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Research Article

Design and Development of Spherical Agglomerates of Drug for the Enhancement of Solubility

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ABSTRACT

The aim of this research attempts was to improve the micrometric properties and solubility enhancement of spherically agglomerated crystals of Aceclofenac by using spherical agglomeration technique. The oral route of administration is the most important method of administering drugs for systemic effects. In this, the solid dosage form, particularly, tablets are the dosage form of a choice because of their special characteristics like unit dosage form with greatest dose precision and least content variability, lower cost, easy administration by a patient Aceclofenac is an orally effective non-steroidal anti-inflammatory drug (NSAID) of the phenyl acetic acid group which possesses remarkable anti-inflammatory, analgesic and antipyretic properties. Aceclofenac agglomerates were prepared with Poloxamer 188 and PEG 4000 using acetone-dichloromethane (DCM), water as the crystallization system. Various process variables such as selection of bridging liquid and good solvent, agitation speed, agitation time and mode of agitation of bridging liquid were optimized. The prepared aceclofenac spherical agglomerates were evaluated by micromeritic properties like optical microscopy, tapped density, bulk density, Carr's index, drug content, and also carried out by FTIR, DSC, PXRD pattern, and Electron Scanning microscopy. The conclusion of this study was the agglomerates of Aceclofenac prepared with PEG 4000 and Poloxamer 188 showed improved solubility and dissolution in addition to improving the micromeritic properties. The solubility study reveals that the solubilizing efficiency of hydrophilic polymers enhances the drug solubility significantly as compare to plain agglomerates and Aceclofenac alone. The increase in drug release could be attributed to deposition of polymers on the recrystallized surface and better wettability of spherical agglomerates.

INTRODUCTION

The oral route of administration is the most important method of administering drugs for systemic effects. In this, the solid dosage form, particularly, tablets are the dosage form of a choice because of their special characteristics like unit dosage form with greatest dose precision and least content variability, lower cost, easy administration by a patient [1]. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and which determines the rate and degree of absorption [2]. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.

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Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability [3]. Poor aqueous solubility of drugs is a major limiting factor with many new drugs in their successful launch in market in spite of their potential pharmacokinetic activity. Poor solubility (less than 10 %) of a drug, leads to poor dissolution in the gastro intestinal tract (GIT) hence, incomplete and erratic absorption ultimately limits its clinical utility. Further, poorly soluble drugs are generally administered at much higher doses than the actual dose in order to achieve necessary drug plasma levels leading to increased adverse reaction & cost of therapy and often yields erratic pharmacological response and hence poor patient compliance. About 40 % of drugs being in the pipeline of pharmaceutical companies are poorly soluble.[4]

Therefore, the improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system.[5] A number of approaches are practiced to improve the aqueous solubility of poorly soluble drugs such as solid dispersion (solvent evaporation method, fusion process melt-mixing, freeze-dried, fusion-solvent method, kneading technique, coprecipitation), spherical agglomeration, evaporative precipitation in aqueous solution, microcrystallisation, supersaturation, pro drug approach, polymorphism, complexation, pH adjustment, co-solvents, use of surfactant, and particle size reduction[4]. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected and nature of intended dosage form [5]. The quality of solid dosage form is primarily influenced by micromeritic characteristics such as the shape and size of drug crystal, especially in the case of poorly soluble drugs. To improve the dissolution rate of poorly soluble drugs, fine crystals are referred and this micronisation can change drug powder properties such as wettability, compressibility, packability and flow. Further, it is more beneficial to convert micro crystalline drugs into an agglomerated form using spherical crystallization technique. The resulting spherically agglomerated crystals can be directly prepared into a tablet, thus direct tabletting saves time and reduces cost [6].

MATERIALS AND METHODS

Aceclofenac obtained from gift sample Arati Drugs Ltd, Tarapur Mumbai, Dichloromethane, Acetone, PEG 4000, Polaxamer 188 are obtained from SD fine Lab Mumbai. All chemicals are used analytical grades.

Method of preparations of Aceclofenac agglomerates [7]

Preparation of Aceclofenac agglomerates without polymers

Spherical agglomeration of Aceclofenac was carried out by simple spherical agglomeration technique using Acetone, Distilled water, Dichloromethane as good solvent, poor solvent and bridging liquid respectively. The clear solution of Aceclofenac (1gm) in acetone (6ml) was added drop wise in the 100 ml solution of distilled water (bad solvent) under continuously stirring at 700 rpm using mechanical stirrer. When fine crystals of Aceclofenac begun to form then Dichloromethane (bridging liquid) was added drop wise to obtain spherical agglomerates. The agglomerates were filtered through whatmann filter paper to separate the agglomerates and the product was air dried in desiccators until further use.

Preparation of Aceclofenac agglomerates with polymers

Spherical agglomeration of Aceclofenac was carried out by simple spherical agglomeration technique using Acetone, Distilled water, Dichloromethane as good solvent, poor solvent and bridging liquid respectively. The clear solution of Aceclofenac (1 gm) in acetone (6 ml) was added drop wise in the 100 ml solution of hydrophilic polymers such as PEG 4000 or Poloxamer 188 in distilled water (bad solvent) at different concentration (0.1-1 % w/v) under continuously stirring at 600 rpm using mechanical stirrer. When fine crystals of Aceclofenac begun to form then Dichloromethane (bridging liquid) was added drop wise to obtain spherical agglomerates. The agglomerates were filtered through whatmann filter paper to separate the agglomerates and the product was air dried in desiccators until further use. The formulation is shown in Table 1.

Table 1: Formulations of Spherical Aceclofenac agglomerates

Formulation Code	Aceclofenac (gm)	Poloxamer 188 (gm)	PEG 4000 (gm)
RK1	1	0.10	-
RK2	1	0.25	-
RK3	1	0.50	-
RK4	1	1	-
RK5	1	-	0.10
RK6	1	-	0.25
RK7	1	-	0.50
RK8	1	-	1
RK9	1	-	-

Characterization of Spherical agglomerates of Aceclofenac[8-16]

Micromeritic properties

The prepared spherical crystals of Aceclofenac were evaluated for angle of repose, bulk density tapped density, Carr's index and Hausner's ratio.

Determination of Particle size

Optical microscopy

Particle size determination was carried out using optical microscopy with a calibrated eye piece

micrometer and stage micrometer by taking a small quantity of formulation on slide. About 100 spherical agglomerates size was measured individually, average was taken and their size range and mean diameter was calculated. Average Particle size is calculated by the formula:

$$\text{Average Particle size} = \sum nd / n$$

Drug content

Agglomerates (equivalent to 100 mg of Aceclofenac) were triturated and dissolved in phosphate buffer pH 6.8 and sonicated for 15 minutes and finally volume was made up to 100 ml with phosphate buffer pH 6.8. The solution was filtered through whatman filter paper. After appropriate dilution with phosphate buffer pH 6.8 it was analysed spectrophotometrically at 273 nm.

***In vitro* Dissolution of Aceclofenac agglomerates**

Dissolution studies were performed using USP type 2 dissolution apparatus. Dissolution test of Aceclofenac agglomerates was performed using 900 ml of Phosphate buffer pH 6.8 dissolution media at a temperature of 37±0.5ºc and stirring speed of 50 rpm for 60 minutes. Aliquot of 5 ml was withdrawn at regular intervals of time (i.e. 5 min) and replenished the same volume with fresh medium. The samples were filtered through Whatman filter paper and after appropriate dilution samples were analysed spectrophotometrically at 273 nm by UV-Visible spectrophotometer. (Shimadzu, Model: Pharmaspec1800).

FTIR spectroscopy

The FT-IR spectrum of agglomerate was obtained using FT-IR spectrophotometer. Sample was prepared by KBr disc method, and examined in the transmission mode. Each spectrum was measured over a frequency range of 4000–400 cm^{-1} and the resolution was $1cm^{-1}$.

Differential scanning calorimetry (DSC)

Agglomerate of drug was placed in an aluminium crucible and the DSC thermograms were recorded at a heating rate of 10ºC/min in the range 0ºC to 300ºC. Nitrogen gas was purged at the rate of 50 ml/min. to maintain inert atmosphere. The enthalpy of fusion and melting point could be obtained from the thermogram using the instrumental software.

Powder X-ray diffraction of (XRD)

The X-ray diffraction pattern of sample were obtained using X-ray diffractometer operated at 40kV, 30mA and a scanning rate of 0.06^0/min over the range 5-40 2θ, using Cu $K\alpha_1$ radiation of wavelength 1.5405 A^0. The cavity of metal sample holder of X-ray diffractometer was filled with the ground sample powder.

Scanning electron microscopy

The shape and surface topography of agglomerate were observed using scanning electron microscope (JSM 5600 LV Joel, Japan), after coating with gold.

RESULTS AND DISCUSSION

Micromeritic Properties

The prepared spherical crystals of Aceclofenac were evaluated for angle of repose, bulk density tapped density, Carr's index and Hausner's ratio. All parameters are mention in Table 2.

Drug content:

The drug content of spherical agglomerates was in the range 97.01 ± 0.35 to 98.93 ± 0.23, Indicating negligible loss of drug during the crystallization process.

***In vitro* Dissolution of Aceclofenac agglomerates**

The result of *in-vitro* dissolution studies are shown in Table 3. Pure drug exhibited less release 49.64±0.14% at the end of 60 minutes, while spherical agglomerates without polymer (RK9) released 54.49±0.18% at the end of 60 minutes. The polymeric spherical agglomerates showed significant increase in drug release as compare to pure drug. In vitro release profile of the formulations (RK1-RK6) was ranging from 62.96±0.18 to 79.61±0.03%. Among the formulations prepared, RK3 (prepared with 0.50 w/w of Poloxamer 188) showed highest drug release, 98.51±0.10%. The increase in drug release of agglomerates could be attributed to deposition of polymer onto the drug surface and better wettability of the spherical agglomerates. The drug Release is shown in Fig. 1.

FTIR spectroscopy study

The possible interaction between the drug, polymer were studied by FTIR spectroscopy shown in Fig. 2. The spectrum of pure Aceclofenac presented characteristic peaks at 3319 cm^{-1} (NH group), 1770 cm^{-1} (Carbonyl of Ester), 1716 cm^{-1} (Carbonyl of -COOH), 617 and 663 cm^{-1} (C-Cl bonding) and 750 cm^{-1} (trisubstituted Phenyl ring).

Table 2: Micromeritic properties of spherical agglomerates of Aceclofenac

Formulation Code	Loose Bulk density (LBD) (gm/ml)	Tapped Bulk density (TBD) (gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of repose(⁰)	Particle Size (µm)
RK1	0.421±0.021	0.468±0.026	10.01±0.50	1.11±0.006	25.68±0.44	172.14±05.01
RK2	0.422±0.019	0.464±0.023	09.10±0.41	1.10±0.005	23.88±0.59	243.57±06.10
RK3	0.443±0.017	0.482±0.021	08.00±0.32	1.08±0.003	22.54±0.56	295.35±08.70
RK4	0.416±0.006	0.456±0.008	08.73±0.14	1.09±0.001	22.71±0.48	360.07±06.40
RK5	0.393±0.001	0.450±0.001	12.64±2.30	1.14±0.002	25.43±0.43	142.14±09.33
RK6	0.397±0.017	0.449±0.012	11.54±2.14	1.13±0.027	24.54±0.28	216.42±06.40

Table 3: *In- vitro* Dissolution of spherical agglomerate RK1 - RK 6

Time	RK1	RK2	RK3	RK4	RK5	RK6
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
5	09.01±0.10	15.22±0.19	19.23±0.14	16.32±0.14	08.02±0.23	14.41±0.27
10	16.24±0.19	23.56±0.27	32.42±0.19	26.66±0.18	14.47±0.14	23.42±0.23
15	25.44±0.14	32.45±0.23	42.40±0.23	37.59±0.19	23.81±0.27	32.42±0.16
20	32.15±0.23	39.89±0.16	50.37±0.24	45.48±0.10	28.69±0.18	39.88±0.24
25	38.15±0.18	48.43±0.18	59.73±0.18	53.56±0.18	34.93±0.14	48.43±0.10
30	47.19±0.14	56.89±0.14	68.45±0.18	61.62±0.16	40.88±0.16	56.88±0.18
35	52.13±0.24	62.58±0.23	76.99±0.14	71.23±0.19	45.34±0.14	62.54±0.23
40	57.12±0.23	69.13±0.19	84.78±0.23	78.34±0.14	51.52±0.18	69.11±0.19
45	61.64±0.19	74.23±0.18	90.88±0.14	85.87±0.18	56.21±0.24	74.22±0.23
50	64.64±0.24	78.88±0.24	95.35±0.19	91.09±0.23	59.09±0.23	78.87±0.18
55	67.99±0.14	80.15±0.37	98.23±0.23	93.94±0.24	62.23±0.14	79.37±0.14
60	68.45±0.23	81.68±0.40	98.51±0.10	94.23±0.19	62.96±0.18	79.61±0.23

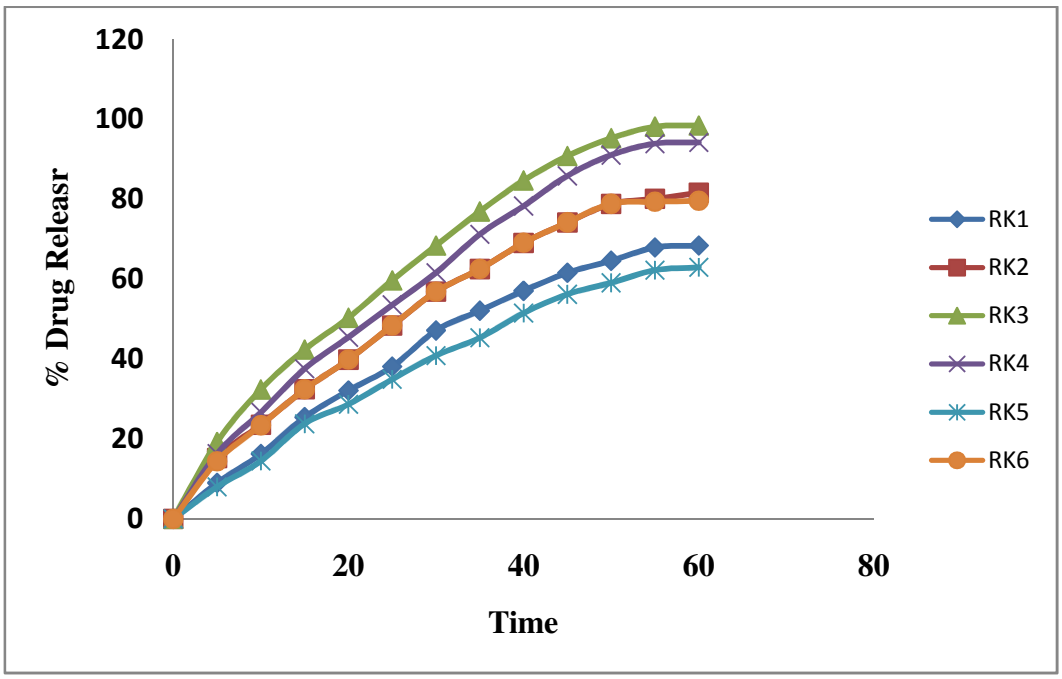

Figure 1: *In- vitro* Dissolution of Spherical agglomerates RK 1 to RK 6

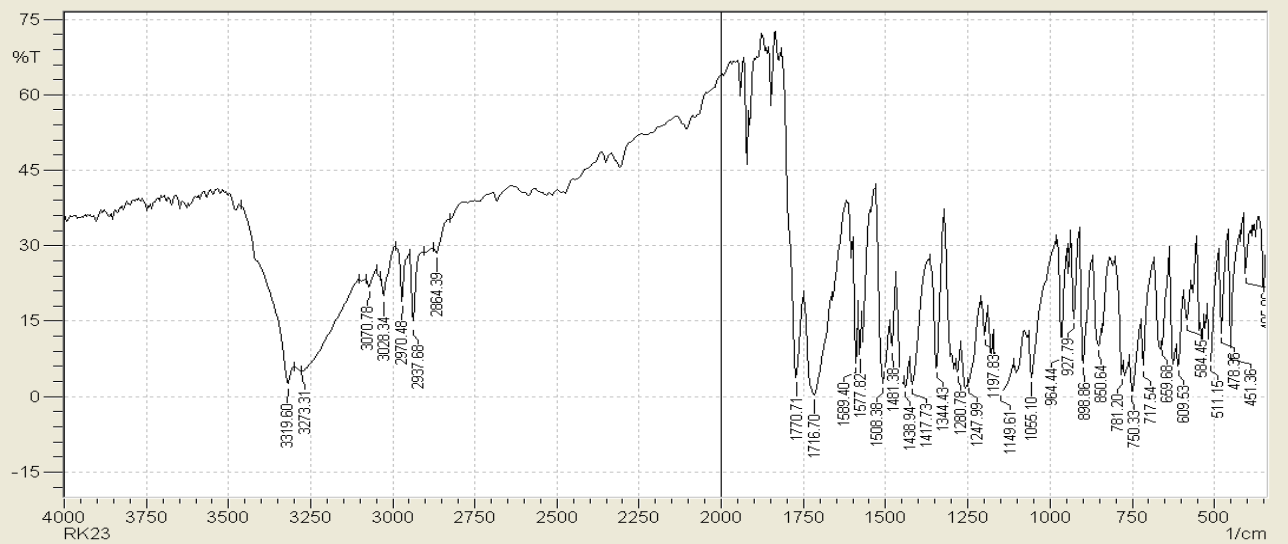

Figure 2: The FTIR spectroscopy for Aceclofenac agglomerates RK 3

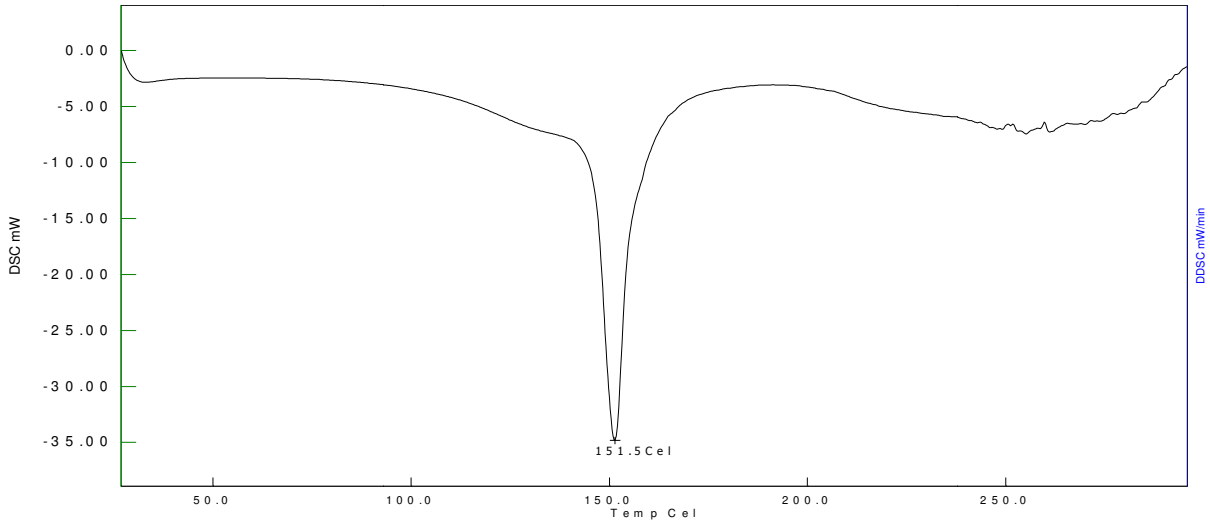

Figure 3: The DSC thermogram of the Formulation RK3 agglomerates

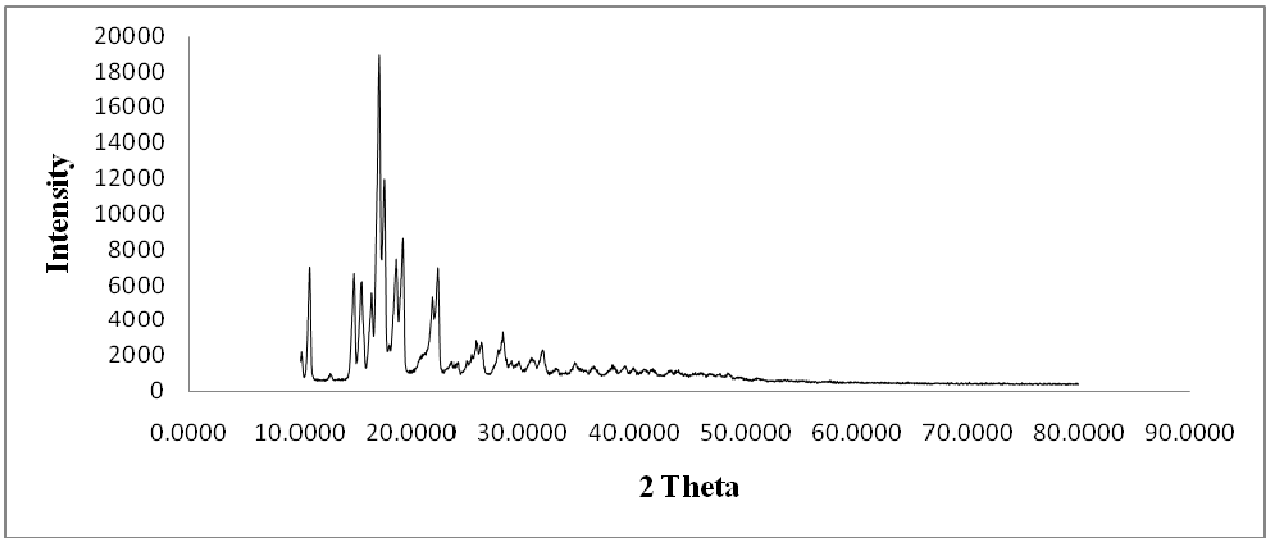

Figure 4: The X-ray diffraction pattern of spherical agglomerates formulation RK3

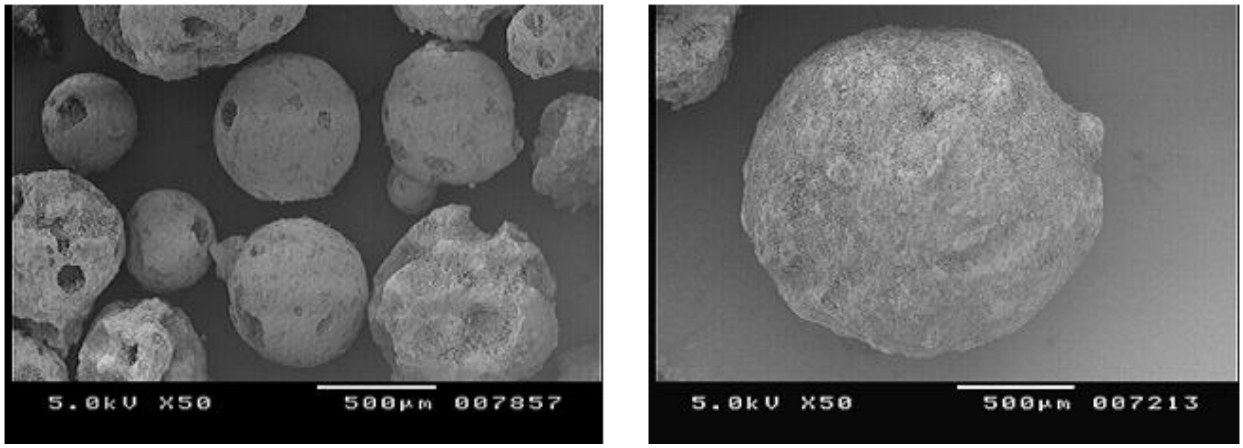

Figure 5: SEM images of spherical agglomerates formulation RK3

The result revealed no considerable change in Aceclofenac in formulation in comparison to pure drug that means all the above characteristics peaks of Aceclofenac appear in the spectra of formulation at same wave number thereby, indicating no modification or interaction between drug and the polymer.

Differential scanning colorimetry (DSC)

The DSC thermogram of the (RK3) agglomerates is presented in Fig. 3. The DSC thermogram of Aceclofenac showed a single melting endotherm at 151.5 ^{0}C, which was ascribed to drug melting. There was a negligible change in the melting endotherm of the prepared spherical agglomerates compared to pure drug (RK3 = 151.8 ^{0}C) this observation further supports the IR spectroscopy results, which indicated the absence of any interaction between the drug and additive used in the preparation. However, there was a decrease although small melting point of the pure drug in the spherical agglomerate compared to that of pure drug. This indicates little amorphization of Aceclofenac when prepared in the form of agglomerates

Powder X-ray diffraction of (XRD)

The results of X-ray diffraction pattern of spherical agglomerates (RK3) are shown in Fig. 4. Pure drug exhibited intense and long peaks whereas spherical agglomerates showed a halo pattern with less intense peaks, which indicate a considerable decrease in crystallinity or partial amorphization of the drug in its agglomerated form. This further supports the DSC results which demonstrated partial amorphization of the drug agglomerates.

Scanning electron microscopy

The results of surface morphology studies are shown in figure. The pure drug is characterized by presence of crystalline particles. Presence of the polymers contributes improved sphericity and roughness of the agglomerates. Improved sphericity may be attributed to coating developed on the crystals before binding into agglomerates, which results into sphericity. SEM obtained at higher magnifications revealed that the agglomerates were formed by very small crystals, which were closely compacted into spherical form. These photo-micrographs show that the prepared agglomerates were spherical in shape which enabled them to flow very easily. The SEM images are shown in Fig 5.

CONCLUSION

The data obtained from the study of preparation and characterization of agglomerates of Aceclofenac by simple spherical agglomeration technique, the following conclusions were made; the spherical agglomerates of Aceclofenac prepared and evaluated for various parameters were found to be within specifications. From Drug-polymer compatibility study by DSC and FTIR, drug was found to be compatible with the Poloxamer 188 and PEG 4000. The agglomerates of Aceclofenac prepared with PEG 4000 and Poloxamer 188 showed improved solubility and dissolution in addition to improving the micromeritic properties. The solubility study reveals that the solubilizing efficiency of hydrophilic polymers enhances the drug solubility significantly as compare to plain agglomerates and Aceclofenac alone. The increase in drug release could be attributed to deposition of polymers on the recrystallized surface and better wettability of spherical agglomerates. All the spherical agglomerates were evaluated for drug content showed negligible loss of drug during crystallization process. The micromeritic properties of

Aceclofenac were highly indicating poor flow and packability properties. On other hand prepared spherical agglomerates exhibited improved flow and packability properties. The formulation RK3 was selected as optimized batch as it showed maximum solubility and drug release from the formulations. This formulation was further evaluated for DSC, FTIR, PXRD and SEM. The DSC results showed that there are no polymorphic changes during the process of crystallization and it further interpreted by peaks found in IR spectrum. The X-ray diffraction pattern of the formulation showed all principle peaks if Aceclofenac, however the peak intensities of spherical agglomerates are lower than corresponding Aceclofenac. The SEM result revealed that the agglomerates formed by very small crystals, which are closely compacted into spherical form and having excellent flow property.

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