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Research Article

Formulation and Evaluation of Poorly Soluble Aceclofenac by Complexation With β-Cyclodextrin

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ABSTRACT
Aceclofenac is an effective analgesic and anti-inflammatory drug prescribed widely in various types of pain and inflammation. Aceclofenac is partially insoluble in water and aqueous fluid and as such it exhibits poor variable oral bioavailability. Aceclofenac needs enhancement of solubility and dissolution rate to improve its oral bioavailability and therapeutic efficacy. Among the various approaches to enhance the solubility and dissolution rate of poorly soluble drugs complexation with cyclodextrin is an effective and industrially accepted technique. In the present investigation, Complexation of aceclofenac with β-CD was carried out by using various techniques like kneading method, co-precipitate method & solvent evaporation method and compared with physical mixture method. From the various characterization studies like drug content, production yield & in vitro dissolution study, batch abc-3 by kneading method was selected as optimised batch. Optimised batch was also studied for FTIR and DSC.

Key words: Aceclofenac, β-cyclodextrin, FTIR, DSC, Solid Dispersion.

INTRODUCTION

The rate of absorption and bioavailability of poorly water soluble drugs is often controlled by the rate of dissolution of the drug in the gastrointestinal tract. Many technological methods of enhancing the dissolution characteristics of slightly water-soluble drugs are solid dispersions, micronization, solvent deposition, prodrugs, use of surfactants and inclusion complexation etc. Among the various methods, cyclodextrin complexation is an industrially accepted technique.[1]

Aceclofenac is a NSAID with good analgesic and anti-pyretic properties. Chemically it is [[[2-[(2, 6-Dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid. It is used in various pain conditions like rheumatoid arthritis, osteoarthritis and ankylosing spondylitis**.** Aceclofenac is practically insoluble in water and aqueous fluids.[1] Cyclodextrins are cyclic oligosaccharides, containing six, seven or eight glucopyranose units (α, β or γ respectively) obtained by the enzymatic degradation of starch. These are torus shaped molecules with a hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs. Cyclodextrins are able to form inclusion complexes with poorly water-soluble drugs and have been shown to improve pharmaceutical properties like solubility, dissolution rate, bioavailability, stability and even palatability without affecting their intrinsic lipophilicity or pharmacological properties. Out of the three parent cyclodextrins, β-cyclodextrin (β-CD) appears most useful as a pharmaceutical complexing agent because of its complexing ability, low cost and other properties. Natural cyclodextrins have limited water solubility. However, a significant increase in water solubility has been obtained by alkylation of the free hydroxyl groups of the cyclodextrins resulting in hydroxyalkyl, methyl and sulfobutyl derivatives. The ability of cyclodextrins to form inclusion complexes may also be enhanced by substitution on the hydroxyl group. The objective of present study is to prepare inclusion complexes of aceclofenac with cyclodextrins in different molar ratios by different methods such as physical, kneading and co-precipitation method and increase the solubility of Aceclofenac for improvement of dissolution rate and bioavailability of the drug.[2,3]

MATERIALS & METHODOLOGY

Aceclofenac was gift sample obtained from Umedica Laboratory Pvt. Ltd. Vapi, India. B-cyclodextrin was gift sample obtained from Triveni Interchem Pvt. Ltd. Vapi, India.

Formulation of inclusive complex of aceclofanac with β-cyclodextrin[5,6]

Method of preparation:

The inclusive complex of Aceclofenac with β-Cyclodextrin may be prepared by one of the following methods:

Physical mixture (Standard method): Aceclofenac with β-Cyclodextrin in different molar ratios (i.e. 1:1M, 1:2M & 1:3M) were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 80 and stored in desiccators over fused calcium chloride and Batches were encoded as PM1, PM2 and PM3.

Co-precipitate method: Aceclofenac was dissolved in ethanol at room temperature and β-Cyclodextrin was dissolved in distilled water. Different molar ratios of Aceclofenac and β-Cyclodextrin (1:1M, 1:2 M & 1:3M) were taken. The mixture was stirred at room temperature, for one hour and then slowly evaporated on a boiling water bath. The inclusion complex precipitated as a crystalline powder was pulverized and passed through sieve No. 80 and stored in a desiccator till free from any traces of the organic solvent. Batches were encoded as abc4, abc5 and abc6.

Kneading method: Aceclofenac with β-Cyclodextrin in different molar ratios (i.e. 1:1M, 1:2M) were taken shown in Table 1. First β-Cyclodextrin is added to the mortar, small quantity of 50% ethanol is added while triturating to get slurry like consistency. Then slowly drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried at 25 °C for 24 hours, pulverized and passed through sieve No. 80 and stored in desiccators over fused calcium chloride. Batches were encoded as abc1, abc2 and abc3.

Solvent Evaporation Technique: In this method the drug and carrier are used in different ratios (1:1, 1:2 & 1:3). The respective amount of carrier was dissolved in methanol (20ml) and aceclofenac was added in parts with continuous stirring the solvent was then removed by evaporation. The prepared dispersion were pulverized and sifted through 100# and stored in desiccator for further studies. Batches were encoded as abc7, abc8 and abc9.

Table 1 Composition of complex of aceclofanac with β-cyclodextrin [14, 15]

Batch	Aceclofenac (Drug)	β-Cyclodextrin (carrier)	Method of Preparation
PM1	100	100	Physical mixture
PM2	100	200	
PM3	100	300	
abc1	100	100	Kneading method
abc 2	100	200	
abc 3	100	300	
abc 4	100	100	Co-precipitate
abc 5	100	200	
abc 6	100	300	
abc 7	100	100	Solvent Evaporation
abc 8	100	200	
abc 9	100	300	

*All quantity is in milligrams

Evaluation of inclusive complex of aceclofenac with β- cyclodextrin [12,13,14,15]

Physico-mechanical characterization:[7,8,9]

Bulk Density: Weigh accurately 25 g of drug (M), which was previously passed through 20# sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm / cm^3 by the following formula.

$$\text{Bulk Density } (\rho_b) = \frac{\text{Weight of powder}}{\text{Bulk Volume}}$$

Tapped bulk Density: Weigh accurately 25 g of drug, which was previously passed through 20# sieve and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V_2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V_2). Calculate the tapped bulk density in gm/cm^3 by the following formula.

$$\text{Tapped Density } (\rho_p) = \frac{\text{Weight of powder}}{\text{Tapped Volume}}$$

Compressibility Index: The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's Index} = \frac{(\rho_p - \rho_b)}{\rho_p} \times 100$$

H**ausner's Ratio:** It is calculated from bulk density and tap density. Values less than 1.25 indicate good flow (20% Carr index.) and the value greater than 1.25 indicates poor flow (33% Carr index.). If it is between 1.25-1.5 added glidants normally to improve flows.

$$\text{Hausner's Ratio} = \frac{\rho_p}{\rho_b}$$

Angle of Repose: The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} h/r$$

Where, h and r are respectively height and radius of the powder cone.

Compatibility study:[10]

FT-IR Study:

Infrared spectra of pure drug, polymer, as well as for combination of drug-polymer were taken by KBr pellet technique and were recorded in the range of 4000 – 400 cm^{-1} by using FT-IR Spectrophotometer Shimadzu.

DSC Study:

Differential scanning Calorimetry (DSC) was performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter. The instrument comprised of calorimeter (DSC 60), flow controller (FCL 60), thermal analyzer (TA 60) and operating software (TA 60). The samples (drug alone or mixture of drug and excipients) were heated in sealed aluminum pans at a scanning rate of 5°C/min from 24±1 to 350°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the drug and drug-polymer mixture. The physical mixtures of drug with different Excipients for compatibility studies were prepared by triturating drug and additives in a dried mortar for 5 min.

Production yield: The yield was calculated by dividing the weight of the collected solid dispersion by the weight of all the non-volatile components used for preparation of the solid dispersion and expressed in terms of percentage. [11]

$$\text{Percentage Yield} = \frac{\text{Weight of solid dispersion recovered}}{\text{Weight (Drug + polymer)}} \times 100$$

Table 3 Drug Content and production yield of Aceclofenac β-cyclodextrin solid dispersion.

Batch	Drug Content (mg)	Drug Content (%)	Mean Production Yield (%)
PM1	47.07±0.21	94.15	91.83±1.89
PM2	31.20±0.10	93.63	91.22±1.01
PM3	23.77±0.15	95.12	92.08±0.38
abc1	43.19±0.21	86.38	78.33±0.76
abc 2	29.83±0.10	89.53	83.44±1.38
abc 3	23.04±0.16	92.18	90.08±1.18
abc 4	35.51±0.10	71.03	72.33±1.04
abc 5	25.20±0.12	75.55	76.21±0.50
abc 6	20.69±0.10	82.79	83.33±0.76
abc 7	38.14±0.10	74	74±1.32
abc 8	27.06±0.16	80.55	80.55±1.16
abc 9	22.05±0.10	88	88±0.25

Drug content estimation: 200 mg of complex was accurately weighed and transferred to 50 ml volumetric flask and volume was made up to the mark with methanol. From this 1ml was taken in 10ml volumetric flask and the volume is adjusted up to the mark with same solvent. The absorbance of the solution was measured at 275nm using appropriate blank. The drug content Aceclofenac was calculated using calibration curve. [12]

***In vitro* dissolution study**

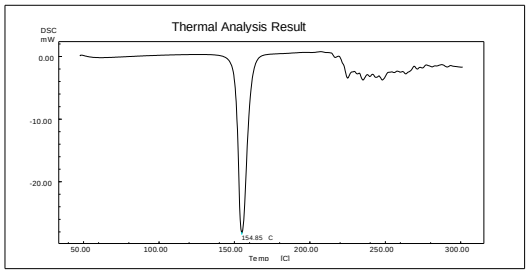
In vitro dissolution studies for Aceclofenac β-cyclodextrin complexes. In-vitro dissolution of Aceclofenac inclusion complex was studied in USP XXIV dissolution apparatus (Electro lab) employing a paddle stirrer. 900 ml of phosphate buffer of pH 7.2 was used as dissolution medium at 50 rpm. The temperature of 37±0.5°C was maintained throughout the experiment. Complex equivalent to 50 mg of Aceclofenac was used in each test. 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 275 nm after suitable dilution with phosphate buffer. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. The amount of Aceclofenac released was calculated and plotted against time and compared with pure drug. [13]

Stability study [15]

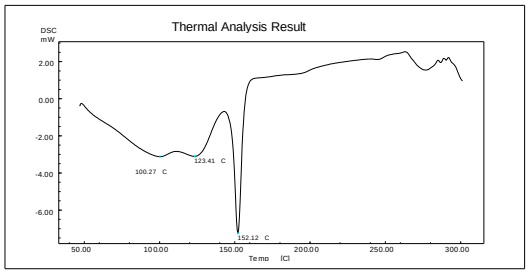
The stability study was carried out for optimized formulation as per ICH guidelines (Feb. 2003). Various ICH storage conditions are available which are as 25^{0}C ± 2^{0}C (60% ± 5%RH), 30^{0}C ± 2^{0}C (65% ± 5%RH) and 40^{0}C ± 2^{0}C (75% ± 5%RH). The Solid Dispersion of the best formulation were placed in screw capped glass container and stored at various ICH storage condition for a period of 60 days. The samples were analyzed for physical appearance and for the drug content at regular interval of 15 days.

RESULTS AND DISCUSSION

The purpose of the present study as to formulate and evaluate solid dispersion of aceclofenac. Where solid dispersion was prepared by various methods namely physical mixture, kneading method, co-precipitate and solvent evaporation using complexing agent (β-cyclodextrin).



(a)



(b)

Figure 1 DSC Thermograph analysis of (a) Aceclofenac and Formulation abc -3

Before the development of solid dispersion various preformulation test was also carried out to determine melting point, λmax, Bulk density, Tapped density, Carr's index, Hausner's ratio and angle of repose.

From the melting point determination it has been found that melting point of Aceclofenac was found in the range of 148°c-154°c. λmax was determined for drug, Aceclofenac in phosphate buffer pH 7.2. It was found to be 275 nm, which was exactly similar to the earlier reported λmax.

Then after Calibration curve was determined for Aceclofenac in phosphate buffer pH 7.2 at λmax 275 nm. This shows the linearity in the range of 5 to 30 µg/ml. The compatibility study for drug, complexing agent and for optimized batch was performed by using FTIR spectrophotometric analysis and DSC. From the results of FT-IR and DSC. It was observed that there was no drug-polymer interaction.

From the values of bulk densities of various formulations indicated good packing character show in table 2. The compressibility index for all the formulations was found to be below 18%, indicating desirable flow properties. The flow properties of solid dispersion were further analyzed by determining the angle of repose for all formulations; ranges were less than 31°. The hausner's ratio for all the granules formulated was less than 2%.

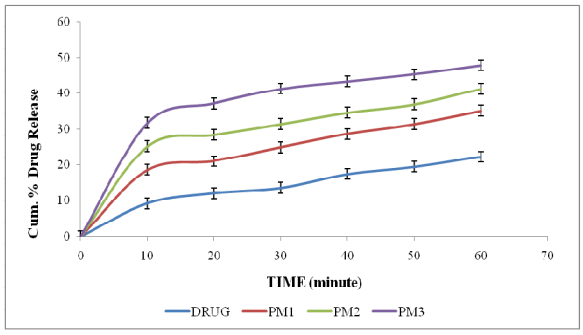


Figure 2 Dissolution profile of PM1, PM2, and PM3

Table 2 Physico-mechanical property of Solid dispersion

Formulation	Bulk Density g/cm^3	Tapped Density g/cm^3	Compressibility Index (%)	Hausner Ratio	Angle of Repose (θ)
Aceclofenac	0.65±0.04	0.77±0.006	15.28±0.70	1.18±0.009	24.18±0.32
PM1	0.59±0.046	0.75±0.019	17.39±0.32	1.21±0.0047	30.47±0.73
PM2	0.54±0.019	0.66±0.020	17.09±0.099	1.20±0.0014	29.30±1.05
PM3	0.59±0.017	0.68±0.016	15.42±0.45	1.18±0.0063	31.03±1.89
abc1	0.59±0.017	0.71±0.011	15.09±0.70	1.18±0.0090	27.15±0.59
abc 2	0.54±0.014	0.65±0.020	17.68±0.26	1.21±0.0038	30.50±1.47
abc 3	0.55±0.010	0.66±0.015	16.67±0.31	1.20±0.0026	28.63±1.01
abc 4	0.55±0.019	0.62±0.032	15.30±0.58	1.18±0.0083	30.23±0.85
abc 5	0.53±0.013	0.71±0.017	17.25±0.38	1.20±0.0056	30.50±1.47
abc 6	0.58±0.049	0.76±0.051	17.37±0.31	1.21±0.0046	31.82±0.68
abc 7	0.62±0.039	0.69±0.038	15.58±1.03	1.41±0.40	28.21±1.35
abc 8	0.55±0.049	0.67±0.049	15.89±0.98	1.18±0.013	29.06±0.67
abc 9	0.59±0.019	0.72±0.036	16.76±1.09	1.20±0.015	30.50±1.47

Various batches were prepared by physical mixture bearing batch no: PM1-PM3. Remaining nine batches had been prepared batch no: abc1-abc9.

Each prepared batch was then subjected to post formulation evaluation like drug content, production yield and *in vitro* drug release study. Release profile of Aceclofenac was compared with physical mixture and pure drug.

After performing various evaluation tests for all the batches, it was observed that as ratio of drug: complexing agent increases, there was increasing in the dissolution rate of drug. So batch no abc3 have been selected as optimised batch as it has shown good production yield (90.08±1.18%), Drug content (92.18%) and %CDR (87.29±0.54).

The selected formulation was subjected to accelerated stability studies by storing at 25^{0}C ± 2^{0}C/60% ±5% RH, 30^{0}C ± 2^{0}C/65% ± 5% RH and 40^0 C ± 2^{0}C/75% ± 5% RH for 60 days. The samples were analyzed for its drug content and physical appearance at an interval of 15 days. It shows better storage at 25° C ± 2°C/60% RH.

Results of physical appearance, % drug content and In vitro dissolution studies was shown that there was no any change at different storage conditions and there was not significant change in the release pattern.

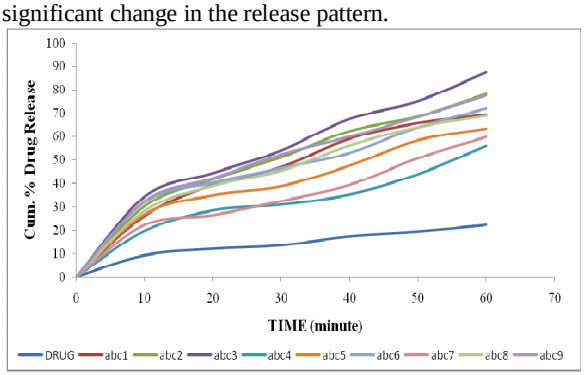


Figure 3 Dissolution profile of complex of aceclofenac with β- cyclodextrin of batch abc1 to abc-9**.**

CONCLUSION

The present study was an attempt to develop solid dispersion of Aceclofenac using β-cyclodextrin as complexing agent by different technique like physical mixture, kneading method, co-precipitate method and solvent evaporation technique. FT-IR and DSC results shows there were no drug-polymer interaction. The influences of drug – polymer ratio on the physical characteristics of solid dispersion (kinetic of release) were investigated. From the various characterization studies like drug content, production yield & in vitro dissolution study, batch abc-3 by kneading method was selected as optimised batch. The optimized batch abc3 formulation was subjected to DSC analysis and accelerated stability studies by storing at various ICH storage conditions for 60 days. Thus, from the obtain data it can be concluded that abc3 formulation shows better dissolution rate hence, Aceclofenac as anti-inflammatory can be successfully formulated as solid dispersion.

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