

Significant Increasing of Gastrointestinal Dissolution of Aceclofenac via Florite

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Abstract

It has been reported that about 40% of the compounds being developed by the pharmaceutical industries are poorly water soluble. The limiting factor to the in vivo performance of poorly water soluble drugs after oral administration their inadequate ability to be wetted by and dissolved into the fluid in the gastrointestinal (GI) tract. Therefore, increasing the dissolution rate of poorly water soluble drugs is an important and significant challenge to pharmaceutical scientists in order to maximize absorption. Aceclofenac is a nonsteroidal anti-inflammatory drug (NSAID), used for rheumatoid arthritis, osteoarthritis and other joint pains. The oral bioavailability of aceclofenac was found to be very poor likely due to the very poor dissolution in aqueous fluids especially in acidic medium. The study utilized the solvent evaporation method for preparation of stable amorphous solid dispersions of Aceclofenac by adsorbing it on porous carrier (Florite).

Keywords: Solid dispersion technique; Fast dissolving tablets; Aceclofenac;

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1. Introduction

In case of pharmaceutical materials, the importance of amorphous solid system form:

- Useful properties: amorphous solid have higher dissolution rate higher solubility.
- Instability: amorphous solid are generally less stable physically and chemically than corresponding crystals.[1-3]

Amorphous substances form a separate class of solids, distinct from the more common and well-known crystalline solids. The three-dimensional long-range order that normally exists in a crystalline material does not exist in the amorphous state and the position of the molecules relative to one another is more random. Pharmaceutical materials that are processed by high-energy processes such as jet milling, melt extrusion, freeze drying, spray drying and so forth, are often rendered at least partially amorphous [4-5].

This occurs by the virtue of the fact that these processes create conditions that can prevent crystallization or mechanically disrupt the structure of an existing crystalline material. The

specific volume of the amorphous state and high internal energy relative to the crystalline state can lead to enhanced dissolution and bioavailability but can also create a possibility that it may spontaneously convert back to the more stable crystalline state during processing or storage. As stated earlier, the application of spray drying technique to obtain amorphous form of the drug substance, either alone or in combination with a hydrophilic polymer is now well known [6-10]. Aceclofenac is a nonsteroidal anti-inflammatory drug (NSAID), used for rheumatoid arthritis, osteoarthritis and other joint pains. The oral bioavailability of aceclofenac was found to be very poor likely due to the very poor dissolution in aqueous fluids especially in acidic medium. The present work is to evaluate the potential of the solid dispersion technique for the development of fast dissolving tablets of Aceclofenac using Florite as hydrophilic porous carrier.

In order to achieve the following objectives:

- To adsorb Aceclofenac over Florite resulting in microparticles and to evaluate them.

- To improve the dissolution of Aceclfenac using porous calcium silicate (Florite RE).
- To formulate and evaluate (*in-vitro*) immediate release of directly compressed tablets using above microparticles with improved drug dissolution.
- To formulate and evaluate (*in-vitro*) immediate release of dispersible tablets prepared by Direct compression method using above microparticles with improved drug dissolution.

2. Material and Methods Preparation of microparticles

2.1 Adsorption of Aceclofenac over Florite

Accurately weighed quantity of Aceclofenac (500mg) was dissolved completely in minimum quantity of acetone into a 100 ml round bottom flask. Accurately weighed quantity of adsorbent (1, 2, 3 times of drug weight) was dispersed into drug solution with shaking the resulted batched (FLR-1, FLR-3) were designated. Acetone was allowed to evaporate completely under vacuum in rotary evaporator at constant temperature and speed of 60° C and 80 rpm respectively. Collected free flowing powder was Vacuum dried for 24 hrs. [11]

2.2 Characterization of microparticles Yield and drug content

Microparticle samples were weighed and process yield were calculated. Drug content was determined by dissolving exactly weighed amount (10 mg) of each formulation in 7.4 Phosphate buffer [12]. After filtration through membrane filter of pore size 0.45 µm and sufficient dilution samples were analyzed spectrophotometrically at 275 nm. Drug content was calculated from the standard curve of aceclofenac in 7.4 Phosphate buffer.

2.3 Infrared spectroscopy

IR spectra of Drug Florite drug loaded microparticles, Physical mixture were obtained on Jasco V5300 FI-11R. The pellets were prepared on KBr press. The spectra were recorded over the wave number range of 2000 to 400 cm⁻¹ [13].

2.5 Powder X-ray diffraction

PXRD data of drug (Florite) drug loaded microparticles Physical mixture were collected using a Philips PW 1729 Xray diffractometer. Drug and microparticles samples were irradiated with monochromatized Cu- α radiation ($\lambda=1.1542\text{Å}$) at 30 Kv and 30mA of 2° to 60° at a scanning rate of 5 x 10³ cps using a chart speed of 10mm/2θ.[14]

2.5 Differential Scanning Calorimetry

Aceclofenac (Florite RE) drug loaded microparticle Physical mixture prepared were separately weighed and hermetically sealed in the aluminum pans[15]. A Mettler Toledo DSC 821 equipped with

intracooler a refrigerated cooling system was used. Indium standard was used to calibrate the DSC temperature and enthalpy scale [16]. The system was purged with nitrogen gas at a flow rate of 5 ml/min. and heating was performed from 10 to 175° C at a rate of 5°C/min.

2.6 Surface Topography

Aceclofenac Florite and drug loaded microparticles were mounted on the specimen stabs using fevicol adhesive. Small samples were mounted directly on scotch double adhesive tape[17]. Samples were coated with gold to a thickness of 100 Å using Hitachi vacuum evaporator Model HVS 5GB. Coated samples were analyzed in a Hitachi scanning electron microscope model operated at 15 Kv and photographed.

2.7 Tablet Prepared By Direct Compression Method

Following formulations were passed through a 16 mesh sieve and were directly compressed using 10 punch station tablet machine using 13mm diameter circular punches with flat faces. Tablets equivalent to 100mg aceclofenac with hardness of about 5 to 6 were produced. [18].

1) Aceclofenac tablets : Aceclofenac: (100 mg) with primo gel (5% w/w), PVP-K30 (3% w/w) and directly compressible lactose IP (q.s) were geometrically mixed and lubricated with 1% w/w magnesium stearate IP.

2) Microparticle without disintegrant: Drug loaded microparticles (FLR-1 and FLR-3) equivalent to 100mg of aceclofenac were compressed using PVP-K30 (3% w/w) as binder and directly compressible lactose IP (q.s.) and 1% w/w magnesium stearate IP as lubricant [19].

3) Microparticle with disintegrant: Drug loaded microparticles (FLR-1 and FLR-3) equivalent to 100mg of aceclofenac, with primogel (5% w/w), PVP-K30 (3% w/w) and directly compressible lactose IP (q.s) were geometrically mixed and lubricated with 1% w/w magnesium stearate IP [20].

2.8 Evaluation of tablets

Uniformity of dispersion: Two tablets were placed in 100ml of water and stirred gently until forms complete dispersion. Obtained smooth dispersion was passed through a sieve screen with a nominal mesh aperture of 710 µm (sieve no. 22).

Weight variation: Twenty tablets were selected at random and average weight was calculated and checked for criteria that 'not more than 2 of individual weight deviate from average weight.

Hardness and friability: Friability of tablets (n = 10) was determined by using a Roche friabilator. Hardness tester was used to determine the hardness of tablet

Disintegration test: The disintegration time of tablets (n = 6) was determined using disintegration test apparatus in distilled water maintained at 37 ± 0.5 °C

Dissolution studies: The tablets were tested for dissolution in 900ml 0.1 M HCl and water using USP XXIV type II dissolution apparatus at 75 rpm and maintained at 37 ± 0.5 °C. Drug dissolved content was determined using UV spectrophotometer at 275 nm. Dissolution of a commercial tablet was also simultaneously studied [21].

3. Results and Discussion

3.1 Preparation of Microparticles: Process Design

Porous carriers have been used to improve dissolution rate of the poorly water soluble drugs. Florite is porous calcium silicate that possesses many interpartical, intrapartical pores, particularly of size 12 and 0.15 μm respectively on its surface [22]. It is hydrophilic and easily dispersible in water. Large surface area and hydrophilic surface of florite are useful for adsorption of drug and quick dispersion in to water respectively. Secondly the fineness of carrier makes it suitable to attain uniformity of dispersion. Therefore florite was selected as adsorbent. Aceclofenac was dissolved in minimum amount of acetone that is sufficient to dissolve the drug and wet the carrier particles. Adsorbent was dispersed in drug solution and it was evaporated in vacuum rotary evaporator. The obtained microparticles were then evaluated. The yield of the adsorption process is between 80- 90%.

Table 1: Solubility Profile of Aceclofenac

Solvent	Solubility (mg/ml)
Distilled Water	0.086 \pm 0.017
0.1 N HCl	0.0180 \pm 0.34
Phosphate Buffer pH 7.4	5.691 \pm 0.017

3.2 Microparticle Characteristics Infra-Red Spectroscopy (IR)

The intermolecular interaction of microparticles system was established by FT-IR. Figure 1 shows aceclofenac presenting the characteristic peak of C=O absorption band at 1770 cm^{-1} and the OH stretch at 3319 cm^{-1} . The spectra of all physical mixtures (1:1, 1:3 ratio) seemed to be only summation of aceclofenac, florite spectra. This observation indicated that no intermolecular interaction occurred in the physical mixtures. However the spectra from microparticles (1:1, 1:3 ratio) showed that the C=O absorption band of aceclofenac was shifted towards lower wave number and the OH stretching of aceclofenac was broadened and reduction in intensity was observed. Their results suggested that intermolecular hydrogen bonding between the aceclofenac and carrier (Florite). Furthermore this also indicated

that the formation of hydrogen bonding in the aceclofenac system correlated with the change in crystalline nature of aceclofenac and there are several studies that have demonstrated that hydrogen bonding can affect the transformation of drug crystal [23].

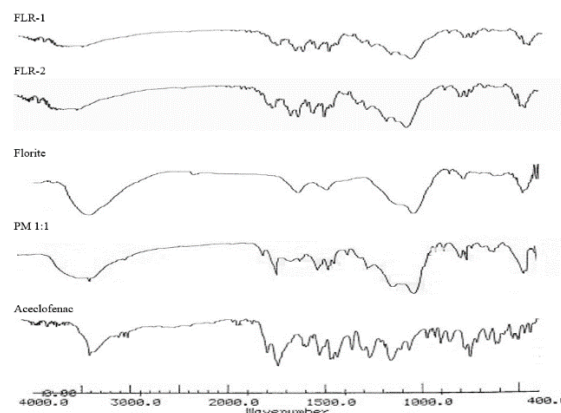


Figure 1: IR Spectra

3.3 X-Ray Diffraction (XRD)

The X-ray diffraction patterns of pure drug, florite, microparticles of FLR-1, FLR-3, PM-1:1, PM-1:3 shown in Figures 2-7. The XRD scan of plain aceclofenac showed intense peaks of crystallinity. Characteristic peaks of aceclofenac appeared at a diffraction angle of 2θ at 16.8, 22.1, 24.5, 25.9, whereas the XRD pattern of the prepared microparticles exhibited reduction in both number and intensity of peaks compared to plain aceclofenac indicating the decrease in crystallinity or partial amorphization of the drug in microparticles of FLR-1 and FLR-3. The XRD pattern of aceclofenac was similar to those of physical mixtures indicating that the crystallinity of aceclofenac did not change in the physical mixture [24]. This was consistent with the results obtained by FTIR, and DSC studies.

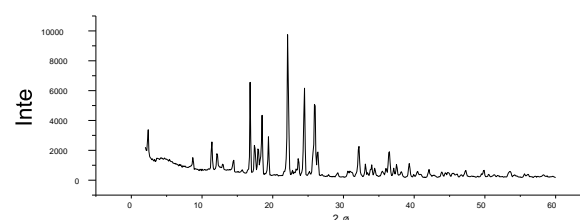


Figure 2: XRD of Aceclofenac

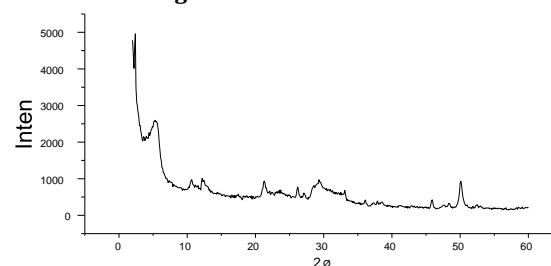


Figure 3: XRD of Florite

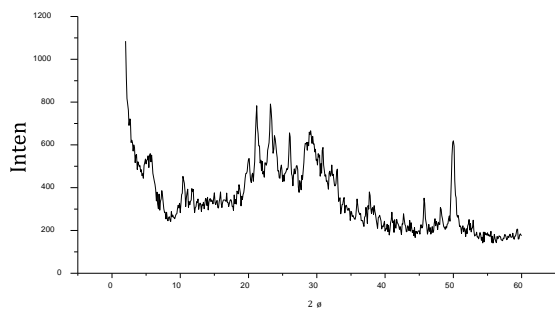


Figure 4: XRD of FLR-1:3

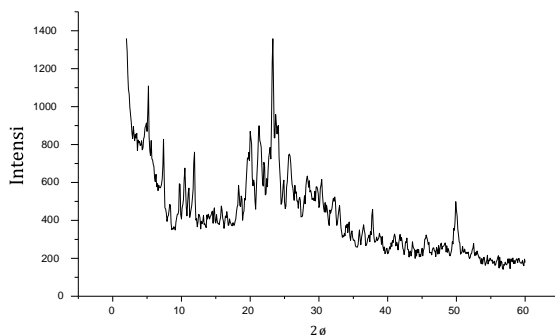


Figure 5: XRD of FLR-1:1

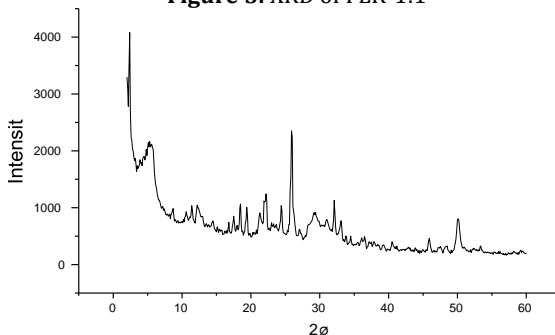


Figure 6: XRD of FLR-1:1

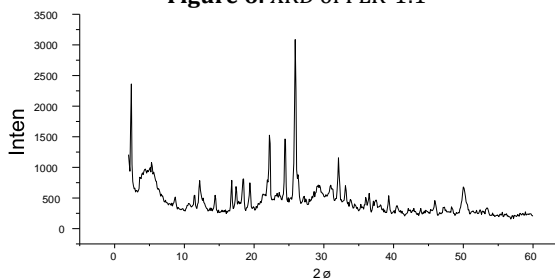


Figure 7: XRD of PM-1:1

3.4 Scanning electron microscopy (SEM)

The SEM photomicrographs of pure aceclofenac, microparticles (1:1 and 1:3), Florite are given in figures 8-9. The pure aceclofenac was characterized by crystals of bigger size and regular shape with an apparently smooth surface. The microparticles (FLR-1 and FLR-3) were fluffy and possess porous and rough surface which might have resulted in the enhanced dissolution rate as compared to pure drug. The surface cavities may be either filled or covered by drug crystals. No unadsorbed drug was seen in the microphotographs. In case of FLR-3, the recrystallized drug was distributed more evenly

covering larger FLR surface as compared to FLR-1. No agglomeration of drug crystals was seen in case of microparticles. It indicates that in spite of small crystal size, drug possesses poor wettability due to agglomeration and air adsorption over surface [25].

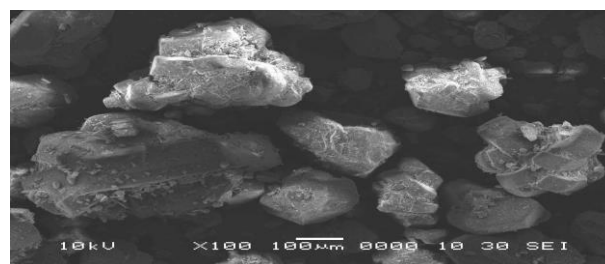


Figure 8: SEM of Aceclofenac

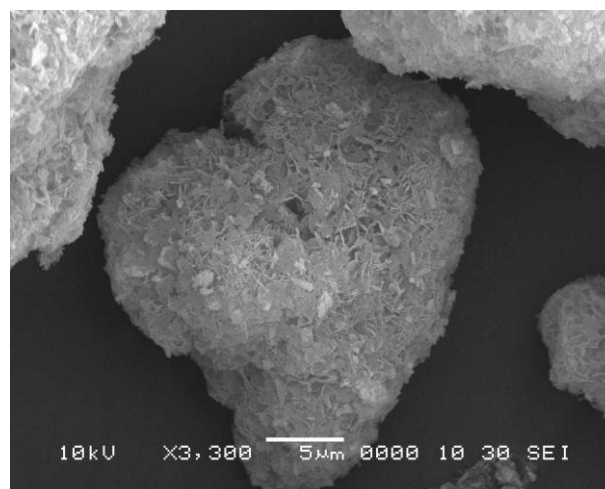


Figure 9: SEM of Florite

3.5 Dissolution Studies

Dissolution of pure aceclofenac and from microparticles was determined in distilled water and 0.1N HCl. In water and HCl, dissolution rate of drug from microparticles was significantly rapid compared to pure drug and the dissolution increased with increase in proportion of adsorbent. The increase in the aceclofenac solubility, although little, are explained as follows-

Calcium silicate (Florite) has been proposed by useful adsorbent for enhancing the bioavailability of poorly water soluble compounds.

- Significant size reduction to micro or sub micron level with narrow size distribution considerably enhances the dissolution due to the increase surface area³⁰
- The earlier literature reveals that dissolution rate not only depends on the surface area and particle size of the process micro particles but is greatly affected by crystal morphology and wettability.
- In order to clarify the causes of significant difference in the dissolution rate, the surface morphology of the micro particles was examined by SEM. Thus the fine and fluffy physical state of FLR-

1:1 and FLR-1:3 micro particles along with their porous and rough surface. As supported by SEM

- photomicrographs might also have contributed to the enhanced solubility and dissolution rate of aceclofenac from these microparticles.
- Decrease crystallinity or partial amorphization of the drug in FLR-1:1 microparticles as supported by XRD and DSC studies.

3.6 Dissolution in Distilled Water

In distilled water the Florite containing microparticles showed maximum drug release. It may be attributed to the greater surface area provided by the porous adsorbent particles for drug. The SEM also reveals the thin coat of drug on the particles. Thus the reduced crystallinity with increased surface area may be responsible for the almost complete drug release from the Florite containing microparticles. Sharma and Pawar reported similar results for meloxicam.

Table 2: Drug released parameters of microparticles of different batches Containing Florite and Aceclofenac, in Distilled Water.

Time (Min)	% Release of Microparticles in Distilled Water		
	Pure Drug	FLR-1:1	FLR-1:3
5	12.67±1.34	48.35±3.60	52.85±1.65
10	15.34±0.39	55.95±2.91	60.44±2.11
30	20.56±1.23	64.09±1.55	78.32±1.01
60	24.45±2.03	75.86±3.04	83.55±1.98

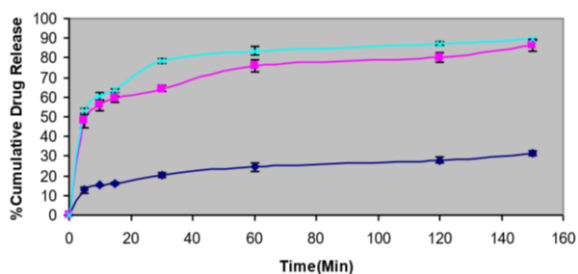


Figure 10: Graph of dissolution studies of Aceclofenac, FLR-1:1, FLR-1:3, in Distilled Water.

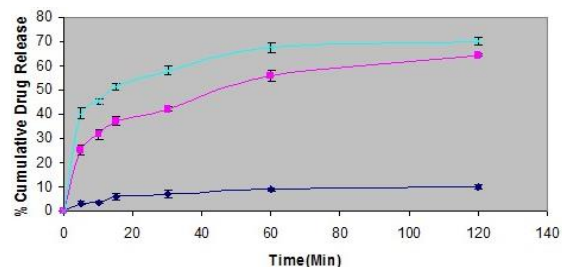


Figure 11: Graph of dissolution studies of Pure Drug, FLR-1:1, FLR-1:3 in 0.1 N HCl

3.7 Dissolution in 0.1 N HCl

In general lower drug dissolution of aceclofenac was observed in an acidic dissolution medium than the water. Florite microparticles(1:3 ratio) showed

around drug 60-67% release at 60 min and it is highest among all the proportion of adsorbent used. The drug released in acidic medium can be explained as describe for the drug release in water.

Table 3: Drug released parameters of microparticles of different batches containing Florite and Aceclofenac, in 0.1 N HCl.

Time (Min)	% Release of Microparticles in 0.1 N HCl		
	Pure Drug	FLR-1:1	FLR-1:3
5	3.08±0.84	25.34±1.97	40.21±2.10
10	3.45±0.45	31.66±2.01	45.38±1.19
15	5.91±1.34	37.24±1.57	51.22±1.56
30	6.88±1.58	42.11±0.79	54.39±1.85
60	8.78±0.64	59.99±1.53	67.45±2.32

4. Conclusion

Aceclofenac is a nonsteroidal anti-inflammatory drug (NSAID) used for rheumatoid arthritis osteoarthritis and other joint pains. Aceclofenac is often used orally. The oral bioavailability of aceclofenac was found to be very poor likely due to the very poor dissolution in aqueous fluids especially in acidic mediums. The present study successfully utilized the solvent evaporation method for preparation of stable amorphous solid dispersions of Aceclofenac by adsorbing it on porous carrier (Florite). Aceclofenac solution in acetone was dispersed with adsorbent (1:1, 1:3) parts by weight of Aceclofenac, adsorbent). FLR-1:1, FLR-1:3 showed maximum release in 0.1 N HCl. Study concluded that the dissolution rate of Aceclofenac significantly enhanced by use of adsorbent. In present study dispersible tablets was prepared using drug loaded porous adsorbent microparticles and sodium starch glycolate (primogel) PVP-K 30 magnesium stearate and lactose. During initial characterization PXRD and dissolution analysis confirmed the presence of less crystallinity of aceclofenac in drug microparticles. IR spectrum has shown formation of hydrogen bonding in the solid dispersion of aceclofenac system correlated with the crystalline conversion of aceclofenac to amorphous form. Comparison study revealed that FLR-1:1, FLR-1:3; showed better dissolution due to increase in the surface area of drug proper dispersion and increase in the amorphicity of drug by adsorption on the surface of adsorbent. The results indicate that FLR can be used as a potential pharmaceutical excipient. The present study demonstrates high potential of solvent evaporation method for obtaining large surface area and amorphicity of drug. The present study demonstrates no significance difference in dissolution study between solid dispersion powder and dispersible tablets. Thus present study fulfills the objective of

preparation and evaluation of Aceclofenac loaded adsorbent microparticles and dispersible tablets.

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