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DISSOLUTION ENHANCEMENT 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 recent years for 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 physical mixture, kneading method, co-precipitate method& solvent evaporation method. From the various characterization studies like drug content, production yield & in vitro dissolution study, batch abc-6 by kneading method was selected as optimised batch. Optimised batch was also studied for FTIR.

Key words: Aceclofenac, β-cyclodextrin, FTIR, 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.[3]

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 TriveniInterchem Pvt. Ltd. Vapi, India.

Formulation Of Inclusive Complex Of Aceclofenac With B-Cyclodextrin[12,13]

Method of preparation:

The inclusive complex of Aceclofenac with β-Cyclodextrin was prepared by following methods[14,15]:

Physical mixture:

Aceclofenacwith 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.

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.

Kneading method:

Aceclofenac with β-Cyclodextrin in different molar ratios (i.e. 1:1M, 1:2M) were taken. 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.

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.

Table 1: Experimental design

Batch	Aceclofenac (Drug)	β-Cyclodextrin (carrier)	Method of Preparation
abc1	100mg	100mg	**Physical mixture**
abc2	100mg	200mg	**Physical mixture**
abc3	100mg	300mg	**Physical mixture**
abc4	100mg	100mg	**Kneading method**
abc 5	100mg	200mg	**Kneading method**
abc 6	100mg	300mg	**Kneading method**
abc 7	100mg	100mg	**Co-precipitate**
abc 8	100mg	200mg	**Co-precipitate**
abc 9	100mg	300mg	**Co-precipitate**
abc 10	100mg	100mg	**Solvent Evaporation**
abc 11	100mg	200mg	**Solvent Evaporation**
abc 12	100mg	300mg	**Solvent Evaporation**

EVALUATION OF INCLUSIVE COMPLEX OF ACECLOFENAC [16, 17, 18, 19]

Compatibility Study:[5,6]

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

Physico-mechanical characterization:[9,10,11]

By bulk density, tapped density, hausners's ratio, compressibility index and angle of repose.

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.

$$\textbf{Percentage Yield} = \frac{\textbf{Weight of solid dispersion recovered}}{\textbf{Weight (drug + polymer)}} \textbf{X 100}$$

Drug content estimation:

50 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.

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.

Kinetics of Drug Release:

In order to investigate the mechanism of drug release from microspheres of different ratios, the release date obtained from dissolution studies were fitted to various kinetic equations.

Stability Study [20]

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□C ± 2□C (60% ± 5%RH), 30□C ± 2□C (65% ± 5%RH) and 40□C ± 2□C (75% ± 5%RH). The Microspheres 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

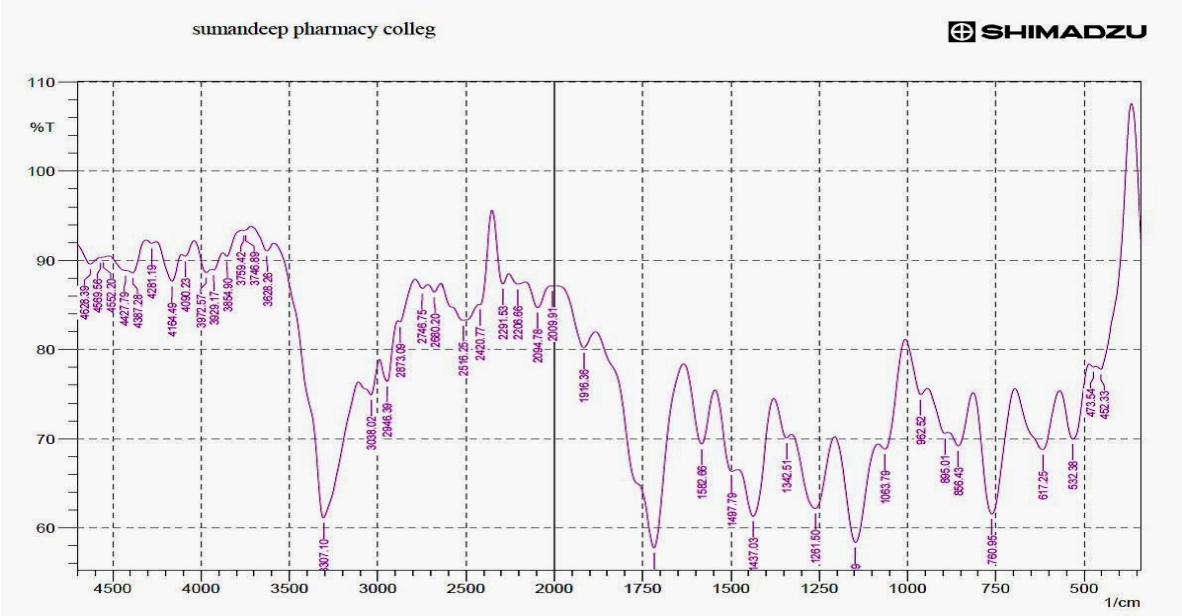

Figure 1: FT-IR Spectrum of pure drug aceclofenac in range 4000 to 400 cm^{-1}

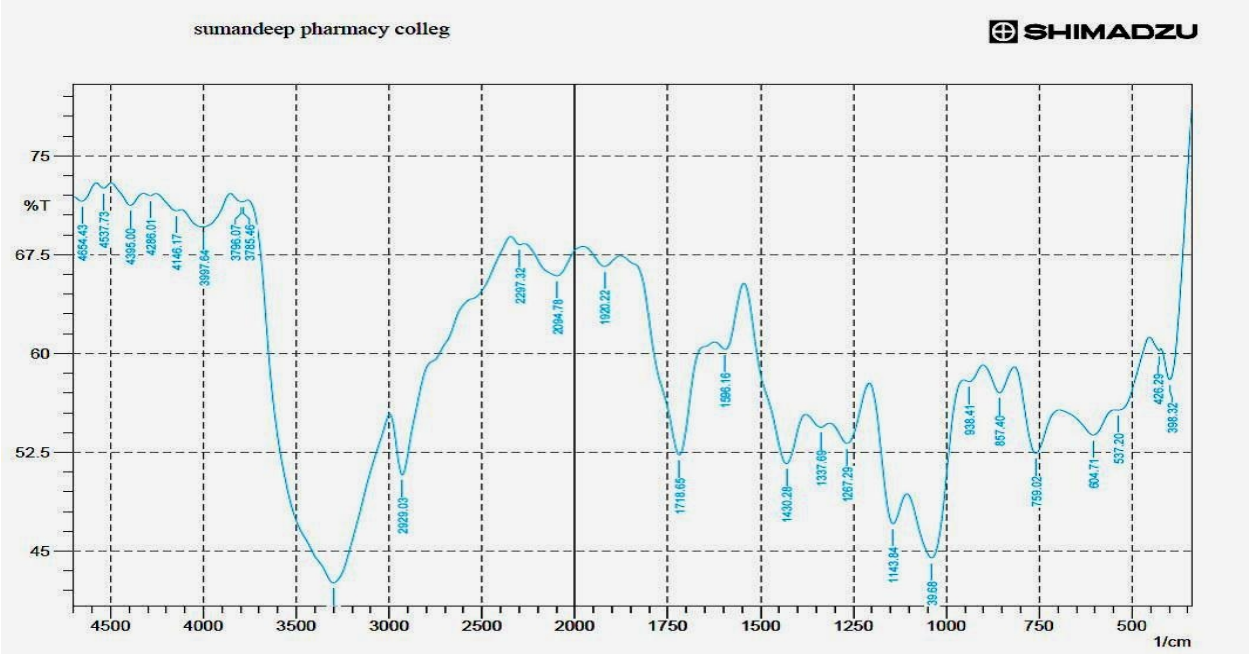

Figure 2: FT-IR Spectrum of abc6 in range 4000 to 400 cm^{-1}.

Table 2: Physico-mechanical property of Solid dispersion

Sr. No	Formulation	Bulk Density g/cm^3	Tapped Density g/cm^3	Compressibility Index (%)	Hausner Ratio	Angle of Repose (θ)
1	abc1	0.59±0.046	0.75±0.019	17.39±0.32	1.21±0.0047	30.47±0.73
2	abc2	0.54±0.019	0.66±0.020	17.09±0.099	1.20±0.0014	29.30±1.05
3	abc3	0.59±0.017	0.68±0.016	15.42±0.45	1.18±0.0063	31.03±1.89
4	abc4	0.59±0.017	0.71±0.011	15.09±0.70	1.18±0.0090	27.15±0.59
5	abc5	0.54±0.014	0.65±0.020	17.68±0.26	1.21±0.0038	30.50±1.47
6	abc6	0.55±0.010	0.66±0.015	16.67±0.31	1.20±0.0026	28.63±1.01
7	abc7	0.55±0.019	0.62±0.032	15.30±0.58	1.18±0.0083	30.23±0.85
8	abc8	0.53±0.013	0.71±0.017	17.25±0.38	1.20±0.0056	30.50±1.47
9	abc9	0.58±0.049	0.76±0.051	17.37±0.31	1.21±0.0046	31.82±0.68
10	abc10	0.62±0.039	0.69±0.038	15.58±1.03	1.41±0.40	28.21±1.35
11	abc11	0.55±0.049	0.67±0.049	15.89±0.98	1.18±0.013	29.06±0.67
12	abc12	0.59±0.019	0.72±0.036	16.76±1.09	1.20±0.015	30.50±1.47

CHARACTERIZATION OF SOLID DISPERSION:

Production yield:

% yield was found between 74% (abc10) to 92.08% (abc3).

Drug content:

The drug content of all prepared batches were in accepted range.

In vitro release studies:

The in vitro release studies are carried out for a period of 60 min.

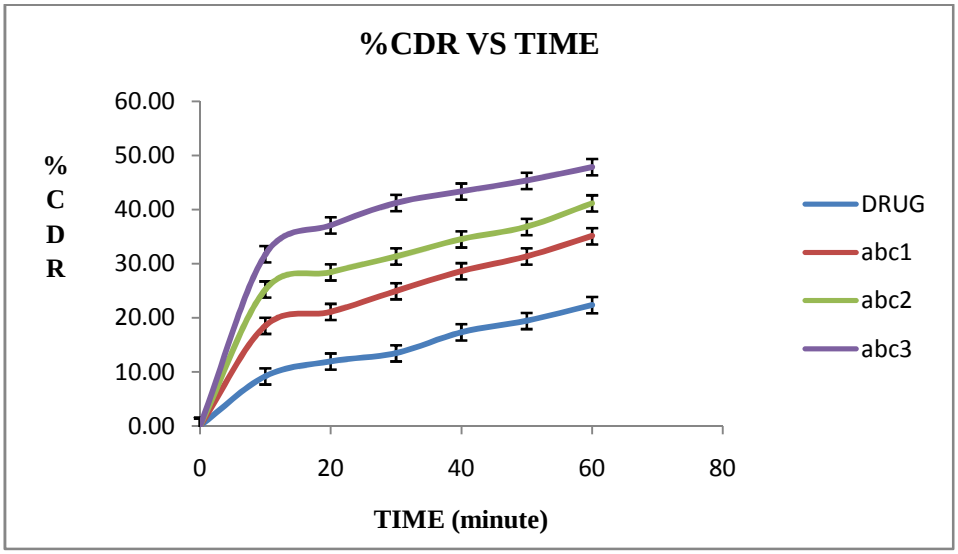

Figure 3: Dissolution profile of abc1, abc2, and abc3

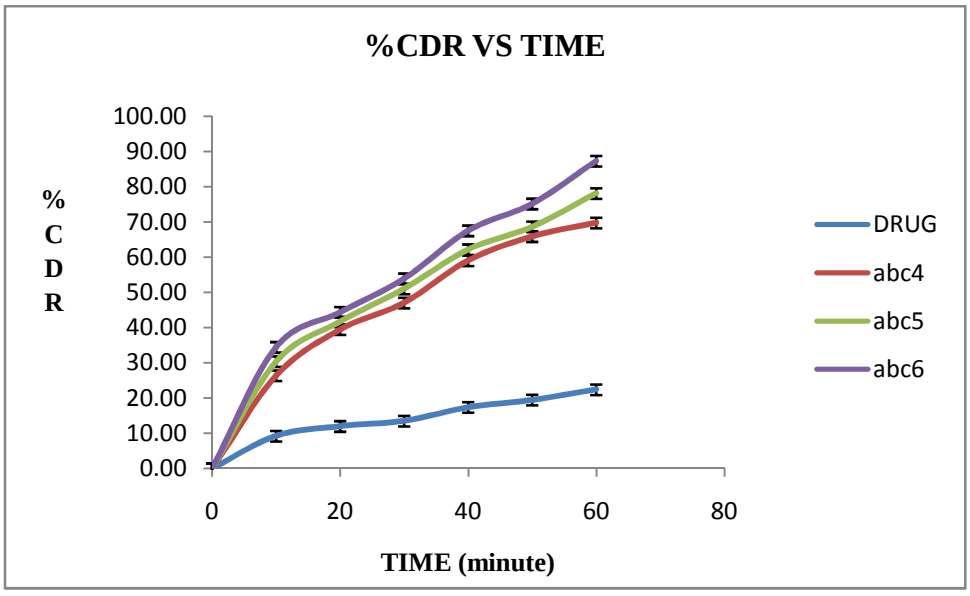

Figure 4: Dissolution profile of abc4, abc5 and abc6.

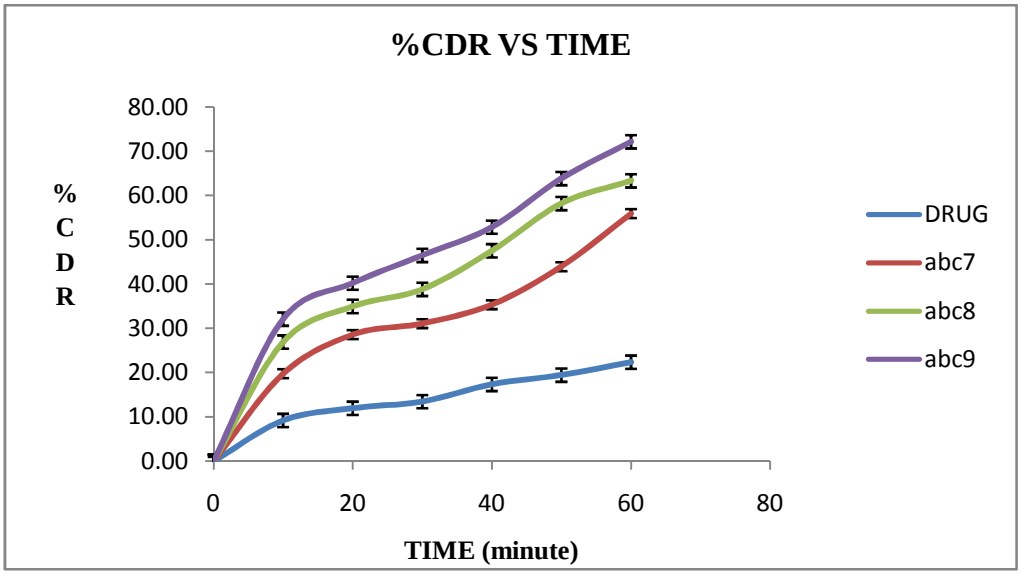

Figure 5: Dissolution profile of abc7, abc8 and abc9.

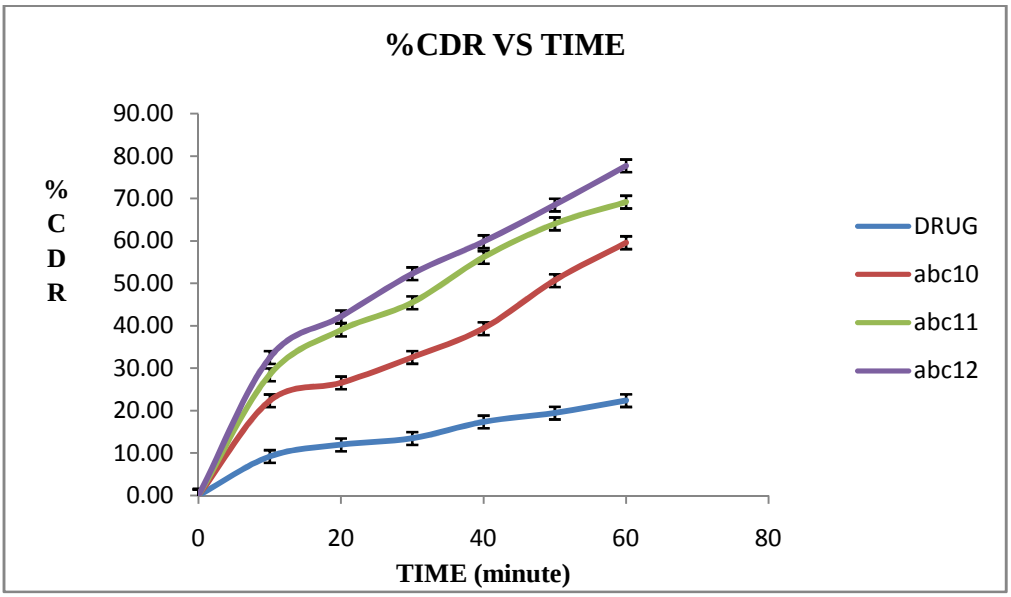

Figure 6: Dissolution profile of abc10, abc11 and abc12.

Kinetics of drug release:

Data obtained from dissolution studies was fitted to various kinetic equations.

Table 3: Parameters of Release Kinetics Model for Prepared Formulations.

Batch	Zero Order		First Order		Higuchi
	R^2	K_0	R^2	K	R^2
abc1	0.8514	1.7209	0.8958	0.0062	0.9823
abc2	0.7599	1.392	0.8225	0.0072	0.9458
abc3	0.6902	1.0914	0.7662	0.0089	0.9155
abc4	0.9288	0.8448	0.988	0.0197	0.9954
abc 5	0.9349	0.79	0.9882	0.0235	0.9965
abc 6	0.9412	1.3088	0.959	0.031	0.99
abc 7	0.9336	1.1726	0.943	0.0117	0.9576
abc 8	0.9245	0.9762	0.9712	0.0155	0.9855
abc 9	0.9093	0.8699	0.9668	0.0191	0.9873
abc 10	0.9551	1.0776	0.9638	0.0136	0.9576
abc 11	0.9238	0.8747	0.9854	0.0187	0.9965
abc 12	0.9212	0.7497	0.9821	0.0228	0.9964

Stability study:

The stability study carried out for formulation abc6 is given in table 24 25, 26.

Table 4:Stability studies of formulations abc6 stored at 25▫C ± 2▫C (60% 5%RH)

Formulation	Tested after time (days)	Physical appearance	Drug content (%)
abc6	15	No Change	92.10
	30	No Change	91.95
	45	No Change	91.74
	60	No Change	91.63

Table 5: Stability studies of formulations abc6 stored at30▫C ± 2▫C (65% 5%RH)

Formulation	Tested after time (days)	Physical appearance	Drug content (%)
abc6	15	No Change	92.00
	30	No Change	91.86
	45	No Change	91.61
	60	No Change	91.56

Table 6: Stability studies of formulations abc6 stored at40▫C ± 2▫C (75% 5%RH)

Formulation	Tested after time (days)	Physical appearance	Drug content (%)
abc6	15	No Change	91.92
	30	No Change	91.73
	45	No Change	91.53
	60	No Change	91.44

Table 7:% CDR of abc6 stored at 25▫C ± 2▫C/60% ±5% RH, 30▫C ± 2▫C/65% ± 5% RH, 40▫ C ± 2▫C/75% ± 5% RH

TIME	25▫C ± 2▫C/60% ±5% RH	30▫C ± 2▫C/65% ± 5% RH	40▫ C ± 2▫C/75% ± 5% RH
0	33.91	33.51	33.25
10	43.69	43.16	42.9
20	53.34	52.81	52.68
30	66.68	66.15	65.88
40	73.59	73.06	72.79
50	86.51	85.85	85.32
60	33.91	33.51	33.25

DISCUSSION

The purpose of the present study was 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).

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. From the results of FTIR, it was observed that there was no drug-polymer interaction.

From the values of bulk densities of various formulations indicated good packing character. 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%.

Various batches were prepared by physical mixture bearing batch no: abc1-abc3. Remaining twelve batches had been prepared by 3^2 factorial design bearing batch no: abc4-abc12.
Each prepared batch was then subjected to post formulation evaluation like drug content, production yield.

Each of the prepared batches was then subjected to 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 abc6 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 25C ± 2C/60% ±5% RH, 30C ± 2C/65% ± 5% RH and 40 C ± 2C/75% ± 5% RH for 60 days. 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.

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 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-6 by kneading method was selected as optimised batch. In vitro release of Aceclofenac from prepared solid dispersion was found to be satisfactory. From in-vitro drug release profile of optimized batch abc6, release pattern could be better expressed by higuchi model as they showed good linearity with “R” value. The optimized batch abc6 formulation was subjected to DSC analysis and accelerated stability studies by storing at various ICH storage conditions 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.

Thus, from the obtain data it can be concluded that abc6 formulation shows better dissolution rate hence, Aceclofenac as anti-inflammatory can be successfully formulated as solid dispersion.

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