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FORMULATION AND EVALUATION STUDIES OF FLOATING MATRIX TABLETS OF NIFEDIPINE

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ABSTRACT

The main aim of the study was to design and evaluate nifedipine floating matrix tablets. Hydroxyprophyl methyl cellulose (HPMC K100M) was used as a polymer. 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* release data were fitted to different order of reactions such as zero order, first order, higuchis reaction, Hixson crowell reaction and korsmeyer peppas reaction. The drug release follows Korsmeyers – Peppas reaction. The mechanism of drug release is by non-fickian motion. 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.

KEY WORDS

Nifedipine, Floating matrix tablets, HPMC K100M, Buoyancy studies

INTRODUCTION

Oral controlled release (CR) dosage forms generally have a transit time of 1–3 hours in the stomach, 3–5 hours in the intestine and 4–11 hours in the colon. However, some drugs require more retention time in the stomach for better results[1]. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged 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 results in an

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increased GRT and a better control of the fluctuations in plasma drug concentration. The FDDS can be divided into gas-generating and non-effervescent systems[2].

Nifedipine (4-(2-nitrophenyl)-2, 6-dimethyl-3, 5-dicarbomethoxy-1, 4-dihydropyridine) is a calcium channel blocking agent used in the treatment of various cardiovascular diseases[3], long term treatment of hypertension[4] and anginapectoris[5]. Earlier, short acting nifedipine was used sublingually (10 mg) in emergency management of severe hypertension. Later it was established that there is an increased risk of myocardial infarction or mortality in patient receiving short acting nifedipine for hypertensive emergencies[6, 7].

In the present work, floating Nifedifine matrix system has been developed using HPMC polymer with different ratios. *In vitro* drug release study was carried out in simulated gastric fluid (pH1.2) for about 10 hours using Disso-2000 dissolution apparatus.

MATERIALS AND METHODS

Materials:

Nifedipine was donated by Unichem laboratories Ltd, Mumbai. Sodium bicarbonate was obtained from Paxmy speciality chemicals-Chennai. Talc, HPMC, magnesium stearate and lactose monohydrate were obtained from Loba chemie Pvt. Ltd-Mumbai. PVP K30 was obtained from Sd. fine chemi Ltd-Mumbai. Isopropyl alcohol was obtained from Nice chemicals Pvt. Ltd-Cochin. All other reagents and chemicals used were of analytical grade.

TABLET PREPARATION – WET GRANULATION METHOD:

The different formulations of nifedipine floating tablets were prepared by wet granulation method (Table 1). Pure nifedipine, sodium bicarbonate, HPMC K100M and lactose were mixed together. 5% of PVP K30 was dissolved in isopropyl alcohol, and this solution was added into the above drug mixture to form a coherent mass. The wet mass was passed through Sieve No.16 and dried at 45-50ºC for 20 minutes in a hot air oven. The dried granules were passed through Sieve No: 20. Then the sieved granules were evaluated. After evaluation, the granules are mixed with magnesium stearate and talc and compressed into tablets[8] (Rimek mini press-1, Model RSB-4, Karnavathi Engineering, Ahmedabad). The compressed tablets were evaluated for various parameters.

Table 1

Preparation of Nifedipine Floating Tablet.

Formulation Code	Nifedipine (mg)	HPMC K100M (mg)	Sodium Bicarbonate (mg)	Lactose (mg)	PVP K 30 (mg)	Magnesium stearate (mg)	Talc (mg)	Iso propyl alcohol
F1	40	80	200	135	25	10	10	q.s
F2	40	100	200	115	25	10	10	q.s
F3	40	120	200	95	25	10	10	q.s
F4	40	140	200	75	25	10	10	q.s
F5	40	160	200	55	25	10	10	q.s
F6	40	180	200	35	25	10	10	q.s
F7	40	-	200	215	25	10	10	q.s

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EVALUATION OF NIFEDIPINE FLOATING GRANULES:

Angle of repose[9]:

Angle of repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. The angle of repose of the granules was determined by fixed funnel method to assess the flow property of the granules. The diameter of the granules cone (d) and the height (h) of the pile were noted. From the diameter, radius (r) was calculated. The angle of repose (θ) was calculated using the following formula.

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

Where θ is the angle of repose.

Bulk density[10]:

An accurately weighed quantity of granules (W) was carefully transferred into 250 ml measuring cylinder and initial volume (V_0) was measured. The bulk density is calculated by using following formula.

Bulk Density = Mass of the granules (W)/ Initial volume of the granules (V_0)

Tapped density[11]:

An accurately weighed quantity of granules (W) was carefully transferred into 250 ml measuring cylinder. The cylinder is then allowed to tap on to a wooden surface from the height of 2.5 cm at one second intervals. The tapping was continued until no further change in volume (until a constant volume) was obtained (V_f). The tapped density is calculated by the following formula.

Tapped Density = Mass of the granules (W)/ Tapped volume of the granules (V_f)

Bulkiness[12]:

Bulkiness is a reciprocal of bulk density. It is expressed by cc/gm.

Compressibility index and hausner ratio[9]:

The compressibility index and the hausner ratio are determined by measuring both the bulk density and tapped density of the granules. The compressibility index and the hausner ratio were calculated as follows:

Compressibility Index = 100 × Tapped density / Bulk density

Hausner Ratio = Tapped density/ Bulk density

EVALUATION OF NIFEDIPINE FLOATING TABLETS:

Hardness[13]:

Hardness of five tablets from each formulation was tested using Monsanto hardness tester.

Uniformity of weight[14]:

For uniformity of weight, twenty tablets were randomly selected from each formulation and weighed individually in an electronic balance (Scaltech).

Friability[14]:

The friability of ten tablets was determined using Roche fribilator[13].

Content uniformity[14]:

Ten tablets were weighed from each formulation, powdered and equivalent to 40 mg of nifedipine were weighed and dissolved in sufficient quantity of methanol and make up to 100 ml with methanol. The solutions were suitably diluted with buffer solution pH 1.2 and the content of nifedipine was estimated spectrophotometrically at 238 nm using pH 1.2 as a blank.

Thickness and Diameter:

Five tablets were randomly selected for the determination of thickness and diameter with the help of vernier caliper (Besto).

Buoyancy determination[15]:

The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa et al. The tablets were placed in 100ml beaker containing simulated gastric fluid pH 1.2, as per

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USP. The time taken by the tablet to reach the surface and float was determined as floating lag time (FLT)[16]. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

IR Spectral Analysis:

It is used to study the interactions between the drug, polymer and the excipients. The drug and excipients must be compatible with one another to produce a product stable, efficacious and safe. IR spectral analysis for drug, polymer and formulation F-6 were carried out.

***In vitro* drug release:**

In vitro drug release of the samples was carried out using Disso-2000 dissolution apparatus (paddle type). The dissolution medium, 900 ml pH 1.2, was placed into the dissolution jar maintaining the temperature of 37 $\pm$ 0.5^{o}C and rpm of 50. The apparatus was allowed to run for 10 hours. Samples measuring 10 ml were withdrawn every 30 mts intervals upto 10 hours using 10 ml pipette. The fresh dissolution medium was replaced every time with the same quantity (10ml) of dissolution medium. Collected samples were suitably diluted with pH 1.2 and analyzed in UV double beam spectrophotometer at 238 nm using pH 1.2 as blank.

Kinetic modeling of drug release:

The dissolution profile of all the batches was fitted to various models such as zero-order, first-order[17], Higuchi[18], Hixon-Crowell[19], Korsmeyer and Peppas[20-22] to ascertain the kinetic modeling of drug release.

RESULTS AND DISCUSSIONS

Evaluation of nifedipine granules:

The granules prepared for the composition of floating tablets were evaluated for the flow properties (Table 2).The bulk density was found in the range of 0.2525 – 0.3691 gm/cm^3. The tapped density ranged between 0.3265 – 0.4623 gm/cm^3. The angle of repose of all the formulations was within the range of 31^0 98' - $34^0$75'. The compressibility index of all formulations exists in the range between 11 – 15. The result of the hausner ratio of all the formulations is between 1.12 – 1.18. These values indicate that the prepared granules exhibited good flow properties.

Evaluation of nifedipine floating tablets:

The results of the physico-chemical characterization are shown in Table 3. The hardness of the tablets of all formulations was within the range of 6.0 – 6.4 kg/cm^2 indicating satisfactory mechanical strength. The weight of the tablet varied between 495 – 499 mg for all the formulations. The variation in weight was within the range of ± 5% complying with pharmacopoeial specification. The friability of all the formulated tablets was within 1%, which is an indication of good mechanical resistance of the tablet. The drug content varied between 91 – 102% for all the formulations. Duration of Buoyancy (DB) of all the 6 formulations is more than 16 hours. The Buoyancy Lag Time (BLT) is in between 2.18 to 9.13 minutes. This shows that, the DB and BLT are within the range. The result shows that all the formulations pass the test.

Infrared spectral studies:

Based on the IR Data, it was found that, there is no significant interaction between the drug and polymer as evidenced by the presence of bands due to the corresponding reactive functional groups.

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Table 2

Evaluation of nifedipine granules for all the six formulation.

Parameter	Nifedipine: HPMC K100M					
	F1	F2	F3	F4	F5	F6
Bulk density, (gm/cc)	0.3135	0.3265	0.2525	0.3568	0.3691	0.2723
Tapped density, (gm/cc)	0.3506	0.3469	0.4623	0.3265	0.4126	0.3431
Bulkiness, (cc/gm)	3.12	3.68	2.68	3.83	2.96	3.13
Angle of repose(θ)	34^0 39’	31^0 65’	33^0 98’	33^0 50’	34^0 75’	34^0 65’
Compressibility Index, (%)	12.19	11.56	12.56	12.88	12.43	12.01
Hausner`s Ratio	1.12	1.13	1.12	1.12	1.13	1.12

Table 3

Evaluation of nifedipine floating tablets.

Parameters	F1	F2	F3	F4	F5	F6	F7
Hardness[a] (kg/cm^2)	6.16 ± 0.09	5.92 ± 0.11	6.16 ± 0.22	6.08 ± 0.18	6.20 ± 0.14	6.00 ± 0.20	6.24 ± 0.17
Uniformity of Weight[b] (mg)	499.85 ± 4.94	501 ± 6.16	498.1 ± 6.69	498.75 ± 5.66	497.70 ± 6.39	498.95 ± 6.35	497.95 ± 5.63
Friability[c] (%)	0.25	0.18	0.02	0.01	0.12	0.23	0.31
Drug content[c] (%)	98.86 ± 0.68	99.04 ± 0.77	98.67 ± 0.28	98.82 ± 0.34	98.74 ± 0.54	99.13 ± 0.24	99.08 ± 0.47
Thickness[a] (mm)	4.12 ± 0.05	4.12 ± 0.08	4.06 ± 0.11	4.06 ± 0.05	4.10 ± 0.10	4.00 ± 0.07	4.24 ± 0.09

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Diameter[a] (mm)	12.56 ± 0.05	12.58 ± 0.04	12.60 ± 0.07	12.54 ± 0.11	12.52 ± 0.08	12.52 ± 0.13	12.6 ± 0.12
Buoyancy Lag Time (minutes)	4.25	9.13	3.12	5.31	5.15	2.18	-
Duration of Buoyancy (Hours)	> 16	> 16	> 16	> 16	> 16	> 16	-

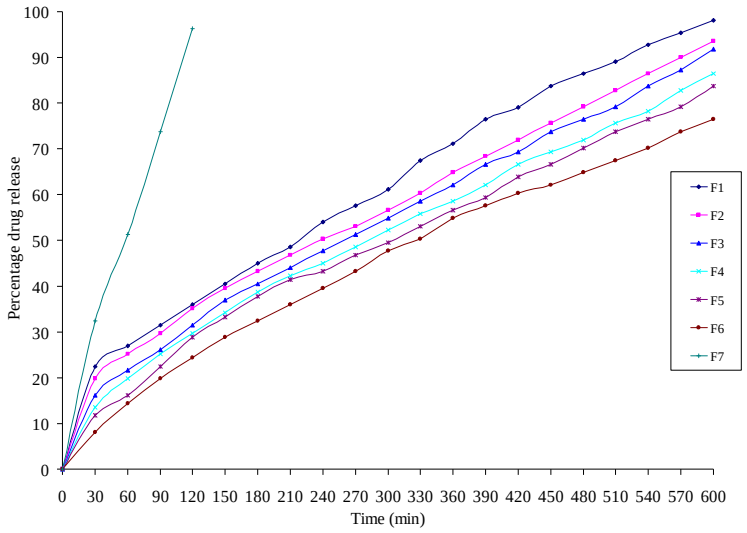
Note : a = 5, b = 20 and c = 10

***In vitro* drug release studies:**

The *in vitro* drug release studies were performed to evaluate the release of nifedipine from floating matrix tablets. The drug release of six formulations was compared with each other and also with pure nifedipine (without polymer). The results are represented by diagrammatically and it is shown in Fig-1. The dissolution study of all the formulations was found to be F-1 98.1%, F-2 93.6%, F-3 91.8%, F-4 86.4%, F-5 83.7%, F-6 76.5% and F-7 96.3% (in 120 min). From all the formulations F6 formulation shows slow drug release when compared to other five formulations.

Figure 1

The in vitro release study of all the seven formulations.



Kinetic modeling of drug release:

All the six formulations were fitted for the release kinetics. The data were processed for regression analysis using Microsoft excel statistical function. It may be concluded that the release of the drug follows Korsmeyers – Peppas reaction. The n values of all the formulations ranged between 0.67-0.74. Values of n between 0.45 and 0.89 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated

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matrix and the polymer relaxation) commonly called anomalous transport. Thus, it was proposed that these formulations delivered their active compound by coupled diffusion and erosion

Table 5

Correlation co-efficient (r^2) and n value of all the six formulations.

Formulation Code	Correlation Co-efficient (r^2) value				Korsmeyers - Peppas	
	Zero order	First order	Higuchi	Hixon crowell	Slope (n)	Correlation Coefficient (r^2) value
F-1	0.8687	0.8781	0.9768	0.9661	0.7321	0.9714
F-2	0.8652	0.9208	0.9780	0.9712	0.7191	0.9753
F-3	0.9053	0.9343	0.9689	0.9773	0.7093	0.9898
F-4	0.9081	0.9642	0.9693	0.9874	0.6986	0.9953
F-5	0.9214	0.9730	0.9628	0.9901	0.6902	0.9985
F-6	0.9400	0.9933	0.9533	0.9979	0.6732	0.9970

CONCLUSION

In this present study nifedipine was successfully formulated as floating drug delivery system using hydrophilic polymer HPMC K100M and sodium bicarbonate as a gas generating agent. It was concluded that the percentage of drug release was prolonged when the concentration of polymer was increased. Nifedipine floating tablets attempt showed encouraging results.

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