large clumps
2.	500	Small-compacted
3.	700	Spherical agglomerates
4.	900	Irregular shaped agglomerates

Table 4: Effect of agitation time on preparation of spherical crystals (agglomerate) of Aceclofenac.

S. No.	Amount of bridging liquid (ml)	Observation
1.	5	Incomplete agglomerates
2.	15	Spherical agglomerates
3.	30	Broken agglomerates

2.3.5 Temperature

The effect of different temperature condition was studied during preparation of spherical agglomerates of aceclofenac and observed.

2.3.7 Amount of non-solvent

The effect of different amount of non-solvent (Water) was seen during preparation of spherical agglomerates of Aceclofenac.

Table 5: Effect of temperature on preparation of spherical crystals (agglomerate) of Aceclofenac.

S. No.	Temperature	Observation
1.	5 ±2^{o}C	Spherical agglomerates
2.	25-30^{o}C (Room- temp.)	No agglomeration
3.	40±2^{o}C	No agglomeration

Table 6: Effect of mode of addition of bridging liquid on preparation of spherical crystals (agglomerate) of Aceclofenac.

S. No.	Mode of addition of bridging liquid	Observation
1.	Drop-wise	Spherical agglomerates
2.	Whole amount at a time	Irregular shaped agglomerates

Table 7: The effect of different amounts of non-solvent (water) on preparation of spherical crystals (agglomerates) of Aceclofenac.

S. No.	Volume of non solvent (ml)	% Yield
1.	40	91.32%
2.	25	96.25%
3.	20	94.17%
4.	15	93.23%

3. Characterization of Spherical Crystals

3.1Yield

Agglomerates were weighed after drying and yield was calculated, considering complete precipitation of drug & polymers. Minimum satisfactory value was set at 90%.

3.2 Particle size distribution-

It was performed by sieve analysis techniques, 5.5001 g of sample (dried) agglomerates of each batch were passed through a nest of sieve containing sieve # 16, 30, 44, 60, 85, 100, 120 for 5 minutes with be coarsest at top. Agglomerates retained on every mesh were weighed & generated data were subjected to analysis for log normal distribution.

3.3 Sphericity

The agglomerates (50 in number) were observed under stereomicroscope (Zeiss Stemi 2000-C, Zeiss. Oberkochen, Germay), and their circularity factor (shape factor) was calculated using Biovis (Image plus, Version 1.50, Expert Vision Labs, Mumbai, India) software. Shape factor = π (major axis)^2 /4 (area)

3.4 Angle of repose

The Aceclofenac power or spherical agglomerates (10g) were carefully poured into a dry glass funnel whose sealed tip was suspended 6cm from the working surface. The seal was removed and the powder was allowed to flow onto a sheet of parchment paper under the force of gravity. The height and diameter of the cone were measured. The angle of repose for standard drug was 40.26^o.

3.5 Friability of Spherical Crystals

Friability of agglomerates were performed after subjecting to attrition, in which sample (10g) of each batch with size (which were retained in between on # 16to #85) and 20 plastic balls (each of 0.95 cm diameter and 500 mg weight) were placed on #85 and shaken for 5,10,5 and 20 minutes. For each time intervals mean geometric diameter was calculated.

Percentage friability index (FI) as a function of time was calculated at each time using the following equation

$$FI = [(df)_t / (dg)_0] \times 100$$

Where, $(dg)_t$ = mean geometric diameter after time t.

$(dg)_0$ = mean geometric diameter at initial time.

3.5 Bulk and Tap density

For the determination of bulk density, 5 g of each sample (Aceclofenac and spherical agglomerates) was carefully introduced in to a 50 ml graduate cylinder separately of Tap Density Test Apparatus Electrolab (Model ETD-10/20/1020). The bulk and tap density for standard drug were 0.16 gm/cm^3 and 0.20 gm/cm^3 respectively.

Table 8: Effect of concentration of PVP K-30 on various parameters

Batch	Conc. of PVP k30 (%w/w)	%yield	Geometric mean diameter (µ m)	Sphericity	Angle of Response (in degree)	Bulk Density (gm/ cm3)	Tap Density (gm/ cm3)	Haussner's ratio	Carr's index (%)
AC1	5	96.42 ± 0.321	824.137± 138.74	1.27± 0.05	28.59± 0.351	0.214	0.2240	1.0461	4.32
AC2	7	95.921± 0.432	860.987± 142.38	1.24± 0.06	29.43± 3.57	0.1818	0.2007	1.1039	9.41
AC3	10	94.213± 1.023	958.167± 60.23	1.17± 0.08	30.98± 2.42	0.1875	0.2069	1.1034	10.68
AC4	12	91.17± 0.837	937.237± 58.237	1.44± 0.30	28.07± 1.83	0.1802	0.1916	1.0632	5.94
AC5	15	89.79± 0.732	896.249± 138.238	1.48± 0.23	28.27± 1.27	0.1792	0.1862	1.0390	3.75

4. Result and Discussion:

The result of % yield, geometric diameter, angle of repose, bulk density, tapped density, sphericity, Haussner's Index, Carr's Index are given in the table 8 for the spherical crystals of Aceclofenac. On the basis of results, two batches (AC3, AC4) were optimized (Table 8). The Particle size distribution of selected batch were observed (Table 9, 10) and friability of these batches represented in the table 11.

Table 9 : Particle size distribution of Batch AC_3 (For Aceclofenac)

Sieve no.	Avg. pore diameter (µm)	Avg. particle size (µm)	Wt. retained (g)	% Wt. retained	Cumulative	Cumulative % frequency
16	1000	1200	0.9920	18.03	81.97	18.03
30	500	780	3.7013	67.29	14.68	85.32
44	355	427	0.2613	4.75	9.93	90.07
60	250	302	0.1713	3.11	6.82	93.18
85	180	215	0.0918	1.66	5.16	94.84
100	150	165	0.0634	1.15	4.01	95.99
120	125	137	0.0137	0.24	3.76	96.24

Total weight of agglomerates taken = 5.5001 g

Mean geometric diameter (by weight) (d_g^1) = 860 µm; by number d_g = 803.52µm

Geometric standard deviation (σ_g) = 1.162

Total weight of agglomerates taken = 5.5001 g

Mean geometric diameter (by weight) (d_g^1) - 910µm; by number d_g=588.04µm

Geometric standard deviation (σ_g) = 1.15

5. Conclusion

From the above it can be concluded that spherical crysllization is a tool of particle engineering which can transform the poorly flowable drug powder into spherical crystals those are best suited for direct compression. The conversion of poorly flowable powder into granular form (agglomerates) enhance the speed of tableting because of elimination of most of steps those are needed in the wet granulation & in dry granulation process

Table 10: Particle size distribution of Batch AC_4 (For Aceclofenac)

Sieve no.	Avg. pore diameter (µm)	Avg. particle size (µm)	Wt. retained (g)	% Wt. retained	Cumulative	Cumulative % frequency
16	1000	1200	1.0120	18.40	81.60	18.40
30	500	780	3.7423	68.04	13.55	86.45
44	355	427	0.2703	4.91	8.63	91.36
60	250	302	0.1623	2.95	5.68	94.31
85	180	215	0.0921	1.67	4.01	95.98
100	150	165	0.0631	1.14	2.86	97.13
120	125	137	0.0132	0.24	2.62	97.37

Table 4: Percent Friability index of Aceclofenac agglomerates.

S. No.	**Time (min)**	**Friability Index (%)**	
		AC_3	**AC_4**
1.	5	49.41	56.20
2.	10	32.56	42.25
3.	15	25.68	37.59
4.	20	19.36	25.64

The angle of repose, carr's index, Haussner's index, particle size, spehricity shows that prepared spherical crystals of Aceclofenac having very good flow properties as compare to pure drug.

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