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Investigation of the effect of different adjuvants on felodipine release kinetics from sustained release monolithic films

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Abstract

A transdermal film was developed employing a calcium channel blocker, felodipine, with two acrylic resin polymers of varying permeability (Eudragit RL 100 and RS 100). The drug and two acrylic co-polymers of different permeabilities at ratio 1:1, with and without adjuvants were used to form films. Adjuvants, including polyethylene glycols (PEG 200, 400, 600, 1000), glycerol, ethoxydiglycol and propylene glycol were incorporated into films. The effect of these adjuvants on the release of drug from the films was investigated by the USP Method Apparatus II. The release data were evaluated kinetically using a computer programme (DISSOL). Drug release from the formulations containing 10% adjuvants showed zero order kinetics. The release profiles of the films which contained 10% glycerol and ethoxydiglycol were in most agreement with the target profile that was plotted based on the pharmacokinetic parameters. The relationship between the in vitro drug release data and moisture permeation constant and glass transition temperature was investigated. The in vitro release rate of drug increased with increasing water vapor transmission. No relationship was established between glass transition temperature values of the films and in vitro release of drug.

Keywords: Felodipine, Eudragit acrylic resin; Transdermal film; Release kinetics; Adjuvants; Physico-chemical properties

1. Introduction

Eudragit acrylic resins have been used for different purposes such as coating (Ghebre-Sellassie et al., 1987), preparation of matrix tablets (Lehmann, 1984), beads (Li et al., 1991), solid dispersions (Kışlalıoğlu et al., 1991), microcapsules (Lin et al., 1991; Kawata et al., 1986, Ueda et al., 1993), and suppositories (Goto et al., 1991). Eudragit acrylic resins are well tolerated by the skin and have a high capacity for incorporating drugs. Recently, the use of acrylic resins as matrix polymers for transdermal systems has been reported. The systems prepared with Eudragit RL 100 were used for transdermal delivery of bromhexidine (Thassu and Vyas, 1991), diclofenac and isosorbit dinitrate (Vyas et al., 1991; Vyas et al., 1994). In another publication, polymeric ma-

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trix films were prepared with Eudragit RLPM and RSPM for transdermal purposes (Jenquin et al., 1990).

Most polymers used for film formation are brittle at room temperature and therefore require the use of plasticizers or adjuvants to improve their handling and processing properties. The addition of adjuvants to polymeric films may make them both softer and flexible due to the decrease in the glass transition temperature of the polymer and may improve the release properties of drug from the films. In addition, adjuvants can influence the transdermal penetration of drugs into the skin. Adjuvants such as propylene glycol, glycerol, polyethylene glycols (Ritschel and Nayak, 1987; Yamada and Tanigawara, 1987; Lin et al., 1991; Sakya and Singh, 1991; Jenquin et al., 1992; Satyanarayana et al., 1993), polyvinylpyrrolidone (Vyas et al., 1991; Vyas et al., 1994; Jenquin et al., 1992), and glyceryl monostearate (Lin et al., 1991) have been incorporated into films for the purposes mentioned above.

Felodipine is a dihydropiridine derivative, a highly selective Ca^{2+} antagonist used for the treatment of hypertension. The absolute extent of bioavailability is reduced because of first pass metabolism. It is marketed in a plain tablet form and it could be a promising candidate in a transdermal system design taking into account its high lipid solubility and penetration behaviour (Diez et al., 1991).

The lipid-water solubility balance of the drug is an important parameter for transdermal systems. The water solubility of felodipine is very low (1.631 μg/ml) therefore, the addition of adjuvant may be needed to enhance the release and penetration characteristics of drug.

In our previous report we studied the effect of polymer ratio and drug loading on felodipine release kinetics from Eudragit RL/RS films (Şencan and Acartürk, 1994).

The objective of this study was to investigate the effect of different hydrophilic polyol adjuvants such as glycerol, ethoxydiglycol, propylene glycol and polyethyleneglycols on the release characteristics of felodipine from sustained release monolithic transdermal films. Some physico-chemical and in vitro release characteristics of the films were evaluated.

2. Materials and methods

2.1. Materials

The felodipine (Astra, Austria) and Eudragit polymers (Röhm Pharma) were kindly supplied by Eczacibasi Pharmaceuticals and Karadeniz Pharmaceutical Warehouse, respectively. Ethoxydiglycol (Transcutol®) was donated by Gattefossé. Polyethylene glycols (PEG) (Aldrich), propylene glycol (Merck) and glycerol (Merck) were purchased.

2.2. Determination of some physico-chemical properties of felodipine

The lipid/water partition coefficient (K_p) of the drug was determined by using an octanol–water system at 32°C.

The solubility of the drug in water and water containing 1% sodium lauryl sulphate (SLS) medium was determined at 32°C by suspending an excess of the drug in the media and stirring until equilibrium.

Investigation of the diffusion coefficient was carried out in a home-made diffusion apparatus in water at 30°C. Caffeine was used to calibrate the apparatus.

The results of the studies are as follows: K_p = 19.3; C_{water} = 1.61 μg/ml; C_{SLS} = 699 μg/ml; $D = 194.10^{-5}$ cm²/s.

2.3. Preparation of the films

Polymer films were prepared by the solvent casting method with acetone into Teflon dishes 6.57 cm in diameter. Ten percent polymer consisting of a Eudragit RL 100 and RS 100 combination (1:1) was used for the preparation of film matrices. The adjuvants (PEG 200, 400, 600, 1000, propylene glycol, glycerol, and ethoxydiglycol) were used in different ratios (2%, 5%, 10%). Adjuvants, polymers and the drug were codissolved in acetone and this film solution (7 ml) was distributed to each dish. Solvent was allowed to evaporate at room temperature. These films were cut and stored in a desiccator. The surface area and average thickness of the films were 16 cm²

Table 1
The formulation of the films

Adjuvants (%)	Code													
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
PEG 200	—	2	—	—	—	—	—	—	—	—	—	—	—	—
PEG 400	—	—	2	—	—	—	—	—	—	—	—	—	—	—
PEG 600	—	—	—	2	—	—	—	—	—	—	—	—	—	—
PEG 1000	—	—	—	—	2	—	—	—	—	—	—	—	—	—
Glycerol	—	—	—	—	—	2	—	—	5	—	—	10	—	—
Propylene glycol	—	—	—	—	—	—	—	2	—	—	5	—	—	10
Ethoxydiglycol	—	—	—	—	—	—	2	—	—	5	—	—	10	—

and 0.197 ± 0.007 mm, respectively. Each film formulation was prepared to contain 10 mg of felodipine. The drug content of the films was determined spectrophotometrically at 241.5 nm (Perkin-Elmer Hitachi 200 spectrophotometer). Table 1 shows contents of the film formulations.

2.4. Drug release studies

Drug release studies were performed by the USP XXII Paddle Method in 900 ml of distilled water containing 1% sodium lauryl sulphate at 32 ± 0.5°C at 75 rev./min. A temperature of 32°C was chosen because of the potential transdermal application of this system. Films were placed between a watchglass and a 18 mesh aluminium screen at the bottom of the vessel. At appropriate intervals, samples were withdrawn and assayed spectrophotometrically at 241.5 nm. Dissolution experiments were done in triplicate. Kinetic assessment of release data was carried out with a programme (DISSOL) (Ağabeyoğlu, 1984) written for this purpose.

2.5. Moisture permeation studies

To determine the moisture permeability constant (P_{erm}) of some film formulations, a moisture permeation cell consisting of a screw-capped bottle with a capacity of 50 ml containing 10 g of anhydrous potassium acetate, was used. A circular piece of film was placed onto the glass bottle and fixed with Parafilm and the screw-cap. The opening of the screw-cap was 1.4 cm in diameter and the total area of the exposed film was 1.54 cm^2. The transmission cell was weighed and then placed over a saturated solution of sodium carbonate in a large glass desiccator. Each day, the cells were weighed and the linear relationship between moisture gain and time was used to calculate the moisture permeability constant (P_{erm}).

2.6. Differential scanning calorimeter (DSC) studies

The glass transition temperature (T_g) of some films was determined with DSC (Mettler). The thermal analyzer was operated at a scanning speed of 10°C/min from 30 to 100°C.

2.7. Plotting of the target profile

The required release rate of the drug was calculated as kr_0 = 0.729 mg/h and the target profile was plotted (Robinson and Eriksen, 1970), on the basis of following pharmacokinetic parameters of felodipine: dose, 5 mg; distribution volume (V_d), 679 l; effective plasma concentration (C_p), 6.24 ng/ml; sustaining dose (D_s), 8.75 mg; disposition constant (K_d), 0.172 h^{-1}; dosing interval (τ), 12 h.

3. Results and discussion

Drug release from a matrix film is a result of a diffusion mechanism which is influenced by the polymer permeability, tortuosity and porosity as well as drug diffusivity and solubility. Eudragit RL and RS 100 polymers have different permeability characteristics. Eudragit RS 100 is slightly permeable to water vapor whereas Eudragit RL 100 is more permeable. It has been reported that the release of felodipine from the Eudragit films which have different polymer ratios depended on the amount of Eudragit RL and RS 100 in the films in the previous study (Sencan and Acartürk, 1994). Increasing the Eudragit RL 100 concentration resulted in increased drug release. The more permeable films which contained higher amounts of Eudragit RL 100 released at a faster rate than those films that contained a lower amount of Eudragit RL 100. To investigate the effect of adjuvants, the polymer ratio was chosen as 50:50 (RL/RS 100) in this study.

When we examine the physical characteristics of the films obtained it was observed that Eudragit RL/RS 100 films without adjuvant were hard and brittle. However, incorporating hydrophilic adjuvants improved the flexibility of the films: adjuvants gave them good handling properties.

It was reported that the addition of adjuvants changes the physicochemical properties of monolithic films such as their polymer tortuosity and porosity which can influence drug diffusion. For example, the addition of PEG 400 enhanced drug release from the Eudragit RSPM films, whereas PEG 8000 decreased the rate of drug release from the Eudragit RSPM films (Jenquin et al., 1992). Drug release from the films containing 2% of different molecular weight PEGs is shown in Fig. 1. Polyethylene glycols (200, 400, 600, 1000) (F2–F5) reduced the felodipine release from Eudragit RL/RS 100 films in comparison to the films without adjuvant (F1). No relationship was found between the molecular weight of polyethylene glycols and drug release.

The required release rate of felodipine based on pharmacokinetic parameters was calculated as 0.729 mg/h. The target profile was plotted dependent on this rate. Fitting to the target profile gave a comparison criterion against which to evaluate the release profile of different formulations. As can be seen from Fig. 2, the other adjuvants including 2% glycerol, propylene glycol and ethoxydiglycol (F6–F8) enhanced felodipine release from the films, but the release profiles of these films did not reach the target profile. In addition, there was no significant difference between the release profiles of the films containing these three adjuvants of the same ratio. Higher concentrations of the adjuvants were therefore needed and accordingly 5% and 10% were incorporated to the films. Figs. 3 and 4 depict the release profiles of the drug from the films that contained 5% and 10% of gylcerol, propylene

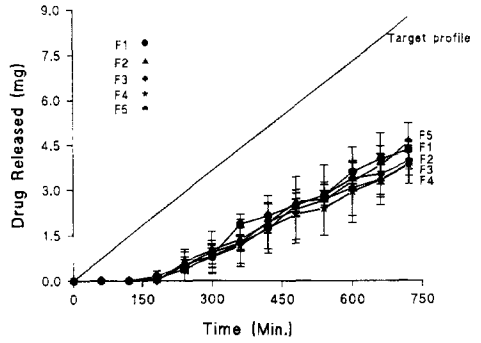

Fig. 1. The release profiles of felodipine from the films containing 2% of different molecular weight PEGs. Studies were done in triplicate. Mean ± confidence interval (C.I.).

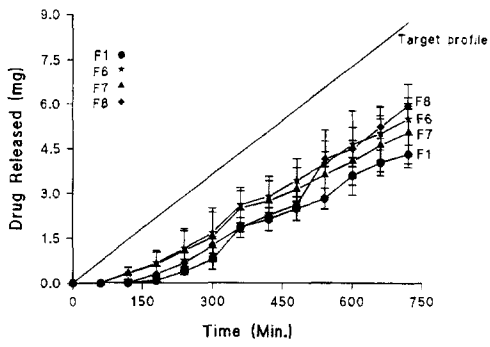

Fig. 2. The release profiles of felodipine from the films containing 2% of glycerol, ethoxydiglycol and propylene glycol. Studies were done in triplicate. Mean ± confidence interval (C.I.).

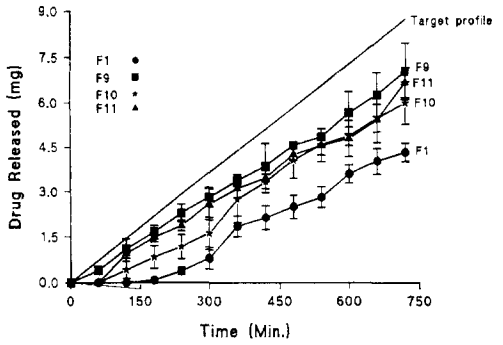

Fig. 3. The release profiles of felodipine from the films containing 5% of glycerol, ethoxydiglycol and propylene glycol. Studies were done in triplicate. Mean ± confidence interval (C.I.).

glycol and ethoxydiglycol. Drug release increased by increasing the adjuvant concentration and the release profiles of the films containing 10% adjuvants were also nearer to the target profile (F12–F14). The total amount of drug released from the films with three adjuvants followed the order glycerol > ethoxydiglycol > propylene glycol.

An increased release rate may be related to the water vapor permeation of the films. Incorporation of the adjuvants into the polymer disturbs the continuity of the polymer chains, thereby decreasing molecular order and increasing the chain mobility of the polymer matrix. As a consequence, permeability is enhanced. Increasing permeability can result in increased drug release.

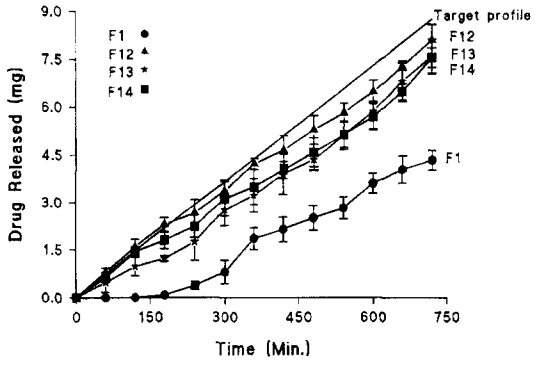

Fig. 4. The release profiles of felodipine from the films containing 10% of glycerol, ethoxydiglycol and propylene glycol. Studies were done in triplicate. Mean ± confidence interval (C.I.).

Table 2
Moisture permeability constants and the glass transition temperature values of the films

Code	$P_{erm} \times 10^{-3}$ ($g \cdot cm^{-1} \cdot day^{-1} \cdot mmHg$)	T_g (°C)
F1	0.710	45
F4	1.73	43.5
F6	1.82	43
F7	1.13	48.5
F8	1.78	44.5
F12	2.18	46
F14	2.40	45.5

Therefore, the moisture permeation constants of some films were determined. As shown in Table 2, the addition of adjuvants (PEG 600, glycerol, propylene glycol, ethoxydiglycol) raised the permeability constant of the films in comparison to those without adjuvant. The moisture permeability constants of the formulations that contained 2% of adjuvants were similar each other (F4–F8), but the highest moisture permeability constants were obtained with glycerol (F6) and propylene glycol (F8). The ratio of adjuvants affected the moisture permeability constant and when the amount of adjuvants increased from 2% to 10%, the moisture permeability constant and the amount of drug released were increased (F12, F14). No relationship could be established between release data and the permeability constants of the films containing polyethyleneglycol 600 (F4).

The glass transition temperature (T_g) of the polymer is an important parameter which is related to the physicochemical properties of the films. A decrease in T_g due to the addition of adjuvant or drug increases the chain mobility of the polymers and decreases the tortuosity of the matrix. Drug release can also be changed due to decreasing T_g. The T_g values of the films that contained different types and ratios of adjuvants are shown in Table 2. Incorporation of 2% adjuvants into the polymers, with the exception of ethoxydiglycol (F7), reduced the T_g value of the polymer films in comparison to those without adjuvant. However, at the higher adjuvant concentration, the T_g values of the F12 and F14 films

Table 3
Kinetic assessment of release data

Code	Kinetic parameters								
	Zero order			First order			$Q-\sqrt{t}$		
	k_0	r^2	SWSD	k_1	r^2	SWSD	k	r^2	SWSD
F1	0.485	0.988	0.148	0.0629	0.986	0.348	0.0130	0.983	0.114
F2	0.404	0.987	0.06	0.0525	0.989	0.165	0.0121	0.988	0.0507
F3	0.455	0.987	0.117	0.0594	0.988	0.297	0.0124	0.985	0.0735
F4	0.419	0.996	0.115	0.0525	0.989	0.248	0.00965	0.983	0.0817
F5	0.481	0.990	0.150	0.0634	0.968	0.382	0.0125	0.967	0.116
F6	0.540	0.996	0.0568	0.0785	0.989	0.249	0.0248	0.983	0.148
F7	0.535	0.993	0.0434	0.0680	0.989	0.169	0.0252	0.982	0.114
F8	0.645	0.982	0.239	0.0966	0.952	0.902	0.0226	0.957	0.238
F9	0.580	0.997	0.00387	0.0988	0.961	0.159	0.0426	0.972	0.157
F10	0.589	0.989	0.0661	0.0900	0.985	0.329	0.0299	0.975	0.186
F11	0.530	0.985	0.0122	0.0875	0.940	0.154	0.0354	0.966	0.119
F12	0.639	0.997	0.00753	0.129	0.938	0.259	0.0595	0.971	0.187
F13	0.649	0.989	0.0349	0.116	0.925	0.467	0.0441	0.941	0.278
F14	0.589	0.991	0.0112	0.106	0.926	0.208	0.0465	0.956	0.173

Summary of output obtained from the program DISSOL; k_0, zero order rate constant ($mg \cdot h^{-1}$); k_1, first order release rate constant (h^{-1}); k, is the rate constant obtained from the slope of the linear regression of cumulative amount released per unit are versus square root of time ($mg \cdot cm^{-2} \cdot h^{-1/2}$); r^2, the coefficient of determination; SWSD, the sum of the weighted squared deviations.

were increased. Therefore, no correlation could be found between the T_g values of the films and the amount of drug released.

The kinetic assessment of release data, as evaluated by computer is shown in Table 3. Upon checking the results according to the values of the determination coefficient (r^2) and the sum of the weighted squared deviations (SWSD), formulations which had been prepared with 2–10% of glycerol, propylene glycol and ethoxydiglycol showed almost zero order kinetics. The release profiles of F12–F14 formulations were parallel to the target profile. The zero order release rates of the films containing 10% glycerol (F12) and ethoxydiglycol (F13) were 0.639 mg/h and 0.649 mg/h, respectively (Table 3). These rates were in greatest agreement with the required drug release rate which was calculated from the pharmacokinetic parameters (0.729 mg/h). As can be seen from Table 3, the release rate of the film with propylene glycol (F8) was also near to the required release rate. However, the release profile of F8 was lower than the target profile (Fig. 1). This may be due to the lag time and the shape of the profile. Therefore, the obtained release rate may not reflect the exact drug release rate from F8 films.

It was concluded that the pattern and the extent of felodipine release from the transdermal monolithic films were found to be related the type and the ratio of the adjuvants. The release of drug from the films containing glycerol, propylene glycol or ethoxydigylycol was relatively faster than those of the films that contained polyethyleneglycols. The polymeric character of the adjuvants may have reduced the amount of drug released. The addition of the adjuvants increased the water permeability of the films, consequently drug release was enhanced. Incorporation of glycerol or ethoxydiglycol into the felodipine–polymer films may be useful in improving the physico-chemical properties of the films and in attaining the target release rate of drug, but more formulation studies are needed to prepare a transdermal system.

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