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FORMULATION AND EVALUATION OF MUCOADHESIVE GEL FOR NASAL DELIVERY OF NOISOME LOADED WITH NIMODIPINE

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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 40 and cholesterol by thin film hydration technique. These formulations were evaluated for entrapmentefficiency, particle size, zeta potential and in vitro drug release. Particle size and zeta potential of the F3 formulation was found to be 736.9nm, -51.9 mV respectively. The highest entrapment efficiency and drug content is observed in F3 niosomal formulation with 96.35% and 94% respectively. Since the formulation F3 showed maximum amount of %drug content, %drug entrapment efficiency, and drug will release in controlled manner for prolonged time. and hence F3 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 (GF3) 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 (9.63±1.02) and viscosity(11450cps). Hence the results clearly showed that the gels have ability to retain the drug for prolonged periods. The % CDR of mucoadhesive niosomal gel formulation GF3 was found to be 94.73% 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.

INTRODUCTION
The nasal route is a significant mode of drug delivery and nasal cavity has been widely explored for more than three decades. This route is a potential alternative routeto parenteral or oral administration for therapeutically active drugs. The nasal route has shown remarkable advantages with an increasing number of products existing for administration through the route for systemic and local administration that include a rapid and high systemic availability. This drug delivery system avoids first pass metabolism by the liver, and the opportunity of targeting drugs directly from the nasal cavity to the brain.[1] Nasal delivery is considered to be a promising administration route to get faster and superior stage of medicine absorption. Nasal mucosa has been considered as a potential since nose has a great surface area existing for remedy absorption.[1]

Niosomes are promising vehicle for drug delivery and being non-ionic; and Niosomes are biodegradable, biocompatible non-immunogenic and exhibit flexibility in their structural characterization. Niosomes have been widely used for controlled release and targeted delivery for the treatment of cancer, viral infections and other microbial diseases. Niosomes are drug carrier systems which have been employed asa substitute to liposomes. They are non-ionic surfactant vesicles in aqueous medium resulting in closed bilayer structure that can be used as carrier of amphiphilic and lipophilic drugs. Main ingredient of niosomes is non-ionic surfactant which give it an advantage of being more stable when compared to liposomes thus overcoming the problems associated with liposomes i.e., susceptibility to oxidation, high cost and the difficulty in producing high purity levels which influence size, shape and stability. Niosomes mainly acts as drug depot in the body which releases the drug in a controlled manner through its bilayer providing sustained release of the enclosed drug.[2] Niosomes are microscopic-lamellar, spherical, unilamellar and multilamellar structures which are formed on the admixture of non-ionic surfactant (span 20, span 40, span 60) and cholesterol with subsequent hydration in aqueous media (distilled water).[3]

Mucoadhesive nasal gels are the most prominent non-invasive dosage forms through which a drug can reach

systemic circulation directly without undergoing first pass effect and this enhances underlying bioavailability of the drug.[4]

Nimodipine is a calcium antagonist of the 1,4-dihydropyridine family that produces relaxation of arterial smooth muscle. In animal models it preferentially dilates cerebral blood vessels and increases cerebral blood flow. It has been suggested that Nimodipine may exert a cytoprotective influence by decreasing calcium influx into nerve cells. These properties constitute the pharmacological basis for investigating the effectiveness of Nimodipine in disorganization such as subarachnoid haemorrhage, stroke, severe head injury, cerebral resuscitation after cardiac arrest, impaired brain function in old-age and senile dementia.[5]

MATERIALS AND METHODS

Nimodipine pure drug was purchased from Nyx pharmaceuticals pvt, ltd, and span 40, cholesterol and soya lecithin, methanol, Carbopol 934 was purchased from the SDfine chemicals, Mumbai.

Method of Preparation of niosomes

Niosomes preparation were prepared by thin film hydration technique Accurately weighed amount of surfactant (span 40), 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 indark condition. Proniosomes were transformed to noisome by hydrating with phosphate buffer saline pH 7.4 by gentle mixing.[6]

Table 1: Formulation design of Nimodipine containing niosomes.

Formulationcode	S:C:D	Drug	Span 40	cholesterol	Soya lecithin
F1	1:0.5	100	100	50	200
F2	1:1	100	100	100	200
F3	0.5:1	100	50	100	200
F4	2:1	100	200	100	200

S-Span 40: 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 permeationstudy.[8-10]

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.[11]

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 homogenous 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.[12]

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°.[13]

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 upperprobe 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 5 min to ensure intimate contact between the membrane and the gel. The surface area of exposed mucous membrane was 1.13 cm^2.[14]

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 the Franz diffusion cell with water bath. At predetermined time intervals, 1 ml of the samples was withdrawn at predermined 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).[15,16]

RESULTS

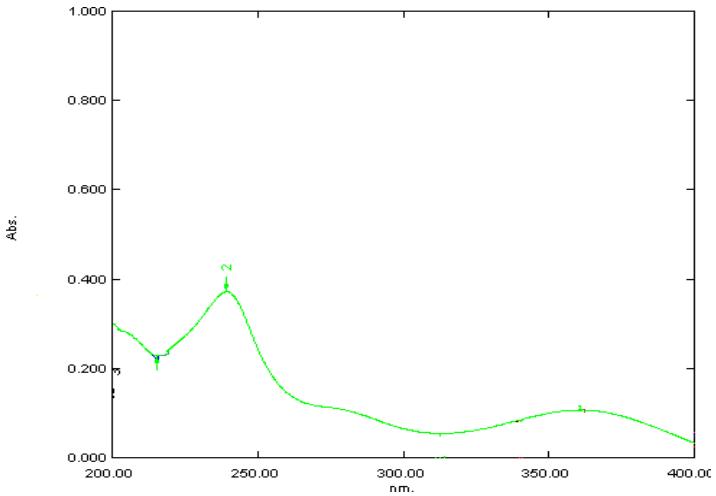

Figure 1: λ max of pure drug Nimodipine.

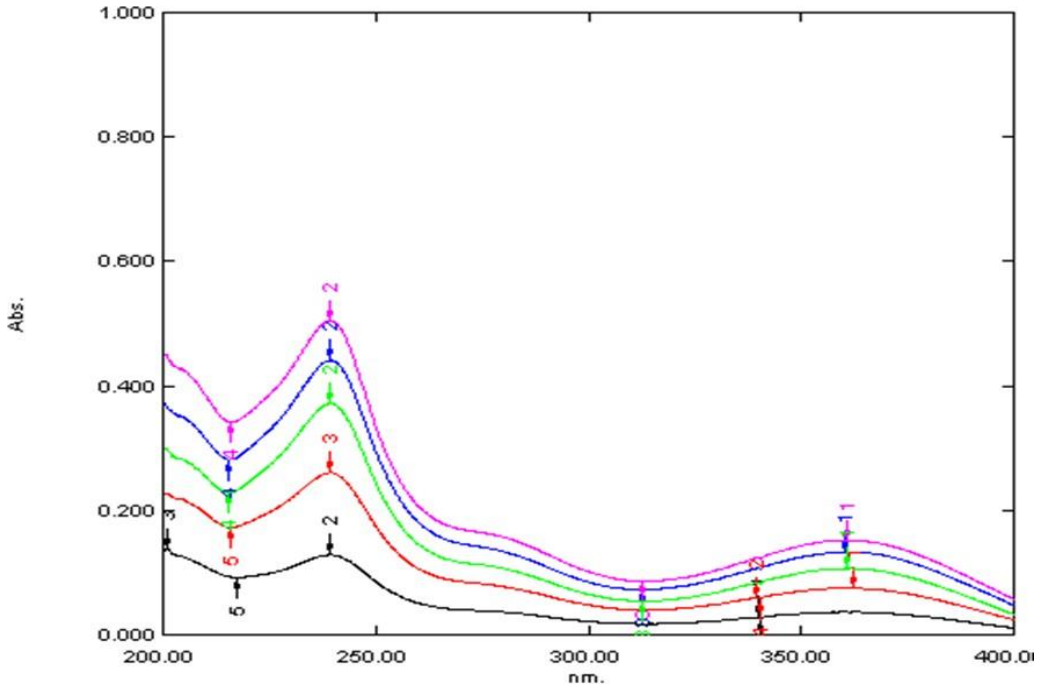

Figure 2: Standard calibration spectra of pure drug Nimodipine.

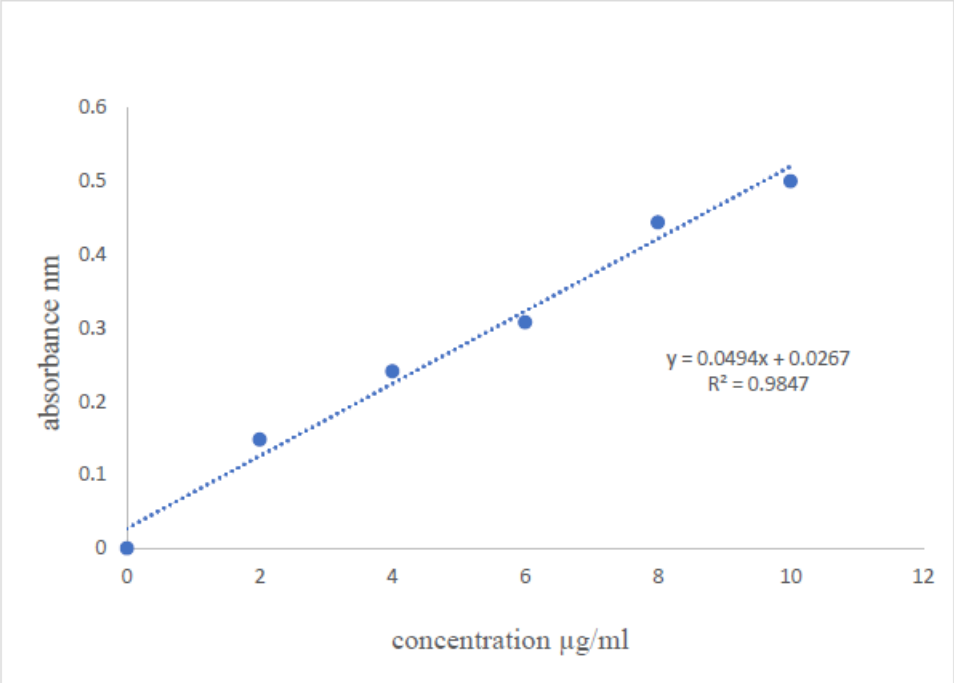

Figure 3: standard calibration curve of pure drug nimodipine.

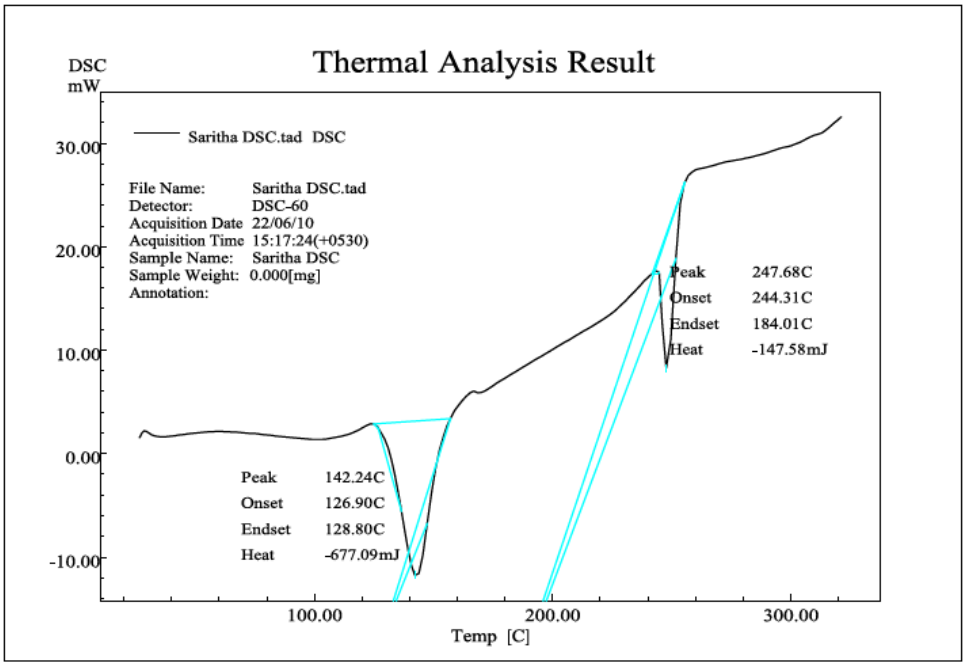

Figure 4: Thermal analysis result.

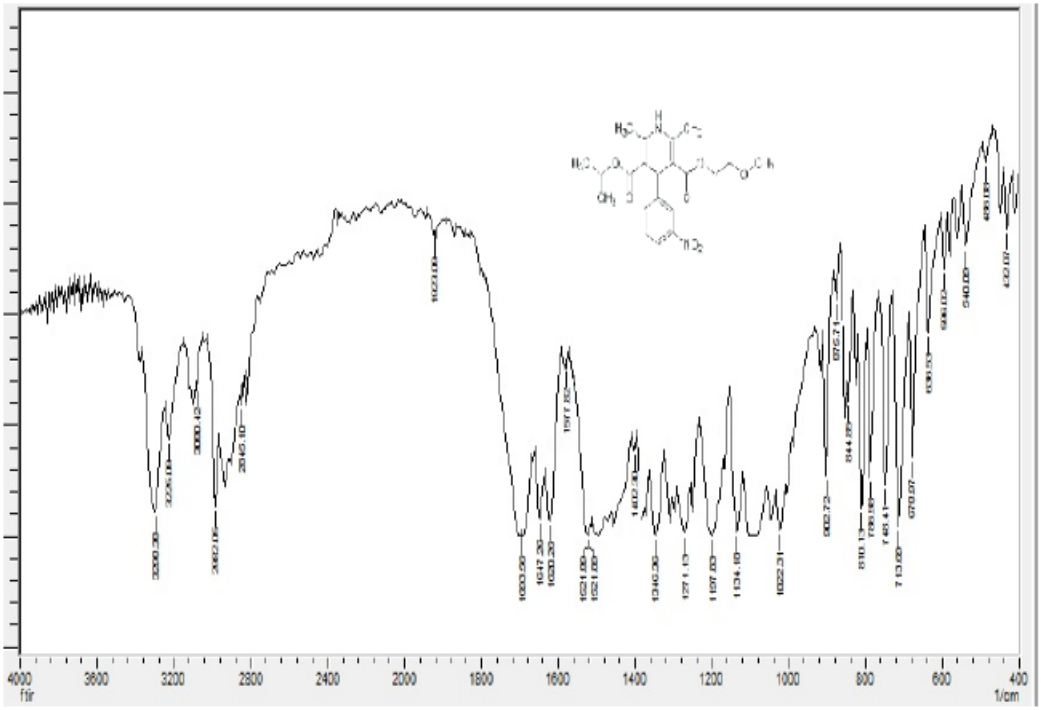

Figure 5: FT-IR spectra of pure drug Nimodipine.

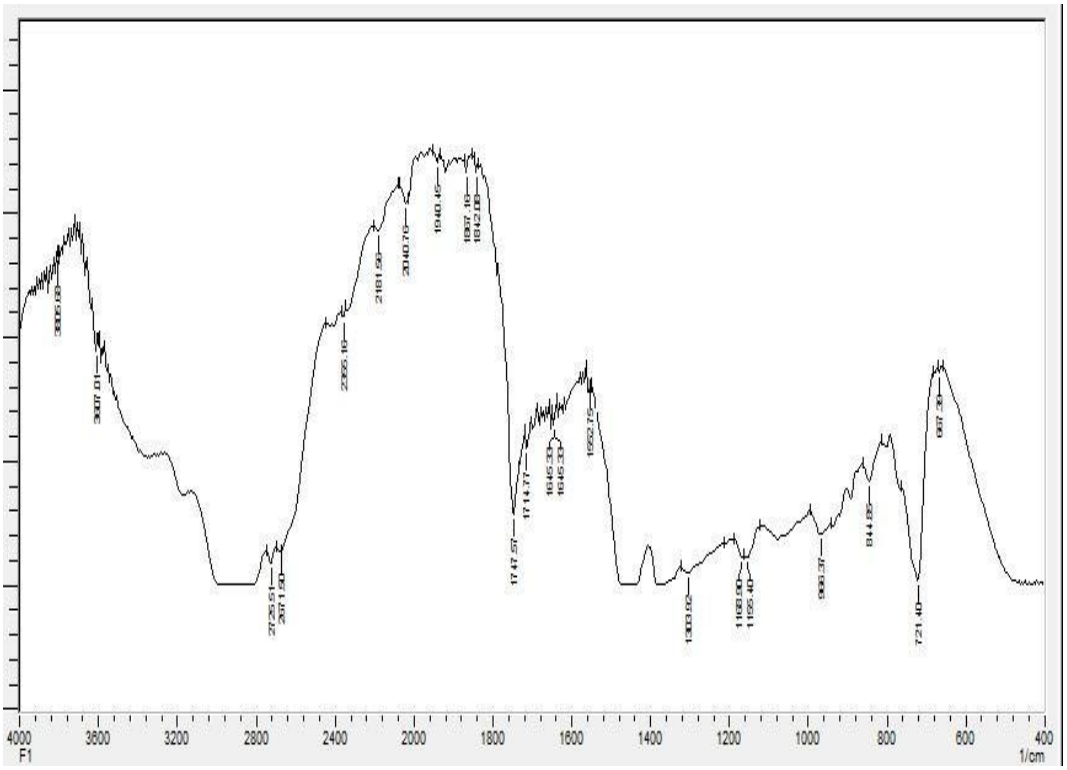

Figure 6: FT-IR spectra of pure drug with span40.

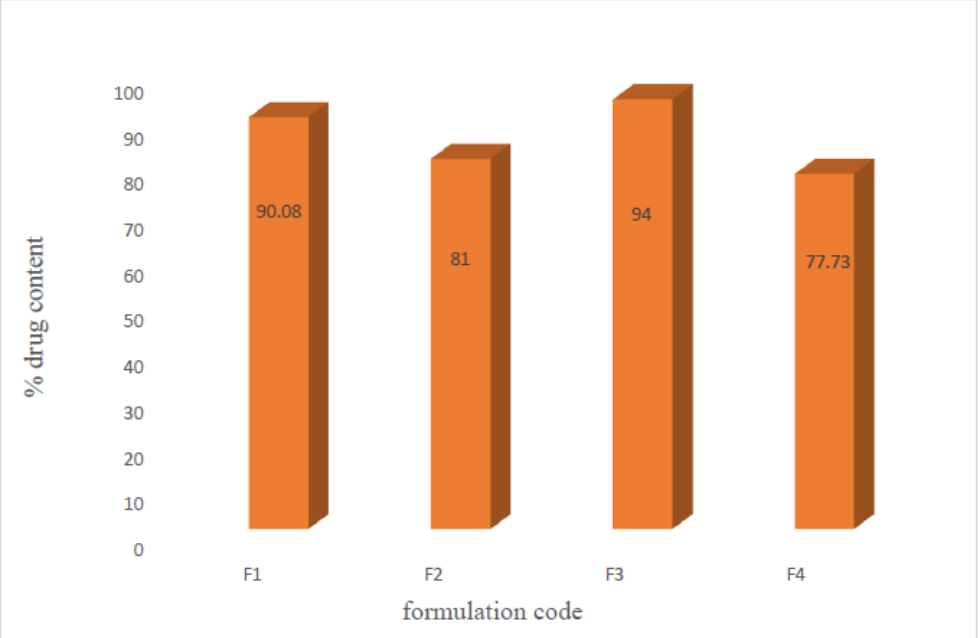

Figure 7: Drug content of formulation F1-F4.

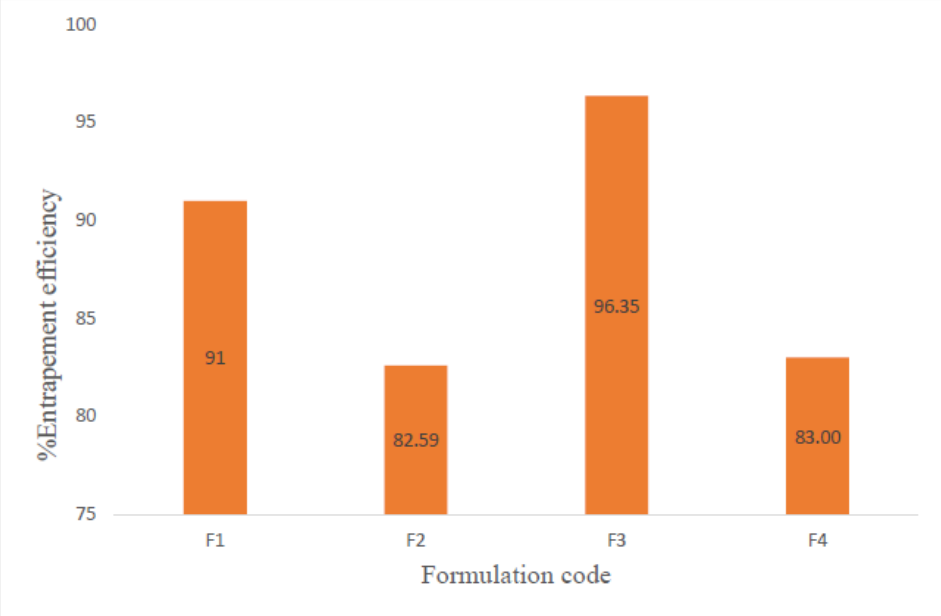

Figure 8: % drug entrapment efficiency of formulation F1-F4.

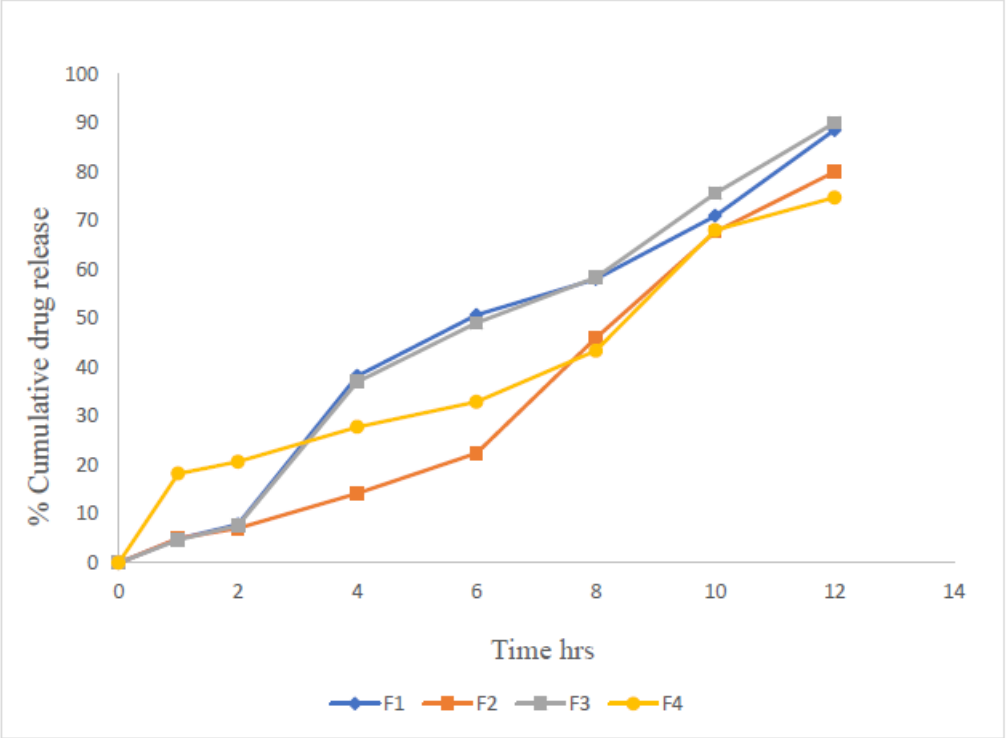

Figure 9: In vitro release profile of niosomal formulation F1-F4.

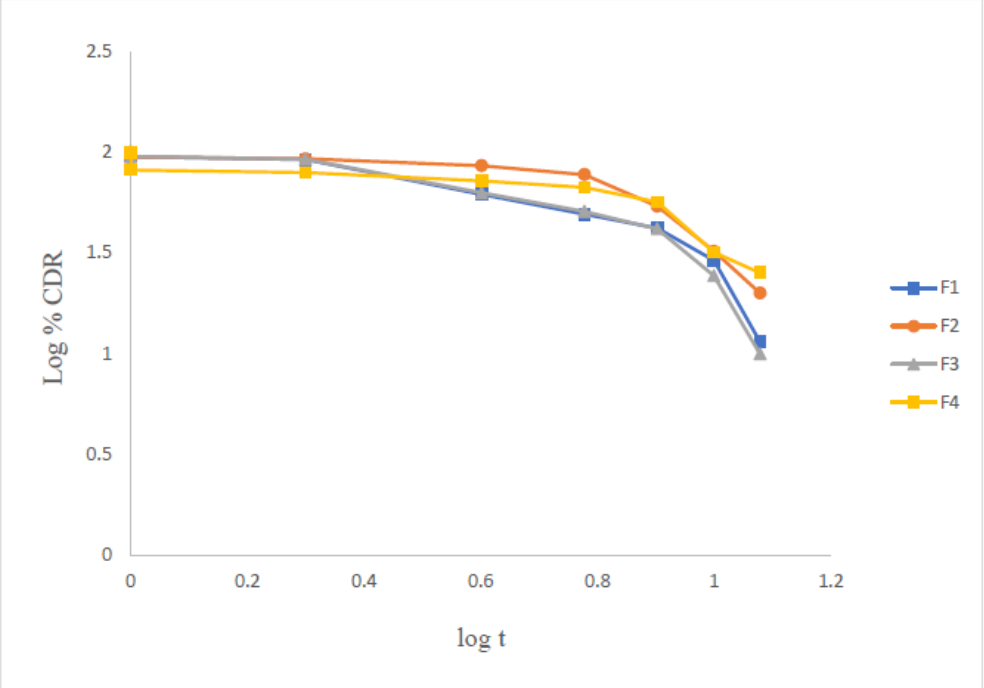

Figure 10: Peppa's order release profile of niosomal formulation F1-F4.

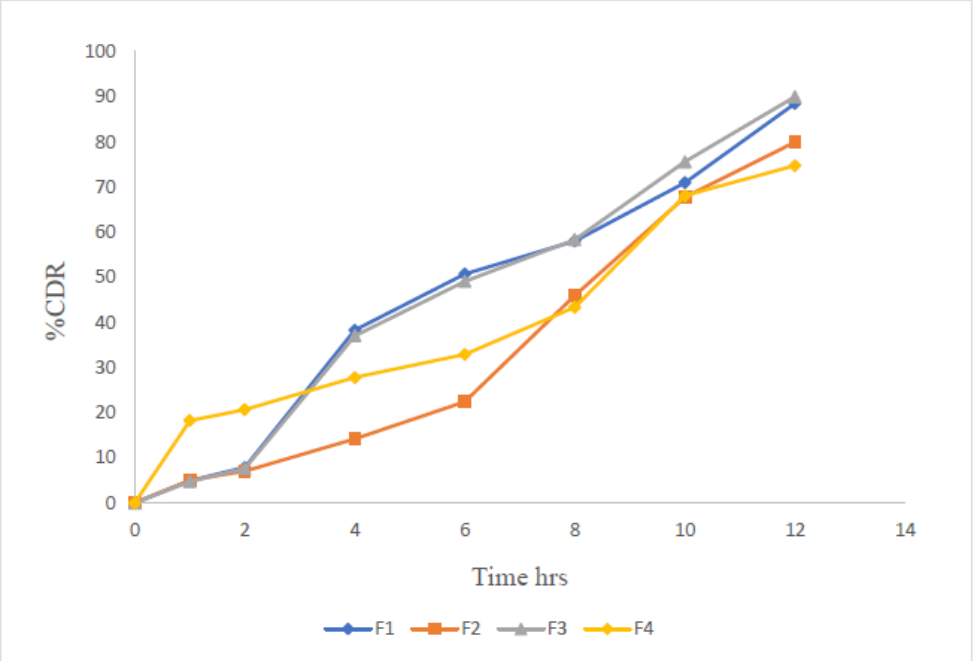

Figure 11: Zero order release kinetics profile of F1-F4.

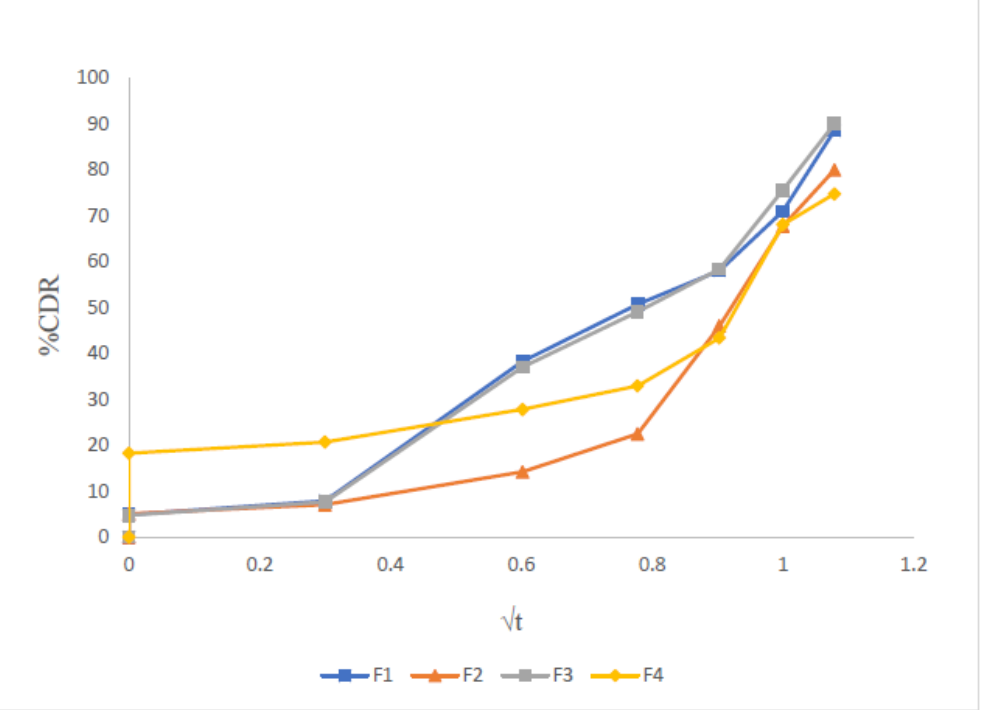

Figure 12: Higuchi order release kinetics profile of F1-F4.

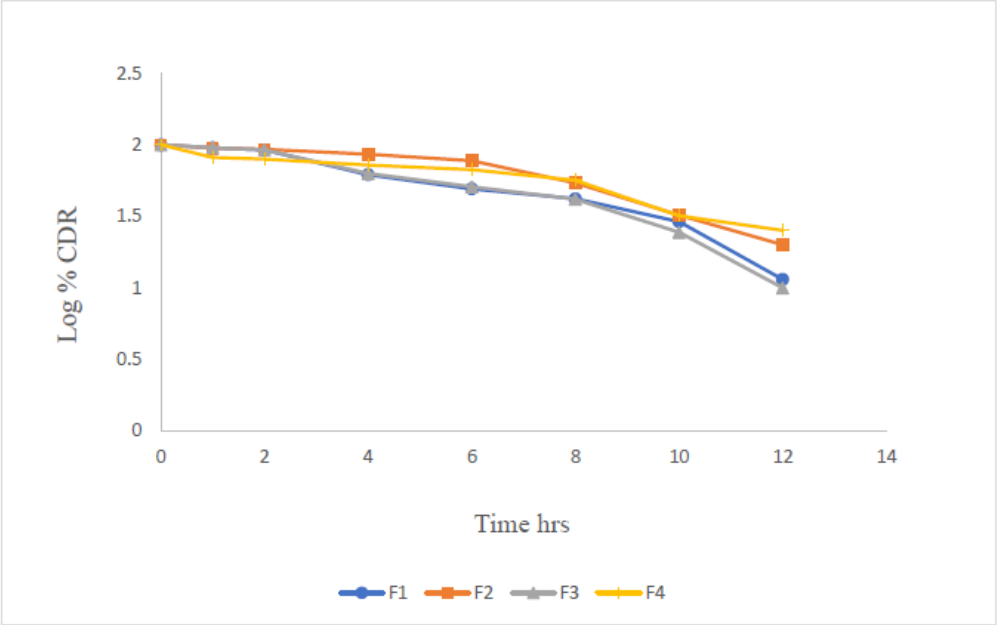

Figure 13: first order release kinetic profile of F1-F4.

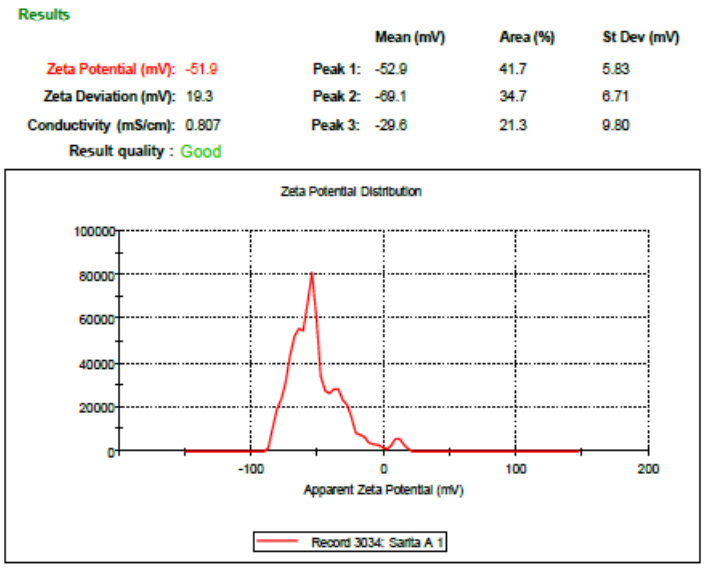

Figure 14: zeta potential.

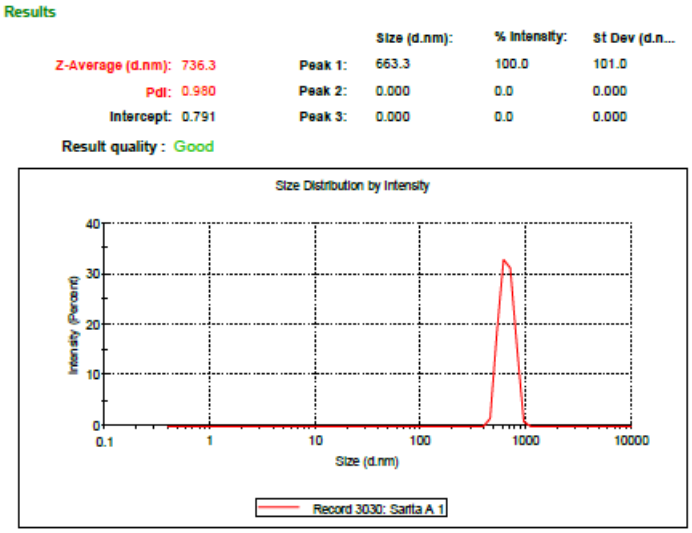

Figure 15: Particle size distribution analysis.

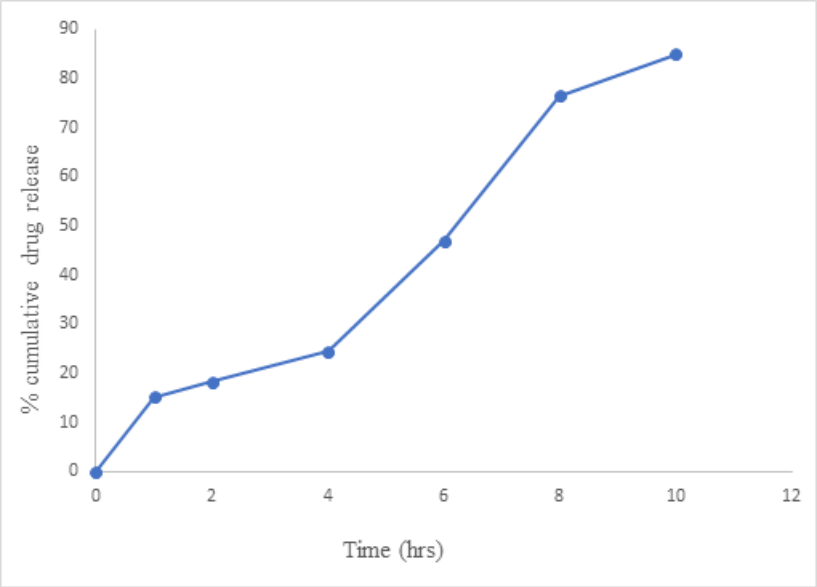

Figure16: Ex-vivo drug permeation GF3 formulation.

Table 2: Data for different kinetic models.

Formulationcode	Zero order	First order	Higuchiplot	Peppa'splot	'n' values for Peppa's
F1	0.9651	0.9184	0.943	0.8945	1.479
F2	0.9481	0.8766	0.7626	0.9229	1.4379
F3	0.973	0.9039	0.9329	0.8945	1.4934
F4	0.9401	0.8771	0.7884	0.6655	1.052

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 Cas 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 r^2= 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 40, 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-40), cholesterol, methanol and chloroform. Span 40 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 F3. The average particle size was found to be 736.9 nm. The data was shown in Figure 15.

The percentage entrapment efficiency of Nimodipine in different niosomal formulations were shown in and Figure 8. Highest Entrapment efficiency was observed in F3 with 96.35%. The high drug entrapment may be observed due to increase in the surfactant ratio. Drug content for all formulation was shown in Figure 8. F1 & F3 formulation having maximum amount of drug content because of increased entrapment efficiency. Formulation F2 & F4 having lesser amount of drug content compare to the formulation F1 and F3 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 F3. The values of zeta potential of Nimodipine loaded niosomal formulation F3 was found to be -51.9mV 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 F1-88.53%, F2 79.97%, F3-90.01%, F4- 74.74%. The increase in surfactant (span 40) ratio from F1 to F4 causes decrease 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 F3 showed maximum amount of %drug content, %drug entrapment efficiency, and drug will release in controlled manner for prolonged time. and hence F3 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 GF3 showed 11450 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 9.63±1.02 g. The result of in vitro release of Nimodipine from the gel formulation is given in Figure 16. However, the results clearly showed that thegels have ability to retain the drug for prolonged periods. The % CDR of mucoadhesive niosomal gel formulation GF3 was found to be 94.73% 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-fickiandiffusion 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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