Department of Pharmaceutics[1], College of Pharmacy, Cairo University, Department of Pharmaceutics[2], College of Pharmacy, Alexandria University, Department of Pharmaceutics[3], College of Pharmacy, Suez Canal University, Ismailia, Egypt

Comparative study of some additives for the improvement of terfenadine performance

M. GHORAB[1], A. H. NADA[2], M. M. GHORAB[3] and T. H. HAMMADY[3]

Terfenadine (Tr) is a H_1-blocker antihistamine that is used in the treatment of allergy and hypersensitivity. Its poor water solubility affects its *in vivo* absorption [1]. We now report the implication of interaction of Tr with maltosyl-β-CD (MCD) and hydroxypropyl-γ-CD (HPCD) on improving drug performance in comparison with those achieved via dispersing the drug with PEG 8000, urea and lactose.

Tr solubility was linearly increased as a function of cyclodextrin (CD) concentrations (1–10 mM) assuming the formation of a 1 : 1 molar complex stability constants were calculated to be 4.53×10^3 and 432 mol^{-1} for Tr-MCD and Tr-HPCD, respectively. Also, drug solubility was linearly increased as a function of urea, PEG-8000 and lactose concentration (1–10%w/w).

The Table shows a dramatic decrease in enthalpy for Tr-CD samples prepared with solvent-kneaded technique, giving an evidence for pronounced interaction between Tr and CD, which may be due to the poor water solubility of the drug that limited its interaction with CD when conducting the water-kneaded technique. The Tr-lactose enthalpic data shows a sort of interaction between the drug and lactose, which is more pronounced in samples prepared by co-evaporation. However, Tr-PEG 8000 solid dispersions samples prepared by the co-melt technique manifested a considerable loss of crystallinity compared to that prepared by co-evaporation and that of the physical mixture [2, 3]. Similarly, Tr-urea samples prepared by co-evaporation shows a little reduction in enthalpy than physical mixture. However, it is completely disappeared in that prepared by co-melt, which may be due to the absence of drug crystallinity or the formation of extremely fine crystalline dispersion of Tr in the carrier [4].

Tr samples were prepared as follows: Tr-CD combinations were prepared using the water-kneaded [4] and solvent-kneaded [5] methods. Physical mixtures of Tr and PEG 8000 or urea in a ratio of 1 : 3.5w/w were prepared by heating on a heating mantle up to 120 and 138 °C, respectively, followed by flash cooling of the dispersion by immersion in a bath of dry ice and acetone. The samples were then dried under vacuum at room temperature for 24 h. Co-evaporates samples of Tr with lactose, PEG 8000 or urea were prepared as described before [6, 7]. All samples were then dried and sieved through a 75–125 μm mesh and filled in hard gelatin capsules.

The dissolution rate (using USP apparatus II, 500 ml 0.1 N HCl of pH 1.2, 100 rpm, and at 37 ± 0.5 °C) of Tr-CD complexes show highly significant fast dissolution rates compared to that of free drug. Also, Tr-additives manifested highly significant enhancement of drug dissolution rate versus drug per se. However, the method of preparation had a significant effect on the dissolution rate of such combinations [8].

A method similar to that previously reported by Simons et al. [9] was used to evaluate the prepared complexes in human subjects, which depend on the suppression of the histamine-induced wheals and flares. In this method six healthy human volunteers (4 males and 2 females) participated in this study. Ages ranged from 21 to 58 years (mean 33.3 ± 4.86), and their weights were from 60 to 97 kg (mean 76.3 ± 5.35). The study was conducted in a crossover design. After an overnight fast, each subject ingested with 150 ml water a hard gelatin capsule containing 60 mg plain Tr or its equivalent from the prepared complex, while placebo was α-lactose.

Epicutaneous tests with 0.1 ml histamine diphosphate (1 mg/ml) (Fluka Chemie AG, Switzerland) were performed on the volar surfaces of the forearms. Tests were performed before medication or placebo administration at hourly intervals for 12 h. Wheal and flare circumferences were traced at 10 min with fine-tip black ink per over

Table: DSC data for terfenadine and each of its combinations with the tested additives

Combination	Type	ΔH (J/gm)	ΔH%	Melting range (°C)	Peak temp. (°C)	Peak slope ratio (a/b)
Terfenadine	Plain	−46.68	100	139.5–168.7	154.4	1.00
Tr-malt-β-CyD	P. M.	−10.93	23.4	146.1–156.1	151.8	1.18
(1 : 1 molar)	W. Knead	−9.16	19.6	153.2–157.5	153.4	0.84
	S. Knead	−1.59	3.4	144.4–153.2	147.4	0.66
Tr-HP-γ-CyD	P. M.	−26.30	56.4	143.0–162.1	152.8	0.87
(1 : 1 molar)	W. Knead	−12.17	26.1	147.6–158.7	153.3	1.17
	S. Knead	−6.73	14.4	144.9–156.0	150.3	1.24
Tr-Lactose	P. M.	−74.54	159.7	141.2–161.7	151.9	1.16
(1 : 3.5w/w)	Coevp.	−24.30	52.1	145.2–158.2	151.6	0.68
Tr-PEG8000	P. M.	−31.50	67.5	126.8–146.3	141.3	1.66
(1 : 3.5w/w)	Coevp.	−12.67	27.1	131.5–149.1	143.6	2.35
	Comelt	−5.76	12.3	127.6–147.2	139.9	2.40
Tr-Urea	P. M.	−5.00	10.7	145.6–153.1	150.0	0.78
(1 : 3.5w/w)	Coevp.	−4.31	9.2	141.4–150.4	144.6	0.54
	Comelt	–	–	–	–	–*

P. M. = physical mixture; W. Knead = Water knead; S. Knead = Solvent Knead; Coevp. = Coevaporate.
* No drug endotherm is associated with the thermogram of this comelt

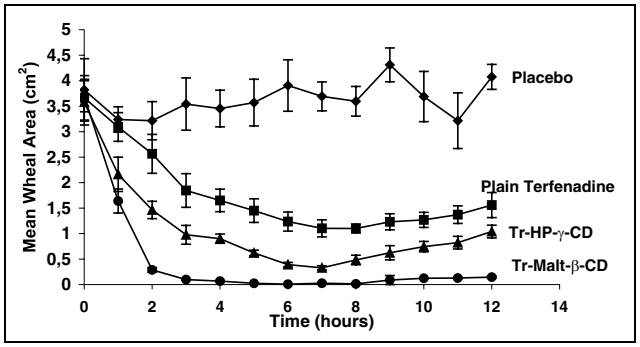

Fig: Mean wheal areas after epicutaneous histamine phosphate (1mg/ml) before and up to 12 hours after single dose of 60 mg terfenadine or its equivalent in prepared products

transport sheets. Wheal and flare area were measured using IBM-PC pen digitizer and an area measurement software (Digital Resource System, British Columbia, Canada).

The histamine-induced wheal and flare areas were analyzed as absolute values and the percent inhibition values were computed [10]. It is clear from the Fig. that treatment with Tr-MCD complex exhibits the most pronounced suppression of the wheal areas, followed by treatment with Tr-HPCD complex than with the drug per se. However, that treatment with Tr-MCD complex induce a highly significant suppression of flare areas, followed by treatment with Tr-HPCD and then Tr. Also the intersubject variability was greatly reduced.

The mean AUC_{wheal} values for treatment with Tr-MCD and Tr-HPCD are significantly higher than that of the drug per se. The maximum percentage of wheal inhibition ($\%WIn_{max}$) for treatment with Tr-MCD and Tr-HPCD exhibits significant increase comparable to that of Tr. Regarding the time for maximum percentage of wheal inhibition (T_{max}), treatment with Tr-MCD induces the shortest T_{max} followed by treatment with Tr-HPCD and than Tr.

That the average AUC_{flare} value following administration of Tr-MCD and Tr-HPCD is highly significant larger than that for treatment with Tr. With regard to the $\%FIn_{max}$ (maximum percentage of flare inhibition) both treatments Tr-HPCD and Tr-MCD exhibited very highly significant difference over treatment with Tr and no significant difference between Tr-HPCD and Tr-MCD. Also, treatment with Tr-MCD manifest the shorter T_{max} followed by Tr-HPCD and than Tr.

In conclusion, complexation of Tr with cyclodextrins may be a promising additive that could be used to improve the biological performance of Tr. Taking in consideration that Malt-β-CD was found to be less toxic than both native cyclodextrins and DM-β-CD [11, 12].

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Mamdouh M. Ghorab, Ph.D.
Department of Pharmaceutics
College of Pharmacy
Suez Canal University
Ismailia
Egypt