JPP Journal of Pharmacy and Pharmacology

JPP 2007, 59: 1501–1507

Received March 10, 2007
Accepted August 6, 2007
DOI 10.1211/jpp.59.11.0006
ISSN 0022-3573

Urea inclusion compounds of enalapril maleate for the improvement of pharmaceutical characteristics

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Abstract

Urea is a well known adductor for linear organic compounds. In the present study, enalapril maleate, a substituted cyclic organic compound, was successfully included in urea together with a suitable rapidly adductible endocyte (RAE). Formation of the urea inclusion compound was confirmed by Fourier transform infrared spectroscopy, differential scanning calorimetry and X-ray diffraction. The modified Zimmerschied calorimetric method was used to estimate the minimum amount of RAE required for adduction of enalapril maleate in urea. Urea–enalapril maleate–RAE inclusion compounds containing varying proportions of guests were prepared and their thermal behaviour studied by differential scanning calorimetry. Regression analysis revealed an excellent r^2 value with regard to the influence of the relative proportion of RAE on the heat of decomposition. The inclusion compounds were found to exhibit good content uniformity and improved dissolution profile as demonstrated by increased dissolution efficiency. Studies revealed that urea inclusion may be a promising alternative for the formulation of potent poorly soluble drugs into immediate release products.

Introduction

Since the serendipitous preparation of urea inclusion compounds by Bengen (1940), considerable scientific endeavour has been devoted towards developing a detailed understanding of the structural, dynamic and chemical properties of urea inclusion compounds (Bishop & Dance 1988; Atwood 2004). In the presence of an adductible guest species, urea is known to crystallize as hexagonal, linear, parallel, essentially infinite, non-intersecting tunnels constructed from an extensively hydrogen-bonded arrangement of urea molecules (Smith 1952; Frank 1975). Thus, a vast array of different urea inclusion compounds containing different types of guest molecules have been isolated and characterized by certain common fundamental features such as parallel, helical host substructure containing guest molecules, an incommensurate relationship between periodicities of host and guest substructures (Harris et al 1991), and substantial dynamic disorder of the guest molecules (Smart et al 1994).

In general, urea is known to form inclusion compounds with straight-chain compounds having a carbon backbone above a minimum length for a homologous series (Schiessler & Flitter 1950). However, guest molecules with non-hydrogen constituents at a position other than terminal carbon atoms also form inclusion compounds, provided certain steric requirements are fulfilled (Atwood et al 1984). Molecules containing benzene or cyclohexane rings do not form inclusion compounds with urea, presumably because these structural components are too wide to fit comfortably inside the narrow tunnel (Bishop & Dance 1988). However 1-phenyloctadecane forms an adduct with urea. The long chain of this compound is readily adducted and apparently the unit cell can easily withstand the distortion caused by an occasional benzene group (Schoen & Mcketta 1962). Moreover, in the presence of a large quantity of a rapidly adductible endocyte (RAE), such as *n*-paraffin, a minor proportion of a branched guest moiety, 3-methyl heptane, a normally non-adductible endocyte (NNAE), may be included in the adduct (Schlenk 1949; Schoen & Mcketta 1962). Steep enhancement of dissolution profile of amiloride hydrochloride, a potent NNAE drug, through co-inclusion in urea has been reported recently (Thakral & Madan 2007a). In the

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Acknowledgements: The authors are very thankful to IIT, New Delhi, for allowing us to conduct X-ray diffraction analysis of the samples and to Roorki Research and Analytical Labs for conducting HPLC analysis.

present study, the possibility of co-inclusion of a small proportion of enalapril maleate, a potent NNAE drug, in the presence of a suitable RAE was investigated (Thakral & Madan 2006), utilizing oleic acid as the RAE.

Enalapril maleate is a highly effective antihypertensive agent, which acts as an angiotensin converting enzyme (ACE) inhibitor (Cleary & Taylor 1986). Enalapril acts as a prodrug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilate, which is the active ACE inhibitor (SOLVD Investigators 1992). The solubility of enalapril maleate in water is poor, however it is highly soluble in methanol (Dominic & Brenner 1987). Two polymorphic forms of enalapril maleate have been identified by X-ray diffraction (Ip et al 1986). In the present study, enalapril maleate was co-included in urea along with a suitable RAE to improve the dissolution profile and other pharmaceutical characteristics.

Materials and Methods

Preparation of urea inclusion compounds of enalapril maleate with RAE

USP grade enalapril maleate was a gift sample from Neuland Laboratories, Hyderabad, India. All chemicals were of analytical grade or HPLC grade. Enalapril maleate (0.5 g) was dissolved in 30 mL methanol containing 5 g urea by gentle heating. Oleic acid (0.6 g) was then incorporated into the above solution, resulting in immediate precipitation of fine crystals. After keeping the solution at room temperature for 2–3 h, crystals were separated by vacuum filtration, dried and stored in suitable containers (Madan & Grover 1993; Madan 1994; Bajaj & Madan 1994).

Characterization of urea inclusion compounds

Fourier transform infrared (FTIR) spectra of the crystals were recorded using a FTIR spectrophotometer (IR 200; Thermo Nicolet, Madison, USA) over the range of 400–4000 cm^{-1} using KBr discs. The IR resolution was 4 cm^{-1}. Differential scanning calorimetry (DSC) thermograms were obtained with a DSC Q10 V 9.0 (275) TA system (Waters Ltd, Vienna, Austria) equipped with a computerized data station, using a nitrogen flow rate of 60 $cm^3 min^{-1}$ and a scanning rate of 10°C min^{-1} from 40°C to 200°C. All samples (~3 mg) were heated in a crimped aluminium pan sealed by application of the minimum possible pressure and an empty aluminium pan was utilized as the reference. X-ray diffractograms of the crystals were recorded using an X-ray diffractometer (X'Pert Pro, PW 3050/PW 3071; Philips, Holland). Experimental settings were as follows: nickel filtered Cu-Kα radiation (λ = 1.540598 Å), voltage 40 kV, current 30 mA, and scanning rate 2° min^{-1} over a 2θ range of 10°–80°.

Determination of the minimum ratio of RAE and NNAE for the formation of co-inclusion compounds with urea

The minimum amount of RAE required for adduction of enalapril maleate per unit quantity of urea was determined by the modified Zimmerschied calorimetric method (Zimmerschied et al 1949; Madan 1994) based on measurement of temperature rise following addition of increments of RAE to a methanolic solution of urea containing excess of the drug. Hence, 5 g enalapril maleate and 10 g urea dissolved in 25 mL of methanol were shaken in a calorimeter until equilibrium temperature was obtained. Increments of 0.1 mL RAE were successively introduced into the calorimeter and the equilibrium temperature was recorded after each successive addition. A plot of temperature rise versus amount of RAE revealed the minimum amount of RAE utilized in the formation of co-inclusion compounds of enalapril maleate and RAE in urea (Zimmerschied et al 1949).

Preparation of urea inclusion compounds containing varying amounts of enalapril maleate and RAE

A number of urea–enalapril maleate–RAE co-inclusion compounds containing varying amounts of enalapril maleate and RAE were prepared using the relative proportions of RAE to enalapril maleate listed in Table 1. DSC scans of these inclusion compounds were conducted over the temperature range of 40–200°C as described above.

Assay procedure

HPLC chromatograms were run on a Shimadzu prominence fitted with a LC-20 AD pump, connected to a UV-Vis detector (SDA-20A) set at 215 nm. A Phenomex Luna L-7 (5 μm) column (250 mm × 4.6 mm) was utilized. A constant chromatographic column temperature of 50°C was maintained with the help of a column oven (CTO-10 AS). The mobile phase used was a mixture of phosphate buffer (pH 2.2) and acetonitrile (75:25) and the flow rate was 1.5 mL min^{-1}. The injection volume was 20 μL. Pure water (purified by the milli-Q system) was used as solvent.

Content uniformity

Content uniformity test was conducted on 10 randomly drawn samples from all the enalapril maleate inclusion compounds (EMIC). Accurately weighed amounts of the adducts containing an equivalent of 20 mg of the drug were dissolved in pH 2.2 phosphate buffer solution to give a concentration of 0.2 mg of enalapril maleate per mL. The solutions were filtered through a 0.45-μm filter. The drug content was determined by the HPLC method used for the content uniformity test.

Dissolution rate studies

The dissolution study was conducted using a USP dissolution apparatus II (Electrolab-TDL-08L) in 900 mL of pH 6.8 phosphate buffer, maintained at 37 ± 0.5°C at a speed of 50 rev min^{-1}. The quantity of enalapril maleate (20 mg) and of inclusion compounds EMIC-2 and EMIC-4 containing an amount of drug equivalent to 20 mg was added to the dissolution medium. At predetermined time intervals (2, 5, 10, 15,

20 and 30 min), 5 mL of the samples was withdrawn with volume replacement. The samples were filtered through a 0.45-μm membrane filter and the content of enalapril maleate released was determined by the HPLC method described above except that pH 6.8 phosphate buffer was used for the preparation of the standard dilution. All experiments were conducted in triplicate.

Statistical analysis

The dissolution rates of enalapril maleate, EMIC-2 and EMIC-4 were compared using one-way analysis of variance (all values were normally distributed). If a significant difference was found, comparisons of the means of individual groups were performed using Tukey's multiple range test at a statistical significance level of $P < 0.05$ (Bolton & Bon 2004).

Results and Discussion

The present study explored the formation of urea–drug adducts as a means to increase the dissolution rate of enalapril maleate. A normally non-adductible endocyte, enalapril maleate was incorporated into the urea adduct in the presence of a suitable RAE (oleic acid). The minimum proportion of RAE required to form the adduct was determined and the physicochemical properties of the resulting adducts were investigated. Finally, it was shown that the complex significantly enhances the dissolution rate of enalapril maleate.

Characterization of urea inclusion compounds

Incorporation of oleic acid into a methanolic solution of urea and enalapril maleate resulted in precipitation of fine, needle-shaped crystals (EMIC). Figure 1 shows FTIR spectra of pure urea, oleic acid, pure drug and its co-inclusion compound in urea. IR spectra of EMIC crystals exhibited vibrations that are characteristic of the hexagonal channel structure of urea (Stuart 1956; Fischer & McDowell 1960; Durie & Harrisson 1962), that is out-of-phase NH stretching vibrations at 3410 cm^{-1} and in-phase NH stretching vibrations at 3226 cm^{-1}. Similar observations were made regarding the occurrence of four bands between 1675 and 1590 cm^{-1} (due to CO stretching and NH_2 bending vibrations), slight raising of the skeletal out-of-phase bending frequency at 791 cm^{-1}, and symmetric C-N frequency increased from 1000 cm^{-1} to 1014 cm^{-1}, which are all characteristic of the hexagonal channel structure of urea (Stuart 1956: Durie & Harrisson 1962). The spectra of EMIC also depicted some peaks that can be attributed to the presence of guest moieties, that is oleic acid (2924 cm^{-1} (asymmetric CH_2 stretch), 2854 cm^{-1} (symmetric CH_2 stretch)) and enalapril maleate (1596 cm^{-1} (monohydrogen maleate carboxyl stretch)). However, host lattice in an inclusion compound is known to give a vibrational spectrum that inevitably obscures some of the guest molecule bands (Davies 1984).

The DSC thermograms obtained for enalapril maleate and EMIC crystals are shown in Figure 2. The thermogram of the drug shows a characteristic endotherm corresponding to the melting point of the crystalline drug (i.e. 151.95°C). The thermogram of the inclusion compound does not show a peak in this region, implying inclusion of the drug into the urea lattice.

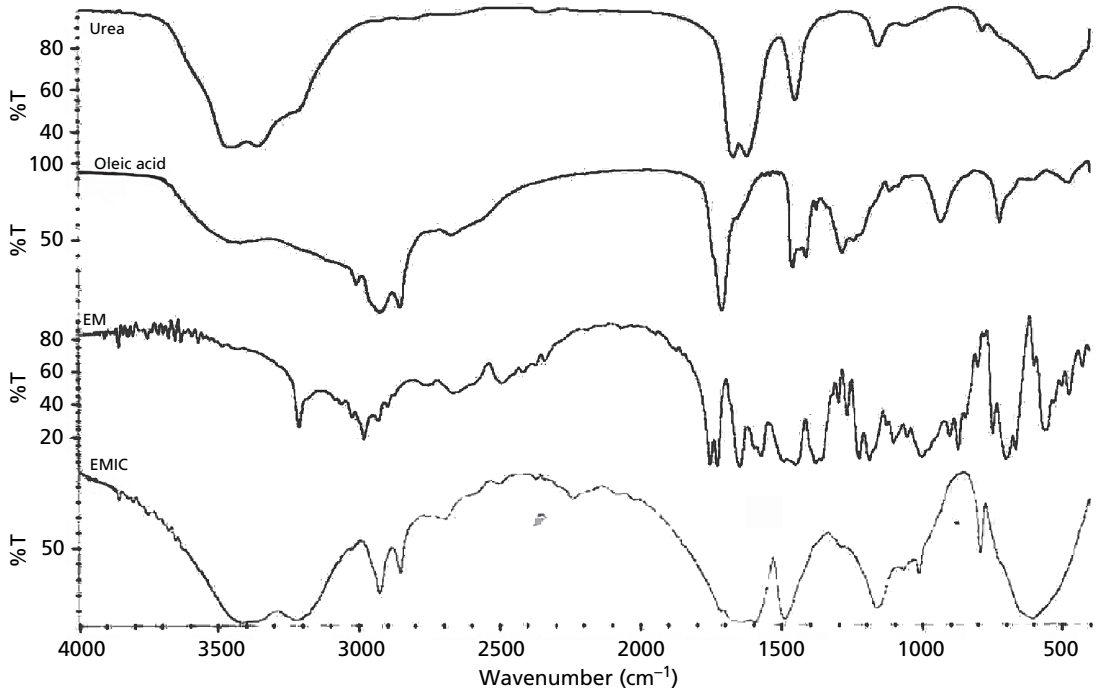


Figure 1 Fourier transform infrared spectra of pure urea, oleic acid, pure drug (EM) and its co-inclusion compound (EMIC) in urea.

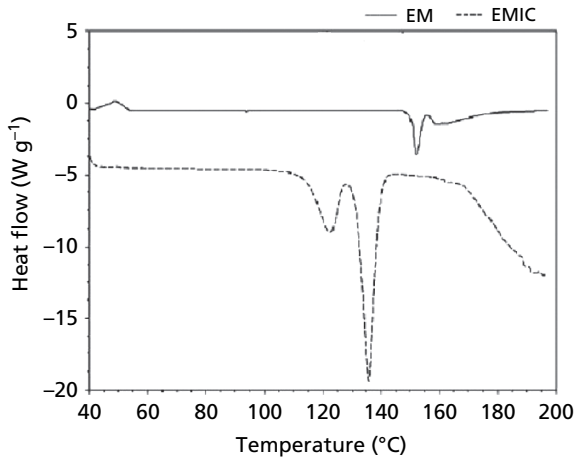


Figure 2 Differential scanning calorimetry thermograms of pure enalapril maleate (EM) and enalapril maleate inclusion compounds (EMIC).

Further, the thermogram exhibits two endothermic events, a characteristic of the hexagonal form of complexed urea (McAdie 1962; Ahmad et al 1994). The first step involves the collapse of the hexagonal form of the urea inclusion compound to yield the guest moiety and tetragonal solid urea, while the second step involves melting of tetragonal urea.

The complexation process of enalapril maleate in urea was confirmed by X-ray diffraction analysis. The diffractograms for the pure drug, urea and EMIC crystals are presented in Figure 3. The diffractogram of the pure drug shows the presence of form II (orthorhombic form) of enalapril maleate, as confirmed by the presence of an extra peak at 13.0° 2θ and the absence of a peak at 14.7° 2θ, which has been reported to correspond to form I of enalapril maleate (Ip et al 1986). The X-ray powder diffraction pattern confirmed the results of DSC analysis. Diffractional peaks relevant to crystalline enalapril maleate were not detectable in EMIC products, indicating that the guest molecules were trapped and isolated from one another in the honeycomb network of urea and do not contribute to the crystal structure except for slight distortions of the hexagonal channels caused by bulky guests (Radell & Connolly 1961). The diffractogram of hexagonal urea (EMIC; important peaks at interplanar spacings at 4.16 (19%), 3.39 (100%) and 7.36 (5%) Å) (Radell & Connolly 1960; Brodman & Radell 1967) was characteristically distinguishable from that of the pure tetragonal form of urea (mainly characterized by the interplanar spacing at 4.04 (100%) Å) (Radell et al 1964), indicating a change in the crystalline form of urea.

Minimum ratio of RAE and NNAE for inclusion of NNAE in urea

The increase in temperature on addition of successive increments of oleic acid to a methanolic solution of urea and enalapril maleate was plotted (data not shown). The curve demonstrated the following sequence of events: an initial temperature rise, followed by an intermediate final temperature, subsequent temperature rise and then achievement of a final temperature. The minimum amount of RAE required for adduction of enalapril maleate in urea was calculated from

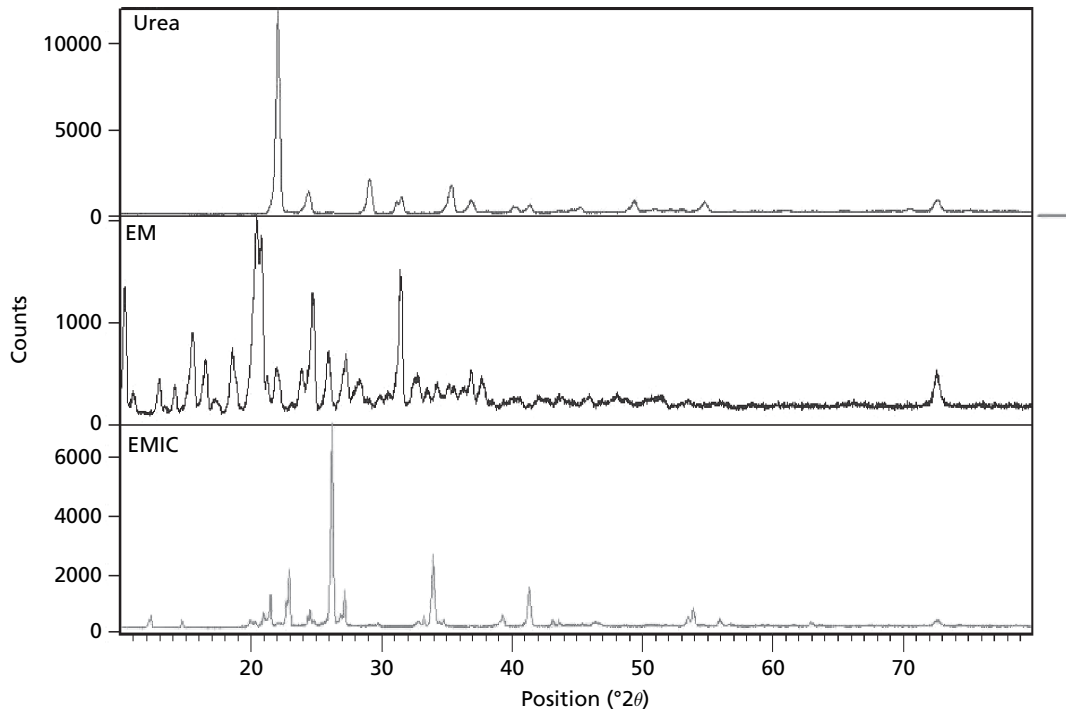


Figure 3 X-ray diffraction patterns of urea, enalapril maleate (EM) and enalapril maleate inclusion compounds (EMIC).

Table 1 Content uniformity in different enalapril maleate inclusion compounds (EMIC)

Product	RAE:drug	Percent drug claimed
EMIC-1	0.45:1	97.3 ± 0.5
EMIC-2	0.6:1	98.1 ± 0.8
EMIC-3	0.8:1	95.7 ± 0.3
EMIC-4	1:1	98.5 ± 0.4
EMIC-5	1.2:1	96.5 ± 0.3

Data are mean ± s.d. for 10 randomly drawn samples of inclusion compounds. RAE, rapidly adductible endocyte.

the point of intersection of the lines of extrapolation of the initial rate of temperature rise and intermediate final temperature. The second stage of temperature rise is due to displacement of NNAE with RAE, as evidenced by the fact that the overall temperature rise is similar to that of RAE alone (Zimmerschied et al 1949). The minimum ratio of RAE to drug for adduction of enalapril maleate in urea was determined to be 0.446:1.

On the basis of calculations of the minimum ratio of RAE to enalapril maleate, urea inclusion compounds containing varying amounts of RAE and drug (Table 1) were prepared and investigated further.

Characterization of inclusion compounds containing varying amounts of enalapril maleate and RAE

Figure 4 presents DSC thermograms of different EMIC containing varying amounts of RAE and enalapril maleate. The enalapril melting endotherm at ~151°C was absent from all the thermograms, indicating the absence of the crystalline form of enalapril maleate. The presence of a low-temperature endotherm in all the thermograms corresponds to the decomposition of the hexagonal inclusion compound and to release of guest molecules and solid tetragonal forms of urea. Heat of decomposition/crystalline transition was found to increase linearly with the quantity of RAE added per gram of enalapril maleate. Regression analysis of the data gave following equation:

$$\Delta H = 24.388\ (\pm 2.488)\ R + 13.508\ (\pm 2.126) \quad (1)$$

$$r = 0.985,\ \sigma = 1.4971,\ F = 96.07$$

where ΔH is the heat of decomposition of the co-inclusion compound and R is the amount of RAE per unit weight of NNAE in the co-inclusion compound.

The above equation clearly shows that as the amount of RAE in the inclusion compound is increased, the heat of crystalline transition increases ($r^2 = 0.969$), indicating improved stability of the co-inclusion compound. Formation of urea inclusion compounds is exothermic in nature, indicating that the resulting compounds are stable. However, substituents in the guest moiety, which do not form part of a linear chain, will naturally lead to distortion and weakening of the host structure comprising narrow channels, with a consequent decrease in the heat of decomposition of urea inclusion compounds (Thakral & Madan 2007b). Enalapril maleate having an aromatic moiety with substitutions in its molecular structure is presumably too wide to fit inside the channels formed by the urea host. However, in the presence of RAE, some proportion of enalapril maleate is included in urea. This is expected to lead to occasional distortions in the host cell in the vicinity of the aromatic ring, the extent of steric strain on the host lattice being proportionate to the amount of NNAE incorporated. However, distortion of the urea host lattice by aromatic groups somewhat weakens the host lattice, as evidenced by the gradual decrease in heat of decomposition, with a corresponding increase in the relative proportion of drug. This weakened/distorted urea host lattice is, however, naturally expected to result in enhancement of the dissolution rate.

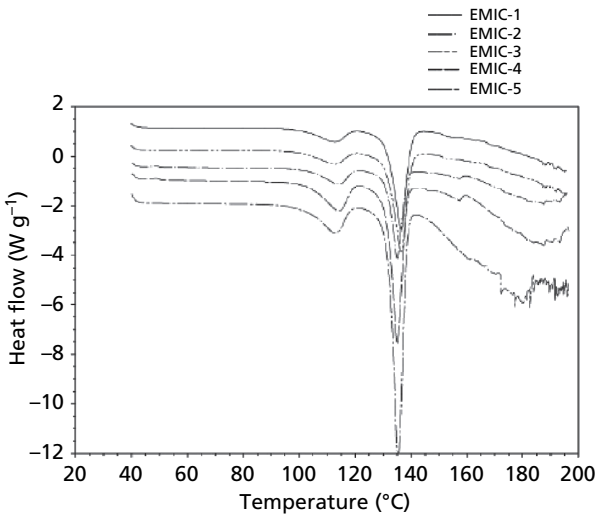


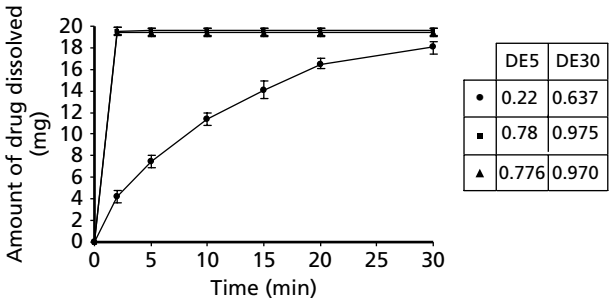
Figure 4 Differential scanning calorimetry thermograms of enalapril maleate–RAE–urea co-inclusion compounds containing varying proportions of enalapril maleate and RAE. RAE, rapidly adductible endocyte.

Content uniformity

The content uniformity data for different EMIC inclusion compounds containing varying RAE to drug ratios are presented in Table 1. From the experimental data, it is apparent that the mean drug content for different inclusion compounds is not significantly different.

Dissolution rate studies

Figure 5 shows the dissolution profiles plotted from the experimental values of pure enalapril maleate and its urea inclusion compounds EMIC-2 and EMIC-4. The dissolution profiles were evaluated by the dissolution efficiency (DE) parameter at 5 min and 30 min (Khan 1975). The extent of pure enalapril maleate released was found to be comparatively low, with dissolution of ~36% of the contents in 5 min. On the other hand, co-inclusion of the drug in urea provided instantaneous dissolution of ~100% within 5 min, as shown by DE_5 ~ 0.78 for both inclusion compounds. Thus enalapril maleate complexation in urea led to a ~2.7-fold increase in the initial dissolution



	DE5	DE30
●	0.22	0.637
■	0.78	0.975
▲	0.776	0.970

Figure 5 Dissolution profiles and dissolution efficiency (DE) parameter at 5 and 30 min (DE5 and DE30, respectively) of enalapril maleate drug and enalapril maleate–RAE–urea co-inclusion compounds containing varying proportions of drug and RAE (●, enalapril maleate; ■, EMIC-2; ▲, EMIC-4). Each point is the average of three measurements; error bars indicate ± s.d. RAE, rapidly adductible endocyte.

efficiency. The improvement in the dissolution rate of drug from inclusion compounds is in agreement with the results of complex characterization, which indicate that the drug is present in the amorphous form. The amorphous nature of the drug in urea compounds led to an increase in the dissolution rate. When such a system is exposed to an aqueous dissolution medium, the urea lattice dissolves, resulting in the release of the included drug at the molecular level.

One-way analysis of variance followed by Tukey's multiple range test revealed that the mean of dissolution profiles of EM were significantly different compared with the means of EMIC-2 and EMIC-4 when tested at a significance level of $P < 0.05$. The mean of dissolution profiles of EMIC-2 and EMIC-4 were not found to be statistically different at a significance level of $P < 0.05$, which indicated the difference in composition of the adduct had no effect on the dissolution profile of the resulting inclusion compounds.

Conclusion

The formation of co-inclusion compounds of enalapril maleate in urea in the presence of a suitable RAE was studied. The higher dissolution rate displayed by inclusion compounds may imply enhanced oral bioavailablity of the drug. The inclusion compounds were also found to show good content uniformity. The overall process of urea inclusion complex formation involves relatively simple preparation steps, reduced processing cost, minimal energy consumption and short processing time. Urea inclusion compounds of enalapril maleate in the presence of a suitable RAE may be a promising alternative for formulation of potent poorly soluble drugs into immediate release products.

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