

EFFECT OF PLATICIZERS ON *IN VITRO* RELEASE AND *EX VIVO* PERMEATION OF CHLORPHENIRAMINE MALEATE FROM ETHYL CELLULOSE POLYVINYL PYRROLIDONE BASED MATRIX PATCHES

RAJAN RAJABALAYA^{*1,2}, SHEBA RANI NAKKA DAVID^{1,3},
JASMINA KHANAM², ARUNABHA NANDA²

¹*Department of Pharmaceutical Technology, School of Pharmacy, International Medical University, No. 126, Jalan Jalil Perkasa 19, Bukit Jalil 57000, Kuala Lumpur, Malaysia.*

²*Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700032, India.*

³*School of Bioscience & Engineering, Jadavpur University, Kolkata-700032, India.*

**corresponding author: rajan_rajabalaya@imu.edu.my*

Abstract

The present release and permeation studies were carried out for developing transdermal therapeutic systems with chlorpheniramine maleate (CPM). The matrix patches were prepared from ethyl cellulose (EC) with polyvinyl pyrrolidone (PVP) as the copolymer and plasticizers like dibutyl phthalate (DBP), dibutyl sebacate (DBS), triethyl citrate (TEC), acetyl triethyl citrate (ATEC), tributyl citrate (TBC) and acetyl tributyl citrate (ATBC) in different percentages. Thickness, tensile strength, elasticity, drug content, moisture content and water absorption studies of the matrix patches were measured. *In vitro* release/permeation of CPM was studied in a modified Keshary - Chien diffusion cell. Experimental release/permeation data (percent release and flux, $\mu\text{g}/\text{cm}^2 \cdot \text{hr}$) of different formulations of the matrix systems are reported. Also the drug-polymer interaction was investigated by ATR-FTIR studies. This study reports the effect of CPM in EC patch and suitable amount of plasticizer for better controlled release/permeation of CPM; hence this drug could be a potential candidate for transdermal antihistamine applications in film device industry.

Rezumat

Studiile de eliberare și de permeabilitate prezentate în articol au fost efectuate pentru dezvoltarea de sisteme terapeutice transdermice cu maleat de clorfeniramină (CPM). Matricele sistemelor terapeutice au fost pregătite din etil celuloză (CE) cu polivinil pirolidonă (PVP), ca copolimer și diferiți agenți plastifianți, cum ar fi dibutilftalat (DBP), dibutil sebacat (DBS), citrat de trietil (TCE), acetil citrat de trietil (ATEC), citrat de tributil (TBC) și acetil citrat de tributil (ATBC), în procente diferite. Au fost măsurate: grosimea, rezistența, conținutul de substanță activă, umiditatea, elasticitatea, studii de absorbție a apei. *In vitro*, eliberarea și penetrarea CPM-ului au fost studiate în celule de difuzie Keshary - Chien modificate. Sunt prezentate în articol datele experimentale privind eliberarea și permeabilitatea diferitelor formule ale sistemelor de matrice. De asemenea, interacțiunea medicament-polimer a fost investigată prin studii ATR-FTIR. Acest studiu prezintă efectul

CPM în sisteme transdermice pe bază de CE și cantitatea adecvată de plastifiant pentru o eliberare controlată optimă și pentru o penetrare mai bună a CPM, prin urmare, acest medicament ar putea fi un candidat potențial pentru formulările antihistaminice transdermice.

Keywords: Matrix patch; Chlorpheniramine maleate; Ethyl cellulose; Polyvinyl pyrrolidone; Plasticizer

Introduction

Ethyl cellulose (EC) is widely used as a coating material in solid dosage forms to provide controlled release profile of drug substances [13, 10]. EC films are prepared by the casting method, using organic solvents with incorporation of some long chain esters plasticizers, such as dimethyl, diethyl, dibutyl phthalates, triethyl and tributyl citrates, dibutyl sebacate, triacetin and also butyl and glycol esters of fatty acids [19]. Bulk of the casting solvent is initially evaporated leading to increased viscosity, which leaves the polymer chains in close proximity. Upon more complete evaporation of the organic solvent, the polymer chains are aligned so that secondary valence forces, either through hydrogen bonds or Van der Waals', are produced between the adjacent chains to further coalesce the polymer into a homogeneous, transparent film [20]. Plasticizers are actually low molecular weight resins or liquids, which hinder a great number of the active centers available for the polymers rigid contacts and increase the free space between the chains and provide a higher rotational freedom for polymer network [4]. A reduction in the volume fraction of the intermolecular cohesive bonds results, in the improvement of polymers flexibility and processability, by lowering the second order transition temperature [17]. Subsequently, a decreased T_g value, provides a superior coalescence of the colloidal particles in the pseudolatex or the polymer in the organic solutions [10]. Thus providing more mobility for the macromolecules, resulting in a softer, more easily deformable mass [15].

CPM is chosen for the present study because of the promising reports of the studies in the literature. Firstly, there is a good release of CPM from polymethacrylate amino-ester copolymer films (Eudragits RLPM and RSPM) [7, 21]. Secondly, 1% CPM, the therapeutic active agent, acts by itself as an excellent plasticizer with hot melt extruded HPC film which has various topical treatment purposes and finally, has an improved mechanical property [11,12]. These reports stimulated the idea for our study with 4% CPM and different plasticizers on EC: PVP matrix patches for its

mechanical and release profile. The EC: PVP (3:1) was reported as the best possible ratio from our earlier studies [12].

Chlorpheniramine, classified as an antihistaminic substance, is a propylamine derivative (alkylamines) and has a molecular weight of 390.87Da. 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, like other antihistamines, CPM produces a drying effect on various mucosas by preventing the responses to acetylcholine that are mediated via muscarinic receptors [11,12]. The CPM is a typical cationic amphiphilic amine drug (CAD) characterized by hydrophobic ring structure and hydrophilic side chain with a charged cationic amino group [16]. This physiochemical property of CPM is similar to other CADs, therefore it was chosen as a model drug for the present study.

Specific aims of the present study are as follows: the primary objective was to study the effects of various plasticizers on CPM loaded EC:PVP matrix patches to utilize them for continuous sustained release. The secondary aim was to evaluate the mechanical properties of various plasticized drug loaded patch. The first part of this work, reported hereafter, concentrates on the physiochemical characterization of the drug loaded ethyl cellulose patches. The second part will focus on identification of the best release/permeation of CPM patch by using modified Keshary Chien diffusion cell and also study the possible drug-polymer interaction by ATR-FTIR studies.

Materials and Methods

Reagents

Ethyl cellulose (EC) was graciously gifted by Signet Chemical Corporation, Mumbai, India. EC had an ethoxy content of 44–51% by weight and a viscosity range from 18 to 24 cps, Aqualon Pharma grade brand, N-22. Polyvinyl pyrrolidone (K-30) was purchased from SRL Pvt. Ltd., Mumbai, India. Chlorpheniramine maleate IP was gifted by Kontest Chemicals, Kolkata, India. Dibutyl phthalate was purchased from Qualigens Fine Chemicals, Mumbai, India. Dibutyl sebacate-N.F. (DBS), triethyl citrate-N.F. (TEC), acetyltriethyl citrate-N.F. (ATEC), tributyl citrate-N.F. (TBC), acetyltributyl citrate-N.F. (ATBC) were kindly gifted by Morflex, Inc., Greensboro, North California, USA. The reagents were used as received without any further purification. All other chemicals used in the study were of analytical reagent grade.

Preparation of the patches

For preparation of the patches, 300 mg of EC was dissolved in a solvent for 30 min, followed by addition of 100 mg PVP, with uniform but slow magnetic stirring, for another 30 min. Then the required plasticizer (10-50% of the total polymer weight) and 16 mg of the drug (CPM) were added to the solution and stirred for 30 min. Next, the total mass was slowly poured into the centre of SS (stainless steel) rings, which had a backing layer of aluminium foil. The total mass was dried at room temperature for 48 h. The dried patches were kept in sealed plastic pouches and stored in desiccators until further use.

Determination of patch thickness

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

Determination of tensile strength

The tensile strength of the patches was evaluated using Instron 4204, UK tensilemeter with a mounted load of 50KN. The patches were tested with extension speed at 5mm/min [American society for testing materials (ASTM); method D 882- 75D]. The test was carried out at $25\pm 2^{\circ}\text{C}$ and $56\pm 2\%$ 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 I).

Drug content

A known area of the 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, we used a spectrophotometric method at 267nm. A control was also performed using a drug free film. An average of six readings was tabulated. (Table II)

Moisture content

The patches were weighed individually and kept in a desiccator containing fused calcium chloride at 40°C for 24 hours [7]. 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 II).

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

***In vitro* release study**

The *in vitro* release studies were carried out in a modified Keshary - Chien diffusion cell. A piece of 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 of pH 7.4. The receptor compartment was maintained at $32 \pm 0.5^\circ\text{C}$ 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 buffer solution. Samples were analyzed spectrophotometrically at 276nm after suitable dilution. An average of three readings was tabulated in table III.

***In vitro* skin permeation study**

A section of 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 used during the release study.

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

The patches were analyzed by attenuated total reflectance-Fourier transform infrared spectrometry (ATR-FTIR) on a Magma-IR™ Spectrometer 750 (Nicolet Instrument Corp.), equipped with a Golden Gate Single Reflection Diamond ATR spectrophotometer (check). 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} .

Results and Discussion

Thickness, tensile strength and modulus elasticity

Tensile test of the patch enables the analysis of mechanical properties, such as strain and stress at failure (strength). These properties are important, since patch needs to exhibit desirable resistance to external forces during storage or use. Drug itself showed to increase the mechanical and plasticizing effect on HPC film [11,12]. In this study, relative series of incremental concentrations of plasticizer were included to ascertain any enhanced effect of mechanical properties of EC patches with CPM.

From table I, it is seen that as the modulus of elasticity value increases the ultimate tensile strength gradually decreases by sequential addition of the plasticizer in the patch. It is obvious that higher amounts of the plasticizer in the patch, make greater the number of molecules to take the possibility of contribution to the extended polymer, superseding the contact polymer–polymer forces of the adjacent chains [15].

Table I

Patch composition, average thickness, tensile strength and modulus of elasticity

EC:PVP:CPM 300:100:16 (mg)	% of plasticizer	Average thickness mm	Tensile Strength MPa	Modulus of elasticity MPa
C1	DBP	20	0.110 ± 0.004	7.267 ± 0.68
C2		30	0.114 ± 0.005	6.923 ± 0.29
C3		40	0.123 ± 0.001	6.343 ± 0.96
C4		50	0.125 ± 0.007	5.824 ± 1.06
C5	DBS	10	0.103 ± 0.002	8.293 ± 0.41
C6		20	0.109 ± 0.004	7.845 ± 0.72
C7		30	0.117 ± 0.003	7.208 ± 0.83
C8		40	0.120 ± 0.006	6.735 ± 0.62
C9		50	0.129 ± 0.005	5.802 ± 0.18
C10	TEC	10	0.110 ± 0.001	5.126 ± 0.53
C11		20	0.119 ± 0.004	5.109 ± 0.47
C12		30	0.121 ± 0.003	5.054 ± 0.49
C13		40	0.125 ± 0.004	4.862 ± 0.62
C14		50	0.127 ± 0.007	4.201 ± 0.80
C15	ATEC	20	0.114 ± 0.005	6.577 ± 0.61
C16		30	0.120 ± 0.003	6.378 ± 0.21
C17		40	0.126 ± 0.007	5.126 ± 0.16
C18		50	0.128 ± 0.004	4.986 ± 0.38
C19	TBC	20	0.109 ± 0.002	8.620 ± 0.72
C20		30	0.115 ± 0.008	7.462 ± 0.64
C21		40	0.119 ± 0.002	6.605 ± 0.51
C22		50	0.124 ± 0.003	5.702 ± 0.91
C23	ATBC	20	0.110 ± 0.005	7.809 ± 0.21
C24		30	0.118 ± 0.006	7.221 ± 0.58
C25		40	0.124 ± 0.008	6.058 ± 0.25
C26		50	0.129 ± 0.005	5.496 ± 0.41

Notation: DBP 10%, ATEC 10%, TBC & ATBC 10% are brittle in nature

The entrapped plasticizer molecules in EC entanglement nullify a great volume of the inter-chain cohesive forces through the new polymer–plasticizer bindings which result in a significant decline in the ultimate strength of the constructed patches. From table I it is clear that the addition of incremental plasticizer increased the local mobility, due to a decrease in the attractive forces of the polymer network which retains the increased elasticity (C1-C29) under mechanical loading. The increased modulus of elasticity, in general, provides a higher protection against the impact of the dynamic loadings [2, 3].

Two conclusions could be derived from these results: plasticizer addition caused a significant decrease of tensile strength (stress at failure) and a significant increase of strain at failure. Among the most widely used plasticizers, such as citrate and phthalate derivatives, no significant differences were observed in the mechanical properties of plasticized EC pseudolatex films [18]. Those properties were influenced by different type, nature and concentrations of traditional plasticizers and moreover, CPM is also believed to increase the plasticization efficiency considerably with the DBS matrix patches (C5-C9). The literature survey shows that less than 30% of DBS produce a stiff, strong structure with brittle natured EC membrane [18], but the present study proves that the drug CPM improves the mechanical properties efficiently even with 10% DBS hence the patch is flexible and not brittle in nature. The rest of the plasticized patches also improved their mechanical properties considerably with drug CPM, thus it may be concluded that CPM influenced the mechanical properties of the EC matrix system very effectively.

Most of the patches were elastic and flexible (except 10% DBP, ATEC, TBC and ATBC are brittle in nature) with an average tensile strength greater than 4.0 MPa. From the literatures [15] and mechanical engineering handbooks, it is well known that the materials having a MPa value more than 4.0 are elastic in nature. Therefore, *in vitro* release studies were carried out for all the patches.

Drug content, moisture content and water absorption studies

Table II shows that the average drug content, CPM, of all the patches is more than 98% and the moisture content percentage and water absorption uptake capacities of the EC patches are purely dependent on type and concentration of plasticizer used in the study. The patches with hydrophilic natured TEC plasticizer (C10-C14) have higher moisture content and water absorption compared to hydrophobic plasticized patches because these allow the water to enter freely into the patch which leads to higher uptake of moisture and water absorption easily by the hydrophilic

nature of PVP, as shown in experiments involving two different moist atmospheres namely have 75% and 93% RH (room humidity). Whereas, hydrophobic nature DBP, DBS, TBC and ATBC patches have difficulty to hydrate the patch during the moisture content and water absorption studies especially in higher percentages.

Table II

Average drug content, moisture content and water absorption capacities

Patch code	% of plasticizer	Drug content (μgm)	Moisture content (wt %)	Water absorption (wt %)	
				75% RH	93 % RH
C1	DBP	20	573 $\pm$ 0.31	1.112 $\pm$ 0.24	1.531 $\pm$ 0.93
C2		30	575 $\pm$ 0.43	1.102 $\pm$ 0.34	1.501 $\pm$ 0.72
C3		40	578 $\pm$ 0.55	1.092 $\pm$ 0.15	1.493 $\pm$ 0.52
C4		50	582 $\pm$ 0.84	1.077 $\pm$ 0.11	1.478 $\pm$ 0.41
C5	DBS	10	571 $\pm$ 0.71	1.123 $\pm$ 0.58	1.471 $\pm$ 0.37
C6		20	574 $\pm$ 0.46	1.118 $\pm$ 0.58	1.412 $\pm$ 0.41
C7		30	577 $\pm$ 0.67	1.094 $\pm$ 0.22	1.346 $\pm$ 0.63
C8		40	578 $\pm$ 0.28	1.083 $\pm$ 0.49	1.312 $\pm$ 0.65
C9		50	581 $\pm$ 0.82	1.073 $\pm$ 0.59	1.301 $\pm$ 0.91
C10	TEC	10	570 $\pm$ 0.18	1.537 $\pm$ 0.42	2.201 $\pm$ 0.72
C11		20	573 $\pm$ 0.45	1.544 $\pm$ 0.27	2.253 $\pm$ 0.32
C12		30	575 $\pm$ 0.61	1.551 $\pm$ 0.37	2.279 $\pm$ 0.71
C13		40	577 $\pm$ 0.11	1.568 $\pm$ 0.67	2.285 $\pm$ 0.48
C14		50	579 $\pm$ 0.26	1.571 $\pm$ 0.54	2.289 $\pm$ 0.41
C15	ATEC	20	568 $\pm$ 0.38	1.312 $\pm$ 0.86	2.103 $\pm$ 0.63
C16		30	570 $\pm$ 0.62	1.325 $\pm$ 0.27	2.112 $\pm$ 0.65
C17		40	574 $\pm$ 0.74	1.339 $\pm$ 0.62	2.126 $\pm$ 0.94
C18		50	577 $\pm$ 0.11	1.346 $\pm$ 0.63	2.151 $\pm$ 0.25
C19	TBC	20	570 $\pm$ 0.42	1.102 $\pm$ 0.56	1.448 $\pm$ 0.12
C20		30	574 $\pm$ 0.68	1.092 $\pm$ 0.54	1.438 $\pm$ 0.82
C21		40	578 $\pm$ 0.28	1.082 $\pm$ 0.94	1.421 $\pm$ 0.37
C22		50	580 $\pm$ 0.84	1.073 $\pm$ 0.41	1.418 $\pm$ 0.19
C23	ATBC	20	570 $\pm$ 0.57	1.064 $\pm$ 0.48	1.346 $\pm$ 0.63
C24		30	575 $\pm$ 0.74	1.053 $\pm$ 0.65	1.332 $\pm$ 0.39
C25		40	577 $\pm$ 0.83	1.049 $\pm$ 0.91	1.331 $\pm$ 0.63
C26		50	579 $\pm$ 0.93	1.037 $\pm$ 0.59	1.314 $\pm$ 0.32

***In vitro* release studies**

The percentage cumulative release and release rate after 8 hr from different plasticized CPM matrix patches are shown in Table III. The cumulative release of drug on a percentage basis from the matrix patch was plotted against time ($t^{1/2}$) in figures 1 and 2. Plots which are having Higuchi pattern and only optimum release formulations are presented. Figures 1 and 2 plots represent cumulative percentage release of CPM from the patches which contain DBP, DBS and citrate group plasticizer (TEC, ATEC, TBC & ATBC) as their plasticizer respectively. From the table and figure of the release pattern from the DBP contained patches C1 – C4, it is observed that they follow Fick's law of diffusion, being also 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 square root of time.

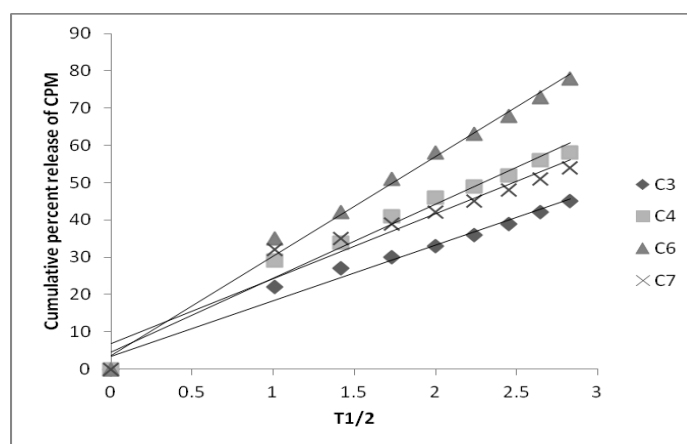


Figure 1

Release profile of DBP and DBS containing patches

From figure 1, C3 and C4, when extrapolated to the origin, fairly follow Higuchi release, also the release rates are fairly uniform in each interval. While C1 and C2 patches released 29 and 44% respectively, this may be due to the reduced amount of DBP which was insufficient to relax the polymer chain and also does not follow the Higuchi release pattern.

The free volume theory of diffusion is absolutely applicable to DBP containing patches. The explanation for this phenomenon is that increasing the amount of plasticizer increases the reduction of inter-molecular attractive forces between the polymer chains, simply due to the higher number of plasticizer molecules located between the macromolecules. Thus,

the mobility of the polymer chains is increased, resulting in higher drug diffusion rates.

In case of DBS, the release profile is higher than DBP patches even at low plasticizer concentrations ($C1 - C5 > C6 - C9$). The patch C5 (10% DBS), with a percent release of 86%, has maximum release which may be due to molecular binding of polymer, copolymer and plasticizer. The molecular binding was not enough to restrict the direct dissolution of PVP in the phosphate buffer solution. Whereas, from the Fig.1 it is clear that the patches C6 and C7 have higher release and follow Higuchi release more regularly. It is in good agreement with J. Siepmann [17], who reported that DBS is suitable for a more 'rapid' release, whereas phthalate groups should be chosen when a more prolonged liberation is desired. Though C8 and C9 patches have reasonable tensile strength, uniform release rates and follow Fickian diffusion and Higuchi release, they were not considered for further studies due to low amount of cumulative release 30% and 42% respectively after 8 hrs of interval.

All citrate group of plasticizer constructed patches and its release profile data from C10 - C26 are presented in Table III, and only Higuchi release pattern obeying formulations are presented graphically in figure 2.

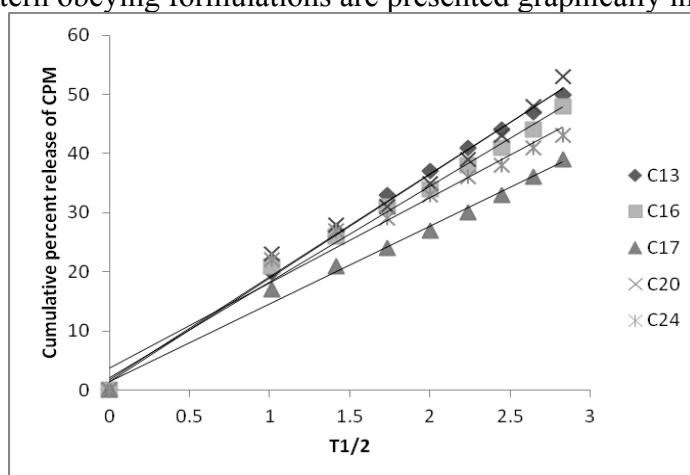


Figure 2

Release profile of citrate group plasticizer containing patches

The matrix patches C10, C11 and C12 give high cumulative releases of 91%, 83% and 77% respectively with partially uniform release rates as well as first hour bursting effect. However after release, all the three patches contained a good number of surface pores. Two reasons may be behind this phenomenon, one is that plasticizing effect of TEC is lesser to that of DBS,

even 30% of TEC is unable to form a strong binding among the ingredients and second is that, due to water soluble nature, TEC in the patches allows the dissolution of PVP easily into the buffer medium during release studies. Obviously, the long chained DBS and acetylated monoglyceride molecules penetrate into the EC chains better than the more spherical TEC molecules. It agrees with the earlier report by Hyppölä R [18] that the DSC measurements revealed a biphasic system in EC films with 10% TEC and also not plasticized effectively.

Table III

Cumulative percent release/permeation and release rate/permeation rate after 8 hours

Patch code	% of plasticizer	% Release	Release rate ($\mu\text{gm}/\text{cm}^2/\text{h}$)	% permeation	Permeation rate ($\mu\text{gm}/\text{cm}^2/\text{h}$)
C1	20	29	6	-	-
C2	30	44	15	-	-
C3	40	50	17	30	9
C4	50	58	18	40	14
C5	10	86	37	-	-
C6	20	78	32	48	16
C7	30	53	20	38	15
C8	40	42	18	-	-
C9	50	29	9	-	-
C10	10	91	28	-	-
C11	20	82	32	-	-
C12	30	77	25	-	-
C13	40	51	21	27	9
C14	50	34	15	-	-
C15	20	37	19	-	-
C16	30	48	19	33	15
C17	40	39	18	25	9
C18	50	38	21	-	-
C19	20	58	14	-	-
C20	30	53	15	29	9
C21	40	40	17	-	-
C22	50	38	33	-	-
C23	20	60	21	-	-
C24	30	43	11	30	10
C25	40	28	14	-	-
C26	50	22	7	-	-

Generally, with increasing plasticizer level the diffusivity of the drug increases due to the higher mobility of the polymer chains [9]. In the present study with TEC, this relationship is inverse and it was found to decrease release percentages and rates of CPM with increasing amounts of TEC in the patch. It may be due to three main reasons (i). hydrophilic TEC leaches from the patch, resulting in decreasing plasticizer content and thus decreasing diffusivity [6] (ii). greater degree of coalescence of the EC particles into a patch for a given set of processing conditions with increasing plasticizer level [8] (iii). during the release studies, the patch is in contact

with the release medium, hence water-filled cavities/channels are created, and drug transport also occurs via diffusion through these domains. It is also evident that this present study of moisture content and water absorption capacities values are higher in TEC patches (Table II). It is interesting to note that C13 patch has optimum cumulative release after 8 hours (51%) and uniform release rate and also shows fickian diffusion and Higuchi release without any deviation (Figure 2).

The release profiles of all ATEC plasticized patches (C15 - C18) follow Higuchi release kinetics but lower percentage release due to very limited water solubility of ATEC, which does not allow the easy dissolution of PVP in the diffusion medium and thus leads to low amount of drug released, though considerable release percentages were obtained from C16 (48%) and C 17 (39%) (Figure 2). The patches containing citrate plasticizer (TBC and ATBC) has release profiles which follow diffusion controlled matrix model – Fick's law of diffusion, but release percentages are insignificant from all the patches. Whereas, from figure 2 it is clear that only C20 and C24 follow Higuchi release ($\% R = KT^{1/2}$) pattern as well as uniform release rate throughout the release study.

The overall percentage release from high molecular weight plasticizer (ATEC, TBC, ATBC > TEC, DBP, DBS) patches is lower compared to low molecular weight plasticized patches. It may be due to the reason that lower molecular weight plasticizers had more molecules per unit weight, and those molecules could more easily penetrate between the polymer chains of the patch and it might lead to higher molecular diffusion, whereas the higher molecular weight plasticizer would decrease the tendency for migration [21]. Another reason may be the sequential addition of the plasticizers, which seems to affect the mass transfer coefficient in the boundary layer, (h) with increasing plasticizer concentration, h increases. In other words, the mass transfer resistance within the boundary layer increases with increasing plasticizer level. In the present study also this phenomenon may affect the overall drug release kinetics because of the dominating mass transfer resistance within the polymer [22-23].

***In vitro* permeation studies**

The cumulative permeation on a percentage basis and permeation rate ($\mu\text{gm}/\text{cm}^2 \cdot \text{hr}$) after 8 hr of permeation through patches (patches chosen which are follows the Higuchi release pattern as well as uniform release rate during release studies) and biological membrane (mouse skin) is shown in Table III. From this data, it can be seen that DBP and DBS matrix patches have the highest permeation, in the range of 30 - 40% and 38-48% respectively compare to citrate based plasticized patches permeated in the

range of 25-33%. The cumulative percent permeation of patches C13 and C17 are smaller than 30% which may be due to swelling or any kind of hydration of the polymer in the TEC patches (as in the drug release studies) did not occur very efficiently during permeation hence did not come into direct contact with the receptor solution. The *in vitro* drug release and skin permeation studies showed that the skin is a 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 DBP and DBS and other citrate group patches was plotted against the permeation time in hours (t) in figure 3 and figure 4 respectively. In each plot, the rate of drug permeation is fairly constant over time and the permeation profiles exhibit concentration dependent first-order kinetics.

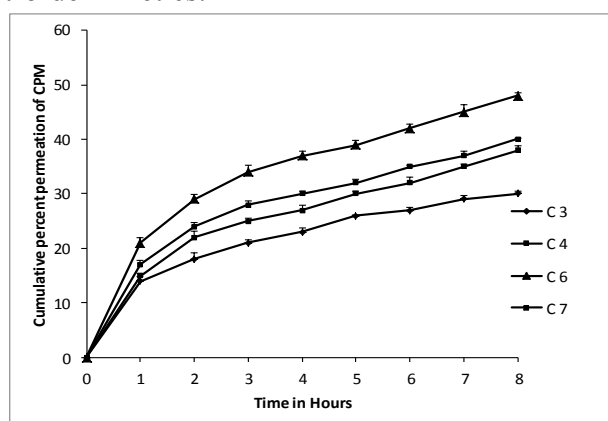


Figure 3.

Permeation profile of DBP and DBS containing patches

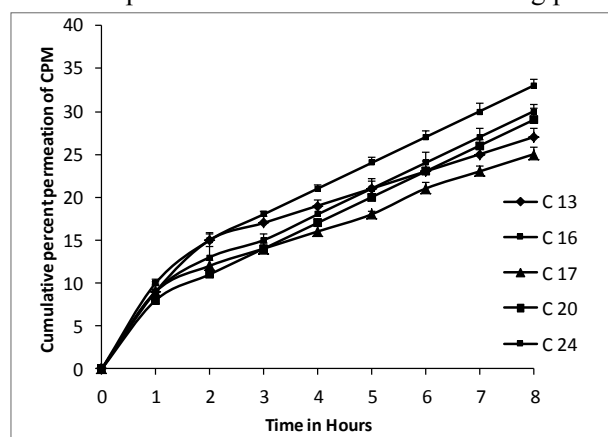


Figure 4

Permeation profile of citrate group plasticizer containing patches

ATR-FTIR studies

A comparison of ATR-FTIR spectrum of the individual polymers EC, PVP and CPM and the formulation matrix patches was performed to observe any spectral shifts in the spectrum. The FTIR spectra of CPM, polymers (EC, PVP) and formulation matrix patches are depicted in figure 5.

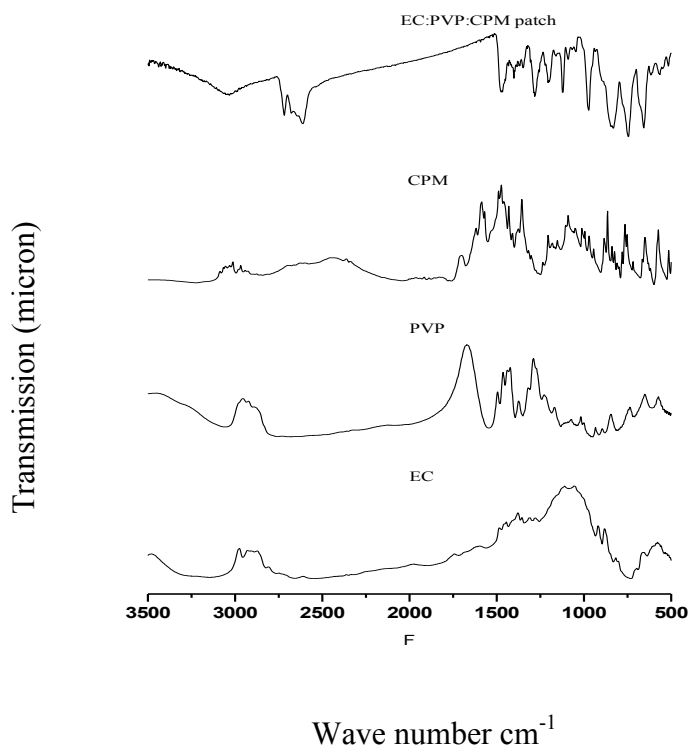


Figure 5

ATR FTIR spectra: EC: Ethyl Cellulose; PVP: Polyvinyl Pyrrolidone; CPM; Chlorpheniramine Maleate: EC:PVP:CPM: Matrix patch

The ATR-FTIR spectra of the optimized formulations EC: PVP: CPM [300:100:16(mg)] revealed all the peaks of the polymers. The characteristics of EC and PVP peaks of the polymer were observed at 2950 cm^{-1} , 1047 cm^{-1} and 1631 cm^{-1} , 1284 cm^{-1} respectively. No significant shifts in the peaks corresponding to the drug or polymers were observed in the formulation matrix. Major frequencies of functional groups of pure drug remained intact in the matrix patch; hence, there is no major interaction between the drug and polymers used in the study.

Conclusions

Many literature studies show that EC patches with less than 30% plasticizer become stiff, strong structure with brittle nature. In the present study most of the EC patches are flexible, in nature, even below 30% plasticizer with 4% CPM. It may be concluded that CPM effectively increased the mechanical properties of the patches. The best suitable plasticizer is DBS when incorporating the CPM in the EC matrix patch whereas TEC from every point of view is inferior to other plasticizers. Therefore, from the above studies, it may be concluded that the formulation [EC: PVP: CPM (300:100:16 mg)] with 30% of any plasticizer except TEC is probably the best possible TD matrix patch composition for uniform and continuous release/permeation of CPM for long period and for maintaining a sustained therapeutic level of the drug in plasma. Considering all the factors, the formulations C3, C4, C6, C7, C20 and C24 patches are useful for further pharmacokinetic and pharmacodynamic studies in suitable animal models.

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