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DESIGN AND EVALUATION OF NIFEDIPINE FLOATING MATRIX TABLETS

Rohit Jaimini[1], Dr. Mayank Bansal[2]
[1]Research Scholar, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India
[2] Professor and Principal, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

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Address for Correspondence: Rohit Jaimini
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ABSTRACT:
Floating drug delivery systems are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluid. Floating drug delivery system have a bulk density less than that of gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period of time. Research work emphasized on design and evaluates nifedipine floating matrix tablets in which polymers i.e. hydroxyprophyl methyl cellulose (HPMC K100M, K4, and K15) was used. About 15-35 % of HPMC can be used as a polymer in the extended release formulations. So, here the polymer was used in the range of 16-36 %. Sodium bicarbonate (40%) is used as a gas generating agent. It can be used in the range of 25-50 %. The granules are prepared by wet granulation method. The prepared granules were evaluated for the bulk density, tapped density, bulkiness, angle of repose, compressibility index and hausner ratio. The values indicate good flow property. The compressed tablets were evaluated for hardness, uniformity of weight, friability, drug content, buoyancy lag time and duration of buoyancy. All the readings are within the prescribed limits. There was no interaction between the drug, polymer and excipients it was found out by IR studies. The in vitro drug release data indicate that the release of the drug depends upon the proportion of polymer present in the formulation. As the polymer ratio increases the release rate of the drug is prolonged.
Keywords: Floating tablet, HPMC K100M, nifedipine, HPMC K4

Introduction

Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Floating drug delivery system have a bulk density less than that of gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased GRT and a better control of fluctuation in plasma drug concentration.

Materials and Methods:

Table 1: The chemical and solvent used in the present investigation

S.NO.	NAME	Supplier / Manufacturer
1	Nifedipine	Unichem laboratories Ltd, Mumbai
2	HPMC K4 M	Anil Enterprises Delhi.
3	HPMC K15 M	samson laboratories pvt .ltd. solan himachal Pradesh
4	HPMC K100 M	samson laboratories pvt .ltd. solan himachal Pradesh
5	Sodium bicarbonate	Central drug house p.ltd. ,New Delhi
6	Lactose	Loba chemie Pvt. Ltd-Mumbai
7	Ethyl Cellulose	Loba chemie Pvt. Ltd-Mumbai
8	Talc	Loba chemie Pvt. Ltd-Mumbai
9	Magnesium Stearate	Loba chemie Pvt. Ltd-Mumbai
10	Poly propyl alcohol	from Nice chemicals Pvt. Ltd-Cochin
11	Starch	Loba chemie Pvt. Ltd-Mumbai

Table 2: List of instruments and equipments

S. No.	Name	Manufacturer with model
1	Melting point Apparatus	Macro Scientific works,403
2	Digital Weighing Balance	Fisher brand ,PS-200
3	Double beam UV Spectrophotometer	Systronics 2203
4	Differential scanning Calorimeter(DSC)	Perkin Elimer,Pyris,DSC,USA
5	Infra Red Spectrophotometer	Shimadzu FTIR,5300
6	Incubator	Instrument India, Mumbai
7	Six Basket Dissolution Appratus	Lab India DT 8000
8	Magnetic stirrer	Instrument India, Mumbai
9	Heating mental	Instrument India, Mumbai
11	pH meter	Instrument India, Mumbai
12	Tablet machine	Shakti Pharma Tech, Gujarat

Calibration Curve of Nifedipine:

Principle: The calibration curve is based on the spectrophotometry. The maximum absorption was observed at 350nm. It obeyed Beer's law in the concentration range of 2-20µg/ml.

Standard stock solution:

The stock solutions was freshly prepared by dissolving 100mg of nifedipine in a 100ml volumetric flask and then make up the solution up to the mark using 0.1N HCl for obtaining the solution of strength 1000 µg/mL (stock I). 10ml of this solution is diluted to 100ml with 0.1N HCl to obtain a solution of strength 100 µg/mL (stock II). From this secondary stock required concentrations 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20µg/mL was prepared. The absorbance was measured at 350 nm using a UV spectrophotometer.

Preparation of Nifedipine floating matrix tablets:

Tablets containing Nifedipine were prepared by wet granulation method. The respective powders drug, polymers (HPMC K4M, HPMC K 15M, HPMC K100M), sodium bicarbonate, lactose were blended thoroughly with mortar and pestle. The powder blend was then lubricated with magnesium stearate and talc mixed for about 3 minutes. The required amount of the blend was weighed and finally this mixture was compressed on a 10-station rotary tablet machine using 10-mm standard flat-face punches

Table 3: Preparation of floating tablet of Nifedipine

Formulation	Z1	Z2	Z3	Z4	Z5	Z6	Z7	Z8	Z9	Z10	Z11	Z12
DRUG(mg)	40	40	40	40	40	40	40	40	40	40	40	40
HPMC K4M(mg)	50	70	50	70	-	-	-	-	-	-	-	-
HPMCK15M(mg)	-	-	-	-	50	60	50	60	-	-	-	-
HPMC K100M(mg)	-	-	-	-	-	-	-	-	70	60	70	60
Sodium Bicarbonate(mg)	50	50	50	50	50	50	50	50	50	50	50	50
Tartaric acid(mg)	20	20	-	-	20	20	-	-	20	20	-	-
Citric acid(mg)	-	-	20	20	-	-	20	20	-	-	20	20
EC	40	50	-	-	50	60	-	-	55	65	-	-
MCC	-	-	40	50	-	-	50	60	-	-	55	65
Lactose	138	108	138	108	128	108	128	108	103	103	103	103
Talc	6	6	6	6	6	6	6	6	6	6	6	6
Mag.Stearate	6	6	6	6	6	6	6	6	6	6	6	6

EVALUATION OF NIFEDIPINE FLOATING GRANULES:

Preformulation studies of powder drug of nifedipine performed according to standard procedure given in IP 1996 i.e. Angle of repose, Bulk density, Tapped density, Bulkiness: Compressibility index and hausner ratio.

EVALUATION OF NIFEDIPINE FLOATING TABLETS:-

Tablet thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using vernier calipers. The average thickness and standard deviation were reported.

Weight variation:

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight and standard deviation were calculated and the results were expressed as compliance or non-compliance of set limits.

Hardness of the tablets:

Ten tablets were measured in the hardness examination. Tablet hardness was measured using a Monsanto hardness tester.

Friability of the tablets:

Twenty tablets of the formulation were weighed and measured in a Roche type friabilator.

The floating lag time and the total floating time:

This test was characterized by floating lag time and total floating time. The test was performed using USP XXIII type II paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 50 rpm at 37 ± 0.5o C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time.

Water uptake studies:

The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900ml of distilled water which was maintained at 37o + 0.5oc, rotated at 50 rpm. At selected regular intervals the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU).

%WU = (Wt - Wo) * 100 / Wo

Where Wt is the weight of the swollen tablet and Wo is the initial weight of the tablet.

Drug–excipients interaction studies:

The infrared spectra of pure drug, physical mixture of drug and excipients, polymer and formulation were recorded between 4000 to 400 cm-1on FTIR.

Dissolution Study of tablets:

The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 0.5, 1, 2, 3, 4, 6, 8, 10 and 12h. The volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after each sampling. The release studies were

conducted with 3 tablets, & the mean values were plotted versus time. Each sample was analyzed at 301 nm using double beam UV and Visible Spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve.

RESULTS AND DISCUSSION:

Differential scanning calorimetry

The sample preparations are sealed in aluminum pan and heated at constant ratio of 10°C/min over a temperature range of 25°C- 65°C.

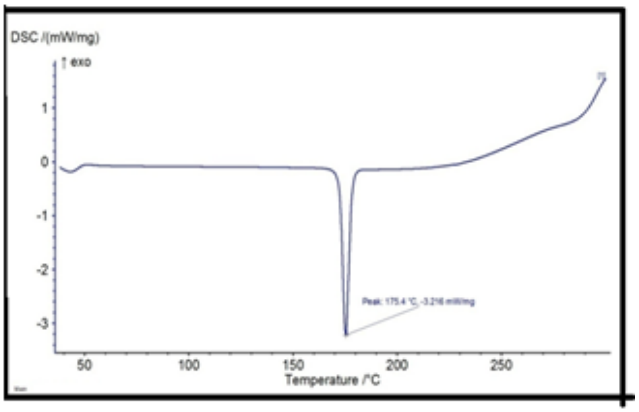

Figure 1: DSC of Nifedipine

Table 4: Determination of UV absorbance maxima of Nifedipine:

Con^c (ug/ml)	Absorbance
0	0.000
2	0.121
4	0.242
6	0.355
8	0.468
10	0.585
12	0.651
14	0.761
16	0.821
18	0.910
20	1.012

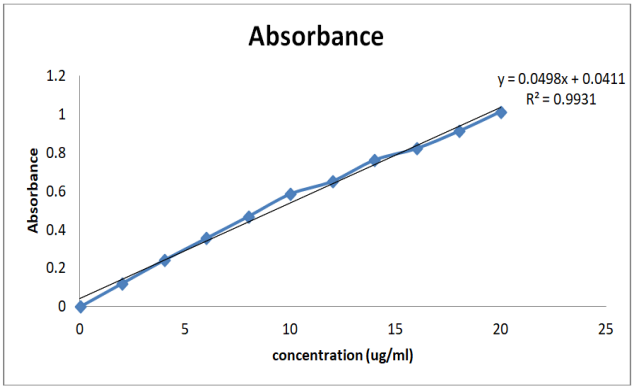

Figure 2: Standard curve of nifedipine in 0.1 N HCL at 350 nm

Table 5: Evaluation of Nifedipine granules for formulation

Parameter	Angle of Repose(θ)	Bulk Density (mg/ml)	Tapped Density (mg/ml)	Hauners Ratio	Compressibility Index (%)
Formulation					
Z1	25.827±1.675	0.673±0.010	0.776±0.029	1.152±0.023	13.265±1.672
Z2	26.406±1.203	0.589±0.023	0.666±0.031	1.131±0.025	11.607±1.262
Z3	25.900±1.109	0.628±0.031	0.702±0.028	1.117±0.027	10.476±1.623
Z4	28.885±1.576	0.661±0.028	0.758±0.039	1.149±0.031	13.065±1.213
Z5	26.575±1.320	0.611±0.033	0.717±0.027	1.148±0.008	12.962±1.278
Z6	25.706±0.923	0.634±0.007	0.634±0.018	1.130±0.023	11.538±1.291
Z7	28.071±1.328	0.568±0.025	0.653±0.016	1.115±0.032	10.344±2.328
Z8	27.348±1.134	0.584±0.027	0.640±0.026	1.118±0.039	10.619±1.259
Z9	26.706±0.914	0.573±0.031	0.694±0.023	1.157±0.029	10.434±1.906
Z10	26.565±0.973	0.603±0.008	0.660±0.013	1.150±0.011	13.636±2.018
Z11	28.787±1.004	0.573±0.023	0.680±0.036	1.134±0.028	11.818±0.775
Z12	28.298±1.281	0.667±0.032	0.715±0.031	1.29±0.031	11.447±1.243

Table 6: Post compression evaluation of nifedipine tablets

Formula code	Weight variation(mg)	Hardness kg/cm2	Thickness (mm)	Friability (%)	Lag time (sec)
Z1	347±2.3	4±0.5	3.21±0.08	0.26	30
Z2	351±3.8	4±0.5	3.23±0.06	0.23	39
Z3	356±4.5	4±0.3	3.21±0.06	0.48	20
Z4	351±8.3	4±0.5	3.22±0.09	0.51	30
Z5	345±5.3	4±0.2	3.26±0.08	0.22	18
Z6	349±2.3	4±0.5	3.21±0.05	0.41	12
Z7	353±5.5	4±0.5	3.24±0.05	0.35	10
Z8	344±5.6	4±0.2	3.28±0.02	0.38	14
Z9	348±3.3	4±0.5	3.23±0.02	0.41	32
Z10	346±6.2	4±0.3	3.21±0.16	0.29	21
Z11	351±4.3	4±0.5	3.28±0.05	0.38	7
Z12	349±2.3	4±0.4	3.19±0.09	0.41	12

Table 7: Swelling index studies of Nifedipine floating tablets

Time (hr)	*Z1*	Z2	Z3	Z4	Z5	Z6	Z7	Z8	Z9	Z10	Z11	Z12
0	0	0	0	0	0	0	0	0	0	0	0	0
2	32	35	35	42	36	38	35	38	36	39	35	34
4	46	48	48	50	49	55	45	48	63	65	62	52
6	52	55	55	58	62	78	54	59	73	75	72	65
8	63	70	70	72	76	89	64	68	84	85	82	72
10	88	91	88	91	99	110	74	79	99	102	110	98
14	108	112	112	113	128	138	142	139	135	140	135	139
18	140	135	130	155	180	177	172	181	160	165	162	174

DRUG RELEASE STUDIES:

Table 8: In vitro release data of nifedipine – Zero-order release

Time hr	**Cumulative % Drug Release**			
0	Z1	Z2	Z3	Z4
0	0	0	0	0
2	24.23	22.35	12.75	21.15
4	35.45	26.21	32.56	34.15
8	37.45	37.51	47.21	46.12
12	45.48	48.24	64.23	52.12
16	65.45	51.12	72.12	72.12
18	77.25	67.25	84.29	78.31

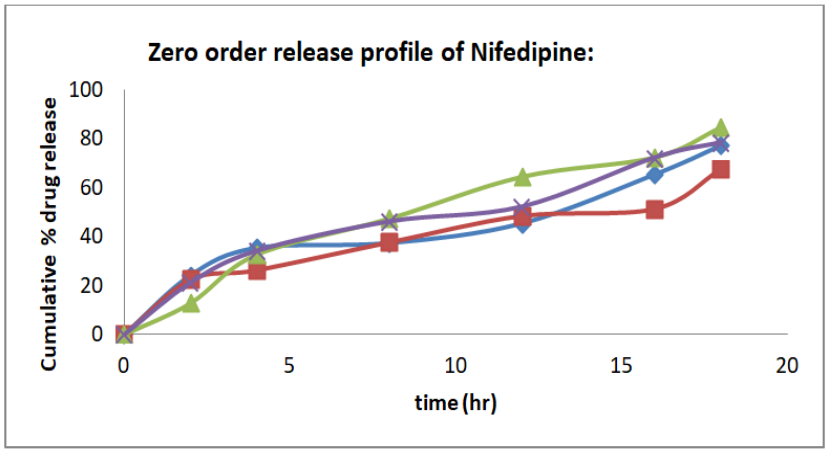

Figure 3: Zero order release profile of Nifedipine

Table 9: In vitro release data of nifedipine – First -order release

	cumulative Log % drug retained			
Time	Z1	Z2	Z3	Z4
0	2	2	2	2
2	1.87	1.89	1.94	1.89
4	1.80	1.86	1.82	1.81
8	1.79	1.79	1.72	1.73
12	1.73	1.71	1.55	1.68
16	1.53	1.68	1.44	1.44
18	1.35	1.51	1.19	1.33

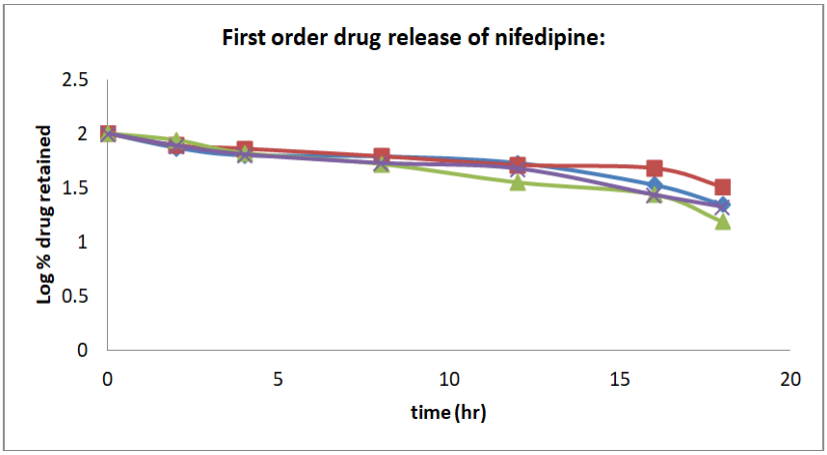

Figure 4: First order drug release profile of Nifedipine

Table 10: Fit of various kinetic models for floating tablet of nifedipine

Formulation code	Zero order R2	First order R2	Higuchi model R2	Korsemeyer model R^2
Z1	0.949	0.932	0.966	0.756
Z2	0.921	0.956	0.970	0.766
Z3	0.966	0.956	0.980	0.745
Z4	0.949	0.938	0.980	0.754
Z5	0.965	0.963	0.970	0.831
Z6	0.957	0.980	0.990	0.830
Z7	0.966	0.874	0.988	0.831
Z8	0.957	0.874	0.970	0.831
Z9	0.963	0.878	0.947	0.794
Z10	0.955	0.972	0.958	0.794
Z11	0.955	0.972	0.958	0.793
Z12	0.956	0.946	0.948	0.836

Conclusion:

Drug delivery system should deliver drug at a dictated by needs of the body over a specified period of time. The newer drug delivery system is being used to body distribution of drug with a view to reduce the toxicity of drug and deliver to their site of action. Floating drug delivery systems are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluid. Floating drug delivery system have a bulk density less than that of gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period of time. About 15-35 % of HPMC can be used as a polymer in the extended release formulations. So, here the polymer was used in the range of 16-36 %. Sodium bicarbonate (40%) is used as a gas generating agent. It can be used in the range of 25-50 %. The granules are prepared by wet granulation method. The prepared granules were evaluated for the bulk density, tapped density, bulkiness, angle of repose, compressibility index and hausner ratio. The values indicate good flow property. The compressed tablets were evaluated for hardness, uniformity of weight, friability, drug content, buoyancy lag time and duration of buoyancy. All the readings are within the prescribed limits.

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