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# DEVELOPMENT OF MUCOADHESIVE GEL FOR NASAL DELIVERY OF NOISOME LOADED WITH NIMODIPINE

**Parthiban S. and Saritha A. N.***

Dept. of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagar, Mandya, Karnataka, India.

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***Corresponding Author**
**Saritha A. N.**
Dept. of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagar, Mandya, Karnataka, India.

## ABSTRACT

The aim of the present investigation was to formulate and evaluate a niosomal mucoadhesive gel containing Nimodipine. Niosomess were prepared by the thin film hydration method by using methanol as a solvent. Niosome containing Nimodipine formulations were prepared by different concentration of span 60 and cholesterol by thin film hydration technique. These formulations were evaluated for entrapment efficiency, particle size, zeta potential and in vitro drug release. Particle size and zeta potential of the F4 formulation was found to be 1256 nm, -48.1 mV respectively. The highest entrapment efficiency and drug content is observed in F4 niosomal formulation with 96.96% and 95.54% respectively. Since the formulation F4 showed maximum amount of %drug content, %drug entrapment efficiency, and drug will release in controlled manner for prolonged time. and hence F4 niosomal formulation were selected as optimized and further used for nasal niosomal mucoadhesive gel by using the Carbopol 934 at 3% w/v as a polymer (gelling agent). Further the prepared gel (GF4) was evaluated for Ex-vivo permeation study for 12 hours and it shows maximum amount of drug release in a controlled manner, further mucoadhesive nasal gel was evaluated for the mucoadhesive strength (13.22±1.05) and viscosity (9450 cps). Hencethe results clearly showed that the gels have ability to retain the drug for prolonged periods. The % CDR of mucoadhesive niosomal gel formulation GF4 was found to be 96.16% and which follows zero order. The ‘n’ values for all the formulation were found to be more than 0.5. this indicates that the release approximates non-fickian diffusion mechanism.

**KEYWORDS:** Niosome, Mucoadhesive gel, Nimodipine, Carbopol 934, nasal drug delivery span 60.

## INTRODUCTION

In the past decade, nasal route for drug delivery has established itself as an important alternative to parenteral route. This route provides higher degree of patient compliance and makes the patient more tractable. Moreover, drugs can be painlessly self-administered by the patient, which adds to the popularity of this route.[1]

Drugs administered through nasal route absorb rapidly and reach therapeutically effective plasma levels quickly due to rich vasculature and highly permeable membranes in nasal cavity. Moreover, nasal route offers additional advantage over oral route, particularly for those drugs that have poor oral bioavailability due to pH instability and enzyme degradation in the gastrointestinal tract (GIT). Further, drugs that undergo gut wall metabolism, P-glycoprotein efflux and high hepatic first pass metabolism are also benefited from nasal route of administration.[2]

In recent times, interest in intranasal route to target drugs to brain and cerebrospinal fluid circumventing blood-brain barrier has gained impetus. Intranasal formulation of drugs for treatment of Parkinson's disease Alzheimer's disease and Psychosis, have been developed and their therapeutic effectiveness over conventional oral formulations has been demonstrated. Comprehensive studies have shown the role of olfactory pathway in transport of nasally administered drugs to Central nervous system (CNS).[3]

Nasal delivery of drugs could improve better patient compliance than intravenous (i.v) administration. The nasal route has been considered as a viable and efficacious alternative for drugs which have extensive first pass metabolism. One of the major disadvantages to deliver drugs through nasal route is the mucociliary clearance. To address this issue, mucoadhesive in situ gel formulation was devised to increase the residence time in the nasal cavity.

Nasal mucosa offers advantages to deliver drugs to brain via olfactory route thus provides rapid onset of drug action and hence faster therapeutic effect. Therefore, various strategies have been proposed to improve the delivery of different drugs to brain including liposomes, colloidal drug carriers, micelles, chimeric peptide technology and nanotechnology through nasal route. The low blood level of folates is the primary cause of depression in Alzheimer's

disease. Folic acid is a water-soluble vitamin showing difficulty in crossing the blood-brain barrier and thus was formulated as niosomal nasal drug delivery systems to target the brain.[4]

The treatment of various CNS diseases has been challenging, despite the rapid development of several novel treatment approaches. The blood-brain barrier (BBB) is one of the major issues in the treatment of CNS diseases, having major role in the protection of the brain but simultaneously constituting the main limiting hurdle for drugs targeting the brain. Nasal drug delivery has gained significant interest for brain targeting over the past decades, wherein the drug is directly delivered to the brain by the trigeminal and olfactory pathway. Various novel and promising formulation approaches have been explored for drug targeting to the brain by nasal administration. Niosome have the potential to avoid problems, including low solubility, poor bioavailability, slow onset of action and enzymatic degradation.[5]

The use of bio adhesive polymers can lengthen the residence time and enhance bioavailability of drugs delivered to the nasal cavity. Chitosan-based mucoadhesive formulation to enhance the retention time and bioavailability of antibiotic to stomach was reported.[6] Polymer gels and mucoadhesive polymers have been studied for the mucosal delivery of various compounds ranging from small molecule to macromolecular drugs. The nasal bio adhesive gels might be used to provide anenhanced bioavailability compared with oral delivery and other route of administration.[7] Nimodipine is FDA-approved drug for treating subarachnoid haemorrhage induced vasospasm. Intravenous (IV) administration, the most common route of Nimodipine, causes several side effects such as hypotension, bradycardia, arrhythmias and inflammation at site of administration. Intravenous administration of Nimodipine is employed for enhancing drug bioavailability. However, it results in severe systemic side effect. But Intranasal administration of Nimodipine loaded niosome could achieve better drug targeting efficiency compared to IV Nimodipine solution with lower systemic side effects.[8]

Hence, the objective of this study is to develop an intranasal delivery system of Niosomal loaded Nimodipine using mucoadhesive gelling system which would enhance nasal residence time and absorption of drug across nasal-mucosal membrane.[9]

## MATERIALS AND METHODS

Nimodipine pure drug was purchased from Nyx pharmaceuticals pvt, ltd and span 60, cholesterol and soya lecithin, methanol, Carbopol 934 was purchased from the SD fine chemicals, Mumbai.

**Method of preparation of niosomes**

**Niosomes preparation were prepared by thin film hydration technique**

Accurately weighed amount of surfactant (span 60), soya lecithin, cholesterol and drug (Nimodipine) were taken in a clean and dry wide mouthed glass vial and methanol(3ml) was added to it. After warming, all the ingredients were mixed well with a glass rod, open end of the glass bottle was closed with a lid to prevent the loss of solvents from it and warmed-over water bath at $60^0$C-$70^0$C for about 5-10min until the surfactant mixture was dissolved completely. Then PBS (pH 7.4) was added and warmed on a water bath till clear solution was formed which was converted in to proniosomal gel on cooling. The obtained gel was stored in the same glass bottle in dark condition. Proniosomes were transformed to noisome by hydrating with phosphate buffer saline pH 7.4 by gentle mixing.[10-12]

**Table 1: Formulation design of nimodipine containing niosomes.**

| Formulation code | S:C:D | Drug | Span 60 | Cholesterol | Soya lecithin |
|---|---|---|---|---|---|
| F1 | 1:0.5:1 | 100 | 100 | 50 | 200 |
| F2 | 1:1:1 | 100 | 100 | 100 | 200 |
| F3 | 0.5:1:1 | 100 | 50 | 100 | 200 |
| F4 | 2:1:1 | 100 | 200 | 100 | 200 |

S:Span 60: C: Cholesterol, D- Drug

**Characterization of prepared niosome**

The prepared niosomes were characterized for various parameter like determination of purity, solubility, compatibility, entrapment efficiency, particle size analysis and in vitro drug release. The optimized nisomes was formulated as mucoadhesive nasal gel and evaluated for viscosity, mucoadhesive strength and Ex-vivo drug permeation study.[13]

**In vitro release study**

In vitro release study pattern of niosomal suspension was carried out in dialysis bag method. Nimodipine niosomal suspension equivalent to 10 mg was taken in dialysis bag and the bag was placed in a beaker containing 100 ml of pH: 7.4 Phosphate buffer. The beaker was placed over magnetic stirrer having stirring speed of 100 rpm and the temperature was maintained at 37+0.5°C. 1 ml sample was withdrawn periodically and were replaced by fresh buffer. The samples were assayed by UV Spectrophotometer at 239 nm using phosphate buffer pH 7.4 as blank and cumulative % of drug released was calculated and plotted against time. The drug

release was fitted to kinetic data analysis to understand the kinetic and mechanism of drug release.[14]

**Preparation of mucoadhesive gel**

Mucoadhesive nasal gels (GF3) were prepared by using Nimodipine loaded noisome (F3-Optimized formulation) in a constant stirring condition. Required amounts of polymer 934P (mixture of Carbopol 934) were added to the niosomal suspension and stirred on a magnetic stirrer until a uniform solution was obtained which was kept at 4°C overnight to allow complete swelling so that a homogeneous gel was formed. The pH of the nasal gel was maintained at 6.4. Nimodipine dose is equivalent to 30mg is incorporated in the gel.[15]

**Determination of viscosity**

Viscosity of the nasal gels was studied using Brookfield Viscometer (DV II+Pro., Brookfield Engineering Labs, USA) at five different speeds of 10, 20, 30, 60 and 100 rpm, respectively using spindle M4 and cord no. 23 at 37±1°.[16]

**Evaluation of mucoadhesive strength**

Mucoadhesive strength of each formulation was determined by measuring force required to detach nasal mucous membrane from the formulation using the same texture analyser. Freshly excised goat nasal membrane was attached to the upper probe of the instrument, and fixed amount of gel was kept below that. The upper probe was then lowered at a speed of 10 mm/min to touch the surface of the gel. A force of 0.1 N was applied for five min to ensure intimate contact between the membrane and the gel. The surface area of exposed mucous membrane was 1.13 cm2.[17]

**Ex-vivo drug permeation study**

Ex-vivo permeation study was conducted using a dialysis bag containing 100 ml of phosphate buffer (pH 6.4 0.1 M) using an excised goat nasal mucosa. The goat nose was obtained from local slaughterhouse within 15 min after the goat was sacrificed. After removing the skin, the nose was stored on ice cold phosphate buffer (pH 7.4, 0.05 M). The septum was fully exposed, and nasal mucosa was carefully removed using forceps and surgical scissors. The mucosal tissues were immediately immersed in Ringer's solution. The freshly excised nasal mucosa was mounted on the diffusion cell, and gel containing equivalent dose 30 mg Nimodipine was placed on it. Throughout the study, the buffer solution in the chamber was maintained at 37±1° by connecting thedialysis bag with water bath. At predetermined time

intervals, 1 ml of the samples was withdrawn at pre-determined time interval and replaced with an equal amount of phosphate buffer. The samples were appropriately diluted, filtered and absorbances were measured spectrophotometrically at 239 nm using Jasco V-550 UV/Vis Spectrophotometer (Tokyo, Japan), taking phosphate buffer (pH 6.4) as the blank (figure 2).[18-19]

## RESULTS

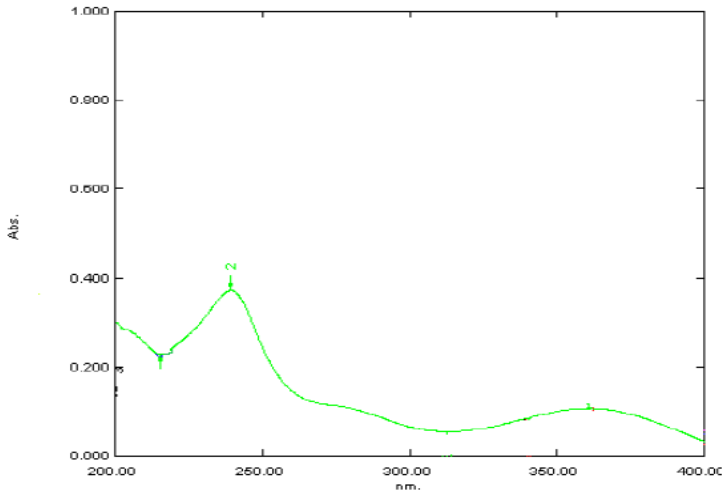


**Figure 1: ʎ max of pure drug nimodipine.**

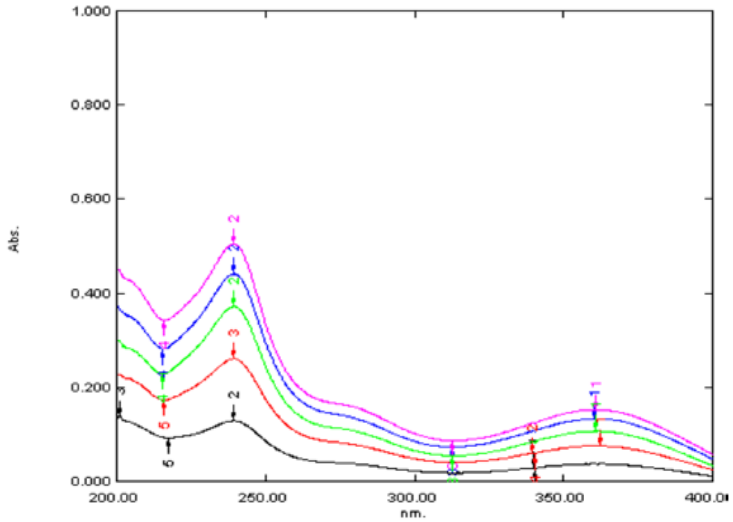


**Figure 2: Standard calibration spectra of pure drug nimodipine.**

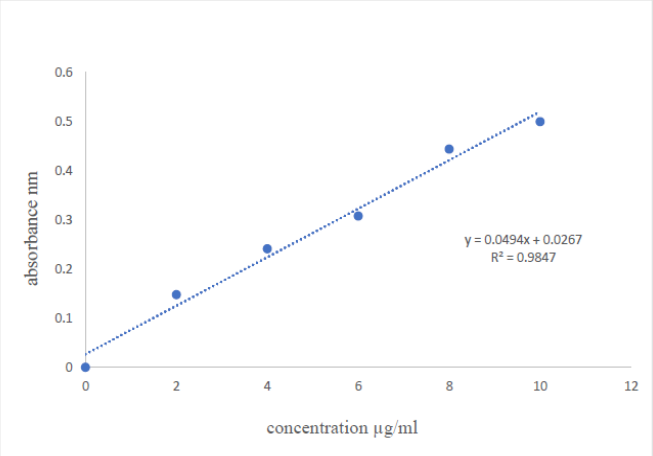


**Figure 3: Standard calibration curve of pure drug nimodipine.**

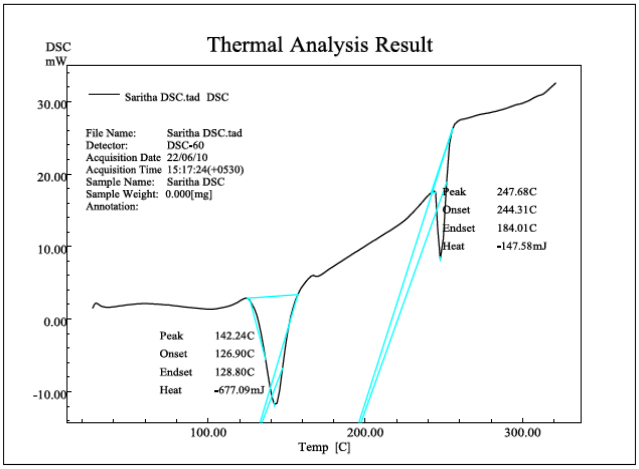


**Figure 4: Thermal analysis result.**

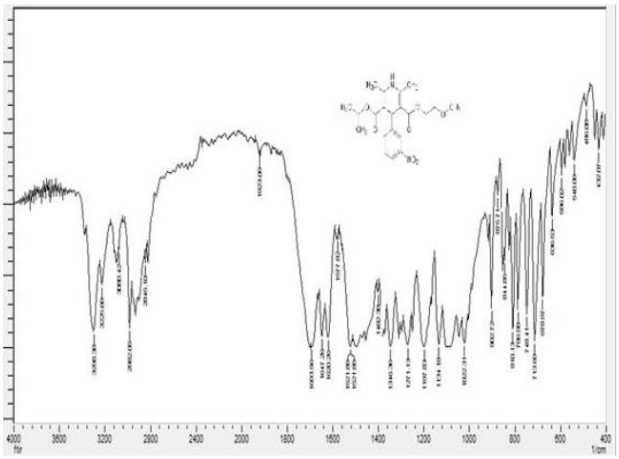

**Figure 5: FT-IR spectra of pure drug nimodipine.**

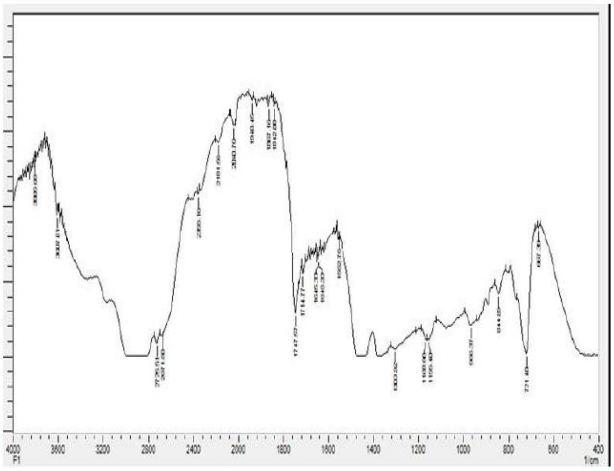

**Figure 6: FT-IR spectra of pure drug and their mixture (Drug, cholesterol, soya lecithin, span 60).**

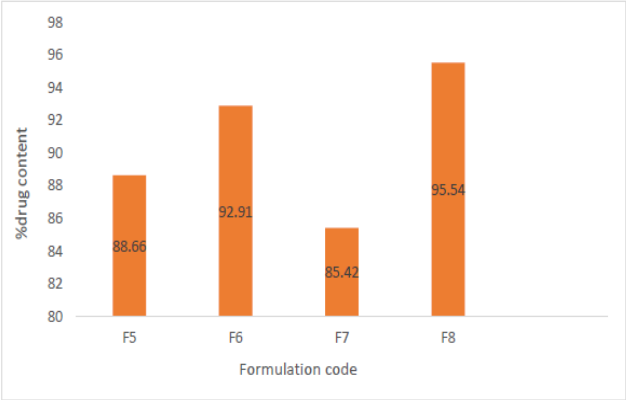


**Figure 7: Drug content of formulation F5-F8.**

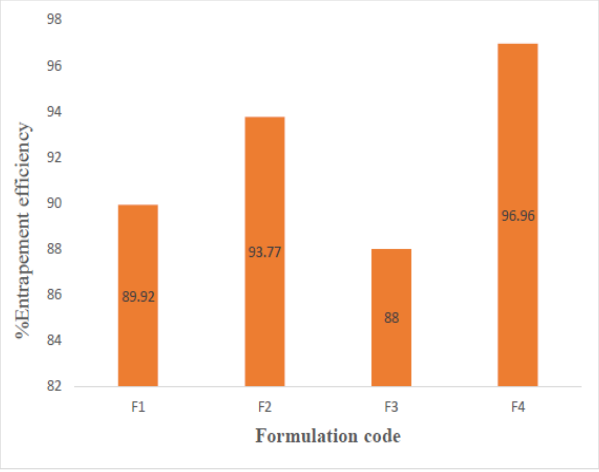


**Figure 8: % Drug entrapment efficiency of formulation F1-F4.**

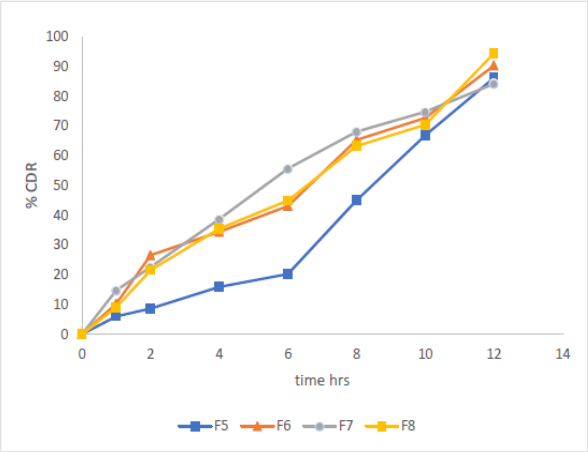


**Figure 9: In vitro release profile of niosomal formulation F1-F4.**

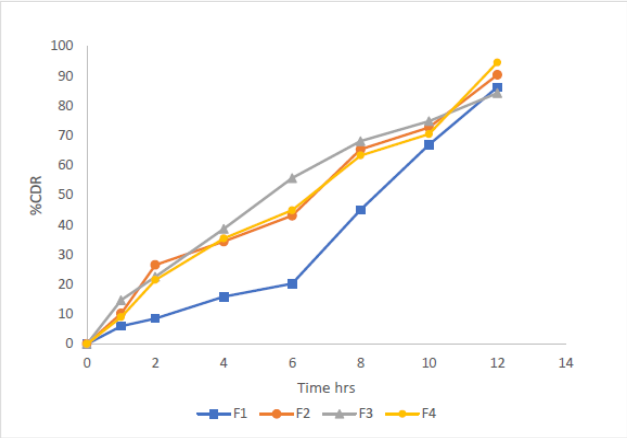


**Figure 10: Zero order release kinetics profile of F1-F4.**

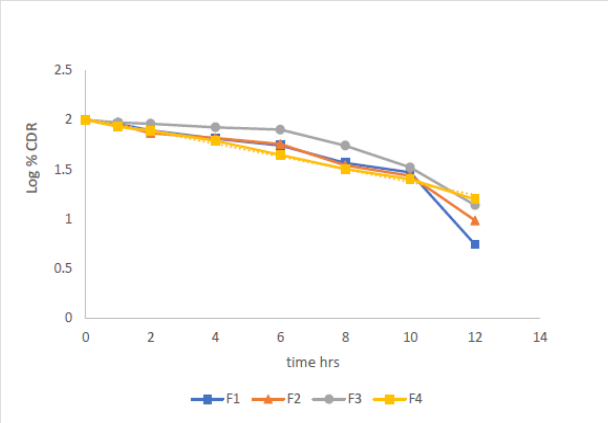


**Figure 11: First order release kinetic profile of F1-F4.**

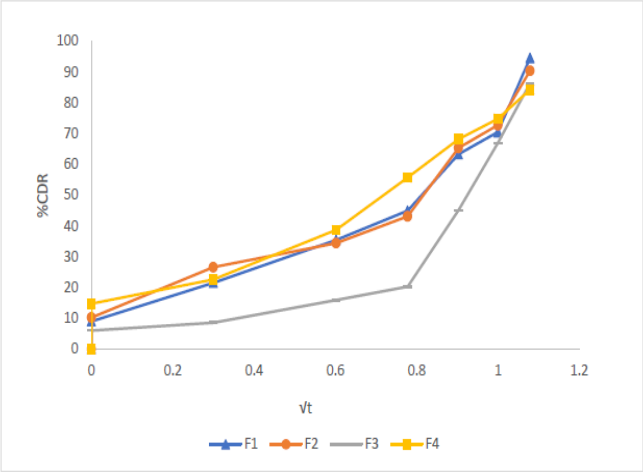


**Figure 12: Higuchi order release kinetics profile of F1-F4.**

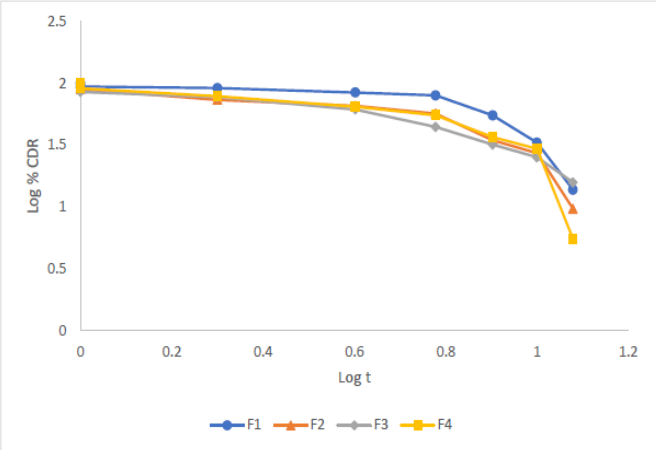


**Figure 13: Peppa's order release profile of niosomal formulation F1-F4.**

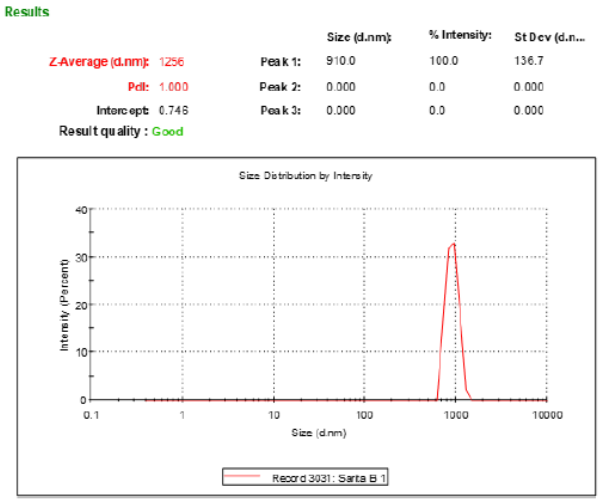


**Figure no. 14: Particle size distribution analysis.**

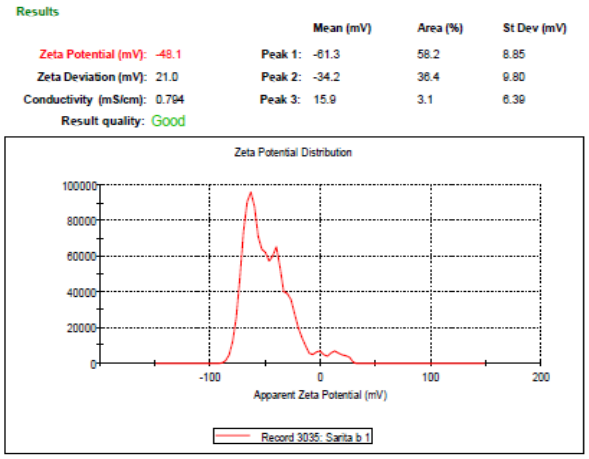


**Figure 15: Zeta potential.**

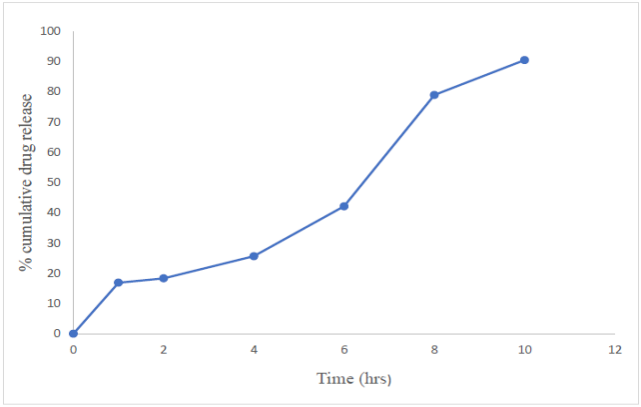


**Figure 16: Ex-vivo drug permeation GF4 formulation.**

**Table 2: Data for different kinetic models.**

| Formulation code | Zero order | First order | Higuchi plot | Peppa's plot | |
|---|---|---|---|---|---|
| | | | | r2 | 'n' |
| F1 | 0.9883 | 0.8104 | 0.9132 | 0.798 | 1.27 |
| F2 | 0.9844 | 0.8975 | 0.9144 | 0.7654 | 1.2319 |
| F3 | 0.9319 | 0.81 | 0.7341 | 0.8953 | 1.3773 |
| F4 | 0.9761 | 0.9907 | 0.9659 | 0.7278 | 1.189 |

## DISCUSSION

The purity of the drug was determined by Differential scanning calorimetry (DSC) we determined melting point of pure drug was found to be 126.09$^0$C as shown in Figure 4, observed that the value within the standard Indian pharmacopoeia (IP) limits confirming the purity of the drug.

The ʎ max of Nimodipine in phosphate buffer pH:7.4 was found to be 239nm and UV spectrum was shown in Figure 1 and 2. Standard curve of Nimodipine obeys the Beer's law

in concentration range 0-10µg/ml (Figure 3) in phosphate buffer pH 7.4 with regression of coefficient of r2= 0.9847 and slope of 0.0494. The calibration spectra of different concentration was shown in figure3.

Drug excipient compatibility studies were carried out using FT-IR. The characteristic peak obtained of pure drug (Nimodipine), and their mixture (drug, cholesterol, span 60, soya lecithin) was shown in Figure 5 and 6. The characteristic peak of pure drug also found in physical mixture indicating there was no significant interaction between the drug and excipients. Different formulations of Nimodipine niosomes were prepared by thin films hydration method using surfactants (span-60), cholesterol, methanol and chloroform. Span 60 were used as surfactants which is used to entrap wide range of drugs in niosomes. The cholesterol improves the stability of bilayer membrane of vesicles and methanol and chloroform was used as nasal penetration enhancer and for providing softness to the vesicles. The particle size analysis also done by using Malvern particle size analyser for the optimized formulation of F4. The average particle size was found to be 1256 nm. The data was shown in Figure 14.

The percentage entrapment efficiency of Nimodipine in different niosomal formulations were shown in and Figure 8. Highest Entrapment efficiency was observed in F4 with 94.46 %. The high drug entrapment may be observed due to increase in the surfactant ratio. Drug content for all formulation was shown in Figure 7. F2 & F4 formulation having maximum amount of drugcontent because of increased entrapment efficiency. Formulation F1 & F3 having lesser amount of drug content compare to the formulation F2 and F4 due to increased surfactant ratio.

Zeta potential is a key factor for evaluation of the stability of colloidal dispersion. It was currently admitted that zeta potentials above -30mV were required for full electrostatic stabilization. The zeta potential was measured for the optimized Formulations F4. The values of zeta potential of Nimodipine loaded niosomal formulation F3 was found to be -48.1mV which are shown in Figure 14

In vitro release study of Nimodipine from various niosomal formulations was conducted for 12 hrs by using dialysis membrane. Cumulative % drug release was plotted against time (t). The % drug release from F1-F4 was observed as follows F1-86.20 %, F2 90.33 %, F3- 84.19 %, F4-94.46 %. The increase in surfactant (span 60) ratio from F1 to F4 causes increase in

the drug release, the release was more controlled by increasing the surfactant ratio. All the formulation released the drug in a controlled manner. The in vitro release data were shown in Figure 9. In vitro release profiles of all the formulation were fitted to various kinetic model and from the results Table 2. and release profile represented graphically in Figure 10,11,12,13 and it was found that all the formulation follows zero order. The 'n' values for all the formulation were found to be more than 0.5. This indicates that the release approximates non-fickian diffusion mechanism. The formulation F4 showed maximum amount of %drug content, %drug entrapment efficiency, and drug will release in controlled manner for prolonged time. and hence F4 niosomal formulation were selected for as optimized and further used for nasal niosomal mucoadhesive gel. The viscosity of gels of various formulations was determined and formulation GF4 showed 9450 cps. Mucoadhesive strength of the formulation was determined by measuring force required to detach nasal mucous membrane from the formulation using the same texture analyser. And the value was found to be 13.22±1.05 g. The result of in vitro release of Nimodipine from the gel formulation is given in Figure 16. However, the results clearly showed that the gels have ability to retain the drug for prolonged periods. The % CDR of mucoadhesive niosomal gel formulation GF4 was found to be 96.16% and which follows zero order. The ‘n’ values for all the formulation were found to be more than 0.5. this indicates that the release approximates non-fickian diffusion mechanism.

## CONCLUSION

The present study demonstrated the successful preparation of Nimodipine loaded niosomes and their evaluation. Since Nimodipine is having poor solubility and stability problem, the entrapment of Nimodipine in to niosomal carrier increases the solubility and stability and when it combined with mucoadhesive gel through nasal route it can overcome the problem associated with poor bioavailability of Nimodipine and also enhances the controlled drug delivery through nasal drug delivery system which could offer better therapeutic effect.

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