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Design, development and evaluation of nifedipine polymeric microspheres

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ABSTRACT

The aim of the study was to prepare Nifedipine microspheres using Solvent evaporation method using different polymer ratio. FT-IR studies revealed that there was no chemical interaction between the drug and polymer.The average particle size of the optimized formulation was found to be 166µm. The *in-vitro* release behavior from all the Nifedipine microspheres was found to be peppas drug release kinetics and produced a sustainedrelease over a period of 12 hours with better entrapment efficiency.

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

INTRODUCTION

Oral route drug administration is by far the most prefer able 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 aSnd improve pharmacokinetic and pharmacodynamics profile isto release the drug in a controlled manner and site specific manner. Microspheres are small spherical particles, with diameters1 µm to 1000 µm. They 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.[1-5]

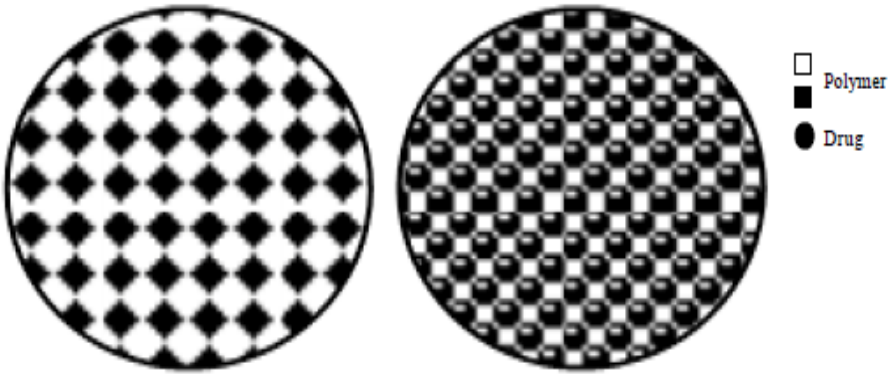

Fig 1: Structure of Microspheres

Ideal characteristics of microspheres [6]

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability.
- Susceptibility to chemical modification.

Advantages of microspheres

- Particle size reduction for enhancing solubility of the poorly soluble drug.
- provide constant and prolonged therapeutic effect.
- provide constant drug concentration in blood there by increasing patent compliance,
- Decrease dose and toxicity.
- Protect the drug from enzymatic and photolytic leavage hence found to be best for drug deliveryof protein.
- Reduce the dosing frequency and thereby improve the patient compliance
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- Microsphere morphology allows a controllable variability in degradation and drug release.
- Convert liquid to solid form & to mask the bitter taste.
- Protects the GIT from irritant effects of the drug.
- 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 microspheresare used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Limitation

Some of the disadvantages were found to be as follows

1. The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to been capsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.

MATERIALS

Nifedipine Provided by SURA LABS, Dilsukhnagar, Hyderabad, Eudragit (Central Institute of Fisheries Technology, Cochin), Carbopol 934p (MerkspecialiitiesPvt Limited, Mumbai), HPMC K4M (Chemical Drug House, New Delhi), Dichloromethane (Chemical Drug House, New Delhi), Methanol (Chemical Drug House, New Delhi), Sodium lauryl sulphate (Chemical Drug House, New Delhi).

METHODOLOGY

PREPARATION OF 0.1N HCl (pH 1.2)

Take 8.5 ml of HCl in a 1000ml volumetric flask and make up the volume with distilled water

Preparation of Standard Calibration Curve of Nifedipine

- 10 mg of Nifedipine was accurately weighed and dissolved in 10ml of methanol (Stock Solution –I) to get a concentration of 1000 µg/ml.
- From the stock solution-I, 1ml of aliquots was taken and suitably diluted with 0.1N HCl (Stock Solution-II) to get concentrations of 100µg/ml.
- From the stock solution-II, aliquots were taken and suitably diluted with 0.1N HCl (pH 1.2) to get concentrations in the range of 2 to 10µg/ml.

The 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. 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 are mentioned in Table.

Table 1: Composition of Nifedipine

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

RESULTS AND DISCUSSION

Preformulation Studies

Spectroscopic Studies

Determination of λmax

A solution of 10µg/ml of Nifedipine was scanned in the range of 200 to 400nm. The drug exhibited a λ_{max} at 231 nm in simulated gastric fluid pH 1.2 and pH 7.4 phosphate buffer respectively. Correlation between the concentration and absorbance was found to be near to 0.998, with a slope of 0.028 and intercept of 0.004.

Calibration curve of Nifedipinein simulated gastric fluidpH 1.2

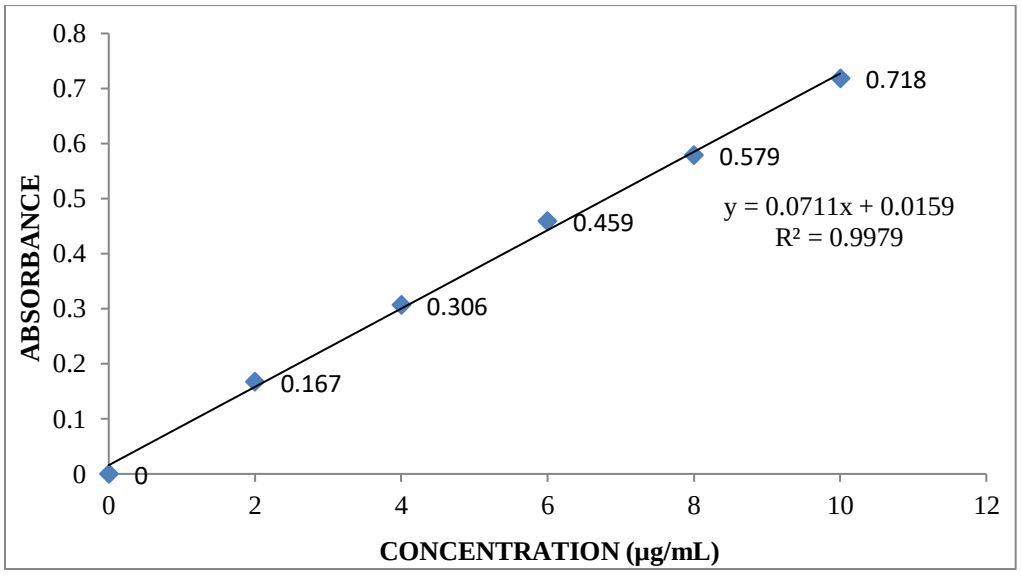

Fig 2: Standard graph Of Nifedipine in simulated gastric fluid pH 1.2

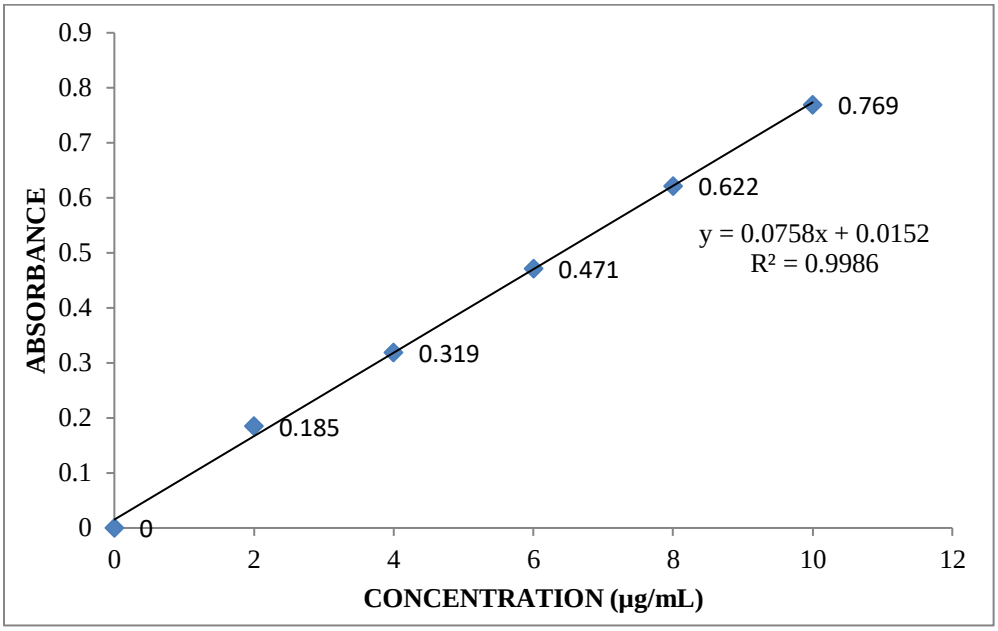

Fig 3: Standard graph of Nifedipine in pH 7.4 phosphate buffer

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

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

In vitro mucoadhesion test

As the polymer to drug ratio increased, microspheres containing Eudragit, Carbopol 934p and HPMCexhibited % mucoadhesion ranging from 72.75 to 96.25 %, the results of *in-vitro*mucoadhesion test are compiled in Table 4.

Table 4: *In Vitro* Mucoadhesion Test of all Formulations

S.NO.	FORMULATION CODE	No. OF MICROSPHERES		PERCENTAGE MUCOADHESION
		INITIAL	FINAL	
1	F1	20	14.55	72.75
2	F2	20	16.12	80.60
3	F3	20	18.14	90.7
4	F4	20	18.92	94.60
5	F5	20	19.25	96.25
6	F6	20	15.72	78.60
7	F7	20	17.32	86.6
8	F8	20	17.86	89.3
9	F9	20	17.89	90.01

Table 5: *In-Vitro* drug release data of Nifedipine microspheres

TIME (h)	CUMULATIVE PERCENT OF DRUG RELEASED								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	12.85	15.75	10.57	12.62	7.82	10.12	15.34	12.31	10.02
2	17.36	20.11	16.31	17.17	13.29	16.72	21.51	17.42	15.36
3	25.17	28.90	20.69	25.34	18.34	21.63	29.86	25.69	23.61
4	30.28	34.71	26.14	32.23	23.71	27.72	35.11	31.34	30.65
5	34.20	40.67	31.52	37.60	27.62	31.34	39.82	36.29	34.92
6	41.63	45.29	37.43	42.57	35.78	37.21	43.51	41.14	40.52
7	47.71	53.75	45.92	47.82	41.83	42.26	49.22	45.28	42.95
8	52.89	59.97	53.21	56.71	56.90	46.33	53.32	56.95	51.82
9	57.40	62.76	60.82	62.22	63.14	52.82	57.81	61.24	56.74
10	65.71	67.34	79.29	77.99	79.57	67.34	61.12	67.32	62.58
11	68.43	74.82	86.32	89.18	86.25	72.21	75.23	71.41	69.25
12	79.30	87.91	91.53	97.29	99.72	86.14	80.15	76.94	73.04

Table 6: Release kinetics studies of the optimized formulation (F5)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
7.82	1	1.000	0.893	0.000	1.965	7.820	0.1279	-1.107	92.18	4.642	4.517	0.124
13.29	2	1.414	1.124	0.301	1.938	6.645	0.0752	-0.876	86.71	4.642	4.426	0.215
18.34	3	1.732	1.263	0.477	1.912	6.113	0.0545	-0.737	81.66	4.642	4.338	0.303
23.71	4	2.000	1.375	0.602	1.882	5.928	0.0422	-0.625	76.29	4.642	4.241	0.400
27.62	5	2.236	1.441	0.699	1.860	5.524	0.0362	-0.559	72.38	4.642	4.167	0.474
35.78	6	2.449	1.554	0.778	1.808	5.963	0.0279	-0.446	64.22	4.642	4.005	0.637
41.83	7	2.646	1.621	0.845	1.765	5.976	0.0239	-0.379	58.17	4.642	3.875	0.767
56.9	8	2.828	1.755	0.903	1.634	7.113	0.0176	-0.245	43.1	4.642	3.506	1.135
63.14	9	3.000	1.800	0.954	1.567	7.016	0.0158	-0.200	36.86	4.642	3.328	1.314
79.57	10	3.162	1.901	1.000	1.310	7.957	0.0126	-0.099	20.43	4.642	2.734	1.908
86.25	11	3.317	1.936	1.041	1.138	7.841	0.0116	-0.064	13.75	4.642	2.396	2.246
99.72	12	3.464	1.999	1.079	-0.553	8.310	0.0100	-0.001	0.28	4.642	0.654	3.987

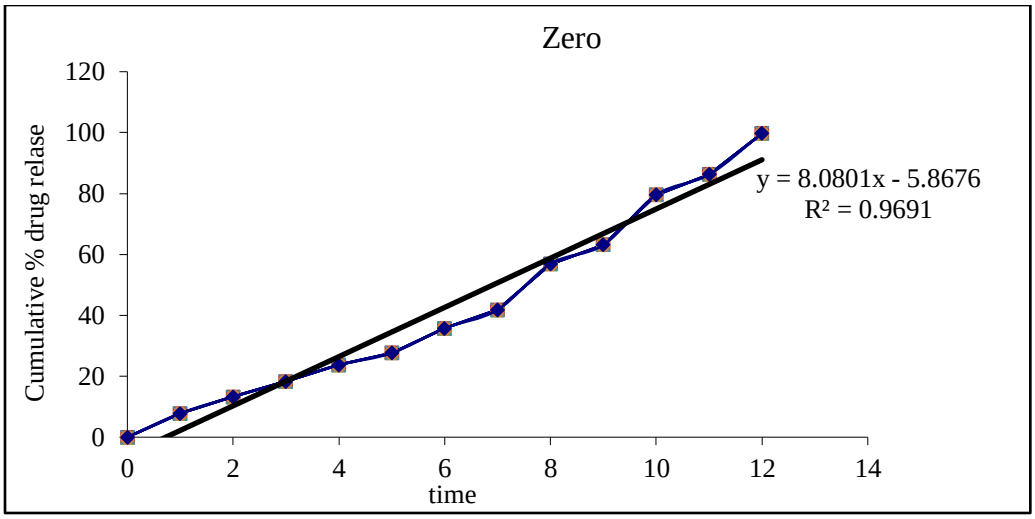

Fig4:Zero order release kinetics graph

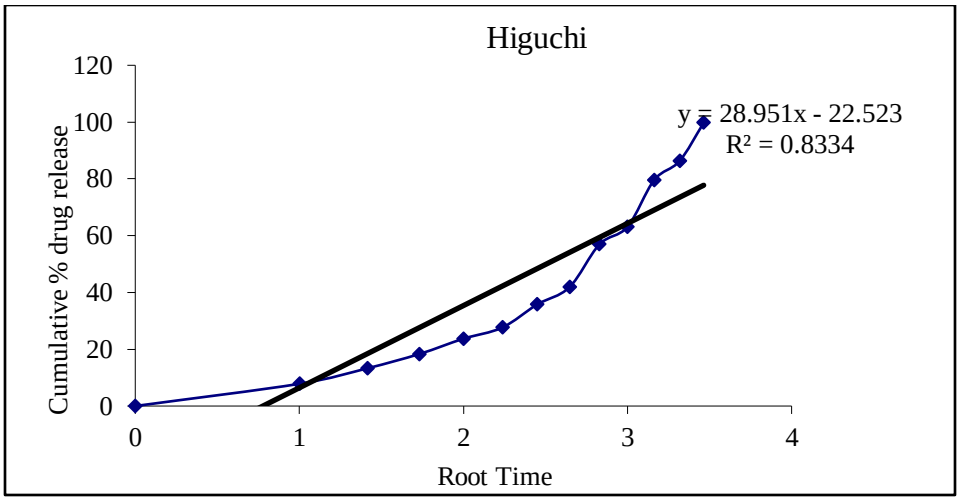

Fig 5: Higuchi release kinetics graph

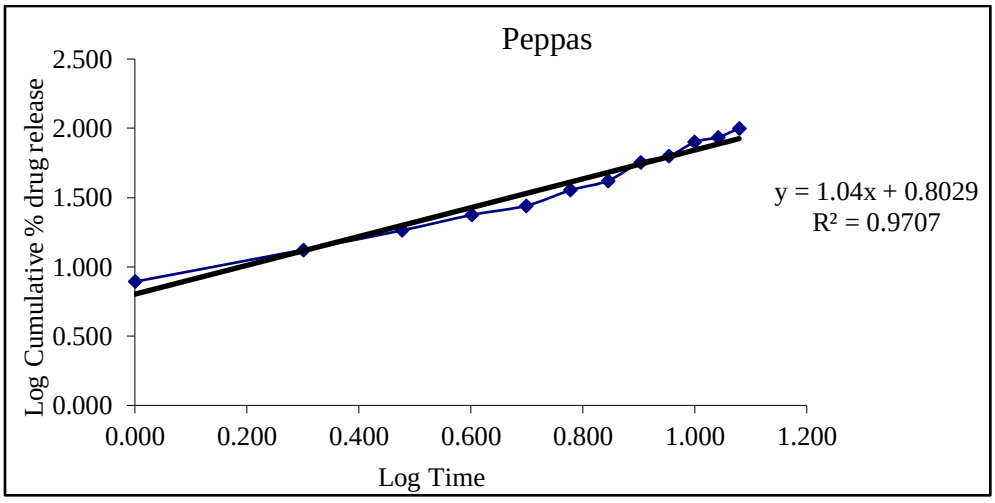

Fig 6: Peppas release kinetics graph

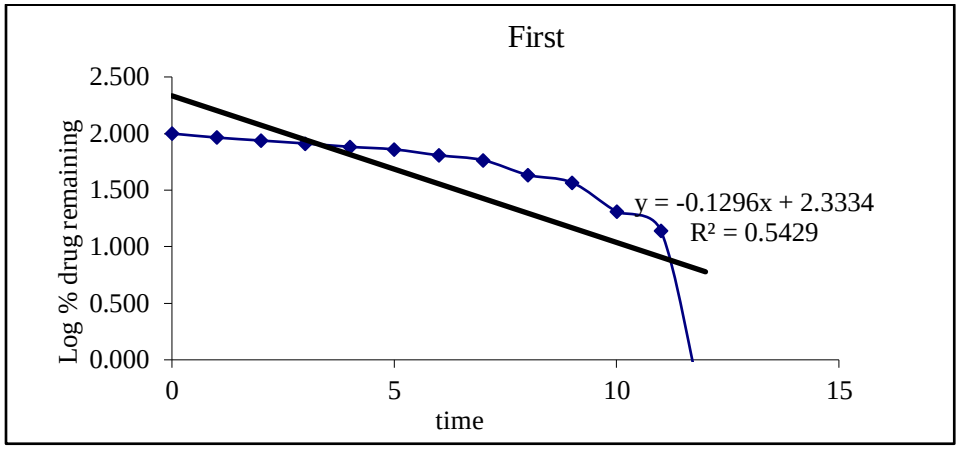

Fig 7:First order release kinetics graph

Drug – Excipient compatibility studies

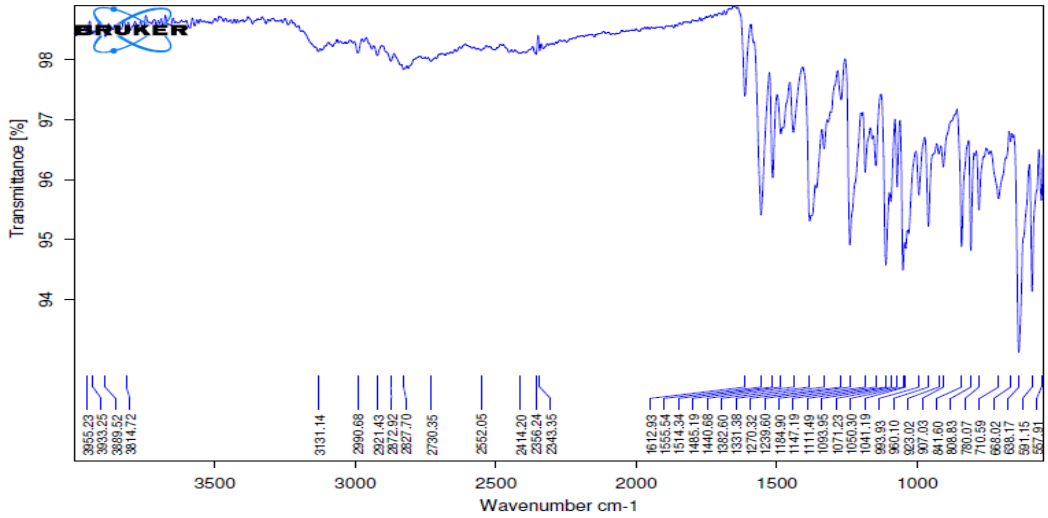

Fig 8:FT-IR spectra of Pure drug

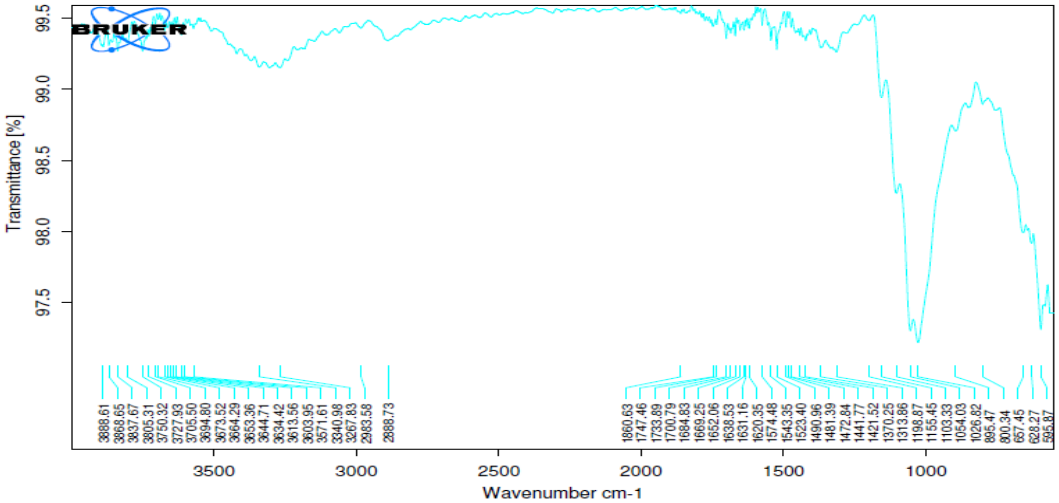

Fig 9:FT-IR spectra of Optimised formulation

SEM

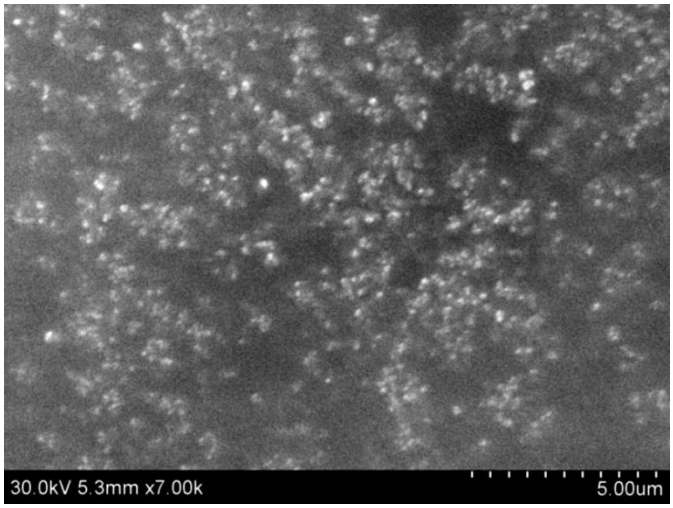

Fig 10: SEM of Optimised formulation

SUMMARY

- An attempt was made to formulate Nifedipine loaded microspheres using Eudragit, Carbopol 934p and HPMC as a mucoadhesive polymer by Solvent evaporation method.
- In the present study F1to F9 formulations were prepared using Eudragit, Carbopol 934p and HPMC as a polymer (1:1, 1:2, and 1:3) in different ratios.
- The FTIR study was carried out for the drug, polymer, physical mixture and optimized formulation F5. In FTIR study, all characteristic peaks in the spectra appeared without any remarkable changes showing that there is no chemical interaction between the drug and polymer used in the preparation of microspheres.
- The mean particle size study was carried out by using microscopic analysis and found that the range for all formulations was varied from 125±0.01 to 191±0.09µm due to change in drug and polymer ratio.
- The drug content for all the formulations was found to be in the range of 95.81 to 99.24%. The formulation F5 had the highest drug content.
- The entrapment efficiency of all formulations was found to be in the range of 72.90 to 99.81 %.
- 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 *in vitro* drug release study was carried out for all the formulations and the formulation F5 (1:1) showed sustained release of 99.72% at the end of 12 h.
- The release rate followed peppas drug release kinetics.

CONCLUSION

The aim of present study is to develop formulation of Nifedipine microspheres.Nifedipine microspheres were prepared through solvent evaporation technique. In the preliminary screening, from the FTIR spectra, it was 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 of action.

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