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FORMULATION AND EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM OF TIMOLOL MALEATE AS A MODEL DRUG.

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ABSTRACT

Timolol maleate, an antihypertensive drug has a half-life of 2-3 hours and a bioavailability of about 60%. It undergoes extensive first pass metabolism. The present study aims to formulate and evaluate Transdermal drug delivery for sustained release of Timolol maleate. The partition coefficient in octanol /water system indicates that the drug is suitable for Transdermal drug delivery. The Physicochemical compatibility of the drug and polymers was studied by IR spectroscopy and the results suggested no physicochemical incompatibility between drugs and the polymers. Total 20 formulations were prepared. The transdermal patches were prepared using different polymers like Hydroxy Propyl Methyl Cellulose, Polyvinyl alcohol and Poly vinyl pyrrolidine in varied ratios, plasticizers like propylene glycol and various permeation enhancers. The patches were evaluated for various parameters like Thickness, weight variation, Water-Vapor Permeability, Tensile Strength, Percent Moisture Uptake, Drug Content, Diffusion and Dissolution studies. The interaction among various components of the matrices was studied by performing Differential Scanning Calorimetry. The Optimized formulation containing PVA: PVP (F 19) in the ratio of 3:2 and containing 30 % propylene glycol as a plasticizer and 2 % Hyaluronidase as a permeation enhancer gave a maximum release 51.68 % (4.75 mg) over a period of 8 hours. Stability studies were carried out as per ICH guidelines and formulations were found to be Stable.

Key words: Transdermal patches; Timolol maleate; Differential Scanning Calorimetry (DSC); Infrared spectroscopy (IR); Partition co-efficient.

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INTRODUCTION

Transdermal drug delivery constitutes one of the most important routes for new drug delivery system (NDDS). Transdermal delivery of drugs offers several advantages over conventional delivery methods including oral and injection methods. Transdermal delivery, that traditionally uses a patch containing drug substances pressed onto the skin, is non-invasive, convenient and painless, and can avoid gastrointestinal toxicity and the hepatic first pass metabolism[1].

Systemic hypertension represents a significant risk factor for the development of atherosclerotic coronary artery disease and myocardial infarction, cerebrovascular accidents and cardiac heart failure[2].

In response to advances, several Transdermal drug delivery systems have been developed to achieve the objective of systemic medication through application on the intact skin surface.[3]

Timolol maleate is a β-adrenoceptor-blocking agent used in treatment of cardiovascular diseases like myocardial infarction, angina pectoris, hypertension, respiratory complications and migraine. The main limitation of therapeutic effectiveness of Timolol maleate is its higher frequency of drug dosing and short biological half-life, high first pass metabolism and poor bioavailability by oral route. It is rapidly absorbed from gastrointestinal tract with peak plasma concentration of 5-10 ng/ ml after 1-2 hr; it is metabolized up to 80% in liver with a mean half-life of 2-3 hr. Thus necessitating frequent administration of larger doses to maintain therapeutic drug level. Therefore, to maintain effective plasma concentration and to avoid sub therapeutic and toxic concentration, a continuous delivery of Timolol maleate is required. The transdermal route is, therefore, a better alternative, to achieve constant plasma level, which additionally warrants less frequent dose regime. The present study has been selected transdermal delivery system to achieve maximum therapeutic benefit.

MATERIALS AND METHODS

Timolol maleate was obtained as gift sample from Van Petro Chemicals Ltd., Mumbai. Hydroxy propyl methylcellulose (HPMC), Polyvinylpyrrolidone (PVP), Polyvinyl alcohol (PVA) was obtained from S. D. Fine chemicals. All other chemicals and reagent used were of analytical reagent grade. The drug samples were characterized by means of UV and IR methods.

Experimental Methods:

Determination of partition coefficient:

The partition coefficient of Timolol maleate was carried out in n-octanol/ distilled water. A drug solution of 5 mg/ml of Timolol maleate was prepared in distilled water, 10 ml of this solution

was taken in a seperating funnel and shake with equal volume of n-octanol/water for 10 minutes and allowed it to stand for 1 hour. Then water phase was seperated, centrifuged for 10 minutes at 2000rpm. The water phase was assayed before and after partitioning using UV-Spectrophotometer to get partition coefficient. Triplicate readings were taken and average was calculated. The partition coefficient was expressed as the concentration of drug in the organic phase divided by the concentration of drug in the aqueous phase[4].

Compatibility Studies:

The proper design and formulation of a formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and Excipients to be used in fabricating the product. The drug and Excipients must be compatible with one another to produce a product that is stable, efficacious, attractive and easy to administer and safe. If the Excipients are new and not been used in formulation containing the active the active the compatibility studies are paramount importance.

Drug+ Excipients 1:1 ratio---> IR and DSC studies---> No interaction---> Recommended Excipients.

Method:

Drug and Excipients in 1:1 ratio were mixed and stored in a glass vials at 50^0C. The samples were analyzed for compatibility by IR and DSC studies after 30days.

Preparation of drug containing polymer matrices:

The transdermal patches were prepared using different polymers like Hydroxy propyl Methylcellulose, Polyvinyl alcohol and Polyvinylpyrrolidone in varied ratios; plasticizers like propylene glycol & glycerin and various permeation enhancers. The composition of various formulations of Timolol maleate was shown in Table 1.The polymer (HPMC//PVA) was taken in a beaker with a minimum quantity of the solvent Then 2/3rd of the solvent was mixed with the other polymers (PVP K-30) and was added with stirring at lower rpm initially and later at a higher speed. The plasticizer and penetration enhancers were added they uniformly mixed and the drug was incorporated with continuing agitation, the volume was made up. This solution was used to cast films. The patches were prepared using Aluminium foil cups, coated with low density polyethylene. The cups had an internal diameter of 3-4 cm. These cups were placed on a level and flat surface. 5 ml of the solution was pipetted into it. These were then dried at 40 -45 ^{0} over night to produce films having an area of 12.56 sq.cm. A 3.14 sq.cm patch was cut out in all

cases and subjected to evaluation studies. The films were then packed in butter paper and stored in dessicator.[5]

Table 1: Composition of Various Formulations of Timolol Maleate

Formulation	Drug (% w/w)	Polymer	Solvent	Plasticizer	Enhancer
F1	0.8	HPMC 2 %	D. Water 100 ml	Propylene glycol 30 %	DMSO 3 %
F2	0.8	HPMC 3 %	"	"	"
F3	0.8	HPMC 1 %	"	"	"
F4	0.8	HPMC 2 %	"	Glycerine 30 %	B-cyclo dextrin 3 %
F5	0.8	HPMC 1 %	"	"	"
F6	0.8	HPMC : PVP (3 : 1)	"	Propylene glycol 40 %	DMSO 3 %
F7	0.8	HPMC : PVP (2 : 2)	"	"	"
F8	0.8	HPMC : PVP (1 : 3)	"	"	"
F9	0.8	HPMC : PVP (2 : 2)	"	Propylene glycol 30 %	Hyaluronidase 3 %
F10	0.8	HPMC : PVP (1 : 3)	"	"	"
F11	0.8	PVA 3 %	"	Propylene glycol 30 %	DMSO 3 %
F12	0.8	PVA 4 %	"	"	"
F13	0.8	PVA 2 %	"	"	"
F14	0.8	PVA 2 %	"	Glycerine 30 %	β -cyclodextrin 3 %
F15	0.8	PVA 3 %	"	"	"
F16	0.8	PVA : PVP (1 : 3)	"	Propylene glycol 40 %	DMSO 3 %
F17	0.8	PVA : PVP (2 : 3)	"	"	"
F18	0.8	PVA : PVP (3 : 1)	"	"	"
F19	0.8	PVA : PVP (3 : 2)	"	Propylene glycol 30 %	Hyaluronidase 3 %
F20	0.8	PVA : PVP (2 : 2)	"	"	"

HPMC = Hydroxy propyl Methylcellulose PVA = Polyvinyl alcohol

PVP = Polyvinyl pyrrolidine DMSO = Dimethyl sulphoxide

Evaluation of Polymer Matrices:

The Polymeric matrices were evaluated for Thickness, Weight variation, Drug content uniformity, Tensile strength, Percentage Moisture Uptake, Water vapor permeability, *In-vitro*

drug release, Compatibility studies and Stability studies. Discs of 3.14 sq. cm patches were subjected to measurement of thickness using Digital Vernier calipers. Discs of 3.14 sq. cm diameters were cut from the film and weights of each determined using single pan electronic balance with sensitivity up to 1 mg. Discs 3.14 sq. cm of the films was cut and each dissolved in sufficient quantity of phosphate buffer of pH 7.4. The volume was made up to 50 ml. 1 ml was then withdrawn from this solution and diluted to 10 ml. The absorbance was measured at 294 nm. From the absorbance and the dilution factor, the drug content in the film was calculated.[6]

The films were casted on mercury and taken in rectangular containers using proportionate quantity of the solution calculated on the basis of area. The films were cut into strips of 1cm width and 15cm length. The films were fixed onto the Tensile strength apparatus in such a way that the length of film between the jaws was initially 10 cm. The trials where the breakage occurred at the jaw were invalid and the result was repeated on another strip.

A weighed film kept in the desicator at room temperature for 24 hrs and exposed to 84 % RH until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between initial and final weight with respect to initial weight. Water vapor permeability was calculated using a glass vials of 5 ml capacity, washed thoroughly and dried to a constant weight in an oven. About 1 gm of fused Calcium chloride was taken in the vials & the polymer films were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber at 85 % RH condition for a period of 24 hours. The vials were removed and weighed at various time intervals like 3, 6, 12, 18 and 24 hr to note down the weight gain.[7]

***In-vitro* drug release:**

Modified Chien diffusion cell was used in our studies for *In-vitro* drug release. The cell consists of two chambers, the donor and the receptor. The effective permeation area of the diffusion cell and receptor volume was 3.14 sq.cm and 50 ml respectively. The donor compartment is open at the top and is exposed to the atmosphere. The receptor compartment is surrounded by a water jacket for maintaining the temperature at $37^{o} \pm 2^{o}$ and is provided with a sampling port. The diffusion medium was phosphate buffer of pH 7.4, which was stirred with Teflon coated magnetic bead (operated by a magnetic stirrer). A treated cellophane membrane was placed between the two chambers. Samples (2 ml) from the receptor compartment were taken at various intervals of time over a period of 8 hours and the concentration of the drug was determined by

UV Spectrophotometric method using the standard curve at 294 nm. Amount of drug diffused at various time intervals was calculated and plotted against time.[8]

Drug Excipients Interaction studies:

The drug excipients interaction studies were done by IR spectroscopy and DSC studies. Drug and excipients in 1:1 ratio were mixed and stored in a glass vials at 50^0C. The samples were analyzed for compatibility by IR after 30days. The IR is the one of the most powerful analytical technique that offers possibility of chemical interaction. The IR spectrum of Timolol maleate and excipients were obtained by using KBR pellet technique using Fourier Transform IR spectrophotometer. In these studies 3 polymers like HPMC, PVA and PVP was used.

Differential Scanning Calorimetry has been one of the most widely used calorimetric techniques employed to characterize the solubility and physical state of drug in the complex. Thermo grams of Timolol maleate, and optimized patch containing Timolol maleate, PVA and PVP were recorded using a differential scanning calorimeter and were compared. The samples (5 mg) were hermetically sealed in flat bottomed aluminum pans and heated over a temperature range of 40-240° at a rate of 10° k/min using alumina as a reference standard.[9]

Stability Studies:

The optimized three formulations F9, F13 and F19 were packed in butter paper, which were tightly plugged with cotton and capped. They were then stored at 0^0, 25^0/ 60% RH and 40^0 / 75% RH for 1 month as per ICH guidelines. The samples were withdrawn every week and the drug content was estimated.

RESULTS AND DISSCUSION

Partition Coefficient:

In this study the partition coefficient value of Timolol maleate in n-octanol/ water system was found to be 1.94. This value is in good agreement with those reported in the literatures. The log K values of Timolol maleate indicates that the drug processes sufficient lipophilicity, which meets the requirements of formulating it into a Transdermal patch.

Drug-excipients compatibility studies:

IR spectroscopy and DSC studies was used as a mean to study drug-excipients interaction. The IR spectrum of pure Timolol maleate, Timolol with individual excipients in the ratio of 1:1 and they are matching with each other and showed finger print region. This shows that Timolol maleate and all the excipients used in the study showed no interaction between them and indicated that they are compatible with each other.

For DSC studies Timolol maleate showed a characteristic exothermic peak at 207.70^0, which corresponds to its melting point. The optimized formulation F19 also showed characteristic

exothermic peak at 210.05^0. This result indicates that drug and polymers are compatible shown in figure 1&2.

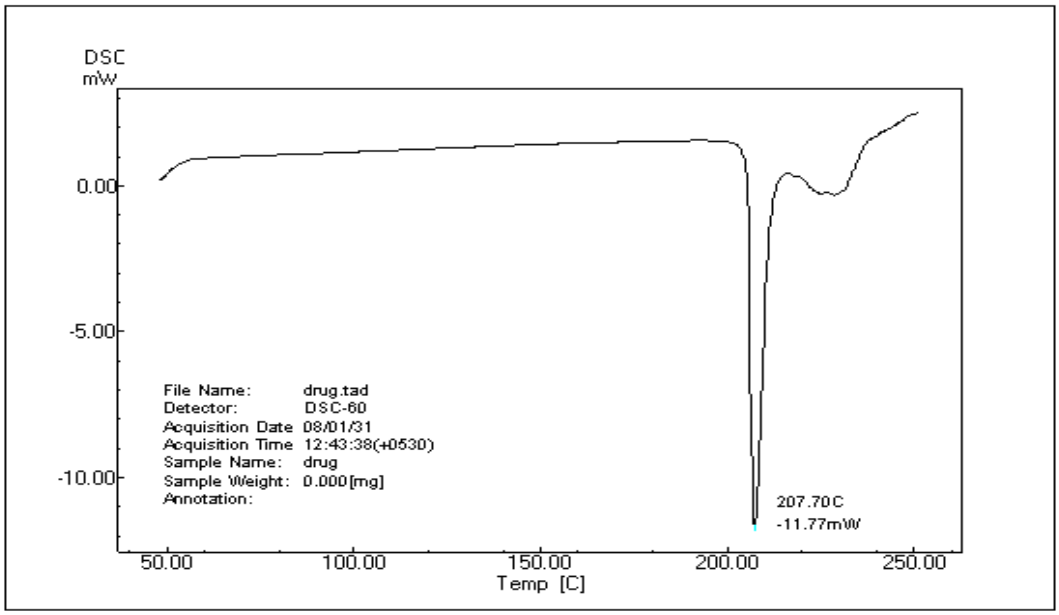

Figure 1: D.S.C. image of Timolol maleate. Timolol maleate showed a characteristic exothermic peak at 207.70^0C, which corresponds to its melting point.

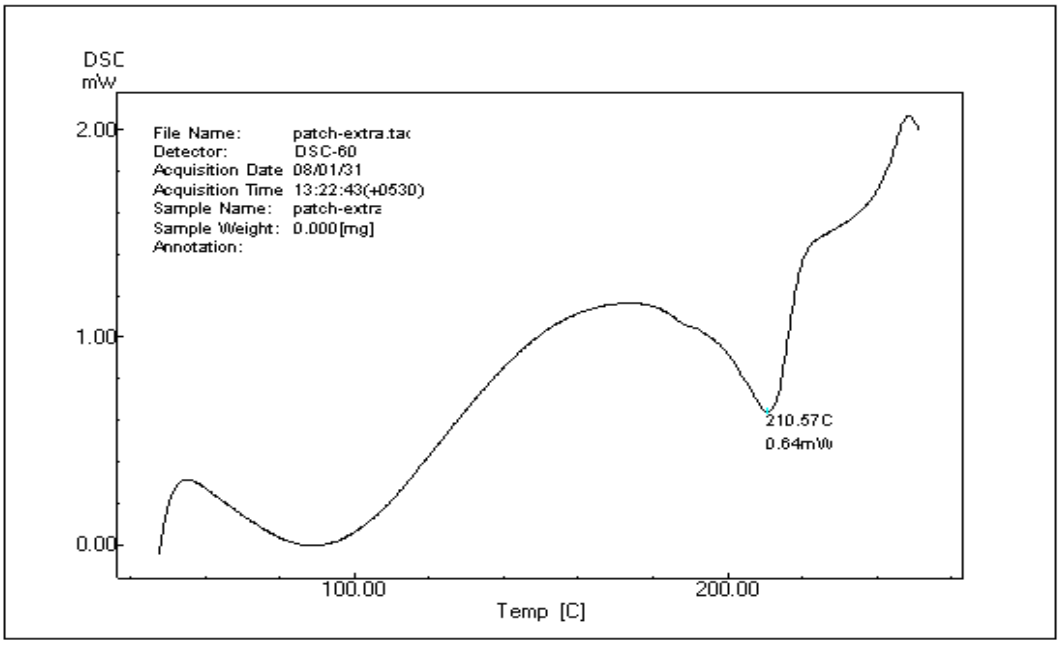

Figure 2: D.S.C. image of Optimized Formulation 19 (Timolol maleate + PVA + PVP)

Evaluation parameters.

The results of physico-chemical parameters were showed in Table 2 & 3. The weight variation of formulated films was found to be in the range of 25.4 ± 1.3 mg to 40.2 ± 2.5 mg and thickness of formulated films was found to be in the range of 0.08 ± 0.02 mm to 0.19 ± 0.04 mm. The drug content of formulated films was found to be in the range of 8.82 to 9.28 mg per 3.14 cm^2 strip. Tensile strength of formulated films was measured using a Bottom loading single pan balance which was found to be 1.5 to 2.86 kg/cm^2. The Percent moisture uptake was found to be more in films containing HPMC polymers because it absorbs moisture.

Table 2: Phsico-Chemical Evaluation of Formulated Patches of Timolol Maleate

Film no	Weight (mg)	Thickness (mm)	Drug content (mg)	Tensile strength (kg/cm^2)	Percent Moisture Uptake
F1	27.5 ± 1.5	0.09 ± 0.03	9.18	1.68	4.36
F2	28.3 ± 1.4	0.1 ± 0.02	9.23	1.82	4.24
F3	25.4 ± 1.3	0.08 ± 0.02	8.82	1.5	4.72
F4	28.6 ± 1.7	0.09 ± 0.03	8.9	1.7	4.19
F5	26.3 ± 1.3	0.08 ± 0.02	9.15	1.74	4.56
F6	32 ± 1.5	0.09 ± 0.03	8.88	1.6	3.43
F7	33.3 ± 1.4	0.11 ± 0.03	9.2	1.9	3.30
F8	29.9 ± 1.3	0.08 ± 0.03	8.9	1.8	3.67
F9	31.5 ± 1.5	0.12 ± 0.03	9.13	1.78	3.49
F10	32.6 ± 1.6	0.09 ± 0.02	9.28	1.94	3.37
F11	34 ± 1.7	0.13 ± 0.02	8.82	2.2	2.94
F12	36.4 ± 1.9	0.16 ± 0.03	8.94	2.28	2.74
F13	33.8 ± 1.7	0.12 ± 0.04	9.16	2.16	2.95
F14	32.2 ± 1.8	0.14 ± 0.03	9.18	2.24	3.10
F15	31.9 ± 1.9	0.12 ± 0.04	8.92	2.1	3.13
F16	35.8 ± 2.2	0.14 ± 0.03	9.12	2.48	2.65
F17	40.2 ± 2.5	0.18 ± 0.03	9.16	2.62	2.36
F18	38 ± 2.3	0.18 ± 0.03	9.2	2.8	2.5
F19	39.4 ± 2.4	0.19 ± 0.04	9.24	2.86	2.41
F20	36.3 ± 2.2	0.16 ± 0.03	8.86	2.32	2.61

Patch size used for evaluation studies: 3.14 cm^2

The *In vitro* permeation data across treated cellophane membrane showed anomalous diffusion (non-fickian) transport and its release mechanism follows Zero order kinetics. The cumulative amount of Timolol maleate released from different polymeric films was found to be between 3.072 to 4.75 mg in 8 hrs using treated cellophane membrane.

The formulation no. F19 (PVA and PVP in the ratio of 3:2) have showed optimum release of 4.75 mg (51.68 %) in 8 hrs using treated cellophane membrane.

Table 3: Evaluation of formulated films for Water vapor permeability.

Film no.	Water vapor permeability (g/cm^2) 1^{st} hour	3^{rd} hour	6^{th} hour	12^{th} hour	24^{th} hour
F1	11.16	11.18	11.19	11.23	11.28
F2	11.18	11.21	11.23	11.24	11.26
F3	11.10	11.12	11.16	11.17	11.20
F4	11.20	11.21	11.23	11.24	11.25
F5	11.10	11.13	11.14	11.48	11.22
F6	11.28	11.30	11.32	11.36	11.40
F7	11.48	11.51	11.52	11.55	11.58
F8	11.24	11.26	11.29	11.30	11.33
F9	11.32	11.33	11.35	11.37	11.41
F10	11.42	11.44	11.46	11.48	11.52
F11	11.68	11.69	11.70	11.70	11.73
F12	11.52	11.52	11.53	11.53	11.55
F13	11.46	11.47	11.48	11.48	11.50
F14	11.36	11.36	11.37	11.39	11.42
F15	11.38	11.39	11.42	11.44	11.45
F16	11.40	11.41	11.42	11.44	11.47
F17	11.76	11.77	11.79	11.80	11.82
F18	11.68	11.68	11.69	11.72	11.75
F19	11.70	11.70	11.71	11.73	11.75
F20	11.38	11.39	11.39	11.40	11.41

The formulation F9 among various HPMC combinations showed an optimum release of 3.67 mg in 8 hrs using treated cellophane membrane and formulation no. F13 among various PVA combinations showed an optimum release of 4.02 mg in 8 hrs using treated cellophane membrane.

In vitro drug release profiles of optimized three formulations of Timolol maleate through treated cellophane membrane in 8 hrs was shown in Fig.3.

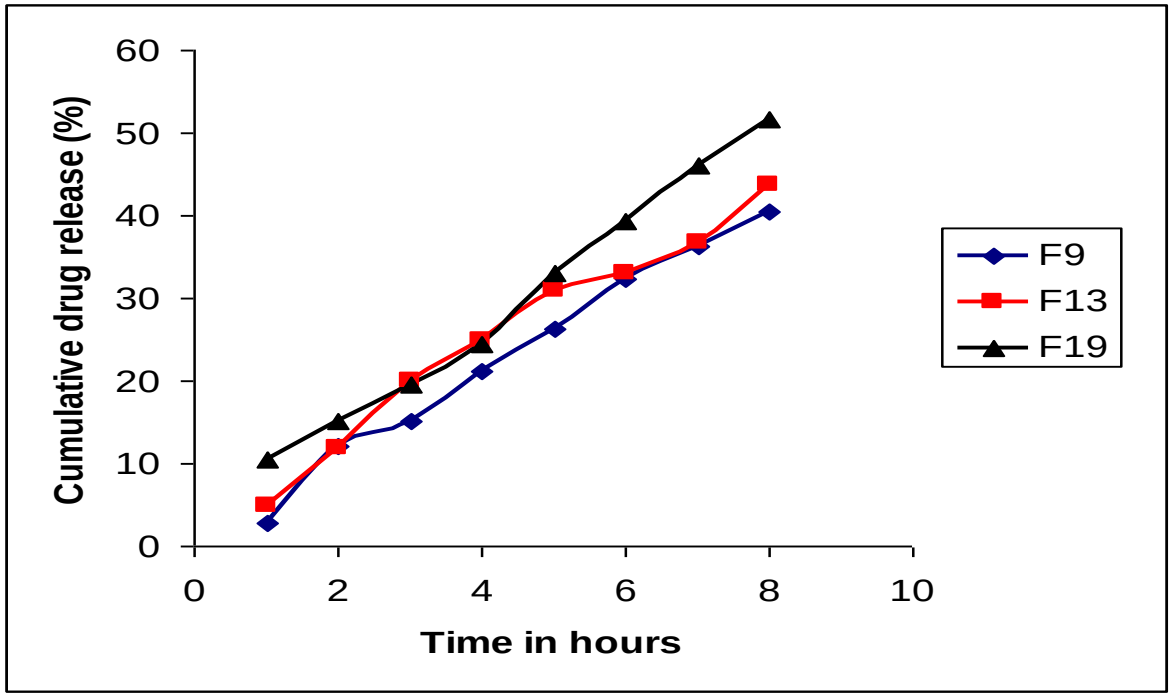

Figure. 3*: In vitro* drug release profiles of optimized three formulations of Timolol maleate through treated cellophane membrane in 8 hrs.

Stability Studies:

The selected three optimized formulation F9, F13 and F19 had a residual drug content of more than 97 % after weekly checking up to 1 month when stored at room temperature, 0^0, 25^0 at 60 % RH and 40^0 at 75 % RH. These results indicate that the selected formulations exhibited good stability during storage and they were stable.

CONCLUSION

Timolol maleate, an antihypertensive drug has been selected which has half-life of 2-3 hours. The study aims to formulate and evaluate Transdermal drug delivery of Timolol maleate. The transdermal patches were prepared using combinations of HPMC, PVP, and PVA in various ratio, Among them PVA: PVP combination in the ratio of 3:2 gave the maximum releasing effect. Formulation 19 was found to be the best formulation and release was carried out using pig skin it was 3.49 mg in 8 hrs 4.75 mg in 8 hrs using treated cellophane membrane. Thus we have succeeded in making Transdermal patches of the drug Timolol maleate.

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