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Aceclofenac Size Enlargement by Non Aqueous Granulation with Improved Solubility and Dissolution

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Present work was designed to investigate the effect of size enlargement methods (Melt granulation and liquisolid technique) on the physicochemical properties (such as solubility and dissolution rate) of a poorly water-soluble drug Aceclofenac (AF). Initially, the granules were prepared by melt granulation technique using melt binders (poloxamer and Polyethylene glycol-PEG), diluent (Microcrystalline cellulose-MCC) and super-disintegrants (Sodium starch glycolate-SSG). The liquisolid systems were also prepared by using non-volatile organic solvent (PEG-400), coating polymer (Hydroxypropylmethylcellulose-HPMC), diluents (dibasic calcium phosphate-DCP and MCC) and super disintegrants (SSG and croscarmellose sodium-CCA). AF and size enlarged granules were characterized by thermal behavior (differential scanning calorimetry-DSC), X-ray diffraction (XRD) and Fourier transforms infra red spectroscopy (FTIR). The size enlarged granules prepared by both techniques exhibited improvement in solubility, dissolution rate, wettability and flowability compared to AF. The melt granules (AFPOLS), containing poloxamer with SSG and liquisolid systems (AFLSM2), containing MCC with CCS showed higher solubility and dissolution rate compared to other melt-granules and liquisolid systems. As observed in DSC studies, the reduced melting point enthalpy of the granules is indicating increased disorder in the arrangement of the atoms focusing towards reduced crystallinity. The XRD and FTIR studies revealed a characteristic decrease in crystallinity of the granules.

KEYWORDS: Liquisolid technique, melt granulation Size enlargement, solubility, wettability.

INTRODUCTION

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and lower medicine production costs. For the drug absorption into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. For hydrophobic drugs, dissolution process is the rate-controlling step and, therefore, determines the rate and degree of absorption. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water (1).About 50% of orally administered drug compounds suffer from formulation problems related to their water insolubility. As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs. One way of improving dissolution involves the reduction of particle size and/or increasing saturation solubility (2).

One of the most common approaches used to reduce particle size is milling, a mechanical micronization process. Milling is a well-established technique which is relatively cheap, fast and easy to scale-up. However, milling has several disadvantages, the main one being the limited opportunity to control important characteristics of the final particle such as size, shape, morphology, surface properties and electrostatic charge. In addition, milling is a high energy process which causes disruptions in the drug's crystal lattice, resulting in the presence of disordered or amorphous regions in the final product (3).

An alternative to milling involves the size enlargement of drug particle with different polymers and excipients, for example compaction, melt granulation and liquisolid technique. The compaction of drug with hydroxypropyl methylcellulose (HPMC) and other hydrophilic polymers shows change in

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crystal form and habit may change the solubility, dissolution rate and other physicochemical properties. These are the easily scalable method to combine poorly water-soluble drugs and dissolution rate enhancing polymers without the use of solvent or heat addition (4-5).

Melt granulation is a process by which pharmaceutical powders like drugs and different excipients were efficiently agglomerated by the use of a binder which can be a molten liquid, a solid or a solid that melts during the process. For accomplishing this process, apparatus of choice are the high shear mixers, where the product temperature is raised above the melting point of the binder either by a heating jacket or, when the impeller speed is high enough, by the heat of friction generated by the impeller blades (6).

The melt granulation technique is mostly now days used to prepare fast release formulations by utilizing water-soluble binders, such as PEG. PEG has been widely used in melt granulation because of its favorable solution properties, low-melting point, rapid solidification rate, low toxicity, and low cost. Another commonly used binder is Gelucire, which is a mixture of glycerides and fatty acid esters of PEGs. Gelucire has been shown to further increase the dissolution rate of poorly water-soluble drugs, attributed to the surface active and self-emulsifying properties of this excipient (7-8). In recent years, the interest in melt granulation has increased due to the advantage of this technique over traditional wet granulation, that is, elimination of water or organic solvents from the melt granulation process. This negates any risk originating from residual solvents; moreover, in melt granulation the drying step is not necessary, thus the process is less consuming in terms of time and energy as compared to wet granulation (9).

Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term 'liquid medication' implies oily liquid drugs and solutions or suspensions of water insoluble solid drugs carried in suitable nonvolatile solvent systems termed the liquid vehicles. Using this new formulation technique, a liquid medication may be converted into a dry-looking, non-adherent, free flowing and readily compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials. Various grades of cellulose, starch, lactose, etc., may be used as the carriers, whereas very fine particle size silica powders may be used as the coating (or covering) materials (10).

The industrial application of liquisolid compacts, however, can be hampered by the poor and erratic flow and compaction properties of the final liquid: powder admixtures. In more recent studies (11), however, the flowability and compressibility of liquisolid compacts were addressed simultaneously resulting in the new formulation mathematical model of liquisolid systems, which enables one to calculate the appropriate quantities of excipients required to produce acceptably flowing and compressible powders. Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability.

Aceclofenac (2-[(2, 6-dichlorophenyl) amine] phenylacetoxyacetic acid) is an orally effective non-steroidal anti-inflammatory drug (NSAID) of the phenyl acetic acid group, which possesses remarkable anti-inflammatory, analgesic and antipyretic properties (12-13). The analgesic efficacy of aceclofenac 100 mg is more prolonged than that of acetaminophen 650 mg. Aceclofenac appears to be particularly well-tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects (14).Aceclofenac exhibits very slight solubility in water and as a consequence it exhibits low bioavailability after oral administration (15-16). There are hardly any reports on the improvement

Table: 1 Formulation of melt granules with different polymers and excipients.

Granule code	Acceclofenac	Poloxamer	PEG-6000	Microcrystalline Cellulose (MCC)	Sodium starch glycolate (SSG)
AF	API	-----	-----	-----	-----
AFPOL	1 gm	1gm	-----	-----	-----
AFPOLM	1 gm	1gm	-----	0.5 gm	-----
AFPOLS	1 gm	1gm	-----	-----	0.25 gm
AFPEG	1 gm	-----	1gm	-----	-----
AFPEGM	1 gm	-----	1gm	0.5 gm	-----
AFPEGS	1 gm	-----	1gm	-----	0.25 gm

of dissolution rate and bioavailability of poorly water-soluble drugs by size enlargement technique. Hence the objectives of present study were to assess the feasibility of size enlargement techniques with different excipients and polymers in enhancing the solubility and dissolution rate of aceclofenac by compaction, Melt granulation and liquisolid technique.

Table: 2 Formulation of liquisolid granules with different polymers and excipients.

Liquisolid system	Non volatile solvent	Carrier (1.5 gm)	Coating material (0.2 gm)	Super disintegrant (0.3gm)
AFLSD1	PEG-400	DCP	HPMC	-----
AFLSD2	PEG-400	DCP	HPMC	SSG
AFLSM1	PEG-400	MCC	HPMC	-----
AFLSM2	PEG-400	MCC	HPMC	CCS

MATERIALS AND METHODS

Materials

Aceclofenac was supplied as a gift sample from Lupin Research Park (Pune, India). Poloxamer 407 (Pluronic F-127) and Polyethylene glycol (PEG-6000) were procured from Alembic Research Ltd (Vadodara, India).Microcrystalline cellulose (MCC), Sodium starch glycolate (SSG), Hydroxypropylmethylcellulose (HPMC), dibasic calcium phosphate (DCP), Croscarmellose sodium (CCA) was obtained as gift sample from Torrent Research Center (Ahmadabad, India). Sodium Laurel Sulphate (SLS), Polyethylene glycol (PEG-400) and other raw materials were procured from S. D. Fine (Mumbai, India).

Preparation of granules by melt granulation technique

Melted granules were prepared in a porcelain dish. Initially, mixtures of ACF with hydrophilic meltable polymer (Polyethylene glycol) or surfactant (poloxamer), as mentioned in Table 1, was dry blended for 10 min .Then these mixtures were placed in hot porcelain dish and heated, around 60^{o}C, on temperature controlled water bath so as to melt the polymers or surfactant in which the drug was dispersed. The molten mass was spread on glass plates and allowed to solidify at room temperature. The solidified mass was passed through sieve no # 20 so as to get uniform sized granules. These granules were stored in sealed bags for evaluation.

Table: 3 Evaluation parameters of Aceclofenac and prepared granules.

Batch ID	Product Yield (%)	Drug Content (%)	Solubility (mg/mL)	Powder bed hydrophilicity test (water raising time-hrs)
AF	-----	98 ± 2.35	0.060 ± 0.004	8.0 ± 0.265
AFPOL	93 ± 2	94 ± 3.21	0.458 ± 0.025	4.0 ± 0.458
AFPOLM	95 ± 3	95 ± 2.58	0.546 ± 0.045	3.5 ± 0.985
AFPOLS	93 ± 2	93 ± 2.58	0.595 ± 0.068	3.0 ± 0.879
AFPEG	94 ± 1	95 ± 1.25	0.356 ± 0.069	5.0 ± 0.578
AFPEGM	95 ± 1	96 ± 2.56	0.425 ± 0.054	4.5 ± 0.896
AFPEGS	93 ± 1	95 ± 3.25	0.410 ± 0.058	5.5 ± 0.867
AFLSD1	95 ± 2	94 ± 2.56	0.365 ± 0.045	4.0 ± 0.954
AFLSD2	92 ± 2	96 ± 3.25	0.345 ± 0.056	4.5 ± 0.678
AFLSM1	94 ± 3	94 ± 2.65	0.378 ± 0.057	5.0 ± 0.689
AFLSM2	96 ± 1	94 ± 3.12	0.405 ± 0.059	5.5 ± 0.789

* Each value represents mean ± S.D. (n = 3)

Preparation of granules by liquisolid technique

Aceclofenac (2gm) was dispersed in a non-volatile vehicle (PEG-400). Then a binary mixture of carrier-coating materials (MCC and DCP as carrier powders and HPMC as coating material at a ratio of 10:0.5) was added to a mixture containing drug and propylene glycol with continuous mixing in a mortar. Finally, superdisintegrant was added to the powder mixture and triturated for a period of 10 minutes (as mentioned in Table: 2). The solidified mass of powder mixture was passed through sieve no #

Table: 4 Flowability Parameter of Aceclofenac and prepared granules.

Batch ID	Bulk Denstidy (gm/mL)	Tap Denstity (gm/mL)	Carr's Index	Hausner Ratio	Angle of Repose (Degree)
AF	0.385 ±0.025	0.555 ±0.035	30.631 ±0.586	1.442 ± 0.085	40.76 ± 1.25
AFPOL	0.296 ±0.035	0.352 ±0.045	16.193 ±0.568	1.193 ± 0.069	23.56 ± 1.35
AFPOLM	0.284 ±0.012	0.328 ±0.065	13.415 ±0.896	1.155 ± 0.056	20.36 ± 1.25
AFPOLS	0.274 ±0.024	0.318 ±0.015	13.836 ±0.869	1.161 ± 0.054	21.58 ± 1.35
AFPEG	0.267 ±0.015	0.308 ±0.035	13.312 ±0.789	1.154 ± 0.025	22.56 ± 1.65
AFPEGM	0.254 ±0.024	0.299 ±0.015	15.050 ±0.896	1.177 ± 0.026	23.75 ± 1.85
AFPEGS	0.257 ±0.015	0.295 ±0.035	12.881 ±0.786	1.148 ± 0.024	24.66 ± 1.57
AFLSD1	0.315 ±0.025	0.386 ±0.042	18.394 ±0.689	1.225 ± 0.025	28.28 ± 1.24
AFLSD2	0.325 ±0.024	0.396 ±0.026	17.929 ±0.769	1.218 ± 0.085	30.68 ± 1.46
AFLSM1	0.356 ±0.016	0.435 ±0.025	18.161 ±0.968	1.222 ± 0.035	29.45 ±1.62
AFLSM2	0.345 ±0.032	0.425 ±0.021	18.824 ±0.689	1.232 ± 0.056	31.63 ± 1.83

* Each value represents mean ± S.D. (n = 3)

20 so as to get uniform sized granules. These granules were stored in sealed bags for evaluation.

Drug content determination

The drug content of granules was determined by pulverizing the granules (10 mg) followed by immersing them in 100 ml phosphate buffer (pH 6.8) with agitating for 10 min at room temperature. After filtration through a 0.2µm membrane filter (Pall Life Sciences, Mumbai), absorbance was measured on UV-Visible Spectrophotometer (Shimadzu UV-1700, Tokyo, Japan) at 273 nm. The samples were analyzed in triplicate and encapsulation efficiency (EE) was calculated using following equation:

$$\% \text{ Encapsulation Efficacy} = \frac{WA}{WT} \times 100$$

Where as WA: actual drug content; WT: theoretical drug content.

Saturation solubility study

An excess quantity of aceclofenac or size enlarged granules was placed in the bottles containing 10 ml of distilled water. The bottles were agitated in a shaking water bath (100 agitations/min) for 24 h at room temperature. Finally, it was filtered through a membrane filter of 0.2µm (Pall Life Sciences, Mumbai) and amount of the drug dissolved was analyzed spectrophotometrically (Shimadzu UV-1700, Tokyo, Japan) at 273 nm. The samples were analyzed in triplicate.

Dissolution studies

The in-vitro dissolution studies were carried out using eight station USP type II (paddle) dissolution test apparatus (Labindia Disso 2000, Mumbai, India). The study was carried out in 900 ml of 0.1N HCl containing 2% Tween 80. Dissolution media was kept in a thermostatically controlled water bath, maintained at 37 ± 0.5°C. The paddles were rotated at 75 rpm. At predetermined time intervals, 5ml of samples were withdrawn and assessed for drug release by UV-Visible spectrophotometer (17). After each withdrawal, 5ml of fresh dissolution media was added to dissolution jar.

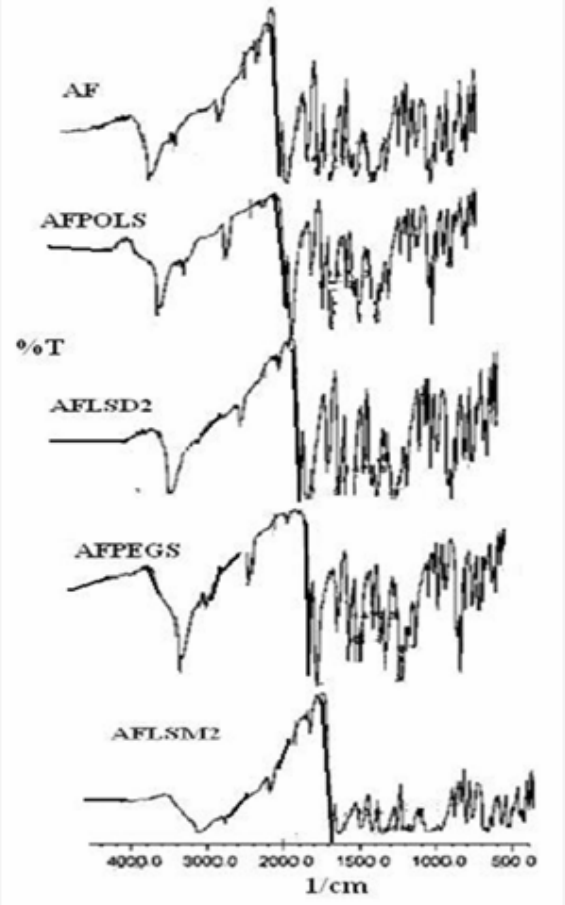

Figure: 1 FTIR spectra of AF and prepared granules

Flow properties

Flow properties of the drug and prepared melt granules were studied by determining the bulk density (σ_b), tap density (σ_t), Carr's Index and Hausner ratio. A weighed quantity of samples was taken to determine the bulk and tap density.

The parameters selected to study flow properties were determined using following equations (18).
Bulk density (σ_b) = Mass / Poured volume (1)
Tap density (σ_t) = Mass / Tapped volume (2)
Carr's Index = $[(\sigma_t - \sigma_b) / \sigma_t] \times 100$ (3)
Hausner ratio = $(\sigma_t / (\sigma_b)$ (4)
Angle of repose (Fixed funnel and free standing cone 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 a flat horizontal surface. The powder sample to be analyzed was carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel (H). The mean diameter (d) of the powder cone was determined and the tangent of the angle of repose was given by the eq:
$\tan\theta = h/r$, $\theta = \tan^{-1} (h/r)$, $\tan\theta = h/0.5d$, (5)
Where
θ = Angle of repose, h = height of the tip of funnel from horizontal plane, r = radius of the pile made by powder, D = diameter of cone.
Values for angle of repose ≤ 30 usually indicate free flowing material and angle ≥ 40 suggested a poor flowing material.

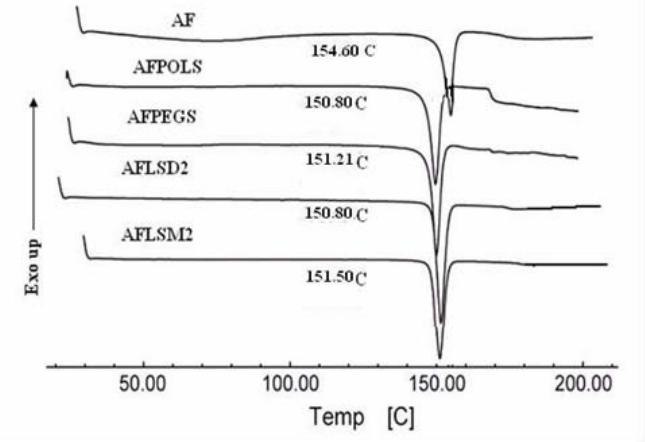

Figure: 2 DSC spectra of AF and prepared granules

Wettability/ Powder Bed Hydrophilicity Study
The untreated drug and prepared granules were placed on a sintered glass disk forming the bottom of glass tube on which methylene blue crystals were placed. The whole device was brought into contact with water. Measure the time taken for the capillary rising of water to the surface so as to dissolve methylene blue crystals was noted. Minimum is the time required to reach the water to surface maximum is its wettability (19).

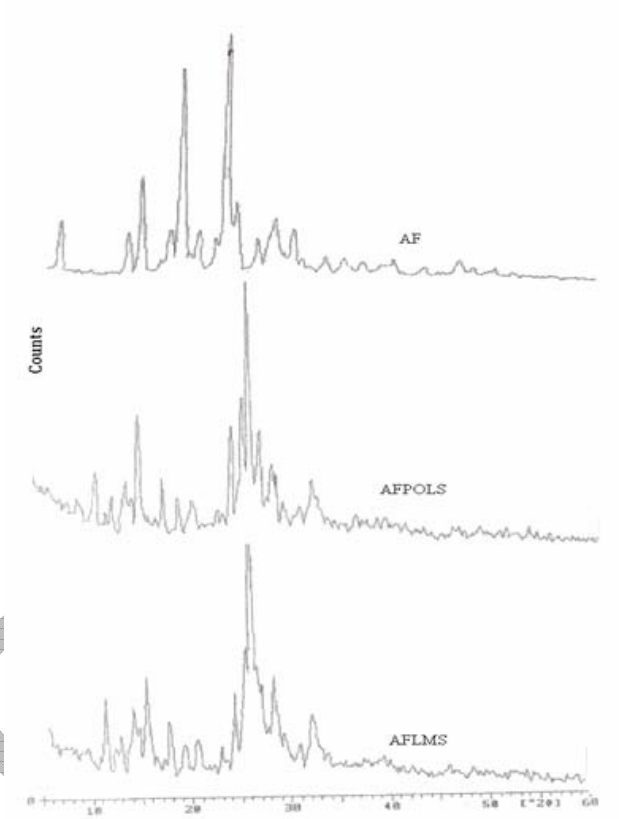

Figure: 3 XRD spectra of AF and prepared granules

Fourier Transform Infra Red Spectroscopy (FTIR)
FT-IR spectra of prepared melt granules were recorded on Shimadzu FTIR-8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 - 4000 cm^{-1} at spectral resolution of 2 cm^{-2} and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

Powder X-Ray Diffraction (PXRD)
Crystallinity of the drug and prepared samples was determined using Philips Analytical X-RD (Model: PW 3710, Holland) with copper target. The conditions were: 40kV voltages; 30mA current; at room temperature. The samples were loaded on to the difffractometer and scanned over

a range of 2θ values form 10 to 80° at a scan rate of 0.05°/0.4 sec.

Differential Scanning Calorimentry (DSC)

Thermal properties of the untreated drug and prepared samples were analyzed by DSC (TA Instruments, USA, and Model: SDT 2960). The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 350°C at a heating rate of 10°C/ min, using nitrogen as blanket gas.

RESULTS AND DISCUSSION

Pure drug, indicating absence of any chemical interaction between the drug and excipients used. Fig. 2 shows the results of DSC studies. Pure aceclofenac showed a sharp endothermic peak at 154.60°C corresponding to its melting point (21). There was no considerable change in the melting endotherms of prepared granules as compared to the pure drug.

Further, these observations support to the results of IR spectroscopy, which indicated absence of any interactions between the drug and excipients used in the preparation. However, there is slight decrease in the melting point of drug when prepared in the form of granules by melt granulation and liquisolid technique. It was also observed that there was a slightly reduction in the enthalpy of the crystals in comparison with pure aceclofenac. The prepared granules showed a lower enthalpy along with a lower melting point. This reduction in melting point along with enthalpy accounts for increased solubility and reduced crystallinity of aceclofenac in the granules (22-23).

The XRD patterns of the pure drug and size enlarged granules are shown in Fig. 3. The XRD scan of plain aceclofenac showed intense peaks of crystallinity; whereas XRD pattern of the optimized granules exhibited reduction in both number and intensity of peaks compared to plain aceclofenac indicating decreased crystallinity or partial amorphization of the drug (24). Thus, XRD data supports to the DSC studies indicating decreased crystallinity of the drug in size enlarged granules by exhibiting lower values of enthalpy and melting point.

Solubility study

FTIR, DSC, XRD studies

The probable interaction between the drug and excipients was studied by FTIR and DSC analysis. FTIR spectra of pure aceclofenac and its size enlarged granules are shown in Fig. 1. Pure aceclofenac showed major peaks at 3319.3, 2970.2, 2935.5, 1716.5, 1589.2, 1506.3, 1479.3, 1344.3, 1280.6, 1255.6, and 665.4 cm^{-1} (20). The Fig.1 illustrated no significant changes in the IR spectra of the granules prepared by melt granulation and liquisolid technique compared to The solubility of aceclofenac and size enlarged granules by both methods in water is given in Table 3. The table shows that the solubility of aceclofenac (0.060 mg/mL) was markedly increased in size enlarged granules by melt granulation and liquisolid technique. Improvement in the solubility was thought to be a synergistic effect of deceased crystallinality confirmed by XRD study and hydrophilic nature of the used polymers which create hydrophilic environment around the drug molecule during dissolution.

Flowability parameters

According to the literature, powders with a Compressibility Index (CI) between 5 to 15%, Hausner ratio below 1.25 and angle of repose below 30 shows good flowability suitable for directly compressible tablets. The prepared melt granules (Table 4) possess a CI between 12 and 16%, Hausner ratio was below 1.15 and angle of repose were below 30. Compared to melt granules the liquisolid systems shows slightly higher values of Compressibility Index , hausner ratio and angle of repose due to presence of non volatile organic solvent (PEG 400) which is not evaporated and remain in liquisold system gives slightly sticky appearance. The rheological properties of prepared melt granules revealed a good flowability because of their granular size which reduces the surface area and increases flow rate.

Wettability/Powder bed hydrophilicity study

Table 3 indicates results of powder bed hydrophilicity study of AF and their granules prepared by melt granulation and liquisolid technique. The melt granules and prepared liquisolid systems showed significantly shortest rising time (** $P<0.01$) of water to its surface

compared to the raw AF crystals represent better wattability of prepared granules as compared to raw AF. The order of wettability was AFPOLS > AFPOLM > AFPOL, AFLSD1 > AFPEGM, AFLSD2 > AFPEG, AFLSM1 > AFPEGS, AFLSM2 > AF .The reason for superior wettability of melt granules and liquisolid systems is due to the presence of polymers with the AF.

Dissolution studies

The results of in vitro drug release studies in 0.1N HCl containing 2% Tween 80 for 3 hrs are depicted in Fig. 4 and 5. The dissolution rate of pure aceclofenac was very low, showed a release of 52% at the end of 3 hrs. The melt granules with poloxamer AFPOL, AFPOLM and AFPOLS shows 86, 89, 95% CDR in three hours comparatively with polyethylene glycol AFPEG, AFPEGM and AFPEGS having 78, 84, 88 % CDR in three hrs. The size enlarged granules prepared by melt granulation method using poloxamer showed highest dissolution rate compared to other granules prepared by melt and liquisolid systems. Compared to liquisolid technique, melt granulation using poloxamer shows higher dissolution rate. In melt granulation technique dissolution rate of melt granules without diluents and super-disintegrants shows on lower side. The impact of super-disintegrants on dissolution rate was slightly on higher side comparative to diluents. The increase in dissolution rate can be attributed to the higher hydrophilic character of the system due to the presence of water-soluble carriers and that part of the drug dissolves in the binder. These results show that melt granulation can be a useful technique to improve the dissolution rate of aceclofenac.

The liquisolid system with dibasic calcium phosphate and microcrystalline cellulose with super-disintegrants shows improvement in dissolution rate comparative to pure aceclofenac. The prepared liquisolid systems AFLSD1, AFLSD2, AFLSM1, AFLSM2 shows 67, 76, 82, 86% CDR within 3 hrs. The increase in dissolution rate may be due to the significantly increased surface of the molecularly dispersed aceclofenac in the liquisolid system which may be mainly responsible for their observed higher and consistent drug dissolution rates.

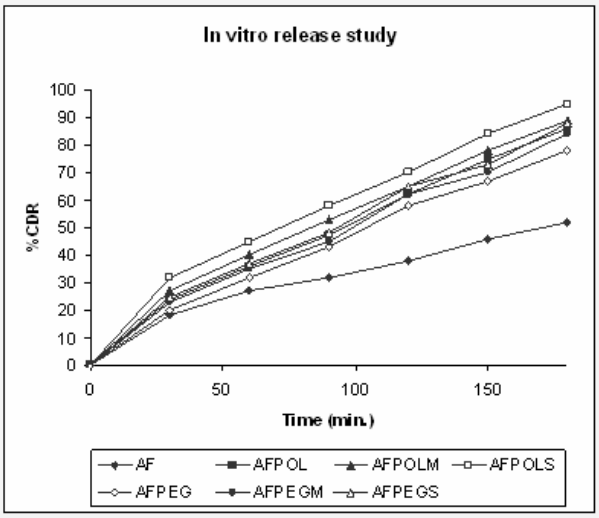

Figure: 4 In vitro release profile of aceclofenac and prepared melt granules.

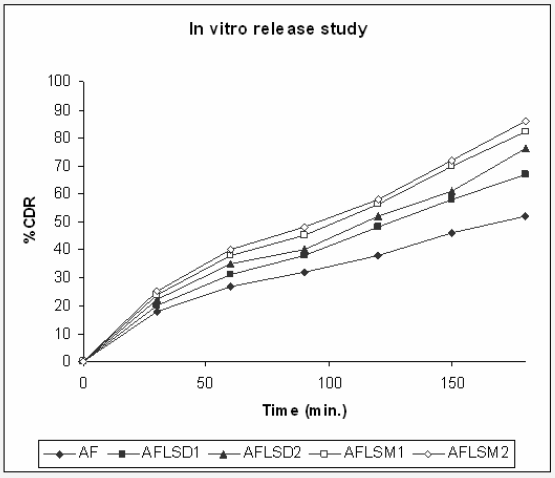

Figure: 5 In vitro release profile of aceclofenac and prepared liquisolid granules.

CONCLUSION

In conclusion, the used size enlargement technique includes melt granulation and liquisolid technique. Melt Granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable polymers; however, liquisolid system refers to formulation of suspension or solution in non-volatile organic solvents into dry, non-adherent, free flowing compressible powder mixtures with selected carriers and coating material. The granules of AF were produced by melt granulation using PEG 400 as a melt binder with

different diluents and super disintegrants. The granules were also prepared by liquisolid technique using non-volatile organic solvent (PEG 400), coating polymer (HPMC), diluents (DCP, MCC) and super disintegrants (SSG and CCS).The granules prepared by both techniques shows improvement in solubility, dissolution, wettability and flowability parameters. The reduction in crystallinity, melting point and chemical interaction was confirmed by XRD, DSC and FTIR.The advantage of this Technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation process.

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