

Enhanced Bromhexine Hydrochloride Solubility and Dissolution by Inclusion Complexation with Methylated β -cyclodextrin

การเพิ่มค่าการละลาย และการละลายของบรอมเฮกซีนไฮโดรคลอไรด์โดยการเกิดสารเชิงซ้อนอินคลูชันกับเมทิลเลเตตเบต้าไซโคลเด็กซ์ตริน

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Abstract

The aim of this study was to enhance the solubility and dissolution of bromhexine hydrochloride by inclusion complexation with the cyclodextrin derivative, methylated β -cyclodextrin (M β CD). Inclusion complexes in 1:1 molar ratio were prepared by the kneading and coevaporation methods. The solubility of drug in methylated β -cyclodextrin was studied. The complexes were characterized by differential scanning calorimetry (DSC), X-ray diffractometry, Fourier transform infrared (FT-IR) spectroscopy and dissolution studies. The solubility of bromhexine hydrochloride increased linearly with the concentration of methylated β -cyclodextrin. The phase-solubility profile was classified as A_L-type, indicating the formation of a 1:1 stoichiometric inclusion complex with an apparent stability constant (K_s) of 110 M⁻¹. The crystallinity of drug from inclusion complexes was reduced. The inclusion complex prepared by the coevaporation method showed interaction between drug and methylated β -cyclodextrin. Both kneaded and coevaporated samples gave similar dissolution profiles; of 50-, and 5-fold increases in drug dissolution were observed within the first 5 mins compared to pure drug and physical mixtures, respectively. These inclusion complexes were effective in enhancing drug dissolution, with bromhexine hydrochloride completely dissolving within 10 mins.

Keywords: bromhexine hydrochloride, methylated β -cyclodextrin, dissolution, solubility, inclusion complex

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บทคัดย่อ

การเตรียมสารเชิงซ้อนอินคลูชันระหว่างบรอมเฮกซีนไฮโดรคลอไรด์และเมทิลเลตเตไซโคลเด็กซ์ตรินมีวัตถุประสงค์เพื่อเพิ่มค่าการละลายและการละลายของบรอมเฮกซีนไฮโดรคลอไรด์ สารเชิงซ้อนอินคลูชันของตัวยาและเมทิลเลตเตไซโคลเด็กซ์ตริน ในอัตราส่วน 1:1 โดยโมลเตรียมโดย 2 วิธีคือการนวดและการระเหยร่วม เมื่อศึกษาค่าการละลายของตัวยาในสารละลายของเมทิลเลตเตไซโคลเด็กซ์ตรินที่ความเข้มข้นต่างๆ และเมื่อนำสารเชิงซ้อนอินคลูชันที่เตรียมได้มาศึกษาถึงคุณลักษณะทางเคมีฟิสิกส์ ได้แก่ การเปลี่ยนแปลงทางความร้อน การเปลี่ยนแปลงรูปผลึก การเกิดอันตรกิริยาและการละลาย ผลการศึกษา พบว่าค่าการละลายของตัวยาเพิ่มขึ้นเป็นสัดส่วนโดยตรงกับความเข้มข้นของเมทิลเลตเตไซโคลเด็กซ์ตรินที่เพิ่มขึ้น ค่าคงที่ของการเกิดสารเชิงซ้อนอินคลูชันระหว่างตัวยากับเมทิลเลตเตไซโคลเด็กซ์ตรินเท่ากับ 110 ต่อโมลสารเชิงซ้อนอินคลูชันที่ได้จากการเตรียมโดยการนวดและการระเหยร่วมทำให้ความเป็นผลึกของตัวยาลดลง สารเชิงซ้อนที่เตรียมโดยการระเหยร่วมเกิดอันตรกิริยาระหว่างตัวยาและเมทิลเลตเตไซโคลเด็กซ์ตริน สารเชิงซ้อนอินคลูชันที่เตรียมได้ทั้งสองวิธีให้การละลายที่นาที่ที่ 5 สูงกว่าสารผสมทางกายภาพและตัวยาเดี่ยวประมาณ 5 เท่า และ 50 เท่า ตามลำดับ และมีการละลายที่รวดเร็วและสมบูรณ์ภายในเวลา 10 นาที

คำสำคัญ: บรอมเฮกซีนไฮโดรคลอไรด์ เมทิลเลตเตเบตาไซโคลเด็กซ์ตริน การละลาย ค่าการละลาย สารเชิงซ้อนอินคลูชัน วารสารเภสัชศาสตร์อีสาน 2552; 5(2): 114-122

บทนำ

Bromhexine hydrochloride (2-amino-3, 5-dibromobenzyl (cyclohexyl) methylammonium chloride) is an oral mucolytic agent used in the treatment of respirator disorders associated with viscid or excessive mucus (Reynolds, 1989). The molecular formula is shown in Figure 1. It is very slightly soluble in water and exhibits slow dissolution characteristics. The rate of absorption and the extent bioavailability for such an insoluble hydrophobic drug are controlled by the rate of dissolution in gastrointestinal fluids (Patel et al., 2008). Therefore, it is important to enhance the solubility and dissolution of the drug in order to improve its bioavailability. Many technological methods of enhancing the solubility and dissolution of poorly water-soluble drugs have been reported such as micronization, complexes, microspheres, and solid dispersions (Shinde, 2007). Among of these methods, complexation with cyclodextrins is one of the most promising ones. Cyclodextrins are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs (Del Valle, 2004; Brewster and Loftsson, 2007). Complexation

with cyclodextrins has been widely used to enhance the oral absorption of poorly water-soluble drug by increasing the solubility and dissolution. Natural cyclodextrins such as β -cyclodextrin is limited in its pharmaceutical applications due to its limited aqueous solubility. Therefore, chemically modified cyclodextrins such as methylated β -cyclodextrin, amorphous derivative, is introduced to overcome this problem. Methylated β -cyclodextrin was reported to improve water solubility, dissolution and complexing power than the parent cyclodextrin (Figueiras et al., 2007; Mura et al, 1999). The objective of this study was to investigate the effect of methylated β -cyclodextrin on improving the solubility and dissolution of bromhexine hydrochloride. The physicochemical properties of bromhexine hydrochloride-methylated β -cyclodextrin inclusion complexes were also evaluated.

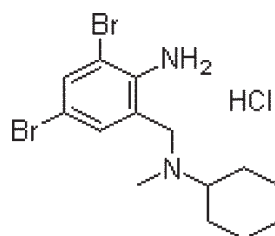


Figure 1 Molecular structure of bromhexine hydrochloride

Materials and Methods

1. Materials

Bromhexine hydrochloride was purchased from High Science Chemical Company (Thailand). Methylated β -cyclodextrin with an average substitution degree per anhydro glucose unit of 1.8 from Wacker-Chemie GmbH (Germany). All other materials and solvents used in this study were of analytical-reagent grade.

2. Methods

2.1 Phase-solubility study

Phase-solubility study was carried out according to the method described by Higuchi and Cornors (1965). In brief, excess amount of bromhexine hydrochloride (100 mg) was added to 10 mL of aqueous solution containing various concentrations of methylated β -cyclodextrin (0, 3, 6, 9, 12 and 15 mM). The dispersions were shaken in a thermostatically controlled water bath shaker at $37 \pm 0.5^\circ\text{C}$ until equilibrium (48 hrs). Afterward, samples were withdrawn, filtered through a $0.45\ \mu\text{m}$ membrane filter and suitably diluted. Drug concentration was analyzed by HPLC with UV detection at a wavelength of 245 nm. Experiments were performed in triplicate. The apparent stability constant (K_s) was calculated from the linear portion of the phase-solubility diagram with the assumption of 1:1 stoichiometry according to the following equation (Higuchi and Cornors, 1965); $K_s = \text{slope}/\text{intercept} (1 - \text{slope})$ where slope is obtained from the initial straight-line portion of the plot of bromhexine hydrochloride concentrations against methylated β -cyclodextrin concentrations and intercept is the intrinsic solubility of bromhexine hydrochloride in the absence of methylated β -cyclodextrin.

High performance liquid chromatography (HPLC)

Bromhexine hydrochloride concentration was analyzed by reverse phase HPLC (Waters, USA) in Waters C18 column ($10\ \mu\text{m}$, $3.9 \times 300\ \text{mm ID}$) with

UV detection at a wavelength of 245 nm and a flow rate of 1.2 mL/min. The mobile phase consisted of acetonitrile: 15 mM triethylamine (50:50) adjusted to pH 3.9 with phosphoric acid. The mobile phase was filtered through a $0.45\ \mu\text{m}$ membrane filter and degassed by ultrasonication before use.

2.2 Preparation of bromhexine hydrochloride-methylated β -cyclodextrin inclusion complexes

Inclusion complexes of bromhexine hydrochloride and methylated β -cyclodextrin were prepared in the molar ratio of 1:1 by the kneading method and coevaporation method.

Preparation of inclusion complex by the kneading method

Methylated β -cyclodextrin was dissolved in small amount of distilled water. Bromhexine hydrochloride was added slowly. The mixture was ground for 1 hr and dried at 45°C for 12 hrs. The dried complex was gently pulverized and sieved through a $50\text{--}250\ \mu\text{m}$ sieve for 5 mins.

Preparation of inclusion complex by coevaporation method

Bromhexine hydrochloride and methylated β -cyclodextrin were dissolved in ethanol. The solvent was evaporated by a rotary evaporator at 45°C . The dried complex was gently pulverized and sieved through a $50\text{--}250\ \mu\text{m}$ sieve for 5 mins. Physical mixture of bromhexine hydrochloride and methylated β -cyclodextrin was prepared by simply mixing of the weighed and previously sieved individual components through a $50\text{--}250\ \mu\text{m}$ until homogeneous.

2.3 Physicochemical characterization

Differential scanning calorimetry (DSC)

DSC curves of bromhexine hydrochloride, methylated β -cyclodextrin, physical mixture and inclusion complex were obtained by a Perkin-Elmer

DSC 7, equipped with a thermal analysis automatic program. Aliquots of about 8 mg of each sample were placed in aluminium pan. Thermograms were measured by heating the sample from 50 to 280°C at a rate of 10°C/min under the nitrogen flow of 20 cm³/min. An empty aluminum pan was used as a reference.

Fourier transform infrared spectroscopy(FT-TR)

FT-IR spectra of bromhexine hydrochloride, methylated β -cyclodextrin, physical mixture and inclusion complexes were analyzed by a Perkin-Elmer 1620 FT-IR spectrophotometer. Samples were ground, mixed thoroughly with potassium bromide and compressed in a hydraulic press. Each spectrum was recorded in the frequency range of 4000–450 cm⁻¹ and 16 scans were obtained at 4 cm⁻¹ resolution.

X-ray diffractometry

The X-ray diffractograms of bromhexine hydrochloride, methylated β -cyclodextrin, physical mixture and inclusion complexes were recorded by using Philips X'Pert MPD (Netherland) diffractometer with tube anode Cu over the interval 4–40°/2 θ . The operation data were as follows: generator tension (voltage) 40kV, generator current 45 mA and scanning speed 2°/min.

2.4 Dissolution studies

Dissolution studies were done by using dissolution apparatus type II (paddle method). Each flask contained 900 ml of simulated gastric fluid TS without pepsin pH 1.2 and maintained at 37±0.5°C. The paddles were rotated at 50±1 rpm. Powdered samples containing 8 mg of bromhexine hydrochloride or its equivalent in inclusion complexes or physical mixture were added on the surface of the dissolution medium. At 5, 10, 15, 30, 45, and 60 mins, the 2 mL aliquot was withdrawn from the dissolution medium, filtered through a 0.45 μ m membrane filter and replaced with a 2 mL of fresh dissolution medium after each sampling. The amount of drug was determined by HPLC. Drug concentration was calculated and expressed as percentage of drug dissolved from the mean of six determinations. The percentage of drug dissolved at 5 mins was statistically validated using analysis of variance (ANOVA) with the level of significance at $p \leq 0.05$.

Results

Phase-solubility Studies

Figure 2 shows the phase-solubility diagram of bromhexine hydrochloride in various concentrations of methylated β -cyclodextrin (0–15 mM). The solubility of bromhexine hydrochloride was approximately 2.2 mM. It can be seen that the solubility of bromhexine hydrochloride was increased linearly with the concentration of methylated β -cyclodextrin.

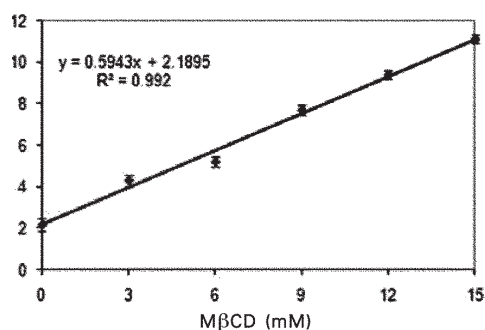


Figure 2 Phase-solubility diagram of bromhexine hydrochloride in various concentrations of methylated β -cyclodextrin (MβCD)

Physicochemical Studies

Differential Scanning Colorimetry

Figure 3 shows the DSC thermograms of bromhexine hydrochloride, methylated β -cyclodextrin, physical mixture and inclusion complexes. The DSC curve of bromhexine hydrochloride showed a sharp melting endotherm (T_{peak}) at 255°C ($T_{\text{onset}} = 244.5^{\circ}\text{C}$; $T_{\text{endset}} = 263.49^{\circ}\text{C}$; $\Delta H = 111.3 \text{ J/g}$). The DSC curves of physical mixture, kneaded and coevaporated samples showed the broadening of the bromhexine hydrochloride fusion peak with a concomitant shift to lower temperature.

Fourier Transform Infrared Spectroscopy

The FT-IR spectra of bromhexine hydrochloride, methylated β -cyclodextrin, physical mixture, kneaded and coevaporated samples are shown in Figure 4. The FT-IR spectrum of methylated β -cyclodextrin showed absorption bands at 3429 cm^{-1} for O-H stretching vibration, 2935 cm^{-1} for C-H stretching vibration and 1044 cm^{-1} for C-O stretching vibration. The FT-IR spectrum of bromhexine hydrochloride showed absorption bands at 3441 , and 3301 cm^{-1} in the region of $3500\text{--}3100 \text{ cm}^{-1}$ for the NH-stretching vibration of Ar-NH_2 and sharp bands

at 1634 and 1483 cm^{-1} in the region of $1700\text{--}1400 \text{ cm}^{-1}$ for the NH-bending vibration of the Ar-NH_2 . The FTIR spectrum of physical mixture was similar to the synthetic spectra producing by the addition of bromhexine hydrochloride and methylated β -cyclodextrin. The FT-IR spectrum of kneaded sample was either identical to or a little different from the corresponding pure molecules. The FT-IR spectrum of coevaporated sample showed almost complete disappearance of the absorption band at 1483 cm^{-1} , the shifts at absorption band from 3301 to 3327 cm^{-1} and the disappeared absorption bands at 865 and 850 cm^{-1} .

X-ray diffractometry

The X-ray diffractograms of bromhexine hydrochloride, methylated β -cyclodextrin, physical mixture and inclusion complexes are presented in Figure 5. The pure bromhexine hydrochloride showed several diffraction peaks, exhibiting a main sharp peak at 7.2 , 21.4 and $36^{\circ} (2\theta)$ and secondary peaks at 14.3 , 15.7 , 18.3 , etc $^{\circ}(2\theta)$. No diffraction peak was observed in the methylated β -cyclodextrin diffractogram. The diffraction patterns of bromhexine hydrochloride-methylated β -cyclodextrin

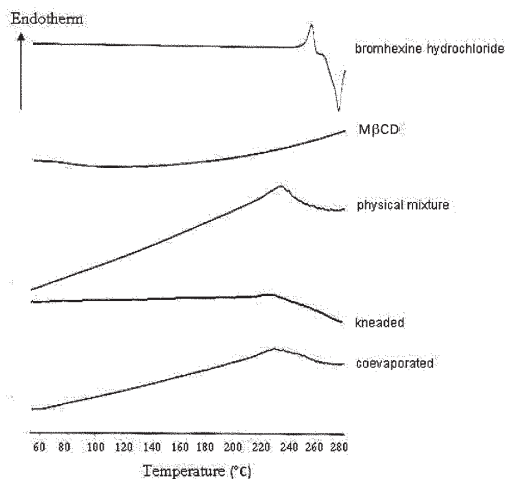


Figure 3 DSC thermograms of bromhexine hydrochloride, M β CD, physical mixture, inclusion complexes prepared by kneading method (kneaded) and coevaporation method (coevaporated).

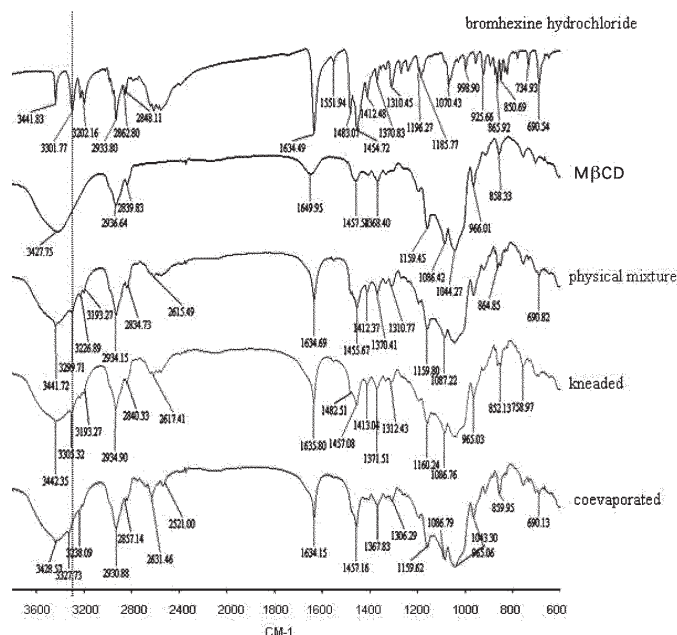


Figure 4 FT-IR spectra of bromhexine hydrochloride, MβCD, physical mixture and inclusion complexes prepared by kneading method (kneaded) and coevaporation method (coevaporated).

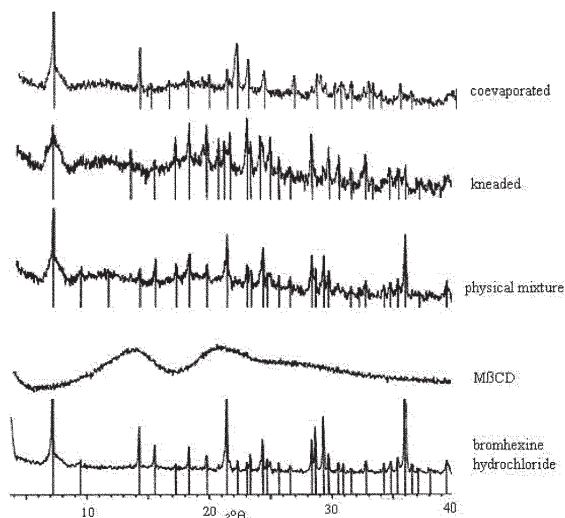


Figure 5 X-Ray diffractograms of bromhexine hydrochloride, MβCD, physical mixture (PM) and inclusion complexes prepared by kneading method (kneaded) and coevaporation method (coevaporated).

physical mixture corresponded to the superimposition of bromhexine hydrochloride and methylated β -cyclodextrin. However, some diffraction peaks of kneaded and coevaporated samples showed fewer

and less intense peaks and a new peak at 22° (2θ) occurs in coevaporated sample compared with the physical mixture and pure drug.

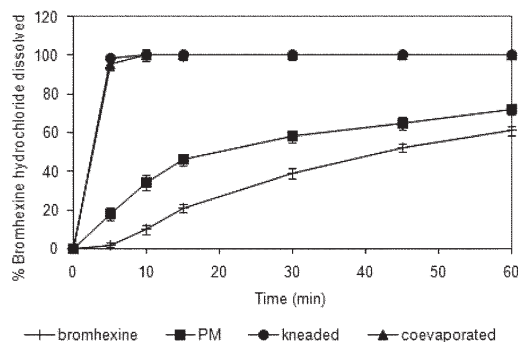


Figure 6 Dissolution profiles of bromhexine hydrochloride powder, physical mixture (PM) and inclusion complexes prepared by kneading method (kneaded) and coevaporation method (coevaporated).

Dissolution studies

The dissolution profiles of bromhexine hydrochloride, physical mixture and inclusion complexes were drawn as the percentage bromhexine hydrochloride dissolved versus time and shown in Figure 6. Bromhexine hydrochloride yielded the lowest dissolution with only 2% of the drug dissolved in the first 5 mins and was incomplete in dissolution (only 60% of drug dissolved) even after 1 hr. The increase in drug dissolution was observed in physical mixture compared to pure drug with about 18% of the drug dissolved in the first 5 mins. All inclusion complexes gave similar dissolution profiles and completely dissolved within 10 mins.

Discussion and Conclusion

Phase-solubility studies

The solubility of bromhexine hydrochloride is increased by 5 fold at 15 mM of methylated β -cyclodextrin. The increase in bromhexine hydrochloride solubility is due to the formation of inclusion complex between bromhexine hydrochloride and methylated β -cyclodextrin. The solubilization performance of methylated β -cyclodextrin could be derived from the presence of the methyl groups, which can extend the hydrophobic region of the cyclodextrin cavity favoring and stabilizing the inclusion complexation of this drug molecule (Mura

et al., 2005). The solubility diagram showed an A_L type as described by Higuchi and Connors (1965) which would lead to the conclusion that soluble complex having 1:1 stoichiometry was formed over the concentration range of this study. The stability constant calculated from the equation $K_s = \text{slope} / \text{intercept} (1 - \text{slope})$ was 110 M^{-1} .

Physicochemical Studies

Differential scanning calorimetry

Some evidence of inclusion complexation was obtained from thermal analysis. When guest molecule is embedded in cyclodextrin cavity or crystal lattice, the melting point of drug generally shift to a different temperature or disappear (Cabral et al., 1990). From Figure 3, the DSC curve of bromhexine hydrochloride with a sharp melting endotherm (T_{peak}) at 255°C indicated that bromhexine is in crystalline form. The DSC curves of physical mixture, kneaded and coevaporated samples which showed the broadening endothermic peak and shift to lower temperature could be ascribed to some interaction between drug and methylated β -cyclodextrin (Mura et al., 1999) but did not seem to be indicative of a true inclusion complex.

Fourier Transform Infrared Spectroscopy

The FT-IR study is a useful technique to determine the interaction and the complex formation

between drug molecules and cyclodextrins in the solid state. Shifts, disappearance, reduction in intensity or appearance of new bands might be related to possible drug-cyclodextrin interactions and/or amorphization of the product (Cirri et al., 2005; Al-Marzouq et al., 2009).

The FT-IR spectra of physical mixture did not show significant changes with respect to that of the pure drug indicating that no important interactions should be involved in these samples. The FT-IR spectrum of kneaded sample showed no or minor drug-methylated β -cyclodextrin interactions. The almost complete disappearance of the absorption band at 1483 cm^{-1} , the shifts at absorption band from 3301 to 3327 cm^{-1} and the disappeared absorption bands at 865 and 850 cm^{-1} in coevaporated sample indicated the interactions between bromhexine hydrochloride and methylated β -cyclodextrin. The assumption for this is part of bromhexine hydrochloride may fit inside the cavity of methylated β -cyclodextrin, whereas the other part may remain outside the methylated β -cyclodextrin.

X-ray diffractometry

The several sharp diffraction peaks from bromhexine hydrochloride diffractogram demonstrated that this drug is in crystalline form. The absence of any peak in the methylated β -cyclodextrin diffractogram revealed the amorphous nature of this compound. The diffraction patterns of physical mixture corresponded to the superimposition of drug and methylated β -cyclodextrin indicated that the crystallinity of bromhexine hydrochloride was not changed. The fewer and less intense peaks of kneaded and coevaporated samples indicating the reduction of drug crystallinity. This may be conclude that the fine crystals either dispersed onto the surface or included in the methylated β -cyclodextrin cavity as crystallites showing a lower melting point than intact bromhexine hydrochloride crystals. In addition, a new peak at 22°

(2θ) occurred in coevaporated sample could be explained by crystallographic modifications performed during the coevaporation process.

Dissolution studies

According to the dissolution profiles (Figure 6), bromhexine hydrochloride exhibited the lowest dissolution compared with physical mixture and inclusion complexes. This effect could be due to the hydrophobic property of drug result in floating of the drug powder on the dissolution medium and prevent drug surface contacting the medium. The faster dissolution of physical mixture compared to pure drug might be attributed to the local solubilization action of the carrier operating in the microenvironment of the drug or the hydrodynamic layer surrounding drug particles in the early stages of the dissolution process, since the methylated β -cyclodextrin dissolve in a short time (Badr-Eldin et al., 2008) and the in situ formation of readily inclusion complex in the dissolution medium (Fernandes et al., 2002). It is evident that the percentage of drug dissolved from inclusion complexes gave significantly ($p < 0.05$) higher dissolution than that of physical mixture and pure drug. The increase of 50-, and 5-fold in drug dissolution within the first 5 mins was observed compared to pure drug and physical mixture, respectively. The fastest dissolution obtained from the inclusion complexes has been attributed to the surfactant-like property of the carrier (which can reduce the interfacial tension between hydrophobic drug and the dissolution medium), an increase in drug solubility upon complexation in the solid state and the reduction of drug crystallinity.

In conclusion, the solubility and dissolution of bromhexine hydrochloride were increased by methylated β -cyclodextrin. The dissolution of bromhexine hydrochloride-methylated β -cyclodextrin inclusion complexes gave much faster than those of pure bromhexine hydrochloride and physical mixture.

Both inclusion complexes gave similar dissolution profiles. The results from this study could be applied for future development of fast released bromhexine hydrochloride tablets or capsules.

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