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PREPARATION AND COMPARITIVE EVAULATION OF NIZATIDINE LOADED SUPER POROUS FLOATING HYDROGELS

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ABSTRACT

The objective of the present investigation is to formulate Nizatidine loaded superporous floating hydrogel tablets. In the present study Nizatidine floating tablets were prepared by effervescence method using sodium bicarbonate as a gas generating agent. The tablets were formulated using direct compression technology by employing polymers like chitosan, carbopol 934p and ethyl cellulose. The prepared superporous floating hydrogel tablets were evaluated for pre compression, post compression and *in-vitro* drug release. The *in-vitro* drug release pattern of Nizatidine loaded superporus floating hydrogel tablets was fitted in different kinetic models which showed highest regression for zero order kinetics with higuchi's type of drug release mechanism. Among all the formulations, F18 which is acombination of chitosan,carbopol 934p and ethyl cellulose was optimized based on desired sustained release time (18hrs) followed by acceptable swelling and floating properties.

Key words: Nizatidine, Superporous Floating Hydrogels, Chitosan, Carbopol934p, Ethyl Cellulose.

INTRODUCTION

Gastro retentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and resultant improve the bioavailability of the drugs. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.[1] Several approaches can be used to prolong gastric retention time, including floating drug delivery systems (i.e., hydrodynamically balanced systems), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, superporous hydrogels and other delayed gastric-emptying devices [2-8]. Among these, superporous hydrogel system has been a promising one. Superporous hydrogel are 3-dimensional net-work of a hydrophilic polymer, they absorbs large amount of water in a very short period of time and hence they remain in stomach for a long time, thereby sustaining the drug release.These dosage forms due to there large volumes cannot be transported through the pylorus and their sheer bulk hinder their transport to the next organ via the narrow pylorus. This unique swelling property allows them to be used as gastric retention carriers providing a sustained release through long residence in the stomach. [9] Nizatidine is a histamine H2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger- Ellison syndrome and gastro esophageal reflux disease (GERD). Its oral bioavailability is about 70% and biological half-life is about 2hrs [10]. The main objective of present investigation was to formulate Nizatidine loaded superporous floating hydrogel tablets using direct compression technology for better delivery to stomach with an aim of increasing the mean residence time in the stomach. The study is carried out using both hydrophilic and hydrophobic polymers and furthermore to assess their influence over gastric retention.

MATERIALS AND METHOD

Materials: Nizatidine was obtained as gift sample from Dr. Reddy's laboratories (Hyderabad, India).

Chitosan, carbopol 934p, Ethyl cellulose were supplied by Aurabindo Pharmaceutical (Hyderabad, India) were supplied by Aurabindo Pharmaceuticals (Hyderabad, India). Sodium bicarbonate was supplied by S.D. Fine Chemicals Pvt (India). All other chemicals used were of analytical grade.

Pre compression parameters:

1. Angle of repose:

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The flow characteristics are measured by angle of repose.

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

Where h = height of pile, r = radius of the base of the pile = angle of repose.

Angle of repose below 25^0 indicates an excellent powder flow.

2. Bulk density:

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the part of the interparticulate void volume. It is expressed as gm/ml and calculated using the equation.

$$P = W/V_b$$

Where P = bulk density. W = mass of the powder blend. V_b = bulk volume of powder blend.

3. Tapped density:

Tapped density is the ratio of mass of powder to the tapped volume. It is calculated using the following equation and expressed as gm/ml.

$$P_{b,\ max} = W/V_{50}$$

Where $P_{b,\ max}$ = tapped density, W = mass of the powder blend.,V_{50} = volume of powder blend at 50 taps.

4. Carr's consolidation index:

It is defined as:

$$\text{Consolidation Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

5. Hausner's ratio: It is defined as

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Method:

The superporous hydrogel tablets of Nizatidne was formulated by incorporating polymers like chitosan, carbopol 934,ethylcellulose and sodium bicarbonate as one of the excipients. Furthermore microcrystalline cellulose was utilized as diluents whereas magnesium stearate functioned as glidant and lubricant respectively.

The ingredient except magnesium stearate were weighed accurately and transferred to a clean mortar and pestle. Chitosan was dissolved in 2% acetic acid and heated, and flakes are formed. The powder blend was mixed for ten minutes after which magnesium stearate was added to the blend and the mixing was continued for another 5 minutes. After obtaining a uniform blend, it was passed through sieve no: 60 and was prepared for compression. The compression of the powder blend was carried out using multi station punching machine (CADMACH MULTI STATION) by employing concave punches of 9mm diameter and adjusting thickness and hardness accordingly.

Evaluation of tablets

Tablet weight variation

Twenty tablets were randomly selected and accurately weighed and their average weight is calculated,such that each tablet weight should within the range of ±5% .Results are expressed as mean values ± SD.

Tablet hardness: The Hardness of tablets were tested using Pfizer hardness tester.

Tablet thickness

A vernier caliper was used to determine thickness of 10 randomly selected tablets. Results are expressed as mean values

***In Vitro* Buoyancy Studies**

The *in vitro* buoyancy was determined by floating lag time as per the method described by Rosa et al [11]. Briefly the tablets were placed in a 200-mL of 0.1 N HCl, maintained in a water bath at 37±0.50C. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time (FLT) and the time period up to which the tablet remained buoyant is determined as Total Floating Time (TFT). The *in vitro* buoyancy time for all the formulation were reported.

Drug content uniformity

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (400 mg) was extracted in 100 mL of 0.1N HCl. The solution was centrifuged at 3000 rpm for 15 min. The drug content was analyzed at 314 nm using a UV/ visible spectroscopy after suitable dilution with 0.1 N HCl.

Tablet friability

According to the BP specifications [12], 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus and rotated 100 times in 4 min at 25rpm.. The percent weight loss was calculated for all formulation and was reported.

Water Uptake Studies

The swelling index of tablet was determined by placing the tablets in 200 ml beaker using 0.1 N HCl. After every one hour up to 12 hours, each tablet was removed and blotted with tissue paper to remove the excess water and weighed on the balance..The swelling index is expressed as a percentage and was calculated from the equation Swelling Index

(S.I.) = {(Wt-Wo)/Wo} × 100

Where, Wt = weight of tablet at time t Wo = weight of tablet before immersion.

***In- vitro* Drug release studies:**

Dissolution test was carried out using USP XXIV rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 0.1 N hydrochloric acid was used as dissolution medium (900ml). It was maintained at 37 ± 1˚C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the Nizatidine at 314 nm by using a double beam UV spectrophotometer.

RESULTS AND DISCUSSION

A standard concentration of Nizatidine was prepared in 0.1N HCl and the absorbances were measured at 314 nm as shown in Fig 1. Nizatidine is showing good linearity between 25-250 µg/ml with a correlation coefficient of 0.999 as shown in Table no. 1 and Fig .2. The floatation was accomplished by incorporating gas generating agent, sodium bicarbonate into a swellable polymer. FTIR studies of the pure drug Nizatidine and formulations showed that there was no drug polymer interaction. Superporous floating hydrogel tablets were formulated by using both hydrophilic and hydrophobic polymers such as chitosan, carbopol 934p, ethyl cellulose. The Pre Compression parameters for the powder blend was carried out and the result were shown in Table. No. 4.the angle of repose of all the formulations was found to be in the range of 27.50^0 - 31.29^0. The Bulk and Tapped density of powder blends were from 0.532-0.559gm/ml and 0.619-0.669gm/ml respectively. Carr's index calculated showed to vary from 13.24-17.7% and Hausner ratio ranged from 1.15-1.22 . These values indicate that the the powder blend exhibited good flow properties and were within the official limit.

All the evaluated parameters result obtained from different formulations of tablet is shown in Table.No.5. Hardness of various tablet were in range of 5.9-6.5kg/cm^2 enabling good mechanical strength. The thickness observed was 4.3-4.5mm. The tablets selected from different formulation passed the uniformity of weight test prescribed in IP. The individual tablet weights when compared with average weight were within the official limit (±5%) of % deviation. The friability of tablet formulations were within the acceptable limits and ranged from 0.36-0.42%.

Tablet formulations containing chitosan ,carbopol 934p,ethyl cellulose(F16) showed less floating lag time than other formulation and a total floating time of 18 hrs.as shown in Table No.6.

Swelling study was performed on all the batches for 5 hr. The result of swelling index is given in Table No.7,8. While the plot of swelling index against time (hr) is depicted in Fig. 4&5.From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The results acquired from the dissolution study of tablets are shown in Table.No 9.Among the 16 formulations, F1 - F4 were chitosan based formulations which showed sustain action for a period of 6-10hrs. Depending upon the observed results, F2 was selected as a base for the remaining formulations Formulations F5 - F8 were prepared using carbopol in 0.25:1, 0.5:1, 0.75:1 and 1:1 ratio with chitosan respectively, provided a sustained release for a period of 7 – 12hrs. The sustained drug release period of 4 – 8hrs was observed in batches F9 – F12 which were prepared using ethyl cellulose in 0.25:1, 0.5:1, 0.75:1 and 1:1 ratio with chitosan respectively..Polymer combination of carbopol934p and ethyl cellulose in 0.25:1, 0.5:1, 0.75:1 and 1:1 ratio with chitosan were used in formulating batches F13 – F16. Compared to the above formulation, the drug release was found to be sustained for a period of 10 – 18hrs. A drug release of 100.25% at 18^{th} hour was provided by F16 which was considered as best formulation based upon the results obtained from dissolution study performed.

CONCLUSION

The floating tablets of Nizatidine were successfully formulated by effervescent technique. The floating tablets containing Chitosan, carbopol 934p and ethyl cellulose (F16) showed satisfactory results with respect to floating lag time, total floating duration, swelling ability and sustained drug release properties. The optimized formulation F16 followed zero order kinetic and the mechanism of drug release was found to be Higuchi mechanism.

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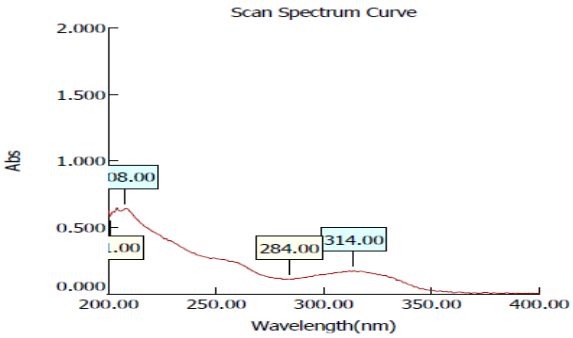

Fig.1. λmax in 0.1N Hcl (pH 1.2).

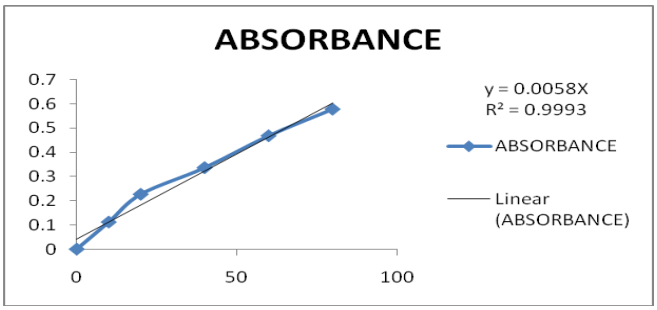

Fig.2. Calibration curve in 0.1N Hcl (pH 1.2)

INTIALLY

AFTER 65 SEC

AFTER 6HRS

AFTER 12HRS

Fig.3.*in-vitro* Buoyancy test

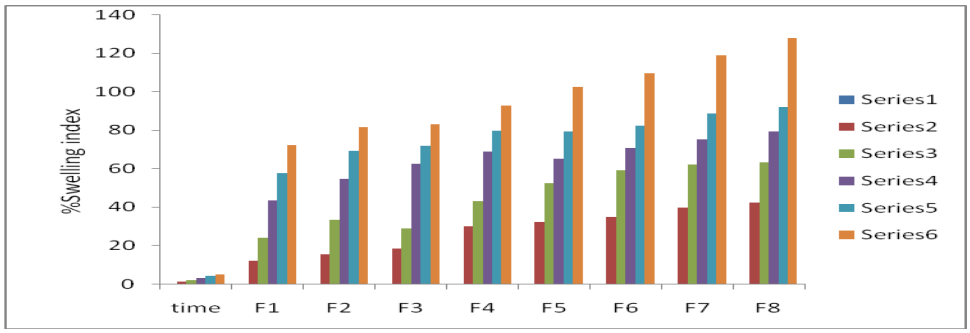

Fig.4. Swelling Index For Batches F1 To F8

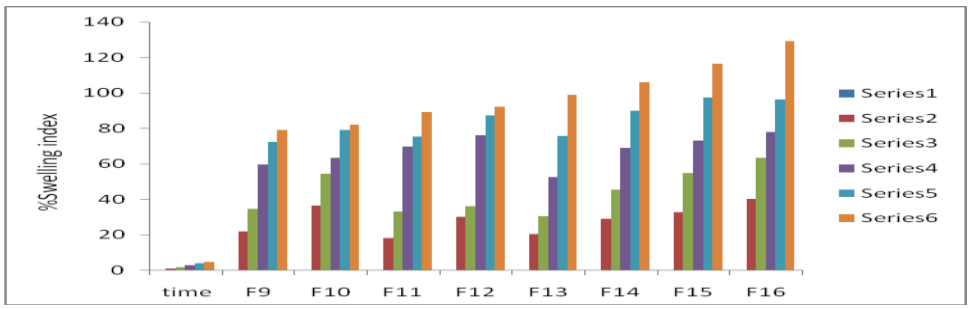

Fig.5. Swelling index for batches F9 to F16

Table No.1.Measured absorbance in 0.1 N Hcl (pH 1.2).

Sno	Concentration	Absorbance
1	10	0.112
2	20	0.227
3	40	0.337
4	60	0.469
5	80	0.579

Table .No.2 .Formulation chart for superporous floating hydrogel Tablets for Batche F1 To F8.

Ingredients(in mgs)	F1	F2	F3	F4	F5	F6	F7	F8
Nizatidine	150	150	150	150	150	150	150	150
Chitosan	37.5	75	112.5	150	75	75	75	75
Carbopol	-	-	-	-	18.75	37.5	56.25	75
Ethyl cellulose	-	-	-	-	-	-	-	-
Mico crstalline cellulose	184.5	147	109.5	72	128.5	109.5	72	34.5
Sodium bicarbonate	20	20	20	20	20	20	20	20
Mag.stearate	8	8	8	8	8	8	8	8

Table .No.3 Formulation chart for superporous floating hydrogel tablets for Batche F9 To F16.

Ingredients(in mgs)	F9	F10	F11	F12	F13	F14	F15	F16
Nizatidine	150	150	150	150	150	150	150	150
Chitosan	75	75	75	75	75	75	75	75
Carbopol	-	-	-		9.37	18.75	28.12	37.5
Ethyl cellulose	18.75	37.5	56.25	75	9.37	18.75	28.12	37.5
Mico crstalline	128.25	109.5	90.75	72	128.5	109.5	90.75	72
Sodium bicarbonate	20	20	20	20	20	20	20	20
Mag.stearate	8	8	8	8	8	8	8	8

Table.No.4.Results showing Flow properties of tablet blend.

Formulation	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	28.16^{o} ±0.88	0.533±0.03	0.621±0.32	14.17±0.86	1.16±0.04
F2	29.49^{o} ±1.15	0.537±0.01	0.632±0.36	15.03±0.84	1.17±0.02
F3	31.29^{o} ±0.66	0.541±0.03	0.638±0.39	17.78±0.90	1.17±0.04
F4	28.12^{o} ±0.32	0.532±0.03	0.619±0.34	14.05±0.71	1.16±0.07
F5	29.28^{o} ±0.32	0.539±0.08	0.645±0.37	16.43±1.46	1.19±0.05
F6	30.31^{o} ±1.73	0.555±0.02	0.661±0.33	16.03±1.26	1.19±0.08
F7	27.50^{o} ±0.65	0.539±0.08	0.622±0.38	13.34±1.23	1.15±0.12
F8	28.22^{o} ±0.95	0.538±0.02	0.643±0.31	16.32±0.78	1.19±0.03
F9	29.28^{o}±0.32	0.550±0.10	0.634±0.38	13.24±1.22	1.15±0.10
F10	31.29^{o}±0.66	0.537±0.01	0.633±0.46	15.16±0.81	1.17±0.02
F11	29.28^{o}±0.32	0.523±0.08	0.626±0.28	16.45±1.19	1.19±0.12
F12	31.21^{o}±0.56	0.535±0.07	0.632±0.36	15.04±0.74	1.18±0.02
F13	27.50^{o}±0.65	0.554±0.08	0.625±0.37	13.50±1.21	1.16±0.12
F14	31.14^{o}±0.14	0.541±0.07	0.655±0.29	17.77±0.92	1.22±0.04
F15	28.22^{o}±0.95	0.534±0.02	0.644±0.36	14.88±0.75	1.17±0.03
F16	30.31^{o}±1.73	0.559±0.02	0.669±0.31	17.43±1.23	1.21±0.08

SD= n±3

Table.No.5. Results Showing Postcompression parameter's

FORMULATION	**Hardness (Kg/cm^2)**	**Thickness (mm)**	**Uniformity of wt (%)**	**Friability %**	**Drug content (%)**
F1	6.1 ±0.19	4.5 ± 0.04	400.41 ±1.12	0.40	98.95±0.88
F2	6.2±0.15	4.5 ± 0.02	401.65 ±1.49	0.37	100.1±0.83
F3	6.4±0.04	4.5 ± 0.02	400.68 ±1.35	0.39	99.73±0.87
F4	6 ±0.11	4.4 ± 0.03	400.05 ±1.37	0.38	100.8±0.64
F5	5.9 ±0.10	4.3 ± 0.02	400.50 ±1.74	0.36	99.4±0.58
F6	6.5 ±0.18	4.5 ± 0.04	400.03 ±1.11	0.38	99.99±0.8
F7	5.9 ±0.16	4.3 ± 0.02	399.85 ±1.65	0.42	99.8±0.42

F8	6.3±0.32	4 .3± 0.03	399.85 ±1.65	0.42	99.9±0.5
F9	6.2±0.26	4.5 ± 0.06	398.27 ± 1.09	0.40	98.84±0.69
F10	6.5±0.15	4.3 ± 0.05	399.41 ± 2.44	0.32	99.98±0.62
F11	5.9 ±0.16	4.4 ± 0.03	399.85 ±1.65	0.42	98.8±0.42
F12	6.3±0.32	4.5 ± 0.03	399.85 ±1.65	0.42	99.9±0.5
F13	6.2±0.26	4.5 ± 0.02	398.27 ± 1.09	0.40	99.74±0.69
F14	6.5±0.15	4.4 ± 0.05	399.41 ± 2.44	0.32	98.18±0.62
F15	6.1 ±0.11	4.3 ± 0.04	400.50 ±1.74	0.36	99.4±0.58
F16	6.5 ±0.18	4.5 ± 0.03	400.03 ±1.11	0.38	101.5±0.8

SD= n±3

Table.No.6.Results Showing In-*vitro* buoyancy test

Batch	Buoyancy lag time (sec)	Total floating time(Hrs)
F1	54	6
F2	58	7
F3	62	9
F4	65	10
F5	69	7
F6	72	9
F7	64	10
F8	70	>10
F9	57	4
F10	68	5
F11	61	6
F12	53	8
F13	60	>10
F14	59	>10
F15	60	>12
F16	50	>12

Table.No.7.Results Showing Swelling Index For Batches F1 To F8

TIME	% SWELLING INDEX							
	F1	F2	F3	F4	F5	F6	F7	F8
1	12.11	15.29	18.27	29.95	32.06	34.87	39.86	42.21
2	23.88	33.39	28.77	42.93	52.28	59.22	62.04	63.12
3	43.52	54.83	62.47	68.92	65.07	70.76	75.38	79.53
4	57.68	69.09	71.7	79.83	79.38	82.47	88.66	92.26
5	72.22	81.66	83.06	92.86	102.41	109.5	118.90	128.15

Table No.8.Results Showing Swelling Index For Batches F9 To F16

TIME	% SWELLING INDEX							
	F9	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**
1	21.9	36.52	18.22	30.06	20.54	29.3	32.86	40.24
2	34.8	54.68	33.39	36.28	30.72	45.64	55.04	63.58
3	59.7	63.43	69.87	76.07	52.49	69.2	73.07	78.17
4	72.52	79.28	75.45	87.38	75.72	90.12	97.38	96.19
5	79.24	82.17	89.24	92.15	99.87.	105.9	116.66	129.17

Table 9. Cumulative drug release for batches F1-F16

Time in Hrs	Cumulative % drug release															
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**
1	50.89	46.84	27.90	25.64	30.67	25.32	20.66	17.66	63.45	61.47	53.29	40.29	23.19	20.72	17.99	13.56
2	69.36	59.64	35.49	36.80	40.88	32.45	31.59	27.46	79.78	74.87	66.78	53.33	35.68	29.81	26.46	20.99
3	78.47	65.85	43.95	45.23	52.38	40.67	42.88	38.81	84.46	89.56	73.19	64.6	42.99	39.53	33.05	28.45
4	86.96	79.78	55.66	51.46	60.99	52.53	55.28	49.98	98.71	93.82	88.96	77.11	51.82	49.81	44.37	36.23
5	94.26	83.46	61.48	60.87	75.31	63.8	59.11	53.19	-	99.86	93.47	82.19	63.18	57.26	51.46	42.69
6	99.51	92.15	74.68	68.94	89.18	72.19	69.36	68.36	-	-	98.45	90.28	74.88	68.67	62.12	49.78
7	-	98.97	82.75	74.36	98.45	84.36	73.18	77.26	-	-	-	94.7	82.92	76.23	70.86	57.32
8	-	-	93.51	85.68	-	91.18	81.05	83.31	-	-	-	99.62	90.25	83.44	79.99	64.32
9	-	-	99.86	94.32	-	99.96	87.29	90.78	-	-	-	-	94.27	90.65	85.23	70.88
10	-	-	-	97.36	-	-	98.21	95.59	-	-	-	-	99.88	94.92	91.98	78.92
12	-	-	-	-	-	-	-	99.96	-	-	-	-	-	98.67	96.58	83.95
14	-	-	-	-	-	-	-	-	-		-	-	-	-	99.89	89.99
16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	93.65
18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100.25

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