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Solubility Enhancement of Poorly Water Soluble Drug by Using β Cyclodextrin

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ABSTRACT:
Aceclofenac complex is prepared by kneading method of inclusion complexation. The aim of present work is to improve the solubility and dissolution properties of a poorly water soluble drug aceclofenac, by inclusion complexation technique. Two components namely β cyclodextrin and span 60 were used in this study, β CD is used as complexing agent and span 60 as surfactant which helps in increasing solubility and dissolution. The prepared Aceclofenac complex is evaluated in terms of compatibility, solubility, dissolution behavior with the help of FTIR, DSC, *In vitro* dissolution studies. The complexation parameter of β CD had an impact on the solubility of drug. The solubility of complexes was progressively improved when compared to pure Aceclofenac drug in water. The prepared Aceclofenac complexes were subjected to dissolution study. At the end of 60 min of dissolution study 22.32±0.42 of pure drug was dissolved. The prepared complexes showed 85.35±0.71 at 60 min. The percent of drug dissolved increased for the complexes prepared with high concentration of β CD. The study showed that complexing property of β CD and surfactant action of span 60 has its influence on both solubility and dissolution of the prepared inclusion complexes. MDT and % DE was evaluated for the all the prepared complexes. Aceclofenac complexes prepared with high concentration of β CD showed lower MDT and higher % DE compared to pure Aceclofenac. The pure and complexed Aceclofenac were characterized by DSC studies. DSC studies showed that there was no appreciable change in the melting endotherm of prepared complexes compared to that of pure drug. The drug release from the above follows Korsemeyer-Peppas model and release mechanism was Non- Fickinian.
Keywords: Aceclofenac, inclusion complex, kneading method, complexing agent, solubility, dissolution.

Introduction

Oral delivery system is the most convenient and commonly employed route of drug delivery system as it is easiest way of drug delivery system and also for its high patient compliance, least sterility constraints, cost effectiveness and flexibility in the design of dosage form. As a result, many of the drug companies are more intended to produce bioequivalent oral drug products. The major challenge associated with these delivery systems is its poor bioavailability i.e. it depends on several factors including aqueous solubility, permeability, dissolution rate and pre systemic metabolism. The most frequent causes of low bioavailability are attributed to poor solubility and low permeability.[1] In order to achieve a better/desired therapeutic effect of a drug, it must reach a reasonable significant

concentration in plasma, which is mainly co-related with the solubility of drugs in GIT fluids. Except pinocytosis all other mechanisms of drug absorption requires presence of drug concentration in the solution form. Solubility is the main parameter for drug dissolution and drug absorption [2]. Nearly one- third of the drug which are developed are water insoluble and one-half of the developed drug will fail in trials because of their under privileged pharmacokinetics i.e. their poor water solubility. Therefore, it is essential to enhance the drug dissolution is the rate limiting step for various lipophilic drugs [3]. Solubility can be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. Drug solubility is the one in which the maximum concentration of the drug dissolved in the solvent under specific standard conditions. The need of drug solubility is to increase the drug absorption rate. The drug absorption from the GIT is low/limited due to various significant factors like poor aqueous solubility were classified under BCS classification.[4]

Class I - High solubility, high permeability

Class II - Low solubility, high permeability

Class III - High solubility, low permeability

Class IV - Low solubility, low permeability

The BCS class II drugs which are having low solubility and high permeability. A success of any formulation depends on how efficiently solubility makes the dug available at the site of action. So, solubility of the drug is the important parameter to increase drug availability.[5]

The various methods to increase the solubility of BCS class II drugs include both traditional and novel techniques.

Traditional techniques include, Use of co-solvents and surfactants, Hydrotophy, Micronization, Inclusion complexation, Solvent deposition and precipitation,
The novel approaches of drug solubility include, Size reduction technique Nanoparticle technology, Nanocrystal technology, Super critical technology Nanosuspensions and Microemulsion technology [6].

Inclusion Complexation

Inclusion complexation is a traditional technique of enhancing the solubility of poorly aqueous soluble drugs. The method involves the formation of complex with the cyclodextrin and the drug molecules. The complexation occurs when an aqueous solution of the cyclodextrin is shaken with the drug molecule or its solution. In aqueous solution the hydrophobic cavity of cyclodextrin are occupied by water molecules, which can be replaced by appropriate drug molecule that are less polar than water.

The formation of complexes by inclusion complexation method involves several techniques. They are Physical blending/ grinding method, kneading method, co precipitation, solid dispersion, neutralization, lyophilization, melting, microwave irradiation method, spray drying [7].

Materials and Methods

Aceclofenac was obtained as a gift sample from Sangus Life Science Pvt.ltd Bengaluru. Cyclodextrin was obtained as a gift sample from HiMedialaboratories Pvt. Ltd. Mumbai. Span 60 was obtained from Ozone International, Mumbai. Distilled water and phosphate buffer pH 6.8 were collected from laboratory.

Methods:

Determination of λ_{max} of drug:

A diluted solution of aceclofenac in phosphate buffer solution (pH 6.8) was scanned for absorption maxima against blank between 200-400 nm using UV- visible spectrophotometer (UV-1700. Shimadzu, Japan). The maximum absorbance was found to be 275nm.

Preparation of phosphate buffer solution (pH 6.8):

Dissolved 28.80 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen orthophosphate in sufficient water to produce a 1000 ml in volumetric flask.

Calibration curve of Aceclofenac in phosphate buffer solution (pH 6.8)

Accurately weighed Aceclofenac (100 mg) was transferred into a 100 ml volumetric flask, dissolved and adjusted the volume up to 100 ml with phosphate buffer solution (pH 6.8) to get stock solution A. From the stock solution A, 10 ml was pipetted out into a 100 ml volumetric flask and volume was made up to mark with phosphate buffer solution (pH 6.8) to get stock solution B. From the stock solution B, known volume were pipetted out and made up to 10 ml with phosphate buffer solution (pH 6.8)of aliquots such as 0.4, 0.8, 1.2, 1.6, 2.0, 2.4, 2.8, 3.2, 3.6 and 4.0 ml are pipetted out and made up to marin 10 ml volumetric flask to get 4-40 µg/ml concentration solutions and absorbance was recorded at 275 nm by UV-visible spectrophotometer (UV-1700. Shimadzu, Japan)[8].

Preparation of Complexes:

Complexation of drug and β-CD by kneading method:

The required quantity of β cyclodextrin and span 60 was weighed and little amount of water added to get paste like consistency. To the paste, weighed quantity of Aceclofenac was added the mixture by kneading in a mortar. Then this mixture was transfer into Petri dish and completely dried in hot air oven at 60ºC for 48h. Dried product was passed through sieve no #80 to obtain fine powder. Total weight of the powder was taken.[9]

Table 1:.Composition of aceclofenac complexes

Sl. Num.	Drug (mg)	Span60(mg)	β Cyclodextrin(mg)
F1	250	50	50
F2	250	50	100
F3	250	50	150
F4	250	50	200
F5	250	50	250

Characterization Studies of Inclusion Complexes:

Fourier transfer infrared spectroscopy: -

The FTIR spectrum of the Aceclofenac formulations was compared with the standard FTIR spectra of pure drug Aceclofenac. The FTIR spectral measurements were taken in ambient temperature using Bruker FTIR (ATR) spectrometer to ascertain compatibility.[10]

Differential scanning calorimetry studies :- (DSC Studies)

The DSC curves were obtained in a DSC-Q 200 calorimeter which was calibrated according to manufacture recommendation. (Standard indium 99.99% purity, melting point 156.1ºC). A mass sample was around 2mg and the sample was heated from 130ºC-180ºC using an aluminum crucible with perforated lid of 1.00mm orifice, under nitrogen atmosphere with a flow rate of 50ml/min and heating rate of 1ºC /min.[11]

Evaluation Studies of Inclusion Complexes

Solubility studies:

Solubility studies of Pure Drug

Solubility analysis was done which include the selection of suitable solvent system to dissolve the drug. Dissolve accurately 10mg of drug in 10ml of water, 10 ml of 0.1N HCL and 10 ml of Phosphate buffer pH 6.8 in 100ml conical flask separately. The samples were kept on rotary shaker at 100rpm for 24 hours. After that the volumes were made up to100ml mark with respective solvents, then filter the solutions. The filtrate was analyzed at 275nm by using UV - visible spectrophotometer (UV-1700. Shimadzu, Japan).

Solubility studies of prepared inclusion complexes

Solubility analysis was done which include the soluble of complexes in water. Dissolve accurately 10mg of F1, F2, F3, F4 and F5 in 10ml of water in 100ml conical flask separately. The samples were kept on rotary shaker at 100rpm for 24 hours. After that the volumes were make up to 100ml mark with water then filter the solutions. The filtrate was analyzed at 275nm by using UV - visible spectrophotometer (UV-1700. Shimadzu, Japan).[12]

***In vitro* dissolution studies:**

Dissolution studies were performed with different formulation of Aceclofenac complexes and compared with the pure Aceclofenac drug. The dissolution studies were performed in distilled water using USP II paddle dissolution apparatus at 50rpm. Dissolution medium consisted of 900ml distilled water maintained at 37±0.5°C. At a specific time intervals (5 to 60 min), an aliquot was withdrawn and replenished with fresh medium. Amount of dissolved drug in each aliquot was measured on a UV- Visible spectrophotometer (UV-1700. Shimadzu, Japan) at 275 nm using suitable blank. All the trails were conducted in triplicate and the average (± S.D) reading was noted.[13]

Results

Calibration Curve of Aceclofenac:

Table 2: Calibration curve of aceclofenac in phosphate buffer solution (pH 6.8)

Sl.No	Concentration (µg/ml)	Absorbance
1	0	0
2	4	0.11
3	8	0.188
4	12	0.285
5	16	0.352
6	20	0.443
7	24	0.527
8	28	0.61
9	32	0.673
10	36	0.763
11	40	0.855

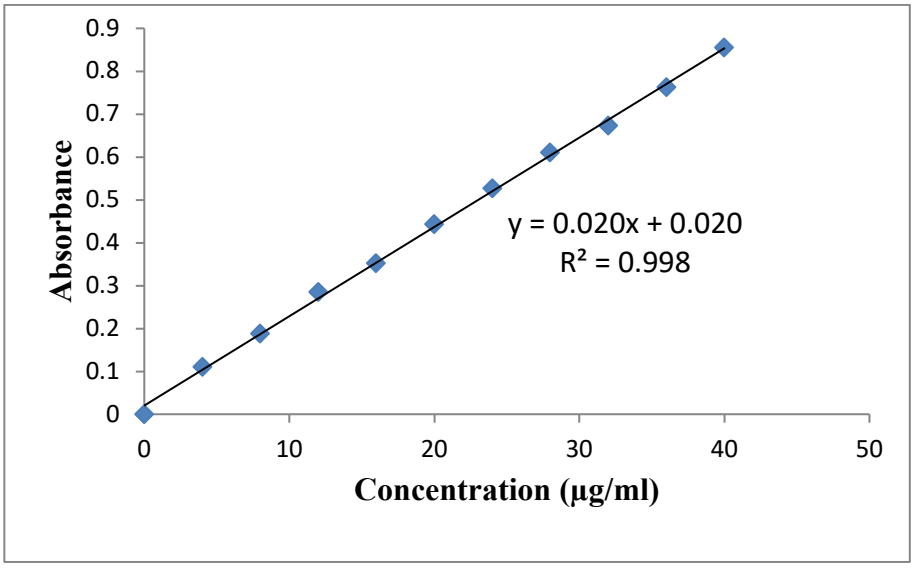

Figure 1: Calibration curve of aceclofenac in phosphate buffer solution (pH 6.8)

Solubility study of aceclofenac

Table 3: Solubility study of aceclofenac in different media

Drug	Solubility in distilled water (mg/ml)	Solubility in 0.1N HCl (pH 1.2) (mg/ml)	Solubility in phosphate buffer (pH 6.8) (mg/ml)
Aceclofenac	0.000765±0.000143	0.0707±0.007259	0.1197±0.01

Values are mean ±SD, n=3

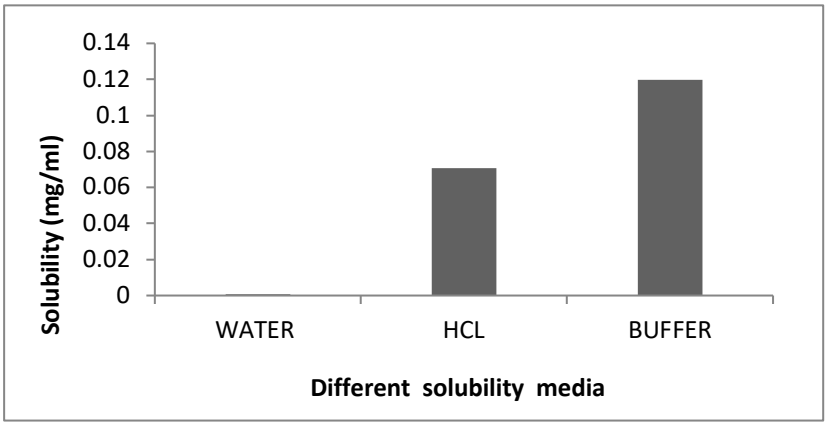

Figure 2: Comparison of solubility of aceclofenac in distilled water, 0.1 N HCl and phosphate buffer solution (pH 6.8).

Solubility study of Aceclofenac and prepared complexes in water

Table 4: Solubility of aceclofenac and prepared complexes in water

Complexes	Solubility in water (mg/ml)
Aceclofenac	0.000765±0.000143
F1	1.762333±0.0351
F2	1.808333±0.0251
F3	1.958667±0.0595
F4	1.963±0.008
F5	2.247667±0.117

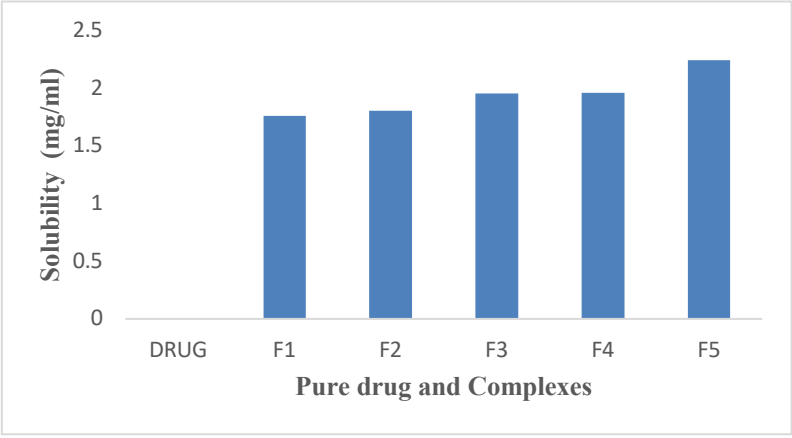

Figure 3: Comparison of solubility study profile of aceclofenac and complexes in distilled water.

Compatibility studies by FTIR

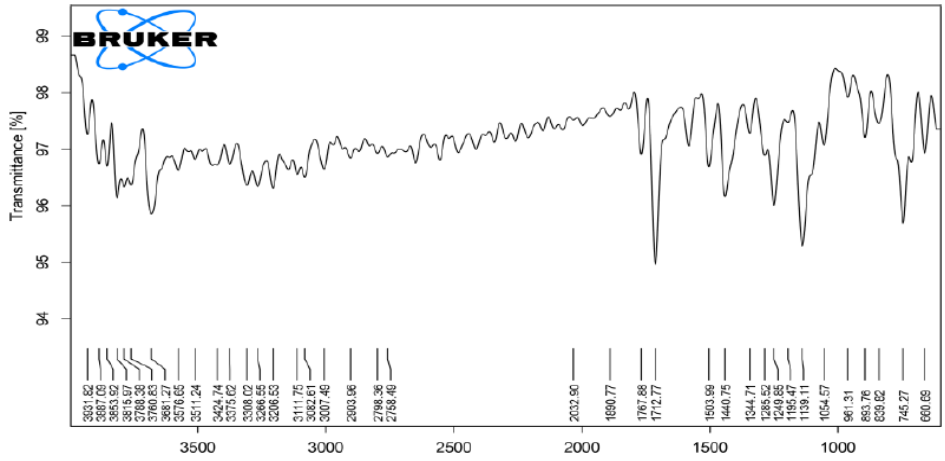

Figure 4: IR spectra of Aceclofenac

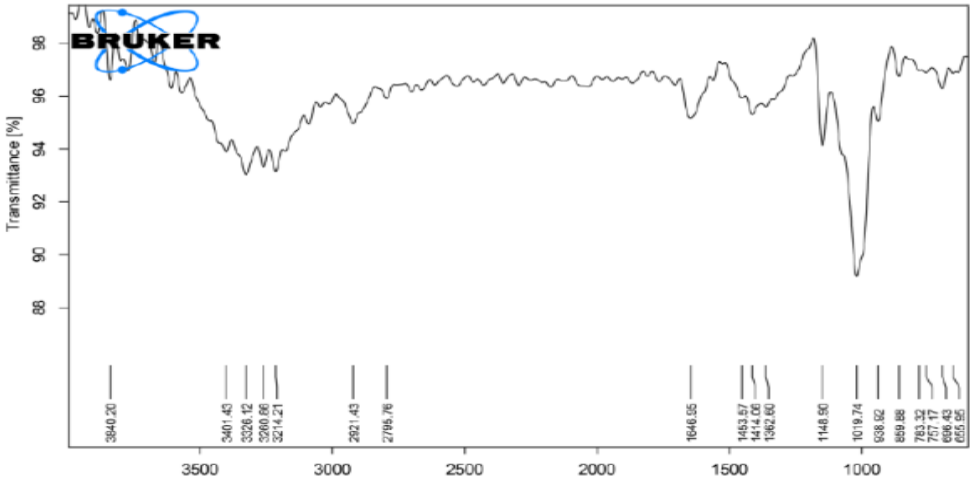

Figure 5: IR Spectra of β-Cyclodextrin

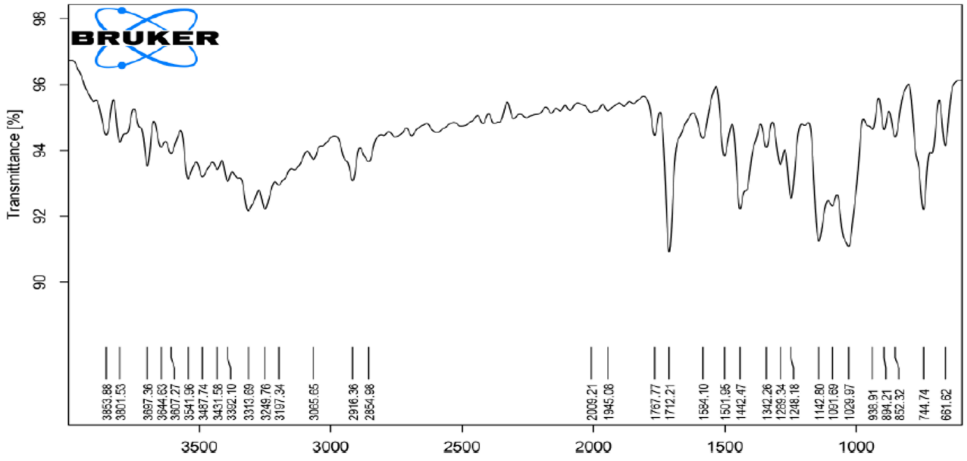

Figure 6: IR Spectra of F1

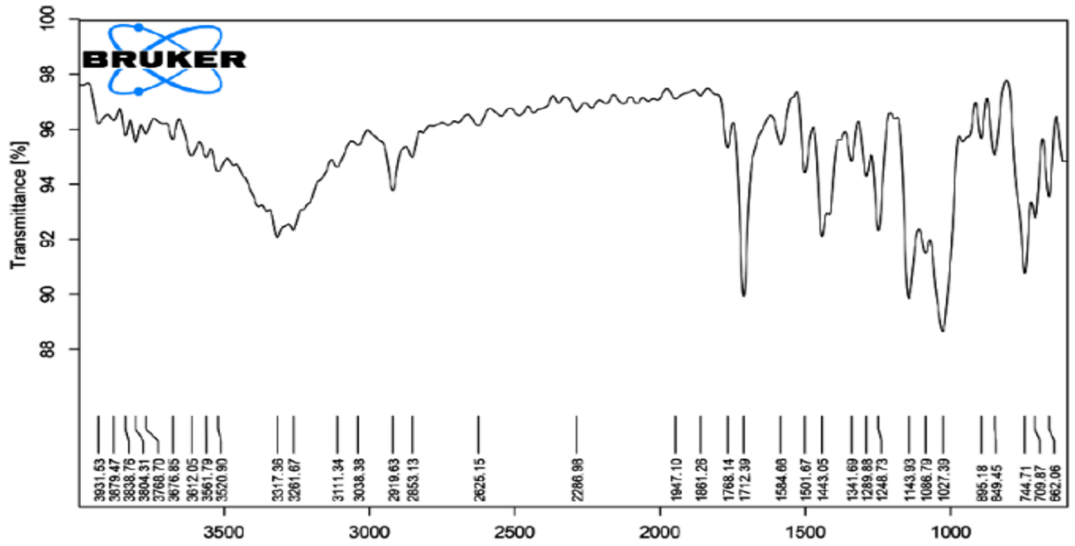

Figure 7: IR Spectra of F2

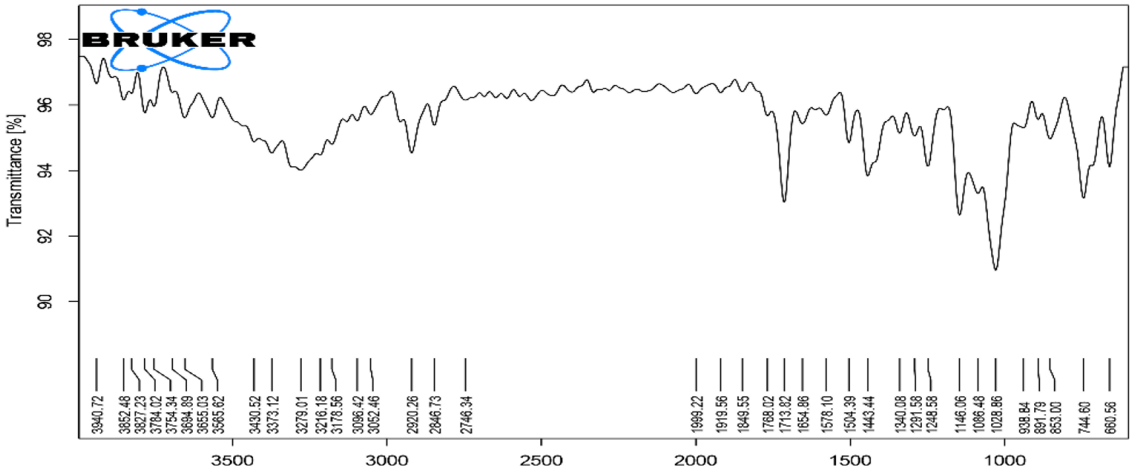

Figure 8: IR Spectra of F3

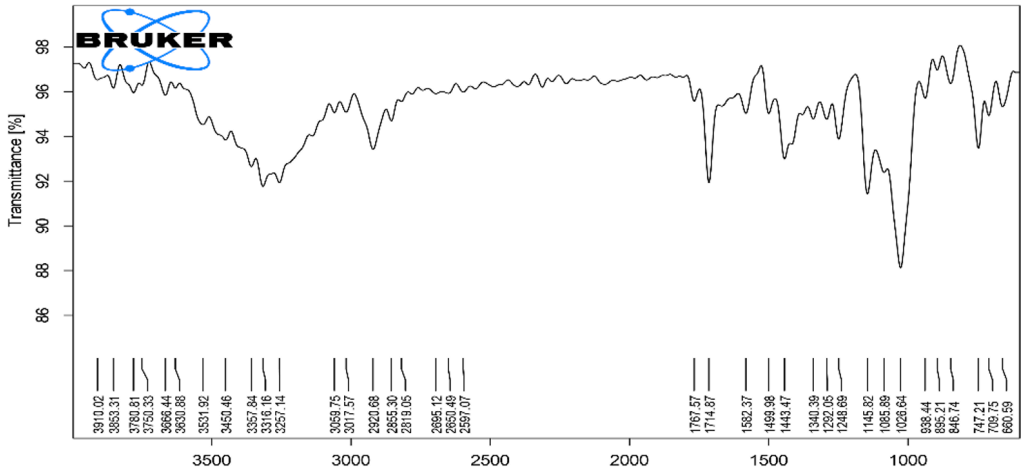

Figure 9: IR Spectra of F4

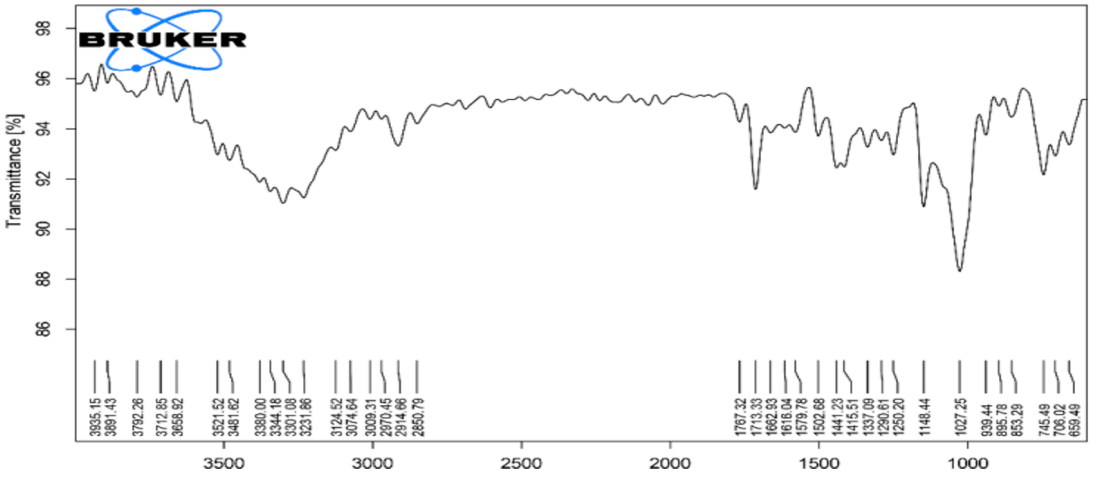

Figure 10: IR Spectra of F5

DSC studies of pure drug and F5

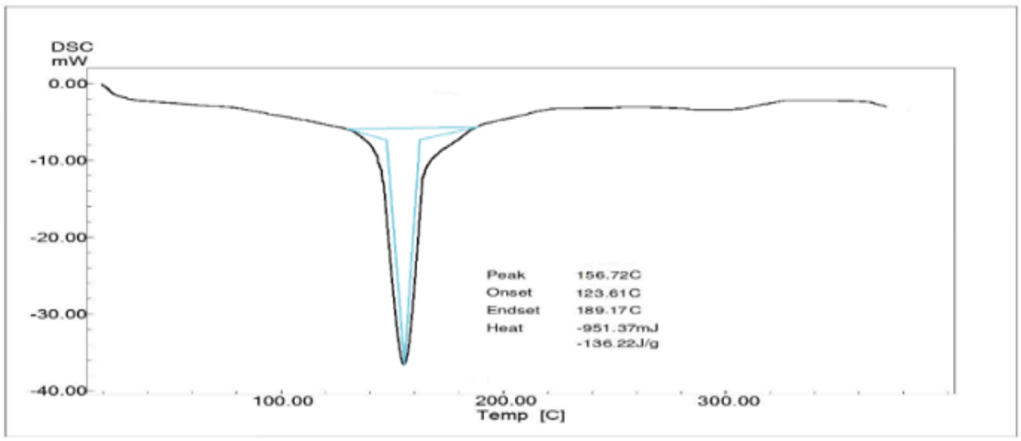

Figure 11: DSC thermogram of aceclofenac

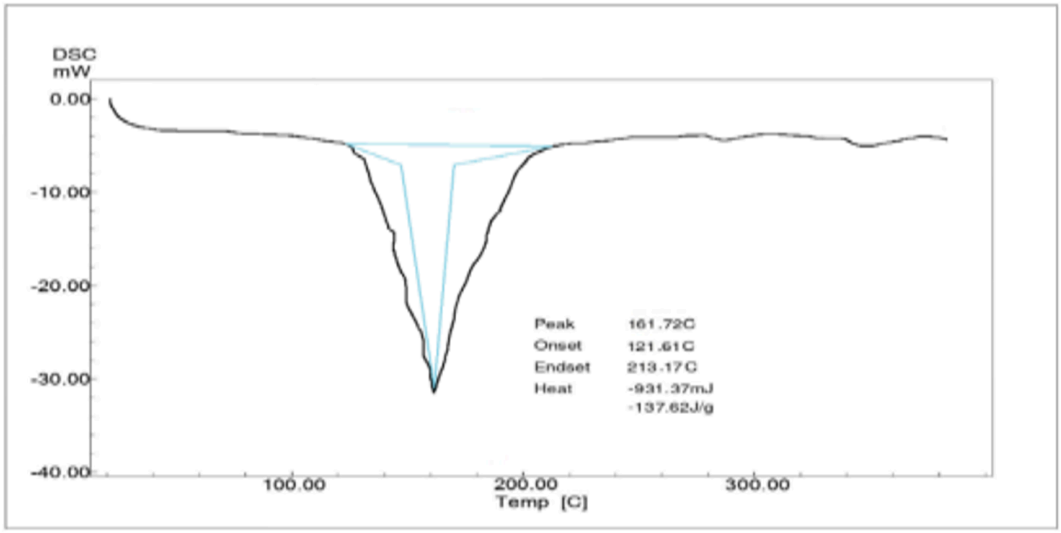

Figure 12: DSC thermogram of F5

***In-Vitro* Dissolution Studies**

Table 5: In vitro dissolution profile of Aceclofenac, F1 to F5.

Cumulative drug release						
Time (min)	**Pure Drug**	**F1**	**F2**	**F3**	**F4**	**F5**
0	**0**	**0**	**0**	**0**	**0**	**0**
5	5.68±0.43	60.10±0.72	61.44±0.30	62.73±0.79	64.38±2.03	68.03±3.39
10	10.39±0.23	61.12±0.94	63.46±0.26	64.70±0.70	66.82±1.38	71.57±3.61
20	13.84±1.42	62.73±0.92	64.49±0.32	66.52±1.35	69.75±1.59	74.20±2.52
30	15.74±0.52	63.68±0.75	65.77±0.43	68.92±1.36	72.86±1.09	77.67±2.06
40	20.15±0.25	64.54±0.72	67.39±1.08	71.25±1.73	74.93±0.92	80.15±1.26
50	21.26±0.12	66.03±0.71	68.51±1.14	73.10±0.97	76.87±0.27	82.67±0.95
60	22.32±0.42	67.29±0.75	70.94±0.89	75.77±0.94	80.09±0.78	85.35±0.71

Values are mean ± SD, n=3

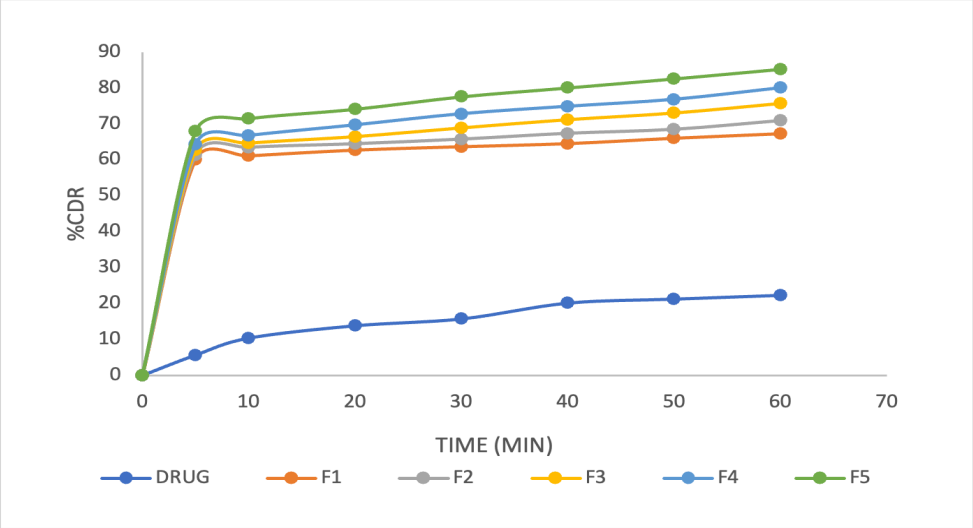

Figure 13:Comparison study of *In- vitro* dissolution profile of Aceclofenac, F1 to F5.

Table 6: First order kinetics of Aceclofenac, F1 to F5

Log% Drug Remaining						
Time(min)	**Pure Drug**	**F1**	**F2**	**F3**	**F4**	**F5**
0	2	2	2	2	2	2
5	1.974	1.601	1.586	1.571	1.552	1.505
10	1.952	1.590	1.563	1.548	1.521	1.454
20	1.935	1.571	1.550	1.525	1.481	1.411
30	1.925	1.560	1.534	1.492	1.434	1.349
40	1.902	1.550	1.513	1.459	1.399	1.298
50	1.896	1.531	1.498	1.430	1.364	1.239
60	1.890	1.515	1.463	1.384	1.299	1.166

Figure 14: Comparison study of first order kinetics of Aceclofenac, F1 to F5

Table 7: Higuchi model for Aceclofenac, F1 to F5

% Cumulative Drug Release						
$\sqrt{t}$	PURE DRUG	F1	F2	F3	F4	F5
0	0	0	0	0	0	0
2.236	5.686	60.107	61.440	62.730	64.382	68.034
3.162	10.397	61.121	63.469	64.701	66.802	71.571
4.472	13.846	62.730	64.498	66.527	69.759	74.208
5.477	15.744	63.686	65.773	68.962	72.860	77.672
6.324	20.150	64.542	67.397	71.252	74.933	80.150
7.071	21.266	66.034	68.513	73.107	76.875	82.672

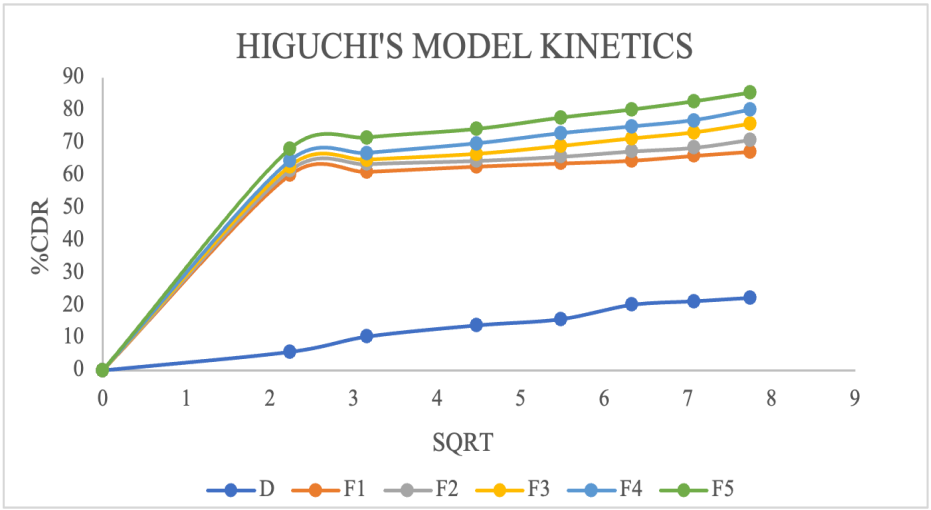

Figure 15: Higuchi model for Aceclofenac, F1 to F5

Table 8: Korsemeyer peppa's model for Aceclofenac, F1 to F5

Log % Drug Release						
Log Time	**Pure Drug**	**F1**	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0	0
0.698	0.754	1.779	1.788	1.797	1.809	1.833
1	1.016	1.786	1.802	1.810	1.824	1.854
1.301	1.141	1.797	1.809	1.823	1.843	1.870
1.477	1.197	1.804	1.818	1.838	1.862	1.890
1.602	1.304	1.809	1.828	1.852	1.874	1.903
1.698	1.327	1.819	1.835	1.864	1.885	1.917
1.778	1.348	1.828	1.850	1.879	1.903	1.931

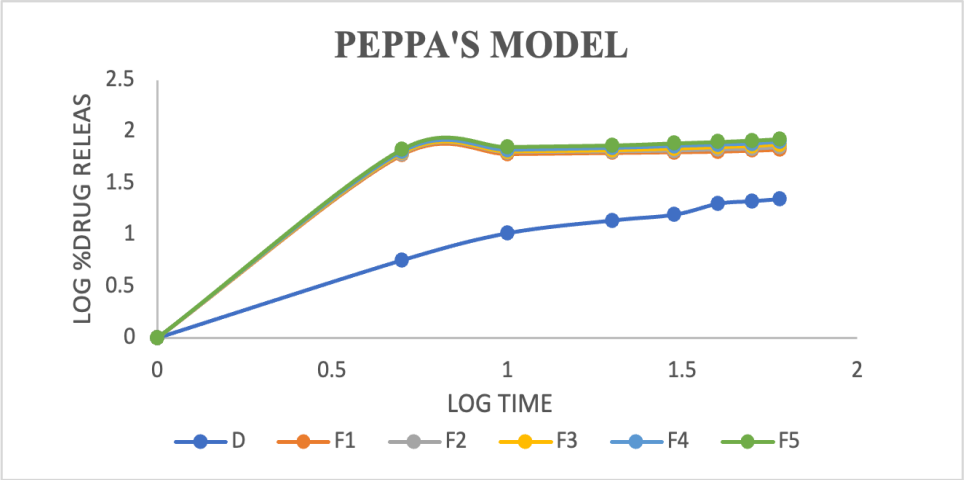

Figure 16: Korsmeyer Peppas model graph for Aceclofenac, F1 to F5

Table 9: Regression Co-efficient values (R^2) and n values of Aceclofenac, F1 to F5 according to different kinetic models

Formulation code	**Zero order**		**First order**		**Higuchi**	**Peppas**	
	N	**R^2**	**n**	**R^2**	**R^2**	**n**	**R^2**
F1	0.604	0.341	0.011	0.415	0.593	0.053	0.939
F2	0.647	0.361	0.012	0.459	0.613	0.051	0.917
F3	0.726	0.410	0.015	0.562	0.660	0.072	0.929
F4	0.784	0.433	0.018	0.624	0.684	0.084	0.958
F5	0.844	0.439	0.022	0.678	0.691	0.087	0.960

Model independent analysis

Mean dissolution time and drug efficacy

Table 10: MDT and DE of drug and formulation.

SI Num	Formulations	MDT	DE
1	Pure Drug	18.527	69.12
2	F1	5.365	91.05
3	F2	6.073	89.87
4	F3	6.302	89.49
5	F4	6.760	88.73
6	F5	6.676	88.87

Discussion

Calibration study of aceclofenac was developed and good linearity with regression coefficient of 0.998 (r^2 value) was observed so the tested concentration range obeyed Beer-Lambert's law. In the determination of solubility of aceclofenac maximum absorbance was shown by drug which was dissolved in phosphate buffer (pH 6.8) at 275nm. For the compatibility studies between drug and excipients, IR spectrum of pure drug and formulations and excipients was recorded. The similar peaks are obtained in drug and formulations which indicates that the pure drug functional group were present in all formulations. The DSC thermogram containing the drug shows the peak at 156^{o}C and formulation F5 shows the peak at 161^{o}C.In the solubility studies of complexes in water, the complex F5 showed highest solubility compared to other complexes and pure drug. The results of *in-vitro* dissolution studies are shown in table number 5**.** The cumulative percentage of drug dissolution from pure drug to F5 ranges from 22.32 % to 85.35% and from the graph it shows that, the drug release was maximum in F5 compared to others. It indicates that the formulation which has more quantity of cyclodextrin shows more drug release due to complexation of cyclodextrin with drug. Here Aceclofenac inclusion complexes release kinetics are fitted in Korsemeyer Peppas equation. The n values are in between 0.5-1, so the release is following non fickinian dissolution kinetics. MDT and % DE was determined for the drug and prepared complexes are shown in the table 10 and the values varied between 18 to 40 min and 5.365 to91.05% respectively. The model independent parameters calculated for different complexes further supports the influence of concentration of complexing agent and surfactant on solubility. Aceclofenac complexes prepared were showed lower MDT and higher %DE compared to pure drug. This supports the observation that dissolution of drug is influenced by concentration of complexing agent.

Conclusion

Aceclofenac complexes are successfully prepared with different concentration of β cyclodextrin and span 60 by inclusion complex technique using kneading method. Complexes exhibited improved solubility and dissolution properties. Amount of complexing agent and surfactant affected the solubility of prepared complexes. The solubility and dissolution of the prepared complexes were improved compare to the pure drug. The complexes prepared at different concentration of βCD and span 60 i.e. F1, F2 F3, F4, F5. showed 67.29±0.75, 70.94±0.89, 75.77±0.94, 80.09±0.78, 85.35±0.71% CDR, at 60min. Variation in concentration of complexing agent and surfactant during complexes preparation significantly enhanced the dissolution of the Aceclofenac . The F5 complex showed better dissolution compared to other complexes and pure drug. Among the prepared complexes F1 complex showed better results in MDT and % DE studies. The FTIR studies of the complexes show good compatibility with drug and complexing agent. DSC studies showed that there was no appreciable change in the melting endotherm of prepared complexes compared to that of pure drug. The prepared formulation follows Korsemeyer- peppa's kinetics and shows non- fickinian phenomena.

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