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Formulation and Evaluation of Transdermal Patches of Carbamazepine

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A B S T R A C T

The aim of the present investigation was to prepare Carbamazepine Transdermal patches of matrix type and membrane controlled type using the HPMC, NaCMC and PVP in different ratios by the solvent casting method. The systems were evaluated for various *in vitro* parameters like Thickness, Folding endurance, Moisture content, Moisture uptake, Drug content, Drug permeation. The drug- Polymer interactions were studied by FTIR. And in vivo studies like Skin irritation studies. The Drug content of the patches was found to be more than 95%, *In-vitro* permeation studies were performed by using chein diffusion cells for 6 hrs.

Keywords: Transdermal drug delivery, Matrix patch, Membrane controlled Patch, Carbamazepine, PVP, *In-vitro* and In vivo skin permeation studies.

A R T I C L E I N F O

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1. Introduction

Throughout the past two decades, the Transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood-level profile resulting in reduced systemic side effects and sometimes, painless and offer multi-day dosing. Transdermal therapeutic systems are defined as 'self-contained discrete dosage forms which, when applied to the intact skin, deliver

the drug(s), through the skin, at a controlled rate to the systemic circulation [1].

Approaches Used in the Development of Transdermal Drug Delivery Systems

Membrane Permeation – Controlled Systems

In this type of system, the drug reservoir is totally encapsulated in a shallow compartment moulded from a drug-impermeable metallic laminate and a rate controlling membrane which may be micro porous or non-porous [2].

Adhesive Dispersion-Type Systems: This system is a simplified form of the membrane permeation-controlled system. Here the drug reservior is formulated by directly dispersing the drug in an adhesive polymer e.g., Poly (isobutylene) or Poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer.

Matrix Diffusion-Controlled Systems: In this approach, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness.

Micro reservoir Type or Micro sealed Dissolution Controlled Systems

This system is a combination of the reservoir and matrix diffusion type drug delivery systems. The drug reservoir is formed by first suspending the drug solids in an aqueous solution of water-soluble liquid polymer viz. silicone Elastomers by high-energy dispersion technique to form several discrete, unleachable microscopic spheres of drug reservoirs.

Pathways of Transdermal Permeation

Permeation can occur by diffusion via:

a. Transcellular permeation, through the stratum corneum
b. Intercellular permeation, through the stratum corneum
c. Transappendageal permeation via the hair follicles, sebaceous and sweat glands.

2. Materials and Methods

Carbamazepine, HPMC, Sodium CMC, PVP K-90, PEG 400, Ethanol 90% were used to formulate the transdermal patches by using solvent casting technique. UV-Spectrophotometer, Digital pH Meter, Melting Point Apparatus, Electronic Balance, Mechanical Stirrer, Thickness tester, Hot Air Ovenwere used to evaluate the formulated patches.

Preparation of transdermal films:

The solvent casting technique was used to formulate the patches using varying concentrations individually, keeping drug concentration constant. The drug, polymer ratios used were 1:2, 1:3, and 1:4. The drug will be dissolved in ethanol and the 1% of polymeric solutions have been prepared that is HPMC 1%, Na CMC 1%, PVP 1% solutions and taken all the polymeric solutions in different concentrations. The drug solution and the polymeric solutions and the plasticizer (PEG 400) 2ml are stirred for 4 hours and then sonicate the solution to clear the air bubbles from the mixture and then casted the solution in a petridish and dry it for 24hours in an hot air oven.

Table 1: Formulations of Transdermal Patches

Formulation	HPMC 1% (mL)	NaCMC 1% (mL)	PVP 1% (mL)	PEG (mL)	Drug conc. (mg)
F1	15	15	5	2	480
F2	15	10	10	2	480
F3	15	5	15	2	480
F4	10	15	10	2	480
F5	5	15	15	2	480
F6	20	10	5	2	480
F7	10	20	5	2	480
F8	25	5	5	2	480
F9	5	25	5	2	480
F10	10	10	15	2	480

Evaluation parameters for transdermal patches of Carbamazepine

The Transdermal films prepared were evaluated for the following parameters

Thickness

The thickness of patches was measured at three different places using an Absolute Digital verniercalipers [3].

Folding Endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance [4].

Percentage of Moisture Content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight [5].

Percentage of Moisture Uptake

A weighed film kept in desiccators at room temperature for 24 hrs was taken out and exposed to 84% relative humidity (a saturated solution of aluminium chloride) in a Desiccator until a constant weight for the film was

obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight [6].

Weight uniformity study: Patches sizes of 2x2 cm^2 were cut. The weights of all patches were taken and the weight variation was calculated [7].

Drug Content Analysis

The patches of specified area were taken into a 100 ml volumetric flask and dissolved in methanol and volume was made up with phosphate buffer pH 5.2. Subsequent dilutions were made and analyzed by UV spectrophotometer at 285 nm [8].

Skin irritation study

The skin irritation study has to be studied on rabbit skin. The hair of rabbit has to be removed by shaving from the dostal area of both the sides one is used as control for the test and the other for the test. Medicated patch has to be placed in the test area and keep in observation for 48 hrs and then examine for any erythema and oedema [9].

***In- vitro* dissolution study of transdermal patches of Carbamazepine**

900mL of pH 5.2 phosphate buffer is prepared and taken in a dissolution jar and the Carbamazepine transdermal patch is placed in it. The program is set to the temperature at 37^0c and the rpm at 50. The dissolution process is started and the samples of 1mL were collected at regular interval of time period that is 15, 30, 60, 90, 120, 150, 180, 210, 240, 270 and 360mins for 6 hours, the dilutions are made. The dilutions absorbance has checked at the 285nm, by using pH5.2 phosphate buffer as blank.

3. Results and Discussion

Melting Point:

Melting point of carbamazepine was determined by capillary tube method and it was found to be 191.3°C (*n* = 3). This value is same as that of the literature citation.

Drug – Excipient Compatibility Studies

The infrared spectroscopy studies were carried out for pure drug and along with polymers. IR spectra of Carbamazepine, HPMC, NaCMC, PVP, alone and their combinations and found no interaction.

Evaluation of Formulated Transdermal Patch:

The thickness, folding endurance, weight variation studies of the patches were measured. And all the results were found in the standard range.

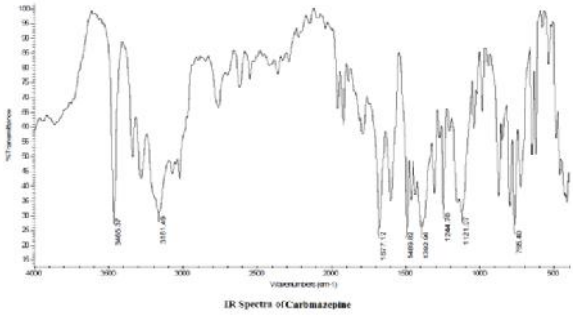

Figure 1

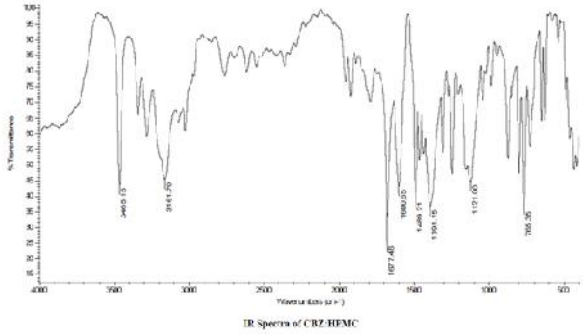

Figure 2

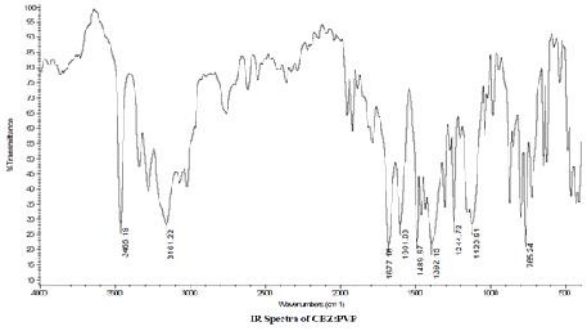

Figure 3

Table 2: Thickness, Folding Endurance weight uniformity, Moisture Content and Moisture Uptake

Formulation Code	Thickness (µm)	Folding Endurance	Weight uniformity (mg)	Moisture Content (%)	Moisture Uptake (%)
F1	79.238 ± 1.541	> 245	201.1±0.763	3.281 ± 0.011	2.634 ± 0.014
F2	78.126 ± 1.346	> 250	198.031±0.219	5.266 ± 0.011	1.552 ± 0.013
F3	89.251 ± 0.792	> 220	200.112±0.368	2.462 ± 0.013	3.253 ± 0.015
F4	84.597 ± 1.266	> 240	203.452±0.412	2.671 ± 0.012	3.319 ± 0.011
F5	75.993 ± 1.514	> 230	201.203±0.156	3.448 ± 0.012	4.332 ± 0.013
F6	82.328 ± 0.544	> 250	196.107±1.003	5.126 ± 0.011	2.116 ± 0.014
F7	83.411 ± 1.424	> 235	200.988±0.224	2.892 ± 0.015	3.527 ± 0.015
F8	87.273 ± 1.316	> 250	201.166±0.438	1.925 ± 0.014	1.495 ± 0.017
F9	76.622 ± 1.110	> 240	196.31±0.294	3.690 ± 0.015	4.278 ± 0.019
F10	79.489 ± 1.218	> 235	204.624±0.708	2.925 ± 0.012	3.765 ± 0.013

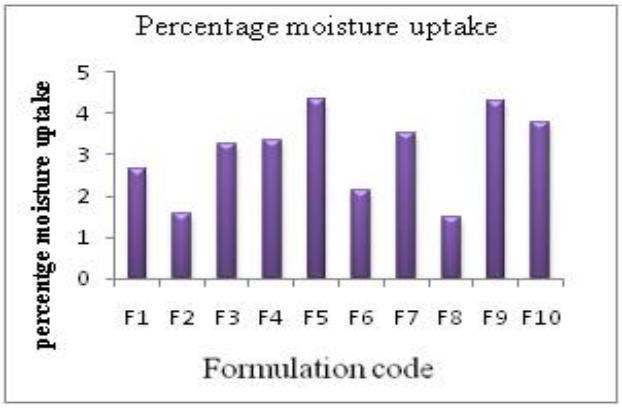

Figure 4

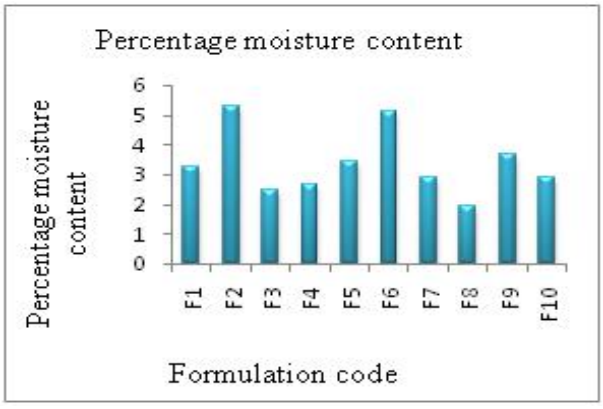

Figure 5

Drug Content Analysis: The drug content analysis of different formulations was done. The drug content ranged between 95.857 ± 0.2073% and 97.770 ± 0.1992%.

Table 3: *In-Vitro* dissolution Studies (%)

Time (mins)	F 1	F2	F3	F4	F 5	F6	F7	F 8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
15	8.82	2.16	8.91	6.21	5.04	1.26	7.29	11.88	8.28	3.24
30	10.898	8.394	11.439	8.979	7.436	2.534	9.621	16.87	9.182	8.136
60	18.038	14.967	16.245	11.058	10.938	8.862	17.197	24.346	15.223	11.016
90	22.286	17.652	19.573	16.759	17.628	12.2	24.046	28.564	20.88	16.987
120	29.369	23.605	26.446	21.712	19.351	18.094	27.639	38.7835	27.498	23.833
150	37.158	27.642	32.403	28.608	24.331	22.342	33.969	46.4045	32.477	28.773
180	30.72	34.511	39.143	36.478	27.114	26.725	40.996	57.3455	38.228	35.205
210	54.896	40.733	49.554	42.272	28.845	28.094	46.657	65.6125	46.199	39.275
240	56.207	47.02	57.286	46.866	41.212	37.215	50.126	74.3245	48.044	46.446
270	62.026	56.252	74.638	51.236	46.963	39.324	55.788	76.9155	58.724	54.232
360	72.943	67.381	78.766	62.579	56.103	48.652	66.277	85.5565	66.547	68.039

Skin irritation studies:

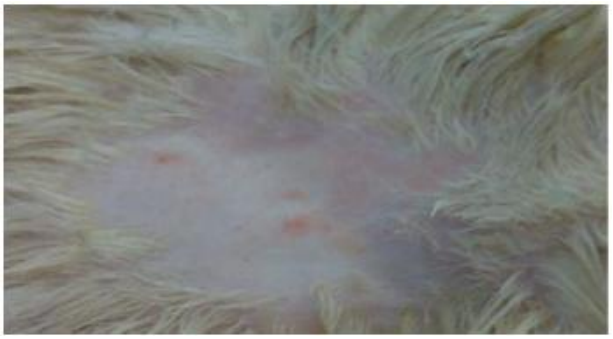

Figure 6: Rabbit Skin After Shaving

Figure 7: After Application of Patch

Figure 8: After Removal of Patch

There is no Erythma or Edema Found on Rat Skin.

4. Conclusion

Transdermal patches of Carbamazepine were found to be satisfactory. Among the different formulations of matrix type (F1 to F10), the formulation F8 was selected as best formulation, after considering its low percentage moisture content (1.925%), percentage moisture uptake (1.495%), better % drug content (89.010%) and maximum 76.361 % drug permeated through the skin at the end of 24 hrs. The drug permeation profile was found to follow zero order kinetics. The patches were thin, flexible and transparent.

The patch was evaluated for the skin irritation study and as well as skin permeation study and it has shown the best results without any adverse reactions like erythma and edema on the rabbit skin. These carbamazepine transdermal patches have been formulated to use as the maintenance dose in cases where the patient forgets consuming the regular dose of Carbamazepine, and this formulation has an advantage since it can be used in the unconscious patients when the patient is attacked by seizures.

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