WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 15, Issue 2, 571-590. Research Article ISSN 2277–7105

FORMULATION, CHARACTERIZATION AND EVALUATION OF SOLID DISPERSION FOR CNS DRUG LOADED IN TRANSDERMAL PATCH

Rajashree Gude[1]*, Eliska D'Souza[2], Akshata Shirodker[3], Raunak Rai[4]

[1,2,3,4]Department of Pharmaceutics, Goa College of Pharmacy, Panaji- Goa, 403001.

Article Received on 15 Dec. 2025,
Article Revised on 05 Jan. 2026,
Article Published on 16 Jan. 2026,

https://doi.org/10.5281/zenodo.18264818

***Corresponding Author**

Rajashree Gude

Department of Pharmaceutics, Goa College of Pharmacy, Panaji- Goa, 403001.

How to cite this Article: Rajashree Gude[1]*, Eliska D'Souza[2], Akshata Shirodker[3], Raunak Rai[4] (2026). Formulation, Characterization And Evaluation Of Solid Dispersion For Cns Drug Loaded In Transdermal Patch. World Journal of Pharmaceutical Research, 15(2), 571–590.

ABSTRACT

Bromocriptine Mesylate (BM) solid dispersion (SD) was formulated and loaded into matrix type transdermal patch, optimized and characterized. BM, an anti-Parkinson's agent, belonging to BCS Class II, has low aqueous solubility and high permeability. Solubility and bioavailability was enhanced by SDs using Hydroxy propyl beta cyclodextrin (HP-b-C) and Hydroxy propyl cellulose (HPC), by Solvent evaporation and Kneading method. The SD was selected based on %yield, %drug content and *in vitro* dissolution data. The SD prepared by kneading method using combination of 2 carriers in a drug carrier ratio of 1: 0.5 :3 (F4), exhibited highest percentage yield of 97.640 ± 0.7692%, percentage drug content of 98.770 ± 0.8129 % and *in vitro* release 98.85 % in 60 mins. Hence, F4 was used. Concentration of HPMC K4M, Eudragit RL 100 and Propylene glycol were selected as independent variables for design of experiment (DoE) using 2^3 Full factorial design. A formula for 8 runs was generated, and formulated. Diffusion study and folding endurance were selected as dependent variables. Based on response data, a formula was generated for the optimized transdermal patch (E9) and evaluated for thickness, weight variation, %drug content, %elongation, folding endurance, surface pH, *in-vitro* diffusion study, *ex-vivo* permeation study and skin irritancy study. BM-SD transdermal patch was successfully developed with improved dissolution profile, avoidance of extensive first-pass metabolism, improved patient compliance, effective and safe for use.

KEYWORDS: Bromocriptine Mesylate, Transdermal patch, Solid dispersion, Kneading method, 2^3 Full factorial design.

1.0 INTRODUCTION

Transdermal drug delivery systems (TDDS), are dosage forms that provide a controlled release of therapeutically effective amount of drug across a patient's skin. For decades, TDDS has drawn deliberate consideration for either local or systemic drug delivery.[1]

Bromocriptine Mesylate (BM) is the most widely prescribed drug in treatment of PD. In patient having PD, 60-80% of the dopamine producing cells are damaged, as a result not enough dopamine is produced. BM belongs to a class of medication called Dopaminergic agonist, it functions by mimicking the action of Dopamine. It stimulates the centrally located dopaminergic receptors resulting in movement. BM has also been used in the treatment of menstrual disorders, inhibition of lactation, breast tumors, acromegaly, infertility and brain tumors as a dopamine agonist.[2]

A potential solution to the issues with conventional BM treatment is the TDDS. Due to its ideal property of small dosing range, short plasma half-life, poor oral bioavailability, and high first pass metabolism, making it suitable to formulate as a transdermal patch.[3]

1.1 PARKINSON'S DISEASE

Parkinson's disease is characterised by the loss or degeneration of dopaminergic (dopamine-producing) neurons in the substantia nigra as well as the development of Lewy Bodies in these neurons, which is a pathologic hallmark. Pathologic alterations may take two decades or longer to become visible.[4]

1.2 Skin as a barrier to drug transport

The skin's barrier function is accomplished, entirely and quite remarkably, by the outermost few microns of the skin – the stratum corneum (SC), a compositionally and morphologically unique. The **epidermis** is the most superficial layer of the skin. The dermis and hypodermis are the next two layers below the epidermis. The epidermis is made up of 5 layers. The thickness and number of layers in the epidermal layer vary depending on its location in the body. For instance, the epidermis covering the area of the heel is significantly thicker than the epidermis covering the eyelid.

The primary **functions** of the epidermis are to protect the deeper tissues from water, microorganisms, mechanical and chemical trauma, and damage from UV light. In addition, the epidermis continuously produces new skin cells that replaces the old one.[5]

i) Dermis - The dermis is the middle layer of the skin, that exists between your epidermis and hypodermis. It made of two layers, the reticular dermis and the papillary dermis. It is the thickest layer of skin which is made up of collagen and elastin. This layer contains all of your connective tissues, nerve endings, sweat glands, oil glands, and hair follicles. The dermis serves a variety of purpose s, including supporting the epidermis and maintaining the epidermis by transporting nutrients. Different sensations as pressure, pain, heat, cold, and itching can be felt with the help of nerve endings.[6]

ii) Hypodermis -The hypodermis shields the skeletal system, organs, muscles, and tissues from harm together with your other layers of skin. The hypodermis also performs a variety of other functions such as, joining the dermis layer to the muscles and bones, protecting the body from heat and cold, producing sweat to control body temperature, and allows the skin to move smoothly over the tissues. Additionally, it serves as a shock absorber to shield the bones, muscles, and organs from injury. The fat cells (adipocytes), aid in energy storage.[7]

1.3 Solid Dispersion (SD) Technique

The term 'Solid Dispersion' refers to a group of solid products consisting of at least two different components, generally 'a Hydrophobic Drug and a Hydrophilic Carrier'. The carrier can be either crystalline or amorphous. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug gets released as fine colloidal particles and as a result there is enhancement of solubility/dissolution rate of poorly water-soluble drugs.[8]

1.4 OBJECTIVES

1) To reduce the side effects, improve the efficacy of the drug, and patient compliance.
2) To perform preformulation studies on the drug BM.
3) To perform compatibility studies between drug and excipients by FTIR.
4) To enhance solubility of BM using the solid dispersion technique.
5) To prepare and optimize the prepared SDs by comparative evaluation based on

percentage yield, percentage drug content values and *in vitro* dissolution study.

1.5 Literature Review

1) **Talaulikar *et. al.* (2016)** formulated a matrix diffusion controlled transdermal patch of Bromocriptine Mesylate using ratios of hydrophilic and hydrophobic polymeric. The effects of combinations were studied. The formulation having 1.5:1 ratio of Hydroxypropyl methyl cellulose K15 and Ethylene cellulose produced the optimized results.[9]

2) **Farooqui *et al.* (2023)** prepared an oral disintegrating films (ODFs) containing Glimepiride solid dispersion. The solubility and dissolution were enhanced by preparing solid dispersion using Polyethylene Glycol 4000. The optimised solid dispersion was selected based on the drug content and *in vitro* dissolution data. Films were formulated using Solvent casting method. It was concluded that the oral disintegrating film loaded with Glimepiride SD was developed with improved dissolution profile, avoiding extensive first-pass metabolism and improved patient compliance.[10]

3) **Sita *et al.* (2020)** developed, characterized, and statistically optimized Bromocriptine nano-emulsion loaded into a gel to evaluate its potential. BCM-NE was prepared by o/w emulsification method and a factorial design examined the impact of various variables. *Ex-vivo* permeation tests on rat skin revealed that permeability was enhanced. *In-vivo* studies on rats demonstrated a higher and prolonged drug release compared to oral suspension. All results proved that the BCM-NE gel could be a superior and patient- compliant alternative.[11]

2) MATERIALS AND METHODOLOGY

2.1 Pre-formulation Studies

2.1.1 General appearance

BM powder was examined for physical appearance such as colour and texture.

2.1.2 Melting Point

The melting point of BM was determined by taking a small amount of sample in a capillary tube closed at one end and placed in the melting point apparatus.

2.1.3 Solubility Studies Saturated solubility studies

The pure BM drug, was taken and added separately into 10 mL of distilled water, methanol, ethanol and phosphate buffer pH 7.4. The content dissolved was determined by measuring

absorbance at λmax of 303 nm using UV–Visible spectrophotometer.

2.1.4 Partition coefficient

Partition coefficient the drug was determined by allowing 100 mg of the BM to equilibrate in Octanol: Distilled water. The flask is shaken for 24hr and kept overnight in separating funnel. The two layers were separated and the filtrates were analyzed spectrophotometrically. Standard curve of the drug was plotted and partition coefficient was calculated.[12]

2.1.5. FT-IR Spectroscopy

$$K\ o/w = \frac{\text{Conc. in Octanol}}{\text{Conc. in Distilled water}}$$

Pure BM was subjected to Fourier Transform Infrared Spectroscopy for characterization. The spectra were obtained by scanning the samples over the range of 4000-400 cm-1.

2.1.6 X-ray Diffraction Study

X-ray diffractometer was utilised to examine the X-ray diffraction pattern of Pure BM powder. The instrument was operated at a voltage of 40 kV and a fixed tube current of 15 mA. Continuous scanning was performed from 10-80° 2θ at a rate of 10°/min.

2.2 Compatibility Studies

2.2.1 FT-IR Spectroscopy Analysis

spectra of the pure BM, and mixtures of BM and excipients and carrier such as HPC and HP-b-C were separately recorded using FTIR spectrophotometer by scanning the sample from 4000-400 cm^{-1}. Any possible interactions in the peaks of BM were identified by comparing them with the standard spectra of BM.

2.2.2 Determination of λmax of Bromocriptine Mesylate

The spectrum of the working stock was recorded over the wavelength range of 400-200 nm taking Phosphate buffer pH 7.4 as the blank, using UV-Visible spectrophotometer.

2.2.3 Preparation of Standard Calibration Curve of Bromocriptine Mesylate in Phosphate buffer pH 7.4

Accurately weighed 25 mg of BM was transferred to a 25 mL volumetric flask and dissolved in a small amount of methanol, and the volume was made up with phosphate buffer. 10 mL of this solution was transferred to a 100 mL volumetric giving a working stock of 100 µg/ml.

Series of dilutions were made of 1, 2, 3, 4, 5, 6, 7 and 8 ml. The absorbance of these solutions was measured at 303nm. The standard calibration curve was obtained by plotting a graph of absorbance v/s concentration.

2.3. Preparation by Solvent Evaporation Method

Accurately weighed drug and carriers were placed in a beaker containing 10 mL of ethanol. The resultant mixture was heated on a water bath at 40-45ºC and then placed in a vacuum oven at 40ºC till the solvent evaporated completely. The obtained mass was pulverized and passed through sieve no. 80 to obtain a free-flowing powder.

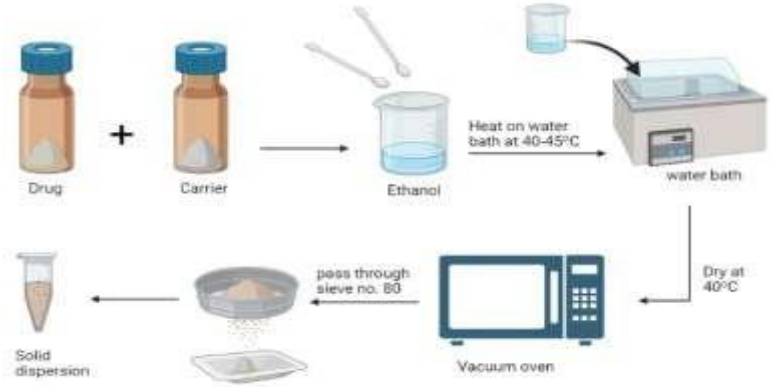

Fig. 2.1: Schematic representation of Solid dispersion preparation by Solvent evaporation method.

2.4 Preparation by Kneading Method

Accurately weighed drug and carrier were placed in a mortar. A sufficient quantity of water: methanol mixture (1:1) was added to the blend and kneaded rigorously to obtain a paste like consistency which was then dried in a vacuum oven, pulverized and passed through sieve no. 80 to obtain a free-flowing powder, as depicted in Fig: 2.2.

Fig.2.2: Schematic representation of Solid dispersion preparation by Kneading method.

Table 2.1: list of Formulations.

Method	Formulation code	Composition	Ratio
Solvent evaporation method	F1	BM: HP-b-C: HPC	1: 0.5 :2
	F2	BM: HP-b-C: HPC	1: 0.5 :3
Kneading method	F3	BM: HP-b-C: HPC	1: 0.5 :2
	F4	BM: HP-b-C: HPC	1: 0.5 :3
Solvent evaporation method	F5	BM: HPC	1:2
	F6	BM: HPC	1:3
Kneading Method	F7	BM: HPC	1:2
	F8	BM: HPC	1:3
Solvent evaporation method	F9	BM: HP-b-C	1:2
	F10	BM: HP-b-C	1:3
Kneading Method	F11	BM: HP-b-C	1:2
	F12	BM: HP-b-C	1:3

2.5 Optimization of the Transdermal patch using DoE

The 2^3 full factorial was used to optimize the composition of excipients in patch. The three independent variables, concentration of film former (HPMC K4M), concentration of hydrophobic film former (Eudragit RL100) and concentration of permeation enhancer (Propylene glycol) were selected and 8 runs were generated. Patches were formulated and evaluated for effect on *in-vitro* diffusion study and folding endurance. Based on data obtained, formula for the preparation was system generated (E9).

2.6 Evaluation of the Optimized Transdermal patch (E9)

2.6.1 General Appearance

The optimized patches were examined for size, colour, odour, surface texture, and any visible physical flaws. Using ttriplicates, mean and standard deviation was calculated.

2.6.2 Thickness

The thickness of the optimized transdermal patches of 2 x 2 cm^2 were measured using a digital vernier calliper. The thickness was measured at three different locations, the test was carried out in triplicates, and the mean and standard deviation was calculated.

2.6.3 Weight Variation

The optimized transdermal patches of 2 x 2 cm^2 were individually weighed on a balance, using triplicates and the mean weight with standard deviation was calculated.

2.6.4 Folding Endurance

The optimized transdermal patches were evaluated for folding endurance by folding them

repeatedly until it showed signs of breakage or visible cracks. The folding endurance was determined by the number of folds required to break the transdermal patch, the test was carried out in triplicates, and the mean and standard deviation was calculated.

2.6.5 Tensile Strength

To test the tensile strength, one end of a 2 x 2 cm^2 optimized transdermal patch was clamped at the static end and the other end was attached to the hanging pan. The pan's weight was gradually increased until the transdermal patch breaks. The tensile strength was calculated using the formula given below.

2.6.6 Percent Elongation

When stress is applied on the optimized transdermal patch of 2 x 2 cm^2 until it elongates or stretches. Percent elongation is calculated by comparing the length of the transdermal patch before and after the stress is applied. The test was carried out in triplicates, and the mean and standard deviation was calculated.

2.6.7 Percent Drug Content

The percent drug content was determined by dissolving the optimized transdermal patch of 2x2 cm^2 in a volumetric flask with 100 mL of phosphate buffer pH 7.4. A volume of 1 mL was taken from the stock solution and adjusted to 10 mL in a volumetric flask. The resulting solution was examined using a UV-visible spectrophotometer at the wavelength of 303 nm. The values were taken in triplicate (n=3), and the mean and standard deviation was calculated.

2.8 Surface pH

This test is used to determine the surface pH of the optimized transdermal patch because changes in the pH can irritate the skin at the site of application. The pH was measured by moistening the transdermal patch with 0.5 mL of distilled water using a pH meter. The test was carried out in triplicates (n=3), and the mean and standard deviation was calculated.

2.9 Percent Moisture Uptake

The optimized transdermal patches of 2x2 cm^2 (n=3) were weighed individually and stored in a desiccator containing a fused saturated solution of potassium chloride to maintain 84 % RH for 24 h at room temperature. After 24 h, the transdermal patches were reweighed and the percentage moisture uptake was calculated. The test was carried out in triplicates, and the mean and standard deviation was calculated.[13]

2.10 Percent Moisture Loss

The optimized transdermal patches of 2x2 cm^2 were sampled and precisely weighed on an analytical weighing balance. After weighing, the transdermal patches were stored for 72 h in a desiccator containing silica. The transdermal patches were weighed again, and the percent moisture loss was calculated using the formula given below. The test was carried out in triplicate, and the mean and standard deviation was calculated.

2.11 Water Vapour Transmission Test

It is the quantity of moisture transmitted through unit area of the transdermal patch in unit time. Glass vials of equal volume and diameter were used as the transmission cells. The cells were washed properly and dried in the oven. Then, about 1 g of silica crystals were placed in each vial, and the optimized transdermal patch was fixed over the brim of the vial with the help of an adhesive tape. These vials were then weighed and placed in a desiccator containing saturated solution of potassium chloride to maintain 84%RH. These cells were removed from the desiccators and weighed after 24 and 48 h. The water vapor transmission rate was determined.

2.12 Swelling Index

Optimized transdermal patches of 2x2cm^2 were immersed in distilled water. The soaked transdermal patches were removed from the medium at 5, 10, 30 and 60 min and blotted with filter paper to remove excess liquid and weighed immediately. The swelling index was calculated using the formula given below. The test was carried out in triplicate, and the mean and standard deviation was calculated.

2.13 Scanning Electron Microscopy (SEM)

A scanning electron microscope was used to examine the surface morphology.

2.14 *in-vitro* Diffusion Studies

In-vitro diffusion study was performed in house fabricated modified Franz diffusion cell. Dialysis membrane-70 which was soaked in phosphate buffer for 12 h before use. Dialysis membrane was secured to the donor compartment and was mounted between donor and receptor compartments. The assembly was fixed in a way that the lower end of tube containing the transdermal patch just touches the surface of diffusion medium. Aliquots of 5 mL were withdrawn from the receptor compartment at time intervals of 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 h and were analyzed using UV-Vis spectrophotometer at 303 nm and

%CDR at the end of 72 h was calculated.

2.14 *in-vitro* permeation studies

The *in-vitro* permeation of the optimized transdermal patch was studied using in-house modified Franz diffusion cell. The donor compartment was in contact with ambient conditions of atmosphere, while the receptor compartment was in contact with phosphate buffer. The transdermal patch with a support of backing membrane was kept in the donor compartment and separated from the receptor compartment using human cadaver skin which was soaked in phosphate buffer for 10 to 20 min. Aliquots of receptor fluid was withdrawn at 2h for 24 h and same volume of solution was replenished with fresh buffer. The aliquots samples were analysed for drug content using UV visible spectrophotometer.

2.15 Skin Irritation Study

Skin irritation study was performed on healthy female rats. The rats were randomly divided into three experimental groups. Group 1 was taken for optimized transdermal patch (E9), Group 2 was taken for drug Blank transdermal patch and Group 3 was taken as control. The responses were recorded after 24, 48 and 74 h after the application of the transdermal patch. The test sites were examined and scored according to Draize Index.

Table 2.2: Draize scoring index.

Sr. No.	Erythema	Edema	Score assigned
1	No erythema	No edema	0
2	Very slight erythema	Very slight edema	1
3	Well defined erythema	Slight edema	2
4	Moderate to severe erythema	Moderate to severe edema	3
5	Severe erythema	Severe edema	4

3.0 RESULTS AND DISCUSSIONS

3.1 Pre-formulation Studies

3.1.1 Physical Characterization of BM Color – white powder

Odor -odorless

Melting point – 193 ± 0.57735 Solubility – water = 0.0811 ± 0.0056

3.1.2 Partition Coefficient

The partition coefficient value of octanol/ distilled water was found to be 3.358 ± 0.123. The result indicates that drug has sufficient lipophilicity, and fulfills the requirement.

3.1.3 FTIR Spectroscopy

The drug BM was characterized by FTIR spectroscopy and the spectrum was recorded using FTIR Spectrophotometer. The spectrum of BM with a scanning range of 4000 to 400 cm¯.

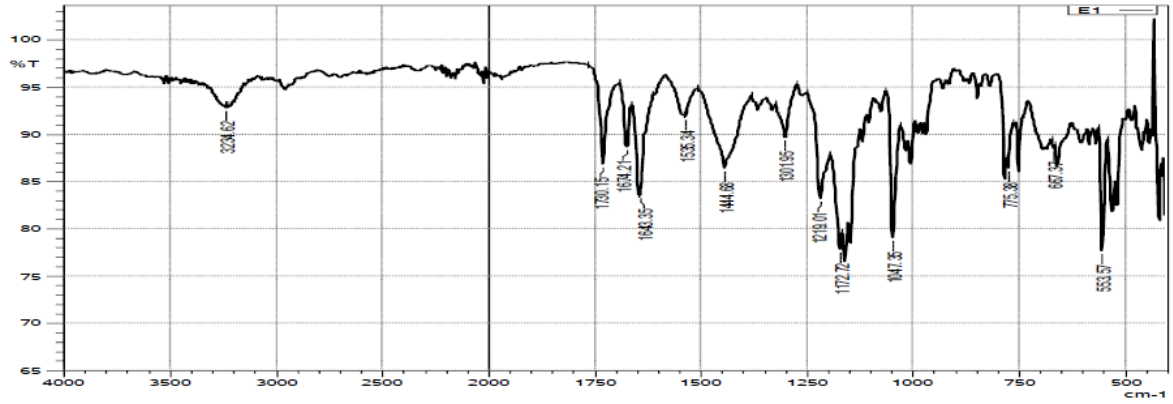

Fig 3.1: FTIR Spectrum of Bromocriptine Mesylate.

Table 3.1: Characteristic peaks of pure drug BM.

Peak/ stretch	Literature value cm^{-1}	Observed value cm^{-1}
Amide N-H	3350-310	3234.62
Alcoholic -0H	1260-1000	1047.35
Alkyl halide C-Br	1300-1150	1210.01
Aromatic ring	1500-1400	1444.68
Sulphonate S=0	1372-1300	1301.95
Ketone C=0	1870-1540	1674.21

3.1.4 X-ray Diffraction Analysis

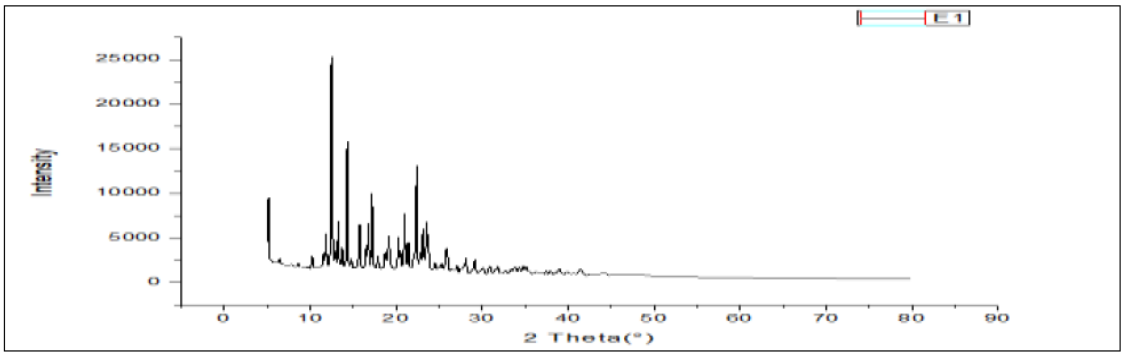

Fig 3.2: XRD pattern of pure drug Bromocriptine Mesylate.

In the X-ray, sharp and intense peaks at a diffraction angle of 2θ were seen at 5.14°, 12.48°, 14.32° and 22.38°, and smaller peaks at 2θ of 12.90°, 16.52°, 20.96°, 21.42° and 23.54 were present. These sharp peaks suggested that drug is present in crystalline state.

3.2 Standardization of the Drug

3.2.1 Determination of λmax of Bromocriptine Mesylate

A solution of 20 µg/mL of BM was prepared in phosphate buffer pH 7.4 and it was scanned in the UV range of 400-200 nm. λmax of the BM was observed at 303 nm.

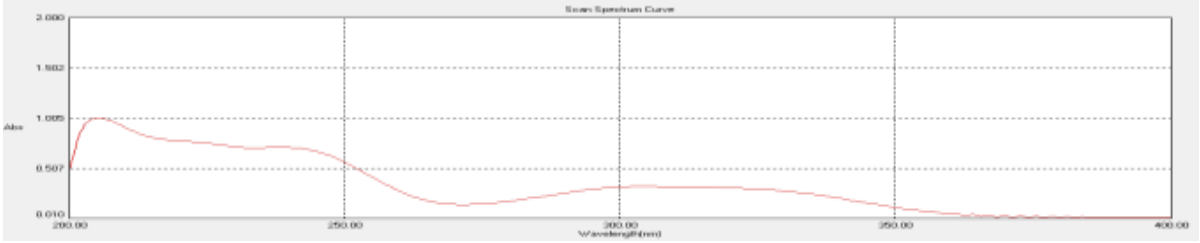

Fig. 3.3: UV spectrum of Pure drug Bromocriptine Mesylate.

3.2.2 Calibration Curve

The standard calibration curve of BM by plotting graph of absorbance at 303 nm v/s concentration (µg/mL). The absorbance values at different concentrations are shown in fig 3.4.

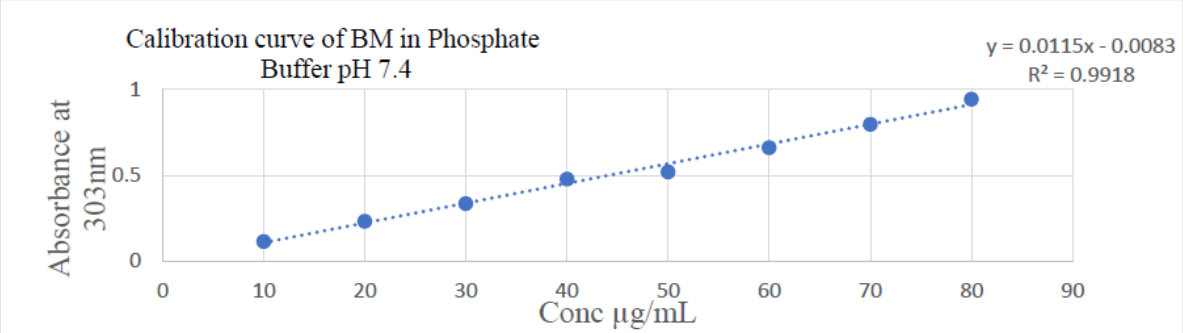

Fig 3.4: Calibration curve of Drug in Phosphate butter pH 7.4. Graph of Abs vs conc.

3.3 Preparation of Solid Dispersion

Solid dispersions of BM were successfully formulated by using carriers such as HP-β-C and HPC individually and in combination. Two different methods were employed in order to prepare the Solid dispersions such as the Solvent evaporation method and Kneading method. The composition of prepared solid dispersions of BM with their formulation.

Fig 3.5: Formulated Solid Dispersions F1-F123.

3.4 Optimization of Bromocriptine Mesylate Solid Dispersion

The BM-SDs (F1-F12) were optimized based on Percentage yield, Percentage drug content and *in-vitro* dissolution study.

3.4.1 Percent Yield and Drug content

The percent yield of all the prepared BM-SD (F1- F12) are displayed in Table 3.2.

Table 3.2: Results of % yield of the prepared BM-SDs F1-F12.

Formulation code	Ratio	% yield	% DRUG CONTENT	%CDR at 60 min
F1	1: 0.5 :2	91.43 ± 0.7926	75.393 ± 0.9321	67.68
F2	1: 0.5 :3	96.35 ± 1.4251	96.866 ± 0.7102	94.12
F3	1: 0.5 :2	92.08 ± 0.7302	93.030 ± 1.504	80.69
F4	1: 0.5 :3	97.640 ± 0.7692	98.770 ± 0.8129	98.85
F5	1:2	44.893 ± 2.1194	39.020 ± 1.632	53.14
F6	1:3	53.450 ± 1.4525	64.020 ± 0.3686	64.08
F7	1:2	56.493 ± 1.6613	42.666 ± 2.013	56.88
F8	1:3	61.836 ± 1.2554	71.020 ± 1.142	60.62
F9	1:2	75.796 ± 0.435	63.473 ± 1.248	78.92
F10	1:3	88.583 ± 1.3562	91.640 ± 1.1511	87.68
F11	1:2	72.396 ± 2.1650	70.276 ± 0.293	80.33
F12	1:3	87.830 ± 0.4648	94.193 ± 1.486	89.42

3.5 Characterization of Optimized Bromocriptine Mesylate Solid Dispersion (F4)

3.5.1 Solubility Study

Table 3.3: solubility profile.

Sr. no.	Solvent	Solubility of BM-SD (F4) (mg/mL)	Solubility of pure drug BM (mg/mL)
1.	Distilled Water	3.848 ± 1.1533	0.0811 ± 0.0056
2.	Phosphate buffer pH 7.4	4.046 ± 0.1202	0.121 ± 0.0095

3.5.2 FT-IR Spectroscopy

The FT-IR spectrum of the optimized BM-SD (F4) showed presence of all the characteristics peaks of pure drug. Although, slight changes in the intensities and some broadening of peaks could be observed, this could be due to the binding of the drug molecule during the formulation of the SD.

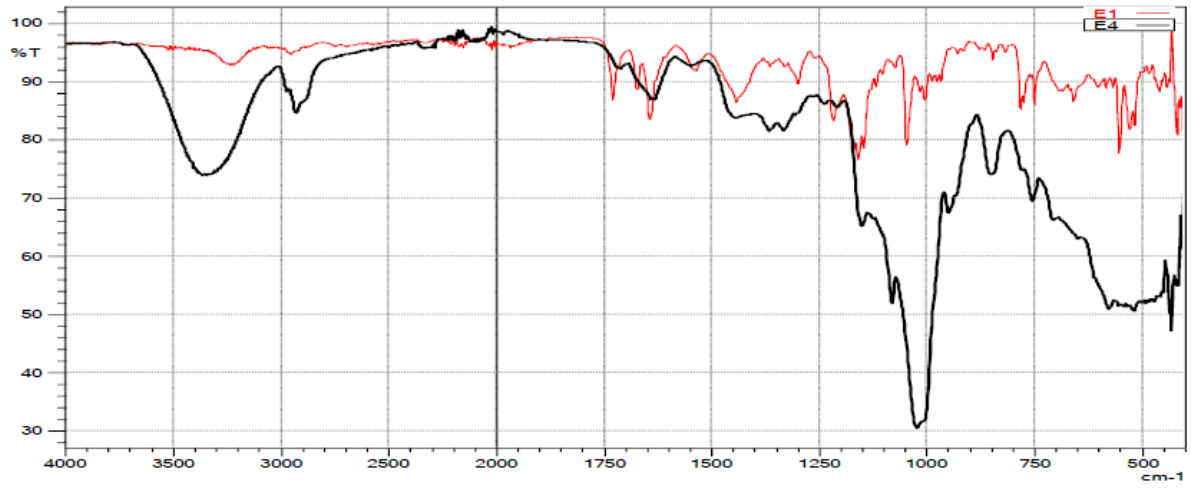

Fig. 3.6: FTIR Overlay of BM and Optimized BM-SD (F4).

3.5.3 X-Ray Diffraction Study

The XRD of optimized BM-SD (F4) as shown in Fig. 5.18, does not exhibit any sharp and intense peaks that were observed in the XRD of the Pure drug BM in Fig 5.4. This absence of these sharp and intense peaks confirms the conversion of drug from its crystalline form to amorphous form.

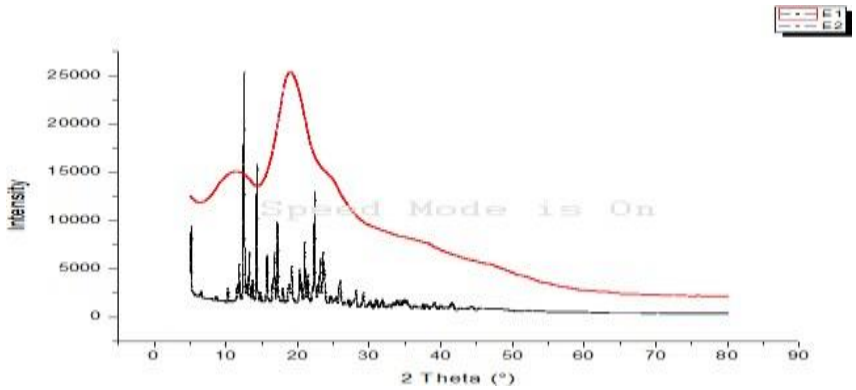

Fig. 3.7: Overlay of the XRD spectrum of BM and optimized BM-SD (F4).

3.6 Optimization of Transdermal Patch by DoE

The design of experiment (DoE) of 2^3 Full Factorial design (Response Surface

Methodology) was used to analyse and optimize the data statistically and graphically using the Design Expert® 360 software. Transdermal patches (E1-E8) were formulated and evaluated on the basis of the 2 dependent variables selected i.e. Diffusion study and Folding endurance.

Table 3.4: Optimization of Transdermal patch using 2^3 full factorial design.

Formulation code	Factor 1	Factor 2	Factor 3	Response 1	Response 2
	A: HPMC K4M (mg)	B: EUDRAGIT RL100 (mg)	C: Propylene Glycol (mg)	Diffusion Study (%)	Folding Endurance
E1	200	100	125	75.96	306
E2	200	200	175	81.09	378
E3	300	100	125	57.87	399
E4	300	200	125	56.13	387
E5	300	100	175	65.71	332
E6	200	100	175	82.98	380
E7	200	200	125	73.62	328
E8	300	200	175	65.16	349

3.7 Evaluation of Optimized BM-SD Loaded Transdermal Patch (E9)

Fig.3.8: Optimized Bromocriptine Mesylate Solid Dispersion loaded transdermal patch (E9).

3.7.1 General Appearance

The optimized transdermal patch (E9) of 2x2 cm^2 appears to be transparent to semi-transparent, with flat surfaces, having a smooth texture and there was absence of any odour and physical flaws.

3.7.2 Thickness

The thickness of optimized transdermal patch (E9) was taken(n=3) and measured using a digital vernier calliper and the mean and standard deviation was found to be 0.05667± 0.0057 mm indicating uniformity.

3.7.3 Weight Variation

The weight of the optimized transdermal patch (E9) of 2 × 2 cm^2 was conducted in triplicates

(n=3) and their mean and Standard deviation was found to be 26.633± 1.379g.

3.7.4 Folding Endurance

The folding endurance of the optimized transdermal patch (E9) was conducted(n=3) and their mean and Standard deviation was found to be 371.66 ± 3.055. As the folding endurance values are >300, this indicates good folding endurance.

3.7.5 Tensile Strength

The stress experienced during the manufacture, handling and use should be able to be The tensile strength of the optimized transdermal patch (E9) was taken(n=3) and the mean and standard deviation was found to be 0.1223 ± 0.006 Kg/cm^2, indicating that the optimized transdermal patch has good tensile strength.[14]

3.7.6 Percent Elongation

The % elongation of the optimized transdermal patch (E9) was taken in triplicates (n=3) and the mean and standard deviation was found to be 23.333 ± 0.006 %, indicating that the optimized transdermal patch has good elasticity.

3.7.7 % Drug Content

The % Drug content of the optimized transdermal patch (E9) was taken in triplicates (n=3) and the mean and standard deviation was found to be 99.193 ± 0.3557%.

3.7.8 Surface pH

pH of the skin should not be changed by the transdermal patch as this could cause irritation. The pH of the optimized transdermal patch (E9) was taken(n=3) and the mean and standard deviation was found to be 5.6±0.3605, indicating no irritation to the skin.[15]

3.7.9 Percent Moisture Loss

The optimized transdermal patch (E9) was taken (n=3) and the mean and standard deviation showed a percent moisture loss of 1.3296 ± 0.4154 % at 24 h and 3.337 ± 0.1718 % at 48 h, this demonstrate a small amount of moisture helps to keep it stable and prevent it from being brittle.

3.7.10 Percent Moisture Uptake

The optimized transdermal patch (E9) was taken and the mean and standard deviation of the percent moisture uptake was found to be 2.593 ± 1.080 % at 24 h and 3.769 ± 1.388 % at

48 h. Higher concentration of the hydrophilic polymer aids in moisture uptake.

3.7.11 Swelling Index

Swelling index was performed on the optimized transdermal patch (E9) of 2x2cm^2 (n=3) for 30 min, The mean and standard deviation of the % Swelling at 5, 10, 15 and 30 min were found to be 14.88 ± 0.815 %, 40.28 ± 1.1985 %, 62.68 ± 0.577 % and 66.62 ± 1.034 % respectively.

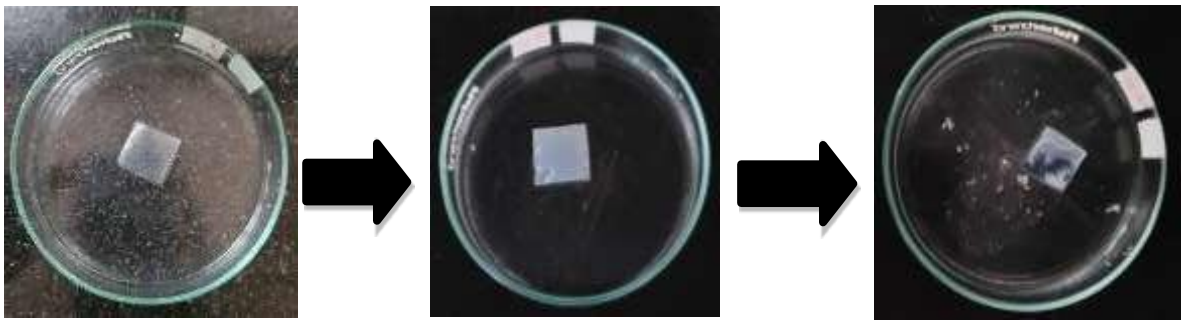

Fig. 3.9: Swelling index.

3.7.12 *ex vivo* permeation study

ex-vivo permeation study of the formulated optimized transdermal patch (E9) through human cadaver skin using a modified Franz diffusion cell was performed and sustained release up to 24 h was obtained and %cumulative drug permeated was found to be 67.49% as shown in Table 3.5, and flux was 0.0135 mg/cm^2/h. This indicates that there is sufficient drug permeation taking place through the human cadaver skin.

Table 3.5: Reported values of the *ex-vivo* permeation study.

Time (h)	Absorbance	Conc.	Amt mg/5mL	Amt mg/50mL	CDR	% CDR
1	0.052	5.243478	0.026217	0.262174	0.262174	10.48696
2	0.088	8.373913	0.04187	0.418696	0.444913	17.79652
3	0.134	12.37391	0.06187	0.618696	0.686783	27.4713
4	0.135	12.46087	0.062304	0.623043	0.753	30.12
5	0.137	12.63478	0.063174	0.631739	0.824	32.96
6	0.148	13.5913	0.067957	0.679565	0.935	37.4
8	0.155	14.2	0.071	0.71	1.033391	41.33565
10	0.225	20.28696	0.101435	1.014348	1.408739	56.34957
12	0.239	21.50435	0.107522	1.075217	1.571043	62.84174
24	0.241	21.67826	0.108391	1.083913	1.687261	67.49043

3.7.13 Skin Irritation Study

The optimized transdermal patch (E9) of 2 x 2 cm^2 and the blank transdermal patch of 2 x 2 cm^2 were casted onto the PU films with a thin layer of pressure sensitive adhesive and were applied on the rat's skin for dermal observations.

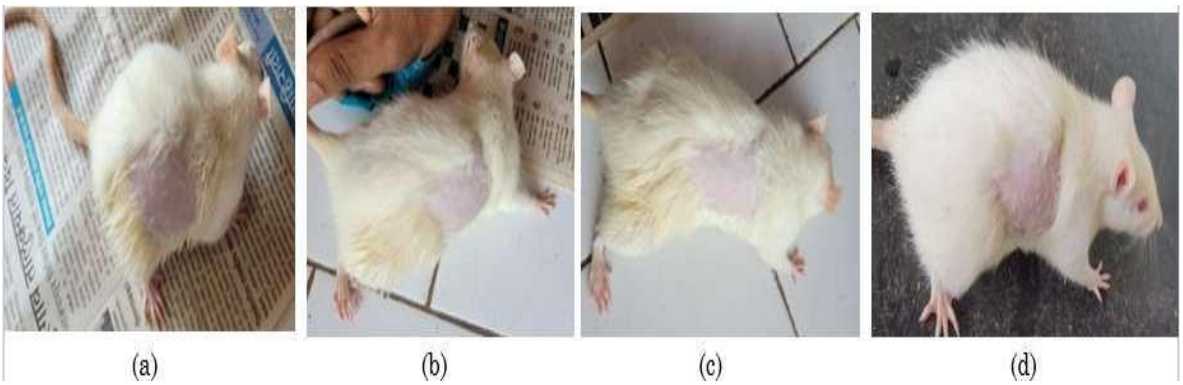

Fig. 3.10 a) Control b) 24h after c) After 48h d) After 72h.

The skin irritation study was conducted on healthy female rats, and it was observed that there were no traces of edema, erythema or any sign of skin irritation.

3.7.14 Stability study

Stability studies on transdermal patches were carried out at room temperature (25 ± 2 ^{0}C, 60% ± 5%) for 120 days. Samples were collected at 0, 30, 60, 90 and 120 days and analysed for appearance, % Drug content and folding endurance.

The transdermal patch remains stable even after 120 days, although sight changes in its % drug content and folding endurance have been observed.

Table 3.6: Results of Stability studies.

Time (Days)	Appearance	%Drug content	Folding endurance
0	Translucent	99.193 ± 0.355	371.66 ± 3.055
30	Translucent	98.88 ± 0.111	375.33 ± 0.577
60	Translucent	97.66 ± 0.455	363.49 ± 1.527
90	Translucent	95.30 ± 0.442	354.33 ± 2.516
120	Translucent	92.97 ± 0.080	342.33 ± 1.732

4.0 CONCLUSION

The prepared transdermal patch offered sustained release action and enhanced *in-vitro* drug release as comparison to the conventional dosage forms thereby eliminating the drawbacks of conventional oral dosage forms. From the study it can be concluded that BM-SD loaded

transdermal patches are a very promising approach to enhance the solubility and sustained release of the drug thereby improving the oral bioavailability of the drug.

5.0 ACKNOWLEDGEMENT

I thank the Almighty for his immense blessings bestowed upon me.

I am greatly indebted to my Guide, Dr. Rajashree Gude, Associate Professor, Department of Pharmaceutics, Goa College of Pharmacy.

6.0 conflict of interest

The authors confirm that there are no known conflicts of interest associated with this publication.

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