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Design, Development and Characterization of Nifedipine Microspheres

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ABSTRACT

Back ground: Nifedipine is a calcium channel blocker and is used in treatment of angina of angina pectoris and hypertension. Nifedipine readily and almost completely absorbed from GIT, but undergoes first pass metabolism, resulting in low oral bioavailability is about 50%.

Aim: The aim of the present study was to prepare and evaluate the microspheres of nifedipine with a goal of improving the bioavailability and giving a prolonged release of drug.

Method: Emulsification (o/w) solvent evaporation method was employed in the preparation of nifedipine microparticles using ethyl cellulose and combination of ethyl cellulose and hydroxypropyl methylcellulose as the polymers.

Results: FT-IR spectra of physical mixture showed no significant shifting of the peaks therefore it reveals that the drug is compatible with the polymer used. The percentage yield obtained in all the formulations was good and in the range of 59.25-94.44%. Among all the formulations, formulation with combination of ethyl cellulose and hydroxypropyl methylcellulose polymers M_9 showed high amount of drug release i.e. (91.23%) in 12hrs. Drug release from microspheres with small mean particle size was faster than those with large mesh particle size and followed Higuchi model of kinetics.

Conclusion: The obtained results could be used as essence to develop microspheres, which bypasses first-pass metabolism and results in the improvement of bioavailability. Hence, the present study has been a satisfactory attempt to formulate microspheres of nifedipine, with a view of improving its oral bioavailability and giving a prolonged release of drug.

Keywords: Microspheres, nifedipine, hydroxypropyl methylcellulose E5, ethyl cellulose.

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INTRODUCTION

Microencapsulation is one of the newly developed techniques. Microencapsulation for oral use has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided. Microencapsulation is used to modify and retard drug release. Due to its small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa[1].

Microencapsulation is a process of incorporating drugs into small size multi particulate units. As a process it is a means of applying relatively thin coatings to small particles of solids or droplets of liquids. Microencapsulation developed for use in medicine consists of solid or liquid core material containing one or more drugs enclosed in coating material[2]. The core may also be referred as nucleus and the coating as wall or sheet. In the present study microencapsulation was selected as a method to design sustained release dosage forms because it is a rapidly expanding technology. In this method relatively thin coatings are applied to small particles of solids or droplets of liquids and dispersions. Microencapsulation also used in converting liquids to solids, altering colloidal and surface properties, providing

environmental protection and in controlling the release characteristics or availability of coated materials.

Nifedipine is a calcium channel blocker available in yellow, crystalline powder, thermostable and non-hygroscopic in nature. It is insoluble in water, freely soluble in acetone and sparingly soluble in ethanol[3,4]. The bioavailability of nifedipine is 50% and it binds with plasma to about 96%. Its half-life is 2-3hrs and effective concentration is about 15ng/ml. Nifedipine readily and almost completely absorbed from GIT, but undergoes first pass metabolism. The volume of distribution after oral administration was found to be 1.32L/kg[5]. Nifedipine is used in treatment and prophylaxis of angina of angina pectoris, Reynaud's syndrome and hypertension. Therefore, preparation of a sustained release formulation may be desirable.

MATERIALS AND METHODS

Materials

Nifedipine was a gift sample from Medreich Ltd., Bengaluru, Karnataka, India. Hydroxypropyl methylcellulose E5 and ethyl cellulose were gift samples from Dr. Reddy's Laboratories, Hyderabad, Telangana, India. Dichloromethane AR and acetone were procured from Merck Ltd., Mumbai, India. PVP was purchased from Fine chemicals, Chandigarh, India. Disodium hydrogen Phosphate was purchased from SD Fine Chem Ltd., Mumbai, India.

Methods

Pre-formulation studies

Organoleptic properties

The organoleptic character of the drug like color, odor and appearance play an important role in the identification of the sample, and hence they should be recorded in a descriptive terminology.

Solubility studies

It is important to know about solubility characteristics of a drug in aqueous systems, since they must possess some limited aqueous solubility to elicit a therapeutic response. Solubility was carried out in water, 0.1N HCl, 0.1N NaOH, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer.

Determination of melting point

Melting point of the drug was determined by capillary tube method. Take a small amount of the drug in a capillary tube closed at one end and was placed in Thieles melting point apparatus and the temperature at which the drug melts were noted. Average of triplicate readings was taken.

Determination of absorption maxima values (λ_{max})

Standard stock solution of drug (100µg/ml) was prepared in 7.4 pH phosphate buffer. For the selection of analytical wavelength, solution of nifedipine of concentration 30µg/ml was prepared by appropriate dilution of standard stock solution with phosphate buffer pH 7.4 and scanned in the spectrum range from 200 to 400nm. From this overlain spectrum of the drug, the wavelength with maximum absorbance was chosen for further analysis.

Construction of standard calibration curve of nifedipine:

Preparation of standard calibration curve of nifedipine in 7.4 pH phosphate buffer

Procedure:

Preparation of standard solution

1st Stock: 1000µg/ml solution of nifedipine was prepared by dissolving 100 mg of nifedipine in 10ml methanol and the volume was made up to 100ml with 7.4 pH phosphate buffer.

2nd Stock: Pipette 10ml of above solution into another 100ml of volumetric flask and the volume was made up to mark with the 7.4 pH phosphate buffer. (i.e.: 100µg/ml in 7.4 pH buffer).

The above second stock solution was serially diluted with 7.4 pH phosphate buffer to get the final concentrations of 10, 20, 30, 40, 50 and 60µg/ml. The absorbance of each concentration was measured 254nm using UV-Visible spectrophotometer and graph was plotted against the concentration and absorbance[6].

Drug and excipients compatibility study

To investigate any possible interactions between the drug and excipients used, the FT-IR spectra of pure nifedipine and its physical mixture with ethyl cellulose and hydroxylpropyl methylcellulose were carried out using Bomem FT-IR MB-II spectrophotometer. The samples were prepared as KBr (potassium bromide) disks compressed under a pressure of 10 Ton/nm^2. The wave number selected ranged between 400 and 4800cm^{-1}.

Preparation of nifedipine microspheres

Emulsification (o/w) solvent evaporation method was employed in the preparation of nifedipine microparticles using ethyl cellulose and combination of ethylcellulose and hydroxylpropylmethylcellulose as the polymers. Polymer was dissolved in 10ml of dichloromethane. To this 45mg of drug was added and mixed thoroughly. The above organic phase was added drop wise to 100ml of 1% PVA solution under magnetic stirrer at 800 rpm by keeping at 40 ^{0}C and stirring is continued until total evaporation of dichloromethane[7,8]. Then the solution was filtered and product was dried. Different formulations were prepared by taking different drug to polymer ratios 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5 and 1:4 and 1:1, 1:2, 1:3 and 1:4 of ethylcellulose and combination of equal ratios of ethylcellulose and hydroxylpropylmethylcellulose respectively. The prepared particles were evaluated for particle size, encapsulation efficiency, drug-polymer interaction by FT-IR and *in-vitro* drug release.

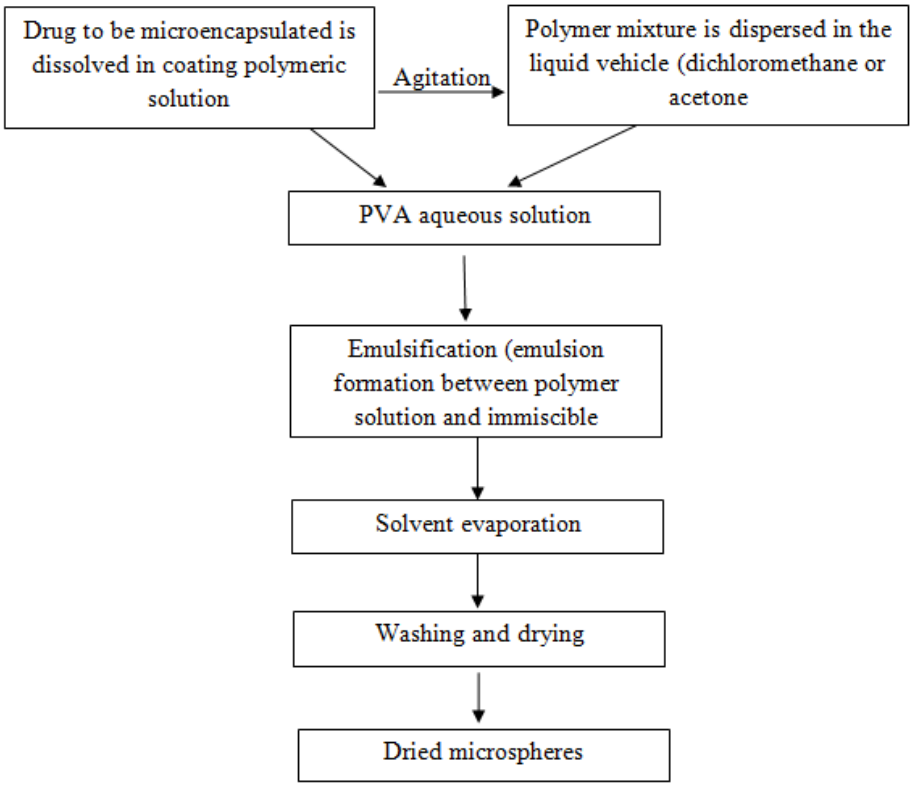

Figure 1: Formulation of nifedipine microspheres

Table 1: Formulation composition of nifedipine microspheres

Formulation code	Drug(mg)	HPMC E5 (mg)	Ethyl cellulose N50 (mg)	DCM (ml)	Acetone (ml)	PVA (%)	Drug : Polymer
M_1	45	22.5	_	10	_	1	1:0.5
M_2	45	45	_	10	_	1	1:1
M_3	45	67.5	--	10	_	1	1:1.5
M_4	45	90	_	10	_	1	1:2
M_5	45	112.5	_	10	_	1	1:2.5
M_6	45	135	_	10	_	1	1:3
M_7	45	157.5	_	10	_	1	1:3.5
M_8	45	180	_	10	_	1	1:4
M_9	45	22.5	22.5	5	5	1	1:1
M_{10}	45	45	45	5	5	1	1:2
M_{11}	45	67.5	67.5	5	5	1	1:3
M_{12}	45	90	90	5	5	1	1:4

Characterization of microspheres[9-12]

Percentage yield

Microspheres dried at room temperature were weighed and the yield of microspheres was calculated using the formula[11,12].

$$\text{Percentage yield} = \frac{\text{The amount of microspheres obtained}}{\text{The amount (gm)of non} - \text{volatile material taken}} \times 100$$

Encapsulation Efficiency

To determine encapsulation efficiency, 100mg accurately weighted microspheres were washed and dissolved in 100ml with phosphate buffer pH 7.4 solution. The microspheres were kept to soak for overnight. After 12hrs the solution was filtered through membrane filter. The volume was made up to 100ml with phosphate buffer pH 7.4 and analyzed for drug content spectrophotometrically at 254 nm[13].

Entrapment Efficiency

$$= \frac{\text{Estimated \% amount of drug encapsulated}}{\text{Theoretical \% drug content in microspheres}} \text{X100}$$

Determination of mean particle size of microspheres

Particle size distribution of microspheres was carried out by optical microscopy. A minute quantity of dried microspheres was suspended in glycerin and the particle size of 100 microspheres was determined in each batch and the mean particle size was calculated. The average particle size was determined by using the Edmondson's equation[9].

$$\text{Edmondson's equation } D = \frac{Snd}{n}$$

Scanning electron microscopy (SEM)

For the external morphology studies, air dried particles were visualized using scanning electron microscopy (FEI-Quanta 200F) operating at 15 kv. The samples were mounted on a

metal slab with double adhesive tape and coated with platinum under vacuum[9-11].

In-vitro release studies

In-vitro release profile for microspheres performed using USP type 1 dissolution apparatus[11,12]. Sample equivalent to 45mg of nifedipine was added to 900ml phosphate buffer of pH 7.4 at 37±0.5 ^{0}C and stirred at 100rpm. Aliquot of 5ml was withdrawn at time intervals of 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10 and 12 hrs. The withdrawn volume was replenished with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at 254nm using phosphate buffer of pH 7.4 as blank. Results of *in-vitro* drug release studies obtained from absorbance data were tabulated and shown graphically as Cumulative % drug released Vs Time.

Kinetics analysis of dissolution data

There are a number of kinetic models, which described the overall release of drug from the dosage forms[14]. Data obtained from the *in-vitro* release was fit into different equations and kinetic models to explain the release kinetics of nifedipine from these microspheres. The kinetic models used were a zero-order equation, first order equation, Higuchi and Korsmeyer-Peppas model. Higuchi model is the most widely used model to describe drug release from pharmaceutical matrices system[15].

The Peppas model is widely used, when the release mechanism is not well known and when more than one type of release is involved. To find out the mechanism of drug release, drug release data were fitted in Korsmeyer-Peppas model[16]. To study the diffusional release mechanism, data obtained from *in-vitro* drug release studies were plotted against log cumulative percentage drug release versus log time. The value of n was estimated by linear regression of log Mt/M∞ versus log t.

$$\frac{Mt}{M\infty} = Kt^n$$

Where,

$\frac{Mt}{M\infty}$ is fraction of drug released at time t.

t is release time,

K is Kinetic constant (incorporating structural and geometric characteristics of preparation),

n is Diffusional exponent indicative of the mechanism of the drug release.

RESULTS AND DISCUSSION

Preformulation studies

The solubility of drug in water, 0.1N HCl, 0.1N NaOH, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer were determined and results are shown in Table 2. The organoleptic properties of nifedipine were performed and physical appearance was good, elegant and results were compiles with pharmacopoeia values of drug characteristics. The melting point of drug was determined and was found to be 172-174 ^{0}C.

Table 2: Solubility studies of nifedipine

S. No.	Medium	Solubility
1	Water	29mg/ml
2	0.1N HCl	15mg/ml
3	0.1N NaOH	18mg/ml
4	6.8 pH phosphate buffer	11mg/ml
5	7.4 pH phosphate buffer	10mg/ml

Determination of absorption maximum values

An UV-Spectrophotometric method was used for determination of absorption maxima. The λ_{max} of nifedipine (30µg/ml) in 7.4 pH phosphate buffer was scanned in UV-Visible Spectrophotometer in the wavelength range of 200-400nm and found to have maximum absorbance at 254nm.

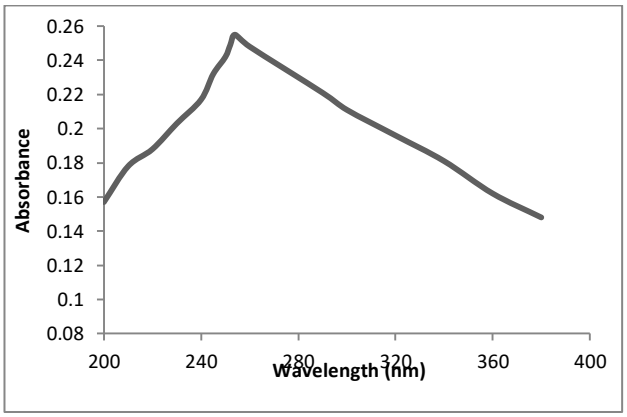

Figure 2: UV absorption spectrum of nifedipine in phosphate buffer pH 7.4

Preparation of standard calibration graph of nifedipine in pH 7.4 phosphate buffer

The solutions of nifedipine were prepared in phosphate buffer pH 7.4 (10- 60µg/ml) and the absorbance of resulting solutions was measured at 254nm using UV spectrophotometer. The calibration curve showed a good linearity with correlation coefficient of R^2 0.999.

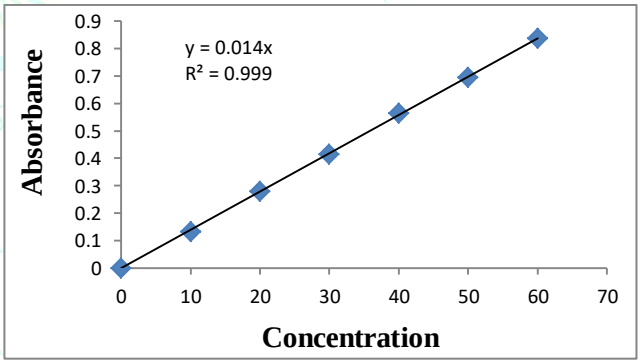

Figure 3: Standard graph of nifedipine in buffer pH 7.4

Drug and excipients compatibility studies

Fourier Transform Infra-Red Spectroscopy (FT-IR)

FT-IR spectroscopy was used to ensure that no chemical interactions between the drugs and polymer had occurred. The presence of interaction is detected by the disappearance of important functional group of the drug. The FT-IR spectra of nifedipine and polymer mixture showed several characteristic peaks. The FT-IR spectrum of pure nifedipine showed the characteristic peaks at wave numbers of 3320 cm^{-1} due to >N–H stretching (>N–H of pyridine), at 1680 cm^{-1} due $(N=O)_2$ asymmetric stretching (Aryl-$NO)_2$, at 1220 cm^{-1} is due to $(N=O)_2$ symmetric stretching (Aryl-NO_2) and at 1520 cm^{-1} due to asymmetric carboxylate anion confirming the drug structure. The spectrum of nifedipine and polymer mixture also showed the characteristic peaks for nifedipine indicating no interaction between the drug and polymers used. This indicates that there is no chemical interaction between drug and polymer mixture, that the molecular structure of nifedipine remained completely intact.

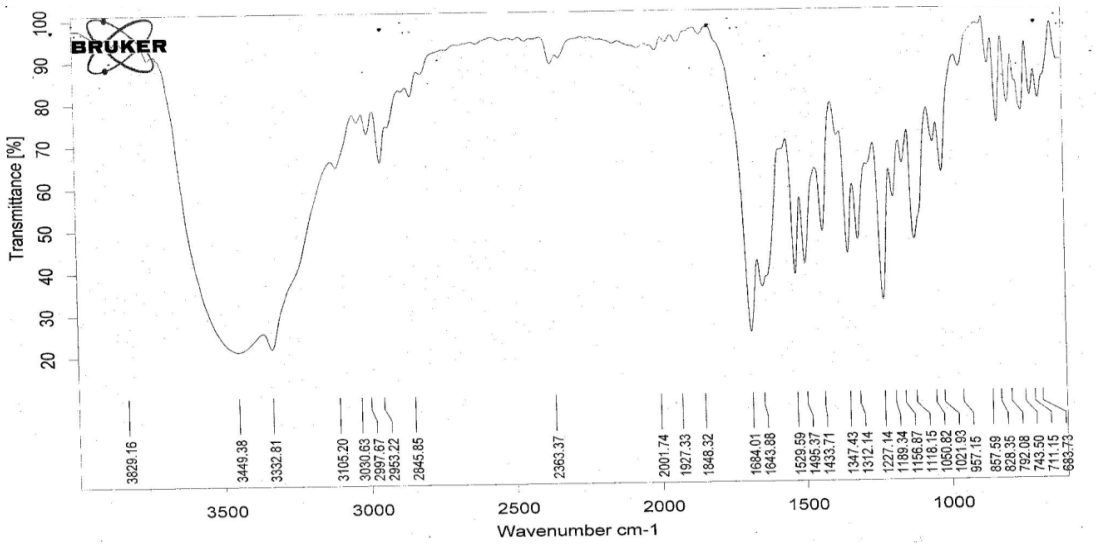

Figure 4: FT-IR spectrum of pure drug (nifedipine)

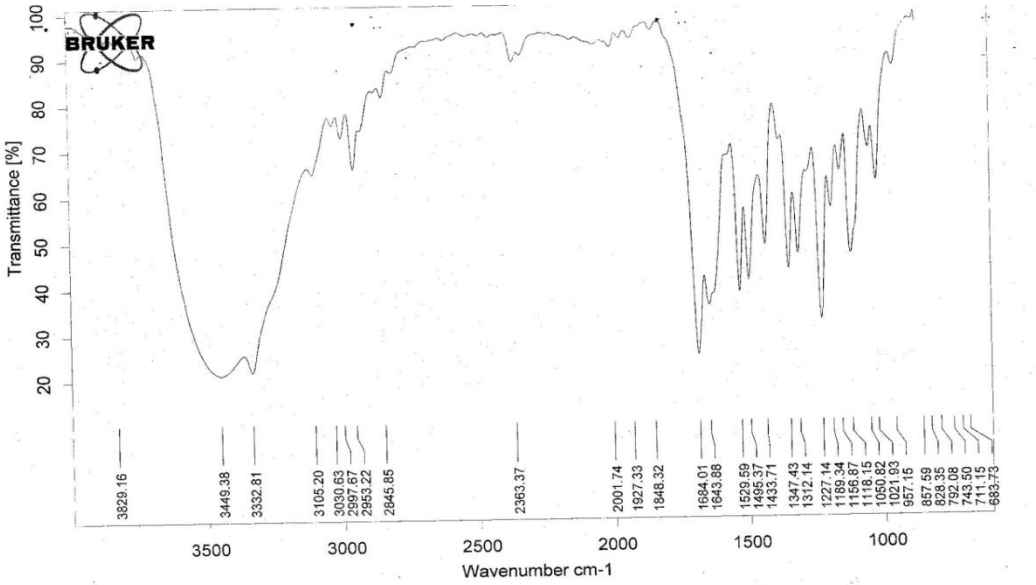

Figure 5: FT-IR spectrum of mixture of drug and polymers

Percentage yield

Percentage yield of microspheres is calculated and the percentage yield for all the ratios of microspheres were found to be in the range of 59.25-93.33% and 60.55-94.44% for ethylcellulose and combination of ethylcellulose and hydroxypropyl methylcellulose respectively in which batch MP_{12} shows highest percentage yield 94.44%. The loss of material during preparation of microspheres may be due to process parameters as well as filtration of microspheres. Percentage yield of all batches is shown in Table 3.

Encapsulation efficiency

The encapsulation efficiency of all the formulations was found to be in the range of 65.87-94.75% and 70.15-95.23% for formulations composed of ethyl cellulose and combination of ethylcellulose and hydroxypropyl methylcellulose respectively in which batch MP_{12} shows highest entrapment efficiency 95.23% and batch MP_1 shows lowest entrapment efficiency 65.87%. From the results it was seen that as the polymer concentration increased, viscosity of the dispersed phase increased, the encapsulation efficiency increased. This may be because of the availability of high amount of polymer to encapsulate the drug. The values of percentage encapsulation efficiency were shown in Table 3.

Particle size determination

The mean particle size of microspheres containing ethyl cellulose was found to be 133.5µm, 157.4µm, 189.3µm, 200.5µm, 215.6µm, 223.5µm, 234.7µm, 246.1µm for MP_1 to MP_8 batches and mean particle size of microspheres containing ethylcellulose and hydroxypropyl methylcellulose combination was found to be 210.1µm, 235.4µm, 243.9µm, 250.6µm for MP_9 to MP_{12} batches respectively. In which MP_{12} shows highest particle size. As the polymer ratio increased the size of the particles increased. This may be because of viscosity of the polymer solution which increases as the polymer concentration increases and availability of high amount of polymer to coat the drug particles and deposition of many polymer layers.

Table 3: Particle size, % encapsulation efficiency and percentage yield of microspheres

Formulation	Particle size (µm)	Encapsulation efficiency (%)	Percentage yield (%)
MP_1	133.5±1.25	65.87±1.56	59.25
MP_2	157.4±1.34	67.13±1.84	63.88
MP_3	189.3±1.28	68.24±0.97	68.88
MP_4	200.5±.87	68.55±2.34	74.07
MP_5	215.6±2.34	74.44±1.39	78.73
MP_6	223.5±1.84	79.04±1.52	83.33
MP_7	234.7±1.57	86.17±1.13	91.35
MP_8	246.1±0.96	94.75±1.40	93.33
MP_9	210.1±1.23	70.15±2.15	60.55
MP_{10}	235.4±1.45	75.87±0.80	74.07
MP_{11}	243.9±1.72	88.88±1.62	86.11
MP_{12}	250.6±1.34	95.23±1.55	94.44

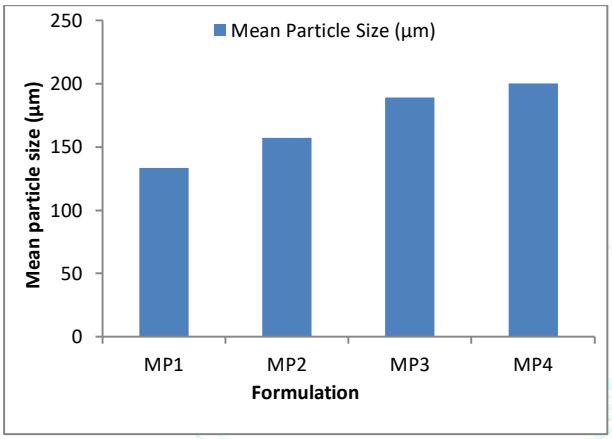

Figure 6: Mean particle size of formulations (MP_1-MP_4)

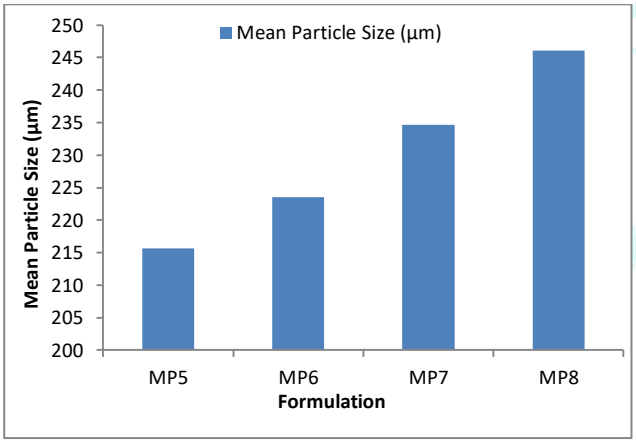

Figure 7: Mean particle size of formulations (MP_5-MP_8)

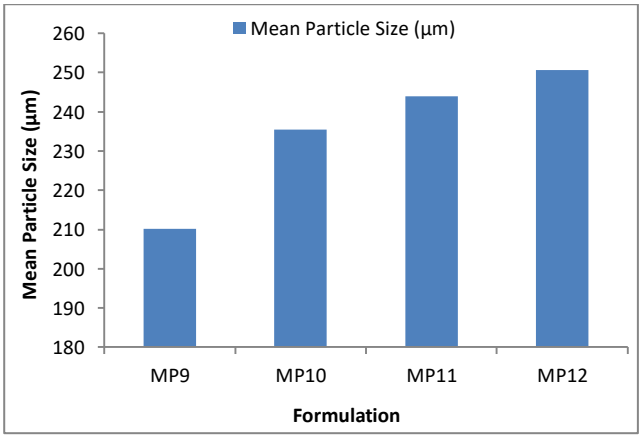

Figure 8: Mean particle size of formulation (MP_9-MP_{12})

Scanning electron microscopy

The microspheres prepared by solvent evaporation method showed a good spherical shape, with smooth surface and the particles are distributed uniformly without any lumps as shown in the Figure 9.

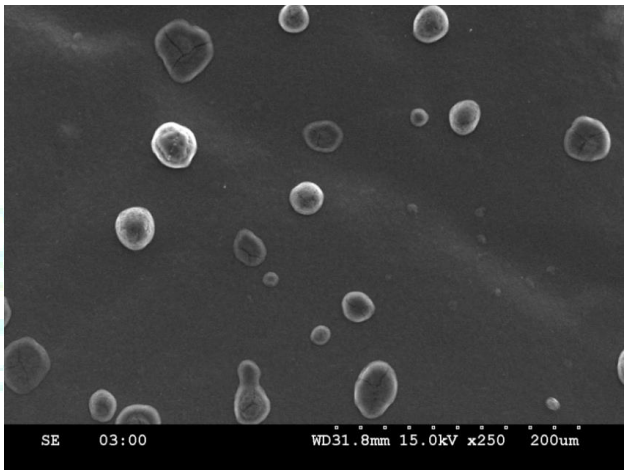

Figure 9: SEM analysis of prepared microspheres

In-vitro release studies

The *in-vitro* release profile of nifedipine microspheres were conducted in pH 7.4 phosphate buffer for 12hrs. The *in-vitro* drug release data for each of the formulations is shown in Figures 10-12. The cumulative percentage drug release after 12hrs was found to be 88.29%, 84.30%, 80.80%, 75.73%, 70.23%, 66.19%, 61.42%, 58.29% for formulations MP_1 to MP_8 and 91.17%, 86.85%, 82.12%, 78.47% for formulations MP_9 to MP_{12} respectively. The release profile was gradually decreased by increasing the polymer ratio.

From the released data observed that increase in the polymer content delays the drug release due to increased particle size and decreased surface area available for drug release. Among all the formulations prepared with ethyl cellulose polymer MP_1 showed high amount of drug release i.e. (88.25%) and among all the formulations prepared with combination of ethyl cellulose and hydroxylpropyl methylcellulose polymers MP_9 showed high amount of drug release i.e. (91.23%) in 12hrs.

From all the twelve formulations improved drug release was observed with combination of polymers i.e. (91.23%) as it contained both hydrophilic polymer with hydrophobic one compared to formulation prepared with ethyl cellulose i.e. (88.25%) as it contained hydrophobic polymer. This might be due to addition of hydrophilic nature of the polymer

which has more affinity for water results in increased thermodynamic activity of the drug in the microspheres.

At lower polymer concentration, a burst release was seen, which was more in case of ethyl cellulose and HPMC containing formulations as compared to single ethyl cellulose formulations, which may due to surface drug present on the microspheres.

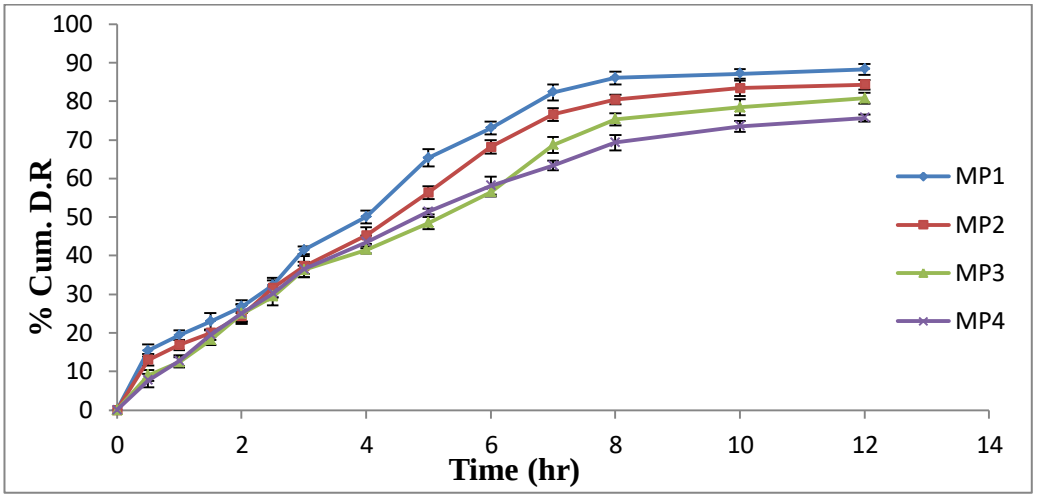

Figure 10: % drug release of nifedipine microspheres (MP_1-MP_4)

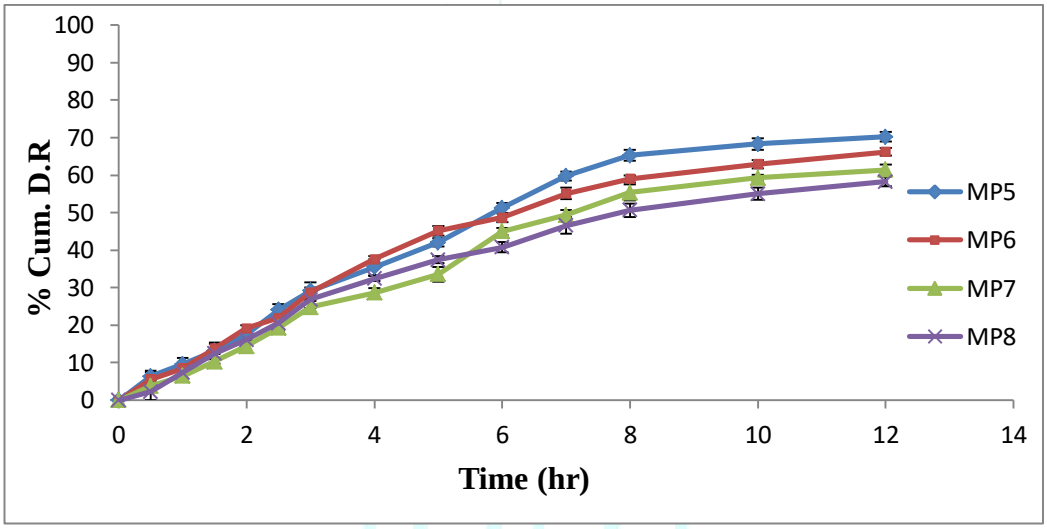

Figure 11: % drug release of nifedipine microspheres (MP_5-MP_8)

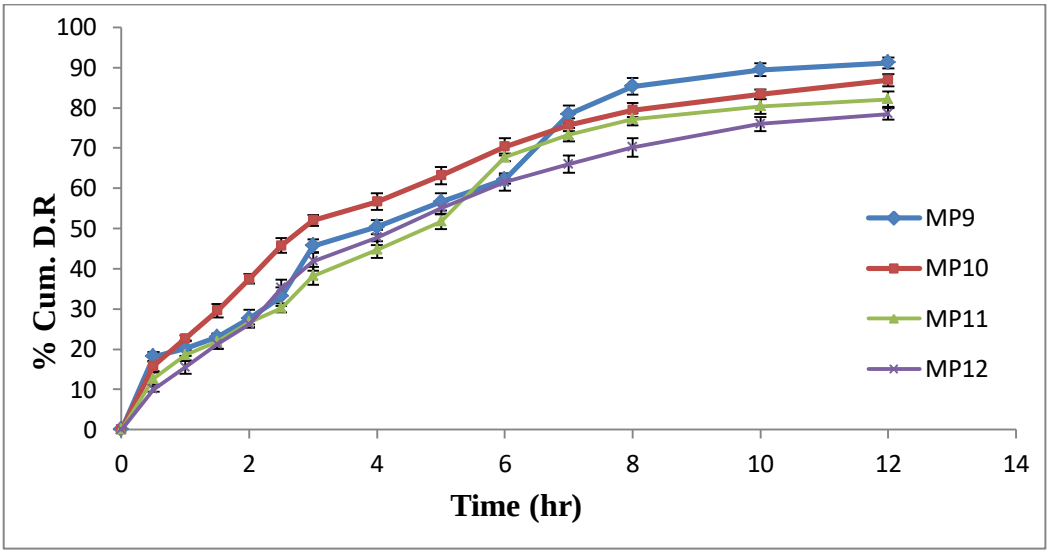

Figure 12: % drug release of nifedipine microspheres (MP_9-MP_{12})

Release kinetic plots for best formulation (MP_9) microspheres containing nifedipine

The kinetic data of various models revealed that formulations MP_1, MP_2, MP_4, MP_6, MP_8, MP_9, MP_{11} followed zero order release kinetics with diffusion controlled mechanism and MP_3, MP_5, MP_7, MP_{10} followed first order release kinetics. The kinetic data of optimized formulation MP_9 was shown in the Figures 13-16.

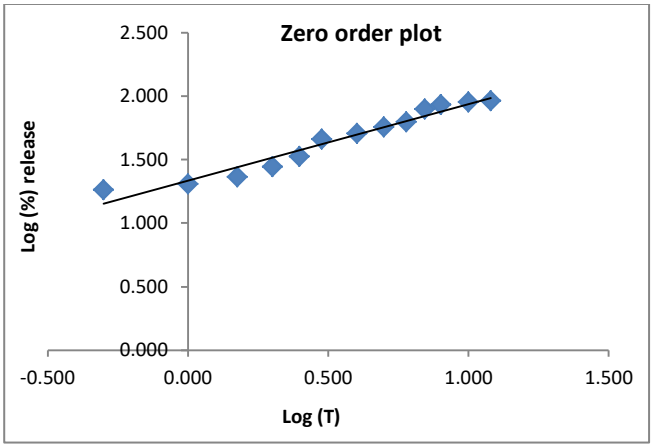

Figure 13: Plots of Log (T) Vs Log (%) release for formulation MP_9

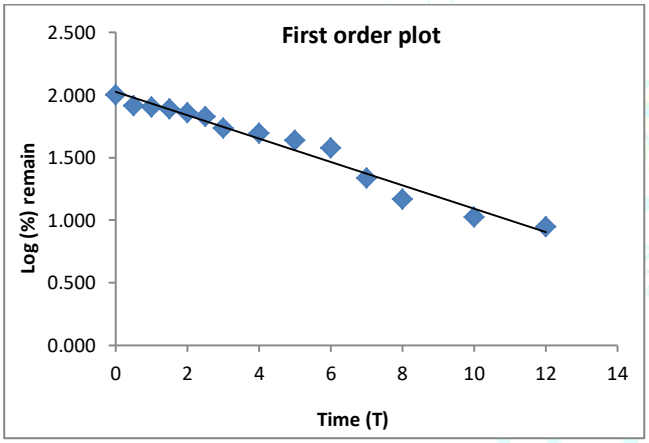

Figure 14: Plots of Time (T) Vs Log (%) Remain for formulation MP_9

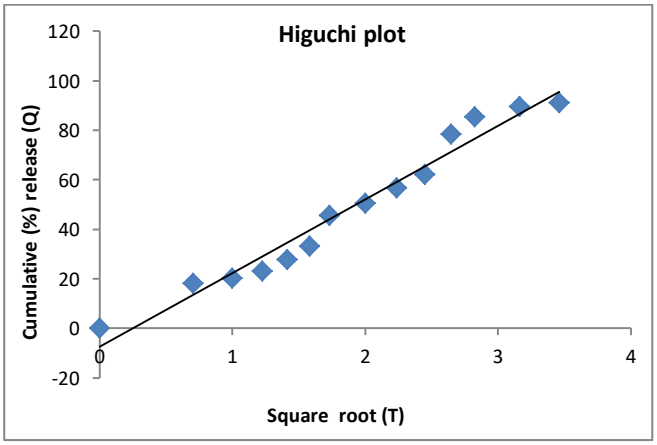

Figure 15: Plots of square root (T) Vs Cumulative (%) release (Q) for formulation MP_9

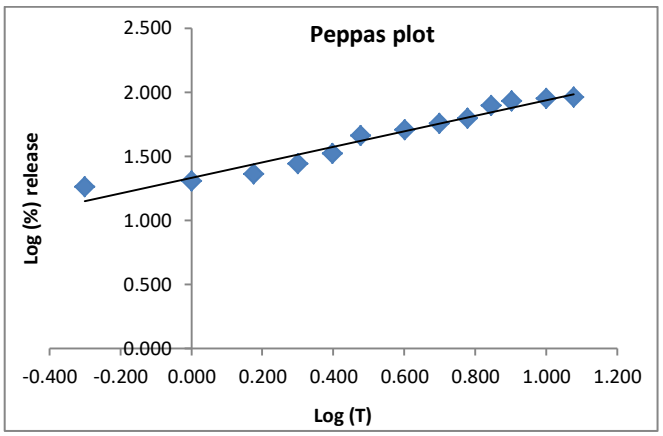

Figure 16: Plots of Log (T) Vs Log (%) release (Q) for formulation MP_9

CONCLUSION

The present study had been a satisfactory attempt to formulate microspheres of nifedipine, an orally administered calcium channel blocker used in the treatment of angina pectoris drug with a view of improving its oral bioavailability and giving a prolonged release of microspheres with polymers such as ethyl cellulose and hydroxypropyl methylcellulose were successfully prepared by emulsification solvent evaporation method.

Based on the results obtained it can be concluded that MP_9 was found to be the ideal formulation considering its size and release profile. Hence microspheres were better choice of drug delivery system than many other types of drug delivery system and plays vital role in place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted, specific drug delivery.

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AUTHORS CONTRIBUTION

All the authors contributed equally.

CONFLICT OF INTEREST

Author declares that there is no conflict of interest to disclose.

SPONSORSHIP

Nil.

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