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NASAL DELIVERY OF FELODOPINE USING HYDROGEL MATRIX

[1]Bhanu P Sahu, [2]H. K. Sharma and [2]Malay K Das*

[1]GIPS, Guwahati University, Azra, Guwahati 781017

[2]Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh 786004, India

*Corresponding author E-mail: du_mkd@yahoo.co.in

ABSTRACT

The very poor oral bioavailability of felodipine due to CYP3A-dependent first-pass metabolism can be attenuate using nasal route of administration. The present work is aimed to develop the hydrogel matrix for nasal delivery of felodipine with improved bioavailability in the treatment of hypertension. The drug containing HPMC gels were prepared by swelling in nasal solution. The prepared gels were evaluated for various physicochemical properties. The ex vivo permeation of felodipine from gel matrix was investigated using goat nasal mucosa in Keshary-Chien Glass diffusion cell. The HPMC based gels showed good surface morphology with higher drug loading efficiency. The viscosities of the preparations were found to be within suitable range for nasal administration. The permeation was more controlled due to higher viscosities of the formulations at higher concentration of HPMC. A higher permeation flux was observed with the formulations containing PEG 400 than with the formulations containing Tween 80. The FT-IR analysis and

DSC scans confirmed no interaction between Felodipine and HPMC. This study shows the feasibility of the hydrogel matrix for nasal deliveries of felodipine with improve bioavailability.

Key words: Felodipine, Nasal delivery, Hyrogel matrix, Hydroxypropyl methylcellulose, Nasal mucosa.

INTRODUCTION:

The nasal route of administration has received a great deal of attention in recent years as a convenient and reliable method (Schipper et al, 1991; Marttin et al, 1998.; Chou et al, 2001). The nasal route is especially advantageous as an alternative means for the delivery of drugs that undergo extensive first-pass metabolism or are sensitive to gastrointestinal decomposition. Many small molecules (dihydroergotamine, metaclorpramide, butarphanol tartrate, su-bistorphanol succinate) and larger molecules (vitamin B_{12}, vasopressin, calcitonin, and insulin) have been successfully delivered intranasally (Zia et al, 1993). Morimoto et al 1987 reported the nasal absorption of nifedipine from gel preparations in rat model. The several nasal gel compositions have been patented for the delivery of erythropoietin (Shimoda and Igusa 1987), Insulin (Zirinis 1995), Tamoxifen (Hussain and Dittert 2001), Oxybutynin (Sherrat and Houdi 2002). The aqueous solubility of the poorly soluble drug is an important prerequisite for nasal permeation of drug. Sambhaji et al 2004 investigated the *in vitro* nasal delivery of Propanalol HCl in gel form using Tween 80. They reported the higher drug flux due to micellar solubilization. The present work is aimed to develop the hydrogel matrix for nasal delivery of felodipine with improved bioavailability in the treatment of hypertension.

Felodipine, a calcium channel blocker, used in the treatment of hypertension due to its vasodilation effect. It

undergoes significant CYP3A-dependent first-pass metabolism in the intestine and liver and thus the oral bioavailability is only 15 %. The drug is practically insoluble in water and its biological half-life is 14±4 h. The nasal delivery of felodipine using hydrogel matrix is expected to improve it bioavailability at the site of action avoiding the first-pass metabolism.

MATERIALS AND METHODS:

Materials:

Felodipine was kindly provided by Glenmark Pharmaceutical laboratories, Mumbai, India.Acetone, Ethanol, Benzalkonium Chloride, Tween 80, Sodium Chloride, Formalin (Ranbaxy Fine Chemicals Ltd, New Delhi); Disodium hydrogen orthophosphate (Qualigens fine chemicals, Mumbai) Potassium dihydrogen orthophosphate (Rankem, New Delhi); Sodium dihydrogen orthophosphate (Loba Chemicals Pvt. Ltd., Mumbai); Polyetyleneglycol 400 (Merck, Mumbai); Hematoxylin, Eosin (BDH Laboratories, Mumbai); Hydroxypropyl methylcellulose, Paraffin wax, Polyethyleneglycol 400 (E. Merck, Mumbai) were used.

Methods:

Solubility of felodipine:

The saturation solubility felodipine was obtained in water, phosphate buffer saline (pH 6.5)-Tween 80 (0.5% v/v) system and ethanol-water system (50% v/v). An excess amount of felodipine was taken in 5 ml each of the solvent systems and magnetically stirred for 48 hours at 37±0.5ºC. The samples were filtered through membrane filter (pore size 0.45 µm) and analyzed spectrophotometrically 363 nm using Spectrascan UV 2600 spectrophotometer.

Preparation of gels:

The felodipine gels were prepared using the formulations shown in Table 1. The drug was solubilised in nasal solution containing the required amount of Tween 80

and/or PEG 400 as the solubiliser. To this required amount of HPMC was added with gentle stirring and then kept overnight to allow it to swell properly for higher drug loading. The swollen system was then stirred with heating at 60^{o}C for 0.5 h and then constantly for 3 h magnetically to form a homogenous gel. Finally the prepared gel were filled in suitable container and kept for 24 hours to allow equilibrating. The nasal solution was prepared using the composition from literature (Kuotsu and Bandopyadhyay 2007).

Drug content in gel:

About 500 mg of gel was taken into 20 ml ethanol and stirred magnetically for 48 hours. It was filtered through a whatman filter paper and the filtrate was suitably diluted and assayed spectrophotometrically at 363 nm. The drug loading efficiency was determined from the following relation: Drug loading efficiency (%) = (Experimental drug content / Theoretical drug content) × 100

pH of gels:

pH was determined for the freshly prepared gels using a pH meter. The glass electrode was calibrated with two standard buffers (pH of 4.00 and 9.00). The preparation was left for about 15 minutes for attaining equilibrium while measuring.

Viscosity of gels:

Viscosity of the prepared and properly equilibrated gels were determined using Brookfield DVE Viscometer with spindle size 63 at 50 rpm (Srividya et al 2001).The viscometer was calibrated using standard solution of glycerine provided by manufacturer.

***Ex vivo* mucodahesive test:**

The *ex vivo* mucoadhesive test was performed in the modified mucoadhesive force measuring device (Robinson et al 2000) using nasal mucosa from sacrificed goat. The collected mucosal

membrane was kept in saline phosphate buffer of pH 7.4 at room temperature. The membrane was secured, keeping the mucosal side upward, on to each glass vial using nylon thread. The exposed area of mucosal membrane was 2 cm. The vials with the nasal tissue were kept at 37ºC for 10 minutes. A constant amount of the gel was applied on the exposed nasal membrane. The height of the vial was adjusted so that the gel could adhere to the mucosal tissues of both vials. A constant weight was placed on the upper vial for 2 minutes, after which it was removed. Water was added at a constant rate to the pan on the other side of the modified balance until the two vials were separated. The weight of water gives the weight required for displacement of two vials. The adhesive force (dyne-cm^{-2}) was determined from the minimum weights to detach the two vials using the following equation (Robinson et al 2000):

Detachment stress (dyne-cm^{-2}) = m × g /A, where m is the weight added to the balance in gram, g is the acceleration due to gravity (980 cm/sec^2) and A is the area of tissue exposed (πr^2).

***Ex- vivo* drug permeation study:**

Fresh nasal tissues were carefully removed from nasal cavity of goat obtained from the local slaughterhouse. Tissue samples were inserted in Kisery-Chein glass diffusion cell displaying a permeation area of 1.13 cm^2. Sixty milliliters of ethanol-water (50:50) system at 37± 0.05°C was added to the receptor chamber. The temperature within the chambers was maintained at 37± 0.05°C. After a pre-incubation time of 20 minutes 1g gel was placed on the donor chamber. At predetermined time intervals, 2 ml samples were withdrawn from the receptor compartment, replacing the sampled volume with fresh dissolution medium after each sampling, for a period of 8 hours. The

samples withdrawn were filtered and used for analysis (Majithiya et al, 2006) spectrophotometrically at 363 nm. The amount of drug (µg) permeated per square centimeter (cm^2) of mucosal membrane at each time interval was calculated from the calibration curve equation, Absorbance = 0.024 × Concentration – 0.009 (R^2 = 0.999).

Calculation of Permeation Parameters:

The cumulative amount of felodipine permeated per unit of nasal mucosal membrane (µg/cm^2) was plotted as a function of time (t, h). The permeation rate of felodipine at steady-state (Jss, µg/cm^2/h) was calculated from the slope of the linear portion of the plot. The permeability coefficient (Kp, cm/h) was calculated using the equation: Kp = Jss / Cd, where Cd is the concentration of drug in donor compartment (10 mg/ml) and it is assumed that under sink conditions the drug concentration in the receiver compartment is negligible compared to that in the donor compartment. The data are expressed as mean ± S.D (n = 3).

Surface morphology of gels:

The surface of the gel was observed using a Phase Contrast Microscope and photomicrographs were recorded at 100X magnification (Devrakonda et al 2005).

Fourier Transform Infrared Spectroscopy (FT-IR):

Drug polymer interactions were studied by FT-IR spectroscopy. The spectra were recorded for drug, polymer, drug-polymer physical mixture (1:5). Samples were prepared in KBr discs (2 mg drug in 8 mg KBr) with a hydrostatic press at a force of 8 t cm^{-2} for 2 minutes. The scanning range was 450-4000 $cm^{-}1$ at the resolution of 2 cm^{-1}.

Differential scanning electron microscopy (DSC):

The DSC analysis of pure drug, HPMC, and HPMC-drug physical mixture

(1:5) was carried out using Mettler Toledo (Model SW 810) DSC to evaluate any possible drug-polymer interaction. Samples (5.5 - 8 mg) were weighted accurately using a single pan electronic balance and heated in sealed aluminum pan at the rate of 5^{o}C/min in the temperature range of 25 - 450^{o}C under a nitrogen flow of 35 ml/min.

RESULTS AND DISCUSSION:

Solubility of felodipine:

The saturation solubility of felodipine in different solvent systems was presented in the Table 2. The drug was found to be sparingly soluble in water. The saturation solubility of drug in phosphate buffer saline (pH 6.5) containing Tween 80 (0.5 %) was found to be considerably lower than that in Ethanol-Water (1:1) system.

Surface Morphology of Gels:

The photomicrographs of gels showed that the drug was homogenously dispersed as discrete particles in the HPMC gel matrix. The addition of Tween 80 or PEG 400 to increase the matrix solubility of felodipine significantly decreased the size of the dispersed particles. The photomicrographs of blank HPMC gel and felodipine loaded HPMC gel are shown in the Fig. 1.

Drug content:

The felodipine content in the gel was found to be in the range of 90.40±0.75 to 105.14±0.94 (Table 3). The higher drug loading obtained may be accounted to the method of preparation, since the drug had been loaded at the time of gel formation. Moreover the sparingly soluble nature of felodipine may also account to better entrapement in HPMC gel network.

pH:

The pH of the felodipine gel was found to be in the range of 6.42 ± 0.48 to 6.55± 0.54 (Table 3) indicating their nonirritating nature towards nasal mucosa.

Viscosity:

It is found from the Table 3 that the viscosity increased with increasing concentration of HPMC and there was a sharp rise for 6% HPMC gels (F3, F6 and F7). The addition of Tween 80 had no significant effect on viscosity of the formulations, but slight decrease in viscosity has been observed with formulations containing 10 % PEG 400 (F5 and F7).

***Ex vivo* Mucoadhesive test:**

The prepared gels (Formulation F3) showed substantial adhesiveness towards nasal mucosa and adhesiveness increased with increase in contact time as can be seen in Fig. 2.

***Ex vivo* Drug permeation study:**

The effect of polymer concentration and permeation enhancer on felodipine permeation across nasal mucosa was investigated using Keshary-Chien glass diffusion cell. The permeation profile and flux values are presented in Fig. 3 and Table 3, respectively. The results show a decreasing trend in permeation flux with increasing the concentration of HPMC (Formulation F1, F2 and F3). The permeation was more controlled due to higher viscosities of the formulations at higher concentration of HPMC. A higher permeation flux was observed with the formulations (F5 and F7) containing PEG 400 than with the formulations (F1, F2, F3, F4 and F6) containing Tween 80. It may due to the intimate contact with higher partitioning of PEG 400 at higher concentration.

FT-IR analysis:

Infrared spectra of Felodipine and physical mixture (1:5) of Felodipine and HPMC were comparable and the peaks of Felodipine in the physical mixture are of lower intensity than pure drug. The characteristic peaks at 1021cm^{-1},1425 cm^{-1},1625 cm^{-1},2922 cm^{-1} and 3420 cm^{-1} which corresponding to aromatic C-Cl, aromatic ring stretch, C=O, C-H stretch and

heterocyclic secondary amine stretch, respectively, were found to be intact in the physical mixture, which indicates the absence of drug interactions. This was further confirmed by DSC studies.

Differential Scanning Calorimetry (DSC):

DSC scans of Felodipine, HPMC and Felodipine–HPMC physical mixture (1:5) were studied for the compatibility of drug with HPMC. DSC scan of Felodipine showed a sharp endothermic peak at 141.5º C corresponding to its melting point (Fig. 4). Felodipine in the physical mixture also showed a similar peak at 139.4º C with decreased intensity revealing its unchanged nature in presence of HPMC. Besides, a characteristic peak at the range of 108-110º has also been seen for the HPMC both in pure and physical mixture. Thus, the FT-IR analysis and DSC scans confirmed no interaction between Felodipine and HPMC, when presented as physical mixture.

Table 1: Formulations of Felodipine Gels.

Formulation Code	HPMC (mg)	FELODIPINE (mg)	TWEEN 80 (mg)	PEG 400 (gm)	NASAL SOLUTION	TOTAL QTY (gm)
F1	400	100	100	-	q s	10
F2	500	100	100	-	q s	10
F3	600	100	100	-	q s	10
F4	500	100	200	-	q s	10
F5	500	100	-	1	q s	10
F6	600	100	200	-	q s	10
F7	600	100	-	1	q s	10

Table 2: Saturation Solubility Data of Felodipine.

SOLVENT SYSTEM	SATURATION SOLUBILITY (μg/ml)
Water	19.7
Phosphate buffer saline, pH 6.5-Tween 80 (0.5%)	260.9
Ethanol-Water (50:50)	1123.66

Table 3: Physicochemical parameters of gel formulations

Formulations	pH	Drug content (Mean± S.D)%	Viscosity (Mean± S.D)cp	Flux(Mean ± S.D) μg/cm^2/h.
F1	6.55±0.54	97.22±0.63	288±9.54	419.50±62.72
F2	6.49±0.51	95.50±0.71	488±14.51	407.50±52.16
F3	6.44±0.49	92.50±0.82	1183±20.49	398.50±32.69
F4	6.52±0.53	105.14±0.94	492±10.53	469.50±62.72
F5	6.42±0.48	96.20±0.62	438±9.48	556±60.12
F6	6.47±0.51	90.40±0.75	1182±21.51	486.50±27.31
F7	6.53±0.49	94.31±0.96	980±15.49	521±36.18

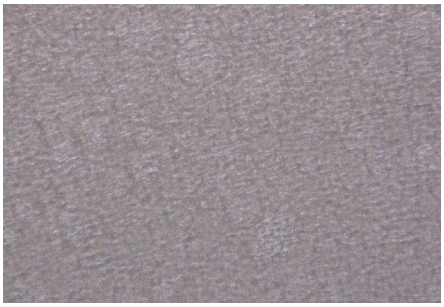

Fig 1 (a): Photomicrograph of Fresh HPMC gel Blank

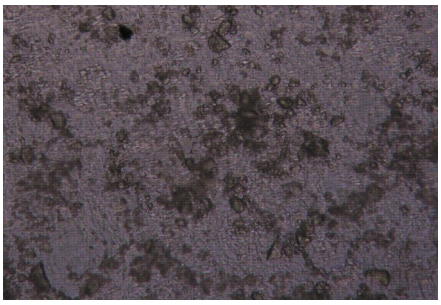

Fig 1 (b): Photomicrograph of Felodipine (1%) loaded HPMC gel (F-2)

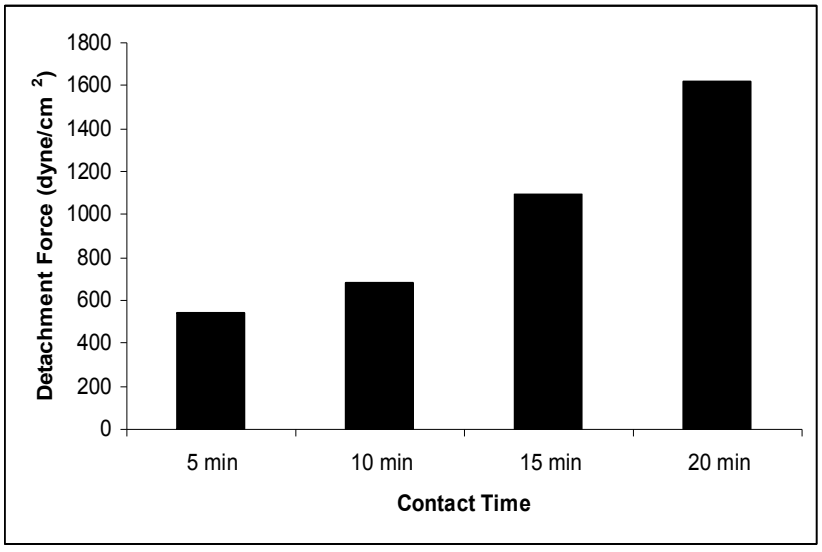

Fig 2: Mucoadhesive behavior of formulation F3.

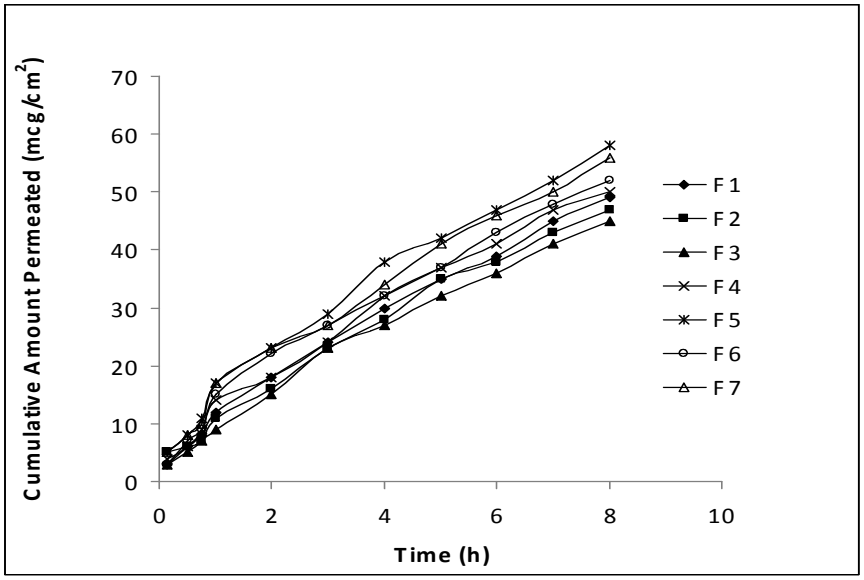

Figure 3: *Ex vivo* permeation profile of felodipine from various nasal gels.

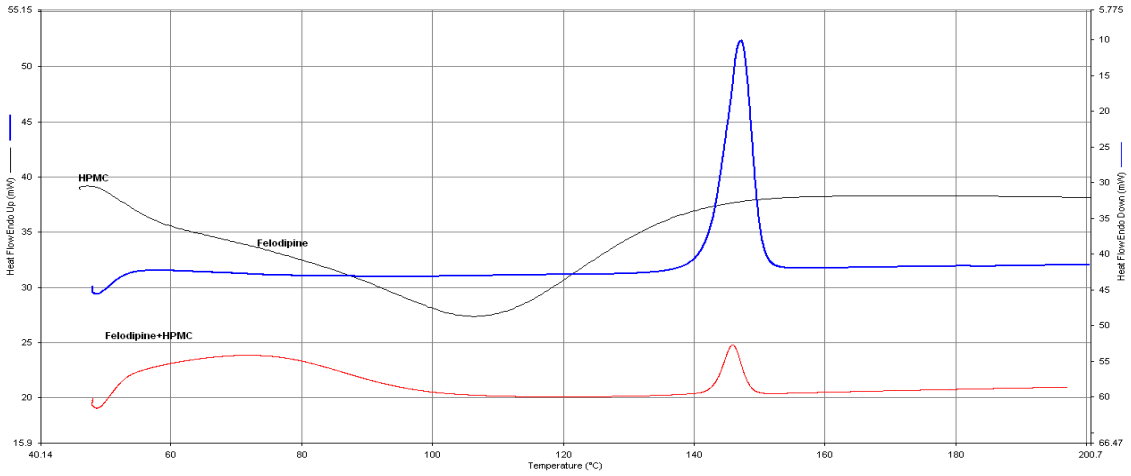

Fig 4: DSC curves of pure drug (A), pure HPMC (B) and Felodipine-HPMC physical mixture (1:5).

CONCLUSION:

The nasal route holds promise for administration of drugs with very poor oral bioavailability like felodipine. The HPMC based gels showed good surface morphology with higher drug loading efficiency. The viscosities of the preparations were found to be within suitable

range for nasal administration. The permeation was more controlled due to higher viscosities of the formulations at higher concentration of HPMC. A higher permeation flux was observed with the formulations containing PEG 400 than with the formulations containing Tween 80. The FT-IR analysis and DSC scans confirmed no interaction between Felodipine and HPMC. It may be concluded that bioavailability of felodipine can be increased by nasal delivery of the drug

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