

# Characterization of Sulfobutyl Ether Beta-cyclodextrin Binary and Ternary Inclusion Complexes of Loratadine

K. V. R. N. S. Ramesh<sup>1</sup>, Hemant Kumar Singh Yadav<sup>1</sup>, Omar Sarheed<sup>1</sup>,  
Tamer Salama Elmarsafawy<sup>2</sup>, Quamrul Islam<sup>1</sup>

<sup>1</sup>Department of Pharmaceutics, RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, Ras Al Khaimah, United Arab Emirates, <sup>2</sup>Department of Institutional Research, RAK Medical and Health Sciences University, Ras Al Khaimah, United Arab Emirates

## Abstract

**Background:** Poor solubility and dissolution of drugs are major hindering factors in the development of their oral dosage forms with acceptable bioavailability. Of the various approaches, employing amorphous form of drugs is frequently utilized to develop drug products. Inclusion complexation is widely employed to prepare stable and fast dissolving forms of drug compounds. **Objective:** The objective of this work was to characterize the inclusion complexes of a poorly soluble drug loratadine prepared by employing sulfobutyl ether beta-cyclodextrin (SBE<sub>7</sub>-β-CD) in the presence or absence of water-soluble polymers. The investigation aims to find out the effect of water-soluble polymers on complexation efficiency and enhanced dissolution of the ternary complexes (TC). **Materials and Methods:** Binary and ternary inclusion complexes of loratadine in SBE<sub>7</sub>-β-CD were prepared by freeze drying method. TC were prepared using gelucire (50/13) and soluplus as the auxiliary hydrophilic polymers and formulated as tablets. The prepared complexes are evaluated by X-ray diffraction, differential scanning calorimetry, Fourier-transform infrared, and dissolution study. **Results:** X-ray diffraction and DSC studies confirmed that inclusion complexation converted crystalline loratadine into an amorphous form enhancing its dissolution. Gelucire and soluplus were effective in promoting dissolution and forming complexes of higher efficiency at a low concentration of 0.3% w/v and 0.6%w/v, respectively. The formulated tablets of inclusion complexes exhibited satisfactory pharmaceutical properties. **Conclusion:** Employing ternary inclusion complexes prepared by utilizing gelucire (50/13) and soluplus is a promising approach to develop fast dissolving formulations of poorly soluble drugs such as loratadine.

**Key words:** Amorphous form, dissolution, gelucire, soluplus, ternary complex

## INTRODUCTION

A number of formulation strategies have been developed in the past two decades to address the development of dosage forms of poorly soluble drug molecules. <sup>[1]</sup> Among these approaches, employing the amorphous form of compounds has attracted a wide attention of researchers to address the absorption problems after oral administration. <sup>[2]</sup> The use of the amorphous form to enhance oral bioavailability is found to be beneficial for many drugs because of their higher solubility relative to the crystalline form of the drugs. However, the high dissolving forms are unstable and this is due to their physical instability (i.e., crystallization). For a successful formulation development, the physical instability is a source of concern

because the beneficial effect amorphous forms are nullified. <sup>[3]</sup> Various methods are reported to prepare the fast dissolving forms which include spray drying, coprecipitation, hot melt extrusion, and inclusion complexation with cyclodextrins. <sup>[4-6]</sup> Among the various cyclodextrins (CDs), sulfobutyl ether beta-cyclodextrins (SBE<sub>7</sub>-β-CD) are found to be exhibiting high potential in increasing the dissolution of poorly soluble

### Address for correspondence:

K. V. R. N. S. Ramesh, Department of Pharmaceutics, RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, Ras Al Khaimah, United Arab Emirates. Phone: 00971503716203. Fax: 971-7-269997. E-mail: venkatramesh@rakmhsu.ac.ae

**Received:** 20-08-2020

**Revised:** 18-09-2020

**Accepted:** 24-09-2020

drugs by forming inclusion complexes of drugs.<sup>[7-8]</sup> However, these high dissolving forms are inherently unstable and need to be stabilized. Different approaches are employed to stabilize the inclusion complexes. One such approach is to develop ternary inclusion complexes in which an additional or supportive complexing agent is added in the complexation process.<sup>[9,10]</sup> In addition, higher solubility of the complexes in aqueous media and an enhanced efficiency of complexation can be achieved by the incorporation of small amounts of water-soluble polymers in complexation medium. Higher stability constants for the ternary complex (TC) formed by the inclusion of auxiliary substance polyethylene glycol and a marked enhancement in the complexation efficiency are reported for the inclusion complex of artesunate in beta-cyclodextrin.<sup>[11]</sup> There are various reports of different hydrophilic polymers, such as arginine, lecithin and polyethylene glycol employed to enhance the complexation efficiency, and stability constants of cyclodextrin complexes.<sup>[12-14]</sup> The synergistic influence of water-soluble polymers on the solubility enhancing effect of CDs can be advantageously utilized in the formulation of dosage forms.

Not much work is reported on the characterization of ternary inclusion complexes of SBE<sub>7</sub>-β-CD complexes employing gelucires and soluplus. SBE<sub>7</sub>-β-CD is a modified β cyclodextrin that has higher drug entrapment ability, better physical, and chemical properties than the parent cyclodextrin. It is reported to be having high solubility (excess 70 g/100 ml) and minimal toxicity.<sup>[15,16]</sup> SBE<sub>7</sub>-β-CD, which is being explored in the development of injectable products and found to be useful to stabilize drugs, is reported to be safe after intensive chronic safety evaluation.<sup>[17]</sup>

Gelucires are a novel class of synthetic polymers derived from mixtures of mono-, di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucires are available with a range of properties depending on their hydrophilic-lipophilic balance (1–18) and melting point (33°C–65°C) range. The gelucires containing only PEG esters (Gelucire 44/14 or 50/13) are hydrophilic and generally are used in preparation of fast-release formulations.<sup>[18]</sup> Soluplus, a new highly water-soluble polyvinyl caprolactam –polyvinyl acetate – polyethylene glycol graft copolymer, combines the features of water solubility and amphiphilicity and can thus function as a polymeric solubilizing agent. Soluplus is miscible with water in any ratio and also shows good solubility in many organic solvents.<sup>[19]</sup> Ternary inclusion complex of itraconazole in beta-cyclodextrin employing soluplus as an auxiliary substance is prepared to improve the dissolution of the drug.<sup>[20]</sup>

The objective of this work was to characterize the ternary inclusion complexes of loratadine prepared by employing SBE<sub>7</sub>-β-CD in association with water-soluble polymers such as gelucire (50/13) and soluplus as the auxiliary hydrophilic polymers. Such characterization is essential to assess the physicochemical characteristics of the prepared complexes to design oral formulations of the complexes with improved drug

dissolution. A poorly soluble drug, loratadine was employed as model drug in the present study. Loratadine belongs to biopharmaceutical classification system Class II which exhibits poor solubility. Loratadine is an anti-allergic drug used in the treatment of allergic rhinitis.<sup>[21]</sup> However, a large intra- or inter-subject variability in the oral bioavailability of loratadine was reported to correlate with the poor water-soluble property and dissolution rate limited absorption of loratadine.<sup>[22]</sup> Therefore, the solubility and dissolution behavior of loratadine are challenging aspects in formulation design.

## MATERIALS AND METHODS

Loratadine (gift sample from Julphar Gulf Pharmaceutical Industries UAE), sulfobutyl ether-beta-cyclodextrin sodium (SBE<sub>7</sub>-β-CD average molecular weight 2163 g/mol) is a gift sample from Cydex Corporation, USA, soluplus was kindly donated by BASF (Ludwigshafen, Germany), gelucire (50/13) is obtained from Genova Lifesciences, Bengaluru. All other excipients, chemicals and solvents are of analytical grade and were purchased commercially.

### Inclusion complexation of loratadine in SBE<sub>7</sub>-β-CD

#### Phase solubility study

Phase solubility studies were done to know the molar ratio of complex formation between loratadine and SBE<sub>7</sub>-β-CD as per Higuchi and Connors method.<sup>[23]</sup>

Excess amounts of loratadine were added to 15 ml of distilled water containing increasing concentrations of SBE<sub>7</sub>-β-CD with or without addition of auxiliary substance gelucire (50/13) (0.3% w/v) or soluplus (0.6% w/v) in 25 ml stoppered glass bottles. The resulting dispersions were shaken at 25°C ± 0.5°C for 3 days in a temperature controlled shaking water bath (SceichemTech SK 330 Pro). At the end of 3 days, dispersions were filtered through a 0.45 μm membrane and estimated spectrophotometrically at 248 nm (Shimadzu Model UV 1600) for the amount of loratadine dissolved.

Phase solubility studies were performed in triplicate. Solubility diagrams were drawn between the molar concentration of loratadine dissolved and the molar concentration of SBE<sub>7</sub>-β-CD. From the resulting plot, the stability constant and complexation efficiency (CE) for the formation of complex between loratadine and SBE<sub>7</sub>-β-CD were determined by employing the below formulae:

$$K_s = \text{Slope}/S_0 (1 - \text{Slope})$$

$$\text{Complexation efficiency (CE)} = \text{Slope}/(1 - \text{Slope})$$

The slope was calculated from the plot [Figure 1] and S<sub>0</sub> is the equilibrium solubility of loratadine. The details of stability constant and complexation efficiency are given in Table 1.

**Table 1:** Phase solubility data of binary and ternary inclusion complexes of loratadine

Product	Slope	r <sup>2</sup>	K <sub>s</sub> (Mol <sup>-1</sup> )	K <sub>STC/BC</sub>	CE	CE <sub>STS/BS</sub>	K <sub>S<sub>Ge</sub>/Sol</sub>	CE <sub>Ge/Sol</sub>
Binary complex	0.0275	0.9984	207	--	0.02	--	--	--
Ternary complex (soluplus)	0.1131	0.9563	380	1.83	0.13	6.5	--	--
Ternary complex (gelucire)	0.1896	0.9924	449	2.16	0.23	11.5	1.18	1.76

### Saturation solubility studies (the synergistic effect of SBE<sub>7</sub>-β-CD and gelucire or soluplus)

The increase in solubility of loratadine in a medium of SBE<sub>7</sub>-β-CD containing either gelucire (50/13) or soluplus was determined to evaluate the effect of the auxiliary hydrophilic polymers on the solubility of loratadine. To 15 ml of distilled water containing 6 mM of SBE<sub>7</sub>-β-CD, different concentrations of gelucire (0.1, 0.2, 0.3, 0.4, and 0.5% w/v) or soluplus (0.2, 0.4, 0.6, 0.8, and 1.0% w/v) were added and the various resulting dispersions were shaken in 25 ml stoppered glass bottles at 25 ± 0.5°C for 3 days in a temperature controlled shaking water bath. The various mixtures were filtered and assayed for the content of loratadine soluble. The results of solubility studies are given in Tables 2 and 3.

### Preparation of inclusion complex

The inclusion complexes of loratadine with SBE<sub>7</sub>-β-CD were prepared by freeze-drying procedure in a 1:1 M ratio.

### Freeze-drying method

Appropriate amounts of loratadine and SBE<sub>7</sub>-β-CD were dissolved in methanol (8 ml) and water (32 ml), respectively. In case of TC, gelucire 0.3% w/v (TC-G), or soluplus 0.6% w/v (TC-S) were added to the aqueous solution. The aqueous and methanolic solutions were then mixed for 24 h at 25°C using a magnetic stirrer. The blended solution was subjected to freezing at -70°C and latter freeze-dried for 48 h at -50°C using a freeze dryer (SP Scientific, Model PRO 3XL). The freeze dried powder was sifted through a 100-mesh sieve and stored until further use.

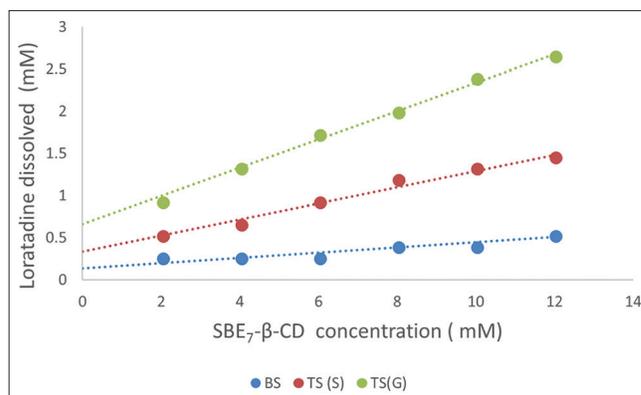
### Evaluation/characterization of inclusion complexes

#### Dissolution

The dissolution pure drug loratadine and of the complexes was studied using USP Type II dissolution rate test apparatus (Lab India Model DISSO). Loratadine or its complexes equivalent to 10 mg of loratadine were added to 900 ml of dissolution medium (simulated intestinal fluid of pH 7.4). The paddle was operated at 50 rpm and temperature was maintained at 37 ± 0.5°C. The samples of dissolution medium were removed at various time points and after filtration, they were assayed for loratadine dissolved by measuring the absorbance at 248 nm employing Shimadzu Model UV 1800

**Table 2:** Solubility of loratadine determined in various media

Medium	Solubility (µg/ml)	Solubility enhancement ratio
Water	3.47	--
Water containing 6 mM of SBE <sub>7</sub> -β-CD	8.05	2.31
Water containing 0.6% w/v of soluplus	8.49	2.44
Water containing 0.3% w/v of gelucire (50/13)	23.3	6.71
Water containing 6 mM of SBE <sub>7</sub> -β-CD and 0.6% w/v of soluplus	22.27	6.41
Water containing 6 mM of SBE <sub>7</sub> -β-CD and 0.3% w/v of gelucire (50/13)	44.31	12.76



**Figure 1:** Phase solubility diagrams of binary and ternary systems of loratadine with SBE<sub>7</sub>-β-CD: BS – binary system; TS(s) – ternary in the presence of soluplus; TS(g) –ternary system in the presence of gelucire

spectrophotometer. The findings of dissolution studies are shown in Figure 2 and give in Table 4.

### X-ray diffraction

The powder X-ray diffraction studies of loratadine and complexes were carried out employing X-ray powder diffractometer, PANalytical, Model No. X Pert pro employing Cu Kα radiation. The diffractograms were obtained between 2° and 40° in terms of 2θ angle. A generator current of 30 mA at a generator tension (voltage) 40 kV was used. The diffractograms of loratadine and complexes are shown in Figure 3.

**Table 3:** Effect of concentration of soluplus or gelucire (50/13) on the solubility ( $\mu\text{g/ml}$ ) of loratadine

Water	Water containing various concentrations (% w/v) of soluplus					Water containing various concentrations (% w/v) of gelucire (50/13)				
	0.2	0.4	0.6	0.8	1.0	0.1	0.2	0.3	0.4	0.5
3.47	13.62	17.25	22.27	24.01	25.72	27.65	36.28	44.31	46.11	48.22

**Table 4:** Dissolution parameters of loratadine and its inclusion complexes

Product	Dissolution parameter		
	Dissolution efficiency (%) $DE_{30}$	Dissolution rate constant ( $K_1$ ) ( $\text{min}^{-1}$ )	$T_{50}$ (min)
Loratadine	5.21 $\pm$ 1.45	0.0023	>60
Binary inclusion complex	29.88 $\pm$ 2.07	0.0197	31.76 $\pm$ 2.06
Ternary inclusion complex (soluplus)	48.14 $\pm$ 1.97	0.0442	12.45 $\pm$ 1.85
Ternary inclusion complex (gelucire)	71.36 $\pm$ 2.11	0.1259	7.35 $\pm$ 1.23

### Differential scanning calorimetry (DSC)

DSC studies were performed to know the physical nature of drug in the prepared complex. The calorimeter (Shimadzu DSC 60+) was run at a scanning speed of 10°C/min. The temperature range of heating was 25–260°C. After sealing the samples in aluminum pans, heating was carried out in an inert atmosphere which is maintained by circulating nitrogen gas. The results of the DSC studies are shown in Figure 4.

### Fourier-transform infrared (FTIR) spectroscopy

The infrared spectroscopic analysis of loratadine and the complexes was performed by attenuated total reflectance sampling interface technique using Agilent Model Cary 630. Different spectra obtained are shown in Figure 5.

### Tablet formulation studies

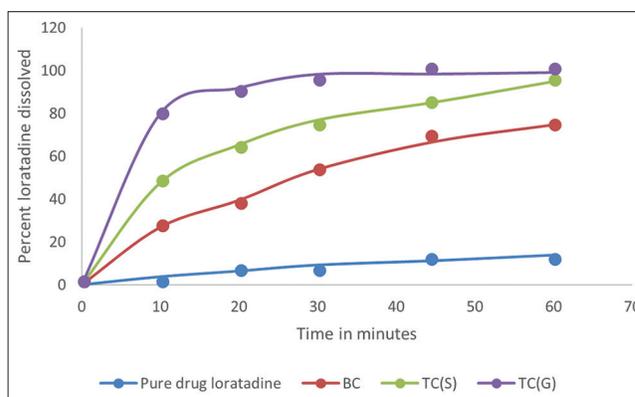
Tablet formulations containing loratadine or the binary and ternary inclusion complexes (equivalent to 10 mg of the loratadine) were prepared, according to the formulae given in Table 5. The appropriate quantities of pure drug loratadine or the inclusion complexes are mixed with various ingredients in a mortar and then the blend is mixed with talc and magnesium stearate in a plastic bag and the resulting mixture is directly compressed employing rotary tablet punching machine (Cadmach model No: CMD<sub>3</sub>-D16) using 7 mm round convex punches.

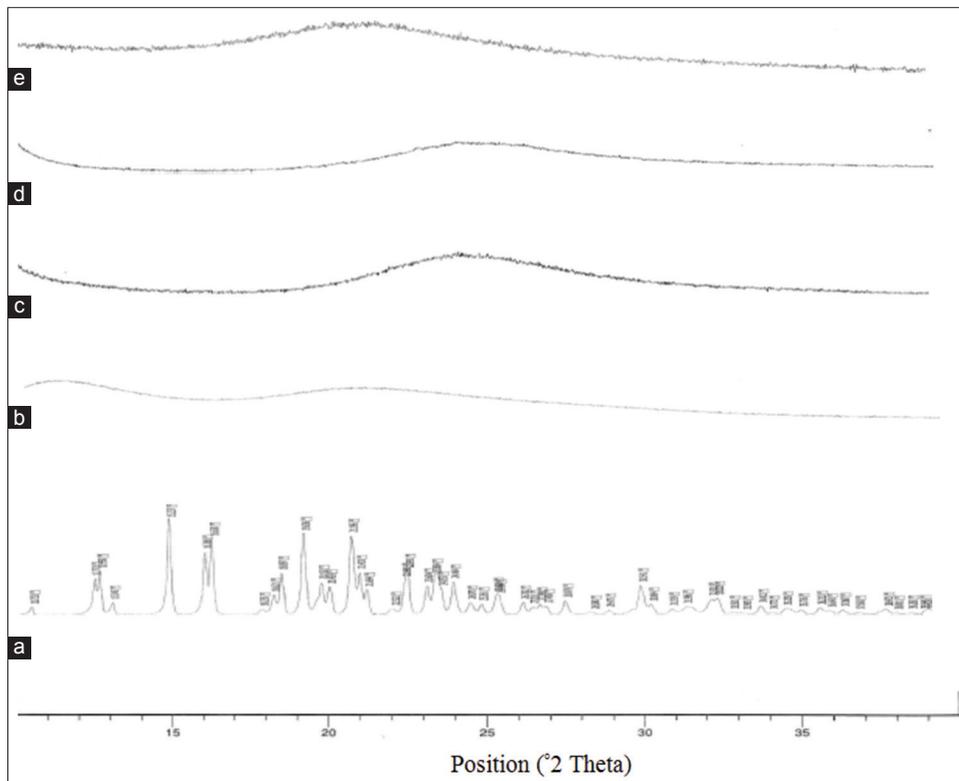
### Evaluation of tablets

The various tablet formulations are evaluated for weight variation, hardness, friability, disintegration, and drug dissolution characteristics. The details of the results obtained are given in Table 6 and shown in Figure 6.

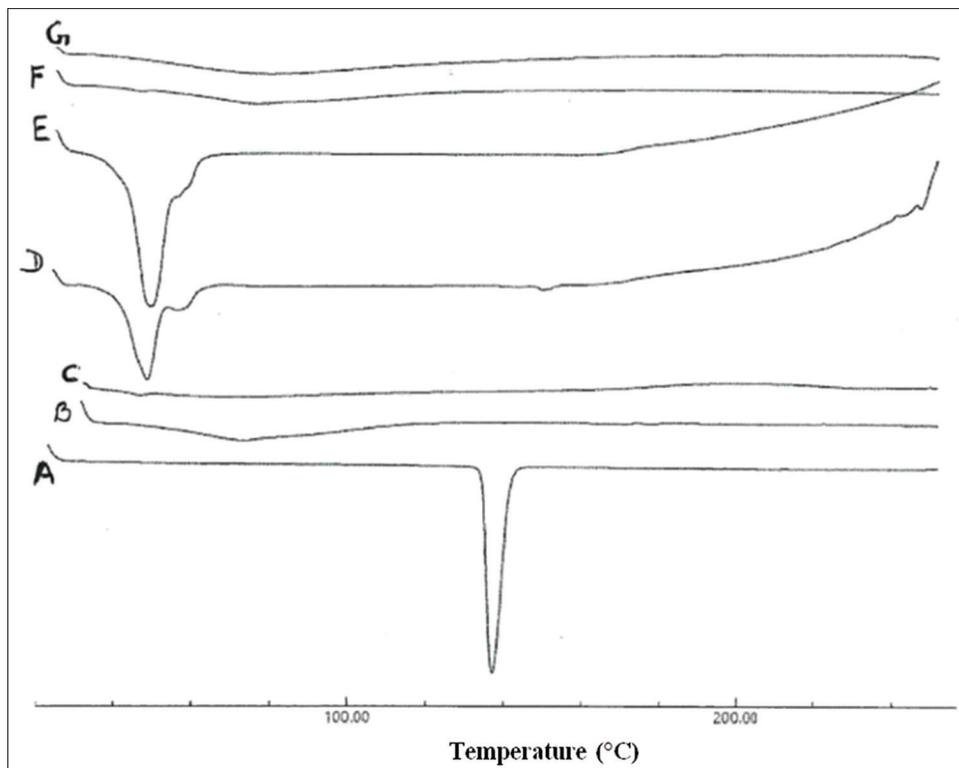
**Table 5:** Composition of different tablet formulations prepared by employing loratadine or its inclusion complexes

Ingredient (in mg)	F1	F2	F3	F4
Loratadine	10	--	--	--
Binary complex	--	65	--	--
Ternary complex (Gelucire)	--	--	70	--
Ternary complex (Soluplus)	--	--	--	75
Spray dried lactose	130	75	70	65
Sodium starch glycolate	15	15	15	15
Croscarmellose sodium	15	15	15	15
Microcrystalline cellulose	20	20	20	20
Talc	5	5	5	5
Magnesium stearate	5	5	5	5
Total weight	200	200	200	200

**Figure 2:** Dissolution profiles of pure drug loratadine and the inclusion complexes: BC-binary complex; TC(s) – ternary complex (soluplus); TC(g) – ternary complex (gelucire)



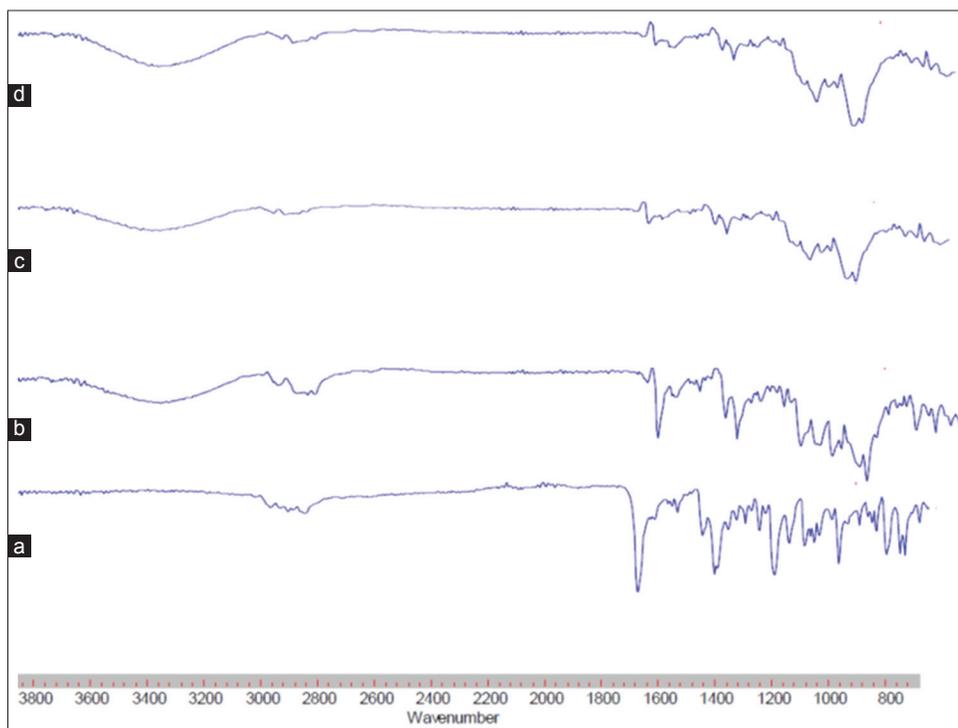
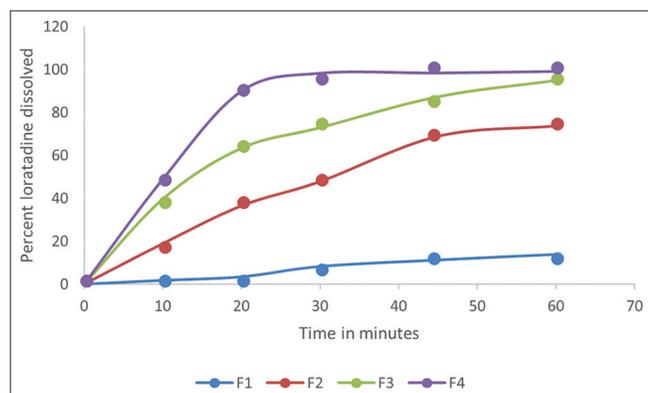
**Figure 3:** X-ray diffractograms of pure drug loratadine (a); binary complex (b); ternary complex with soluplus (c); ternary complex with gelucire (d) and SBE<sub>7</sub>-β-CD (e)



**Figure 4:** DSC thermograms of pure drug loratadine (A); binary complex (B); ternary complex with soluplus (C); ternary complex with gelucire (D); gelucire (E); soluplus (F); SBE<sub>7</sub>-β-CD (G)

**Table 6:** Hardness, average weight, friability, and disintegration time of different formulations

Formulation	Hardness (kg/cm <sup>2</sup> )	Average weight (mg)±SD	Friability (%)	Disintegration time (min)
F1	3.47±0.21	202.12±1.12	0.47±0.14	7.54±1.12
F2	3.39±0.31	199.05±0.78	0.52±0.31	8.21±1.38
F3	3.29±0.19	201.21±1.01	0.69±0.22	7.65±0.87
F4	3.51±0.29	200.78±1.18	0.73±0.17	7.21±1.05

**Figure 5:** FTIR spectra of pure drug (a); binary complex (b); ternary complex (soluplus) (c); and ternary complex (gelucire) (d)**Figure 6:** Dissolution profiles of tablet formulations of pure drug (F1); binary complex (F2); ternary complex (soluplus) (F3); ternary complex (gelucire) (F4)

## RESULTS AND DISCUSSION

### Phase solubility study

The phase solubility curves of loratadine in aqueous solutions of SBE<sub>7</sub>-β-CD in the presence or absence of gelucire

(0.3% w/v) or soluplus (0.6% w/v) are shown in Figure 1. The phase solubility diagram in all the three cases exhibited A<sub>L</sub> type curve as the solubility of loratadine increased linearly with the SBE<sub>7</sub>-β-CD concentration. The slopes of the curves are <1 suggesting that water-soluble complexes are formed in 1:1 molar ratio between loratadine and SBE<sub>7</sub>-β-CD.<sup>[23]</sup> The different phase solubility parameters investigated are shown in Table 1. The stability constant values are found to be higher in the case of ternary systems. Formation of such TC is observed as an increase in the K<sub>s</sub> value.<sup>[24]</sup> The solubility of loratadine is significantly promoted in the presence of gelucire or soluplus. The slopes of the phase solubility curves are higher in case of ternary systems than in the case of binary system. The slope value and the corresponding stability constant value of ternary system where gelucire is employed as the auxiliary compound are higher than that of ternary system prepared by employing soluplus. The complexation efficiency of the ternary systems is also found to be 6.5 and 11.5 times higher where soluplus or gelucire are employed, respectively, than the binary system. As shown in Table 1, the values of slope, K<sub>s</sub>, and CE of complex increased with the addition of either gelucire or soluplus to the complexation media, indicating greater effectiveness of ternary systems over the binary one.

Water-soluble polymers along with beta-cyclodextrins are reported to exhibit a synergistic solubilization effect on the solubility of poorly soluble drugs.<sup>[25]</sup> That is, the apparent solubility of drug is greater than the solubility obtained when the hydrophilic polymers were assessed individually. Loftsson *et al.* reported that the maximum CE is typically obtained at relatively low polymer concentrations of between 0.1% and 1% (w/v).<sup>[26]</sup> The results of our studies are also in agreement with the reported findings. Gelucire and soluplus exhibited significant synergistic effect on solubility and also at low concentrations in which they were employed resulted in enhanced complexation efficiency.

### Saturation solubility studies

Studies were carried out to evaluate the solubility enhancing effect of the third component (gelucire or soluplus) at different concentrations. The results of the synergistic effect of the third component on the solubility of loratadine are given in Table 2. While the solubility of loratadine was 3.47 µg/ml in water and 8.05 µg/ml in water containing only SBE<sub>7</sub>-β-CD (6 mM), respectively, it has sharply increased to 44.31 µg/ml when the medium also contained gelucire at 0.3% w/v exhibiting a solubility enhancement by 12.76 times. Similarly, in the presence of soluplus (0.6%w/v), the solubility of loratadine has increased to 22.27 µg/ml showing a solubility enhancement by 6.41 times.

To determine the appropriate amount of soluplus or gelucire that can be employed for preparing the inclusion complex, studies were carried out to find the solubility of loratadine at different concentrations of soluplus or gelucire. The results are shown in Table 3. As the gelucire percent in the medium increased, the solubility of loratadine also increased. However, beyond 0.3% w/v of gelucire, the increase in solubility is not significant, so in the phase solubility studies and for the complex preparation, a gelucire percentage of only 0.3% w/v is employed. Similar results are observed with soluplus also as the third component. It was observed that beyond 0.6% w/v of soluplus, there is no significant raise in the solubility of loratadine. Hence, as such during phase solubility studies and during the complex preparation, 0.6% w/v of soluplus was employed.

### Evaluation/characterization of inclusion complexes

#### Dissolution studies

Zahirul *et al.* carried out *in vitro* and *in vivo* correlation studies of loratadine bioavailability and found that the predicted profiles based on dissolution studies done at gastric pH values were in reasonable agreement with the mean bioavailability data suggesting dissolution testing should be done at gastric pH values. However, they reported that the bio-data was highly variable and it is suggested this may be due, at least in part, to high individual gastric pH

variability, and dissolution occurring in the intestine on some occasions, and therefore, dissolution testing should also be done in simulated intestinal fluid.<sup>[27]</sup> Furthermore, loratadine is a highly ionizable drug and exhibits high dissolution in gastric medium (pH1.2), so to correctly assess the dissolution characteristics of high dissolving forms, the drug dissolution should be evaluated in a medium in which the drug remains unionized so that the actual beneficial influence of the polymers or excipients on the dissolution of the drug will be revealed. Loratadine remains unionized in alkaline medium. There are reports of dissolution studies of loratadine performed in simulated intestinal fluid for characterization of inclusion complexes of loratadine.<sup>[28]</sup> Furthermore, Nacsaa *et al.* reported in their work that loratadine has different solubility properties at the various pH levels in the gastrointestinal tract and loratadine can undergo protonation in acidic media, forming salts with good solubility whereas in contrast, in simulated intestinal medium, it is practically insoluble.<sup>[29]</sup> Since loratadine is a weak base, it is absorbed from the intestine and accordingly, the dissolution properties of the inclusion complexes in their study were done in simulated intestinal fluid. So as such in our investigations, we employed simulated intestinal fluid of pH7.4 to carry out the dissolution studies. The results of the dissolution studies are shown in Figure 2 and Table 4.

It is observed that the complexes exhibited a rapid dissolution compared to the pure drug loratadine. Furthermore, relative to the binary complex (BC), the TC showed higher dissolution. In between the TC(G) made by the addition of gelucire and the TC(S) made by the incorporation of soluplus, and TC(G) exhibited higher percentage of dissolution. This could be because of more synergistic effect on the solubility of loratadine by the combination of gelucire and SBE<sub>7</sub>-β-CD than the combination of soluplus and SBE<sub>7</sub>-β-CD [solubility results are shown in Tables 2 and 3]. The various dissolution parameters and profiles are shown in Table 4 and Figure 2.

At the end of 60 min, the pure drug showed <15% dissolution while the BC, TC(S), and TC(G) inclusion complexes exhibited 53%, 76%, and 98% dissolution, respectively. To assess the increase in dissolution, Khan has suggested the term dissolution efficiency (DE).<sup>[30]</sup> Pure loratadine showed DE<sub>30</sub> of 5.21% and the complexes showed 29.88% (BC), 48.14% [TC(S)], and 76.36% [TC(G)]. The K<sub>1</sub> values for the binary and TC are higher than the values, respectively, compared to that of pure drug.

The extent of increase in dissolution observed from the complexes compared to the pure drug was assessed by finding out the difference (f1) and similarity factors (f2) as per the model proposed by Moore and Flanner.<sup>[31]</sup> The difference factor f1 is proportional to the average difference between the two profiles, whereas similarity factor f2 is inversely proportional to the average squared difference between the two profiles. In general, if the f1 values are above 15, then the two profiles compared are considered as different.

In the present investigation, when the dissolution profile of pure drug is compared with the complexes, the values are found to be 81.76, 88.42, and 91.31 for (BC), [TC(S)], and [TC(G)], respectively. These high values suggest a significant difference in the extent of dissolution between the pure drug and the complexes.

### Mechanism of increased dissolution from inclusion complex

To assess the reason for the hike in the dissolution rate of loratadine from the prepared complexes, X-ray diffraction and DSC studies were carried out.

#### X-ray diffraction

X-ray diffraction is commonly employed for characterizing the physical state of the drug in solid state in inclusion complexes. The diffraction behavior will throw light on the crystalline or amorphous nature of the drug. The X-ray diffraction spectra of loratadine and its inclusion complexes are shown in Figure 3. Pure drug loratadine exhibited several well-defined diffraction peaks. This phenomenon was also observed by Skapin and Matijevec,<sup>[32]</sup> who studied the preparation of colloidal particles of loratadine. Pure SBE<sub>7</sub>- $\beta$ -CD showed no diffraction peaks which re characteristic of its amorphous state. Similar observations are reported by Laura *et al.* in their work on cyclodextrin inclusion complexation of vinpocetine.<sup>[33]</sup> As shown in Figure 3, the diffraction peaks of loratadine have completely disappeared in both the binary and ternary inclusion complexes. The diffractograms of the complexes are more diffuse which thus indicates that the drug has failed to diffract the X-rays and this could be because it is converted into an amorphous state in the inclusion complexes.

#### DSC

The endotherms of loratadine and the inclusion complexes are shown in Figure 4. Pure drug loratadine showed a sharp endothermic peak at 137°C which is due to its melting point. Gelucire (50/13) showed its endothermic peak around 49°C. While the thermograms of pure soluplus displayed a broad endothermic peak at 73°C due to the glass transition of amorphous soluplus, which is in agreement with the reported finding of Terife *et al.*<sup>[34]</sup> No specific endothermic transformation was observed in case of SBE<sub>7</sub>- $\beta$ -CD and there is seen only a broader endotherm at 80°C which is consistent with the reported finding of Laura *et al.*<sup>[33]</sup>

No thermodynamic transformation of loratadine (melting endotherm) was observed in all the inclusion complexes. The sharp endothermic peak observed in case of pure loratadine disappeared completely. This could be due to the presence of the drug in soluble amorphous state in the polymers and loss of crystallinity. This conversion of drug into amorphous

form and getting entrapped in the cavity of SBE<sub>7</sub>- $\beta$ -CD is the reasons for the higher dissolution of loratadine from the complexes compared to that of the pure drug. Hence, the X-ray diffraction and DSC studies confirm the existence of loratadine in amorphous state in the inclusion complexes resulting in higher dissolution.

#### FTIR spectroscopy

IR spectra for pure drug loratadine, binary, and TC are shown in Figure 5. Loratadine exhibited two major characteristic absorption peaks at 1702 cm<sup>-1</sup> (C=O stretching) and at 1226 cm<sup>-1</sup> (C-O stretching).<sup>[29]</sup> The spectrum of loratadine also shows bands at 1559 cm<sup>-1</sup> (C=C stretching) and 1432 cm<sup>-1</sup> (C=N stretching). Fernando *et al.* reported in their work that the C=O and C-O bonds (absorption bands at 1702 cm<sup>-1</sup> and 1226 cm<sup>-1</sup>) from the amide or ester groups can potentially have intermolecular interaction.<sup>[35]</sup> In the case of all inclusion complexes, the stretching frequencies at 1702 cm<sup>-1</sup> and 1226 cm<sup>-1</sup> have moved to the lower and higher wavenumbers, respectively, suggesting that C=O and C-O groups were involved in the complex forming bonds with SBE<sub>7</sub>- $\beta$ -CD. Nacsa *et al.* in their work on loratadine and dimethyl beta-cyclodextrins have observed similar spectral changes and surmised that -COO group provides the complex forming bonds with the cyclodextrins and that during the formation of the inclusion complex hydrogen bonds develop between loratadine and the cyclodextrin.<sup>[28]</sup> The absorption bands at 1702 cm<sup>-1</sup> and 1226 cm<sup>-1</sup> are also found to be diminished in their intensity suggesting formation of hydrogen bonds between the carbonyl groups of loratadine and the hydroxyl groups of the host cavity during inclusion process. Otero *et al.* have reported similar observations of reduction in peak intensity in their work on the inclusion complexation of naproxen with beta-cyclodextrin.<sup>[36]</sup>

#### Tablet formulation studies

To evaluate the suitability of formulating the prepared inclusion complexes into tablets, formulations were developed employing commonly used excipients. The details of various tablet formulations are shown in Table 5.

The various tablet formulations showed satisfactory properties [Table 6]. The different tablets had a hardness of 3–4 kg/cm<sup>2</sup> and disintegrated well within 15 min. The loss of weight observed in the friability tests was <1%. And the tablets exhibited high uniformity in weight with a very low percentage of deviation.

The various dissolution profiles are shown in Figure 6. Compared to tablet formulations containing the binary complex, the formulations of TC showed much higher dissolution rate. In between the formulations containing ternary systems made of soluplus and gelucire, as expected the formulation with TC of gelucire exhibited higher dissolution.

**Table 7:** Analysis of variance of the drug dissolution from different formulations

Source	Degrees of freedom	Sum of squares	Mean of squares	F value	P value
Percent drug					
Dissolved (A)	3	60188.575	20062.858	5712.4746	0.000 **
Error	8	28.097	3.512		
Time (B)	4	7803.375	1950.844	2634.4310	0.000**
Interaction					
(AB)	12	2385.615	198.801	268.4624	0.000**
Error	32	23.697	0.741		
Total	59	70429.358			

\*\*Highly significant

Thus, the tablet formulations studies indicate that the fast dissolving characteristics of the binary and TC of loratadine were preserved and did not undergo any change in character after formulation and compression into tablets.

### Statistical analysis of drug dissolution profiles

A statistical analysis is performed to compare the drug dissolution profiles of various tablet formulations. Analysis of variance (ANOVA) was performed using two factor completely randomized design by employing MSTATC statistical analysis software. The results of ANOVA analysis for products are shown in Table 7.

According to the results of ANOVA, the percent drug dissolved was found to be significantly different at each time level ( $P = 0.000$ ) and among the tablet formulations ( $P = 0.000$ ), implying time with formulation interaction was highly significant (at  $P = 0.000$ ), that is, that the dissolution profiles were not parallel. This interaction indicated that the mean difference of percent drug dissolved among different formulations was not constant at any two points of time considered. The calculated F value of treatment groups is greater than tabulated F value (at 0.01 level of probability). The results of ANOVA also showed that the tablet formulations prepared by employing the binary and ternary inclusion complexes were significantly different in terms of percent dissolved at each time point.

### CONCLUSION

Inclusion complexation of loratadine with SBE<sub>7</sub>- $\beta$ -CD resulted in increased dissolution. The ternary systems prepared by employing the two hydrophilic polymers, gelucire (50/13) or soluplus exhibited much higher dissolution rate than the binary systems. Higher stability constant values for the TC suggest an improved complexation which is also reflected in the higher complexation efficiency. A synergistic effect in the solubility and dissolution of loratadine was observed in the presence of the two hydrophilic polymers with SBE<sub>7</sub>- $\beta$ -CD. Gelucire (50/13) is found to be showing more solubility and

dissolution promoting effect than soluplus. The crystalline drug loratadine is converted into amorphous form in the inclusion complex. The increase in solubility and dissolution of loratadine is due to the combined effect of inclusion complexation and conversion of the drug into an amorphous form. The ternary inclusion complexes could be formulated into fast dissolving tablets of loratadine without loss of the high dissolving nature of the complexes. In summary, the TC prepared with either gelucire or soluplus have a high potential in the development of a fast dissolving tablet dosage forms.

### ACKNOWLEDGMENT

The authors express their gratitude to the President of RAK Medical & Health Sciences University, UAE and Dean RAK College of Pharmaceutical Sciences for their encouragement and support in carrying out the research.

### CONTRIBUTION OF AUTHORS

All authors have made substantial contribution to the work and approved it for publication.

### REFERENCES

- Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, *et al.* Strategies to address low drug solubility in discovery and development. *Pharmacol Rev* 2013;65:315-499.
- Miller JM, Beig A, Carr RA, Spence JK, Arik D. A win-win solution in oral delivery of lipophilic drugs: Supersaturation via amorphous solid dispersions increases apparent solubility without sacrifice of intestinal membrane permeability. *Mol Pharm* 2012;9:2009-16.
- Singh A, van den Mooter G. Spray drying formulation of amorphous solid dispersions. *Adv Drug Deliv Rev* 2016;100:27-50.
- Lang B, McGinity JW, Williams RO. Hot-melt extrusion-basic principles and pharmaceutical applications. *Drug*

- Dev Ind Pharm 2014;40:1133-55.
5. Mahmah O, Tabbakh R, Kelly A, Paradkar A. A comparative study of the effect of spray drying and hot-melt extrusion on the properties of amorphous solid dispersions containing felodipine. *J Pharm Pharmacol* 2014;66:275-84.
  6. Thomas Z, Jennifer BD, Sandra K. Application of a ternary HP beta CD-complex approach to improve the dissolution performance of a poorly soluble weak acid under biorelevant conditions. *Int J Pharm* 2012;430:176-83.
  7. Farouk S, Nida EI, Xue YL, Wu ZM, Bo W. Effects of the preparation method on the formation of true nimodipine SBE- $\beta$ -CD/HP- $\beta$ -CD inclusion complexes and their dissolution rates enhancement. *AAPS Pharm Sci Tech* 2015;16:704-15.
  8. Cutrignelli A, Lopodota, A, Denora N, Rosa MI, Elisabetta F, Valentino L, *et al.* A new complex of curcumin with sulfobutylether- $\beta$ -cyclodextrin: Characterization studies and *in vitro* evaluation of cytotoxic and antioxidant activity on HepG-2 cells. *J Pharm Sci* 2014;103:3932-40.
  9. Jug M, Mennini N, Kover KE, Mura P. Comparative analysis of binary and ternary cyclodextrin complexes with econazole nitrate in solution and in solid state. *J Pharm Biomed Anal* 2014;91:81-91.
  10. Atul PS, Forum P, Manikanta M, Vasanti S, Kavatkumar P. Study on effect of L-arginine on solubility and dissolution of zaltoprofen: Preparation and characterization of binary and ternary cyclodextrin inclusion complexes. *Chem Phys Lett* 2018;694:120-8.
  11. Renu C, Gups S, Shukla G, Jain DV, Pissurlenkar RR, Coutinho ES. Interaction of artesunate with beta-cyclodextrin: Characterization, thermodynamic parameters, molecular modeling, effect of PEG on complexation and antimalarial activity. *Results Pharma Sci* 2011;1:38-48.
  12. Sarika S, Yogesh P. Inclusion complexes of cefuroxime axetil with  $\beta$ -cyclodextrin: Physicochemical characterization, molecular modeling and effect of L-arginine on complexation *J Pharm Anal* 2016;6:300-6.
  13. Dan W, Haiyan L, Jingkai G, Tao G, Shuo Y, Zhen G, *et al.* Ternary system of dihydroartemisinin with hydroxypropyl-beta-cyclodextrin and lecithin: Simultaneous enhancement of drug solubility and stability in aqueous solutions. *J Pharm Biomed Anal* 2013;83:141-8.
  14. Chowdary KP, Srinivas SV. Influence of hydrophilic polymers on celecoxib complexation with hydroxypropyl beta-cyclodextrin. *AAPS Pharm Sci Tech* 2006;7:184-9.
  15. Jain AS, Date AA, Nagarsenker MS, Pissurlunkar RR, Coutinho EC. Sulfobutyl ether,  $\beta$ -cyclodextrin (SBE,  $\beta$ -CD) carbamazepine complex: Preparation, characterization, molecular modeling, and evaluation of *in vivo* anti-epileptic activity. *AAPS Pharm Sci Tech* 2011;12:1163-75.
  16. Lockwood SF, O'Malley S, Mosher GL. Improved aqueous solubility of crystalline astaxanthin (3, 3'-dihydroxy- $\beta$ ,  $\beta$ -carotene-4, 4'-dione) by captisol (sulfobutyl ether  $\beta$ -cyclodextrin). *J Pharm Sci* 2003;92:922-6.
  17. Rajewski RA, Traiger G, Bresnahan J, Jaberaboansar P, Stella VJ, Thompson DO. Preliminary safety evaluation of parenterally administered sulfoalkyl ether  $\beta$ -cyclodextrin derivatives. *J Pharm Sci* 1995;84:927-32.
  18. Hussein A, El-Menshawe S, Afouna M. Enhancement of the *in vitro* dissolution and *in vivo* oral bioavailability of silymarin from liquid-filled hard gelatin capsules of semisolid dispersion using Gelucire 44/14 as a carrier. *Pharmazie* 2012;67:209-14.
  19. Beaulieu PL, de Marte J, Garneau M. BASF: Technical Information Soluplus. Ludwigshafen: BASF; 2010. p. 1-8.
  20. Thomas T, Jennifer BD, Charles MB, Sandra K. Cyclodextrin-water soluble polymer ternary complexes enhance the solubility and dissolution behaviour of poorly soluble drugs. Case example: Itraconazole. *Eur J Pharm Biopharm* 2013;83:378-87.
  21. Gerald KM. American Society of Health System Pharmacists. Bethesda, Maryland: AHFS Drug Information; 2018. p. 15.
  22. Ramirez E, Laosa O, Guerra P, Duque B, Mosquera B, Borobia AM, *et al.* Acceptability and characteristics of 124 human bioequivalence studies with active substances classified according to the biopharmaceutic classification system. *Br J Clin Pharmacol* 2010;70:694-702.
  23. Higuchi T, Connors A. Phase-solubility techniques. In: *Advances in Analytical Chemistry Instrumentation*. New York: Wiley Interscience; 1965. p. 117-211.
  24. Loftsson T, Marcus EB. Cyclodextrins as functional excipients: Methods to enhance complexation efficiency. *J Pharm Sci* 2012;101:3019-32.
  25. Mohammad A. Investigations of polyethylene glycol mediated ternary molecular inclusion complexes of silymarin with beta cyclodextrins. *J Appl Pharm Sci* 2015;5:26-31.
  26. Loftsson T, Fridriksdottir H, Sigurdardottir AM, Ueda H. The effect of water-soluble polymers on drug-cyclodextrin complexation. *Int J Pharm* 1994;110:169-77.
  27. Zahurul MI, Dragica R, Ruzica Z, Snjezana Z, Jasna HM, Lara K, *et al.* Classification of loratadine based on the biopharmaceutics drug classification concept and possible *in vitro in vivo* correlation. *Biol Pharm Bull* 2004;27:1630-5.
  28. Nacsá A, Berkesi O, Szabo RP, Aigner Z. Achievement of pH-independence of poorly-soluble, ionizable loratadine by inclusion complex formation with dimethyl-beta-cyclodextrin. *J Incl Phenom Macrocycl Chem* 2009;64:249-54.
  29. Nacsá A, Ambrus R, Berkesi O, Szabo RP, Aigner Z. Water-soluble loratadine inclusion complex: Analytical control of the preparation by microwave irradiation. *J Pharm Biomed Anal* 2008;48:1020-3.
  30. Khan KA. The concept of dissolution efficiency. *J Pharm*

- Pharmacol 1975;27:48-9.
31. Moore JW, Flanner HH. Mathematical comparison of dissolution profiles. *Pharm Technol* 1996;20:64-75.
  32. Skapin SD, Matijevic E. Preparation and coating of finely dispersed drugs 4. Loratadine and danazol. *J Colloid Interface Sci* 2004;272:90-8.
  33. Laura SS, Domingos CF, Francisco JB. Physicochemical investigation of the effects of water soluble polymers on vinpocetine complexation with beta cyclodextrin and its sulfobutyl ether derivative in solution and solid state. *Eur J Pharm Sci* 2003;20:253-66.
  34. Terife G, Wang P, Faridi N, Gogos GC. Hot melt mixing and foaming of soluplus and indomethacin. *Polym Eng Sci* 2012;52:1629-39.
  35. Fernando F, de Oliveira EJ, Carmen MS, Marcia LM, Julian MM. Dissolution rate enhancement of loratadine in polyvinylpyrrolidone K-30 solid dispersions by solvent methods. *Powder Technol* 2013;235:532-9.
  36. Otero EF, Anguiano IS, Garcia GN, VilaJato JL, Blanco MJ. Interaction of naproxen with  $\beta$ -cyclodextrin in solution and in the solid state. *Int J Pharm* 1992;79:149-57.

**Source of Support:** Nil. **Conflicts of Interest:** None declared.