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Designing and Characterization of Drug Free Patches for Transdermal Application

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ABSTRACT
The present investigation was taken up to prepare and evaluate drug free polymeric patches using different polymers and to study the effect of different plasticizers on physicochemical properties of the patches to explore their feasibility for transdermal application. Polyethylene glycol (PEG 400), Dibutylphthalate (DBP) and Propylene glycol (PG) were used as plasticizers at a concentration of 40 % w/w of dry polymer weight. Drug free polymeric patches were prepared by the casting method on mercury surface and evaluated for weight variation, thickness, flatness, tensile strength, folding endurance, surface pH, hardness, swellability, water vapour transmission rate and skin irritation studies. The mercury substrate method was found to give thin uniform patches.
The weight and thickness of the patches was found to be uniform. Tensile strength and folding endurance of the patches prepared with DBP as plasticizer was high compared to patches plasticized with PG and PEG. All the formulations show 100 % flatness. HPMC K4M: PVP patches plasticized with PEG 400 showed higher swellability and water vapour transmission rates. The patches were found to be free of any skin irritation. Based on the above observations, it can be reasonably concluded that plasticizers have a significant influence on the mechanical properties of the transdermal patches.

Keywords: Transdermal, PEG400, Dibutylphthalate, Propylene glycol, Eudragit, Cellulose acetate.

INTRODUCTION

The development of technology for release of drug at a controlled rate into systemic circulation using skin as a port of entry has become popular for various reasons. [1] Transdermal patches are innovative drug delivery systems and can be used for achieving efficient systemic effect bypassing hepatic first pass metabolism and increasing the fraction absorbed. [2] The transdermal therapeutic system provide for continuous drug release through intact skin into the systemic blood stream during a prolong time at a preset rate. [3] The screening and testing of polymers for use in transdermal drug delivery needs the knowledge of placebo patches. Formulation of polymeric patches for transdermal drug delivery system requires plasticizers. Plasticizers are added to polymeric system to modify their physical properties and to improve their film forming characteristics. Plasticizers can change the viscoelastic behaviour of polymers significantly. Plasticizers can turn a hard brittle polymer into a softer, more pliable material and possibly make it more resistant to mechanical stress. [4] The plasticizer will interpose itself between the polymer chains and interact with the forces held together by extending and softening the polymer matrix. [5] The commonly used plasticizers include phthalate esters, phosphate esters, fatty acid esters and glycol derivatives. [6] In the present investigation drug free patches of different polymers were formulated and evaluated. The effect of three different plasticizers viz. Polyethylene glycol 400, Dibutylphthalate and Propylene glycol on physicochemical properties of placebo patches was also studied.

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MATERIALS AND METHODS

Eudragit RL100 and Eudragit RS100 was gifted sample from Wockhardt Pharmaceutical Ltd, Hyderabad. HPMC K4M, HPMC K15M, HPMC K100M was gifted sample from Colorcon Pvt. Ltd., Goa. Cellulose acetate (Ottokemi, Mumbai), PVP K-30 and PEG 4000 (CDH (P) Ltd., New Delhi), Dibutyl Phthalate (S. D. Fine Chem. Ltd., Mumbai), PEG 400 (Lobachemie Pvt. ltd) and Propylene Glycol (Merck Ltd, Mumbai) were used. All other chemicals used were of analytical grade.

Methods

Formulation of drug free patches

Transdermal patches were prepared by solvent casting technique employing mercury as a substrate. [7] The casting solutions were prepared by dissolving appropriate polymers and plasticizers in suitable solvents using magnetic stirrer for 20 min to get uniform dispersion. Plasticizers were added at a concentration of 40 % w/w of polymers. The solution was then transferred quantitatively to glass ring kept on the surface of mercury in petridish. Controlled solvent evaporation was achieved by placing an inverted funnel over the petridish. These were left undisturbed at room temperature for one day. The patches could be retrieved intact by slowly lifting the rings from the mercury substrate and kept in the dessicator until used. The composition of transdermal patches is shown in Table 1.

Characterization of Transdermal Patches

The composition of transdermal patches has a profound influence on the physical, mechanical properties as well as the permeability of drugs. Transdermal patches of 3.14 cm^2 were taken out from each casted film after complete drying and evaluated for the following physicochemical properties.

Thickness

The thickness of transdermal patches was measured at three different places using a micrometer and the mean values were calculated. [8]

Weight variation

The patches were subjected to weight variation by individually weighing five randomly selected patches. Such determinations were carried out for each formulation. [9]

Flatness

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, three longitudinal strips were cut out from each patch: 1 from the centre, 1 from the left side, and 1 from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0 % constriction equivalent to 100 % flatness.

$$\% \text{ constriction} = l_1\text{-}l_2/\ l_2 \times 100$$

Where l_1 = initial length of each strip

l_2 = final length of each strip [10]

Tensile strength

Mechanical properties of the polymeric patches were conveniently determined by measuring their tensile strength. [11] The tensile strength of the patches was determined by using a tensile strength instrument. Tensile strength is the maximum stress applied to a point at which the specimen breaks, and can be computed from the applied load at rupture and the elongation of the patch as described from the following equation.

$$T.S. = \text{break force}/\ a.b\ (1+\Delta L/L)$$

Where a,b and L are width, thickness and length of the strip respectively.

ΔL is the elongation of patch at break point.

Break force = Weight required to break the patch (Kg.) [12]

Hardness

Hardness test was performed on three different patches individually from each batch by fabricated hardness instrument and the average was calculated. Hardness apparatus consists of a wooden stand of 8 cm in height, and a top area of 8 × 8 cm. A hole of 0.2 cm diameter was made in the center of the wooden top. A small plastic pan was fixed horizontally on to one end of a 2 mm thick smooth iron rod, whose other end had been reduced to sharp point. This rod, having the pan on its upper end, was inserted into the hole of the wooden top and its lower sharp end was placed on a metal plate.

An electric circuit was made through a 3-volt battery in such a way that the bulb lighted up only when the circuit was completed through the contact of the metal plate and the sharp end of the rod. The sample patch was placed between the metal plate and the sharp end of the iron rod and weights were gradually added on to the pan and the total weight required to penetrate the patch, which was indicated as lighted bulb, was noted. [13]

Folding Endurance

The folding endurance is defined as the number of folds required to break any polymeric patch. [14] This test was carried out to check the efficiency of the plasticizer and the strength of the patch prepared using different polymers. [15] This was determined by repeatedly folding one patch at the same place until it broke. The number of times the patch could be folded at the same place without breaking/cracking gave the value of folding endurance. [16]

Swellability

The patches of 3.14 cm^2 was weighed and put in a petridish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed.

The degree of swelling (S) was calculated using the formula

$$S\ (\%) = W_t - W_o/W_o \times 100$$

Where S is percent swelling

W_t is the weight of patch at time t and W_o is the weight of patch at time zero. [17]

Surface pH

Surface pH of the patches was determined by the method described by Bottenberg et al. The patches were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1 hour in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute. [18]

Water vapour transmission

For water vapour transmission studies glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried to constant weight in an oven.

About 1 g of fused calcium chloride as a dessicant was taken in the vials and the polymeric patches were fixed over the brim with the help of an adhesive tape. These preweighed vials were stored in a humidity chamber at an RH of 80 % with the temperature set to 30ºC for a period of 24 h. The weight gain was determined every hour up to a period of 24 h. [19]

Water vapour transmission (Q) usually expressed as number of grams of moisture gain per 24 h per square centimeter, was calculated using the equation

$$Q = WL/S$$

Where W is gm of water transmitted / 24 h [20]

L is patch thickness in cm

S is surface area in cm^2

Skin Irritation Study

The hair on the dorsal side of Wister albino rats was removed 1day before the initiation of this study. The rats were divided

Table 1: Composition of Drug Free Transdermal Patches

Formulation Code	Polymers (4:1)	Polymer Concentration (% w/v)	Casting Solvent	Plasticizer Concentration (% w/w)*		
				PEG 400	DBP	PG
F_1	CA +PVP	5	Acetone	40	-	-
F_2	CA +PVP	5	Acetone	-	40	-
F_3	CA +PVP	5	Acetone	-	-	40
F_4	CA + HPMC	5	Acetone	40	-	-
F_5	CA + HPMC	5	Acetone	-	40	-
F_6	CA + HPMC	5	Acetone	-	-	40
F_7	CA + PEG 4000	5	Acetone	40	-	-
F_8	CA + PEG 4000	5	Acetone	-	40	-
F_9	CA + PEG 4000	5	Acetone	-	-	40
F_{10}	HPMC K4M + PVP	2	Ethanol:dichloromethane	40	-	-
F_{11}	HPMC K4M + PVP	2	Ethanol:dichloromethane	-	40	-
F_{12}	HPMC K4M + PVP	2	Ethanol:dichloromethane	-	-	40
F_{13}	HPMC K15M + PVP	2	Ethanol:dichloromethane	40	-	-
F_{14}	HPMC K15M + PVP	2	Ethanol:dichloromethane	-	40	-
F_{15}	HPMC K15M + PVP	2	Ethanol:dichloromethane	-	-	40
F_{16}	HPMC K100M + PVP	2	Ethanol:dichloromethane	40	-	-
F_{17}	HPMC K100M + PVP	2	Ethanol:dichloromethane	-	40	-
F_{18}	HPMC K100M + PVP	2	Ethanol:dichloromethane	-	-	40
F_{19}	Ed RL100 + Ed RS 100	5	Acetone	40	-	-
F_{20}	Ed RL100 + Ed RS 100	5	Acetone	-	40	-
F_{21}	Ed RL100 + Ed RS 100	5	Acetone	-	-	40
F_{22}	Ed RL100 + HPMC	5	Acetone	40	-	-
F_{23}	Ed RL100 + HPMC	5	Acetone	-	40	-
F_{24}	Ed RL100 + HPMC	5	Acetone	-	-	40
F_{25}	Ed RS100 + HPMC	5	Acetone	40	-	-
F_{26}	Ed RS100 + HPMC	5	Acetone	-	40	-
F_{27}	Ed RS100 + HPMC	5	Acetone	-	-	40

* % w/w of polymer

Table 2: Characterization of transdermal patches

Code	Weight variation (mg)	Thickness (mm)	Tensile strength (kg/ mm^2)	Folding Endurance	Surface pH	Hardness (gm)	Swellability (%)	Water vapour transmission ($gmcm/cm^2.24h$)	Flatness (%)
F_1	143.7 ± 2.25	0.238±0.0041	0.373±0.0042	243±3.56	5.2±0.06	263±3.32	17.28±0.41	$6.64*10^{-4}$	100
F_2	154.6 ± 1.65	0.267±0.0042	0.393±0.0065	262±4.68	5.3±0.05	301±4.11	13.81±0.39	$5.72*10^{-4}$	100
F_3	148.3 ± 1.28	0.243±0.0034	0.386±0.0053	254±5.34	5.1±0.11	282±3.52	14.92±0.45	$6.19*10^{-4}$	100
F_4	151.9 ± 2.34	0.245±0.0016	0.367±0.0068	275±4.87	5.5±0.10	273±3.41	15.41±0.53	$5.63*10^{-4}$	100
F_5	155.2 ± 1.72	0.291±0.0031	0.385±0.0076	298±5.21	5.7±0.07	307±3.56	12.52±0.60	$4.93*10^{-4}$	100
F_6	158.6 ± 1.82	0.274±0.0041	0.378±0.0081	283±4.33	5.5±0.12	291±2.87	13.95±0.42	$5.15*10^{-4}$	100
F_7	161.3 ± 1.67	0.241±0.0023	0.353±0.0036	218±5.77	5.2±0.11	261±4.13	13.23±0.46	$5.03*10^{-4}$	100
F_8	165.1 ± 1.42	0.283±0.0035	0.371±0.0056	241±2.89	5.3±0.07	298±3.61	10.24±0.51	$4.51*10^{-4}$	100
F_9	159.4 ± 2.18	0.264±0.0061	0.362±0.0074	238± 3.62	5.3±0.09	271±3.23	11.47±0.38	$4.89*10^{-4}$	100
F_{10}	161.3 ± 1.64	0.292±0.0052	0.258±0.0068	267±5.04	5.4±0.11	248±3.48	39.23±0.44	$8.17*10^{-4}$	100
F_{11}	153.4 ± 1.33	0.336±0.0038	0.272±0.0058	286±4.70	5.5±0.10	281±2.92	36.63±0.43	$7.99*10^{-4}$	100
F_{12}	158.8 ± 1.40	0.331±0.0045	0.269±0.0047	284±4.19	5.3±0.08	262±4.33	37.76±0.50	$8.05*10^{-4}$	100
F_{13}	162.3 ± 2.27	0.338±0.0059	0.281±0.0036	276±3.45	5.9±0.13	258±4.22	35.20±0.42	$8.01*10^{-4}$	100
F_{14}	166.4± 1.82	0.447±0.0039	0.303±0.0026	315±2.32	6.0±0.09	289±3.53	33.32±0.54	$7.76*10^{-4}$	100
F_{15}	168.7± 1.73	0.417±0.0024	0.288±0.0051	298±3.53	5.5±0.13	275±2.64	34.52±0.37	$7.92*10^{-4}$	100
F_{16}	170.8± 1.87	0.423±0.0043	0.298±0.0067	293±4.76	5.8±0.09	268±4.53	33.19±0.44	$7.11*10^{-4}$	100
F_{17}	178.6± 2.38	0.463±0.0026	0.332±0.0045	324±5.37	5.7±0.08	290±2.76	31.16±0.32	$6.68*10^{-4}$	100
F_{18}	175.7± 1.79	0.451±0.0047	0.314±0.0072	302±5.76	5.0±0.07	281±4.15	32.25±0.46	$6.91*10^{-4}$	100
F_{19}	152.6± 1.56	0.187±0.0038	0.157±0.0066	246±4.23	5.8±0.14	132±3.35	27.81±0.55	$3.75*10^{-4}$	100
F_{20}	157.3± 1.43	0.198±0.0031	0.171±0.0054	273±3.11	5.2±0.08	185±4.06	24.31±0.41	$3.26*10^{-4}$	100
F_{21}	158.9± 1.29	0.191±0.0046	0.165±0.0044	268±2.56	5.7±0.05	146±3.18	25.28±0.56	$3.50*10^{-4}$	100
F_{22}	149.3± 1.21	0.194±0.0049	0.197±0.0036	288±4.52	5.9±0.10	159±4.45	28.39±0.51	$4.51*10^{-4}$	100
F_{23}	151.4± 1.34	0.199±0.0055	0.233±0.0049	316±3.66	5.8±0.12	190±3.51	25.44±0.42	$4.32*10^{-4}$	100
F_{24}	157.8± 1.71	0.195±0.0061	0.215±0.0076	271±3.51	5.3±0.13	173±4.13	26.13±0.45	$4.44*10^{-4}$	100
F_{25}	160.7± 1.50	0.207±0.0034	0.183±0.0037	262±4.65	5.5±0.08	142±3.26	25.27±0.36	$4.21*10^{-4}$	100
F_{26}	161.5± 1.32	0.213±0.0048	0.204±0.0064	290±3.02	5.7±0.09	187±4.63	23.91±0.47	$3.93*10^{-4}$	100
F_{27}	159.9± 1.73	0.211±0.0043	0.190±0.0065	286±4.16	5.6±0.10	154±3.37	24.18±0.40	$4.16*10^{-4}$	100

into three groups. Group I served as the control, group II received optimized transdermal patch, and group III received a 0.8 % (v/v) aqueous solution of formalin as a standard irritant. [21] A new patch or new formalin was applied daily for 7 days. Finally the application sites were graded always by the same investigator according to the method of Draize et al. [22] Prior permission was obtained from Institutional Animal Ethics Committee (IAEC) to carry out the irritation study.

RESULT AND DISCUSSION

Transdermal drug delivery system is one of the promising alternatives to oral dosage forms especially for drugs that are subjected to first pass metabolism. Evaluation of free patches has proved a popular means of assessing the properties of polymeric patches. The use of mercury substrate method for the preparation yielded transparent, smooth and uniform patches. The transparency, uniformity and flexibility are needed for transdermal drug delivery system fabrication to provide uniform drug distribution and proper handling. The drug free patches of different polymers were prepared by solvent casting technique employing mercury as a substrate

to explore their feasibility for transdermal application. Non plasticized patches were smooth and transparent but were very brittle, and hence addition of plasticizer was found to be essential to improve the mechanical properties of placebo patches. Plasticizer shifts the glass transition temperature to lower temperature and is an important formulation factor. PEG 400, DBP and PG at a concentration of 40 % w/w of polymer were used as a plasticizer. Preliminary experiments indicated lower concentrations were found to give rigid and brittle patches whereas higher concentrations gave soft patches. So plasticizers at a concentration of 40 % was found to give good flexible patches and easily removed from the mercury surface without any rupture. The physicochemical evaluation study reveals that there were no physical changes like appearance, colour and flexibility when the patches were stored at room temperature. The weight of the patches varied between 143.7 g to 178.6 g. All the formulations exhibited uniform weight with low standard deviation values. The thickness of the patches varied between 0.187 mm to 0.463 mm. The area of the patch was found to be 3.14 cm^2. An ideal patch should be formulated in such a way that it should possess a smooth surface and it should not constrict with time. Flatness studies were performed to assess the same. 100 % flatness of all the formulation indicates no amount of constriction in formulated transdermal patches. Thus this could better maintain a smooth surface when applied onto the skin. The folding endurance measures the ability of patch to withstand rupture. The result indicated that the patches would not break and would maintain their integrity with general skin folding when used.

HPMC K100M: PVP polymer combination with DBP as plasticizer has maximum folding endurance while CA: PEG4000 with PEG400 showed least folding endurance. The tensile strength of the patches was found to vary with the nature of polymer and plasticizer. A soft and weak polymer is characterized by low tensile strength and low elongation, a hard and brittle polymer is defined by a moderate tensile strength and low elongation, and a soft and tough polymer is characterized by moderate tensile strength and high elongation, whereas a hard and tough polymer is characterized by high tensile strength and high elongation. Polymer combination CA: PVP plasticized with DBP possessed high tensile strength while polymers plasticized with Eudragit RL100: EudragitRS100 plasticized with PEG possessed low tensile strength. Among the plasticizers the tensile strength of the patches decreased in the following order DBP>PG>PEG400. Patches require certain amount of hardness to withstand the mechanical shocks in handling, packaging and at the time of application. The hardness of the patch varied from 132 g to 307 g. Surface pH varied between 5.1 to 6.0 indicating that no irritation will occur on the skin after applications of the patches.

Swelling varied between 10.24 to 39.23 for different polymeric patches. The swellability varied with nature and composition of patches. Hydrophilic polymers showed considerable swelling, as it increased the surface wettability and consequently water penetration within the matrix. The polymer combination HPMC K4M: PVP with PEG 400 as plasticizer have highest swelling index. PEG 400 could leach out from the patches when immersed in double distilled water, the loss of plasticizer from the patches made it more penetrable to the water molecule; this caused an increase in the weight of patches.

Water vapour transmission determines the permeability characteristics of the patches. The results of water vapour transmission revealed that all the formulations are permeable to water vapour. The water vapour transmission of the patches with different plasticizers was decreased in the following order PEG400 > PG > DBP. Therefore the physicochemical properties of the patches may vary with the nature of polymer and type of plasticizer. The plasticizer diffuses into and softens the polymer particles. This softening promotes latex coalescence and film formation. Incorporation of the adjuvants into the polymer disturbs the continuity of the polymer chains, thereby increasing molecular order and increasing the chain mobility of the polymer matrix. Physical studies conducted on different polymeric patches favoured the combination of these polymers for the preparation of transdermal patches.

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