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# PREPARATION AND EVALUATION OF TRANSDERMAL FILMS OF VERAPAMIL

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**ABSTRACT**

The aim of present study was to formulate and evaluate drug loaded transdermal films by solvent casting method. Verapamil loaded films by sod.CMC 3%+PG 10% and PVA 8% + glycerin 5%.The prepared films were studied for their peelability, tanness, film endurance, weight uniformity, thickness, *in vitro* release and % moisture uptake. Screening of different polymers and plasticizers for preparation of transdermal films were done and from the observations polymers such as PVA 8 %, EC 5 %, sod. CMC 3 % were found to be ideal and were selected for drug loaded film preparation. Finally sod.CMC (3%) with PG 10%; 8% PVA + Glycerin 5% and 5 %EC + DBP were found to be good. So these films were selected for the further considerations with drug. The formulations were prepared and characterization of transdermal patches**,** *invitro* release and moisture uptake test was done. Peelability and tachyness was found to be good for both films film endurance was in range of 330 to 350 times for verapamil films. Thickness was found to be in the range 170- 195µm for verapamil films. % moisture uptake was found to be in range of 10 – 15% for verapamil films. The *in vitro* release of the formulation of verapamil was performed and data was treated for zero and first order release kinetics. % release of verapamil films it was in range of 90 – 100%. Verapamil with PVA8% + glycerin 5% showed more thicker films and film endurance is also more for that film. % moisture uptake was found to be more for verapamil + sodium CMC film. Drug release was found to be more from verapamil + sodium CMC film.

**Key words**: Verapamil, Transdermal films, Sodium CMC, Poly vinyl alcohol.

## INTRODUCTION

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Due to an advantage of being non-invasive, this delivery has to fulfill some parameters such as high potency, better permeability through skin and non-irritation for better compliance. Avoidance of 'first-pass' metabolism of drugs, Reduction of dosing frequency and enhancement of patient compliance, avoiding the fluctuation in drug level, Ability to deliver drug more selectively to a specific site, Provide suitability for self-administration (Kusum DV *et al*., 2003)

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### Skin structure

The skin is the largest organ in the body; it protects against the influx of toxins and the efflux of water and is largely impermeable to the penetration of foreign molecules. Human skin consists of three main layers: the epidermis, dermis, and hypodermis (Fig. 1). The epidermis, in particular the stratum corneum, acts as the major barrier to drug absorption. The stratum corneum contains only 20% of water and is a highly lipophilic membrane; it is 10–20 µm thick depending on its state of hydration. The thickness of the epidermis varies from 0.06 mm on eyelids to 0.8 mm on the soles of the feet (Limpongsa E, Umprayn K, 2008).

An applied drug must traverse these structural layers, encountering several lipophilic and hydrophilic domains on the way to the dermis where absorption into the systemic circulation is rapid due to the large capillary bed. Removing the stratum corneum speeds the diffusion of small water-soluble molecules into the systemic circulation by up to 1000 times. Alternatively, hydrophilic compounds can reach the dermis via shunt pathways such as hair follicles, sweat glands, nerve endings, and blood and lymph vessels. These routes contribute minimally to steady-state drug flux. The dermis is the thickest layer of the skin (3–5 mm) and possesses hair follicles, sweat glands, nerve endings, and blood and lymph vessels. It acts as the systemic absorption site for drugs (Sakellariou P *et al*., 1986).

There are variations between individuals in the rate at which drugs are absorbed via the skin due to factors such as thickness of the stratum corneum, skin hydration, underlying skin diseases or injuries, ethnic differences, and body temperature (Cooper ER, 1984).

The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007.Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl CII (marketed as Duragesic) and Buprenorphine CIII (marketed as BuTrans)Hormonal patches .Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis.contraceptive patch (marketed as Ortho Evra or Evra) and testosterone CIII patches for both men (Androde) and women (Intrinsa). Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills. Transdermal scopolamine is commonly used as a treatment for motion sickness. The anti-hypertensive drug Clonidine is available in transdermal patch form under the brand name Catapres-TTS. Emsam, a transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant approved for use in the U.S. in March 2006. Daytrana CII, the first transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD) drug methylphenidate (otherwise known as Ritalin or Concerta), was approved by the FDA in April 2006. Its key formulator, Juan Mantelle, is one of the leading transdermal developers in the nation. He is currently serving as CEO for ProSolus Pharmaceuticals. Vitamin B12 may also be administered through a transdermal patch. Cyanocobalamin, a highly stable form of vitamin B12, is compatible with transdermal patching. Rivastigmine, an Alzheimer's treatment medication, was released in patch form in 2007, under the brand name Exelon (Goodman M, Barry BW, 1989).

Verapamil is an ant hypertensive drug that acts through the mechanism by blocking the L-type of calcium channels and thereby reducing the contraction of the cardiac muscle by reducing the ionotropy and chronotropy of the cardiac muscles (Hu JH, Zhu Y, 1996).Present study is to formulate verapamil transdermal patch and evaluate for different evaluation tests of the transdermal patches.

## MATERIALS AND METHODS

### Materials

Verapamil (Aurobindo Pharma Ltd, Hyderabad), Ethyl cellulose(Loba Chemie Pvt Ltd, Mumbai), Sodium CMC(phenar chemical ltd Ahmedabad), Polyvinyl alcohol (PVA) (Loba Chemie Pvt Ltd, Mumbai), DCM (dichloro methane), IPA (iso propyl alcohol), PG(propylene glycol), methanol, UV spectrophotometer (JASCO V-650), all the chemicals and the solvents used are analytical grade

### Method

### Screening Of Different Polymers And Plasticizers For Preparation Of Transdermal Films

The polymers and the plasticizers that are to be used were selected by preparing the drug free patches, and from that the best suit polymer and plasticizer were selected

### Formulation of drug free patches

Transdermal patches were prepared by solvent casting technique. The casting solutions were prepared by dissolving appropriate polymers and plasticizers in suitable solvents using sonicator for 10 min to get uniform dispersion. Plasticizers were added at a different concentration of %w/w of polymers. The solution was then transferred to Petridish. Controlled solvent evaporation was achieved by placing an inverted funnel over the Petridish. These were left undisturbed at room temperature for one day (Chi SC *et al*., 1995)

### SELECTION OF POLYMER

The polymers 3% Sod.CMC, PVA 8% were found to be ideal and were used to prepare drug loaded films.

### SELECTION OF PLASTICIZER

The plasticizers DBP 18%, PG 10%, Glycerin 5% were found to be ideal and were used to prepare drug loaded films.

### Optimization of the formula for patches:

Patches were prepared from different polymers with and without plasticizer and they were evaluated for their physical properties. Finally sod.CMC (3%) with PG 10%; 8% PVA + Glycerin 5%, 5% EC + DBP 18% were

found to be good. So both these films were selected for the further considerations with drug.

**PREPARATION AND EVALUATION OF DRUG LOADED FILMS**

B) Preparation and evaluation of Verapamil transdermal film

1) Weighed amount of drug i.e 200 mg verapamil was dissolved in10 ml water and to that 1 ml of 10 % PG was added.

2) Then sodium CMC was added to that. The solution was then casted on petri plate and kept for drying at $45^0$C overnight. The film is removed by sharp blade and evaluated.

3) Weighed amount of drug i.e. 200 mg verapamil was dissolved in 10 ml water and to that 1 ml of 5 % glycerin was added.

4) Then PVA 8 % was added to that. The solution was then casted on petri plate and kept for drying at $45^0$C overnight. The film is removed by sharp blade and evaluated.

Diameter of the plate 9.5 cm (Radius 4.75 cm)

Hence Area is 70.91 $Cm^2$

Dose: 70.91 $Cm^2$ will Contain 2.82 mg/$Cm^2$ (200 mg / 70.91 $Cm^2$= 2.82 mg/$Cm^2$)

**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 square cm were taken out from each casted film after complete drying and evaluated for the following physicochemical properties (Kim DD, Chien YW, 1996).

**1) Thickness -** The thickness of transdermal patches was measured at three different places using a micrometer and the mean values were calculated.

**2) Weight variation -** The patches were subjected to weight variation by individually weighing five randomly selected patches. Such determinations were carried out for each formulation.

**3) Folding endurance -** The folding endurance is defined as the number of folds required to break any polymeric patch. This test was carried out to check the efficiency of the plasticizer and the strength of the patch prepared using different polymers. 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.

**4) Percentage Moisture uptake -** The weighed films were kept in a desiccators at room temperature for 24hrs containing saturated solution of KCl in order to maintain 88% RH( 5.41 g KCl in 100 ml water gives saturated solution to give 88 % RH). After 24hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula (Arora P, Mukherjee P, 2002).

$$\% \text{ moisture uptake} = \frac{Final\ wt - Initial\ wt}{Initial\ wt} 100$$

**5) In vitro drug diffusion studies –** The in vitro diffusion study was carried out with the films using Franz diffusion cell. The cylinder consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at 37 ± 0.5o C and receptor compartment was provided with sampling port. The diffusion studies were done to get an idea of permeation of drug through barrier from the transdermal system. In vitro studies are also done for TDDS development. Diffusion cells generally comprise two compartments, one containing the active component (donor compartment) and the other containing receptor solution (receptor compartment), separated by film. The cell consisted of sampling port and temperature maintaining jacket. The outlet and inlet was connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate. The magnetic bead was used to stir the receptor solution using magnetic stirrer. The film was placed on receptor compartment and both compartments held tight by clamps. The volume of diffusion cell was 25 ml and stirred with the magnetic bead. The temperature was maintained at 37 ± 2°C with the help of magnetic stirrer. The diffusion was carried out for 24 hours and 1 ml sample was withdrawn at an interval of 0, 1, 2, 3, 4, 5, 6, 7 and 8 hour. The same volume was added to receptor compartment to maintain sink conditions and the samples were analyzed in UV spectrophotometer (Ammuaikit C *et al*., 2002).

**RESULTS AND DISCUSSIONS**

Screening of different polymers and plasticizers for preparation of transdermal films were done and given in table 1&2 respectively and from the above observations polymers such as PVA 8 %, EC 5 %, and sod. CMC 3 % were found to be ideal and were selected for drug loaded film preparation.

The formulations were prepared according to the table3&4 and respectively. Characterization of transdermal patches was given in tables 7&8 and moisture uptake values were found to be 14.31 and 11.78 respectively for the films with sao.CMC and PVA. Peelability and tachyness was found to be good for both films film endurance was in range of 330 to 350 times for verapamil. Thickness was found to be in the range of 170- 195µm for verapamil films. % moisture uptake was found to be in range of 10 – 15% for verapamil films respectively. The *in vitro* drug release from the formulation of verapamil is given in Figure 2.

**Table 1. list of polymers screened for the selection of the best fit polymer for the patch**

| S.No | Polymers | % of polymers | Solvents (10 ml) |
|---|---|---|---|
| 1 | Sodium CMC | 1 % | Water |
| 2 | Sodium CMC | 2 % | Water |
| 3 | Sodium CMC | 3 % | Water |
| 4 | Methyl cellulose | 5 % | Water |
| 5 | Eudragit RL 100 | 5 % | IPA & DCM (1:1) |
| 6 | Eudragit RS 100 | 5 % | IPA & DCM (1:1) |
| 7 | Ethyl cellulose | 5 % | IPA & acetone |
| 8 | PVA | 10 % | Water |
| 9 | HPMC 5 C | 5 % | Water |
| 10 | HPMC 15 C | 2 % | Water |

**Table 2. list of the plasticizer that are used to select the best plasticizer to be used.**

| S.No | Plasticizer | Concentration |
|---|---|---|
| 1. | PEG 200 | 10% |
| 2. | PEG 200 | 15% |
| 3. | PEG 200 | 20% |
| 4. | Glycerine | 5% |
| 5. | Sorbitol | 10% |
| 6. | PG | 10% |
| 7. | PG | 15% |

**Table 3. Formulation of verapamil film in sod CMC(3%)**

| S.No. | Ingredients | Quantity(mg) |
|---|---|---|
| 1 | Sodium CMC 3 % | 250 mg |
| 2 | Water | 10 ml |
| 3 | Verapamil | 200 mg |
| 4 | PG 10 % | 1 ml |

**Table 4. Formulation of verapamil film in PVA**

| S.No. | Ingredients | Quantity(mg) |
|---|---|---|
| 1 | PVA 8% | 250 mg |
| 2 | Water | 10 ml |
| 3 | Verapamil | 200 mg |
| 4 | Glycerin 5 % | 1 ml |

**Table 5. Screening of different polymers**

| S.No | Polymers | Sodium CMC 1 % | Sodium CMC 2% | Sodium CMC 3% | MC 5% | Eudragit RL 100 5% | Eudragit RS 100 5% | EC 5% | PVA 10% | HPMC 5 C 5% | HPM C 15 C 2% |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Peel ability | +++ | +++ | +++ | ++ | + | - | +++ | +++ | +++ | +++ |
| 2 | Film endurance | 169 times | 185times | 187 times | 125 | 8 times | - | 30 times | 380 times | 40 times | 100 times |
| 3 | Wt uniformity ( mg ) | 2.98, 2.63, 2.31, 2.4 | 5.88, 4.76, 6.74, 5.24 | 4.7 , 4, 5, 5.6 mg | | 5.2, 4.94, 5.66, 4.62 | - | | | 15, 20, 18, 15 | 6, 5, 4, 4 |
| 4 | Tachyness | +++ | +++ | +++ | ++ | ++ | - | +++ | +++ | +++ | +++ |
| 5 | Thickness ( μm ) | 28, 23, 20, 20, 21, 19, 20, 21 | 30, 29, 33, 35, 34, 30, 32, 30 | 92, 104, 103, 101, 99, 100, 96, 99 | 28, 31, 80, 45, 62, 28, 18, 22 | 98, 72, 64, 69, 79, 87, 91, 71. | - | 120, 110, 105, 115 | 191, 189, 185, 195, 185, 191, 195, 183 | 144, 140, 135, 144, 138, 145, 140, 139 | 89, 90, 92, 95, 100, 90, 85, 81 |

**Table 6. Screening of Plasticizers**

| S.no | Films | | Peel ability | Film endurance | Tachyness | Wt uniformity (mg) | Thickness (µm) |
|---|---|---|---|---|---|---|---|
| | Plasticizer | Conc | | | | | |
| 1 | PEG 200 | 10% | ++ | 125 | + | 8.91, 21.06, 9.7, 24.66 | 367, 355, 421, 457, 111, 92, 439, 457 |
| 2 | PEG 200 | 15% | + | 140 | + | 44.23, 30.75, 34.11, 26.61 | 363, 302, 365, 393, 316, 398, 478, 208 |
| 3 | PEG 200 | 20% | ++ | 200 | ++ | 28.28, 37.72, 24.05, 27.09 | 331, 221, 388, 363, 399, 419, 330, 327 |
| 4 | Glycerine | 5% | +++ | 250 | +++ | 15.13, 10.96, 9.34, 14.53 | 285, 144, 197, 135, 143, 160, 153, 136 |
| 5 | Sorbitol | 10% | +++ | 368 | +++ | 14.61, 11.26, 8.52, 14.51 | 452, 444, 222, 196, 344, 357, 185, 192 |
| 6 | PG | 10% | +++ | 352 | +++ | 15.28, 16.32, 23.21, 26.25 | 157, 156, 326, 283, 260, 207, 179, 183 |
| 7 | PG | 15% | +++ | 329 | +++ | 26.06, 26.86, 20.28, 20.12 | 244, 338, 210, 238, 375, 265, 350, 242 |

**Table 7. Verapamil + sod. CMC 3 % + PG 10 %**

| S.No | Evaluation parameters | Results |
|---|---|---|
| 1. | Peel ability | +++ |
| 2. | Film endurance | 335 times |
| 3. | Tachyness | +++ |
| 4. | Wt uniformity ( mg ) | 7.4, 8.1, 6.9, 7.8 mg |
| 5. | Thickness ( µm ) | 199, 179, 155, 185, 175, 191, 195, 193 µm. |

**Table 8. Verapamil + PVA 8 % + Glycerin 5 %**

| S.No | Evaluation parameters | Results |
|---|---|---|
| 1. | Peel ability | +++ |
| 2. | Film endurance | 342 times |
| 3. | Tachyness | +++ |
| 4. | Wt uniformity ( mg ) | 6.4, 8.1, 7.9, 6.8 mg |
| 5. | Thickness ( µm ) | 191, 189, 185, 195, 185, 191, 195, 183 µm. |

**Fig 1. Structure of skin**

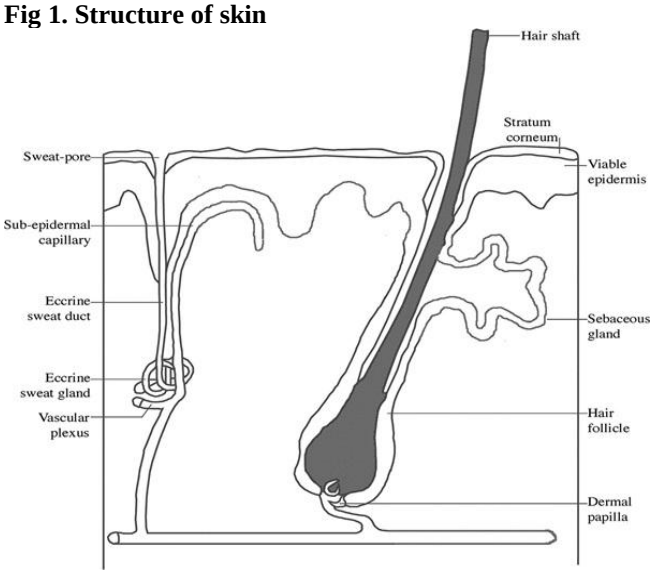



**Fig 2. structure of verapamil**

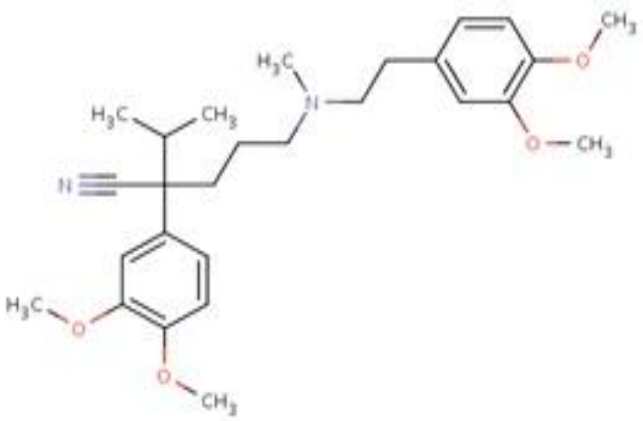


**Fig 2. *in vitro* drug release study for the two formulations of verapamil with sod.CMC and PVA respectively *in vitro* release data was treated for zero and first order release kinetics respectively for verapamil+sod CMC and verapamil+PVA films.**

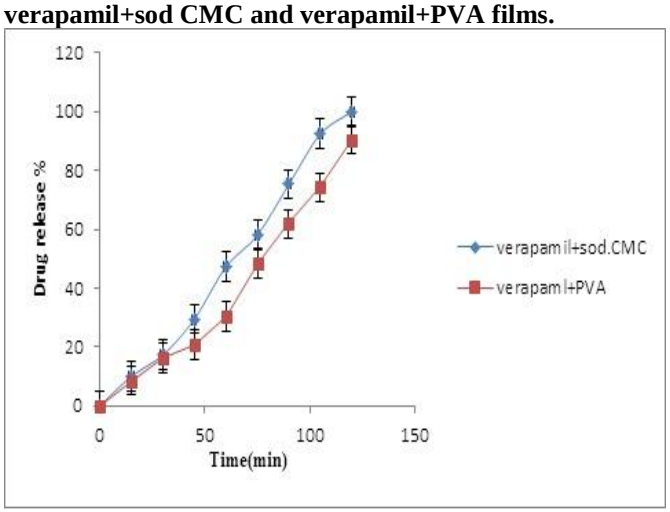



**Fig 3. zero order release kinetics for the two formulations of verapamil with sod.CMC and PVA respectively**

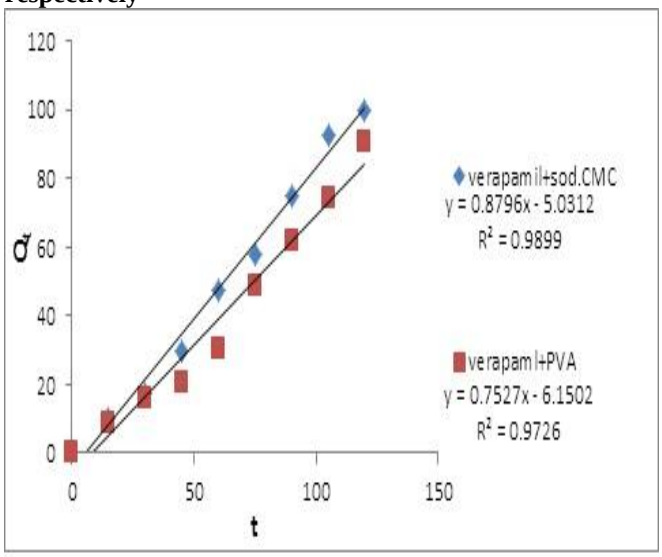
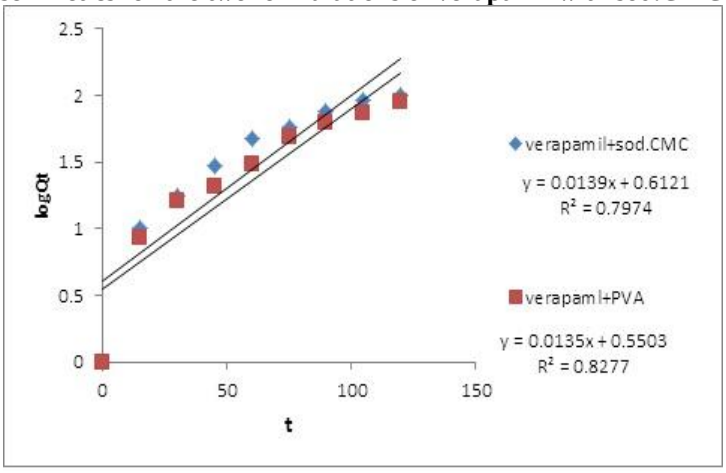



**Fig 4. first order release kinetics for the two formulations of verapamil with sod.CMC and PVA respectively**



## CONCLUSION

The films of verapamil films were prepared and were found to follow zero order kinetics. verapamil with verapamil + sod. CMC 3 % + PG 10 % showed more thicker films and film endurance is also more for that film.% moisture uptake was found to be more for verapamil + sodium cmc film and less for ketorolac + 5%EC film.drug release was found to be more from verapamil + sod. CMC film. All films were found to follow zero order of drug release.

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