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Effect of the wettability characteristics of polyethylene glycol derivatives on the drug release of wax matrices

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The purpose of the present work was to study the relationship between the physicochemical characteristics of different polyethylene glycol aqueous solutions and the kinetics of potassium chloride release from wax matrix samples containing polyethylene glycol derivatives. Potassium chloride was embedded into thermosoftening matrix material to produce a sustained-release dosage form. Potassium chloride release was measured by the rotating paddle method of USP 23 and the dissolution process was characterized by a modified Nernst equation. Physicochemical characteristics – surface tension, dynamic contact angle, viscosity – of the polyethylene glycol aqueous solutions were also determined. The results indicate that the adhesion tension of surfactant containing aqueous solutions has a decisive impact on the prediction of the potassium chloride release rate from wax matrices.

1. Introduction

Drug release from solid dosage forms, based on the disintegration and dissolution process, is a determining factor in the bioavailability of drug products [1]. The successful dissolution of matrices necessitates the penetration of the liquid into the pores of the dosage form. The liquid penetration involves interfacial interactions based on adhesion and spreading of the surfactant containing molten wax mass over the substrate surface. The surface tension and contact angle of surfactant solutions have a decisive impact on these interfacial processes [2–5].

Polyethylene glycols and their derivatives are widely used excipients (solubilizers, complex-forming agents, suppository bases, plasticizers and film coating materials) of pharmaceutical technology [6].

The aim of the present study was to compare the physicochemical characteristics (surface tension, dynamic contact angle, viscosity) of aqueous solutions of different polyethylene glycols, and to find a correlation between the potassium chloride release characteristics of wax matrices containing various polyethylene glycols. The physico-chemical characteristics of the aqueous solutions of polyethylene glycol derivatives were investigated.

2. Investigations, results and discussion

The dissolution-kinetic parameters of different matrix samples were determined by the following equation (eq. 1) which was successfully applied by Rácz for comparing the dissolution rate of more than 40 active ingredients of different chemical structures and properties [1, 7]:

$$M_t/M_\infty = 1 - \exp\,[-a(kt)^\alpha] \qquad (1)$$

where k is the release rate constant, M_t is the amount of drug released at time t, M_∞ is the maximal amount of drug released and a and α are constants that describe structural and geometric characteristics of the systems. According to the calculation, the release rate constant (k) is independent of the sampling time. Fig. 1 illustrates the amount of drug released (% w/w) as a function of time in the case of matrices containing different surfactants at a concentration of 1% w/w.

Table 1 summarizes the drug release characteristics of potassium chloride matrices containing Polysorbate 40. The results indicate that with increasing Polysorbate concentration, the rate of potassium chloride release was also increased. Table 2 summarizes the viscosity, surface tension and adhesion tension values of aqueous solutions of different surfactants. Above 1% w/w (critical micelle concentration of Polysorbate 40) the surface tension value of aqueous Polysorbate 40 solutions leveled out to a constant value (Fig. 2) and their dynamic contact angle values decreased. The decreasing contact angle (increasing cos θ) increased the adhesion tension values. The experimental results obtained relate to the impact of the molecular weight of the surfactant on the contact angle values. The average molecular weight of Lutrol 127 is 12 000 (BASF)

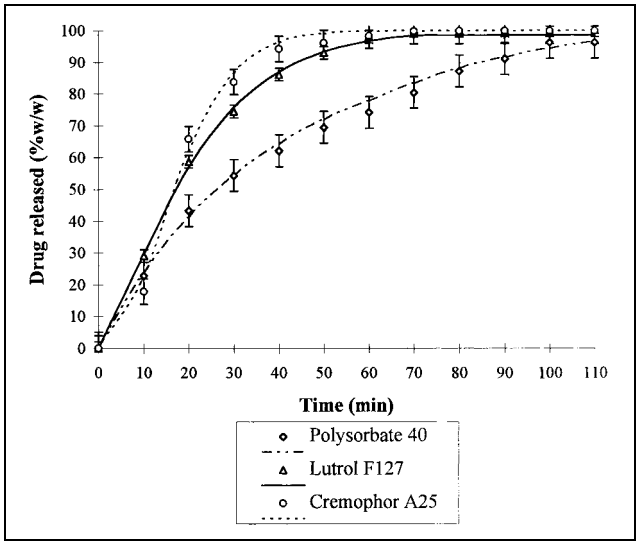

Fig. 1: Measured and calculated released amount of potassium chloride from matrices containing different non-ionic surfactants in 1% w/w (n = 6, ± S.D.)

Table 1: Characteristic parameters (k, α) of drug release from potassium chloride matrices containing Polysorbate 40

Polysorbate 40 concentration (% w/w)	k (min^{-1})	α	Correlation coefficient
0	0.00934	0.7765	0.9933
1	0.01263	0.7107	0.9976
2	0.01807	0.9585	0.9975
5	0.02016	0.7207	0.9899
10	0.02545	1.0508	0.9986

Table 2: Viscosity, surface tension and adhesion tension values of aqueous solutions of polyethylene glycol derivatives

Concentration (% w/w)	Viscosity ± STD (mPa · s)	Surface tension (γ) ± STD (mN/m)	Adhesion tension (τ_0) (mN/m)
Distilled water			
	1.999 ± 0.0099	72.80 ± 0.0245	45.329
Polysorbate 40			
0.1	2.168 ± 0.0097	35.61 ± 0.0874	29.193
0.5	2.170 ± 0.0086	35.86 ± 0.1233	27.917
1.0	2.171 ± 0.0105	32.88 ± 0.3099	26.533
2.0	2.172 ± 0.0084	32.10 ± 0.0998	27.687
5.0	2.179 ± 0.0138	32.62 ± 0.3031	28.809
10.0	2.779 ± 0.0250	31.63 ± 0.2811	28.563
Lutrol F 127			
0.1	2.272 ± 0.0099	39.35 ± 0.0432	36.652
0.5	2.373 ± 0.0057	37.47 ± 0.0152	35.312
1.0	2.517 ± 0.0096	36.80 ± 0.0296	35.586
2.0	2.424 ± 0.0081	35.12 ± 0.0776	33.863
5.0	3.327 ± 0.0094	36.06 ± 0.0354	33.063
10.0	9.459 ± 0.0091	37.28 ± 0.0076	34.178
Cremophor A25			
0.1	2.027 ± 0.0058	46.27 ± 0.0493	38.612
0.5	2.162 ± 0.0057	42.60 ± 0.0569	39.801
1.0	2.339 ± 0.0076	42.43 ± 0.0963	40.139
2.0	2.272 ± 0.0061	42.10 ± 0.1104	40.369

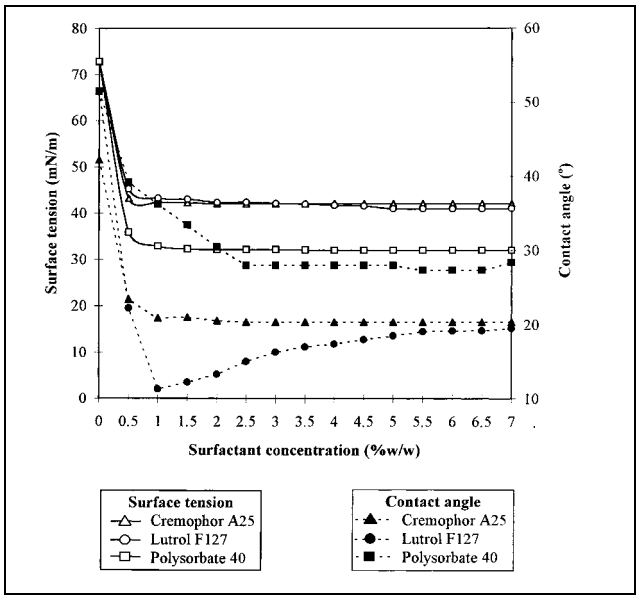

Fig. 2: Surface tensions and contact angles of aqueous solutions of the examined surfactants versus concentration

which is almost ten times higher than that of Tween 40. This phenomenon could be the reason for the increasing contact angle values remaining constant above 6% w/w concentration. Since the polymer contains only hydrophilic monomers, the measured contact angle above 6% w/w concentration is below that of Tween 40 at the same concentration.

The viscosity of 1% w/w aqueous solutions increased as the average molecular weight of the polymer increased. Since the surface tension values of each surfactant solution examined were lower compared to distilled water, their adhesion tension values also decreased. The release rate constants of different matrix samples increased in the

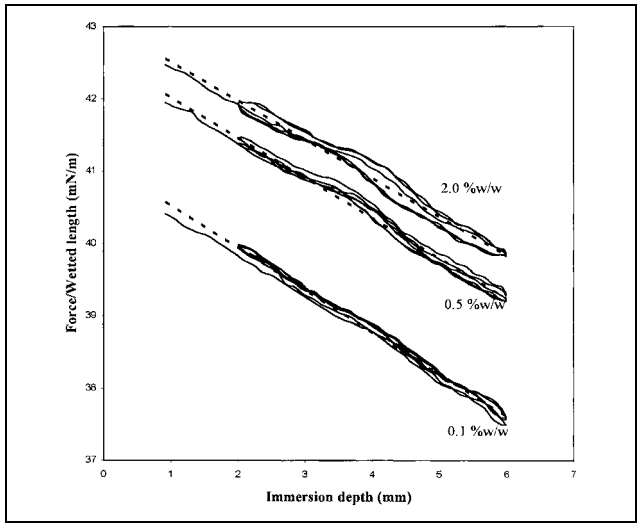

Fig. 3: The buoyancy slopes of receding and advancing contact angles of Cremophor A25 aqueous solutions

Table 3: Calculated linear regression of advancing and receding contact angles of aqueous Cremophor A25 solutions of different concentrations

Concentration (% w/w)	Dynamic contact angle (°)	Linear regression equation	R^2
0.1	33.16	$y = -0.5722x + 41.154$	0.9928
0.5	21.37	$y = -0.5542x + 42.573$	0.9878
2.0	16.81	$y = -0.5555x + 43.047$	0.9780

presence of surfactants, but the most marked increase could be seen with Lutrol F 127. This could be explained by its more hydrophilic chemical character.

Fig. 3 illustrates that the buoyancy slope of receding and advancing contact angles was not altered by increasing concentration of Cremophor A25, while the different forces measured resulted in different contact angle values. Table 3 summarizes the calculated contact angle values and linear regressions using the SIGMA 70 software. The results of this study indicate that with increasing adhesion tension of surfactant containing aqueous solutions, the rate of drug release also increased.

The surface tension, contact angle and calculated adhesion tension values accurately characterize the interfacial interactions of solutions of non-ionic surfactants. The results of these measurements permit predictions about the process of drug release from wax matrices containing the surfactants studied.

3. Experimental

3.1. Materials

The highly watersoluble core material potassium chloride (USP 23) of 160–320 μm (80% 250 μm) particle size was selected as a model drug. The coating material studied was white beeswax, purchased from the Fluka Chemie AG (Buchs,Switzerland). Polysorbate 40 (average molecular weight: 1 280; Sigma Aldrich, Hungary), Lutrol F127 (average molecular weight: 12 000; BASF, Germany) and Cremophor A25 (average molecular weight: 1 610; BASF, Germany) were selected as surfactants. All other chemicals were of analytical grade.

3.2. Determination of surface tension

Aqueous solutions of polyethylene glycol derivatives of different concentrations (0.1, 0.5, 1, 2, 5, 10% w/w) were prepared. The surface tension of each sample was determined after equilibrium at 20 °C for 1 h, applying the Du Nouy ring method with a computer controlled tensiometer (KSV Sigma 70, RBM-R. Braumann GmbH, Germany).

3.3. Dynamic contact angle measurements

The dynamic contact angle of aqueous polyethylene glycol solutions was determined by the Wilhelmy plate method of KSV Sigma 70 tensiometer (KSV Sigma 70, RBM-R. Braumann GmbH, Germany) at $20 \pm 0{,}5\,^{\circ}C$. From the extrapolated bouyancy slope, it is possible to obtain the contact angle:

$$\cos\theta = f/p\gamma_{LV} \quad (2)$$

where θ is the contact angle, f is the force measured on the balance, p is the measured plate perimeter and γ_{LV} is the surface tension of the surfactant solution. The measured contact angle of water is 51.49°, the adhesion tension (τ_0) calculated by the eq. 3 was 45.33 mN/m.

$$\tau = \gamma_{LV} \cos\theta \quad (3)$$

3.4. Determination of viscosity

Viscosity of the aqueous surfactant solutions was determined using a Haake VT550 viscotester (Haake, Germany) equipped with a sensor system NV (resolution factor 5.41, shear rate 4300 s^{-1}, measuring time 120 s), at a temperature of $25 \pm 1\,^{\circ}C$.

3.5. Preparation of the samples

The water-soluble model drug was embedded in a beeswax matrix using a melt method. The beeswax was heated in a double jacketed vessel to a temperature approximately 10 °C above its melting range. The potassium chloride crystals of 160–300 μm particle size were mixed into the melted mass in the proportion of 3 : 1. Surface active agents at different concentrations were added to the resulted mixture. The prepared samples were fractionated with a vibrating sieve (Retsch AS 200 control, Retsch Verder GmbH, Germany) for 5 minutes with 2.5 mm amplitudes without intervals and sieving aids. The sieve fractions were as follows: 1250–1600 μm; 1000–1250 μm; 800–1000 μm; 630–800 μm; 400–630 μm. For the subsequent experiments only the fraction of 400–630 μm particle size and of 0.064 m^2/g specific surface area, calculated according to the B.E.T. model by the multipoint method, was applied.

3.6. In vitro dissolution studies

Potassium chloride release was studied by the rotating paddle method of the USP 23 (Method 2) in a Pharmatest PTW2 dissolution-tester (Pharmatest Apparatebau GmbH, Hainburg). The amount of potassium chloride released was monitored continuously by a digital pH-meter (Radelkis OP 211/1, Budapest) with a chloride-selective electrode (Radelkis OP-Cl 7111P type, Budapest).

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