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Influence of different solid-dispersion techniques upon the release of dimenhydrinate from chewing-gum formulations

Jaleh Varshosaz*, Jabber Emami, Shirin Hashemi

*Department of Pharmaceutics, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, PO Box 81745-359, Iran. Fax: 0098-311-6680011, E-mail: j_varshosaz@hotmail.com

Abstract

Solid dispersions and physical mixtures of dimenhydrinate (I) in polyethylene glycol 6000 (PEG 6000) and urea were prepared by co-evaporation (or solvent) and fusion-solvent method to increase its aqueous solubility. In contrast to the very slow dissolution rate of pure (I), the dispersion of the drug in the polymers considerably enhanced the dissolution rate. Drug-polymer interactions in the solid state were investigated by differential scanning calorimetry (DSC) and infrared (IR) spectroscopy. By these physical determinations no drug-polymer interactions were evidenced. Finally the solid-dispersions were used in the chewing gum formulations to improve the poor solubility of pure (I) in saliva during mastication. The aqueous dissolution of (I) in chewing gums was favored by the presence of urea. The addition of Tween® 80 as the solubilizing agent to the chewing gum, increased the release of (I) about 20%, whereas it only increased the solubility of pure (I) by 3%. Drug release profiles from the chewing gum formulations were compared with Travvell® Gum as the reference standard. The formulation based on solid-dispersion of (I) with urea and Tween 80 released about 60% of the drug after 60 min with a Higuchi kinetic model.

Key words: Chewing gum, Solid dispersion, Dimenhydrinate, Mastication device, Solubilizer

Introduction

Dimenhydrinale is an ethanol-amine derivative of histamine antagonist, which is used as an antiemetic drug in prevention and treatment of motion sickness and emesis caused by menier sickness and pregnancy (1). Chewing gums could constitute a valuable delivery system to act systemically. They are interesting as an alternative delivery system when considering oral or per oral administration of drug substances since they may offer a number of advantages over conventional tablet administration; convenient and individually controlled release of the active substance, effective buccal drug administration for treatment of local oral diseases or avoidance of first pass metabolism, just to mention a few (2). Medicated chewing gums have been formulated

and commercialized for delivery of a number of various active substances, e.g. nicotine, dimenhydrinate, meclizine, aspirin and xylitol (3). An individual with neausea is often frightened to swallow a tablet and might prefer to take a chewing gum. Chewing may distract him for some time and this may have an impact on the well-known high placebo rate in the effect of an antiemetic drug. But this drug shows poor water/saliva solubility (1) and expected to be released very slowly from chewing gum during mastication and even after 30 min, less than 5% of the drug can be released (2). Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs in general, include micronization (4), surfactants (5) and solid dispersions (6). The last method provides a means of reducing particle size to nearly a molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to the dissolution medium as very fine particles for quick dissolution and absorption. In particular, polymers such as PEG and polyvinylpyrrolione have been extensively used as carriers (7) for dispersions due to their low melting point and their hydrophilic environment. Xylitol and urea are among the other carriers reported for this technique (8). Investigations show that solid-dispersion of some water insoluble drugs like itraconazole in superdisintegrants like Primogel, Kollidon and Ac-Di-Sol also can enhance the dissolution rate and efficiency of the drug markedly (9). The aim of this study was to improve the release rate of (I) from its chewing gums by application of solid dispersion technique. Physical characterization of the dispersions was performed based on IR spectroscopy, microscopy, and DSC (7). The effect of solubilizing agents to increase the release of drug from chewing gums was also studied.

Materials and Methods:

Materials:

Dimenhydrinate was obtained from Dr. Abbiddi's Pharmaceutical Company; Iran, gum base and other additives of chewing gum were generous gifts of Industrial Company of Pars-Minoo, Iran. Sucrose, glycerin, polyethylene glycol, urea, Tween® 80, methanol and ethanol were all from Merck Company, Germany, and aspartam from Chemo Iberica, Switzerland. Other chemicals and reagents were of analytical grade and from Merck, Germany.

Methods:

1. Solid-dispersion preparation: In this study solid dispersions of (I) and water-soluble carriers were obtained by co-evaporation (or solvent) and combined fusion-solvent methods. PEG 6000 and urea were tried as carriers for (I). Physical mixtures of the carriers and (I) were prepared by a proportion of 10, 20, and 40% of the drug in each carrier. They were mixed in a mortar and the mixture was sieved through a 300 μm mesh sieve. The mixtures were then used in preparation of solid-dispersions.

1.1. Solvent method: In the solvent method, the physical mixture of (I) and PEG 6000 or urea was dissolved in a minute quantity of absolute ethanol. Then ethanol was evaporated in a rotary evaporator at 50 °C. The obtained sticky mass was kept in an oven at 50 °C for 24 hrs. The solid mass was crushed, sieved through a 300 μm mesh sieve and stored in desicators.

1.2. Fusion/solvent method: A minute quantity of absolute ethanol was added to the physical mixture of (I) and PEG 6000 or urea, to dissolve them. The solution was then transferred to an oil bath at 60 °C. The temperature was increased from 60°C to 110 °C in a course of 20 min and kept al 110 °C for 10 min. The melt was poured on to cold aluminum plate, and the solid mass obtained after 2 hrs, was handled as described under the solvent procedure.

2. Determination of (I) in the solid-dispersions: An accurately weighed amount of dispersions containing 50 mg of (I) was transferred to a 100 ml volumetric flask which was adjusted with methanol. The diluted samples were analyzed spectrophotometrically (Perkin-Elmer, Type: 2380) at 279 nm against similarly prepared methanolic solutions urea or PEG 6000 as the blank.

3. Thermal analysis: Differential scanning calorimetry (DSC) was performed on solid-dispersion system of 20% of (I) with urea and PEG 6000, prepared by solvent method using a Perkin-Elmer DSC7. Samples (5-10mg) were heated in hermetically sealed aluminum pans with a heating rate 10 °C/min under nitrogen atmosphere.

4. Infrared spectroscopy: IR spectra were obtained by an IR spectrometer (1620 Perkin-Elemr). Samples were prepared in KBr discs.

5. Dissolution rate: A stirring paddle method was used to measure the dissolution rates of the solid-dispersions, the pure (I) and physical mixtures of (I) and PEG 6000 or urea. The dissolution studies were run in 900 ml of distilled water (37 ± 0.5°) with 50rpm speed. At predetermined time intervals 3ml samples were withdrawn and analyzed spectrophotometrically at 275nm. Each time the samples were replaced by 37°C fresh distilled water.

6. Chewing gum manufacturing: The chewing gums were manufactured from common gum ingredients with the use of a conventional mixer. Each piece of chewing gum weighed 1g and contained 20mg of pure (I) (GDM), or its equivalent of a 10% solid dispersion of (I) /PEG 6000 prepared by solvent procedure (GP10), or a 20% solid dispersion of (I) /urea prepared by solvent method (GU20). In each case the amount of pure drug was adjusted to 20mg.

Some chewing gum formulations were prepared by incorporating a mixture of (I) and Tween® 80 as the solubilizing agent (GMDT) (1:1) to obtain a good contact between the drug and the solubilizer. Furthermore, the chewing gum GU20 was prepared with Tween 80 (GUT20). Equivalent amount of the solubilizing agent with the pure drug in the solid-dispersion was used in the chewing gum.

7. Determination of (I) in chewing gum: A piece of chewing gum was cut up and suspended in 20 ml of methanol on a magnetic stirrer for at least 30min. The solution was paper-filtered into a 100ml volumetric flask that was adjusted with methanol. After dilution of 1ml of this solution to 5ml with methanol, the solution was centrifuged at 2000 rpm for 5min and the absorbance of the solution was measured spectrophotometrically at 279nm against a similarly prepared placebo chewing gum as the blank.

8. In-vitro release of (I) from chewing gums: The *in-vitro* release experiments were carried out using a mastication device described in (10). The mastication device was set at 50 cycles/min. The release test was carried out in 0.05M phosphate buffer pH=6.8 (11). The volume of 10 ml dissolution medium was added to the mastication device at zero time, and the mastication lasted 60min. The temperature was fixed at 37° ± 1°C and 1ml samples were collected from the dissolution medium after 5, 10, 15, 30, 45 and 60 minutes of mastication. The dissolution medium was replaced by 1ml of fresh buffer solution. The samples were filtered through a cellulose acetate filter (0.2μm) and after dilution with phosphate buffer were analyzed spectrophotometrically at 276nm. Each time the sample taken from a placebo chewing gum was used as the blank.

Results and discussion:

1. Determination of drug loaded in the solid-dispersions: Table 1 shows the loaded drug percentage in each solid-dispersion formulation. As this table shows the drug was loaded between 83-100% in the solid formulations.

2. IR spectroscopy: IR spectroscopy was employed to study the interaction in solid-dispersions between drug and urea or PEG 6000. As shown in Fig.1a pure (I) shows a sharp peak at about 1800-1600 cm^{-1} which is related to C=O, a peak between 300-600 cm^{-1} related to benzene ring and C=C stretching vibration at 1650-1560 cm^{-1}. IR spectrum of urea is shown in Fig.1b that displays the N-H stretching vibration at 3500 cm^{-1} and C=O peak is seen at 1715 cm^{-1}. The IR spectrum of the physical mixture of drug : urea still shows the peak of N-H stretching vibration of urea at 3500 cm^{-1} and C=O at 1800-1600. (Fig. 1c). This indicates that physical mixture spectra was only the summation of (I) and urea spectra and reflected that there was no interaction between (I) and urea in physical mixtures. As shown in Fig.1d the same stretching vibrations of solid-dispersion of urea : (I) was similar to their physical mixture. The absence of any shift of the carboxyl and N-H stretching bound suggested that no chemical interaction occurs between (I) and urea. Important vibrations detected in the spectrum of PEG 6000 are the C-H stretching at 2890 cm^{-1} and the C-O (ether) stretching at 1110 cm^{-1} (Fig. 2b). Comparing the spectra of solid dispersions of (I) and PEG 6000 (Fig. 2d) and their physical mixtures (Fig 2c), no interaction was shown in the position of absorption bands. The spectra can be simply regarded as the superposition of those of (I) and PEG 6000.

Although it could be expected to have hydrogen bonding between the hydrogen atom of OH of the drug and one of the lon pairs of the oxygen atom in PEG 6000, this could not be demonstrated.

Table 1: Drug loading and dissolution efficiency percentage after 5 minutes (DE_5%) in solid-dispersions of dimenhydrinate (I) (n=3) prepared by different methods.

Formulation (Preparation method)	Code	Drug loaded (% ± SD)	DE_5 % ± SD
Uera+10%(I)(solvent /melt)	UHM10	98.8 ± 1.20	93.3 ± 0.7
Uera+20%(I)(solvent /melt)	UHM20	100 ± 0.81	94.0 ± 0.5
Uera+40%(I)(solvent /melt)	UHM40	92.8 ± 0.1	85.0 ± 0.5
Uera+10%(I)(solvent)	UH10	98.7 ± 2.8	86.1 ± 1.5
Uera+20%(I)(solvent)	UH20	88.2 ± 0.52	99.1 ± 0.3
Uera+40%(I)(solvent)	UH40	94.6 ± 1.34	82.0 ± 2.0
PEG+10%(I)(solvent /melt)	PHM10	100 ± 0.25	90.2 ± 0.9
PEG+20%(I)(solvent /melt)	PHM20	90.6 ± 1.98	90.4 ± 1.4
PEG+40%(I)(solvent /melt)	PHM40	91.6 ± 1.04	81.0 ± 0.6
PEG+10%(I)(solvent)	PH10	85.4 ± 1.11	86.4 ± 1.4
PEG+20%(I)(solvent)	PH20	83.4 ± 2.56	92.5 ± 0.2
PEG+40%(I)(solvent)	PH40	94.8 ± 1.91	96.8±1.5
(I)	DM	-	0.71 ± 2.9
Physical mixture urea + 10%(I)	PMU10	-	83.0±1.8
Physical mixture urea + 20%(I)	PMU20	-	85.0 ± 2.1
Physical mixture urea + 40%(I)	PMU40	-	75.0 ±0.7
Physical mixture PEG + 10%(I)	PMP10	-	79.0 ± 2.7
Physical mixture PEG + 20%(I)	PMP20	-	64.0 ±1.6
Physical mixture PEG + 40%(I)	PMP40	-	69.0 ± 0.3

3. Differential scanning calorimetry: Considering that the best results of the dissolution profiles of the chewing gums related to the formulation containing urea solid dispersion, just DSC thermograms of (I), urea, their physical mixture and solid-dispersions are shown in Fig. 3. (I) showed a melting endotherm at 107 °C (Fig. 3a) while urea showed its melting temperature at 135°C (Fig. 3b). The second and third endotherms at 250° and 360°C are likely related to the recrystalization and deamintion of urea, respectively. The endotherm seen at 250°C exhibited a shoulder on the leading edge that may indicate the presence of more than one crystal form within the sample due to the grinding effect. A similar situation was reported by Mooter et al. (12) and Craig-Newton (13) for PEG 6000. Physical mixture and 20% solid-dispersion of urea: (I) showed both constant melting endotherms at 107°C and 135°C corresponding to the melting point of pure (I) and urea respectively (Fig. 3c, 3d). A slight change occurs in the shape of (I) endothermic peak that appeared broadened and shortened in the solid-dispersion and physical mixture which is related probably to the low concentration of the drug (20%) but indicates that (I) is still present as a crystalline material. The crystalline morphology of the solid-dispersion of urea : (I) prepared by the solvent procedure was confirmed by the microscopic pictures. The fine particles of crystallization in

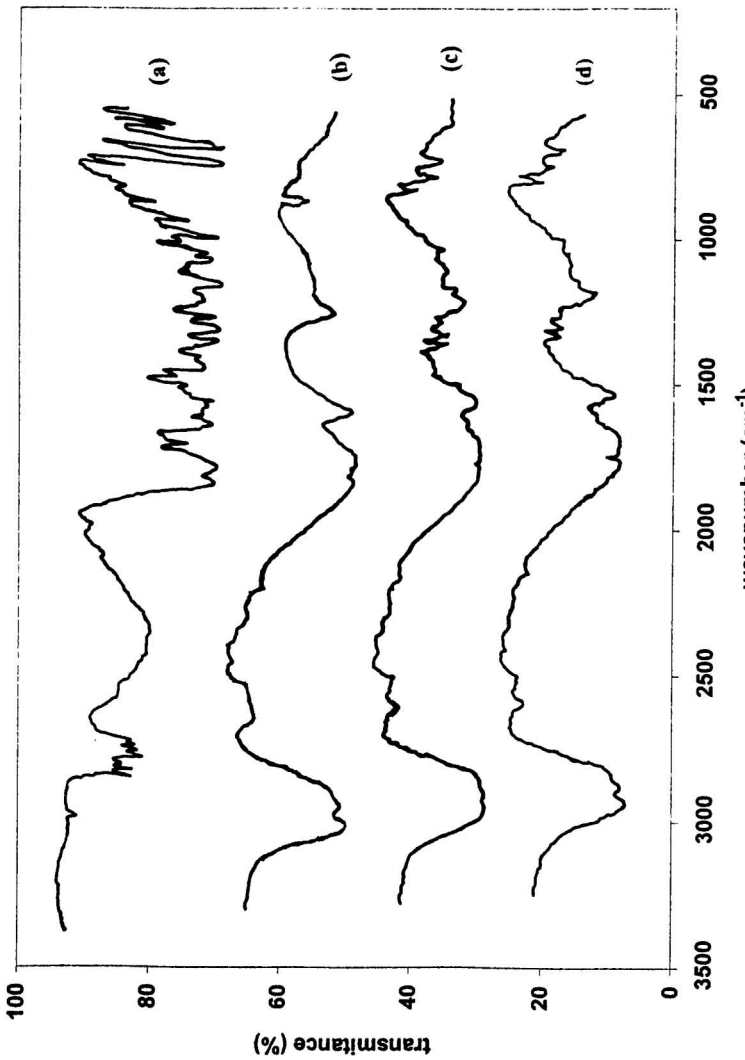

Figure 1: IR spectra of a) pure dimenhydrinate (I), b) urea, c) physical mixture of (I): Urea (20:80; w/w) and d) solid dispersion of (I): urea with the same composition.

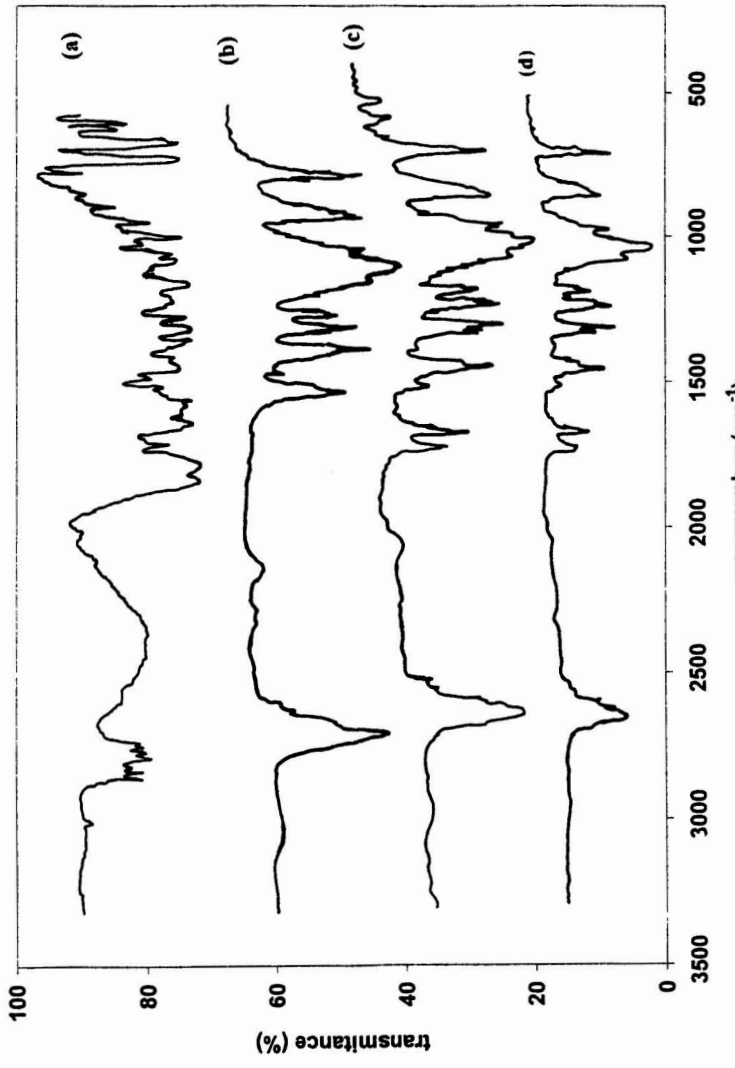

Figure 2: IR spectra of a) pure dimenhydrinate (I), b) PEG 6000, c) physical mixture of (I): PEG 6000 (10:90; w/w) and d) solid dispersion of (I): PEG 6000 with the same composition.

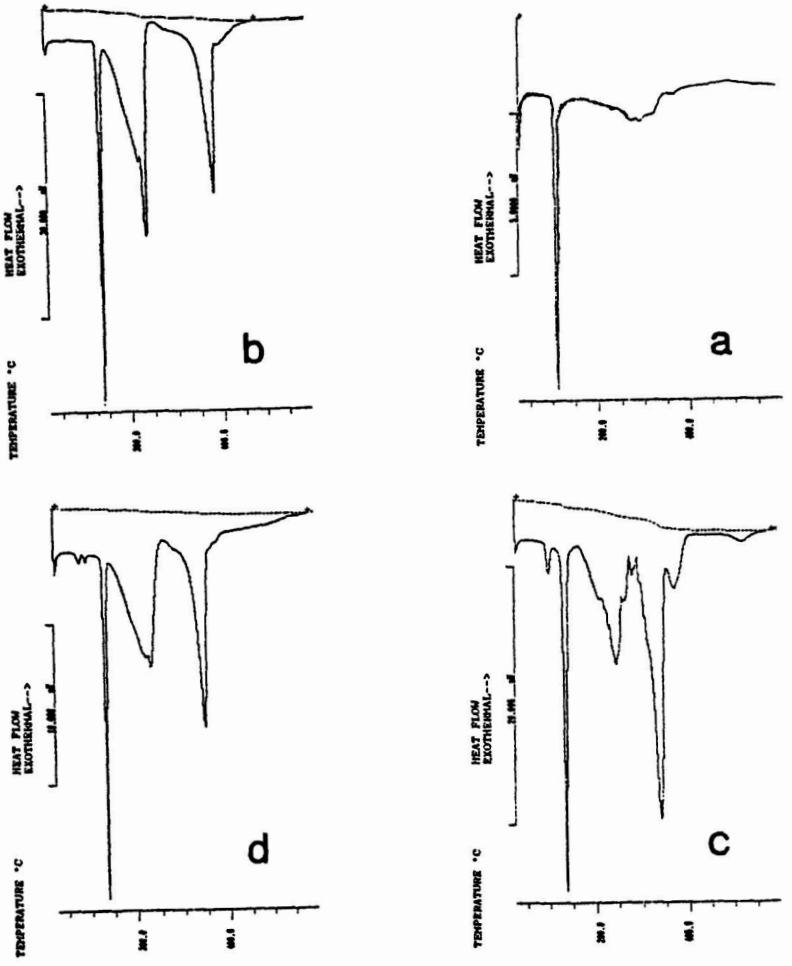

Figure 3: DSC thermograms of a) pure dimenhydrinate (I), b) urea, c) physical mixture of (I): Urea (20:80; w/w) and d) solid dispersion of (I): urea with the same composition

the glassy matrix of urea could be readily detected. Chiou and Rigelman also report the presence of the crystalline structure of the solid-dispersions detected by polarizing microscope (7). In general DSC studies indicated no interaction between (I) and urea or PEG 6000 at the studied concentration.

4. Dissolution studies of solid-dispersions: A stirring paddle method was chosen because it is considered to be the most convenient method to compare dissolution rates of solid dispersions and pure drug and it is widely used (12,14,15). Fig. 4a and 4b illustrates the dissolution profiles of pure (I), its physical mixtures, and solid-dispersions with urea and PEG 6000.

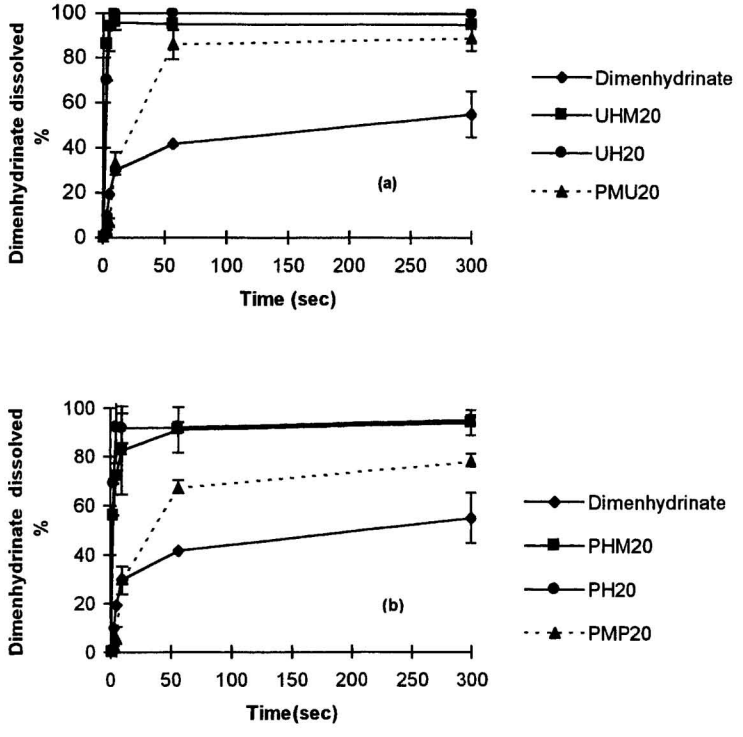

Figure 4: (a) Dissolution profiles of dimenhydrinate, a physical mixture of 20% dimenhydrinate/urea (PMU20) and 20% solid-dispersions of dimenhydrinate/urea prepared by solvent /melt (UHM20) or solvent (UH20) method. (b) Dissolution profiles of dimenhydrinate, a 20% physical mixture of dimenhydrinate/PEG 6000 (PMP20), and 20% solid-dispersions of dimenhydrinate/PEG 6000 by solvent/melt (PHM20) or solvent (PH20) method.

Dissolution efficiency percentage after 5 min ($DE_5\%$) was considered as a basis for comparison of the dissolution rate (16): $DE\% = \frac{\int_0^t y\,dt}{t\,y_{100}} \times 100$. This time was taken because almost all formulations of the solid-dispersions dissolved their content after 5 min. The results are given in Table 1. It is evident that the rate of dissolution of pure (I) is very slow and only shows 0.71% DE compared to 80-100% for different solid-dispersions of (I), and dispersion of the drug in the polymers considerably enhanced dissolution. The difference in dissolution rate of (I)/PEG 6000 dispersions prepared either by fusion/solvent or co-evaporation is negligible, as is the difference between dispersions prepared with PEG 6000 and urea. Similar results have been reported for dissolution rate of different solid-dispersions of temazepam prepared by PEG 6000 and PVP k30 (12). The proposed mechanism for increased dissolution rate from solid-dispersions may be increased wettability and reduction of drug particle size (17). Table 1 shows that increasing the concentration of drug in the dispersions leads to a decrease in the dissolution efficiency ($P<0.05$). Similar findings were reported with solid-dispersions of temazepam-PEG and PVP k30 (12) lorazepam-PEG (18) and ibuprofen-PVP (19). Guyot et al (20) has proposed the formation of a polymer outer layer controlling drug release, formation of a continuous drug layer, or release of intact particles from which dissolution occurs over a large area, are among the reasons for these dissolution profiles. Dissolution efficiency of (I) from its physical mixtures was significantly higher than for the pure drug ($P<0.05$). $DE_5\%$ values for physical mixtures containing 10%w/w of (I) in PEG 6000 and urea reached from 0.71 to 79 and 83% respectively. Dry mixing brings the drug in close contact with the hydrophilic polymer and the increased dissolution rate can thus be explained as a result of increased wettability and dispersibility of (I). Comparing the percentage of drug released in early minutes of dissolution test, shows that physical mixtures of (I) with urea or PEG release between 50-70% of the pure drug while its solid-dispersions release between 90-100% and the difference is significant ($P< 0.05$) (Fig. 4a, 4b). $ED_5\%$ values of the solid-dispersion systems prepared by PEG 6000 and urea by solvent procedure show an optimum at the system containing 10% (I) for PEG and 20% for urea (Table 1). The optimum could be explained as the results of two factors: increased weight ratio of (I) in the solid-dispersion leads to the presence of larger (I) crystals and thus to a decrease in the dissolution rate (Fig. 5). The dissolution rates of the carriers are rate limiting for systems containing a small percentage of (I). To study the kinetic of drug release from different solid-dispersion formulations, the best fitness method was used. Table 2 shows the correlation coefficient (r) and drug release rate constant (k) for each kinetic model. The different r values were studied for their significant difference by ANOVA and LSD post hoc test and the $P< 0.05$ was considered for the difference. According to Table 2, drug release kinetic from physical mixtures of (I) with PEG or urea obeyed a first-order model, while all the solid-dispersion

formulations better fitted with a Higuchi model except in two cases (UHM10 and UHM40) which showed a zero-order release kinetic.

Table 2: The correlation coefficient (r) and release rate constant (k) of release data according to different kinetic models for solid-dispersions of dimenhydrinate with urea and PEG 6000, their physical mixtures and chewing gum formulations. (n=3).

Formulation	Zero-order kinetic $Q=Q_0-Kt$		Higuchi-kinetic $Q=Kt^{1/2}$		First-order kinetic $Q=Q_0\,e^{-kt}$	
	r	k	r	k	r	k
DM	0.965	5.5	0.995	23.83	0.930	-0.024
UHM40	0.996	16.97	0.950	28.65	0.750	-0.058
UH40	0.870	17.7	0.988	30.4	0.645	-0.025
UHM20	0.942	19.5	0.990	40.9	0.888	-0.012
UH20	0.893	15.15	0.987	35.46	0.944	-0.033
UHM10	0.998	20	0.980	45.04	0.692	-0.12
UH10	0.980	15.1	0.999	39.06	0.971	-0.053
PHM40	0.984	11.2	0.999	23.5	0.976	-0.075
PH40	0.880	16.5	0.998	28.40	0.840	-0.021
PHM20	0.866	14.7	0.995	29.41	0.834	-0.062
PH20	0.867	18.7	0.989	32.89	0.506	-0.031
PHM10	0.862	18.3	0.989	33.11	0.561	-0.047
PH10	0.793	17.5	0.995	37.31	0.834	-0.070
PMU40	0.891	1.3	0.969	0.0032	0.999	-0.024
PUM20	0.951	1.4	0.979	0.0080	0.999	-0.036
PMU10	0.940	1.06	0.985	0.0042	0.999	-0.031
PMP40	0.970	1.1	0.950	0.0038	0.999	-0.0104
PMP20	0.909	1.1	0.958	0.0035	0.999	-0.014
PMP10	0.881	1.3	0.962	0.0032	0.999	-0.013
GDM	0.930	1.02	0.998	2.7	0.955	-1.2
GP10	0.912	1.4	0.998	4.6	0.930	-0.03
GU20	0.950	2.4	0.999	5.9	0.950	-0.01
GUT20	0.917	3.3	0.991	8.7	0.903	-0.89
GDMT	0.970	1.3	0.991	3.3	0.946	-0.12

5. Determination of (I) in chewing gums: Under the proposed experimental conditions and at 279nm a linear relationship was obtained between absorbance and concentration of (I) in the test solution over the 0.5-16 μg/ml range, correlation coefficient, r^2= 0.9987, with the intercept close to zero. Pieces of chewing gum were manufactured with known amounts of pure (I). The results are presented in Table 3.

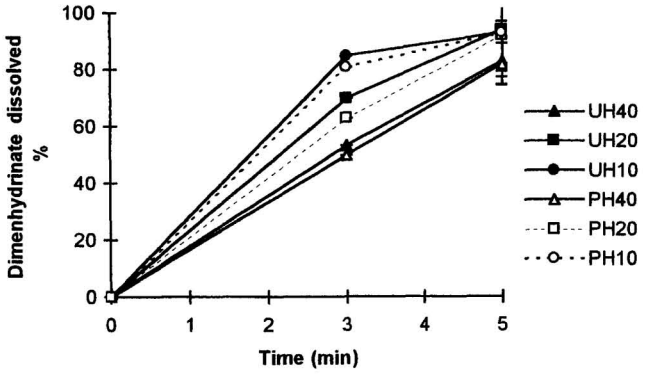

Figure 5: Comparison of dissolution profiles of solid-dispersions of different percentages of dimenhydrinate (10-40%) with urea (U) or polyethylene glycol (P) prepared by solvent method (H) in distilled water (n=3).

Table 3: Recovery and precision data for determination of dimenhydrinate in chewing gum.

Amount added (mg)	Amount found (mg)	Percent recovery of amount added
20.0	19.6	98.0
20.3	20.8	102.5
22.1	23.2	105.0
21.4	20.5	95.8
21.2	20.7	97.6

The recovery and precision data indicate that the method can be satisfactorily applied to the estimation of (I) in chewing gum. The content of (I) in the chewing gum formulations is presented in Table 4. According to this table the contents of (I) in all formulations are almost similar.

Table 4: Content of pure dimenhydrinate (I) and drug release after 60 min from different chewing gum formulations in phosphate buffer pH= 6.8

Formulation	Code	Mean drug content (% ± SD)	CV%	Drug released (%± SD)
Pure (I)	GDM	90.3 ± 1.8	2.0	19.14± 0.11
PEG +10% (I), solvent method	GP10	86.8±5.0	5.8	30.17± 0.05
Urea +20% (I), solvent method	GU20	95.1±1.5	1.6	38.54± 2.45
Urea +20% (I)+ Tween 80	GUT20	93.6±2.1	2.2	58.65± 1.82
Pure (I) + Tween 80	GDMT	91.2±1.3	1.4	22.00± 0.31

6. In vitro release of (I) from chewing gums:

The release profiles of (I) from different chewing gum formulations in phosphate buffer (pH=6.8) are shown in Fig. 6. According to this figure, it is expected that chewing gum containing a 20% solid-dispersion based on urea and prepared by the solvent procedure released the drug faster than both the chewing gums prepared by pure (I) or the solid-dispersion of 10% (I) /PEG 6000. However to improve the release of the drug from chewing gum GU20, a solubilizing agent (Tween 80) was added to the formulation and to compare its effect on the solid-dispersion used in the chewing gum, the same amount of Tween 80 was added to the GDM. As it can be seen from Fig. 6, adding the solubilizing agent to the chewing gum containing (I) causes a significant 20% GDM just about 3% (Fig. 6).

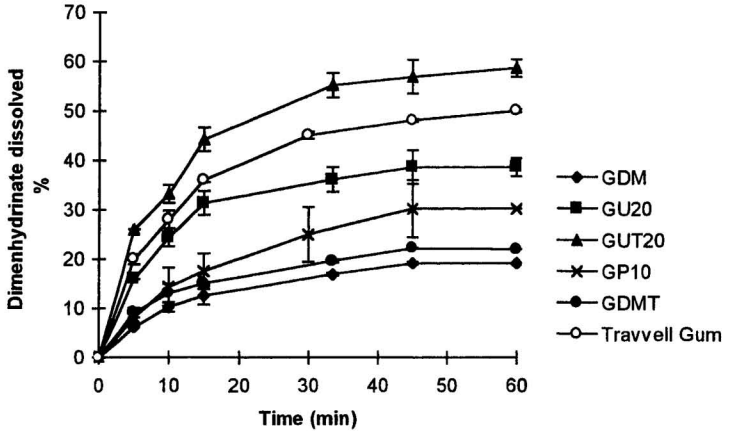

Figure 6: Dissolution profiles of different chewing gum formulations in phosphate buffer solution (pH= 6.8) containing pure dimenhydrinate (I) (GDM), (I)+ Tween 80 (GMDT) or solid-dispersions prepared by solvent method, of (I) : PEG 6000 (10: 90; w/w) (GP10), (I): Urea (20:80; w/w) (GU20), or (I): urea (20:80)+ Tween 80 (GUT20).

The results of the study on the miconazole chewing gums show that the gums prepared from pure drug has only 1.5% release, while the formulations prepared from solid-dispersion of the drug with PEG 6000, xylitol and PVP 40000 release about 30.8, 10.2 and 14.6, respectively (21). The percentage of nystatin released from its chewing gum has been reported 1.4% while including the solubilizing agents like polyoxyethylene glycol trihydroxy stearate 40, Tween 60 or monoglyceride diacetyl tartrate to the chewing gum increased the drug release to 71.5, 70.4 and 95.0, respectively

(22). It seems that the effect of solubilizing agent in the (I) chewing gums can not be explained by its ability to increase the solubility of (I) but may also be seen as a result of the manufacturing process, and the presence of urea promotes its solubilizing effect. In general, it may be concluded that the addition of the solubilizing agents accompanied with the use of solid-dispersion of the insoluble drugs is a valuable method to increase the release of these drugs from their chewing gum formulations.

The dissolution data obtained from the chewing gum formulations were studied by different release kinetic models. The results are shown in Table 2. According to this table, the Higuchi model better fits the drug release profiles from all the studied formulations.

The percentage of drug release from the formulation GUT20 and Travvell® Gum after 60 minutes were about 60 and 48% respectively, which was significantly higher for GUT20 ($P< 0.05$). The composition of Travvell® Gum is: 10mg (I), 3mg aspartam, 2mg sodium saccharin, 10mg glucose, 285mg sorbitol and 406mg gum base. This formulation contains as much as 28 fold sorbitol more than our formulations, which probably causes a higher and better dissolution profile than all tested formulations except GUT20. This is perhaps related to the hygroscopic properties of this substance, which causes better wetting of the chewing gums in the dissolution medium and faster release of (I). The apparatus for *in vitro* drug release testing of medicated chewing gums is very important and perhaps if the device used by Kvist et al (3, 23) was used for release testing of the chewing gums, the higher percentage could have been obtained than 60% for GUT20, because the Travvell gum which showed about 50% by our apparatus showed about 80% release by their mastication device. Some other *in vitro* dissolution chewing apparatuses have been used so far but no international standards have been set for controlled release of medicated chewing gums (10, 24-28). Anyway, pharmacopoeia guidelines state that in general, solid oral dosage forms in which absorption of the drug is essential for the therapeutic effect should be tested for *in vitro* drug release to guarantee the biopharmaceutical quality of the product (29, 30). The apparatus used in this study for *in vitro* drug release testing from chewing gums has been shown to be proper to compare different formulations just from a rank order point of view and its usefulness should be checked for *in vivo/ in vitro* correlations.

Conclusion:

As a conclusion, in this paper we showed the increased dissolution rate of (I) when dispersed in PEG6000 and urea. Solid-dispersions demonstrated a higher dissolution rate than physical mixtures. Drug release kinetic from solid-dispersions better fitted with a Higuchi model while the physical mixtures released the drug with a first-order kinetic. The increased dissolution rate in systems of urea was probably the result of increased wettability and dispersibility of (I), since IR

and DSC could demonstrate no interactions in the solid state. The chewing gums prepared by solid-dispersions proved to be superior in drug release rate than formulations prepared from pure (I). The addition of a non-ionic surfactant Tween® 80 increased the release of (I) from chewing gums. Further improvements of (I) chewing gums are currently under investigation. *In vivo* release experiments form the proposed formulation are planned in the near future.

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