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Development of sustained release Aceclofenac lipid matrix tablet using continuous melt granulation technique

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ABSTRACT

The present study deals with application of melt granulation technology to develop sustained release formulation of aceclofenac with lipidic excipients (Compritol 888 ATO). This approach is concerned with the use of minimum number of excipients to reduce the tablet weight and increase the compatibility of the drug. The continuous melt granulation/extrusion was done by optimizing the formulation as well as processing parameter such as drug loading, operating temperature, screw speed and feed rate during the process. The FTIR study revealed that there is no chemical interaction exists in between the drug and lipidic excipients while DSC and XRD studies exhibited crystalline state of the drug after melt granulation. The scanning electron microscopic examination of melt extrudates revealed the agglomerated particles with porous network and rough surface. The developed tablet (80% drug loading) has weight of 250 mg (mini tablet) containing 200mg of aceclofenac and it showed sustained release profile upto 24h.

Keywords: Aceclofenac, Melt granulation, extrudates, drug release.

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INTRODUCTION

Sustained release drug delivery systems are effective approach to achieve the optimal profile of those drugs having short elimination half-life and narrow therapeutic window, thus reducing the dose frequency and improving the patient compliance. Matrix system is one of the most widely used to achieve sustained drug release property and it is easy to formulate and manufacture the dosage forms with common techniques and instruments.¹

Lipids are biodegradable products with nontoxic properties which have been enormously used as pharmaceutical excipients to develop sustained release formulation, bioavailability enhancement of poorly soluble drugs², taste masking of bitter drugs³, development of floating dosage form.^{4,5} Glycerides used in sustained release drug delivery systems are solid material, with a high melting point around 60–80°C, they are chemically inert and practically insoluble in polar solvents.⁶ Many research data reported the use of lipids for sustained release formulations.⁷⁻¹⁰ The inert matrix formed by the lipidic excipients prevents the drug excipients interaction and penetration of water due to hydrophobic nature, thus control the diffusion and dissolution of the drug from the matrix formed around the drug.¹¹ Compritol 888 ATO (Glyceryl behenate) is fatty acid ester of glycerol (HLB = 1) with melting point around 70° C which has been used for melt coating for modified release formulation, as binder in extended release formulation and as a lubricant in tablet.¹²⁻¹⁵ Compritol 888 ATO has also been employed for the preparation of sustained release formulation as it forms a lipophilic matrix with the drug and allows penetrating the dissolution fluid slowly and control the release by diffusion mechanism through the matrix channel¹⁶. Drug release from such type of matrix is mainly depends upon the rate and extent of permeating hydrophilic media and solubility of drug in aqueous media.¹⁷ There are various techniques to process API with lipidic excipients like direct compression, wet/ dry granulation, spray congealing, melt pelletization, melt granulation/extrusion, melt coating etc.¹⁸⁻²⁰

Hot Melt granulation/extrusion is an interesting approach to develop sustained release formulation using twin screw extruder system. It is rapid, single step solvent free method for development of sustained release formulation with high drug loading. The powder agglomeration is assisted by addition of meltable binder which is solid at room temperature and melts at low temperature (60-80°C). The demand of the melt granulation technique over conventional or other extended release drug delivery technologies has increased due to ease of scale up, solvent and drying free operation and hence it comes under time and energy saving cost effective technology.^{9,21,22} Recently the melt granulation technique has been employed for dissolution rate enhancement of poorly soluble APIs

and in development of prolong/sustained release formulation.²³⁻²⁷. Recently various polymeric binders has been used in melt granulation such as polyethylene glycol,^{28,29} cellulosic derivatives like hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC)³⁰ and hydroxypropyl methylcellulose and polyethylene oxide (PEO) in combination with lipids.³¹

Aceclofenac is 2-[(2,6-dichlorophenyl) amino] phenylacetoxyacetic acid, as a non-steroidal anti-inflammatory drug (NSAID) with short biological half -life (~4h) used extensively in treatment of pain and inflammation.³² Aceclofenac blocks PGE2 secretion at inflammation site by inhibiting the IL beta and tumor necrosis factor (TNF) in the inflammatory cells.³³ It is also used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The long term use of aceclofenac leads to gastrointestinal complication such as gastric irritation, ulcer, nausea, perforation and obstruction. Aceclofenac have short biological half-life hence more dosing frequency (200mg daily in two divided dose). To reduce the dosing frequency and to improve patient compliances, aceclofenac is ideal for making sustain release formulation.^{34,35,36}

The aim of the present study was to develop the lipid matrix tablet for sustained release of aceclofenac by using continuous hot melt granulation/extrusion technique. Compritol 888 A TO (glyceryl behenate) was used as lipophilic matrix former in the development of sustained release formulation. The study investigated the process parameters like effect of processing temperature and screw speed on melt granulation process. The effect of addition of hydrophilic component (hydroxypropyl cellulose) in the formulation and processing condition on drug release was also investigated.

MATERIALS AND METHOD

Aceclofenac was purchased from Alka Laboratories Pvt Ltd Mumbai, Compritol® 888 ATO was obtained as gift sample from Gattefosse India Pvt Ltd, Mumbai India. Klucel EF was kindly supplied by Ashland Specialty Ingredient Mumbai, India.(Head office Wilmington US) as gift sample. All chemicals and reagent used were of analytical grade.

Preparation of blend

The physical blends for melt granulation were prepared by mixing the dry API powder with different ratio (w/w) of polymer and solid lipidic excipients as described in Table.1.The mixture was blended in V-shaped blender (Wintech Pharmachem equipment Pvt Ltd. Mumbai, India) at 30 rpm for 20minutes.

Hot melt extrusion process

Hot melt granulation/extrusion process was performed by twin screw extruder made by ACG

Pharma Ltd Pune India. The hot melt extruder was attached with a gravimetric feeder (Coperion k-TRON Germany). The extruder consist of 9 zones including hopper and die .The screw design was fixed for all experiment which includes kneading elements at zone 5 and zone 6.The preblended physical blends of aceclofenac and lipidic excipients were transferred to a feeder of the extruder which passes in the barrel on the rotating screws operated at 30-35rpm in the barrel with a feeding rate of 1-2kg/hr. The temperature profile of the respective individual zones is given in Table.2.The schematic representation of overall melt extrusion/ granulation process is described in figure.1.

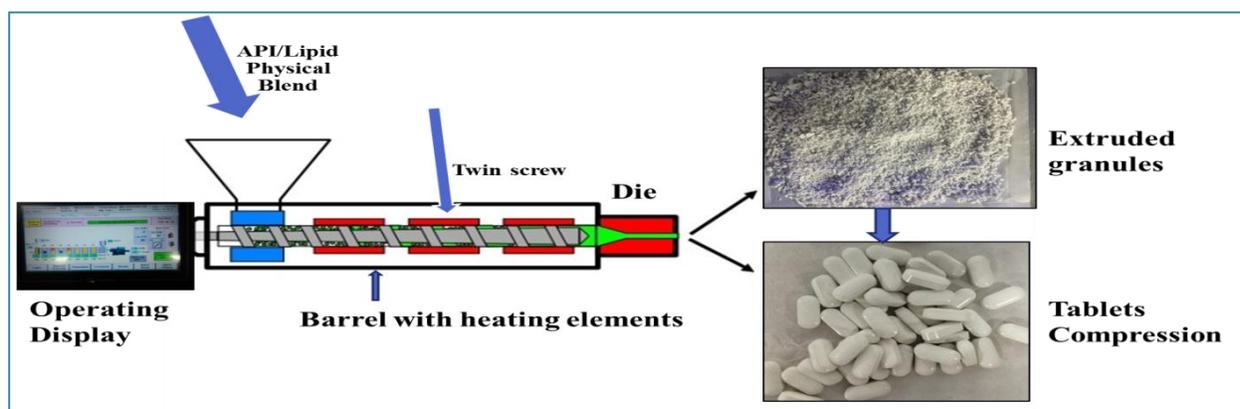


Figure 1: Hot Melt granulation/extrusion process

Table 1: Composition of the blend

Component (%w/w)	Formulation code				
	F1	F2	F3	F4	F5
Aceclofenac	90	80	80	75	70
C888 ATO	9	19	14	24	24
Klucel EF	--	--	5	--	5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5
Aerosil 200	0.5	0.5	0.5	0.5	0.5

Micrometrics of the granules

The granules obtained after melt extrusion process were evaluated for physicochemical properties. The Angle of repose of the granules was determined by fixed funnel method and calculated by the formula

$$\tan\theta = \frac{h}{r} \quad (1)$$

where θ is angle of repose, r is a radius of powder circumstances and h is the high of the powder cone.

Bulk density was determined by filling the pre weighed granules in to graduated 100ml measuring cylinder upto the defined volume and bulk density value was calculated by dividing the weight of the granules with acquired volume of the powder in measuring cylinder. Tapped density was

calculated by dividing the filled weight of the granules with new volume of the powder after tapping in tapped density apparatus (Veego Instrument Corporation Mumbai, India). The Hausner's ratio and compressibility index of the granules were determined by following equations

$$\text{Compressibility Index (CI)} = \frac{\text{TD}-\text{BD}}{\text{TD}} \times 100 \quad (2)$$

$$\text{Hausner's Ratio (HR)} = \frac{\text{TD}}{\text{BD}} \quad (3)$$

Granules particle size distribution

The extruded granules particle size distributions were measured by sieve analysis. 30gm of samples placed on the top sieve of the stacked sieves and subjected for agitation for 20min. The weight of granules retained on each stacked sieves was calculated as a percentage of the weight and used to determine the granule particle size distribution.

Differential scanning calorimetry

DSC analysis of plain API, Compritol 888 ATO, physical mixture and extruded batches were carried out using Perkin Elmer differential scanning calorimeter operated by Pyris manager software (Perkin Elmer life & Analytical Sciences Inc., USA). Approximately 4mg of finely powdered sample was accurately weighed and placed in empty aluminum pan and crimped with lid to seal it. The sample was heated from 30-300°C at 10°/min heating rate under continuous purging of nitrogen gas with 20ml/min flow rate. An empty sealed aluminum pan was used for reference.

FTIR Studies

FTIR studies were performed using Perkin Elmer FTIR (Spectrum Two L160000A) spectrometer to examine the interaction between aceclofenac, polymer and Compritol 888 ATO. The sample pellets were prepared by mixing with KBr and compressed by hydraulic press. The sample spectra were recorded at scanning range 4000-400cm⁻¹.

X-ray diffraction analysis

X-ray diffraction study was performed to examine the crystalline nature of the APIs and melt extrudates. The powder samples were analyzed using Bruker AXS D8 Advance diffractometer (Germany) in theta –theta mode with Cu x-ray tube operated at 40kV with 30mA current. The powder samples were scanned from 5° to 60° using scanning speed of 2.0 degree/min and 0.02degree step size.

Scanning electron microscopy

The surface morphology of the plain API and extrudates were studied by scanning electron microscope (Jeol JSM 6380LA Japan) operated at 20-25kv voltage. The sample were placed on the

adhesive carbon tape and sputtered coated with platinum for 50s using Autofine coater and the morphology of the extrudates were examined.

In vitro drug release

The In vitro release study was carried out for 24 hours using USP II paddle type dissolution apparatus in phosphate buffer (pH 6.8) at 100 rpm maintaining temperature 37 ± 0.5 . A 10ml samples were collected from each vessel at 2, 4, 8, 12, 16 and 24 hour and analyzed by UV spectrophotometer at 275 nm. The withdrawn sample was immediately replaced by equal volume of fresh buffer. The dissolution study was performed using 6 tablets in triplicate. The cumulative percentage of drug release was calculated and plotted against time.

RESULTS AND DISCUSSION

Melt extrusion/granulation process

Sustained release formulation approach mainly depends on the matrix former (ratio of polymer/lipidic excipients), since drug release rate is mainly depend on it. The processing temperature during the melt granulation process should be near to the melting point or Tg of the lipids/polymer. It was observed that Compritol 888 ATO itself exhibiting plasticizing effect without increasing the torque value during melt granulation. So there was no additional plasticizer added in the blend. The processing temperature for all the formulations was optimized at 65-80°C with screw speed of 30-35 rpm. The torque value at this temperature range was observed around 5-10% (except batch F1 which showed 18% torque value) with continuous extrusion and granulation of blend with feed rate of 1-2kg/hr. It was observed that decreasing the temperature below 60°C causes increase in the torque parameter up to 40% and hardening of the material at kneading zone, which was observed in case of batch F1 during optimization. It might be due to less content of C888 ATO (only 9%) in the formulation and operation at temperature below the melting point of the C888 ATO. The granules obtained after melt granulation showed excellent flowability and compactibility (Carr's indices from 9 to 17%) Table.3. Figure.2 described the broad particle size distribution of extruded granules which exhibited the good compressibility.

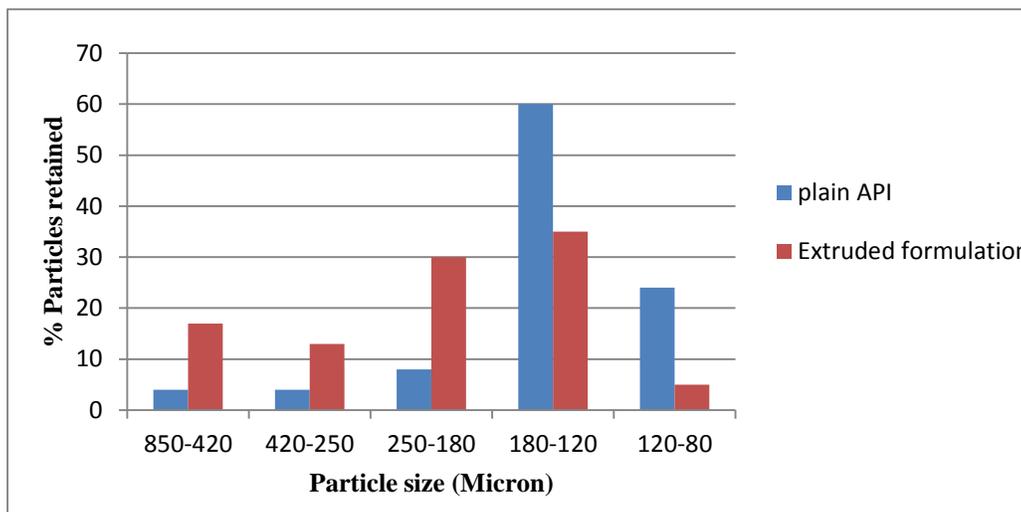


Figure 2: Particle size distribution of extruded granules

Table 2: Melt granulation processing parameter in twin screw extruder

Batch	Processing parameters										Screw speed (rpm)	Torque (%)	Residence time(min)
	Feed rate(kg/hr)	Temperature of screw zones (°C)											
		Z-1	Z-2	Z-3	Z-4	Z-5	Z-6	Z-7	Z-7	Z-9			
F1	1	70	70	70	75	80	80	75	75	70	30	18	15-16
F2	1.5	70	70	70	75	80	80	75	75	70	35	10	12-13
F3	1.5	70	70	70	70	75	75	70	70	70	35	7	11-12
F4	1.5	65	65	65	70	75	75	70	65	65	35	5	9-10
F5	1.5	65	65	65	65	70	75	75	65	65	35	5	9-10

Z-1 is Feeder zone, Z-9 is ejection die, Z-5 and Z-6 are kneading zones.

Table 3: Micromeritics properties of melt extruded granules

Properties	Aceclofenac	Formulations				
		F1	F2	F3	F4	F5
Angle of repose (°)	47 ±0.51°	32±0.21°	27.9±0.62°	21±0.71°	23±0.64°	18±0.31°
Bulk density (g/ml)	0.4012±0.102	0.5452±0.071°	0.5791±0.33	0.5891±0.43	0.5334±0.63	0.5228±0.051
Tapped density (g/ml)	0.5760±0.082	0.6382±0.046	0.6121±0.061	0.6431±0.084	0.6152±0.046	0.6021±0.061
Carr's Index	30.66±0.62	14.54±0.50	17.91±0.82	9.16±0.60	15.33±0.76	15.17±0.56
Hausner ratio	1.4421±0.071	1.170±0.049	1.178±0.061	1.09±0.053	1.151±0.059	1.15±0.021

The extrude or granules obtained with the batches containing only drug and Compritol 888 ATO were easily breakable and difficult to process due to sticking of the material during size reduction, screening and compression. Hence the binder needs to be added in the blend to overcome this issue. The batches processed in combination with Hydroxypropyl cellulose (Klucel EF) didn't exhibited the sticking during the milling and compression. The Co-processing of lipid with polymer during melt extrusion/granulation resulted in improvement in sustaining the release profile along with increase in the tablet hardness.

Differential scanning calorimetry

The DSC analysis was performed to examine the drug excipients compatibility and physical changes in drug after melt granulation. The DSC thermogram of plain aceclofenac showed endothermic peak at 158°C ($\Delta H = 451.2$ J/g) which is corresponding to its melting point. Figure.3. Compritol 888 ATO® showed the melting peak at 76.6°C. The physical mixture & melt extruded formulations with Compritol 888 ATO shown the melting endotherm between 155-160°C with similar peak that of plain aceclofenac which confirm that crystalline form of drug in formulation. A slight reduction in peak intensity was observed, it might be due solubilisation of drug in lipidic matrices. However there is no conversion of crystalline drug to amorphous form.

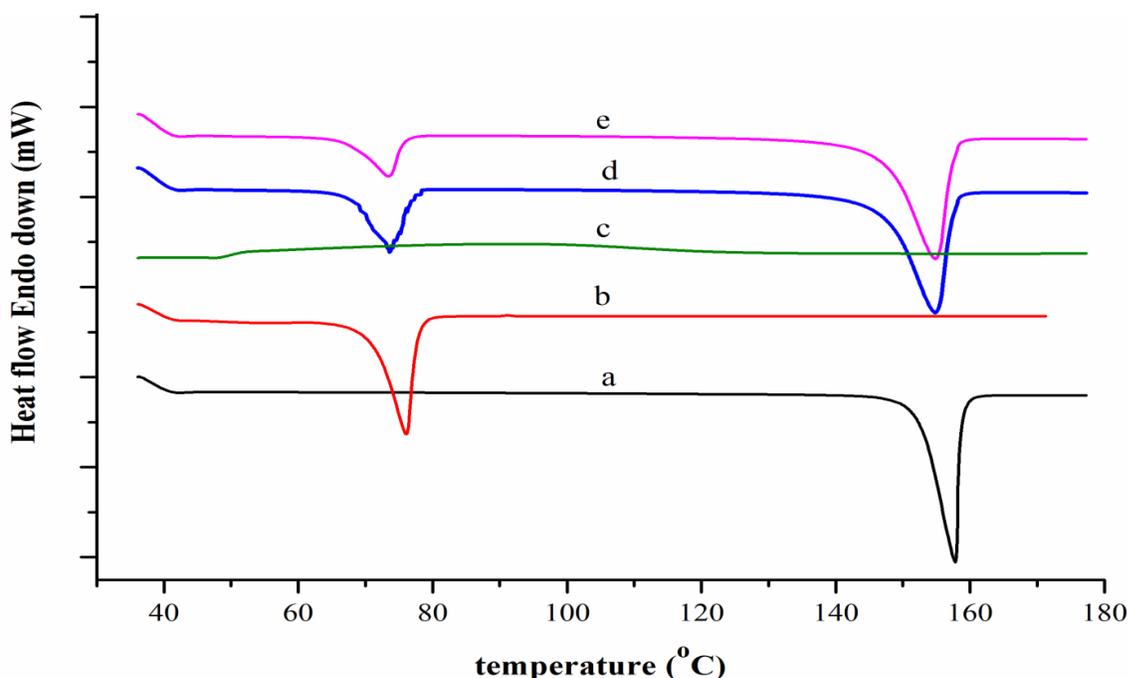


Figure 3: Differential scanning calorimetry thermograms of (a) Plain aceclofenac (b) C888 ATO, (c) HPC EF (d) AC:C888ATO PM and (e) Melt extrudates.

FTIR Studies

The FTIR spectra of aceclofenac showed principle characteristic aliphatic C-H (stretch) peak at 2913 cm^{-1} while a band at 1728 cm^{-1} indicates C=O stretch of ester. A sharp peak of C=O of carboxylic acid observed at 1772 cm^{-1} . A peak at 3319 cm^{-1} due to N-H (secondary amine rocking vibration) which merged with O-H stretch of acid, two sharp peaks at 764 cm^{-1} and 748 cm^{-1} observed in fingerprint region due to 1,2-disubstituted C-Cl stretching. In case of Compritol 888ATO, a sharp peak observed at 2916 cm^{-1} and 2849 cm^{-1} indicates C-H stretch (aliphatic). While peak at 1738 cm^{-1} due to C=O stretch of ester, a band at 1468 cm^{-1} indicates CH₂ deformation of alkane, peak at 1175 cm^{-1} , and 1109 cm^{-1} is due to C-O-C stretch. The peaks of

pure aceclofenac match with the peaks of physical mixture so there was neither masking of single characteristic peak nor existence of additional peak in drug spectra figure.4 indicates that drug and Lipidic excipients are compatible with each other.

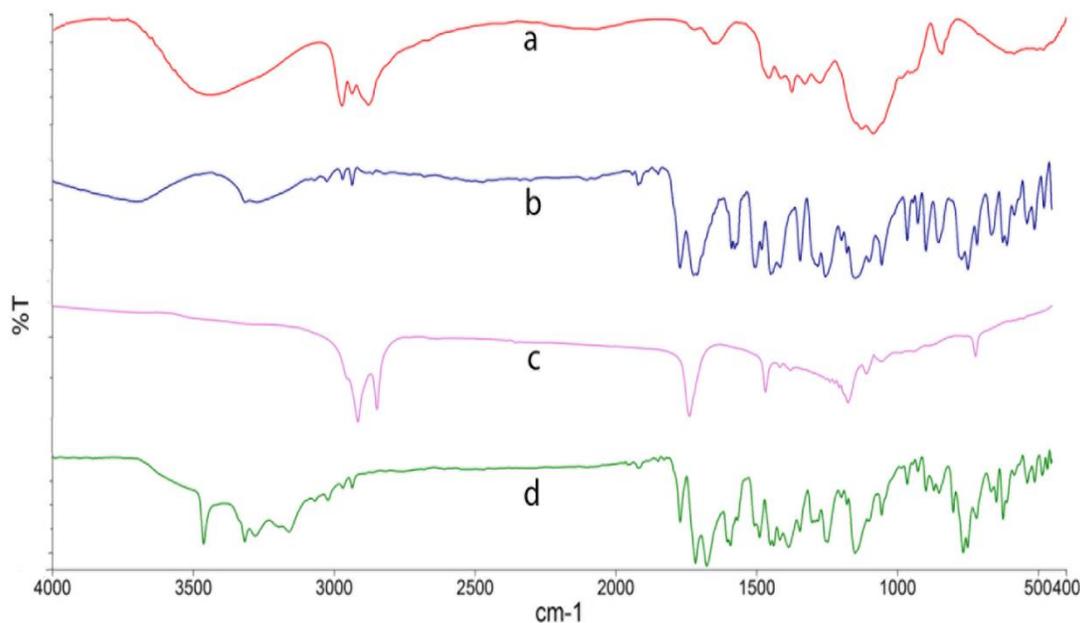


Figure 4: FTIR spectra of (a) HPC (b) Plain Aceclofenac (c) C888 ATO and (d) Physical mixture

X-ray diffraction analysis

The XRD study was used to investigate the crystalline state of aceclofenac with lipid matrices. The x-ray diffraction studies of plain aceclofenac, Compritol 888 ATO, physical mixtures and extrudates were performed to determine the crystalline state as shown in Figure.5. The pure aceclofenac showed distinct peaks at 2θ values of 17.1° , 18° , 19° and 20° but these peaks are small while at 26° and 28° sharp peaks were observed, Compritol 888 ATO exhibited sharp peaks at 21° and 24° . The melt granulated formulation exhibited the characteristics and similar peaks that of pure aceclofenac but relatively with lower intensities. This reveals that the crystallinity of aceclofenac retained in extruded formulation, but slight decrease in crystallinity was observed after melt granulation with lipidic material.

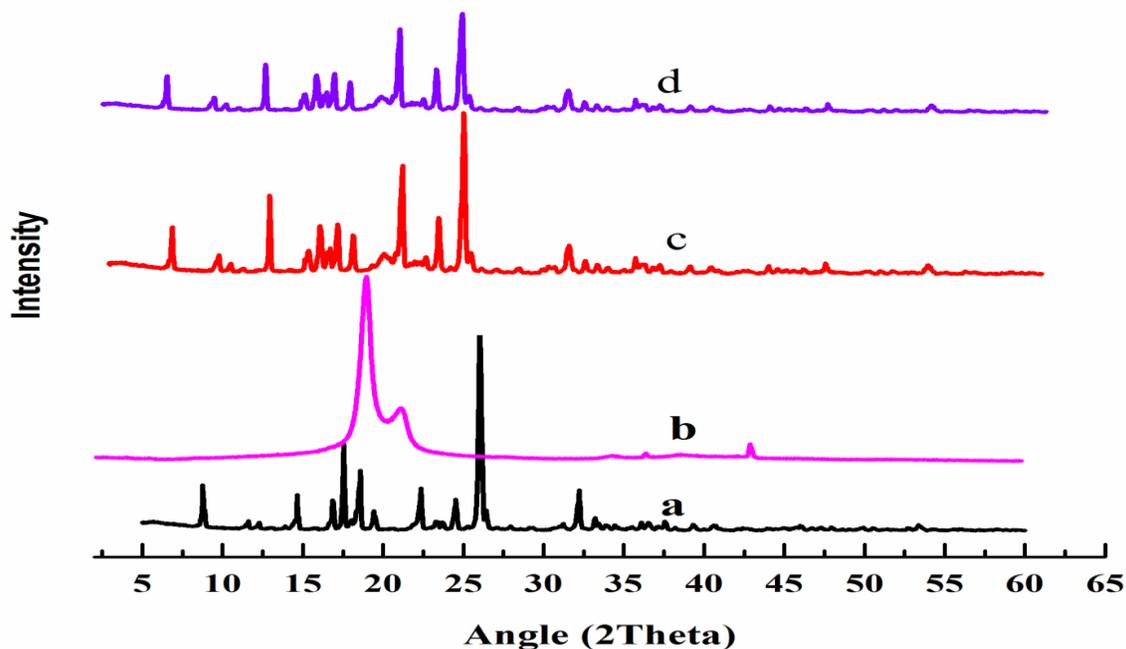


Figure 3: X-ray diffraction analysis of (a) pure aceclofenac, (b) C888 ATO, (c) AC: C888 ATO PM and (d) Melt extrudates

Scanning electron microscopy

The scanning electron microscopic study revealed the surface morphology and shape of the API, lipidic material and extruded formulation. The pure aceclofenac shown 50-100 μ m size with rod and spherical shape, the extruded batches with Compritol 888 ATO[®] exhibited agglomerated particles with voids between them as described in figure 6. The surface topography melt granulated granules exhibited the porous network and rough surface which indicates the excellent melt granulation processing of granules. The voids spaces between the agglomerated particles improved the compressibility to achieve required hardness.

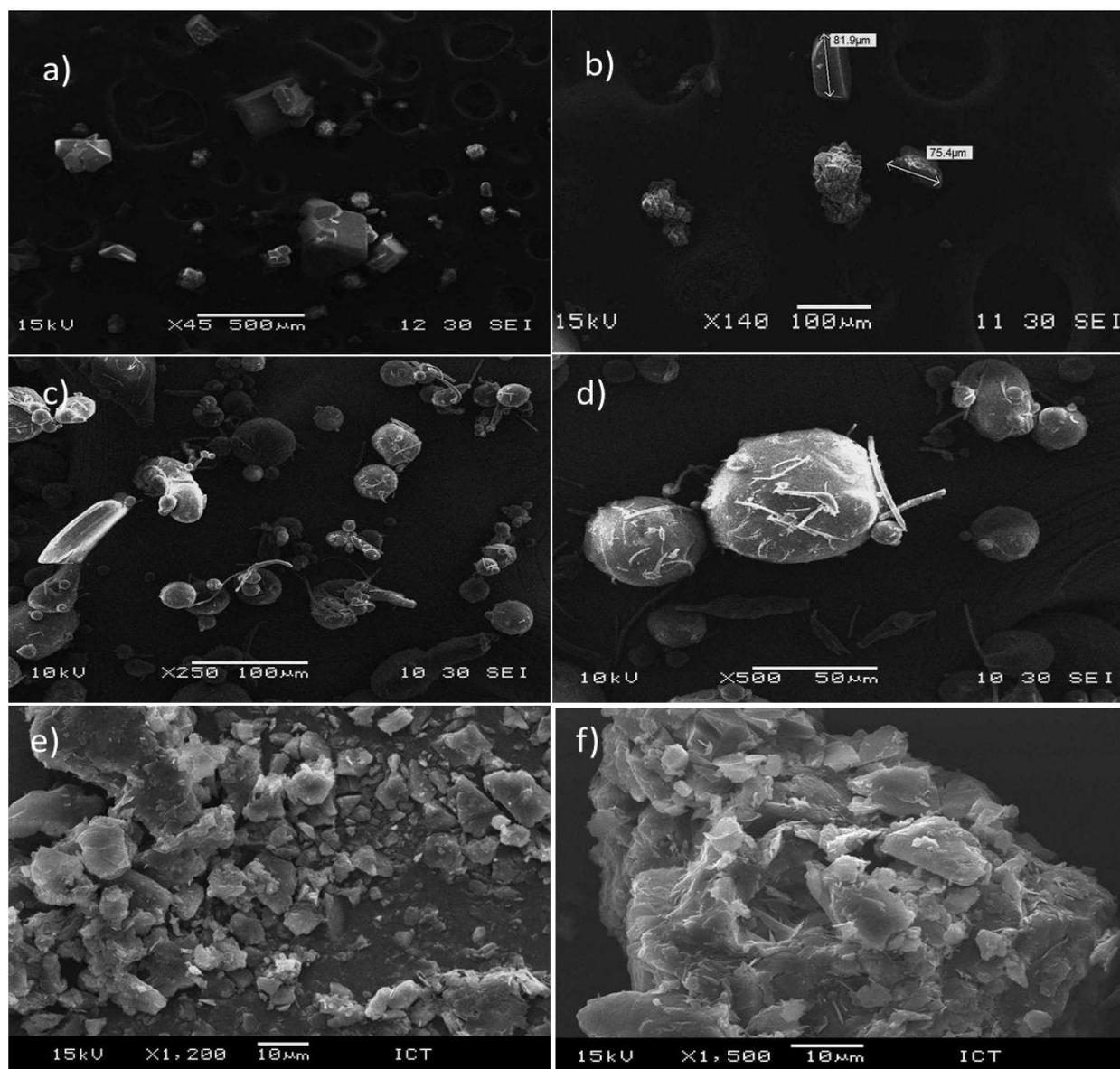


Figure 4: SEM images of (a, b) Pure aceclofenac, (c, d) plain Compritol 888 ATO and (e, f) Melt extrudates

In vitro drug release

The dissolution study revealed that formulation of aceclofenac with Compritol 888 ATO[®] gives different release profile which is depicted in figure 7. Batch F1 contained 9% Compritol 888 ATO[®] did not gave well extruded material and proper binding to the granules and unable to achieve desired hardness to the tablet hence it showed release up to 80% in 4 h due to erosion. The batches processed with 20 -30% C888 ATO (Batches F2 to F5) gave well extruded material and sufficient hardness to the tablet. Batches F2 and F4 (20-25% C888 ATO) with drug loading 80-75% showed the release rate too slow, only 60-65 % drug release in 12h which is not complying with innovator product sample. While batch F3 processed with 14% Compritol in combination

with 5% Hydroxypropyl cellulose had given the excellent hardness along with the glossy and shiny surface to the tablet which obviate tablet coating step. Batch F3 exhibited desired release profile which might be due to presence of matrix former hydrophilic polymer (Hydroxypropyl cellulose) which produces gelling and helped in the diffusion of the drug from the tablet and considered as optimized formulation. Formulation F5 (75% drug loading) processed with 24 % Compritol 888 ATO and 5% hydroxypropyl cellulose (Klucel EF) showed slower drug dissolution due to excessive hardness. The batch F3 showed similar release profile that of market sample ($f_2 > 50$).

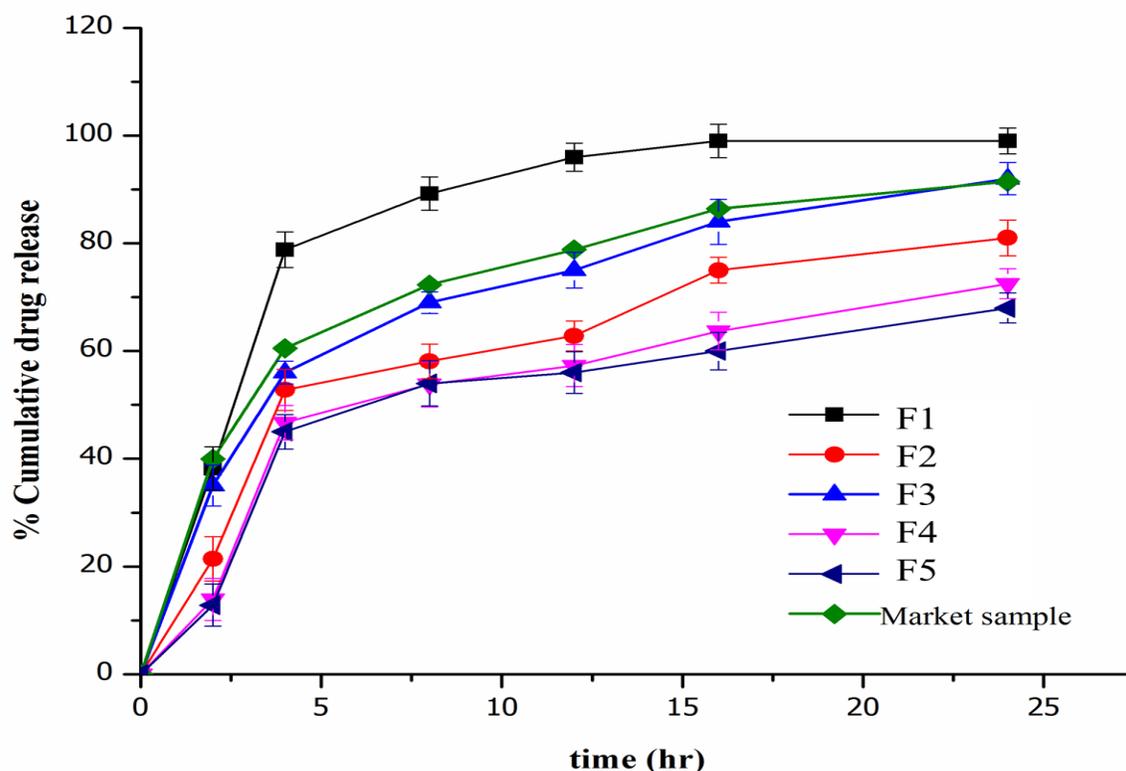


Figure 7: *In vitro* drug release studies of compressed tablets of extruded formulations (Mean \pm SD, n=3)

Table 4: Drug release kinetics data of different mathematical model in terms of regression coefficient

Batches	Kinetic Model (Correlation Coefficient- R^2)				n
	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	
F1	0.84	0.96	0.98	0.92	0.90
F2	0.82	0.96	0.99	0.93	0.53
F3	0.79	0.92	0.98	0.91	0.64
F4	0.85	0.93	0.99	0.92	0.47
F5	0.82	0.94	0.99	0.96	0.58

Drug release kinetics

To understand the drug release mechanism from the formulation, the dissolution data obtained were fitted to different mathematical model like zero order, first order, Higuchi model and Korsmeyer and Peppas equation and correlation coefficient were calculated and used to find the best fitness of the data. Table 4. describes the kinetic release of aceclofenac lipid matrix tablet. The kinetic studies revealed that the in vitro release pattern of all the formulation followed Higuchi's model as the plotting data showed the high linearity (R^2 value in between 0.98 to 0.99). The release of the drug (in matrix tablet) in dissolution media generally follows the diffusion mechanism with respect to concentration gradient. The diffusion mechanism was understood by analyzing the data with Korsmeyer and Peppas equation. The values of n in Korsmeyer and Peppas model indicated batches (F2-F5) followed nonfickian diffusion mechanism ($0.45 < n < 0.89$), while batch F1 showed super case II transport relaxational mechanism ($n > 0.89$).

CONCLUSION

Melt granulation/extrusion with Compritol 888 ATO is an effective approach to develop sustained release formulation of high dose drugs. The plasticizing effect of Compritol 888 ATO played an important role in extruding the material without producing torque on machine. Binder was added in the formulation to increase the particle bonding in the granules and tablet hardness which further influenced the drug release. Batch F3 was found good with respect to extrusion and compression thus it was considered as optimized formulation. The addition of the hydrophilic binder hydroxypropyl cellulose in the formulation resulted not only improved the compressibility and tablet strength but also acted as carries and hence sustained the release profile.

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