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DESIGN AND EVALUATION OF CONTROLLED POROSITY OSMOTIC PUMP TABLET OF NIFEDIPINE FOR BUCCAL DELIVERY

R. Kumaravelrajan[1]*, L. Abungsana Singh[1], Priyanka Mitra[1] and V. Suba[2]

[1]Department of Pharmaceutics, C.L.Baid Metha College of Pharmacy, Chennai.
[2]Department of Pharmacology, National Institute of Siddha, Chennai.

Corresponding Author: R. Kumaravelrajan
Department of Pharmaceutics, C.L.Baid Metha College of Pharmacy, Chennai.

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ABSTRACT

The objective of the present study is to develop, optimise and evaluate of Buccal Osmotic Pump Tablet (BOPT) of Nifedipine. Nifedipine was choosen as drug candidate to carry out the objective of the study. The DSC thermograms were clearly proved that there was no specific interaction between the drug and polymer used in the formulation. Lactose and lactose-dextrose combined was used as osmogent. Different drug: osmogent ratios are used to investigate the study. The release of drug from the osmotic pump is dependent on Osmotic pressure inside the system. The percentage of pore former concentration was directly proportional to the drug release. 30% pore forming agent concentration, drug release rate is only at the end of 8 hr however, release rate was increased as increased the % of pore former concentration, 40% showed 74.8% and 50% (F3) showed 83.2%. The formulations with 4% coating thickness showed greater amount of release rate when compared with other formulations with 7% and 10% coating thickness. Thickness of the membrane is inversely proportional to the drug release. The optimised batch (F9) showed good ex vivo permeation of the drug, around 80% of the drug permeated at the end of 6th hour, muco adhesive strength and wash off test results showed good adhesive property on buccal membrane. SEM study showed the porosity of the membrane in situ condition of the Nifedipine BOPT, before contact to aqueous environment there was no pores on the membrane but after contact pores were formed was observed.

KEYWORD: Osmotic pump, Nifedipine, Buccal delivery.

INTRODUCTION

Hypertension (high blood pressure) is a condition in which the blood pressure in the arteries is persistently elevated.[1] High blood pressure usually does not cause symptoms. Long term high blood pressure is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease.[2-3] About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors.[4-6] Lifestyle factors that include excess salt, excess body weight, smoking, and alcohol. The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills.[7-9]

Approximately one billion adults or ~22% of the population of the world have hypertension as of 2014. It is slightly more frequent in men, in those of low socioeconomic status and prevalence increases with age. It is common in high, medium and low income countries.[10]

The prevalence of raised blood pressure is highest in Africa, (30% for both sexes) and lowest in the WHO Region of the Americas (18% for both sexes). In Europe hypertension occurs in about 30-45% of people as of 2013.[11-12] In 1995 it was estimated that 43 million people (24% of the populations) in the United States had hypertension or were taking antihypertensive medication. By 2004 this had increased to 29% and further to 34% (76 million US adults) by 2006.[12-13]

Lifestyle changes such as weight loss, decreased salt intake, physical exercise, and a healthy diet. If lifestyle changes are not sufficient to control blood pressure then medications are used.

First line medications for the treatment of hypertension are thiazide-diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers.[14]

The objective of the present study is to develop, optimise and evaluate of Buccal Osmotic Pump Tablet (BOPT) of Nifedipine. Nifedipine was choosen as drug candidate to carry out the objective of the study. Nifedipine is an anti-hypertensive calcium channel blocker with dose of 20 – 40 mg thrice a day and belongs to Class II drug with high permeability (3.4 *clog p*) and low solubility (0.0177 mg/ml) of BCS. The solubility of Nifedipine to be modulated using HP-β-CD to enable the faster drug release rate to achieve the desire drug concentration profile. The buccal route has excellent accessibility, relatively low enzymatic activity, robustness of the epithelium, natural clearance mechanism for elimination of drug from buccal area, satisfactory patient acceptance, avoiding hepatic first pass metabolism and increased bioavailability etc., are the advantages of buccal route. Therefore, Buccal route of administration is selected for the present study. The flux rate of water through the cellulose acetate membrane and the type of osmogent to be studied at preformulation level. The other objectives of the investigation is to study the effect of different drug and osmogent ratio, variable concentration of pore forming agent and thickness of the membrane is included. Further investigation includes *ex vivo* permeation study, swelling study, strength of the membrane, muco adhesive strength, wash off test, SEM test to be performed for the optimised formulation. The optimized formulation to be subjected for short term accelerated stability study.

MATERIALS AND METHODS

Nifedipine BMR Pharma& Chemical Suppliers (Hyderabad), 2-Hydroxypropyl-β-cyclodextrin (HP-β-CD) Sigma-Aldrich, Lactose-Chemspure (Chennai), Cellulose Acetate*(CA 398-10 NF)Eastman Chemicals Company, Kings port, USA. Dextrose-Chemspure (Chennai).

Magnesium Stearate Lobachemie,(Chennai),Talc-Lobachemie(Chennai),polyvinyl pyrrolidone- Sd Fine Chemicals Limited (Mumbai), Dicalcium Phosphate-Sd Fine Chemicals Limited (Mumbai),Aerosil-Chemspure (Chennai), Isopropyl Alcohol-Chemspure (Chennai)-Methanol-Sd Fine Chemicals Limited (Mumbai)-Acetone Sd Fine Chemicals Limited (Mumbai).Poly ethylene Glycol 400 Chemspure (Chennai) Hydroxpropyl Methyl Cellulose E-15 Chemspure (Chennai).

Preparation of inclusion complex[15]

Solid complex of NHP-β-CD was prepared in 1:1 ratio by co-precipitation method. Nifedipine was first dissolved in a small volume of acetone and then thoroughly mixed with 100 ml of ethanolic solution of HP-β-CD in a round bottom flask. The solvent was evaporated under reduced pressure at 40.0°C.

Preparation of Nifedipine granules

The solid complex NHP-β-CD and the powder materials were weighed, (Lactose, di-calcium phosphate) of required quantity andreduced their particle size by using mortar pestle. The powder mixtures were transferred into a beaker and mixed it properly. PVP was dissolved in IPA in a beaker separately; this solution was poured into the beaker which contained mixtures. The powder mixtures were mixed thoroughly by using a glass rod, until to get dough mass. Then the wet mixture was kept inside hot air oven for half drying at 50.0°C for 10min. The half dried mass was passed through sieve 22, then the Nifedipine granules were formed. The Nifedipine granules were kept inside hot air oven for further drying for 15min. to remove moisture completely.

For blending process, the prepared granules were mixed with glidant and lubricant like talc, magnesium stearate and aerosil. Finally, the granules were compressed into tablet at 5-7kg/cm2 on a single stoke by, Rotary tablet punching machine (Cadmach) with 8mm round shape flat punch. 159 mg, 189 mg and 219 mg weights of tablets were prepared **(Table 1).**

Solubility Study of Nifedipine HP-β-CD complex

Excess amounts of NHP-β-CD complex were added to 10 ml distilled water. After vertical rotation for 24 h at 30^{o}C, samples were withdrawn, filtered through 0.45 µm membrane filters, diluted with methanol and analyzed by the spectrophotometric method.

Table 1: Compositions of different batches of NifedipineBuccal Osmotic pump core tablet.

Formula (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Nifedipine (HP-β-CD)	100	100	100	100	100	100	100	100	100	100	100	100	100
Lactose	30	30	30	60	90	90	90	90	-	-	-	-	-
Lactose- Dextrose	-	-	-	-	-	-	-	-	90	90	90	90	90
PVP	6.3	6.3	6.3	6.3	6.3	6.3	6.3	6.3	6.3	6.3	6.3	6.3	6.3
DCP	13.7	13.7	13.7	13.7	13.7	13.7	13.7	13.7	13.7	13.7	13.7	13.7	13.7
Aerosil	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc	6	6	6	6	6	6	6	6	6	6	6	6	6
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight (mg)	159	159	159	189	219	219	219	219	219	219	219	219	219

Coating of core tablets

The coating of the core tablet had been done by using 2% w/v solution of Cellulose acetate in acetone. PVP was also dissolved in IPA. Both solutions are mixed together and used as a coating solution. Coating was carried out by dip coating method. The core tablets were dipped into coating solution and then dried at 50.0°C in hot air oven, taking care to prevent adherence to one another. For obtaining more perfect or heavier coats, the dipping and drying steps repeated several times one after another (**Table 2**). The thickness of all coated tablets was measured by Vernier caliper.

Table 2: Core variables of the of Nifedipine Buccal Osmotic Pump tablet.

Formula Code	Variables		
	Drug : Osmogent	Pore forming agent (%)	Thickness (%)
F 1	1:1	30	4
F 2	1:1	40	4
F 3	1:1	50	4
F 4	1:2	50	4
F 5	1:3	50	4
F 6	1:3	50	7
F 7	1:3	50	10
F 8	1:3	50	4
F 9	1:3	50	4
F 10	1:3	30	4
F 11	1:3	50	4
F 12	1:3	30	4
F 13	1:3	50	4

Evaluation

Swelling index [16]

The previously weighed (W_1) tablets were placed individually in the petri dish containing 10 ml of distilled water. The weight of the tablet (W_2) was noted after 30 min after wiping out the excess water by filter paper. The swelling study was carried up to 6hr. The swelling index was calculated using the formula.

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 100$$

In vitro drug release study[17]

The developed formulations were subjected to release studies using USP-II dissolution apparatus (Electrolab, India) at 100 rpm. Dissolution medium used was phosphate buffer (pH 6.8, 900 ml) and bath temperature was $37^0C \pm 0.5^0C$. The samples were withdrawn at 0, 1, 2, 3, 4, 5, 6, 7, 8 hr intervals and replaced with an equal amount of fresh medium. The dissolution samples were filtered and analysed using a validated UV spectrophotometric method at 236 nm. Each study was done in triplicate and the mean values were reported. All the experiments were carried out under strict protection from light to prevent undesirable photo-degradation of Nifedipine throughout the entire experimental procedure.

Wash- off test[18]

The mucoadhesive properties of the tablets were evaluated by wash-off method. A piece of buccal mucosa of goat was mounted on the glass slide provided with suitable support. After fixing the 2 tablets to this glass slide by pressing them to the pre wet tissue for 30 sec, it was tied to the arm of the tablet disintegration test apparatus (Electrolab) and was run at $37^0C \pm 0.5^0C$ in pH 6.8 buffer. Time taken for the detachment of both the tablets was noted down.

Ex *vivo* mucoadhesive strength[19]

A modified balance method used for determining the *ex vivo* mucoadhesive strength. Fresh buccal mucosa obtained (goat) within 2 hours of local slaughter. The mucosal membrane separated by removing underlying fat and loose tissues. The membrane washed with distilled water and then with phosphate buffer pH 6.8 at 37^0C. The buccal mucosa cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The two sides of the balance made equal before the study, by keeping a 5gm weight on the right-hand pan.

A weight of 5gm was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8, at 37°C ±0.5°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of arubber stopper with cyanoacrylate adhesive.The muco adhesive strength was assessed in terms of weights (gm) required to detach the tablet from the membrane.Mucoadhesive strength which was measured as force of adhesion in Newton's by using following formula:

Force of adhesion (N) = $\frac{\text{Mucoadhesive strength x 9.81}}{100}$

Tensile strength of the membrane[20]

Mechanical properties of the membranes were evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with a 25kg load cell.

Film strip with the dimensions 60 x 10 mm and without any visual defects were cut and positioned between two clamps separated by a distance of 3cm. Clamps were designed secure the patch without crushing it during the test, the lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2mm/sec until the strip broke.

The force and elongation of the film at the point when the strip broke was recorded. The tensile strength was calculated using the formula:

$$\text{Tensile strength (kg. mm}^{-2}) = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample (mm}^2)}$$

Scanning Electron Microscopy study (SEM)[21-22]

A scanning electron microscope was used to observe the mechanism of drug release from the developed formulations. This study was performed on the surface of coated tablets before and after dissolution studies. Membranes were dried at 45 °C for 12 h and stored between sheets of wax paper in a desiccator until examination. The samples (membranes) were fixed on a brass stub using a double sided tape and then gold coated in vacuum by a sputter coater. Scans were taken at an excitation voltage of 20KV in SEM (FEI Quanta 200 FEG) fitted with ion sputtering device. The surface morphology of coated membrane of optimized formulation film coating before and after dissolution was examined and by comparing the porous morphology the capability of porogen and drug release can be evaluated from this study.

Ex-vivo drug permeation study[23]

Ex-*vivo* permeation study was carried out using fresh buccal mucosa of goat. The pieces of buccal mucosa of goat was procured from local slaughter house and placed in phosphate buffer. The study was carried out using open end cylinder method. The mucous membrane was tied to one end of the two sided open ended cylinder, this will act as donor compartment. The buccalosmotic pump tablet containing 31 mg of Nifedipine was kept on the mucous membrane, in such a way that the lower surface of the tablet was in contact with the mucous membrane. Then the donor compartment was fixed, so that mucous membrane was in contact with the receptor medium (beaker), 100 ml of phosphate buffer pH6.8 in the receptor compartment. Samples was withdrawn at 0, 1, 2, 3, 4, 5 and 6 hrintervals and replaced with fresh buffer and drug content was analysed.

RESULTS AND DISCUSSION

The dosage form was developed as a tablet core with rate controlling membrane. Tablet core consist of the drug along with HP-β-CD, osmogent and other excipients to form the core compartment. For this purpose, lactose and dextrose was used as an osmogent. The core tablet surrounded by rate controlling membrane that consist of semi permeable membrane and plasticizer which are capable of forming pores of the polymer. Cellulose acetate with acetyl content 38.9 % was used as a semi permeable membrane. PVP, PEG 400 and HPMC E15 were used as pore forming agents. During the preformulation, flux of water through cellulose acetate membrane was determined using the Franz Diffusion cell. Almost 5.6 ml of water was permeated per hour without the addition of pore forming agent. The above observation gave the idea of drug molecules with water passed across the membrane. However, by increasing the flexibility of membrane upon the addition of pore forming agent, the desire drug release rate can be achieved.

DSC Thermogram of Nifedipine with excipients depicted in the **Fig 1** showed no changes in melting endotherms when compared with the thermogram of pure Nifedipine. Both the pure Nifedipine and coated Nifedipine powder exhibited melting point at (175.10°C). From the DSC Thermograms it was concluded that there is no specific interaction between the drug and polymer used in the formulation.

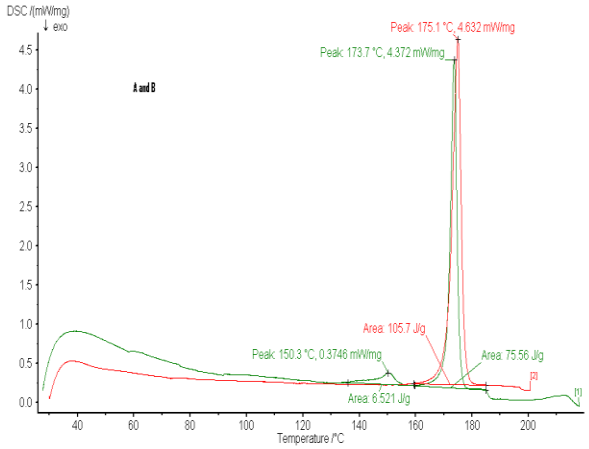


Figure 1: DSCThermogram of Nifedipine with excipients.

Solubility Study

The increase in solubility observed was due to the formation of an inclusion complex. The driving force for inclusion complexation between β-cyclodextrin and Nifedipine may include vander Waals interaction, hydrogen bonding, and hydrophobic interaction, resulting in release of high energy water molecules from the cavity of β-cyclodextrin and release of strain energy in the ring of cyclodextrin. NP solubility was 17.7 µg/ml which was increased to 28.32µg/ml by complexing with

1:3 ratio drug and carrier. Therefore, it may be concluded that the binary complex are capable of improving the solubility and stability of Nifedipine. The compressibility index for all the 13 batches was found between 14.09 and 17.48. Angle of Repose was found between 23.16 and 25.63. Hausner's ratio was found between 1.15 and 1.23. The evaluation of physical mixture expresses that the values of compressibility index, angle of Repose and Hausner's ratio were found within the specified limits. From this it is clear that all the batches have good flow property and are suitable for compression.

Swelling index

Swelling index of the Nifedipine Buccal Osmotic Pump tablet as the concentration of osmogent increased the extent of swelling index also increased. The Swelling index is also dependent on the membrane thickness. The increase in the membrane thickness decreased the swelling index.

Formulation **F9** showed highest swelling index (3.47 %). The least swelling index was shown by **F7** (1.62 %). **Fig. 2** showed the swelling index of Buccal Osmotic Pump Tablets of Nifedipine.

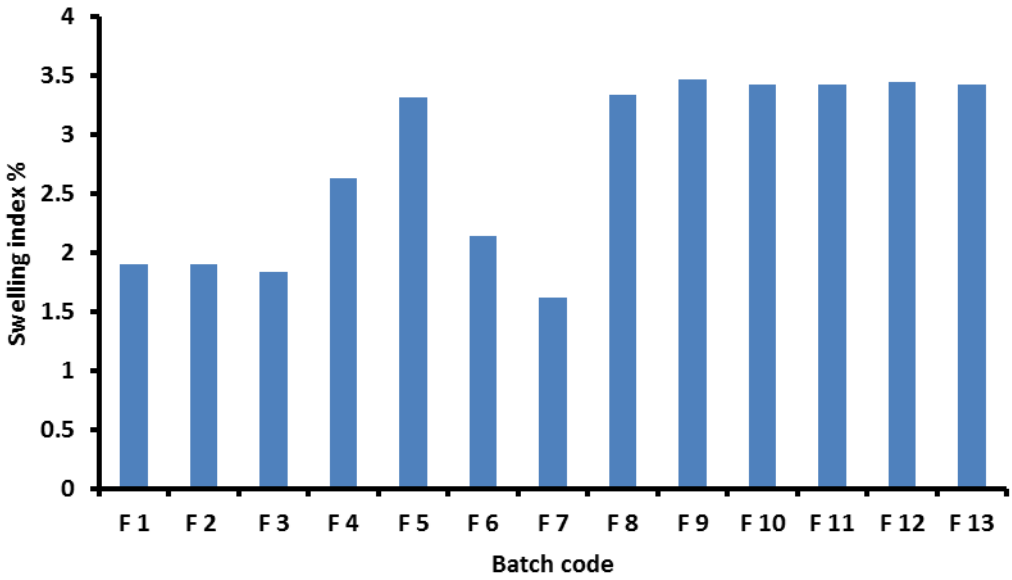


Figure 2: Swelling index of Buccal Osmotic Pump Tablets of Nifedipine (F1-F13).

Effect of drug: osmogent ratio on drug release

To study the influence of drug: osmogent ratio, the osmogent level was kept constant (1:1) initially but different in concentration the pore forming agent. 2% cellulose acetate was used to coat the core tablet by dip coating method. At the end of the coating the weight gained of the tablet was found to be 22%. PVP was used as pore forming at 30% (F1), 40% (F2) and 50% (F3). The percentage of pore forming agent was calculated with reference to the total solid content of cellulose acetate. The in vitro release profile of F1 indicate around 70% of drug release achieved at end of 8th hour, 80% and 90% of drug release achieved for F2 and F3 respectively. By increasing the concentration of pore forming agent the release was increased. All the 3 formulations shown the higher release initially gave the rate of release (7 mg/hr). Later from the period of 3 to 6 hours the release rate was consistent. Only F3 showed higher the Nifedipine release rate at 3-6 hours as compared to other formulation **(Fig.4).** Therefore 50% of PVP used as a pore forming agent for subsequent batches.

Effect of level of pore former on drug release

It was found that the drug release was directly proportional to the pore forming agent. As the level of pore former increase the membrane become more porous after coming in contact with aqueous environment resulting in faster drug release. The similar results reported by others workers. The level of pore former affects the extent of drug release .The maximum drug release was obtained around 90 % with 50 % of pore former. In case of formulation with 30 % and 40 %, the percentage of drug release was found to be around 70 % and 80 % respectively **(Fig. 3).**

Up to 40% of pore forming agent concentration, there was no significant increase in percentage of drug release. This may be because of less number of pores formed in situ to contribute the desire drug release and the size of the pores might be small enough to release the drug in suspension form. This observation came to notice during evaluation of SEM study. In SEM images, it appeared that increase the pore forming agent the number and size of pores increase, thereby drug release. Therefore, we can conclude that the drug release is directly proportional to the pore former in the membrane.

Effect of thickness of coating membrane on drug release

To study the effect of thickness of membrane, the core tablet of Nifedipine coated with cellulose acetate of different thickness 4 % (F5), 7 % (F6) and 10 % (F7). The maximum weight gained after coating was 28 % of the tablet weight. Coating was done by dip coating method. The drug release was found to be decreased by 85.5 % and 77% with the 7% and 10% cellulose acetate respectively.

Although the desire percentage of drug release achieved within in 6-8 hours, the linearity in release rate is one of the parameter to optimise the formulation. 4% cellulose acetate gives the desire release fashion from 2 to 7 hours. Fig 5 showed, release rate as function of reciprocal of membrane thickness.

The water influx is related to osmotic pressure and the thickness of the coating membrane. It is inversely related to the thickness of the coating membrane and is directly related to the osmotic pressure developed inside the system. When the coating thickness is increased it decreases the water imbibing through the membrane, thus the hydration of the tablet will be decreased and this further decreases the release rate of the drug from the osmotic pump tablet.

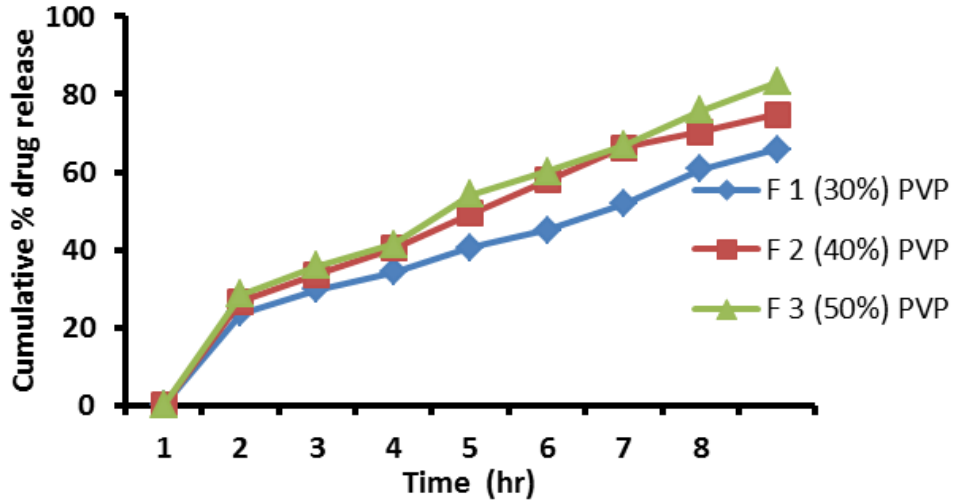


Figure 3: Comparison based on different pore forming %, *in vitro* cumulative drug release between F 1, F 2 and F 3*.

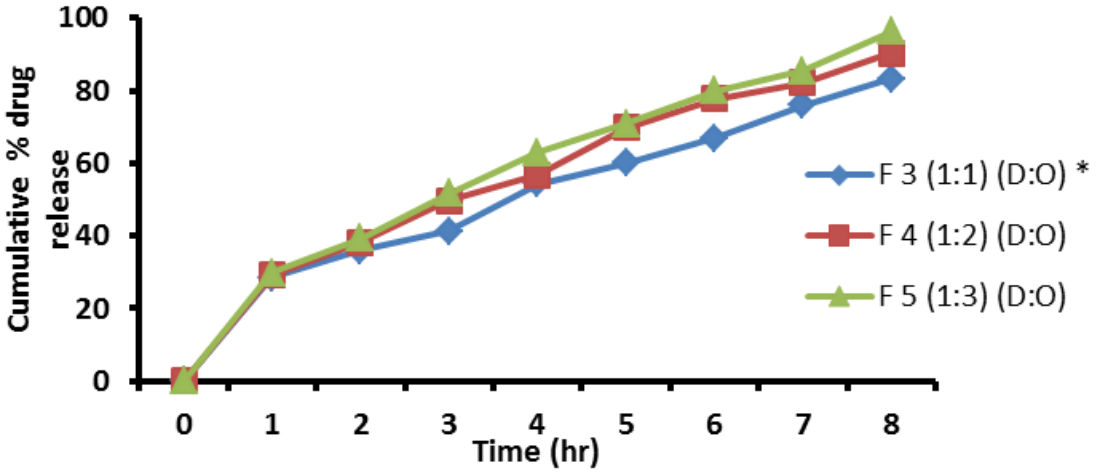


Figure 4: Comparison based on different drug: osmogent concentration,*in vitro*cumulative drug release between F 3, F 4 and F 5.

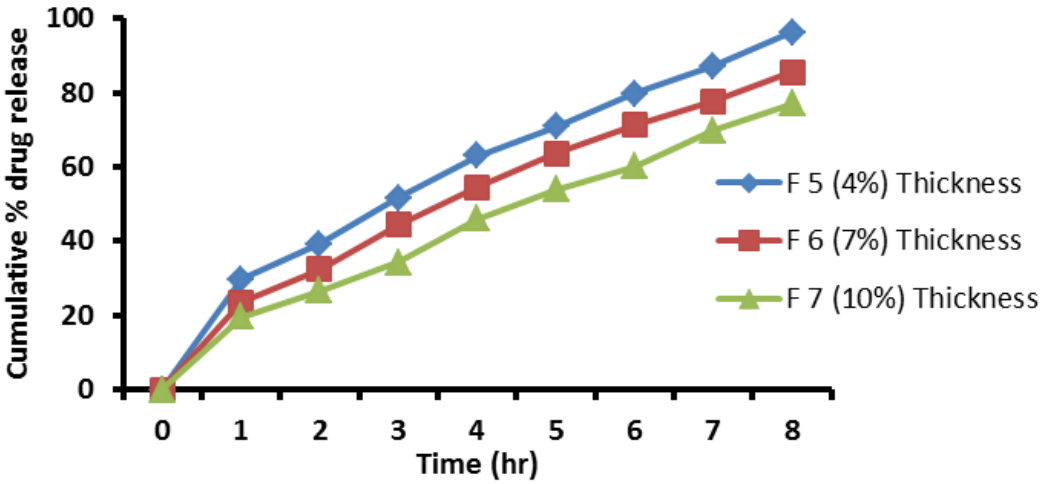


Figure 5: Comparison based on different coating thickness (%), *in vitro* cumulative drug release between F5, F6 and F7.

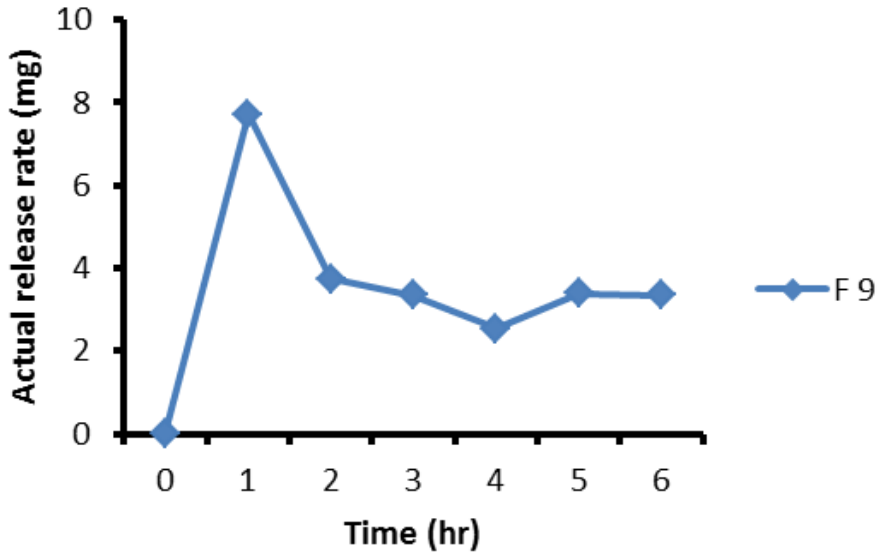


Figure 6: *Ex vivo* drug permeation profile of Nifedipine BOPT from F 9.

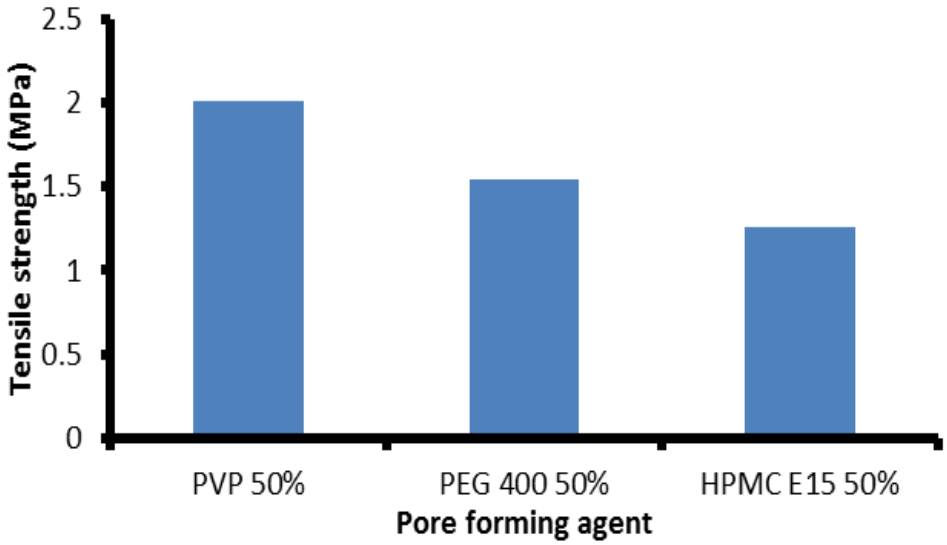
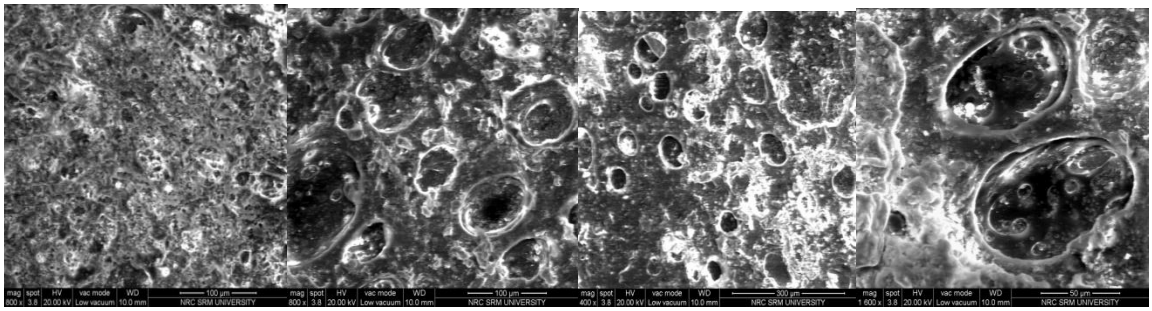


Figure 7: Strength of the membrane with different pore forming agents and thickness.



A B C D

Figure 8: Scanning Electron Microscopy study (Before, A and after, B dissolution C-50%. PVP, D- high magnification 1600x).

Wash off test

The optimised batches of Nifedipine buccal osmotic pump tablet adhered up to 218 mins to the tissue. This shows the good adhesion nature of the tablet. From this test, it is cleared that the Nifedipine BOPT has enough time to stick on buccal membrane during this period drug can release in controlled manner from the core of tablet by osmosis process.

Muco adhesive strength

The muco adhesive strength of the optimised Nifedipine buccal osmotic pump tablets from mucous membrane was found out by using the modified balance method. So the required force in terms of amount of the water used to detach the tablet from the membrane was found to be 12.7 gm. It can conclude that Nifedipine BOPT adhered properly so that it cannot detach from the membrane by lightly movement of saliva and tongue.

Ex *vivo* Permeation of the Optimized Batch

The result of the ex vivo permeation study of the optimized batch (F9) was tabulated in Table 41. The optimised batch showed good ex vivo permeation of the drug. Around 81% of the drug permeated at the end of the 6th hour **(Fig 6)**. From this test, it can show that the optimised batch Nifedipine BOPT can permeate the buccal membrane and release drug in a controlled manner. So, at the end of 6th hours ex vivo study of F9 drug release rate are showing quite similar.

Tensile Strength study

The tensile strength test of the membrane was carried out with 3 different membranes having different pore forming agent. The strength data of the membranes. Fig. 7 shows graphically the different tensile strength of the membrane. The membrane which contains PVP as pore forming agent shows average value of 2.01 MPa. This indicates that the coating membrane has enough strength to hold the osmotic pressure which creates by osmogent. This study showed the integrity of the membrane.

Scanning Electron Microscopy study

The mechanism of the drug release from the Nifedipine BOPT can be concluded by this study. Pore forming agent is used in the coating solution. The outer layer of the tablet membrane forms numbers of pores when contact with the aqueous medium, from these pores drug are fluxed from the core of the tablet in a controlled manner. Fig.8 shows the SEM study of F9 before dissolution, there is no pore on the membrane but the SEM study after dissolution, there are number of pores formed on the membrane. So, the drug can release from the core of tablet in a controlled manner.

From SEM study, it can co relate the concentration of pore forming agent to be optimised. When the concentration of pore forming agent increases as 30% (F1), 40% (F2) and 50% (F3), the release rate of drug also increase, due to increase number of pore formation and increase the size of pores on membrane, Fig 8 (A); (B), (C) and (D at higher maginification). Therefore F 3 (50 %) pore former released more drug as compare to other formulation.

Kinetics study

Dissolution data of the optimized formulation was fitted to various mathematical models (zero-order, first-order, and Higuchi) in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR) and Akaike information criterion (AIC), best goodness-of-fit test (R^2) and High value of MSE were taken as criteria for selecting the most appropriate model

Stability studies

The optimised batch (F9) were selected for stability studies and were carried out according to ICH guidelines at $40^oC \pm 2^oC$ for a specific period of time indicated that the physical parameters and the drug release characteristic were not altered significantly showing good stability on storage.

CONCLUSION

The Controlled porosity osmotic system comprising a monolithic tablet coated with cellulose acetate as a semipermeable membrane containing pore forming agents has been developed for Nifedipine. The solubility of Nifedipine was improved by the addition of 2-HP-β-CD. The desired zero order release profile was obtained by optimizing: 1. Drug: osmogent ratio 2. Concentration of pore forming agent, 3. Coating thickness of CA membrane. The drug release increased with the amount of osmogent due to the increased water uptake, and

hence increased driving force for drug release. This was retarded by the proper choice of channelling agent with adequate coating thickness in order to achieve the desired zero order release profile. The optimized system found to have sufficient strength and adhesion time in the buccal mucosa. Similarly *ex vivo* permeability study indicated release rate can be correlated to that of *in vitro* drug release profile. The formulations were found to be stable at room temperature. Results of SEM studies showed the formation of pores in the membranes after coming into contact with the aqueous environment, the number of pores being dependent on the initial level of pore former in the membrane. The system was found to deliver Nifedipine at a zero order rate for a period of **4-8**hr independent of the environmental pH and agitation intensity. This system is simple to prepare with no drilling required and can be used in the field of controlled delivery of drugs.

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