Journal of Pharmaceutical and Biological Research

Journal Home Page: www.pharmaresearchlibrary.com/jpbr

Research Article Open Access

Formulation and Evaluation of Nizatidine Hydrogel Beads

T. Satyanarayana*[1], Saritha Priya Vattikuti[1], K. Someshwar[2]

[1]*Department of Pharmaceutics, Browns College of Pharmacy, Khammam, Telangana, India.*
[2]*Managers, Formulation R&D, KP Labs (A Division of KDPL), Kothapet, Hyderabad, Telangana, India*

A B S T R A C T
The objective of the present study was to prepare and evaluate Hydrogel Beads for the controlled release of Nizatidine from the prepared Hydrogel beads using different polymers. The Hydrogel beads were prepared by ionotropic gelation method. The prepared Hydrogel beads were characterized for FTIR, scanning electron microscopy (SEM), the percentage drug content, entrapment efficiency, *in vitro* dissolution studies, Release order kinetics, Stability studies. The Particle size of hydrogel beads was determined with the help of SEM and it was found to be ranging from 500-650 µm. The swelling Index of Nizatidine containing Hydrogel beads F 11 formulation contains the value 28 ±1 %. The FT-IR and DSC study confirmed that no chemical interaction took place during encapsulation process. Entrapment efficiency was in range of all formulation 76.2-77.3%. The drug entrapment of various batches varied from 47.35% to 99.68%. The F_{11} formulation observed a zero order release based on the regression coefficient value in kinetics study.
Keywords: Hydrogel Beads, controlled release, ionic gelation, entrapment efficiency.

A R T I C L E I N F O

CONTENTS

1. Introduction 09
2. Materials and Methods 11
3. Results and discussion 13
4. Conclusion 16
5. Acknowledgement. 16
6. References 16

Article History: Received 29 January 2016, **Accepted** 28 February 2016, **Available Online** 21 June 2016

***Corresponding Author**
T. Satyanarayana
Department of Pharmaceutics,
Browns College of Pharmacy,
Khammam, Telangana, India
Manuscript ID: JPBR2925

PAPER-QR CODE

Citation: T. Satyanarayana, *et al.* Formulation and Evaluation of Nizatidine Hydrogel Beads. *J. Pharm. Bio. Res.*, 2016, 4(1): 09-17.

Copyright© 2016 T. Satyanarayana, *et al.* This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

1. Introduction

The Term beads are defined as a “spherical particle with a size varying from 50 nm (or) 2 mm, containing a core substance”. The Beads are Targeted drug delivery systems have been designed on the concept of magic bullets given by “Dr. Paul Ehrlich”. This concept is associated with the

development of such systems which when introduced in the body, direct the drug only to its site of action there by providing maximum therapeutic response accompanied with reduced toxic effects due to decreased distribution of drug to other body tissues [1].

Hydrogels:

Since the establishment of the first synthetic hydrogels by Wichterle and Lim in 1954. The growth of hydrogel technologies has advanced many fields ranging from food additives to pharmaceuticals to biomedical implants. Hydrogels can be prepared from natural or synthetic polymers [2]. Hydrogels are three dimensional hydrophilic polymer networks capable of swelling in water or biological fluids, and retaining a large amount of fluids in the swollen state. Their ability to absorb water is due to the presence of hydrophilic groups such as –OH, -CONH-, $-CONH_2$, -COOH, and - SO_3H. The water content in the hydrogels affects various properties like permeability, mechanical properties, surface properties and biocompatibility [3].

Hydrogels have similar physical properties as that of living tissue, and this similarity is due to the higher water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids. The ability of molecules of different size to diffuse into (drug loading), and out (release drug) of hydrogels, permit the use of hydrogels as delivery systems. Since hydrogels have high permeability for water-soluble drugs and proteins, the most common mechanism of drug release in the hydrogel system, is diffusion. Factors like polymer composition, water content, cross-linking density and crystalline can be used to control the release rate and release mechanism from hydrogels [4].

Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. New synthetic methods have been used to prepare homo- and co- polymeric hydrogels for a wide range of drugs, peptides, and protein delivery applications. Random copolymers with balanced hydrophobicity or hydrophilicity, can offer desirable release rates and dissolution profiles, for the development of oral sustained drug delivery [5].

Hydrogel beads:

A hydrogel is a cross linked polymer network that is insoluble in water but swells to an equilibrium size in the presence of excess water. In chemical gels, the polymer chains are cross linked by covalent bonding. If the polymer chains are cross linked by non-covalent bonding, such networks are called physical gels. The research on hydrogels started in 1960s with a landmark paper on poly(hydroxyl ethyl methacrylate) by Wycherley and Lim. Since then, various types of hydrogels have been synthesized and characterized due to the unique properties of hydrogels and potential applications in various areas including sustained drug delivery [6]. Much of the work on hydrogels has been concentrated on lightly cross linked homogenous homo-polymers and copolymers. One of the first applications of hydrogels in sustained drug delivery was slow release of the loaded drugs from dried hydrogels exposed to an aqueous environment. For dried hydrogels to swell, water has to be absorbed into the glassy matrix of the dried hydrogels. The swelling kinetics of the dried hydrogels thus depends on the absorption of water occurring by a diffusion process and the relaxation of the polymer chains in the rubbery region. This is a slow process. Although the slow swelling of dried hydrogels has been useful in many applications, there are situations where faster swelling of dried hydrogels is desirable [7].

Nizatidine is a histamine H_2-receptor antagonist that inhibits stomach acid production, and commonly used in the treatment of peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD). It is chemically *N*-(2-[(2-[(dimethylamino) methyl] thiazol-4-yl) methylthio] ethyl)-*N*-methyl-2-nitroethene-1, 1-diamine Nizatidine competitively inhibits the action of histamine at parietal cell receptor sites reducing the volume and hydrogen ion concentration of gastric acid secretions [8]. Nizatidine accelerates the healing of most ulcers. Nizatidine is a competitive, reversible inhibitor of histamine at the histamine H2-receptors, particularly those in the gastric parietal cells.

Pharmaceutical Applications:

A new dimension for the use of sodium alginate hydrogel polymeric beads as drug delivery device in pharmaceutical and biomedical science has been explored. Some important applications are as follows [9, 10]:

Drug Delivery to Colon:

As sodium alginate is biodegradable by the colonic bacterial flora, it is a promising polymer for colon drug delivery. Alginate-chitosan beads loaded with a model protein, bovine serum albumin, were investigated to explore the temporary protection of protein against acidic and enzymatic degradation during gastric passage.

Mucosal Delivery:

In recent times, mucosal surfaces such as nasal, peroral, and pulmonary surfaces are receiving a great deal of attention as alternative routes of systematic administration. Alginate has mucoadhesive properties, and therefore it seems particularly useful to formulate the bioadhesive dosage forms for mucosal administration. Alginate has been found to enhance drug absorption through mucosa without damaging the biological system.

Nasal Delivery:

Nasal mucosa has high permeability and can provide easy access of the drug to the absorption site. The particulate delivery to peroral mucosa is easily taken up by the peyer's patches of the gut-associated lymphoid tissue.

Gastro Enteric Delivery:

Alginate has effects on the intestinal epithelium, and they studied the effects of alginates with varying molecular weights The observations suggest that alginate had pronounce effect on the permeability of mucous free epithelial layer and enhanced the permeation of atenolol.

Ocular Delivery:

The primary requirement for an ocular delivery system is bioadhesiveness that increases the contact time with the cornea, leading to improved drug absorption at the site. In consideration of the alginate bioadhesiveness, attempts

were made to take advantage of cationic properties of alginate in ocular delivery.

2. Material and methods

Material:

Nizatidine is obtained from Atlas chemicals, Pune. The Excipients like Sodium alginate, Pectin, is obtained from Varuna bio products, Tamilnadu, Hydroxy propyl methyl cellulose (E 15 & K4M), Sodium carboxy methyl cellulose is obtained from Neha chemicals Mumbai Calcium chloride is obtained from Chlorides India, Baruch, Mumbai, Sodium dihydrogen ortho phosphate & Distilled water is analytical grades.

Methodology:

The following preformulation studies were performed for Nizatidine and polymers.

1. Determination of Solubility studies of Nizatidine
2. Physical appearance
3. Drug – polymer compatibility studies

1. Solubility studies

Solubility studies are carried out by preparing saturated solutions of drug in solvent and analyzing them spectro-photometrically. Saturated solutions are prepared by adding excess of drug to solvent and shaking them on shaker for specific time period under constant vibration. After this, the solutions are filtered and analyzed spectro-photometrically. Solubility can be determined by adding the solute in small incremental amount to fixed volume of the solvents. After each addition, the system is vigorously shaken and examined visually for any un dissolved solute particles [11].

% solubility = sample absorbance / standard absorbance x dilution factor x 100

1 mg of drug is added to 1ml of water or any other solvent in a test tube and shaken. A soluble organic compound will form a homogenous solution with water or any other solvent while an insoluble organic compound will remain as a separate phase.

2. Physical appearance:

These are preliminary characteristics of any substance which is useful in identification of specific material. The physical properties like color, odour of API were studied. The appearance of the active pharmaceutical ingredient was done by visual observation [13].

Pre-Formulation Study of Nizatidine and Excipients:

Drug –Polymer Compatibility studies:

FT-IR Spectra: Prior to the development of the dosage forms, infrared spectra of the physical mixture of the Nizatidine, polymers individually and the mixture of drug and polymer were taken [14]. The drug-Polymer Interaction were studied by FTIR spectrometer, shimadzu 8400S 2% w/w of the sample with respect to a potassium Bromide (KBr) was mixed with drug KBr. The mixture was mixed into a fine powder using mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned for 10 times at a resolution of $2cm^{-1}$ using Happ-Genzel apodization. The characteristic peaks were recorded.

Preparation of Nizatidine containing Sodium alginate beads:

Preparation of hydrogel beads [15]:

Hydrogel beads of nizatidine were prepared by ionotropic gelation technique. Accurately weighed quantity of nizatidine was added to 50 ml of sodium alginate solution and thoroughly mixed with a magnetic stirrer. For the formation of hydrogel beads, 50 ml of this solution was extruded dropwise from needle into aqueous solution of calcium chloride and stirred for 10 minutes.

The obtained hydrogel beads were washed with water and dried at 70°C for 6 hr in an oven. Total two sets of hydrogel beads were prepared using only sodium alginate in different concentrations. In second set, hydrogel beads are prepared in a combination of polymers like HPMC, sodium CMC, pectin and sodium alginate combination. No beads are formed for formulations F_3, F_4, F_5, F_6, F_{12}, F_{13}. So, some of the evaluation tests were conducted on remaining formulations. The prepared beads F_1 to F_6 were dropped in 2 % calcium chloride solution and F_7 to F_{14} in 4 % calcium chloride solution.

Characterization of Nizatidine Hydrogel Beads

a) Scanning electron microscopy (SEM):

The surface morphology of the hydrogel beads was examined using scanning electron microscopy. The samples were mounted directly onto the SEM sample holder using double-sided sticking tape and were gold spray coated [16].

Evaluation of nizatidine hydrogel beads:

1. Particle size determination:

Measurement of the particle size distribution and mean diameter of hydrogel beads was carried out with an optical microscope. Stage micrometer was used to calculate calibration factor. 10 deviation of stage micrometer was matched with the deviation of ocular disc and calibration factor was calculated [17]. The particle size was calculated by multiplying the number of deviation of the ocular disc occupied by the particle with calibration factor. 50 randomly chosen hydrogel beads were taken to measure their individual size.

2. Drug entrapment efficiency:

Accurately weighed hydrogel beads equivalent to 150 mg were suspended in 100 ml of pH 6.8 buffer solution using 100 ml volumetric flask and kept for 24 hr [18]. Next day it was stirred for 5 min and filtered. From this, further suitable dilutions were made and the drug content analyzed by UV spectrophotometrically at 272 nm. The blank solution was prepared in the same manner as above using hydrogel beads without the drug.

$$\text{Entrapment efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

3. *In-vitro* swelling study

The swelling study of hydrogel beads was carried out in two aqueous media, 0.1 N HCl for 2hr and pH 6.8 buffer solution for next 6 hr. Accurately weighed hydrogel beads were immersed in 25 ml of 0.1 N HCl, after 2 hr the hydrogel beads were transferred to 25 ml of pH 6.8 buffer solution. At fixed time intervals, the hydrogel beads were separated from the medium, immediately they were wiped

gently with paper and weighed [19]. The dynamic weight change of the hydrogel beads with respect to time was calculated according to the formula.

Degree of swelling = (wet weight – original dry weight) / original dry weight x 100

4. *In-vitro* release study

The *in vitro* drug release studies of nizatidine was carried out using USP dissolution apparatus type II (Paddle type) at 50 rpm at 37± 0.50°C using 0.1 N Hcl for 2 h and phosphate buffer (pH 6.8) for 10 h [20]. From each batch 150 mg of nizatidine hydrogel beads containing enteric capsules were taken and subjected to dissolution studies. 5 ml of dissolution medium was withdrawn at every 1 hr and the medium was replaced with equal quantity of fresh dissolution medium. The sample withdrawn was suitably diluted and nizatidine content was analyzed by using spectrophotometer at 272nm [20].

Evaluation of Degradation Kinetics:

The degradation kinetics of hydrogel is examined by measuring the swelling ratio as a function of water retention. The hydrogel are placed in 0.1N HCl medium at 37°c for 24h and the samples are periodically weighed at 6h interval. Water retention capacity as a function of time is assessed by the following equation:

$$WRt = (Wp-Wd)/(Ws-Wd)$$

Where,

Wd is the weight of the dried hydrogel,

Ws the weight of the fully swollen hydrogel,

Wp the weight of the hydrogel at various exposure times.

Release profile comparison:

In the development of oral controlled release preparations, an ethical or proprietary product, which has been available in the market and established its efficacy clinically, is usually selected as a reference. The generic preparation is always formulated with its dissolution profile as similar as possible to that of proprietary product. *In vitro* dissolution can be considered as a surrogate tool for the assessment of bioequivalence. There are several methods to compare the dissolution profiles of test with reference [21].

Model dependent methods:

The model dependent methods all rely upon a curve fitting procedure. Different mathematical functions have been used to model the observed data. Both the linear and non-linear models are being used in practice for dissolution modeling. Linear models include Zero order, Higuchi, Hixson-Crowell where as the nonlinear models include First order, Korsmeyer-Peppas, etc. The kind of drug, its polymorphic form, crystallinity, particle size, solubility and amount in the pharmaceutical dosage form can influence the release kinetics. A water soluble drug incorporated in a matrix is mainly released by diffusion, while for a low water soluble drug the self erosion of the matrix will be the principal release mechanism [22].

Model dependent models:

Zero Order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that the area does not change and no equilibrium conditions are obtained) can be represented by following equation.

$$W_o - W_t = K\,t$$

Where

W_o is the initial amount of the drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at the time t and K is the proportionality constant. The following relation can in a simple way, express the Zero order kinetic model:

$$Q_1 = Q_o + K_o t$$

Where Q_1 is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution and K_o is the zero order release rate constant.

First order kinetics: the following equation can express this model:

$$\text{Log } Q_1 = \text{Log } Q_o + K_1 t/2.303$$

Where Q_1 is the amount of drug released in time t, Q_o is the initial amount of drug in solution and K_1 is the first order release constant. In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in porous matrices, release the drug in a way proportional to the amount of drug remaining in its interior.

Higuchi model:

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid matrixes. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. To study the dissolution from a planar system having a homogeneous matrix, the relation obtained was the following:

$$f_t = K_H t^{1/2}$$

Where f_t = amount of drug released at time t

K_H = the Higuchi release rate.

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship of square root of time versus concentration indicates that the drug release follows Fickian diffusion.

Korsmeyer- Peppas model:

For prediction of mechanism of drug release through polymeric system Korsmeyer and Peppas, in 1983 developed a mathematical equation, relating exponentially the drug released to the elapsed time. It is a simple semi empirical equation also called as Power law.

$$M_t/M \;= Kt^{\,n}$$

Where, M and M are the absolute cumulative amount of drug released at time t and infinite time, k is a constant incorporating structural and geometric characteristics of the device, n is the drug release exponent, indicative of the mechanism of drug release. The values of n representing drug release mechanism for different geometry.

Stability study [23]:

An ethical drug manufacturer is committed to provide to his consumers drug products, which are efficacious and safe. This can be ensured only by instituting a sound

programmed to study the stability of a product during its various phases of development and to arrive at the proper storage conditions and the expiry period under those conditions. This is a requirement in most of the countries and is stipulated by the regulatory agencies of those countries.

These studies would very quickly identify the need, if any, to stabilize the active substance or the formulation, and save invaluable time and effort from being spend on an unmarketable formulation. With the recent trend towards globalization of manufacturing operation, it is imperative that the final product be sufficiently rugged for marketing worldwide under various climatic conditions including tropical, subtropical and temperate.

Table 2: Conditions for Stability According To ICH-Guidelines

Study	Storage conditions	Minimum time period covered by data at submission
Long term	25 ± 2°C/ 60 ± 5% RH or 30 ± 2°C / 65 ± 5% RH	12 months
Interme diate Accelera ted	30 ± 2°C / 65 ± 5% RH 40 ± 2°C / 75 ± 5% RH	6 months 6 months

To obtain information on the stability of hydrogel beads, the effects of storage on the release profile and the crushing strength of liquisolid compacts were investigated. Stability studies of hydrogel beads conducted at 40 °C/ 42 and 75 % R.H., 12 weeks, 25 °C/ 75 % R.H., 6 months, 25 °C/ 75 % R.H., 12 months, 25 °C/ 75 % R.H., 6 and 9 months, respectively, 20 °C/ 76 % R.H., 4 weeks showed that storage at different conditions neither had an effect on the hardness nor on the release profiles of hydrogel beads.

3. Results and Discussion

Determination of Solubility studies of Nizatidine is a crystalline and amorphous was done in methanol at 370 °C. or 10-33 mg/mL.

Physical appearance:

The organoleptic properties of Nizatidine are white color, Amorphous in nature and also odorless.

Drug-Excipient Compatibility Study by FTIR

FT-IR spectroscopy to find out the compatibility of drug with polymer: FT-IR spectroscopy study was carried out separately to find out, the compatibility between the drug nizatidine and the polymers hydroxypropyl methylcellulose E-15. The FT-IR was performed for drug, polymer and the physical mixture of drug-polymer. The spectral obtained from FT-IR spectroscopy studies at wavelength between 4000cm to 400 cm.

FT- IR interpretation of drug, polymer and physical mixture of drug- polymer

Table 3: FT-IR absorption bands $(cm)^{-1}$

S.No.	Interpretation	Pure Drug (cm^{-1})	Drug +HPMC E 15 (cm^{-1})
1	NH	1613.67	1618.97
2	N=O	1516.19	1518.22
3	C=N	1219.21	1212.24
4	C-H	685.99	685.48
5	C=C	1580.76	1582.27

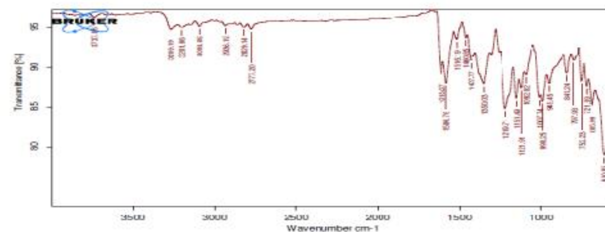

Figure 1: FT-IR Spectra of Nizatidine pure drug

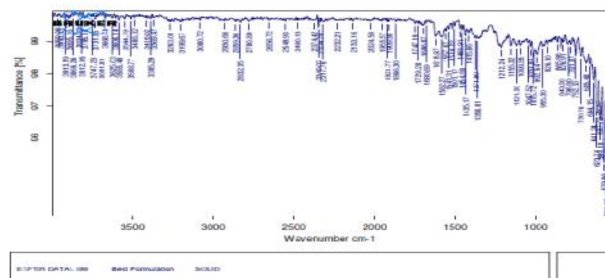

Figure 2: FT-IR Spectra of best formulation (F_{11}) of nizatidine hydrogel beads

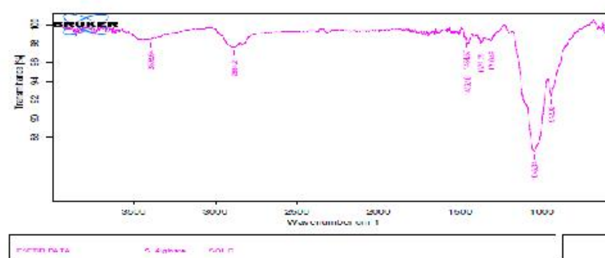

Figure 3: FT-IR Spectra of sodium alginate

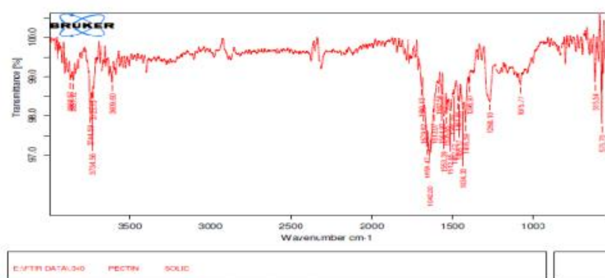

Figure 4: FT-IR Spectra of Pectin

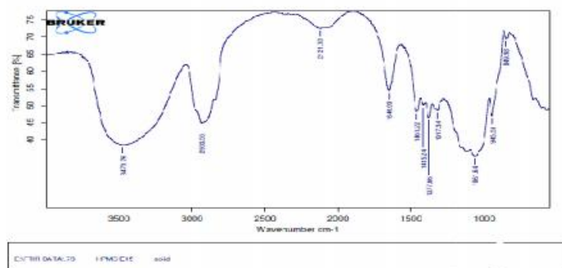

Figure 5: FT-IR Spectra of HPMC E15

Morphological Characters of Hydrogel Beads:
Scanning electron microscopy (SEM):

The surface morphology of the hydrogel beads was examined using scanning electron microscopy. The samples were mounted directly onto the SEM sample holder using double-sided sticking tape and were gold spray coated. By using SEM, the particle size, surface morphology and diameter of nizatidine hydrogel beads can be measured.

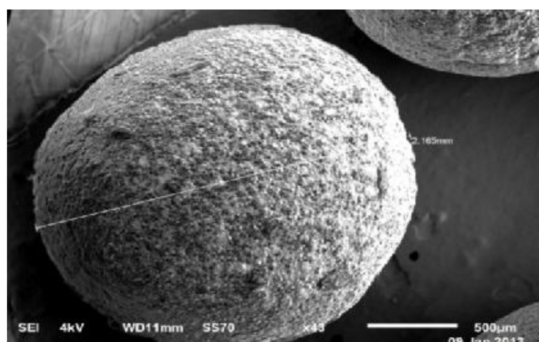

Figure 6: Diameter of Nizatidine hydrogel bead

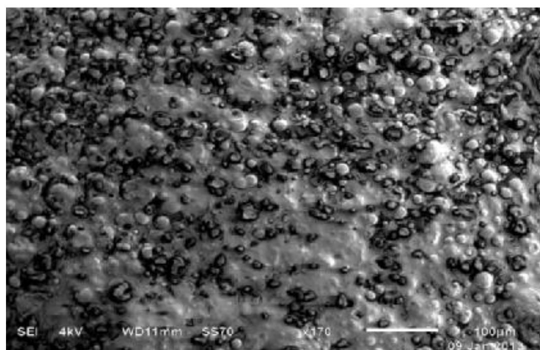

Figure 7: Surface morphology of Nizatidine hydrogel bead(x170 at 100µm)

Particle Size Determination

Table 3: Particle size values of nizatidine hydrogel beads

Formulation code	Mean Particle size (µm) ±SD, n=20
F_1	**500±42.85**
F_2	**618±72.88**
F_7	**575±69.67**
F_8	**510±66.59**
F_9	**650±44.21**
F_{10}	**536±82.10**
F_{11}	**550±75.54**
F_{14}	**614±59.26**

% Drug Entrapment Efficiency Determination

Accurately weighed hydrogel beads equivalent to 150 mg were suspended in 100 ml of pH 6.8 buffer solution using 100 ml volumetric flask and kept for 24 hr. Next day it was stirred for 5 min and filtered. From this, further suitable dilutions were made and the drug content analyzed by UV spectrophotometrically at 272 nm. The blank solution was prepared in the same manner as above using hydrogel beads without the drug.

$$\text{Entrapment efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Table 4: Drug entrapment efficiency values

Formulation code	% Drug entrapment mean value ±SD, n=3
F_1	47.35±0.32
F_2	51.85±0.56
F_7	77.56±1.08
F_8	88.75±1.12
F_9	90.16±1.23
F_{10}	91.44±0.45
F_{11}	95.68±1.75
F_{14}	92.26±1.38

***In-vitro* swelling study**

The swelling study of hydrogel beads was carried out in two aqueous media, 0.1 N HCl for 2hr and pH 6.8 buffer solution for next 6 hr. Accurately weighed hydrogel beads were immersed in 25 ml of 0.1 N HCl, after 2 hr the hydrogel beads were transferred to 25 ml of pH 6.8 buffer solution. At fixed time intervals, the hydrogel beads were separated from the medium, immediately they were wiped gently with paper and weighed. The dynamic weight change of the hydrogel beads with respect to time was calculated according to the formula.

Degree of swelling = (wet weight – original dry weight) / Original dry weight x 100

Table 5: Swelling study values

Formulation code	Swelling study mean value ±SD
F_1	11±1
F_2	14±2
F_7	16±2
F_8	19±1
F_9	21±2
F_{10}	25±3
F_{11}	28±1
F_{14}	33±2

Dissolution studies:

The dissolution was carried out for different experimental trials. The various results that are obtained are tabulated below. Dissolution studies are carried out in the following media.

Table 14: Cumulative % drug release of F1, F 2, F 7, F8 formulation

Time (min.)	Formulation codes			
	F 1	F2	F 7	F 8
0	0	0	0	0
1	22.28 ± 1.6	21.38 ± 2.6	47.43 ±3.1	24.38 ± 2.6
2	30.59 ± 1.2	31.69 ± 2.2	49.41 ±2.2	32.89 ± 2.2
3	37.34 ± 2.8	39.34 ± 2.8	63.00 ±1.3	37.34 ± 2.8
4	43.98 ± 1.5	42.98 ± 1.9	67.34 ±3.6	43.98 ± 1.95
5	50.63 ± 2.8	50.63 ± 1.4	76.58 ±3.3	60.63 ± 3.4
6	63.36 ± 2.2	58.36 ± 2.3	78.20 ± 2.8	63.36 ± 3.3
7	71.68 ± 2.5	61.68 ± 1.8	85.22 ± 2.7	81.68 ± 2.8
8	80.34 ± 1.6	70.34 ± 1.6	96.24 ± 3.2	90.34 ± 2.6
9	89.32 ± 1.1	78.32 ± 2.1	---	99.32 ± 2.15

Table 15: Cumulative % drug release of F9, F 10, F 11, F 14 formulation

Time (min.)	Formulation Codes			
	F 9	F 10	F 11	F 14
0	0	0	0	0
1	50.88 ±2.5	33.74 ± 3.6	10.76 ± 1.3	15.45 ± 2.5
2	89.16 ±1.82	44.52 ± 2.8	16.72 ± 3.2	29.64 ± 3.2
3	97.30 ±2.2	51.46 ± 2.4	18.69 ± 3.6	33.46 ± 2.8
4	--	62.68 ± 3.2	18.76 ± 2.9	37.84 ± 3.5
5	--	68.29 ± 2.5	21.74 ± 3.4	42.31 ± 2.7
6	--	71.27 ± 2.7	34.61 ± 1.9	49.09 ± 1.9
7	---	84.75 ±1.6	43.79 ± 1.9	54.83 ± 2.8
8	---	97.57 ± 3.1	56.66 ± 2.7	57.96 ± 3.2
9	---	--	--	74.02 ± 2.6
10	----	--	--	89.15± 3.6
11	--	--	--	96.96 ± 2.5

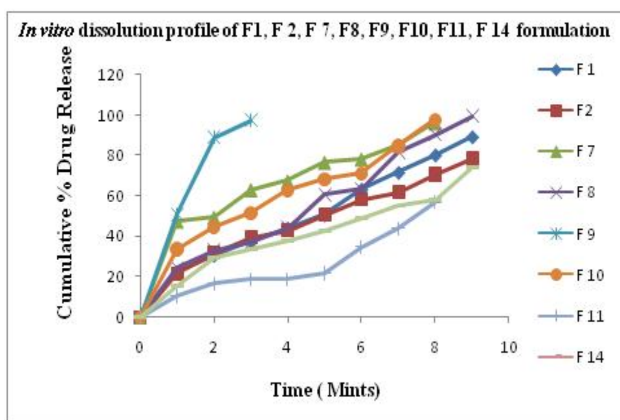

Figure 16: *In vitro* dissolution profile of F1, F 2, F 7, F8, F9, F10, F11, F 14 formulation

Table 17: kinetics study data of F_{11} formulation

Variables	Zero order	First order	HIGUCHI	PEPPAS
R^2	0.95	0.79	0.80	0.82
K_0	8.33	0.123	29.66	1.31

Stability studies: The best formulations of hydrogel beads were packed in aluminum foil and were placed in the stability test chamber and subjected to stability studies at accelerated testing (50°C, 75 % RH) for 3 months. After maintaining such conditions, the samples were tested for In vitro drug release and kinetics studies.

Table 18: Kinetics study for stability testing

S. No	Release order kinetics				*In vitro* release study for stability testing
	Zero order % CDR of F_{11} After 3 Months	First order % CDR of F_{11} after 3 months	Higuchi plot of F_{11} after 3 months	Peppas plot of F_{11} after 3 months	% CDR F_{11} formulation after 3 months
1	10.36	1.04	10.2	0.98	10.42
2	16.54	1.18	16.4	1.18	16.36
3	18.24	1.32	17.5	1.22	18.21
4	19.33	1.35	18.6	1.26	19.04
5	21.75	1.41	20.8	1.29	20.96
6	34.75	1.58	33.7	1.45	33.54
7	42.98	1.66	42.9	1.58	43.57
8	56.44	1.72	56.1	1.67	56.48
9	73.21	1.83	73.1	1.75	73.49
10	80.12	1.89	78.8	1.89	80.26
11	91.85	1.94	90.8	1.94	92.35
12	98.46	1.96	98.2	1.96	98.20

Table 1: Composition of nizatidine hydrogel beads

Formulation code	Drug : polymer	Nizatidine (mg)	Sodium alginate (mg)	pectin (mg)	HPMC E15 (mg)	HPMC K4M (mg)	Sodium CMC (mg)
F_1	1:0.5	500	250	---	---	---	---
F_2	1:1	500	500	---	---	---	---
F_3	1:1	500	---	500	---	---	---
F_4	1:1	500	---	---	500	---	---
F_5	1:1	500	---	---	---	---	500
F_6	1:1	500	---	---	---	500	---
F_7	1:2	500	500	500	---	---	---
F_8	1:2	500	500	---	500	---	---
F_9	1:2	500	500	---	---	500	---
F_{10}	1:2	500	500	---	---	---	500
F_{11}	1:2	500	500	250	250	---	---
F_{12}	1:2	500	500	250	---	250	---
F_{13}	1:2	500	500	---	---	250	250
F_{14}	1:2	500	500	---	250	---	250

4. Conclusion

There is no compatibility is found in the drug & other polymers. From scanning electron microscopy, it was concluded that the shape of beads found to be spherical to disc shape, the surface of nizatidine hydrogel beads was found to be rough and each bead had a diameter range of 2-3 mm and the particle size ranged from 500-650 µm. From the above results it was concluded that the particle size of nizatidine hydrogel beads ranges from 500-650 µm. The above results revealed that all the formulations showed varied entrapment efficiencies while F_{11} formulation showed the highest percentage of entrapment efficiency of 95.68 % compared to all other formulations. The above results that all the formulations showed varied swelling study 11±1 to 33±2. The *In vitro* drug release study of all formulations is performed and the F_{11} formulation was found to be the best formulation as it showed the maximum sustained drug release of 98.23% at 12th hour. The formulation was observed to follow zero order kinetics based on the regression co-efficient value, $R^2 = 0.95$. After the kinetics stability study and *In vitro* drug release stability study, it was concluded that the formulation remained stable even after maintaining stress conditions for 3 months also.

5. Acknowledgement

The authors are thankful to my principal Browns College of Pharmacy, Ammapalem, Near Thanikella, Kanijerla, Khammam, Khammam Dist. for providing the all facilities for carried out this research work.

6. References

[1] Saleem M.A., Murali Y.D., Naheed M.D., Patel Jaydeep., and Malvania Dhaval. Preparation and evaluation of Valsartan loaded hydrogel beads. *International research journal of pharmacy.* **2012**; Vol.3 (6): 80-81.

[2] Gupta V.N., and Siva Kumar H.G. Preparation and characterization of superporous hydrogels as gastro retentive drug delivery system for

rosiglitazone maleate. *International research journal of pharmacy*. **2010**; Vol.18: 200-201.

[3] Peeush Singhal., Kapil Kumar., Manish Pandey., and Shubini Saraf., Evaluation of acyclovir loaded oil entrapped calcium alginate beads prepared by ionotropic gelation method. *International journal of chemtech research*. **2010**, 2(4):2076-2085.

[4] Abdul Altaf Sheikh., Umal Altaf Sheikh and Praneeta. Preparation and evaluation of chitosan-carrageenan., chitosan-alginate beads for controlled release of nateglinide. Pelagia research library. **2011**; Vol.2(2): 375-384.

[5] Leena M Thomas., Yehia Khaleel. Preparation and evaluation of atenolol floating beads as a controlled drug delivery system. *Iraqi journal of pharmaceutical sciences*. **2011**; Vol.20(1):70-80.

[6] Behin Sundar Raj., and Puneetha S R. Formulation and evaluation of chitosan-prazosin beads by ionotropic gelation method. *International journal of research in pharmacy and chemistry*. **2012**; Vol.2(4): 974-982.

[7] Amrindar Singh., K K Jha., Prabh Simran Singh and Gagan Shah. Formulation and evaluation of cefixime beads. *International journal of research in pharmacy and chemistry.* **2011**; Vol.1(4): 922-924.

[8] SivaKumar R., Rajendran N and Narayanan N. Design of mucoadhesive hydrophilic beads entrapped with ketoprofen for delivery into small intestine. *International journal of research in pharmaceutical, biological and chemical sciences.* **2011**, 1(2): 704-712.

[9] Loyd V Allen., Leon Shargel., Lawrence H Block., Andrew Wilson. "Peptic ulcer disease and related acid-associated disorders". Textbook of clinical pharmacy. 7th ed. **2008**. Vol.2. 1128-1129.

[10] Bhavisha B Rabadiya and Biswajit Basu. Design and development of inter-penetrating polymeric hydrogel beads as delivery carrier for modified release of simvastatin. Inventi raid: NDDS. March **2013**; 2(4): 374-382.

[11] Sanjay K Jain., Anikant Jain., Yashwant Sinha and Manisha Ahiwar. Design and development of hydrogel beads for targeted drug delivery to the colon. AAPS Pharma science technology. **2007**. 8(3):1-8.

[12] Radhika Shah S., Kanu Raj Patel, Mukesh R Patel and Patel N M. A novel approach of gastro retentive dosage forms. *Asian journal of pharmaceutical research and technology*. **2013**. 3(1): 15-22.

[13] Poonam Patil., Daksha Chavange., and Milind Wagh. A review on ionotropic gelation method. Novel approach for controlled gastro retentive gelispheres. *International journal of pharmacy and pharmaceutical sciences*. **2012**, 4(2): 27-32.

[14] Chan Ma and Sunil Prabhu. Characterization of a novel lyophilized chitosan hydrogel beads for the controlled release of a highly water soluble drug, niacinamide. *International journal of drug delivery*. **2011**; Vol.3: 55-63.

[15] Alaa Eldeen B Yaseen., Ibrahim A Al Saria and Abdullah M Al Mohizea. Chitosan beads as a new gastro retentive system of verapamil. Scientia pharmaceutica. **2006**. Vol.74: 175-178.

[16] Biswajit Basu. Design and development of inter-penetrating polymeric hydrogel beads as delivery carrier for modified release of simvastatin. Bioavailability & bioequivalence: pharmaceutical research and development summit. **2013**.

[17] Afifa Bathool., Gowda D Vishakante., Mohammad S Khan and Sivakumar H G. Development and characterization of atorvastatin calcium loaded chitosan nanoparticles for sustain drug delivery. Advanced materials letters. **2012**. Vol.3(6): 466-470.

[18] Sudiptha Chatterjee., Min W Lee and Seung H Woo. Enhanced mechanical strength of chitosan hydrogel beads by impregnation with carbon nanotubes. *International journal of chemtech research*. **2009**. Vol.4: 2933-2939.

[19] Badarinath A V., Ravi Kumar Reddy J., Mallikarjun Rao K., Alagusundaram M., Gnana Prakash K and Madhusudhan Shetty. Formulation and characterization of alginate hydrogel beads of flurbiprofen by ionotropic gelation technique. *International journal of chemtech research*. **2010**; Vol.2(1):361-367.

[20] Durga Jaiswal., Arundhathi Battacharya., Indranil Kumar Yadav., Hari Pratap Singh., Dinesh Chandra., Jain D A. Formulation and evaluation of oil entrapped floating alginate beads of ranitidine hydrochloride. *International journal of pharmacy and pharmaceutical sciences*. **2009**; Vol.1:128-140.

[21] Mahale A M., Panigrahy R N., Sreeniwas S A. Formulation and *In vitro* evaluation of gastro retentive drug delivery system for acyclovir. *International journal of comprehensive pharmacy.* 2011; 2(5):1-4.

[22] Deshmukh V N., Jadav J K.,Masirkar V J., Sakarkar D M. Formulation, optimization and evaluation of controlled release alginate microspheres using synergy gum blend. *International journal of pharmaceutical sciences and research*. **2009**, 2(2):324-327.

[23] Ganesh N S., Bharathi G., Hanumanthachari Joshi., Jayanthic., Devendra pratap Singh. Buoyant multiparticulate drug delivery- Afocus on hydrogels. *World journal of pharmacy and pharmaceutical sciences.* **2013**; Vol.2:450-464.