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DESIGN AND DEVELOPMENT OF SPHERICAL AGGLOMERATED CRYSTALS LOADED FAST DISSOLVING TABLETS FOR ENHANCING THE SOLUBILITY OF IBUPROFEN

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Abstract:

The main focus of this work was to enhance the solubility and bioavailability of Ibuprofen by using spherical crystallization technique. This technique was developed by Kawashima and their coworkers in 1986, by which crystallization and agglomeration can be carried out at once in a single step to convert crystals straight into compressed spherical form. Spherical agglomerates were obtained by the quasi-emulsion solvent diffusion method, in which ibuprofen was dissolved in the mixture of methanol (good solvent), dichloromethane (bridging liquid) and poor solvent (distilled water containing polymer PVP K-30) with a stirring rate of 500 rpm at room temperature and filtered through Whatman filter paper no.42. Evaluation of agglomerates showed that drug content ranged from 98.18% to 99.27% and agglomerates prepared with ibuprofen and PVP K-30 in 1:1 ratio showed the highest drug release in 60 minutes. This technique enhanced the Physico-chemical properties such as solubility and also enhanced the bioavailability of Ibuprofen as compared with the plain drug, which indicates that the spherical agglomerates can suitable for direct compressible tablet process. Direct compression is a modern method in tablet manufacturing which involves simple mixing and compression and it is both efficient and economical, well suited to the production of high-quality tablets. The formulation prepared with crospovidone was offered the rapid release of ibuprofen when compared to other superdisintegrants. Evaluation tests of tablets exhibit hardness, low friability, excellent dissolution rates and also improve the physical and chemical stability of tablets as compared to wet granulation technique.

Keywords: *Spherical agglomerates, Physico-chemical properties, Bioavailability, Direct compression, superdisintegrant*

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1. INTRODUCTION

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used for the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis and is used in chronic and acute conditions of pain and inflammation. As its serum concentrations and analgesic effect are correlated, rapid absorption of ibuprofen could be a prerequisite for the quick onset of its action. The major problems with the drug are its very low solubility in biological fluids, gastric irritation and its short biological half-life of 2 h. It is practically insoluble in water and so possesses poor solubility and subsequent poor GI absorption and bioavailability. Thus, rapid ibuprofen absorption could be a prerequisite for the quick onset of its action. Because of its high membrane permeability characteristic, the extent of ibuprofen absorption approaches up to 100 %. Therefore, dissolution becomes the rate limiting step for absorption and the quick release of ibuprofen in the gastrointestinal tract following oral administration is desirable. The major problem of ibuprofen is its very low water solubility, which results in poor dissolution rate. The purpose of the present work was to improve the solubility, dissolution rate and micromeritic properties of ibuprofen through spherical crystallization by quasi-emulsion solvent diffusion technique [1,2]. The resultant crystals can be designated as spherical agglomerates. Spherical crystallization is an effective alternative to improve the dissolution rate of drugs. This can be achieved by various methods such as spherical agglomeration, quasi-emulsion solvent diffusion and neutralization methods. Many of the drugs, evolving from these techniques, can be categorized as class II drugs according to Biopharmaceutical classification system. These drugs are poorly water soluble, but once they are dissolved they easily absorbed through the gastrointestinal membrane. Therefore, bioavailability after oral administration can be improved by enhancement of the dissolution rate. One of the approaches dissolution rates is the use of spherical crystallization technique [3-6].

2. MATERIALS AND METHODS

2.1 MATERIALS

Ibuprofen was obtained from Dr.Reddy's labs, Hyderabad, India. Poly ethylene glycol 4000, polyethene glycol 6000 and PVP k-30 were purchased from SD Fine Chemicals Ltd, Mumbai. All other materials used were of analytical grade.

2.2 PREPARATION OF SPHERICAL AGGLOMERATES

All spherical agglomerates were obtained by the quasi-emulsion solvent diffusion method [7]. Spherical agglomerates were prepared with and without stabilizers by spherical crystallization technique. The stabilizers composition was given in **Table 1**. Ibuprofen (1.0 g) was dissolved in good solvent methanol (4.0 mL). The bridging liquid dichloromethane (1.0 mL) was added to it. The resulting solution was then poured dropwise into the poor solvent distilled water (100 mL) containing different polymers like PEG-6000 and PVP K-30 with a stirring rate of 500 rpm using propeller type agitator (Remi Motors Ltd., Mumbai, India) at room temperature [8]. After agitating the system for 30 minutes, the prepared agglomerates were collected by filtration through Whatman filter paper no.42.

2.2.1. EVALUATION OF SPHERICAL AGGLOMERATES

a) Particle size determination

Particle size determination was carried out using optical microscopy with a calibrated eyepiece micrometer and stage micrometer by taking a small quantity of formulation on slide8. About 100 spherical agglomerates size was measured individually, an average was taken and their size range and mean diameter frequency was calculated. Average Particle size is calculated by the following formula,

Average Particle size= £nd/ n

b) Drug Content Estimation

The percentage drug content in spherical agglomerates was estimated by dissolving spherical agglomerates equivalent to 100 mg of ibuprofen in methanol, mixed thoroughly by shaking and the volume was made up to the mark within 6.8 pH phosphate buffer. The solution was filtered and the filtrate was diluted suitably with 6.8 pH phosphate buffer and absorbance was measured at 221 nm using UV/Visible spectrophotometer [9].

c) Dissolution studies of agglomerates

In-vitro dissolution studies of pure drug and spherical agglomerates were carried out for 60 minutes using USP Dissolution test apparatus type II (Lab India DISSO 2000, eight stages) at 50 rpm. Spherical agglomerates equivalent to 100 mg of ibuprofen was used for dissolution study at 37±0.5^{0}C in 900ml of 6.8 pH phosphate buffer as dissolution medium. Aliquot equal to 5 ml were withdrawn at regular time intervals (10, 20, 30, 40, 50, 60 min), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and aliquots were measured at 221 nm UV/Visible spectrophotometer. DE30%, T50, T90 and k-1 values were calculated from dissolution data.

2.3 PREPARATION OF IBUPROFEN TABLETS

Tablets were made from blends by direct compression method. All the ingredients (shown in Table 4) were mixed [11]. The resulting blend was lubricated with magnesium stearate and compressed into tablets using the Cadmach single punch (round shaped, 7mm thick) machine.

2.3.1 EVALUATION OF IBUPROFEN TABLETS

a) Weight variation test [12]

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

b) Drug content [13]

Twenty tablets were powdered, and powder equivalent to 100 mg of Ibuprofen was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 5 ml methanol was added and shaken for 10 min. Then, the volume was made up to 100 ml with 6.8 phosphate buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 221 nm.

c) Disintegration Time [14]

The disintegration time was determined in distilled water at 37±0.50 C using disintegration test apparatus USP ED-2L (Electro lab, Mumbai).

d) Friability [14]

Roche friabilator was used to determine the friability. Pre-weighed tablets were placed in friabilator and rotated at a speed of 25 rpm for 4 minutes or up to 100 revolutions. The tablets are dropped from a distance of 6 inches in each revolution. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

e) Hardness [14]

The hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was computed by deducting the initial pressure from the final pressure.

f) Wetting Time [14]

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. 10 mL of water-containing amaranth a water-soluble dye is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet is noted as a wetting time.

g) Water Absorption Ratio [14]

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using the following equation.

$$R = [(Wa - Wb)/Wb] \times 100$$

Where Wb and Wa were the weights of the tablet before and after water absorption**.**

h) In vitro dispersion time [14]

Tablet was added to 10 ml of phosphate buffer solution pH 6.8 (pH of saliva) at 37± 0.5°C. The time required for complete dispersion of tablet was measured.

i) The fineness of dispersion [14]

This test was performed by placing two tablets in 100 ml of water and stirring it gently until the tablets get completely disintegrated. Then the dispersion is passed through a sieve screen with a nominal mesh aperture of 710 µm.

j) Dissolution studies [14]

Dissolution studies for Ibuprofen fast dissolving tablets were performed in pH 6.8 phosphate buffer using USP dissolution test apparatus (Electrolab, Mumbai, India) with a paddle stirrer. The paddles are allowed to rotate at speed of 100 rpm. The dissolution medium was maintained at a temperature of 37+0.5 OC and samples are withdrawn at an interval of every 5 min the volume of the withdrawn samples are replaced by fresh dissolution medium in order to keep the volume of the dissolution medium as constant. The withdrawn samples are filtered and absorbance was measured at absorption maxima of 221 nm using the UV-visible spectrophotometer.

k) In-vitro dissolution kinetic studies [14]

The drug release data were plotted and tested with zero order (cumulative % drug released Vs time), First order (Log % remained Vs time). The *in-vitro* dissolution kinetic parameters, dissolution rate constants (K), correlation coefficient (r), the times (t50) for 50 % drug released (half-life) and dissolution efficiency [D.E.] were calculated. From the slopes of linear plots, the dissolution rates were calculated.

l) FTIR (Fourier Transform Infra-red Spectroscopy) Studies [15]

Infrared (IR) spectroscopy studies of Ibuprofen and its optimized formulations with PVP and cross-povidone were recorded in an FTIR spectrophotometer (Thermo-IR 200) Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The spectrum for each sample showed the wavelength of absorbed light which is a characteristic of the chemical bonds in the sample. Each spectrum was derived from 16 single average scans collected in

the region of 400 - 4000 cm-1 at a spectral resolution of 2 cm-1.

3. RESULTS AND DISCUSSION

Spherical agglomerates of ibuprofen were prepared by quasi-emulsion solvent diffusion method (QESD) using a three-solvent system. It involves good solvent, poor solvent and a bridging liquid. The selection of these solvents depends on the miscibility of the solvents and the solubility of the drug in the individual solvent. Accordingly, methanol, dichloromethane, water were selected as a good solvent, bridging liquid, and a poor solvent, respectively. Ibuprofen is highly soluble in methanol but poorly soluble in water. Also, it is soluble in dichloromethane which is immiscible in water. Hence, this solvent system was used in the present study. In QESD method, when a good solvent solution of drug plus bridging liquid were poured in the poor solvent (containing different polymers) under agitation, quasi-emulsion droplets of bridging liquid and good solvent were produced. Then the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter-diffusion of the poor solvent into the droplets induces the crystallization of the drug within the droplet due to the decrease in solubility of the drug in the droplet containing the poor solvent. The bridging liquid wets the crystal surface to cause binding and promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals are formed by the coalescence of these dispersed crystals. In the present study effect of different polymers on solubility and dissolution rate of spherical agglomerates of ibuprofen were studied. Incorporation of the polymer during agglomeration significantly enhanced the dissolution. Mixing of the drug with a hydrophilic carrier (polymer) results in greater wetting and increase surface available for dissolution by reducing interfacial tension between the hydrophilic drug and dissolution media. It was noted that the drug carrier system sinks immediately, while pure drug keeps floating on the surface for a longer time interval. The cumulative percentage of drug released from different agglomerates was increased in the following order: Ibuprofen spherical agglomerates prepared with PVP > Ibuprofen spherical agglomerates prepared with PEG6000. Among all the formulations prepared, spherical agglomerates prepared Ibuprofen and PVP in 1:1 ratio showed the highest drug release in 60 minutes.

To study the influence of superdisintegrants on the performance of Ibuprofen Orodispersible Tablets, a set of three formulations (F7, F8 and F9) were prepared using three different superdisintegrants viz, Sodium starch glycolate (5%), Croscarmellose sodium (5%), Crospovidone (5%) respectively. The dissolution rate followed first-order kinetics as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Ibuprofen was found to be affected by the nature of the superdisintegrant used in the preparation of tablets. Based on the dissolution rate, superdisintegrants can be rated as SSG < Croscarmellose sodium < Crospovidone. The formulation prepared with Crospovidone was offered the relatively rapid release of Ibuprofen when compared with other superdisintegrants used in this investigation.

4. CONCLUSION

Present study concluded that spherical agglomerates prepared by the quasi-emulsion solvent diffusion method showed an improvement in the solubility, dissolution rate, compatibility, wettability, flowability and bioavailability. These spherical agglomerates also showed excellent physicochemical characters as compared with the plain drug which indicates that the spherical agglomerates can suitable for directly compressible tablet process.

Table 1: Composition of Ibuprofen Spherical Agglomerates

Ingredients	F1	F2	F3	F4	F5	F6
Ibuprofen(g)	1	1	1	1	1	1
PEG 6000(g)	0.5	0.75	1	-	-	-
PVP K-30 (g)	-	-	-	0.5	0.75	1
Methanol(ml)	4	4	4	4	4	4
Dichloromethane(ml)	1	1	1	1	1	1
Water (ml)	100	100	100	100	100	100

Table 2: Particle size and % of Drug content of Ibuprofen spherical agglomerates

Formulation	Particle size(µm)	% of Drug content
FI	215	98.18
F2	247	98.63
F3	267	99.23
F4	276	98.44
F5	293	98.88
F6	312	99.27

Table 3: *In-vitro* dissolution kinetics of Ibuprofen spherical crystals prepared with different carriers.

S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{30} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_1	38.6	126.8	19.8	0.018	0.9890	0.9940
2	F_2	33.6	111.7	22.44	0.020	0.9875	0.9949
3	F_3	27.6	91.7	27.93	0.0251	0.9741	0.9939
4	F_4	28.5	94.6	27.05	0.024	0.9770	0.9940
5	F_5	22.0	73.1	34.34	0.032	0.9480	0.9888
6	F_6	17.2	57.0	39.51	0.040	0.9250	0.9836

Table 4: Composition of ingredients for Ibuprofen fast dissolving tablets

S.No.	Ingredients	F_7	F_8	F_9
1	Ibuprofen crystals prepared with PVP in 1:1 ratio	200	200	200
2	Sodium starch glycolate	10	-	-
3	Croscarmellose sodium	-	10	-
4	Crospovidone	-	-	10
5	Mannitol	44	44	44
6	Microcrystalline cellulose	40	40	40
7	Talc	3	3	3
8	Magnesium stearate	3	3	3
	Total weight	**300**	**300**	**300**

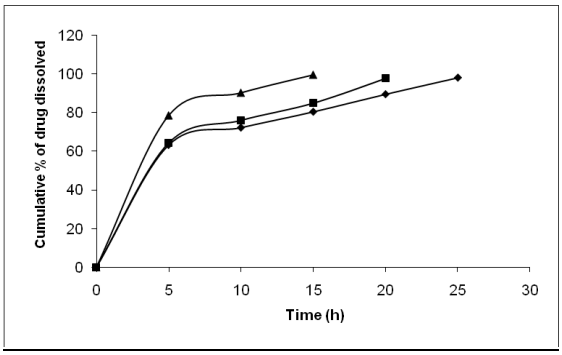
Table 5: Physical parameters of Ibuprofen fast dissolving tablets

S.No.	Parameters	F_7	F_8	F_9
1	Average weight (mg)	300±0.2	299±0.1	200±0.1
2	Drug content (%)	99.46	99.33	100.1
3	Disintegration time (sec)	65	46	39
4	Friability (%)	0.86	0.6	0.78
5	Hardness (kg/sq cm)	4	3.5	4
6	Wetting time (sec)	50	41	33
7	Water absorption ratio	89	95	103
8	*In-vitro* dispersion time (min)	2.3 ± 0.11	1.9 ± 0.08	1.4 ± 0.13
9	Fineness of dispersion	Pass	Pass	Pass

Table 6: *In-vitro* dissolution kinetics of Ibuprofen fast dissolving tablets

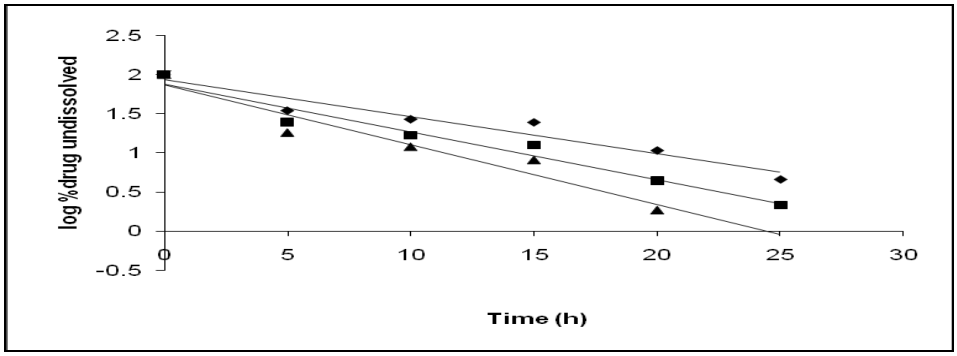
S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_7	5.16	17.14	61.31	0.1343	0.7490	0.9760
2	F_8	4.22	14.01	70.44	0.1641	0.8193	0.9869
3	F_9	2.20	7.33	75.13	0.314	0.8237	0.9858

Figure 1: *In-vitro* dissolution profile of Ibuprofen fast dissolving tablets formulated with different superdisintegrants



(♦) F_7 -Tablets prepared with 5% sodium starch glycolate
(■) F_8 -Tablets prepared with 5% Croscarmellose sodium
(▲) F_9 - Tablets prepared with 5% crospovidone

Figure 2: First order plots of Ibuprofen tablets formulated with different superdisintegrants



(♦) F_7 -Tablets prepared with 5% sodium starch glycolate
(■) F_8 - Tablets prepared with 5% Croscarmellose sodium
(▲) F_9 - Tablets prepared with 5% crospovidone

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