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CHARACTERIZATION OF FASTER RELEASE TABLET OF ACECLOFENAC USING BETA-CYCLODEXTRIN IN PRESENCE OF SODIUM STARCH GLYCOLATE

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ABSTRACT

Phase solubility profile of aceclofenac with beta – cyclodextrin (B-CD) classified as an AL - type, confirming 1:2 stoichiometric inclusion complex. Along with ratio 1:2 the nearer ratios 1:1 and 2:1 was also prepared by kneading method and those were characterized by X – ray diffraction and FTIR spectra. The above complexes were prepared as tablets with and without sodium starch glycolate (2%) (SSG) (sarsija et.al,2006) as superdisintegrate. Precompression parameters like tapped density, Carr's index, bulk density and angle of repose were determined. The tapped density of complex were found between 0.55 and 0.57 g/cc and the carr's index were 16.0 and 18.0% .Average bulk density and angle of repose was found to be 0.46 g/cc and less than 40^{o} respectively indicate a good flow property of the kneading complex.

The post compression physical parameter like width, thickness and diameter of the tablets were recorded. Friability, hardness, drug content was found to be in normal range limit. However disintegration test of tablet contain B-CD and SSG result in 2-3 min. The order of faster dissolution rate observed in various ratios with SSG was 1:2 complex > 1:1 complex > 2:1 complex > pure drug, in acidic medium contains 1% SLS. Another batch was also prepared in the same ratio with BCD, this batch have higher solubility of

aceclofenac when 2% SSG added; the release was 30 min faster in 1.2 pH medium containing 1% sodium lauryl sulphate (SLS). From the above result we conclude the Inclusion complex of drugs and B-CD ratio 1:2 with SSG as superdisintegrate could be used as an effective technique for immediate release of aceclofenac.

Key words: Faster release tablet; β- Cyclodextrin; Sodium starch glycolate; Aceclofenac

INTRODUCTION

Faster relief of pain is always a demand from athlete to ordinary person to avoid unpleasant sensation. Most of the NSAIDs are poorly soluble and their solubility is less than 1mg/ml. Aceclofenac is a NSAID having very sparingly solubility of 0.01mg/ml. This raises difficulties in pharmaceutical formulation and leads variation in bioavailability of oral and parental dose.

The β and γ - cyclodextrin [CD] and several of their derivations are unique in having the ability to form molecular inclusion complexes with hydrophobic drugs having poor solubility.

Cyclodextrins are cyclic malto – oligosaccharide consisting of 6, 7 and 8 glucose units and are called α, β and γ respectively. These three CD are having differentiated by MW, cavity diameter, cavity depth and solubility.

The B-CD is known to be harmless to all living organisms. Its oral administration does not result in any acute toxicity and even the highest, does not lead mortality when CD is fed to animal simultaneously long term administration does not result in any significant change in the organs or biological blood values. However intramuscular administration of higher dose of B-CD results in the ulceration and IV administration leads to nephrotoxicity and hemolytic effect (Challa R. et.al 2005).

Sarsija et.al., (2006) have studied tablets with superdisintegrate could be used as an effective and efficient technique for enhancing the dissolution rate of poorly soluble NSAID's like aceclofenac. We made an attempt of using both BCD and super disintegrate to increase the dissolution rate.

MATERIALS AND METHODS

Aceclofenac was received as a gift sample from M/s. Khandelwal laborations Ltd Mumbai. Beta Cyclodextrin and SSG were purchased from S.D fine chemicals. All the other chemicals used were of Analytical grade.

Phase Solubility Studies

This study permits to evaluate the affinity between B-CD and aceclofenac in water and it was performed according to the method reported by Higuchi and Connors. Aceclofenac amount that exceeded its solubility was taken in a screw cap vials containing 20ml of various concentration of B-CD (1-5mm) solution in water. The vial is shaken for 48 hrs in 25^{o}c. The aliquots were filtered through Whattman filter paper and a portion of sample was analyzed by UV spectrophotometer (UV – 1700, Shimadzu Japan), no shift in λ max was confirmed the complex at 275 nm. These procedures were conducted in triplicate. The stability constant K_c was calculated in linear region by the equation K_c = slope / S_0 (1-slope). The K_c values indicated that the inclusion complex formed by kneading method were quite stable.

Aceclofenac and B-CD was weighted in 1:1 ratio, the B-CD is kneaded like a paste with small amount of water in mortar. Aceclofenac was dissolved in methanol and added to the above mortar. Several hours of grinding of paste in mortar and result in evaporation of solvent leads the powder. This powder was dried in hot air oven at 40 – 45^{0}C and passed through sieve no. 44 and stored in airtight container and the same procedure was repeated for various ratios of drug and BCD complex.

X-ray Diffraction study

X-ray diffraction furnishes a rapid and accurate method for the interaction and identification. The sample was recorded by using automated Philips Holland-PW 1710 scanner at 35KV power input and 20mA current. Scanning speed of the goniometer used through the study was 1^{0} / min.

FT-IR spectra

The FT-IR Spectra were recorded in Jasco FT/IR – 4100 type A model. Samples were prepared in KBr disc (2mg sample in 200mg KB). The scanning range was 400 – 4000 cm^{-1}, resolution was $4cm^{-1}$.

Pre compression parameters

Bulk density was determined by 10gm of complex powder which were introduced into a clean, dry 100ml measuring cylinder, the volume was recorded as triplicate and the bulk density was calculated by using formula. The same procedure is repeated after tapping 25 times to find out tapped density. Ratio of both densities was used to finding out carr's index. The angle of repose was calculated by height and radius ratio of pile.

Post compression study

Width, thickness, diameter and hardness were measured by tablet tester model C-WW TDH 500N, Campbell electronics. Roche friabilator at the speed of 25rpm for 4 mins dropping the tablets at a distance of six inches with each revolution were used to find the tablet strength. 20 tablets were randomly weighed and average weight was calculated for weight variation test.

Content Uniformity of aceclofenac

Aceclofenac contents were estimated by UV spectrophotometer at 275nm. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range 0-10mg/ml. The standard drug solution was assayed repeatedly (n=6) the mean error and relative standard deviation was found to be 0.8% and 1.4% respectively.

In-Vitro disintegration Time

The in vitro disintegration test was performed by Campbell disintegration test apparatus. The tablet was placed in each of the 6 tubes and the assembly was suspended in liquid medium in a 1000ml beaker. The beaker filled in such a way that the wire mesh at the highest point was at least 35mm below the surface of the liquid and its lowest point was at least 25mm above the bottom of the beaker.

In- Vitro Drug Release Studies

The prepared tablet drug release was studied using USP XXII type 1 apparatus, with 900 ml of 1.2 pH with 1% sodium lauryl sulphate (SLS) as dissolution medium maintained at 37 ± 0.5^0c for 2 hours at 50 rpm. 1ml of sample was withdrawn after every 10mins and was replaced by an equal volume of fresh dissolution

medium of same pH solution. Collected samples were analyzed spectro photometerically at 275nm and release were recorded.

RESULT AND DISCUSSION

The phase solubility study of Higuchi confirmed the ratio AL type 1:2, and nearer ratios 1:1 and 2:1 was also prepared as complex and evaluated. Inclusion complex of aceclofenac with beta-cyclodextrin was prepared by kneading method. Various batch prepared were evaluated for its physical properties like bulk-density, tapped density, angle of repose and carr's index are mentioned in table 2. Tapped density of complex mixture were found between 0.55 and 0.57 g/cc and also the carr's index of complexes were found between 16.0 and 18.0%. Average bulk density and angle of repose was found to be 0.46 g/cc and less than 40^0 respectively indicate a good flow property of the kneading complex.

Table No.2: Precompression study of Aceclofenac complex

S.No.	Parameters	1:1	1:2	2:1
1	Bulk density(g/cc)	0.46	0.47	0.45
2	Tapped density(g/cc)	0.55	0.56	0.55
3	Angle of repose(Ɵ)	29.86	30.11	39.68
4	Carr's index	17.85	16.07	18.18

DRUG AND CARRIER INTERACTION:

The result obtained from TLC was not conclusive as the R_f value of complex and reference were not significantly different and no shift in $\lambda_{max.}$ So the X- ray diffraction analysis was carried out to confirm the change in the crystalline nature of the drug in inclusion complex and pure form. The X – ray diffraction pattern shows sharp intense and characteristics multitude of peaks, indicating that the crystalline solid phase

had been attained. The characteristic peaks are situated 0^0 to 40^0 (2 θ) were used for conformation studies. X-Ray diffraction analysis of aceclofenac and cyclodextrin is given in figure 4.

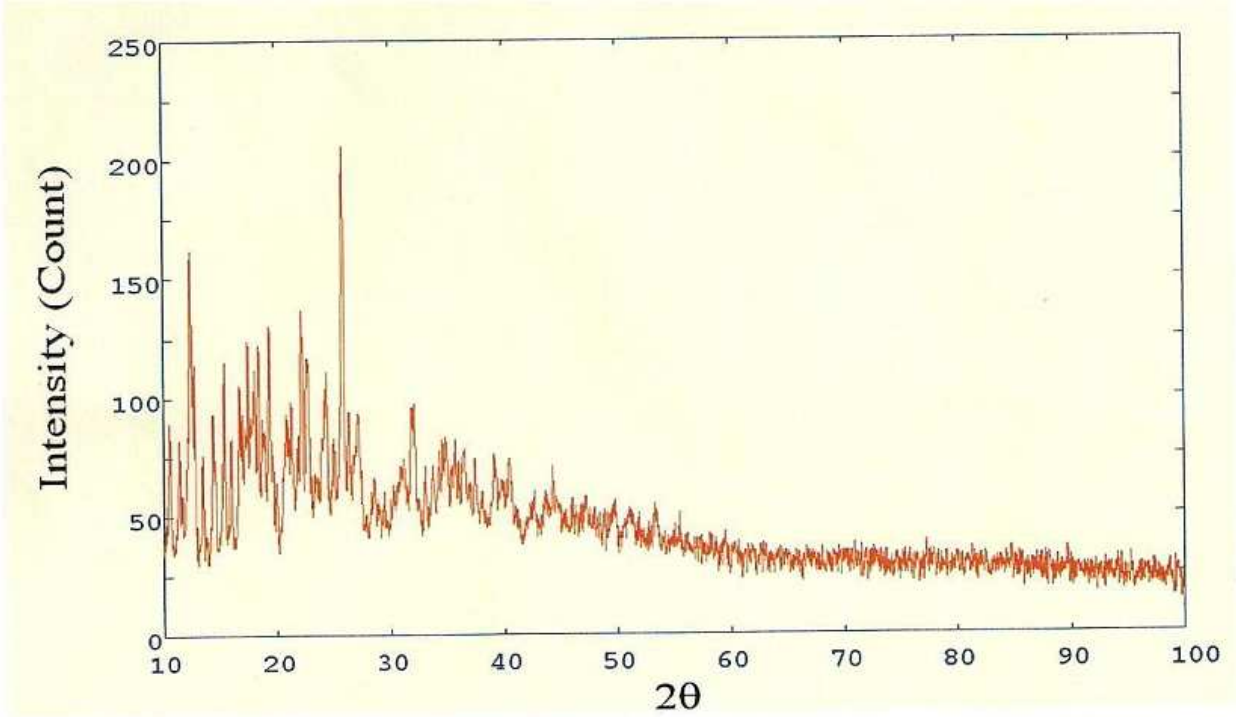

Fig. 4.: X-Ray diffraction pattern of Kneading Method of 1:2

The drug characteristics peaks were observed at 6, 10, 18 and 28 at 2θ values with intensities of 1100, 1350, 820 and 790 respectively. The X-ray diffraction pattern of B-CD also exhibited well defined peaks at 8, 13 and 25 at 2θ values with intensities of 560, 950 and 650 respectively. The diffractogram of that complex displayed, well defined peaks at 10, 25 and 28 at 2θ with intensities 170, 120 and 220 respectively. Even though the complex displayed characteristic pattern corresponding to the crystalline drug, the peak intensities were reduced, indicating the decrease in the drug crystalinity, which may be responsible for the increased solubility of the solid complex when compared to that of the pure drug. (sarasija et al 2006). The crystalinity was calculated by (RDC) relative degree of crystalline method RDC = Isam/Iref I – peak height.

FT –IR is highly sensitive spectral analytical method for all complexes and individual components were given in the figure 1-3. No significant charge in IR-spectra of kneaded complex was observed except broadening of peaks. This broadening was probably due to the restriction of bending and stretching vibration of the aceclofenac due to the B-CD cavity. A significant shift of carbonyl absorption band at 1769cm^{-1} assigned to carboxyl stretching. This may be indicative of the monomeric dispersion, as a consequence of the interaction with CDs through hydrogen bonding, which could result in its inclusion into the hydrophobic cavity of the B-CD.

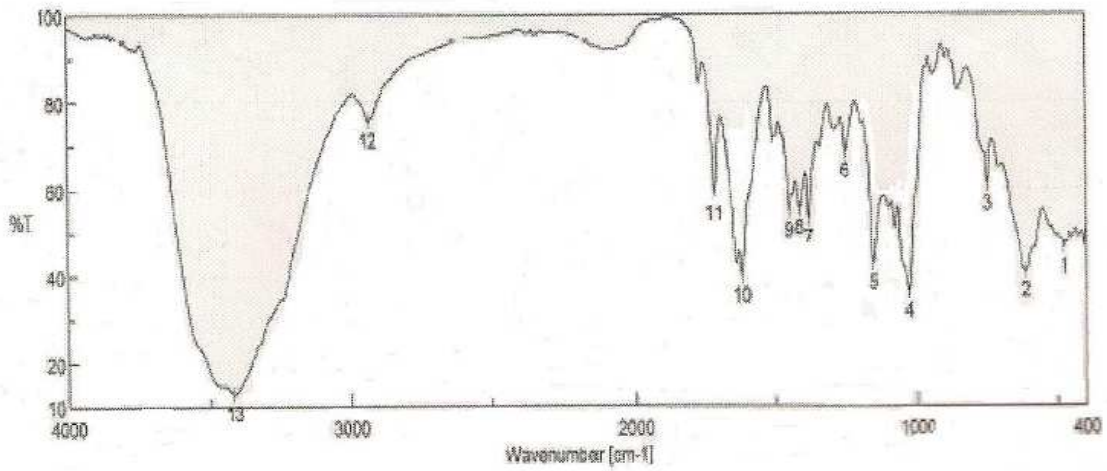

Fig. 1. FTIR spectra of Aceclofenac β-Cyclodextrin Complex (1:2)

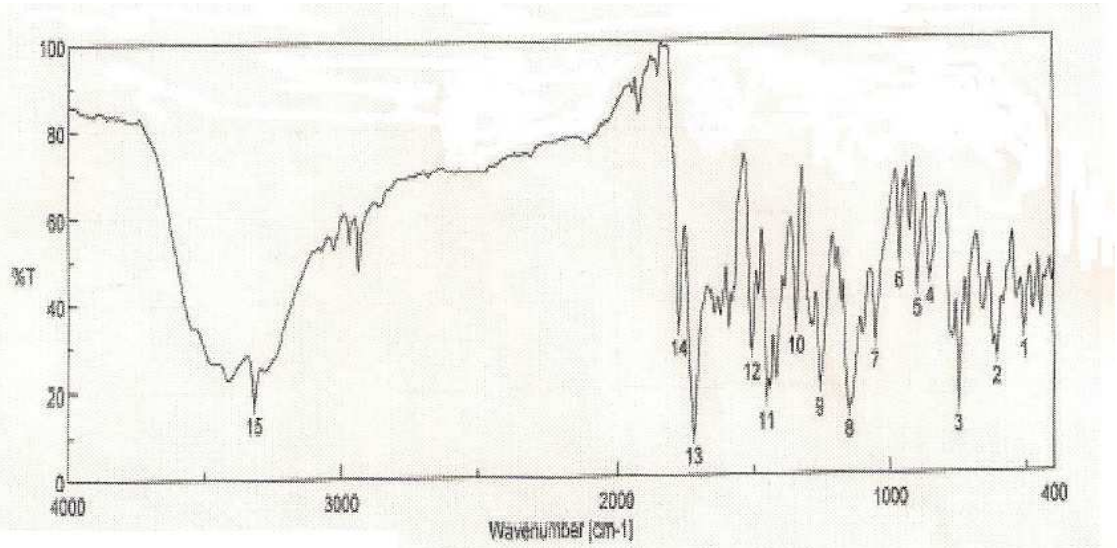

Fig. 2. FTIR spectra of Aceclofenac

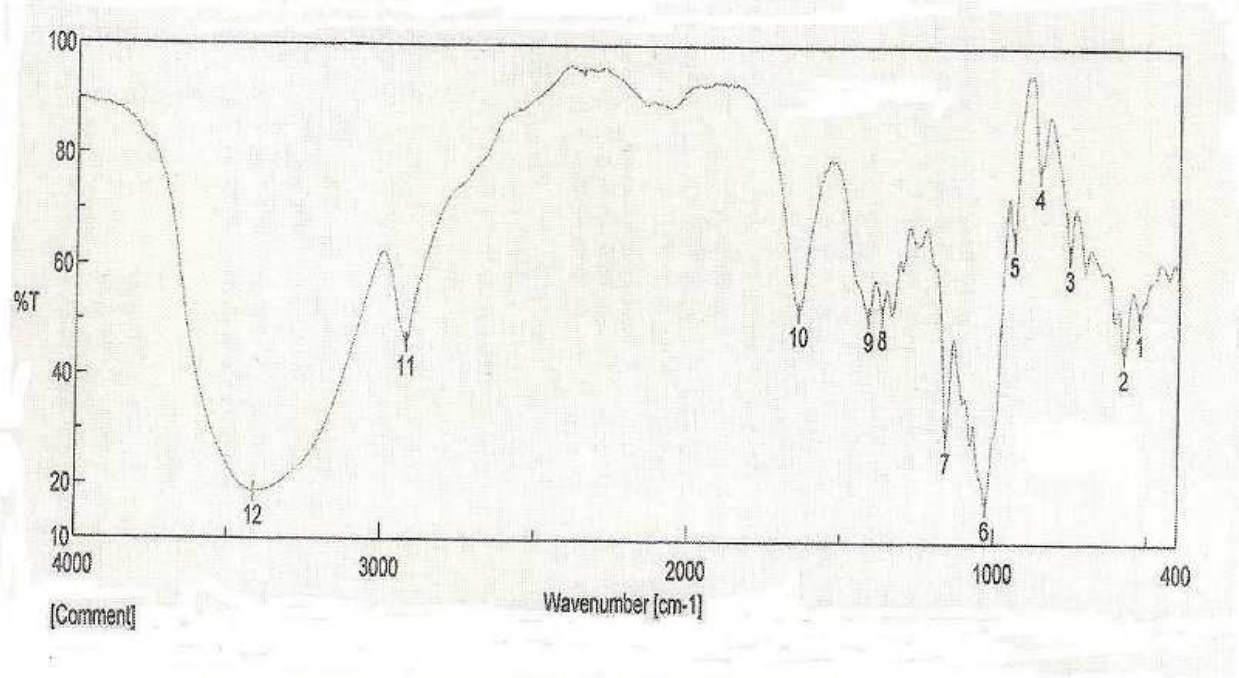

Fig. 3. FTIR spectra of β-cyclodextrin.

The complex mixture was then directly compressed as tablet with 2% sodium starch glycolate as super disintegrate by the following formula, given in table 1.

Table No.1: Formulation for Aceclofenac- β Cyclodextrin complex 2:1 ratio BP 100 mg.

S.No.	Ingredients	Formula for 1 tablet in (mg)	Formula for 50 tablets in (mg)
1	Aceclofenac-β CD complex	190	9500
2	Lactose	100	5000
3	Starch	10	500
4	S.S.G (Sodium starch glycolate)	6 (2%)	300
5	Talc	3 (3%)	150
6	Magnesium stearate	6 (2%)	300

The Hardness of tablets was found between 10.5 and 12.4 gm/tab. The friability of the all ratio tablets were found in acceptable limit (0.38 to 0.48%) and the disintegration time(2-3 mins) was exceptionally faster in tablets containing 2% SSG given in table 3.

Table No. 3: Evaluation of compressed different ratio aceclofenac tablets.

Tablets ratio	Width mm	Thickness mm	Hardness kg/tab	Friability %	Disintegration
1:1	8.38	4.5	10.50	0.38	18.5
1:2	12.93	4.10	10.60	0.42	22.0
2:1	12.98	3.72	11.44	0.48	20.4
SSG 1:1	11.90	4.8	10.96	0.42	4.5
SSG 1:2	13.45	5.2	11.90	0.56	3.0
SSG 2:1	14.10	5.2	10.53	0.52	5.2

The dissolution of drug aceclofenac from B-CD-aceclofenac complex was much higher than plain aceclofenac. Further SSG and B-CD- aceclofenac complex have showed higher and also rapid release than the plain aceclofenac in acidic (pH1.2) medium contain 1% SLS. The overall SSG containing tablets showed same amount of release but 30 min earlier than drug and BCD complex tablets given in table 4.

Table No. 4: SD± Percentage cumulative drug release of Aceclofenac in pH 1:2, Containing 1% SLS.

S.No.	Time (mins)	1:1	1:2	2:1	SSG + 1:1	SSG + 1:2	SSG + 2:1	Marketed formulations(Tablets)
1	10	42.62	46.42	30.10	54.63±0.3	69.56±0.9	66.46±0.2	54.36±0.5
2	20	48.12	51.67	42.40	62.34±0.7	74.74±0.7	68.44±0.7	62.34±0.3
3	30	54.45	67.31	51.92	66.18±0.2	83.60±0.6	69.36±0.4	66.18±0.7
4	40	60.03	72.45	56.25	66.89±0.8	87.84±0.2	70.97±0.5	66.89±0.4
5	50	69.36	74.06	66.46	72.36±0.6	89.60±0.3	74.20±0.5	69.21±0.2
6	60	70.97	77.65	68.44	74.33±0.4	90.18±0.1	76.40±0.3	69.65±0.6
7	70	74.20	79.93	74.55	77.29±0.5	90.91±0.9	78.80±0.6	71.62±0.7
8	80	75.66	82.59	77.15	80.26±0.6	91.64±0.3	78.10±0.4	72.59±0.3
9	90	79.49	83.12	78.23	81.61±0.2	94.34±0.8	85.80±0.2	74.36±0.5
10	100	80.57	86.91	79.11	81.41±0.1	94.24±0.6	86.02±0.1	76.63±0.8
11	110	81.56	89.26	80.92	81.31±0.9	94.04±0.9	86.50±0.5	77.01±0.4
12	120	82.46	90.98	81.61	81.30±0.4	94.00±0.3	86.60±0.7	82.40±0.3

N= 3 Values are average of triplicates

Among all ratio complex tested, the ratio 1:2 with SSG gave highest enhancement of dissolution rate and rapid release. The order of increasing dissolution rate with various complex ratios and superdisintegrate was, all complexes prepared SSG > 1:2 complex > 2:1 complex > 1:1 complex > plain aceclofenac.

The 1:2 ratio with SSG have a 69.56% of release at first 10min as compared but the marketed tablet have 74.36% at 90 min, So the entire release pattern is faster in 1:2 ratio containing SSG among all other ratios including marketed tablet. Further this investigation may suggest the formula given in table 1 for immediate release tablets of aceclofenac.

CONCLUSION

Thus aceclofenac and beta cyclodextrin ratio 1:2 contain 2% SSG as super integrant tablets found to be optimized for faster release of aceclofenac effectively. This may suggest the formula of table no.1 can be used to prepare oral immediate release conventional tablets of aceclofenac.

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