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Design and evaluation of floating osmotic tablet of Nizatidine

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ABSTRACT

Conventional drug delivery systems have little control over their drug release and almost no control over the effective concentration at the target site. The present work investigates the design of a novel floating osmotic tablet to prolong the gastric residence of a highly water-soluble drug. Nizatidine was chosen as a model drug. Floating Osmotic tablets of Nizatidine were prepared by direct compression method using polymers like HPMC, Carbopol in different proportions along with sodium bicarbonate as a gas generating agent. The prepared mass was passed through sieve and was evaluated for angle of repose, compressibility index and Hausner's ratio and results obtained were satisfactory. Compressed formulations were further evaluated for weight variation, hardness, thickness, friability, buoyancy studies, drug content and in-vitro dissolution studies. All the formulations showed good results which were in compliance with pharmacopoeial standards. Among all formulations it was concluded that the F4 batch is optimized since it showed better drug release.

Key words: Osmotically controlled drug delivery, direct compression, Hydroxy Propyl Methyl Cellulose, Carbopol, Nizatidine.

INTRODUCTION

Gastro-retentive drug delivery systems [1] are designed to prolong overall gastrointestinal transit time and improve the oral bioavailability of drugs that are having site-specific absorption in the stomach or in the upper part of the small intestine, drugs acting locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid. Different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems swelling and expanding systems floating systems and delayed gastric emptying devices.

Osmotically controlled oral drug delivery systems [2] utilize osmotic pressure as the energy source for the controlled delivery of drugs. Drug release from these systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system.

Floating drug delivery systems [1] have bulk density less than gastric fluids and so they remain buoyant in the stomach where the drug is released slowly. Floating drug delivery systems can be divided into effervescent and non-effervescent systems. The effervescent systems prepared with swellable polymers and effervescent components that upon arrival in the stomach; carbon dioxide is released and entrapped within the jellified polymer causing the formulation to float in the stomach. Non-effervescent systems prepared by mixing the drug with a gel, which swells

in contact with gastric fluid and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these systems.

Nizatidine[3] is a histamine H2- receptor antagonist that inhibits stomach acid production, and commonly used in the treatment of peptic ulcer and gastro esophageal reflux. Nizatidine has short biological half life[3] of 1-2 hours and is susceptible to metabolism by colonic bacteria. It has been reported that [4] the local delivery of H2- receptor antagonists increases the stomach wall receptor site bioavailability and increases efficacy of these drugs to reduce acid secretion. Based on the mentioned criteria, Nizatidine is a suitable candidate for gastro retentive drug delivery system.

MATERIALS AND METHODS

MATERIALS:

Nizatidine was obtained from Dr. Reddy's Lab Hyderabad as gift sample. HPMC, Carbopol 940, sodium bicarbonate, microcrystalline cellulose, talc, magnesium stearate were obtained from Research-Lab Fine Chem Industries, Islampur. All ingredients used were of analytical grade only.

Preparation of floating and osmotically controlled tablets of Nizatidine:

Tablets were prepared by direct compression method as shown in table 1. Formulations F_2 to F_6 were composed with HPMC as a hydrophilic polymer and Carbopol 940 was incorporated as an osmotically controlled polymer. The polymers were added in increasing concentration of Carbopol 940 and decreasing concentration of hydrophilic polymer. Formulation F_1 was prepared without osmotically controlled polymer.

Accurately weighed quantities of hydrophilic polymers, osmotically controlled polymer, and microcrystalline cellulose were taken in a mortar and mixed geometrically. To this mixture, weighed quantity of Nizatidine was added and mixed with pestle. This mixture was passed through 40# and later collected in a plastic bag and blended for 5 min. Then sodium bicarbonate was added and again mixed for 5 min. followed by the addition of magnesium stearate and talc. The final blend was again triturated and was passed through 40#. The obtained granules were compressed into tablets with 8 mm die.

Table 1: Formulation table

Ingredients	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)
Nizatidine	50	50	50	50	50	50
HPMC	100	70	60	50	40	30
Carbopol 940	-	30	40	50	60	70
Microcrystalline Cellulose	50	50	50	50	50	50
Sodium Bicarbonate	45	45	45	45	45	45
Magnesium Stearate	3	3	3	3	3	3
Talc	2	2	2	2	2	2

Evaluation Parameters

Pre-compression parameters:

Following the standard procedures, pre-formulation studies including compressibility index, Hausner's ratio and angle of repose was performed for the powder.

Post compression parameters:

1. Weight Variation Test:

20 tablets of each formulation were weighed individually using digital weighing balance and their average weight was calculated. Then individual tablet weight was compared with average weight.

2. Hardness:

The tablet hardness was measured using Monsanto tablet hardness tester. The force required to crush the tablet was recorded as hardness in Kg/cm^2.

3. Thickness:

The thickness of the tablets was determined using a Screw gauge.

4. Friability:
10 tablets were weighed accurately and then placed in Roche-type friabilator which was rotates at 25 rpm for 4 min (i.e. 100 revolutions).

Then tablets were taken out of the friabilator and again weighed after dusting. The percent friability was calculated as follow:

% Friability = $(W_i - W_f / W_i) \times 100$

Where, W_i – initial weight of tablets,
Wf – final weight of tablets.

5. Drug content:
10 tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (100 mg) was extracted with 0.1N HCl (pH 1.2 buffer) and the solution was filtered through 0.45 µ membrane filter. Each extract was suitably diluted and analyzed spectrophotometrically at 314nm.

6. Buoyancy studies:
The *in-vitro* floating behavior (buoyancy) of the tablets was determined by floating lag time. The tablets were placed in 100 ml beaker containing 0.1 N HCl (pH 1.2). The floating lag time (time taken by the tablet to reach the surface) and total floating time (floating duration of the tablet) were determined.

7. *In-vitro* drug release studies:
Release rate of drug from floating and osmotically controlled tablets was determined using USP type II apparatus. The dissolution test was performed in triplicate, using 900ml of 0.1N HCl, at 37± 0.5˚C at 50 rpm for 6 hrs. A 5ml sample was withdrawn from the dissolution apparatus at specified time points and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted if necessary. Absorbances of these solutions were measured at 314 nm using U.V Visible Spectrophotometer.

8. Curve fitting analysis:
To study the drug release kinetics, the data obtained from in vitro drug release studies were plotted in various kinetic models such as a zero-order, first order and Higuchi plot.

9. Stability studies:
The optimized formulation was subjected to stability studies at 40±2^{o}C and 75±5% RH for a period of three months. After each month, tablet was analyzed for drug content and *In-vitro* drug release along with other physical parameters.

RESULTS AND DISCUSSION

Pre-compression parameters:
The properties like compressibility index, angle of repose, and Hausner ratio were calculated and all estimated parameters found within the limits (Table 2)

Table 2: Precompression Parameters Of All Formulations

Formulation Code	Compressibility Index (%)	Angle of repose	Hausner Ratio
F1	11.2	27º.9'	1.13
F2	15.7	28º.1'	1.17
F3	12.8	27º.6'	1.13
F4	12.5	28º. 7'	1.15
F5	15.9	29º.3'	1.19
F6	12.5	28º. 7'	1.15

Post-compression parameters:
All formulations were tested for Physical parameters likehardness, thickness, weight variation, friability and found to be within the pharmacopoeial limits. The results of the tests were tabulated in Table 3. The drug content of all the

formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table 3: Post-compression parameters

Formulation Code	Hardness (Kg/cm^2)	Weight Variation (mg)	Thickness (mm)	Friability(%)	Drug Content (%)
F1	5.1	249	3.21	0.65	99.23%
F2	6.4	251	3.19	0.67	101.42%
F3	5.9	248	3.16	0.71	99.67%
F4	6.8	250	3.19	0.69	100.07%
F5	5.4	249	3.20	0.68	100.01%
F6	5.8	250	3.14	0.69	100.34%

Floating properties:

The results of the tests were tabulated in table 4.Tablets of all batches had floating lag time below 2 minutes regardless of content of HPMC because of evolution of CO_2 resulting from the interaction between sodium bicarbonate and dissolution medium, entrapment of gas inside the hydrated polymeric matrices enables the dosage form to float by lowering the density of the matrices. It was clearly observed that the reduction in concentration of HPMC in each batch the floating lag time increased as well as floating duration decreased.

Table 4: Floating properties

Formulation code	Floating Lag Time (sec)	Floating Time (hrs)
F1	30	15
F2	18	20
F3	21	24
F4	17	26
F5	18	24
F6	21	21

***In-vitro* drug release data:**

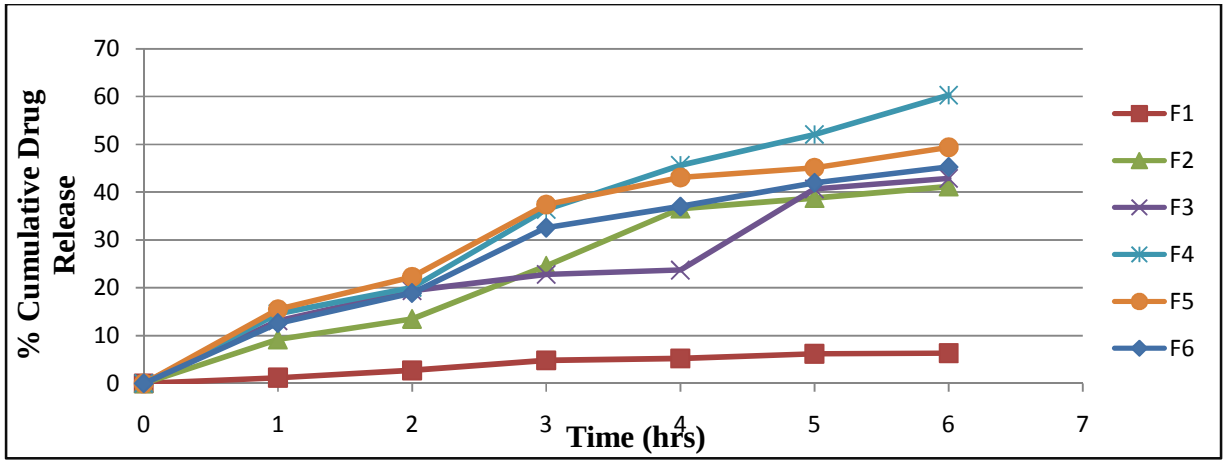
Formulations F2 to F6 are composed with HPMC as a hydrophilic polymer and an osmotically controlled polymer carbopol 940, in increasing concentrations of Carbopol 940 and decreasing concentrations of hydrophilic polymer. Formulation F1 is composed without osmotically controlled polymer, which is designed to find out the difference in drug release rate compared to floating and osmotically controlled tablets. Here the effect of concentration of hydrophilic polymer to carbopol 940 is observed.

The graph shows that, the decrease in concentration of HPMC retards the drug release from formulation. This may be expected due to the increase in concentration of carbopol 940 which is having high molecular weight as well as more drug release retarding property compared to that of HPMC. There is no much difference in drug release was observed with formulations of F2 –F6 to that of F1 which has no osmotically controlled polymer in its formulation.

Table 5: Drug release profile of Nizatidine floating osmotically controlled Tablets

Time (hrs)	% cumulative drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	1.7	9.2	13.1	14.6	15.5	12.6
2	2.4	13.5	19.4	20.1	22.3	18.9
3	4.8	24.6	22.8	36.4	37.4	32.6
4	5.2	36.6	23.7	45.6	43.1	37.0
5	6.2	38.8	40.7	52.1	45.1	42.0
6	6.3	41.2	42.9	60.3	49.4	45.3

Fig 1: Graphical representation of cumulative % drug release of Nizatidine floating and osmotically controlled tablets



Curve fitting analysis:

Dissolution data of the optimized formulation (batch F4) was fitted to various mathematical models (zero-order, first-order and Higuchi plot) in order to describe the kinetics of drug release. Drug release from optimized formulations fitted well into zero-order kinetics, confirming that the release from formulations is close to the desired release profile and drug load dependent.

Fig 2: Zero Order Release Kinetics for F4

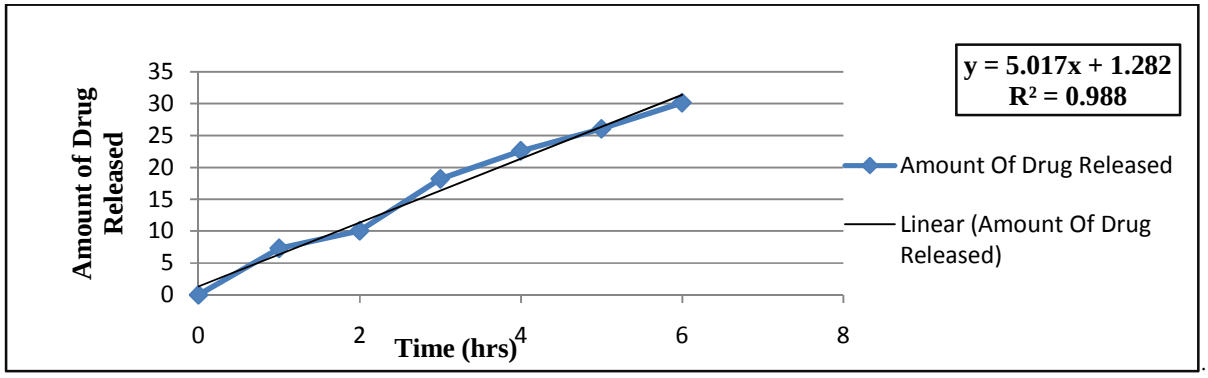


Fig 3: First order release kinetics for F4

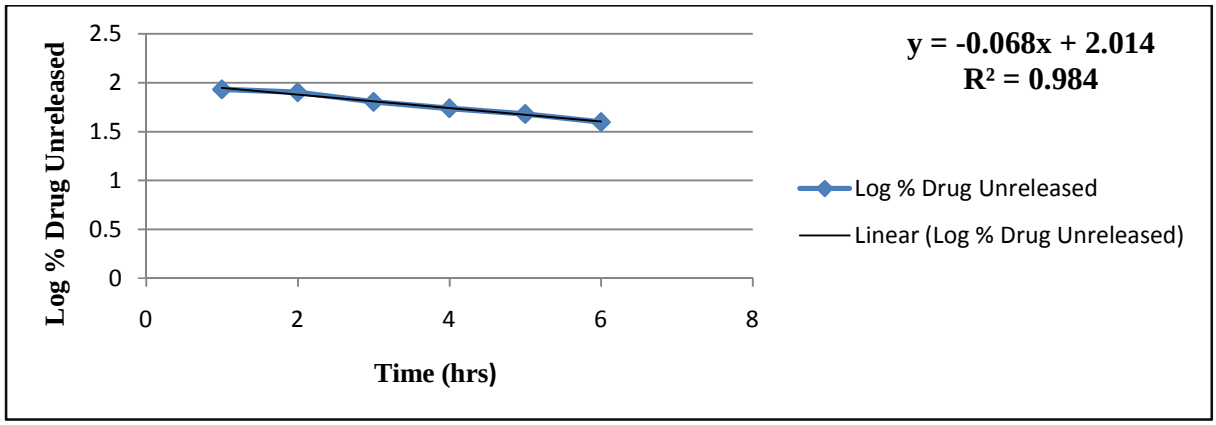
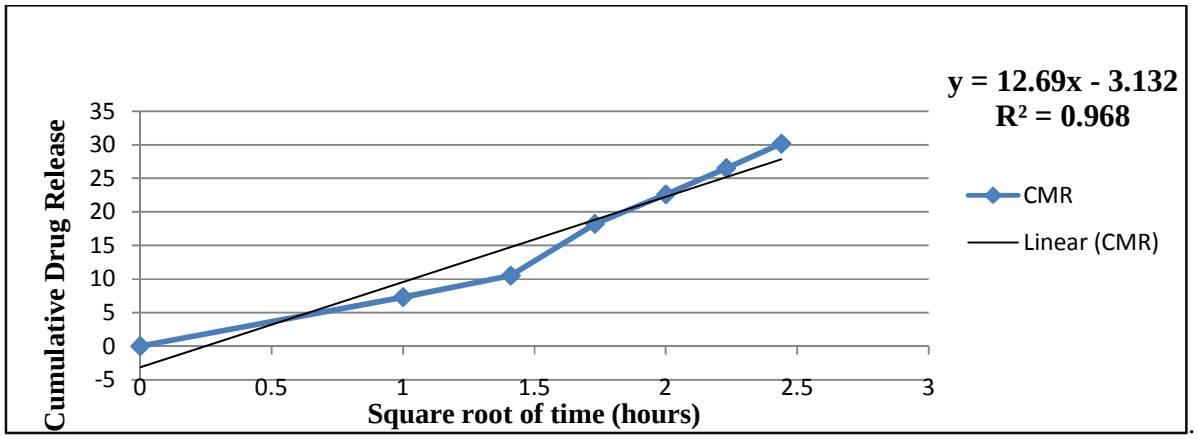


Fig 4: Higuchi drug release kinetics for F4



Stability studies:

The optimized tablets batch F4 was charged for stability studies. There was no change in physical appearance, color. Formulations were analyzed at the end of 3 months for the assay and dissolution studies. *In vitro* dissolution profile showed that there was no significant change in the release rate of the drug from optimized tablets at the end of 3 months.

CONCLUSION

Formulated tablets gave satisfactory results for various evaluation parameters like tablet, hardness, friability, weight variation, Thickness, floating lag time, floating duration, content uniformity, and *in-vitro* drug release. In all formulations Carbopol 940 is used to add osmotically controlled strength but the concentration of this polymer has significantly influenced the drug release due to its retarding property. All the formulated tablets from F_2 to F_6 shown the excellent osmotically controlled property compared to formulations with no osmotically controlled property i.e., F_1. Floating and osmotically controlled tablets of Nizatidine can be formulated as an approach to increase gastric residence time thereby improve its bioavailability and to overcome the limitations of conventional approaches of gastric retention.Drug release profiles are fitted to kinetic modes like zero order, first order and Higuchi model. It was found that the formulations were best fitted to zero order model. Stability studies were conducted for optimized formulation at different conditions. And the formulation is found stable in all the conditions. It was concluded that the F_4 formulation is optimized because of its equal combination of osmotically controlled polymer and hydrophilic polymer.

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REFERENCES

[1] Suresh P. Vyas and Roop K. Khar; *Controlled Drug Delivery System*, Vallabh Prakashan, India, **2012**.
[2] N.K.Jain, Advances *in Controlled and Novel Drug Delivery*, CBS Publishers and Distributors, **2011**.
[3] http://en.wikipedia.org/wiki/Nizatidine
[4] http://www.webmd.com/heartburn-gerd/h2-blockers-acid-reducers-for-gastroesophageal-reflux-disease-gerd
[5] Jadhav S.L and Banerjee S.K., *Int. J. Res. Pharm. Sci*, **2013**,4, 250.
[6] Sharma Tejal, Solanki NS, Mahatma OP, *Res. J. Pharm. Bio. Chem. Sci*, **2012,** 3, 396.
[7] Kapoor D, Chauhan CS and Gupta A.K, *Int. J. Pharm. Bio Arch*, **2011**, 2, 967.
[8] Zhihong Zhang, Bo Peng, Xinggang Yang, Chao Wang, Guangmei Sun and Weisan Pan, *J. Pharm. Sci***, 2009**, 12, 129 .
[9] Gehan Balata, *Int. J. Pharm. Pharm Sci*, Design and evaluation of gastro retentive floating tablet of nizatidine: A trial to improve its efficacy, **2014**, 6, 423.

[10] Rashmin S Thakor, Falguni D Majmudar, Jayvadan K Patel, Ganesh C Rajput and Manish P Patel, *Scholars Research Lib***, 2010**, 2, 43.
[11] Srinivas Pannala, Mahalaxmi Rathnanand; *Int. J. PharmTech R*, **2011**, 3, 1688.
[12] Suvakanta Dash, Padala Narasimha Murthy, Lilakanta Nath, Prasanta Chowdhury, *Acta Poloniae Pharmaceutica Drug*, **2010**, 67, 217.