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Research Article

DESIGN AND EVALUATION OF ACECLOFENAC FAST DISSOLVING TABLETS PREPARED BY CRYSTALLO-CO-AGGLOMERATION TECHNIQUE

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ABSTRACT

Aceclofenac is a novel anti-inflammatory, analgesic and antipyretic drug that is currently approved for the treatment of acute and chronic rheumatoid arthritis and osteoarthritis. It exhibits very slight solubility in water, poor flow and compression characteristics. Hence directly compressible aceclofenac-disintegrant agglomerates with improved water solubility, flow and compression characteristics were obtained by novel crystallo-co-agglomeration (CCA) technique. Aceclofenac agglomerates were prepared by using a three solvent system comprising of acetone: DCM: water. Acetone-water containing PEG 6000, HPC and disintegrants like SSG, CP and pregelatinised starch in different concentrations were used as the crystallization medium. Precompressional parameters of agglomerates were found within limits. The prepared tablets were evaluated for weight variation, thickness, hardness, friability, *in vitro* dispersion time, wetting time, *in vitro* disintegration time, drug content and *in vitro* drug release. Optimized fast dissolving tablets were characterized by FTIR, DSC and PXRD studies. *In vitro* dispersion time decreases with increase in concentration of all superdisintegrants. Among all the formulations studied, F6 prepared by incorporation of CP (18.43%) had shown short dispersion time with maximum drug release. Formulation F6 showed least disintegration time (18.03 sec) and optimized the drug release (99.13% in 8 min).

Keywords: Aceclofenac, Fast dissolving tablets, Superdisintegrants, Crystallo-co-agglomeration, Direct tableting.

INTRODUCTION

Oral route of drug administration have wide acceptance and hence up to 50-60% of total dosage forms are administered orally. The most popular dosage forms being tablets and capsules[1]. About 35% of the general population in addition to 30-40% of elderly institutionalized patients and 18-22% of all persons in long term care facilities suffer from dysphagia, i.e. difficulty in swallowing[2]. A constant focus on Novel Drug Delivery systems that offer greater patient compliance, effective dosages and minimal chances of side effects has led to the development of fast dissolving tablets[3]. During the last decade, fast disintegrating tablet (FDT) technologies have drawn a great deal of attention. Recently, US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an FDT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". When such tablets are placed in the oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. Their characteristic benefits in terms of patient compliance, rapid on-set of action, increase bioavailability and good stability make these tablets popular as a dosage form of choice[4]. These FDTs can be prepared by lyophilization, tablet moulding, sublimation and direct compression etc[5].

Aceclofenac (2-[[2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetyl]oxy] acetic acid), a nonsteroidal anti-inflammatory drug has been recommended for the treatment osteoarthritis, rheumatoid arthritis and inflammatory disease of the joints. Aceclofenac proved as effective as other NSAIDs with lower indications of gastro-intestinal adverse effects and thus, resulted in a greater compliance with treatment. Aceclofenac is well absorbed after oral administration with hepatic first pass metabolism. It exhibits very slight solubility in water, poor flow and compression char acteristics. Because of the poor aqueous solubility, aceclofenac poses a dissolution- related absorption problem[6,7].

Direct compression is the modern and the most efficient process used in tablet manufacturing due to its low manufacturing cost and high mechanical integrity of tablets. There are currently limited pharmaceutical tablets on commercial production that can be made by direct tabletting because most powders lack the proper characteristics of binding or bonding together into a compact entity[8]. Crystallo-co-agglomeration (CCA) technique involves simultaneous crystallization and agglomeration of drug/s with/without excipient/s from good solvent and /or bridging liquid by addition of a non-solvent. The spherical agglomerates obtained by CCA can be used as intact beads (encapsulated spansules) or directly compressible tablet intermediates having satisfactory micromeretic (flowability), mechanical (friability, crushing), compressional (compressibility, compactibility) and drug release properties[9].

In the present work aceclofenac fast dissolving tablets were prepared by direct compression of aceclofenac-disintegrant agglomerates with improved solubility, flow and compressibility. The rational for preparing was to make the drug available in a soluble form in the mouth, which would facilitate its absorption from the buccal cavity. This would help to overcome its first-pass metabolism and thereby improve bioavailability.

MATERIALS AND METHODS

Aceclofenac was received as gift sample from Aristo Pharmaceuticals Pvt. Ltd, Mumbai. Hydroxypropylcellulose was generously donated by Nippon Soda Co., Ltd, Tokyo. Crospovidone was obtained as a gift sample from Torrent Pharmaceuticals Ltd, Kalol. Pregelatinised starch was obtained as a gift sample from West Bengal Chemical Industries Ltd, Kolkata. Sodium starch glycolate was obtained as a gift sample from Vijalak pharma Pvt. Ltd, Hyderabad. Directly compressible mannitol was obtained as gift sample from Torrent Pharma Ltd, Ahmedabad. All other chemicals/solvents used were of analytical grade.

Crystallo-co-agglomeration technique

Aceclofenac agglomerates were prepared using a three solvent system comprising acetone: dichloromethane: water (good solvent, bridging liquid and bad solvent, respectively). In a vessel, mixture of polyethylene glycol 6000 (6.5% w/w of total solid content) and hydroxypropylcellulose (10% w/w of drug and disintegrant amount) was dissolved in distilled water (50 ml) and 1/3 of the total disintegrant was uniformly dispersed in the solution. Acetone (4 ml) at 50 ^{0}C containing 1 gm aceclofenac and the other 2/3 of disintegrant was separately stirred for 20 min. The latter dispersion was added immediately to the dispersion containing dissolved polymer under constant stirring conditions (400 rpm, paddle type

agitator with 4 blades) kept at room temperature. The stirring was continued for 20 min and bridging liquid dichloromethane was added drop wise to obtain agglomerates, which were then filtered and dried overnight. The dried crystals were stored in screw-capped jars at room temperature before use. As a reference, the aceclofenac agglomerates in the absence of disintegrant were prepared. Different compositions of aceclofenac agglomerates are shown in Table 1.

Table 1: Compositions of the aceclofenac-disintegrant agglomerates

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Aceclofenac (gm)	1	1	1	1	1	1	1	1	1	1
SSG (mg)	-	250	300	350	-	-	-	-	-	-
CP (mg)	-	-	-	-	250	300	350	-	-	-
Pregelatinised Starch (mg)	-	-	-	-	-	-	-	250	300	350
HPC (%w/w of drug and disintegrant amount)	10	10	10	10	10	10	10	10	10	10
PEG-6000 (%w/w of total solid content)	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Formulation of the aceclofenac fast dissolving tablets										
Agglomerates equivalent to 100 mg of drug	105	112	116	119	113	116	118	114	118	120
Spray dried mannitol (mg)	91	84	80	77	83	80	78	82	78	76
Sodium saccharin (mg)	2	2	2	2	2	2	2	2	2	2
Talc (mg)	2	2	2	2	2	2	2	2	2	2
Total weight (mg)	200	200	200	200	200	200	200	200	200	200

Precompressional studies of aceclofenac agglomerates

Yield and drug-loading efficiency of agglomerates

The practical yield of agglomerates was calculated by weighing the prepared agglomerates after drying stage. For the determination of drug content, agglomerates (100 mg) were powdered and dissolved in 10 ml phosphate buffer (pH 6.8) and vortexed for 20 min. The solution wasfiltered and after sufficient dilution with phosphate buffer (pH 6.8) analyzed spectrophotometrically at 247 nm for drug content[10].

$$\% \text{ Yield} = \frac{\text{Total weight of agglomerates}}{\text{Total weight of drug and polymer}} \times 100$$

$$\text{Drug loading efficiency} = \frac{\text{Drug entrapped}}{\text{Theoretical drug content}} \times 100$$

Determination of the amount of disintegrant in agglomerates

Agglomerates (1 gm) were powdered and samples equivalent to approximately 100 mg of aceclofenac were weighed accurately and dispersed in acetone, such that any drug dissolved whereas the disintegrant remained dispersed. The dispersion was then filtered to separate aceclofenac solution from the disintegrant. After filtration the acetone solution was diluted with phosphate buffer (pH 6.8) and the samples were analyzed spectrophotometrically at 274 nm. The drug content was determined by reference to an appropriate standard curve and the amount of disintegrant was taken as the difference between total amounts of powder and the spectrophotometrically determined weight of aceclofenac.

Particle size distribution

This was performed by sieve analysis techniques, 5.0 gm sample (dried) agglomerates of each batch were passed through a nest of sieve containing sieve # 16, 30, 44, 60, 85, 100 and 120 with the coarsest at the top. The vibration rate was set at 200 strokes/ min and the sieving time was 10 min. agglomerates retained on every mesh were weighed and generated data were subjected for analysis for log normal distribution. In case of untreated aceclofenac, particle size of crystals was measured using scanning electron micrographs[11].

Angle of Repose

This was measured according to the fixed funnel method. A funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip 2.5 cm height (h), above graph paper placed on aflat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. The mean diameter (2r) of the powder cone was determined and the angle of repose of the powder material was calculated using the formula.

$$\text{Angle of repose } (\theta) = \tan^{-1} h/r$$

Where, h is height of the pile and r is radius of the pile.

Compressibility index measurement

Flowability of untreated and agglomerated samples was also assessed from Hausner's ratio and Carr's Index (CI). The Hausner's ratio and CI were calculated from the bulk and tapped densities. Tapped density was determined by tapping the samples (10 g) into a 10ml measuring cylinder using a tapping machine. The Hausner's ratio and CI were calculated from the following equations[12].

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

$$\% \text{ Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{ X } 100$$

Determination of shape factor

The agglomerates were photographed using an image analysis (scion image analyzer-Scion CG-7 RGB, USA). Area (A) and perimeter (P) obtained from tracings of enlarged photomicrographs of agglomerates were used to calculate the shape factor (S).

$$S = 4\pi (A_{actual})/P_{actual}^2$$

Preparation of aceclofenac FDTs by direct compression technique

The quantity of aceclofenac-disintegrant agglomerates equivalent to 100 mg of drug was taken, then mixed with direct compressible diluent and sweetener in a plastic container. The diluents and sweetening agents were passed through sieve no.40 before mixing. Talc was passed through mesh no.80, then mixed and blended with above mixture followed by compression of the blend. The tablets were prepared by direct compression method using 4 mm flat punches on a 10 station rotary compression machine.

Evaluation of aceclofenac FDTs

Thickness and diameter

Thickness and diameter of prepared tablets were tested by vernier callipers and the average was calculated.

Hardness

The prepared tablets hardness was measured by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Friability

Ten tablets were weighed collectively and placed in the chamber of the friabilator. After 100 rotations (i.e. in 4 minutes), the tablets

were taken out from the friabilator and intact tablets were again weighed collectively[13].

Weight variation

Twenty tablets from each formulation were selected at a random an d average weight was determined. Then individual tablets were weig hed and was compared with average weight[14].

Drug content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 100mg of aceclofenac was dissolved in 100ml of pH 6.8 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 274 nm using UV-Visible spectrophotometer (UV 160- Shimadzu, Japan.

Wetting time

A piece of tissue paper folded twice was placed in a small petridish (internal diameter of 5 cm) containing 6 ml of distilled water. A tablet was placed on the paper and the time required for complete wetting of the tablet was measured.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the tissue paper. The wetted tablet was weighed. The test was done in triplicate. The water absorption ratio(R) was determined according to the following equation

$$\text{Water absorption ratio (R)} = \frac{W_a - W_b}{W_a} \text{ X } 100$$

Where, W_a and is W_b are the weights of the tablets before and after water absorption[15].

***In vitro* disintegration time**

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water was maintained at a temperature of 37° ± 2°C and time taken for the entire tablet to disintegrate completely was noted[14].

***In vitro* dispersion time**

In vitro dispersion time was measured by dropping a tablet in a 10 ml measuring cylinder containing 6ml of buffer solution simulating saliva fluid (pH6.8)[16].

***In vitro* drug release studies**

The prepared FDT's were subjected to *in vitro* dissolution studies using an 8 station USP (Type-II) dissolution apparatus (Electro Lab, TDT-O8L, Mumbai). The dissolution studies were carried out in 900 ml of phosphate buffer pH 6.8 at 37 ± 0.5°C. The speed of the paddle was set at 50 rpm. Sampling was done every 2 minutes interval. For each sample, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium. The samples withdrawn were analyzed in the UV spectrophotometer at 274 nm.

Fourier Transform Infrared Spectroscopy (FTIR) studies

The pure drug, physical mixtures and best formulation (F7) were subjected for FTIR analysis. The samples were prepared on KBr-press (Startech Lab, India). The samples were scanned over a range of 4000-400 cm^{-1} using Fourier transformer infrared spectrophotometer (8600, Shimadzu Corporation, Japan). Spectra were analyzed for drug polymer interactions.

Differential scanning calorimetry (DSC) studies

The pure drug and best formulation (F7) were subjected to differential scanning calorimeter equipped with an intracooler (Mettler, Switzerland). Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample were sealed in aluminum pans and heated at a constant rate 20°C/min over a temperature range of 20-250°C. An inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

X-ray diffraction of powder (XRDP)

The X-ray powder diffraction patterns were recorded on an X-ray diffractometer (PW 1729, Philips, Netherland). The samples were irradiated with monochromatized CuK-α radiation (1.542A°) and analyzed between 10-50° 2θ. The voltage and current used were 30kV and 30mA, respectively. The range and the chart speed were $1x10^4$ CPS and 5mm/2θ respectively.

Scanning electron micrographs (SEM) analysis

The shape and surface topography of agglomerated crystals and conventional crystals were observed through a scanning electron microscope (JEOL USA Inc., Peabody, MA). Dried samples were fixed on aluminum stubs using double-sided copper tape and coated with gold palladium in the presence of argon gas using a Hummer I sputter coater (Anatech Ltd., Denver, NC), under vacuum (0.1 mm Hg).

RESULT AND DISCUSSION

Crystallo-co-agglomeration mechanism

Aceclofenac agglomerates were prepared using a three solvent system comprising acetone: dichloromethane: water. Water containing PEG-6000, HPC and 1/3 disintegrant (aqueous dispersion) was used as the crystallization medium. The acetone dispersion containing the drug and 2/3 disintegrant was added immediately to the aqueous dispersion with constant stirring and DCM was added drop wise to obtain quasi-emulsified droplets of drug solution. The crystallization of the drug then proceeded from the outer surface of the droplet due to both decreasing temperature and counter diffusion of both solvents through the interface of emulsion droplets. The batch processing time of 20 min is necessary to produce agglomerates with good sphericity and flowability. The end-point of the process was apparent when the dispersion (comprised primarily of suspended disintegrant) became transparent continuous phase containing spherical agglomerates.

Precompressional studies of aceclofenac agglomerates

The results of various precompressional evaluations of agglomerates are given in Table 2. The practical yield was found satisfactory and ranged from 77.4 to 82.2%. The drug loading efficiency was found to be in the range of 95.2-99.2% w/w. As both phases (acetone and aqueous) contain the disintegrant, then it is likely that it is distributed both inside the agglomerates (intagranularly) and outside the agglomerates (extragranularly), attached to the surface. The maximum amount of disintegrant incorporated in to agglomerates was pregelatinised starch (19.95% in F10). The geometric mean diameters of the agglomerates (451-542 μm) were approximately 23 times larger than those of the untreated aceclofenac (22.49 ± 10.4 μm). The data indicate that the original single crystals of drug were uniformly agglomerated by the spherical crystallization process employed.

The micromeretic properties of aceclofenac agglomerates are shown in Table 3. The prepared agglomerates showed improved flowability when compared to pure drug as observed from the values of angle of repose (23.04–28.5°), Hausner's ratio (1.0–1.22) and Carr's index (8.86–12%). Among different agglomerates prepared, formulation F7 showed maximum flowability as evident by low values of angle of repose (23.04°), Hausner's ratio (1.0) and Carr's index (8.86). Pure drug exhibited poor flowability and compressibility as indicated by high value of angle of repose (46.57 ± 0.625°), Hausner's ratio (1.45 ± 0.04) and Carr's index (29.63 ± 0.29%). This is because of irregular shape and small size of the crystalline powder, which put hurdles in the uniform flow of powder from the funnel. The improved flowability of spherical agglomerates is due to increase in the sphericity of agglomerates, since the agglomerates displayed shape factor values close to 1.

Table 2: Precompressional parameters of the aceclofenac-disintegrant agglomerates

Formulation code	Yield (% w/w)	Drug loading (% w/w)	Ratio of disintegrant/drug measured in agglomerates (%)	Geometric mean diameter (µm)
Pure drug	---	---	---	22.49 ± 10.4
F1	82.25 ± 0.18	95.21 ± 0.14	---	508.23 ± 0.55
F2	80.91 ± 0.11	96.82 ± 0.16	12.46	465.41 ± 0.14
F3	78.17 ± 0.14	99.22 ± 0.11	13.26	485.41 ± 0.1
F4	78.57 ± 0.21	98.12 ± 0.14	13.59	501.15 ± 0.12
F5	80.33 ± 0.09	97.0 ± 0.11	16.44	451.2 ± 0.24
F6	79.15 ± 0.12	98.82 ± 0.20	16.07	472.12 ± 0.14
F7	80.25 ± 0.24	99.2 ± 0.16	16.39	493.31 ± 0.2
F8	77.47 ± 0.15	98.29 ± 0.18	19.67	512.12 ± 0.13
F9	79.5 ± 0.14	98.60 ± 0.16	18.43	533.17 ± 0.21
F10	79.45 ± 0.18	98.76 ± 0.15	19.95	542.1 ± 0.18

Table 3: Micromeretic propereties of aceclofenac-disintegrant agglomerates

Formulation code	Angle of repose (θ)	Hausner`s ratio	Carr`s index (%)	Shape factor
Pure drug	46.57 ± 0.625	1.45 ± 0.04	29.63 ± 0.29	---
F1	28.55 ± 0.17	1.2 ± 0.02	10.34 ± 0.03	1.06 ± 0.11
F2	27.3 ± 0.23	1.01 ± 0.02	11.69 ± 0.21	0.84 ± 0.11
F3	26.1 ± 0.13	1.05 ± 0.01	10.06 ± 0.34	1.05 ± 0.04
F4	25.2 ± 0.23	1.03 ± 0.02	9.69 ± 0.21	1.07 ± 0.10
F5	25.04 ± 0.2	1.04 ± 0.02	9.6 ± 0.39	1.032 ± 0.12
F6	24.1 ± 0.11	1.02 ± 0.01	9.04 ± 0.23	0.96 ± 0.08
F7	23.04 ± 0.26	1.0 ± 0.02	8.86 ± 0.39	1.01 ± 0.14
F8	25.2 ± 0.21	1.18 ± 0.08	12.00 ± 0.12	0.94 ± 0.08
F9	24.7 ± 0.2	1.12 ± 0.01	11.16 ± 0.07	1.00 ± 0.06
F10	23.69 ± 0.21	1.18 ± 0.06	10.00 ± 0.12	1.04 ± 0.10

Physico-chemical evaluations of aceclofenac FDTs

The results of physicochemical evaluations of aceclofenac FDTs are given in Table 4-5. The thickness and diameter of all tablets was found in range of 3.23-4.35 mm and 7.1- 7.18 mm respectively. Hardness of tablets was between 3.0-4.2 kg/cm^2 for all the formulations. This ensures the good handling characteristics of all the formulations. Friability was found in between 0.28-0.43% in all the formulation ensuring that the tablets were mechanically stable. The drug content and weight variation were found to be in the range of 98-99.89% and 0.28-0.43% respectively which were within the acceptable limits.

Dissolution of a FDT is dependent on wetting time, disintegration time and dispersion time. Wetting time is related to inner structure of tablet and hydrophobicity of components. The wetting time for all the formulations ranged 21.14-35.33 sec. The formulation F7 containing crospovidone as disintegrant showed least wetting time of 21 sec among all the formulations. The water absorption ratio of all the formulations ranged 60.21-76.12%. Disintegration time is very important for FDT which is desired to be less than 60 sec. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity. The disintegration time for all the formulations ranged 18-25 sec. The formulation F7 containing crospovidone as disintegrant showed least disintegration time of 18 sec among all the formulations. Dispersion time is used as an indication for the ease of tablet disintegration in buccal cavity. The dispersion time for all the formulations ranged 24.34-28 sec. The formulation F7 containing crospovidone as disintegrant showed least dispersion time of 20 sec among all the formulations.

From the results it is evident that the wetting time decreases with increase in the concentration of superdisintegrants. It was observed that as the concentration of superdisintegrants increases water absorption ratio increases and disintegration time decreases. There is a good relationship between disintegration time and dispersion time (Fig. 1). The faster disintegration of crospovidone tablets when compared to tablets with other disintegrants may be attributed to its rapid capillary activity and pronounced hydration with little tendency to gel formation. SSG swells 7-12 folds in less than 30 sec thus forming a thick barrier to the further penetration of the disintegration medium and retard the disintegration of tablet contents.

Table 4: Physico-chemical evaluation of aceclofenac FDTs

Formulation Code	Thickness (mm) (±SD), n=4	Diameter (mm), (±SD), n=3	Hardness test (Kg/cm^2) (±SD), n=3	Weight variation(%), (±SD), n=20	Friability (%), (±SD), n=10
F1	3.23 ± 0.04	7.13 ± 0.01	3.0 ± 0.12	0.38 ± 0.01	1.35 ± 0.12
F2	4.25 ± 0.12	7.18 ± 0.05	3.2 ± 0.14	0.36 ± 0.04	2.32 ± 0.17
F3	4.28 ± 0.05	7.18 ± 0.05	3.4 ± 0.13	0.42 ± 0.18	2.1 ± 0.15
F4	4.25 ± 0.12	7.18 ± 0.05	3.4 ± 0.14	0.36 ± 0.04	2.31 ± 0.12
F5	4.33 ± 0.04	7.14 ± 0.02	4.1 ± 0.15	0.28 ± 0.14	1.67 ± 0.24
F6	4.35 ± 0.03	7.11 ± 0.03	4.1 ± 0.12	039 ± 0.24	1.32 ± 0.13
F7	4.33 ± 0.04	7.14 ± 0.02	4.2 ± 0.15	0.28 ± 0.14	1.6 ± 0.2
F8	4.25 ± 0.17	7.12 ± 0.03	3.8 ± 0.14	0.41 ± 0.02	2.17 ± 0.15
F9	4.35 ± 0.03	7.10 ± 0.03	3.4 ± 0.14	0.43 ± 0.10	1.32 ± 0.15
F10	4.25 ± 0.17	7.12 ± 0.04	3.8 ± 0.14	0.41 ± 0.02	2.7 ± 0.13

Table 5: Physico-chemical evaluation of aceclofenac FDTs

Formulation Code	Drug content (%) (±SD), n=5	Wetting time (sec) (±SD), n=4	Water absorption ratio (%) (±SD), n=4	Disintegration time (sec) (±SD), n=6	Dispersion time (sec) (±SD), n=4
F1	99.04 ± 0.34	84.6 ± 0.42	66.81 ± 1.4	75.43 ± 0.51	80.78 ± 0.64
F2	98.79 ± 0.18	30.14 ± 0.2	62.12 ± 1.2	25.03 ± 0.64	28.01 ± 0.13
F3	98.86 ± 0.2	28.15 ± 011	67.13 ± 1.91	24.34 ± 0.11	27.6 ± 0.2
F4	99.6 ± 0.12	25.73 ± 0.13	71.15 ± 1.43	22.58 ± 0.21	24.34 ± 0.14
F5	99.08 ± 0.29	28.91 ± 0.12	51.15 ± 1.41	22.95 ± 0.22	24.55 ± 0.21
F6	99.53 ± 0.18	25.21 ± 0.27	61.81 ± 1.86	20.59 ± 0.31	23.91 ± 0.11
F7	99.89 ± 0.18	21.14 ± 0.24	63.24 ± 1.75	18.03 ± 0.5	20.01 ± 0.15
F8	98.08 ± 0.15	35.33 ± 0.14	60.21 ± 1.5	26.71 ± 0.5	30.01 ± 0.43
F9	98.59 ± 0.22	32.26 ± 0.22	74.16 ± 1.16	24.12 ± 0.9	26.83 ± 0.13
F10	99.10 ± 0.39	29.18 ± 0.2	76.12 ± 1.78	22.42 ± 0.6	25.28 ± 0.1

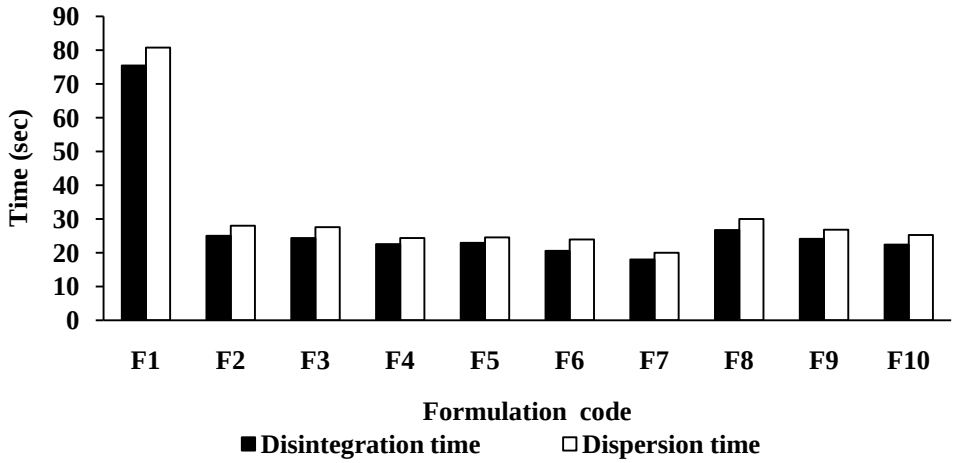

Fig. 1: Comparison between disintegration and dispersion time of aceclofenac FDTs

***In vitro* release study**

In vitro release profile of all formulations (F1-F10) in phosphate buffer pH 6.8 was ranging from 99.13-99.96% (Fig. 2-3). The formulation F1 containing untreated aceclofenac showed 99.41% release in 28 min. The dissolution profiles of tablet were influenced by nature of superdisintegrants. The best formulations in case of each superdisintegrant with respect to drug release were F4 in case of SSG (99.88% in 14 min), F7 for CP (99.13% in 8 min) and F10 for pre gelatinized starch (99.85% in 20 min). The release profiles indicated the faster and maximum drug release due to easy breakdown of particles due to porous structure formation after agglomeration of drug crystals. The investigated superdisintegrants can be ranked based on overall *in-vitro* release profile of aceclofenac FDTs as CP > SSG > pregelatinized starch. Among all the formulations F7 was selected as best formulation which gave 99.13% drug release in 8 min.

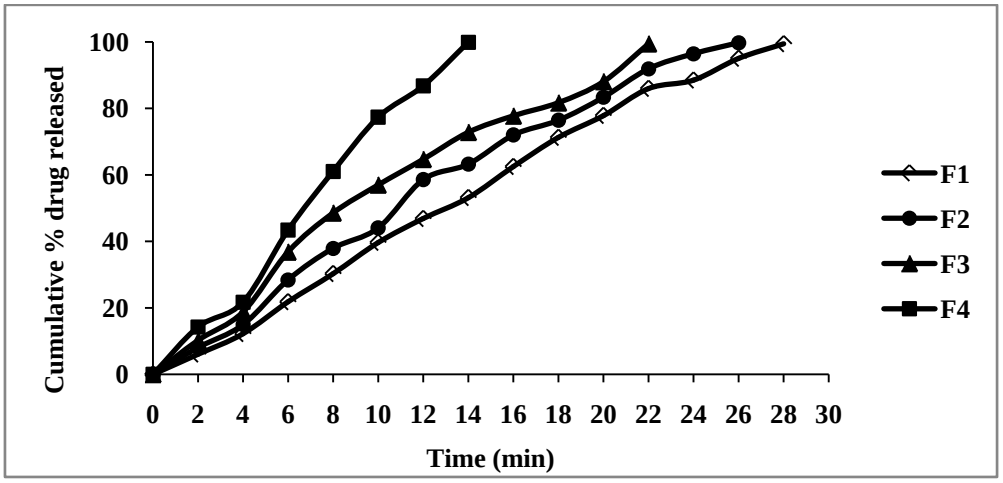

Fig. 2: Comparative dissolution profile of aceclofenac FDTs containing different disintegrants (F2-F4: 250 mg)

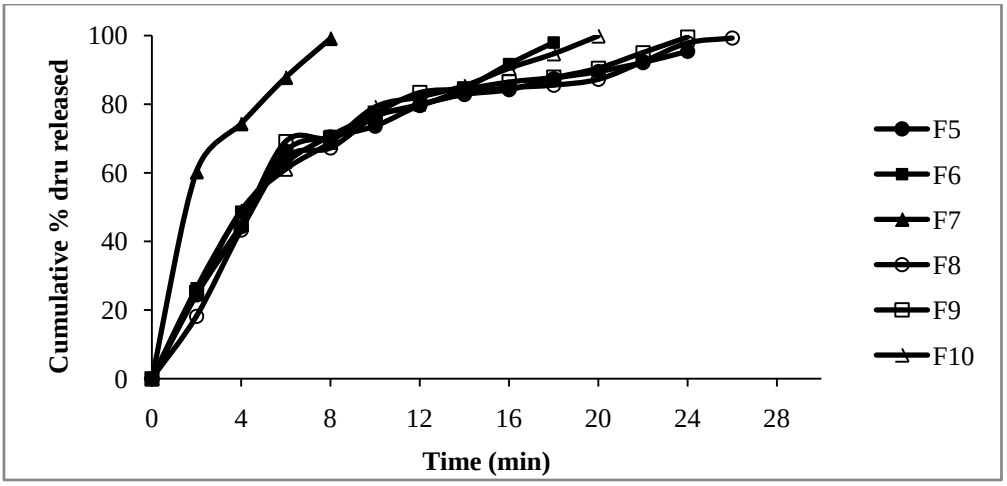

Fig. 2: Comparative dissolution profile of aceclofenac FDTs containing different disintegrants (F5-F7: 300 mg, F8-F10: 350 mg)

FTIR Studies

The FT-IR spectra of pure drug, best formulation (F7) and its physical mixture are taken for the characterization studies (Fig. 4). As there is no change in the positions of characteristic absorption bands and bonds of various functional groups present in the drug. This observation clearly suggests that the drug remains in its normal form with no prominent change in its characteristics even in its physical mixture and formulation.

DSC Studies

In the DSC studies pure aceclofenac showed a sharp endotherm at 152.51^{0}C corresponding to its melting point. There was no appreciable change in the melting endotherm of spherical agglomerates compared to that of pure drug (F7 agglomerates = 153.27 ^{0}C). The DSC results (Fig. 5) also revealed little amorphization of aceclofenac when prepared in the form of agglomerates with HPC. This is evident by a decrease, although little, in the enthalpy changes of agglomerates when compared with that of pure drug (pure aceclofenac = -391.59 mJ/mg; F7 agglomerates = -388.45 mJ/mg).

PXRD Studies

The X-ray powder diffraction pattern (PXRD) of best formulation (F7) in 10–50^0, 2θ range showed that the diffraction peaks, characteristic of aceclofenac were still detectable in the crystallized samples suggesting that the particles crystallized in the presence of HPC, PEG-6000 and disintegrants did not undergo structural modifications (Fig. 6). However, the XRD scan of plain aceclofenac showed intense peaks of crystallinity, whereas the XRD pattern of the agglomerates exhibited halo pattern with less intense and denser peaks compared to plain aceclofenac indicating the decrease in crystallinity or partial amorphization of the drug in its agglomerated form.

SEM studies

An examination of the SEMs, confirm that the aceclofenac pure drug (Fig. 7a) was markedly smaller in particle size than the prepared agglomerates and was plate-like in appearance with no evidence of porosity. Aceclofenac-crospovidone agglomerates (Fig. 7b) illustrate aceclofenac particles crystallized from acetone-water system containing HPC, PEG-6000 and disintegrants. SEMs obtained at higher magnifications (Fig. 7c) revealed that agglomerates were spherical aggregates of plate-shaped crystals with clear evidence of porosity. It was also apparent that the presence of disintegrating agent in crystallization medium produced agglomerates with a high surface roughness. Aceclofenac agglomerates prepared by CCA technique but without disintegrant were also found to be spherical (Fig. 7d). The higher magnifications of aceclofenac agglomerates without disintegrating agent (Fig. 7e) indicate uniform surface with no evidence of porosity. The Fig. 7b and 7d clearly indicate that the use of disintegrant in the crystallization media had no major effect on the overall shape of aceclofenac crystals.

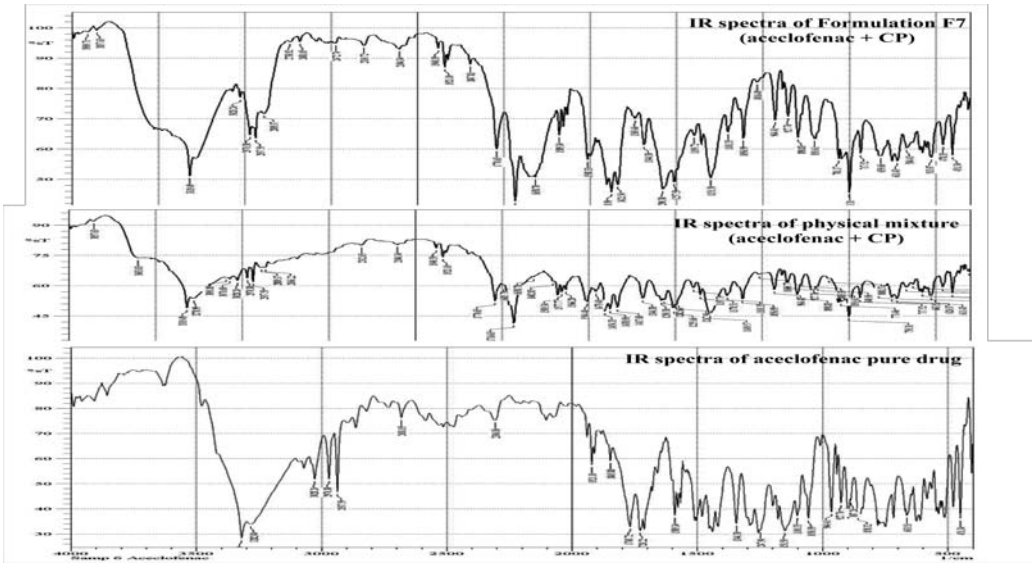

Fig. 4: Comparison between FTIR spectrum of pure drug, Formulation F7 and its physical mixture

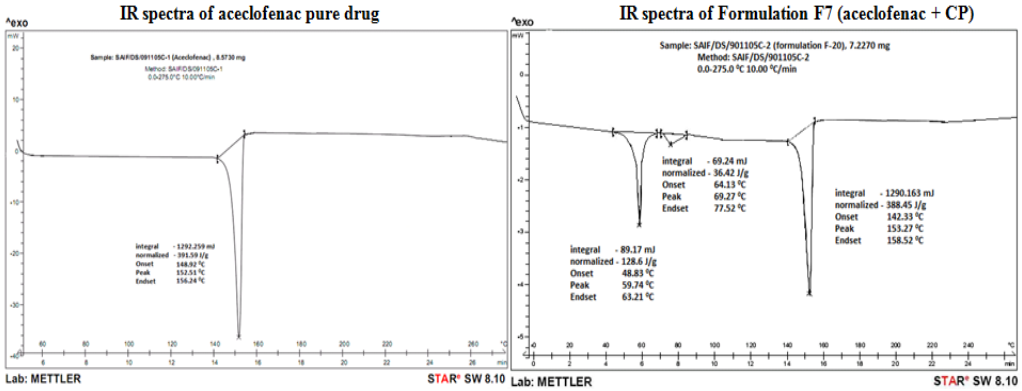

Fig. 5: Comparison between DSC thermograms of pure drug, Formulation F7

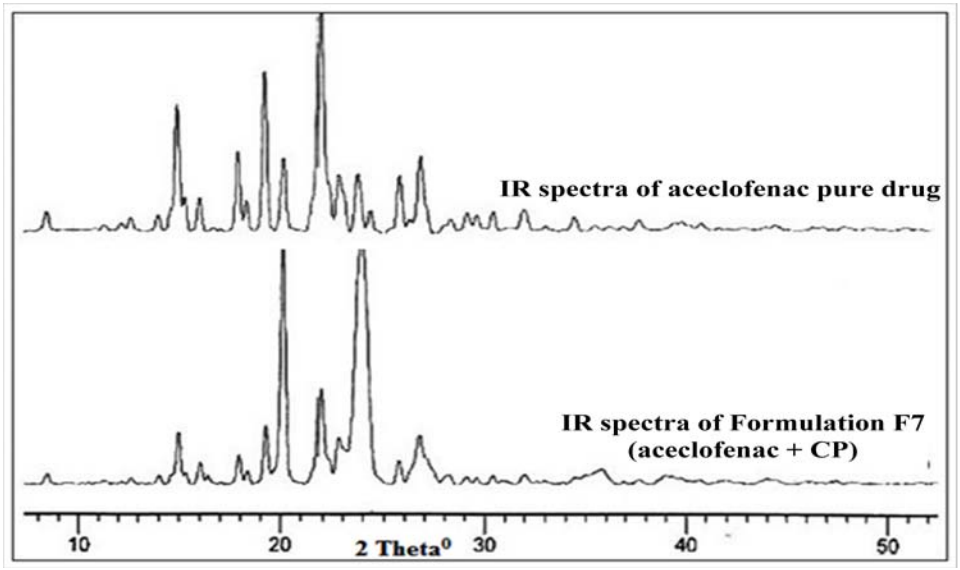

Fig. 6: Comparison between PXRD patterns of pure drug, Formulation F7

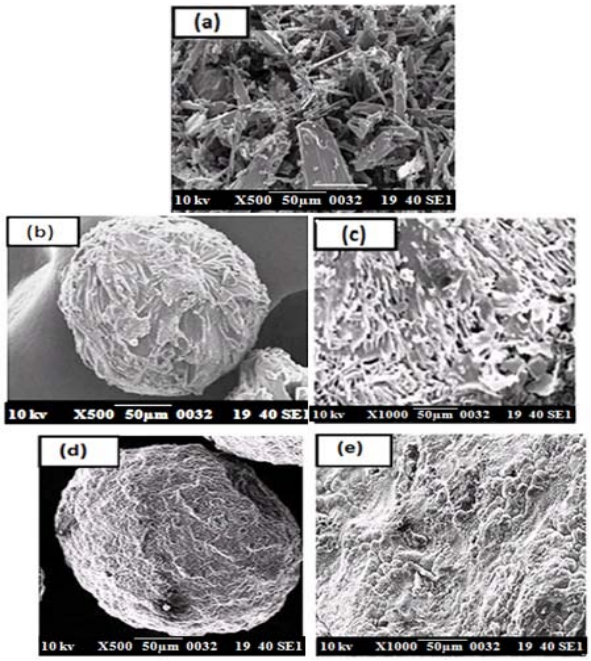

Fig. 7: SEM of (a) Aceclofenac pure drug crystals, (b) Shape and (c) Surface of aceclofenac-crospovidone agglomerates (F7), (d) Shape and (e) Surface of aceclofenac agglomerates without disintegrant (F1)

CONCLUSION

Aceclofenac-disintegrant agglomerates were successfully pre- pared for direct tableting by use of a crystallo-co-agglomeration technique. The micromeritics of the agglomerates, such as flowability, packability and compactibility were dramatically improved, resulting in successful direct tableting without capping. The main factor in the improvement of the flowability and packability was a significant reduction in interparticle friction, due to the spherical shape of the tableted particles. Compactibility of the agglomerates was much improved. The dissolution rate of aceclofenac from the aceclofenac-disintegrant agglomerates was enhanced significantly with increasing the amount of disintegrant.

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REFERENCES

1. Mohire NC and Yadav AV. Novel approach to formulate ß-cyclodextrin complexed mouth dissolving tablet of metronidazole and its *in-vitro* evaluation. Journal of pharmacy research 2010; 3(3): 662-67.
2. Wagh MA, Dilip KP, Salunkhe KS, Chavan NV and Daga VR. Techniques used in orally disintegrating drug delivery system. International journal of drug delivery 2010; 2: 98-107.
3. Arjun G, Prasad MS, Santhosha D and Achaiah G. Formulation and evaluation of rosiglitazone mouth dissolving tablet. International Journal of Pharma and Bio Sciences 2010; 1: 1-9.
4. Patel HA, Patel JK, Patel KN and Patel RR. Studies on formulation and *in vitro* evaluation of fast dissolving tablets of domperidone. Int.J.Ph.Sci 2010; 2(1): 470-76.
5. Rao NGR, Patel T, Gandhi S. Development and evaluation of carbamazepine fast dissolving tablets prepared with a complex by direct compression technique. Asian J Pharm 2009: 97-103.
6. Alvarez-Larena A, Piniella JF and Carrasco E. Crystal structure and spectroscopic study of 2-[(2, 6-dichlorophenyl) amino] phenylacetoxyacetic acid (Aceclofenac). J. Chem. Crystallography 1992; 22: 323–28.
7. Shakeel F, Ramadan W and Shafiq S. Solubility and dissolution improvement of aceclofenac using different nanocarriers. J Bioequiv Availab 2009; 1(2): 39-43.
8. Yadav VB and Yadav AV. Comparative Tabletting behavior of Carbamazepine granules with spherical agglomerated crystals prepared by spherical crystallization technique. Int.J. ChemTech Res 2009; 1(3): 476-82.
9. Paradkar AR, Pawar AP and Jadhav NR. Crystallo-co-agglomeration technique: A novel particle engineering technique. Asian journal of pharmaceutics 2010; 4-10
10. Usha AN, Mutalik S, Reddy MS, Ranjith AK, Kushtagib P and Udupa N. Preparation and, *in vitro*, preclinical and clinical studies of aceclofenac spherical agglomerates. European Journal of Pharmaceutics and Biopharmaceutics 2008; 70: 674–83.
11. Gupta MM and Srivastav B. 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. International Journal of Current Pharmaceutical Review and Research 2010; 1(1): 12-23.
12. Maghsoodia M, Taghizadeh O, Martin GP and Nokhodchic A. Particle design of naproxen-disintegrant agglomerates for direct compression by a crystallo-co-agglomeration technique. International Journal of Pharmaceutics 2008; 351: 45-54.
13. Alfred Martin. Physical Pharmacy. 4th ed. Philadelphia: Lippincott Willams & Wilkins; 1993.
14. Mohsin AA, Nimbalakr NE, Sanaullah S, Aejaz A. Formulation and evaluation of mouth dissolving tablets of amitryptyline hydrochloride by direct compression technique. Int J Pharm Pharm Sci 2010; 2(1): 204-210.
15. Swamy PV, Areefulla SH, Shirsand SB, Gandra S, Prashanth B. Orodispersible tablets of meloxicam using disintegrant blends for improved efficacy. Indian J Pharm Sci 2007; 69(6): 836-40.
16. Kumar R, Patil MB, Patil SR, Paschapur MS. Development and characterization of melt-in-mouth tablets of haloperidol by sublimation technique. Int J Pharm Pharm Sci 2009; 1(1): 65-73.