Enhancement of the Aqueous Solubility and Masking the Bitter Taste of Famotidine Using Drug/SBE-β-CyD/Povidone K30 Complexation Approach

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ABSTRACT: The objective of the present study was to evaluate the potential of ternary system (comprised of famotidine, β-cyclodextrin (β-CyD) or its derivatives and a hydrophilic polymer) as an approach for enhancing the aqueous solubility and masking the bitter taste of famotidine. The aqueous solubility of famotidine increased in the presence of β-CyDs, particularly sulfobutyl ether β-CyD (SBE-β-CyD), and it was further enhanced by the combination of SBE-β-CyD and polyvinyl pyrrolidone (Povidone) K30. The solid binary (drug-β-CyDs) and ternary (drug-β-CyDs-Povidone K30) systems were prepared by the kneading and freeze-drying methods. The dissolution rates of these solid systems were much faster than that of the drug alone. A taste perception study was carried out, initially using a taste sensory machine and subsequently on human volunteers to evaluate the taste masking ability of the ternary complexation. Our results indicated that the combination of SBE-β-CyD and Povidone K30 is effective not only in the enhancement of the solubility and dissolution rate of famotidine, but also in masking of the bitter taste of the drug. This technique may be of value for the pharmaceutical industries, especially in preparation of rapidly disintegrating tablets dealing with bitter drugs to improve patient compliance and thus effective pharmacotherapy. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:4285–4294, 2010

Keywords: famotidine; cyclodextrins; sulfobutyl ether β-cyclodextrin; Povidone K30; dissolution; masking of bitter taste

INTRODUCTION

Cyclodextrins (CyDs) interact with poorly water soluble compounds to increase their apparent solubility. This occurs as the results of the formation of an inclusion complex formation, in which the guest and host molecules are in dynamic equilibrium with the complex.[1] However, the natural CyDs, in particular β-CyD, are of limited aqueous solubility. As a result, complexes formed *via* interactions between lipophilic compounds and these CyDs may also be poorly soluble resulting in the precipitation of the solid CyD complexes from water and other aqueous systems. Substitution of any of the hydrogen bond-forming hydroxyl groups, even by lipophilic functions, results in dramatic improvement in their aqueous solubility.[2] Hydrophilic CyDs, namely 2-hydroxylpropyl-β-CyD (HP-β-CyD) and sulfobutyl ether β-CyD (SBE-β-CyD), are generally considered to be nontoxic at low to moderate oral and intravenous doses.[3,4] In addition, human experience with CyD derivatives, specifically SBE-β-CyD and HP-β-CyD, indicates that these two CyDs are well tolerated by humans and have no adverse effects on the kidneys or other organs following either oral or intravenous administration.[5] Sometimes, large amounts of CyD are needed to solubilize small amounts of the drug, which makes CyD solubilization of the drugs impractical. The addition of a small amount of water-soluble polymer to an aqueous complexation medium frequently

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results in an increase in the complexation efficiency (CE) and, consequently, is less demanding on the formulation bulk. It is well-known that water-soluble polymers form complexes with a wide variety of compounds[6,7] and that they stabilize micelles and other types of aggregates in aqueous solutions.[8] It is also known that water-soluble polymers can solubilize β-CyD and its complexes[9] and apparent stability constants between polymers and CyDs, as well as between polymers and CyD complexes, have been determined.[10] The effect of pharmaceutical polymers such as methyl cellulose (MC), hydroxypropylmethyl cellulose (HPMC) and polyvinyl pyrrolidone (Povidone) has traditionally been attributed to several of the effects.[11] Polymers are known to interact with CyDs[12] although the exact nature of the polymer/CyD interaction is still not known. It has also been shown that at low concentrations, polymers increase the complexing abilities of CyDs[6,13] and enhance drug availability in aqueous CyD solutions.[14] Ternary complexation in the presence of suitable auxiliary substances has proved to be an effective method for increasing the stability constant.[9,14,15] Povidone, a synthetic polymer composed of linear groups of 1-vinyl-2-pyrrolidone (VP) monomers, forms molecular adducts with a wide variety of compounds and is frequently used in pharmaceutical formulations involving anti-inflammatory nonsteroidal drugs.[16,17] Extensive literature reports indicate that ternary complexation is a potentially useful approach for improving the complexation efficiency of β-CyD by increasing the stability constant of the resulting complex. In addition, it has also been suggested that ternary complexation can be effectively used as a novel approach for taste masking.[18]

Famotidine-[*N*′-(Aminosulfonyl)-3-(((2-((diaminomethylene)amino)-4-thiazolyl)methyl)thio)propanimidamide] (MW 337.43), is a potent H_2 receptor antagonist and is used in the treatment of duodenal ulcers, gastric ulcers, prevention of ulcer recurrence, treatment of gastritis, gastro-esophageal reflux disease, Zollinger–Ellison syndrome, acute upper gastrointestinal hemorrhage and for protection against the pulmonary aspiration of acid during anesthesia. In humans, famotidine selectively inhibits basal and simulated gastric acid secretion and has no clinically significant activity on histamine H_2 receptor sites outside the gastrointestinal tract. It has been reported that poor lipophilicity, poor aqueous solubility and susceptibility to gastric degradation may contribute to the low and variable oral bioavailability of famotidine.[19] It is white to off-white crystalline powder, insoluble in cold water. Its solubility at 20°C: 80% w/v in dimethyl formamide, 50% w/v in acetic acid, <0.01% w/v in ethanol, ethyl acetate and chloroform. It also has an extremely bitter taste. The pK_a of famotidine has been reported to be 6.45 at 37°C.[20] In recent years, the importance of patient compliance, not only in drug efficacy, but also in the overall economics of health care, has been increasingly recognized. Efforts to improve patient compliance have included attempts to improve the palatability of orally administered pharmaceutical agents especially for children and the elderly.[21] In particular, the bitter taste is known to decrease patient compliance, and thus reduce effective pharmacotherapy. Many reported techniques such as polymer coating, microencapsulation, use of lecithins and related substances, liposomes and various polymeric materials mask the bitterness by controlling drug release at salivary pH.[21] However, it is a major challenge to develop taste-masked formulation with improved drug release. Thus, in the present work, the interaction between famotidine and β-CyD or two of its derivatives (SBE-β-CyD and HP-β-CyD) in absence and presence of Povidone K30 was investigated, with a focus on the basis of its effect on the aqueous solubility of famotidine and on masking of its bitter taste.

MATERIALS AND METHODS

Materials

Famotidine was supplied by El-Mehan Pharmaceutical Company (Al-Ismailia, Egypt); β-CyD (MW 1135) and HP-β-CyD (average MW 1402, degree of substitution is 4.6) were generously donated by Nihon Shokuhin Kako (Tokyo, Japan); SBE β-CyD (Captisol®) (average MW 2163, the average degree of substitution is 6–7.1) was generously donated by Cydex Company (Lenexa, KS); Povidone K30 was obtained from Tokyo Chemical Industry Co. Ltd (Tokyo, Japan); All other chemicals and solvents used were of pharmaceutical and analytical grade. Double distilled water was used throughout the study for experimental work.

Methods

Phase Solubility Studies

Phase solubility equilibrium diagrams (in water at 25°C) were obtained for both binary and ternary systems as per method described by Higuchi and Connors.[22] Studies for binary systems were carried out by adding an excess amount of the drug to 25 mL of aqueous solutions containing increasing concentrations of β-CyD, HP-β-CyD, and SBE-β-CyD (from 0 to 15 mM) or Povidone K30 (from 0% to 3% w/v).

Experiment dealing with the ternary systems were performed analogously to those for the binary systems, but in the presence of 1%w/v Povidone K30. These series of suspensions were equilibrated for 48 h on a mechanical shaker (30 spm) followed by filtration and analysis. The samples were filtered

through a 0.45 μm membrane filter (Millex-HV filter units, Millipore, Carrigtwohill, County Cork, Ireland) and suitably diluted for analysis. The drug content was determined by UV spectrophotometry (Hitachi, U-2900 Spectrophotometer, Tokyo, Japan) at 269 nm. The presence of CyD and Povidone did not interfere with the spectrophotometric assay of the drug. Each experiment was performed in triplicate. For a 1:1 drug/CyD complex, the stability constants (K_c) can be determined using Eq. (1), assuming that the intrinsic solubility (S_0) is equal to the y-intercept of the linear phase solubility profile. However, because of hydrophobic interactions of lipophilic water-insoluble drugs, the presence of multiple complex structures and nonideality of saturated drug solutions, the value of S_0 is frequently much greater than that indicated by the y-intercept.[23] A better way to compare the solubilizing effects of CyDs is to compare their complexation efficiency (CE) which is calculated from the slope of the phase solubility diagram according to Eq. (2);[23,24]

$$K_c = \frac{\text{slope}}{S_0(1 - \text{slope})} \quad (1)$$

$$\text{CE} = \frac{\text{slope}}{(1 - \text{slope})} \quad (2)$$

where S_0 is the solubility of famotidine at 25°C in absence of CyD and the slope represents the corresponding slope of the phase solubility diagrams, that is, the slope of the drug molar concentration versus CyDs molar concentration graph.

Preparation of Famotidine–CyD Systems

Complexes of drug: β-CyD derivatives were prepared by the solution method. The required amounts of CyDs were initially dissolved in double distilled water to give a clear solution. The drug was then dispersed into this aqueous solution of CyD in molar ratio (1:1) followed by continuous stirring for 24 h at room temperature. The resulting solution was then freeze-dried using a freeze dryer FD-1 (EYELA, Tokyo Rikakikai, Co. Ltd, Tokyo, Japan). Ternary systems were prepared by the same procedures but with the addition of 1% w/v Povidone K30 to the aqueous solution of CyDs.

Binary and ternary CyD systems (1:1 molar ratio) were also prepared by the kneading method. Famotidine and CyDs (with or without Povidone K30) were triturated in a mortar with a small amount of water. The thick slurry formed was kneaded for 45 min and then dried at 40°C. The dried mass was powdered and sieved through mesh no. 100.

Also physical mixtures (PM) of drug-CyD-polymer were prepared by mixing all three components in geometric proportion followed by passing through a no. 100 sieve with minimum abrasion. All samples were stored in dessicator until used.

^1H NMR Spectroscopy

All NMR measurements were done on a JNM-ECA 500 model 500 MHz spectrometer (Tokyo, Japan). Famotidine and its CyDs complexes were dissolved in D_2O with the addition of 5 μL of CD_3COOD (The concentration of the drug was about 5 mg/mL and the pH was 4.2). The samples were transferred to a capillary and spectra obtained. Chemical shifts were calibrated indirectly using tetramethylsilane as an external standard.

Differential Scanning Calorimetry (DSC) Studies

The samples (5 mg of famotidine or its equivalent amount of CyD systems) were subjected to DSC studies using (Thermoplus Rigaku TG-DTA, Tokyo, Japan), Samples were sealed in 40 μL aluminum pans. An identical pan containing Al_2O_3 was used as a reference; all samples were scanned at 20°C/min with a 20 mL/min nitrogen purge.

Powder X-Ray Diffraction (PXRD) Studies

PXRD patterns were obtained by using a Rigaku X-ray diffractometer (RINT Ultima+/PC, Rigaku Corporation, Tokyo, Japan) equipped with Ni-filtered Cu Kα radiation (1.542 Å). The tube was operated at 40 kV, 40 mA and the scan range used was 10–50° of the diffraction angle 2θ.

Dissolution Studies

Dissolution tests of the binary and ternary systems (20 mg of famotidine or its equivalent amount of the CyD systems) were carried out according to JPXV paddle method. The temperature of the dissolution fluid was 37 ± 0.5°C and the speed of rotation was 50 rpm, using a rotating paddle. The tests were made with dissolution medium: 900 mL of phosphate buffer pH 6.8. Samples were taken at predetermined time intervals. The sample volume was 5 mL, and was replaced each time with an equivalent volume of fresh dissolution medium. The active content of the samples was determined using a UV/VIS spectrophotometer at 269 nm on the basis of a previously recorded calibration curve. The relationship between the absorbance and concentration of the active material was found to be linear between 3 and 30 μg/mL with a correlation coefficient of 0.9996. The experiments were performed in triplicate.

Sensor Measurement

The taste-responding system (SA402B of Intelligent Sensor Technology, Inc., Atsugi, Japan) was used to

measure the electric potential of solutions of famotidine, binary and ternary CyDs systems. The electrode set is attached to a mechanically controlled robot arm. The detecting sensor part of the equipment consists of four electrodes made of lipid/polymer membranes (channels). The lipid components of the sensors used in the present study are shown in Table 1. The difference between the electric potential of the working electrode and the reference electrode was determined by means of a high input impedance amplifier connected to a computer. We searched for sensors that responded to the bitterness of famotidine. The identified sensor was sensor channel 2, which consists of phosphoric acid didodecyl ester and dioctylphenyl phosphonate.

Samples consisting of solutions of 0.6 mg/mL famotidine, binary β-CyD, ternary β-CyD, binary HP-β-CyD, ternary HP-β-CyD, binary SBE-β-CyD and ternary SBE-β-CyD systems in 10 mM KCl solution were used in the study. A freshly prepared 30 mM KCl solution containing 0.3 mM tartaric acid (corresponding to saliva) was used as the reference sample and also to rinse the electrodes after each measurement.[25] The following method was used to measure the sensitivity and the selectivity of adsorption of the samples. The electrode was first dipped into the reference solution (V_r) and then into the sample solution (V_s). The sensor output is taken as the difference ($V_s - V_r$) between the potentials of the sample and the reference solution. Each measurement interval was set at 30 s, and electrodes were thoroughly rinsed after each measurement. The concentrations of all samples were adjusted with 10 mM KCl, which has no taste, to improve conductibility. Analysis application for artificial taste sensor SA402B Ver. 1.0.0.4 Rev.5 (Tokyo, Japan) was used as calculation software for regression analysis.

Gustatory Sensation Test

A gustatory sensation test was carried out according to the method described by Mou-ying et al.[26] Twelve healthy human volunteers, of either sex; in the age group of 23–27 years were selected. The protocol for the investigation was signed by the volunteers before starting the study. Before testing, the volunteers (n = 12) were asked to retain the reference solutions in their mouths for 10 s, and provided information on their concentrations and their bitterness intensities. All unknown samples were randomly supplied to each volunteer in a blind manner. They were then asked to taste 3 mL aliquots of the sample solutions and to assign each sample a bitterness score. All samples were kept in the mouth of the volunteers for 10 s. After tasting the sample, subjects gargled well and waited for at least 10 min before tasting the next sample.

Table 1. Lipid Component Used in the Sensor Membranes

Channel	Lipid Component
1	Palmitic acid, dioctyl phenyl phosphonate
2	Phosphoric acid didodecyl ester, dioctyl phenyl phosphonate
5	Tetradodecyl ammonium bromide, 2-nitro phenyloctyl ether
6	Tetradodecyl ammonium bromide, dioctyl phenyl phosphonate

For comparison, pure famotidine was subjected to taste evaluation by the panelist. For this purpose, two reference concentrations of the drug were used (A) 6 mg/mL and (B) 3 mg/mL. The determination of the threshold was carried out as follows. The volunteers were asked to taste reference (B), and retain in their mouths for 10 s, the volunteers were then asked to recognize this taste and consider it as score 3, the same procedures were done with reference (A) and also the volunteers were also requested to recognize this taste and consider it as score 6.

Immediately after the preparation, each volunteer held about 3 mL of each sample in their mouth for 10 s. After expectoration, the bitterness level was recorded. A numerical scale was used with the following values: 0 = tasteless, 1 = very slightly bitter, 2 = slightly bitter, 3 = moderately bitter, 4 = moderate to strong bitter, 5 = strongly bitter, 6 = very strongly bitter. This numerical scale was validated by testing samples randomly. The oral cavity was rinsed with distilled water three times to avoid bias. The wash out period between testing different samples was 10 min.

RESULTS AND DISCUSSION

Interaction of Famotidine with β-CyDs in Aqueous Solution

It has been reported that hydrophilic polymers tend to have solubility enhancement effect on poorly soluble drugs *via* the formation of weak water soluble complexes.[9,27] Thus, the aqueous solubility of famotidine in the presence of various concentrations of Povidone K30 was examined. The results showed that the solubility of the drug increased with the increasing concentrations of Povidone K30 up to an optimal concentration of almost 1% w/v, and reached a plateau thereafter, suggesting no significant increase in the solubility with further addition of polymer (Fig. 1). Thus, 1% w/v of Povidone K30 was chosen for the phase solubility studies of the ternary system of β-CyD, HP-β-CyD, and SBE-β-CyD. Phase solubility curve for both the binary and ternary systems, that is, with or without polymer was found to be of Higuchi's A_L type: that is, a linear increase in drug concentration was observed as a function of CyD

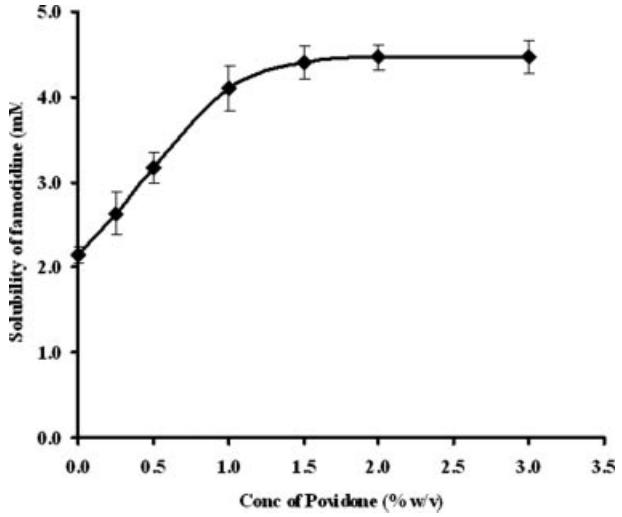


Figure 1. Phase solubility diagram of famotidine in the presence of Povidone K30 (mean ± SD).

concentration (Fig. 2). The slopes in both cases were less than unity, thus confirming the formation of 1:1 complexes.[28] The values of (K_c) and (CE) of drug-CyD systems both in the absence and presence of 1% w/v polymer were calculated (Tab. 2). It was also found that the presence of Povidone K30 resulted in a significant increase in the stability constants. The stability constant, complexation efficacy and solubility of famotidine determined with the three CyDs were in the order SBE-β-CyD > HP-β-CyD > β-CyD in the absence or presence of Povidone K30. The ratio between the K_c values of ternary and binary systems were 1.12, 1.41, and 1.67 for β-CyD, HP-β-CyD, and SBE-β-CyD, respectively. This indicates that adding of Povidone K30 produced a synergistic effect in the solublization of famotidine. The increase in the

Table 2. Values of Apparent Stability Constant (K_c) and Complexation Efficiency of Different Binary and Ternary Systems

Type of CyD	Slope	K_c (M^{-1})	CE
β-CyD binary	0.302	200 ± 7	0.43 ± 0.01
HP-β-CyD binary	0.372	280 ± 11	0.59 ± 0.02
SBE-β-CyD binary	0.437	370 ± 12	0.79 ± 0.1
β-CyD ternary	0.439	223 ± 8	0.75 ± 0.03
HP-β-CyD ternary	0.588	395 ± 9	1.26 ± 0.12
SBE-β-CyD ternary	0.689	620 ± 17	1.91 ± 0.22

K_c, stability constant; CE, complexation efficiency.

stability constant and complexation efficiency can be attributed to the increase in the complexing ability of cyclodextrin towards the drug *via* the formation of interactions such as hydrophobic bonds, Van der Waals dispersion forces, or hydrogen bonds and/or promoting the release of high-energy water molecules present in the cyclodextrin cavity.[29] In this case, the ternary complexes (cocomplexes) of β-CyDs may be similarly formed, as previously reported for methazolamide and HP-β-CyD in the presence of different hydrophilic polymers.[30]

The interaction between famotidine and the three β-CyDs was examined using ^{1}H NMR spectroscopy. ^{1}H NMR spectroscopy is one of the most useful techniques for investigating the stability and stoichiometry of complexes. Changes in hydrogen signals in an interacting molecule can be detected in a single ^{1}H NMR spectrum. To analyze the molecular interactions with saccharide molecules, signal assignments are necessary in the first stages of the study. However, it is very difficult to completely assign proton signals because saccharide molecules show severely overlapped signals in a limited range in the

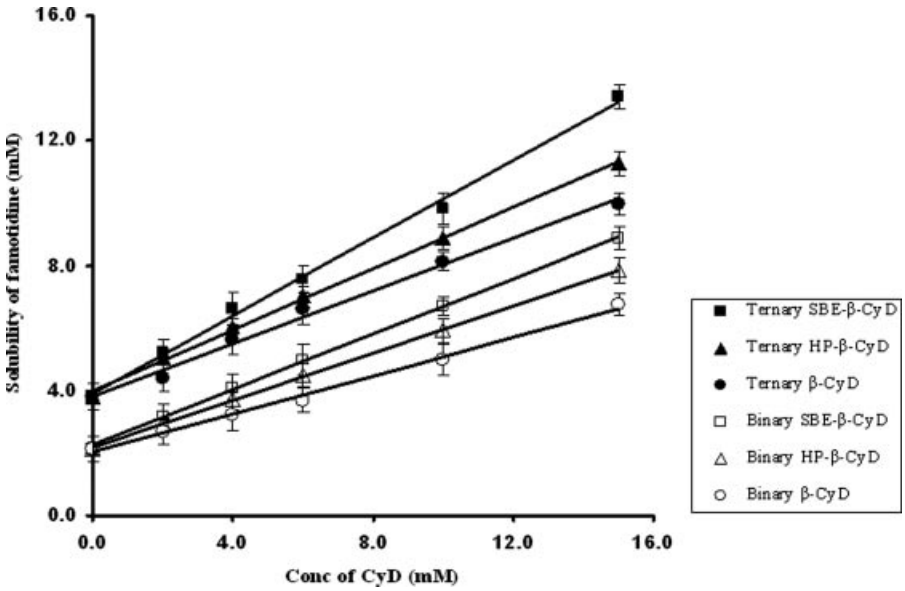


Figure 2. Phase solubility diagram of binary drug CyD and ternary drug-CyD-polymer systems (mean ± SD).

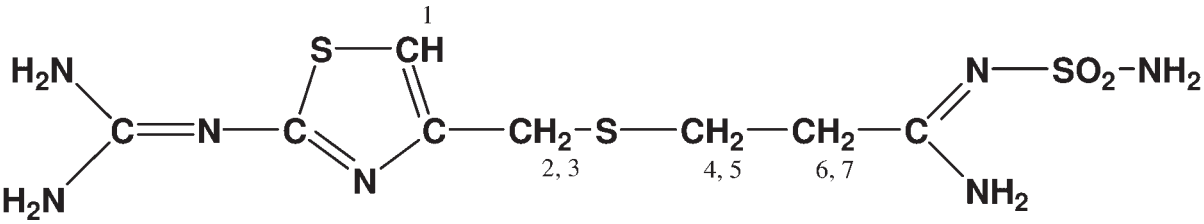
^{1}H NMR spectra.[31] The assignment of famotidine was done according to a previous report.[32] Table 3 summarizes the effects of the three β-CyDs including SBE-β-CyD on the ^{1}H-chemical shifts of famotidine. Unfortunately, amino protons were not detected owing to H–D exchange in D_2O solution. However, some protons were clearly observed. Upon addition of β-CyDs, most of famotidine protons observed were shifted downfield. The changes in the chemical shifts were particularly dramatic in the case of SBE-β-CyD compared with β-CyD and HP-β-CyD. In the case of SBE-β-CyD system, H-1 at the thiazole ring was shifted downfield significantly. In sharp contrast to SBE-β-CyD, no significant chemical shift changes were observed for β-CyD and HP-β-CyD systems. This suggested that the free rotation of the thiazole ring may be inhibited by the interaction with SBE-β-CyD. Furthermore, H-2,3, H4,5, and H6,7 at the sulfide moiety underwent downfield shifts in the order of SBE-β-CyD > HP-β-CyD > β-CyD. These results indicate that famotidine binds with SBE-β-CyD *via* relatively strong hydrophobic and electrostatic interactions. Unfortunately, it was too difficult to analyze the molecular interactions in case of ternary β-CyDs systems due to the increase in viscosity of the ternary β-CyDs solutions (data not shown).

Interaction of Famotidine with β-CyDs in Solid State

DSC thermograms of famotidine, β-CyD, HP-β-CyD, SBE-β-CyD, physical mixture, binary systems (prepared by the kneading method) and the ternary systems (prepared by the kneading method), binary systems (prepared by freeze drying) and ternary systems (prepared by freeze drying) are illustrated in Figure 3. Famotidine exhibited a sharp peak at 161–163°C which corresponds to its melting point. Moreover, β-CyD and HP-β-CyD exhibited a broad endothermic event at 80–100°C which corresponds to the release of water content from the cavity of CyD. The existence of an interaction between two components can be obtained by DSC. When guest molecules are included in the CyD cavity, their melting, boiling and sublimation points usually shift to a different temperature or disappear. The magnitude of the peak area provides an estimation of the number of molecules undergoing the transition.[33–35] Thus, a decrease in the peak area value for the ternary system of β-CyD, and or the complete disappearance of the drug peak of ternary systems of HP-β-CyD and SBE-β-CyD suggests that the complexation efficiency is enhanced due to the presence of the hydrophilic polymer leading to a decrease in the amount of free drug in the ternary system as compared to both binary systems and physical mixtures.

PXRD analyses were carried out to confirm that a new solid state was formed. PXRD patterns and data for the samples are shown in Figure 4. Famotidine exhibited a series of intense peaks at 11.56, 15.70, 17.94, 20.00, 20.80, 22.02, 24.00, 27.05, and 31.22°(2θ), which are consistent with the crystalline nature of famotidine. On comparing the diffratograms of all the samples, it can be concluded that the formation of ternary systems of HP-β-CyD and SBE-β-CyD resulted in the formation of an apparently amorphous solid system. However, the diffratogram of the ternary system of β-CyD shows a decrease in the intensity of the peaks of famotidine but not complete disappearance of these peaks which indicates the presence of free crystalline drug. Moreover, the diffratograms of the binary systems of CyDs show a decrease in the peak intensities of famotidine but not a complete disappearance of these peaks which is also indicative of the presence of free crystalline

Table 3. Experimental ^{1}H NMR Chemical Shift Displacements of Famotidine in the Presence of CyDs in D_2O at 25°C



Atom Number	Chemical Shift Displacement of Famotidine $\triangle\delta$ (ppm)[a]		
	β-CyD	HP-β-CyD	SBE-β-CyD
H1	0.001	−0.002	0.042
H2,3	0.005	0.014	0.076
H4,5	0.010	0.009	0.159
H6,7	0.018	0.025	0.115

[a]Chemical shift displacements were expressed as $\triangle\delta = \delta_{withCyD} - \delta_{withoutCyD}$.

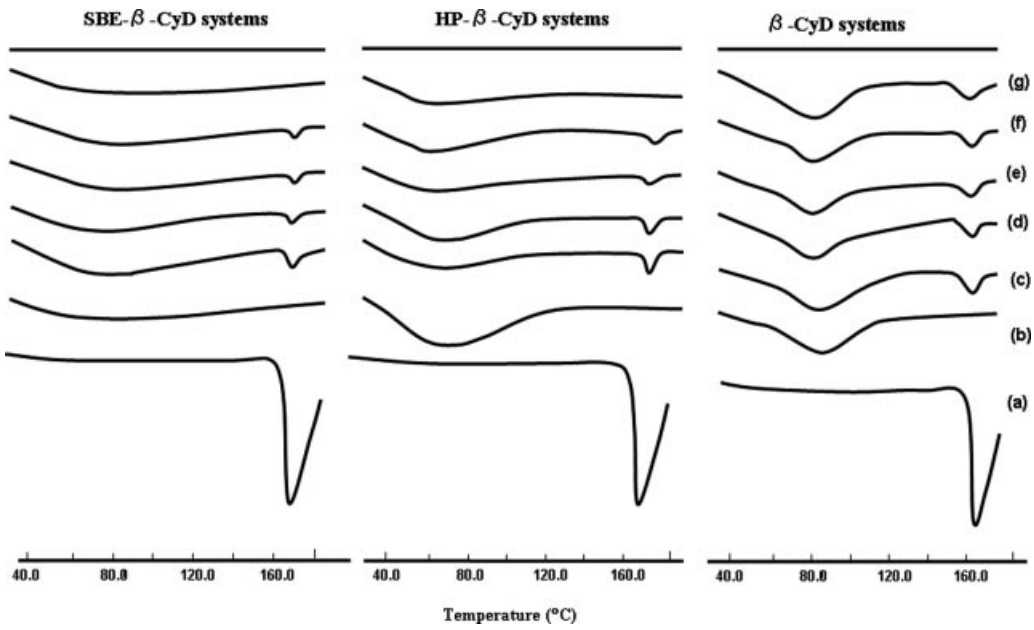


Figure 3. DSC of (a) famotidine, (b) CyD, (c) physical mixture1:1, (d) binary kenading system, (e) ternary kneading system, (f) binary freeze drying system, and (g) ternary freeze drying system.

drug. The increased complexation of famotidine led to a decrease in its free concentration in the ternary systems. Moreover, the PXRD patterns of ternary systems were found to be more diffuse compared to both the binary systems and the physical mixtures. Thus, it can be concluded that the ternary systems resulted in an increase in the complexation efficiency, resulting in the formation of an amorphous solid state.

Dissolution Studies

In the present study, an in vitro drug release study was carried out to evaluate the effect of the enhanced stability constant on dissolution rate of the ternary system. It was found that ternary system of SBE-β-CyD resulted in a complete release with a dissolution percentage (DP_{10min}) of about 100% as compared to about 93.1% and 85.6% in the case of ternary systems

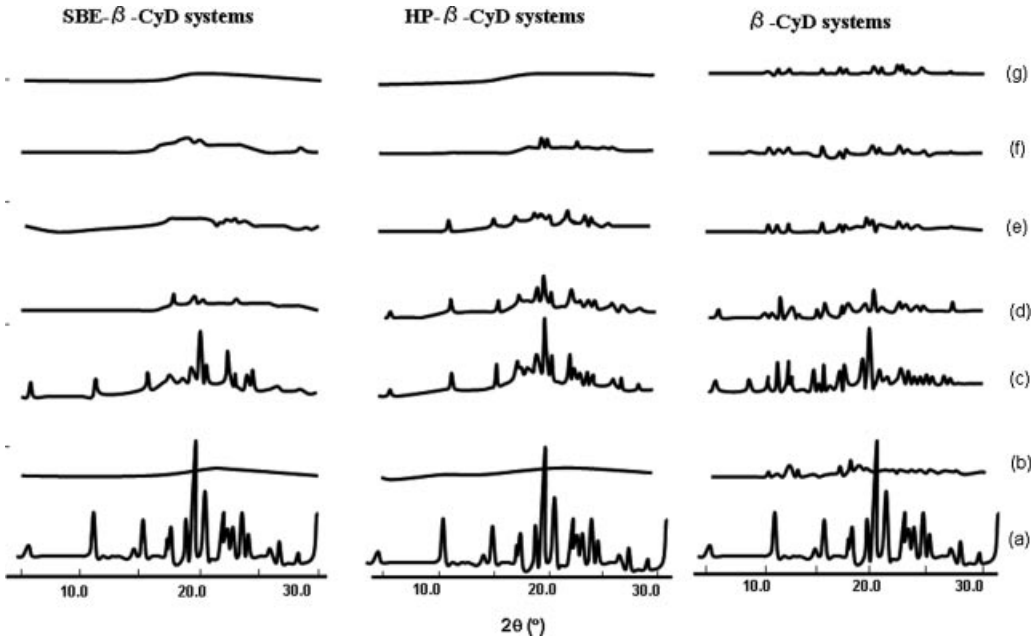


Figure 4. X-ray pattern of (a) famotidine, (b) CyD, (c) physical mixture 1:1, (d) binary kneading system, (e) ternary kneading system, (f) binary freeze drying system, and (g) ternary freeze drying system.

of HP-β-CyD and β-CyD, respectively and 45.5% for the plain drug. On the other hand, in the case of binary systems, the values were 95.7%, 88.4% and 78.5% for SBE-β-CyD, HP-β-CyD, and β-CyD binary systems, respectively. It was found that at higher dilutions (900 mL), ternary SBE-β-CyD, HP-β-CyD, and β-CyD systems resulted in an almost complete release with DE_{10min} of 75.5%, 62.5%, and 54.7% as compared to 27.1%, 66%, 57.2%, and 47.4% in the case of plain drug, SBE-β-CyD, HP-β-CyD, and β-CyD binary systems respectively. Also, the calculated $t_{1/2}$ for the ternary system of SBE-β-CyD was about 2 min compared with about 12 min in the case of the plain drug (Fig. 5). The significant improvement in dissolution characteristics of the complexes can be attributed to the concurrence of several factors: increased particle wettability, and a reduction in the degree of crystallinity of the product.[36,37] Improved dissolution may be attributed to the high energetic amorphous state and reduction in crystallinity of famotidine following complexation in kneaded systems and freeze drying systems, a conclusion that is confirmed by PXRD and DSC studies.

Gustatory Sensation Test

Table 4 shows the results obtained from the electrical sensor machine which indicates that the ternary system comprising of famotidine-SBE-β-CyD-Povidone K30 gave the lowest bitterness value, suggesting that this ternary system is the most promising for masking the bitter taste of famotidine. This conclusion was confirmed in the human gustatory sensation tests.

The results concerning the bitterness evaluation using consensual, trained persons are listed in Table 5. Eight of 12 panelists give a bitterness score of 1 for the ternary SBE-β-CyD system compared to eight of the panelists giving a score of 3 and eight giving a score of 5 for the ternary HP-β-CyD and ternary β-CyD systems, respectively. Moreover, the bitterness score for the binary SBE-β-CyD system was decreased to 2 by eight of the panelists compared to eight of the panelists giving a score of 5 and nine giving a score of 6 for the binary HP-β-CyD and binary β-CyD systems, respectively. Nearly no bitterness was detected in the ternary system of SBE-β-CyD, when compared to the other ternary systems, binary systems and pure drug. The order of improvement of the bitter taste was ternary SBE-β-CyD system > binary SBE-β-CyD system > ternary HP-β-CyD > binary HP-β-CyD > ternary β-CyD > binary β-CyD. This masking ability of SBE-β-CyD may be attributed to the increase in complexation efficiency of SBE-β-CyD-Povidone K30 system, that is, lower free drug results in a lower bitter taste sensation. Szejtli and Szente[38] explained how CyD can eliminate the bad taste. They suggested that there are only two theoretical possibilities: the CyD enwraps the bad tasting molecule (inclusion complex formation), impeding its interaction with the taste buds, or the CyD interacts with the gate-keeper proteins of the taste buds, paralyzing them. In addition, the sweet taste of CyD may impart an additive effect.

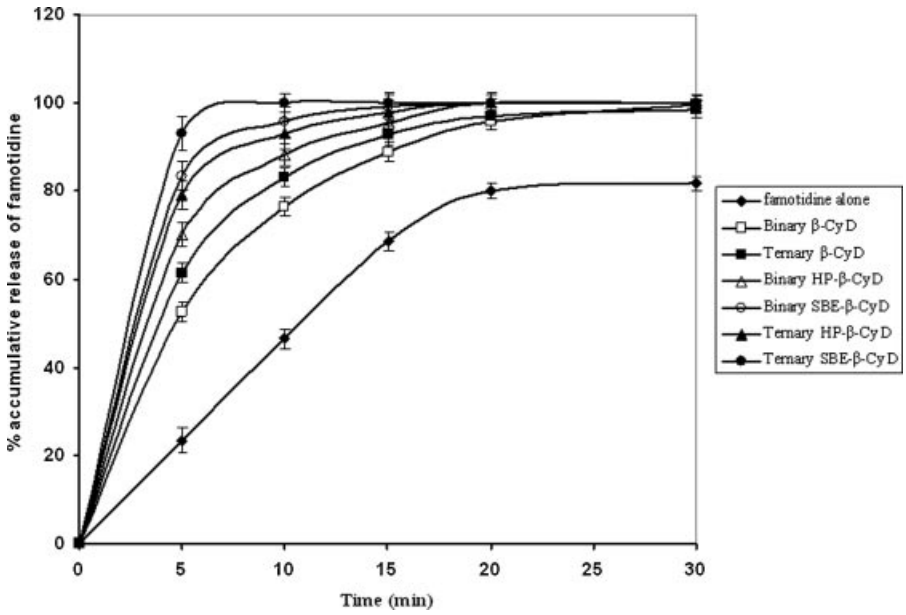


Figure 5. Dissolution profile of famotidine and different β-CyD systems in phosphate buffer at pH 6.8 and 37°C (mean ± SD).

Table 4. Results of the Electrical Sensor Machine

Formulations	Bitterness Value (Mean ± SD)	% Relative
Pure drug	22.8 ± 0.1	100.0
β-CyD binary system	19.5 ± 0.7	85.5
HP-β-CyD binary system	17.6 ± 0.1	77.3
SBE-β-CyD binary system	13.2 ± 0.2	57.9
β-CyD ternary system	18.1 ± 0.5	79.4
HP-β-CyD ternary system	11.1 ± 0.4	48.6
SBE-β-CyD ternary system	8.5 ± 0.1	37.1

Table 5. Bitterness Score Evaluation by a Panelist of 12 Human Volunteers

	Number of Volunteers Rating the Preparation as						
Formulations	0	1	2	3	4	5	6
Binary β-CyD					1	2	9
Binary HP-β-CyD						8	4
Binary SBE-β-CyD		4	8				
Ternary β-CyD					1	8	3
Ternary HP-β-CyD				8	2	2	
Ternary SBE-β-CyD	2	8	2				

CONCLUSION

This study conclusively demonstrates a procedure that permits the complete masking of the bitter taste of famotidine with improved dissolution *via* the use of a ternary SBE-β-CyD-Povidone K30 system. The effective taste masking can be attributed to the enhanced complexation of famotidine in ternary SBE-β-CyD system compared with β-CyD and HP-β-CyD systems and this conclusion was confirmed in the characterization studies. This approach may be of value for the pharmaceutical industries especially for producing rapidly disintegrating tablets dealing with bitter drugs and could lead to improve patient compliance and thus effective pharmacotherapy.

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