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Research Article

FORMULATION AND *IN*-VITRO EVALUATION OF TRANSDERMAL PATCHES OF METHYL SALICYLATE

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Abstract

The purpose of this research work was to develop and evaluate transdermal therapeutic system containing Methyl salicylate with different polymeric combinations by the solvent evaporation technique. Five transdermal patch formulations (F1, F2, F3, F4 and F5) consists of HPMC and PVP were prepared. All formulations carried menthol as penetration enhancer and glycerin as plasticizer. The prepared transdermal patches were evaluated for *in vitro* release, moisture absorption, moisture loss and other physico-chemical properties. The diffusion studies were performed by using modified Franz diffusion cells. The formulation, F5 showed maximum release of 95.72±1.07% in 24 h, followed Higuchi kinetics and the mechanism of release was diffusion mediated.

Key words: Methyl salicylate, transdermal patches, menthol, glycerin.

Introduction

The first transdermal systems were simply pieces of plastic dipped into a drug that was dissolved in alcohol. The plastic had an adhesive around the edges. Although revolutionary in their day, they created a significant number of skin reactions. The next generation still in use today uses a "drug in the adhesive" model. This is a significant improvement, as the skin irritation is diminished and the adhesive serves two functions: It is the glue that keeps the patch attached to the skin and it acts as the suspension that holds the drug. Third generation patches have solved some of these issues by using an acrylic reservoir that holds

the drug. Silicon adhesive is added to create a semisolid suspension of microscopic, concentrated drug cells. Now, fourth generation transdermal systems involve the addition of an enhancer, a mechanism to increase the permeability of the skin and in some of the technology, a mechanism to time the delivery and create bolus dosing. FDA approved the first transdermal patch products in 1981. These delivery systems provided the controlled systemic absorption of scopolamine for the prevention of motion sickness and nitroglycerine for the prevention of angina pectoris associated with coronary artery disease[1]. Methyl salicylate is an active ingredient of semisolid formulations[2]. Methyl salicylate is an NSAID and act as inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid itself derived from the cellular phospholipid bilayer by phospholipase A2, Prostaglandins act as messenger molecules in the process of inflammation[3]. Topical NSAIDs are an alternative route of administration with advantages including avoidance of hepatic first-pass metabolism and limitation of gastrointestinal disturbance[4]. While it is generally accepted that topical NSAIDs are therapeutically beneficial for soft tissue inflammation and arthritis pain, reduced systemic drug concentrations following topical administration of NSAIDs will minimise the incidence of adverse drug effects[5]. The present investigation deals with the formulation of transdermal patches of methyl salicylate to reduce the frequency of administration to obtain greater therapeutic efficacy to improve patient compliance.

Materials and Methods

Drugs and Chemicals

Methyl salicylate was obtained from Ranbaxy, Gurgaon, Hydroxy propyl methyl cellulose (HPMC 15 cps) and PVP (15 cps) received as gift samples from BPRL, Banglore.

Estimation of Methyl salicylate

UV spectrum of methyl salicylate showed maxima at 237 nm (Fig. 1) which is comparable with the reference spectrum of the drug[6]. Stock solution was prepared in methanol and was further diluted to

concentrations of 1 to 10µg/ml. Absorbance of these solutions (Fig. 2) was recorded in accordance with Beers's law at λ_{max} 237 nm against methanol as blank using UV-visible spectrophotometer (Shimadzu 1201

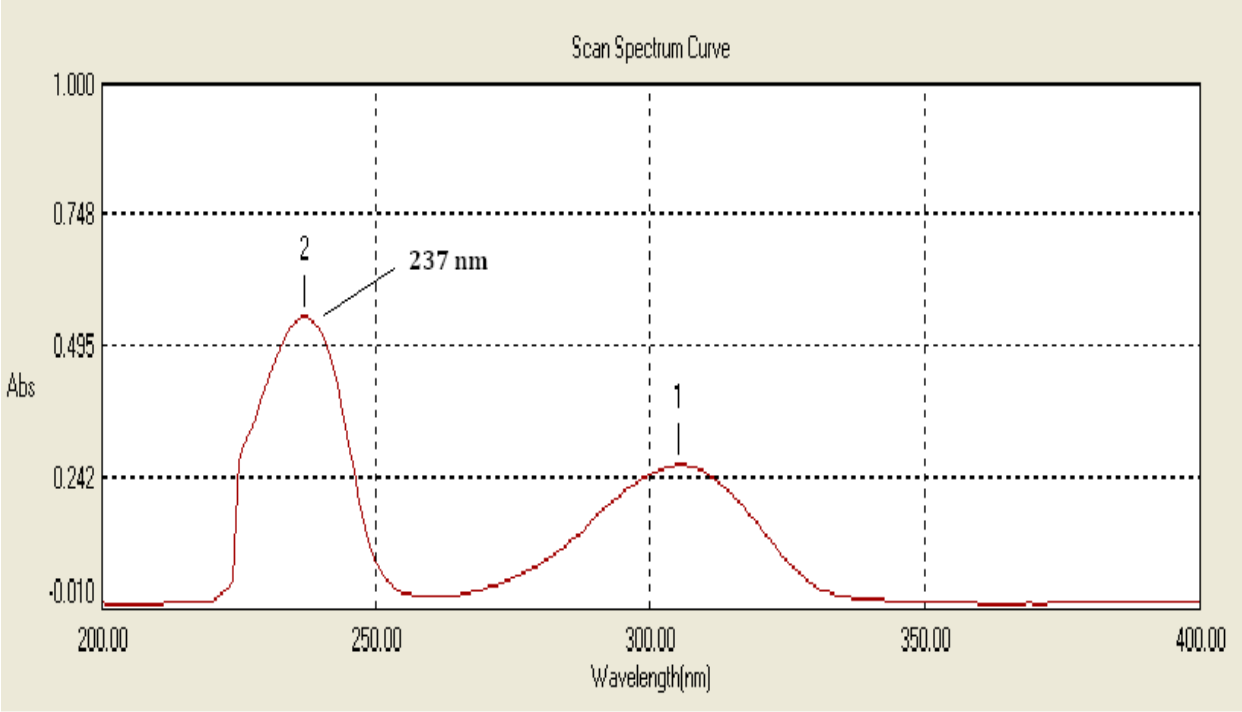

Fig-1: UV Scan of Methyl Salicylate.

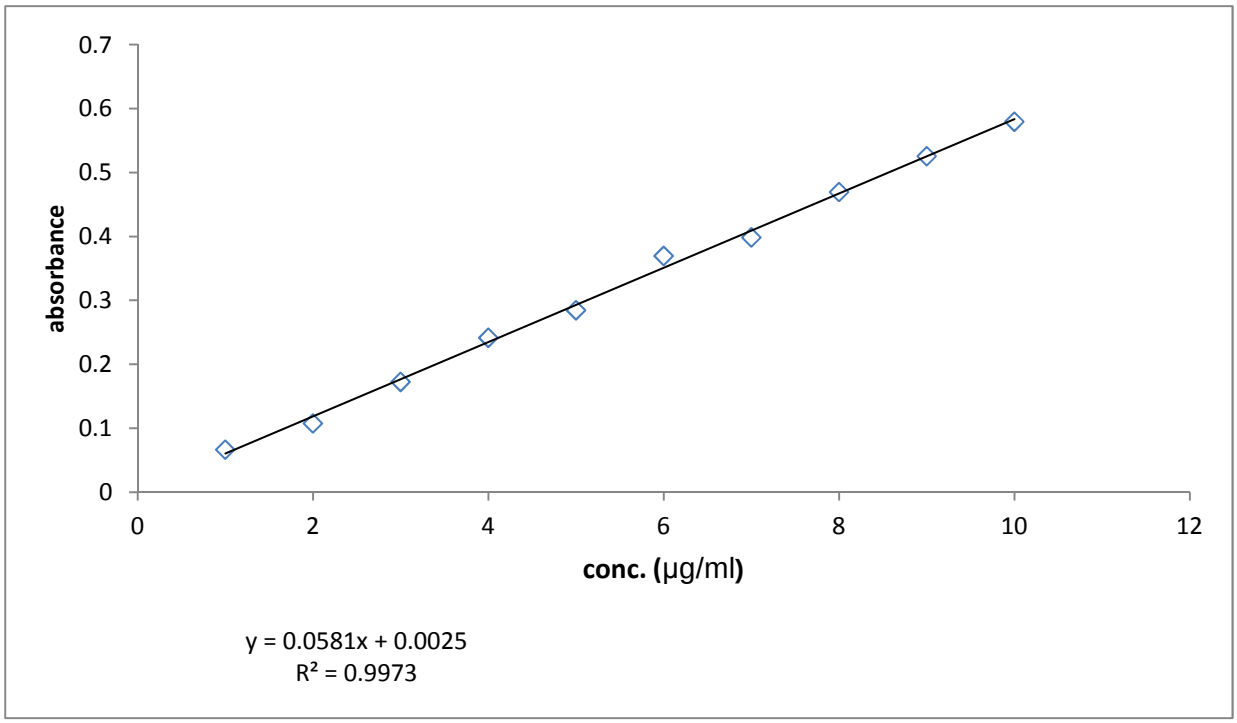

Fig-2: Calibration curve of Methyl Salicylate.

Formulation of transdermal patches

A fabricated mould was used and solvent evaporation method was adopted. The bottom of the mould was wrapped with aluminium foil, 300 mg of the polymer(s) was accurately weighed and dissolved in 8 mL of methanol and kept aside to form clear solution. Glycerin was used as plasticizer and menthol was used as permeation enhancer. 50 mg of drug was dissolved in the above solution and mixed for 15 min. The resulted uniform solution was cast on the aluminium foil and dried at 40ºC in the hot air oven for 24 h. An inverted funnel was placed over the mould to prevent fast evaporation of the solvent. After 24 h the dried films were taken out and stored in a desiccator for further studies. Different compositions of formulations are represented in Table 1.

Table-1: Composition of different formulations containing Methyl Salicylate.

Composition	F1	F2	F3	F4	F5
Methyl salicylate (mg)	50	50	50	50	50
HPMC (mg)	30	60	90	120	150
PVP (mg)	270	240	210	180	150
Glycerin (mL)	0.12	0.12	0.12	0.12	0.12
Menthol (mg)	0.06	0.06	0.06	0.06	0.06
Methanol (mL)	8	8	8	8	8

Physico-chemical and In-*vitro* drug release evaluation of formulations.

1. Percentage moisture loss[7]

The films were weighed accurately and kept in the desiccator containing anhydrous calcium chloride. After 3 days the film were taken out and weighed then moisture loss was calculated using the formula:

$$\text{Percentage moisture loss} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

2. Percentage moisture absorption[7]

The percentage moisture absorption was studied by placing reweighed films of six numbers in each formulation in a desiccator containing 100ml of saturated solution of aluminum chloride, maintained at 80% RH. After 3 days, the films were taken out and weighed and calculations were done as per formula:

$$\text{Percentage moisture absorption} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100$$

3. Film thickness:

The thickness of the film was measured at three different points using a screw-gauge and average thickness was determined.

4. Weight variation

Each film was weighed individually & average weight of three films was determined.

5. Folding endurance[8]

It was determined by repeatedly folding a small strip of film at the same place till it break. The number of time, the film could be fold at the same place without breaking gave the folding endurance value.

6. Drug content uniformity

A fabricated film was cut into small pieces and put in a 100ml of phosphate buffer 7.4 pH solution. This is then stirred in a mechanical stirrer to get a homogenous solution and filtered. The filtrate of 1ml was withdrawn and made up to 100 ml again from this 1 ml was pipette out and made up to 10 ml with buffer 7.4 pH. The drug content was analyzed at 237 nm by UV spectrophotometer (Shimadzu 1201)

7. *In vitro* drug release studies

In vitro skin permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 30 mL. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into size of $1cm^2$ and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer and the solution in the

receptor compartment was constantly and continuously stirred using magnetic beads at 40 rpm, the temperature was maintained at 37 ± 0.5º C. The samples of 1 mL were withdrawn at time interval of 2, 4, 6, 8, 10, 12, 16, 20, 24 h and analyzed for drug content spectrophotometrically at 237 nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The release kinetics of drug was graphically analysed for zero order (Fig. 4), first order (Fig. 5), higuchi (Fig. 6) and peppas (Fig. 7) exponential equations.

Results and discussions

In the present study, efforts have been made to prepare Methyl salicylate transdermal patches using solvent evaporation technique. The films were prepared by using different hydrophilic polymers such as HPMC and PVP. Physico-chemical evaluation data indicates that the formulation F5 has shown highest maximum moisture absorption than the other formulation. This may be due to the presence of high hydrophilicity of HPMC and PVP. Formulation F1 has shown maximum moisture loss may be due lower concentration of HPMC as compared to other formulations (Table 2). The thickness of the films varied from 0.10 to 0.21 mm. The minimum Standard deviation values assured that the process used for preparing the delivery system is capable of giving reproducible results also confirmed by drug content and weight uniformity studies. In order to evaluate the flexibility, the films were subjected to folding endurance studies, values in the range of 78 to 84 were observed in all batches. This revealed that the prepared films were having capability to withstand the mechanical pressure along with good flexibility (Table 2, 3). The cumulative percentage (Table 4) (Fig. 3) drug release for F5 was found to be 95.72±1.07 at 24 hrs., where the concentration of hydrophilic polymers is in equal ratio. It is considered as the best formulation, since it shows maximum *in-vitro* drug release as compared to other formulations. The drug release kinetics (Table 5) studies showed that F2, F3 and F3 were governed by first order release whereas F1 and F5 followed higuchi kinetics depicting slow diffusional process of release of drug. (Fig. 4-7)

Table 2: Evaluation of formulated patches for Percent moisture absorption (%), Percent moisture loss (%) and Film Thickness (mm)

Formulation code	Percent moisture absorption (%) ± SD	Percent moisture loss (%) ± SD	Film Thickness (mm) ± SD
	(`x ± s.d., n = 3)		
F1	19.87±0.17	10.24±0.66	0.20±0.11
F2	21.32±0.36	9.57±0.76	0.25±0.59
F3	23.34±0.34	8.43±0.35	0.19±0.52
F4	20.54±0.55	8.76±0.21	0.21±0.85
F5	24.12±0.12	8.54±0.63	0.13±0.18

Table 3: Evaluation of formulated patches for Weight variation (g), Folding endurance and Drug content uniformity (%).

Formulation code	Weight variation (g) ± SD	Folding endurance ± SD	Drug content uniformity (%) ± SD
	(`x ± s.d., n = 3)		
F1	0.203±0.88	78±2	93.65±0.39
F2	0.234±0.51	80±1	93.67±0.22
F3	0.123±0.37	81±3	95.12±0.17
F4	0.254±0.28	79±2	94.99±0.57
F5	0.156±0.70	84±1	95.16±0.50

Table -4: Results of *in-vitro* drug release.

Time (hrs.)	Percentage cumulative drug release (`x ± s.d., n = 3)				
	F1	F2	F3	F4	F5
2	3.62±0.34	4.58±0.34	3.05±0.34	3.14±0.78	2.63±0.54
4	10.85±0.98	26.21±0.45	26.05±0.56	31.07±0.23	33.41±0.33
6	27.77±1.76	38.35±0.97	33.52±1.46	40.63±0.53	40.54±0.76
8	36.23±0.54	46.82±1.11	49.45±1.98	51.54±1.98	46.00±0.65

10	43.85±1.46	53.42±1.99	57.74±0.88	63.09±1.54	54.10±0.11
12	52.10±1.54	61.94±0.68	64.86±0.30	69.65±1.75	66.06±0.19
16	63.98±1.76	72.26±0.39	74.29±2.20	79.33±1.54	75.28±1.99
20	75.65±0.43	79.88±1.24	83.87±0.54	88.84±0.22	88.95±1.86
24	87.47±2.01	88.47±1.65	92.65±0.33	93.21±0.87	95.72±1.07

Table -5: R^2 value of kinetic model fitting of Methyl salicylate.

Formulation code	Zero order	First order	Higuchi kinetics	Peppas kinetics
F1	0.9732	0.972	0.9951	0.9512
F2	0.9198	0.9915	0.9834	0.8696
F3	0.9174	0.9818	0.9812	0.8484
F4	0.885	0.9954	0.9651	0.8119
F5	0.9242	0.9505	0.976	0.7971

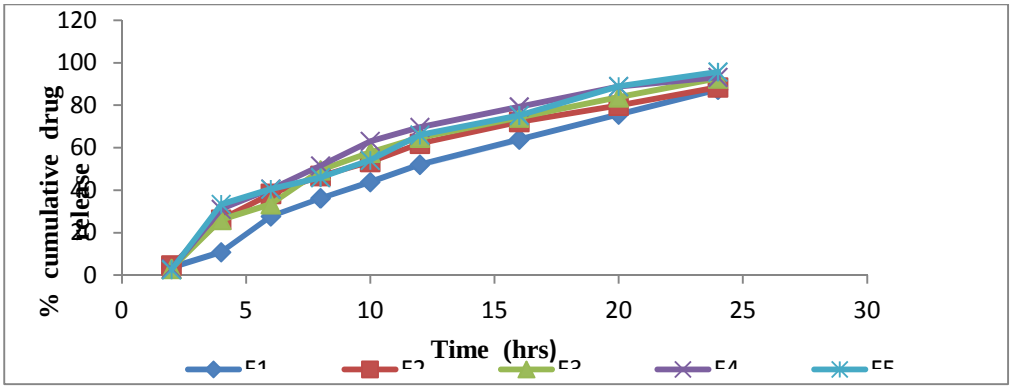

Fig-3: Drug release profile of patches.

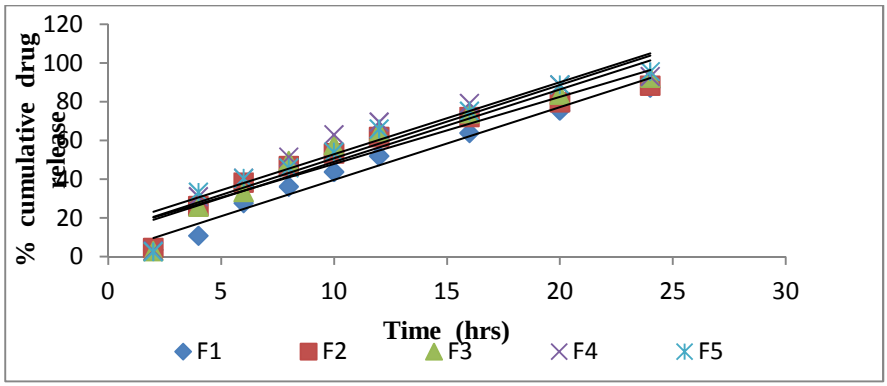

Fig-4: Zero order release plot of Methyl salicylate from patches.

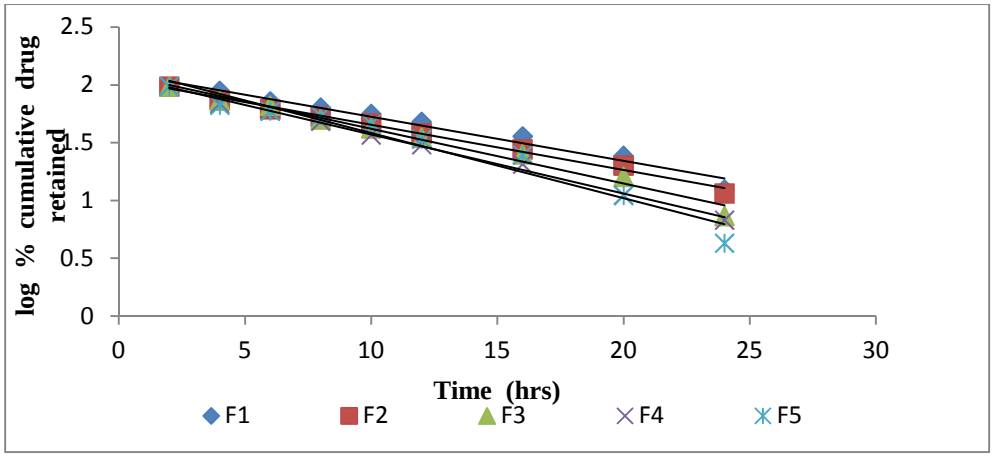

Fig-5: First order release plot of Methyl salicylate from patches.

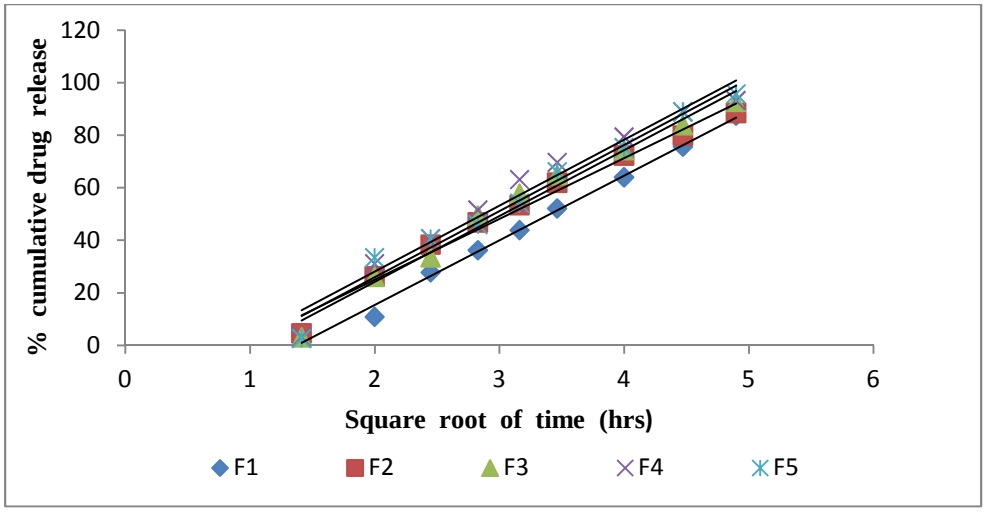

Fig-6: Higuchi kinetics release plot of Methyl salicylate from patches.

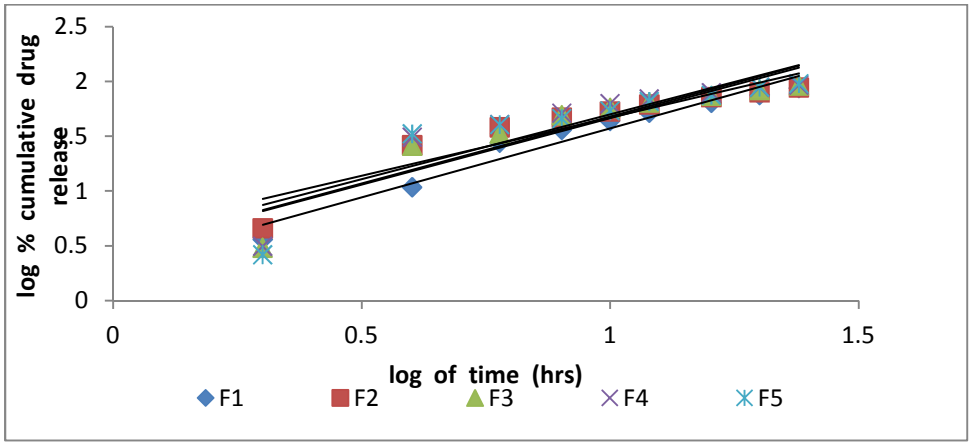

Fig-7: Peppas kinetics release plot of Methyl salicylate from patches.

Conclusion

In conclusion formulation F5 has achieved the targets of present study such as prolonged release, reduced frequency of administration, and thus may improve the patient compliance.

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