



APPLICATION OF ACECLOFENAC SOLID DISPERSION TO TABLET FORMULATION AND MANUFACTURING USING CROSSPOVIDONE AND PVP-K 30 AS DISSOLUTION ENHANCING CARRIERS

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ABSTRACT

The objective of the present study is to develop solid dispersion tablet formulation of aceclofenac, a novel non steroidal anti inflammatory drug, mainly used for rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The major problem with this drug is its very low solubility in biological fluids, which results in poor bioavailability after oral administration. Therefore, solid dispersion of aceclofenac with crosspovidone and polyvinyl pyrrolidone K-30 were prepared with a view to increase its water solubility. Aceclofenac solid dispersion with crosspovidone showed maximum drug release and hence, the tablet formulation containing aceclofenac, crosspovidone and polyvinyl pyrrolidone K-30 solid dispersion, was prepared with a view to improve its water solubility. The dissolution profile of best laboratory developed formulation (F-III) was compared with marketed tablet product.

The drug release profile was studied in 2 % w/v sodium lauryl sulphate in distilled water. F-III gave far better dissolution than other laboratory developed formulations. The dissolution efficiency of F-III was compared with pure drug, conventional tablets. F-III showed maximum dissolution efficiency. F-III was considered better than the conventional tablet, as far as the cost of raw materials used in the product is concerned. F-I to F-IV were subjected to stability studies. The formulation was found to be stable for 30 days at 40° C ± RH 75 % as per ICH guidelines, with insignificant change in the hardness, disintegration time, and in vitro drug release pattern.

Key words : Aceclofenac, Crosspovidone, Polyvinyl pyrrolidone K-30, Solid dispersion tablets.

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INTRODUCTION

Aceclofenac is a new non-steroidal anti-inflammatory drug (NSAID), acting by inhibition of the synthesis of prostaglandins, by inhibiting the activity of the enzyme, cyclooxygenase -2 (COX-2). Aceclofenac is preferred over conventional NSAIDs, as the latter may lead to serious gastrointestinal complications such as peptic ulcer, severe bleeding and perforation, resulting in hospitalization and even death. It is mainly used for rheumatoid arthritis, osteoarthritis and ankylosing spondylitis¹⁻⁴. The drug is available in tablet form. Aceclofenac is practically insoluble in water, and peak blood level reaches between 2-3 hr after oral administration.

The rate and extent of dissolution of the drug from any solid dosage form, determines the rate and extent of absorption of the drug. In the case of poorly water-soluble drugs, dissolution is the rate limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/mL at 37°), due to erratic or incomplete absorption from GIT⁵. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates, and consequently, the bioavailability of poorly water-soluble drugs. A number of drugs have been shown to improve their dissolution character, when converted to solid dispersions⁶⁻⁸. To date, some reports on the formulation of these systems have appeared⁹⁻¹². Because of its poor aqueous solubility, aceclofenac may possess dissolution-related absorption problem. Hence, an attempt was made to improve the dissolution of aceclofenac through the formulation of tablets containing solid dispersion of aceclofenac and crospovidone and polyvinyl pyrrolidone K-30 (PVP K-30), used as dissolution enhancing agents¹³.

EXPERIMENTAL

Materials and methods

Materials

Crospovidone, polyvinyl pyrrolidone K-30 were purchased from Loba Chemie (Mumbai, India). Lactose was purchased from Cipla Pharma (Mumbai, India). Aceclofenac was a gift from Caplin Point Laboratories (Pondicherry, India). All the other chemicals used were of high analytical grade.

Methods

Preparation of solid dispersions of aceclofenac with carriers

Solid dispersions containing aceclofenac and carrier in the proportion of 2 %, 3 %, 4 %, and 5 % of crosspovidone and 10 % and 20 % PVP K-30, were prepared by solvent evaporation method. In this method, the solvents employed to dissolve polymers for preparing solid dispersions were methanol to get the clear polymer solution. To these solutions of polymers, weighed amounts of aceclofenac were added into boiling test tubes individually. The solvent was allowed to evaporate with adsorbent (10% Aerosil) at room temperature for 1 h, and then dried at 65°C for 6 h in a tray dryer. The mass obtained in each case was crushed, pulverized and shifted through mesh 80 mesh.

Formulation and preparation of tablets of aceclofenac solid dispersion

Different tablet formulations were prepared by direct compression technique (Formulations I-VI, Table 1).

Table 1. **Tablet formulations***

Ingredients (per tablets)	F-I	F-II	F-III	F-IV	F-V	F-VI
Acelofenac (mg)	100	100	100	100	100	100
Cross povidone (mg)	4	6	8	10	-	-
Polyvinyl pyrrolidone K-30 (mg)	-	-	-	-	20	40
Aerosil % (wt/wt)	qs (20)	qs (20)	qs (20)	qs (20)	qs (20)	qs (20)
Starch % (wt/wt)	20	20	20	20	20	20
Direct compressible lactose (% wt/wt)	74	72	70	68	58	28
Aerosol (%wt/wt)	1	1	1	1	1	1
Magnesium stearate (% wt/wt)	1	1	1	1	1	1

* qs indicates quantity sufficient.

All the powders were passed through ASTM (American society of testing and materials) 80 mesh. Starch, direct compressible lactose, aerosil and magnesium stearate were added as disintegrant, diluents, glidant and lubricant. All the ingredients were mixed intimately, and the mixture was compressed into tablets (220 mg weight) on a rotary tablet machine (Cadmach, Ahmedabad, India). Each tablet contained 100 mg of aceclofenac and other pharmaceutical ingredients as listed in Table 1. Prior to the compression, the solid dispersion granule were evaluated for angle of repose¹⁴ and Carr's Index¹⁵.

Evaluation of solid dispersion powder

Angle of repose

The angle of repose of powder was determined by the funnel method. An accurately weighed about 10 g of powder were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation⁴.

$$\tan \theta = h/r \quad \dots(1)$$

where h and r are the height and radius of the powder cone.

Compressibility index

The compressibility index of solid dispersion powder was determined by Carr's compressibility index¹⁵.

$$\text{Carr's Index (\%)} = [(TBD-LBD) \times 100/TBD] \quad \dots(2)$$

where LBD and TBD are weight of powder / volume of the packing and weight of powder / tapped volume of packing.

Drug content

An accurately weighed amount of solid dispersions equivalent to 100 mg of aceclofenac was dissolved in methanol and the solution was filtered through 0.45 μm membrane (Nune, New Delhi, India). Then it was diluted with methanol and the drug content was estimated by measuring absorbance at 275 nm in UV-visible spectrophotometer (Shimadzu, UV-1700).

Solubility studies

Pure aceclofenac (100 mg) was weighed and placed into each of the four conical flasks, having teflon lined screw caps, containing 50 mL of 0.5, 1.0, 1.5 and 2.0 % w/v sodium lauryl sulphate in water. Samples were placed on a shaker, agitated at 37 ° C, until equilibrium was achieved (48 h) and the aliquots were filtered through 0.45 µm Millipore filter. The filtered samples were diluted suitably and assayed spectrophotometrically at 275 nm.

Evaluation of tablets

Thickness

The thickness of the tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used, and average values were calculated.

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX - 100, Arrada, Colorado), and the test was performed according to the official method¹⁶.

Drug content

Twenty tablets were accurately weighed and finely powdered. The quantity of powder, equivalent to 100 mg of aceclofenac was extracted in methanol. The drug content was determined as described above.

Hardness and Friability

For each formulation, the hardness and friability of 10 tablets were determined using the Monsanto hardness tester (Cadmach, Ahemadabad, India) and Roche friabilator (Model Ef-2 Electrolab, Mumbai, India), respectively.

***in vitro* disintegration study**

One tablet was placed in each tube of disintegration apparatus (Model ED-2L, Electro lab, Mumbai, India) and the test was carried out using distilled water as a disintegrating media at $37 \pm 2^\circ\text{C}$ ¹⁶.

***in vitro* dissolution study of tablets**

in vitro dissolution study of the tablets were conducted using USP apparatus type II (Model TDT- 067, Electrolab, Mumbai, India) at 50 rpm using 2% w/v sodium lauryl sulphate in water as a dissolution media maintained at $37^{\circ} \pm 0.5^{\circ}\text{C}$. Samples were withdrawn at various time interval, filtered through a 0.45 micron membrane filter, diluted, assayed at 275 nm using a UV/visible double beam spectrophotometer. The release studies were conducted in triplicate.

Stability studies

In order to determine any change in *in vitro* drug release profile on storage, stability study was carried out at 45°C in a humidity chamber having 75 % RH as per ICH guidelines. The formulation F-I to F-IV were stored as per ICH guideline condition, and the formulations were withdrawn after 30 days, and evaluated for change in *in vitro* drug release pattern, hardness, and disintegration time.

RESULTS AND DISCUSSION

The solid dispersion powder of different formulations were evaluated for angle of repose, compressibility index and drug content (Table 2).

Table 2. Properties of the solid dispersion powder*

Tablets	Angle of repose	Compressibility index (%)	Drug content (%)
F - I	19.97 ± 0.06	13.74 ± 0.07	95.48 ± 0.02
F - II	23.22 ± 0.02	11.81 ± 0.02	96.16 ± 0.03
F - III	21.70 ± 0.02	12.10 ± 0.03	97.68 ± 0.02
F- IV	24.48 ± 0.07	13.41 ± 0.03	96.16 ± 0.04
F- V	21.05 ± 0.08	11.58 ± 0.04	96.49 ± 0.01
F - VI	24.18 ± 0.07	12.24 ± 0.04	95.70 ± 0.02

* All values are expressed as mean \pm SE, n = 3.

The results of angle of repose and compressibility index (%) ranged from 19.97 ± 0.06 , to 24.48 ± 0.07 and 11.58 ± 0.04 to 13.74 ± 0.07 , respectively. The drug content in weighed amount of powder of all the formulations ranged from 95.48 ± 0.02 to $97.68 \pm$

0.02%. Solubility of aceclofenac in purified water was $51.26 \pm 0.18 \mu\text{g} / \text{mL}$ where as in 2.0 % w/v sodium lauryl sulphate in water was $115.72 \pm 1.25 \mu\text{g} / \text{mL}$ (Table 3)

Table 3. Solubility of pure aceclofenac *

Solvents	Saturation solubility ($\mu\text{g} / \text{mL}$)
Purified water	51.26 ± 0.18
0.5 % w/v Sodium lauryl sulphate	53.68 ± 0.24
1.0 % w/v Sodium lauryl sulphate	75.68 ± 0.72
1.5 % w/v Sodium lauryl sulphate	85.14 ± 0.27
2.0 % w/v Sodium lauryl sulphate	115.72 ± 1.25

* All values are expressed as mean \pm SE, n = 3.

Table 4. Properties of the compressed tablets

Tablets	Thickness * (mm)	Deviation in weight variation test [†] (%)	Drug content* (%)	Hardness [‡] (Kg/cm ²)	Friability [‡] (%)
F - I	4.39 ± 0.01	1.819 ± 0.001	95.45 ± 0.015	3.1 ± 0.1	0.28 ± 0.005
F - II	4.58 ± 0.01	1.356 ± 0.005	96.18 ± 0.015	3.0 ± 0.05	0.47 ± 0.005
F - III	4.64 ± 0.005	0.908 ± 0.000	97.63 ± 0.015	4.1 ± 0.05	0.28 ± 0.005
F- IV	4.71 ± 0.005	3.179 ± 0.001	96.11 ± 0.01	4.1 ± 0.05	0.11 ± 0.005
F- V	4.70 ± 0.005	3.179 ± 0.001	96.47 ± 0.0115	4.1 ± 0.01	0.15 ± 0.005
F - VI	4.70 ± 0.15	0.908 ± 0.000	95.70 ± 0.01	3.1 ± 0.01	0.20 ± 0.005

* All values are expressed as mean \pm SE, n = 3

[†]All values are expressed as mean \pm SE, n = 20

[‡]All values are expressed as mean \pm SE, n = 10

The thickness of the tablets ranged from 4.39 ± 0.01 to 4.70 ± 0.015 mm. The

average percentage deviation of 20 tablets of each formula was less than $\pm 5\%$. Drug content was found to be uniform among different batches of the tablets and ranged from 95.45 ± 0.01 to 97.63 ± 0.01 . The hardness and percentage friability of the tablets of all the batches ranged from 3.0 ± 0.05 to 4.1 ± 0.05 kg/cm² and 0.11 ± 0.005 to $0.47 \pm 0.05\%$ respectively (Table 4).

The results of the dissolution studies of formulations with pure drug, F-I, F-II and F-III composed of crosspovidone and PVP K-30 in varying drug to carrier polymer ratio, are shown in Fig. 1.

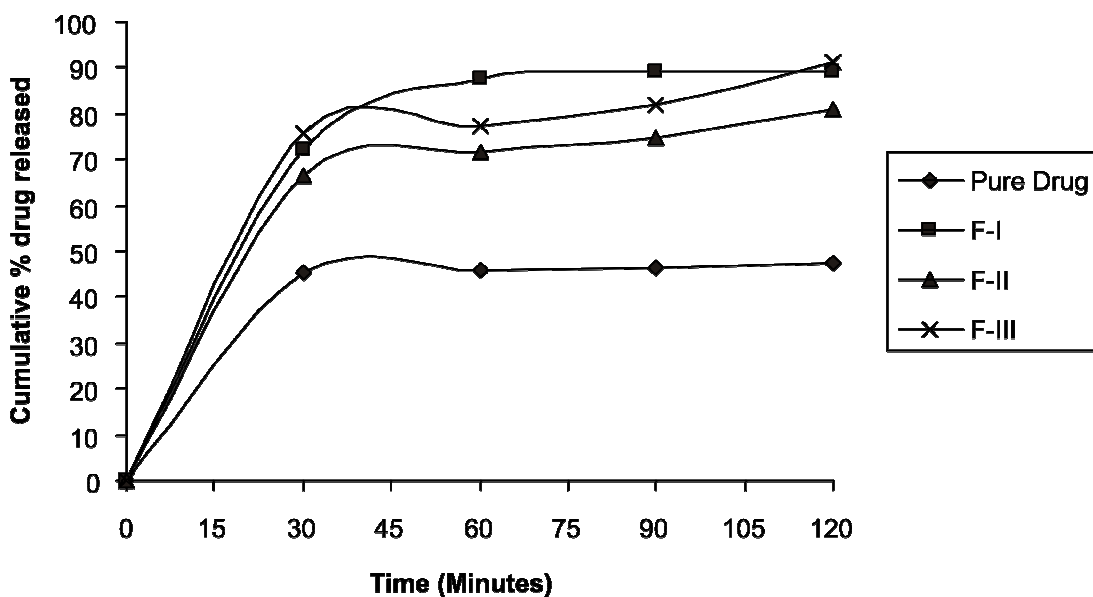


Fig. 1: The *in vitro* release profiles of aceclofenac from pure drug, F-I, F-II and F-III formulations. Each point represents. Mean \pm SE; n = 3.

Tablets with pure drug, F-I, F-II and F-III released 47.38%, 89.06%, 80.82% and 91.40% of aceclofenac at the end of 2 hours, respectively. The results of dissolution studies of formulations F-IV, F-V, F-VI and conventional tablet are shown in Fig. 2. It indicates that F-IV, F-V, F-VI and conventional tablet released 88.51%, 62.48%, 78.01% and 80.00% of aceclofenac at the end of 2 hours, respectively. The *in vitro* release profile on storage, stability study of F-I, F-II, F-III and F-IV was compared with conventional tablet. The values are shown in Table 5. It indicates that formulation F- III gave higher *in vitro* dissolution and no change in physical characteristics.

Table 5 . Results of stability study

Time (min)	Cumulative percentage released after storage at 40°C for 30 days			
	F - I	F - II	F - III	F-IV
0	0.00	0.00	0.00	0.00
30	68.48	58.91	70.48	52.18
60	70.60	67.12	75.08	64.52
90	74.18	70.46	79.98	72.64
120	80.40	72.34	90.08	78.48

Each values represents mean \pm SE: n = 3.

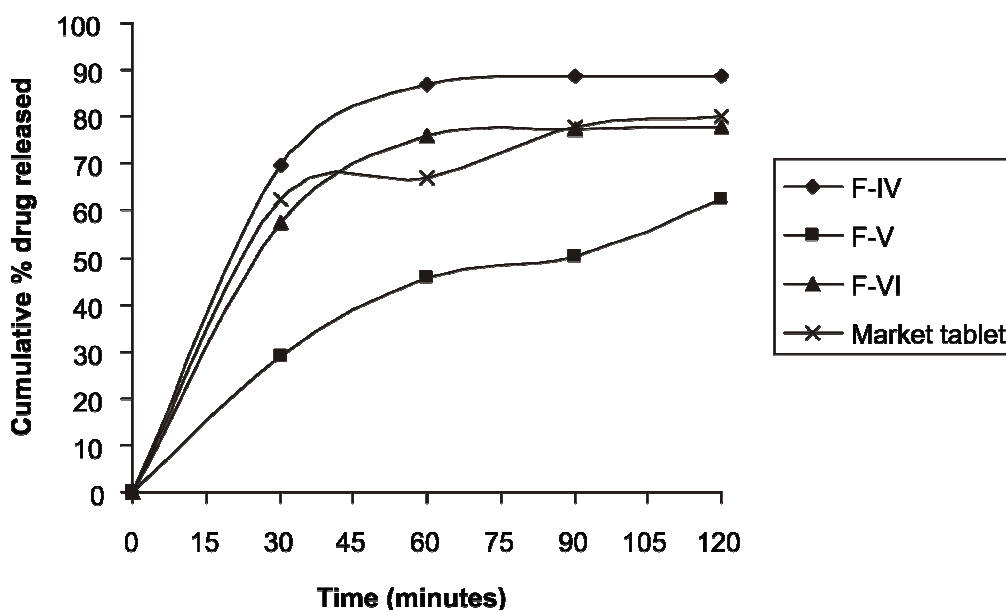


Fig. 2: The *in vitro* release profiles of aceclofenac from F-IV, F-V, F-VI and marketed tablet formulation. Each point represents. Mean \pm SE; n = 3.

Aceclofenac is a potent non-steroidal anti-inflammatory drug for the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The major problem with this drug is its very low solubility in biological fluids, which results in poor bioavailability after oral administration. In case of inflammatory diseases, successful treatment can be achieved by increasing solubility in biological fluids through solid dispersion tablet formulation. In

the present study, croscopolidone, and PVP K-30, which are commonly used dissolution enhancing carriers in solid dispersion systems, have been employed to formulate fast release tablets of aceclofenac.

The tablets were prepared according to the formula given in Table 1. Physical properties of mixtures such as specific surface area, shape, hardness, surface characteristics, and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous formulation¹⁷. The powder of different formulations were evaluated for angle of repose, compressibility index and drug content (Table 2). The results of angle of repose (< 25) indicate excellent flow properties of the powder. This was further supported by lower compressibility index values (Table 2). Generally, compressibility index values upto 15% result in good to excellent flow properties¹⁵.

The drug content in the weighed amount of powder of all formulations was found to be uniform. All these results indicate that the powder possessed satisfactory flow properties, compressibility and drug content. Solubility studies on sodium lauryl sulphate have shown to satisfy these needs. Based on these facts, dissolution of tablets were carried out in 2.0 % w/v sodium lauryl sulphate in water as dissolution medium.

The tablets of different formulations were subjected to various evaluation tests, such as thickness, diameter, uniformity of weight, drug content, hardness, friability, *in vitro* disintegration, *in vitro* dissolution and stability studies. All the formulations showed uniform thickness. In a weight variation test, the pharmacopoeial limit for the percentage deviation for tablets of more than 250 mg is $\pm 5\%$. The average percentage deviation of all tablet formulations was found to be within the limit, and hence, all formulations passed the test for uniformity of weight as per official requirements¹¹. Good uniformity in drug content was found among different batches of the tablets and percentage of drug content was more than 95 %. The formulation F-III, F-IV and F-V showed comparatively high hardness value of 4.1 Kg/cm². This could be due to the presence of more hydrophilic carriers of the tablet. The low hardness value observed with formulation F-I, F-II and F-VI may be due to the presence of low hydrophilic carriers, which generally decreases the hardness of tablets¹³. Tablet hardness is not an absolute indicator of strength¹⁷. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits¹⁷. The *in vitro* drug disintegration were studied in distilled water using disintegration apparatus. The results revealed that all the formulations have faster disintegration and disintegrated within three minutes. All the tablet formulations

showed acceptable pharmaco-technical properties and complied with the in-house specifications for weight variation, drug content, hardness, friability and *in vitro* disintegration.

The results of dissolution studies indicated that formulations with pure drug, F-I, F-II and F-III released 47.38%, 89.6%, 80.82% and 91.40% of aceclofenac at the end of 2 h respectively (Fig. 1). The results of dissolution studies of formulations F-IV, F-V, F-VI and conventional tablet, are shown in Fig. 2. Among these formulations, the release rate was increased in the following polymer order : F-III > F-I>F-II >F-IV> conventional tablet > pure drug. The carriers like crosspovidone and PVP K-30 have been well known as dissolution enhancing agent in aqueous media¹³. It is clear that the dissolution of aceclofenac has improved considerably from crosspovidone and PVP K-30 solid dispersion tablets as compared to conventional tablet. The reason for the poor dissolution of pure drug could be poor wettability, and/or agglomeration of particles.

From Fig. 1 and 2, it can be seen that dissolution of aceclofenac increases with increase in crosspovidone, upto 4% and in PVP K-30, with 10%. This increase in the dissolution rate may be due to improved wettability by dissolution enhancing carriers. At higher level, the negative effect on dissolution appears. That may be due to distortion of molecular dispersion structure, which leaves an insoluble base particle and increased accumulation of carrier molecule in the bulk, to cause saturation, by which further solubility of aceclofenac retarded.

In order to determine the change in *in vitro* release profile on storage, stability study of F-I, F-II, F-III and F-IV was carried out at 40° C for 30 days. Appreciable change in the physical characteristics and the release profile, was not observed at the end of 30 days. Stability study results were shown in Table 5, that the effect of storage is in significant at 5% level for F-III. Hardness, disintegration time, as well as *in vitro* release pattern of aceclofenac from F-III, were almost the same before and after storage for 30 days at 40°C.

CONCLUSION

The hydrophilic enhancing agent like crosspovidone and PVP K-30 alone could gave better release effectively within 2 h. It is evident from the results that a formulation F-III is a better system for fast dissolving of a poorly water soluble drug like aceclofenac.

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