Studies on the effect of plasticizer on *in vitro* release and *ex vivo* permeation from Eudragit E 100 based chlorpheniramine maleate matrix type transdermal delivery system.

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ABSTRACT

Release and permeation studies were carried out with the objective of developing transdermal therapeutic systems with chlorpheniramine maleate (CPM). The patches were prepared with Eudragit E 100 with/without polyvinyl pyrrolidone (PVP) and dibutyl phthalate (DBP), as well as, dibutyl sebacate (DBS) as the plasticizer in different compositions. Thickness, tensile strength, modulus of elasticity, drug content, moisture content and water absorption studies of the patches were measured. *In vitro* release/permeation of CPM was studied using a modified Keshary-Chien diffusion cell. Chemical enhancers like l-menthol, oleic acid and phospholipon 80 were added to compare the release pattern of the drug. The percent release of the drug from matrix patch increased with higher amounts of PVP and plasticizers, but the tensile strength decreased. Experimental release/permeation data of different formulations of these systems are reported. Additionally the drug-polymer interaction was investigated using an ATR-FTIR. This study shows that these are suitable plasticizers and chemical enhancers for Eudragit E 100 polymer for controlled release/permeation of CPM; hence this drug could be a potential candidate for transdermal antihistamine and wound healing applications in film device industry.

KEY WORDS: Chlorpheniramine maleate, Eudragit polymer, Polyvinyl pyrrolidone, Dibutyl phthalate, Dibutyl sebacate, Chemical enhancers

INTRODUCTION

Eudragit polymers are widely used as coating materials in pharmaceutical formulations (1). These polymers are well tolerated by the skin and have a high capacity for loading drugs. A formulation containing Eudragit E 100 (E 100) has gained wide commercial acceptance due to a resistance to oxidation and thermal degradation, as well as, being of moderate cost (2). Self adhesive E 100 polymers are suitable for both hydrophilic and hydrophobic plasticizers (3). Recently studies have been carried out to investigate the transdermal drug delivery of different drugs using mixed ratios of Eudragit polymers without any copolymers (4-6). The

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present studies investigate the role of plasticizers and enhancers, such as L-menthol and Phospholipon 80, on the release and permeation behavior of chlorpheniramine maleate (CPM) transdermal patch formulations. Unlike in previous studies, the Phospholipon 80 was added in a polymeric matrix film to study its enhancing performance rather than to the drug in solution. The primary role of plasticizers is to improve the flexibility and the processability of polymers by lowering the second order transition temperature (7). Plasticizers are actually low molecular weight resins or liquids which form secondary bonds with polymer chains and separate them. Thus, plasticizers reduce polymer-polymer chain secondary bonding and provide more mobility for macromolecules, resulting in a softer, more easily deformable mass (8).

CPM is an antihistaminic propylamine derivative, and has a molecular weight of 390.87 Da. Antihistamines such as CPM are H1-receptor antagonists, and are used in the treatment of allergy. They prevent, but do not reverse, the responses mediated by histamine. CPM antagonizes most of the pharmacological effects of histamine, including urticaria and pruritus. In addition, CPM, like other antihistamines, produces a drying effect on various mucosae by preventing the responses to acetylcholine mediated via muscarinic receptors (9-10). The CPM is a typical cationic amphiphilic amine drug (CAD); characterized by the hydrophobic ring structure of the molecule and the hydrophilic side chain with a charged cationic amino group. The chemical structure of CPM is similar to other CADs, therefore it was chosen as a model drug for the present study (11).

The specific objectives were: (1) to prepare CPM matrix patches with Eudragit E 100 polymer, with and without, povidone (PVP) as the copolymer, but with different percentages of dibutyl phthalate (DBP) and dibutyl sebacate (DBS) as the plasticizers, and with and without permeation enhancers, (2) to measure thickness and tensile strength of the matrix patches, (3) to measure the drug content and moisture content and calculate water absorption capacities of high tensile strength patches, (4) to study the percentage release with and without permeation enhancers and permeation properties of CPM from the matrix patches by using a modified Keshary-Chien diffusion cell, (5) to evaluate the addition of Phospholipon 80 in the matrix polymeric patch and its effect on the permeation behavior of CPM, (6) to study the possible drug-polymer interaction using an ATR-FTIR and (7) to develop a transdermal therapeutic system on the basis of the above data.

MATERIALS

Eudragit E 100 was a gift from Degussa India Ltd., Mumbai, India. Povidone (K-30) was purchased from SRL Pvt. Ltd., Mumbai, India. Chlorpheniramine maleate IP was a gift from Kontest Chemicals, Kolkata, India. L- Menthol B.P and Phospholipon 80 were provided by Hindustan Mint and Agro Products Ltd, India and Natterman Phospholipid GMBH, Germany respectively. Oleic acid was purchased from Loba Chemie Pvt Ltd, Mumbai, India. Dibutyl Phthalate was purchased from Qualigens Fine Chemicals, Mumbai, India. All other chemicals used in the study were of analytic reagent grade.

METHODS

Preparation of the patches

The patches were prepared by dissolving 400 mg of Eudragit E 100 in a 3 ml solvent mixture comprising isopropyl alcohol: acetone (IPA: Acetone 1:1), followed by the addition of 0 mg, 30 mg or 60 mg PVP with uniform, but slow magnetic stirring at room temperature. The plasticizer (DBP or DBS), 5 or 10% of the total polymer weight, and 16 mg of the drug CPM were added to the solution and stirred for 15–20 minutes. The total solution was slowly poured into SS rings (cross sectional area of the patch = 27.3258 cm^2) with a

backing layer of aluminium foil. The total mass was dried at room temperature for 48 hours.

Determination of patch thickness

Patch thickness was measured using a digital micrometer (Mitutoyo, Japan). The results are reported as an average of six readings (Table 1).

Determination of tensile strength

The tensile strength of the patches was evaluated using Instron 4204 Tensile tester, with a 50KN load cell (Instron, UK). Six samples of each formulation were tested at an extension speed of 5mm/min [American Society for Testing Materials(ASTM); method D 882- 75D]. The test was carried out at 25±2°C and 56± 2% RH. The tensile strength was calculated as follows :

$$\tau = L_{max}/A_i \qquad \text{Eq. 1}$$

Where τ is the tensile strength; L_{max} is the maximum load, and A_i is the initial cross sectional area of the sample. The results are reported as an average of six readings (Table 1).

Determination of Modulus of Elasticity

Modulus of elasticity was calculated as follows:

$$E = \text{Modulus of Elasticity} = \Delta\sigma/\Delta\varepsilon \qquad \text{Eq. 2}$$

Where, E = Modulus of elasticity, psi (N/m^2)
σ = Stress, psi (N/m^2), ε =Strain, in/in (m/m)

The results are reported as an average of six readings (Table 1).

Drug content

A 1 cm^2 area of each patch was cut and weighed accurately, dissolved in 2 ml of IPA: acetone (1:1), further diluted with distilled water and filtered. The drug content in each formulation was analyzed spectrophotometrically at 267nm. A blank was also prepared using a drug free film. The results are reported as an average of six readings (Table 2).

Moisture content

The patches were weighed individually and kept in a desiccator containing fused calcium chloride at 40º C for 24 hours (8). The patches were re-weighed until a constant weight was obtained. Moisture content was calculated as a percentage, based on the difference between the initial and the constant final weights of the patches. The results were reported as an average of three readings (Table 2).

Water absorption studies

For the determination of water absorption capacity, the weighed patches were allowed to remain at room temperature for 24 hours, exposed to two relative humidities of 75% (containing saturated solution of sodium chloride) and 93% (containing saturated solution of ammonium hydrogen phosphate) in different desiccators. The water absorption capacity of the patches was determined in terms of percentage increase in the weight of the patch over its initial weight. The patch weights were determined periodically until constant weight was obtained. The results are reported as an average of three readings (Table 2).

In vitro release study

The *in vitro* release studies were carried out using a modified Keshary–Chien diffusion cell. A piece of circular matrix patch was mounted carefully on the donor compartment. The donor compartment was empty and the backing membrane side of the matrix patch was open to the atmosphere but the receptor compartment was filled with freshly prepared phosphate buffer saline solution at pH 7.4. The receptor compartment was maintained at 32 ± 0.5°C by circulating water in the surrounding jacket and by slow stirring of the receptor liquid using a magnetic stirrer at 40-50 rpm.

The volume of the receptor liquid was such that the matrix patch piece (drug side; 2.5cm^2) just touched the receptor liquid surface horizontally for molecular diffusion. Samples were withdrawn at different intervals and replaced immediately with the same volume of saline solution. Samples were analyzed spectrophotometrically at 276nm after suitable dilution. The results are reported as an average of three readings (Table 3).

The percentage release and release rate for all the formulations containing 1% permeation enhancer, L-menthol, oleic acid or Phospholipon 80 are reported as averages of three readings and included in Table 3.

Ex vivo skin permeation study

A section of freshly excised albino mouse abdominal skin treated in isotonic solution was bound intimately with a matrix patch (2.5cm^2) with the aid of adhesives and without any air gap on the donor compartment side. The dermal side of the skin just touched the receptor liquid surface horizontally for permeation of the drug. All other analysis conditions were similar to those for the *in vitro* release study. The results are presented as an average of three readings in Table 4.

Attenuated total reflectance-Fourier transform infrared (ATR-FTIR) Studies

The patches were analyzed by attenuated total reflectance-Fourier transform infrared (ATR-FTIR) studies on a Magma-IR™ Spectrometer 750 (Nicolet Instrument Corp.), equipped with a Golden Gate Single Reflection Diamond ATR. Spectra were recorded on an average of 32 scans with a resolution of 4 cm^{-1} and in the frequency range of 400 - 4000 cm^{-1} (Table 5).

RESULTS AND DISCUSSION

Thickness, tensile strength and modulus of elasticity

The results from these studies are presented in Table 1. Tensile testing of the patch allows analysis of mechanical properties, such as stress-strain curves and stress at failure (strength). These properties are important since the patch must remain intact during storage or use. Previous studies have shown that CPM itself acts as an effective plasticizer and hence modifies the mechanical properties of HPC films (10-11). In this study two hydrophobic plasticizers, DBP and DBS, were added to determine if there were difference in release, physiochemical and mechanical properties of films prepared from E 100 containing CPM.

Table 1 shows that the modulus of elasticity value increases and the ultimate tensile strength gradually decreases as the plasticizer concentration in the patch is increased.

Table 1 Patch thickness, Tensile strength and Modulus of Elasticity

Patch Code: E 100:CPM 400:16 (mg)	PVP (mg)	% of plasticizer		Average thickness, mm	Tensile Strength, MPa	Modulus of elasticity, MPa
E1	-	DBP	5	0.110 ± 0.001	7.208 ± 0.83	27.17 ± 1.61
E2	-		10	0.117 ± 0.003	6.735 ± 0.62	29.47 ± 1.34
E3	30		5	0.119 ± 0.004	5.802 ± 0.18	31.56 ± 1.75
E4	30		10	0.121 ± 0.003	5.126 ± 0.53	33.19 ± 1.64
E5	60		5	0.124 ± 0.005	5.109 ± 0.47	36.21 ± 2.43
E6	60		10	0.129 ± 0.005	5.054 ± 0.49	38.75 ± 1.77
E7	-	DBS	5	0.103 ± 0.002	8.293 ± 0.41	31.31 ± 2.93
E8	-		10	0.109 ± 0.004	7.845 ± 0.72	34.10 ± 1.62
E9	30		5	0.110 ± 0.004	7.267 ± 0.68	37.22 ± 1.09
E10	30		10	0.114 ± 0.005	6.923 ± 0.29	39.07 ± 1.67
E11	60		5	0.123 ± 0.001	6.343 ± 0.96	42.18 ± 2.95
E12	60		10	0.125 ± 0.007	5.824 ± 1.06	44.59 ± 1.87

Notes:

E – Eudragit E 100, Example: E 1 means: E 100 - 400mg + PVP-Nil + CPM-16mg + DBP-5%

Higher amounts of the plasticizer in the patch disrupt the contact between the polymer strands in adjacent chains (10). The entrapped plasticizer molecules in the E 100 matrix patch considerably reduce the inter-chain cohesive forces. This leads to new polymer–plasticizer interactions which result in a significant decrease in the ultimate strength of the patches. Table 1 shows clearly that there is no significant difference in mechanical properties between these two plasticizers. However, the DBS containing patches are slightly superior than DBP containing patches in terms of tensile strength, modulus of elasticity and physical appearance. This may be due to a

higher miscibility of DBS plasticizer with the polymer and CPM.

Additionally, Table 1 shows that increasing the level of PVP in the patches, decreases the tensile strength of all formulations. The increase in PVP also reduces the matrix tensile strength. This observation was in good agreement with the results obtained by other workers (12-13). This is because either the PVP interrupted the continuity of the polymer chain molecules, resulting in a decrease in the blended polymer strength, or it decreased internal stresses of the E 100 (14).

Two conclusions may be derived from these results: adding the plasticizer caused a significant decrease of tensile strength and significant increase in elasticity. The patches containing plasticizers, either DBP or DBS, show no significant differences regarding the mechanical properties of plasticized E 100 films (15). These present studies show that the CPM loaded E 100 patches containing DBS as the plasticizer have slightly higher mechanical strength than DBP patches. Small differences were observed only in those patches that contained 10% of plasticizer. Additionally CPM is also believed to increase the plasticization efficiency of the matrix patches (E1-E12). The present study shows that CPM improves the mechanical properties efficiently even with 5% DBS. Hence the patch is flexible and not brittle in nature. Thus it may be concluded that CPM influences the mechanical properties of the E 100 matrix system. Most of the patches were elastic and flexible with an average tensile strength greater than 5.0 MPa. Literature (16) and mechanical engineering handbooks show that materials that have an average tensile strength of more than 4.0 MPa are elastic in nature.

Drug content, moisture content & water absorption studies

The results of these studies are presented in Table 2. Water absorption and moisture content studies show that the storage and handling of such transdermal patches would be difficult if they did not have suitable properties. Table 2 shows that the average drug content of all the patches is more than 98% of the intended amount, and that moisture content and water absorption capacities of the E100 patches are purely dependant on the concentration of plasticizer used in the study. The patches with and without PVP, and with 5% of plasticizer (E1-E3-E5-E7-E9-E11), have higher moisture contents and water absorption compared to the 10% plasticized patches (E2-E4-E6-E8-E10-E12). Another important reason is the hydrophilic nature of PVP which may account for the higher moisture content of the patches containing higher PVP levels (E5, E6, E11 and E12).

Table 2 Drug content, moisture content and water absorption studies

Patch Code	Drug content ($\mu gm/cm^2$)	Moisture content (wt %)	Water absorption (wt %)	
			75% RH	93 % RH
E1	570 ± 0.08	0.683 ± 0.29	0.912 ± 0.11	1.633 ± 0.13
E2	572 ± 0.05	0.673 ± 0.31	0.871 ± 0.17	1.616 ± 0.10
E3	574 ± 0.11	0.702 ± 0.24	1.112 ± 0.15	1.721 ± 0.13
E4	576 ± 0.17	0.692 ± 0.15	1.046 ± 0.13	1.702 ± 0.16
E5	577 ± 0.09	0.748 ± 0.18	1.186 ± 0.12	1.921 ± 0.08
E6	579 ± 0.12	0.733 ± 0.12	1.134 ± 0.11	1.913 ± 0.12
E7	571 ± 0.13	0.583 ± 0.29	0.846 ± 0.12	1.478 ± 0.19
E8	573 ± 0.11	0.573 ± 0.31	0.832 ± 0.07	1.421 ± 0.15
E9	575 ± 0.14	0.602 ± 0.24	0.931 ± 0.08	1.495 ± 0.18
E10	577 ± 0.05	0.592 ± 0.15	0.914 ± 0.15	1.402 ± 0.10
E11	578 ± 0.07	0.723 ± 0.18	1.041 ± 0.13	1.647 ± 0.13
E12	581 ± 0.13	0.718 ± 0.12	0.987 ± 0.10	1.567 ± 0.09

Similarly the water absorption at both RH conditions was also higher at higher PVP contents, because PVP allows the water to more easily diffuse into the patch which leads to higher uptake of moisture and water absorption (17). The relatively more hydrophobic DBS containing patches are more difficult to hydrate during the moisture content and water absorption studies, especially at 10%. From Table 2 it is clear that the water uptake and capacity of both types of patches remain intact when fully hydrated.

ATR-FTIR studies

A comparison of the ATR-FTIR spectrums of the individual materials including E 100, PVP

and CPM, together with a formulated matrix patch, was carried out to observe any spectral shifts in the matrix. The FTIR spectra of the drug CPM, E 100, PVP and formulated matrix patches (400:60:16mg) are shown in Figure 1.

The group assignments are given in Table 3. The FTIR spectra of the formulation containing E 100: PVP: CPM showed all the peaks for the polymers. The characteristic peaks of E 100 and PVP were observed at 2954cm^{-1} and 1724cm^{-1}, 1643cm^{-1}, 1656cm^{-1}, 1643cm^{-1}, 1438 cm^{-1}, and 842cm^{-1} respectively.

No significant shifts in the peaks corresponding to the drug or polymers were observed in the formulation matrix. Some characteristic peaks corresponding to the drug were found to overlap those of the polymer.

In vitro release studies

The percentage cumulative release and release rate (μgm/cm^2/hr) after 8 h from E 100 matrix patches are shown in Table 4. It can be seen that as the level of plasticizer in matrix patch increases, the percentage release also increases; however in the case of DBS, the release is significantly faster even without any permeation enhancers (E12 – 73%) than for the corresponding DBP containing patch (E6 – 63%). This is in good agreement with Siepmann *et al.* (18), who reported that DBS is a suitable plasticizer for a more 'rapid' release, whereas phthalate groups should be chosen when a more prolonged release is desired.

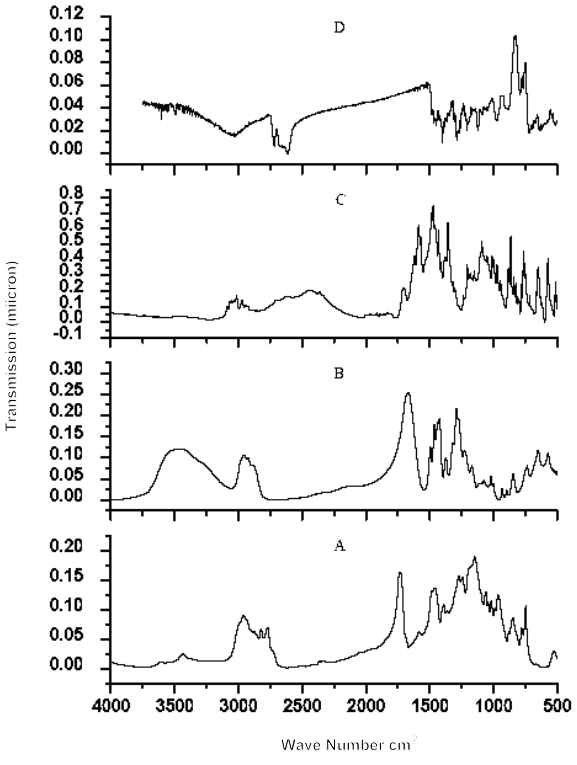

Figure1 ATR-FTIR Spectra: A: Eudragit E100; B: PVP; C: CPM; D: E 100:PVP:CPM matrix patch.

Table 3 Functional group assignment ATR- FTIR studies

Materials	Wave number (cm^{-1})		Peaks for functional groups assignment
	Standard	Test	
E100	2962-2853	2958, 2821	C–H Stretching, alkane
	~1340	1386	C–H Stretching, alkane (RS&RL100)
	1485-1445	1459	C–CH2 Stretching, alkane
	1750-1735	1731	RCOO - Strong band of ester group
	~1410	1388	N–R quaternary amine salts
	1220-1020	1147,1060	C–N Vibration, aliphatic
	800-600	748	C–Cl Vibration, aliphatic
PVP	2962-2853	2954	C–H Stretching, alkane
	1680-1630	1672	N-C=O carbonyl stretching vibrations on amides
	1485-1445	1463	C– CH_2 Bending, alkane
	~1340	1375	C–H Bending, vinyl
	1360-1310	1290	C–N Vibration, aromatic tertiary
	~830	844	C–H Bending aromatic 2 adjacent hydrogen atom
CPM	~3030	3012	C–H Stretching aromatic vibration
	2962-2853	2942	C–H Stretching, alkane
	~1450	1473 HI	C–C Multiple bond stretching, aromatic
	1400-1300	1357	COOH carboxylate anion Stretching
	1350-1280	1205	C–N Vibration, aromatic 2° amine
	1220-1020	1151	C–N Vibration, aliphatic tertiary amine
	995-985	971	CH=CH Bending, alkene
	800-600	717,649	C–Cl Vibration, aliphatic
	~780	763	C–H Bending aromatic adjacent 3 hydrogen atom
E100:PVP:CPM patches	2962-2853	2950	C–H Stretching, alkane
	1750-1735	1764	RCOO - Strong band of ester group
	1680-1620	1631	C–C Multiple bond stretching
	1485-1445	1484	C–CH2 bending, alkane
	~1410	1427	N–R quaternary amine salts
	1400-1300	1390	COOH carboxylate anion Stretching
	1360-1310	1355	C–N Vibration, aromatic tertiary
	1350-1280	1326	C–N Vibration, aromatic 2° amine
	1220-1020	1263	C–N Vibration, aliphatic tertiary amine
	1220-1020	1191	C–N Vibration, aliphatic
	800-600	732	C–Cl Vibration, aliphatic
	~830	806	C–H Bending aromatic 2 adjacent hydrogen atom

Table 4 Cumulative percentage release and rate after 8 hours with and without permeation enhancer

Patch Code	% Release	Release rate μgm/cm^2/hr	1% permeation Enhancer					
			% Release			Release rate μgm/cm^2/hr		
			M	O	P	M	O	P
E1	33	10.40	38	35	41	12.18	9.97	14.74
E2	42	29.16	45	44	48	31.09	25.89	35.76
E3	46	18.38	48	46	52	20.06	15.18	22.45
E4	50	32.90	55	51	58	34.07	29.43	35.19
E5	51	21.51	61	54	64	24.19	16.03	27.37
E6	63	35.09	71	65	76	37.11	31.50	39.23
E7	35	19.23	40	30	43	21.49	16.60	23.69
E8	41	20.12	47	39	51	23.96	17.03	26.41
E9	42	21.45	48	40	53	23.76	19.19	27.38
E10	54	25.78	59	51	63	25.78	23.15	29.02
E11	57	28.17	64	54	74	30.69	25.03	31.95
E12	73	35.52	83	68	86	37.93	31.18	39.04

Notes: M- L-menthol; O- Oleic acid; P- Phospholipon 80

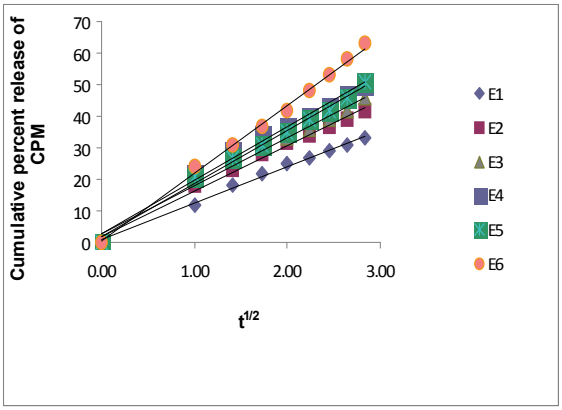

Figure 2 Release profile of DBP containing patches.

The cumulative release of drug on a percentage basis from both the DBP and DBS containing matrix patches was plotted against the square root of time ($t^{1/2}$) in Figures 2 and 3 respectively. From the plots presented in Figure 2 it is clear that the release of the drug from the patches followed the diffusion controlled matrix model in which the total percentage of drug released is proportional to the square root of time.

The cumulative release from all the matrix patches shown in Figures 2 and 3 follows Fick's law of diffusion. All the plots, when extrapolated to the origin, may be considered as linear and follow Higuchi release. The release rate of the DBS containing patches is higher compared to DBP containing patches This is probably due to two reasons; first the greater the uniformity of distribution of drug in the polymer matrix, the higher surface diffusion and second the DBS relaxes the polymer chains more effectively thus increasing the rate of diffusion. The DBS reduces the secondary

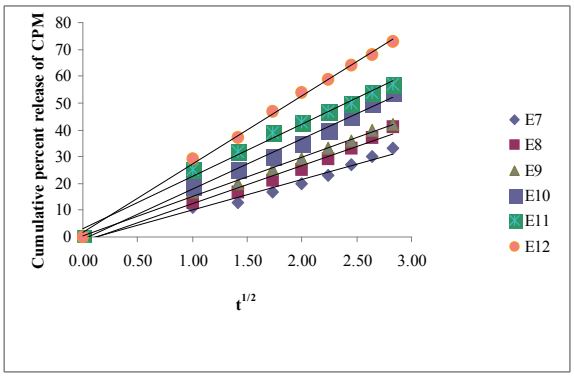

Figure 3 Release profile of DBS containing patches.

polymer chain bonding and provides more mobility for the CPM, resulting in an increased release rate. Release of a drug from a transdermal drug delivery system mainly involves diffusion (20).

The data presented in Figure 3 show that the rate of release of CPM is higher from DBS containing patches than from DBP containing patches. This may be due to either the porosity of the matrix or the solubility of CPM in the release medium. The cumulative amount of CPM released after 8 hours was in the order of E1-6< E7-12.

Effect of permeation enhancers on the release of CPM

Based on release studies the percentage release and release rate were not high, especially from DBP containing patches. It was decided to add 1% of a permeation enhancer, L-menthol, oleic acid or Phospholipon 80 to all the formulations. Their compositions are presented in Table 4. The percent release is only slightly increased with oleic acid. The oleic acid may be blocking the polymer chain spacing and retarding the diffusion channels created by the primary plasticizer DBP. Many literature reports have stated that oleic acid acts as a secondary plasticizer (21). This may be the reason it reduces the release of the drug.

When Phospholipon 80 was added to the

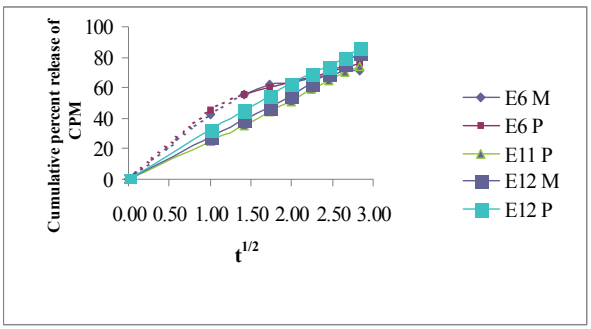

Figure 4 Release profiles of DBP and DBS containing patches with enhancers.

patches both the mechanical properties and the release percentages increased considerably due to greater miscibility of CPM in the polymer matrix and thus increasing the average polymer chain spacing. Many studies have used phospholipids as vesicles (liposomes) to carry drugs into and through human skin. However, we are not aware of studies that have used phospholipids in a non-vesicular form as penetration enhancers (22).

Figure 4 shows only the formulations that have a cumulative percent release above 70% after 8 hours. The cumulative percent released was plotted against $t^{1/2}$. From Figure 4 it is clear that the cumulative percent releases from DBP patch appreciably increased with an initial burst effect during the first 1-2 hours when either 1% L-menthol or Phospholipon 80 was included in the formulation (E6 M and E6 P; 71 and 76% respectively).

The release from the DBS plasticized patches was a maximum from the E12 patches containing 1% of L-menthol or Phospholipon 80 (83% and 86% respectively, Table 4). And even for the 5% of DBS containing patch (E11), the formulation containing Phospholipon 80 had a significantly increased percent release (74%) compared to DBP containing patch (E5-64%). The release pattern from the DBS plasticized patches containing L-menthol or Phospholipon 80, such as E11P, E12, E12M and E12P, follow Fick's law of diffusion. It is also clear that the release of the drug from the patches follow the Higuchi relationship, and that the release rates are fairly uniform for each interval.

Ex vivo skin permeation study

After review of all the factors including mechanical and physiochemical properties, percent release, release rate, patch quality before and after release by visual examination, surface smoothness and the effect of permeation enhancers, patches E6 M, E6 P (DBP) and E11, E11 P, E12, E12 M, E12 P (DBS) were selected for skin permeation studies. Each selected formulation was evaluated using the mouse skin model, and the average of three determinations reported. The cumulative percent permeation after 8 hours through E 100 matrix patches and mouse skin are shown in Table 5.

Table 5 Cumulative percentage permeation and rate after 8 hours.

Patch Code		% Release	Release rate µgm/cm²/hr	% Permeation	Permeation rate µgm/cm²/hr
E6	M	71	37.11	25	13.83
E6	P	76	39.23	29	15.72
E11	P	74	31.95	23	13.09
E12		73	35.52	27	15.26
E12	M	83	37.93	35	16.84
E12	P	86	39.04	40	18.43

From this data, it can be seen that the E12 M and E12 P matrix patches have the highest permeation, 35% and 40% respectively. Hence Phospholipon 80 is a more suitable enhancer with E 100 as reported earlier, it can occlude the skin surface and thus can fuse with stratum corneum lipids and increase tissue hydration, which, as shown above, can increase CPM permeation (22). Phospholipids are hygroscopic in nature and bind easily with water. For this reason we assume that this property increases the skin humidity and that leads to maximal hydration of the horny layer. In addition any residual ethanol would be synergistic with the Phospholipon 80.

The cumulative percent permeation from patches containing L-menthol (E6 M – 25; E12 M - 35) was also appreciably higher. This may be due to L-menthol which acts by disrupting the lipid structure of the stratum corneum, thereby increasing the diffusion coefficient of the drug in the skin (23-24). The *in vitro* drug release and skin permeation studies showed that the skin is the rate-limiting factor because the *in vitro* release of the drug was greater from each type of the matrix patch compared with the respective *in vitro* drug permeation rate. The

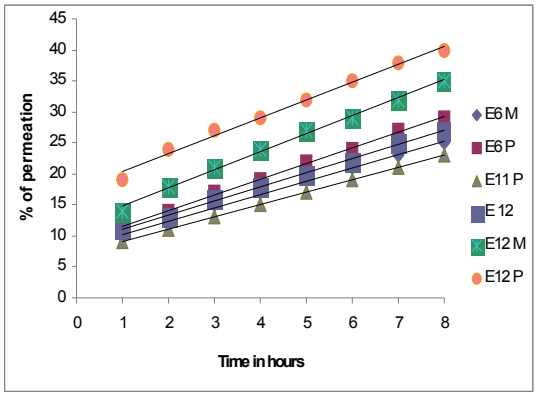

Figure 5 Permeation profile of DBP and DBS containing patches

cumulative drug permeation as a percentage from E 100 patches was plotted against the permeation time in hours (t) in Figure 5. In each plot, the rate of drug permeation is fairly constant over time and the permeation profiles exhibit the concentration dependent first-order kinetics.

CONCLUSION

The percentage release and permeation from the E 100 patch formulations plasticized with DBS and containing either L-menthol or Phospholipon 80 are higher than for the corresponding DBP containing formulations. Patch thickness was lower and tensile strength and modulus of elasticity were higher compared to DBP containing patches, whereas there was no significant difference in the value of the average moisture content and water absorption capacities. From the above observations, it may be concluded that (1) E 100 is suitable for preparing CPM matrix patches, () DBS (5-10%) is the plasticizer of choice, however 1% L-menthol or 1% Phospholipon 80 as permeation enhancers may also be needed (3) addition of the copolymer PVP to the E 100 patches is necessary to increase the release percentages.

The patch formulations E12 M, E12P were the best TD matrix patch compositions in this present study for the uniform and continuous release/permeation of CPM over an extended period, and to maintain a sustained therapeutic level of the drug in plasma. These selected formulations may be used for further pharmacokinetic and pharmacodynamic studies in suitable animal models.

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