DOI: 10.21276/IJIPSR.2018.06.04.683

International Journal of Innovative Pharmaceutical Sciences and Research
www.ijipsr.com

FORMULATION AND COMPARATIVE EVALUATION OF ACECLOFENAC ORODISPERSIBLE TABLETS PREPARED BY DIFFERENT GRANULATION METHODS

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Abstract

Oral dosage forms are limited by first pass metabolism and non-compliance of tablets especially in case of paediatric and geriatrics. Oral dispersible tablets (ODT's) are a novel form of oral dosage systems which disintegrate in a couple of seconds so that the proportion of drug that reaches the systemic circulation is increased. Aceclofenac is poorly aqueous soluble, so it can be formulated as oral dispersible tablets, which enhances its solubility and ultimately its bioavailability is increased. The main objective of the study is to develop, optimize, evaluate and compare the percentage release of Aceclofenac ODT's prepared by using Sodium starch glycollate as a super-disintegrant in four different concentrations i.e., 0, 4, 6, 8% w/w of tablet weight and MCC, mannitol as other excipients by two granulation methods i.e., Wet and Melt granulation methods. It was found that the melt granulation formulations (FM, F4, F5, and F6) having PEG-4000 as melt binder showed faster release compared to that of wet granulation tablets (FW, F1, F2, and F3) prepared by using HPC 5% as wet binding agent. F5 formulation consisting of 6% SSG showed best results with a disintegration time of 21 secs and about ≤ 90% drug release within 20 min. From this a conclusion may be drawn that the melt granulation technique is more advantageous for Aceclofenac Orodispersible tablets than the conventional wet granulation method.

Keywords: Aceclofenac, Oro-dispersible tablets, Sodium starch glycollate, PEG 4000, Melt granulation method, Wet granulation method.

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DOI: 10.21276/IJIPSR.2018.06.04.683

INTRODUCTION

Among all dosage forms tablet is the most popular because of its major advantages like scope for self - administration, compactness and ease in the manufacturing. Oro-dispersible tablets have emerged as an alternative to the traditional tablets when an immediate onset of action is required. Oro-dispersible tablet dosage forms disintegrates rapidly usually within a matter of seconds when placed upon the tongue results in a quick dissolution, fast absorption and bioavailability of the drug [1]. The use of Super-disintegrants like sodium starch glycolate, micro crystalline cellulose and mannitol etc. is the basic approach in the development of these oro-dispersible tablets [2]. Aceclofenac is a widely prescribed analgesic useful for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis than conventional NSAIDS [3]. The plasma elimination half-life of the drug is approximately 4 hours [4].

Aceclofenac belongs to BCS class II (poorly soluble and highly permeable) and exhibits low oral bioavailability due to its poor solubility and dissolution rate [5]. An oro-dispersible tablet decreases the time for onset of action and increases patient compliance. The objective of the present study was to design Aceclofenac oro-dispersible tablets by wet granulation and melt granulation methods employing sodium starch glycollate, MCC and mannitol. The specific objective of the research includes comparing the two granulation methods i.e., wet granulation and melt granulation methods. When comparing the two granulation methods melt granulation method produces fast release of the drug from the tablet dosage form with enhanced dissolution characteristics. Melt granulation is a process by which granules are obtained through the addition of either a molten binder or a solid binder (at 10–30% w/w) which melts during the process [6,7]. This process is also called melt agglomeration and thermoplastic granulation. In the present research, melt granulation process was carried out using a hydrophilic melt binder PEG 4000 to prepare immediate-release dosage forms. All the formulations were evaluated for their pre and post compression parameters and in vitro dissolution studies.

MATERIALS AND METHODS

Materials collection: Aceclofenac was received as gift sample from Swiss Garnier Life Sciences, Himachal Pradesh, India. Sodium starch glycollate, Talc, Mannitol and Microcrystalline cellulose were received from Loba chemicals Mumbai India. Magnesium Stearate was received from SD fine-chem Ltd. Mumbai India.

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Pre-formulation studies

Pre-formulation studies like determination of melting point, infrared spectral analysis and physical compatibility were performed for Aceclofenac.

Analytical method used for the estimation of aceclofenac [8]

25 mg of Aceclofenac drug was taken into a 25 ml volumetric flask as a standard solution and subsequently diluted with Phosphate buffer solution (pH-7.4) to obtain a series of dilutions containing 2,4,6,8 and 10 µg/ml of Aceclofenac in 1 ml solution. The absorbance of these solutions was measured in ELICO-SL159, UV-VIS Spectrophotometer at λ_{max} 273 nm using Phosphate buffer solution (pH-7.4) as blank and a calibration curve was plotted.

Formulation development

Table 1: Formulation for aceclofenac ODT's by wet granulation method.

S.No.	Ingredients	Fw (mg)	F1 (mg)	F2 (mg)	F3 (mg)
1	Aceclofenac	100	100	100	100
2	Microcrystalline Cellulose	212	196	188	180
3	Sodium Starch Glycollate	--	16	24	32
4	Hydroxy Propyl Cellulose (5%) aqueous solution	Q.S	Q.S	Q.S	Q.S
5	Mannitol	80	80	80	80
6	Magnesium Stearate (1%)	4	4	4	4
7	Talc (1%)	4	4	4	4
8	Total Wt	400	400	400	400

Table 2: Formulation for aceclofenac ODT's by melt granulation method.

S.No.	Ingredients	Fw (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1	Aceclofenac	100	100	100	100
2	Microcrystalline Cellulose	112	96	88	80
3	Sodium Starch Glycollate	--	16	24	32
4	PEG 4000	100	100	100	100
5	Mannitol	80	80	80	80
6	Magnesium Stearate (1%)	4	4	4	4
7	Talc (1%)	4	4	4	4
8	Total Wt	400	400	400	400

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Method of tablet preparation

Preparation of aceclofenac ORD tablets by wet granulation method [9,10]

Immediate release tablets of Aceclofenac were prepared by wet granulation method employing Sodium starch glycollate in four different concentrations i.e., 0, 4, 6, 8% as per formulae given in table-1. Aceclofenac, Microcrystalline cellulose, mannitol and super-disntegrant were blended thoroughly in a dry mortar and granulated using HPC(5%) solution in water. The wet mass formed was sieved through mesh no 12 and granules were dried at 60 ºC for 1 hour. The dried granules were again sieved through mesh no.10 to break the aggregates formed and to obtain discrete granules. Talc, magnesium stearate were passed through mesh no.85 and mixed with the granules. The granules were blended thoroughly in a closed polythene bag. The obtained granules were evaluated for their flow properties and compressed into 400 mg tablets with 9 mm diameter using tablet punching machine.

Preparation of aceclofenac ORD tablets by melt granulation method [11,12]

A powdered mixture of meltable and non-meltable materials i.e., PEG 4000 having M.P. 53-58 ^{o}C [13] and Aceclofenac, MCC, SSG, Mannitol respectively, were weighed and then heated in a porcelain dish on a water bath maintained at 65 ºC for 3 minutes with continuous stirring. By the distribution mechanism, small agglomerates (nuclei) are formed by initial solid particles being wetted by distribution of molten binder on their surface enabling agglomerate formation by coalescence between the wetted solid particles. Further agglomerate growth occurs by coalescence between the nuclei, provided that the liquid saturation is suf!ciently high. When it is about to solidify 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 12 mesh sieve and finally lubricated with magnesium stearate and talc. The obtained mixture was evaluated for its flow properties and compressed into tablets.

Characterization and Evaluation

Pre-compression properties [14, 15]

The powder blends of different formulations of wet granulation and melt granulation techniques were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio.

Angle of repose: The angle of repose of powder mixtures of all the formulations were determined by fixed funnel method.

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ISSN (online) 2347-2154
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Post-compression properties [16]

The tablets of different formulations prepared by wet granulation and melt granulation techniques were evaluated by characterizing their hardness, friability, weight variation, wetting time, in-vitro dispersion time and in- vitro dissolution study.

Hardness was determined by Pfizer hardness tester, Friability by Roche friabilator, Disintegration time was measured using USP disintegration tester (Electrolab ETC 11L) and the Dissolution rate was studied using LAB-INDIA DISSO-2000 dissolution rate test apparatus. All the studies were done in triplicate.

RESULTS AND DISCUSSION

FTIR Spectroscopy:

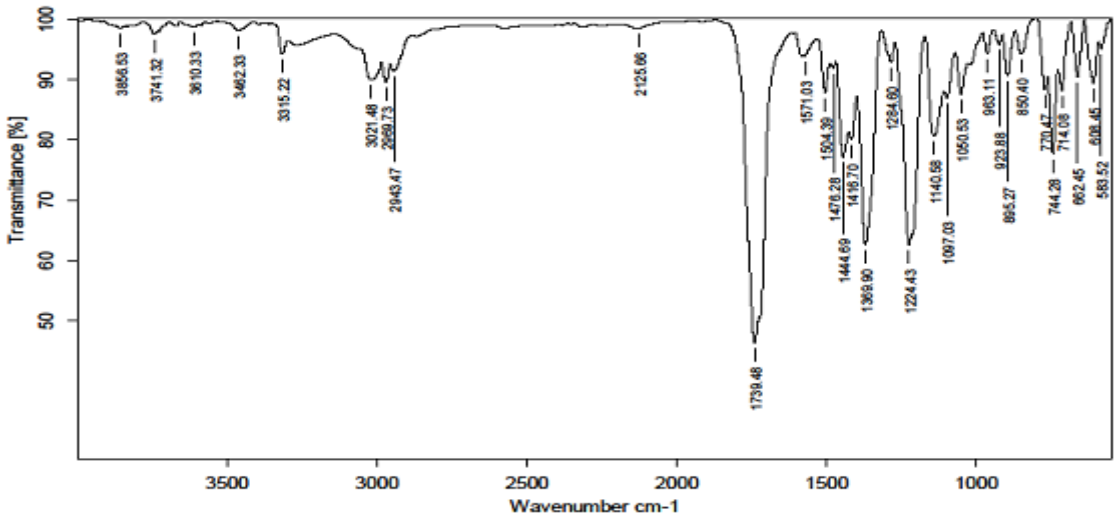

Fig. 1: FTIR spectra of aceclofenac

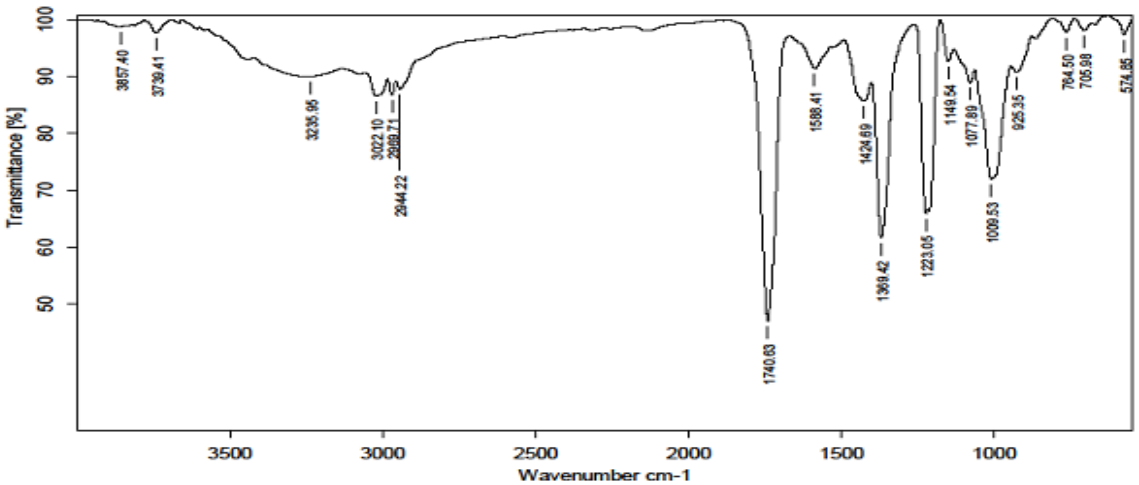

Fig. 2: FTIR spectra of sodium starch glycolate

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ISSN (online) 2347-2154
DOI: 10.21276/IJIPSR.2018.06.04.683

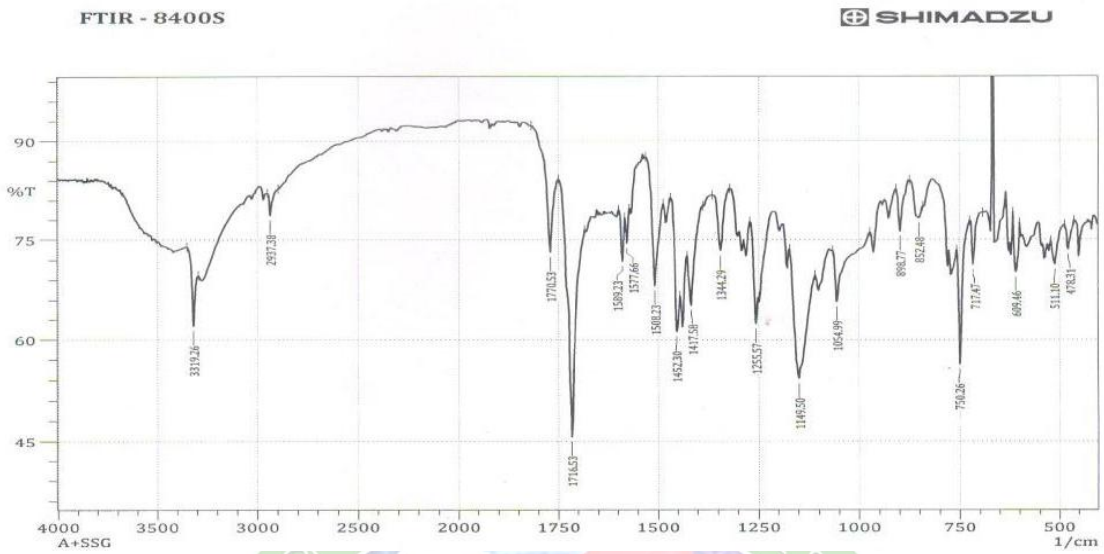

Fig. 3: IR spectra of physical mixture of aceclofenac and sodium starch glycolate

FTIR spectra determine interactions between drug and excipients in the formulation. FTIR spectra ruled out any incompatibility.

Calibration:

Table 5: Absorbance data for calibration curve of Aceclofenac in 7.4 pH buffer at λ_{max} 273 using UV-vis spectrophotometer

Sl. No	Concentration	Absorbance
1	0	0
2	2	0.111
3	4	0.221
4	6	0.326
5	8	0.435
6	10	0.544

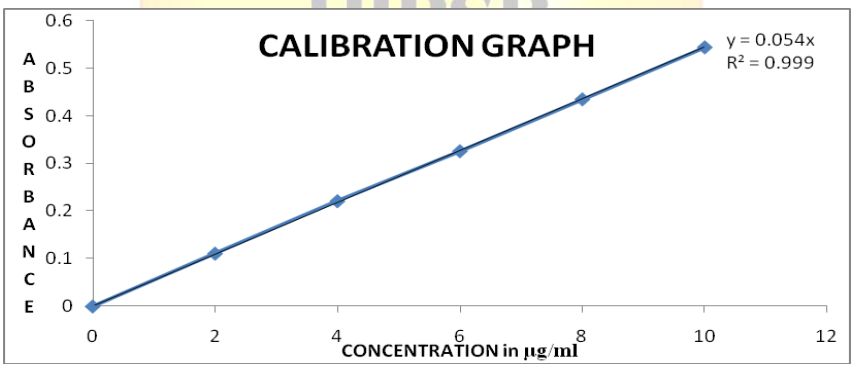

Fig. 4: Calibration plot of Aceclofenac

Validation of the calibration method reveals that it has reproducibility, robustness and obeys Beer Lambert's law

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Evaluation of orodispersible tablets of Aceclofenac

Table-6: Pre-compression evaluation

Sl.No	Formulation	Angle of Repose (ø) ± S.D (n=3)	Bulk Density (g/cc) ± S.D (n=3)	Tapped Density(g/cc) ± S.D (n=3)	Carr's index ± S.D (n=3)	Hausner's ratio ± S.D (n=3)
1	Fw (wet)	26.19±1.03	0.55±0.04	0.65±0.03	15.45±2.25	1.18± 0.06
2	F1	24.03±0.83	0.53±0.01	0.63±0.05	16.23±1.06	1.18±0.03
3	F2	25.96±0.54	0.52±0.01	0.62±0.01	12.77±5.15	1.19±0.04
4	F3	26.61±0.45	0.53±0.02	0.63±0.01	15.72±1.86	1.18±0.02
5	F_M (Melt)	24.39±0.24	0.54±0.04	0.64±0.04	15.09±1.73	1.18±0.06
6	F4	25.44±0.48	0.52±0.01	0.62±0.05	16.49±1.07	1.19±0.02
7	F5	26.95±0.47	0.51±0.05	0.61±0.05	16.75±0.86	1.19±0.04
8	F6	24.34±0.55	0.53±0.01	0.63±0.05	15.70±1.56	1.18±0.05

Table 7: Post compressional evaluation parameters

Sl. No	Formulation	Thickness (mm) (n=3)	Hardness (kg/sq.c) (n=3)	Avg. Wt (mg) (n=20)	Friability (%)	Wetting time (sec)	Disintegration time (sec)	% Drug content
1	Fw (wet)	4.34±0.07	4.54±0.08	402±2.46	0.51	296	19 (min)	97.41
2	F1	4.34±0.08	4.14±0.05	408±3.12	0.47	84	64	96.83
3	F2	4.32±0.06	4.24±0.05	404±3.15	0.61	59	54	98.54
4	F3	4.34±0.06	4.32±0.08	406±2.98	0.63	45	31	102.31
5	F_M (Melt)	4.35±0.08	3.38±0.08	396±2.75	0.54	141	14 (min)	97.98
6	F4	4.38±0.08	3.96±0.05	405±2.70	0.51	17	24	103.56
7	F5	4.38±0.07	4.14±0.05	407±2.60	0.57	22	23	99.12
8	F6	4.22±0.10	4.24±0.05	401±3.10	0.53	21	21	103.17

All the formulations have shown pre-formulation tests results within the limits and also passed the post-compression parameters (within the limits).

DOI: 10.21276/IJIPSR.2018.06.04.683

In-vitro dissolution

Table 8: *In-vitro* dissolution profiles of all the Aceclofenac Tablets (FW, FM, F1-F6)

Time (min)	FORMULATIONS (Percent drug released)							
	FW	F1	F2	F3	FM	F4	F5	F6
0	0	0	0	0	0	0	0	0
5	14.53	26.39	27.1	24.78	16.83	29.63	34.27	26.18
10	29.73	41.24	43.54	39.7	32.06	46.45	51.25	40.83
15	51.49	63.43	65.15	60.57	54.31	69.45	73.43	62.28
20	65.57	81.72	83.21	78.16	66.36	87.18	89.09	83.6
25	70.44	87.27	89.31	85.83	71.75	93.99	96.67	89.54
30	73.03	89.17	91.84	88.36	75.47	97.35	98.67	93.6

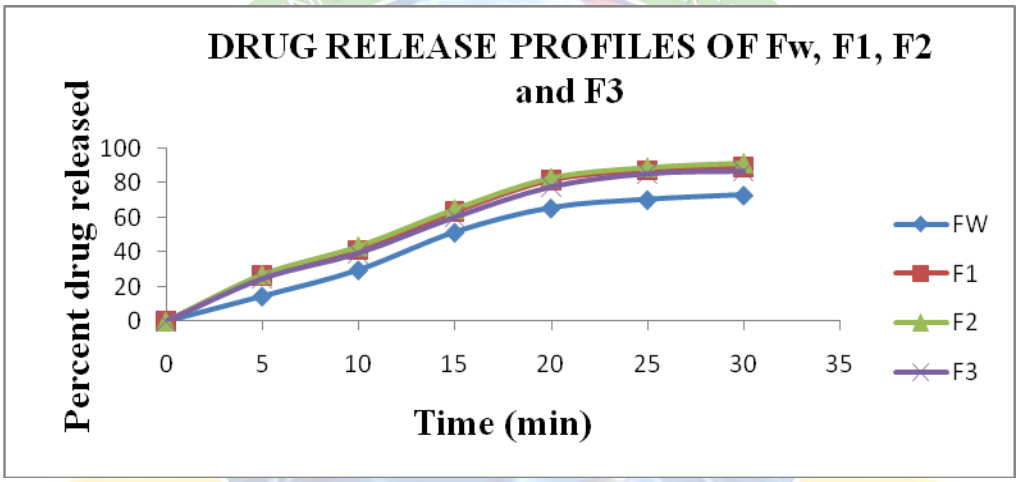

Fig. 5: In-vitro dissolution profiles of FW, F1, F2, F3

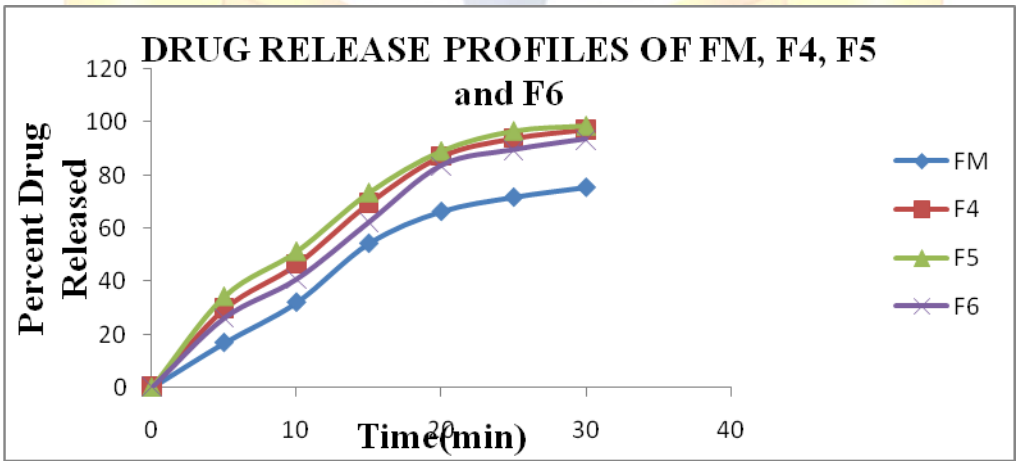

Fig. 6: *In-vitro* dissolution profiles of FM, F4, F5, F6

Siva et.al / IJIPSR / 6 (04), 2018, 48-58
ISSN (online) 2347-2154
DOI: 10.21276/IJIPSR.2018.06.04.683

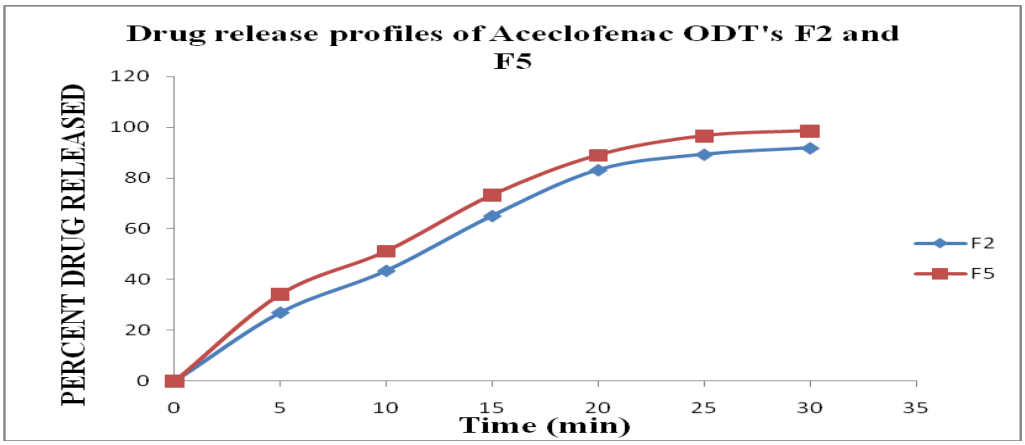

Fig. 7: Comparison of % drug release of best formulation of wet and melt granulation methods

The tablets prepared by melt granulation method showed less wetting time compared to that of wet granulation method indicating a tendency to disintegrate at faster. F6 formulation showed faster disintegration than all the other formulations (i.e., with in 21 sec). Among all the formulations prepared by wet granulation method F2 formulation containing 6% Sodium starch glycollate showed better drug release i.e; ≥80% within 20 min and the formulations containing super disintegrant showed faster drug release than the test formulation FW i.e., without super disintegrant. Among all the formulations prepared by melt granulation method; F5 formulation containing 6% Sodium starch glycollate showed better drug release i.e., ≤90% within 20 min and the formulations containing super disintegrant showed faster drug release than the test formulation FM i.e., without super disintegrant. Comparing the better formulations of both wet and melt granulation methods i.e., F2 and F5; it was found that the F5 formulation consisting of 6% of SSG prepared by melt granulation method showed faster drug release i.e., ≤90% within 20 min than the formulation F2 containing 6% of SSG prepared by wet granulation method.

CONCLUSION

Aceclofenac Orodispersible tablets were prepared by wet and melt granulation methods by using different concentrations of super-disintegrant Sodium starch glycollate with HPC 5% solution as wet binder and PEG 4000 as melt binder. The prepared Wet granulation formulations FW, F1, F2, F3 and Melt granulation formulations FM, F4, F5, F6 were evaluated for their flow properties. All the blends showed good to excellent flow. The blends were compressed into tablets and evaluated for their hardness, thickness, friability, weight variation, assay, disintegration time and the test results were within official limits. The formulations of melt granulation method showed faster

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disintegration time and dissolution profiles when compared with that of wet granulation formulations. Among the melt granulation formulations, the F5 formulation consisting of 6% SSG prepared by using PEG4000 for melt granulation showed disintegration time of 21 sec and about ≤ 90% drug release within 20 min. From the research work a conclusion may be drawn that the melt granulation technique by using PEG 4000 and SSG at 6% can be more advantageous for Aceclofenac Orodispersible tablets than the conventional wet granulation method.

ACKNOWLEDGEMENT

The authors are thankful to the management, principal and faculty of Nalanda Institute of Pharmaceutical Sciences for rendering their assistance in this work.

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