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FORMULATION AND EVALUATION OF MATRIX DIFFUSION CONTROLLED TRANSDERMAL PATCH OF BROMOCRIPTINE MESYLATE

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ABSTRACT

The aim of the present study was to design and formulate matrix diffusion controlled transdermal patch of Bromocriptine Mesylate using different ratios of hydrophilic and hydrophobic polymeric combinations by solvent evaporation technique. The effects of the different ratios of polymeric combinations were studied. All the formulations were examined for several evaluation parameters like physicochemical properties, compatibility, in vitro release, and stability studies. IR results showed that there was no incompatibility between the drug and the excipients used. The prepared formulations which were evaluated for different physicochemical properties like thickness, folding endurance, drug content, surface pH, percentage moisture absorbance, percentage moisture loss, tensile strength, percentage elongation, flatness, water vapour permeation rate and skin irritancy testing exhibited satisfactory results. The drug release followed first order and Higuchi's kinetics, which was evident from regression value. Formulation F5 was considered as optimized formulation which showed highest drug release (59.20% after 120 hours). All formulations were found to be stable after 3 months stability studies under accelerated conditions (400C and 75%RH). It was concluded that (1.5:1) ratio of Hydroxypropyl methyl cellulose K15/Ethylene cellulose produced best optimized results and can be used to enhance the transdermal permeation of the drug.

KEYWORDS: Transdermal drug delivery, Bromocriptine Mesylate, Hydrophilic and Hydrophobic Polymers.

INTRODUCTION

The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs. In comparison to conventional pharmaceutical dosage forms, transdermal delivery system offers many advantages, such as elimination of first pass metabolism, sustained drug delivery, reduced frequency of administration, reduced side effects and improved patient compliance.[1,2] Bromocriptine Mesylate is the most widely prescribed drug in the long term treatment of Parkinson‘s disease, Hyperprolactinemia and Acromegaly. Following oral administration, Bromocriptine Mesylate is extensively metabolized in the liver (up to 70%) and the oral bioavailability remains low (e.g. 30%), because of significant first-pass hepatic metabolism. Bromocriptine also has a short plasma half-life of 2-8 hours. Long term therapy of Bromocriptine by oral administration may result in poor patient compliance because of low bioavailability and short plasma half-life, leading to increased frequency of administration. Transdermal administration is a potential approach to overcome these problems with Bromocriptine Mesylate treatment.[3] Bromocriptine Mesylate possesses ideal characteristics such as low molecular weight, smaller dose range, short plasma half-life and poor oral bioavailability; for formulation as a transdermal patch.[3] The need and objective of any study is to improve the efficacy of the medication, reduce the side effects, and increase the patient compliance for maximum desirable effect. Bromocriptine is prescribed widely in treatment of Parkinson‘s alone or to supplement other antiparkinsonian drugs (Levodopa). The objective of this study was to design and evaluate transdermal patch of Bromocriptine Mesylate as a model drug using hydrophilic polymer such as HPMC K15 and hydrophobic polymer such as EC. The research further includes optimization of release patterns of the drug and to study mechanism of drug release from six prototype formulation batches along with *in-vitro* permeation study and other physicochemical tests.

The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. The prepared formulations were evaluated for different physicochemical properties like thickness, folding endurance, drug content, surface pH, percentage moisture absorbance, percentage moisture loss, tensile strength, percentage elongation, flatness, water vapour permeation rate and skin irritancy test.

MATERIALS AND METHODS

Materials

Bromocriptine Mesylate was received as a gift sample from Abbot India Pvt. Ltd., Goa. Hydroxypropyl Methyl Cellulose K15 and Ethyl cellulose was procured from Colorcon Asia Pvt. Ltd., Goa. All other materials used in the study were of analytical grade.

Formulation of Bromocriptine Mesylate transdermal patch

The matrix type transdermal patch was prepared by employing solvent evaporation method. Accurately weighed quantities of the polymers HPMC K15, Ethylcellulose in different ratios were added to 15ml of solvent mixture (Ethanol) and were kept on magnetic stirrer. Plasticizer Di-butyl phthalate was added to the polymer solution and mixed using magnetic stirrer. Accurately weighed amount of Bromocriptine Mesylate was dissolved in 5ml solvent. Drug solution was added to the polymer solution and mixed.

Propylene glycol (Permeation enhancer) was then added to the solution and mixed for 1 hour to ensure uniform distribution. This was set aside for 2 hours to eliminate entrapped air, transferred to a petriplate having a surface area of 63.585cm^2 and dried at room temperature. Controlled solvent evaporation was achieved by inverting a funnel and allowing drying at room temperature for 24 hours. The developed patches were removed carefully, cut to size (each having an area of 4 cm^2) and stored in a desiccator away from light in a cool place. Each patch of area 4cm^2 contained 15mg of Bromocriptine Mesylate. The compositions of patches are given in Table 1.

Evaluation of patches[4,5]

General Appearance

In the study, patches were tested for size, shape, colour, presence or absence of odour, surface texture, physical flaws, consistency and legibility of any recognizable markings.

Patch weight and thickness uniformity

For the evaluation of patch weight three patches of every formulation were taken and weighed individually on a digital balance. The average weights were calculated. Similarly, three patches of each formulation were taken and the patch thickness was measured using digital vernier caliper at three different places and the mean value was calculated.

Folding Endurance

The flexibility of patches can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the patch was determined by repeatedly folding a small strip of the patch (approximately 2 x 2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gave the value of folding endurance. The test was performed on three patches from each formulation.

Content Uniformity

4 cm^2 area of the patch was cut and shaken with 25ml of methanol for 4 hours to extract the drug. The volume was made up to 100ml using methanol. 1 ml was then withdrawn from this solution and diluted to 10 ml with phosphate buffer pH 7.4. The absorbance was then measured at 303nm. From the absorbance and the dilution factor, the drug content in the patch was calculated.

Determination of surface pH of the patches

The surface pH of the patches was determined in order to investigate the possible side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the skin. The patch to be tested was placed in a petridish and was moistened with 0.5 ml of distilled water and kept for one hour. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulations.

Percentage Moisture Loss

The transdermal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The percentage moisture absorption was calculated using the formula:

$$\% \text{ Moisture loss} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

Percentage Moisture Absorption

The percent moisture absorption test was carried out to check the physical stability and integrity of the patches at high humid conditions. The patches were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of potassium chloride, which maintains 80-90% RH. After 3 days, the patches were taken out and weighed. The study was performed at room temperature. The percentage moisture absorption was calculated using the formula:

$$\% \text{ Moisture loss} = \frac{\text{(Final weight-Initial weight)}}{\text{Final weight}} \times 100$$

Tensile Strength Measurement

The instrument for measurement of tensile strength was designed in our laboratory as per literature. The strip (2x2 cm) was clamped at the static end and was attached to the movable rod on a railing with the help of a clip. The weights were gradually added to the pan to increase the pull force till the patch was cut. The elongation was determined simultaneously by noting the distance travelled by the pointer before break of the patch on the graph paper. The weight required to break the patch was noted as the break force. The tensile strength was calculated as follows:

$$\text{Tensile strength } (kg/cm^2) = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area sample } (cm^2)}$$

$$\% \text{ Elongation at break} = \frac{\text{Length of patch at break (cm) - Original length (cm)}}{\text{Original length (cm)}} \times 100$$

Flatness

The construction of a patch strip cut out from drug-loaded matrix patch is an indicator of its flatness. Longitudinal strips (1.5cm x 0.75cm) were cut out from prepared medicated matrix patch. Initial length of the film was measured and then it was kept at room temperature for 30 mins. The variation in length due to non- uniformity of the flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percent of constriction was considered to be equal to 100 percent flatness.

$$\% \text{ constriction} = \frac{L1 - L2}{L2}$$

where, L1=initial length of each strip (cm)

L2= final length of each strip (cm)

Water Vapour Transmission Rate (WVTR)

The water vapour transmission is defined as the quantity of moisture transmitted through unit area of a patch in unit time. The water vapour transmission data through transdermal patches are important in knowing the permeation characteristics. The film was fixed over the brim of glass vial, containing 3g of fused calcium chloride as dessicant, with an adhesive tape. The vial was weighed and kept in dessicator containing saturated solution of potassium chloride

to provide relative humidity of 84%. The vial was taken out and weighed at every 24 hr intervals for period of 72 hrs. The WVT was calculated by taking the difference in the weight of the patches before and at regular intervals of 24 hrs. The water vapour transmission was calculated using the equation:

$$\text{WVT rate} = \frac{WL}{S}$$

where, W = g of water transmitted

L = thickness of the patch

Skin irritation study[5]

Skin irritation studies were performed on healthy rats. The dorsal surface of the rats was cleaned and their hair was removed by the use of electric shaver, skin was cleaned using rectified spirit. The rats were divided into two groups, group I received prepared Transdermal patch and group II received 0.8% formalin as standard irritant. After 24hr and 74 hr after test article application, the test sites were examined for dermal reactions in accordance with the Draize scoring criteria as tabulated in Table 2.

In-vitro diffusion studies[5,6]

In-vitro diffusion studies were performed using cellophane membrane soaked overnight in phosphate buffer pH 7.4. The study was performed using Modified Franz Diffusion cell, containing donor and receptor compartments. This apparatus was setup in-house. The donor compartment consisted of a cylinder with both ends open. The cellophane membrane was fixed to one end of this cylinder and dipped in the dissolution medium (Phosphate Buffer pH 7.4) present in the receptor compartment such that the skin just touched the surface of the dissolution medium. The temperature of the medium was kept at 37 ± 1°C and was stirred continuously at low speed using magnetic stirrer. The volume of dissolution medium used was 100 ml. 5 ml of the sample was withdrawn every 4 hour for the 1st day and replenished using Phosphate Buffer pH 7.4. For the next for 4 days sample was withdrawn after every 24th hours. The samples were analyzed using UV spectrophotometer at the wavelength of 303 nm.

Release Kinetics[7,8,9]

To investigate the possible mechanism of the drug release from the prepared matrix patch, the release data were analyzed mathematically according to the following models:

Zero order

To study Zero order release kinetics, release rate data is fitted to the following equation,

$At = A_o - K_o t$.

where, At = drug release at time t,

A_o= initial drug concentration,

K_o = release rate constant

If the plot of cumulative % drug release versus time is linear then the data obeys zero order kinetics with slope equal to K_o.

First order

The release rate data are fitted to the following equation,

$\text{Log } C = \text{Log } C_o/2.303 - Kt$.

C = amount of drug remained in matrix at time t‘

C = is initial amount of drug in matrix.

K = is first order rate constant [hr^{-1}].

If a plot of log % drug remained versus time is linear it indicates that the release follows first order. The constant K can be obtained by multiplying the value (-2.303) with slope.

Higuchi’s model

Drug release matrix has been described by Higuchi‘s classical model equation,

$F = k\, t^{1/2}$.

where, k = Higuchi constant.

In Higuchi model, if a plot of % drug release versus square root of time is linear, it indicates that the drug is released by diffusion mechanism. The slope is k.

Peppa’s release model:

The release rate data were fitted to the following equation,

$\text{Log } M_t / M_0 = \text{Log } K + n \text{ Log } t$.

If n is equal to 1.0, the release is zero order.

If n is < 0.5 the release is best explained by Fickian diffusion and

If 0.5 < n < 1.0 then the release is through anomalous diffusion or Non Fickian diffusion (Swellable & Cylindrical Matrix).

In this model, a plot of log (Mt/Mo) versus log (time) is linear.

Stability Studies

The patches were sealed in aluminium packaging and subjected to room temperature (25+2^{o}C) and to elevated temperature conditions of 40±2^{o}C for 180 days at 75%RH. Samples were withdrawn at the end of 30th day and evaluated for,

- Physical Appearance.
- Active drug content.
- *In-vitro* drug release.

RESULTS AND DISCUSSIONS

General Appearance

Patches of all the formulations were square in shape, transparent to semi-transparent, with flat surfaces and having a smooth texture. The size of the patch was 20mm in diameter and there was absence of any odour and physical flaws.

Patch weight and Thickness

The weight of the patches ranged between 138.7±2.25mg to 146.2±2.72mg. The weight of patches from each formulation is reported in the following Table 3(a). The Thickness of the Patch from batch F1 to F6 of size 4sq.cm area is reported in Table 3(a). The patch thickness was measured using digital vernier caliper and was found to be in the range of 0.25 to 0.35mm. The variations in weight and thickness among the formulations may be the consequence of difference in molecular weight and the proportion of polymer used in the patch.

Folding Endurance

All patches did not show any cracks even after folding for more than 300 times, hence showed good folding endurance. The folding endurance of each patch from F1 to F3 is reported in Table 3(a).

Content uniformity

For various formulations, the drug content was found to be 93.73% to 102.2%. The results are tabulated in Table 3(a). The result indicated that the process employed to prepare patches in this study was capable of giving patches with uniform drug content and minimum batch variability. The data was analyzed for mean and standard deviation. The percent drug content was found to be within acceptable limits. Drug distribution in the matrix (i.e., drug concentration profile) can heavily affect drug release kinetics.

Surface pH of the patches

The surface pH for all the formulations is shown in Table No 3(a). The values represent the mean of the three replicate determinations. The surface pH for all the formulations was almost within the range of skin pH thereby showing better patient acceptability.

Percentage moisture loss

The moisture loss was found to be between 0.143% to 2.33%. Percent moisture loss for all formulations is given in Table 3(b). A small amount of moisture in the patches helps to keep patch stable and prevent it from being brittle. Overall, it was observed that, hydrophilic polymers tend to absorb more moisture in comparison to hydrophobic polymers.

Percentage Moisture Absorption

The percent moisture absorption was found to be between 0.21 % to 4.03%. Moisture absorption values for all the formulations are given in Table 3(b). Patches containing higher amount of hydrophobic polymers (EC) showed least moisture absorption in contrast to other formulations with hydrophilic polymers.

Tensile strength measurement

The tensile strength gives an indication of the strength and elasticity of the patch reflected by the parameters, Tensile strength (TS) and elongation at the break (EB). A soft and weak polymer is characterized by a low TS and EB; a soft and tough polymer is characterized by a moderate TS and a very high EB(20-1000%); a hard and brittle polymer shows moderate TS and very low EB (<2%); a hard and strong polymer shows a high TS and moderate EB(~5%) whereas a hard and tough polymer shows a high TS and high EB, Hence it is suggested that a suitable transdermal patch should have relatively high TS and high EB.

The tensile strength of the transdermal patch was in the order of: F1>F2>F3>F4>F5>F6 % Elongation of the transdermal patch was observed to be in the order of: F6>F5=F4=F3>F2=F1. The highest tensile strength was observed in case of F1 and F2. High elongation was observed in films containing more HPMC K15 than EC. All the formulations possessed good tensile strength and elongation. The tensile strength and % elongation for the transdermal patches is shown in Table 3(b) and Figure 3.

Flatness

The construction of a patch strip cut out from a drug-loaded matrix patch is an indicator for its flatness. Longitudinal patch (1.5x0.75cm) was cut out from prepared matrix patch. The initial lengths of the films were measured and then it was kept at room temperature for 30 minutes. The variations in the length due to non- uniformity in flatness were measured. Flatness was calculated by measuring constriction of strips and zero percent of constriction was considered to be equal to 100% flatness. Readings are plotted in table 3(c).

Water vapour transmission rate (WVT)

The water vapour transmission rate is defined as the quantity of the moisture transmitted through unit area of a patch in a unit time. The water vapour transmission data through transdermal patches are important in knowing the permeation characteristics and also helps in understanding the permeability. Table 3(c) gives the WVT values.

Skin irritation study

The optimized patch F5 was tested for their potential to cause skin irritation/sensitization in rats. Skin irritation studies were performed on healthy rats (CPCSEA approval number GCP/IAEC/15/06).

Dermal observation of skin irritation test of optimized F5 patch is shown in Table 4. Skin irritation study was conducted on healthy male rats, there was no trace of edema, erythema or any skin irritation on site of application of the patch, hence these formulations are non irritable to the skin tissue and can be considered as safe. In group II which contained formalin as irritant, showed slight to severe skin irritation reaction.

***In-vitro* diffusion Studies**

The *in-vitro* release study was carried out in phosphate buffer pH 7.4 for a period of 120 hrs using modified diffusion cell. The cumulative percentage drug release at the end of 120 hours

of *in vitro* release study is shown in descending order: F6>F5>F4>F3>F2>F1 (70.04>59.20>52.46>39.92>31.90>27.61) Formulation F6 containing EC and HPMC K15 (1:2.3) exhibited a significantly higher rate and extent of drug release of 70.04% in 120 hrs. The differences in release profiles may be due to differences in the characteristics and presence of different functional groups of different polymers. The effect of polymer content on the drug release rate could be explained in two ways; (i) an increase in the total porosity of the matrices (initial porosity plus porosity due to drug diffusion) and (ii) an increase in the hydrophobicity of the matrix leading to decreased penetration of the solvent molecules into the system, which in turn decreases diffusion of the drug from the matrix. The drug-release rate appeared to increase with increasing amount of the hydrophilic polymers. Drug release from hydrophilic matrices is dependent on factors like swelling and diffusion of the drug through the porous matrix of the polymers, giving rise to mass erosion of the system, concomitantly with dissolution and diffusion of the drug. Initially, the matrix thickness increases due to hydration and swelling of polymer then the matrix thickness decreases and finally disappears due to polymer dissolution as well as dissolution of the drug. This phenomenon has been referred to as ―Swellable soluble matrix. This can be seen with F5, F6 (HPMC and EC), containing higher percentage of hydrophilic polymer.

The high drug release from these patches was possible because of the formation of more pores and channels due to presence of hydrophilic polymers. Formulations containing higher amount of EC showed slower drug release rates. This can be attributed to the lower solubility of EC relative to HPMC, which is soluble in water only at a temperature below 38°C; in addition the drug was hydrophobic in nature. Incorporation of Ethylcellulose in higher concentration then HPMC K15 was found to retard the drug release (F1, F2, F3), which could be attributed to the decreased penetration of the solvent molecules in the matrix due to the presence of hydrophobic polymer leading to decreased diffusion of the drug from the matrix. The minimum percent drug released was observed from F1 (EC alone), where only 27.61% was released in 120 hours compared to other patches. This may be attributed to the hydrophobicity of EC that reduces the amount of water uptake which in turn diminishes polymer swelling and hence reduces the drug release. These results clearly indicated that increase in amount of hydrophilic polymer HPMC K15 showed an increase in the drug release whereas increase in concentration of the hydrophobic polymers retarded the drug release in the transdermal formulations. As the formulation was intended for delivering

Bromocriptine for longer duration, combining the hydrophilic and hydrophobic polymers in the optimum range gave patches with desired drug release.

Kinetic Treatment

In-vitro release data of all 6 transdermal patches formulations was fitted in 4 mathematical models viz; Zero order, First order, Higuchi & Peppa's. The model that best fits the release data was evaluated by correlation coefficient (R). The R values for First order plots were higher when compared to Zero order plots which indicates that all formulations best fitted in first order kinetics. The best fit with higher correlation was found with the Higuchi's equation for most of the formulations with the highest correlation coefficient (R^2= 0.993) nearly approaching 1.0. The results indicated that all formulations exhibited diffusion mechanism in drug release. The data was subjected to Peppa's model where R value revealed that Peppa's model best fitted in all dissolution profiles having the highest correlation coefficient approaching 0.972. The values of n as derived from Peppa's model ranged between 0.362 and 0.515. Hence it was concluded that the drug release in Transdermal patches occurred via Fickian diffusion. Thus the drug release from the transdermal patches is Diffusion Controlled and followed First order kinetics.

Figure 1: Percentage Moisture Loss

Figure 2: Percentage Moisture Absorption

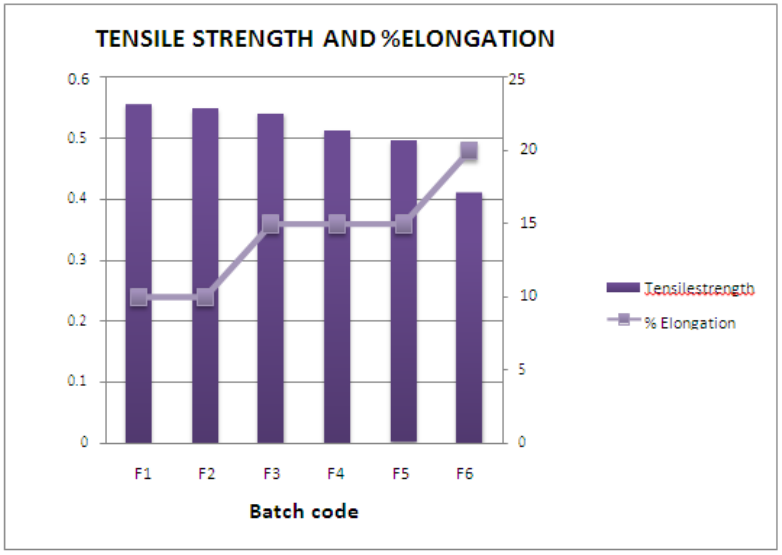

Figure 3: Graph of Tensile strength and Elongation

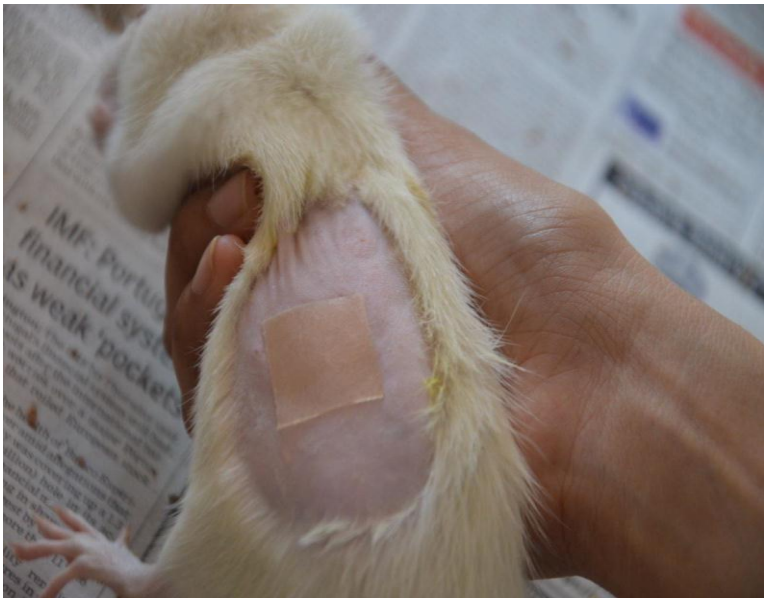

Figure 4: Rat after application of patch

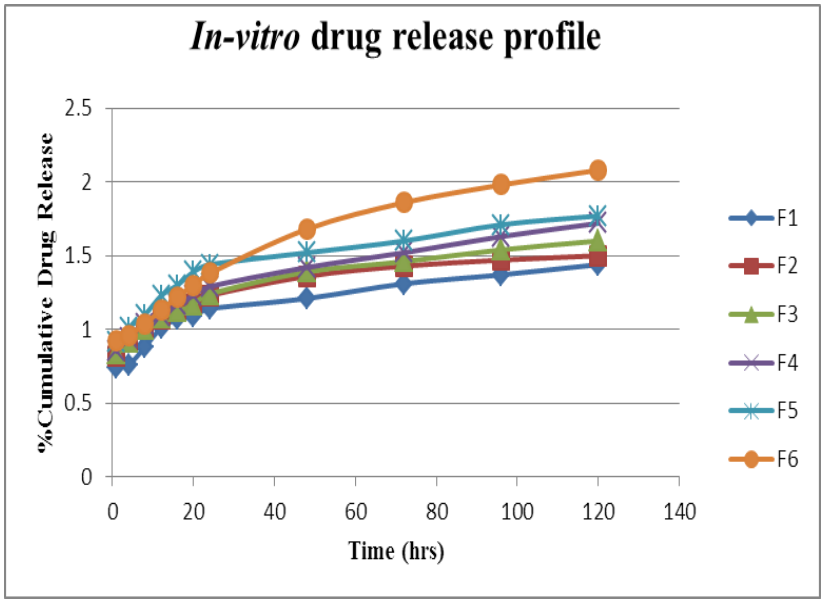

Figure 5: *In-vitro* drug release profile

Table 1: Formulation of Matrix Diffusion Controlled Transdermal Patch of Bromocriptine Mesylate

Constituents	F1	F2	F3	F4	F5	F6
Bromocriptine Mesylate	238.4mg	238.4mg	238.4mg	238.4mg	238.4mg	238.4mg
Ethyl cellulose	1400mg	980mg	840mg	700mg	560mg	420mg
HPMC K4M	----	420mg	560mg	700mg	840mg	980mg
Dibutylpthalate	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
Propylene glycol	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml

Table 2: Draize scoring index

Score	Reaction	
	Erythematic	**Edema**
1	No erythema	No edema
2	Very slight erythema	Very slight edema
3	Well-defined erythema	Well-defined edema
4	Moderate to severe erythema	Moderate to severe edema
5	Severe erythema	Severe edema

Table 3(a): Physiochemical evaluation data for transdermal patch of Bromocriptine

Batch code	Film appearance	Weight variation (mg) ±SD	Thickness (mm)	Folding Endurance	% Drug content	Surface pH ±SD
F1	Good	138.7±2.25	0.25	>300	102.2	5.58±0.10
F2	Good	139.4±1.80	0.25	>300	98.2	5.64±0.13
F3	Good	144±1.55	0.29	>300	95.53	5.45±0.11
F4	Good	145.5±2.15	0.32	>300	100.4	5.6±0.12
F5	Good	145.7±1.90	0.34	>300	96.73	5.42±0.12
F6	Good	146.2±2.72	0.35	>300	99.06	5.52±0.15

Table 3(b): Physiochemical evaluation data for transdermal patch of Bromocriptine

Batch code	%Moisture loss	%Moisture absorption	Tensile strength Kg/cm^2	% Elongation
F1	0.14398	0	0.556	10
F2	0.49964	0.2152	0.550	10
F3	1.36986	1.18055	0.541	15
F4	0.95302	2.68041	0.513	15
F5	1.75320	2.88263	0.496	15
F6	2.33800	4.03556	0.412	20

Table 3(c): Physiochemical evaluation data for transdermal patch of Bromocriptine

Formulation code	%Flatness	Water vapour transmission
F1	100	0.0084
F2	100	0.0151
F3	100	0.0235
F4	100	0.0239
F5	100	0.0351
F6	100	0.0369

Table 4: Dermal Observation of skin irritation test of optimized F5 patch

Rat No	Reaction	Group I (Test patch)		Group II (Standard irritant)	
		24 hour	72hour	24 hour	72 hour
1	Erythema	0	0	1	1
	Edema	0	0	2	1
2	Erythema	0	0	1	1
	Edema	0	0	1	1
3	Erythema	0	0	2	1
	Edema	0	0	1	1
4	Erythema	0	0	1	1
	Edema	0	0	2	1
5	Erythema	0	0	1	1
	Edema	0	0	2	1
6	Erythema	0	0	1	1
	Edema	0	0	2	1

CONCLUSION

In the present study, attempts were made to fabricate and evaluate transdermal matrix type patch using HPMC K15 and EC by solvent evaporation method. The value of partition co-efficient of Bromocriptine in n-octanol/water system was found to be favorable for transdermal drug delivery system. FTIR studies were carried out to rule any drug and polymer incompatibility. The results of the physicochemical tests were interpreted and found satisfactory. *In-vitro* release showed that the transdermal patch could deliver the drug over

the period of 120 hrs, showing sustained delivery and following first order and Higuchi's kinetic profiles of drug release. Based on the release profile and other physicochemical results F5 formulation was considered as optimized (59.60% release) and skin irritancy and stability studies were carried out on the optimized patch. The *in-vitro* release study indicated first order kinetics. The Higuchi's plot revealed that the release was by diffusion and Peppa's plot indicated that it was Fickian diffusion. Stability studies conducted at room temperature and at 400C and 75% RH for a period of 3 months gave satisfactory results confirming that the devised formulation was stable. There were no significant physical and chemical changes in the patch at the end of the stability. From the above study, it was concluded that the therapy in Parkinson's, Acromegaly and Hyperprolactinemia can be dramatically improved by application of transdermal patch.

As Bromocriptine is mostly used in long term therapy, more work can be done to formulate a transdermal patch which will deliver the drug for a longer period of time. Thus, further research on this dosage form is definitely desirable.

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