BJPS

Brazilian Journal of
Pharmaceutical Sciences
vol. 47, n. 4, oct./dec., 2011

Article

Formulation and *in vitro* evaluation of taste-masked oro-dispersible dosage form of diltiazem hydrochloride

Swati Changdeo Jagdale*, Vaibhav Uttam Gawali, Bhanudas Shankar Kuchekar, Aniruddha Rajaram Chabukswar

Department of Pharmaceutics, MAEER's Maharashtra Institute of Pharmacy, Maharashtra, India

Diltiazem hydrochloride is a calcium channel blocker generally indicated for the treatment of angina and hypertension, and it is extensively metabolized due to the hepatic metabolism. Formulation of diltiazem hydrochloride into an oro-dispersible dosage form can provide fast relief with higher bioavailability. The bitter taste of the drug should be masked to formulate it in a palatable form. In the present work, an attempt was made to mask the taste by complexation technique, with a formulation into an oro-dispersible dosage form, using superdisintegrants Doshion P544, crospovidone (CP) and sodium starch glycolate (SSG). The complexes of diltiazem hydrochloride with β-CD (1:1 molar ratio) were prepared by kneading, co-evaporation, co-grounding, freeze-drying and melting methods. Phase solubility showed stability constant 819.13M_{-1}. Prepared inclusion complexes were evaluated for taste masking and characterized by I.R, XRD, DSC. Using the drug β-CD complex, oro-dispersible tablets were prepared and evaluated for hardness, friability, weight variation, thickness, disintegrating time (DT), dissolution rate and taste. Formulations with 4 % Doshion, 8 % CP and 4 % SSG showed DT of 0.54, 0.35 and 1.23 minutes, respectively.

Uniterms: Diltiazem hydrochloride. Cyclodextrin. Drugs/taste-masking. Freeze-drying.

O cloridrato de diltiazem é bloqueador do canal de cálcio geralmente indicado para o tratamento de angina e de hipertensão e é extensamente biotransformado devido ao metabolismo hepático. A formulação do cloridrato de diltiazem em orodispersão pode prover rápida liberação com maior biodisponibilidade. O sabor amargo do fármaco deve ser mascarado para ser formulado em forma palatável. No presente trabalho tentou-se mascarar o sabor pela técnica de complexação, com uma orodispersão, usando superdesintegrantes, como Doshio P544, crospivodina (CP) e glicolato de amido sódico (SSG). Os complexos de cloridrato de diltiazem com β-CD (razão molar 1:1) foram preparados por mistura, coevaporação, comoagem, liofilização e métodos de fusão. A solubilidade de fase mostrou estabilidade constante de 819,13 M^{-1}. Os complexos de inclusão preparados foram avaliados com relação ao mascaramento do sabor e caracterizados por IV, Difração de Raios X e DSC. Empregando-se o fármaco complexado com β-CD, prepararam-se comprimidos dispersíveis e avaliaram-se os mesmos quanto à dureza, friabilidade, variação de peso, espessura, tempo de desintegração (DT), taxa de dissolução e sabor. Formulações com 4% de Doshion, 8% de CP e 4% de SSG mostraram DT de 0,54, 0,35 e 1,23 minutos, respectivamente.

Unitermos: Cloridrato de diltiazem. Ciclodextrina. Fármacos/mascaramento de sabor. Liofilização.

INTRODUCTION

The development of drug delivery technology to any molecule is based on market needs, product differentiation and patient compliance. In the present scenario, there is an ever-increasing demand for more patient-compliant dosage forms. One important innovation in this direction is the development of fast dissolving/disintegrating dosage forms. These have been proved ideal for the geriatric and pediatric populations, bedridden or traveling patients, people suffering from dysphasia, clinical conditions in which water intake is limited, and situations in which water is not available.

***Correspondence:** Dr. Swati Changdeo Jagdale. Department of Pharmaceutics, MAEER's Maharashtra Institute of Pharmacy, MIT Campus, S.No.124, Ex-serviceman colony, Kothrud, Pune- 411038, Maharashtra, India. E-mail: jagdaleswati@rediffmail.com

Rapidly disintegrating/dissolving dosage forms are further categorized as oro-dispersible tablets and dispersible tablets. Oro-dispersible tablets are uncoated tablets intended to be placed in the mouth, where they rapidly disperse before swallowing. There are many methods for formulation of rapidly disintegrating/dissolving dosage forms. Practically reviewing these methods with respect to the ease of preparation and cost-effectiveness, the direct compression method was found to be the best option. Probably one of the least recognized advantages of direct compression is the optimization of tablet disintegration, in which each primary drug particle is liberated from the tablet mass and available for dissolution. (Dandagi *et al.,* 2006; Fini *et al.,* 2008; Hisakadzu *et al.,* 2002)

Cyclodextrins (CD) are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. On account of their relatively hydrophobic interiors, CDs have the ability to form inclusion complexes with a wide range of substrates (Loftson *et al.,* 1996). This complex-forming ability of CD have been widely exploited in the pharmaceutical field for various applications, including taste-masking of bitter drugs (Giancarlo *et al.,* 2006; Sohi *et al.,* 2004; Szejtli, 2004). The use of CD as a taste-masking agent has been widely reported (Noriaki *et al.,* 2006; Patel *et al.,* 2008; Rajewski *et al.,* 1996).

Diltiazem hydrochloride is a BCS Class-I drug. It is very bitter and has an after taste. Diltiazem hydrochloride is a calcium channel blocker generally indicated for the treatment of angina and hypertension, and it is extensively metabolized, predominantly due to hepatic metabolism. At present, there is no ODT in the market; the drug is marketed as immediate sustained-release tablets, extended sustained-release capsules, and injections. Complexation with β-CD will mask the bitter taste of diltiazem HCl (Indian Pharmacopeia, 2007; Nappini *et al.,* 2007). The formulation of ODT will show rapid onset of action and avoid the hepatic metabolism.

MATERIAL AND METHODS

Material

Diltiazem hydrochloride was a generous gift from Themis Lab (Mumbai, India). The β-cyclodextrin (β-CD) was purchased from Gangwal Chemicals (Mumbai, India). Microcrystalline cellulose (MCC), mannitol, lactose, aspartame, ice cream flavor, magnesium state, talc, crospovidone, sodium starch glycolate, and Doshion P 544 were procured from SD Fine Chemicals (Mumbai, India). All reagents were of analytical grade. Double distilled water was used for all the experiments.

Methods

Complexation

Phase solubility study

Phase solubility studies were carried out at room temperature and in triplicate, according to the method reported by Higuchi and Connors (Higuchi *et al.,* 1965; Loftsson *et al.,* 2005). An excess amount of diltiazem hydrochloride was added to double distilled water containing various concentrations of β-CD (0.002-0.1 M) in a series of stoppered conical flasks and then shaken for 3 days on a rotary flask shaker. The suspensions were filtered through Whatman filter paper and assayed for diltiazem hydrochloride using a UV spectrophotometer (Varian Cary 100, Australia) at 236 nm against blank prepared using same concentration of β-CD in double distilled water. The association constant (Ka) was calculated from the slope of the linear portion of the phase solubility diagram. According to Equation (1), Ka = Slope / Intercept (1- Slope).

Preparation of solid complexes

The solid complexes of diltiazem hydrochloride with β-CD (1:1 molar ratio) were prepared (Emara *et al.,* 2002; Franco *et al.,* 2008; Rawat *et al.,* 2004) by the following method.

- Kneading method (Kn)

Diltiazem hydrochloride and β-CD were triturated in a mortar with a small volume of water-methanol solution. The thick slurry was kneaded for 45 minutes, then dried at 40 ºC. The dried mass was pulverized and sieved through. (#100)

- Co-evaporation method

The aqueous solution of β-CD was added to an alcoholic solution of diltiazem hydrochloride. The resulting mixture was stirred for 1 hour and evaporated at a temperature of 45 ºC until dried. The dried mass was pulverized and sieved through (#100)

- Co-grounding

The drug was triturated with a minimum quantity of methanol in a glass mortar until it dissolution. Then, β-CD was added, and the suspension was triturated rapidly at room temperature until solvent was evaporated.

- Freeze-drying method

Physical mixtures of diltiazem hydrochloride and β-CD in a molar ratio of 1:1 were added to 500 mL of double distilled water and stirred for 5 days. The suspension was freeze-dried (Ilshin® Freeze Dryer). The freeze-dried complex was pulverized and sieved through (<38 μm).

- Physical mixture (PM)

The physical mixtures of diltiazem hydrochloride

and β-CD [1:1 molar ratio] were obtained by mixing together the pulverized powders (#100) using a mortar and pestle.

Evaluation of solid complexes

Evaluation of taste of complexes

The sample of drug-β-CD complex underwent sensory evaluation by a panel of five members with respect to the bitter taste; the evaluation was performed by classifying the bitter taste into the following five classes.

Class 5:Very strong bitter taste
Class 4:Strong bitter taste
Class 3:Moderately bitter taste
Class 2:Slightly bitter taste
Class 1:No bitter taste

The pure drug was used as a standard control, with a mean bitter taste of 5.0. Written consent was obtained from the members of the panel and it was explained that the procedure involved testing the taste of complexes. Each of the members was given the control, *i.e.*, the pure drug. They were asked to compare the bitterness of each of the ratios of the complex with that of the control, indicating the level of bitterness perceived by them. The members of the panel were asked to gargle and wait for 20 minutes before another sample was given to them for tasting. The mean bitterness value of each of the ratios was calculated based upon the level of bitterness sensed by each individual member of the panel.

Drug content

A drug-β-CD complex equivalent to 10 mg of the drug was stirred with 100 mL of 0.1 N HCl for 60 minutes. The solution was then filtered and treated as a stock solution, containing 100 µg/mL of the drug. From this stock solution, the concentration of 10 µg/mL was prepared. Drug content was determined using the calibration curve of the pure drug in 0.1 N HCl spectrophotometrically at 236 nm, using 0.1 N HCl as blank.

Infrared Spectroscopy

Infrared (IR) spectra of diltiazem hydrochloride, β-CD and complexes were obtained by using a Varian 640 IR spectrophotometer (Varian, Australia) with KBr pellets. The scanning range used was 4000 to 400 cm^{-1}.

X-ray Diffractometry

Diltiazem hydrochloride, β-CD, drug-β-CD complexes and a physical mixture of drug-β-CD were subjected to powder X-Ray Diffraction (XRD). To study the XRD pattern, the sample was placed into an aluminum holder and the instrument was operated between an initial and final 2θ angle of 5-50°, respectively, in increments of 0.2°2θ.

Differential Scanning Calorimetry

Diltiazem hydrochloride, β-CD, and drug-β-CD complexes were subjected to a Differential Scanning Calorimetry (DSC) study. DSC was performed on a Mettler DSC 30. Initially, 1.60-2.80 mg of the sample was weighed into an aluminum crucible and analyzed by heating at a scanning rate of 20 ºC/minute, over a temperature range of 25 to 300 ºC (Ramana *et al.,* 2008; Mura *et al.,* 2005)

In vitro dissolution studies

Dissolution studies of samples were performed using USP 23 type II apparatus in 900 mL of 0.01 N HCl and phosphate buffer with a pH of 6.8. Temperature was maintained at 37 ± 0.5 °C, and rotation speed was 100 rpm. The samples were withdrawn at time intervals of 5, 10, 15, 20, 30, 45, 60, and 90 minutes, and analyzed spectrophotometrically at 236 nm.

Formulation of tablets

The tablet consisted of a drug-β-CD freeze-dried complex equivalent to 30 mg of drug, mannitol, lactose, aspartame, ice cream flavor, magnesium stearate, talc, microcrystalline cellulose (PH102) and various concentrations (2%, 4%, 8% and 12%) of superdisintegrant (Doshion P 544, crospovidone, sodium starch glycolate). The weight of tablets in each batch was kept constant. All the batches were prepared by direct compression using an 8-station rotary tablet machine Minipress-II (Rimek Ltd.).

Blending and tablet compression

Tablets containing 86.07 mg of drug-β-CD freeze-dried complex equivalent to 30 mg of the drug were prepared by direct compression method. The various formulae used in the study are shown in Table I. The drug, diluents, superdisintegrant and sweetener were passed through a ≠ 40 sieve. All the above ingredients were properly mixed together (in a polybag). Talc and magnesium stearates were passed through a ≠ 80 sieve, mixed, and blended with the initial mixture in a polybag. The powder blend was compressed into tablets on an 8-station rotary tablet machine Minipress-II (Rimek Ltd.).

Evaluation of rapidly disintegrating tablets

All the formulations were evaluated for characteristics such as hardness, friability, weight variation, thickness, disintegrating time, dissolution rate and taste. In the weight variation test, twenty tablets were selected at random, and mean weight was determined using an electronic balance. Tablets were weighed individually and compared with mean weight. A Pfizer hardness tester and a Roche friabilator were used to test hardness and friability loss, respectively. Disintegration time was determined using a USP tablet disintegration test apparatus in 900 mL of distilled water, without disk, at room temperature. For the *in vivo* test, the tablets were given to volunteers and they were asked to note the disintegration time. Thickness of tablet was determined by using a dial caliper.

Dissolution studies

The tablets underwent a dissolution test using USP type II apparatus (paddle) using 900 mL of dissolution medium (0.1 N HCl, pH 6.8 buffer), at a speed of 100 rpm and at a temperature of 37.0 ± 0.5 ºC. Five-milliliter aliquots were withdrawn at time intervals of 0, 1, 3, 5, 10, 15, 30, and 60 minutes. Every time, an equal volume of fresh dissolution medium, which was maintained at same temperature, was added to the bulk. Samples were filtered through Whattman filter paper, dilutions were carried out as per calibration curve, and absorbance was recorded at 236 nm. The percentage of the labeled amount of drug released at each time point was calculated and a graph was plotted.

Assay method

Twenty tablets were accurately weighed and then powdered. Tablet powder equivalent to 10 mg of the drug was stirred within 100 mL of 0.1 N HCl for 60 minutes, and the solution was then filtered and treated as a stock solution containing 100 µg/mL of the drug. From this stock solution, further dilutions were performed for each formulation. Absorbance was measured and the concentration of the drug in the tablet was determined, using the calibration curve of pure drug in 0.1N HC1 spectrophotometrically at 236 nm, using 0.1N HC1 as blank (Kaushik *et al.,* 2004; Malke *et al.,* 2008; Sekar *et al.,* 2008).

Percentage Assay = Absorbance of Sample / Absorbance of Standard x 100

Stability testing

Temperature-dependent stability studies were carried out with the optimized batches Dosh II, CP III, SSG II. They were packed in Alu-Alu pouches and stored under the following conditions for a period prescribed by the ICH guidelines for accelerated studies in stability chambers (Thermolab).

(i) 30 ± 2 °C and RH 65 % ± 5%

(ii) 40 ± 2 °C and RH 75 % ± 5%

The tablets were withdrawn after a period of 7, 14 days, 1, 2, and 3 months, and then analyzed for visual defects, hardness, friability, disintegration, dissolution and percentage assay.

RESULTS AND DISCUSSION

The phase solubility diagram for the complex formation between diltiazem hydrochloride and β-CD is shown in Figure 1. The association constant (Ka) was calculated as 819.13M^{-1} which was within the range of 200-5000 M^{-1}. The phase solubility diagram shows that the aqueous solubility of diltiazem hydrochloride increased linearly with a slope of 0.933 (r^2 = 0.997), as a function of β-CD concentration. 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 freeze-dried complex was selected for formulation, because it masked the bitter taste, showed maximum drug content and better dissolution profile. Table I shows the formulae used in the preparation of the tablets containing the freeze-dried complex of the drug.

The bitter taste of the drug was masked after complexation. The freeze-dried method resulted in the complex that showed maximum masking of bitter taste of the drug during *in vivo* studies (Table II).

The drug content percentages of the complexes are shown in Figure 2, and were found to be within the range of 94 ± 0.5 to 99 ± 0.5%.

The infrared spectra of diltiazem HCl, β-CD, physical mixture and CD complexes prepared by various methods are shown in Figure 3a, 3b, 3c, 3d, 3e, 3f , 3g and 3h, respectively. Drug spectrum shows prominent peaks at 3035 cm^{-1}, 2966 cm^{-1}, 2837 cm^{-1}, and 781 cm^{-1}, corresponding to aromatic C-H stretch, aliphatic C-H stretch, O-CH_3 C-H stretch and C-H stretch (Figure 3a). The prominent peaks of β-CD are at 3326 cm^{-1}, 2950 cm^{-1}, 1200 cm^{-1}, and 1000 cm^{-1}, corresponding to C-H stretching, C-H stretching-C-O asymmetric stretching, and OH bending, respectively (Figure 3b). The physical mixtures of the drug with β-CD (1:1) and of the drug with β-CD complexes show prominent peaks of the drug, but there was a reduction in peak intensity of the drug peak, which

TABLE I - Formulae used in the preparation of tablets

Ingredients (mg)	Control formulation	Dosh I (2 %)	Dosh II (4%)	Dosh III (8 %)	Dosh IV (12%)	CP I (2%)	CP II (4%)	CP III (8%)	CP IV (12 %)	SSG I (2%)	SSG II (4%)	SSG III (8%)	SSG IV (12%)
Drug-β-CD complex	86.07	86.07	86.07	86.07	86.07	86.07	86.07	86.07	86.07	86.07	86.07	86.07	86.07
MCC PH 102	58.43	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5
Lactose	50	50	50	50	50	50	50	50	50	50	50	50	50
Manitol	43.4	38.2	33	22.6	12.2	38.2	33	22.6	12.2	38.2	33	22.6	12.2
Doshion P544	-	5.2	10.4	20.8	31.2	-	-	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	5.2	10.4	20.8	31.2	-	-	-	-
Sodium starch glyolate	-	-	-	-	-	-	-	-	-	5.2	10.4	20.8	31.2
Aspartame	13	13	13	13	13	13	13	13	13	13	13	13	13
Magnesium stearate	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2
Talc	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
Ice cream flavor	1.30	1.23	1.23	1.23	1.23	1.23	1.23	1.23	1.23	1.23	1.23	1.23	1.23
Total (mg)	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**

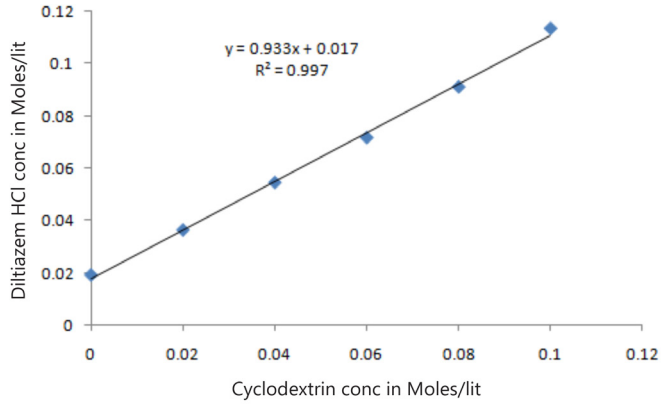


FIGURE 1 - Phase solubility analysis plot for diltiazem hydrochloride inclusion complexes.

TABLE II - Taste evaluation of the complexes

Drug-Drug-β-CD	Mean bitterness value	
	Drug	Drug-β-CD (1:1)
Kneading	5	3
Co-evaporation	5	3
Co-grounding	5	4
Freeze-drying	5	2
Melting method	5	4
Physical method	5	5

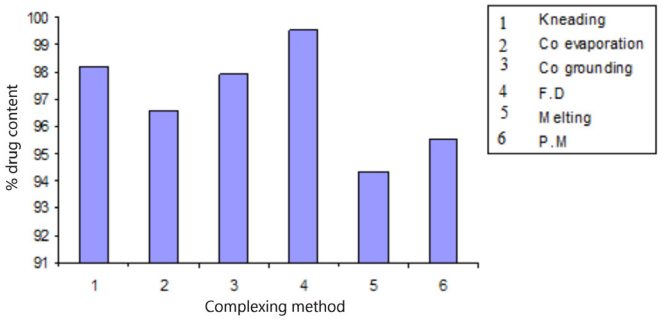
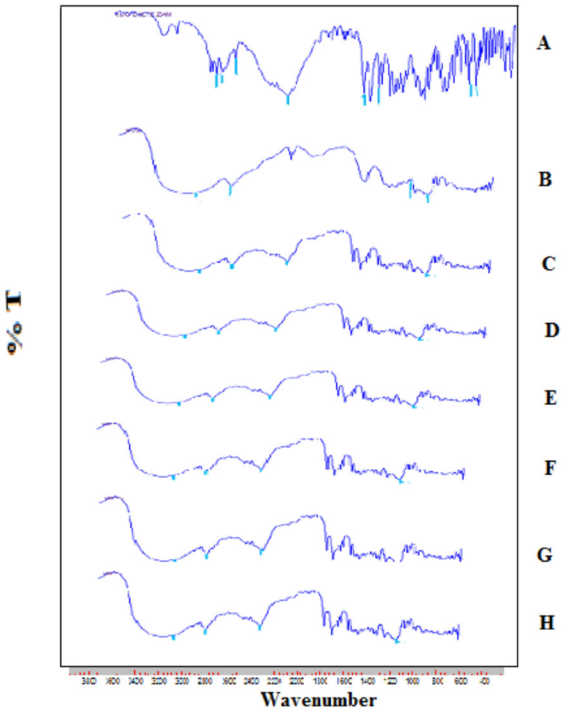


FIGURE 2 - Drug content in drug-β-cyclodextrin (1:1) complex.

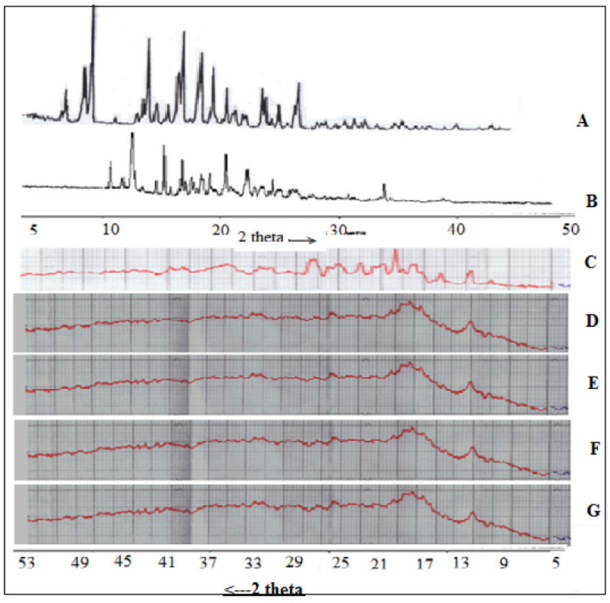
was obscured by the CD peak, indicating the formation of inclusion complexes. (Figure 3c, 3d, 3e, 3f, 3g, 3h).

The XRD analysis (Figure 4) was carried out to confirm the formation of a new solid state, *i.e.*, the formation of amorphous solid state (inclusion complex formation). The diffractograms of the drug (4a) exhibited characteristic peaks at 5.85, 9.18, 10.60, 12.54, 15.23, 19.53, 20.80, 20.02, 25.933, and 27.331, due to the crystalline nature of the drug. The diffractograms of β-CD (4b) exhibited characteristic peaks at 10.62, 12.46, 15.42, 16.98, 20.94, and 22.80 due to its crystalline nature. The physical mixture (4c) exhibited peaks at 10.6, 12.6, 15.4, 19.6, 23, 25.2, and 27.4 both for the drug and for β-CD, *i.e.*, it is crystalline in nature, and there is no inclusion complex formation. The diffractograms for the kneading method



(A) Drug, (B) β-Cyclodextrin, (C) Physical mixture, (D) Kneading method:(Kn), (E) Coevaporation method, (F) Co-grounding , (G) Freeze –Drying Method, (H) Melting method

FIGURE 3 - Infrared spectroscopy study.



(A) Drug, (B) β-Cyclodextrin, (C) Physical mixture, (D) Kneading method:(Kn), (E) Coevaporation method, (F) Co-grounding, (G) Freeze –Drying Method

FIGURE 4 - X-ray diffraction studies.

(Kn) (4d), co-evaporation method (4e), co-grounding (4f), and freeze–drying method (4h) were found to be more diffuse, when compared to the physical mixture, *i.e.*, there is no characteristic peak which confirms the formation of an amorphous solid state (inclusion complex formation).

Figure 5 show the DSC thermograms of drug, β-CD and drug-β-CD (1:1) complexes. The DSC studies were carried out to confirm the interaction of the drug with β-CD. The DSC studies showed that endothermic peaks for pure diltiazem HCl and β-CD were obtained at 212 °C and 85.11 °C, respectively. The thermogram of the drug-β-CD (1:1) complex showed complete disappearance of peak of diltiazem HCl and shift of the endothermic peak of β-CD. These indicate the successful inclusion complexation of the drug with β-CD.

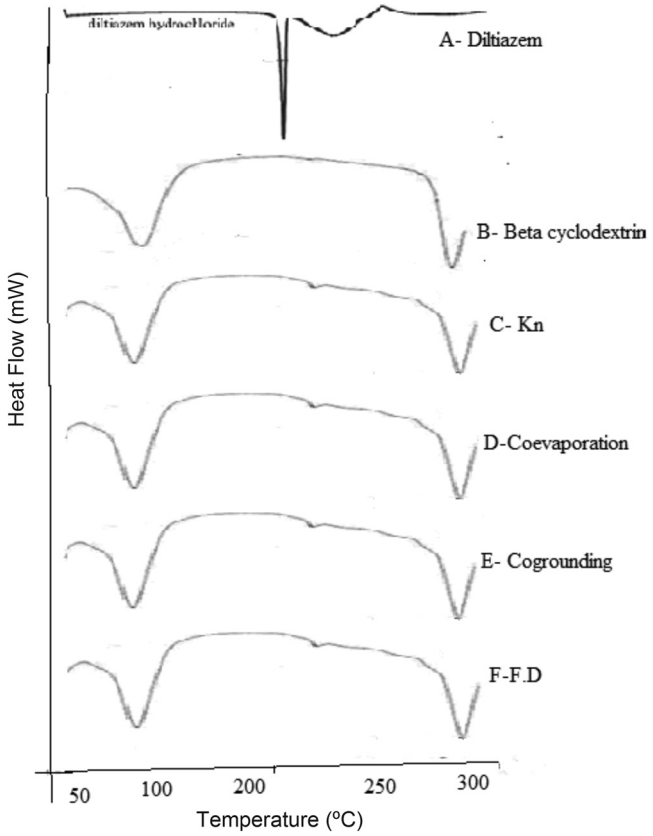


FIGURE 5 - Differential scanning calorimetry study.

From the *in vitro* release study (Figures 6 and 7), it was found that the freeze-dried complex showed improvement in dissolution behavior as compared to the drug and other complexes. The freeze-dried complex presented better dissolution performance in 0.1 N HCl and pH 6.8 phosphate buffer. This might be due to the inclusion complex formation.

The prepared tablets were evaluated for weight variation, hardness, friability, disintegration time, and taste. Table III shows that the prepared formulations mask the bitter taste of the drug, which may be due to complex-

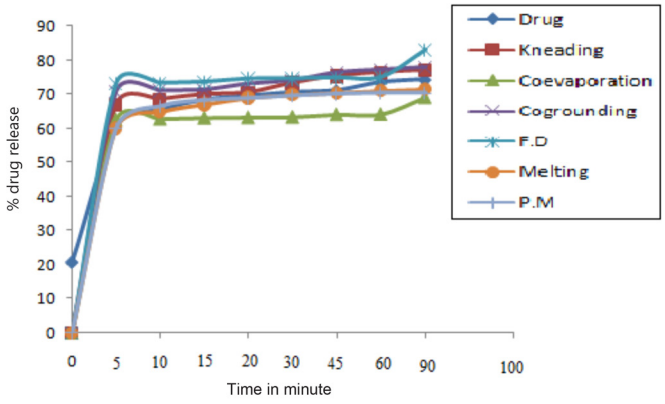


FIGURE 6 - Drug release of the drug and its complexes in 0.1 N HCl.

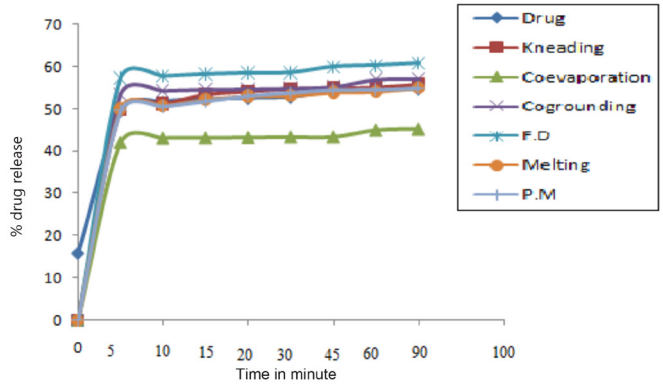


FIGURE 7 - Drug release of drug and its complexes in pH 6.8 phosphate buffer.

ation with β-CD, as well as the use of a sweetener in the formulation. Formulations Dosh II (4 % Doshion), CP III (8% CP) and SSG II (4 % SSG) show decreased DT, *i.e.*, 0.54, 0.35 and 1.23 minutes, respectively. Doshion consists of ion exchange resins. Doshion (Table IV) showed a reduction in the disintegration time from 2% to 12%, but at 4% Doshion showed reduction in DT, when compared to 2%, 8% and 12%. Hence, 4% Doshion (Dosh II) was selected. CP (Table IV) showed a trend of decrease in DT as concentration increased. This was because CP shows a capillary mechanism of disintegration. When in contact with water, it replaces the air absorbed by particles. This weakens the intermolecular bond, breaking the tablet into smaller particles. As the concentration of CP increased, the number of capillaries also increased, thus increasing the channeling of water. Hence, the rate of liberation to primary particles increased. As compared to other superdisintegrants, CP showed much better disintegration time drop and was much more effective than others. At 8%, CP showed decrease in DT, as compared to 2%, 4% and 12 %. Hence, 8% CP (CP III) was selected. SSG (Table IV) showed a reduction in DT at 4 % (SSG II), but at 2%, 8%, and 12% there was an increase in disintegration time. Swelling of the disintegrant particles caused expansion of the compact – this effect is proportional to the disintegrant concentration. The rate of swelling was initially very fast, leveling off after a few minutes, probably due to confinement of the tablet and change in the viscosity of the penetrating liquid. This behaviour is explained by the fact that SSG, at higher concentrations, may act as a binder, and instead of swelling immediately, it binds to the particles surrounding it. Later on, gelling takes place. This creates a viscous barrier. As a result, DT increases. As compared to the other formulations, SSG showed higher DT.

TABLE III - Taste evaluation of the formulations

Formulation	Mean bitterness value	
	Drug	Formulation
Dosh I (2%)	5	2
Dosh II (4%)	5	2
Dosh III (8%)	5	2
Dosh IV (12%)	5	2
CP I (2%)	5	2
CP II (4%)	5	2
CP III (8%)	5	2
CP IV (12%)	5	2
SSG I (2%)	5	2
SSG II (4%)	5	2
SSG III (8%)	5	2
SSG IV (12%)	5	2

Formulations Dosh II, CP III and SSG II showed maximum release in pH 6.8 phosphate buffer and 0.1N HCl, as compared to the other formulations (Figures 8 and 9).

In vivo DT for Dosh II, CP III and SSG II was almost the same as the *in vitro* time, which indicates a good *in vitro-in vivo* correlation (Table IV).

Stability data is shown in Tables V and VI. There was no major change in hardness, friability, disintegration, dissolution, and percentage assay for Dosh II, CP III and SSG II, when compared with the initial batch, which indicates that formulations remained stable.

CONCLUSION

Diltiazem hydrochloride, a bitter drug, could be successfully taste-masked using β-CD by freeze-drying method. The taste-masked complex was incorporated to

TABLE IV - Evaluation of the formulation

Parameter	Control formulation	Dosh I (2%)	Dosh II (4%)	Dosh III (8 %)	Dosh IV (12%)	CP I (2%)	CP II (4%)	CP III (8%)	CP IV (12 %)	SSG I (2%)	SSG II (4%)	SSG III (8%)	SSG IV (12%)
Hardness (Kg/cm2)**	2.6 ± 0.1732	2.9 ± 1.31	3.2 ± 1.06	3.4 ± 0.89	3.1 ± 0.19	2.56 ± 0.032	2.50 ± 0.10	2.63 ± 0.152	2.66 ± 0.057	2.62 ± 0.158	2.53 ± 0.152	3 ± 0.100	3.1 ± 0.100
Friability (%)	0.70	0.76	0.63	0.72	0.89	0.69	0.62	0.65	0.63	0.78	0.79	0.74	0.78
Thickness (mm)**	3.3 ± 0.0173	3.3 ± 0.02	3.4 ± 0.04	3.1 ± 0.02	3.2 ± 0.03	3.4 ± 0.02	3.5 ± 0.03	3.02 ± 0.02	3.01 ± 0.02	3.2 ± 0.03	3.2 ± 0.03	3.4 ± 0.03	3.5 ± 0.02
DT (min)**	2.09-2.20	1.60 ± 0.577	0.51 ± 0.577	0.72 ± 0.577	0.80 ± 1.00	1.10 ± 1.0	0.4 ± 2.0	0.32 ± 1.52	0.50 ± 2.60	1.54 ± 0.036	1.23 ± 0.026	1.40 ± 0.05	1.45 ± 0.02
DT (in vivo, min)**	2.10-2.25	1.63 ± 0.562	0.54 ± 0.534	0.75 ± 0.567	0.82 ± 1.00	1.15 ± 1.04	0.42 ± 1.80	0.35 ± 1.46	0.54 ± 2.10	1.60 ± 0.040	1.25 ± 0.030	1.45 ± 0.05	1.48 ± 0.03
Mean weight (mg)*	256.77 ± 0.56	255.70 ± 0.6083	255.6 ± 0.5292	255.2 ± 1.058	256.83 ± 0.5923	256.93 ± 0.9018	256 ± 1.00	256.06 ± 0.702	254.73 ± 0.25	257.16 ± 1.04	256.83 ± 0.763	255.5 ± 0.500	255.5 ± 1.322

* Mean ± SD, n = 20, ** Mean ± SD, n = 6

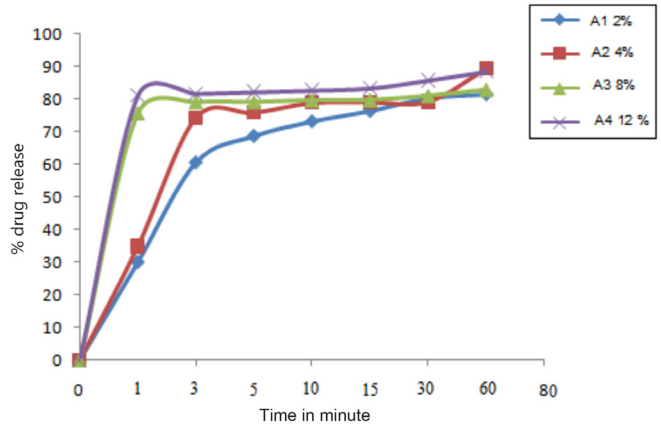


FIGURE 8 - Drug release from tablet in pH 6.8 phosphate buffer.

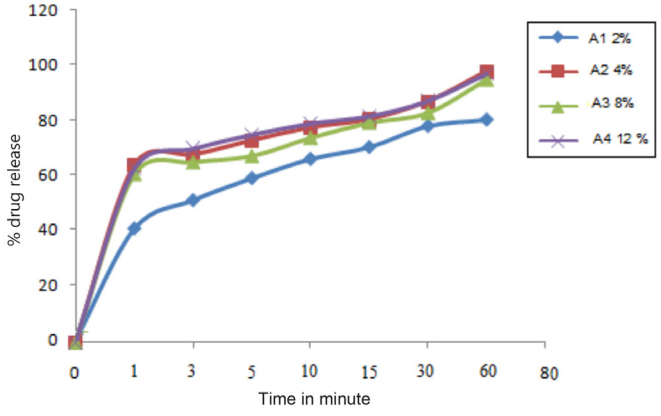


FIGURE 9 - Drug release from tablet in 0.1 N HCl.

TABLE V - Stability Testing-i) 30 ± 1 °C and RH 65 % ± 5%

Formulation	Parameter	Initial	30 °C / 65% RH 7 days	30 °C / 65% RH 14 days	30 °C / 65% RH 1 month	30 °C / 65% RH 2 months	30 °C / 65% RH 3 months
Dosh II	Hardness** (Kg/cm²)	3.2 ± 1.06	3.1 ± 0.19	3.2 ± 0.10	3.13 ± 0.057	3.3 ± 0.34	3.2 ± 0.15
	Friability (%)	0.63	0.63	0.69	0.71	0.72	0.69
	Thickness (mm)**	3.4 ± 0.04	3.3 ± 0.02	3.2 ± 0.11	3.2 ± 0.057	3.3 ± 0.04	3.2 ± 0.02
	DT (min)**	0.51 ± 0.577	0.51 ± 0.577	0.51 ± 1.00	0.53 ± 1.154	0.52 ± 1.20	0.51 ± 0.546
	Assay (%)	92.87	92.38	92.48	92.50	92.45	92.58
	Mean weight (mg)*	255.6 ± 0.5292	255.70 ± 0.6083	254.66 ± 0.57	254 ± 1.00	255.23 ± 0.489	255.30 ± 0.372
CP III	Hardness (Kg/cm²)**	2.63 ± 0.152	2.66 ± 0.057	2.66 ± 0.010	2.65 ± 0.0153	2.64 ± 0.149	2.61 ± 0.042
	Friability (%)	0.65	0.65	0.67	0.65	0.70	0.68
	Thickness (mm)**	3.02 ± 0.02	3.02 ± 0.02	3.03 ± 0.0058	3.02 ± 0.015	3.1 ± 0.02	3.05 ± 0.06
	DT (min)**	0.32 ± 1.52	0.33 ± 1.52	0.34 ± 0.577	0.35 ± 1.00	0.33 ± 1.47	0.34 ± 1.53
	Assay (%)	93.67	93.15	93.29	93.20	93.38	93.40
	Mean weight (mg)*	256.06 ± 0.702	256.93 ± 0.9018	256.33 ± 0.577	255.66 ± 0.577	256.70 ± 0.356	255.43 ± 0.521
SSG II	Hardness** (Kg/cm²)	2.53 ± 0.152	2.53 ± 0.152	2.56 ± 0.0346	2.55 ± 0.0153	2.60 ± 0.054	2.55 ± 0.0134
	Friability (%)	0.79	0.78	0.76	0.79	0.75	0.78
	Thickness (mm)**	3.2 ± 0.03	3.2 ± 0.03	3.2 ± 0.100	3.23 ± 0.057	3.1 ± 0.10	3.2 ± 0.04
	DT (min)**	1.23 ± 0.026	1.23 ± 0.026	1.24 ± 0.010	1.24 ± 0.015	1.23 ± 0.025	1.25 ± 0.014
	Assay (%)	91.34	91.21	90.89	91.37	91.45	91.69

* Mean ± SD, n = 20, ** Mean ± SD, n = 6

TABLE VI - Stability Testing-i) 40 ± 2 °C and RH 75 % ± 5%

Formulation	Parameter	30 ºC / 65% RH 7 days	30 ºC / 65% RH 14 days	30 ºC / 65% RH 1 month	30 ºC / 65% RH 2 months	30 ºC / 65% RH 3 months
Dosh II	Hardness (Kg/cm^2)**	3.1 ± 0.200	3.13 ± 0.1528	3.2 ± 0.100	3.2 ± 0.150	3.1 ± 0.260
	Friability (%)	0.67	0.74	0.78	0.72	0.70
	Thickness (mm)**	3.2 ± 0.100	3.16 ± 0.152	3.16 ± 0.0577	3.3 ± 0.100	3.18 ± 0.0512
	DT (min)**	0.52 ± 0.57	0.51 ± 1.00	0.52 ± 1.52	0.53 ± 1.00	0.51 ± 0.58
	Assay (%)	92.30	92.42	92.53	93.10	92.81
	Mean weight (mg)*	255.33 ± 0.57	255.66 ± 0.57	255.33 ± 0.57	255.40 ± 0.56	256.20 ± 0.58
CP III	Hardness (Kg/cm^2)**	2.66 ± 0.057	2.7 ± 0.100	2.73 ± 0.152	2.60 ± 0.054	2.75 ± 0.052
	Friability (%)	0.68	0.73	0.79	0.70	0.75
	Thickness (mm)**	3.02 ± 0.010	3.03 ± 0.010	3.016 ± 0.015	3.1 ± 0.012	3.08 ± 0.021
	DT (min)**	0.33 ± 0.57	0.35 ± 1.00	0.36 ± 1.52	0.34 ± 1.00	0.35 ± 1.42
	Assay (%)	93.10	93.39	93.45	93.12	92.90
	Mean weight (mg)*	256.66 ± 0.57	256 ± 1.00	256 ± 0.42	256 ± 1.00	257.10 ± 0.564
SSG II	Hardness** (Kg/cm^2)	2.55 ± 0.020	2.56 ± 0.0153	2.56 ± 0.010	2.58 ± 0.06	2.57 ± 0.01
	Friability (%)	0.68	0.76	0.81	0.75	0.70
	Thickness (mm)**	3.16 ± 0.057	3.2 ± 0.10	3.1 ± 0.10	3.2 ± 0.05	3.1 ± 0.10
	DT (min)**	1.22 ± 0.010	1.23 ± 0.020	1.23 ± 0.010	1.24 ± 0.021	1.23 ± 0.022
	Assay (%)	91.20	91.43	91.62	91.70	91.60
	Mean weight (mg)*	256.66 ± 0.577	256 ± 1.00	257 ± 1.00	256.70	258.10

* Mean ± SD, n = 20, ** Mean ± SD, n = 6

prepare oro-dispersible tablets. Tablets formulated with Doshion P544 (4%), crospovidone (8%), and sodium starch glycolate (4%) as superdisintegrant showed faster disintegration and drug release. The prepared formulation offered significant results in terms of improving taste and bioavailability.

ACKNOWLEDGEMENTS

The authors are grateful to University of Pune, India, for providing financial assistance (BCUD Project Grant) for the present research work. The authors are also thankful to the Management of MAEER's Maharashtra Institute of Pharmacy, Pune, India.

REFERENCES

DANDAGI, P.M.; HALKATTI, P.K.; MASTIHOLIMATH, V.M.; PATIL, M.B.; MANVI, F.V. Rapidly disintegrating domperidone tablets. *Ind. Drugs,* v.43, n.7, p.594-597, 2006.

GIANCARLO, C., ARIANNA, B.; ENZO, B. Cyclodextrins as food additive and in food processing. *Curr. Nutr. Food Sci.*, v.2, n.4, p.343-350, 2006.

EMARA, L.H.; BADR, R.M. Improving the dissolution and bioavailability of nifedipine using solid dispersions and solubilizers. *Drug. Dev. Ind. Pharm.,* v.28, n.7, p.795-807, 2002.

FINI, A.; BERGAMANTE, V.; CESCHEL, G.C.; RONCHI, C.; FONSECA, D.E., MORAES, C.A. Fast dispersible/slow releasing ibuprofen tablets *Eur. J. Pharm. Sci. Biopharm*., v.69, n.1, p.335-341, 2008.

FRANCO, C.; SCHWINGEL, L.; LULA, I.; SINISTERRA, R. D.; KOESTER, L. S.; BASSANI, V. L. Studies on coumestrol/β-cyclodextrin association: Inclusion complex characterization. *Int. J. Pharm.*, v.369, n.1/2, p.5-11, 2009.

HIGUCHI, T.; CONNORS, K.A. Phase solubility techniques. *Adv. Anal .Chem. Instr*., v.4, p.117-212, 1965

HISAKADZU, S.; YUNXIA, B.I. Preparation, evaluation and optimization of rapidly disintegrating tablets. *Powder Tech.,* v.122, n.2-3, p.188-198, 2002.

INDIAN PHARMACOPEIA. Delhi: Indian Pharmacopoeia Commission, 2007. v-II, p.1041-1043.

KAUSHIK, D., SAINI, T.; DUREJA, H. Development of melt-in-mouth tablets by sublimation technique. *J. Pharm. Res.,* v.3, n.2, p.35-37, 2004.

LOFTSON, T.; BREWSTER, M.E. Pharmaceutical applications of cyclodextrin: 1.Drug solubilization and stabilization. *J. Pharm. Sci.*, v.85, n.10, p.1017-1025, 1996.

LOFTSSON, T.; HREINSDOTTIR, D.; MASSON, M. Evaluation of cyclodextrin solubilization of drugs. *Int. J. Pharm.,* v.302, n.1-2, p.18-28, 2005.

MALKE, S.; SHIDHAYE, S.; KADAM, V.J. Formulation and evaluation of oxcarbazepine fast dissolve tablets. *Ind. J. Pharm. Sci.*, v.69, n.2, p.211-214, 2008.

MURA, P.; BETTINETTI, G.P. Solid- state characterization and dissolution properties of naproxen arginine hydroxypropyl β-cyclodextrin ternary system. *Eur. J. Pharm. Sci. Biopharm.,* v.59, n.1, p.99-106, 2005.

NAPPINI, M.; KISHORE, V.S. Formulation and evaluation of microspheres of diltiazem hydrochloride. *Ind. J. Pharm Sci.*, v.69, n.4, p.511-514, 2007.

NORIAKI, F.; IKUMI, U.; TAKASHI, O.; SHUN, H. Masking mechanisms of bitter taste of drugs studied with ion selective electrodes. *Chem. Pharm. Bull.,* v.54, n.8, p.1155-1161, 2006.

PATEL, A.R.; VAVIA, P.R. Preparation and evaluation of taste masked famotidine formulation using drug/β-cyclodextrin/ polymer ternary complexation approach. *AAPS PharmSciTech.,* v.9, n.2, p.544-550, 2008.

RAJEWSKI, R.A.; STELLA, V.J. Pharmaceutical applications of cyclodextrin II: *In vivo* drug delivery. *J. Pharm. Res.,* v.85,n.11, p.1142-1169, 1996.

RAMANA, M.V.; HIMAJA, M.; DUA, K. A new approach: Enhancement of solubility of rofecoxib. *Asian J. Pham*., v.2, n.2, p.96-101, 2008.

RAWAT, S.; JAIN, S.K. Solubility enhancement of celecoxib using β-cyclodextrin inclusion complexes. *Eur. J. Pharm. Sci. Biopharm.,* v.57, n.2, p.263-267, 2004.

SOHI, H., SUTANA, Y.; KHAR, R. Taste masking technologies in oral pharmaceutical: Recent developments and approaches. *Drug. Dev. Ind. Pharm.,* v.30, n.5, p.429-448, 2004.

SEKAR, V.; CHELLAN, V.R. Immediate release tablets of telmisartan using superdisintegrant formulation and stability studies. *Chem. Pharm. Bull.,* v.56, n.4, p.575-577, 2008.

SZEJTLI, J. Past, present and future of cyclodextrin research. *Pure Appl. Chem*., v.76, n.10, p.1825-1845, 2004.

Received for publication on 31st January 2011
Accepted for publication on 19th September 2011