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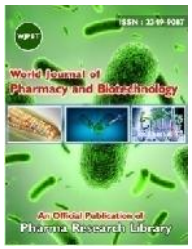

Research Article Open Access

Development and *In-vitro* Characterization of Gastro Retentive Floating Tablets of Nefidipine Using Various Polymers

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A B S T R A C T

The aim of the present study was to develop sustained release formulation of Nifedipine to maintain constant therapeutic levels of the drug for over 12 hrs. Various natural polymers such as Guar gum Sodium CMC and Chitosan were employed as polymers. Nifedipine dose was fixed as 50 mg. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 60, 90 and 180 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F3) showed better and desired drug release pattern i.e., 97.30 % in 12 hours. It followed zero order release kinetics mechanism.

Keywords: Nifedipine, Guar gum, Chitosan, Sodium CMC and sustained release tablets.

A R T I C L E I N F O

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1. Introduction

Conventional Drug Therapy: Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional drug delivery is effective, but some drugs which posses narrow

therapeutic window and which cause irritation to gastric mucosa require modified drug delivery system to achieve desired therapeutic effect. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience. The main goal of modified drug delivery systems is to improve the effectiveness of drug therapies. Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentrations versus time curve reflecting primarily the rate of absorption and elimination, respectively. Because of the rapid rate of absorption from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on biological half life (t½) and duration of pharmacological effect. The time of dosing may also be effected by therapeutic index of a drug.

Disadvantages of Conventional Drug Delivery Systems

- In conventional oral drug delivery systems, there is little or no control over the release of the drug and effective concentration at the target site.
- The dosing pattern in conventional dosage forms results in constantly changing, unpredictable and often sub-therapeutic plasma concentrations, leading to marked side effects in some cases.
- Conventional drug delivery system is not suitable for the drugs, which cause irritation to the gastric mucosa.
- The rate and extent of absorption of drug from conventional formulations may vary greatly, depending on the factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the gastrointestinal tract, gastrointestinal motility and so on.

Modified Drug Delivery Systems

Dosage forms can be designed to modify the release of the drug over a given time or after the dosage, form reaches the required location. Drug release occurs only after some time of the administration or for a prolonged period of time or to a specific target in the body. Modifications in drug release are often desirable to increase the stability, safety and efficacy of the drug, to improve the therapeutic outcome of the drug treatment and/or to increase patient compliance and convenience of administration.

Classification: Modified Release dosage form may be classified as

Extended Release

- Sustained Release
- Controlled Release

Delayed Release

Extended Release: This type of oral DDS allows the drug to be released over prolonged time periods. By extending the release profile of a drug, the frequency of dosing can be reduced. Extended release can be achieved using sustained or controlled-release dosage forms.

Sustained Release: This term is constantly used to describe a pharmaceutical dosage form formulated to retard the release of the therapeutic agent such that its appearance in the systemic circulation is delayed and prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed, and the duration of its therapeutic effect is sustained. In orally administered dosage forms, this duration is in hours and critically depends on the residence time of the dosage form in GI tract, where as in the case of injectables this period may vary from days to months.

2. Materials and methods

Materials: Nifedipine, Guargum, Chitosan, Sodium CMC, Magnesium stearate, Talc, Micro crystalline cellulose.

Analytical method development:

Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation calibration curve: 100 mg of Nifedipine pure drug was dissolved in 100 ml of 0.1 N HCl (stock solution) 10 ml of solution was taken and make up with 100 ml of 0.1 N HCl (100 µg/ml).from this 10 ml was taken and make up with 100 ml of 0.1 N HCl (10 µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20,25,30,35 and 40 µg/ml of Nifedipine per ml of solution. The absorbance of the above dilutions was measured at 298 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 1. The tablets were prepared as per the procedure given below and aim is to prolong the release of Nifedipine. Total weight of the tablet was considered as 300 mg.

Procedure:

Nifedipine and all other ingredients were individually passed through sieve no ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method.

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test: To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the

percentage shown in the following table and none deviates by more than twice the percentage. The mean and deviation were determined.

Hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness: Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability: It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre-weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations).

***In vitro* drug release studies:** As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure: 900 ml of 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 2 hours and then the medium 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 298 nm using UV-spectrophotometer.

3. Result and Discussion

The present study was aimed to developing extended release tablets of Nifedipine using various polymers. All the formulations were evaluated for physicochemical properties and *in-vitro* drug release studies.

Analytical Method:

Graphs of Nifedipine was taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 298 nm and 294 nm respectively.

Table 2: Observations for graph of Nifedipine in 0.1N HCl (298 nm**)**

Conc [µg/l]	Abs
5	0.104
10	0.205
15	0.302
20	0.411
25	0.503
30	0.608
35	0.710
40	0.808

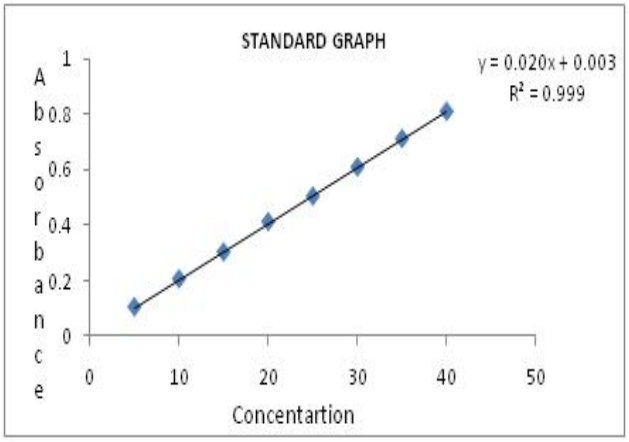

Figure 1: Standard graph of Nifedipine in 0.1N HCl

Table 3: Observations for graph of Nifedipinein pH 6.8 phosphate buffer (294 nm)

Conc [µg/l]	Abs
5	0.098
10	0.195
15	0.298
20	0.392
25	0.490
30	0.595
35	0.690
40	0.776

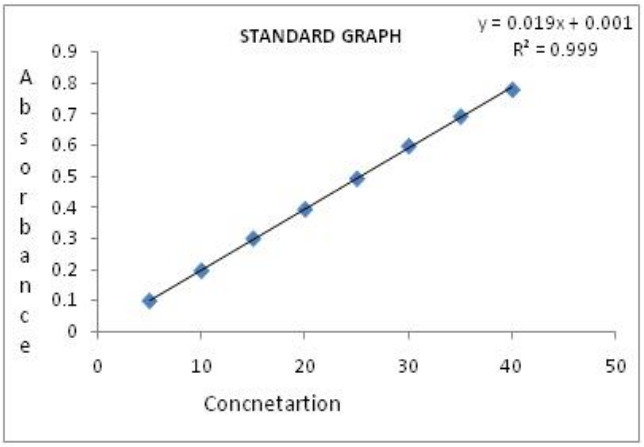

Figure 2: Standard graph of Nifedipinep H 6.8 phosphate buffer (294nm)

Pre-formulation parameters of powder blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations has shown the Hausner ratio ranging between

0 to 1.2 indicating the powder has good flow properties.

Quality Control Parameters For tablets: Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

***In-vitro* quality control parameters for tablets**

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies**

Table 5: Dissolution Data of Nifedipine Tablets Prepared With Sodium CMC in Different Concentrations

Time (hr)	Cumulative percent drug dissolved (n=3±sd)		
	F1	F2	F3
0.5	25.5	20.1	16.4
1	46.7	39.4	26.7
2	76.5	55.3	34.6
3	98.4	75.3	42.4
4		87.3	55.4
5		99.4	67.4
6			85.4
7			91.5
8			97.3

Table 6: Dissolution Data of Nifedipine Tablets Prepared with Guar gum In Different Concentrations

Time (hr)	Cumulative percent drug dissolved (n=3±sd)		
	F4	F5	F6
0.5	17.25	16.42	14.62
1	38.26	25.73	19.86
2	54.16	36.63	22.35
3	72.01	45.04	31.45
4	88.26	58.25	39.80
5	97.10	65.33	45.25
6		76.41	58.24
7		84.84	66.73
8		97.80	71.34
9			75.52
10			82.17
11			87.10
12			96.10

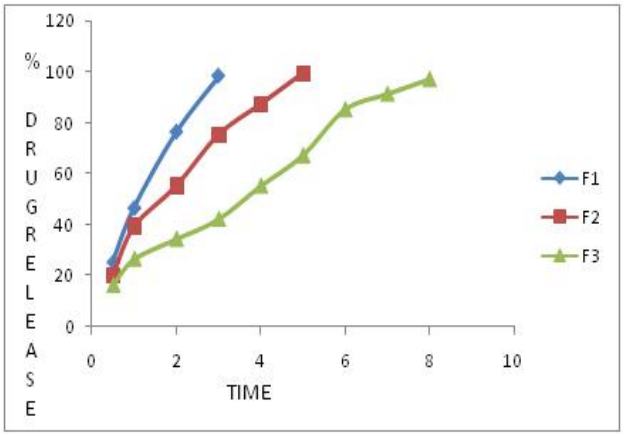

Figure 3: Dissolution profile of Nifedipine (F1, F2, F3 formulations**).**

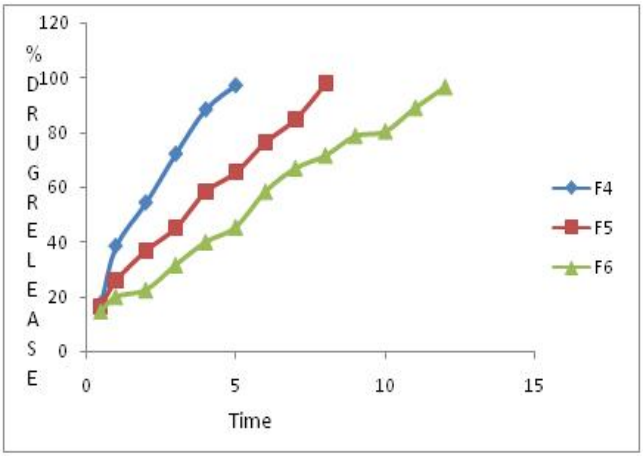

Figure 4: Dissolution profile of Nifedipine (F4, F5, F6 formulations)

Table 7: Dissolution Data of Nifedipine Tablets Prepared With Chitosan in Different Concentrations

Time	Cumulative Percent Drug Dissolved		
	F7	F8	F9
0.5	10.4	9.4	8.5
1	16.5	15.6	14.5
2	28.6	21.4	18.4
3	39.5	36.7	23.4
4	48.5	42.4	28.2
5	59.4	49.6	34.8
6	69.2	55.3	40.2
7	74.5	60.3	44.8
8	82.3	72.8	50.4
9	87.78	83.52	63.34
10	98.78	88.65	69.27
11		96.56	74.86
12			79.97

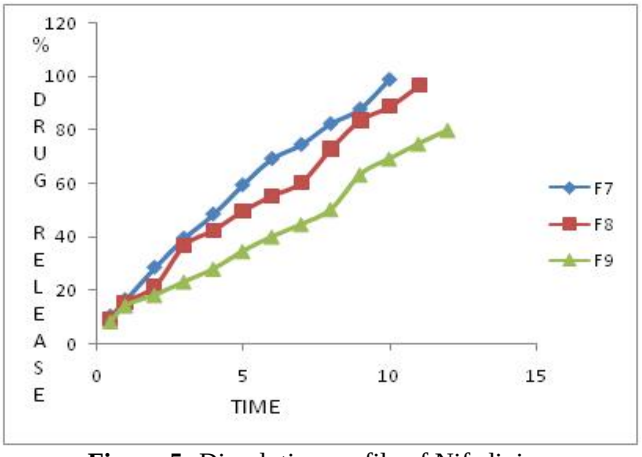

Figure 5: Dissolution profile of Nifedipine (F7, F8, F9 formulations)

From the dissolution data, it was evident that the formulations prepared with Sodium CMC as polymer were unable to retard the drug release up to desired time period

i.e., 12 hours. Whereas the formulations prepared with Guar gum retarded the drug release in the concentration of 180 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.10% in 12 hours with good retardation. The formulations prepared with Chitosan showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Table 1: Formulation composition for tablets

Formulation No.	Nifedipine	Sodium CMC	Guar Gum	Chitosan	Mag. Stearate	Talc	MCC pH 102
F1	50	60			6	6	QS
F2	50	90			6	6	QS
F3	50	180			6	6	QS
F4	50		60		6	6	QS
F5	50		90		6	6	QS
F6	50		180		6	6	QS
F7	50			60	6	6	QS
F8	50			90	6	6	QS
F9	50			180	6	6	QS

All the quantities were in mg

Table 4: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11	0.49±0.04	0.54±0.04	16.21±0.06	0.86±0.06
F2	25.67	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05
F3	25.54	0.50±0.05	0.58±0.05	17.11±0.01	0.64±0.03
F4	25.43	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04
F5	25.34	0.52±0.03	0.57±0.03	16.92±0.04	1.2±0.08
F6	24.22	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09
F7	25.18	0.54±0.06	0.59±0.04	16.43±0.05	0.76±0.03
F8	24.22	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09
F9	25.05	0.55±0.08	0.5 2±0.03	17.54±0.09	1.17±0.02

Table 5

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	312.5	4.5	0.50	6.8	99.76
F2	305.4	4.5	0.51	6.9	99.45
F3	298.6	4.4	0.51	4.9	99.34
F4	310.6	4.5	0.55	6.9	99.87
F5	309.4	4.4	0.56	6.7	99.14
F6	310.7	4.5	0.45	6.5	98.56
F7	302.3	4.1	0.51	6.4	98.42
F8	301.2	4.3	0.49	6.7	99.65
F9	298.3	4.5	0.55	6.6	99.12

4. Conclusion

The aim of the present study was to develop sustained release formulation of Nifedipine to maintain constant therapeutic levels of the drug for over 12 hrs. Various natural polymers such as Guar gum Sodium CMC and Chitosan were employed as polymers. Nifedipine dose was fixed as 50 mg. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 60, 90 and 180 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F3) showed better and desired drug release pattern i.e.,97.30 % in 12 hours. It followed zero order release kinetics mechanism.

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