Int. j. adv. multidisc. res. stud. 2024; 4(4):125-133

Received: 19-05-2024
Accepted: 29-06-2024

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Enhancing Aceclofenac Solubility and Dissolution with PVP K30 and β-Cyclodextrin

[1] Manju Singh, [2] Vijay Kumar

[1] Department of Pharmaceutics, Dr. KN Modi Institute of Pharmaceutical Education & Research, Modinagar, Utter Pradesh, India

[2] Department of Pharmaceutics, School of Pharmaceutical Education and Research (SPER), Jamia Hamdard, New Delhi, India

DOI: https://doi.org/10.62225/2583049X.2024.4.4.3012

Corresponding Author: **Manju Singh**

Abstract

Aceclofenac (AC) is a potent non-steroidal anti-inflammatory drug (NSAID) known for its anti-inflammatory, analgesic, and antipyretic properties. Its effectiveness is comparable to other NSAIDs, with a similar onset of action. As a Biopharmaceutical Classification System (BCS) Class II compound, the oral bioavailability of AC is limited by its dissolution rate in the gastrointestinal tract. Enhancing the dissolution rate of AC is crucial for improving its bioavailability and therapeutic efficacy. This study aimed to prepare and characterize solid dispersions of AC using a mixed excipient system of β-cyclodextrin and polyvinylpyrrolidone K30 (PVP K30) as carriers, and to examine their effect on the drug's dissolution rate. Solid dispersions were created via physical mixture and solvent evaporation methods using different ratios of AC to the excipient system. The formulations were evaluated for parameters such as practical yield, drug content, bulk and tapped density, Hausner's ratio, Carr's index, angle of repose, and *in vitro* drug release. The results showed a significant increase in drug release for the solid dispersions compared to the pure drug, with the solvent evaporation method proving more effective than the physical mixture method. Solid dispersion techniques offer numerous benefits by altering drug release characteristics, leading to faster drug release within the body. The study demonstrated that the solubility of poorly soluble drugs like AC can be significantly improved through solid dispersion methods. The use of water-soluble carriers such as PVP K30 and β-cyclodextrin effectively modified the drug release profiles. Solid dispersions of AC with PVP K30 were prepared in drug-to-carrier ratios of 1:1 to 1:5 using the solvent evaporation method, while inclusion complexes with β-cyclodextrin were prepared by the kneading method in similar ratios. The formulations were screened for yield, texture, color, physical characteristics, and suitability.

Keywords: Aceclofenac, Phase Diagram, Solvent Evaporation, Aqueous Solubility and Dissolution Rate

Introduction

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. More than 40% of new drug candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties. Over the years, tools of drug discovery have caused a perceptible shift in biopharmaceutical properties. Poorly water-soluble drugs involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bio-availability. Almost more than 90% drugs are orally administered [1, 2, 3]. Drug absorption sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium [1, 4, 5].

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include enhancing solubility and

dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly permeable drugs. Various methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction have been utilized to improve the dissolution properties of poorly water-soluble drugs. In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs [6, 7, 8].

The solubility and dissolution rates of Aceclofenac, a non-steroidal anti-inflammatory drug (NSAID) widely used for its analgesic and anti-inflammatory properties, are critical factors influencing its bioavailability and therapeutic efficacy. However, Aceclofenac poor water solubility often limits its clinical performance. To address this challenge, the use of solubility-enhancing agents such as Polyvinylpyrrolidone K-30 (PVP K-30) and beta-Cyclodextrin has been explored. These agents can form inclusion complexes and improve the drug's solubility and dissolution characteristics, thereby enhancing its absorption and therapeutic effectiveness. This study focuses on the formulation and evaluation of Aceclofenac using PVP K-30 and beta-Cyclodextrin to optimize its solubility and dissolution profile [9, 10, 11].

Methods

Reagents and chemicals

Aceclofenac was procured as a gift sample from Wockhardt Pharmaceuticals Ltd, Aurangabad, PVP K-30 purchased from Ponmani Chemicals, Coimbatore, β-Cyclodextrin purchased from Wokhhardt Pharmaceuticals, Ltd, Aurangabad, Ethanol purchased from Ponmani Chemicals, Coimbatore, Methanol purchased from Fisher Scientific India Pvt. Ltd, MTT {3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide} obtained from HR institute of pharmacy, Utter Pradesh, Sodium Hydroxide, Potassium Dihydrogen orthophosphate, and Disodium hydrogen orthophosphate purchased from Thomas Baker, New Delhi [11, 12].

Preformulation studies

Determination of the absorption maximum of Aceclofenac in ethanol

The absorption maximum of Aceclofenac was determined as per the standard protocol with some modification. In brief, the stock solution of Aceclofenac was prepared at the concentration of 1 mg/ml in methanol. Further, it was followed by serial dilution to get the concentration of Aceclofenac as 2, 4, 6, 8 and 10µg/ml, and then it proceeded to UV spectrophotometric analysis at the λmax of 275 nm. The measurement was taken in triplicate and obtained data were analyzed statistically [13, 14].

Determination of Solubility

Accurately weighed quantity (5, 10, 15, 20 and 25mg) of Aceclofenac was placed in screw capped bottles. Then freshly prepared distilled water was added (50ml) to each bottle and kept at 37^0C, with occasional stirring, for 24hrs. After 24hrs content of each bottle was filtered using whattman filter paper. The filtrate was diluted appropriately with buffer pH 1.2 and absorbance of the resultant solution was measured at 275nm and extrapolated on standard graph to determine the concentration solubilized [15, 16].

Screening of Carriers

Carriers used for study were, PVP K-30, and β-Cyclodextrin. The solid dispersion of PVP K30, were prepared by solvent evaporation method, and solid dispersion of β-Cyclodextrin was prepared by kneading method using ratio1:1 of Drug: Carrier were screened for yield, texture and color, physical characteristics and suitability in preparation [17].

Melting point determination

Melting point of Aceclofenac was determined by capillary method. A small amount of drug was placed in thin walled capillary tube, closed at one end. The capillary and thermometer were then inserted into melting point apparatus. The instrument was kept on and allowed to heat slowly and evenly. The temperature range, over which the sample was observed to melt, was taken as the melting point.

Bulk Density

Bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume. About 10 gm. of Aceclofenac was taken and poured into 50 ml measuring cylinder. The poured volume was measured. Bulk density was calculated from the formula:

Bulk density = Amount of drug taken / Poured volume

Tapped Density

The tapped density is an increased bulk density attained after mechanically tapping a container containing a powder sample. About 10 gm. of Aceclofenac was poured into 50 ml capacity measuring cylinder and the cylinder was mechanically tapped the mechanical tapping was achieved by raising the cylinder and allowing it to drop. The tapped density was calculated using the formula:

Tapped density = amount of Aceclofenac taken / tapped volume

Hausner's Ratio

The Hausner's ratio and Carr's index are both measures of the flow properties of powders. A Hausner's ratio of < 1.25 indicates a powder that is free flowing whereas > 1.25 indicates poor flow ability. Hausner's ratio can be determined by:

Hausner's ratio = tapped density / poured density

Carr's Index

The smaller the Carr's index the better the flow properties. For example, 5-15 indicates excellent; 12-16 good; 18-21 fair and > 23 poor flow.

Carr's index = tapped density-bulk density × 100 / tapped density

Formulation of Solid Dispersions

Preparation of PVP K30 solid dispersions

Solid dispersions of Aceclofenac with PVP K-30 were prepared by solvent evaporation method Accurately weighed quantity of Aceclofenac and PVP K-30 in

proportions of 1:1, 1:2, 1:3, 1:4 and 1:5 were mixed thoroughly and dissolved in minimum amount of ethanol. Then the solvent was evaporated completely on water bath with constant stirring. The resultant dry products were powdered and passed through sieve no.80 mesh [18, 19, 20].

Preparation of cyclodextrin inclusion complexes

Inclusion complexes of Aceclofenac with β-Cyclodextrin were prepared by kneading method Accurately weighed quantity of β-Cyclodextrin for the ratio, 1:1, 1:2, 1:3, 1:4 and 1:5, was taken in mortar and slurry was prepared by using distilled water, in this douch mass drug was added and kneaded for 1hr. The resulting product was dried for 2hrs at 60^0C and passed through sieve no. 80 mesh [19, 21].

Preparation of physical mixtures

The physical mixtures of Aceclofenac with all carriers i.e. PVP K-30, and β-Cyclodextrin, were prepared in various ratio, as like solid dispersions, by mixing Aceclofenac with carrier for 1hr in mortar and pestle. The resultant powders were dried at 60^0C and passed through sieve no. 80 mesh.

***In-Vitro* Release Studies**

Aceclofenac, equivalent to 25mg was filled in hard gelatin capsule from each formulation. The dissolution study was conducted in 900ml of simulated gastric fluid (1.2 pH acid buffer) using type-I **(LABINDIA, DISSO2000**) basket type dissolution apparatus. The temperature of dissolution medium was maintained at 37 ± 0.5 ^{0}C and stirring speed was 100 rpm. 5ml of sample solution was withdrawn at the time interval 10, 20, 30, 40, 50 and 60min. and filtered through whattman filter paper. The volume of the dissolution fluid was adjusted by replacing 5ml of dissolution medium after each sampling. The samples were diluted properly and the absorbance was measured at 275nm [22, 23].

Following samples were subjected to the *in-vitro* dissolution studies in simulated gastric fluid (pH 1.2 acid buffer).

Pure Aceclofenac

- Solid Dispersions of Aceclofenac with PVP K-30 in the following ratio (1:1, 1:2, 1:3, 1:4 and 1:5) of Drug: Carrier.
- Physical Mixtures of Aceclofenac with PVP K30 in the following ratio (1:1, 1:2, 1:3, 1:4 and 1:5) of Drug: Carrier.
- Inclusion complexes of Aceclofenac with β-Cyclodextrin in the following ratio (1:1, 1:2, 1:3, 1:4 and 1:5) of Drug: Carrier.
- Physical Mixtures of Aceclofenac with β-Cyclodextrin in the following ratio (1:1, 1:2, 1:3, 1:4 and 1:5) of Drug: Carrier.

Characterization of Solid Dispersions

Estimation of Drug Content

The drug content was estimated in all solid dispersions and physical mixtures prepared from various carriers as per the method described by Chowdary & Ramesh. Accurately weighed 50mg equivalent of Aceclofenac solid dispersions and physical mixtures were transferred to 50ml volumetric flask and was extracted with ethanol suitably and the amount of Aceclofenac was determined by spectrophotometrically at 275nm [24, 25].

Particle Size Analysis

An ordinary compound microscope was used for this purpose. The ordinary microscope is used for the measurement of particle size in the range of 0.2 to 100 μm. Test material, diluted or undiluted is mounted on a slide and placed on a mechanical stage. The eyepiece of the microscope is fitted with a micrometer, using which the sizes of particles are determined. Eyepiece micrometer should be calibrated using a standard stage micrometer. In this, one millimeter is divided into 100 equal divisions and hence, each division is equal to 10 μm. The eyepiece micrometer, which is linear, consists of 100 divisions. Calibration is undertaken to find out the measure of each division [26, 27].

Procedure

A small amount of prepared solid dispersions and physical mixtures were diluted with petroleum ether. A few drops of this suspension were transferred onto a glass slide and focused in a microscope. The number of division of eyepiece micrometer determined the diameters of 300 particles randomly. This is then converted into microns and then average particle size was determined [28].

Powder X-Ray Diffractrometry

X-ray powder diffraction patterns were recorded on *X' Pert Pro- PANALYTICAL* diffractrometer. The scanning was employed over a 2θ range of 5-900 at normal resolution. The initial value of omega was 2.50. X-ray have been used in crystal structure studies in two different ways (1) single crystal X-ray crystallography dealing with the determination of bond angles and interatomic distances, and (2) powder X-ray diffraction dealing with the study of crystal lattice parameters, where the X-ray diffraction intensity from a sample is measured as a function of the diffraction angles. Thus, changes in the diffraction pattern indicate changes in crystal structure. The relationship between the wavelength(λ) of the X-ray, the angle of diffraction and the distance between each set of atomic planes of crystal lattice (*d*) is given by Bragg's equation [29].

$$M\lambda = 2d\sin\theta$$

Where,

M represents the order of diffraction.

X-ray diffraction spectra of simple eutectic systems show peaks of each crystalline component. Any change in the crystal lattice parameter will displace the diffraction peaks; Solid solutions exhibit a gradual shift in the positions of the diffraction lines with changes in composition. The lattice parameters of complexes are markedly different from those of pure components. Hence, the X-ray diffraction method can also be used in detecting complex formation. However its major drawback has been the inability to differentiate between amorphous precipitation and molecular dispersion of the lattice parameter of the solvent component is unchanged. The techniques have been frequently used by researchers to characterize solid dispersions [29, 30, 31].

Scanning Electron Microscopy

The optimized batches were evaluated for morphology using scanning electron microscopy. A minute amount of sample

was gold coated with the help of sputter coating and then viewed on ZEISS's Smart SEM EVO 40 [32].

Stability Studies

To evaluate the stability of the drug, Aceclofenac, and the effect of carriers on drug after storing at different temperature for 30 days the stability studies were carried out.

About 100mg equivalent of Aceclofenac formulations were taken in well closed containers from ideal batches and stored separately at 4^0C in freeze, at room temperature and at 60^0C hot air oven. From these, sample equivalent to 20mg of Aceclofenac was removed at the interval of 10, 20 and 30 days and analyzed the drug content by spectrophotometrically at 275 nm [33, 34].

Result and Disscussion

Preformulation study of drug

Determination of the absorption maximum of Aceclofenac in ethanol

The potential drug absorption was calculated as per standard protocol through the absorption maximum of Aceclofenac at 275 nm λmax against the concentration 2-10 µg/ml. The regression equation and coefficient were found to be 0.0272x - 0.0035 and 0.999 respectively. The associated aim to determine the Luliconazole absorption maxima and method validation is for qualitative and quantitative analysis.

Table 1: Absorption maxima of aceclofenac and regression coefficient against the different concentration of aceclofenac (µg/ml)

S. No	Concentration (µg/ml)	Absorbance
1	2	0.05
2	4	0.105
3	6	0.163
4	8	0.21
5	10	0.269

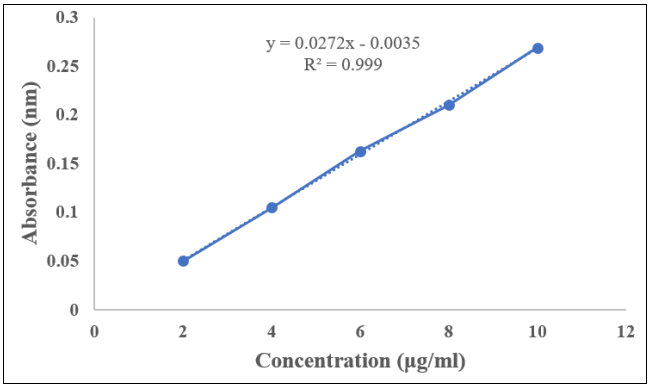

Fig 1: Absorption maxima of aceclofenac and regression coefficient against the different concentration of aceclofenac (µg/ml)

Determination of Solubility

Table No-2 shows the solubility profiles of Aceclofenac in pH 6.8 phosphate buffer influenced by carrier material concentration at room temperature. Solubility of Aceclofenac was determined at 37ºC in distilled water. The results are shows in table 2 was noted that solubility of Aceclofenac in water, calculated form the average of five determinations was 0.334 mg/ml.

Table 2: Solubility analysis of aceclofenac

	Amount of drug use				
	5 mg	10 mg	15 mg	20 mg	25 mg
Amount of drug dissolved (mg/ml)	0.3	0.31	0.35	0.35	0.36

Screening of Carriers

For the screening study, the carriers PEG 6000, PEG 4000, PVP K-30, HPMC, HPC, UREA and β-Cyclodextrin were used to prepare solid dispersions of Aceclofenac, only PVP K-30, β-Cyclodextrin were used to prepare solid dispersions. The observations of the screening study are shown in table 3. From these screening studies, it was possible to prepare the solid dispersion system of Aceclofenac by solvent evaporation method with PVP K-30, by kneading method with β-Cyclodextrin and by fusion method with Urea.

Table 3: Screening of carriers (Drug: Polymer = 20:20 mg)

Carrier	Miscible/ immiscible	Discoloration	Final texture	Final color	Yield
PVP K-30	Miscible	--	Crystalline solid	Pale Yellow	34 mg
β-CD	Miscible	--	Soft and fine	White	36 mg

Effect of Carriers on Solubility of Aceclofenac

To find out the effect of carriers on solubility of pure drug, solubility study was carried out using a 1:1 solid dispersion of drug and carrier in distilled water. The results are shown in Table-4.

Table 4: Effect of carriers on solubility of Aceclofenac

Composition	Solubility (mg / ml)
Aceclofenac	0.334
Aceclofenac + PVP K-30 (1:1)	1.28
Aceclofenac + β-Cyclodextrin (1:1)	1.32

From the above study, it was concluded that the solubility of the drug was increased with the use of different carriers. In this study, β-Cyclodextrin has shown highest effect on the solubility of Aceclofenac.

Melting point determination

Melting point of pure Aceclofenac was determined by the capillary tube method. The result was observed to be 152 ^{0}C.

Table 5: Melting point determination of Aceclofenac

Actual melting point	Observed melting point
149^0C-153^0C	152^0C

Bulk density

Bulk density of pure Aceclofenac was determined by graduated cylinder method and it was found to be 0.72 g/cm^3.

Table 6: Bulk density determination of Aceclofenac

Amount of drug taken (gm)	Bulk volume (cm^3)	Bulk Density (g/cm^3)
10 gm	14	0.72 g/cm^3.

Tapped density

The tapped density of pure Aceclofenac was found to be 0.79 g/cm3.

Table 7: Tapped density determination of Aceclofenac

Amount of drug taken (gm)	Tapped volume (cm^3)	Tapped density (g/cm^3)
10 gm	13	0.79 g/cm3

Hausner's ratio

Hausner's ratio value for pure Aceclofenac was found to be 1.075 which indicates towards the poor flowability of Aceclofenac. Actually, a Hausner's ratio value < 1.25 indicates powder that is free flowing.

Carr's index

The value of Carr's index was found to be 9.19 (< 23) which also indicates towards the excellent flowability of the drug.

***In-Vitro* Release Studies**

In vitro drug release and kinetics study Statistical models are commonly used to forecast the release mechanism and compare the release profile. The *in-vitro* release profile of the drug was performed in a prepared buffer system using the dialysis bag technique for 60 min. The desolvation percentages of acelcofenac from PVP K-30 and Cyclodextrin are increased in the proportion of time as illustrated in Figure 2 and Table 8 [35, 36].

Table 8: Percentage drug release profile of aceclofenac

Time (min)	Cumulative drug % Release
0	0
10	2.17
20	4.25
30	6.98
40	8.65
50	11.65
60	16.32

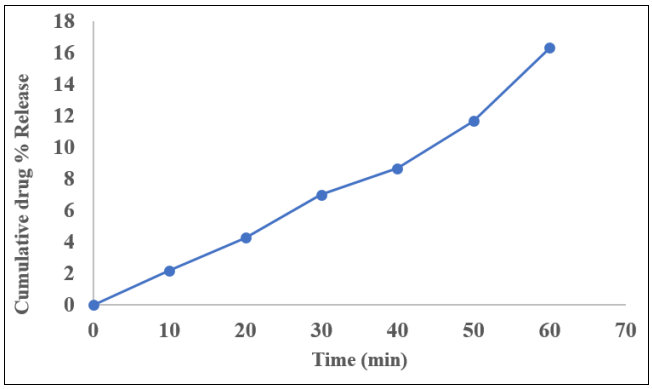

Fig 2: *In-vitro* drug release profile of aceclofenac

The ultimate aim of this work was to develop a suitable formulation for Aceclofenac, which can dissolve maximum amount of drug in 1 hour. Hence, different batches of solid dispersions were studied for *in-vitro* dissolution. The results are shown in Tables 9, 10, 11, 12 the results are also plotted in the form of % drug release vs. time as shown in Figures 3, 4, 5, 6 respectively.

Table 9: *In-vitro* drug release of aceclofenac solid dispersions with PVP k30

Time	% Release of Aceclofenac				
(min)	1:1	1:2	1:3	1:4	1:5
0	0	0	0	0	0
10	9.26±0.12	10.81±0.67	11.97±0.56	13.50±0.54	14.74±0.78
20	11.29±0.23	14.99±0.43	17.27±0.76	25.52±0.22	28.90±0.45
30	19.91±0.31	22.60±0.87	26.10±0.78	33.26±0.19	40.46±0.39
40	27.10±0.21	34.30±0.78	41.56±0.87	48.31±0.67	52.62±0.89
50	33.18±0.27	42.85±0.56	51.23±0.64	58.11±0.44	62.67±0.86
60	41.42±0.54	53.65±0.67	62.14±0.76	69.12±0.47	73.46±0.75

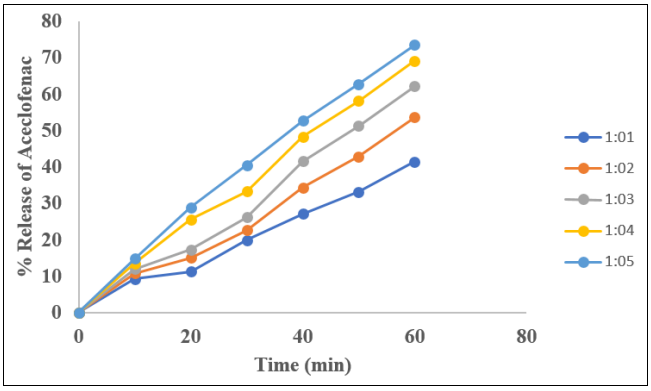

Fig 3: *In-vitro* release profile of aceclofenac solid dispersions with PVP k-30

Table 10: *In-vitro* drug release of aceclofenac physical mixtures with PVP k30

Time	% Release of Aceclofenac				
(min)	1:1	1:2	1:3	1:4	1:5
0	0	0	0	0	0
10	5.21±0.78	6.18±0.76	9.31±0.12	10.42±0.29	11.65±0.66
20	9.36±0.54	10.17±0.20	11.97±0.09	13.52±0.65	14.75±0.70
30	11.44±0.89	14.14±0.56	17.21±0.67	25.26±0.42	28.72±0.54
40	19.26±0.32	22.75±0.50	26.48±0.56	33.50±0.69	40.46±0.80
50	27.40±0.90	34.30±0.63	41.26±0.87	48.30±0.42	52.61±0.38
60	33.81±0.76	42.71±0.54	51.58±0.35	58.90±0.57	62.67±0.67

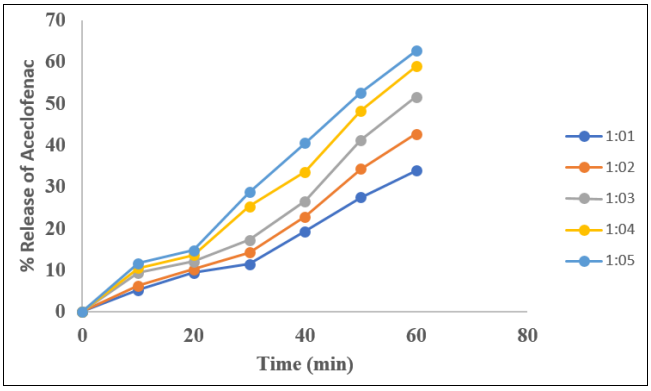

Fig 4: *In-vitro* drug release of aceclofenac physical mixtures with PVP k30

Table 11: *In-vitro* drug release of aceclofenac solid dispersions with β-Cyclodextrin

Time	% Release of Aceclofenac				
(min)	1:1	1:2	1:3	1:4	1:5
0	0	0	0	0	0
10	9.83±0.56	10.88±0.97	11.11±0.25	12.70±0.71	13.81±0.87
20	13.10±0.99	16.60±1.15	18.00±0.96	18.50±0.98	19.70±0.78
30	18.50±0.83	22.70±0.65	24.20±0.82	23.10±0.84	26.19±1.27
40	29.50±0.67	33.30±0.75	35.20±0.58	35.29±0.61	39.55±0.86
50	36.30±0.88	41.60±0.79	44.00±0.53	47.30±0.55	52.86±0.67
60	39.10±1.03	52.61±0.86	58.62±0.69	62.00±0.58	65.92±0.69

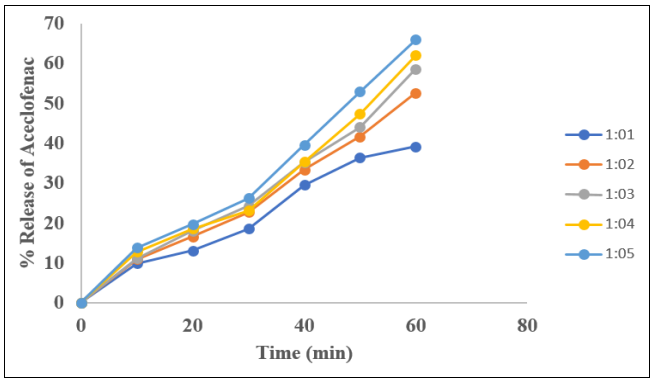

Fig 5: *In-vitro* release profile of aceclofenac solid dispersions with β-Cyclodextrin

Table 12: *In-vitro* drug release of aceclofenac physical mixtures with β- Cyclodextrin

Time (min)	% Release of Aceclofenac				
	1:1	1:2	1:3	1:4	1:5
0	0	0	0	0	0
10	12.45±0.98	13.50±1.31	14.60±0.91	17.00±0.51	20.90±1.29
20	19.27±1.07	19.60±0.59	20.41±0.78	22.66±0.59	25.23±0.53
30	26.89±0.56	27.40±0.89	28.00±1.02	30.90±0.81	35.34±0.39
40	34.28±0.67	36.52±1.67	39.12±0.79	43.51±1.05	48.25±0.69
50	42.81±1.23	46.50±1.09	49.61±1.12	56.00±1.13	61.30±1.06
60	45.68±0.43	55.69±0.27	61.98±0.69	68.25±0.63	71.20±1.09

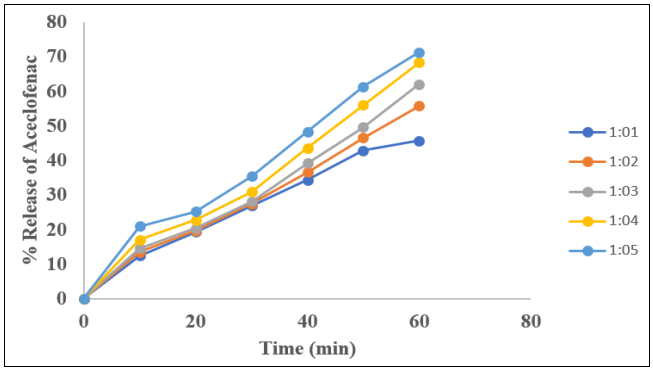

Fig 6: *In-vitro* release profile of aceclofenac physical mixtures with β-Cyclodextrin

In the batches of solid dispersions prepared with PVP K-30, the maximum dissolution of Aceclofenac, at the end of 1 hour, was observed with 1:5 combination of solid dispersion. At the end of 1 hour, this combination was able to release 73.46% of drug. The least dissolution of Aceclofenac was observed with 1:1 combination, which was able to release only 41.42% of Aceclofenac. Whereas, the other combinations have released only 53 to 69 % of drug after 1hr. In the batches of physical mixtures prepared with PVP K-30, the maximum dissolution of Aceclofenac, at the end of 1 hour, was observed with 1:5 combination of physical mixture. At the end of 1 hour, this combination was able to release 62.67% of drug. The least dissolution of Aceclofenac was observed with 1:1 combination, which was able to release only 33.18% of Aceclofenac. Whereas, the other combinations could release only 42-58% of drug after 1 hr.

Solid dispersion prepared by solvent evaporation method showed more release than physical mixtures of Aceclofenac with PVP K-30.

In both the cases, solid dispersion and physical mixtures, a linear relationship between the percentage of drug released and concentration of carrier. The dissolution was increased with increase in concentration of PVP K-30 as shown in Table no 9 and 10 and respective graphs are plotted in Figure no 3 and 4.

In the batches of solid dispersions prepared with β-Cyclodextrin by kneading method, the maximum dissolution of Aceclofenac at the end of 1 hour was achieved with 1:5 combination of solid dispersion. At the end of 1 hour, this combination was able to dissolve 65.92% of drug. The least dissolution of Aceclofenac was observed with 1:1 combination, which was able to release only 39.10% of Aceclofenac. Whereas, the other combinations has released only 52 to 62 % of drug after 1hr.

In the batches of physical mixtures prepared with β-Cyclodextrin, the maximum dissolution of Aceclofenac at the end of 1 hour was observed with β-Cyclodextrin of physical mixture in ratio of 1:5. At the end of 1 hour, this combination released 71.20% of drug. The least dissolution of Aceclofenac was observed with 1:1 combination, which was able to release only 33.18% of Aceclofenac. Whereas, the other combinations could release only 42-58% of drug after 1 hr.

Here the physical mixture of Aceclofenac with β -Cyclodextrin showed comparatively more dissolution than the inclusion complex prepared by kneading method.

In the both cases, solid dispersion and physical mixtures, a linear relationship between the percentage of drug released and concentration of carrier. The dissolution was increased with increase in concentration of β -Cyclodextrin as shown in Table no 11 and 12 and respective graphs are plotted in Figure no 5 and 6. In the both cases, solid dispersion and physical mixtures, a linear relationship between the percentage of drug released and concentration of carrier. The dissolution of respective graphs are plotted in Figure no 2.

Comparison of dissolution of pure drug with solid dispersions

At the end of 60 minutes, the pure drug showed only 16.32% dissolution, (Table no 8, Figure-2) whereas, the solid dispersions and physical mixtures have achieved release up to 73.46% and 62.67% (with PVP K30), 65.92% and 71.20% (with B-Cyclodextrin). Hence, the solid dispersions showed a marked increase in the dissolution of drug. It was observed that solid dispersions of drug with PVP K30 showed highest dissolution followed by B-Cyclodextrin the physical mixtures also improved the dissolution of Aceclofenac but in case of β-Cyclodextrin, more release than solid dispersion which is not case with PVP.

Characterization

Estimation of Drug Content

All the solid dispersions and physical mixtures were extracted with ethanol and the extract was suitably diluted with acid buffer 1.2 pH. The Aceclofenac content was estimated spectrophotometrically at 275nm. The results are presented in Table no 13 & 6.14. The results showed that the percentage of Aceclofenac was ranging from 96-98% in all formulation. This reveals that the drug, in all dispersed and confirms homogeneous mixing of drug and carriers. However slight variation of percentage of Aceclofenac may be due to the physical loss of drug and instrumental or handling error [37].

Table 13: Estimation of aceclofenac in solid dispersions

S. No	Drug: Carrier ratio	% Aceclofenac
1	1:1 PVP K 30	96.2
2	1:2 PVP K 30	96.1
3	1:3 PVP K 30	97.1
4	1:4 PVP K 30	97.8
5	1:5 PVP K 30	97.5
6	1:1 β- Cyclodextrin	94.2
7	1:2 β- Cyclodextrin	96.1
8	1:3 β- Cyclodextrin	97.2
9	1:4 β- Cyclodextrin	98.4
10	1:5 β- Cyclodextrin	98.94

Table 14: Estimation of aceclofenac in physical mixtures

S. No	Drug: Carrier ratio	% Aceclofenac
1	1:1 PVP K 30	96.7
2	1:2 PVP K 30	97.5
3	1:3 PVP K 30	97.2
4	1:4 PVP K 30	97.9
5	1:5 PVP K 30	97.5
6	1:1 β- Cyclodextrin	98.2
7	1:2 β- Cyclodextrin	97.5
8	1:3 β- Cyclodextrin	96.3
9	1:4 β- Cyclodextrin	97.1
10	1:5 β- Cyclodextrin	98.2

Particle Size Analysis

Particle size of best releasing formulations were analyzed by using compound microscope the results are tabulated in Table no. 15:

Table 15: Particle size of ideal batches of solid dispersions and physical mixtures

Formulation		Average particle size (□)
Drug +PVP K30 (1:5)	SD	165.46
	PM	170.1
Drug +β-Cyclodextrin (1:5)	SD	167.64
	PM	185.36

Powder X-Ray Diffractrometry

One of the most useful parameters for the characterization of a crystalline polymer is its degree of crystallinity (C.I.).Various methods have been developed for the determination of the crystallanity of polymers, one of which is x-ray diffraction analysis. Powder X-ray diffraction as a consequence of the importance of solid drug substance characterization, analytical tools such as X-ray diffractometry are usually employed in the pharmaceutical PXRD diffractograms of pure drug, carriers and various SD systems were investigated in figure 7. The incorporation of different carriers with AC showed a great impact on AC characteristic peaks.

The X ray diffraction of ACF, inclusion complex with β-CD, and solid dispersions with PVP K30, The diffraction pattern of pure AC was indicated by numerous peaks. Several peaks at 8.75°, 11.5°, 16.75°, 17.5°, 18°, 18.5°, 19.5°, 21.75°, 22°, 24°, 26°, 26.5°, 32°, 33° and 37.5° were noticeable and the main peak at 26° was particularly distinctive. It is known that the lack SD systems reveals the high concentration in the solid state. Moreover, a large reduction in characteristic peaks indicates an amorphous state. Nevertheless; the spectrum of SD of PVP K30 were characterized by the complete absence of any diffraction peak which is characteristic of an amorphous compound [38, 39, 40].

Hence, increased dissolution of the drug was observed since an amorphous form will dissolve at the faster rate owing to its higher internal energy and thermodynamic properties relative to crystalline materials (Goddeeris *et al*, 2008).

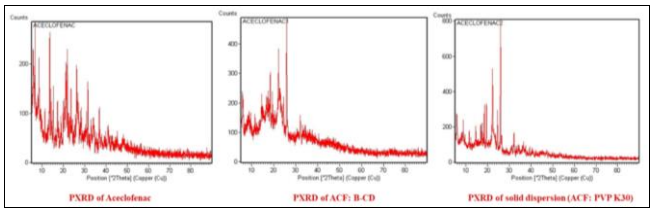

Fig 7: PXRD analysis of aceclofenac and excipients

Scanning Electron Microscopy

SEM images of ACF, inclusion complex with β-CD and solid dispersions of PVP K30, were shown in. Pure drug consisted of mixture of amorphous particles (14 to 43 μm). Results of pure drug shows the particles are irregular in shape (figure 8). The morphology of particles indicates that they are amorphous in nature. The morphology of solid dispersion with PVP K30 indicates the reduction in particle size and hence results in a mass or reduced agglomeration of drug and carrier molecules. Particle size in all images is irregular but when compared with pure drug, the particle size was found to be smaller. All the carriers used for formulation of solid dispersions were found to increase the solubility of Aceclofenac significantly. Among these carriers, PVP K-30 was found to possess highest solubilizing character and dissolution following to that β-Cyclodextrin was possessing high dissolution in physical mixture. When dissolution rate of pure drug was compared with that of various solid dispersions and physical mixtures at different ratio, all the polymers showed significant increase in the rate of dissolution in both solid dispersions and physical mixtures. The study further revealed that PVP K-30 was found to be a better polymer to be used in the solid dispersions of Aceclofenac [41, 42].

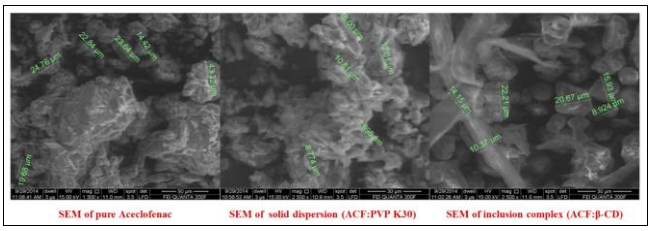

Fig 8: SEM analysis of aceclofenac and excipients

Stability Studies

Formulations were stored at 4^0C in freeze, room temperature and at 60^0C in hot air oven. After 30 days of storage, the formulations were observed physically and no color change and hardness was perceptible. The content of Aceclofenac in all formulations at various intervals of 10, 20 and 30 days was calculated. The result proved that the percentage of Aceclofenac was not less than 4-6 % in all the formulations after storing different temperatures, as shown in Table no 16. It reveals that there was no degradation of Aceclofenac in all formulations when stored under room and freeze temperature but at elevated temperature, the little degradation was found [43, 44].

Table 16: Stability study of aceclofenac

Formulation	Temperature (^{0}C)	% of Aceclofenac			
		0 days	10 days	20 days	30 days
Pure Aceclofenac	4	98.98	98.97	98.96	98.96
	Room temp	98.98	98.98	98.98	98.98
	60	98.98	97.15	96.45	95.29
ACE:PVP (1:5)	4	97.5	975	975	975
Solid dispersion	Room temp	97.5	975	974	971
	60	97.5	96.42	94.2	93.32
ACE:PVP (1:5)	4	97.5	97.83	97.83	97.83
Physical mixture	Room temp	97.5	97.5	97.5	97.5
	60	97.83	95.5	94.3	91.21
96.00β-CD (1:5)	4	98.94	98.94	98.94	96.01
Solid dispersion	Room temp	98.94	98.94	98.94	98.94
	60	98.94	98.72	97.21	96.1
ACE: β-CD (1:5)	4	98.2	98	98	98
Physical mixture	Room temp	98.2	98.2	98.2	98.2
	60	98.2	97.32	96.32	94.98

Conclusion

The solubility and dissolution rate of Aceclofenac were significantly enhanced by employing PVP K30 and beta-Cyclodextrin as carriers. These excipients function synergistically to improve the drug's aqueous solubility, thereby enhancing its bioavailability. PVP K30, a hydrophilic polymer, acts as a solubilizing agent, increasing the wettability and dispersibility of Aceclofenac. Beta-Cyclodextrin, a cyclic oligosaccharide, forms inclusion complexes with Aceclofenac, further augmenting its solubility. The combined use of these carriers results in a substantial improvement in the dissolution profile of Aceclofenac, making it a promising approach for enhancing the therapeutic efficacy of this anti-inflammatory drug.

References

1. Dr. Senthilkumar KL, Sirisha Y. Enhancement of Dissolution Rate Studies on Solid Dispersion of Aceclofenac. Ijpbs. 2011; 2(2).
2. Natarajan R, Komala G, Ramcy Swathi Polineni TR, Mohan S. Dissolution Enhancement of Aceclofenac Solid Dispersion Prepared With Hydrophilic Carriers By Solvent Evaporation Method. IJRPC. 2014; 4(1):83-89.
3. Himansu Bhusan Samal, Jitendra Debata, Naveen Kumar N, Sneha S, Pratap Kumar Patra. Solubility and Dissolution Improvement of Aceclofenac using _Cyclodextrin. International Journal of Drug Development & Research. 2012; 4(4). ISSN 0975-9344
4. Şeyda Akkuş Arslan, Figen Tirnaksiz. A Nonsteroidal Antiinflammatory Drug: Aceclofenac. Fabad J. Pharm. Sci. 2010; 35:105-118.
5. Mohomad J Habib. Pharmaceutical Solid Dispersion Technology. Technomic Publishing Company, pg. no. 1, 7,14,27,28, 65, 70, 72-74, 87-93.
6. Martin A. Physical Pharmacy, 3rd edition Lea and Febiger, Philadelphia, 1983, 313, 408.
7. Lachman L, Lieberman HA, Kiang JL. Theory and Practice of Industrial Pharmaceutics, Second edition, lea Febiger, Philadelphia, 1976, 99-104.
8. Martindale. The Extrapharmacopoeia: Third edition, Royal pharmaceutical society London, 1996, 2,3,13.
9. Bramankar DM, Sunil B Jaiswal, Biopharmaceutics and Pharmacokinetics A treatise, 1977, 25, 18-40, 297302.
10. Gopalrao M, Suneetha R. Indian Journal of Pharma. Sci, 2005, 26-29.
11. Soniwala MM, Patel PR. Indian Journal of Pharma. Sci, 2005, 61-65.
12. Choudhary KPR, Shaikh Srinivasa. Indian Journal of Pharma. Sci, 2001, 438-444.
13. Khadilkar M, Avari j, Gudsookar VR. Eastern pharmacist, 1997, 129.
14. Choudhary KPR, Hymin R. Indian Journal of Pharma. Sci, 2001, 150-153.
15. Nagarsenker MS, Musale JM. Indian Journal of Pharmaceutical Sciences, 1997, 34-42.
16. Choudhary KPR, Kamalkara G. Indian Journal of Pharma. Sci, 2002, 142-145.
17. Kusum Devi V, Vijayalaxmi P. Indian Journal of Pharma. Sci, 2003, 542-545.
18. Neelam Seedher. American Association of Pharmaceutical Sciences. 2003; 33:185-194.
19. Taneja LN, Khopade AJ, Jain NK. Indian Drugs. 1997; 34(2):72.
20. Furquan Nazimuddin Khan, Mohamed Hassan G. Dehghan Enhanced Bioavailability and Dissolution of Aceclofenac Calcium from Floating Microcapsules Using Minimum Additives sci pharm. 2012; 80:215-228.
21. Gehan Balata, Mahmoud Mahdi, Rania Abu Bakera. Improvement of Solubility and Dissolution Properties of Ketoconazole by Solid Dispersions and Inclusion Complexes. Asian Journal of Pharmaceutical Sciences. 2010; 5(1):1-12.
22. Gurjer M, Patidar A, Agrawal S, Maheshwari R. Analytical application of hydrotropic solubilization in spectrophotometric determination of naproxen in tablet dosage form. IJPBA. 2011; 2(5).
23. Halle Pradeep D, Sakhare Ram S, Dadage Ketan K, Birajdar Ganesh O, Raut Deepika B, Manasa Gangotri Peddi. Novel Drug Delivery System: Liquid Solid Compacts. J Mol Pharm Org Process Res. 2013; 1:3.
24. International Journal of Health Research Peer-Reviewed Online Journal. http://www.ijhr.org.
25. Kausalya J, Suresh K, Padmapriya S, Anusha Rupenagunta, Senthilnathan B. Solubility And Dissolution Enhancement Profile of Telmisartan Using Various Techniques. IJPRIF. 2011; 3(3):1737-1749.
26. Jitendra T Lalwani, Vaishali T Thakkar, Harsha V Patel. Enhancement of Solubility and Oral Bioavailability of Ezetimibe by a Novel Solid Self Nano Emulsifying Drug Delivery System (SNEDDS). int j pharm pharm sci. vol 5, issue 3, 513-522.
27. Jonathan Evans, Brian Scherzer, James Hitt, Gary Kupperblatt, Shakil Saghir, Edmund Elder. Enhanced Dissolution of Poorly Water Soluble Model Drugs Utilizing a Novel Spray Freezing into Liquid (SFL) and Atmospheric Freeze Drying (ATMFD) Technology. The Dow Chemical Company Midland, Mi 48674, Usa.
28. Kanika Sarpal, Yogesh B Pawar, Arvind K Bansal. Self Emulsifying Drug Delivery System: A Strategy to Improve Oral Bioavailability. Crips. 2010; 11(3).
29. Kavita Sapraa, Ashu Saprab, Singha SK, Saloni Kakkarb. Self Emulsifying Drug Delivery System: A Tool in Solubility Enhancement of Poorly Soluble Drugs. Indo Global Journal of Pharmaceutical Sciences. 2012; 2(3):313-332.

30. Kokare CR, Kumbhar SA, Archana Patil. Formulation and Evaluation of Self-Emulsifying Drug Delivery System of Carbamazepine. Ind J Pharm Edu Res. 2013; 47(2).
31. Komal R Parmar, Sunny R Shah, Navin R Sheth. Studies in Dissolution Enhancement of Ezetimibe by Solid Dispersions in Combination with a Surface Adsorbent. Dissolution Technologies, August, 2011.
32. Sunitha Reddy M, Srinivas Goud P, Apte SS. Solubility Enhancement of Candesartan Cilexetil by Self Emulsifying Drug Delivery Systems. IJPSR. 2012; 3(7):2098-2104.
33. Pawar Anil R, Choudhary Pravin D. Novel Techniques for Solubility, Dissolution Rate and Bioavailability Enhancement of Class Ii and Iv Drugs. Asian Journal of Biomedical and Pharmaceutical Sciences. 2012; 2(13):9-14.
34. Puckhraj Chhaprel, Amit Talesara, Amit K Jain. Solubility Enhancement of Poorly Water-Soluble Drug Using Spray Drying Technique. International Journal of Pharmaceutical studies and research. 2012; 3(2), 01-05.
35. Maheshwari RK, Narendra Govil, Mayank Rai, Mithun Singh Rajput. New Titrimetric Estimation of Naproxen Bulk Drug Sample Using Ibuprofen Sodium as Hydrotropic Solubilizing Agent. International Journal of Pharma and Bio Sciences. 2010; V1(1).
36. Maheshwari RK, Navneet Upadhyay, Jitendra Jain, Mittal Patani, Khem Chand Mathuria. New Spectrophotometric Estimation of Naproxen Tablets Formulations Employing Mixed Solvency Concept. IJPT. 2011; 3(4):3618-3623.
37. Rajendra Chouksey, Harish Pandey, Jain AK, Himesh Soni, Saraogi Gk. Preparation and Evaluation of the Self Emulsifying Drug Delivery System: A Acontaining Aceclofenac Hmgcoa –Inhibiter. IJPPS. 2011; 3(3).
38. Rajesh A Keraliyaa, Tejal G Sonib, Vaishali T Thakkarb, Tejal R Gandhib, Rajanikant C Patel. Physical Characterization of Microcrystals for Dissolution Rate Enhancement of Tolbutamide. Int. J. Res. Pharm. Sci. 2010; 1(1):69-77.
39. Rajkumar Gudikandula, Kalla Madhavi, Swathi Rao Thakkalapally, Anilkumar Veeramalla, Indarapu Rajendra Prasad. Enhancement of Solubility and Dissolution Rate of Ezetimibe through Liquisolid Technique. Gudikandula *et al*., IJPSR. 2013; 4(8):3229-3238.
40. Ravi S Wanare. Studies on the Enhancement of Dissolution of Poorly Water Soluble Drug by Solid Dispersion Technique. Wanare RS Pharmacie Globale (IJCP). 2013; 03(05).
41. Stegemanna S, Leveillerb f, Franchic D, De jongd H, Lindéne H. When Poor Solubility Becomes An Issue: From Early Stage to Proof of Concept. Capsugel, RIJKSWEG 11, 2880 Bornem, Belgium.
42. Bhanja SB, Ellaiah P, Nayak Bs, Mahapatra DK, Sahu A, Padhyand SK, *et al*. Enhancement of Dissolution Properties, Preparation and Evaluation of Immediate Release Tablets of Poorly Soluble Drug Repaglinide. IJPT. 2011; 3(3):2961-2991.
43. Sahil M Gavali, Sharad S Pacharane, Shirish V Sankpal, Kisan R Jadhav, Vilasrao j Kadam. Liquisolid Compact: A New Technique for Enhancement of Drug Dissolution. IJRPC. 2011; 1(3) Jadhav *et al*. ISSN: 2231 -2781.
44. Sameer Singh, Raviraj Singh Baghel, Lalit Yadav. A Review on Solid Dispersion. (IJPLS). 2011; 2(9):1078-1095.