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Research

Formulation and evaluation of microspheres encompass nifedipine by solvent evaporation method

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Abstract

Basically, oral route drug administration is far the most preferable route for taking medications. However, their short circulating half-life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmaco kinetic limitation leads in many cases to frequent dosing of medication to achieve therapeutic effect. Rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamics profile is to release the drug in a controlled manner and site-specific manner. Hence only our current research work is to prepare Nifedipine microspheresusing Solvent evaporation method using different polymer ratio. FT-IR studies revealed that there was no chemical interaction between the drug and polymer. The in vitro mucoadhesion study was conducted for all the formulations and the results were found in the range of 73.05 to 99.72%.The average particle size of the optimized formulation was found to be 166µm. The *in-vitro* release behavior from all the Nifedipine microspherewas found to be peppas drug release kinetics and produced a sustained release over a period of 12 hours with better entrapment efficiency.

Keywords: Nifedipine, Eudragit, Carbopol 934P, HPMC, Solvent evaporation method and microspheres.

INTRODUCTION

Microspheres are spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature. There are two types of microspheres; microcapsules and micromatrices, which are described as, Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall. and micromatrices in which entrapped substance is dispersed throughout the matrix. Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Microsphere play an important role to improve bioavailability of conventional drugs and minimizing

side effects. Ideal characteristics of microspheres [1-6].Microspheres provide constant drug concentration in blood there by increasing patent compliance, Decrease dose and toxicity. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.

Out of all the biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion[7,8]. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeuticaction.

MATERIALS AND METHODS

Materials utilized for our current research work are Nifedipine, Sigma Aldrich, Eudragit, Central Institute of Fisheries Technology, Cochin, Carbopol 934P, Merk specialties Pvt Limited, Mumbai, Hydroxy propyl methyl cellulose, Chemical Drug House, New Delhi,

Standard Calibration Curve of Nifedipine

Absorbance of these samples were analyzed by using UV-Visible Spectrophotometer at 231nm against reference solution 0.1N HCl (pH 1.2). The procedure repeated to pH 6.8 phosphate buffer and pH 7.4 phosphate buffer.

Method of Preparation

Nifedipine microspheres were prepared using Eudragit, Carbopol 934p and HPMC K4M and distilled water as continuous phase by solvent evaporation technique. Initially dichloromethane (DCM) and methanol was mixed uniformly at room temperature, then Eudragit, Carbopol 934p and HPMC K4M in various proportions was dissolved in the above solution[9-13]. To this mixture, a drug solution corresponding was added and mixed thoroughly and injected drop wise in to the continuous phase consisting of 100mL of 0.2% (w/v) SLS (Sodium Lauryl sulphate) at 250 rpm. The microspheres obtained was washed for 2-3 times with distilled water and dried at room temperature. Different concentrations and ratios of polymers used in the formulation of microspheres.

Table 1: Concentrations and ratios of polymers

Ingredients (mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nifedipine	10	10	10	10	10	10	10	10	10
Eudragit	100	200	300	-	-	-	-	-	-
Carbopol 934p	-	-	-	100	200	300	-	-	-
HPMC K4M	-	-	-	-	-	-	100	200	300
Dichloromethane (mL)	20	20	20	20	20	20	20	20	20
Methanol (mL)	30	30	30	30	30	30	30	30	30
Sodium lauryl sulphate (mg)	25	25	25	25	25	25	25	25	25

Characterization of Microspheres

Micromeritic properties

The microspheres were characterized by their micromeritic properties such as Particle size, Bulk density, Tapped density, Compressibility index, Hausners ratio and Angle of repose.

Bulk density

In this method floating microspheres are transferred to a measuring cylinder and is tapped manually till a constant volume is obtained. This volume is bulk volume and it includes true volume of the powder and the void space among the microspheres.

$$\text{Bulk density} = \frac{\text{Mass of microspheres}}{\text{Bulk volume}}$$

Tapped density

In this method floating microspheres were transferred to a measuring cylinder & tapped for 100 times. After tapping volume of microspheres was visually examined. The ratio of mass of microspheres to volume of microspheres after tapping gives tapped density floating microspheres.

Percent Compressibility index was determined by using the formula,

Carr's Index = (tapped density – bulk density) x 100 / tapped density

Hausners ratio

Hausners ratio of microspheres was determined by comparing tapped density to bulk density using the equation

Hausner ratio = tapped density / bulk density

Angle of repose

Angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method4. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed microspheres were allowed to pass through the funnel freely on to the surface. The height and radius of the powder cone was measured and angle of repose was calculated using the following equation.

$\theta = \tan^{-1} h / r$

Here,

θ - Angle of repose

h - Height of granules above the flat surface

r - Radius of the circle formed by the granule heap.

Percentage yield

The percentage of production yield was calculated from the weight of dried microspheres recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical mass (Microspheres)}}{\text{Theoretical mass (Polymer + Drug)}} \times 100$$

Drug entrapment efficiency

Weighed number of microspheres (100 mg) with phosphate buffer pH 7.4 (10 ml) was added in a vial. The solution was stirred vigorously for 24 hours with mechanical stirrer. Supernatant was collected by centrifugation and drug content in supernatant was determined by using UV spectrophotometer at wavelength 231nm[14-23]. The amount of drug entrapped in the microspheres was calculated by the following formula,

$$\% \text{ Drug Entrapment Efficiency} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Swelling study

Swelling ratio of different dried microspheres were determined gravimetrically in simulated gastric fluid pH 1.2. The microspheres were removed periodically from the solution, blotted to remove excess surface liquid and weighed on balance. Swelling ratio (% w/v) was determined from the following relationship:

$$\text{Swelling ratio} = \frac{(Wt - W0)}{(W0)} \times 100$$

Where W0 & Wt are initial weight and Final weight of microspheres respectively

***In vitro* drug release study**

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5^0C, 50 rpm) using the USP type – I rotating basket method in simulated gastric fluid pH 1.2 (900ml) for 2 hours then replace the media with pH 6.8 phosphate buffer for 3 hours, then replace the media with pH 7.4 Phosphate buffer. A quantity of accurately weighed microspheres equivalent to 100mg Nifedipine each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 231nm[24-29]. At the same time the volume withdrawn at

each time intervals were replenished immediately with the same volume of fresh pre-warmed simulated gastric fluid pH 1.2 maintaining sink conditions throughout the experiment.

***In Vitro* drug release kinetics**

The release data obtained was fitted into various mathematical models. The parameters 'n' and time component 'k', the release rate constant and 'R', the regression coefficient were determined by Korsmeyer-Peppas equation to understand the release mechanism [30,31].

To examine the release mechanism of Nifedipine from the microspheres, the release data was fitted into Peppa's equation,

$Mt / M\infty = Ktn$

\Where, $Mt / M\infty$ is the fractional release of drug,'t' denotes the release time, 'K' denotes a constant incorporating structural and geometrical characteristics of the device, 'n'is the diffusional exponent and characterize the type of release mechanism during the release process.

RESULTS AND DISCUSSION

The mean size increased with increasing polymer concentration which is due to a significant optimum in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing Eudragit as a polymer had a size range of 125±0.01µm to 187±0.05µm. Microspheres containing Carbopol 934p as polymer exhibited a size range between 137±0.08µm to 191±0.09 µm.

The carr's index of formulation F1 to F9 containing different grades of Eudragit, Carbopol 934p and HPMC K4M11.86to 19.18respectively. The angle of repose of formulation F1 to F9 containing Eudragit, Carbopol 934p and HPMC formulation was in the range <31.45 respectively(as shown in table 8.3) The values of carr's index and angle of repose indicate good flow properties.

Table 2: Micromeritic property of microspheres of Nifedipine

Formulation code	Mean partical size	Bulk density (gm./cm^3)	Tapped density (gm./cm^3)	Hausener's ratio	Carr's index	Angle of repose
F1	125±0.01	0.59	0.73	1.237	19.18	31.45
F2	171±0.06	0.58	0.71	1.224	18.31	30.64
F3	187±0.05	0.58	0.70	1.207	17.14	30.05
F4	191±0.09	0.50	0.57	1.140	12.28	23.49
F5	166±0.02	0.52	0.59	1.135	11.86	23.82
F6	137±0.08	0.53	0.62	1.170	14.52	24.50
F7	152±0.04	0.55	0.64	1.164	14.06	24.68
F8	185±0.07	0.56	0.67	1.196	16.42	25.07
F9	191±0.01	0.54	0.65	1.194	16.40	25.05

Percentage yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle andwastage of the drug-polymer solution, adhesion ofpolymer solution tothe magnetic bead and microspheres lost during the washing process.

Drug entrapment efficiency

Percentage Drug entrapment efficiency of Nifedipine ranged from 72.90 to 90.45 % for microspheres containing Eudragit, Carbopol 934p and HPMC polymer, the drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity.

Table 3: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

Formulation code	% yield	Drug Content (mg)	% Drug entrapment efficiency
F1	96.25	96.14	72.90
F2	86.21	98.39	84.63
F3	90.14	98.50	90.25
F4	94.31	97.19	82.70
F5	97.35	99.24	89.12
F6	97.51	98.76	90.45
F7	87.64	95.81	82.63
F8	92.32	98.63	86.81
F9	94.14	97.58	89.69

Swelling studies

Swelling ability is an indicative parameter for rapid availability of drug solution for diffusion with greater flux. Swellability data revealed that amount of polymer plays an important role in solvent transfer.The effect of drug to polymer ratio on percentage swelling is displayed. amount of polymer directly affects the swelling ratio. As the polymer to drug ratio increased, the percentage of swelling increased from 12.33 to 34.26% for microspheres containing Eudragit as polymer, 15.53 to 38.8 % for microspheres containing Carbopol 934p as polymer. As shown in the figure 1,2&3.

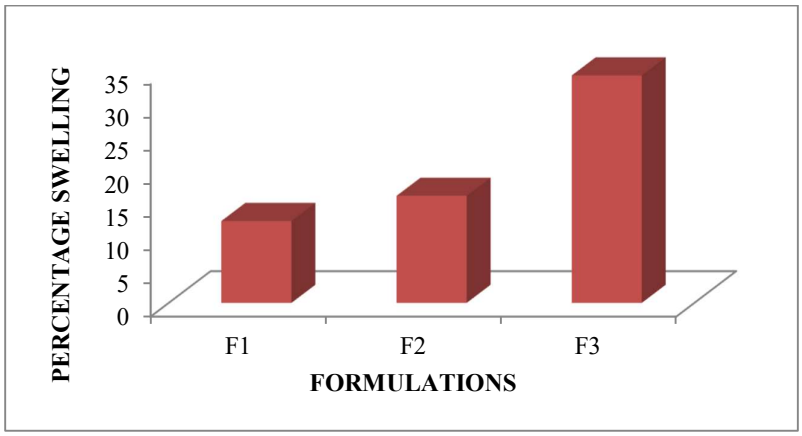

Fig 1: Percentage swelling of microspheres containing Eudragit

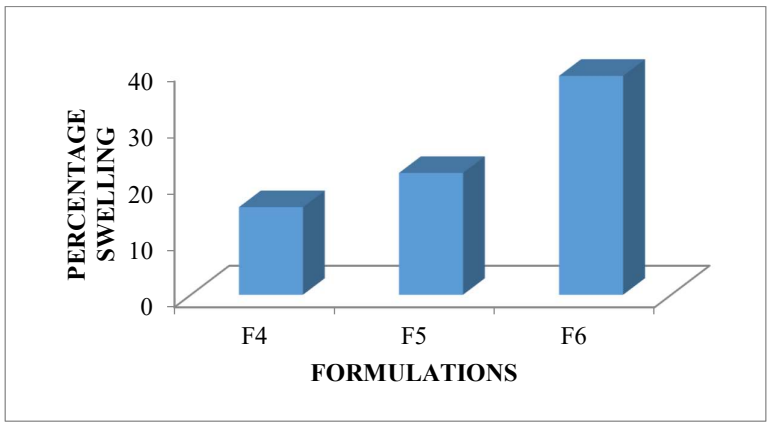

Fig 2: Percentage swelling of microspheres containing Carbopol 934p

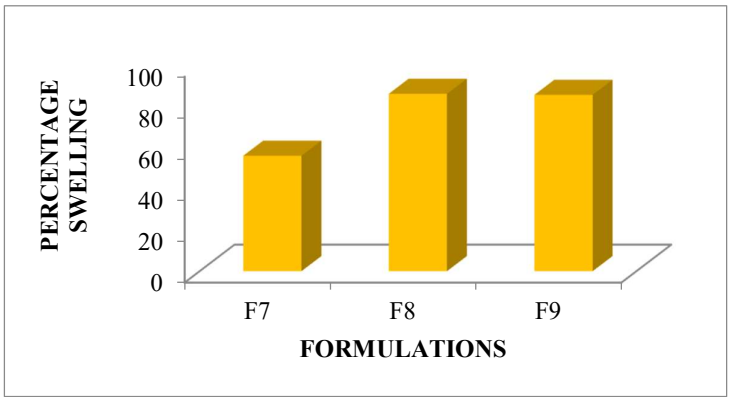

Fig 3: Percentage swelling of microspheres containing HPMC K4M

***Invitro* Mucoadhesion Test**

As the polymer to drug ratio increased, microspheres containing Eudragit, Carbopol 934p and HPMC exhibited % mucoadhesion ranging from 72.75 to 96.25 %, the results of *in-vitro* mucoadhesion test. As shown in the figure 4.

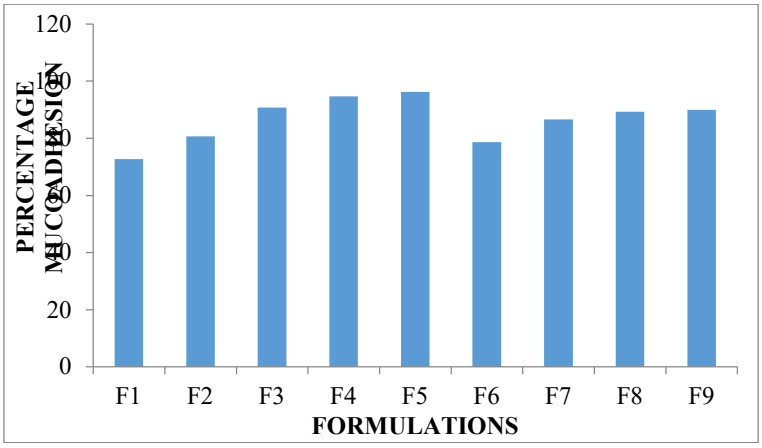

Fig 4: Percentage mucoadhesion of microspheres

***Invitro* Drug Release Studies**

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type I. The release patterns rae shown in the figure 5

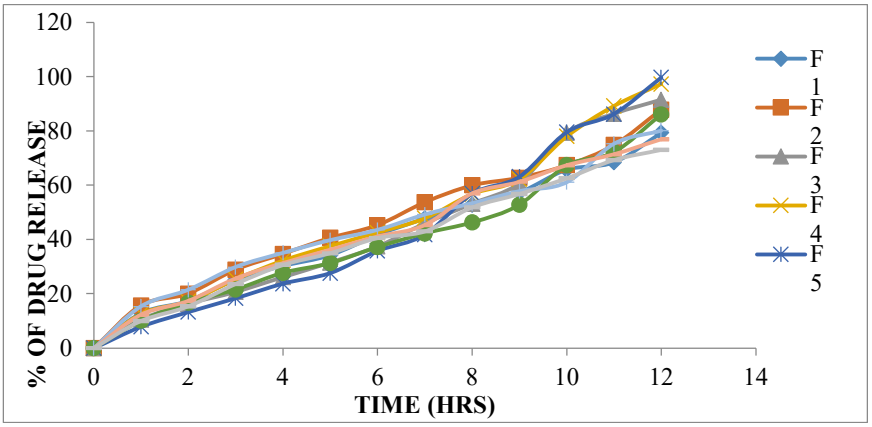

Fig 5: *In-Vitro* drug release profile of Nifedipine microspheres

Compatibility Studies

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish any possible interaction of Drug with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug. As shown in the figure 6&7. The Scanning electron microscopy studies are shown in the figure 8.The release kinetics of the drug follows peppas release model shown in the fig 9.

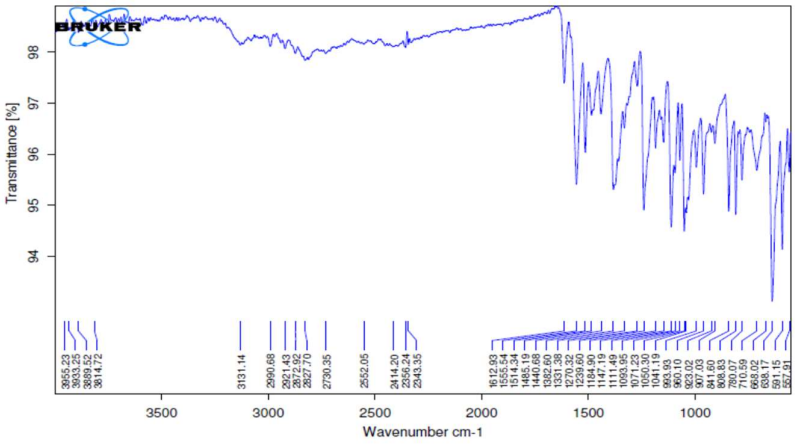

Fig 6: FT-IR spectra of Pure drug

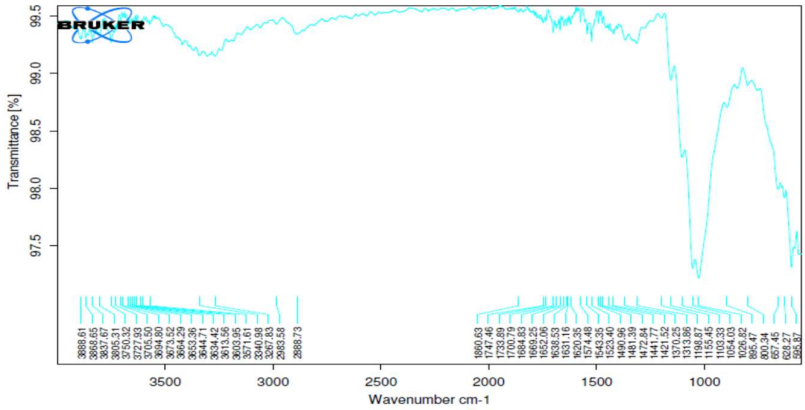

Fig 7: FT-IR spectra of Optimised formulation

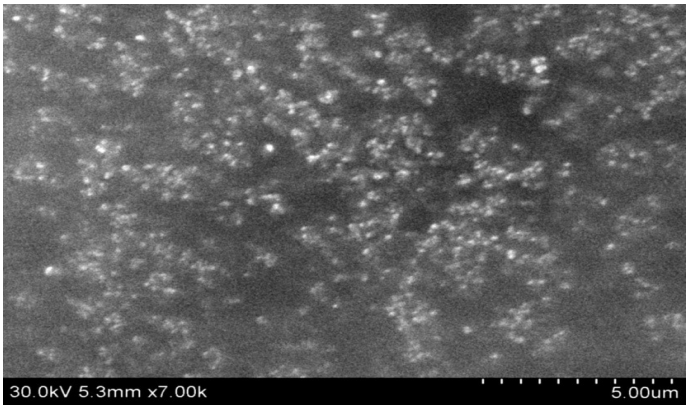

Fig 8: SEM images of Optimised formulation

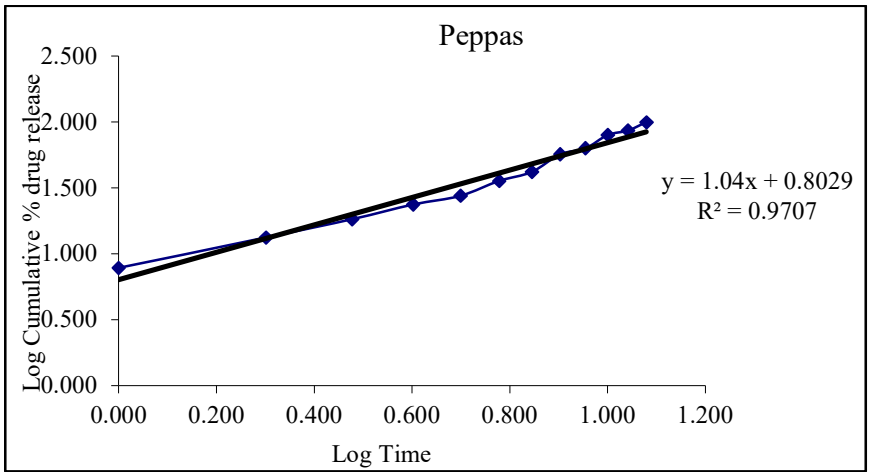

Fig 9: Graph of peppas drug release kinetics of optimized formula

CONCLUSION

At this juncture, the formulation of Nifedipine microspheres were prepared through solvent evaporation technique.In the preliminary screening, from the FTIR spectra, itwas observed that similar functional groups appear for the drug and the formulation. Hence it shows that there was no chemical interaction between drug and polymer used. The formulations F1 to F9 prepared by solvent evaporation technique. F5 Selected as an optimized formulation, because of better entrapment efficiency and *in vitro* drug release of about 99.72 % in 12hours.It follows peppas drug release kinetics. Hence it can be concluded that Nifedipine can be prepared in the form of microspheres by solvent evaporation technique to improve the drug targeting efficiency and also to prolong the duration as far its action in concerned.

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