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SYNTHESIS AND EVALUATION OF β-CYCLODEXTRIN-EPICHLOROHYDRIN INCLUSION COMPLEX AS A PHARMACEUTICAL EXCIPIENT

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ABSTRACT

A water soluble *Beta*-cyclodextrin-epichlorohydrin complex (*β*-CDEPI) was synthesized by one-step condensation polymerization. Drug- *β*-CDEPI inclusion complexes were prepared and characterized. Inclusion complexes prepared using lyophilization technique was used to formulate orodispersible tablets. Compatibility studies showed no interaction and characterization proved substantial inclusion complex formation. Drug content was found between 97-99%. *In-vitro* disintegration time was found to be less than 3 minutes and all the formulations showed complete drug release of 100% within 15 minutes. The formulations were found to be stable for a period of 6 months. *β*-CDEPI polymer enhances the solubility and thus effectively can be utilized to improve the aqueous solubility of poorly water soluble drugs.

Keywords: *β*-cyclodextrin, epichlorohydrin, condensation polymerization, inclusion, complexation, famotidine.

1. INTRODUCTION

Cyclodextrins are cyclic oligosachharides with a hydrophilic external surface and a hydrophobic interior cavity. Of the cyclodextrins, β- cyclodextrin (β-CD) is the most widely used, because of its readily availability and pharmaceutically useful complexation characteristics with the widest range of drugs.

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But it suffers from drawback of low aqueous solubility due to which it has restricted applications in the pharmaceutical field[1].

To overcome these difficulties, the hydrophilic cyclodextrin derivatives have been developed to enhance the solubility, stability and oral bioavailability of the poorly water soluble drugs[2]. Two different ways have been reported to produce water soluble CD-polymers. The first type was prepared by radical polymerization of acryloyl cyclodextrin monomers. The synthesis of these monomers was carried out by acylation[3]. An alternative way to synthesize such CD- polymers is to chemically modify a pre- existing polymer. Methylated amorphous β-CD and crystalline heptakis- (2, 6- di- O- methyl) -β-CD were the most efficient chemically modified cyclodextrins[4]. However, methylated Cd- derivatives show high surface- activity and, as a consequence, are more systemically toxic than parent CDs. An alternative approach to CD modification is the use of CD polymers, which can offer the advantages of the amorphous state and CD- type complexation without toxic effects. Polycondensation of CD or CD derivatives with epichlorohydrin or other epoxy compounds such as ethylene glycol bis (epoxypropyl) ether or butylenes glycol bis (epoxypropylether) in aqueous solution offers the formation of β-CDEPI[5]. Water soluble, high molecular mass cross- linked β-CDEPI polymers increases the solubility, dissolution rate and bioavailability of poorly water- soluble drugs, often more effectively than the parent CDs[6]. Preparation of water soluble β-CD polymers was achieved by the reaction of β-CD with epichlorohydrin (EP) in an alkaline medium by a two-step procedure. First the β-CD was stirred with an excess of NaOH in order to form alcoholate sites. Then, EP was added to the suspension obtained. Hydroxyl groups can react with one reactive group of the bifunctional agent. The side chain obtained can further react in two different ways: the epoxy ring can react with another hydroxyl group of a second β-CD molecule, resulting in a glyceryl bridge connecting two CD cavities, or, the epoxy ring is hydrolyzed[7].

In this work famotidine was selected as model drug due to its poor aqueous solubility and evaluated whether the prepared β-CDEPI enhances the solubility, dissolution rate and hence the bioavailability of the poorly water soluble drug.

2. MATERIALS AND METHODS

2.1 Materials

Famotidine was obtained from strides Arco labs Ltd, Bangalore. β-cyclodextrin was purchased from S.D.Fine chemicals, Mumbai. Epichlorohydrin was purchased from Spectrochem Pvt Ltd, Mumbai. All other reagents used were of analytical reagent grade.

2.2 Synthesis of β-Cyclodextrin-epichlorohydrin (β-CDEPI) Complex

β-Cyclodextrin-epichlorohydrin (β-CDEPI) complex was synthesized by the modified method as reported earlier[8]. Briefly 5g of the β-CD was mixed with 10.00ml of 50%w/w sodium hydroxide solution and stirred for 24 hours at 25°C using a magnetic stirrer. To this mixture, 6.0 ml of epichlorohydrin was added rapidly and stirred continuously for 40 min at 400rpm. The reaction was stopped by the addition of 15ml of acetone. The reaction mixture was set aside for 30 min and acetone was removed by decantation. The solution was maintained at 50˚C overnight. After cooling, the solution was neutralized by the addition of 6N HCl (19.9ml). The resulting clear solution was evaporated to dryness in tray dryer at 50˚C. Absolute alcohol (44ml) was added to the obtained residue that resulted in formation of a white precipitate. The solution was decanted and the white product was dried at 50˚C for 24 hours. The product was size reduced to 1-2mm size.

2.3 Characterization of β-CDEPI complex

2.3.1 Phase aqueous solubility studies

Phase aqueous solubility studies were carried out according to the method reported by Higuchi and Connors[9]. An excess of famotidine was added to 10ml various concentrations of β- CDEPI solution, water and β- CD solution each containing 0, 2, 4, 6, 8 and 10 millimoles/ liter. All the above solutions were shaken in rotary shaker for 72 hours. After shaking, the solutions were filtered and their absorbance was measured spectrophotometrically at 287.5nm.

2.3.2 Melting point determination

Melting point of the β- CDEPI complex was determined by placing the β- CDEPI complex in a capillary tube and it was placed in thermoionic melting point apparatus and the temperature at which the complex melted was noted.

2.3.3 pH of 1% solution

The pH of 1%w/v solution of β- CDEPI complex in water was measured using a digital pH meter.

2.3.4 ^{1}H Nuclear Magnetic Resonance Studies

^{1}H Nuclear Magnetic Resonance spectra were recorded on Mercury- 300BB NMR spectrometer. Chemical shifts (δ) were reported in parts per million downfield using the internal reference standard dimethyl sulphoxide (DMSO)[10].

2.3.5 Determinationofmolecular weight by mass spectroscopy

Mass spectrometry is an analytical technique that measures the mass-to-charge ratio of charged particles. The detection was carried out by LCMS Shimadzu, Japan, using diethyl ether as solvent. The solvent used is methanol: water in the ratio 8:2 at a flow rate of 0.2ml/ min. The sample is analyzed using atomic pressure chemical ionizer.

2.3.6 Determination of residual solvent analysis by gas chromatography

Residual organic volatile impurities were determined as per ICH Harmonized Tripartite Guideline on Impurities[11]. Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specification.

The instrument used to measure residual solvent by GC chromatography was 1080- GCHR-0004, Agilent 7890A.Standard solution was prepared using mixture of methanol and acetone. 1µl of the prepared sample and standard solutions were injected into the system and run for 14 minutes. Flame ionization detector was used.

2.3.7 Micromeritic properties

Micromeritic properties such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio was determined for the prepared β- CDEPI complex[12]**.** All the analysis was carried out in triplicate.

2.3.8 Loss on drying

0.5 g of β-CDEPI polymer powder was weighed and placed in a dry china dish and maintained at 105ºC for 1h in a hot air oven. The china dish was removed and the weight of the polymer complex was determined.

2.3.9 Moisture content

Moisture content was determined using IR moisture balance. 0.5g of β-CDEPI complex powder was placed on an infra-red balance maintained at 105°C until the weight was constant for 5 minutes[13].

2.3.10 Particle size distribution

The prepared β-CDEPI complex was observed under 100X magnification in an optical microscope (Olympus LITE image) and an average of 100 particles were counted.

2.3.11 Surface tension

The surface tension of 1%w/v solution of β- CDEPI complex in water was determined using stalagmometer[14].

2.4 Preparation of famotidine-β-CDEPI inclusion complexes

β-CDEPI–famotidine inclusion complexes were prepared in molar ratio of 1:1, 1:3 and 1:5 by physical mixing, kneading, co-evaporation and freeze drying methods.

2.4.1 Physical mixture

Famotidine and β-CDEPI was mixed for one hour with constant trituration in a mortar, and then passed through sieveNo.100.The resulting sample was stored in a dessicator.

2.4.3 Kneading method

β-CDEPI complex was mixed with 5ml of 50% ethanol and triturated in a mortar to get slurry like consistency. Then famotidine was incorporated into the slurry and trituration was further continued for one hour. Slurry was then air dried at 25°C for 24hours, pulverized and passed through sieveNo.100 and stored in a dessicator.

2.4.5 Co- evaporation method

β-CDEPI and famotidine was mixed with 10ml of 50% aqueous ethanol. The resulting mixture was stirred till a clear solution was obtained and the solution was then evaporated under vacuum at a temperature of 45°C. The solid residues was further dried completely at 45°C for 48h, the dried complex was pulverized and stored in a dessicator.

2.4.6 Freeze- drying method

Famotidine and β-CDEPIs were taken with 20 ml of water and mixed thoroughly using a magnetic stirrer. The resultant solution was frozen in a deep freezer at-20°C for about 12h. The frozen mixture was then freeze dried in the freeze dryer (Martin Christ, Germany) for 8h at 50°C under vacuum and was stored in a dessicator.

2.5 Drug content estimation

100mg of drug β-CDEPI complex was accurately weighed and transferred to 25ml volumetric flask and volume was made up with 6.8 pH phosphate buffer. The resulting solution was diluted suitably and the absorbance of the solution was measured at 287.5nm using appropriate blank. The drug content of famotidine was calculated using calibration curve.

***2.6 In-vitro* dissolution profile of famotidine-β-CDEPI complexes**

In-vitro dissolution studies were studied using USP type II dissolution apparatus. 900 ml of 6.8 pH phosphate buffer was used as dissolution medium at 50 rpm and at temperature of 37±0.5°C. Complex equivalent to 50mg of famotidine was used in each test. 5ml samples

of dissolution medium was withdrawn at predetermined time intervals, diluted suitably and analyzed for drug release by measuring the absorbance spectrophotometrically at 287.5nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium.

2.7 Formulation of orodispersible tablets of famotidine-β-CDEPI complexes

β-cyclodextrin-epichlorohydrin-famotidine complex along with mannitol, crospovidone, croscarmellose sodium, sodium starch glycolate, aspartame, aerosil and talc as excipients were used to formulate orodispersible tablets. All the ingredients were sifted through sieve no. 12 prior to granulation. The drug and other excipients were mixed together and granulated with alcohol. The granules were dried at 40°C for 20 minutes in a tray dryer (Lab Instruments, Mumbai). The dried granules were dry screened by passing through mesh no. 16 and then the granules were lubricated with the mixture of talc. Lubricated granules were compressed into tablets using rotary punching machine (Rimek RSB-4 mini press). (Table 1)

Table 1. Composition of orodispersible tablets

S. No	Ingredients*	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	FAD-β-CDEPI complexes (famotidine equivalent to-20mg)	122.4	122.4	122.4	122.4	122.4	122.4	122.4	122.4	122.4
2	Mannitol	8.6	6.1	3.6	8.6	6.1	3.6	8.6	6.1	3.6
3	Crospovidone	5	7.5	10	-	-	-	-	-	-
4	Croscarmellose sodium	-	-	-	5	7.5	10	-	-	-
5	Sodium starch glycolate	-	-	-	-	-	-	5	7.5	10
6	Aspartame	5	5	5	5	5	5	5	5	5
7	Aerosil	3	3	3	3	3	3	3	3	3
8	Talc	6	6	6	6	6	6	6	6	6

*****_All quantities in mg_

2.8 Pre compression studies of granules

The prepared granules for all the formulations were subjected to pre-compression studies, such as, Angle of repose, Bulk density, Bulkiness, Tapped density, Carr's index and Hausner's ratio.

2.9 Post compression studies[15]

The prepared tablets were evaluated for its weight variation, hardness, friability, thickness and disintegration time.

2.10 Determination of drug content

10 tablets were selected randomly, crushed to powder and amount equivalent to 150 mg of tablet was accurately weighed and transferred into 25 ml volumetric flask, volume made up with phosphate buffer pH 6.8.The resulting solution was diluted suitably and the absorbance of was measured spectrophotometrically at 287.5 nm.

2.11 Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. The selected formulations were closely packed in aluminum foils and then stored at 40°C±2° C with 75%RH±5% in stability chamber for 6 months[16] and evaluated for their physical appearance, drug content, percent friability and *in-vitro* disintegration time at intervals of 2 months.

3. RESULTS AND DISCUSSION

3.1 Evaluation studies of β-CDEPI polymer

The β-Cyclodextrin-epichlorohydrin polymer was synthesized by one step condensation polymerization process using acetone and methanol as organic solvents in alkaline medium. The practical yield of β-CDEPI was found to be 7.86g. The solubility studies of β- CDEPI polymer were performed in various solvents such as distilled water, ethanol, acetone, propylene glycol and dichloromethane. The synthesized polymer was completely soluble in distilled water and dichloromethane. The 1% w/ v solution of β-CDEPI polymer showed a pH of 7. The melting point of the β- CDEPI polymer was found to be 232°C. The surface tension of 1% w/v solution of β-CDEPI polymer was found to be 89.16 dynes/cm. The moisture content of β- CDEPI polymer was found to be 6.6%. The average particle size of β- CDEPI was found to be 19.52µm. Loss on drying of the β- CDEPI polymer was found to be 8%.

On carrying out the micromeritic properties of β-CDEPI bulk density was found to be 0.866g/ml and tapped density was found to be 0.9941g/ml. Hausner's ratio was 0.1479g/ml. Hausner's ratio with values less than 1.5 indicated good flow property. The Carr's index value was 12.88%, which confirmed good flow property and compressibility of the β- CDEPI polymer. The angle of repose for β-CDEPI was found to be 24˚62', thereby confirming the good flow property of the β- CDEPI polymer.

Phase aqueous solubility studies revealed that there was an increase in the solubility of poorly water soluble drug famotidine due to molar interaction with β- CDEPI. Famotidine soluble complexes with β- CDEPI in water showing a typical AL- type solubility diagrams where the

regression co- efficient of the curve and inclusion stability constant (Kc), was found to be 0.9923 and 0.01474M^{-1}. The lower values of the stability constants (Kc) suggest that the famotidine-β-CDEPI interaction is weak.

3.2 Mechanism of complex formation

Preparation of water soluble β-CD polymers was achieved by the reaction of β-CD with epichlorohydrin in an alkaline medium by a two-step procedure. First the β-CD was stirred with an excess of NaOH in order to form alcoholate sites. Then, epichlorohydrin was added to the suspension obtained. Hydroxyl groups can react with one reactive group of the bifunctional agent. The side chain obtained can further react in two different ways: the epoxy ring can react with another hydroxyl group of the second β-CD molecule, resulting in a glyceryl bridge connecting two β-CD cavities, or, the epoxy ring is hydrolysed. The end result is a β-CD molecule with a glycerol moiety. Moreover, epichlorohydrin has the capability to react on itself to form homopolymers of epichlorohydrin. Consequently, the glyceryl bridges and the glycerol tails can have different lengths.

3.3 Mass spectral studies

Mass spectroscopic studies were carried out to find out the molecular weight of the β- CDEPI. The molecular ion peak was observed at 2360.89 on m/z scale. The intensity of the peak was found to be high and abundance. Minor fragments obtained were at 2452.35 and 2632.78 on m/z scale. (Figure 1)

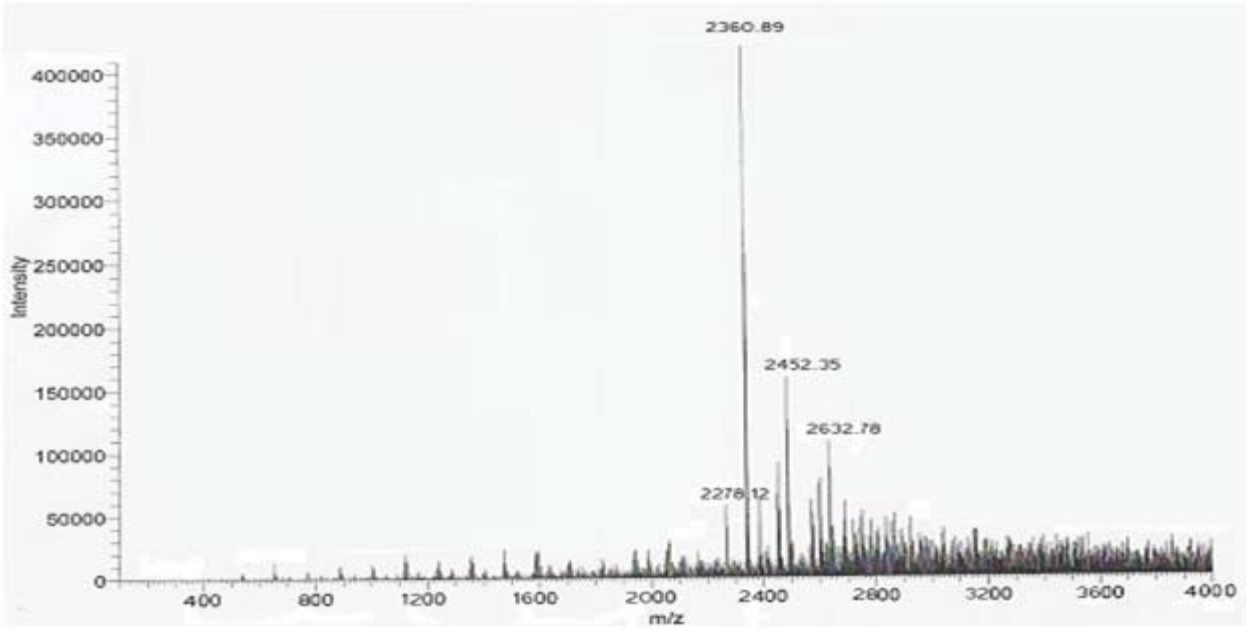

Fig.1. Mass spectra of the prepared β- CDEPI

3.4 ^{1}H Nuclear Magnetic Resonance Studies

NMR Spectral studies reveals the chemical shift for each proton of famotidine, β-CD and β-CDEPI were evaluated to confirm the formation of new β-CDEPI polymer. The chemical shifts for protons were observed from 2.8–6.2 ppm for famotidine and the number of protons was 14.612 (fig. 2a). The chemical shifts for protons were observed from 3.6–5.4 ppm for β-cyclodextrin and the number of protons was 69.846 (fig. 2b). The chemical shifts for protons were observed from1.6–8.8 ppm for β- CDEPI polymer and the number of protons was 149.012(fig. 2c). These chemical shifts confirmed the formation of β- CDEPI complex.

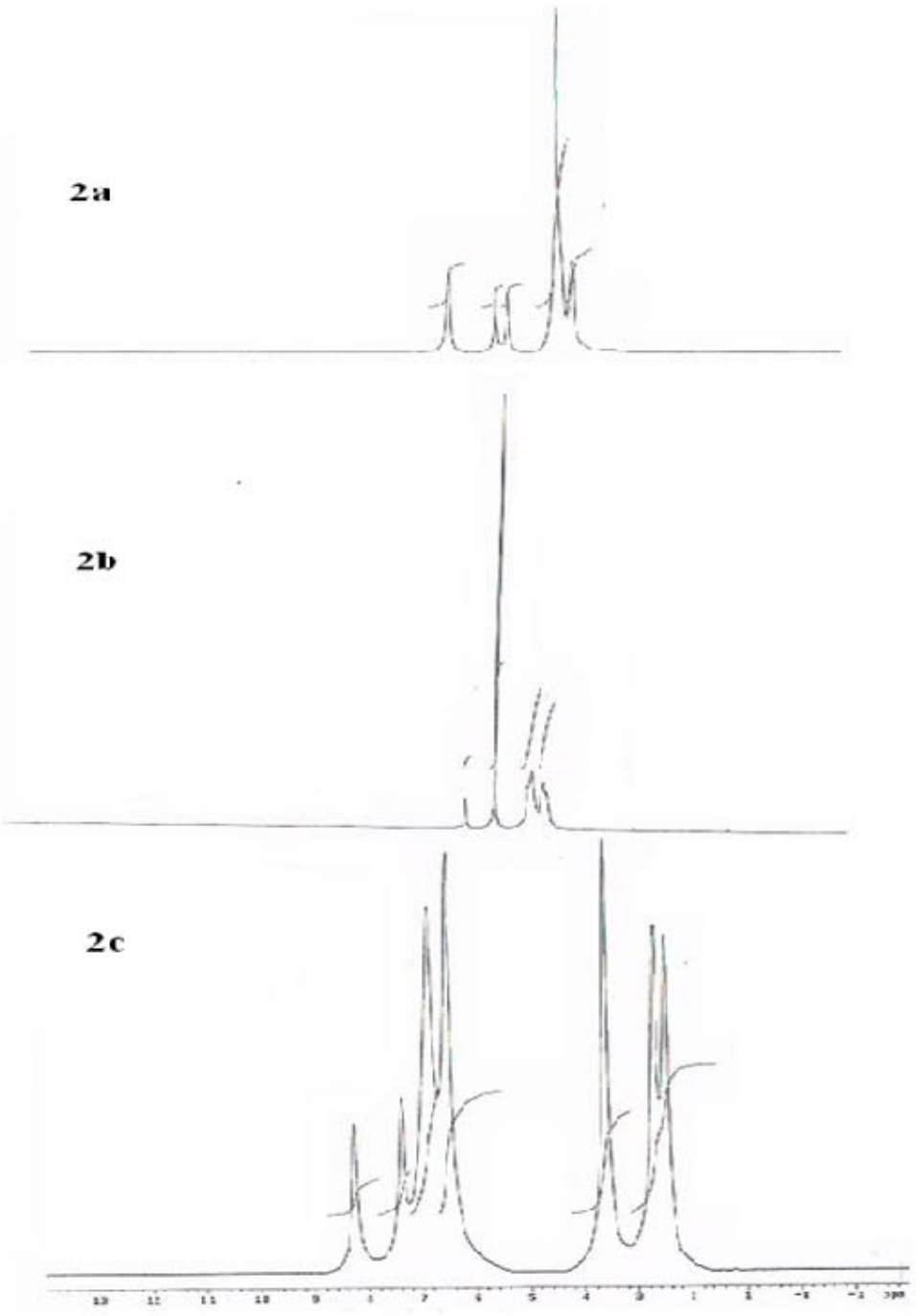

Fig.2. NMR spectral studies, 2a - Spectrum for famotidine, 2b - Spectrum for β- cyclodextrin, 2c - Spectrum for β- CDEPI complex

3.5 Residual solvent analysis

Residual solvent analysis was done by Gas Chromatography. The limit for acetone and methanol as specified by ICH guidelines is 5000ppm and 3000 rpm respectively. The

estimated amount of acetone found in the synthesized β- CDEPI was 0.04 ppm and estimated amount of methanol was found to be 0.03 ppm. Hence the synthesized β- CDEPI was found to be safe and it can be effectively used in pharmaceutical formulations.

3.6 FT-IR spectral studies

The FT-IR spectra of the pure famotidine had shown characteristic peaks at 3503.45 cm^{-1}, 1324.04 cm^{-1},1582.48 cm^{-1},777.26 cm^{-1},1147.57 cm^{-1},2930.63 cm^{-1},1532.48 cm^{-1},1434.94 cm^{-1},1582.48 cm^{-1} and 1635.52 cm^{-1} due to primary amine NH stretch, primary amine CN stretch, NH bend, CS stretch, S =O stretch, CH alkane stretch and C = N stretch (fig. 3a). The IR peaks of β- cyclodextrin has shown characteristic peaks at 1185.18cm^{-1}, 3472.59cm^{-1}, 2961.49 cm^{-1} due to C – O – C epoxy stretch, OH primary alcohol and CH cyclic alkanes (Fig. 3b).The characteristic IR peaks for β- CDEPI polymer was shown at 1259.43 cm^{-1}, 2907.49cm^{-1} due to C – O – C ether stretch, C – H alkane stretch and showed all characteristic peaks of β-CD (fig. 3c). This confirmed the formation of complex between cyclodextrin and epichlorohydrin. The characteristic IR peaks for physical mixture of FAD-β- CDEPI showed presence of characteristic peaks of both pure famotidine and β- CDEPI polymer (fig. 3d). Thus the FT-IR spectral analysis confirmed the formation of β- CDEPI polymer and absence of interaction between the synthesized polymer and drug.

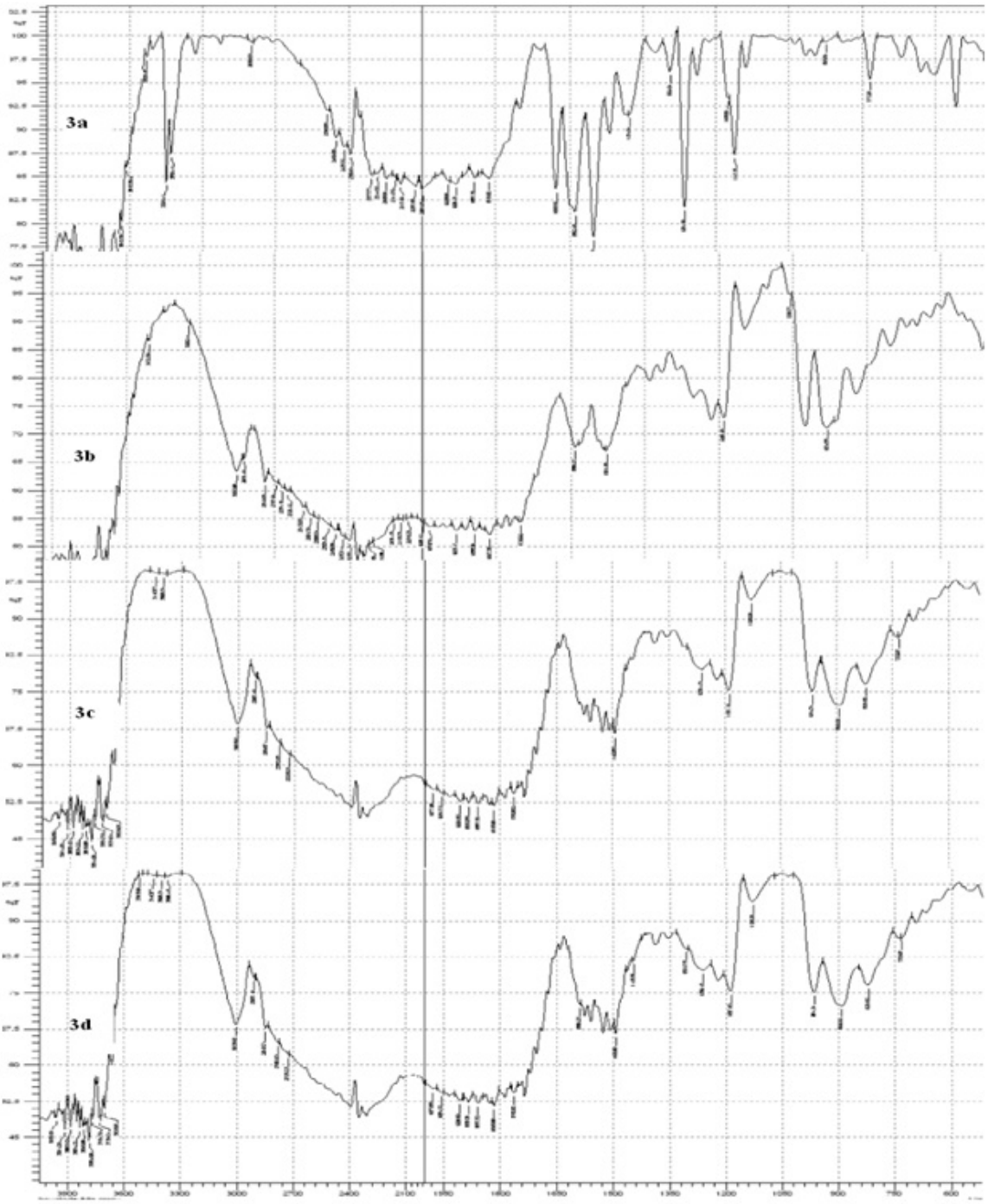

Fig.3. FT-IR spectral studies, 3a - Pure famotidine, 3b - β- cyclodextrin, 3c - β- CDEPI polymer, 3d - physical mixture of famotidine with β- CDEPI

3.7. DSC studies

The DSC thermogram of the famotidine showed a sharp endothermic peak at 163.65°C (fig. 4a). Such endothermic peak signifies that famotidine used was in pure crystalline state. β-cyclodextrin showed endothermic peak at 157.45°C corresponding to its melting temperature

and it indicated the crystallinity of β- cyclodextrin (fig. 4b).The thermal behavior of β-CDEPI in did not show any sharp peaks, proving that the new polymer was in an amorphous state (Fig. 4c).

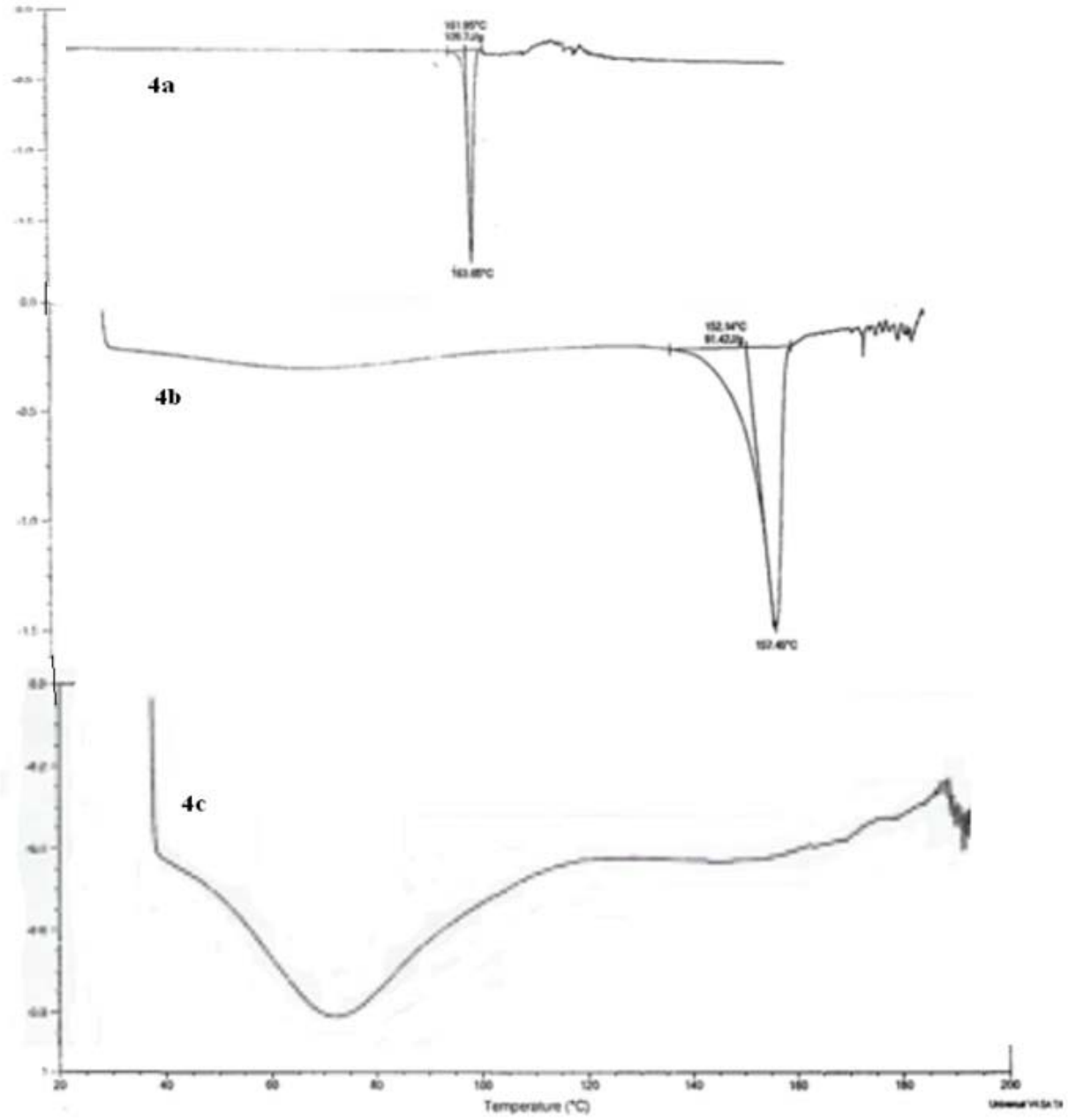

Fig.4. DSC thermograms, 4a - Famotidine, 4b - β- cyclodextrin, 4c - Inclusion complex of famotidine with β- cyclodextrin

3.8 *In-vitro* dissolution profile of famotidine- β- CDEPI inclusion complexes

FAD- β-CDEPI inclusion complexes were prepared by various methods such as physical mixture, co- evaporation, kneading and lyophilization method in 1:1, 1:3 and 1:5 molar ratios of FAM-β-CDEPI. *In- vitro* release studies were carried out using USP type I tablet dissolution test apparatus. Of all the inclusion complexes prepared by different methods, the one that was found to be efficient in terms of dissolution studies was by lyophilization method in the molar ratio 1:5.Pure famotidine showed 100.02% drug release at the end of 65minutes, whereas complexes prepared by physical method (1:1, 1:3, 1:5 molar ratio) released 99.83%, 99.99% and 100.00% drug at the end of 55, 50 and 52 minutes respectively. Co- evaporated complexes prepared in molar ratio 1:1, 1:3 and 1:5 showed drug release of 99.86%, 99.78% and 99.99% at the end of 55, 55 and 50 minutes. Complexes prepared by kneading method in molar ratio 1:1, 1:3 and 1:5 showed drug release of 99.86%, 100.005 and 100.00% at the end of 55, 50 and 45 minutes. Lyophilized product in molar ratio 1:1, 1:3 and 1:5 showed drug release of 100%, 99.97% and 100% at the end of 45, 40 and 35 minutes. The maximum drug release was observed in formulation F12, which was prepared by lyophilization process and it showed 100.00% drug release at the end of 35 minutes. Based on the dissolution profile formulation F12 was selected for further studies of orodispersible tablets formulation as it had the maximum drug dissolution in least time.

3.9 Formulation of famotidine- β- CDEPI orodispersible tablets

Formulation F12 which is famotidine- β-CDEPI inclusion complex prepared by lyophilization method in the 1:5 molar ratio was selected for formulation into orodispersible tablets. The formulations were prepared by wet granulation technique. Total of 9 formulations were prepared using three different superdisintegrants such as crospovidone, croscarmellose sodium and sodium starch glycolate in three different concentrations (3.33 %, 5 % and 6.66 %). Aspartame was incorporated as sweetener, mannitol as diluent, and aerosil and talc were used as lubricant and glidants respectively.

3.10 Precompression studies of granules

The bulk density of all 9 formulations ranged between 0.40 to 0.56 g/ml and tapped density ranged from 0.45 to 0.63 g/ml. Bulkiness was between 1.78 and 2.48. Hausner's ratio ranged from 1.09 to 1.12. The Carr's index value was between 8.99 to 11.13%. The angle of repose was found to be between 16°69' to 21°20'. All the precompression parameters confirmed that the powder blends possess good compressible and flow properties (table 2).

Table 2. Data for pre compression studies of the prepared granules

Formulation code	Bulk density* (g/cc)	Tap density* (g/cc)	Bulkiness	Angle of repose* (θ)	Carr' s index	Hausner' s ratio
F1	0.43±0.015	0.47±0.015	2.29	16°69'	8.99±0.498	1.09±0.100
F2	0.56±0.015	0.63±0.015	1.78	17°48'	11.11±0.291	1.12±0.041
F3	0.52±0.015	0.58±0.030	1.90	19°69'	9.93±0.440	1.11±0.040
F4	0.49±0.015	0.55±0.030	2.03	18°41'	11.05±0.304	1.12±0.047
F5	0.43±0.020	0.48±0.010	2.32	21°20'	11.13±0.194	1.12±0.095
F6	0.55±0.020	0.62±0.010	1.80	20°29'	11.09±0.174	1.12±0.095
F7	0.44±0.017	0.49±0.010	2.25	19°29'	9.93±0.185	1.11±0.110
F8	0.40±0.015	0.45±0.035	2.48	20°70'	11.06±0.353	1.12±0.110
F9	0.48±0.010	0.54±0.035	2.08	17°95'	11.11±0.293	1.12±0.038

**Values are represented as mean± SD (n=3)*

3.11 Post- compression parameters for prepared orodispersible tablets

The hardness of all the tablet formulations was measured using Monsanto hardness tester and the hardness ranged between 4.2 to 5.8 kg/cm^2.The thickness of the tablet formulations were determined using screw gauge and the thickness of tablets was found to be in the range of 3.93- 4.71 mm.The percentage friability of all the formulations were measured using Roche friabilator and the percentage friability were found between 0.42 to 0.79%. The friability results indicated that the tablets were mechanically stable. The weights of all tablet formulations were found to be between 140 to 160 mg. The actual weight of the tablets were 150mg, the acceptable weight variation range is between 138.75mg to 161.25 mg (±7.5%). All the tablet formulations were within the pharmacopoeial limit. The drug content determination of all 9 formulations were found to be in the range of 97.15- 99.86 % of famotidine. *In- vitro* disintegration time of all the formulations showed that the formulations

disintegrated within three minutes (table 3).

Table 3. Data for post compression studies of the prepared formulations

Formulation code	Hardness *(kg/cm^2)	Friability* (%)	Weight variation* (mg)	Drug content*(%)	Thickness* (mm)	Disintegration time (sec)
F1	4.2±0.152	0.66±0.020	140±2.588	98.86±0.056	4.25±0.125	94±3
F2	5.8±0.378	0.71±0.152	160±2.659	98.14±0.066	4.71±0.201	81±5
F3	4.6±0.208	0.68±0.252	150±1.104	99.4±0.217	4.37±0.254	74±6
F4	5.2±0.152	0.54±0.151	150±2.588	98.62±0.065	3.93±0.189	143±4
F5	4.6±0.404	0.69±0.020	140±2.663	97.87±0.087	4.11±0.185	112±6
F6	5.4±0.152	0.42±0.020	160±2.472	99.24±0.069	4.49±0.216	80±7
F7	5.8±0.264	0.50±0.055	160±2.104	97.55±0.087	4.14±0.245	88±5
F8	4.4±0.264	0.79±0.0499	150±2.456	97.13±0.058	3.97±0.164	79±7
F9	4.2±0.152	0.63±0.015	140±4.104	99.38±0.049	4.23±0.133	66±6

* Values are represented as mean ± SD (n=3)

3.12 *In- vitro* dissolution studies of the prepared orodispersible tablets

In- vitro dissolution studies were performed for all the formulated tablets using USP XXIII tablet dissolution apparatus employing rotating paddle method at 50rpm using 900ml of 6.8pH phosphate buffer. The temperature of the dissolution medium was maintained at 37±0.5°C.The results showed that formulation F1 complete drug release of 99.08% at the end of 15 minutes, F2 released 99.31% at the end of 15 minutes, F3 showed 99.87% at the end of 10 minutes, F4 released 98.44% at the end of 15 minutes, F5 released 99.10% at the end of 15 minutes, F6 complete drug release of 100.08% at the end of 10 minutes, F7 released 99.11% at the end of 15 minutes, F8 showed drug release of 99.56% at the end of 15 minutes and F9 released 98.99% at the end of 10 minutes(fig.5). Formulations F3, F6 and F9 were found to possess the desirable *in-vitro* drug release characteristics. So these formulations were considered for stability studies based on the other parameters such as *in-vitro* disintegration

time, *in-vitro* drug release profiles and percent drug content.

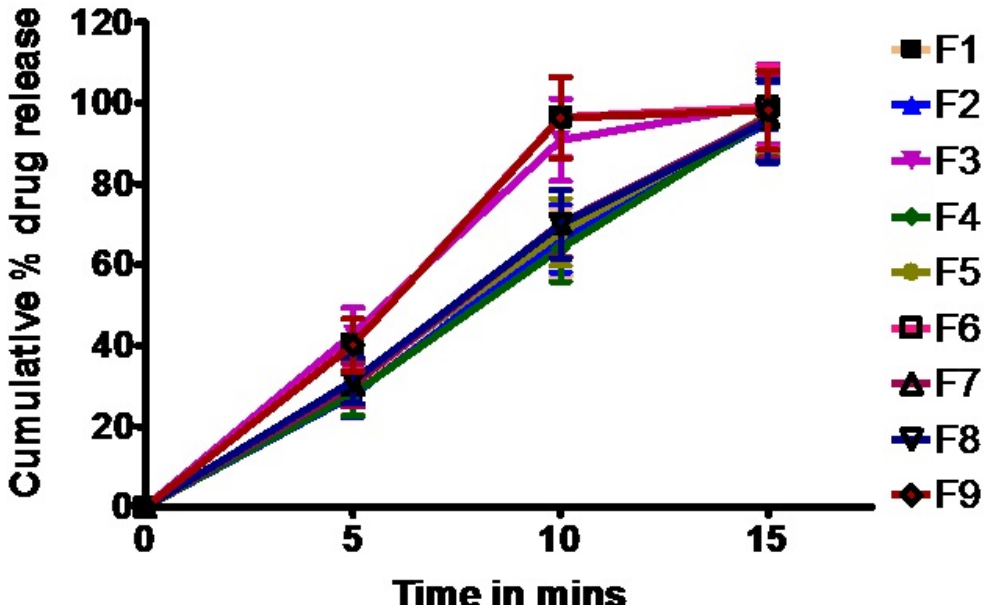

Fig.5. In-vitro release studies of formulations F1 to F9

3.13 Stability studies

Formulations F3, F6 and F9 were subjected to accelerated stability studies as per ICH guidelines; stored at 40°C/75% relative humidity for a period of 6 months and evaluated for physical appearance, percent drug content, hardness, percent friability and *in-vitro* disintegration time at the interval of 2 months. The results revealed that there were no significant changes observed in the physical appearance and marginal decrease of 2-3% was observed in the drug content. The tablets were found to have sufficient mechanical strength at the end of the study. This study confirmed that the prepared orodispersible tablets were physically and chemically stable and it may have profound stability.

4. CONCLUSION

Synthesis of β-cyclodextrin-epichlorohydrin polymer (β-CDEPI) has shown good practical yield. The synthesized polymer was evaluated and the results proved that the synthesized polymer was safe for pharmaceutical use. The synthesized polymer was further evaluated for its improvement in dissolution by converting into orodispersible tablets. Thus the prepared β-CDEPI was found to be an effective polymer in terms of enhancement in solubility, dissolution rate and thereby bioavailability of the poorly water soluble drug, famotidine

effectively than the parent cyclodextrins. This polymer can be adopted to formulate orodispersible tablets in routine manufacturing operations. But the scale up of the synthesis needs to be studied in future.

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6. CONFLICT OF INTERESTS

The authors report no conflict of interests.

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