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INCLUSION COMPLEXES OF TERFENADINE-CYCLODEXTRINS

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ABSTRACT

Terfenadine, a poorly soluble, H_1-antihistamine was solubilised using B-cyclodextrin and its derivatives. A molar ratio of 1:1 of the drug and cyclodextrin was prepared by the kneading method. The inclusion complex was characterised and evaluated by Differential Scanning Calorimetry & X-ray Diffractometry. *In vitro* dissolution profile of the inclusion complex was studied. Dissolution rates of the drug-cyclodextrin complexes were more as compared to the drug alone. An attempt was also made to prepare a palatable syrup of terfenadine-cyclodextrin complex. Various combination of co-solvents and additives were used to formulate a stable and an acceptable liquid oral.

INTRODUCTION

Terfenadine, is a non-sedating H_1 receptor antagonist which is practically insoluble in water (1). Current research shows that cyclodextrin derivatives display an ability to entrap molecules and have the advantage of a much higher solubility (2,3). Potent solubilisers like B-cyclodextrin, 2-hydroxy propyl B-cyclodextrin and dimethyl-B-cyclodextrin were used. Thus inclusion abilities have been reported to

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be largely magnified depending on the chemical modification.

EXPERIMENTAL

Materials:

Terfenadine, U.S.P. (Cipla, Bombay) & Cyclodextrins: B-Cyclodextrin (B-CD), 2-hydroxypropyl B-Cyclodextrin (2-HP B-CD) and dimethyl B-Cyclodextrin (DM B-CD) were obtained as gift samples from Nihon Shokuhin Kako Co. Ltd. (Japan). All reagents and solvents were of analytical grade.

Methods:

Preparation of Inclusion Complexes (4):

Terfenadine and cyclodextrins were weighed accurately in a molar ratio of 1:1. Terfenadine was added to a slurry of cyclodextrin prepared in water and the mixture kneaded in a mortar for 30 min. The paste was dried at 60°C for 12 hr and sieved through # 100. Physical mixtures of terfenadine and the respective cyclodextrins were prepared in the same molar ratio. A comparison of the physical mixture and the inclusion complex was made.

Characterisation of Terfenadine-B Cyclodextrin Complexes:

1. Differential Scanning Calorimetry (DSC) Studies:

10 mg each of the drug, inclusion complex and physical mixture were subjected to DSC studies using Perkin Elmer DSC7 Model. Alumina was used as a reference standard and the scanning rate was 10°/min.

2. Powder X-ray Difffraction Studies:

This was carried out using Philips Powder Diffractometer Model PW 17291 with a gonoimeter using a Nickel filter $Cu_{\alpha}K$ radiation operating at 30 KW and 20 mamps in the range of 5-35°. Scanning rate was 1° per min.

***In vitro* Dissolution Studies**:

In vitro dissolution of the pure drug, inclusion complex and physical mixture of the drug and cyclodextrin was carried out on USP XXII, type II Dissolution Apparatus using 900 ml of 0.1 N HCl at 37±0.5°C (100 rpm). Aliquots were analysed for the drug content spectrophotometrically at λ = 257 nm.

Preparation of Liquid Oral:

A specified amount of propylene glycol was taken in which methyl and propyl paraben (0.1% w/v & 0.02% w/v respectively) were dissolved. Weighed amount of the inclusion complex equivalent to 0.6% w/v of the drug to the total volume of the liquid oral was added and stirred well.

To the above mixture, specified amount of citric acid dissolved in water was added. The mixture was mixed properly at 40°C. Glycerin was then added followed by addition of prepared syrup base.

Taste Evaluation:

Taste evaluation was carried out on volunteers consisting of adults, male and female, who were in good general health and not affected by conditions which would interfere with the sense of taste and smell. The subjects were first instructed to rinse their mouth with 10 ml distilled water followed by 5 ml portion of the formulation. The grading system used was an increasing order of + signs, indicating improved palatability. Latin Square Method was used as the basis of statistical evaluation.

RESULTS AND DISCUSSION

Characterisation of Inclusion Complex:

1. **DSC Studies**:

Fig. 1 shows the DSC thermograms of the drug, cyclodextrin and its derivatives, their physical mixtures and their inclusion complexes. (A) shows an endothermic peak at 151°C for pure terfenadine. (E), (F) & (G) show endothermic peaks for the physical mixture of Drug-BCD; Drug-HP B-CD and Drug-DM B-CD. It

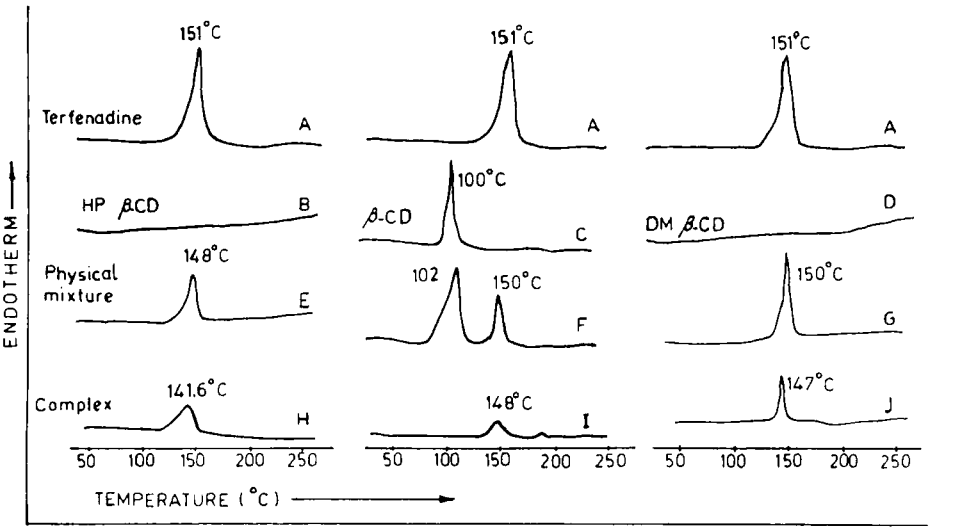

FIG. 1: DSC SCANS OF TERFENADINE-CYCLODEXTRIN SYSTEMS

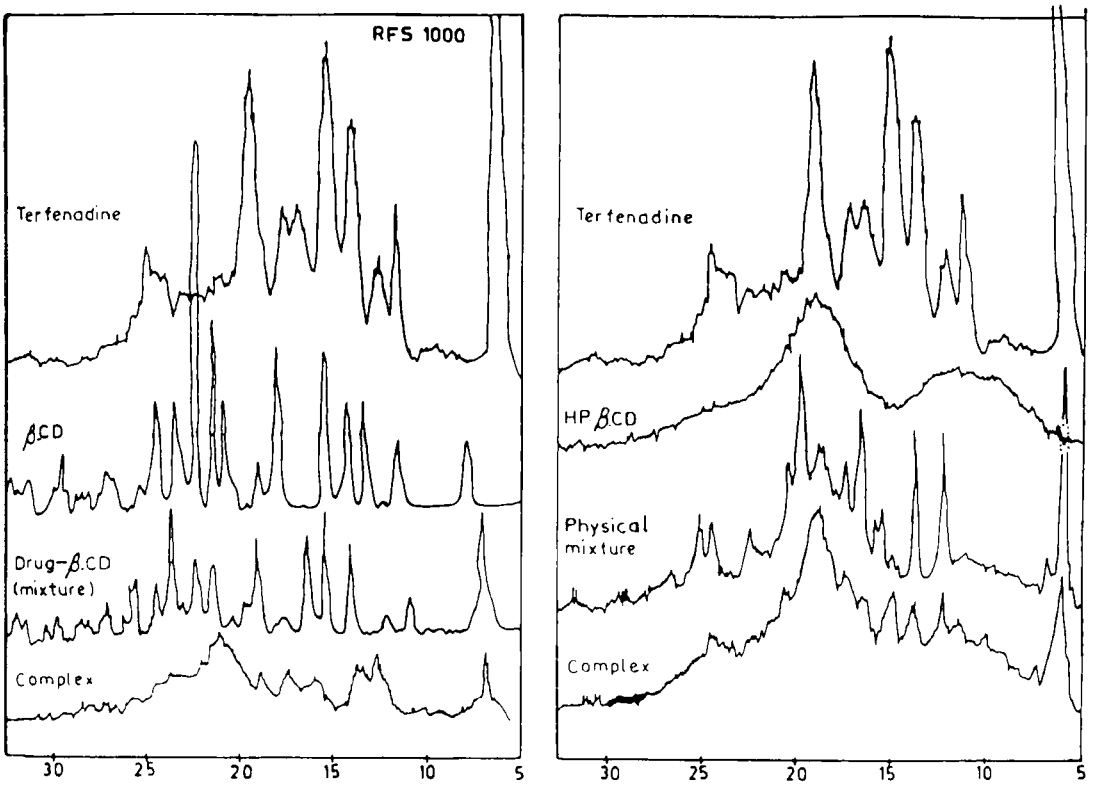

FIG. 2: X-RAY DIFFRACTION PATTERN OF TERFENADINE-CYCLODEXTRIN SYSTEMS

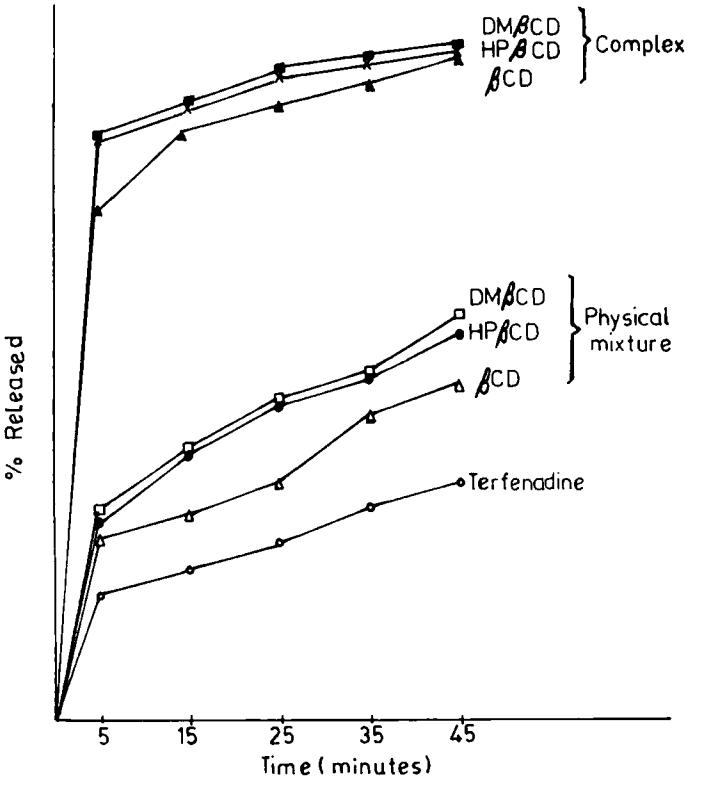

FIG. 3: In Vitro Drug Release Profile

is evident that the thermogram of the physical mixtures are a mere superimposition of both, the drug and cyclodextins. However, in case of inclusion complexes (H), (I) and (J), the endothermic peak of pure drug is shifted to a lower temperature coupled with a decrease in intensity, indicating inclusion complex formation.

2. **X-ray Diffraction Studies**:

From Fig. 2 , the X-ray diffraction pattern of the inclusion complex was found to be diffused and different, confirming that, a new, less crystalline solid phase was formed as compared to the physical mixture. This can be attributed to complex formation.

Table 1: Formulations of Cyclodextrin Complexes

Formulation Ingredients	Pure Drug	Drug: B-CD	Drug: HP B-CD	Drug: DM B-CD
Drug (% w/v)	0.60	2.036	2.25	2.29
Propylene glycol (% v/v)	25.0	20.0	12.0	16.0
Citric acid (% w/v)	0.16	0.10	0.06	0.08
Sucrose (% w/v)	6.00	10.0	16.0	14.0
Sorbitol (% v/v)	8.00	16.0	20.0	12.0
Glycerin (% v/v)	12.0	12.0	15.0	12.0
Invert Syrup (% v/v)	20.0	20.0	20.0	20.0
Water	---------- to 100 ml ----------			
pH	3.14	4.39	4.95	4.60
Viscosity (cps) (at 10 rpm)	70.4	73.6	80.0	76.8
Drug content	99.95	99.86	100.20	99.85
Taste	+	+++	++++	+++++

***In vitro* Dissolution Studies**:

Fig. 3 shows the release profile of various physical mixtures and inclusion complexes. Only 35.02% of the pure drug was dissolved at the end of 45 min, while the release of drug from the inclusion complex was comparatively enhanced. This implies the solubility enhancing effect of cyclodextrins. DM B-CD complexes gave higher t_{90} values as compared to B-CD complexes due to the higher solubility of the former. All physical mixtures gave higher dissolution rates as

compared to the pure drug due to improved wetting of the drug.

Preparation of Liquid Oral:

Propylene glycol and citric acid were used in different combinations to solubilise the drug, as per literature report (1) (Table 1).

It was observed that the amount of propylene glycol required was in the order:

Drug:B-CD > Drug: DM B-CD > Drug: HP B-CD

Also the syrup containing only the drug, without cyclodextrin, had a very low pH due to excess amount of cirtic acid. Also its palatability was poor. The taste masking ability of the formulations were in the order

Drug: DM B-CD > Drug: HP B-CD > Drug: B-CD

All formulations showed acceptable viscosity and drug content.

CONCLUSIONS

The solubility of terfenadine can be improved by forming inclusion complexes with various B-cyclodextrin derivatives. The solubilising effect of 2-hydroxypropyl B-cyclodextrin and dimethyl B-cyclodextrin was higher than B-cyclodextrin itself. Also the taste masking ability of these cyclodextrins substantiate the viability of making inclusion complexes of drugs, where such a palatable effect is desired.