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RESEARCH ARTICLE

Formulation and Evaluation of Floating Drug Delivery of an Anti-Hypertensive Drug

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ABSTRACT:
Nifedipine is an anti-hypertensive drug which belongs to the dihydropyridine (DHP) class of calcium channel blockers (CCBs). The drug has short half-life of 2 hours and exhibits low bioavailability (45-55%). Hence the purpose of this study is to design Floating drug delivery system so as to prolong the gastric residence time as well as the drug release. Floating hollow micro particles (Microballoons) of Nifedipine were prepared using Eudragit S100 as polymer by solvent evaporation method. The effect of variables like drug to polymer ratio and volume of solvents on the physical characteristics of micro particles was investigated. The particle size distribution of the micro particles was determined using optical microscopy. The % drug loading and % entrapment efficiency of the micro particles were estimated by UV spectrophotometry. The surface morphology of micro particles was evaluated using scanning electron microscopy. *In vitro* buoyancy studies were performed in USP Type II (rotating paddle) dissolution apparatus. *In vitro* dissolution studies were performed in USP Type I dissolution apparatus with 0.1 N HCl (pH 1.2). Micro particles of F2 were found to demonstrate an average particle size of 227µ, prolonged buoyancy and complete drug release in 8 hours. Therefore, it can be concluded that F2 would be most suitable formulation which is likely to deliver most of the drug following oral administration.

KEYWORDS: Floating drug delivery, Nifedipine, Polymers, Micro Particles, Microballons.

1. INTRODUCTION:

Oral controlled drug delivery system:

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site of the body, to achieve and then maintain the desired therapeutic drug concentration that elicits the pharmacological action and to minimize the incidence and the severity of unwanted adverse effects. To achieve this goal, it would be advantageous and more convenient to maintain a dosing frequency to once daily, or at most, a twice-daily regimen dose. An appropriately designed extended release dosage form can be a major advantage in this direction.[1]

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Oral route is the most convenient and extensively used route for drug administration. This route has high patient compliancy, due to ease of administration. This route of administration has received more attention in the pharmaceutical field because of the flexibility in the designing of dosage. Most of the oral controlled drug delivery systems rely on diffusion and dissolution or combination of both mechanisms, to release the drug in a controlled manner to the Gastrointestinal Tract (GIT). The drug profile data, such as dose, absorption properties and the quantity of drug needed, is helpful to determine the desired release rate of the drug from controlled release dosage form.[2, 3]

Drugs that are easily absorbed from the G.I.T and having a short half-life are eliminated quickly from the blood circulation. To avoid this problem the oral Controlled release formulations have been developed, as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period of time.[4, 5]

The real challenge in the development of an oral controlled drug delivery system is not just to sustain the drug release but also to extend the presence of the dosage form in the stomach or the upper small intestine until all the drug release completely in the desired period of time. Gastro retentive systems can remain in the gastric region for several hours and significantly prolong the gastric residence time of drugs. Gastro retention helps provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

The residence of a drug delivery in the upper part of the GIT can be accomplished by several drug delivery systems, such as intragastric floating systems, swelling and expandable systems, bio adhesive systems, delayed gastric emptying systems and low density super porous systems. Floating dosage forms are designed to prolong the gastric residence time, increase the drug bioavailability, diminish the side effects of irritating drugs.[5] To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (~1.004 g/cm^3).[6, 7]

Certain types of drugs can benefit from using gastro retentive devices. These include drugs that act locally in the stomach, are primarily absorbed in the stomach; are poorly soluble at an alkaline pH, have a narrow window of absorption, and degrade in the colon.[8, 9]

Many attempts have been made to develop sustained-release preparations with extended clinical effects and reduced the frequency dosing. In order to develop oral drug delivery systems, it is necessary to optimize both the release rate of the drug from the system and the residence time of the system within the gastrointestinal tract.

FACTORS AFFECTING GASTRIC RETENTION:

There are several factors that can affect gastric emptying and hence gastric retention time of an oral dosage forms.[10, 11]

Density:
Gastric retention time is a function of dosage form buoyancy that isdependent on the density.

Size: Dosage form units with a diameter of more than 7.5 mm are reported to have ahigh GRT compared with those with a diameter of 9.9 mm.

Shape of dosage form:
Tetrahedron and ring shaped devices with a flexural modulusof 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

Single or multiple unit formulation:
Multiple unit formulations show a morepredictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Fed or unfed state:
Under fasting conditions, the GI motility is characterized byperiods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Nature of meal:
Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

Caloric content:
GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

Frequency of feed:
The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender:
Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface).

Age:
Elderly people, especially those over 70, have a significantly longer GRT.

Posture:
GRT can vary between supine and upright ambulatory states of the patient.

Concomitant drug administration:
anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.

Biological factors:
Diabetes and Crohn's disease etc.[10, 11]

APPROACHES TO GASTRIC RETENTION:

Various approaches have been used to increase the gastric retention time (GRT) of a dosage form in the stomach: [12, 13]

a) Floating Systems
b) Swelling and Expanding Systems
c) High density systems
d) Incorporation of passage delaying food agents
e) Ion exchange resins
f) Osmotic regulated systems

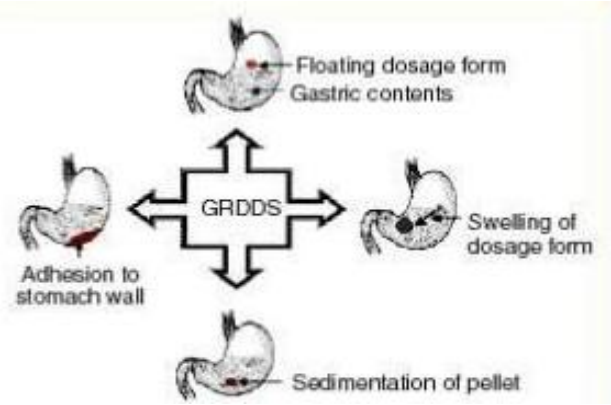

Figure.1. Approaches for gastro retentive drug delivery systems

Floating Systems:

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.[14]

2. METHODOLOGY:

1. Standard preparation of calibration curve of nifedipine:

a) Determination of absorption maxima (λmax):

A solution of Nifedipine having a concentration of 10µg/ml was prepared in 1.2pH buffer. The solution was scanned in the range of 200 - 400 nm and UV spectrum was taken.[15]

b) Preparation of calibration curve:

About 50 mg of pure Nifedipine was accurately weighed and transferred into 50 ml volumetric flask and dissolved in small quantity of Methanol. The volume was made upto the mark with Methanol to produce a standard stock solution I (SS-I) having a concentration of 1000 µg/ml. From the stock solution (SS-I) 2.5 ml was transferred into 25 ml volumetric flask and the volume was made up with pH 1.2 buffer solution to get stock solution II (SS-II) having a concentration of 100 µg/ml. From the stock solution II, aliquots were taken and diluted suitably with pH 1.2 buffers to obtain working standard solutions having concentrations of 2, 4, 6, 8, 10, 12, 14, and 16µg/ml. The absorbance of the solutions was measured at 237 nm using pH 1.2 buffers as reference in a spectrophotometer. Each concentration was analyzed in triplicate. Linearity of standard curve was assessed from the square of correlation coefficient (r^2) which was determined by least-square linear regression analysis. A graph was plotted for absorbance versus concentration.[15-18]

2. Preformulation studies:

2.1 Drug- Excipient Compatibility Studies:

Assessment of drug-excipients compatibility is very important to identify product's stability as well as its reproducibility with ensured therapeutic efficacy. IR spectral studies were done to study drug and polymer compatibility.

Method:

In order to check the integrity (Compatibility) of drug in the formulation, IR spectra of the selected formulation along with the drug and other excipients were recorded and compared using JASCO V460 PLUS IR spectrometer by diffuse refluctance technique. The samples were thoroughly mixed with dry powdered potassium bromide. The powder samples were placed in the spectrophotometer and the spectrum was recorded.

3. Preparation of holllow microspheres of nifedipine:

Microspheres were prepared by solvent evaporation method. Dispersed phase was added to the continuous phase at a pre-determined temperature and stirring speed to obtain hollow drug containing microspheres.

Preparation of solution for dispersed phase:

Required amount of polymer was taken in a 50 ml beaker. To this required amount of Dichloromethane and Ethyl alcohol were used as solvents in appropriate ratio (5:3 or 3:5). Total volume of the solvents was kept constant at 8ml. The mixture was stirred using a magnetic bead over a magnetic stirrer to obtain a clear transparent polymeric solution. Accurately weighed quantity of drug was added to this polymeric solution, and further stirred to obtain a completely homogenous solution containing the drug and polymer.

Table 1: Composition of formulations F1 to F8

INGREDIENTS	FORMULATIONS							
	F1	F2	F3	F4	F5	F6	F7	F8
Nifedipine (mg)	200	200	200	200	200	200	200	200
Eudragit S100 (mg)	100	200	400	600	100	200	400	600
Dichloromethane(ml)	5	5	5	5	3	3	3	3
Ethanol(ml)	3	3	3	3	5	5	5	5
Polyvinylalcohol(w/v)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15

Preparation of solution for continuous phase:

About 0.15% Solution of PVA (Mol. Wt. 125000) in Distilled water was prepared by heating the required quantity of PVA in a 500 ml. beaker on a hot plate at a temperature of 85º C. The setup was stirred at a constant speed of 500 RPM for approximately 30 minutes, till a clear solution was obtained. The solution was cooled using a water bath to room temperature. The pH of this solution was adjusted to the appropriate value (pH 2.0) using freshly prepared solutions of 0.1 N HCl.

Preparation of microspheres:

About 200 ml. of 0.15% PVA solution in a 500 ml beaker, adjusted to required pH was kept over a hot plate and maintained to 40º C, with constant stirring speed of 400 RPM, employing a variable speed propeller stirrer. The temperature was constantly monitored using a Celsius thermometer. As soon as required temperature of 40°C was attained, the previously prepared drug-polymer solution was added to the continuous phase immediately, to obtain a dispersion of microspheres, which were stirred constantly at 400 RPM at a temperature of 40º C for approximately 1hour, till the solvents of dispersed phase (i.e. DCM and Ethyl alcohol) were completely removed by evaporation, leaving behind hardened microspheres. The freshly prepared microspheres were filtered using a Whattman filter paper and dried in a Hot air oven at 40ºC to obtain dry uniformly sized microsphere.

4. Characterization of prepared nifedipine hollow microspheres (Microballoons):

4.1 Percentage yield:

The percentage yield of Nifedipine microballoons was calculated by the following formula

Percentage Yield = Actual weight of the product/Total weight of the Product X 100

4.2 Micromeritic studies:

Nifedipine microballoons were characterized for theirmicromeritic properties such as particle size and shape.

Particle size and shape:

The surface morphology and internal structure of the products were observed by Scanning electron microscopy.

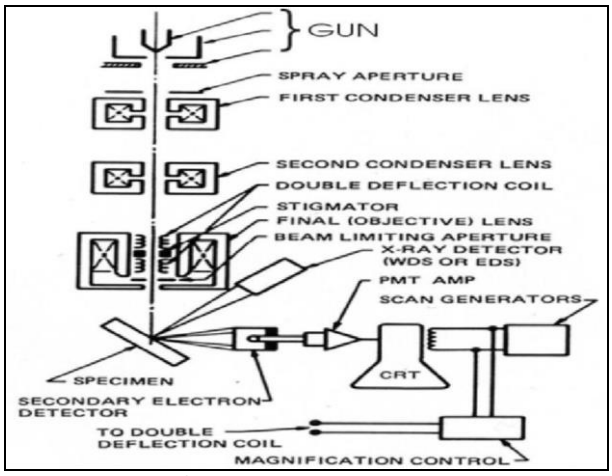

Figure.2 Diagram of Scanning Electron Microscope

Cleaned brass specimen studs were used for mounting the samples. Wet solvent paint was applied on these studs. While the paint was wet, the pellets were placed on each stud and allowed to dry. Then the samples were observed in the JSM -6440 scanning electron microscope and the photographs were taken.

Optical microscopy:

Nifedipine Hollow microspheres (Microballoons) wereobserved under 4X magnification in an optical microscope and an average of 200-400 particles were counted.

4.3. Hausner's ratio:

Hausner's ratio of microspheres is determined by comparing the tapped density to the Bulk density using the equation:

Hausner's ratio=Tapped density/ Bulk density

Bulk Density= Weight of Powder/ Bulk volume

Tapped density= Weight of powder/ Tapped volume

4.4. Drug encapsulation efficiency:

Microballoons containing 10 mg equivalent of Nifedipine were finely triturated and taken in 10 ml volumetric flask. The content was dissolved in methanol by sonication for about 15 min. From the above solution 0.1 ml of sample was withdrawn and transferred into 10 ml volumetric flask and the volume was made with methanol. The absorbance of the resulting solution was measured at 237 nm, using pH 1.2, 0.1 N HCl as blank. All the analysis was carried out in triplicate. The

percentage drug encapsulation efficiency was determined using the following equation,

$$\% \text{ Drug Encapsulation efficiency} = \frac{\text{Actual drug content of microballons}}{\text{Theoretical drug content of microballons}} \times 100$$

4.5. *In-vitro* buoyancy studies:

In-vitro buoyancy studies were performed in dissolution test apparatus USP type II(rotating paddle). About Microballoons containing 10 mg equivalent of Nifedipine were taken and added to the dissolution flask containing 0.1N HCl as medium (500 ml) containing Tween 20 (0.02%). Temperature was maintained at 37ºC ± 0.5 ºC for 8h at a paddle speed of 50 rpm. The floating and the settled portion of hollow microspheres (microballoons) were recovered separately after 8h. Buoyancy percentage was calculated as the ratio of the weight of microballoons that remained floating and the total weight of hollow microspheres (microballoons) taken.

$$\textit{Buoyancy (\%)} = \frac{Q_f}{Q_f + Q_t} \times 100$$

Where,
Q_f and Q_s are masses of floating and settled microspheres respectively.

4.6. *In-vitro* drug release studies:

In-vitro drug release was studied using dissolution test apparatus USP type 1 method. The drug loaded microballons equivalents to Nifedipine were tied in muslin cloth. The muslin bag was placed in the basket of the dissolution apparatus containing 500 ml of 0.1N HCl with 0.02 w/v% Tween 20. The temperature was maintained at 37±0.5 ºC and basket rotating speed at 100 rpm. About 10 ml of aliquot was withdrawn at regular predetermined intervals and equal volume of fresh dissolution medium was replaced each time. The samples taken were analyzed spectrophotometrically at 237 nm using 0.1N HCl as blank. All the analysis was carried out in triplicate.

5. RELEASE KINETICS:

To analyze the *in vitro* release data, various kinetic models were used to describe the release kinetics. The drug release profile obtained in dissolution test was plotted in different models.

5.1 Zero order rate kinetics describes the system where the drug release rate is independent of concentration and plotted as amount of drug release versus time.

$$\mathbf{C = K_0 t \text{.....eq}}$$

Where,
K_0 is the zero order rate constant, expressed in units of concentration/ time. t is the time in hours.

5.2 First order rate kinetics describes the release from system where release rate is concentration dependent and shows the log cumulative percentage of drug remaining in insoluble matrix as a time dependent process (log% drug remained v/s time in hr).

$$\mathbf{\log C = \log C_0 - kt/2.303 \text{.....eq}}$$

C_0 is the initial drug concentration. C is the drug concentration at time t.

K is the first order rate constant reflecting the design variables of the system. t is the time in hours.

5.3 Higuchi square root kinetics describes the release of drug from insoluble matrix as a square root of time dependent process based on Fickian diffusion equation. (% cumulative release v/s square root of time).

$$\mathbf{Q = Kt^{1/2} \text{.....eq}}$$

Where, Q is the percentage of drug release at time t.
K is Higuchi release rate constant that reflects the shape and the internal structure of the matrix as well as the drug concentration and solubility .

5.4 Korsmeyer-peppas model which is log cumulative % drug release vs. log time is used to find out the mechanism of drug release (log % cumulative release v/s log time)

$$\mathbf{Q = K_2 t^n \text{..... eq}}$$

Where, K_2 is a constant incorporating the structural and geometric characteristics of the matrix tablets
n is the release exponent indicating the drug release mechanism.

Table.2 Diffusion exponent and release mechanism

N	Mechanism
0.48	Fickian Diffusion
0.48<n<1	Anomalous Transport/non fickiandiffusion (First Order)
0.85	Case-II Transport (Zero Order)
n>0.85	Super Case-II Transport

3. RESULTS:

3.1 Preparation of calibration curve of nifedipine:

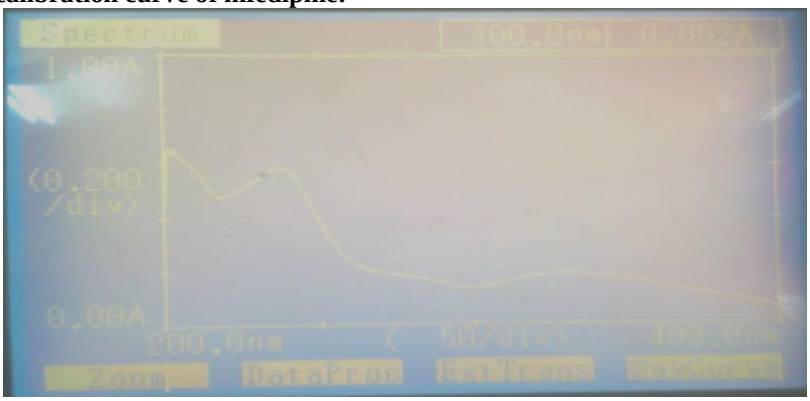

Figure.3: UV Spectrum of Nifedipine

Data for Calibration curve of Nifedipine

Table no. 3. Calibration curve of Nifedipine

S. No	Vol. of SS-II (ml)	Vol. made up to	Conc. (µg/ml)	Absorbance at 237 nm			Average	±SD
				Trail-I	Trail-II	Trail-III		
1	0.2	10 ml	2	0.1419	0.1423	0.1421	0.1421	0.00020
2	0.4		4	0.2734	0.2735	0.2736	0.2735	0.00010
3	0.6		6	0.3913	0.3915	0.3916	0.3915	0.00015
4	0.8		8	0.5227	0.5225	0.5229	0.5227	0.00020
5	1		10	0.6526	0.6527	0.6530	0.6527	0.00020
6	1.2		12	0.8219	0.8218	0.8221	0.8219	0.00015
7	1.4		14	0.8933	0.8930	0.8931	0.8931	0.00015

Standard graph of Nifedipine:

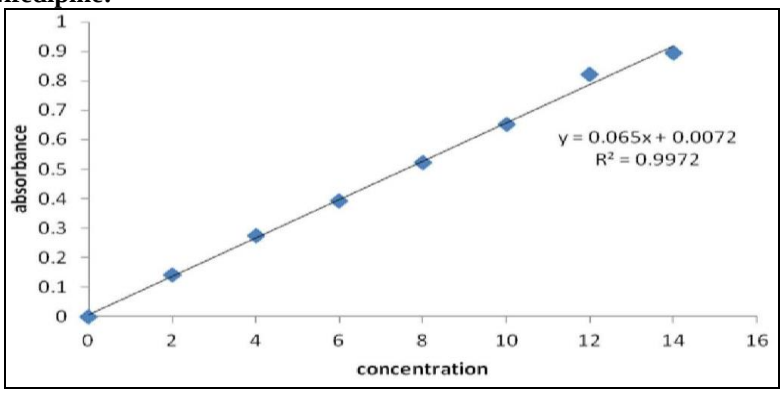

Figure.4: Standard plot of Nifedipine

3.2. PREFORMULATION STUDIES:

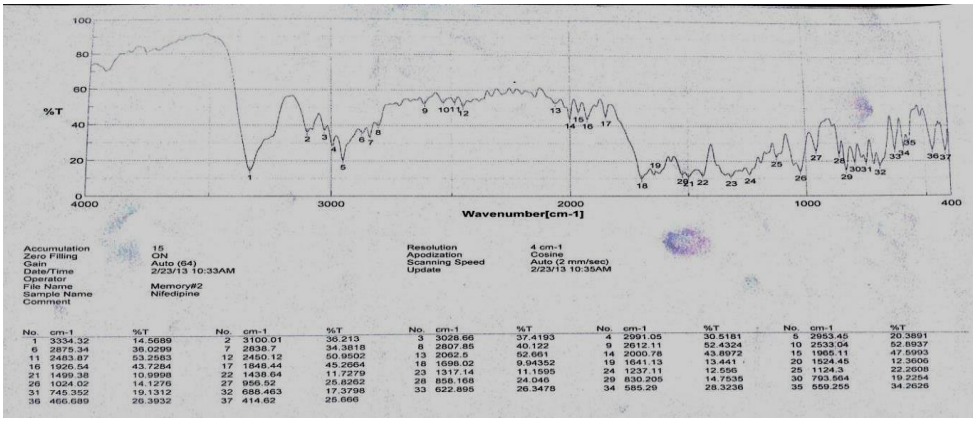

Figure.5: IR spectrum of pure Nifedipine

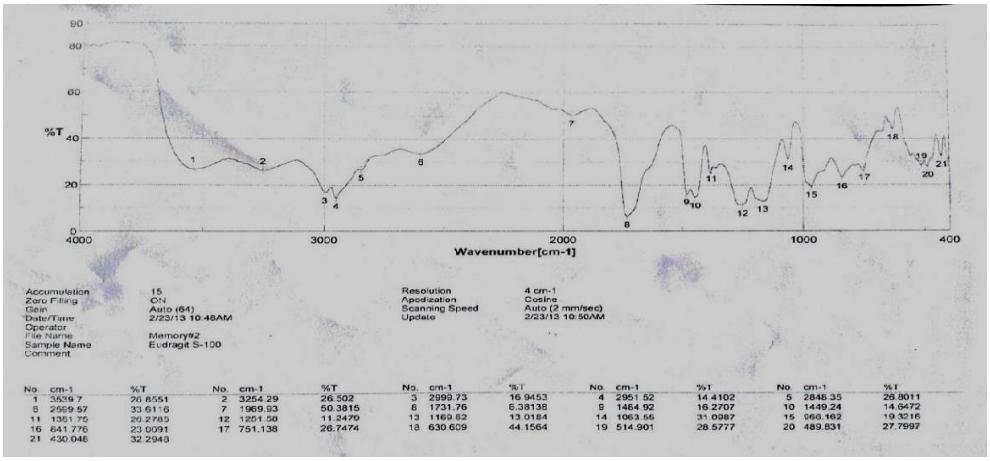

Figure.6: IR spectrum of Eudragit S100

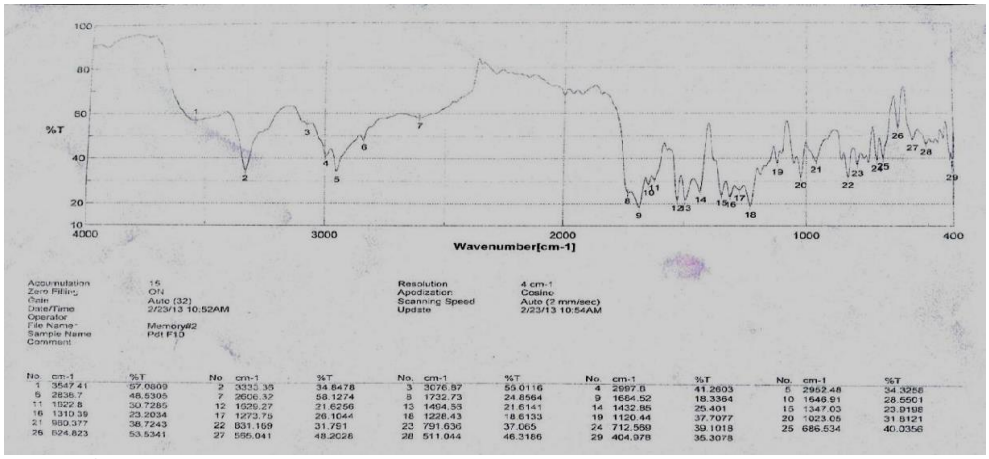

Figure.7: IR spectrum of product

Table no.4 Compatibility Studies: Fourier transform infrared (FTIR) spectrum

Group	Literature value	Nifedipine	Eudragit S100	Formulation of Nifedipine Microballoons
-NH	3250-3400	3334	-	3333
-CHAromatic	3000-3100	3100	-	3076
-CH Alkane	2850-3000	2875	2999	2997
-C=O	1690-1760	1698	1731	1732
N-O	1475-1550	1499	-	1494
Asymmetric N-O	1290-1360	1317	-	1310
C-O	1000-1320	1237	-	1228
OH	2500-3300	-	3254	3076

3.3 EVALUATION PARAMETERS OF FLOATING MICROPARTICLES:

3.3.1 EFFECT OF STRING RATE:

Table no: 5. Effect of stirring rate

S. No	Ratio	Stirring in rpm	Physical Appearance	Particle size	% Yield
1		100	_		_
2	1:1	200	Irregular Large		71.1
3	1:1	300	Spherical	650	76.9
4	**1:1**	**400**	**UniformSpherical**	**402**	**89.68**
5	1:1	500	Uniform Spherical	361	74.32
6	1:1	800	Uniform Spherical	312	60.96
7	1:1	1000	Uniform Spherical	204	43.18

3.3.2 EFFECT OF CONCENTRATION OF PVA IN CONTINOUS PHASE:

Table no: 6. Effect of Concentration of PVA in Continuous Phase

S. No.	Drug: polymers	PVA (%W/V)	Physical Appearance	Particle size µm	% Drug content	% Entrapment
1	1:1	0.05	Micro particles were not formed	_	_	_
2	1:1	0.1	Spherical	353	43.64	87.29
3	**1:1**	**0.15**	**Uniform Spherical Rigid**	**289**	**41.79**	**83.58**
4	1:1	1.00	Fibrous product few spherical	258	36.54	73.08
5	1:1	5	Viscous and foaming solution	_	_	_

3.3.3EFFECT OF DISPERSED PHASE VOLUME ON MICROBALLOONS:

Table no: 7 Effect of Dispersed Phase volumes on Microballoons

S. No.	Internal Volume (ml) (Dichloromethane : Ethanol)	Physical Appearance	% Yield	% Drug Content
1	10:10 (20)	Fibrous product	10	_
2	7:7 (14)	Fibrous product	23	_
3	7:5 (12)	Irregular large	35	47.12
4	5:5 (10)	Few Spherical	30	38.53
5	**5:3 (8)**	**Spherical**	**78.33**	**46.91**

FORMULATION OF MICROBALLOONS:

Table no: 8. Variables used for the formulation of microballoons

S No.	Variables	Essential consideration
1	Dispersed phase	Dichloromethane: Ethanol
2	Continuous phase	Water
3	Nifedipine	200 mg
4	Concentration of polymer	200 mg
5	Concentration of PVA	0.15 (%w/v)
6	External volume	200 ml
7	Internal volume	8 ml
8	Stirring speed	400 rpm
9	Stirring time	1 hr
10	Temperature	40^0C

3.3.4 THE SUITABLE VARIABLES FOR THE

3.4 CHARACTERIZATION OF PREPARED NIFEDIPINE MICROBALLOONS

3.4.1 Characterization of formulations F1 to F8

Table no.9.: Characterization of formulations F1 to F8

S. No	Formulation code	% yield	Mea Particle n Size µm	% buoyancy after 8 hrs	%Drug content	% Entrapment efficiency
1.	F1	70.00	135	93	46.65	69.98
2.	F2	83.00	227	91	42.01	84.02
3.	F3	72.00	386	83	29.36	88.02
4.	F4	52.00	510	75	23.16	92.64
5.	F5	68.33	169	73	39.89	59.84
6.	F6	71.66	271	86	40.06	80.06
7.	F7	55.00	355	74	27.37	82.11
8.	F8	74.00	190	68	22.91	91.64

3.4.2 Micrometrics properties:

Table no:10. Micromeritic properties of formulation F1 to F8

S. No	Formulation code	Bulk density	Tapped density	Hausner's ratio
1	F1	0.303	0.380	1.25
2	F2	0.310	0.360	1.16
3	F3	0.301	0.380	1.26
4	F4	0.321	0.390	1.21
5	F5	0.324	0.390	1.20
6	F6	0.352	0.436	1.23
7	F7	0.361	0.432	1.19
8	F8	0.381	0.455	1.22

3.4.3 *In vitro* drug release profile

Table no: 11.*In vitro* drug release profile of formulations F1 to F4

Time (hour)	F1	F2	F3	F4
1	14.7788	14.1095	10.9918	6.0167
2	24.1170	23.5518	15.3675	12.5369
3	33.1415	32.6171	27.4561	23.1574
4	42.6601	39.0064	31.1234	28.1851
5	51.8634	45.8116	38.5518	34.2259
6	49.5416	51.5421	44.8852	37.0706
7	57.7399	62.3143	56.4970	45.4230
8	66.9181	72.4761	64.3321	57.0736

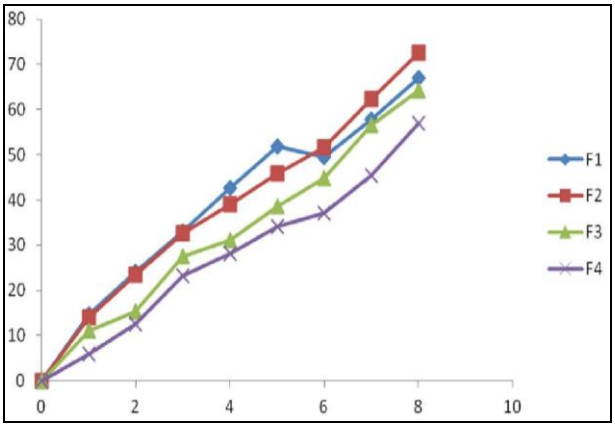

Figure.8. *In vitro* drug release profiles of the formulations F1to F4

Table no: 12*In vitro* drug release profile of formulations F5 to F8

Time (hour)	F5	F6	F7	F8
1	13.7784	13.9964	9.0001	5.7932
2	22.7153	25.7732	13.8927	10.9783
3	31.9891	31.4456	24.0341	19.0541
4	41.1130	38.6645	28.9978	23.9786
5	49.8869	44.2532	35.1193	31.0001
6	47.1077	50.6317	39.2194	36.6783
7	55.9324	63.5621	45.1127	43.0987
8	63.4511	66.4352	59.1028	51.1337

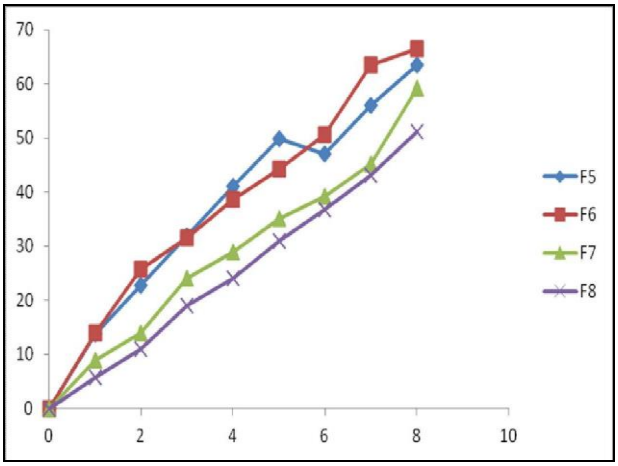

Figure.9: *In vitro* drug release profiles of the formulations F5 to F8

3.4.4 Scanning Electron Microscopy (SEM):

SEM photographs of hollowmicrospheres loaded with NFD showing surface dents and hollowness.

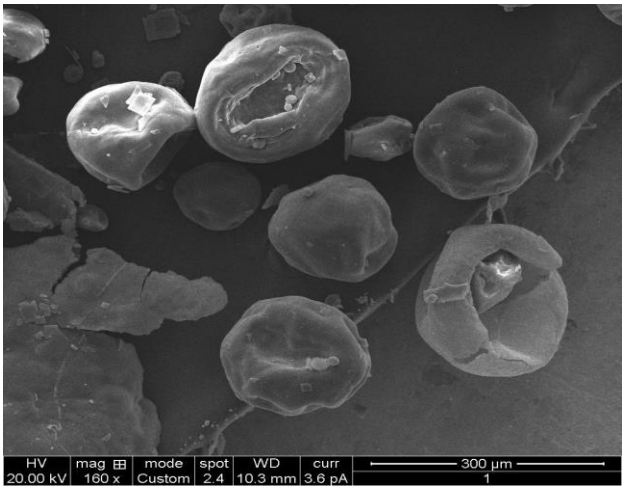

Figure.10: SEM pictures of Microballoons

3.5 RELEASE KINETICS:

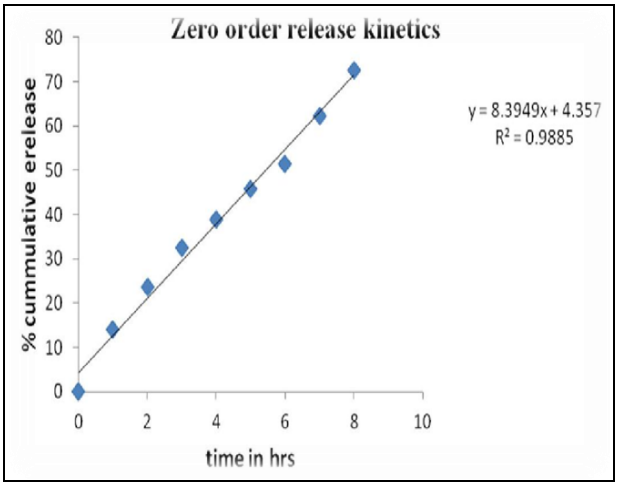

Figure.11: Zero order plot of optimized formulation

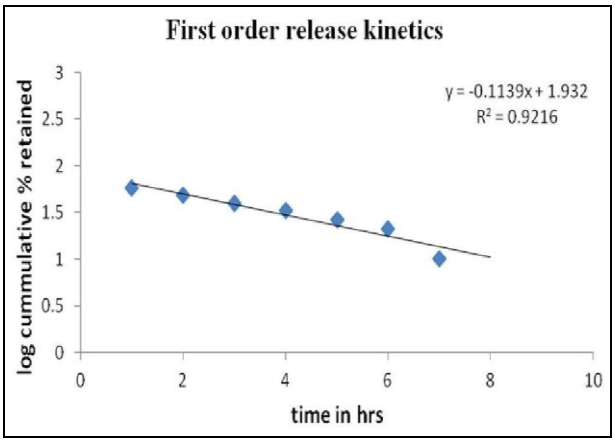

Figure.12: First order plot of optimized formulation

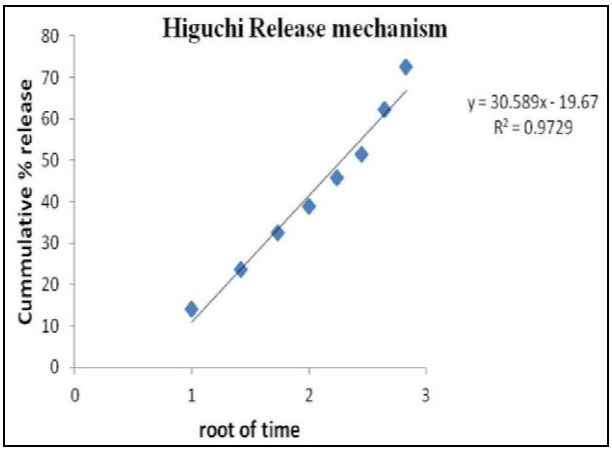

Figure.13: Higuchi plot of optimized formulation

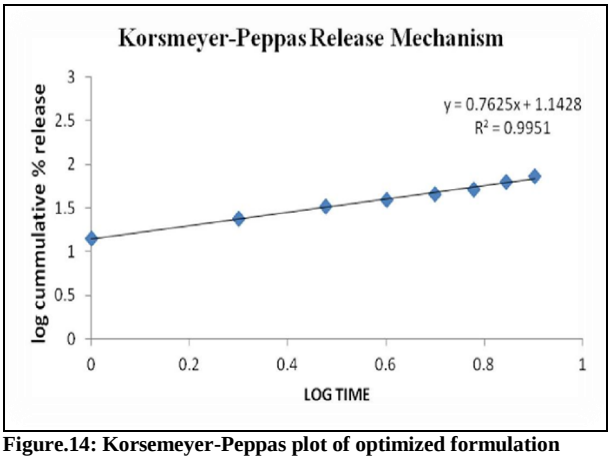

Figure.14: Korsemeyer-Peppas plot of optimized formulation

3.5.1 Regression Coefficient and Slope values for various kinetic models

Table no 13: R^2 and slope values for various kinetic models

	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
R^2	0.9626	0.9216	0.8835	0.9951
Slope	9.1638	0.1139	21.68	0.7625

4. DISCUSSION:

4.1 Standard graph:

When standard solution of Nifedipine (NFD) scanned in pH1.2, the peak position was observed at 237 nm in all cases. Calibration curve of NFD was developed using 0.1 N HCl (pH 1.2). A simple reproducible method of estimation of NFD in 0.1 N HCl (pH 1.2) was developed at 237 nm. The procedure was repeated for three times and average value of absorbance was obtained. Average value of absorbance vs. concentration was plotted and the data was subjected to regression analysis. The standard curve (Fig.4) was found to be linear in the concentration range of 2 - 14 µg/ml in pH 1.2 with a regression coefficient of 0.997 and slope 0.0657.

4.2. Preparation of Microballoons of NFD and selection of formulation:

Nifedipine is a potent vasodilator used in the management of hypertensive emergencies particularly in patients with impaired renal efficiency during pregnancy and also used as a single drug in hypertensive patients with diabetes mellitus, as it does not affect the secretion of gluco regulatory hormones1[1]. It acts as an efficient calcium channel blocker with short half-life of 2 hours and bioavailability (45-55%). Drugs that are easily absorbed from the gastrointestinal tract (GIT) and having a short half-life are eliminated quickly from the blood circulation. To avoid this problem, the oral controlled-release (CR) formulations have been developed as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period of time. Such oral drug delivery devices have a restriction due to the poor gastric retention time (GRT), a physiological limitation. The GRT can be increased by loading NFD in floating hollow microspheres (Microballoons), which are useful in the effective management of hypertension with a single dose.

For the preparation of microballoons of NFD, solvent evaporation method was applied. Eudragit S100 was used as polymer. Preformulation studies indicated absence of interaction between the drug and the polymer. Initial trails were done to identify the right processing parameters like stirring rate, concentration of the continuous phase, volume of solvents in dispersed phase and the drug polymer ratio. The prepared initial formulations were evaluated for percentage yield, particle size and shape and % drug entrapment.

Based on the initial trials the right parameters were: stirring speed was 400 rpm and the temperature was maintained at 40ºC. Acceptable microparticles were obtained with 0.15% PVA solution as a continuous phase.

Eight Formulations (F1-F8) were prepared using various drug polymer ratios (1:0.5, 1:1, and 1:2) and different volumes in dispersed phase. The microballoons were evaluated for yield, surface morphology, drug entrapment, buoyancy and *in vitro* cumulative release.

Various factors that influence the properties of microballoons includes

1. Stirring speed:

Stirring speed is the dominating factor because it provides the energy to disperse the oil phase in water. Our experimental results demonstrate that a high stirring speed yields smaller microparticles because the emulsion formed is broken up into smaller droplets at a higher input power. However, yield was lower because microparticles are broken down into finer globules at a higher input power. Thus, the stirring speed needs to be optimized in order to obtain a sufficiently high yield of microparticles with a desired size distribution.[24]

2. Effect of concentration of PVA in continuous phase:

PVA concentration in the external water phase is known to be a key factor to influence the size of microspheres. Since PVA is a polymer with a high molecular weight, the presence of PVA in the external water phase may increase the viscosity of the emulsion, resulting in an increased difficulty in breaking up the emulsion into smaller droplets[25]. Thus, this yields bigger microspheres. On the other hand, the presence of PVA in the external water phase stabilizes emulsion droplets against coalescence, resulting in smaller emulsion droplets. In the present work on increasing concentration of PVA affected the particle size appreciably and high concentration of PVA gave threading and film on drying resulting on fibrous product.

3. Effect of dispersed phase volume:

Many trails were conducted with varying the Dichloromethane and Ethanol ratio. High volumes did not give the product. The volumes of 5:3ml of Dichloromethane:Ethanol respectively was most suitable. The gas generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The volume of Dichloromethane affected the % buoyancy as it is responsible for the formation of cavity.

4.3 Evaluation of Hollow microparticles (Microballoons):

(a) Scanning Electron Microscopy (SEM):

The scanning electron microscope (SEM) uses a focused beam of high-energy electrons to generate a variety of signals at the surface of solid specimens. The signals that derive from electron-sample interactions reveal

information about the sample including external morphology (texture), chemical composition, and crystalline structure and orientation of materials making up the sample. Areas ranging from approximately 1cm to 10µ in width can be imaged in a scanning mode using conventional SEM techniques. SEM is an electron optical imaging technique that provides photographic images and elemental information. The sample was placed in the evacuated chamber and scanned in the controlled pattern by an electron beam. Interaction of the electron beam on the specimen produces a variety of physical phenomena that when detected were used to form images and provided elemental information about the specimen(Fig.10).

SEM studies were carried out for the formulations. Microballoons were found to be spherical with a surface dents and hollow cavity. However, the particles were found to be aggregated as the amount of polymer increased.

(b) Drug content and % entrapment:
Better drug loading and encapsulation efficiency was observed in formulation with higher amount of Eudragit S100. Eight different formulations were formulated and all the formulations gave satisfactory product. The entrapment efficiency was found to depend upon drug loading. Drug content and % entrapment of these formulations were calculated. Among these formulations, F2 have the highest drug content and % entrapment efficiency.

(c) *In vitro* buoyancy studies:
The prepared formulations F1-F8 were subjected to *in vitro* buoyancy study using dissolution test apparatus USP type II at pH 1.2 for 8 hours. Among all formulations % Buoyancy was found to be higher for F2 formulation. The formulations performed with low DCM volume (F5-F8) showed very low % buoyancy comparatively than the formulations performed with high DCM volume (F1-F4). DCM was responsible for the formation of cavity in microparticles.

(d) *In vitro* release study of Nifedipine loaded microballoons:
The prepared formulations F1-F8 were subjected to *in vitro* dissolution study in USP apparatus type I at pH 1.2 for 8 hours. Among all formulations, F2 formulation was found to be the most buoyant and released most of the drug i.e 72.4761 % in 8h. As the polymer ratio increased the drug release decreased.

To know the mechanism of drug release from these formulations, the data was fitted to different kinetic models and based on correlation coefficients (R), the best fitted models were determined. The drug release rate kinetics was calculated for zero order, first order, Higuchi model and Peppas-Korsemeyermodels(Fig.13).

5. MECHANISM OF RELEASE:
The release mechanism of optimized formulation F2 was determined by subjecting the dissolution data to different kinetic models such as Zero order, First order, Higuchi model and Korsemeyer-Peppasequations (Fig.14).

The R^2 values of Korsemeyer-Peppas release as well as R^2 values of zero order release pattern of formulation F2 was near to one. Formulation F2 follows zero order kinetics and super case II transport as "n" value was found to be 0.9626 and 0.9951 respectively (Table.13).

6. SUMMARY AND CONCLUSION:
In the present study an attempt was made to formulate and evaluate gastroretentive floating hollow microspheres (Microballons) of Nifedipine.

The main objective was to enhance gastric residence time and drug release. Many trails were conducted in order to optimise stirring speed, effect of concentration of PVA in continuous phase, effect of dispersed volume. The initial trials of formulated floating hollow microspheres were evaluated for parameters like shape, yield and drug entrapment to optimize the formulation. Dichloromethane, ethanol, PVA were employed in formulation of Eudragit S100 floating hollow microspheres (Microballons). Concentrations of polymer and volume of solvents were varied to achieve best results which were evaluated for buoyancy and *in vitro* drug release.

In formulation F2, mean particle size was 227µm, percentage buoyancy was 91 after 8h, drug entrapment was found to be 86%. The drug release in the acidic buffer pH 1.2 was found to be 72.47% after 8h. The SEM photographs of hollow microspheres loaded with NFD revealed the surface was dents and hollowness. The I.R spectra of prepared microballons showed no major variations in the peaks of the drug, indicating that the drug and excipients were compatible.

Thus the formulated floating hollow microspheres (Microballons) of Nifedipine were successful in achieving the enhancement of gastric residence time and drug release.

- The floating hollow microspheres (Microballoons) of Nifedipine were successfully developed as gastro retentive drug delivery system by solvent evaporation method. The microparticles developed were having hollow cavity, suitable for floating.
- Microparticles prepared with more Dichloromethane

(DCM) showed good floating ability comparatively. So, we can conclude that suitable volume of DCM is responsible for the formation of hollow cavity.

- The suitable conditions for the formation of Microballoons are: Stirring speed is 400 rpm, Temperature is maintained at 40º C and 200 ml of 0.15 % (w/v) of PVA are selected.
- Analysis of Nifedipine loaded microballoons has shown that they have smooth surface with size range of 227µ showing surface dents and hollow cavity. The bulk density and Hausner's ratio indicated that they were having moderate flow properties. The microballoons were found to exhibit high drug loading(42.01%) and encapsulation efficiency(84.02%). The formulated gastroretentive floating hollow microspheres (Microballoons) of Nifedipine floated more than 8h in 0.1N HCl. The % buoyancy of microballoonswas estimated for all the formulations.
- As the drug to polymer ratio was increased the particle size of microspheres increased and drug release decreased. Drug to polymer ratio of 1:1 gave better release i.e 72.4761 % among all formulations. The formulated gastroretentive floating hollow microspheres (Microballoons) of Nifedipine floated more than 8h in 0.1N HCl.

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8. CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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