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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF NARATRIPATAN HCL TO IMPROVE AND SUSTAINED ITS ANTIMIGRAINE EFFECT

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ABSTRACT

Transdermal drug delivery system (TDDS) was designed to sustain the release and improve the bioavailability of drug and patient compliance. Among the various types of transdermal patches, matrix dispersion type systems disperse the drug in the solvent along with the polymers and solvent is allowed to evaporate forming a homogeneous drug-polymer matrix. The objective of the present study was to design and formulate TDDS of Naratriptan hydrochloride and to evaluate their sustained release. **Materials and Methods:** In the present study, an attempt has been made to develop a matrix-type transdermal therapeutic system comprising free film method with different ratios of hydrophilic and hydrophobic polymeric combinations using solvent casting technique. **Results:** The physicochemical compatibility of the drug and the polymers was studied by Fourier transform infrared spectroscopy. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. The patches were further subjected to various physical evaluations.

KEYWORDS: Transdermal Drug Delivery System (TDDS), hydroxy propyl methyl cellulose (HPMC), Polyethylene glycol, Isopropyl myristate, Anti-migraine effect.

INTRODUCTION

During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed. The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent. Transdermal Drug Delivery System (TDDS) are defined as self-contained, discrete dosage forms which are also known as "patches" , when patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation. TDDS are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin.

Basic principle of transdermal permeation

Transdermal patch is based on passive diffusion. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimetre of tissue separate its surface from the underlying capillary network. The release of a therapeutic agent from a formulation applied to skin surface and its transport to systemic circulation is a multistep process, which include

1. Diffusion of drug from drug to the rate controlling membrane
2. Dissolution within and release from the formulation
3. Absorption by stratum corneum and penetration through viable epidermis
4. Uptake of drug by capillary network in the dermal papillary layer
5. Effect on target organ
6. Partitioning into skin 's outermost layer, the stratum corneum
7. Diffusion through the stratum corneum, principal via a lipidic intercellular pathway[4]

Components of Transdermal Drug Delivery System

a) Polymer matrix/ Drug reservoir
b) Drug
c) Permeation enhancers.
d) Pressure sensitive adhesive (PSA).
e) Backing laminate.
f) Release liner.
g) Other excipients like plasticizers and solvents

Methods of Preparation of TDDS

a) Asymmetric TPX membrane method.
b) Circular Teflon mould method.
c) Mercury substrate method.
d) By using "IPM membranes" method.
e) By using "EVAC membranes" method.
f) Preparation of TDDS by using Proliposomes.
g) By using free film method

a) **Asymmetric TPX Membrane Method**: This method was discovered by Burner and John in 1994. By this method prototype patch can be prepared by using heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter as the backing membrane. Drug dispersed on concave membrane, covered by a TPX [poly (4-methyl-1- pentene)] asymmetric membrane, and sealed by an adhesive.

Preparation: These are prepared by using the dry or wet inversion process. In this TPX is dissolved in a mixture of solvent (cyclohexane) and non- solvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs. and cast on a glass plate. Then casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath (temperature maintained at 25°C). After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs.

b) **Circular Teflon Mould Method**: It was discovered by Baker and Heller in 1989. Polymeric solution in various proportions is used as an organic solvent. Then that solution is divided in two parts. In one parts calculated amount of drug is dissolved & in another part enhancers in different concentration are dissolved, and then two parts mixed together. Then plasticizer (e.g., Di-N-butyl phthalate) is added into the drug polymer solution. The total contents are to be stirred for 12 hrs. And then poured into a circular Teflon mould. The moulds are to be placed on a levelled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. After which a dried film formed & that is to be stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects.

c) **Mercury Substrate Method:** In this method drug & plasticizer get dissolved in polymeric solution. It stirred for 10-15 min to produce homogenous dispersion then it is poured into levelled mercury surface, covered with inverted funnel to control solvent evaporation.

d) **"IPM Membranes" Method:** In the mixture of water & polymer (propylene glycol containing Carbomer 940 polymer) drug get dispersed and stirred for 12 hrs. in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. If the drug solubility in aqueous solution is very poor then solution gel is obtained by using Buffer pH 7.4. The formed gel will be incorporated in the IPM membrane.

e) **"EVAC Membranes" Method:** Preparation of TDS, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membrane is needed as rate control membrane. If the drug is insoluble in water then use propylene glycol for gel preparation. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

f) **Preparation of TDDS by Using Proliposomes:** By carrier method using film deposition technique proliposomes are prepared. Drug and lecithin ratio should be 0.1:2.0 taken as an optimized one from previous references. For the preparation of proliosome in 100ml round bottom flask take 5mg of mannitol powder, then it is kept at 60-70°c temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20- 30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator overnight and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

g) **Free Film Method:** In this process firstly cellulose acetate free film is prepared by casting it on mercury surface. And 2% w/w polymer solution is prepared by using chloroform. Plasticizers are to be added at a concentration of 40% w/w of polymer weight. Then 5 ml of polymer solution is poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent can be controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. By this process we can prepare free films of different thickness can be prepared by changing the volume of the polymer solution.[4]

EXPERIMENTAL WORK

1. Materials used

Table no 1: List of materials used and their suppliers.

Sr. No.	Materials	Suppliers
1	Naratriptan hydrochloride	Hetro Drugs Limited Hyderabad (India)
2	HPMCk4M	Research-Lab Fine Chem Industries Mumbai 400002 (India)
3	Polyethylene glycol400	Oxford Laboratory Mumbai-400002 (India)
4	Isopropyl myristate	LobaChemie Laboratory Chemicals Ltd,Mumbai
5	Ethanol	Jiangsu Huaxi International Trade Co. Ltd
6	Potasium dihydrogen phosphate	LobaChemie Laboratory Chemicals Ltd,Mumbai
7	Disodium hydrogen phosphate	LobaChemie Laboratory Chemicals Ltd,Mumbai

2. Instruments Used

Table no. 2: List of instruments used and their manufacturer.

Sr.No	Instruments	Manufactures
1	Digital Balance	Contech Instruments Ltd.(Model no.CAH-223)
2	Digital pH meter	Elico-Li-120
3	Double beam UV-Spectrophotometer	Shimadzu UV1800
4	Diffusion cells	Franz diffusion cell
5	FTIR Spectrophotometer	Shimadzu (Model no 00346
6	Digital Vernier Caliper	Mitutoyo CD6CSX, Japan
7	Ultrasonicator	MVTEX

EVALUTION OF RAW MATERIAL

Prior to development of new dosage from with a drug candidate, it is essential that certain fundamental physical and chemical properties of the drug candidate and excipients are to be determined.

1. Characterization of Drug

The characterization of drug was carried out by conducting various test, including.

- **Appearance**

Appearance of drug was visually recorded by physical texture of drug.

- **Organoleptic properties**

These are preliminary characteristics of any substance, which are useful in the identification of specific material. Following physical properties of drug were studied. Colour, Taste, Odour.

- **Determination of melting point**

Glass capillary method was used to determine the melting point. Drug was filled in glass capillary tube and tied with a thermometer and then immersed in Thiele's tube (containing liquid paraffin as heating medium) which was heated slowly. The temperature at which drug started melting and temperature at which it melted completely was noted. Reading were recorded in triplicate and mean value has been reported.

- **PH**

The PH value of a Naratriptan HCl is usually determined by putting the Naratriptan HCl in petri dish and subsequently drug is made wet by using distilled water and noting pH by touching the drug with a pH meter electrode.

Evaluation of Naratripatan Hcl

Table. No. 3: Analysis report of NaratriptanHCl

Sr. no	Test	Properties	Reorted	Observed
1	Organoleptic Peoperties	Appearance	Amorphous powder	Amorphous powder
		Taste	Slightly bitter	Slightly bitter
		Odour	Odourless	Odourless
		Colour	White	White
2	Melting Point	Melting range	234-236	232-235
3	Identification Test	Ph	6.4	6.2
4	Solubility Study	Phosphate buffer 6.8	Freely soluble	Freely soluble

❖ **Spectral analysis of drug**

- **Determination of $\lambda_{max:}$ -**

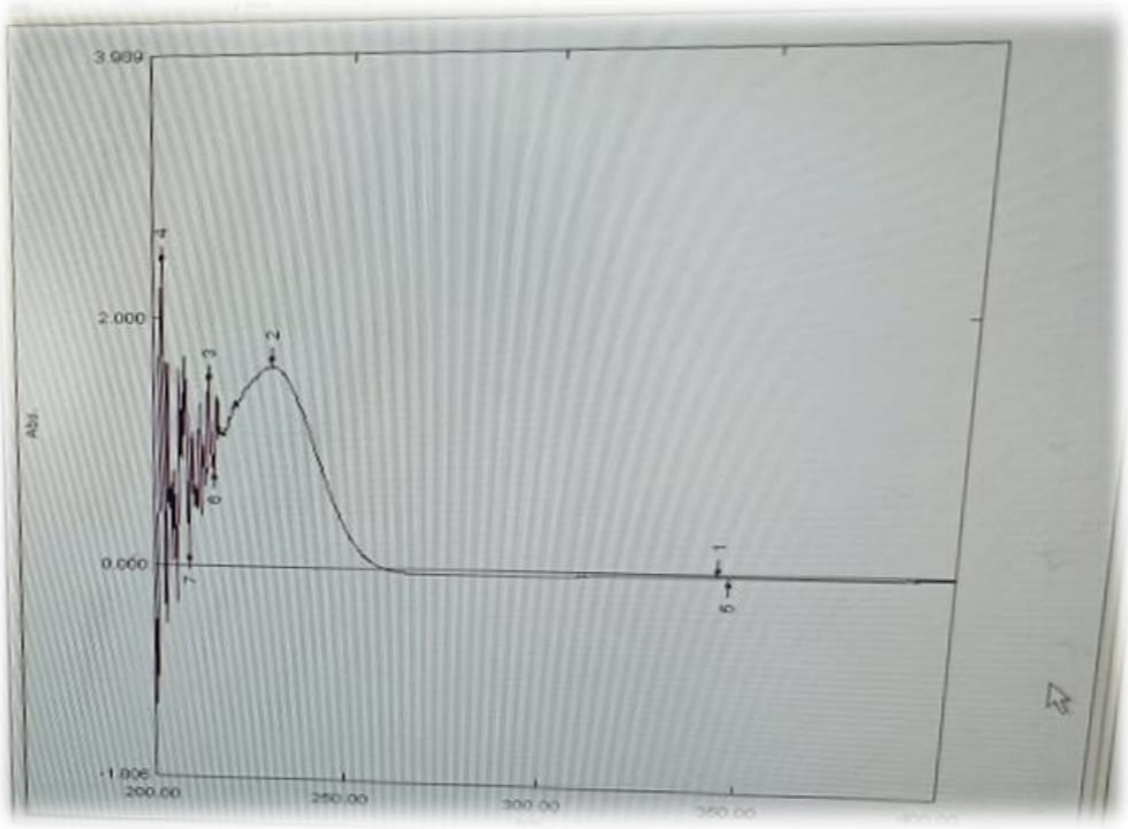

Figure 1: Scanning of Naratriptan HCl phosphate buffer 6.8ph buffer.

The λ_{max} Naratripatan HCL was found to be 237 nm as shown in figure.

Preparation of working stock solutions of Naratriptan HCl

The linearity of the response of the drug was verified at 2 to 10µg/ml concentration. Accurately weighed 10mg of NH was dissolved in phosphate buffer 6.8 to get the stock solution of 100µg/ml. From this stock solution aliquots of 0.1, 0.2, 0.4, 0.6, 0.8 and 1ml were withdrawn and further diluted to 10 ml with phosphate buffer pH 6.4 to obtain concentrations range of 1 to 10µg/ml. The absorbance for different concentration was measured at 281nm by using UV spectrophotometer. The calibration curve was obtained by plotting the absorbance versus con-centration data and were treated by linear regression analysis.

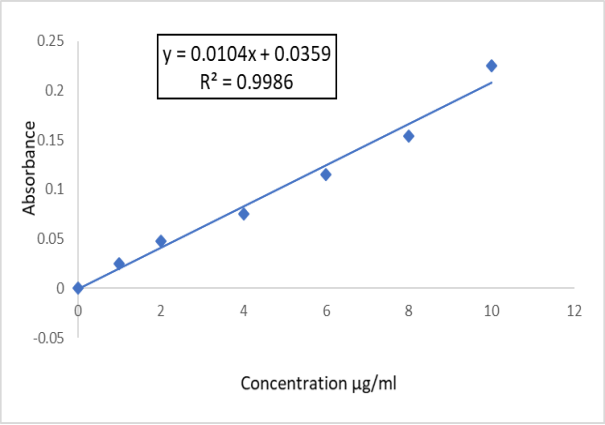

Figure 2: Standard Calibration curve of Naratriptan HCL in 6.8 phosphate buffer.

Sr no	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	1	0.025
3	2	0.048
4	4	0.075
5	6	0.115
6	8	0.154
7	10	0. 225

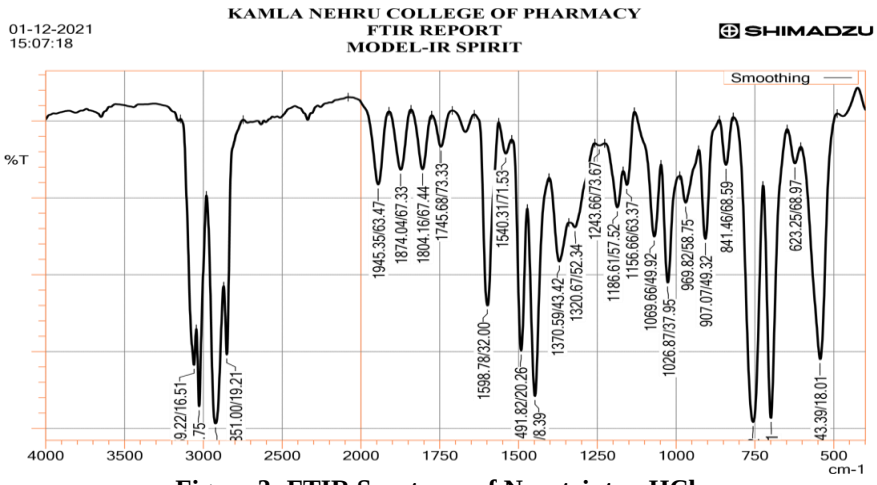

Figure 3: FTIR Spectrum of Naratriptan HCl.

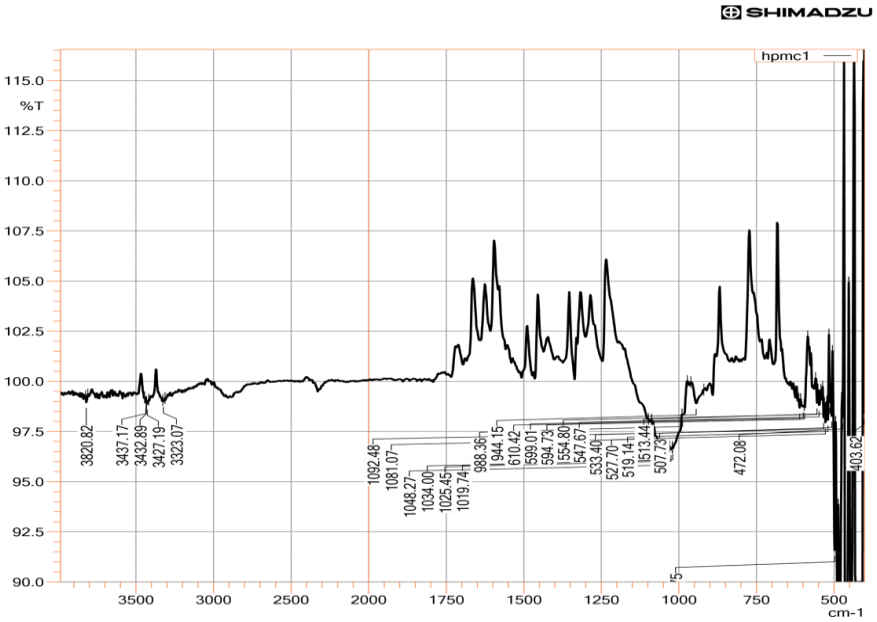

Figure 4: FTIR Spectrum HPMCK4M.

Compatibility Study

Study of physical interaction between Naratripatan HCl and HPMCK4M

The polymer

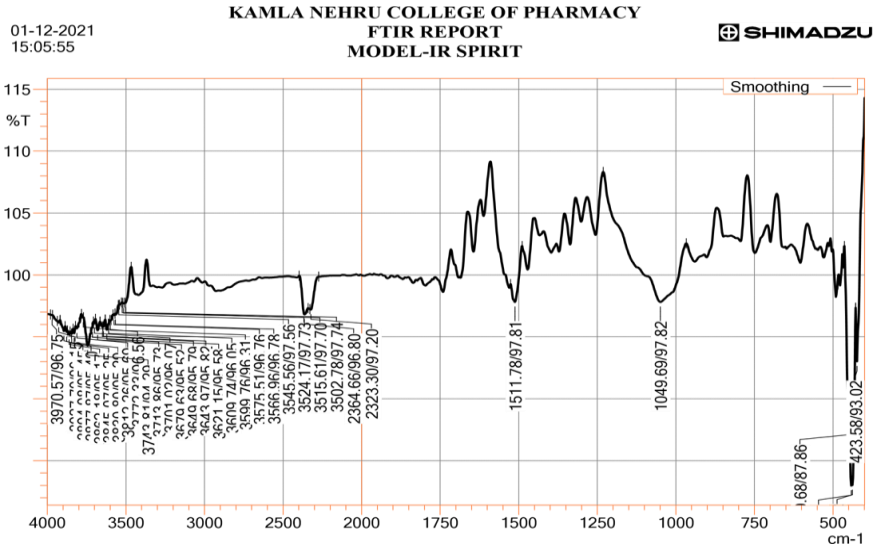

Figure 5: FTIR Spectrum of Naratriptan HCl and HPMCK4M.

Formulation of Transdermal Patch without Drug

Transdermal patch was prepared by using solvent casting method. All the ingredients mentioned in table below were weighed accurately and dissolved in the solvent system ethano1: water (1:1) in the 50ml beaker. This polymeric solution was then placed on the magnetic stirrer 30min until homogeneous solution formed. Then solution was sonicated for 20min to remove entrapped bubbles. The resulting solution was poured in a petri dish and dried at room temperature. The rate of evaporation of solvent was controlled by inverting a funnel over the petri dish. After drying at room temperature for 24 hours, films are taken out, packed in aluminium foil and stored in desiccator until further use.

Table no 4: Formulation of preliminary batches of transdermal patch without drug.

Ingredients	Batch F-1	Batch F-2	Batch F-3	Batch F-4	Batch F-5	Batch F-6	BatchF-7	Batch F-8	Batch F-9	Batch F-10	Batch F-11
HPMCK4M (%)	60	65	70	75	80	85	89	90	91	92	93
Isopropyl myristate (%)	–	–	–	–	–		6	8	7	5	4
Polyethylene glycol400 (%)	7	6	5	4	4	3	5	2	2	3	2
Ethanol: water Ratio (ml)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)

Formulation of Transdermal Patch

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Figure 6: Formulated Transdermal patches with drug.

Table No. 5 Formulation of preliminary batches of Transdermal patch with drug.

Ingredients	Batch F-12	Batch F-13	Batch F-14	Batch F-15	Batch F-16
Drug (mg)	3	3	3	3	3
HPMCK4M (%)	89	90	91	92	93
Isopropyl myristate (%)	6	8	7	5	4
Polyethylene glycol 400 (%)	5	2	2	3	2
Ethanol : water ratio (ml)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)

RESULT AND DISCUSSION

Table No.7: Result of Transdermal patch without drug.

Sr. no	Test	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11
1	Thickness (mm)	_	_	_		_	_	0.049± 0.11	0.050± 0.08	0.051± 0.11	0.051± 0.08	0.054± 0.08
2	Weight uniformity (mg)	–	–	–		–	–	28 ± 0.11	29 ± 0.12	30±0.12	30 ±0.12	28 ± 0.11
3	Folding endurance	_	_	_		_	_	300	200	220	210	199
4	PH	_	_	_		_	_	6.67	6.88	6.90	6.88	6.89
5	Moisture uptake	_		_		_	_	29.5	30.5	31.5	30.5	33.5
6	Moisture loss	_		_		_	_	25	28	28	25	28

Table No.8 Result of Transdermal patch with drug.

Sr. no	Test	F-12	F-13	F-14	F-15	F-16
1	Thickness (mm)	0.050±0.10	0.050±0.12	0.052±0.12	0.053±0.08	0.053±0.08
2	Weight uniformity (mg)	28±0.11	29.5 ± 0.12	30±0.12	28±0.12	29±0.11
3	Folding endurance	250	200	210	240	190
4	pH	6.66	6.50	6.51	6.54	6.55
5	Moisture uptake	28.5	29	30	28	32.5
6	Moisture loss	25	28.5	28	28.5	27.5

Table no.9: % Drug release from transdermal patch with drug.

Sr.no	Time (h)	F-1(%)	F-2(%)	F-3(%)	F-4(%)	F-5(%)
1	1	8.0	13.1	12.2	10.3	4.7
2	2	26.1	30.1	20.1	18.0	11.4
3	3	30.1	36.2	28.2	25.2	19.3
4	4	35.2	38.6	30.0	30.0	25.3
5	5	39.3	40.2	35.0	36.7	30.1
6	6	41.2	45.0	38.3	41.6	37.6
7	7	45.6	70.1	48.2	45.6	42.1
8	8	48.2	75.0	60.3	57.8	49.1
9	9	52.5	80.1	69.4	66.7	59.8
10	10	56.3	82.1	87.0	79.2	72.3
11	11	70.0	86.1	94.6	92.2	80.0
12	12	80.1	95.0	97.8	94.0	81.6
13	24	88.3	98.5	99.0	95.1	87.6

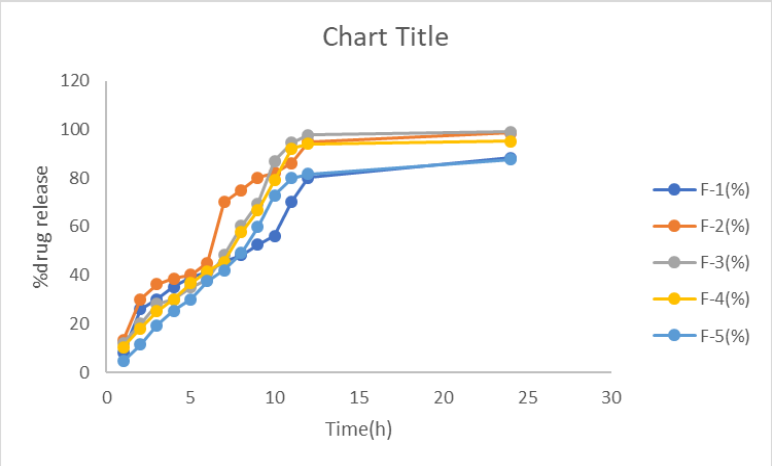

Figure 7: Cumulative % drug release from F-1 to F-5.

DISCUSSION

1. Physical appearance

The use of solvent the casting method for the preparation of transdermal patches yielded smooth, flexible, transparent, non-sticky, by using HPMCK4m polymer. The result indicated that the method used for casting film on a petri dish was found to be satisfactory.

2. Weight Variation

The weight of the patches ranged from 28±0.11mg to 30±12mg for HPMCk4m prepared with ethanol : water (1:1) (F-12, F-13, F-14, F-15, F-16) shows satisfactory result and transdermal patches prepared with lower concentration of HPMCK4m polymer 60% batch no.(F-1), 65% (F-2), 70% (F-3), 75% (F-4), 80% (F-5), 85%(F-6) get failed.

3. Thickness of patch

Thickness of the transdermal patch varied from 0.050±0.10mm to 0.053±0.08.the result were shown in Table No. 2 The thickness of the patches were found to increased in following order

4. without Drug

F-7 HPMCK4M 89% with ethanol: water (1:1) (0.049±0.11)
F-8 HPMCK4M 90 %(0.050±0.08)
F-9 HPMCK4M 91% (0.051±0.11)
F-10HPMCK4M 92 %(0.051±0.08)
F-11HPMCK4M 93 %(0.054±0.08)
With Drug

F-12 HPMCK4m 89 % with Ethanol: water (0.050±0.10),
F-13 HPMCK4m 90% (0.050±0.12mm),
F-14HPMCK4m 91% (0.052±0.12mm), F-15HPMCK4m 92% (0.053±0.08mm),
F-16 HPMCK4m (0.053.0.08mm)
From the results it was observed that thickness of the patches increased with increased in concentration of polymer, all the batches showed satisfactory result.

5. Folding Endurance
This test was carried out to check the efficiency of the plasticizer and strength of the prepared patch the folding endurance were shown in Table no 1, 2. The folding endurance of HPMCK4M patches with and without drug (F-7 TO F-16) was ranged from 300 to 199
From the result it was observed that the folding endurance was found to be high in patches containing high concentration (5%, 3%) of plasticizer polyethylene glycol 400 as compared to the transdermal patch containing lower concentration of polyethylene glycol400 shown in Table no.8.1, 8.2.Batch no F-13 to F-14 showed satisfactory results with (2%) concentration of polyethylene glycol 400.

6. PH
PH of all transdermal film of all batches showed satisfactory results.

7. Moisture uptake
This test was carried out to check uniformity of transdermal film. Results shown in table no 1,.2. All batches showed satisfactory results.

8. Moisture loss
Moisture loss studies was carried out in order to determine the stability of the prepared patches under dry ambient condition. Shown in table no 1, 2 (F-7 to F-16) all batches showed satisfactory results.

9. % Drug release
The results of drug permeation from transdermal patches of Naratripatan HCl through the cellophane membrane shown in table no.8.3.cumulative drug release showed satisfactory results with containing high concentration of permeation enhancer (8%,7%,6%5%)batch no (F-1,F-3,F-4,F-3) (99.0%,98.5%,95.1)there is decrease in drug release with decrease in concentration of permeation enhancer (4%) batch no.(F-5) (87.6%).

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