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Formulation and evaluation of controlled release Eudragit buccal patches

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Abstract

Controlled release buccal patches were fabricated using Eudragit NE40D and studied. Various bioadhesive polymers, namely hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose and Carbopol of different grades, were incorporated into the patches, to modify their bioadhesive properties as well as the rate of drug release, using metoprolol tartrate as the model drug. The in-vitro drug release was determined using the USP 23 dissolution test apparatus 5 with slight modification, while the bioadhesive properties were evaluated using texture analyzer equipment with chicken pouch as the model tissue. The incorporation of hydrophilic polymers was found to affect the drug release as well as enhance the bioadhesiveness. Although high viscosity polymers can enhance the bioadhesiveness of the patches, they also tend to cause non-homogeneous distribution of the polymers and drug, resulting in non-predictable drug-release rates. Of the various bioadhesive polymers studied, Cekol 700 appeared to be most satisfactory in terms of modifying the drug release and enhancement of the bioadhesive properties.

Keywords: Controlled release buccal patch; Bioadhesive; Dissolution.

1. Introduction

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Problems such as high first-pass metabolism, and drug degradation in the harsh gastrointestinal environment, can be circumvented by administering the drug via the buccal route (Gibaldi, 1985; Harris and Robinson, 1992). Moreover, buccal drug delivery offers a safer method of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route. Therefore, adhesive mucosal

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dosage forms were suggested for oral delivery, which included adhesive tablets (Davis et al., 1982; Schor et al., 1983), adhesive gels (Ishida et al., 1983; Bremecker et al., 1984) and adhesive patches (Anders and Merkle, 1989; Guo, 1994).

Metoprolol tartrate is a selective β_1 adrenergic antagonist with no intrinsic sympatomimetic activity, and is widely used to treat essential hypertension (Robertson, 1983) and angina pectoris (Benfield et al., 1986). Although it is completely absorbed from the gastrointestinal tract, the systemic availability is only approximately 50% because of high first-pass metabolism (Johnsson et al., 1975; Jordo et al., 1980). Hence, it is a suitable candidate for administration via the buccal route.

A suitable buccal drug delivery system should be flexible and possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a controlled and predictable manner to elicit the required therapeutic response. Hydrogels are able to meet these requirements and they swell to a certain extent when placed in aqueous medium (Graham and McNeill, 1984). In the present study, a flexible buccal patch for the controlled delivery of metoprolol was developed using water-insoluble Eudragit NE40D as the base matrix. Several polymers with known bioadhesive properties were incorporated into the Eudragit patches, both to provide the patches with bioadhesive properties, and to modify the rate of drug release. The in-vitro release characteristics of the prepared systems were evaluated using a new design closely similar to the USP dissolution apparatus 5. On the other hand, the adhesive measurements were conducted using texture analyzer equipment with chicken pouch as the model mucosa.

2. Materials and methods

2.1. Materials

Metoprolol tartrate was purchased from Xiamen Chemical (Xiamen, China) and poly(ethylacrylate methylmethacrylate) copolymer (Eudragit NE40D) was purchased from Rohm GmbH (Darmstadt, Germany). Hydroxypropylmethyl cellulose (Methocel K4M and K15M) were gifts from Colorcon (UK). Sodium carboxymethyl cellulose (SCMC 400) was obtained from Euro Chemo Pharma (Malaysia), while sodium carboxymethyl cellulose, Cekol 700 and Cekol 10000 were purchased from Metsa-Serla (Sweden). Carbopol (CP 934P, CP 971P and CP 974P) were gifts from BF Goodrich (Cleveland, OH, USA). All other chemicals and reagents used were of AR grade purchased from BDH Chemical (Poole, UK). All the materials were used as received.

2.2. Fabrication of bioadhesive patches

Patches containing different proportions of metoprolol and Eudragit NE40D were prepared by dissolving the metoprolol tartrate in the Eudragit NE40D dispersion and then cast onto a petri dish and dried in the oven at 60°C until completely dry. The drug to Eudragit NE40D ratios studied were 1:1, 1:2.5, 1:5, 1:7.5 and 1:10. Various hydrophilic polymers, namely Methocel K4M, Methocel K15M, SCMC 400, Cekol 700, Cekol 10000, CP 934P, CP 971P and CP 974P, were incorporated into the Eudragit patches to modify the drug-release profile and the bioadhesiveness of the Eudragit-based buccal patch. These polymers were prepared as a 2% solution, and allowed to stir and hydrate for 24 h before being incorporated into the mixture drug and Eudragit NE40D. However, in the case of Carbopol, the gel solution was neutralized with 18% sodium hydroxide solution to pH 6.5–7.5 before being added, to avoid incompatibility. The composition of the patches are summarized in Table 1, where the percentage of the hydrophilic polymers refers to the total solid content in the patch. The buccal patches were circular in shape with a diameter of 9.70 cm (surface area, 73.90 cm^2) and thickness of 1.09–1.99 mm. The metoprolol content for patches containing only drug and Eudragit NE40D ranged from 1.20 to 10.00 g per patch dependent on the formulations, whereas for all other patches, they were 2.00 g per patch. These patches were then cut into a circular shape of smaller size for studying the in-vitro drug

Table 1
Composition of the patches and their bioadhesive strength

PRIVATE Formulations	Work of adhesion (mJ) mean ± S.D. ($n = 4$)	Force of detachment (N) mean ± S.D. ($n = 4$)
Drug(D):Eudragit(E)		
1:1	0.147 ± 0.025	1.068 ± 0.419
1:2.5	0.064 ± 0.006	0.747 ± 0.101
1:5	0.051 ± 0.009	0.726 ± 0.209
1:7.5	0.041 ± 0.008	0.574 ± 0.147
1:10	0.088 ± 0.018	1.306 ± 0.295
D:E:SCMC 400		
1:5:1	0.091 ± 0.009	1.314 ± 0.304
1:5:5	0.123 ± 0.014	1.635 ± 0.228
1:5:10	0.591 ± 0.079	5.214 ± 1.586
D:E:Cekol 700		
1:5:1	0.132 ± 0.010	1.614 ± 0.130
1:5:5	0.181 ± 0.016	2.353 ± 0.310
1:5:10	1.117 ± 0.215	7.784 ± 1.410
D:E:Cekol 10000		
1:5:1	0.155 ± 0.018	2.026 ± 0.455
1:5:5	0.180 ± 0.034	2.067 ± 0.593
1:5:10	1.599 ± 0.210	9.032 ± 1.096
D:E:Methocel K4M		
1:5:1	0.047 ± 0.003	0.588 ± 0.097
1:5:5	0.136 ± 0.016	1.879 ± 0.222
1:5:10	0.090 ± 0.020	0.759 ± 0.356
D:E:Methocel K15M		
1:5:1	0.032 ± 0.005	0.361 ± 0.102
1:5:5	0.214 ± 0.020	2.378 ± 0.517
1:5:10	0.139 ± 0.017	1.220 ± 0.304
D:E:CP 934P		
1:5:5	0.231 ± 0.021	2.002 ± 0.149
1:5:10	0.970 ± 0.079	4.706 ± 0.581
D:E:CP 974P		
1:5:5	0.078 ± 0.015	0.956 ± 0.193
1:5:10	0.489 ± 0.069	3.069 ± 0.619
D:E:CP 971P		
1:5:5	0.619 ± 0.092	3.802 ± 0.434
1:5:10	1.777 ± 0.290	8.182 ± 1.265

release (diameter, 2.40 cm; surface area, 4.52 cm^2) and bioadhesive strength (diameter, 1.20 cm; surface area, 1.13 cm^2).

2.3. In-vitro drug-release studies

The in-vitro metoprolol release was evaluated using a design closely similar to the USP 23 dissolution test apparatus 5 (paddle over disk). It was performed using a dissolution tester (Sotax AT7, Switzerland) equipped with a Fractional Collector (SDX Pharmaceutical, Penang, Malaysia). The dissolution medium comprised 500 ml of distilled water maintained at a temperature of 37 ± 0.5°C and a paddle rotation speed of 100 rev/min was used. The patch of circular shape of 4.52 cm^2 surface area was placed in a self-fabricated basket (50 mm diameter and 6 mm height)

made from stainless steel with a sieve opening of approximately 850 μm (size No. 20, USP 23). The basket containing the sample was submerged into the dissolution medium at approximately 10 mm from the base of the dissolution vessel (Fig. 1). Five milliliters of sample were collected at predetermined time intervals over 14 h. The drug concentration was measured by a UV spectrophotometer (Model U-2000, Hitachi, Japan) at a detection wavelength of 274 nm. Six patches of each formulation were tested.

2.4. Evaluation of bioadhesive strength

The bioadhesive strength of the buccal patches was determined using a TA.XT_2 Texture Analyser (Stable Micro Systems, Haslemere, Surrey, UK), equipped with a 5-kg load cell. The inverted surface of chicken pouch, removed of its contents and surface fats, was used as the model tissue to study the bioadhesion. The chicken pouches were kept frozen at −20°C in a phosphate buffer saline solution (pH 6.75), and only thawed to room temperature before use. The chicken pouch was mounted onto a cylindrical perspex support of 2 cm diameter and 4 cm length and secured with a string. A foam tape was placed on the perspex support (underneath the chicken pouch) at the cross-sectional end to provide a cushioning effect. The chicken pouch was further secured and fastened to the foam tape by placing an aluminium cap over the perspex support. This was to ensure that the tissue adhered firmly to the foam tape and perspex support so that no movement of the tissue from the foam tape occurred during measurements. A circular hole of 17 mm diameter was made on the top of the cap to expose the chicken pouch for contact with the patches during measurements. The whole perspex support was then positioned at the bottom of the measuring system and held in place by a clamp. The circular patches of 12 mm diameter were affixed to other perspex supports of similar dimension using double-sided tape and the support was then screwed onto the upper probe of the instrument. The two perspex supports were aligned to ensure that the patches come into direct contact with the exposed surface of the chicken pouch when the upper support was lowered. The whole assembly is shown in Fig. 2. All measurements were conducted at room temperature of 21°C and relative humidity 50–60%.

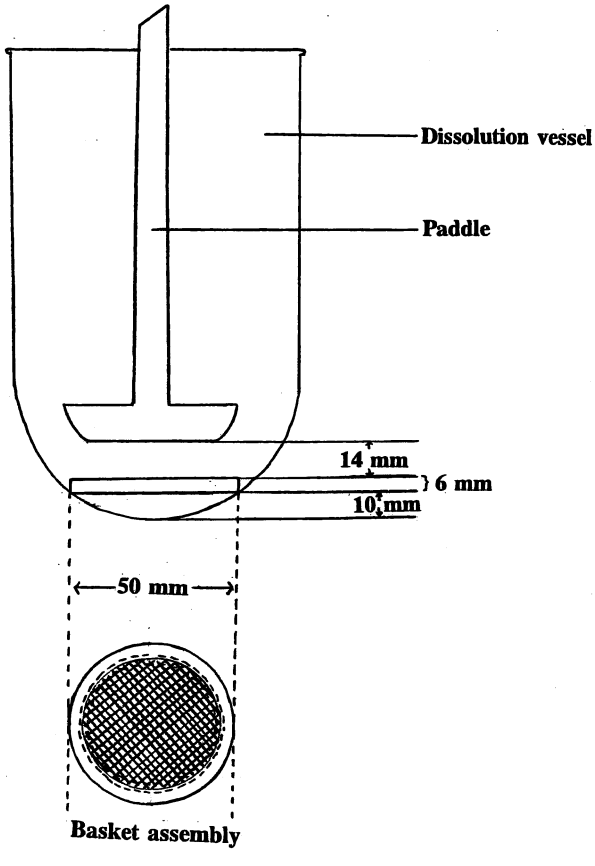

Fig. 1. Schematic illustration of the dissolution test apparatus.

During measurement, 200 μl of simulated saliva solution was evenly spread on the surface of the tissues. The upper perspex support was lowered at a speed of 0.5 mm/s to contact with the tissue at a contact force of 2 N and a contact time of 300 s. It was then withdrawn at a speed of 1.0 mm/s to a distance of 15 mm. An acquisition rate of 25 points/s was chosen for the mucoadhesive analysis. Data collection and calculation were performed using the XTRA Dimension software package of the instrument. The work of adhesion and peak detachment force were used to evaluate the bioadhesive strength of the patches. The work of adhesion was calculated from the area under the force–distance curve, whereas the peak de-

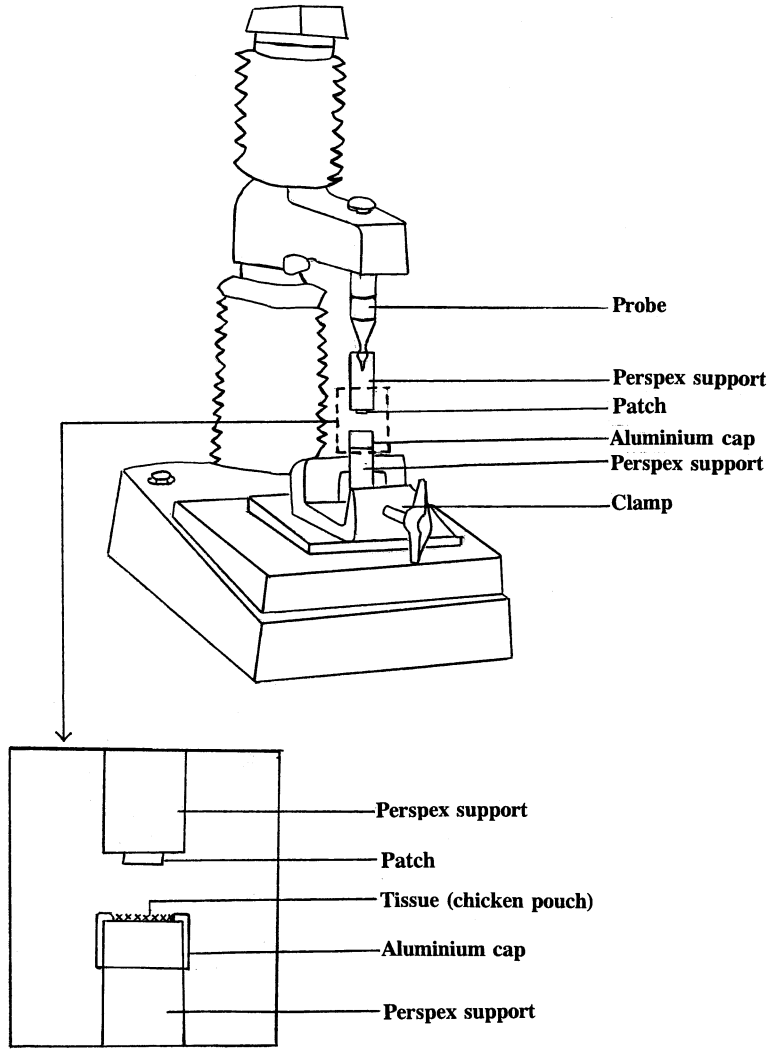

Fig. 2. Bioadhesive testing system utilizing the texture analyzer equipment.

tachment force was the maximum force needed for detaching the patch from the tissue. Each measurement was repeated four times.

3. Results

3.1. Drug-release profiles of the patches

Fig. 3 shows the drug-release profiles of Eudragit patches containing different ratios of the polymer to the drug. It is apparent from the plots that the drug release could be sustained and was governed by the Eudragit content. An increase in the polymer content was associated with a corresponding decrease in the drug-release rate.

The formula with a drug to polymer ratio of 1:5 was chosen to evaluate the drug-release and bioadhesive properties of the patches after incorporation of various hydrophilic polymers. Figs. 4–11 show the drug-release profiles of the patches after incorporating the hydrophilic polymers. Referring to Figs. 4 and 5, it can be seen that the rate of drug release could be modified in a pre-

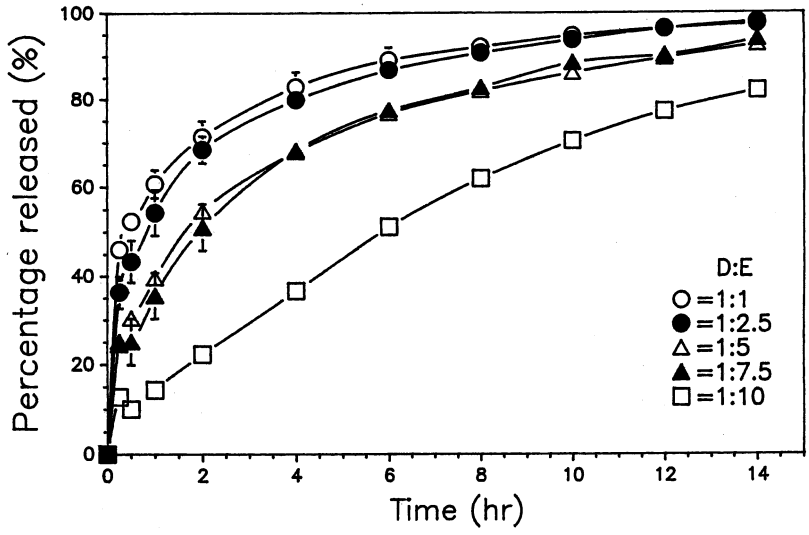

Fig. 3. Release profiles of metoprolol (D) from patches comprising Eudragit NE40D (E); error bar ± S.D. ($n = 6$).

dictable manner by varying the Cekol 700 and Methocel K4M content. The drug-release rate appeared to increase with increasing amount of the hydrophilic polymers.

For the other hydrophilic polymers, namely SCMC 400, Cekol 10000, Methocel K15M and CP 934P, although the rate of drug release could be modified after their incorporation into the patches, there was no direct relationship between the rate of drug release and the amount of polymer added, as shown in Figs. 6–9, respectively. In all these cases, the rate of drug release was increased when the polymers were incorporated at low concentrations, but was decreased when incorporated at higher concentrations. Examination of the patches during the dissolution studies revealed that the patches showed considerable swelling and gel formation, especially when the hydrophilic polymers were incorporated at higher concentrations. This may help to explain the decrease in drug-release rate observed with higher concentrations of the polymers.

In the case of the polymer CP 971P, no significant change in the drug-release rate was observed when it was incorporated at the 5% level, but a decrease in the release rate was apparent when the polymer content used was 10% (Fig. 10). This was probably due to the gel formation and swelling of the patches observed at a higher concentration of the polymer. With the polymer CP 974P, the plots in Fig. 11 show that the rate of drug release was increased after incorporation of the polymer at 10% but declined rapidly after approximately 3 h. In this case, the gelling and swelling of the patches occurred slowly, reaching a maximum at approximately 3 h, and corresponded with the decline in the rate of drug release.

3.2. Bioadhesive properties of the patches

Two parameters, namely work of adhesion and peak detachment force, were used to measure the bioadhesive properties of the patches before and after incorporating various hydrophilic polymers. Both were calculated from the measurements taken using the texture analyzer and the values are shown in Table 1. Patches containing only drug and Eudragit appeared to have low bioadhesive properties, as indicated by the work of adhesion and force of detachment. As for the other patches incorporated with the various hydrophilic polymers, the bioadhesiveness appeared to increase with a corresponding increase in the hydrophilic polymer content, except for Methocel K4M and Methocel K15M. For these two polymers, there was an increase in bioadhesiveness

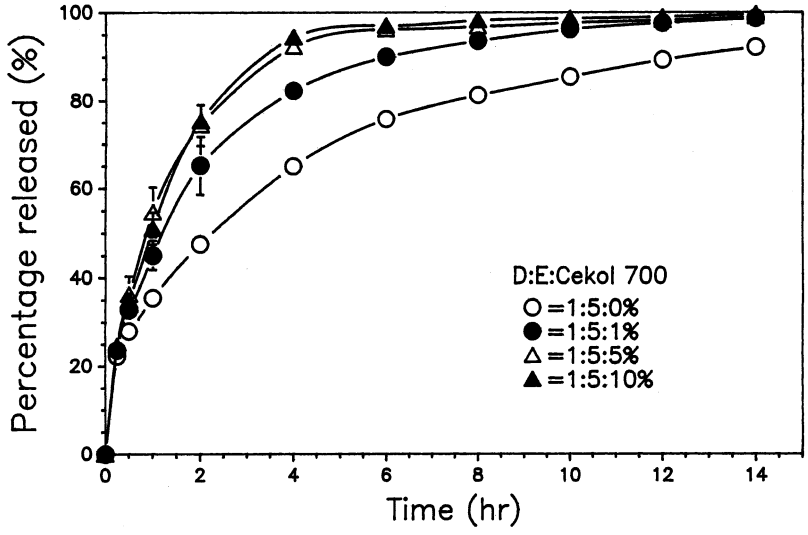

Fig. 4. Release profiles of metoprolol (D) from patches comprising Eudragit NE40D (E) and sodium carboxymethyl cellulose (Cekol 700); error bar ± S.D. ($n = 6$).

when the polymer content was increased from 1 to 5%, but appeared to decrease at a polymer content of 10%.

It can be inferred from Table 1 that CP 971P achieved the highest value for work of adhesion, followed by Cekol 10000, Cekol 700, CP 934P, SCMC 400, CP 974P, Methocel K15M and, finally, Methocel K4M. In terms of the force of detachment, the ranking was closely similar, except for CP 971P and Cekol 10000. The former recorded a higher value than Cekol 10000 for work of adhesion, but was lower than the latter in terms of the detachment force. Notwithstanding this discrepancy, these two polymers appeared to

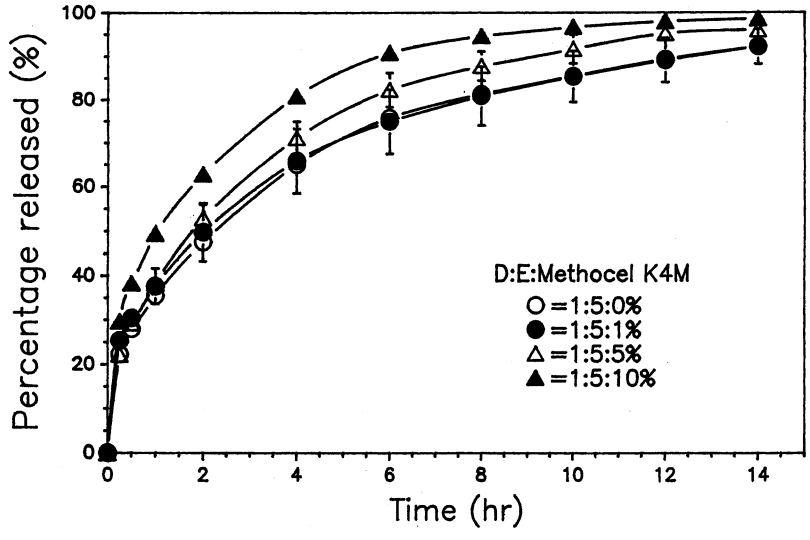

Fig. 5. Release profiles of metoprolol (D) from patches comprising Eudragit NE40D (E) and hydroxypropylmethyl cellulose (Methocel K4M); error bar ± S.D. ($n = 6$).

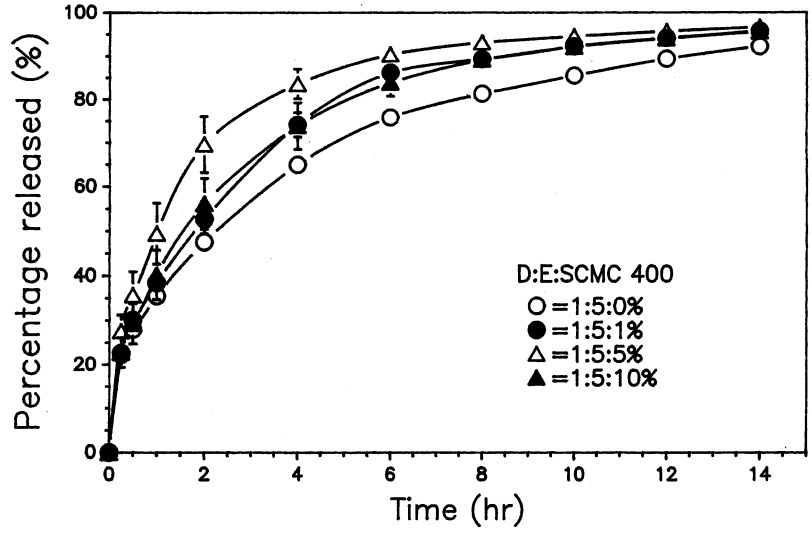

Fig. 6. Release profiles of metoprolol (D) from patches comprising Eudragit NE40D (E) and sodium carboxymethyl cellulose (SCMC 400); error bar ± S.D. ($n = 6$).

be most effective in conferring bioadhesive properties to the patches, followed closely by Cekol 700.

However, after taking into consideration both the drug-release and the bioadhesive properties, Cekol 700 appeared to be the most suitable polymer to be used with the Eudragit patches. Although the bioadhesive strength conferred by Cekol 700 was slightly less than those of CP 971P and Cekol 10000, it has the advantage of a more reliable and predictable drug-release profile compared with the latter two.

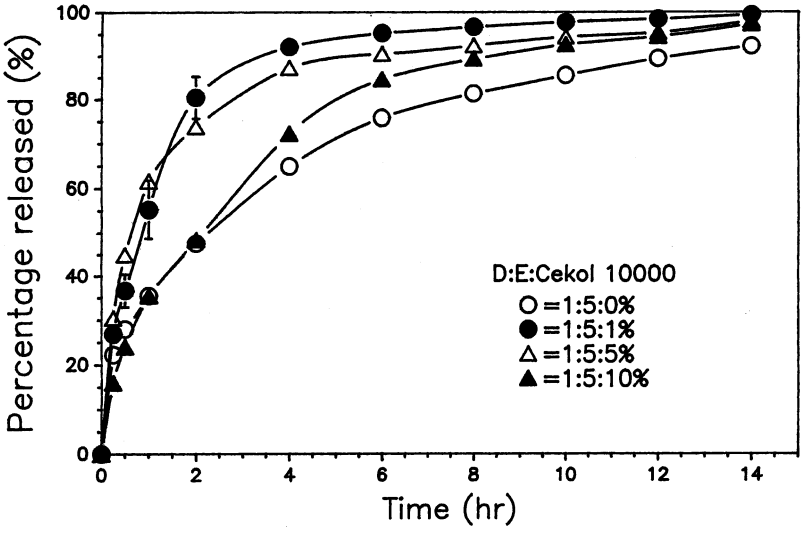

Fig. 7. Release profiles of metoprolol (D) from patches comprising Eudragit NE40D (E) and sodium carboxymethyl cellulose (Cekol 10000); error bar ± S.D. ($n = 6$).

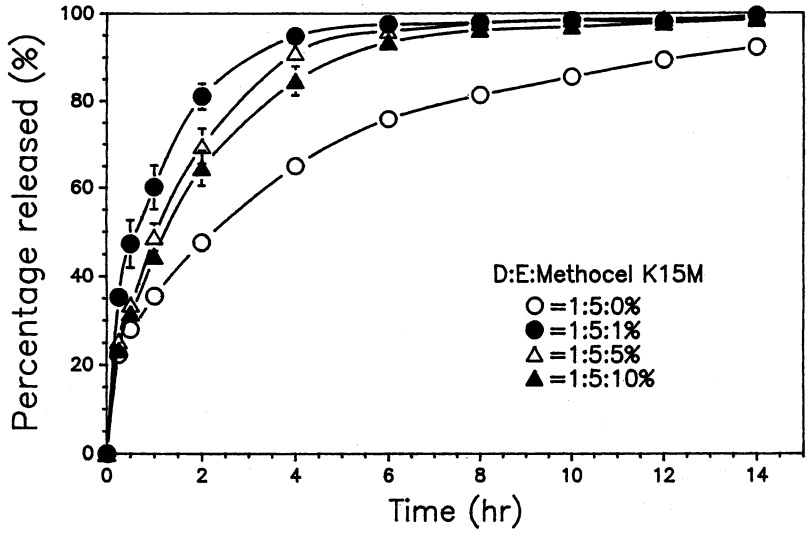

Fig. 8. Release profiles of metoprolol (D) from patches comprising Eudragit NE40D (E) and hydroxypropylmethyl cellulose (Methocel K15M); error bar ± S.D. ($n = 6$).

4. Discussion

Eudragit NE40D is a neutral poly(ethylacrylate methylmethacrylate) copolymer prepared by emulsion polymerization (Lehmann, 1989), and is widely used in the development of controlled-release delivery systems and film coating technology. This aqueous colloidal dispersion (latex) is insoluble and inert in aqueous media at all pH values and is preferred over the use of organic solvent casting, which posed undesirable hazards to environment and overall health. In the present study, the drug was dissolved in the latex prior to casting and drying. Upon evaporation of water, the polymer particles are forced into a close packing, followed by deformation and coalescence of

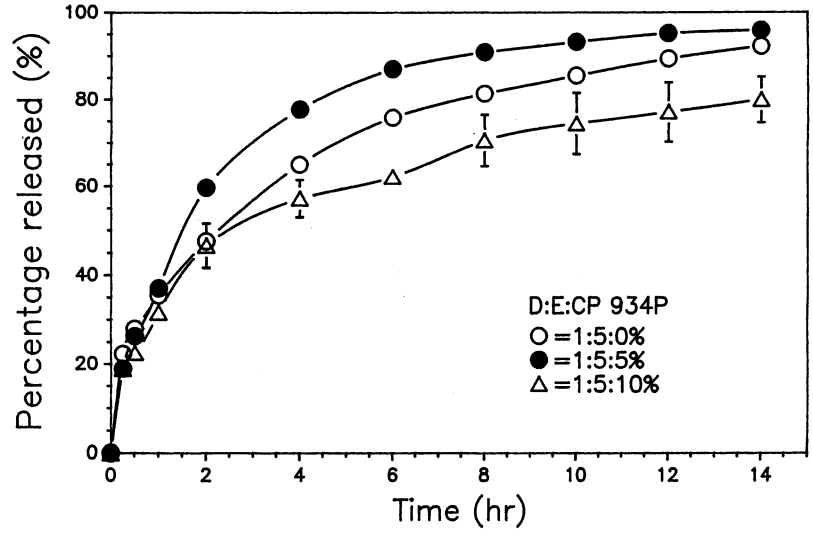

Fig. 9. Release profiles of metoprolol (D) from patches comprising Eudragit NE40D (E) and Carbopol (CP 934P); error bar ± S.D. ($n = 6$).

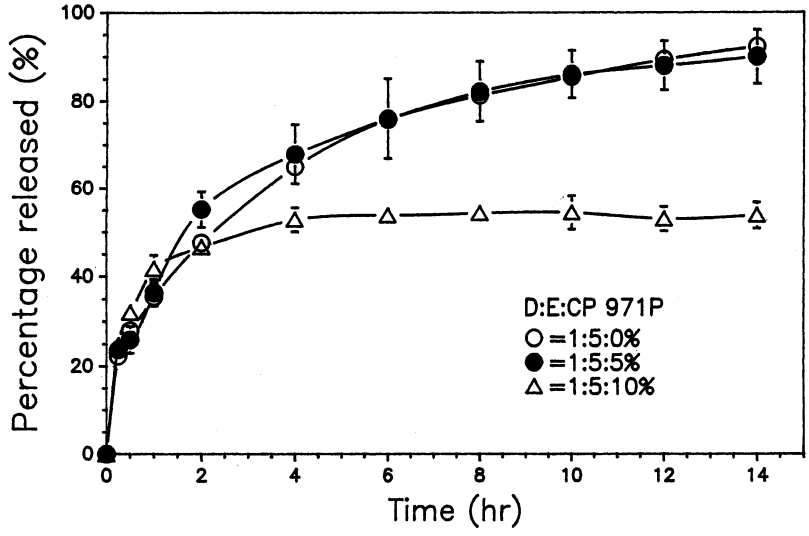

Fig. 10. Release profiles of metoprolol (D) from patches comprising Eudragit NE40D (E) and Carbopol (CP 971P); error bar ± S.D. ($n = 6$).

the particles into a continuous film. The latex is sensitive to temperature, pH changes, high shear, and, in particular, the addition of electrolytes. Hence, precautions should be taken when incorporating the hydrophilic polymers into the latex dispersion. Addition of highly acidic Carbopol solution into the mixture of drug and colloidal polymer dispersion resulted in latex coagulation. This incompatibility could be overcome by neutralizing the Carbopol solution to pH 6.5–7.5 prior to addition to the drug and latex dispersion. However, upon neutralization, the viscosity of Carbopol gel increased greatly, which prevented homogeneous mixing. In addition, casting was difficult as the preparation was hard to flow and may necessitate the aid of a spatula. No inco

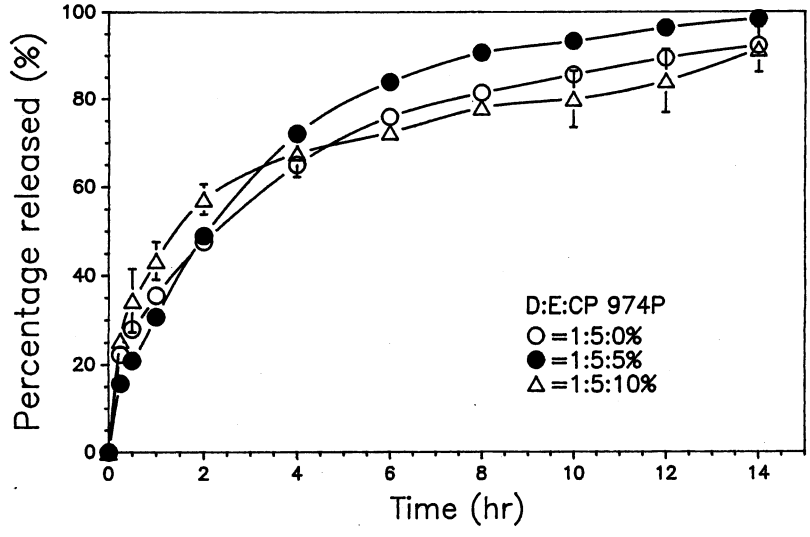

Fig. 11. Release profiles of metoprolol (D) from patches comprising Eudragit NE40D (E) and Carbopol (CP 974P); error bar ± S.D. ($n = 6$).

patibility was observed in the addition of hydroxypropylmethyl cellulose and sodium carboxymethyl cellulose into the system and flexible patches were obtained.

Presently, no universal method has yet been developed for studying the in-vitro dissolution of buccal formulations. Various methods have been employed for evaluating the in-vitro release of different dosage forms, such as the J.P. IX disintegration tester (Machida and Nagai, 1978), the Toyamo-Sangyo TR-553 dissolution tester (Ishida et al., 1982), the USP type II apparatus (Chen and Hwang, 1992) and Plexiglass sample blocks placed in a flask (Guo, 1994). In the present study, a design closely similar to the USP 23 dissolution tester apparatus 5 (paddle over disk) was employed to investigate the in-vitro dissolution. From the results obtained from the present study, the drug release from the Eudragit patches could be modified by addition of the hydrophilic polymers. This observation was in good agreement with those obtained by Bodmeier and Paeratakul (1989). The increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the highly water-soluble drug. Moreover, the hydrophilic polymers would leach out and, hence, create more pores and channels for the drug to diffuse out of the patches. For patches incorporated with the higher viscosity polymers, namely SCMC 400, Cekol 10000, Methocel K15M, CP 934P, CP 971P and CP 974P, the drug release did not change in accordance with the amount added. An increase in the rate of drug release was observed only at lower concentrations of the hydrophilic polymers, not when more was incorporated. This could be due to the extensive swelling of the polymers, which created a thick gel barrier for drug diffusion. In addition, a sponge-like structure with a non-homogeneous distribution or clustering of the individual components was observed upon drying of the patches. Shah and Sheth (1972) have also reported that the dispersion of a hydrophilic polymer within a hydrophobic polymer matrix could result in non-uniform distribution of the individual components.

Several methods have been employed to determine the in-vitro bioadhesion of mucoadhesive dosage forms. These included the tensile testing method (Park and Robinson, 1987), Wilhelmy plate method (Smart et al., 1984), adhesion weight method (Smart and Kellaway, 1982), fluorescent probe method (Park and Robinson, 1984), flow channel techniques method (Mikos and Peppas, 1986) and colloidal gold staining method (Park, 1989). More recently, the texture analyzer has been used for mucoadhesiveness measurements (Tobyn et al., 1995) and was used in the present study. The use of chicken pouch as a model mucosa has been reported by Mumtaz and Ch'ng (1995) and was chosen for the present study because it is easily available. Work of adhesion was used to evaluate the bioadhesiveness performance, and was reported to be a more reliable and accurate predictor of mucoadhesion (Lejoyeux et al., 1989). The other parameter, force of adhesion was also reported in the present study, although this parameter was claimed to be less reliable (Lejoyeux et al., 1989). However, in the present study, the values obtained with the two parameters appeared to be well correlated.

The incorporation of hydrophilic polymers was found to enhance the bioadhesiveness of the patches. The work of adhesion increased with increasing content of the bioadhesive polymers for all the polymers studied. From the results obtained, it can be seen that patches consisting of CP 971P showed the most promising adhesiveness properties, followed by Cekol 10000 and Cekol 700. Methocel did not seem to appreciably improve the adhesiveness of the patches. On the other hand, the neutralized CP 934P and CP 974P exhibited only intermediate bioadhesiveness strength. This may be caused by the non-uniform dispersion within the patches. In addition, the degree of neutralization and interaction between the metoprolol tartrate (cation), latex (highly ionic) and polymer could also contribute to the results observed. It has been reported that the bioadhesive work of CP 934P was reduced in the presence of ions, especially cations (Lejoyeux et al., 1989). This may be due to the recoiling of the Carbopol on itself, with the influence of cations that shield the negative carboxylic charge of Carbopol, making it difficult to diffuse, penetrate and to form secondary chemical bonds with the biological tissue.

5. Conclusions

Insoluble, flexible, organic solvent-free, controlled release patches could be fabricated using Eudragit NE 40D as the base matrix. The drug release as well as the adhesive properties of the patches could be modified by incorporating bioadhesive polymers. For the above purposes, Cekol 700 appeared to be the most suitable since it provided both satisfactory bioadhesion and a predictable rate of drug release.

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