

Research Article

Formulation and Comparative Evaluation of Aceclofenac Tablets by Two Granulation Methods

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ABSTRACT

The objective of the present investigation was to design suitable Immediate release tablet formulation of Aceclofenac by using cross carmellose sodium as super-disintegrant in four different concentrations i.e., 0, 4, 6, 8% w/w of tablet weight by two granulation methods i.e., Wet and melt granulation methods. The objective of the research was to compare the two granulation methods i.e., wet and melt granulation methods. Melt granulation provides an advantageous method of granulation which results in a tablet dosage form showing immediate and fast release of drug. The main scope of this research work was to compare pre-compression, post-compression and in Vitro drug release properties of the tablets prepared by two granulation methods. Aceclofenac is an analgesic belonging to the class of NSAIDs. Four formulations (F_w, F₁, F₂, and F₃) of IR tablets were prepared by wet granulation method and four formulations of melt granulation (F_M, F₄, F₅, and F₆) were prepared. All the formulations were evaluated for their pre and post compression properties and also the in Vitro dissolution tests were carried out. It was found that the melt granulation formulations showed faster and immediate release compared to that of wet granulation method. Among all the formulations F₆ formulation containing 8% CCS showed the faster drug release. Also the best formulations of both the granulation methods i.e., F₃ and F₆ were compared.

Keywords: Aceclofenac, Immediate release tablets, Cross carmellose sodium, PEG 6000, Melt granulation method, Wet granulation method.

INTRODUCTION

Among all dosage forms tablet is the most popular one existing in the field of pharmacy because of its major advantages like self-administration, compactness and ease in the manufacturing. But sometimes immediate onset of action is required than convention therapy in many cases. So that to meet that requirements immediate release dosage forms has emerged as an alternative oral dosage forms. Immediate drug release dosage forms disintegrate rapidly immediately after the administration with enhanced rate of dissolution. The use of Super-disintegrants like sodium starch glycolate, cross carmellose sodium, crospovidone etc. is the basic approach in the development of these immediate release tablets. Aceclofenac is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac has higher anti-inflammatory action than conventional NSAIDs. It is a cytokine inhibitor. Aceclofenac is the glycolic acid ester of diclofenac. The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. The plasma elimination half-life of the drug is approximately 4 hours¹⁻³. Aceclofenac is a widely prescribed analgesic belonging to BCS class II and exhibit low and oral bioavailability due to its poor solubility and dissolution rate. So an immediate release

dosage form of the drug is necessary for its fast onset of action in relieving the pain and inflammation. The objective of the present study was to design Aceclofenac immediate release tablet dosage form by wet granulation and melt granulation methods employing cross carmellose sodium as super-disintegrant. The specific objective of the research includes comparing the two granulation methods i.e., wet granulation and melt granulation methods. Wet granulation method is a conventional method of granulation and has several disadvantages. When comparing the two granulation methods melt granulation method combined with the use of super-disintegrant., cross carmellose sodium produces immediate release of the drug from the tablet dosage form with enhanced dissolution characteristics. Melt granulation is process by which granules are obtained through the addition of either a molten binder or a solid binder which melts during the process. This process is also called melt agglomeration and thermoplastic granulation⁴⁻⁷. In the present research, melt granulation process was carried out using a melt binder PEG 6000. All the formulations were evaluated for their pre and post compression parameters and in vitro dissolution studies.

MATERIALS AND METHODS

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Table 1: Formula for wet granulation method

Ingredients	F _w	F ₁	F ₂	F ₃
Aceclofenac	100	100	100	100
Lactose	267.87	249.875	240.875	231.87
	5			5
C.C.S	-	4%	6%	8%
PVP K30 solution (10%)	q.s	q.s	q.s	q.s
Mannitol	67.5	67.5	67.5	67.5
Sodium saccharin	4.5	4.5	4.5	4.5
Magnesium stearate	4.5	4.5	4.5	4.5
Talc	4.5	4.5	4.5	4.5
Flavour	1.125	1.25	1.125	1.125

Aceclofenac was obtained as a gift sample from Aurobindo pharma., Hyderabad. Anhydrous lactose (LOBA CHEMICALS), Poly vinyl pyrrolidone (PVP K30, BASF Germany), Cross carmellose sodium was received from OZONE international, PEG 6000, Mannitol, sodium saccharin, Magnesium stearate, talc was purchased from S.D fine chemicals limited., Mumbai. All other chemicals used were of analytical reagent grade, available commercially and used as such without further processing.

Preparation of Aceclofenac IR tablets by Wet granulation method⁸

Immediate release tablets of Aceclofenac were prepared by wet granulation method employing a super disintegrant i.e., Cross carmellose sodium in four different concentrations i.e., 0, 4, 6, 8% as per formula given in the table 3. Aceclofenac, lactose, mannitol, sodium saccharin and super-disintegrant were blended thoroughly in a dry mortar and granulated using PVP K30 solution in isopropyl alcohol (q.s) as granulating fluid. The wet mass formed was pressed through mesh no 16. The wet granules were dried at 60°C for 1 hour. The dried granules were again passed through mesh no.20 to break the aggregates formed and to obtain discrete granules. Super-disintegrant, talc, magnesium stearate was passed through mesh no.60 and collected on to the bed of tablet granulation and mixed. The tablet granulations were blended thoroughly in a closed polyethylene bag. The obtained granules were evaluated for their flow properties and compressed into 450mg tablets using tablet punching machine.

Preparation of Aceclofenac IR tablets by Melt granulation method⁹

PEG 6000 was weighed and then melted in porcelain dish on a water bath maintained at 75°C for 3 minutes. Aceclofenac was exactly weighed and it was passed through sieve no 16. Gradually Aceclofenac was added to melted compound with continuous stirring when it is about to solidify and it should be added at a temperature slightly more than the melting point of PEG. The contents were transferred to a glazed tile by spreading them in thin layers. The molten mixture was then allowed to solidify at room temperature. The solidified mass was crushed in

mortar and passed through a 10 mesh sieve. The granules are evaluated. Dried granules were mixed with lactose, sodium saccharin, mannitol and finally lubricated with magnesium stearate and talc. The obtained mixture was evaluated for its flow properties and compressed into tablets using tablet punching machine.

Evaluation tests for prepared Immediate release tablets of Aceclofenac

The formulated tablets were evaluated for the following Pre, post compression quality control studies and dissolution studies.

Pre Compression studies

Angle of Repose¹⁰⁻¹¹

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose of granules was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} (h/r)$$

Where:

θ = angle of repose

h = height in cms

r = radius in cms

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

Bulk density (BD)

It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula.

$$\text{Bulk density} = \text{weight of powder} / \text{Bulk volume. } D_b = \frac{M}{V_0}$$

M = mass of the powder;

V₀ = bulk volume of the powder.

Tapped density (TD)

It is the ratio of total mass of powder to the tapped volume of powder

Weigh accurately 25 g of granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula. Tapped density = Weigh of powder / Tapped volume

$$D_t = (M) / (V_t)$$

M = mass of the powder; V_t = tapped volume of the powder.

Carr's Index

It is a simple test to evaluate the BD and TD of a powder

Table 2: Formula for melt granulation method

Ingredients (mg)	F _w	F ₁	F ₂	F ₃
Aceclofenac	100	100	100	100
Lactose	167.875	149.875	140.875	131.875
C.C.S	-	4%	6%	8%
PEG 6000	100	100	100	100
Mannitol	67.5	67.5	67.5	67.5
Sodium saccharin	4.5	4.5	4.5	4.5
Magnesium stearate	4.5	4.5	4.5	4.5
Talc	4.5	4.5	4.5	4.5
Flavour	1.125	1.125	1.125	1.125

and the rate at which it was packed down. The formula for Carr's index is as below:

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Hausner's Ratio

Hausner's Ratio is a number that is correlated to the flow ability of a powder.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Post compression studies

General appearance

The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

Weight Variation test¹²

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

% weight variation

$$= \frac{\text{average weight} - \text{weight of each tablet}}{\text{average weight}} \times 100$$

Average weight

Thickness¹²

Thickness of the tablets (n=3) was determined using a Vernier Callipers.

Hardness test¹²

Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) 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 turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Friability test¹²

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage.

t should be preferably between 0.5 to 1.0%.

$$\% \text{ Friability} = \left[\frac{(W_1 - W_2)}{W_1} \right] \times 100$$

Where, W₁ = weight of tablets before test,

W₂ = weight of tablets after test

Assay of tablets

Weigh and finely powder not less than 20 tablets. Transfer an accurately weighed portion of the powder equivalent to about 10mg of model drug a 10 ml volumetric flask. Add approximately 6ml of 6.8 phosphate buffer and shake and sonicate for 10 min to complete the extraction. Dilute the methanol to volume and mix. Pipette 1ml aliquot into a 10ml volumetric flask, dilute with mobile phase to volume, mix and filter. From it withdraw take 1ml aliquot and make up to mark with buffer.

Calculate the quantity in mg of model drug phosphate buffer in the portion taken by the formula

$$\% \text{ drug content} = \frac{\text{actual drug content}}{\text{total drug content}} \times 100$$

Wetting time¹²

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a petri-dish with a 10cm diameter. 10 ml of water-soluble dye solution was added to petri-dish. A tablet was carefully placed on the surface of the tissue paper. The time required to wet the tablet with dye is known as wetting time.

Disintegration test¹²

The disintegration test was carried out using USP disintegration test apparatus type-2. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed over each tablet. Distilled water was used as the medium maintained at 37°C ± 0.5°C and the time taken for each tablet to disintegrate completely was recorded.

In vitro Dissolution Study¹³

900 ml of pH-6.8 phosphate buffer was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37°C ± 0.5°C. A tablet was placed in the vessel and was covered; the apparatus was operated for 1 hour at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} of 275 nm using a UV-spectrophotometer (LABINDIA).

Table 3: Acceptance criteria for tablet weight variation (USP 29-NF 34)

Average weight of tablet(mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

Table 4: Dissolution Parameters

Parameter	Details	
Dissolution apparatus	USP -Type II (paddle)	
Medium	PH-5.6 phosphate buffer	
Volume	900 ml	
Speed	50 rpm	
Temperature	37 ± 0.5 °C	
Sample volume	5 ml	
Time points	0, 5, 10, 15, 20, 25, 30, 40, 50, 60 min	
Analytical method	Ultraviolet Spectroscopy	Visible
λ_{\max}	275 nm	

RESULTS AND DISCUSSION

Evaluation of pre-compression properties Aceclofenac IR tablets

Physical properties such as bulk density, tapped density, angle of repose, compressibility index and hausner's ratio were determined for the prepared tablet blend.

DISCUSSION

The wet granulation blends showed the angle of repose values in the range from 26.03 ± 0.83 to 29.19 ± 1.03 and the melt granulation blends showed the values from 26.95 ± 0.47 to 29.39 ± 0.24 . All formulations showed excellent to good flowability. Wet granulation blends showed bulk density and tapped density in the range from 0.52 ± 0.01 to 0.55 ± 0.04 and 0.62 ± 0.01 to 0.65 ± 0.03 gm/ml respectively and melt granulation blends showed bulk density and tapped density in the range from 0.51 ± 0.005 to 0.54 ± 0.04 and 0.61 ± 0.005 to 0.64 ± 0.04 gm/ml respectively having good packability of the granules. The carr's index of wet and melt granulation blends were in the range from 12.77 ± 5.15 to 16.75 ± 0.86 . All formulations showed excellent to good compressibility. The Hausner's ratio of wet and melt granulation tablet blends were found to be in the range from 1.18 ± 0.02 to 1.19 ± 0.04 . All formulations showed excellent to good flow property.

Evaluation of Aceclofenac IR tablets

Aceclofenac immediate release tablets were prepared using three different concentrations of super disintegrant., Cross carmellose sodium and evaluated to check the effect of method of granulation on the disintegration and release parameters of the tablets prepared by two granulation methods., Wet granulation and Melt granulation.

Results

The prepared tablets were evaluated for average weight, weight variation, thickness, hardness, friability, assay, *in-vitro* disintegration time, and *in-vitro* drug release for all the batches.

Discussion

The wet granulated tablets have showed the thickness ranges from 4.32 ± 0.06 to 4.34 ± 0.07 . The melt granulated tablets have showed the thickness ranges from 4.22 ± 0.10 to 4.38 ± 0.08 . The wet granulated tablets have showed the hardness ranges from 4.14 ± 0.05 to 4.54 ± 0.08 . The melt granulated tablets have showed the hardness ranges from 3.38 ± 0.08 to 4.24 ± 0.05 kg/cm². All the formulations of wet and melt granulated tablets passes the weight variation and they showed the % deviation of tablets within the IP limit of $\pm 5\%$. The wet and melt granulated tablets were showed the friability ranges from 0.047 to 0.063. The wet granulated tablets showed the wetting time from 49 to 300 sec and the melt granulated tablets showed the wetting time ranges from 21 to 144 sec. The tablets prepared by melt granulation method shows less wetting time compared to that of wet granulation method indicating tendency to disintegrate at faster rate. The tablets prepared by wet granulation method have showed the higher disintegration time compared to that of melt granulation method. F₃ formulation shows faster disintegration than all the remaining wet granulation formulations and F₆ formulation disintegrate faster than all the other formulations i.e., within 25 sec. The wet and melt granulated tablets were showed the assay values from 97.9 to 101.7.

In Vitro Dissolution test

Dissolution test was carried out on 3 tablets from every batch prepared by both wet and melt granulation methods and reported as percent drug release with respect to time.

Discussion

Among all the formulations prepared by wet granulation method F₃ formulation consisting of 8% Cross carmellose sodium showed the complete drug release in 50 min and the formulations consisting of superdisintegrant showed faster drug release than the test formulation F_w i.e., without superdisintegrant.

Discussion

Among all the formulations prepared by melt granulation method F₆ formulation consisting of 8% Cross carmellose sodium showed the complete drug release in 20 min and the formulations consisting of superdisintegrant showed faster drug release than the test formulation F_M i.e., without superdisintegrant.

Comparison of percent drug release of best formulations of wet and melt granulation methods

Discussion

The best formulations from both the granulation methods i.e., F₃ and F₆ were compared. From the graph it was found that the F₆ formulation consisting of 8% of CCS prepared by melt granulation method have shown the faster drug release i.e., within 20 min than the formulation F₃ consisting of 8% of CCS prepared by wet granulation method.

SUMMARY AND CONCLUSION

Table 5: Precompression studies of Wet and Melt granulation blends

Batch	Angle of Repose (°) ± S.D	Bulk Density (g/cc) ± S.D	Tapped Density(g/cc) ± S.D	Carr's index ± S.D	Hausner's ratio ± S.D
F _W (wet)	29.19±1.03	0.55±0.04	0.65±0.03	15.45±2.25	1.18± 0.06
F ₁	26.03±0.83	0.53±0.01	0.63±0.005	16.23±1.06	1.18±0.03
F ₂	27.96±0.54	0.52±0.01	0.62±0.01	12.77±5.15	1.19±0.04
F ₃	26.61±0.45	0.53±0.02	0.63±0.01	15.72±1.86	1.18±0.02
F _M (Melt)	29.39±0.24	0.54±0.04	0.64±0.04	15.09±1.73	1.18±0.06
F ₄	28.44±0.48	0.52±0.01	0.62±0.005	16.49±1.07	1.19±0.02
F ₅	26.95±0.47	0.51±0.005	0.61±0.005	16.75±0.86	1.19±0.04
F ₆	28.34±0.55	0.53±0.01	0.63±0.005	15.70±1.56	1.18±0.05

Table 6: Evaluation of Aceclofenac IR tablets prepared by wet granulation and Melt granulation methods

Batch	Thickness (mm) (n=3)	Hardness (kg/sq.cm) (n=3)	Avg. Wt (mg) (n=20)	%Friability	Wetting time(sec)	In vitro disintegration time	% Drug content
F _W	4.34±0.07	4.54±0.08	450±2.46	0.051	300	20 min	98.11
F ₁	4.34±0.08	4.14±0.05	458±3.12	0.047	87	65 s	101.7
F ₂	4.32±0.06	4.24±0.05	444±3.15	0.061	61	53 s	97.93
F ₃	4.34±0.06	4.32±0.08	453±2.98	0.063	49	32 s	99.88
F _M	4.35±0.08	3.38±0.08	433±2.75	0.054	144	58 s	98.21
F ₄	4.38±0.08	3.96±0.05	454±2.70	0.051	19	30 s	99.72
F ₅	4.38±0.07	4.14±0.05	462±2.60	0.057	22	31 s	97.94
F ₆	4.22±0.10	4.24±0.05	461±3.10	0.053	21	25 s	100.6

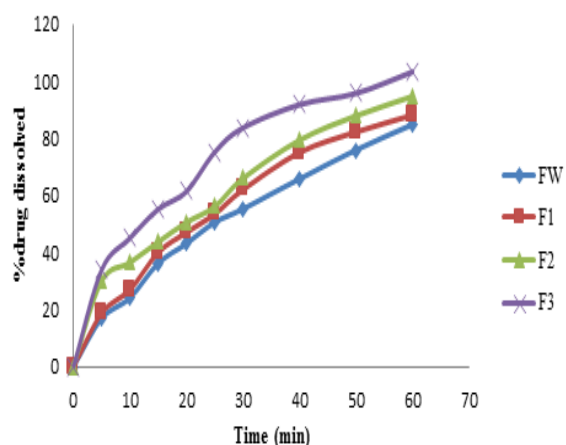


Figure 1: Dissolution profile studies of F_w, F₁, F₂, F₃

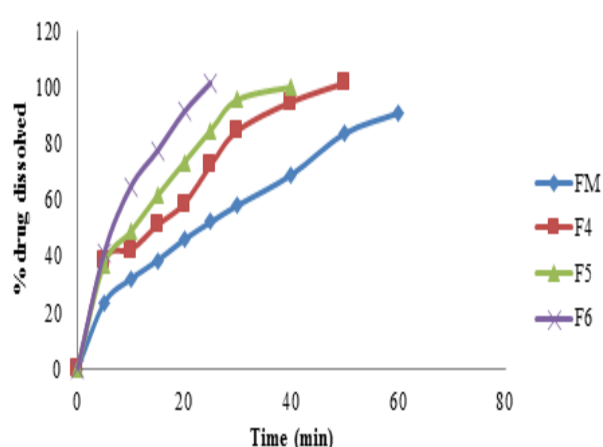


Figure 2: Dissolution profile studies of F_M, F₄, F₅, F₆

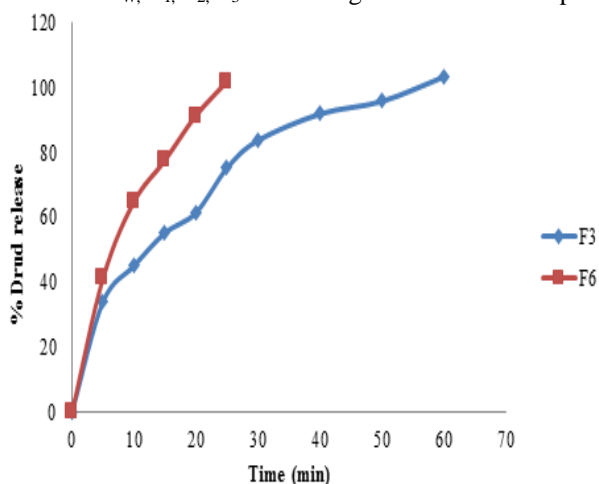


Figure 3: Comparison of %drug release of best formulation of wet and melt granulation methods

Aceclofenac immediate release tablets were prepared by wet and melt granulation methods by using three different concentrations of super-disintegrants such as 4, 6, 8% of croscarmellose sodium with PVP solution in isopropyl alcohol as wet binder and PEG 6000 as melt binder and other excipients like mannitol, sodium saccharin, magnesium stearate and talc. The prepared Wet granulation blends of formulations F_w, F₁, F₂, F₃ and Melt granulation blends were evaluated for their flow properties. All the blends showed good to excellent flow. The blends were compressed into tablets and the tablets were characterized based upon their physicochemical characteristics like hardness, thickness, friability, weight variation, assay, disintegration test, *in-vitro* dissolution studies. The formulations of melt granulation method showed faster disintegration rate and faster dissolution profiles when compared with that of wet granulation formulations. Among the melt granulation formulations, the F₆ formulation consisting of 8% CCS showed higher disintegration rate i.e., within 20 secs and about 100% drug release within 20 min. From the research work a conclusion may be drawn that the melt granulation technique can be of more advantageous than the conventional wet granulation method showing its maximum acceptance in the pharmaceutical industry.

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