Research Article

Formulation Development and Characterization of Frovatriptan Transdermal Patches

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ABSTRACT

The present research work was aimed to develop matrix type transdermal patches of Frovatriptan using polymers HPMC K 15M, ERS 100 and EC and plasticizers DBP & PEG 400 via solvent casting method for low dose (6.25 mg) & high dose (12.5 mg) of drug. Frovatriptan the highly selective serotonin 5-HT1B/1D receptor agonist, used in the acute treatment of moderate to severe migraine attacks in adults and adolescent patients with a history of migraine with or without aura, is reported to have the best sustained pain-free rate and the lowest adverse events rate of all the triptans. Surface pH of all the films were found to be in the range of 5-6, indicating that irritation will not occur on the skin after applications of the patches. A percentage moisture loss test was used to determine how sensitive the patch was to moisture while being stored, and a percentage moisture absorption test was used to determine the films' physical stability and integrity under extremely humid conditions. In the current study, the optimisation response parameters of percentage moisture loss and cumulative percentage medication release at 12 hours were examined. It offers flexibility and prioritises each response separately.

Keywords: Frovatriptan, migraine, polymers, transdermal patches.

INTRODUCTION

The transdermal mode of administration involves delivering active substances via the skin for systemic dispersion. All topically applied medication formulations (patch, ointment, cream, gel, specifically prepared sprays, etc.) meant to release the active component into the general circulation are broadly referred to as TDDS. In the past, topically applied lotions and ointments for dermatological conditions were the most often used systems [1,2]. Compared to other drug delivery methods as oral, topical, intravenous, intramuscular, etc., a transdermal drug delivery route has the benefit that the patch allows the patient to get their medication in a regulated manner, typically by melting tiny layers of drug contained in the adhesive or by using a porous membrane to cover a reservoir of medication.

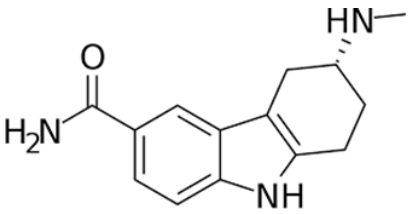

Figure 1: Structure of Frovatriptan

Migraine is painful primary headache that associated with different combinations of pain symptoms in neurological, gastrointestinal, autonomic parts. Frovatriptan affects blood flow redistribution by binding to the serotonin 5-HT1B/1D receptor on extracranial and intracranial blood vessels, causing vasoconstriction of cranial (brain) blood arteries. Importantly, it decreases blood flow via extra-cranial cranial arteries while increasing cerebral blood flow. In both young and old healthy volunteers, a single dose of frovatriptan has no clinically meaningful effect on heart rate or blood pressure. Larger dosages, however, appear to raise blood pressure marginally but not enough to be clinically significant [3-5].

METHODOLOGY

Preformulation Studies:

The general information provided by preformulation studies is meant to assist formulators in developing stable and bioavailable dosage forms. Utilising preformulation parameters increases the likelihood that a product will be formulated that is acceptable, safe, effective, and stable while also serving as the foundation for improving the quality of the drug product [6,7].

Solubility Profile of Frovatriptan

Frovatriptan's solubility was examined in a range of solvents. At room temperature, 10 ml of each solvent were used to dissolve a specific amount of medication (10 mg). The solubility was observed by visual inspection [8-10].

Preparation of pH 6.5 Phosphate Buffer:

60.5g of disodium hydrogen phosphate and 46g of potassium dihydrogen phosphate were dissolved in water to make 1000 ml, and then 20 mg of mercuric chloride and 100 ml of 0.02M disodium edetate were added [11-13].

Calibration Curve of Frovatriptan

After precisely weighing 100 mg of Frovatriptan, it was placed to a 100 ml volumetric flask and dissolved in methanol. With pH 6.5 phosphate buffer solution the volume was made up to 100ml to get a concentration of 1000µg/ml. From this 10ml was withdrawn and diluted to 100ml with pH 6.5 phosphate buffer solution to get a concentration of 100µg /ml. From this standard stock solution 0.2ml, 0.4ml, 0.5ml, 0.8ml and 1ml were

withdrawn and volume was made up to using pH 6.5 phosphate buffer solution to get a concentration of 2, 4, 6, 8 and 10µg/ml. Absorbance of these solutions were measured against blank of pH 6.5 phosphate buffer solution at 227nm.

Compatibility Studies of Drug & Excipients

The FTIR studies were carried out by KBr disc pellet method. 10mg of the samples and 400mg of KBr were taken in a mortar and triturated. A small amount of the triturated sample was taken into the pellet marker. It was compressed at 10kg /cm² using a hydraulic press. The sample was taken on the sample holder, it was then scanned from 4000cm^{-1} to 400cm-1 in FTIR spectrophotometer. Samples were prepared for drug and excipients also, the spectra obtained were compared and interrupted for functional group peaks[14-17].

Formulation of Frovatriptan

In the present study, matrix-type transdermal patches of Frovatriptan for its low (6.25mg) and high dose (12.5mg) were prepared by solvent evaporation technique. A glass mold of diameter 9.6cm having surface area 72.34cm^2 were used for casting the patches. By measuring the entire surface of the petri dish in which the patch was cast, the total amount of medicine that needed to be injected into the patch was determined [18-20].

Frovatriptan Loaded HPMC K 15M - ERS 100 Transdermal Patches

Polymeric solutions of HPMC K 15M and ERS 100 were prepared using DCM and methanol in 1:1 ratio (20ml) and specified amount of Frovatriptan and DBP were added and stirred well in a magnetic stirrer for 30min to get a homogenous solution. 5 ml of the casting solution was poured into glass a mold which was lubricated with glycerin; entrapped air bubbles were removed and dried at room temperature for 24 hours for solvent evaporation[21-23]. By inverting a glass funnel over the petri plate, rate of solvent evaporation was controlled. After 24 hours the patches were removed by peeling and cut into a circle of radius 2.1cm having surface area 13.85cm^2. These patches were wrapped in aluminium foil and placed in self-sealing covers after being left in the desiccator for two days to dry further. The same procedure was followed for preparing transdermal patches of high dose of Frovatriptan.

Drug Loaded HPMC K 15M – EC Transdermal Patches

Matrix patches containing Frovatriptan were prepared by dissolving HPMC K15M and EC polymers in suitable solvents namely DCM and methanol. PEG 400 is used as a plasticizer. The beakers were kept on the magnetic stirrers for continuous stirring to get a homogenous solution. The solution was poured into a petri plate which was lubricated with glycerin and covered with a funnel in an inverted position. The solvent was allowed to evaporate in ambient conditions for 24 hours. After 24 hours the patches were removed by peeling and cut into a circle of radius 2.1cm having surface area 13.85cm^2. These patches were kept in the desiccator for 2 days for further drying and wrapped in aluminum foil, packed in self-sealing covers. High dose of Frovatriptan were also prepared [24-27].

Drug Loaded HPMC K 15M Transdermal Patches

The transdermal patches of Frovatriptan were prepared using HPMC K15M polymer by solvent evaporation method. 250mg of HPMC K15M polymer was weighed accurately and kept aside. The specified amount of the drug was weighed accurately and is dissolved in 20ml of distilled water. The beakers were kept continuously stirring at room temperature. While stirring the polymer is added into the beaker slowly. As the drug & polymer both are hydrophilic in nature they get completely dissolved in solvent. PEG 400 is added to the solution. The whole solution was mixed thoroughly with the help of a magnetic stirrer for 30minutes. To avoid sudden evaporation, an inverted funnel was placed over the plate. Then the petri plates were kept for 12 hours in hot air oven at 40^{o}C for drying & the dried patches were taken out, cut to a circle of radius 2.1 cm having surface area 13.85 cm^2 and preserved in aluminum foil for further studies. Same composition was used for the other dose of the drug [28,29].

RESULTS AND DISCUSSIONS

Preformulation Studies

Solubility Profile of Frovatriptan

Solubility studies were carried out to select a suitable solvent to dissolve the drug and to select the dissolution medium.

Table 1: Solubility studies

Solvent	Solubility
Water	Soluble
Phosphate buffer pH 6.5	Soluble
Dichloromethane	Soluble
Methanol	Soluble

Development of Calibration Curve of Frovatriptan

Calibration Curve of Frovatriptan

In the validation studies, it was found that the estimation of Frovatriptan by spectrophotometric method at 227 nm has good reproducibility, at the concentration between 2-10 µg/ml. Correlation between concentration and absorbance was found to be 0.999845 which is closer to 1.

Table 2: Calibration curve of Frovatriptan

Concentration (µg/ml)	Absorbance
0	0
2	0.2166
4	0.4085
6	0.6155
8	0.8098
10	1.0031

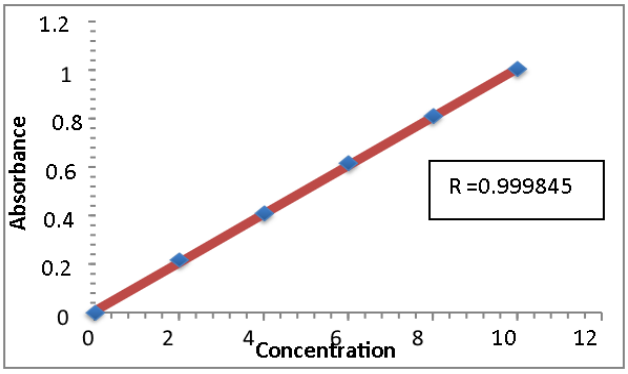

Figure 2: Calibration curve of Frovatriptan

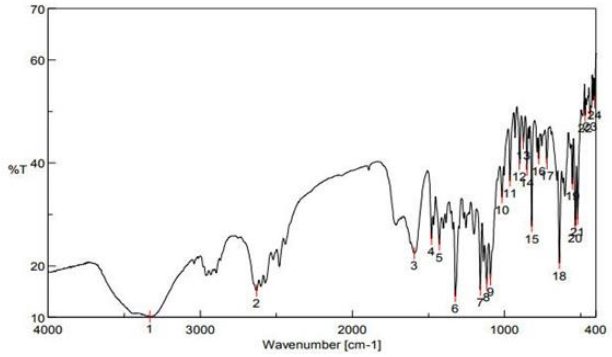

Figure 3: FTIR of Frovatriptan

Compatibility Studies of Drug & Excipients

In the present study, physical mixture of Frovatriptan in solid form along with different polymers were prepared and analyzed by FTIR to find out the compatibility between the drug and polymers. The IR spectra of Frovatriptan along with the physical mixture of Frovatriptan with different polymers are shown from the graph 2-5, which showed that the drug and excipients.

Formulation of Frovatriptan Loaded Transdermal Patches

The formulation of the patch was made in such a way that each small circular patch of 2.1cm radius (which is the radius of the Franz diffusion cell) contains the desired amount of the drug. By measuring the entire surface of the petri dish in which the patch was cast, the total amount of medicine that needed to be injected into the patch was determined.

Table 3: FTIR interpretation of Drug Frovatriptan

Samples	Functionalgroup		Type of vibration	Characteristic absorption (cm^{-1})	Test absorption (cm^{-1})
Frovatriptan	CH		Stretching	2840-3000	2976.59
			Bending	1350-1480	1433.82
	NH		stretching	3400-3500	3429.78
	C=C			1400-1600	1433.82
	S=O			1030-1060	1038.45
	COOH	OH		2500-3300	2563.21
		C-O		1210-1320	1229.12

Table 4: Calculation of total amount of drug to be loaded

Desired drug content	6.25 mg	12.5 mg
Area of the small circular patch (which is the area of Franz diffusion cell)	13.8474cm ^{2}	13.8474cm ^{2}
Area of the petri dish inwhich the patch is molded	72.3456 cm^2	72.3456 cm^2
Total amount of drug tobe loaded	(72.3456 / 13.8474) × 6.25 = 32.65mg	(72.3456 / 13.8474) × 12.5 = 65.31mg

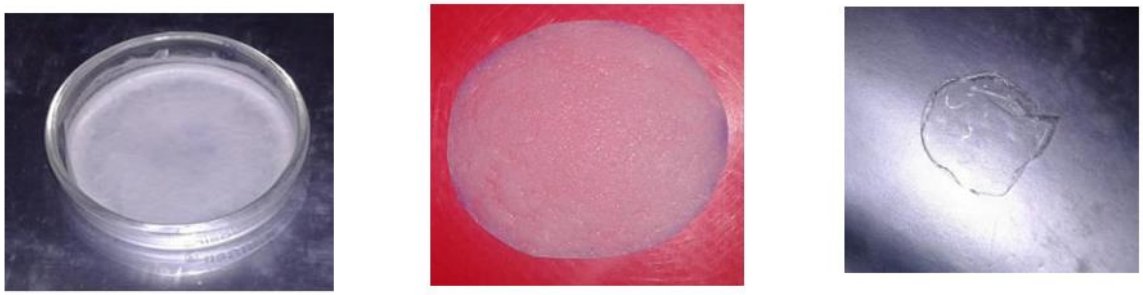

Figure 4: Prepared formulations

Table 5: Physical characters of formulated transdermal patches

Formulation	Formulation code	Evaluation Parameters			
		Colour	Flexibility	Smoothness	Stickiness
Frovatriptan Loaded HPMC ERS100 patches	F A1	White	Flexible	Smooth	Non-sticky
	F A2	White	Flexible	Smooth	Non-sticky
Frovatriptan loaded HPMC – EC patches	F B1	White	Flexible	Smooth	Non-sticky
	F B2	White	Flexible	Smooth	Non-sticky
Frovatriptan loaded HPMC patches	F C1	Clear & transparent	Flexible	Smooth	Sticky
	F C2	Clear & transparent	Flexible	Smooth	Sticky

CHARACTERIZATION OF FROVATRIPTAN LOADED TRANSDERMAL PATCHES

Transdermal patches of Frovatriptan were successfully prepared by solvent casting technique using HPMC K 15M as the hydrophilic polymer, ERS 100 and EC as the hydrophobic polymer and DBP & PEG 400 as plasticizer. The physicochemical properties, in-vitro drug release tests, and in-vitro drug release kinetic studies of each produced formulation were assessed.

Physical Appearance

Physical appearances of the films were evaluated, without any recrystallization, all the films are simply removable from the mould. All the systems were thin, flexible, smooth and without the entrapment of air but formulation having only the polymer HPMC K 15M were found to be clear and transparent. For casting the system, the adopted method was good.

Thickness of each film of all formulations were found uniform and ranged from 0.105 mm to 0.341 mm.

Folding Endurance

According to the results of the folding endurance test, the patches exhibited good elasticity and retained their integrity when folded like normal skin, even after 300 folds. The patch's capacity to resist rupture is determined by its folding endurance.

Drug Content

Drug content in each small circular patches were analysed spectrophotometrically, and it was noted that all the formulations shown a satisfactory drug content values ranging from 88 – 99% release of the drug from the patch ensures the uniform reproducible sustained.

Weight Uniformity

From each batch, five patches were taken on a digital balance to weight and observed that weight of the entire film sample in each formulation was uniform.

Surface pH

The surface pH for all the formulations was well and the optimum range of 5-6, hence no skin irritation was expected to occur after applications of the patches.

Percentage Moisture Absorption

Percentage moisture absorption for HPMC-ERS 100, HPMC-EC and HPMC alone was observed, 14.72%, 9.5% and 4.94% respectively; it may be due to hydrophilic and hydrophobic nature of the polymer. The lower moisture content in the formulation made the patches to stay steady and dry completely and brittle film and protects the material from microbial contamination and bulkiness.

Percentage Moisture Loss

According to a study on moisture loss, the formulation exhibited the greatest level of moisture loss because of HPMC K 15M when it was exposed to dry conditions; yet, even after this, the patches were found to retain their physical stability.

Water Vapour Transmission Rate

Patches having ERS 100 as the hydrophobic polymer shown least transmission rate than the patches with EC. All the formulations were permeable to water vapour, low water vapor transmission rate also indicates high degree of stability even in high humid conditions.

CONCLUSION

The present study demonstrated the optimization of Frovatriptan loaded transdermal patches. The independent variables selected were HPMC K 15M and ERS 100. The effect of these variables on drug content, %moisture absorption, %moisture loss and cumulative % drug release at 12hrs were investigated as optimization response parameters in the current study. It provides inflexibility and giving significance for each response collectively. Optimization aided in understanding the interaction of formulation parameters, which can be exemplified by increase in both the polymer concentration decreases drug release and it was found that concentration of HPMC K 15M were found to have individual effect on moisture uptake and loss. Analysis of the release data as per zero order and first order kinetic models indicated that the drug release from TDDS patches formulated followed zero order kinetics. When the release data were analysed, used to characterize different release mechanisms was found in the range 0.45-0.89 in the case of TDDS patches diffusion as the release mechanism. Transdermal patches of Frovatriptan provide sustained transdermal delivery for prolonged periods in the management of migraine, which can be a good way to

bypass the extensive hepatic first pass metabolism. The result of the study showed the feasibility of formulating rate-controlled transdermal films of Frovatriptan for effective control and prophylaxis of migraine. Further in-vivo investigations are required to correlate in-vitro permeation studies for the development of suitable transdermal system of Frovatriptan.

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