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Triamterene-β-cyclodextrin Systems: Preparation, Characterization and In Vivo Evaluation

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Alka Pravin Mukne[1] and MS Nagarsenker[1]

[1]Bombay College of Pharmacy, Kalina, Santacruz (East), Mumbai - 400098, Maharashtra, India

ABSTRACT

The purpose of this research was to improve the solubility and therefore dissolution and bioavailability of triamterene, a poorly water soluble diuretic, by complexation with β-cyclodextrin. Triamterene has been reported to show low bioavailability after oral administration, with wide intersubject variation. This study presents the formulation of solid dispersions of triamterene with β-cyclodextrin—by cogrinding, kneading, and coevaporation, using low pH conditions—and their characterization, evaluation of improvement in dissolution profiles, and in vivo advantage. Phase solubility studies indicated complex with possible stoichiometry of 1:1 and a stability constant of 167.67M^{-1}. The solid dispersions were characterized by Fourier transform infrared spectroscopy, nuclear magnetic resonance, x-ray diffraction, and differential scanning calorimetry studies. The characterization studies confirmed inclusion of the phenyl ring of triamterene within the nonpolar cavity of β-cyclodextrin in the coevaporate. Remarkable improvement in in vitro drug release profiles in 0.1N HCl and pH 6.8 phosphate buffer was observed with all dispersions, especially the coevaporate. The coevaporate, when administered orally in rats, also exhibited improved in vivo activity, as measured by net sodium ion excretion, as compared with triamterene powder. Thus, coevaporation of the drug and β-cyclodextrin from acidified alcohol provide the optimum condition for inclusion complexation to give a binary system with remarkable improvement in in vitro drug release profile and in vivo performance.

KEYWORDS: triamterene, β-cyclodexrin, coevaporate

INTRODUCTION

Triamterene (2,4,7-triamino-6-phenylpteridine) (Figure 1) is a mild potassium-sparing diuretic used either alone or as an adjunct to thiazide and loop diuretics. It is very poorly soluble in water but soluble in organic acids and dilute mineral acids.[1] Bioavailability of triamterene in normal subjects after oral administration has been found to be as low as 30% with wide intersubject variation.[2] Improvement in aqueous solubility is expected to improve the bioavailability of the drug on oral administration. Triamterene has 3 primary amino groups but remains weakly monobasic (pk_a = 6.2).[3] Because of this weak basicity, most attempts to form more soluble classical salts of triamterene have failed. In view of this information, formulation of solid dispersions of triamterene with hydrophilic polymers was considered worthwhile for improving solubility and availability. Triamterene-urea systems, prepared by melting carrier method, showed an improvement in dissolution rates of the drug from the solid dispersions as compared with the pure drug and physical mixtures.[4] Thermal analysis and equilibrium solubility determinations are reported in order to elucidate the mechanism of interaction at the solid state in triamterene/D-mannitol dispersions prepared by melting carrier method.[5] A linear increase in the solubility of triamterene with increasing mannitol concentration, possibly due to complexation processes and hydrogen bonding formation, was observed. Triamterene/D-mannitol systems have also been prepared by spray drying, with better dissolution rates obtained for the spray-dried outputs.[6] Solid dispersions of triamterene with polyethylene glycols prepared by melting carrier method have demonstrated improved dissolution efficiency and pharmacologic effect.[7]

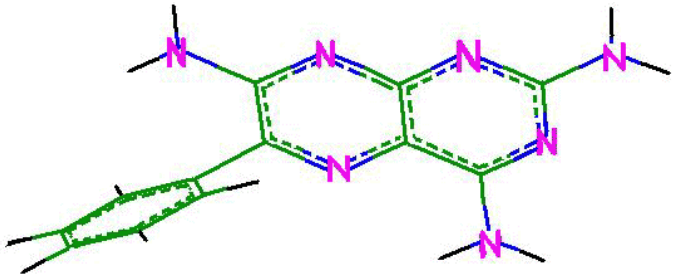

Figure 1. Structure of triamterene.

Complexation with cyclodextrins has been reported to enhance the solubility, dissolution rate, and bioavailability of poorly water soluble drugs.[8] Among the commercially

Corresponding Author: MS Nagarsenker, Bombay College of Pharmacy, Kalina, Santacruz (East), Mumbai - 400098, Maharashtra, India; Tel: +91 022 26670871; Fax: +91 022 26670816;
Email: mangal_nag511@yahoo.co.in

available cyclodextrins, β-cyclodextrin is reported to be stable and has been found safe for oral delivery. β-cyclodextrin is a cyclic oligosaccharide containing 7 α-(1,4)-linked glucopyranose units that delimit a relatively nonpolar cavity (Figure 2). Triamterene/β-cyclodextrin systems have been prepared by spray drying and cogrinding.[9,10] The improvement in dissolution achieved by these systems has been attributed to amorphization. However, details of complexation in these systems have not been reported.

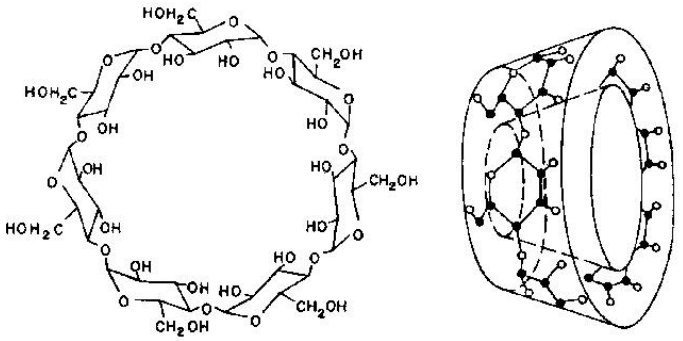

Figure 2. Spatial orientation of the different groups in β-cyclodextrin molecule.

This study presents formulation of solid dispersions of triamterene with β-cyclodextrin—by cogrinding, kneading, and coevaporation, using low pH conditions—and their characterization, evaluation of improvement in dissolution profiles, and in vivo advantage.

MATERIALS AND METHODS

Materials

Triamterene was obtained as gift sample from Smithkline Beecham (I) Pvt Ltd, Bangalore, India. Free samples of β-cyclodextrin were obtained from Cerestar, Cedar Rapids, IA. The other reagents such as HCl were from SD Fine Chemicals, Dubai, India.

Preliminary Studies

Phase-Solubility Studies

The aqueous solubility of triamterene at various concentrations of β-cyclodextrin was studied by the method reported by Higuchi and Connors.[11] Accurately weighed samples of triamterene in quantities exceeding its aqueous solubility were shaken at room temperature with aqueous solutions of β-cyclodextrins in increasing concentrations (0-10 mmol/L), for a period of 72 hours, until equilibrium was established. The solutions were then analyzed by spectrophotometer (Shimadzu 160A UV/Vis spectrophotometer, Shimadzu Corp, Kyoto, Japan) at 365 nm. The standard plot of triamterene in distilled water over a concentration range of 0 to 12 μg/mL at 365 nm was linear with a correlation coefficient of 0.99 ($r^2 = 0.9999$). The apparent stability constant was calculated from the phase-solubility diagram, using the following equation:

$$k_{1:1} = \frac{slope}{intercept\,(1 - slope)} \qquad (1)$$

Preparation of Solid Dispersions

Physical mixtures (PM) and solid dispersions of triamterene and β-cyclodextrin in 1:1 molar ratios were prepared. PM were prepared by mixing in geometric proportion followed by passing through no. 80 sieve with minimum abrasion. Coground samples (CG) were prepared by grinding the drug and β-cyclodextrin with intense trituration for over 30 minutes. Solid dispersions were prepared by kneading and coevaporation. The kneaded dispersions were prepared by grinding the drug and β-cyclodextrin together for approximately 30 minutes. The powder was then kneaded with (1) alcohol (K-1), (2) acidified alcohol (K-2), and (3) aqueous alcohol (K-3) to get a pasty consistency. The mass was dried at 40°C for 1 hour, stored overnight in a vacuum dessicator, and passed through no. 80 sieve. The coevaporated product was prepared by dissolving triamterene and β-cyclodextrin in (1) acidified alcohol (C-1) and (2) aqueous alcohol (C-3) and then evaporating the solvents at controlled temperatures of 40°C to 45°C. The contents were then dried overnight in a vacuum dessicator and then passed through no. 80 sieve. The same procedure was repeated for triamterene alone, without β-cyclodextrin (C-2).

Characterization of Samples

Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FTIR) spectra of the samples were obtained in the range of 400 to 4600 cm^{-1} using a Jasco-FTIR spectrophotometer (Jasco, Essex, UK) by the KBr disc method.

Nuclear Magnetic Resonance Studies

The ^1H spectra of the samples in D_2O were performed on Bruker AMX-500 Fourier transform nuclear magnetic resonance (FTNMR) spectrophotometer (Bruker AXS Inc, Madison, WI) at 298°K and 500 Mhz.

X-Ray Diffraction Studies

X-ray diffraction (XRD) patterns were recorded on a Philips X-ray diffractometer (PW 1710, Philips Analytical, Almelo, The Netherlands) with a copper target, voltage 40KV, current 30 mA, and a scanning rate of 1°/min.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) studies were performed on samples weighing 5 mg in flat-bottomed aluminum pans using a Shimadzu DT-40 thermal analyzer. The samples were heated from 30°C to 350°C at a heating rate of 10°C/min.

In Vitro Dissolution Studies

The physical mixture and solid dispersion samples equivalent to 100 mg of triamterene were analyzed for drug release profiles using *United States Pharmacopeia (USP)* 23 paddle dissolution apparatus at a temperature of 37°C and a stirring rate of 100 rpm, using 900 mL of 0.1N HCl and pH 6.8 phosphate buffer as the dissolution medium.

In Vivo Studies: Pharmacodynamic Evaluation in Rats

Male Wistar rats were used to compare the diuretic efficacy of C-1 with that of triamterene. Animals in the weight range of 150 to 200 g were used in the study. The rats were orally administered an initial saline load of 25 mL/kg, followed by either triamterene or coevaporate C-1, dispersed in tragacanth suspension. They were divided into the following 4 groups:

1. Control group—treated with tragacanth suspension;
2. Standard group—administered triamterene in tragacanth slurry;
3. Test group—treated with C-1 in tragacanth suspension; and
4. Carrier group—administered β-cyclodextrin in tragacanth slurry.

The animals were placed individually in metabolic cages, and urine samples were collected over a period of 5 hours. The extent of diuresis was estimated based on net sodium ion excreted. Baseline studies were conducted on all the animals prior to the drug studies, wherein net sodium ion excretion was determined after oral administration of only saline load. The percentage increase in net sodium ion excreted for each animal was calculated with respect to the baseline excretion of sodium ion. Thus, each animal in all the 4 groups, served as its own control. The animals used in the study were handled and taken care of in accordance with the institutional guidelines.

RESULTS

Phase-Solubility Studies

Figure 3 shows the phase-solubility plot for triamterene and β-cyclodextrin.

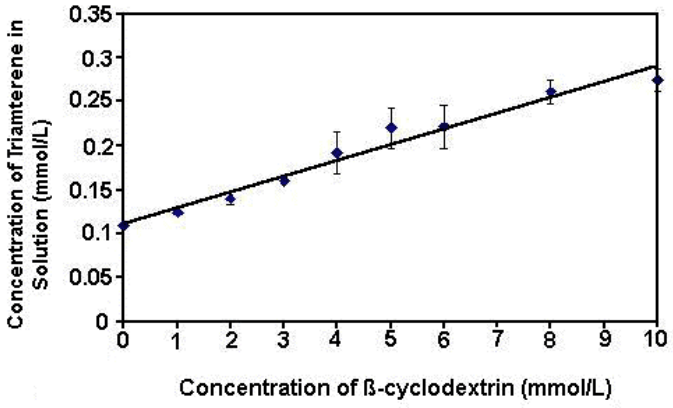

Figure 3. Phase-solubility plot of triamterene-β-cyclodextrin system. The experiments were conducted in replicates of 3 to 6.

The equation after linear regression analysis was found to be as follows:

$$y = 0.0179x + 0.1119 \quad (2)$$

where x is the concentration of β-cyclodextrin in solution (mmol/L); y is the concentration of triamterene in solution (mmol/L); and the correlation coefficient $r = 0.9848$ ($r^2 = 0.97$).

There is a linear increase in solubility of triamterene with increasing concentrations of β-cyclodextrin, with a negative shift from linearity at higher concentrations of β-cyclodextrin. Since the slope of the diagram is less than 1, the complex stoichiometry was assumed to be 1:1. As the purpose of the study was not to prove stoichiometry of the complex, based on this assumption binary systems of triamterene and β-cyclodextrin were prepared using 1:1 molar proportion. The value of the stability constant $k_{1:1}$ was 167.67M^{-1}; well within the range of 100 to 1000 M^{-1} considered ideal.[12] A smaller $k_{1:1}$ value indicates too weak an interaction, whereas a larger value indicates the possibility of limited release of drug from the complex thereby interfering with drug absorption.

Table 1. Chemical Shift Assignments for the Different Protons in Triamterene and β-Cyclodextrin and Changes in the Chemical Shift Values of These Protons in C-1

Protons		Chemical Shift Values	Changes in Chemical Shift Values in C-1
Triamterene	Ortho-	7.70	+0.051
	Meta-para-	7.597	+0.097
β-Cyclodextrin	H_3	4.073	–0.1
	H_6	3.990	–0.053
	H_5	3.965	–0.088
	H_2	3.776	–0.049
	H_4	3.694	–0.048

Fourier Transform Infrared Spectroscopy

Figure 4 illustrates the FTIR spectra of the samples under study. IR spectrum of triamterene is characterized by principal absorption peaks at 3472, 3371, 1614, 1570, 1537, 1421, 819, and 760 cm^{-1}. The peaks observed at 3472 and 3371 cm^{-1} are due to asymmetric and symmetric stretching vibrations of the free amino groups in the molecule of the pure drug, whereas those in the range of 1614 to 1421cm^{-1} can be assigned to the C-N and C=N bonds.[10] Peaks at 819 and 760 cm^{-1} may be assigned to aromatic stretching of the phenyl group in the molecule.

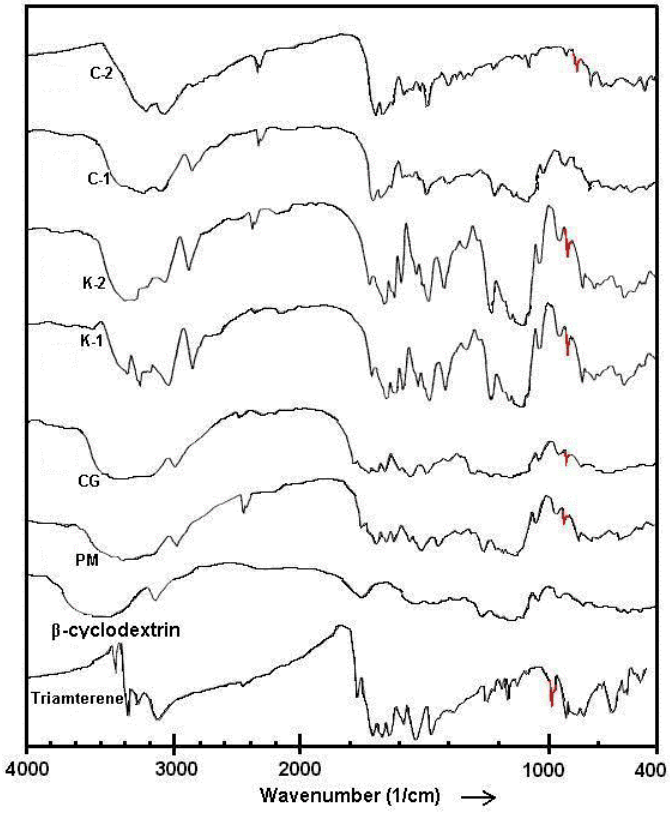

Figure 4. FTIR spectra of triamterene, β-cyclodextrin and their binary systems.

The IR spectra of PM, CG, K-1, K-2, K-3, and C-3 correspond to the superimposition of the spectra of triamterene and β-cyclodextrin, with no significant shift in the major peaks corresponding to triamterene (K-3 and C-3 are not shown in Figure 4). The peaks in the range of 3472 to 3371 cm^{-1} in all these systems except K-1, are smoothened, which could be due to some host-guest interaction between the amino groups of triamterene and β-cyclodextrin in these complexes. The spectral patterns of C-1 and C-2 show a shift of 20 to 50 cm^{-1} for all the principal peaks of triamterene. As these spectral differences are seen in both C-1 and C-2, these could be ascribed to protonation of the nitrogen atom in the pteridine ring of the drug molecule and not to any guest-host interaction. The aromatic stretching vibrations of the phenyl group at 819 cm^{-1} in triamterene disappear completely in C-1 but are present in C-2. This finding suggests interaction of significant magnitude between phenyl group of triamterene and β-cyclodextrin in C-1.

Nuclear Magnetic Resonance Studies

Table 1 shows the chemical shift assignments for the different protons in triamterene and β-cyclodextrin and the changes in the chemical shifts of these protons in C-1. The pattern of triamterene run in D_2O showed a doublet at 7.7 and 7.597 ppm due to the aromatic protons.[13] The spectrum of β-cyclodextrin shows signals at 4.073, 3.99, 3.965, 3.771, and 3.694 ppm corresponding to protons at C3, C6, C5, C2, and C4 positions, respectively, of the glucose units in the β-cyclodextrin molecule.

In the case of the spectrum of C-1, there is downfield shift of 0.051 and 0.097 ppm corresponding to the ortho- and meta-para-protons, respectively, of the phenyl ring. The peaks corresponding to β-cyclodextrin in C-1 shift to 3.973, 3.937, 3.877, 3.727, and 3.646 ppm for protons at C3, C6, C5, C2, and C4, respectively. For protons at C3 and C5, there is a downfield shift of 0.1 and 0.088 ppm, respectively. A shift of 0.1 ppm or more for protons at C3 and C5 indicate inclusion complex formation. This ascertains inclusion of the phenyl group of triamterene within the cavity of the β-

cyclodextrin molecule, with greater involvement of the meta-para-protons of the phenyl ring in the inclusion complex formation, as compared with the ortho-protons as shown in Figure 5.

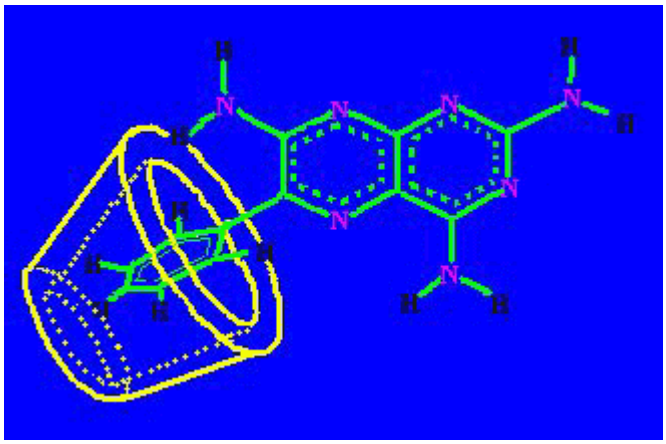

Figure 5. Schematic representation of triamterene-β-cyclodextrin inclusion complex.

The NMR data for the samples are thus in complete accordance with IR results and confirm inclusion of the phenyl ring of triamterene within the nonpolar cavity of the β-cyclodextrin molecule.

X-Ray Diffraction Studies

Figures 6 and 7 show the diffraction patterns for triamterene, β-cyclodextrin, and the various solid dispersions. Triamterene shows 2 major peaks at 2θ values of 9.42° and 26.4°, with a range of smaller peaks between the 2. The peak at 2θ value of 9.42° decreases considerably in intensity in all the solid dispersions as compared with the PM, with the maximum reduction in CG and C-1. The peak at 2θ value of 26.4° also shows a decrease in intensity in all the solid dispersions, with very significant reduction in C-1 and maximum decrease in CG.

β-cyclodextrin is a very crystalline molecule with major peaks at 2θ values of 4.75°, 12.7°, 19.7°, 21.1°, 22.8°, 24.3°, and 35.9°. The peak corresponding to 12.6° in β-cyclodextrin decreases in intensity only in the case of CG and C-1. All these factors indicate some degree of amorphization or inclusion complex formation in CG and C-1. New peaks at 5.4° and 13.6° are observed in diffractograms of both C-1 and C-2, indicative of interaction between the drug and acid used in acidifying alcohol. In the case of the XRD pattern of CG, the number of peaks is the minimum, indicating amorphization of the drug. The number of peaks in the XRD pattern of C-1, however, is the maximum, indicating the possibility of formation of a solid form with different properties or inclusion complex.

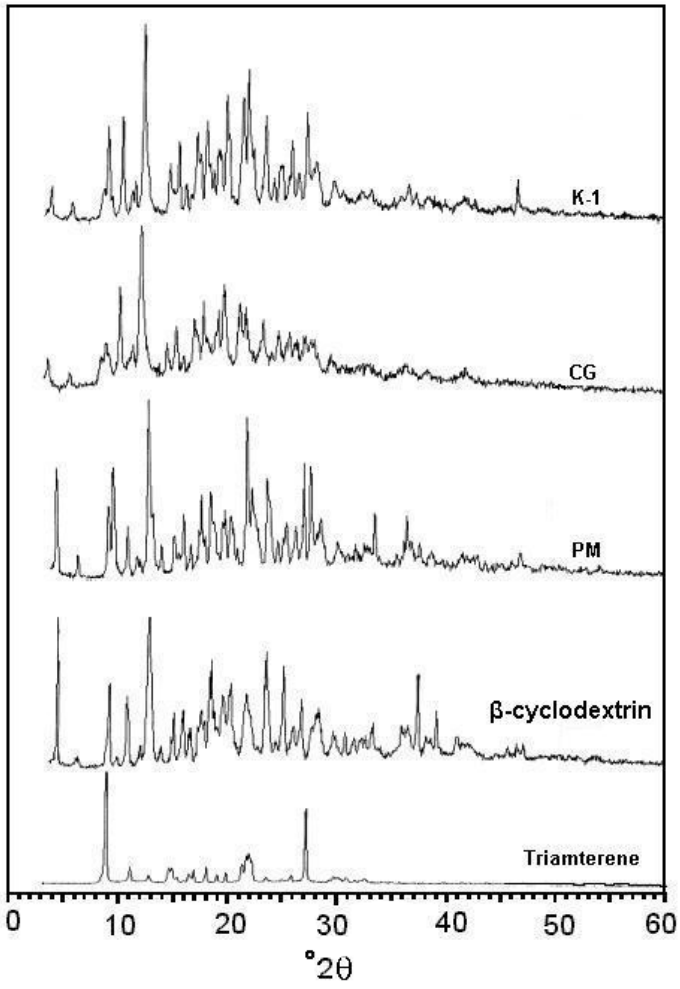

Figure 6. XRD patterns of triamterene, β-cyclodextrin, and their binary systems.

Differential Scanning Calorimetry

The DSC thermograms of triamterene, β-cyclodextrin, and the binary systems are illustrated in Figure 8. The DSC curve of triamterene shows a sharp endotherm at 332.3°C. The DSC curve of β-cyclodextrin shows a broad endotherm in the range of 75°C to 85°C, which can be attributed to desolvation, followed by a melting endotherm at 321.5°C. The DSC thermograms of all the binary systems except C-1 show a typical pattern with a broad endotherm in the range 60°C to 70°C (because of desolvation), followed by decomposition at temperatures above 200°C, with a melting endotherm at around 340°C. The melting endotherm in the binary systems is broader and more flattened compared with that in the pure drug, probably due to greater disorder in the crystal structure. Grinding has been reported to reduce the intensity of the endotherm peak of desolvation in β-cyclodextrin as well as coground triamterene/β-cyclodextrin

systems.[9] This result would explain the flattening of this peak in CG.

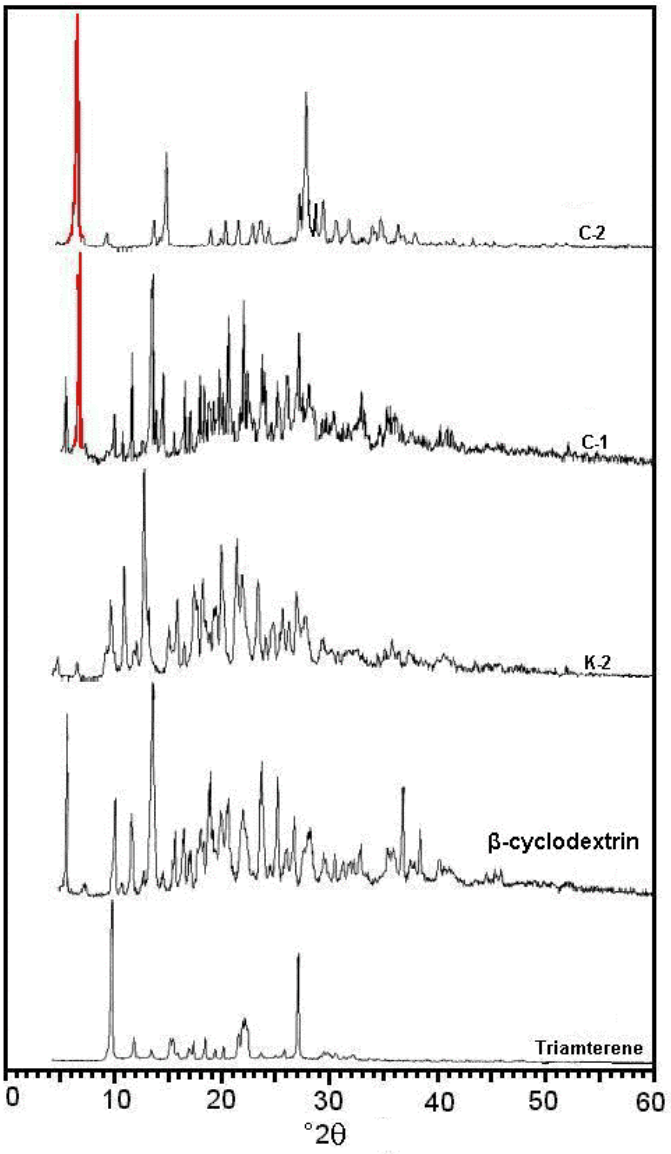

Figure 7. XRD patterns of triamterene, β-cyclodextrin, and their binary systems.

The DSC curve of C-1 shows initial desolvation in the temperature range of 45°C to 122°C, with a melting endotherm at 265°C. This finding probably indicates the formation of a solid form with different properties or inclusion complex in the coevaporate, which melts at 265°C, much lower than the melting point of triamterene. C-2 shows a thermogram similar to triamterene with a slight shifting of the melting endotherm to 321°C, followed by an exothermic peak, along with an additional endotherm of desolvation in the temperature range of 60°C to 100°C. This finding indicates formation of a new metastable form in C-2, which is responsible for its improved dissolution profile as compared with the plain drug.

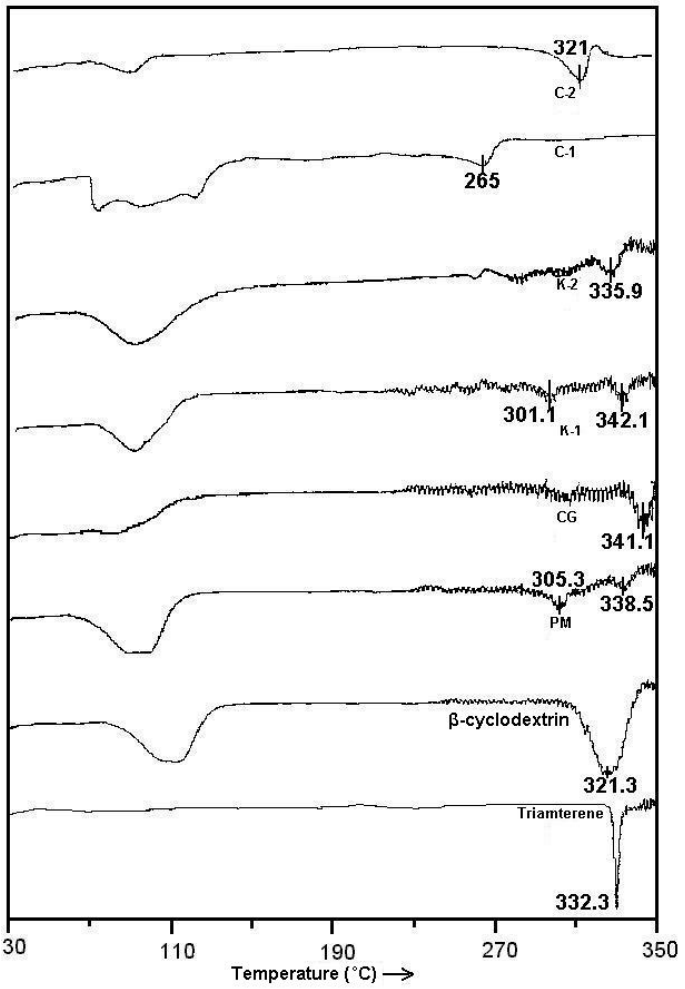

Figure 8. DSC thermograms of triamterene, β-cyclodextrin, and their binary systems.

DSC patterns, thus, confirm the findings of XRD studies indicating formation of a solid form with different properties or drug-β-cyclodextrin inclusion complex in C-1. The possible formation of a metastable form in C-2 is indicated, as evident from the changes in FTIR spectra, diffractogram, and thermogram of C-2.

In Vitro Dissolution Studies

Figures 9 and 10 illustrate the percentage drug release vs time profiles for the systems under study in 0.1N HCl and pH 6.8 phosphate buffer.

In 0.1N HCl, triamterene powder is poorly soluble with ~95% of the drug dissolving in 3 hours. In the case of PM, there is a marginal improvement in dissolution as compared with triamterene powder. Cogrinding resulted in dissolution of 95% of drug in 2 hours, whereas both K-2 and K-3 gave

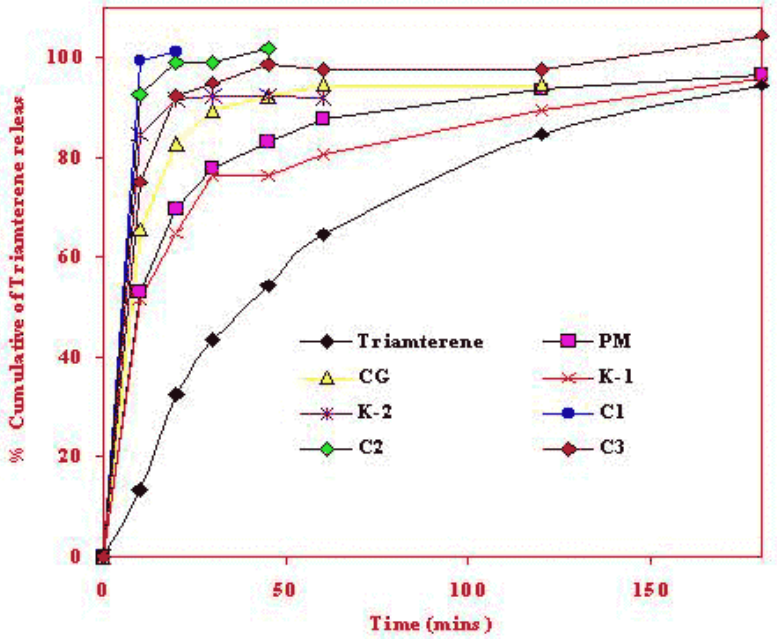

Figure 9. In vitro release profiles of triamterene-β-cyclodextrin systems in 0.1N HCl. Studies were conducted in replicates of 3 to 6. SD in all the cases except for PM was less than 5. In case of PM, the maximum SD was up to 11.

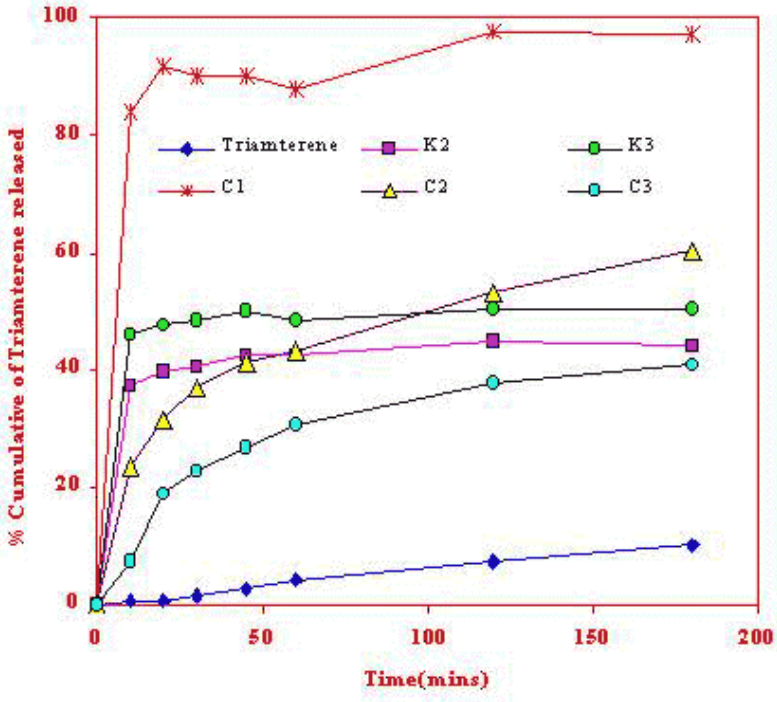

Figure 10. In vitro release profiles of triamterene-β-cyclodextrin systems in pH 6.8 phosphate buffer. Studies were conducted in replicates of 3 to 6. SD in all the cases was less than 5.

better release profiles, with 99% release in 30 minutes. C-3, coevaporate with β-cyclodextrin from aqueous alcohol, showed complete drug release within 45 minutes. C-2, coevaporate without β-cyclodextrin from acidifed alcohol, gave 100% dissolution in 20 to 30 minutes. The faster drug release from C-2 could be attributed to protonation of the drug molecule or formation of a new metastable form with different properties. C-1, coevaporate with β-cyclodextrin from acidified alcohol, gave the fastest release rates, with complete dissolution within 10 minutes, obviously due to drug-β-cyclodextrin inclusion complex formation.

Triamterene powder showed extremely poor dissolution in pH 6.8 phosphate buffer with only ~10% of the drug going into solution in 3 hours. Therefore, only the kneaded and coevaporated solid dispersions—which exhibited good dissolution in 0.1N HCl—were studied for release profiles in pH 6.8 phosphate buffer. All the kneaded and coevaporated systems showed significant improvement in dissolution as compared with triamterene powder. K-2 gave approximately 37% drug release in the first 10 minutes, which increased to 44% in 3 hours. K-3 was marginally better, with 45% release in 10 minutes and approximately 50% release in 3 hours. C-2, coevaporate without β-cyclodextrin from acidified alcohol, gave a better performance with 60% drug release in 3 hours, though only 23% could go into solution in the first 10 minutes. The better initial release with K-2 and K-3 could be attributed to the improved wetting provided by β-cyclodextrin. Only C-1, coevaporate with β-cyclodextrin from acidified alcohol, could bring about complete drug release in pH 6.8 phosphate buffer, with 100% dissolution in 3 hours. This remarkably better performance of C-1 is attributed to inclusion complex formation of triamterene with β-cyclodextrin, as confirmed by FTIR, XRD, DSC, and NMR studies.

In Vivo Studies: Pharmacodynamic Evaluation in Rats

Table 2 shows the average percentage increase in net sodium ion excretion in the 4 groups, after drug treatment. The test group showed a significantly increased average sodium ion excretion, with a lower standard deviation, as compared with the standard group. C-1, coevaporate with β-cyclodextrin from acidified alcohol, gave superior drug bioavailability as compared with triamterene powder. This result could be attributed to enhancement in dissolution of triamterene when it was coevaporated with β-cyclodextrin from acidified alcohol. The findings were subjected to a series of nonparametric tests to ascertain their statistical significance. In order to compare the net sodium ion excreted before and after drug treatment, Wilcoxon signed rank test was applied to all the groups. At 0.05% level of significance, the observations of the test and standard groups showed significant difference in change in sodium ion excretion, whereas in the case control and carrier groups, the difference was not significant, confirming that the increase in sodium ion excretion in the test and standard groups was due to the administration of triamterene as such, and in the coevaporate form. The statistically nonsignificant difference in the control and carrier groups implies that the change in percentage sodium excreted values, before and after drug treatment in both the cases, can be attributed to day-to-day variations in urinary sodium excretion and not to tragacanth and β-cyclodextrin, respectively. Kruskal-Wallis test, the nonparametric equivalent of analysis of variance (ANOVA), revealed significant difference within the 4 groups at 0.05% level of significance. Mann-Whitney *U* test also showed that net sodium ion excretion values for the group administered with coevaporate were significantly higher than those shown by the group treated with triamterene as such. The results suggest in vivo advantage of oral administration of triamterene/β-cyclodextrin system.

Table 2. Average Percentage Increase in Na^+ Excreted in Male Wistar Rats After Oral Administration of Drug

	Average % Increase in Na^+ Excreted
Test	62.24 ± 9.89
Standard	46.62 ± 17.01
Control	–176.91 ± 426.12
Carrier	–92.41 ± 207.65

CONCLUSION

Triamterene/β-cyclodextrin systems show significant improvement in dissolution profiles as compared with triamterene itself; the coevaporate from acidified alcohol showed the maximum enhancement, coupled with improved activity, as measured by net sodium ion excretion, when administered orally in rats. Superior in vitro and in vivo performance of the coevaporate was attributed to the inclusion of the phenyl group of the drug molecule within the nonpolar cavity of β-cyclodextrin molecule, as indicated by the data from the characterization studies.

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