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Design and in vitro evaluation of chlorpheniramine maleate from different eudragit based matrix patches: Effect of platicizer and chemical enhancers

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ABSTRACT

The release and permeation studies were carried out for developing transdermal therapeutic systems with chlorpheniramine maleate (CPM). The patches were prepared with eudragit RS-100 and RL-100 with/without polyvinyl pyrrolidone (PVP) and dibutyl phthalate (DBP) in different compositions. Thickness, tensile strength, drug content, moisture content and water absorption studies of the patches were measured. In vitro release/permeation of CPM was studied in modified Keshary-Chien diffusion cell. Chemical enhancers like l-menthol, oleic acid and phospholipon80 were added to compare the release pattern of the drug. The percent release of the drug from matrix patch increased with increase of PVP & DBP but the tensile strength decreased with the increase of DBP & PVP. Experimental release/permeation data of different formulations of the matrix systems are reported. Also the drug-polymer interaction was investigated by ATR-FTIR studies. The discussion was correlated the efficient matrix dispersion patch from suitable eudragit polymers for transdermal antihistamine applications in film device industry.

KEYWORDS: Matrix patch; Chlorpheniramine malaeate, Chemical enhancers, Dibutyl phthalate, Eudragit polymer, Polyvinyl pyrrolidone.

1. INTRODUCTION

Eudragit polymers are widely used as coating material in the pharmaceutical formulations.[1] These polymers are well tolerated by the skin and have high capacity for loading drugs. Some recent studies have been carried out with mixed ratios of Eudragit polymers (RS 100: RL 100, RLPO: RSPO) and with/without copolymers polyvinyl pyrrolidone (PVP) and polyethylene glycol 4000(PEG 4000) on transdermal drug delivery system.[2-7]. The primary role of plasticizers is to improve the flexibility and processability of polymers by lowering the second order transition temperature.[8] Plasticizers are actually low molecular weight resins or liquids, which form secondary bonds to polymer chains and spread them apart. Thus, plasticizers reduce polymer-polymer chain secondary bonding and provide more mobility for the macromolecules, resulting in a softer, more easily deformable mass.[9] Chlorpheniramine, classified as an antihistamine, is a propylamine derivative (alkylamines) and has a

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molecular weight of 390.87Da (chlorpheniramine maleate, CPM) Antihistamines such as CPM are H1-receptor antagonists and are utilized 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. Also, CPM, like other antihistamines, produces a drying effect on various mucosas by preventing the responses to acetylcholine that are mediated via muscarinic receptors[10,11]. 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. This above physiochemical property of CPM is similar to other CADs; therefore it was chosen as a model drug for the present study[12]. Specific objectives are: (1). to prepare CPM matrix patches with eudragit polymer, with/without PVP as the copolymer, with different percentages of dibutyl phthalate as the plasticizer and with/without enhancers. (2). to measure thicknesses and tensile strength of the matrix patches. (3). to measure the drug content & moisture content and also calculate water absorption capacities of high tensile strength patches. (4). to study the percentage release with/without chemical enhancers and permeation properties of CPM from the matrix patches by using modified keshary chien diffusion cell. (5). to study the possible drug-polymer interaction by ATR-FTIR and (6) to develop transdermal therapeutic system on the basis of the above data.

2. MATERIALS AND METHODS

2.1. Materials

Eudragit RS 100 and RL 100 were gifted by Degussa India Ltd., Mumbai, India. Polyvinyl pyrrolidone (K-30) was purchased from SRL Pvt. Ltd., Mumbai, India. Chlorpheniramine maleate IP was gifted by Kontest Chemicals, Kolkata, India. L- Menthol B.P and Phospholin80 were gifted by Hindustan Mint & 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. These were used as received without any further purification. All other chemicals used in the study were of analytic reagent grade.

2.2. Preparation of the patches

For preparation of the patches, 400 mg of different eudragit grades were dissolved in 4 ml methanol followed by the addition of 20-80 mg PVP with uniform but slow magnetic stirring. Then the plasticizer (DBP:5-25% of the total polymer weight) and 16 mg of the drug (CPM) were added to the solution and stirred for 15–20 min. Next the total mass was slowly poured into the centre of SS rings having a backing layer of aluminium foil. The total mass was dried at room temperature for 48 h.

2.3. Determination of patch thickness

Patch thickness was measured by a digital micrometer (Mitutoyo, Japan). An average of six readings was tabulated (Table 1)

TABLE 1: Patch thickness and Tensile strength

Patch code	PVP (mg)	DBP (%)	Average patch Thickness (mm)		Average patch Tensile Strength (MPa)	
			R - RS 100	L - RL 100	R - RS 100	L - RL 100
R/L 1	-	10	0.11 ± 0.01	0.09 ± 0.01	6.83 ± 0.91	5.86 ± 1.02
R/L 2	-	15	0.11 ± 0.01	0.10 ± 0.05	7.43 ± 0.09	5.71 ± 1.02
R/L 3	-	20	0.11 ± 0.04	0.11 ± 0.03	6.34 ± 1.26	5.60 ± 1.02
R/L 4	-	25	0.11± 0.01	0.11 ± 0.01	6.26 ±0.99	4.27 ± 0.01
R/L 5	40	10	0.11± 0.01	0.11 ± 0.02	4.10 ± 0.62	4.48 ± 0.37
R/L 6	40	15	0.12 ± 0.04	0.11 ± 0.02	5.38 ± 0.05	5.30 ± 0.41
R/L 7	40	25	0.12 ± 0.01	0.11 ± 0.03	3.98 ± 0.88	5.12 ± 0.63
R/L 8	60	10	0.13 ± 0.08	0.11 ± 0.02	3.00 ± 0.21	5.60 ± 0.65
R/L 9	60	20	0.13 ± 0.08	0.12 ± 0.01	4.76 ± 0.10	3.53 ± 1.08
R/L 10	80	15	0.14± 0.02	0.13 ± 0.01	3.52 ± 0.86	3.10 ± 0.99
R/L 11	80	25	0.14 ± 0.05	0.14 ± 0.02	3.17 ±1.13	2.95 ± 1.52

Notations:

R - RS 100; **L** - RL 100

All formulations contain 400 mg of polymer and 16mg of CPM.

Example: **R 1** means: RS 100 - 400mg + PVP-Nil + CPM-16mg + DBP-10%

2.4. Determination of tensile strength

The tensile strength of the patches was evaluated using Instron 4204, UK tensilometer with a mounted load of 50KN. Six samples of same formulation were tested with extension speed at 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

$\tau = L_{max} / A_i$

Where τ is the tensile strength; L_{max} is the maximum load and A_i is the initial cross sectional area of the sample. An average of six readings was tabulated. (Table 1)

2.5. Drug content

A known area of each patch was weighed accurately, dissolved in 2ml of casting solvent and the volume was diluted with distilled water and filtered. For the drug content in each formulation, 6 patches were analyzed spectrophotometrically at 267nm. A control was also performed using a drug free film. An average of six readings was tabulated. (Table 2)

TABLE 2: Drug content and Moisture content

Patch code	Drug content (µgm/cm^2)		Moisture content (Wt %)	
	R - RS 100	L - RL 100	R - RS 100	L - RL 100
R/L 1	567 ± 0.01	564 ± 0.18	0.675 ± 0.57	1.112 ± 0.91
R/L 2	571 ± 0.43	567 ± 0.45	0.663 ± 0.67	1.102 ± 1.02
R/L 3	574 ± 0.53	570 ± 0.61	0.634 ± 0.53	1.002 ± 1.02
R/L 4	579 ± 0.84	574 ± 0.11	0.621 ± 0.48	0.987 ± 0.01
R/L 5	-	563 ± 0.29	-	1.123 ± 0.37
R/L 6	567 ± 0.46	565 ± 0.38	0.743 ± 0.05	1.118 ± 0.41
R/L 7	572 ± 0.76	570 ± 0.43	0.729 ± 0.62	1.004 ± 0.63
R/L 8	-	565 ± 0.74	-	1.217 ± 0.65
R/L 9	573 ± 0.96	-	0.756 ± 0.10	-

2.6. Moisture content

The patches were weighed individually and kept in a desiccator containing fused calcium chloride at 40º C for 24 hours[9]. The patches were reweighed until a constant weight was obtained. Moisture content was calculated in percentage based on the difference between the initial and the constant final weights of the patches. An average of three readings was tabulated (Table 2).

2.7. Water absorption studies

For the determination of water absorption capacity, weighed patches were kept 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 at room temperature. The water absorption capacity of the patches was determined in terms of percentage increase in the weight of the patch over its initial weight. Periodically the weights

were taken until constant weight was obtained. An average of three readings was tabulated (Table 3).

TABLE 3: Water absorption studies

Patch code	Water absorption studies 75% RH (Wt %)		Water absorption studies 93% RH (Wt %)	
	R - RS 100	L - RL 100	R - RS 100	L - RL 100
R/L 1	1.143 ± 0.91	2.231 ± 0.91	2.814 ± 0.57	4.421 ± 0.91
R/L 2	1.132 ± 1.02	2.201 ± 1.02	2.769 ± 0.67	4.403 ± 1.02
R/L 3	1.126 ± 1.02	2.193 ± 1.02	2.682 ± 0.53	4.391 ± 1.02
R/L 4	1.109 ± 0.01	2.178 ± 0.01	2.625 ± 0.48	4.384 ± 0.01
R/L 5	-	2.471 ± 0.37	-	4.478 ± 0.37
R/L 6	1.154 ± 0.41	2.412 ± 0.41	2.873 ± 0.05	4.421 ± 0.41
R/L 7	1.142 ± 0.63	2.346 ± 0.63	2.861 ± 0.62	4.402 ± 0.63
R/L 8	-	2.512 ± 0.65	-	4.493 ± 0.65
R/L 9	1.173 ± 1.08	-	2.903 ± 0.10	-

2.8. Attenuated total reflectance-Fourier transform infrared (ATR-FTIR)

The patches analyzed were by attenuated total reflectance-Fourier transform infrared (ATR-FTIR) 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 to 4000 cm^{-1} (Table 4).

TABLE 4: Functional group assignment ATR- FTIR studies

Materials	Wave number (cm^{-1})		Peaks for functional groups assignment
	Standard	**Test**	

Eudragit RS100/ RL100	2962-2853	2952,2956,2852	C–H Stretching, alkane
	~1340	1386	C–H Stretching, alkane (RS&RL100)
	1485-1445	1456,1481,1479	C–CH_2 bending, alkane
	1750-1735	1733	RCOO - Strong band of ester group
	1680-1620	1635	C–C Multiple bond stretching
	~1410	1386	N–R quaternary amine salts
	1220-1020	1149, 1147	C–N Vibration, aliphatic
	800-600	667,653,651,752	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

RS/RL:PVP:CPM patches **Scanned 1cm^2 patch containing 585µgm**	2962-2853	2954	C–H Stretching, alkane
	1750-1735	1724	RCOO - Strong band of ester group
	1680-1620	1656	C–C Multiple bond stretching
	1680-1630	1643	N-C=O carbonyl stretching vibrations on amides
	1485-1445	1461	C–CH_2 bending, alkane
	~1410	1438	N–R quaternary amine salts
	1400-1300	1384	COOH carboxylate anion Stretching
	1360-1310	1357	C–N Vibration, aromatic tertiary
	1350-1280	1274	C–N Vibration, aromatic 2° amine
	1220-1020	1145	C–N Vibration, aliphatic tertiary amine
	1220-1020	1074	C–N Vibration, aliphatic
	800-600	748	C–Cl Vibration, aliphatic
	~830	842	C–H Bending aromatic 2 adjacent hydrogen atom
	~780	705	C–H Bending aromatic adjacent 3 hydrogen atom

2.9. In vitro release study

The invitro release studies were carried out in a modified Keshary – chien diffusion cell. A piece of matrix patch (circular) 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 of 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 by a magnetic stirrer at 40-50 rpm. The volume of the receptor liquid was such that the matrix patch piece (drug side) just touched the receptor liquid surface horizontally for molecular diffusion. The 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. An average of three readings was tabulated (Table 5).

TABLE 5: Cumulative percentage release and rate after 8 hour

Patch code	Average cumulative release (%)		Average release rate µgm/cm^2.hr	
	R - RS 100	L - RL 100	R - RS 100	L - RL 100
R/L 1	31	32	4	21
R/L 2	38	75	20	25
R/L 3	42	82	22	27
R/L 4	68	89	25	30
R/L 5	36	82	-	13
R/L 6	40	94	6	12
R/L 7	59	-	27	-
R/L 8	-	-	-	-
R/L 9	68	-	17	-

2.10. In vitro skin permeation study

TABLE 7 :Cumulative percentage permeation and rate after 8 hour

Patch code	Average cumulative permeation (%)	Average permeation rate, µgm/cm^2.hr
R 2	16	8
R 3	19	12
R 4	42	29
R 5 Pb	30	16
R 6 Pb	39	17
L1 Mb	56	32
L1 Ob	55	39
ML2	50	20
ML3	56	24
ML4	57	27

A section of the freshly excised albino mouse abdominal skin treated in isotonic solution was bound

intimately with a matrix patch piece without any air gap, on the donor compartment. The dermal side of the skin just touched the receptor liquid surface horizontally for permeation of the drug. The temperature of the receptor liquid, the rate and method of stirring, the sample collection and the sample analysis methods were similar to those during release study (Table 7).

3. RESULTS AND DISCUSSION

3.1. Physiochemical and mechanical properties

RS 100 and RL 100 with/without PVP and with DBP were used to prepare the matrix patches, Table 1 allows some interesting conclusions to be drawn. Patches from RL 100 have a lower tensile strength compared to those with RS 100. This may be due to high miscibility of hydrophobic RS 100 polymer with the drug CPM and DBP. Moreover, increasing PVP, in patches, decreases the tensile strength in all cases. Addition of more PVP, (R/L 5 – R/L 11)) reduces the matrix tensile strength as well as its elasticity[13,14]. This could be due to either PVP destroyed the continuity of polymer chain molecules, resulting in a decrease in the blended polymer strength or decreases internal stresses of main polymer of eudragit[15].

The moisture content of the RL 100 patches was higher compared to relatively hydrophobic nature of Eudragit RS 100 patches and also hydrophilic nature of RL 100 is responsible for increasing the amount of water absorbed by the patches, as shown in experiments involving two different moist atmospheres namely in 75% and 93% RH. Tables 2 & 3 show that the DBP has limited water solubility so it was difficult to hydrate the patch in higher percentage during the moisture content and water absorption studies. The hydrophilic nature of PVP has also to be taken into account with regard to the higher moisture content of the patches due to their higher PVP content. Similarly the water absorption under both RH conditions is also higher at higher PVP contents in the matrix patches. Eudragit RL 100 with PVP patches (L 5 - L 8) showed surface cracks and pores during the water absorption studies. Eudragit RL100 film plasticized with any of the plasticizers took up water a hundred times its weight and this may be attributed to the higher hydrophilic property of Eudragit RL film which rapidly broke during the water absorption studies[16]. Hence these were deleted from in vitro release studies because this type of matrix patches will not be stable during wound care therapy hence the patch needs needed balance in hydrophilic and hydrophobic nature[17-19].

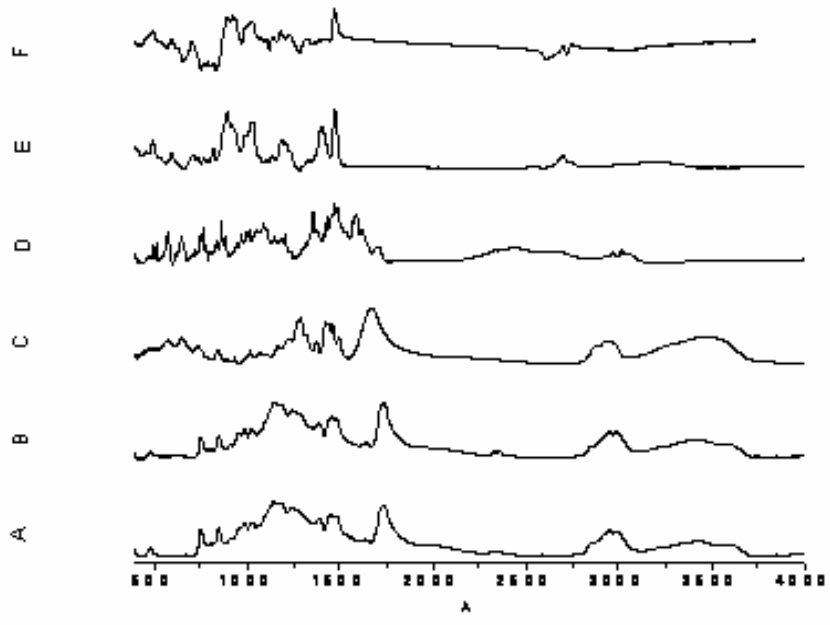
Table 2, the matrix patches having more than 20% of DBP with PVP is more flexible and adhesive in nature due to two important reasons, which is CPM itself acting as a plasticizer. [10] The second reason is that the addition of PVP resulted the significant increase of the matrix cohesion was due to interactions between the amide group of PVP and the carboxylic acid group of PMMA. Solid solutions of chlorpheniramine in Eudragit1 RL or RS films exhibited a decrease of T_g values when the concentrations of the drugs in the polymeric films were increased[20-21]. So the present study report will be promising for possiblilty in potential transdermal, wound care and with hot melt extrusion

technology film fabrication as earlier reported extrusion of CPM with HPC based polymer[11]. From the literatures and mechanical engineering handbooks, it is well known that the materials having a value more than 4.0 MPa are elastic in nature. Therefore in vitro release studies were carried out for only those patches having suitable physiochemical properties and more than 4.0MPa tensile strength.

3.2. ATR-FTIR studies

A comparison of the ATR-FTIR spectrums of the individual polymers/drug like eudragit RS 100, RL 100, PVP and CPM and also formulation matrix patch was carried out to observe any spectral shifts in the matrix. The FTIR spectra of the drug CPM, polymers (eudargit RS 100 & RL 100, PVP and formulation matrix patches are depicted in Fig. **1.** The group assignments are discussed in Table **4.** The FTIR spectra of the optimized formulations RS 100: PVP: CPM as well as RL 100: PVP: CPM [Scanned 1cm^2 patch containing 585µgm] revealed all the peaks of the polymers. The characteristics of eudragit RS 100 and PVP peaks 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 be overlapping in the region as that of the polymer.

FIG. 1: ATR FTIR Graphs: A: Eudragit RS 100; B: Eudragit RL 100; C: PVP; D: CPM; E: RS 100 Matrix patch; Figure: RL 100 Matrix patch



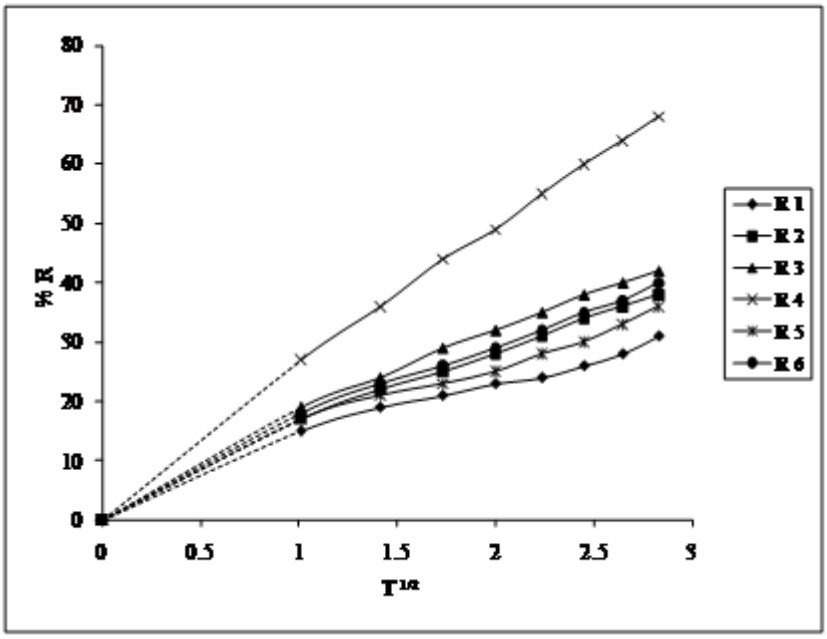
Wave number cm^{-1}

3.3. In vitro release studies

The percentage cumulative release and release rate (µgm/cm^2.hr) after 8 h of diffusion from both RS 100 and RL 100 matrix patches are shown in Table 5. From this data, it can be seen that as the amount

of DBP in matrix patch increases, the percentage release also increases; however in the case of RL 100, the release is maximum (even without PVP: L1 - L4: 32 – 89 %) than RS 100 patches (R1 – R4: 31 – 68 %). As stated earlier above 20% of DBP with PVP like R7 and R9 is sticky in nature though it released 59 & 68%, but in irregular passion. The cumulative release of drug on a percentage basis from the matrix patch was plotted with time ($t^{1/2}$) in Fig. 2 and Fig. 3. From the plots, 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 the RS 100 matrix patches (Fig. 1) follows Fick's law of diffusion. The plots of R2, R3 and R4, when extrapolated to the origin, may be considered as linear and follow Higuchi release while rest of the plots of RS 100 are not linear and do not follow Higuchi release. Higuchi developed an equation (percentage release = $Kt^{1/2}$) for the release of a drug from a homogeneous polymer matrix-type delivery system that indicates the amount of drug released is proportional to the square root of time[22]. In both cases, R/L 4 (25% DBP) exhibit the maximum percentage release compared to others. Release of a drug from a transdermal drug delivery system mainly involves diffusion factors[23]. This is probably due to two reasons the first one is that the greater uniform distribution of drug in the polymer matrix, the greater surface diffusion, while the other reason is the presence of a greater amount of DBP relaxing the polymer chain which increase the rate of diffusion. The patch released cumulative amount of CPM in the order R/L 1 > R/L 2 > R/L 3 > R/L 4.

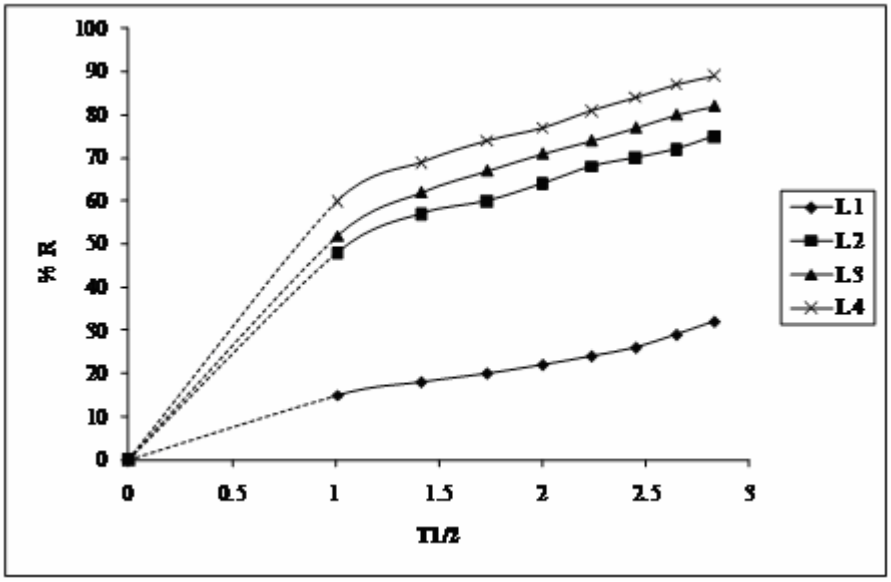
FIG. 2: Release profile of RS 100 patches



A break in each plot in Fig. 3 is observed in RL 100 matrix patches, each plots after the break also follow Fickian diffusion but do not follow Higuchi release. The total drug release increases with the increasing time of release but the total release as a percentage after 8 h is greater in RL 100 compared to the corresponding RS 100 (L1 –L4 >R1- R4) due to higher hydrophilic property of Eudragit RL 100

allow the permeant freely (responsible of its ammonium group), thereby promoting the dissolution, and hence higher release of water-soluble drug[24,25]. Moreover, with PVP patches like (L5 & L6) are polymer would leach out and, hence, create more pores and channels for the higher drug release[26]. Also the active path thickness of diffusion decrease leads to bursting effect as well as the release percentages increases.

FIG. 3: Release profile of RL 100 patches

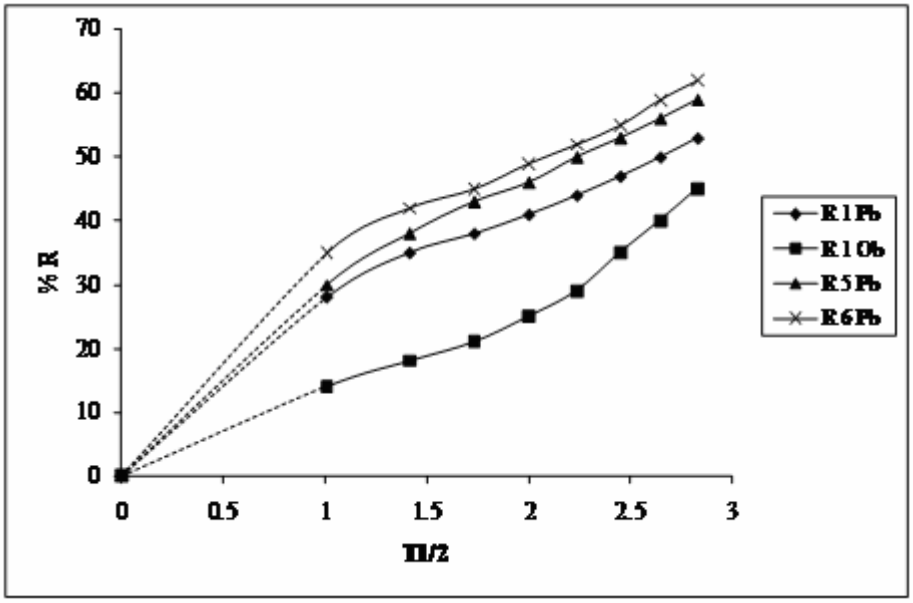


3.4. Effect of chemical enhancers on the release of CPM

To observe the enhancer effect R1, R5 and R6 patches were chosen as its tensile strength is appreciably high and cumulative release is lowest (31 – 40 %). Oleic acid and phospholipon 80 of different percentages were added (Table 6). The percent release increases with oleic acid but not appreciably, may be due filling of oleic acid between the polymer chain spacing and blocks the diffusion path channel with primary plasticizer of DBP. Many literatures have stated that oleic acid acts as a secondary plasticizer leads to lesser release of drug[27]. Phospholipon 80 either patch quality or the release percentages increased may be due to greater miscibility in the polymer drug matrix and thus increasing the average polymer chain spacing.

Many studies have employed phospholipids as vesicles (liposomes) to carry drugs into and through human skin. However, none of the studies have used phospholipids in a non-vesicular form as penetration enhancers[28]. This is the first time this enhancer is incorporated in to the matrix system. All the release profiles follow fickian diffusion, therefore the patches are containing 2% phospholipids 80 (R5 Pb and R6 Pb) considered for permeation (Fig.4).

FIG. 4: Release profile of RS 100 patches with chemical enhancers



The matrix patch L1 having reasonably high tensile strength and fairly uniform release rate was considered for observing the effect of chemical enhancers on its release profiles. The enhancers used were L-menthol, oleic acid and phospholipon 80 (1%, 2% and 3% of the total patch weight). The compositions and experimental release data for different patches are tabulated in Table 6 except phospholipon 80 because it was observed during and after the release studies that the patches were either swollen or the patches contained some surface cracks. The Fig. 5 and table 6 shows that the cumulative percent releases as well as release rate appreciably increased with 2% L-menthol & oleic acid (75 &76%) and show maximum release, incase of 3% L-menthol shows higher release but with few surface cracks, hence only 2% enhancers patches (L1 Mb & L1 Ob) were chosen for the permeation studies.

FIG. 5: Release profile of RL 100 patches with chemical enhancers

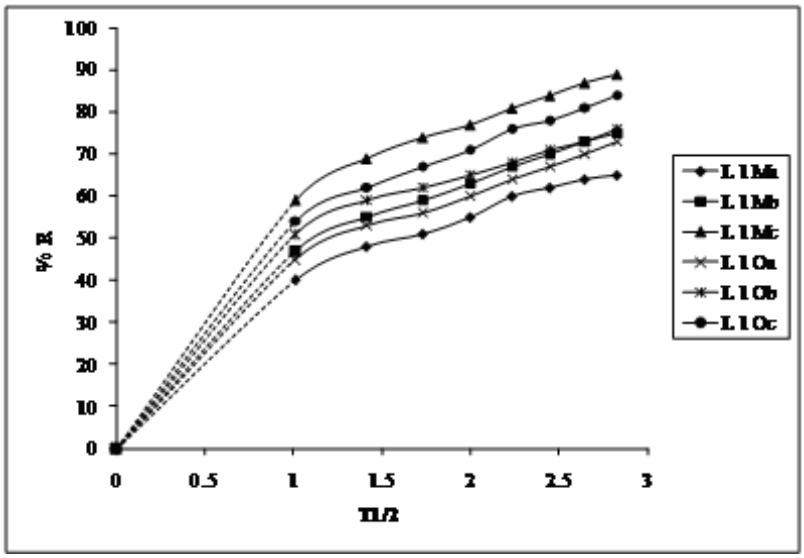


TABLE 6 Cumulative percentage release and rate with enhancers data

Patch code	P/O/M (%)			% Release after 8 hours			Release rate after 8thhour,µgm/cm^2.hr		
	a	b	c	a	b	c	a	b	c
R 1	P	P/O	P/O	44	53/45	54/49	12	13/26	20/21
R 5	P	P	P	36	59	61	13	19	28
R 6	P	P	P	43	62	83	8	21	33
L1	M/O	M/O	M/O	65/73	75/76	89/84	10/6	11/20	18/27

Notations:P: Phospholipon 80;O: Oleic acid; M:L-menthol (a-1%, b-2% and c -3%).

Eg. R5 Pb: 2% phospholipon 80

3.5. In vitro skin permeation studies

Considering all the factors like tensile strengths, better physiochemical properties, percent release, release rate, patch quality before and after release, surface smoothness and initial bursting effect of the patches, R2, R3, R4, R5Pb and R6Pb (RS100) and L1 Mb, L1 Ob, L2, L3 and L4 (RL 100) were selected for permeation studies. The cumulative permeation on a percentage basis after 8 h of permeation through RS 100 and RL 100 matrix patches and biological membrane (mouse skin) are also shown in Table 7. From this data, it can be seen that the R 4 and R 6 Pb matrix patches have the highest permeation, 42 % and 39 % respectively. Hence phospholipids is more suitable enhancer with RS 100 as reported earlier because 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[28].

FIG. 6: Permeation profile of RS 100 patches

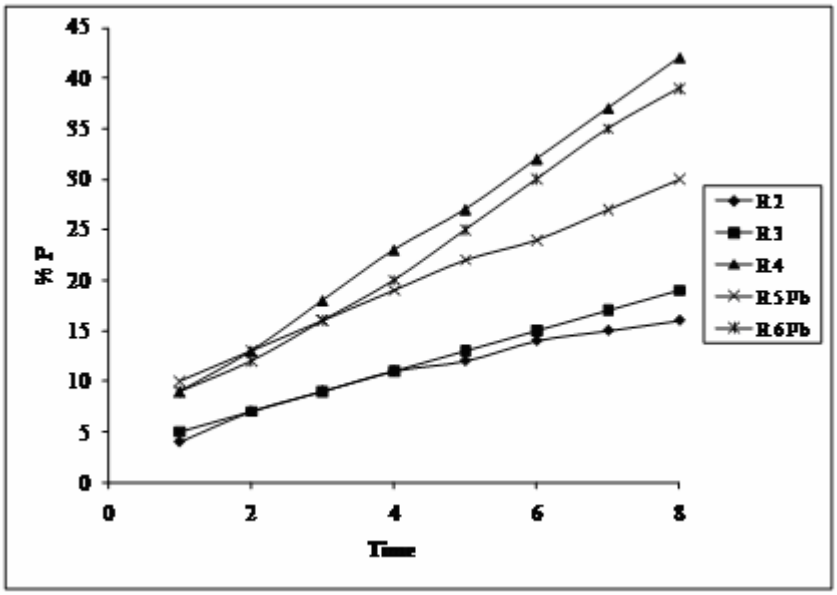
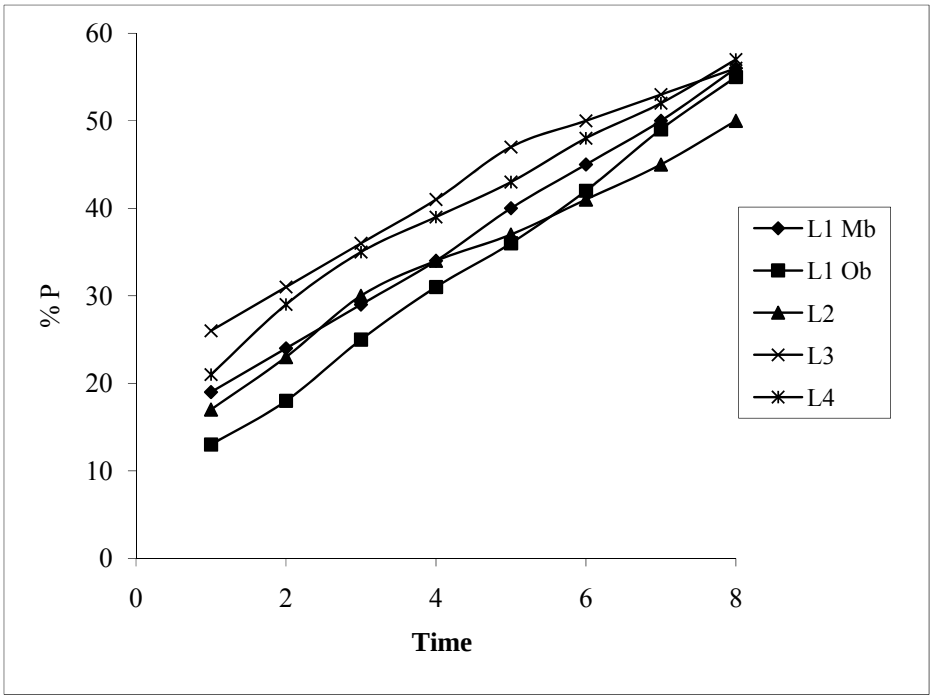


FIG. 7: Permeation profile of RL 100 patches



In the case of RL 100 patches the permeation of all the patches were regular, with higher percent permeation and uniform in nature. The cumulative release rate with L-menthol and oleic acid was higher mainly 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 membrane and a fluidizing action on the ceramide alkyl chains organization, increasing spacing of the lipid bilayer packing of the skin respectively[29-31].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 cumulative drug permeation as a percentage from RS 100 and RL 100 patches was plotted against the permeation time in hours (*t*) in Fig. 6 and Fig. 7 respectively. In each plot, the rate of drug permeation is fairly constant over time and the permeation profiles exhibit the concentration dependent first-order kinetics.

4. CONCLUSIONS

The percentage release and permeation from the RL 100 formulations are greater than the corresponding values of the RS 100 formulations, the other physical properties like patch thickness and tensile strength are slightly lower compared to RS 100 patches. The average moisture content and water absorption capacities of any RL 100 formulation are greater, hence proper packaging and storage of such RL 100 patches would be necessary. Percentages water absorption of RL 100 with PVP patches at different relative humidities is also higher compared to RS 100 patches. These physical properties also rule out the RL 100 with PVP patches from any further studies. Therefore, from the above observations, it may be concluded that (i). Polymer Eudragit RS 100 is suitable for making of

CPM matrix patch. (ii). DBP (25%) is the plasticizer of choice, however with 2% phospholipon80 as the enhancers may need only 15% of DBP for RS 100. (iii). PVP (copolymer) may be added in minimum amount in RS 100 formulation patches however it may require 2% phospholipon 80 as the chemical enhancer. (iv). In the case of RL 100, the copolymer PVP is not required, however it may be added (depends upon the release pattern required by the patient) chemical enhancers like 2% L menthol and oleic acid.

The patches R4, R6 Pb and all rest of the RL 100 patches are probably the best possible TD matrix patch composition for the uniform and continuous release/permeation of CPM for long period and for maintaining 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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