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FORMULATION AND EVALUATION OF HYDROGEL BEADS FOR SUSTAINED DELIVERY OF NIFEDIPINE

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ABSTRACT

The objective of present study was to formulate hydrogel beads for the sustained delivery of Nifedipine using different polymer ratio and to study the *in-vitro* release characteristics of hydrogel beads. The sodium alginate/chitosan crosslinked hydrogel beads of Nifedipine were prepared by the ionotropic gelation method. The hydrogel beads were showed very little drug release under pH 1.5 HCl buffer whereas the release was increased in simulated gastrointestinal fluid (pH 6.8 phosphate buffer). The drug release was found to be affected by the varying ratio of sodium alginate and chitosan as well as percentage of total polymer. The results of stability study indicated that there was no significant variation in the drug release profile of the optimize batch F12 and F13 during the three month study. Therefore, the prepared sodium alginate/chitosan hydrogel beads can be considered as potential candidate for sustained delivery of Nifedipine to the intestine.

Key words: Hydrogel beads, Nifedipine, Sodium alginate, Chitosan.

INTRODUCTION

A basic objective in dosage form design is to optimize the delivery of medication so as to achieve a the desired therapeutic effects in the face of uncertain fluctuations in the *in-vivo* environment in which drug release takes place 9 (Lachman L 1987). In general, goal of sustained release dosage form has to maintain therapeutic blood or tissue level of drug for extended period of time. This is generally accomplished by attempting to obtain "zero order" release from the dosage from (Khan M, 2002).

Hydrogels are three-dimensional, hydrophilic, polymeric network capable of imbibing large amount of water or biological fluids. Hydrogels have similar physical properties as that of living tissue and this similarity has due to the high water content, soft and rubbery consistency and low interfacial tension with water or biological fluids. The beads are discrete spherical microcapsules that serve as the solid substrate on which the drug is coated or encapsulated in the core of the beads. Beads can provide sustained release properties and a more uniform distribution of drugs, include within the gastrointestinal tract. Bioavailability of drugs formulated in beads can be enhanced. A wide variety of biomedical applications such as site specific controlled drug delivery system, wound dressings, gel actuators, artificial organs medical pharmaceuticals and contact lenses. Hydrogel can respond to surrounding conditions such as pH, ionic strength, temperature, electric current and magnetic field. 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, crosslinking density and crystallinity can be used to control the release rate and release mechanism from hydrogel (Satish CS et al., 2006). Hydrogels are mainly classified as, pH sensitive,

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temperature sensitive, enzyme sensitive and electrical sensitive hydrogels based on their nature (Kost J and Langer R, 2001; Satish CS et al., 2006). Generally, the hydrogel beads are prepared by syringe dropping/ extruding and air atomization method depends on the intended particle size.

Cardiovascular diseases are one of the life threatening diseases of the world. Most common cardiovascular diseases are hypertension and angina pectoris, which require constant monitoring. Calcium channel blocker and coronary vasodilator are presently most important class of drug for hypertension and angina pectoris. Nifedipine belongs to dihydropyridine class of compound is calcium ions influx inhibitors. It exhibits 45-65% oral bioavailability due to hepatic first pass metabolism. It has a relative short biological half life of about 2-5 h. It is usually administered as conventional dosage form containing 5-50 mg taken 2 to 3 times a day. Once daily sustained-release formulation of Nifedipine is desirable to reduce the frequency of administration and to improve patient compliance and sustained release delivery in the form of hydrogel beads is a better alternative and advantageous over conventional drug delivery system. The main objective of present study was to formulate hydrogel beads for the sustained release of Nifedipine using different polymer ratio and to study the *in-vitro* release characteristics of hydrogel beads.

MATERIALS AND METHODS

Nifedipine was received as a gift sample from Zim Laboratories Pvt. Ltd., Kalmeshwar, Nagpur. Sodium alginate and chitosan were received as a gift samples from S. D. Fine Chemicals, Mumbai and Oxford Laboratory, Mumbai respectively. All other chemicals were procured from Merck, Loba Chemie and S. D. Fine Chemicals.

Formulation of hydrogel beads

The drug loaded hydrogel beads were prepared by ionic gelation technique. The hydrogel beads were formulated by dropping 10 ml of the polymer-drug dispersion containing sodium alginate and Nifedipine through 0.9 mm syringe needle at a dropping rate of 1.2 ml/min into 30 ml of gelling solution containing chitosan (previously dissolved in 1% acetic acid solution) and calcium chloride used as a crosslinking agent. The distance between the edge of the needle and the surface of the gelling solution was 6 cm. The spherical beads were cured for predetermined time interval in the gelling solution at room temperature with gentle stirring, and then the beads were filtered, rinsed with deionized water to remove any unreacted calcium chloride and then dried overnight (Patil JS et al., 2010).

The hydrogel beads were prepared by keeping the

concentration of Nifedipine at 50mg. Concentration of sodium alginate (polymer 1): 2% w/v, 3% w/v, 6% w/v and 10% w/v; Concentration of chitosan (polymer 2): 2% w/v, 3% w/v, 6% w/v and 10% w/v; Concentration of calcium chloride: 2% w/v, 3% w/v, 6% w/v and 10% w/v (crosslinking agent)

Evaluation of hydrogel beads
Drug content, encapsulation and loading efficiency

Accurately weighed hydrogel beads equivalent to 50 mg of the drug was crushed in glass mortar-pestle and the powdered hydrogel beads were suspended in 100 ml of phosphate buffer (pH 6.8). The solution was filtered after 24 h using Whatmann filter paper and 1ml of the filtrate was taken and diluted to 10ml. The absorbance was measured at 313 nm (Hui-Juan L et al., 2011; Piyakulawat P et al., 2007).

$$\% \text{ Encapsulation efficiency} = \frac{\text{Nifedipine initial amount} - \text{free Nifedipine amount}}{\text{Nifedipine initial amount}} \times 100$$

$$\% \text{ Loading efficiency} = \frac{\text{Nifedipine initial amount} - \text{free Nifedipine amount}}{\text{Weight of drug loaded hydrogel beads}} \times 100$$

Swelling study

Accurately weighed hydrogel beads (50 mg) were placed in petri dish containing pH 1.5 HCl buffer (30 ml) for 2 h, and subsequently transferred into pH 6.8 phosphate buffer (30 ml). At the end of 1 h, the beads were removed from the swelling medium, soaked with tissue paper to absorb excess water on the surface, and weighed. Weights of the beads were noted for every 1h. Percent weight gained by the beads was calculated by the following formula (Farhana Y et al., 2008; George P et al., 2006):

$$\% \text{ Swelling Index} = \frac{Ws - Wd}{Wd} \times 100$$

Where, Ws = weight of swollen beads,
Wd = weight of dried beads.

In-vitro drug release

The *in-vitro* drug release studies were performed using Dissolution Apparatus USP Type I (Rotating Basket DISSO2000, Lab India). The USP rotating basket method was selected to study the dissolution profiles of Nifedipine from all formulations. The study was carried out using 500 ml of pH 1.5 buffer and phosphate buffer pH 6.8, maintained at 37º± 0.5º at a rotation speed of 50 rpm. Withdrawing 10 ml of sample and replacing it with equal amount of fresh medium for preselected interval upto 12 h, monitored progress of the dissolution. The release rate

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from these hydrogel beads were conducted in a medium of changing pH by starting with hydrogel beads in pH 1.5 for 2 h and phosphate buffer pH 6.8 for 10 h. The sample solutions were analyzed for Nifedipine by UV absorbance at 324.5 nm for pH 1.5 HCl buffer and at 313 nm for pH 6.8 phosphate buffer using a UV spectrophotometer (UV-1700). Cumulative percentage of drug released was calculated and the mean of three determinations were used in data analysis (Agnihotri SA, 2006).

Kinetic study of formulation

The kinetics of drug release from the tablet formulations were described using zero-order, first order, Higuchi, Hixon-crowell and Korsmeyer peppas model. The criteria for selection of the best fit model were chosen on the basis of the goodness fit test. The zero-order release kinetic describes the systems in which the drug release rate is independent of its concentration. The first order kinetic described the systems in which the drug release rate was concentration dependent. Higuchi described the release of drug from an insoluble matrix as square root of time dependent process. In case of Korsmeyer peppas model, the drug release from such devices having constant geometry was observed till the polymer chains rearrange to equilibrium state. The Higuchi square root model was gives the drug release from a planer surface of an insoluble heterogeneous matrix by diffusion through the intragranular openings created by porosity of the matrix tablet. The Hixson-Crowell cube root law was described the drug release from systems in which there is a change in the surface area and the diameter of particle present in tablet. Korsmeyer peppas model was described the fraction released Q_t/Q_∞ as power function of time t for short time period (Ford JL et al., 1987; Colombo P et al., 2000; Ritger PA et al., 1987; Ozdemir N et al., 2000).

Particle size analysis

The particle size was determined using imaging system (Biowizard software 4.1). The diameters of about 20 beads were measured and the average particle diameter was determined.

Surface morphology

The surface morphology of the beads of optimized formulation was examined with Scanning Electron Microscopy (SEM) using (JEOJSM 6380A L, Japan at Metallurgy and Material Department, VNIT, Nagpur). The samples were vaccum dried in desiccator and coated with platinum using Vacuum Electric Sputter Coater JFC-1600(JEOL, Japan). Then the beads were mounted on the sample holder and the Scanning Electron Micrographs were taken.

Infrared absorption spectrophotometry

The chemical interaction and crosslinking mechanism of plain and drug loaded beads the FTIR analysis was conducted for plain and drug loaded beads. The plain and drug loaded beads were grounded respectively. For each type of the powder, 1 mg amount of the powder was blended with 100 mg amount of KBr pellets in a mortar and pressed into a tablet.

Stability studies

The stability study of the optimized formulation F12 and F13 was carried in air tight high density polyethylene bottles in incubator at 40º±2º and relative humidity of 75% ± 5% for a period of 3 month. After each month the formulations were analyzed for the drug content and *in–vitro* cumulative drug release (Kyndonieus F, 1980).

RESULTS AND DISSCUSSION

The scanning of drug in simulated gastric fluid and in simulated intestinal fluid was concluded that the drug had λ_{max} of 324.5 nm and 313 nm respectively and the drug obeys Beer-Lamberts law in concentration range of 0-50 µg/ml using simulated gastric fluid (pH 1.5) and in simulated intestinal fluid (pH 6.8).

Hydrogel beads F1- F13 were formulated by ionotropic gelation method using different ratio of sodium alginate and chitosan as shown in (Table 1) and examined the effect of various factors (sodium alginate and chitosan ratio and concentration, calcium chloride concentration and nature of beads). The formation of semi-interpenetrating network was observed due to the blend of sodium alginate and chitosan.

The drug content of all the formulation were found in the range of 38.31±0.08 mg to 42.01±0.4 mg/100 mg of beads. The encapsulation efficiency and loading efficiency of Nifedipine within sodium alginate and chitosan beads were depicted in Table 2.

The drug encapsulation was more than 97% in all formulations and the efficiency was neither affected by the amount of polymers nor the crosslinking agent used. Good drug loading efficiency were achieved for all the formulations (F1-F13) since Ca^{++} and NH_3^+ ions of chitosan competed with each other and reacts with $-COO^-$ ion of sodium alginate resulting in more compact structure. Some drug was lost to the external phase during preparation and recovery. The optimized batch F12 and F13 were showed the loading efficiency of 27.46±0.04 % and 28.76±0.06 % respectively.

The particle size of the beads of batch F12 and F13 were in the range of 31.7 µm and 33.1 µm respectively (Table 3).

The cumulative release profile of Nifedipine from sodium alginate/ chitosan beads in simulated gastric fluid (pH 1.5) for 2 h and simulated intestinal fluid (pH 6.8) for 10 h at 37°±0.5° were shown in Table 4.

The release rate of Nifedipine in simulated intestinal fluid (pH 6.8) was relatively higher than in simulated gastric fluid (pH 1.5). Low release in acidic medium was due to strong interaction between amino groups of chitosan and carboxyl group of alginate which was due to formation of intermolecular and intramolecular hydrogen bonds between the two polymers. Additionally, a repulsive force within the test hydrogel bead was created due to the protonation of primary amino groups ($-NH_3^+$) of chitosan. But, the force of H-bond is greater than the repulsive force, the beads were kept in a shrunken state in acidic medium and the drug was released slowly. However, under alkaline condition there was breakage of H-bond which reduced the interaction between the polyelectrolyte and ionization of carboxylic group of alginate resulted in swelling of hydrogel network (beads) with subsequent imbibitions of fluid and dissolution and release of drug f by diffusion.

The slowest drug release observed in formulations F12 and F 13 (containing 10% w/v polymer) were 98.12% and 98.54% respectively in 10 and 12 h. Thus, these formulations were capable of controlling drug release and considered as optimized. The release rate was rapid with low percent polymer concentration. Beads (F1 to F9) with lowest percent polymer (3% w/v) released more than 90% of drug within 3 to 5 h whereas beads (F10 and F11) with (6% w/v) polymer concentration released more than 90% of drug in 8 to 9 h. These results suggested that, higher polymer concentration formed a highly viscous hydrogel network which sustained the drug release.

The hydrogel beads containing higher amount of chitosan (F12 with 2:1 polymer ratio) gave higher drug release than the beads containing greater amount of sodium alginate (F13 with 1:2 polymer ratio). This was due to the burst effect given by the beads at higher concentration of chitosan, gives faster release than the beads containing higher concentration of sodium alginate. The burst effect was due to increase in osmotic pressure. When the beads were placed in pH 6.8 phosphate buffer, the mechanical strength of the beads decreased because of the displacement of crosslinking calcium by sodium ions, but the osmotic activity of the ions increased. The mechanical strength of the beads was not bear the osmotic pressure and the beads probably burst. The optimized batch F12 and F13 were treated with different kinetic equation to interpret the order of release of Nifedipine and coefficient of regression (Table 5).

As there was very low release in pH 1.5 buffer therefore, dissolution profiles in pH 6.8 phosphate buffer were treated kinetically. The release seems to fit in the Korsemeyer peppas diffusion model and the order of drug release was first order kinetics. Further to characterize the release mechanism of Nifedipine from the beads the dissolution data was subjected to Korse-meyer peppas diffusion model. The value of 'n' (diffusion exponent) was estimated by linear regression of log Mt/M∞ Vs log (t). The value of 'n' was found to be 1.1729 and 1.8327 for F12 and F13 respectively, which suggested that the formulation exhibits a super case II release behavior. All formulations showed comparatively lower swelling index in pH 1.5 buffer than in pH 6.8 phosphate buffer (Table 6).

Table 1. Formulation of batches

Formulation Code	Drug concentration (mg)	Ratio of Sodium Alginate: Chitosan	Sodium alginate (% w/v)	Chitosan (% w/v)	Calcium chloride (% w/v)
F1	50	1:1	1	1	0.5
F2	50	1:2	1	2	0.5
F3	50	2:1	2	1	0.5
F4	50	1:1	1	1	1
F5	50	1:2	1	2	1
F6	50	2:1	2	1	1
F7	50	1:1	1	1	2
F8	50	1:2	1	2	2
F9	50	2:1	2	1	2
F10	50	1:2	2	4	2
F11	50	2:1	4	2	2
F12	50	2:1	4	6	2
F13	50	1:2	6	4	2

Table 2. Percent encapsulation and loading efficiency

Sr. No.	Batch	Drug Content (mg/100mg of beads)	Encapsulation efficiency (%)	Loading efficiency (%)
1	F1	38.31± 0.08	97.43±0.13	26.76±0.07
2	F2	39.42±0.03	98.64±0.06	26.58±0.13
3	F3	39.64±0.10	99.34±0.23	24.83±0.05
4	F4	38.82±0.02	97.64±0.07	21.16±0.08
5	F5	38.97±0.05	98.26±0.08	22.56±0.04
6	F6	39.04±0.015	99.84±0.11	26.08±0.09
7	F7	38.73±0.054	97.69±0.10	24.46±0.03
8	F8	39.32±0.01	98.65±0.04	26.04±0.04
9	F9	39.31±0.06	98.89±0.06	22.84±0.06
10	F10	39.49±0.05	99.75±0.07	20.70±0.11
11	F11	39.64±0.04	99.90±0.05	22.39±0.15
12	F12	40.97±0.02	99.94±0.03	27.46±0.04
13	F13	42.01±0.4	99.98±0.02	28.76±0.06

Represents mean ± S.D (n=3)

Table 3. Mean diameter size of formulations F1- F13

Sr. No.	Formulations	Mean diameter(μm)
1	F1	18.0±0.12
2	F2	18.4±0.21
3	F3	19.0±0.13
4	F4	19.2±0.13
5	F5	22.8±0.10
6	F6	23.9±0.23
7	F7	26.2±0.10
8	F8	27.6±0.22
9	F9	29.2±0.21
10	F10	30.9±0.23
11	F11	31.1±0.12
12	F12	31.7±0.10
13	F13	33.1±0.21

Represents mean ± S.D (n=3)

It was found that the beads shrink in acidic pH, this could be well justified due to the fact that, at acidic pH strong interaction occurs between amino groups of chitosan and carboxyl group of alginate due to formation of intermolecular and intramolecular hydrogen bond (polyelectrolyte complex) between the two polymers. Additionally, a repulsive force within the test hydrogel bead was created due to protonation of primary amino group ($-NH_3^+$) of chitosan.

The increased swelling of beads in pH 6.8 phosphate buffer was due to breakage of H-bond, which reduces the interaction between the polyelectrolytes and ionization of carboxylic group of alginate results in swelling of hydrogel network (beads) with subsequent imbibitions of fluid. The ionization of crosslinked calcium salt was increased and the process of exchange of Ca^{2+} for sodium starts. As Ca^{2+} ions were replaced by Na^+ ions, the dense crosslinked structure starts to get loosened and water starts getting absorbed into the beads.

The beads were prepared in different calcium chloride concentration as formulation F1- F3 in 0.5%, F4 to F6 in 1% and F7 to F13 in 2% respectively. At pH 1.5 and pH 6.8 the swelling index of the beads with different calcium chloride concentration was found in the order of 0.5% > 1% > 2%. At pH 1.5, this effect was due to lower degree of crosslinking between the amino group of chitosan and the carboxyl group of alginate at lower concentration of calcium chloride. At pH 6.8, the lower concentration of calcium chloride leads to lower crosslinking between Ca^{2+} and $-COO^-$ ions and subsequently a very large swelling force was created by the electrostatic repulsion between the ionized carboxyl groups that leads to higher swelling ratio at lower concentration of calcium chloride.

Table 4. Cumulative percent drug release of batch F1- F13

Sr. No	Time (h)	% Cumulative Drug Release												
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
1	0	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00
2	1	7.82± 0.40	6.89± 0.09	4.5± 0.132	5.0± 0.025	4.4± 0.065	4.2± 0.096	4.4± 0.09	3.14± 0.04	11.16± 0.07	8.5± 0.14	9.12± 0.04	10.72± 0.08	9.8± 0.08
3	2	18.32± 0.43	12.85± 0.17	7.8± 0.625	5.8± 0.154	5.0± 0.027	4.8± 0.065	6.9± 0.15	8.33± 0.20	17.02± 0.19	12.62± 0.26	12.3± 0.05	21.66± 0.02	12.73± 0.04
4	3	99.42± 0.26	98.56± 0.27	98.0± 0.048	98.32± 0.1	97.21± 0.17	96.21± 0.08	95.32± 0.17	82.9± 0.29	53.18± 0.15	65.0± 0.65	56.0± 0.10	52.58± 0.12	36.5± 0.195
5	4	-	-	98.85± 0.03	-	98.56± 0.16	96.52± 0.2	97.30± 0.18	88.7± 0.54	86.09± 0.14	68.2± 0.05	62.32± 0.12	63.76± 0.04	44.50± 0.25
6	5	-	-	-	-	-	97.13± 0.04	-	97.32± 0.32	93.16± 0.25	73.0± 0.02	69.25± 0.15	65.88± 0.18	51.30± 0.36
7	6	-	-	-	-	-	-	-	98.16± 0.91	95.12± 0.63	80.73± 0.14	74.0± 0.07	83.27± 0.06	68.01± 0.2
8	7	-	-	-	-	-	-	-	-	98.23± 0.05	86.13± 0.15	83.21± 0.08	87.40± 0.27	76.17± 0.62
9	8	-	-	-	-	-	-	-	-	-	95.13± 0.02	90.44± 0.5	89.98± 0.08	79.07± 0.32
10	9	-	-	-	-	-	-	-	-	-	-	94.56± 0.65	91.65± 0.11	81.77± 0.12
11	10	-	-	-	-	-	-	-	-	-	-	-	98.12± 0.06	86.54± 0.16
12	11	-	-	-	-	-	-	-	-	-	-	-	-	95.53± 0.13
13	12	-	-	-	-	-	-	-	-	-	-	-	-	98.54± 0.09

Represents mean ± S.D (n=3)

The above effects decreased with increase in concentration of calcium chloride from 1% to 2%, since the degree of crosslinking increased. Thus, it can be concluded that with increased in concentration of calcium chloride, the degree of crosslinking was increased and swelling index of the beads decreased.

The sodium alginate and chitosan were prepared in three different ratios i.e. 1:1, 1:2, 2:1.The swelling index observed was in the order of 1:1 > 1:2 > 2:1. The beads with sodium alginate/ chitosan in 1:1 ratio were showed the highest degree of swelling than beads with 1:2 and 2:1 polymer ratio. The highest degree of swelling of beads with 1:1

polymer ratio might be due to lose of physical entanglement between the two polymers. While in case of beads with 1:2 and 2:1 sodium alginate/ chitosan ratio, the beads with higher concentration of chitosan was formed a heavy viscous mass on hydration and persisted in the medium for longer duration on hydration than the beads containing higher concentration of sodium alginate. Thus, the beads with 1:2 polymer ratio was showed greater swelling ratio than the beads with 2:1 polymer ratio.

The beads were prepared using different concentration of polymer (sodium alginate/ chitosan) i.e. 2% w/v, 3% w/v, 6% w/v and 10% w/v. The effect of this polymer concentration on swelling was

Table 5. Kinetic treatment of drug release data of various batches

Batch Code	Kinetic equations				
	Zero order plot	First order plot	Higuchis plot	Korsemeyer Peppas plot	
	R^2	R^2	R^2	R^2	Slpoe (n)
F1	0.933	0.982	0.950	0.9843	0.865
F2	0.947	0.973	0.964	0.9798	0.836
F3	0.952	0.978	0.972	0.9821	0.854
F4	0.9563	0.9684	0.9652	0.9785	0.865
F5	0.9612	0.9736	0.9715	0.9794	0.862
F6	0.964	0.9745	0.9712	0.9817	0.863
F7	0.932	0.9641	0.9821	0.9842	0.854
F8	0.944	0.9735	0.9812	0.9829	0.839
F9	0.954	0.9821	0.9799	0.9843	0.821
F10	0.960	0.9721	0.9591	0.9789	0.837
F11	0.9520	0.9785	0.9810	0.9825	1.057
F12	0.9695	0.9900	0.9478	0.9763	1.1729
F13	0.9550	0.9843	0.9407	0.9853	1.4327

Table 6. Percent swelling index of batch F1- F13

| Sr. No	Time (h)	%Swelling Index												
	FFF1	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
1	0	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00
2	1	68±0.02	64±0.01	57±0.01	54±0.02	52±0.01	30±0.02	25±0.02	20±0.01	18±0.03	42±0.02	33±0.01	49±0.02	38±0.02
3	2	93±0.03	82±0.05	77±0.04	72±0.01	68±0.01	49±0.03	47±0.05	44±0.03	36±0.02	52±0.01	49±0.03	69±0.03	56±0.01
4	3	162±0.01	150±0.04	136±0.03	120±0.03	112±0.02	98±0.04	89±0.04	81±0.01	79±0.01	99±0.03	94±0.02	116±0.04	106±0.03
5	4	189±0.02	182±0.02	152±0.01	142±0.04	135±0.04	122±0.02	116±0.01	102±0.02	98±0.04	118±0.01	108±0.01	130±0.01	122±0.01
6	5	735±0.04	705±0.01	698±0.02	684±0.03	656±0.03	645±0.01	121±0.02	135±0.02	105±0.01	130±0.02	128±0.04	145±0.01	136±0.02
7	6	702±0.01	698±0.03	643±0.02	626±0.02	610±0.01	600±0.01	605±0.03	596±0.04	624±0.01	650±0.04	542±0.03	890±0.03	868±0.01
8	7	693±0.02	684±0.02	618±0.01	600±0.01	592±0.02	584±0.02	594±0.04	588±0.02	610±0.03	856±0.03	850±0.01	930±0.02	892±0.01
9	8	625±0.04	605±0.02	538±0.03	541±0.03	533±0.01	500±0.03	586±0.01	580±0.04	590±0.01	925±0.01	912±0.02	984±0.01	956±0.02

Represents mean ± S.D (n=3)

observed in the order of 10% > 6% > 3%. The formulation F12 and F13 with 10% w/v polymer concentration have the highest concentration of the two polymers and showed the highest swelling index due to formation of highly viscous polymeric network on hydration which increased the weight of swollen bead and sustained the release. While the beads with 6% w/v (F10 and F11) and 3% w/v (F2, F3, F5, F6, F8 and F9) polymer concentrations were formed a less dense viscous mass on hydration. There was decreased in percent swelling index after equilibrium for beads containing 3% w/v polymer. This reduction was due to decreased in weight of beads at higher pH condition and consequently loss of polymeric mass and lower retention. Mean while beads containing 10% w/v of polymer (F12 and F13) were retained for longer with respect to concentration in pH 6.8 phosphate buffer, rather they swelled with highly viscous hydrogel formation and keeping high percent swelling index.

The beads of optimize batch F12 and F13 were spherical in shape but the surface of the bead of batch F12 prepared with higher concentration of chitosan showed cracks and numerous pits while the surface of bead of batch F13 prepared with higher concentration of sodium alginate was smooth (Figure 1).

Figure 1. SEM pictures of Batch F12 and F13.
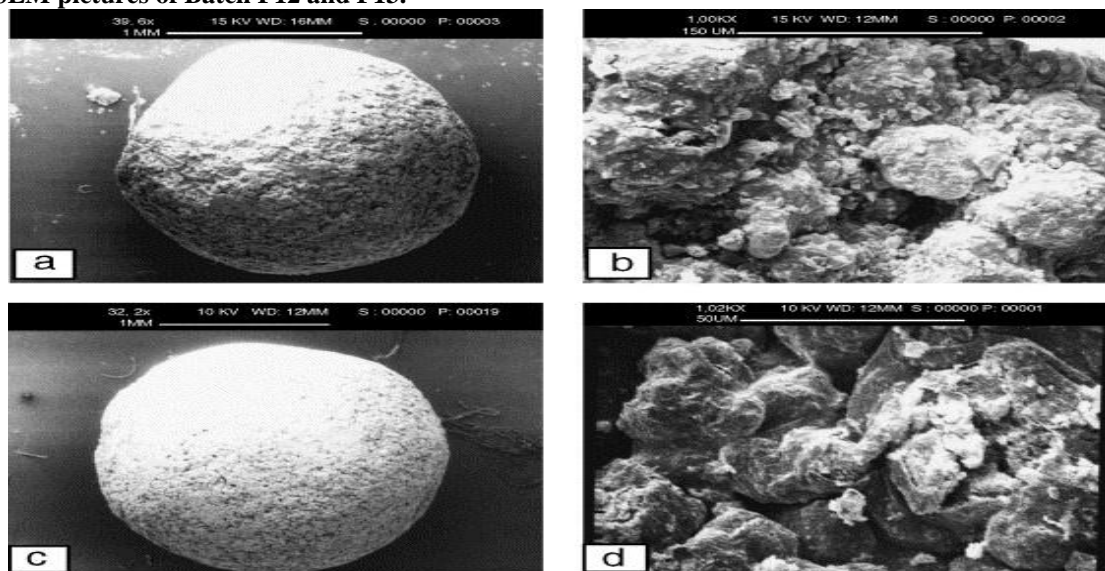
(a and c shows surface morphology of Nifedipine loaded sodium alginate and Chitosan beads, b and d shows cross section of beads)

Figure 2. Cumulative release profile of F12 at time Zero, One, Two and Three Month after storage under 40º±2º and of 75% ± 5% RH

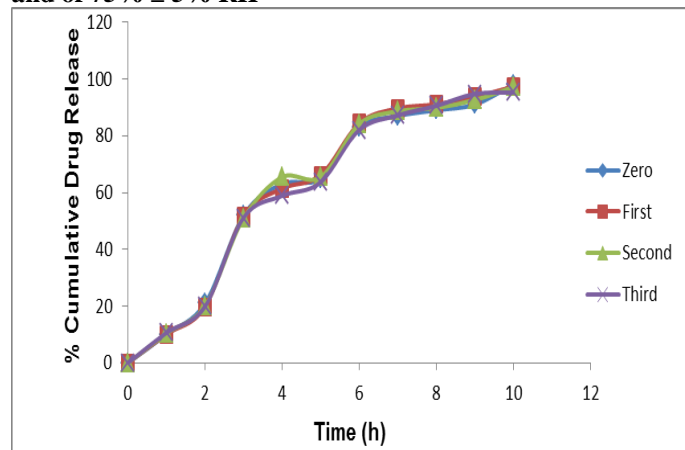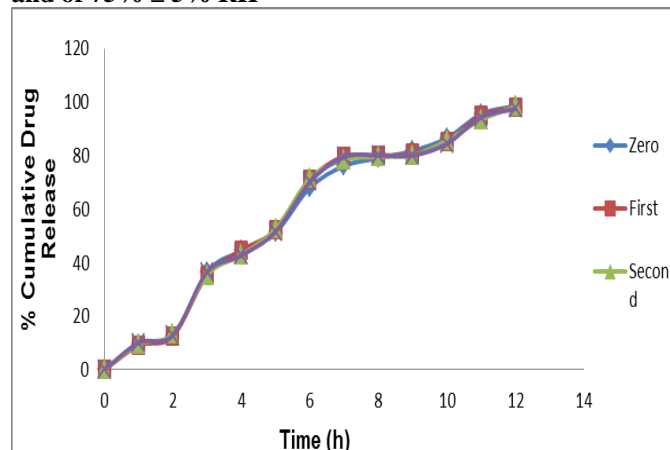**Figure 3. Cumulative release profile of F13 at time Zero, One, Two and Three Month after storage under 40º±2º and of 75% ± 5% RH**

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The peaks at 1770.53 cm^{-1} - 750.26 cm^{-1} were observed in the FTIR spectra of Nifedipine loaded sodium alginate/ chitosan beads, which indicated that Nifedipine was physically filled in the polymeric network. The IR spectra of physical mixture and Nifedipine loaded sodium alginate / chitosan beads showed bands as obtained in the IR spectra of pure drug, this suggests that no chemical interaction was occurred between the two polymers and the drug. The results of stability study (Figure 2 and 3) indicated that there was no significant variation in the drug release profile of the optimize batch F12 and F13 during the three month study therefore, it was concluded that the batch F12 and F13 were stable over the chosen temperature and humidity for 3 month.

CONCLUSION

The sodium alginate / chitosan crosslinked hydrogel beads of Nifedipine were prepared by the ionotropic gelation method. The hydrogel beads was showed very little drug release under pH 1.5 HCl buffer whereas the release was increased in simulated gastrointestinal fluid (pH 6.8 phosphate buffer). The release was found to be affected by the varying ratios of sodium alginate and chitosan as well as percentage of total polymer. Therefore, the prepared sodium alginate/ chitosan hydrogel beads can be considered as potential candidate for sustained delivery of Nifedipine to the intestine.

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