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Research paper

# Improvement of availability of allopurinol from pharmaceutical dosage forms I - suppositories

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**Abstract**

Solid dispersion and crystallization of a very slightly water-soluble drug, allopurinol, were prepared using urea, sodium salicylate and $\beta$-cyclodextrin ($\beta$-CD) as carriers. The spectroscopic infra-red (IR), differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD) data indicate a role of these carriers in decreasing the crystallinity of allopurinol and complexing abilities. Solid dispersion and crystallization of the drug with these carriers were used in suppository formulations to investigate their role in enhancement of drug release through the membrane barrier. The bases used included Suppocire AM and the mixture of polyethylene glycols (PEGs). The release rates of allopurinol from lipophilic and hydrophilic suppository bases were examined and compared with those obtained for their inclusion compounds incorporated in the same bases. The prepared suppositories were evaluated for in-vitro drug release, when fresh and on storage. The release of pure allopurinol from the lipophilic base was remarkably higher than that from the hydrophilic one. The release of allopurinol from lipophilic as well as hydrophilic bases was significantly enhanced by crystallization of the drug from 5% w/v of sodium salicylate. Allopurinol crystallized from sodium salicylate, showed enhanced release reaching about 100% in 1 h from the Suppocire AM base. The obtained data from these experiments proved the superiority of the PEG formulations containing coevaporates of the drug to sodium salicylate, ratio 1:1, or of the drug to $\beta$-CD, ratio 1:2; $T_{90\%}$,12 and 36 min, respectively. A significant decrease of uric acid excretion in rabbits was observed after rectal administration of suppositories containing allopurinol crystallized from sodium salicylate. 

*Keywords:* Solid dispersion; Crystallization; Suppositories; Bioavailability studies

## 1. Introduction

Allopurinol, 1,5-dihydro-4*H*-pyrazolo[3,4–*d*]pyrimidin-4-one, a structural isomer of hypoxanthine was introduced into clinical medicine in 1962 [1]. It is widely used in the treatment of both the primary hyperuricemia of gout and that secondary to hematological disorders or antineoplastic therapy [2]. Allopurinol is a polar compound with strong intramolecular hydrogen bonding and limited solubility in both polar and non-polar media [3]. Consequently, the extremely low availability following administration of rectal suppository dosage forms in humans [4,5] and rabbits [6] may be due to poor partitioning and solubility of allopurinol from the dosage form. Despite availability of allopurinol from the most bioavailable rectal dosage form, a rectal solution was also negligible. Following administration of polyethylene glycol suppositories, neither allopurinol nor oxypurinol were detectable in the plasma [6].

Patel and Kramer [7] reported that the absorption of allopurinol suspension in polyethylene glycol 400 (PEG 400) is erratic and poor after oral administration to rabbits. Allopurinol has been shown to form a reversible, soluble complex with a PEG base [5]. The lower bioavailability and erratic absorption may have been due to differential absorption of allopurinol from different sites, with absorption decreasing as the complex moved down the gastro-intestinal (GI) tract [6].

Crystallization [8] and solid dispersion [9] techniques have been widely used to improve the dissolution properties and bioavailability of poorly water soluble drugs. The use of crystallization of allopurinol in different media (water, Tween 20 and Myrij 59) for the enhancement of drug release from different suppository bases and absorption after rectal administration has been reported [10]. Rectal administration is often used to overcome gastric irritation, nausea and

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vomiting that may be associated with oral administration of allopurinol [11]. Furthermore, drugs are administered rectally when the oral route is not convenient, as in infants and elderly patients. A literature survey of allopurinol pointed out a lack of rectal formulations of this drug. The prepared work has been undertaken to enhance the dissolution rates of allopurinol from rectal suppositories by crystallizing the drug in urea, sodium salicylate or $\beta$-cyclodextrin ($\beta$-CD) media. Solid dispersions of the drug in these carriers prior to its formulation as suppositories using different bases were also prepared. Characterization of such systems were studied by infra-red spectrometry (IR), differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD). Moreover, the inhibitory effect of allopurinol on the action of xanthine oxidase, which reduces the oxidation of hypoxanthine and xanthine to uric acid [12], was utilized for the evaluation of some formulations. The effect of rectal and oral administration of the drug on urinary uric acid excretion in rabbits was investigated.

## 2. Methods and materials

### 2.1. Materials

Allopurinol (Sigma Chem. Co., USA), polyethylene glycol (PEG 1000 and PEG 4000) (Atlas Chem. Ind., USA), Suppocire AM (Gatte Fossé Etablissements, France), B-cyclodextrin ($\beta$-CD, Sigma, USA), sodium salicylate, urea (E. Merck, Darmstadt, Germany), dimethylsulfoxide (DMSO), acetone, ethanol and all other chemicals were either of analytical or reagent-type grade.

### 2.2. Methods

#### 2.2.1. Preparation of solid dispersions

Solid dispersions of allopurinol with each of urea, sodium salicylate or $\beta$-CD were prepared by the solvent method at weight ratios of 1:1 and 1:2, drug to carrier. Allopurinol and these carriers were dissolved in ethanol, the solvent was then removed using a rotary vacuum dryer. The residue was further dried over phosphorous pentoxide in a desiccator for 3 days. Before carrying out the release study, the coevaporates were then powdered in a mortar and particles of a 60–120 μm range were obtained for further investigations.

Allopurinol in urea at weight ratio of 1:1 was prepared by the melting method, making use of the relatively low melting point of urea. After the urea was completely melted in a thermostat-controlled oil bath, allopurinol was dissolved and then solidified by pouring on a glass petri dish stored on an ice bath. After the resulting solid was cooled, it was kept in vacuum, then the powdered sample was pulverized and was fractionated in the particle size range of 60–120 μm by sieving.

#### 2.2.2. Crystallization of allopurinol

Allopurinol (500 mg) was dissolved in 25 ml DMSO at 50°C. The drug was precipitated by adding 5% w/v of aqueous solution of any of urea and sodium salicyate or 1.8 % w/v $\beta$-CD. The obtained crystals were collected by filtration and dried under vacuum at 40°C for 12 h. A particle size range of 60–120 μm was chosen for investigation.

#### 2.2.3. Preparation of suppositories

Suppository formulations were prepared from either fat or water-soluble bases by the melting technique in order to contain 15 mg of allopurinol/suppository. The water soluble base employed was a mixture of PEG 1000/PEG 4000 (96:4% w/w). The fatty base used was Suppocire AM. Allopurinol suppositories in PEG and Suppocire containing the equivalent of 15 mg of the drug in its solid dispersions or crystallized from different hydrotropic materials were prepared. The prepared suppositories were stored in refrigerator, taken out 24 h before investigation and left at room temperature to attain equilibrium.

### 2.3. Evaluation of solid dispersion and crystallizate products

#### 2.3.1. Content uniformity

The uniformity of drug content for each batch (20 suppositories) was determined by dissolving PEG suppositories in phosphate buffer at pH 7.4 and measuring the drug content spectrophotometrically at $\lambda = 249$ nm (UV Spectrophotometer model Uvidec-320 JASCO). The procedure was repeated to determine the uniformity of drug content of fatty base suppositories using repeated extraction with phosphate buffer (pH 8.2), to ensure complete extraction of the drug from the base. In both cases, blank suppositories without the drug were prepared and subjected to the same analytical procedure to serve as the blank for spectrophotometric determination. The mean drug content was found to be 14.8 ± 0.2 mg for the PEG base, and 14.2 ± 0.37 mg for the Suppocire base suppositories.

#### 2.3.2. Infra-red spectroscopy studies

Studies of the IR spectra of the coevaporates and crystallized products were conducted using a Shimadzu spectrophotometer (model 470, Japan) and the KBr disc method.

#### 2.3.3. Differential scanning calorimetry

Samples of the coevaporates of allopurinol with sodium salicylate or $\beta$-CD, crystallized products from sodium salicylate and its physical mixture were studied using a differential scanning calorimetry (DSC, model 50, Shimadzu, Japan). Samples of 2–10 mg accurately weighed in crimp-sealed (non-hermetic) aluminum sample pans, were scanned from 20–450°C, at a heating rate of 10°C/min, and nitrogen purge (40 ml/min). An indium pan served as the reference, and all scans were performed in triplicate. The instrument

was calibrated prior to sample analysis, using an indium standard.

*2.3.4. Powder X-ray diffraction*

PXRD was performed on allopurinol, coevaporates of the drug with sodium salicylate and its physical mixture. Each powder sample was carried out with a Philips diffractometer (PW-1710, The Netherlands); Cu $K_\alpha$ radiation (40 Kv, 30 MA, slit 1.5°).

*2.3.5. In-vitro release studies*

The in-vitro release of allopurinol from the different suppository formulae was performed by a modification of the dialysis method of Othman and Muti [12]. The cellophane membrane (Fisher Sci. Co., UK) was fastened on the open end of a glass tube (20 cm in length) having a surface area of 4.53 $cm^2$, using a rubber band. The tube was then immersed upside-down in a 250-ml beaker containing 200 ml of phosphate buffer (pH 7.4). The temperature was maintained at 37°C and the stirring rate was kept constant at 25 rpm, using a shaker with thermostatically-controlled water bath (Karl Kolb, type FR, Germany). The release of the drug from different suppository formulae was determined by placing the suppositories with 5 ml of the dissolution medium, in dialysis tubes. The drug concentrations were analyzed spectrophotometrically at $\lambda = 249$ nm. Interference experiments showed that the components of the different systems did not interfere with the spectrophotometric measurements of the drug at the specified wavelengths. Each release experiment was performed in triplicate, and the mean readings were used for calculation.

*2.4. Effect of storage on the release of allopurinol suppositories*

Allopurinol suppositories were shelf-stored at room temperature for 4 months. The stored suppositories were those prepared with PEG, Suppocire AM, coevaporates of the drug with sodium salicylate (1:1) and with $\beta$-CD (1:2) in a PEG suppository base. The release of allopurinol from the stored suppositories was performed monthly using the dialysis method as before.

*2.5. Bioavailability studies*

The usual effect of allopurinol administration in man is a decrease in uric acid excretion [13]. Accordingly, uric acid was determined in the urine of rabbits by phosphotungistic reduction in an alkaline medium [14] using a uric acid-kit (BioMe'rieux laboratory reagents and products, France). Specially prepared allopurinol suppositories weighing 0.15 g and containing the calculated dose of the drug were prepared according to formulae $F_7$, $F_{10}$ and $F_{16}$. Ten male healthy rabbits were kept on a standard diet throughout the experimentation period. The volumes of urine were collected for 24 h and the amount of uric acid was determined before administration of allopurinol (Group one, control). Group two were given allopurinol orally in a gelatin capsule (size five). Group three received formula $F_{10}$, suppositories containing the untreated drug in a Suppocire AM base. Group four received formula $F_{16}$, suppositories containing the drug crystallized from sodium salicylate in a Suppocire base. Group five received formula $F_7$, suppositories containing allopurinol crystallized from sodium salicylate in a PEG suppository base. The drug was administered following 24 h of fasting and a minimum of 2 weeks washout period. Allopurinol was given to rabbits at a dose of 7.5 mg/kg, reasonably equivalent to the usual human dose of 300–600 mg/day. To prevent expulsion of the suppository, a bulldog clamp was used to hold the anus for 1 h after dosing.

## 3. Results and discussion

*3.1. Spectroscopic studies*

The spectroscopic survey done in this work to reveal any changes in the absorption maximum and thermal behavior

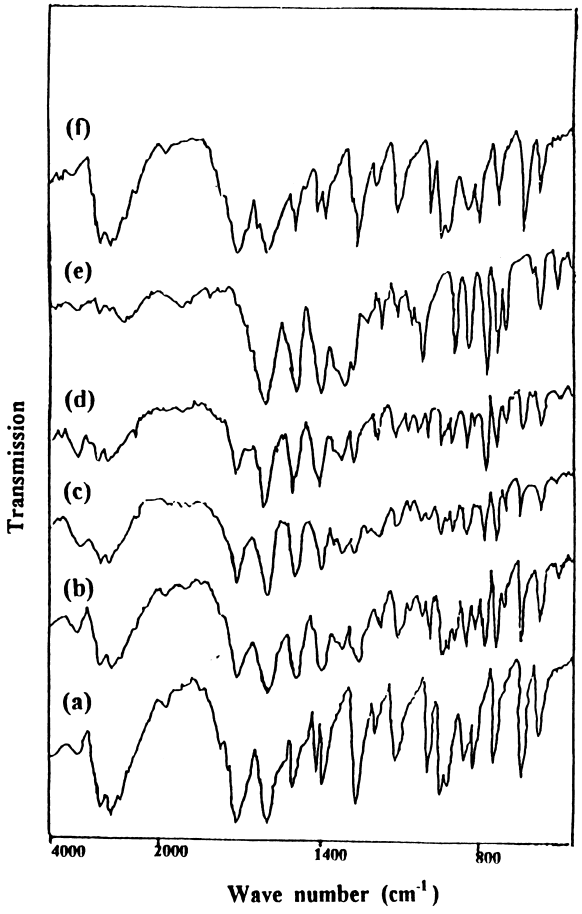


Fig. 1. Infra-red spectra of allopurinol (AL)/sodium salicylate (SS) systems. (a) AL alone; (b), AL/SS coevaporates (1:1); (c), AL/SS coevaporates (1:2); (d), AL/SS physical mixtures (1:2); (e), SS alone; (f), AL crystallized from 5% SS.

of allopurinol as a result of its admixture with urea, sodium salicylate or β-CD in solid dispersion form, crystallized and physical mixture with the possibility of complex formation.

### 3.1.1. Infra-red spectral studies

Fig. 1 shows that the characteristic shoulders of allopurinol in IR are at 790 and 1245 $cm^{-1}$, denoting CH in plane deformation; 1590 $cm^{-1}$ representing ring vibration, 1700 $cm^{-1}$ indicating CO stretching vibration of the keto form of the 4-hydroxytautomer, 3060 $cm^{-1}$ denoting CH stretching vibrations of pyrimidine ring and at 3400 $cm^{-1}$ for NH stretching band [14]. The carbonyl stretching band of allopurinol that appeared at 1700 $cm^{-1}$ shifted in its coevaporates with either sodium salicylate (1:1), urea (1:1) or β-CD (1:2). This band was reduced in intensity and shifted to 1693, 1687 and 1690 $cm^{-1}$ for sodium salicylate, urea and β-CD coevaporates with allopurinol, respectively. Furthermore, the NH stretching band of allopurinol at 3400 $cm^{-1}$ shifted to 3445 $cm^{-1}$ for both coevaporates of the drug with sodium salicylate or urea. Moreover, this band shifted to 3390 $cm^{-1}$ for allopurinol/β-CD coevaporates.

On the other hand, the characteristic shoulders of the melting product of allopurinol/urea (1:1) are shown at 779, 811, 1236, 1589, 1682, 2935, 3080 and 3450 $cm^{-1}$, but missing some of the characteristic peaks of allopurinol (Fig. 2).

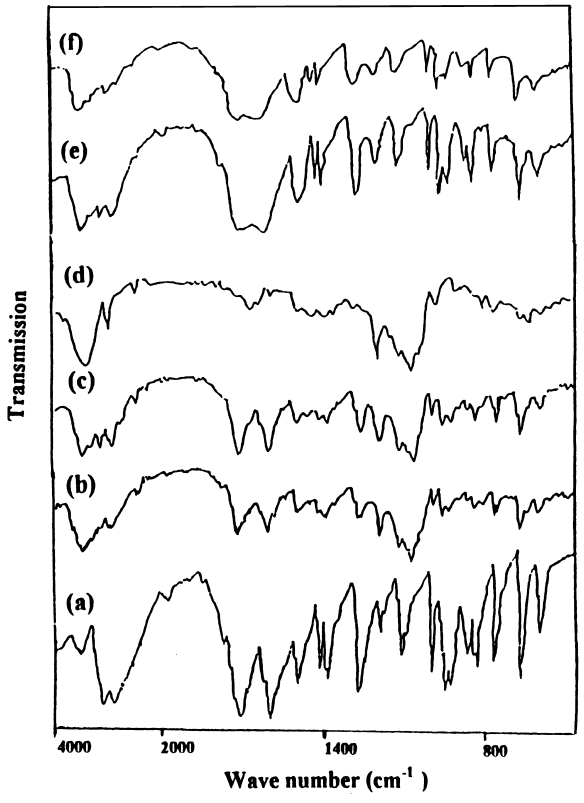


Fig. 2. Infra-red spectra of allopurinol (AL)/carrier systems. (a) AL alone; (b), AL/β-CD coevporates (1:2); (c), AL/β-CD physical mixtures (1:2); (d), β-cyclodextrin alone (β-CD); (e), AL/urea coevaporates (1:1); (f), AL/urea melting (1:1).

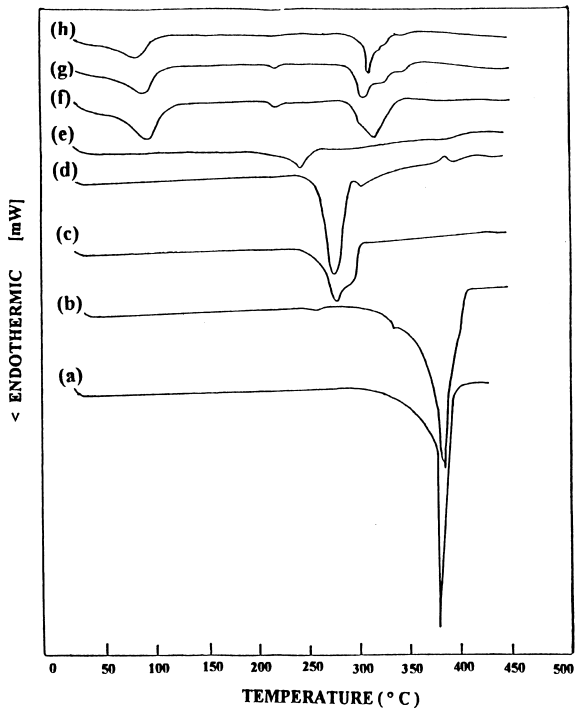


Fig. 3. DSC thermograms of allopurinol (AL)/sodium salicylate (SS) and allopurinol/β-cyclodextrin (β-CD) systems. (a) AL alone; (b), AL crystallized from 5% SS; (c), SS alone; (d), AL/SS physical mixtures (1:2); (e), AL/SS coevaporates (1:2); (f), β-CD alone; (g), AL/β-CD physical mixtures (1:2); (h), AL/β-CD coevaporates (1:2).

On conclusion, these spectral changes would indicate some sort of interaction between allopurinol and sodium salicylate, urea or β-CD that could be via intermolecular hydrogen bonding [15].

The characteristic peaks of both allopurinol and sodium salicylate or β-CD are shown in the given peaks of the physical mixture, which indicate the absence of any interaction between the drug and the carrier upon mixing them together with similar particle size range.

### 3.1.2. Differential scanning calorimetry

Fig. 3 shows DSC thermograms of allopurinol-carrier systems. The thermogram of intact allopurinol showed a characteristic sharp endothermic peak at 381°C corresponding to its melting point. The thermogram of sodium salicylate exhibited a broad endothermic peak between 250 and 300°C (maximum at 277.3°C). While the thermogram of β-CD showed two broad endothermic peaks, one at approximately 96°C, corresponding to the release of the water molecules, and the second at 318°C corresponding to its melting point [16].

Concerning the physical mixture of allopurinol with sodium salicylate or β-CD, the endothermic peak characteristic of the pure drug was found at 343 and 347.7°C, respectively. In the case of the allopurinol/β-CD physical

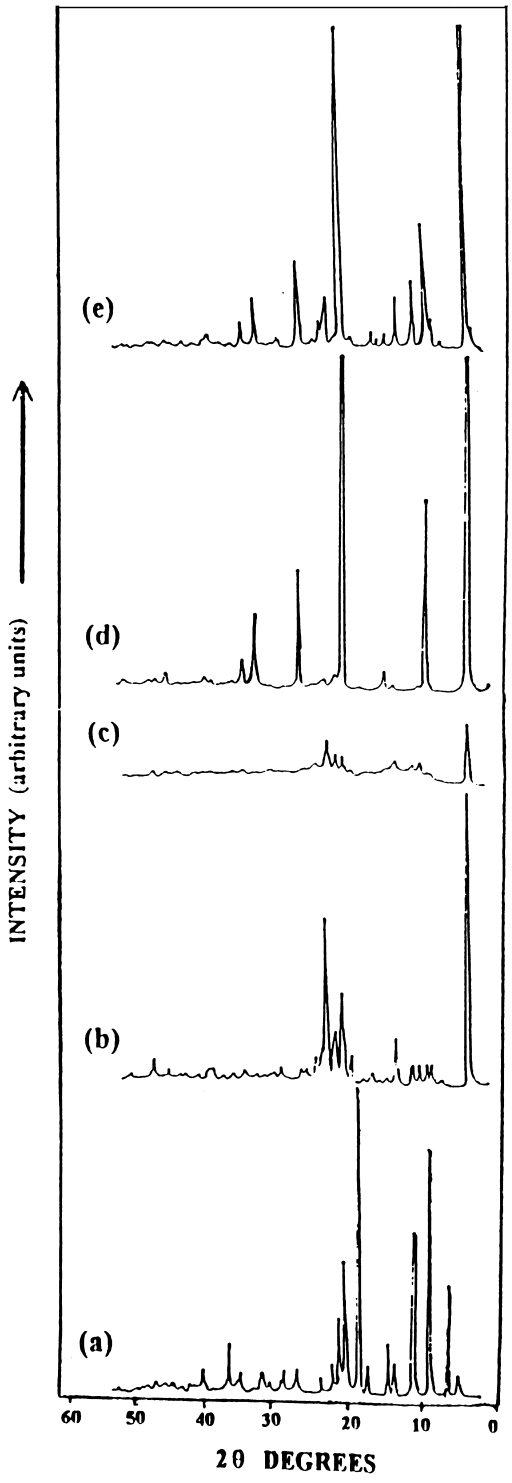


Fig. 4. Powder X-ray diffraction patterns of allopurinol (AL)/sodium salicylate (SS) systems. (a) AL alone; (b), AL/SS coevaporates (1:1); (c), AL/SS coevaporates (1:2); (d), SS alone; (e), AL/SS physical mixtures (1:1).

mixture, the broad thermal rise corresponding to pure $\beta$-CD was also found (maximum around 318°C) as if those thermograms were the superposition of those of the components analyzed separately.

However, in the DSC curves of the coevaporates system, complete disappearance of the endothermic peak of allopurinol was observed. The disappearance of the endothermic peaks of allopurinol is attributed to the amorphous state or inclusion complexation or both [17].

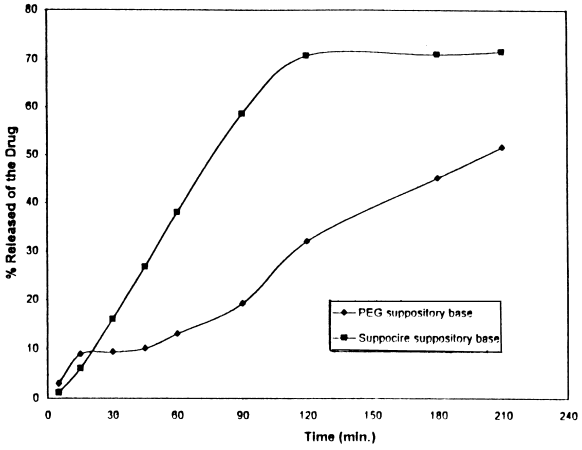


Fig. 5. Release profile of allopurinol from a hydrophilic base (PEG) and a lipophilic base (Suppocire AM) (pH 7.4).

Concerning allopurinol crystallized from sodium salicylate, the thermal characteristic peak appeared around 386°C. These results clearly indicate the existence of interactions between allopurinol and sodium salicylate or $\beta$-CD in the solid state of coevaporate and crystallized systems. The DSC results indicate that the presence of sodium salicylate and $\beta$-CD would affect the crystalline state of allopurinol, and might affect the dissolution of allopurinol from its coevaporates and crystallizates. These results are further confirmed by the PXRD.

### 3.1.3. Powder X-ray diffraction

The crystallinity of the drug allopurinol/sodium salicylate coevaporates and physical mixture at ratios of 1:1 and 1:2 was determined by PXRD (Fig. 4). In the diffractograms, all diffraction peaks were due to carrier crystals and no diffrac-

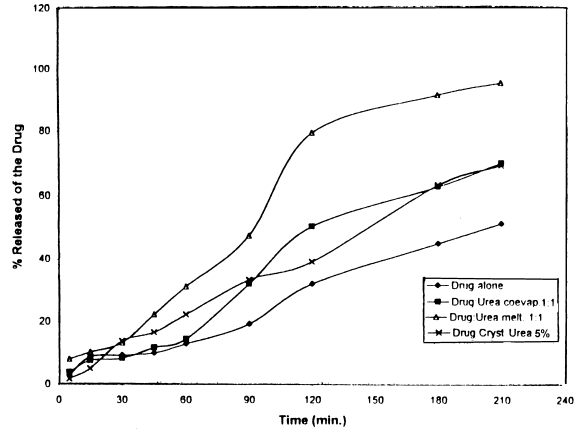


Fig. 6. Effect of urea on the release of allopurinol from PEG suppository bases (pH 7.4).

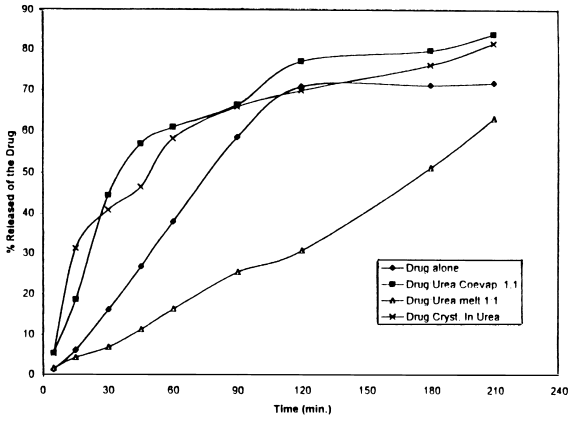


Fig. 7. Effect of urea on the release of allopurinol from Suppocire suppositories (pH 7.4).

tion peaks of allopurinol in the coevaporates were observed. This indicates that the amorphous state of allopurinol was formed in the coevaporates system.

### 3.2. In-vitro release studies

The release of allopurinol from PEG ($F_1$) and Suppocire ($F_{10}$) suppository bases is illustrated in Fig. 5. The results indicated that drug release from the Suppocire base was superior to that from the PEG base. This result is in agreement with Patel and Kramer [8]. It was reported that allopurinol has been shown to form a reversible soluble complex with a PEG base. The release of the drug from suppositories is known to be influenced by various factors, such as drug–vehicle interactions, type of vehicle and the chemical composition of the additives.

Inclusion of urea in some formulations by coevaporation, melting and crystallization methods was carried out to study its effects on drug release. The results are shown in Figs. 6 and 7. This substance was selected on the basis of the osmotic effect of urea, in addition to its compatibility with body fluids, being a normal component of the human body. Basic amino acids have been used successfully to improve rectal absorption of ampicillin sodium [18] and as enamine derivatives [19] to enhance the rectal absorption of different $\beta$-lactam antibiotics. Also, urea and Lysine HCl have been used to enhance the release of verapamil hydrochloride from different suppository bases [20]. The effect of urea on release from PEG, e.g. $F_2$ and $F_4$, was demonstrated by a slight increase in the rate and extent of drug release. The release of allopurinol from the PEG base, e.g. $F_3$, was found to be 95.9% after 210 min. In this case of PEG bases, the effect of urea was more pronounced with bases which did not show initially good drug release, e.g. $F_1$.

Incorporation of sodium salicylate increases the release of allopurinol from its suppository bases. The results are illustrated in Figs. 8 and 9. Crystallization of allopurinol from sodium salicylate (5% w/v) enhances the release of allopurinol from both types of suppository bases. The percentage of drug released after 1 h was found to be 90.7 and 102% for $F_7$ and $F_{16}$, respectively. The enhancement of the release rates of the drug from the suppository bases may be attributed to the interaction of the drug with the carrier and the change in the crystallinity of the drug as illustrated by IR, DSC and P-XRD studies. Moreover, it was reported [21] that the improvement of release rate of allopurinol as a result of crystallization in the presence of hydrotropic agents may be attributed to the surface activity in the microdiffusion layer surrounding the drug particles which increase their wettability and thereby increase their dissolution rates.

Figs. 8 and 9 show the release profiles of allopurinol suppositories containing coevaporates of the drug/sodium salicylate in ratios of 1:1 and 1:2. Formula $F_5$ showed the highest release rate of the drug from PEG suppository bases. The percentage of drug released after 10 min was found to be 100%. In contrast to the PEG base, the complex formation of allopurinol ($F_{14}$) led to much a slower release from the Suppocire base compared to that of the pure drug. This decrease in suppository drug release could be explained by a theory of Frijlink et al. [22,23] that in the case of substances with high lipophilic character after partial complex dissociation, free drug is formed which undergoes back-diffusion to

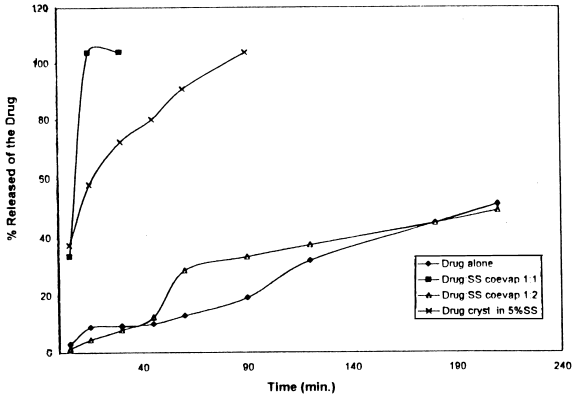


Fig. 8. Effect of sodium salicylate (SS) on the release of allopurinol from PEG suppository bases (pH 7.4).

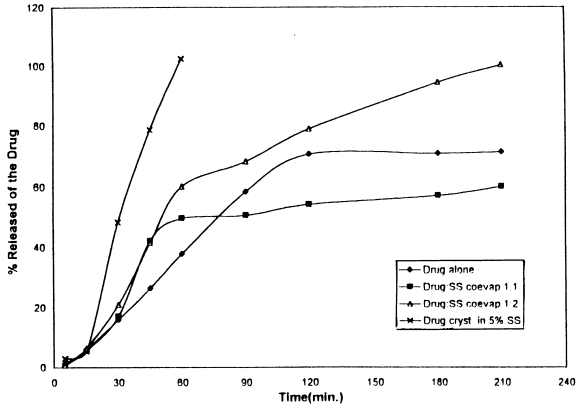


Fig. 9. Effect of sodium salicylate (SS) on the release of allopurinol from suppocire suppository bases (pH 7.4).

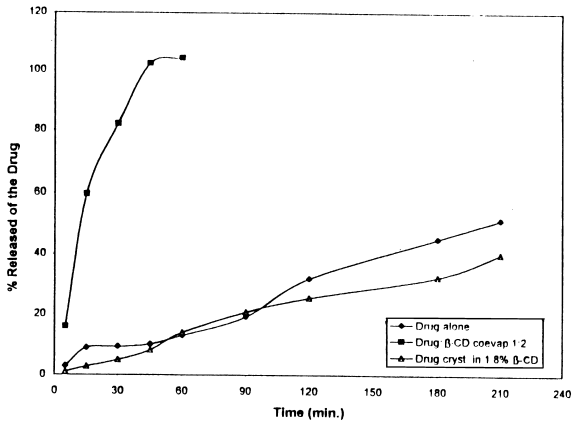


Fig. 10. Effect of $\beta$-cyclodextrin ($\beta$-CD) on the release of allopurinol from PEG suppository bases (pH 7.4).

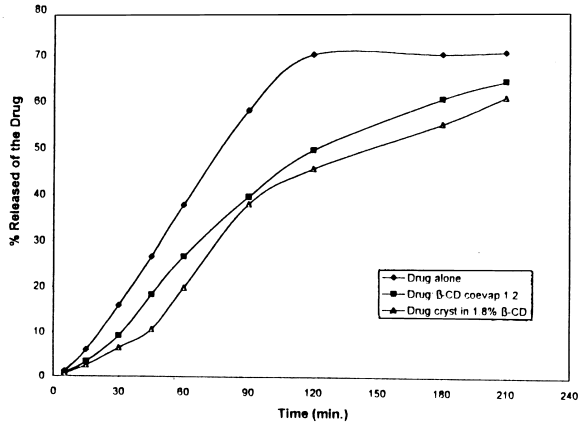


Fig. 11. Effect of $\beta$-cyclodextrin ($\beta$-CD) on the release of allopurinol from Suppocire suppository bases (pH 7.4).

the lipid phase. The final drug concentration in the aqueous phase is by this reason diminished.

The use of $\beta$-CD as a release enhancer of allopurinol from its suppositories was shown in Figs. 10 and 11. For $\beta$-CD complexes (coevaporates), the release rate of allopurinol from the PEG base ($F_8$) was much greater than that from formula ($F_1$) containing the drug alone. This reflects the lesser interaction between the complex and the hydrophilic base [24]. These results are also in agreement with Iwaoka et al. [25], who found that the $\beta$-CD gave a greatly enhanced release rate of phenobarbital from suppositories containing the complex more than the drug alone and produced a net increase in absorption rate. The crystallization of allopurinol from 1.8% w/v $\beta$-CD led to much a slower release from lipophilic and hydrophilic bases compared to the pure drug.

Based on the obtained experimental results, it can be finally concluded that increased solubility of the drug by complex formation with sodium salicylate or $\beta$-CD does not necessarily increase the release rate of the drug from the suppository bases.

The mathematical evaluation of the in vitro release of the drug has been done by using zero, first and diffusion models. The highest values of the correlation coefficients were obtained with the first-order kinetic. Moreover, for easier and more quantitative comparison, the kinetics of the drug release were investigated to enable the calculation of release rate constants, $K$ (Table 1).

### 3.3. Effect of storage on the release of allopurinol suppositories

The effect of shelf storage on the release of allopurinol from its selected suppositories was studied for 4 months. It is clear from this study that shelf storage does not change the amount of drug released for each of the tested bases. The extent of allopurinol released from stored Suppocire AM after 1 h ranged from 70.1 to 72.3% for 1 and 4 months

Table 1
Effect of formulations of allopurinol on their release rate constants (K/min × $10^3$) from PEG and Suppocire AM suppository bases.

| Formulation technique[a] | No. of formula (F) of PEG bases | $K \times 10^{3}$[b] | $r$[b] | $T_{90\%}$ (min) | No. of formula (F) of Suppocire AM bases | $K \times 10^{3}$[b] | $r$[b] | $T_{90\%}$ (min) |
|---|---|---|---|---|---|---|---|---|
| 1. Allopurinol alone | 1 | −1.454 | 0.996 | >210 | 10 | −2.943 | 0.985 | >210 |
| 2. Coevaporates, drug/urea (1:1) | 2 | −2.620 | 0.995 | >210 | 11 | −3.404 | 0.990 | >210 |
| 3. Melting, drug/urea (1:1) | 3 | −6.235 | 0.990 | 166 | 12 | −1.959 | 0.994 | >210 |
| 4. Crystallized, drug in 5% w/v of urea | 4 | −2.475 | 0.995 | >210 | 13 | −2.995 | 0.990 | >210 |
| 5. Coevaporates, drug/SS (1:1) | 5 | −134.3 | 0.982 | 12 | 14 | −1.815 | 0.980 | >210 |
| 6. Coevaporates, drug/SS (1:2) | 6 | −1.437 | 0.993 | >210 | 15 | −6.114 | 0.995 | 165 |
| 7. Crystallized, drug in 5% w/v of SS | 7 | −11.92 | 0.990 | 60 | 16 | −16.96 | 0.997 | 52 |
| 8. Coevaporates, drug/$\beta$-CD (1:2) | 8 | −26.54 | 0.999 | 36 | 17 | −2.331 | 0.999 | >210 |
| 9. Crystallized, drug in 1.8% w/v of $\beta$-CD | 9 | −1.041 | 0.998 | >210 | 18 | −2.132 | 0.995 | >210 |

[a] $\beta$-CD, $\beta$-cyclodextrin; SS, sodium salicylate.
[b] First-order release rate constants ($m^{-1}$) and correlation coefficients.

Table 2
Effect of oral and rectal administration of allopurinol on urinary uric acid excretion (mg/24 h) in rabbits

| Parameter | Control | Oral administration | Rectal administration | | |
|---|---|---|---|---|---|
| | | | Suppocire AM base | | PEG base |
| | | | Untreated drug | Crystallized drug in SS[a] | Crystallized drug in SS[a] |
| Mean amount excreted | 235.1 ± 12.8 | 130.5 ± 5.5 | 189.2 ± 10.8 | 139.8 ± 6.7 | 161.8 ± 8.6 |
| Percentage decrease in uric acid | – | 44.49*[a] | 19.52**[a] | 40.54*[a] | 31.18*[a] |

[a] SS, Sodium salicylate; $*P < 0.001$; $**P < 0.01$

storage, respectively. Similar results were obtained for the other stored bases, where the amount of drug released did not change upon storage of allopurinol suppositories.

### 3.4. Bioavailability studies

Table 2 shows the antigout efficiency of allopurinol suppositories measured as percentage decrease in urinary uric acid in rabbits. The oral administration of allopurinol was more effective than the rectal suppositories in decreasing urinary uric acid excretion in normal rabbits. For both routes, a significant decrease of uric acid excretion was observed. It is clear that the tested suppositories containing allopurinol crystallized from sodium salicylate produce a greater decrease in uric acid excretion compared to those containing the untreated drug in the same bases. Comparing the percentage decrease in uric acid reveals that the effect of Suppocire AM, which contains the drug crystallized from sodium salicylate, is about two times the decrease exhibited by the untreated drug in the same bases. The bioavailability results coincide with the in vitro release results shown in Tables 1 and 2. This observation is in accordance with the finding of Matsumoto et al. [26] in their work on the effect of sodium salicylate as an absorption-enhancing agent of gentamicin from suppositories after rectal administration to rabbits. Hosny et al. [27] proved that sodium salicylate has been used successfully to enhance the rectal absorption of insulin in humans from the investigated suppositories.

## 4. Conclusions

Coevaporation and crystallization of allopurinol in the presence of sodium salicylate exhibited an increase in the rate of drug release from different suppository bases. A greatly enhanced release rate of the drug from suppositories containing sodium salicylate produces a net increase in absorption reflected by lowering uric acid excretion in rabbits.

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