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Enhancement of dissolution rate and bioavailability of Aceclofenac by Complexation with cyclodextrin

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ABSTRACT

Aceclofenac (ACE) is Nonsteroidal anti-inflammatory drug (NSAID). It is practically insoluble in water. In the present study attempt has been made to prepare and characterize inclusion complexes of Aceclofenac with β-CD and HP-β-CD. The phase solubility analysis indicated the formation of 1:1 molar inclusion complex of Aceclofenac with β-CD and HP-β-CD. Apparent stability constant (K_C) was 42.003 M^{-1} and 48.477 M^{-1} for β-CD and HP-β-CD complexes respectively. The inclusion complexes were prepared by three different methods viz. physical, kneading and co-precipitation method. The prepared complexes were characterized using FT-IR and differential scanning calorimetry. The inclusion complex prepared with HP-β-CD by kneading method exhibited greatest enhancement in solubility and fastest dissolution (98.61% ACE release in 60 min) of ACE. The inclusion complex containing ACE: HP-β-CD (1:1) was formulated into tablets using superdisintegrant like crospovidone and microcrystalline cellulose. The prepared tablet were evaluated for various post compression parameters like hardness, friability, weight variation, thickness, drug content and in-vitro dissolution.

Keywords: Aceclofenac, β-CD, HP-β-CD, Physical method, Kneading method, Co-precipitation method.

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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 [1] etc. Among the various methods, cyclodextrin complexation is an industrially accepted technique [2].

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 spondylatis. ACE is practically insoluble in water and aqueous fluids [2-6].

Cyclodextrins are cyclic oligosaccharides, containing six, seven or eight glucopyranose units (α, β or γ respectively) obtained by the enzymatic degradation of starch [7]. 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 [2, 7]. 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.

EXPERIMENTAL

Materials

Aceclofenac was a gift sample obtained from Amoli Pharmaceutical Pvt.Ltd. Mumbai, India. Both β-Cyclodextrin and Hyroxypropyl β-Cyclodextrin were gift samples obtained from Gangwal Chemicals Pvt. Ltd. Mumbai, India.

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Methods

Phase Solubility Studies

Phase solubility studies were carried out according to the method reported by Higuchi and Connors [8]. An excess of Aceclofenac (50 mg) was added to 20 ml portions of distilled water, each containing variable amount of β-CD or HP-β-CD such as 0, 1, 3, 6, 9, 12, and 15 x 10^{-3} moles/liter. All the above solutions with variable amount of β-CD or HP-β-CD were shaken for 72 hours. After shaking, the solutions were filtered and their absorbance was noted at 275 nm [9]. The solubility of the Aceclofenac in every β-CD or HP-β-CD solution was calculated and phase solubility diagram was drawn between the solubility of Aceclofenac and different concentrations of β-CD or HP-β-CD.

Physical mixture [10]

ACE with β-CD in different molar ratios (i.e. 1:1M, 1:2M) and with HP-β-CD in ratio (i.e., 1:1M) were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 80 and stored in a desiccators over fused calcium chloride. The formulation codes are given in table 1.

Kneading method [10]

ACE with β-CD in different molar ratios (i.e. 1:1M, 1:2M) and with HP-β-CD in ratios (i.e.1:1M) were taken. First 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. The formulation codes are given in table 1.

Co-precipitate method [10]

ACE was dissolved in ethanol at room temperature and β-CD & HP-β-CD was dissolved in distilled water. Different molar ratios of ACE and β-CD (1:1M and 1:2 M) and ACE and HP-β-CD (1:1 M) 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. The formulation codes are given in table 1.

Drug Content Estimation [11]

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 10 ml volumetric flask and the volume is adjusted up to the mark with same solvent. The absorbance of the

solution was measured at 275 nm using appropriate blank. The drug content of Aceclofenac was calculated using calibration curve.

IR Spectroscopy

The IR spectra of Aceclofenac and their complexes were obtained by KBr pellet method by JASCO FT/IR-5300 spectrometer.

Differential Scanning Calorimetry (DSC)

The samples were analyzed by DSC using a Mettler Toledo SR System. The samples were placed into pierced aluminum container.

In vitro dissolution studies for Aceclofenac -CD complexes [12]

In-vitro dissolution of ACE inclusion complex was studied in USP XXIV dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of phosphate buffer of pH 7.4 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 ACE 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 ACE released was calculated and plotted against time and compared with pure drug.

Preparation of tablet

The complex of ACE-HP-B-CD was prepared into tablet by direct compression method containing 100 mg of ACE. The complex, crospovidone and microcrystalline cellulose were passed through sieve # 80. All the above ingredients were properly mixed together. Talc and magnesium stearate were mixed. The mixture was then compressed in to tablet. The formulation of tablet is shown in table 2.

Evaluation of Tablet [13]

The prepared tablets were evaluated for weight variation, hardness and friability. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. The hardness of 6 tablets was determined using the Monsanto hardness tester. Friability was determined by first weighing 10 tablets after dusting and placing them in a friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablet was recorded and the percent friability was calculated.

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In vitro dissolution study [14]

In-vitro dissolution of tablet was studied in USP XXIV dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of phosphate buffer of pH 7.4 was used as dissolution medium. The stirrer was adjusted rotate at 75 rpm. The temperature of dissolution media was previously warmed to 37 $\pm$ 0.5°C and was maintained throughout the experiment. 1 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 pH 7.4. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Percentage amount of Aceclofenac released was calculated and plotted against time. For comparison, the dissolution of marketed tablet was studied.

RESULTS AND DISCUSSION

Phase Solubility Studies

The complexation of ACE with β-CD and HP-β-CD was investigated by Phase Solubility Studies. The phase solubility diagram for complex formation is shown in fig.1.The aqueous solubility of ACE was increased linearly as a function of concentration of CD. The phase solubility diagram can be classified as type A_L according to Higuchi and Connors. It is assumed that the increase in solubility observed was due to the formation of a 1:1 M inclusion complex. The solubility constant (Kc) was calculated from the slope of the linear plot of the phase solubility diagram according to equation, Kc = slope / S_0 (1- slope) where S_0 is the solubility of the drug in absence of CD. The calculated Kc value was 42.003 M^{-1} and 48.477 M^{-1} with β-CD and HP-β-CD respectively.

Drug Content Estimation

The inclusion complexes prepared by physical mixture and kneading method showed nearly 100 % drug content. But the inclusion complexes prepared by Co-precipitate method were found to be slightly less.

IR Spectroscopy

IR Spectra of pure drug and inclusion complexes of Aceclofenac with β-CD and HP-β-CD prepared by different methods are given in fig. 2. As clearly seen from the spectra, the characteristic peaks of ACE at 750, 1396, 1627, 3114 and 3319 were modified significantly as a result of complex formation.

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Table 1: Different formulations of Aceclofenac with β-Cyclodextrin and Hydroxypropyl-β-Cyclodextrin

Method	Drug to Carrier	Drug to Carrier ratio	Code
Physical Mixture	ACE: β-CD	1:1	ABP_1
	ACE: β-CD	1:2	ABP_2
	ACE: HP-β-CD	1:1	AHP_1
Kneading Method	ACE: β-CD	1:1	ABK_1
	ACE: β-CD	1:2	ABK_2
	ACE: HP-β-CD	1:1	AHK_1
Co-precipitation	ACE: β-CD	1:1	ABC_1
	ACE: β-CD	1:2	ABC_2
	ACE: HP-β-CD	1:1	AHC_1

Table 2: Formula for Preparation of tablet (Each tablet)

Si. No	Ingredients	Quantity (mg)
1	ACE:HP-β-CD	536
2	Crospovidone	10
3	Microcrystalline cellulose	50
4	Talc	2
5	Magnesium Stearate	2

Table 3: Evaluation of tablets containing Aceclofenac-HP-β-CD

Formulation code	Hardness	% Friability	Deviation in weight variation test (%)	Drug content (%)
AHK_1 Tablet	4.0 ± 0.41	0.87 ± 0.12	600 ± 0.09	98.26 ± 0.11
Marketed Tablet	4.5 ± 0.37	0.76 ± 0.36	300 ± 0.06	97.46 ± 0.41

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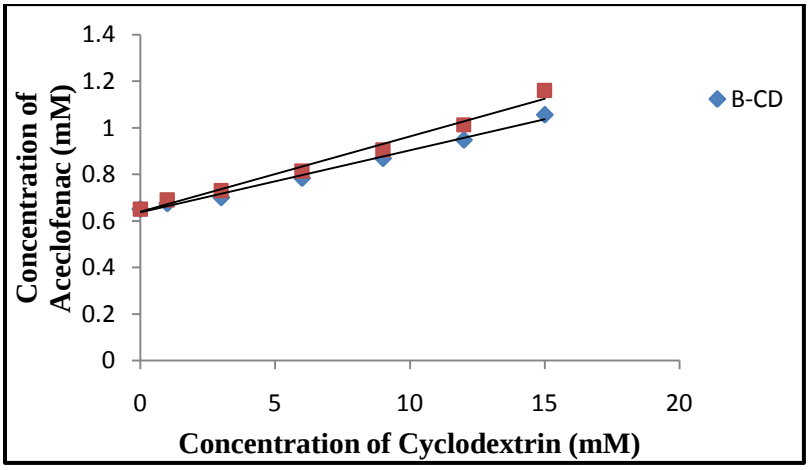

Fig.1: Phase solubility diagram of Aceclofenac with β-CD and HPβ-CD

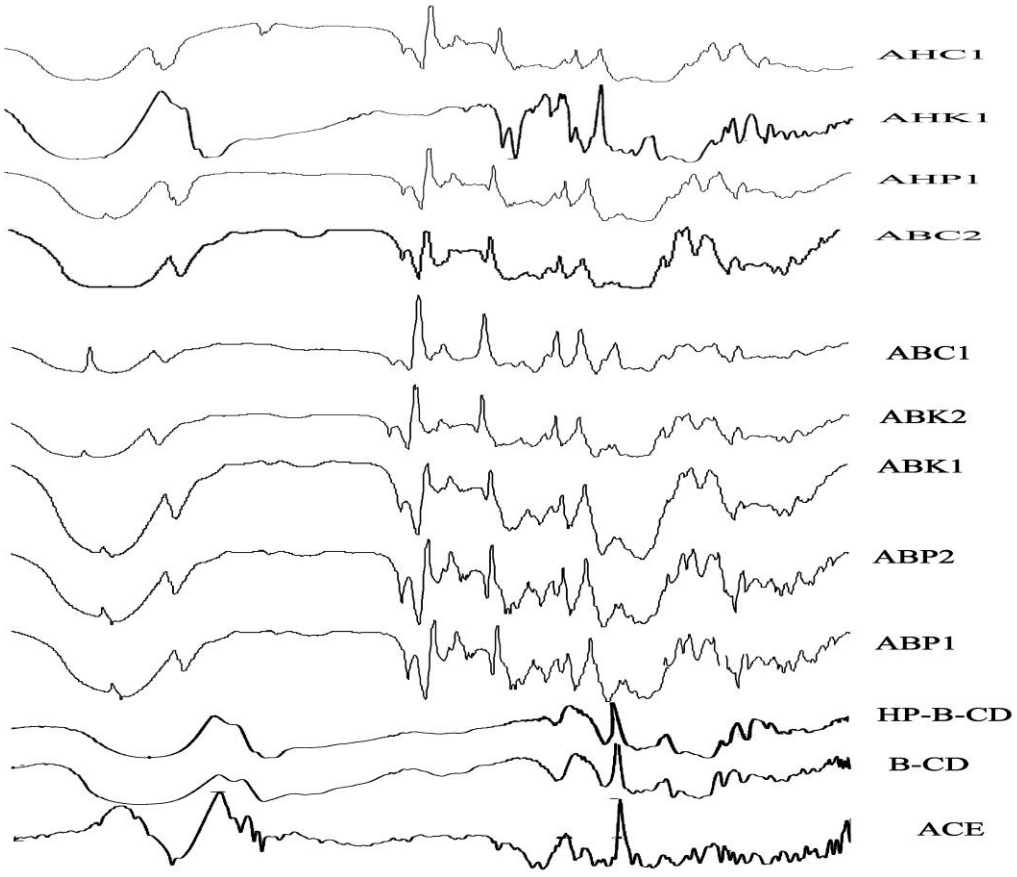

Fig.2: IR spectra of ACE, β-CD, HP-β-CD and complexes

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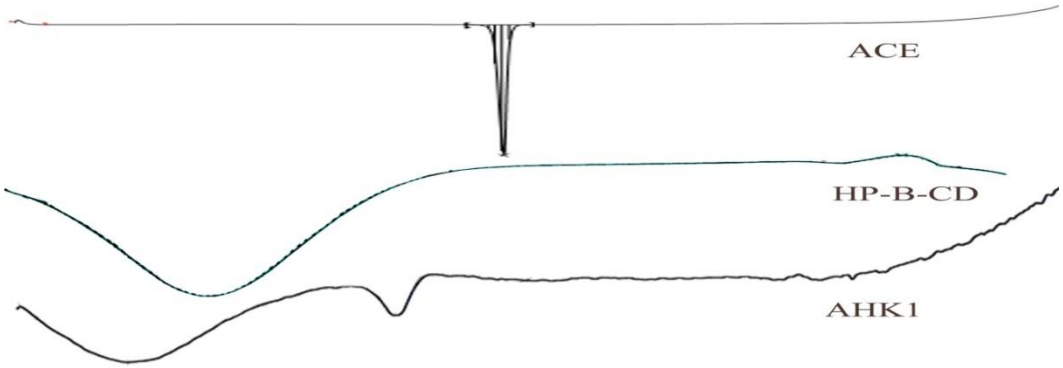

Fig.3: DSC thermogram of ACE, HP-β-CD and AHK_1

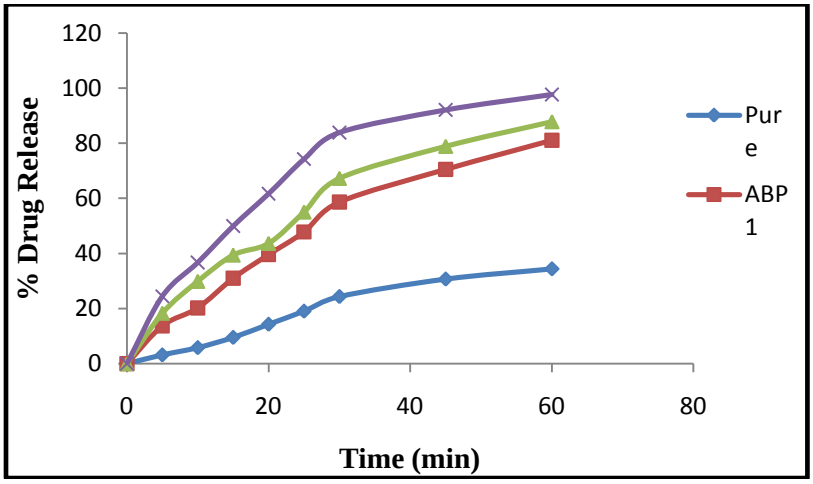

Fig.4: Dissolution profile of pure ACE, ABP_1, ABP_2, AHP_1

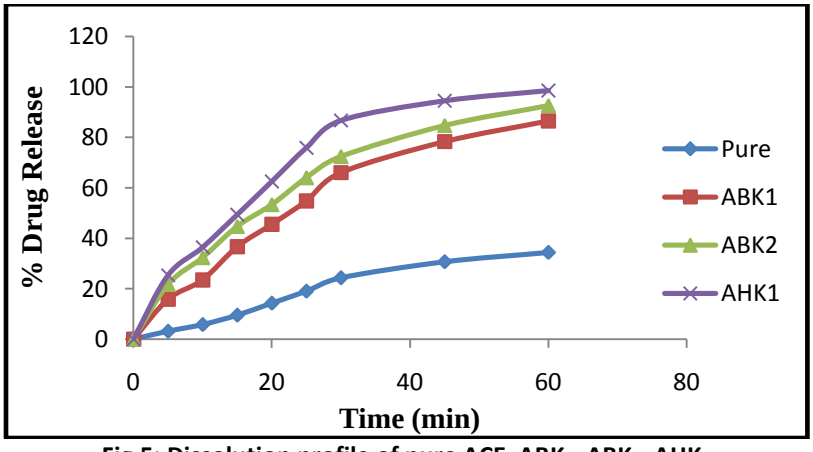

Fig.5: Dissolution profile of pure ACE, ABK_1, ABK_2, AHK_1

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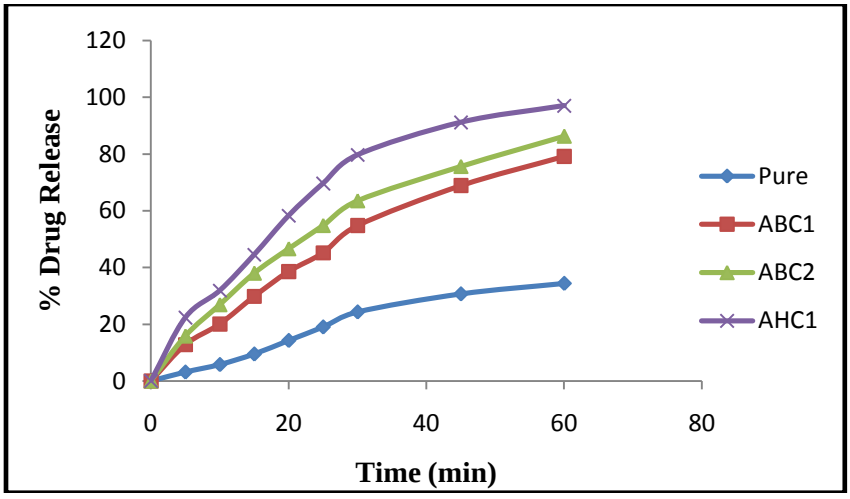

Fig.6: Dissolution profile of pure ACE, ABC_1, ABC_2, AHC_1

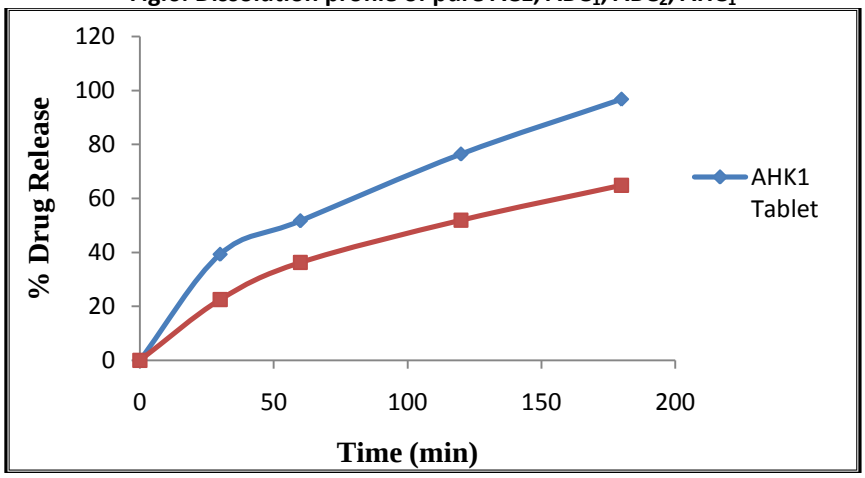

Fig.7: Dissolution profile of AHK_1 Tablet and Marketed tablet

Differential Scanning Calorimetry (DSC)

The thermal behavior ACE-HP-β-CD complex was studied using DSC in order to confirm the formation of complex. DSC thermogram of ACE, HP-β-CD and AHK_1 are shown in fig. 3. The DSC thermogram of ACE showed an endothermic peak at 151^{o}c corresponding to its melting point. The thermogram of AHK_1 showed endothermic peak at 127^{o}c which is different from the pure drug, which gives clear evidence that there is formation of the complex.

In vitro dissolution study

The dissolution characteristics of ACE (pure drug) and complexes are shown in fig. 4, 5 and 6. The inclusion complexes produces pronounced enhancement in its dissolution rate than pure drug. The inclusion complexes prepared with HP-β-CD shows higher dissolution rate than the inclusion complexes prepared with β-CD. Among these the complex prepared with HP-β-CD i.e. formulation AHK_1 shows higher dissolution rate than the other methods.

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Evaluation of tablet

Hardness, % friability, weight variation and drug content of tablet is given in table 3. The hardness of tablet was in the range 4 - 4.5 kg/sq.cm. The percent weight loss in the friability test was less than 1 %. The tablets were found to contain the Aceclofenac within 100 ± 2% of the label claim.

Dissolution of AHK_1 tablet shows higher dissolution (96.77) than the marketed tablet (64.89) shown in fig. 7.

CONCLUSION

Cyclodextrins like β-CD and HP-β-CD can be used to prepare inclusion complexes of ACE with improved solubility of the drug. ACE formed inclusion complexes with β-CD and HP-β-CD in 1:1 M ratio. All inclusion complexes showed increase in dissolution rate than pure drug. The inclusion complex prepared with HP-β-CD by kneading method showed highest enhancement in dissolution profile. AHK_1 Tablet showed higher dissolution rate than marketed ACE tablet.

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