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EMPLOYING COMPRITOL IN A MIXED MATRIX FOR SUSTAINING CHLORPHENIRAMINE MALEATE RELEASE: KINETIC STUDY

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An investigational study aimed for studying the effect of compritol ATO888 (compritol) on the release of chlorpheniramine maleate (CPM) from hydrophilic matrix (HPMC) was conducted. Matrix tablets were manufactured by direct compression using different compritol -HPMC blends. The release kinetics showed anomalous release mechanism. All the tested matrices containing compritol showed an increase in the release of CPM when compared with tablets contain HPMC only. The results revealed that controlling the speed of water soluble drug CPM release from a hydrophilic polymer HPMC can be obtained through designing a mixed hydrophilic lipophilic matrix using compritol. Compritol showed the ability to affect the water uptake of the matrix. Also, compritol was found to affect the relaxation of HPMC. For matrix containing 50% mixture of HPMC and compritol, the contribution of compritol in 17.5 to 25% of this part will result in a suitable release.

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1. Introduction

Behinates has been used as a lubricant in tablet production [1]. Compritol ATO 888 (compritol) has been used for coating oral sustained-release dosage forms [2,3]. Increasing the amount of compritol led to prolonged drug release profile [4]. Compritol (glyceryl behnate) has been used for sustaining the release of drugs from dosage forms. The HLB value of compritol is 2, with a low melting point 71.3°C [5]. Compritol is a mixture of mono-, di-, and tribehenate of glycerol. Depending on many parameters such as crystallization rate or temperature of storage, compritol is known to exhibit a complex polymorphism [6,7]. The lattice structure of Compritol crystals composed usually of very small amounts of the unstable alpha polymorphic form characteristic of triacylglycerols that disappear after thermal stress [8].

Chlorpheniramine maleate (CPM), a low molecular weight organic compound, was used as a model drug. CPM has been used extensively as an antihistamine for symptomatic relief of the common cold and allergy, CPM is typically administered 2 to 3 times daily [9]. CPM has high solubility, 160 mg/ml [10]. The absolute bioavailability from oral solution (10 mg) was 59 and 34%, and from tablets (8 mg) 44 and 25%, respectively, indicating extensive gut first-pass metabolism [11].The relatively small daily dose, undesirable side effects and rapid absorption from the GIT make CPM a good candidate for formulation in a sustained release dosage form. The hepatic first pass metabolism of the drug [12] may discourage the sustaining of its release.

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However, it has been found that, this metabolism is linear as revealed by the bioequivalence of a sustained release dosage form [13]. This linearity does not hinder the formulation of CPM in sustained release dosage form.

The performance of matrix tablets is strongly dependent on the matrix materials used,

which are normally synthetic or semi-synthetic polymer [14]. Semi-synthetic polymers include cellulose ethers such as hydroxypropyl cellulose (HPC), methylcellulose (MC),

hydroxypropyl methylcellulose (HPMC) and sodium carboxy methylcellulose (Na CMC) [15]. According to the used polymer properties, drug release from matrix tablets may be swelling-controlled, erosion-controlled, multiple mechanism controlled.

Moreover, drug release from matrix tablet depends on other factors such as pore permeability, shape and size of matrix, drug solubility, polymer molecular weight, drug

loading, compression force and hydrodynamic conditions [16,17]. Release characteristics affected by compression force and porosity [18]

Drug solubility, hydrophilicity of the polymer and tablet porosity determines the rate of liquid penetration into the tablet [19], so that drug release rate will be affected. The initial wetting of the surface of matrix, hydrophobicity of the drug, amount as well as type of polymer affect its swelling [20]. Khan and Maheshwari prepared CPM using combination of different grades of HPMC, HPMC K4M, HPMC K15M and HPMCK 100M [21]. Also, CPM sustained release tablet prepared by hot-melt extrusion containing Chitosan and xanthan gum as matrix materials was also reported [22].

The aim of the present study is to investigate the potential of using compritol as a lipophilic component with HPMC to form a mixed hydrophilic lipophilic matrix to affect behaviour of CPM as a water soluble drug for sustaining its release.

2. Material and Methods

2.1. Materials

Chlorpheniramine maleate (CPM) was generously obtained from Egyptian Pharmaceutical International Company (EPICO), Egypt. Hydrxypropylmethyl cellulose (HPMC K15M) was purchased from Dow Chemical Company, Midland, Michigan, USA. Compritol® ATO888 (Gglyceryl behenates) was purchased from Gattefossé (Saint Priest, France). Magnesium stearate and hydrochloric acid were obtained from Riedel-de-Haen AG (Seelze-Hanover, Germany). All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Preparation of CPM matrix tablets

Matrix tablets weighing 150 mg and containing CPM (10 % w/w) were prepared by direct compression. Components of each matrix formula as shown in Table 1 were mixed in turbula mixer (type S27, Erweka, Apparatebau, Germany) for 15 min. Finally, the powder was compressed into tablets by an instrumented multiple press rotary tablet machine (Rotab T, kg pharma, Berlin, Germany) using 7 mm diameter, round, flat, and scored punches. Tablets hardness was kept within the range of 4-6 kp.

Table 1. The ingredients of various formulations of CPM matrix tablet.

Formula	Ingredients (%w/w)					
	CPM	Avicel PH102	Compactol	Compritol	HPMC K15M	Mg-Stearate
F1	10	44.5	44.5	-	-	1
F2	10	19.5	19.5	50	-	1
F3	10	19.5	19.5	-	50	1
F4	10	19.5	19.5	25	25	1
F5	10	19.5	19.5	12.5	37.5	1
F6	10	19.5	19.5	37.5	12.5	1
F7	10	19.5	19.5	16.7	33.3	1

2.2.2. Tablet evaluation

Tablet hardness tester (type TBH28, Erweka, Apparatebau, Germany) was used to study the hardness of matrix tablets. The results of ten measurements was listed in table 2 as the mean values ± SD.

The friability of 20 tablets were measured using Roche friabilator (type TA3R, Erweka, Apparatebau, Germany) and the mean values was listed in Table 2.

Weight uniformity test of 20 tablets was carried out according to BP limits and the results were listed in Table 2.

Table 2. Physical properties of CPM Extended release matrix tablets (Mean± SD)

Formula	Weight (mg)	Thickness (mm)	Hardness (Kp)	Friability (%)
F1	151.5±2.17	2.71± 0.01	4.24±0.50	0.40
F2	143.1±1.10	3.17±0.03	5.51±0.28	0.35
F3	139.2±1.14	3.94±0.02	2.58±0.16	0.87
F4	150.2±1.75	3.13±0.04	5.36±0.17	0.43
F5	147.9±1.20	3.25±0.03	4.36±0.21	0.50
F6	151.6±1.17	3.25±0.07	5.43±0.23	0.99
F7	136.6±1.15	2.92±0.25	4.16±0.33	0.76

2.2.3. In-vitro release studies:

The release of CPM from the prepared matrices was carried out in phosphate buffer pH 6.8 using the USP apparatus II (Caleva Ltd., Model 85T). In brief, 900 ml of the buffer was equilibrated to 37±0.5°C at 50 rpm attached to an IBM computer PK8620 series with PU 8605/60 dissolution test software where samples withdrawn automatically with Watson-Marlow peristaltic pump lined to Philips VIS/UV/NIR single beam eight cell spectrophotometer Model PU 8620.

An accurately weighed CPM tablet of each of the prepared formulations was added to each flask. Samples were withdrawn at pre-determined time intervals for 8 hours. For each formula, release runs were performed in triplicate and absorbance was recorded automatically at 265 nm. The cumulative percentage of drug released was determined as a function of time.

2.2.4. Release analysis:

The released CPM was fitted as the fraction of total released (M_t/M_∞) with time t according to different model equations. The best model fitting represent the mechanism of drug release. The following are the used models

2.2.4.1. Zero order

$$M_t/M_\infty = k_0 t \quad (1)$$

Where k_0, is the zero order rate constant

2.2.4.2. First order

$$M_t/M_\infty = 1- \exp^{(-k1t)} \quad (2)$$

Where k_1, is the first order rate constant

2.2.4.3. Higuchi diffusion model

$$M_t/M_\infty = k_h t^{1/2} \quad (3)$$

Where k_h, is the Higuchi diffusion rate constant

2.2.4.4. Peppas and Korsemayer model

$$M_t/M_\infty = k_p t^n \quad (4)$$

Where k_p is the release rate constant at the elapsed time *t, n* is a constant, where the value of $n \leq 0.45$ indicates Fickian diffusion, $0.45 \leq n \leq 0.89$ indicates non-Fickian (anomalous) diffusion, $n = 0.89$ indicates case-II transport (erosion control and zero-order kinetics), and $n \geq 0.89$ indicates Super Case II transport [23].

2.2.4.5. Weibull model

The effect of compritol lipophilicity on drug release from HPMC containing matrices was studied through fitting the released data to the weibull distribution (Eq. 5)

$$M_t/M_\infty = 1 - \{\exp - [(t - t_0)/\tau]^\beta\} \quad (5)$$

Where t_0 is the lag time, τ is the mean release time when 63.2% of M_∞ CPM has been released and β is the shape parameter of the release curve[24,25].

2.2.4.6. Peppas and Sahlin model

The following equation (equ. 6) was applied to estimate the release of CPM through a diffusion/relaxation HPMC matrix system

$$M_t/M_\infty = k_d t^m + k_r t^{2m} \quad (6)$$

Where, k_d is the diffusional constant, k_r , is the relaxational constant and, *m,* is the diffusional exponent which depends on the geometrical shape of the releasing matrix[26].

2.2.4.7. *Water uptake studies*

The mechanism and the rate of water uptake was calculated using (equ. 7) of Davidsons and Peppas model [27]

$$w = k_s t^n \quad (7)$$

where *w, is* the weight gain of the swelled matrix (water/dry polymer); k_s the kinetic constant of water penetration; *t is* the penetration time and *n* is the exponent which depends on the water penetration mechanism.

All equations were fitted using the MULTI computer program with little modifications, the criteria for judging the best fitting includes the examination of the predicted curve fitted to the data, and the sum of the squared residuals (SSR), as well as comparison of the Akaike's information criterion (AIC) [28]. The AIC can be calculated using the equation 8 and SSR using equation 9

$$AIC = n[\ln(SSR)] + 2p \quad (8)$$

$$SSR = \Sigma\Sigma W_{ij}(C_{i,j} - f(t_j,P))^2 \quad (9)$$

Where *n*, is the number of experimental points, and p, is the number of parameters to be estimated.

3. Results and discussion

Table 1 illustrates the composition of the different prepared matrices.CPM matrix tablets were manufactured by using different compritol- HPMC blends of that represents 50% of tablet weight with a constant amounts of avicel PH 102 and compactol and magnesium stearate composing the other 50% for the aim of producing tablets with good organoleptic properties. Table 2 depicts the physical properties of the prepared matrices. Comparing the physical properties of F2 (50% compritol) and F3 (50% HPMC) in matrices the mean weight was higher in case of F2 (143.1 mg) than F3 (139.2 mg) reflecting higher density in case of compritol at the same time the lowest thickness was for F1 (control tablet without HPMC or compritol, 2.71 mm) although the compression conditions were the same for all, each of F2, F3 showed increased thickness (3.17, 3.94 mm, respectively) and hardness (2.85 and 5.36 kP, respectively). The increased thickness reflects a relaxation after compression. Partial substitution of HPMC with compritol will obtain mixed matrices having hydrophilic lipophilic properties. Although there are no correlation between the percent compritol added and thickness, all mixed matrices show decreased thickness than that containing HPMC only. This reflects also that the concentration of the added compritol is not homogeneously affecting the elastic relaxation of HPMC after compression. At the same time compritol was found to increase the hardness of HPMC matrices. Generally all formulations showed accepted hardness and friability.

3.1. Release studies

The release profiles of CPM from the prepared matrices are presented in figure 1. The results revealed a complete release reaching 100% of CPM from matrix containing compritol only after 8 hrs; however matrix containing HPMC only reached 73.71% at the same time. Looking to the release after 6 hrs, it is clear that displacing part of HPMC in the matrix with compritol increases the release rate of CPM from matrices to be 70.96, 62.74, 60.59, 57.08% for F4, F6, F7 and F5 respectively. The same ranking appears after 8hrs but with a decrease in release of CPM from F5 (58.58%) compared to F2 (62%). Using fluorescine, Pham and Kee [29] noticed that the presence of a highly water-soluble compound, in a HPMC matrix generates an osmotic gradient, leads to a faster rate of polymer swelling with a large increase in gel thickness. As a result of exposing the polymer to solvent, an enhancement in the mobility of the polymer chains occurs. This causes gradual transformation of a glassy matrix to a rubbery swollen gel. As the polymer loading increases, the gel matrix viscosity increases resulting in a decrease in the effective diffusion coefficient of the drug [30]. Other factors such as differences in water penetration rate, water absorption capacity and polymer swelling may also contribute to the differences in drug dissolution profile as a function of changes in total polymer concentration [31].

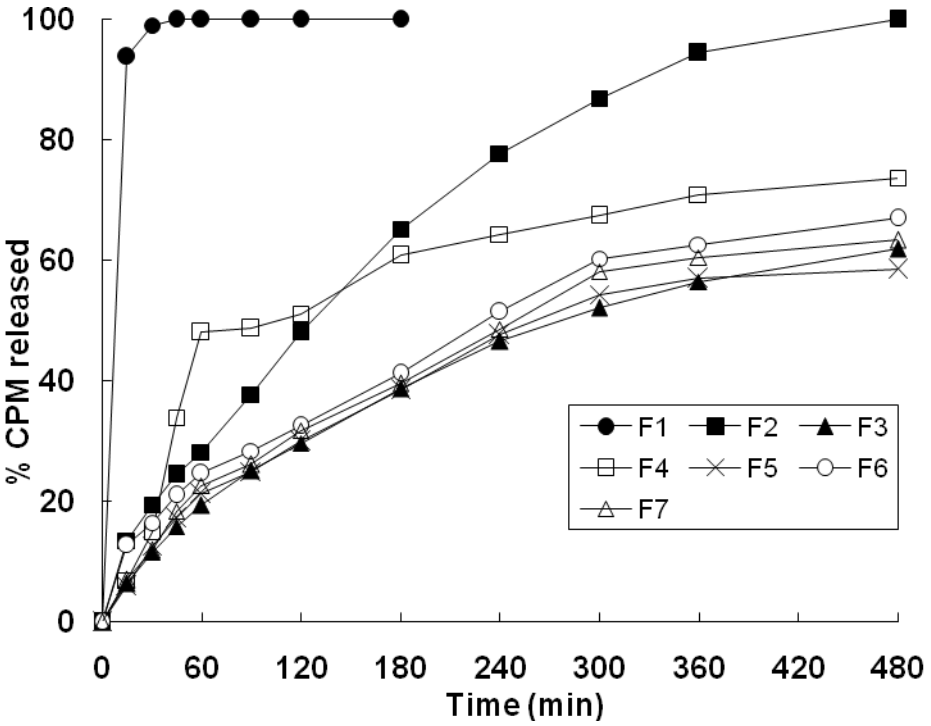

Fig 1: Release profile of CPM from the prepared matrices

Incorporation of varying concentrations of compritol with HPMC (F4, F5,F6 and F7) increased drug release. This may be attributed to increased penetration of the solvent molecules in the presence of the hydrophobic polymer, leading to enhance drug diffusion from the matrix.

According to penetration theory, when a matrix is composed of a water-soluble drug and a water-insoluble polymer, drug release occurs mainly by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network [32, 33].

As drug release continues, the interconnecting clusters increase the pore network through which interior drug clusters can diffuse with more compritol particles present, then fewer clusters of soluble drug are formed. In this case, a finite drug clusters should remain which appear statistically plausible.

Incorporating compritol with HPMC increased drug release rate relative to its increase, combined with decreasing HPMC. This result may recommend that the large hydrophobic molecules of compritol impose a discontinuity in the gel-structure of HPMC leading to formation of a weaker barrier than in matrix containing HPMC gel alone [21].

3.2. Release kinetics

Table 3 represents the fitting data of CPM according to zero order, first order, Higuchi diffusion model and Korsemayer Peppas model. According to n of Korsemayer Peppas, it is clear that CPM release follow the anomalous mechanism (Higuchi + other mechanism). This finding could be observed for all formulae containing compritol concentrations except that of 25% where equality in the amount between compritol and HPMC, the mechanism appears Fickian diffusion this result is strengthen with the lower AIC value in the Higuchi model fitting.

Table 3: Calculated kinetic parameters according to different models

% compritol*	formula	Zero order			First order		
		k_0	SSR	AIC	k_1	SSR	AIC
100%	F2	0.00305	0.1029	-20.741	0.00607	0.0114	-42.764
75%	F6	0.00207	0.0809	-23.14	0.0032	0.0289	-33.453
50%	F4	0.00259	0.3486	-8.538	0.00539	0.1138	-19.731
33%	F7	0.00198	0.0528	-27.403	0.00295	0.014	-40.697
25%	F5	0.00188	0.0506	-27.838	0.00275	0.0157	-39.558
0%‡	F3	0.00186	0.4186	-6.709	0.00266	0.0119	-42.286
% compritol*	formula	Higushi model			Peppas and Korsemayer model			
		k_h	SSR	AIC	k_p	n	SSR	AIC
100%	F2	0.04728	0.03198	-32.426	0.02164	0.647	0.003707	-51.975
75%	F6	0.03256	0.00414	-52.86	0.0249	0.551	0.002469	-56.04
50%	F4	0.04213	0.06599	-25.181	0.06409	0.42	0.056802	-24.682
33%	F7	0.03081	0.01001	-44.041	0.01658	0.617	0.00217	-57.33
25%	F5	0.02933	0.00804	-46.234	0.01647	0.609	0.001779	-59.312
0%‡	F3	0.02868	0.00811	-64.152	0.01523	0.619	0.000938	-65.715

* , percent ratio of compritol with HPMC

‡, 100% HPMC

k(s), represent the rate constant of the model

N. B. Compritol and HPMC represent 50% of tablet weight.

Table 4: Calculated kinetic parameters of Weibull model (Effect of compritol lipophilicity)

% compritol*	formula	Weibull functions			
		τ	β	SSR	AIC
100%	F2	163.7	1.0507	0.010551	-41.515
75%	F6	644.2	0.5247	0.050052	-25.947
50%	F4	213.8	0.6233	0.040544	-28.054
33%	F7	390.9	0.7843	0.002266	-56.897
25%	F5	435.4	0.7636	0.001296	-62.482
0%‡	F3	448	0.7734	0.000152	-83.935

* , percent ratio of compritol with HPMC

‡, 100% HPMC

Table 4 presents the Weibull model fitted parameters for the release data. Langenbucher [24] and Carstensen [25] employed the Weibull distribution for the study of drug dissolution process from different dosage form. In the present study, the Weibull distribution equation 5 was applied to investigate the role of compritol lipophilicity upon addition to HPMC on the shape parameter β, Table 4. The results showed that β parameter increases with decreasing compritol from 75% with HPMC to 0%, where, all having the same mechanism of release. These results appear in agreements with Dredán et al. [35], who found that β values increased significantly by decreasing the proportion of the lipophilic excipient.

Table 5: fitted data of Peppas and Shalin model (equation 6)

Formula	% HPMC	k_d	k_r	m	AIC	SS
F2	0	0.0312	0.003288	0.4382	-46.848	0.00507
F3	100	0.00707	0.011293	0.3277	-61.862	0.00113
F5	75	0.00810	0.011532	0.3265	-56.275	0.00197
F7	66	0.00863	0.011703	0.3294	-54.651	0.00232
F4	50	0.03775	0.017261	0.2945	-21.130	0.03367
F6	25	0.03162	0.002989	0.3959	-56.359	0.00196

k_d, k_r are the diffusional and relaxation constant
m is the diffusion exponent of the model

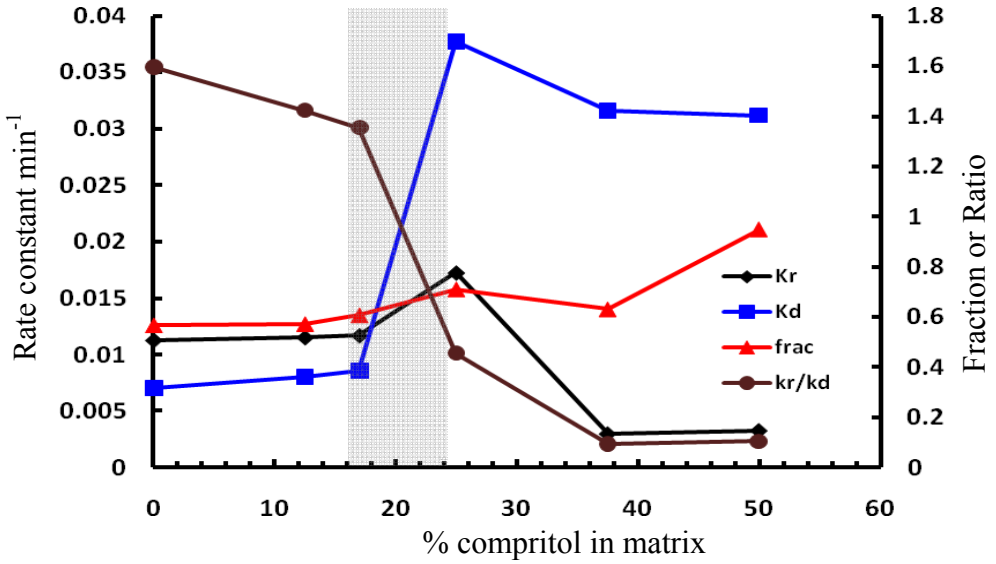

Fig. 2. Effect of compritol concentration on k_r and k_d and k_r/k_d ratio as well as the fraction of CPM released.

To study the release data, empirically, a non linear regression of the Higuchi's model as well as of Korsmeyer and Peppas-Sahlin was applied. Values for kinetic constants indicated that CPM release is faster from matrices containing compritol , where k_h is the lowest in the absence of compritol. There were a linear relationship between the fraction of dose released (frac) after eight hours and the percent compritol (P_{com})[frac= 0.006 X(P_{com}) + 0.513] with a correlation coefficient r= 0.8289, Fig. 2 .

Values of diffusion exponent 0.551 < n < 0.647 (Korsmeyer Peppas equation) for release of CPM correspond to anomalous diffusion mechanism. This anomalous mechanism of diffusion reflects a diffusion relaxation of the polymer chain effect.

In accordance with the aspect ratio obtained for all formulations, values of 0.3265 <m< 0.4382 were found appropriate to be used in Equation 6 . The results obtained are shown in Table 5. The model can identify the different contribution of the relaxation mechanism and of the diffusive mechanism. The values obtained for k_r were lower than k_d for all the dissolution profiles.

Figure 2 represents the effect of compritol concentration on k_d, k_r and the ratio k_r/k_d. It is clear that at higher compritol concentration, k_d value appears higher, however k_r appears lower. At the same time, the ratio of k_r/k_d appears decreasing in a sigmoidal shape. The decrease in the relaxation rate will give the chance for more clusters of drug to release.

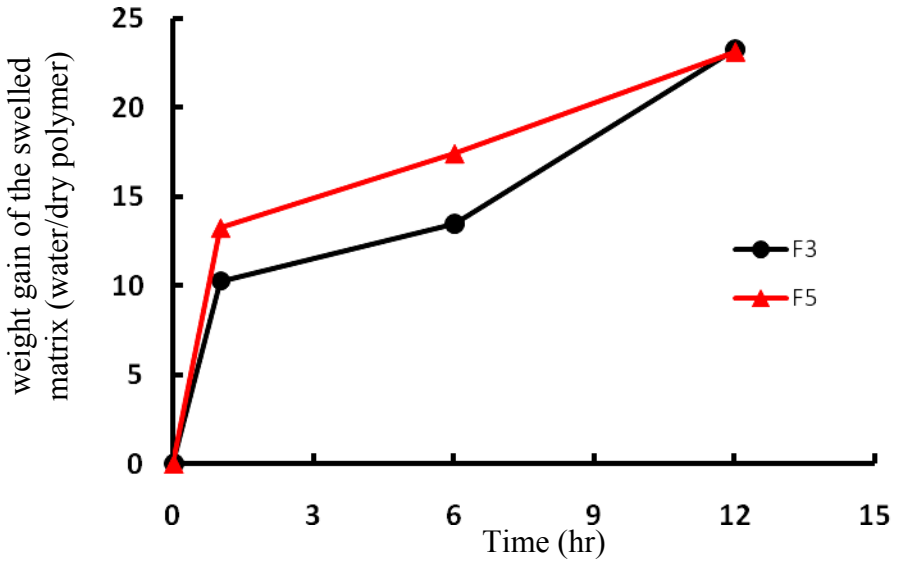

Fig. 3. Water uptake profile by F3 and F5

To investigate the effect of compritol on the uptake of water by matrices, two formulae were selected, namely F3, where no compritol was added (100% HPMC) and F5, where 25% of HPMC displaced with compritol. Figure 3 shows the rate of water uptake of the selected formula. It appears clearly that in presence of compritol the rate of water uptake is higher. Table 6 represents the fitted parameters of Davidsons and Peppas [27] equation. The kinetic constant of water penetration, k_s, increased by about 50% in presence of compritol. In addition, n may reflect a fikian penetration mechanism. This result strengthens the release data that is as water uptake rate increases, the release rate will increase.

Table 6: Fitting parameters of Davidsons-Peppas models (equation 7)

Formula	K_s	n
F3 (100% HPMC)	8.453	0.374
F5 (75% HPMC)	12.595	0.228

According to Figure 2 the inflection of the ratio k_r/k_d from high to low values lies between 17.5 and 25% this area (the gray area) appears the suitable compritol concentration for a suitable hydrophilic lipophilic matrix for CPM sustained release.

4. Conclusion

Controlling the speed of water soluble drug CPM release from a hydrophilic polymer HPMC can be obtained through designing a mixed hydrophilic lipophilic matrix using compritol. Compritol showed the ability to affect the water uptake of the matrix. Also, compritol was found to affect the relaxation of HPMC. For matrix containing 50% mixture of HPMC and compritol, the contribution of compritol in 17.5 to 25% of this part will result in a suitable sustained release.

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