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FORMULATION AND EVALUATION OF MUCOADHESIVE MICROSPHERES OF NIFEDIPINE

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ABSTRACT -The objective of this study is to develop, characterize, and evaluate mucoadhesive microspheres of Nifedipine employing mucoadhesive polymers for prolonged gastrointestinal absorption. Nifedipine, an effective antihypertensive that requires controlled release owing to its short biological half-life of 2.5 hours. The mucoadhesive microspheres were evaluated by in vitro and in vivo methods for controlled release.

Nifedipine has a short biological half-life of 2.5 h and is eliminated rapidly and its antihypertensive effect lasts only for few hours. As such controlled release products are needed for Nifedipine to prolong its duration of action and to improve patient compliance. Controlled release products also avoid the vasodilator related adverse effects such as increase in heart rate, flushing and palpitation associated with conventional Nifedipine tablets and capsules. The prepared microsphere of Nifedipine also gave good Micrometrics result, percent yield, drug entrapment and in-vitro release. In dissolution study of all formulations it was observed that change in process variables during the formulation of microspheres like stirring speed (RPM) and stirring time significantly affect the release rate of drug. The microspheres of F7 batch were found to be satisfactory in terms of percent yield, percent drug entrapment and in-vitro release; Surface morphology by stereomicroscope gives smooth surfaceof all batches.

KEYWORDS - Mucoadhesion, Polymers, Nifedipine, Amlodipine, Microspheres, Carpools

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INTRODUCTION -Over the last few decades the persistent quest for targeting drug delivery and improvement of pharmacokinetic properties of the drug in serum has tremendously grown and led to the development of different types of drug delivery strategies. Mucoadhesive drug delivery system is one such delivery technique which utilizes the properties of the oral mucosa as the site of drug delivery.

Mucoadhesion

Bioadhesion is usually defined as the state in which two materials are held together for an extended period of time by interfacial forces, one of the materials being biological in nature. In biological systems, Bioadhesion can be classified into three types:

- Adhesion between two biological materials, for example, platelet aggregation and wound healing
- Adhesion of a biological material to an artificial substrate, for example, bio- film formation on prosthetic devices and inserts
- Adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydro gels to soft tissues or the adhesion of sealants to dental enamel.

Nifedipine

Nifedipine the prototype of the dihydropyridine class of calcium-channel antagonists is similar to other dihydropyridine including amlodipine,f elodipine, isradipine and nicardipine. Nifedipine is used to treat Prinzmetal's angina hypertension, and other vascular disorders such as Raynaud's phenomenon by blocking the calcium-channels

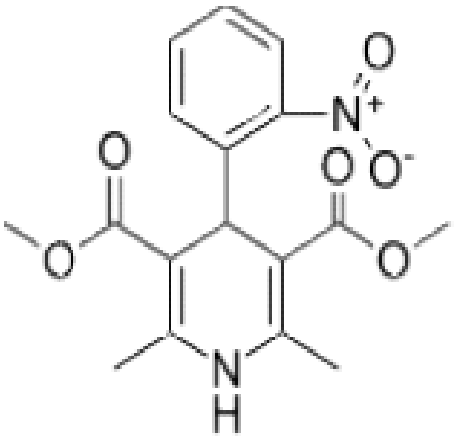

Fig.1: Structure of Nifedipine

Nifedipine inhibits the spasm of the coronary artery and dilates the systemic arteries, result in an increase of myocardial oxygen supply and a decrease in systemic blood pressure.

EXPERIMENTAL ANALYSIS AND RESULTS

PREFORMULATION

Organoleptic evaluation- It refers to the evaluation by sensory characters-taste,appearance, odor etc.

Solubility (at room temp. :)- Solubility is determined in different solvents example water,

methanol, 0.1 N HCL, Ethyl Alcohol, and Chloroform.

Identification Test

FTIR Spectroscopy

Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound. The region from 0.8 μ to 2.5 μ is called Near Infra-red and that from 15 μ to 200 μ is called Far infra-red region.

Loss on drying

Loss on drying is directly measured using IR moisture balance. The instrument is firstly calibrated and then 5.000 gm sample (powder) is weighed and placed on the pan of the balance. The temperature is set at 100°C to 105°C for 5 minutes and constant reading is observed for to check % moisture.

FORMULATION DEVELOPMENT

Preparation of Mucoadhasive Microsphere of Nifedipine

Mucoadhasive microsphere of Nifedipine was prepared by the solvent evaporation of RLPO, Carbopol used as mucoadhesive with HPMC and for solvent evaporation light liquid paraffin is used. All the ingredients along with the drug are dissolved in a slight excess of ethanol. Using a syringe, the solution was sequentially dropped into appropriate quantity into light liquid paraffin. Light liquid paraffin was stirred with a mechanical stirrer at 1000 rpm at 50^0C temperature for 45 min. by filtration. They were washed several times with petroleum ether and dried in vacuum oven at ambient temperature for 24 hr. The yield calculated by dividing the weight of the collected microspheres by the total weight of the non volatile components use for preparing the microspheres.

Table No 1: Formulations of the Mucoadhasive Microspheres Prepared

Sl. No	Formulation Code	Nifedipine(mg)	RLPO (mg)	Carbopol(mg)
1.	F1	50	50	-
2.	F2	50	100	-
3.	F3	50	150	-
4.	F4	50	200	-
5.	F5	50	-	50
6.	F6	50	-	100
7.	F7	50	-	150
8.	F8	50	-	200
9.	F9	50	25	25
10.	F10	50	50	50
11.	F11	50	75	75
12.	F12	50	100	100

EVALUATION OF MICROSPHERES

Measurement of mean particle size

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement.

Determination of zeta potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25 °C in triplicate.

Percentage Yield

The prepared microspheres with a size range of 609-874 µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

$$\% \text{ Yield} = \frac{\text{Actual weight of product x100}}{\text{Total weight of drug and polymer}}$$

In-vitro Release Studies

The drug release rate from Mucoadhasive microspheres was carried out using the USPtype II dissolution paddle assembly. A weighed amount of Mucoadhasive microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. One ml sample was withdrawnat predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition.

Shape and Surface Characterization of Mucoadhasive Microspheres by Scanning Electron Microscopy (SEM)

From the formulated batches of Mucoadhasive microspheres, formulations (F4) which showed an appropriate balance between the percentage releases were examined for surface morphology and shape using scanning electron microscope Joel Japan 6000. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 10 KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

STABILITY STUDIES FOR OPTIMIZED FORMULATION

The optimized formulation F7 was taken and accelerated stability study was performed by taking suitable quantity of microspheres. The microspheres were placed in air-tight glass container at 40±2°C/75±5% RH. At suitable sampling interval the samples were withdrawn and evaluated for various parameters.

Result

Organoleptic property of Nifedipine

Table No. 2 Organoleptic property of Nifedipine

Color	Light yellow to yellow powder
Odor	Odourless
Taste:	Bitter

Solubility studies of Nifedipine in different solvent

Table No. : 3 Solubility studies of Nifedipine in different solvent

Sl. No.	Solvent used	Solubility
1.	Water	Slightly soluble
2.	0.1 N HCL	Slightly soluble
3.	Ethanol	Soluble
4.	Methanol	Freely Soluble

Identification test by FTIR

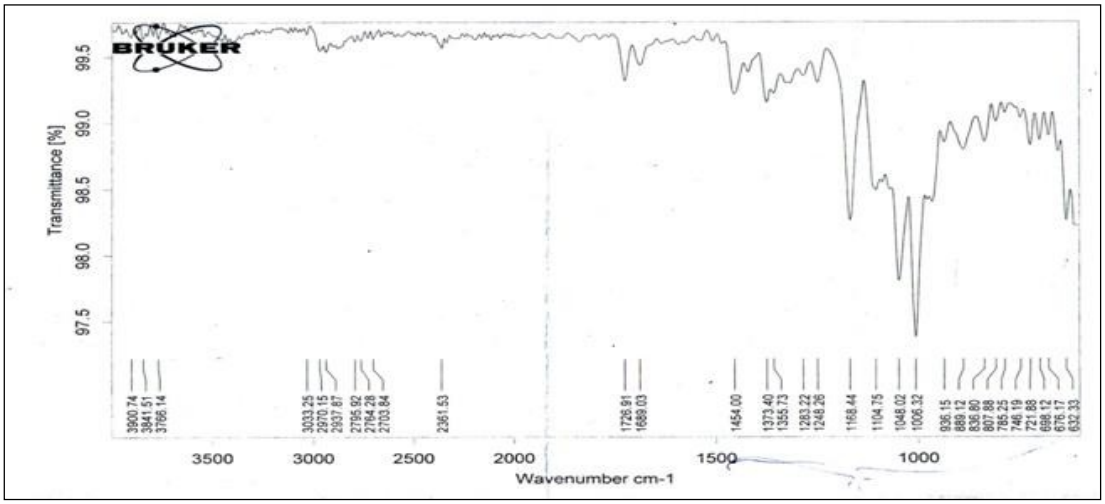

Figure No: 2. FT-IR Spectrum of Pure Drug (Nifedipine)

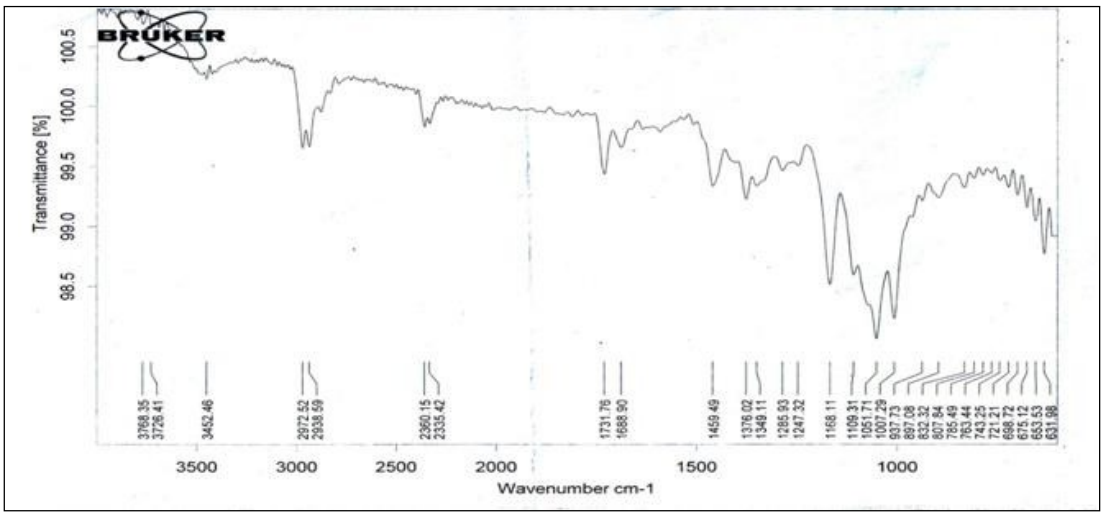

Figure No: 3. FT-IR Spectrum of Drug + Excipients

Loss on Drying (LOD)

Procedure: Loss on drying directly measuring by IR moisture balance. Firstly calibrate the instrument by knob then take 1 gm sample (powder) and set the temp at 100°C to 105°C for 5 minutes and constant reading set the knob and check % moisture.

Result: The percentage of loss on drying of Nifedipine was found to be **1.52**% w/w respectively

EVALUATION OF NIFEDIPINE MUCOADHESIVE MICROSPHERES:

Particle size analysis:

The mean size of the microspheres was determined by photo correlation spectroscopy (PCS) on a submicron particle size analyzer (Horiba Instruments) at a scattering angleof 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement. The results of measurement of mean particle size found: **272.0 nm.**

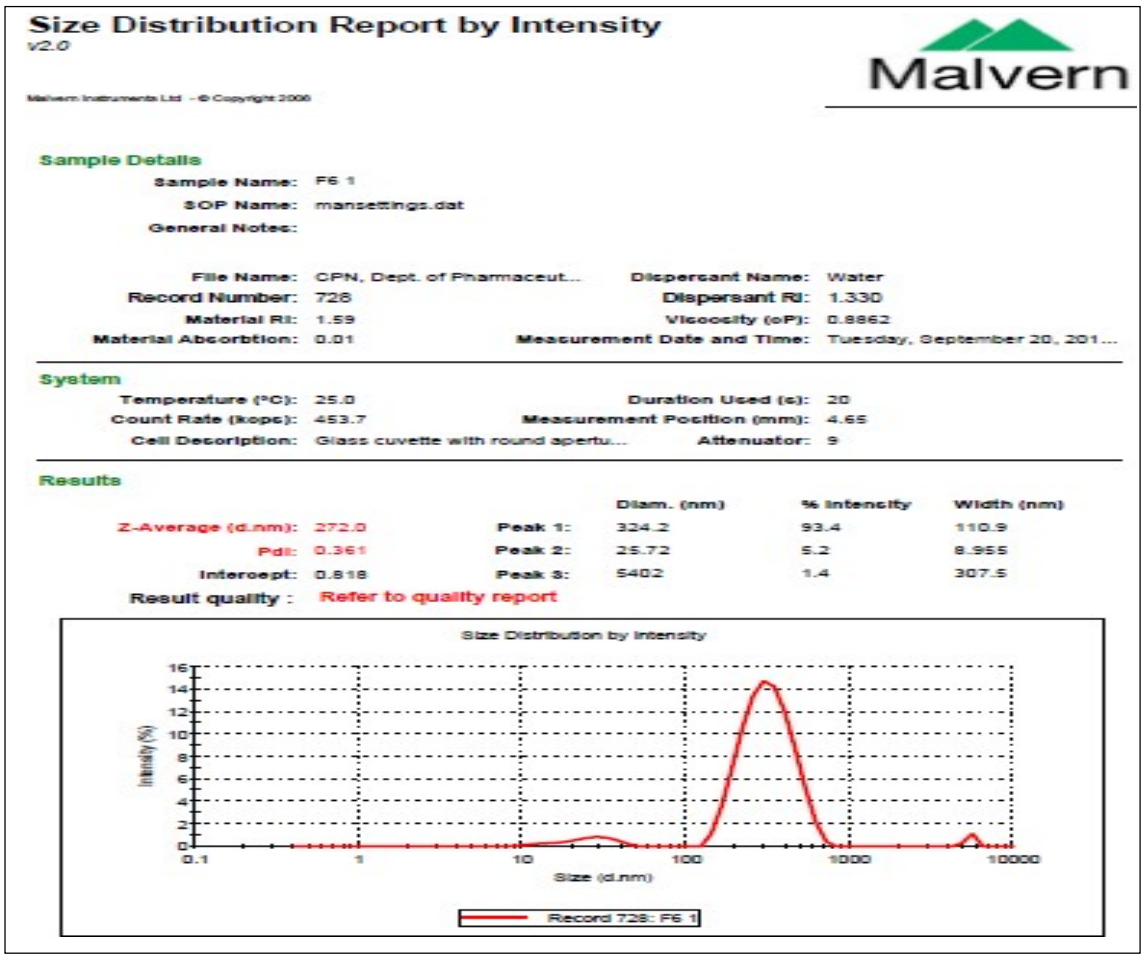

Fig. No. 4. Particle size data

Zeta Potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25 °C in triplicate. Results of zeta potential of optimized formulation F7 found: **-31.1mV.**

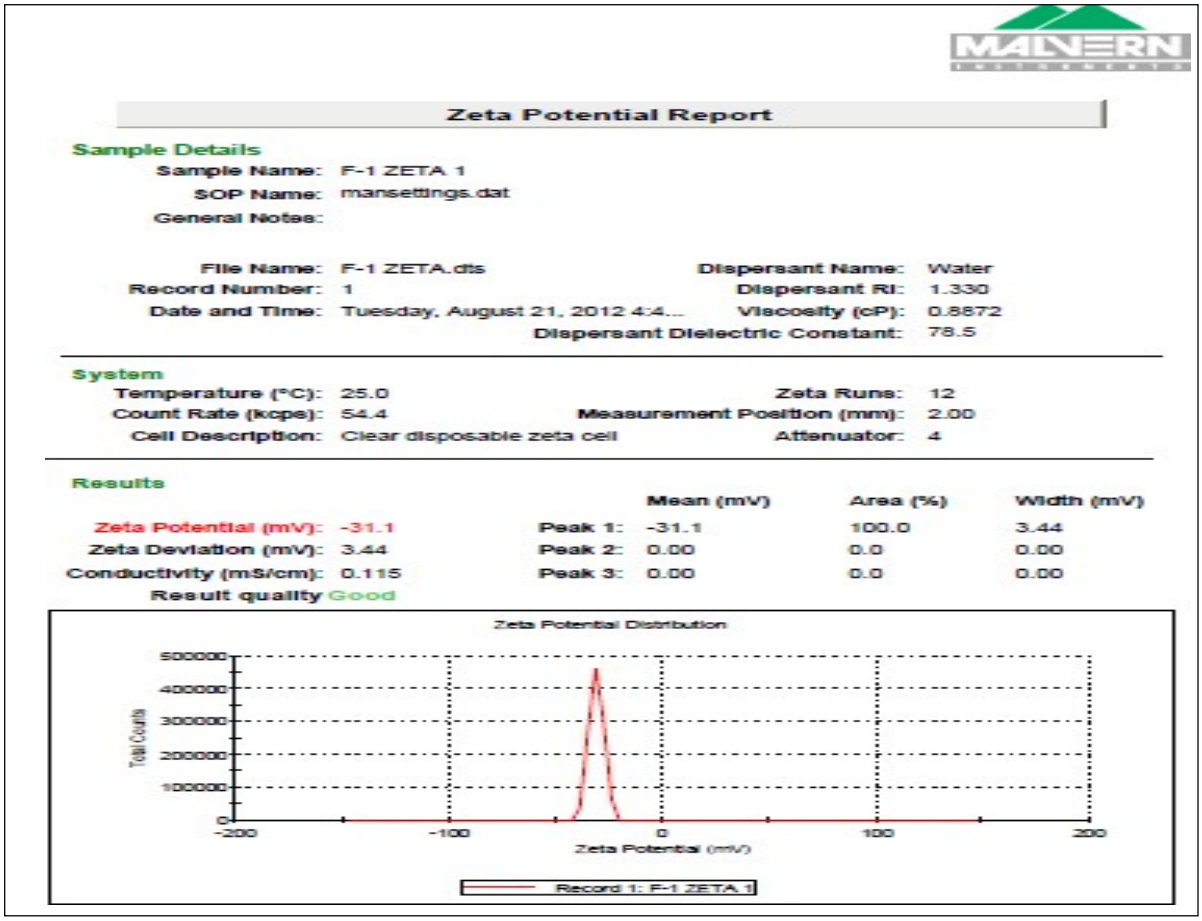

Fig. No.5: Zeta potential data

Percentage Yield Percentage yield of different formulation was determined by weighing the Microspheres after drying. The percentage yield of different formulation was in range of 56.84 - 82.87%.

Table 4: Percentage Yield

Formulation	Percent Yield (%)
F1	82.87
F2	78.53
F3	76.47
F4	71.56
F5	69.31
F6	66.03
F7	89.84
F8	78.89
F9	65.56
F10	60.56
F11	55.56
F12	56.65

IN-VITRO Drug release study

In vitro drug release study of Nifedipine loaded Microsphere

Table-5: *IN-VITRO* Drug release

Time	% of Drug Release											
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.5	9.78	12.00	12.00	11.36	14.21	12.63	14.21	13.25	13.25	12.25	11.25	10.25
1.0	10.16	11.43	11.43	12.06	21.86	14.28	19.65	18.56	15.56	13.25	12.25	11.25
1.5	13.68	13.39	13.39	18.44	25.14	28.25	28.23	25.56	20.25	18.56	15.56	14.56
2.0	15.34	15.36	15.36	24.86	27.49	29.04	36.66	35.59	30.56	25.56	22.12	20.32
3.0	20.16	23.97	23.97	30.36	32.70	32.99	40.33	38.89	35.56	32.25	30.54	25.56
4.0	27.85	31.68	31.68	24.21	35.08	36.01	50.03	48.89	45.56	40.56	35.56	32.56

Release Kinetics of Optimized Formulation

Zero order Release Graph

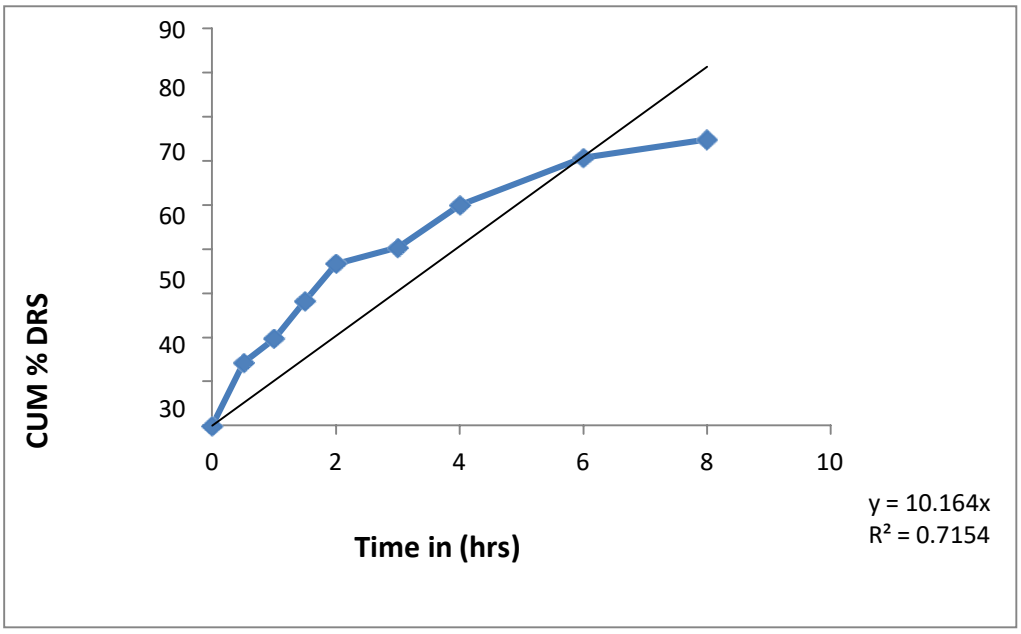

Fig. No. 6 Zero order Release Graph

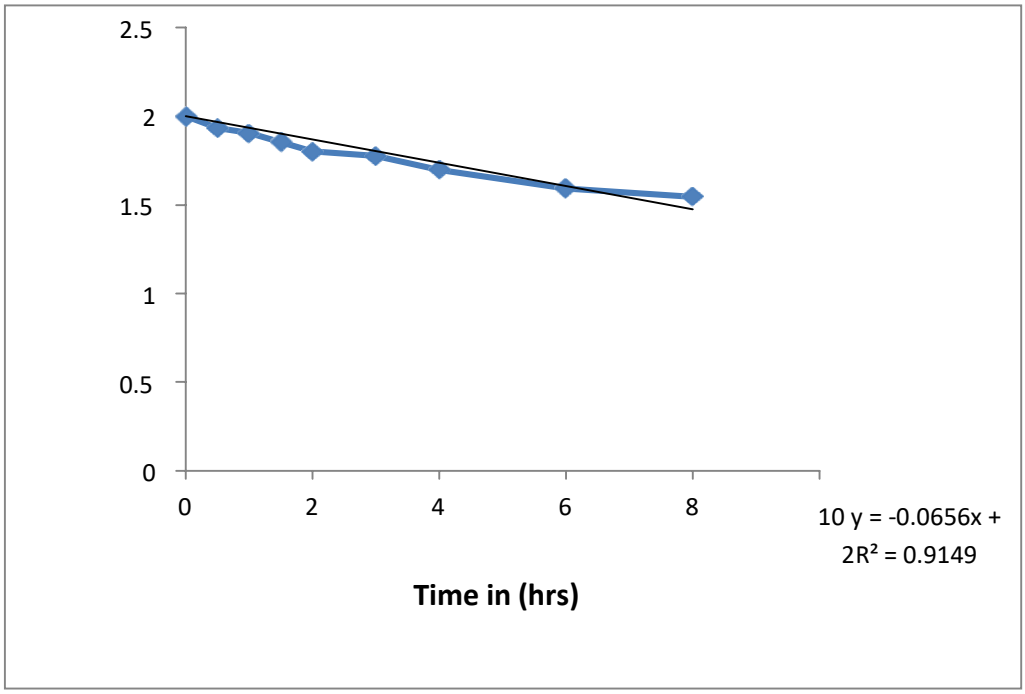

Fig. No. 7. First order Release Graph

STABILITY STUDIES OF FINAL FORMULATION

According to ICH guidelines, 3 months accelerated stability study at 40±2°c and 75±5% RH optimized formulation (F7) was carried. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference in the drug content between initial and formulations stored at 40±2°c & 75±5% RH for 3 months.

CONCLUSION

The objective of this study is to develop, characterize, and evaluate mucoadhesive microspheres of Nifedipine employing mucoadhesive polymers for prolonged gastrointestinal absorption. Nifedipine, an effective antihypertensive that requires controlled release owing to its short biological half-life of 2.5 hours. The mucoadhesive microspheres were evaluated by in vitro and in vivo methods for controlled release.

Nifedipine has a short biological half-life of 2.5 h and is eliminated rapidly and its antihypertensive effect lasts only for few hours. As such controlled release products are needed for Nifedipine to prolong its duration of action and to improve patient compliance. Controlled release products also avoid the vasodilator related adverse effects such as increase in heart rate, flushing and palpitation associated with conventional Nifedipine tablets and capsules

The present study was carried out to develop Mucoadhesive drug delivery System in the form of microsphere dosage form of Nifedipine by using Carbopol and RLPO and thereafter formulating the formulation. From the study it is observed that formulation act as prolonged dosage form. As the stirring speed increased the size of microsphere decreases and increases the released rate drug. The prepared microsphere of Nifedipine also gave good Micrometrics result, percent yield, drug entrapment and in- vitro release. In dissolution study of all formulations it was observed that change in process variables during the formulation of microspheres like

stirring speed (RPM) and stirring time significantly affect the release rate of drug. The microspheres of F7 batch were found to be satisfactory in terms of percent yield, percent drug entrapment and in-vitro release; Surface morphology by stereomicroscope gives smooth surfaceof all batches.

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