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Formulation and evaluation of gastroretentive mucoadhesive tablets of nizatidine

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ABSTRACT

Controlled release gastro-retentive drug delivery systems offer many advantages for drugs having local action in the stomach or upper part of the gastrointestinal tract and control their release in the proximal part of GIT and improve their bioavailability. The objective of this study was to formulate mucoadhesive tablets to enhance the gastric residence time of the drug Nizatidine for the management of peptic ulcer. Nine prototypes, controlled release mucoadhesive tablet formulations were designed using the mucoadhesive polymer Carbopol 934P in combination with swellable polymers HPMC K4M, Polyox WSR303 and Xanthan Gum in different concentrations. The tablets were prepared by a direct compression method. The formulated tablets were evaluated for different quality parameters including in-vitro dissolution and diffusion study, in-vitro bioadhesion strength, drug content. The cumulative percentage drug release data revealed that formulations F2, F4 and F9 were highly effective in retarding drug release up to 12 hrs with 99.863%, 99.657%, 99.384% release respectively. The release mechanism explained with 5 models viz: zero order, first order, Higuchi and Peppa's. The overall drug release was observed to follow zero order kinetics and data obtained fitted well with the Higuchi's equation following non-fickian diffusion mechanism. The bioadhesive strength was found to be the function of nature and concentration of polymer used. Stability study performed for a month (40°C±2°C/75%±5%RH) exhibited no variations. The mucoadhesive gastroretentive formulation could be a promising delivery system for Nizatidine with the controlled release and promote local delivery of the drug to its site of action in the upper GIT.

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INTRODUCTION

The scenario of pharmaceutical drug delivery is rapidly changing. Conventional pharmaceutical dosage forms are now being replaced by new drug delivery system; most importantly controlled release system. This has been due to various factors such as developing new drug entities, expiration of international patents, discovery of new polymeric materials suitable for prolonging the drug release, need of therapeutic safety and efficacy (Gibaldi M *et al.,* 1987).

The basic rationale of a controlled drug delivery system is to optimize the biopharmaceutic, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using small quantity of drug, administered by the most suitable route (Brahmankar D.M. *et al.,* 1995).

A significant obstacle can arise in the development of oral controlled drug delivery system if there is narrow absorption window for the drug in the GIT and if the drug is poorly soluble or slowly degrade in colonic microbe environment or if it has local action in the specific regions of GIT. So, the real issue in the development of oral controlled drug delivery system here is not just to prolong the delivery of drugs for more than 12 hours, but to prolong its presence in upper intestine or stomach until the drug is released for the desired period.

The development of oral CRDDS has been hindered by the inability to localise the system in the selected regions of the GIT. There has been considerable research over the last decade on the possibility of controlled and site-specific delivery to the GIT by controlling the gastrointestinal transit of orally administered dosage forms using gastroretentive DDS (GRDDS). Such GRDDS possess the ability to retain the drug in GIT particularly in the stomach for long periods (Davis S.S. *et al.,* 2005). In general, a controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that i) are locally active in the stomach, ii) have an absorption window in the stomach or the upper small intestine, iii) are unstable in the intestinal or colonic environment, or iv) exhibit low solubility at high pH values (Alexander S. *et al.,* 2006).

Various approaches have been worked out to improve the retention of oral dosage forms in the stomach. One such approach is bioadhesive or mucoadhesive drug delivery system. Mucoadhesive drug delivery system utilizes the mucoadhesive property of certain water-soluble polymers that become adhesive on hydration and hence can be used for targeting a drug of a particular region of the body (Jimenez-Castellanos N.R. *et al.,* 1993).

Mucoadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site-specific manner. This approach involves the use of mucoadhesive polymers, which can adhere to the epithelial surface in the stomach. Nizatidine is an antiulcer drug of the H_2-receptor antagonist class. Nizatidine is well absorbed following oral administration with an oral bioavailability of 70% and half-life of 1-2 hrs. Nizatidine is metabolised in the liver to *N*-desmethyl nizatidine, Nizatidine *N*-oxide. *N*-desmethyl nizatidine metabolite is approximately 60% as active as nizatidine in blocking gastric acid secretion.

The half-life of Nizatidine is very short. Therefore inhibition of gastric acid secretion generally persists for only up to 3-4 hours following a single 150 mg dose of Nizatidine (Katzung G.B. *et al.,* 2007). Therefore, patients are directed to adhere to strict medication routine and multiple dosage regimens which can lead to lack of patient compliance and increased possibilities of drug-related side effects. Therefore, it is advisable to formulate the controlled release drug delivery system of Nizatidine which releases the active ingredient over an extended period thus minimizing the frequency of dosing (Bennett P.N. *et al.,* 2003).

A peptic ulcer is a sore or lesion which occurs in the mucosal lining of the stomach, duodenum which is the upper part of the small intestine or esophagus. This may occur due to excessive acid secretion or bacterial infection which produces lesions which may penetrate through the muscularis mucosa (Walker R. *et al.,* 2007). Hence ulcers are not superficial. Therefore, for effective treatment, the therapeutic agent will have to penetrate the mucus layer.

Thus one of the feasible approaches to improve the efficacy of treatment and promote faster healing of ulcer will be by way of controlled drug delivery system that can be retained in the stomach for a long time and provide sustained local action in the stomach and proximal part of GIT (Duchene D. *et al.,* 1988). The purpose of the study is to formulate the controlled release mucoadhesive drug delivery system of Nizatidine which releases the active ingredient over an extended period of time and delivers the active entity directly to the site of action, thus minimizing or eliminating side effects, minimizing the frequency of dosing and improved treatment of the disease.

MATERIALS AND METHODS

Research design

- To design and evaluate mucoadhesive oral tablets of Nizatidine as a model drug using polymers such as Carbopol 934P, HPMC K4M, Polyox WSR303 and Xanthan Gum.
- To determine the physical parameters such as thickness, hardness, friability, weight variation of the formulations.
- The research further includes optimisation of release patterns of the drug and to evaluate the release profile of drug from 9 prototype formulation batches with respect to mathematical modelling.
- The investigation focusses on studying the effect of the nature of polymers and their different concentrations on drug release, in-vitro diffusion and bioadhesive strength.
- To select the ideal optimised formulation which gives the best results for all the quality evaluation tests.
- Stability studies of the selected optimised batch.

Materials used: Nizatidine (USP) was a gift sample from Watson Pharma Pvt. Ltd. Goa, India. Carbopol 934P, Microcrystalline Cellulose, Magnesium Stearate and Talc were gifted by Centaur Pharma Pvt. Ltd, Goa, India. Hydroxypropyl methylcellulose and Polyox WSR-303 were generously donated by Colorcon Asia Pvt. Ltd, Goa, India., Xanthan was gifted by Wallace Pharmaceuticals, Goa, India. All other chemicals were of research grade.

Preparation of mucoadhesive tablets of Nizatidine: Mucoadhesive Tablets of Nizatidine using different concentrations of Carbopol 934P along with HPMC K4M, Polyox WSR303 and Xanthan Gum and various formulation additives as shown in Table 1 were prepared by Direct Compression technique. All the ingredients, except magnesium stearate, were uniformly blended in a glass mortar. After sufficient mixing of the drug and other ingredients, magnesium stearate was added and further mixed for 2-3 minutes. Tablets were compressed with an 11mm punch using Single Punch Tablet Compression machine. The tablet weighed around 350mg.

Evaluation of Mucoadhesive Tablets of Nizatidine

Tablet thickness and diameter: Thickness of tablets was important for uniformity of tablet size. Thickness and diameter were measured using digital vernier callipers (Lachman L. *et al.*)

Hardness and friability: The hardness of the tablet was measured using Monsanto hardness tester. It is expressed in kg/cm^2.

The Roche type Friability tester was used for testing the friability using the following procedure: Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25rpm dropping the tablets through a distance of six inches with each revolution. After 4mins, the tablets were deducted and reweighed, and the percentage loss in the tablet weight was determined.

$$\%F = \frac{W_{\&n\&(\&)^*} - W_{f\&n)^*}}{W_{\&n\&(\&)^*}} \times 100$$

Weight variation test: The weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average. From this percentage weight difference is calculated and checked for USP specifications (Duchene D. *et al.,* 1988). All the above tests were done in triplicate.

Content uniformity test

The content of Nizatidine in the tablets was performed for three randomly picked samples from each formulation. Three tablets were powdered in a glass mortar, and powder corresponding to the weight of the tablet was taken in a 100ml volumetric flask. The powder was well mixed with 70ml of simulated gastric fluid, and the final volume was made up of the same medium. The solution was filtered, and 1ml of the filtrate was taken in 25ml of volumetric flask and diluted with the media and analysed at λmax (314nm). The concentration of the drug in mg/ml was determined using a standard calibration curve of the drug. The study is done in triplicate for each formulation.

Measurement of bioadhesive strength

Bioadhesive strength of mucoadhesive tablets was measured on a modified physical balance.

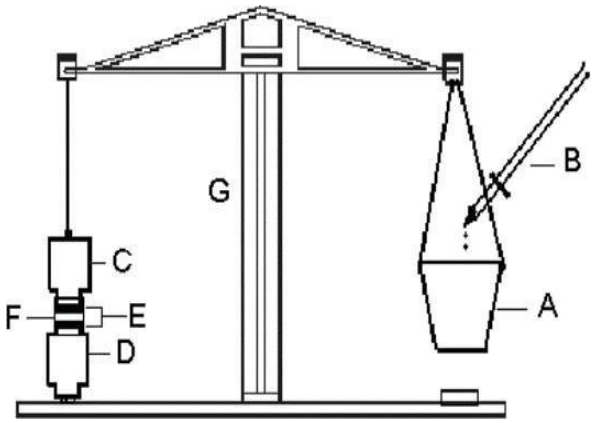


Figure 1: Mucoadhesive force measuring device
Labels represent (A) Light plastic glass; (B)Burette; (C) Upper glass vial; (D) Lower glass vial; (E) Sheep stomach mucosa; (F)Mucoadhesive tablet; (G)Modified balance

A vial (lower vial) was inverted and fixed in a place at the left-hand side of a physical balance. The tablet was attached to the upper end of the vial. A fresh piece of sheep stomach mucosa was fixed to the rubber closure end of a second vial (upper vial) with the mucosal surface facing outward. A string was attached to the left-hand side of a physical balance. The weight of upper vial was 17.24 gms, and it acted as the preload. A plastic container was placed on the right-hand side arm of the physical balance. The surface of the tablet was moistened with simulated gastric fluid [pH1.2], and the upper vial with the mucous membrane was placed on to the tablet, the weight of the upper vial acting as the preload. The balance was kept in this position for 5 mins, and then slowly water was poured into the plastic container on the right-hand side of the pan. The pouring of water was stopped as soon as the detachment of the two surfaces was observed on the left-hand side. The weight on the right-hand side of the plastic container with the poured water was noted. The total weight minus the weight of the plastic container is the weight required for detachment of the tablet from the mucosa which corresponds to the bioadhesive strength of the tablet

in grams (Jadhav B.K. *et al.,* 2004). Sheep stomach mucosa was obtained from the slaughterhouse and washed thoroughly before use. The test was carried out on three tablets from each formulation. The fresh membrane was used for testing of each tablet (Singh B. *et al.*, 2002).

Determination of Swelling Index

The swelling index of the tablets was determined in simulates gastric fluid at 37±0.5°C. Each tablet was weighed and placed in a preweighed stainless steel wire mesh with 40 mesh size. The mesh containing the tablet was then submerged into 900ml of the medium contained in a glass vessel maintained at 37±0.5°C. The increase in the weight of the tablet was determined every 1-hour till 8 hours. Each measurement was repeated three times. The swelling index was calculated by the following equation:

$$\text{Swelling Index} = \frac{W_t - W_;}{W_;}$$

Where W_t is the weight of the tablet at time t and W_0 is the weight of the tablet at time zero (Chaudhari P. *et al.,* 2008).

***In vitro* dissolution study**

The dissolution study of the mucoadhesive tablet was carried out using USP dissolution apparatus type-II using 900 ml of simulated gastric fluid [pH 1.2] as the dissolution medium. The temperature of the medium was maintained at 37.5°C with the stirring paddle rate of 50rpm. The tablet was placed inside the dissolution vessel. This study was done for 12 hours in triplicate. Sample (10ml) was withdrawn from the dissolution apparatus every one hour, and the volume of the dissolution medium was maintained by replenishment with 10 ml of the medium. Absorbance was measured at 314 nm using UV spectrophotometer. The % drug release was determined using a standard calibration curve (Chaudhari P. *et al.,* 2008).

Data treatment

To analyse the in-vitro release data and to understand the release mechanism from mucoadhesive tablet formulations, the results of the in vitro release studies were fitted into various kinetic equations namely the zero order, first order, Higuchi's Korsmeyer-Peppas equation (Raslan H.K. *et al.*, 2006).

***In vitro* diffusion study**

In-vitro diffusion study was carried out using Modified Franz Diffusion Cell. Sheep stomach mucosa was used as a simulated human gastric mucosa (barrier membrane). Fresh sheep stomach mucosa was washed in simulated gastric fluid [pH 1.2] and cut into the desired shape (Ritger P.L. *et al.*, 1987).

Modified Franz Diffusion Cell consists of a donor compartment into which two sides open tube was fixed to allow provision for less surface area and receptor compartment. The mucosal membrane was mounted on the lower end of the open test tube in the donor compartment. The receptor compartment was filled with 10ml phosphate buffer pH 7.4. The two cell compartments were held together with a clamp. It was kept at 37°C by circulating water through an external water jacket. After 30 mins of equilibrium of the membrane with the receptor solution, the tablet was applied to the membrane in such a manner that protective impermeable layer was kept upside. A 2ml of simulated gastric fluid [pH 1.2] was added to the donor compartment. The donor compartment was covered with aluminium foil to prevent evaporation of the solvent. The receptor solution was continuously stirred by means of a spinning bar magnet, at 300-400 rpm. At every time interval (1hr), 1ml aliquots of sample were withdrawn through the sampling port of the receptor compartment. The aliquots were analysed at 314.0 nm spectrophotometrically. The test was done in triplicate (El-Samaligy M.S. *et al.*, 2004).

Stability study

The formulation giving the most satisfactory results (optimized formulation) was subjected to stability testing at 40±2°C/75±5%RH conditions. The tablet samples were withdrawn at the end of 30 days and evaluated for hardness, drug content, weight variation and bioadhesive strength (Deshmukh V.N. *et al.*, 2009).

RESULTS AND DISCUSSION

In the present study, nine batches of mucoadhesive tablet formulations were designed and evaluated for physical characteristics, drug content uniformity, drug release profiles, in vitro diffusion and mucoadhesive strength. Stability study was also carried out for 30 days.

Tablet thickness and diameter of prepared mucoadhesive tablets was almost uniform in all the nine formulations and was found to be in the range 4.64±0.02- 4.7±0.01 mm and 11.00±0.12–11.13±0.1mm respectively. The hardness was found to be in the range of 5.2±0.3-5.6±0.2 Kg/cm^2. The friability of all tablets was less than 1% and the percentage deviation from the average weight of all the batches of tablets was found to be within the prescribed limits as per USP. The drug content was found to be uniform in all batches and within acceptable limits.

Table 1: Composition of different mucoadhesive gastroretentive

Ingredients	Quantity present in each tablet formulation (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nizatidine	150	150	150	150	150	150	150	150	150
Carpobol 934 P	48.61	48.61	48.61	72.92	72.92	97.22	97.22	97.22	97.22
HPMC K4 M	38.89	58.33	77.78	-	-	-	-	-	-
Polyox WSR 303	-	-	-	38.89	58.33	77.78	-	-	-
Xanthum Gum	-	-	-	-	-	-	38.89	58.33	77.78
MCC	105.52	86.06	66.61	81.2	61.75	42.3	56.89	37.45	18
Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5

F1 to F9 represent the various formulations of Nizatidine MCC represents Microcrystalline Cellulose

Table 2: Physical properties of mucoadhesive tablets

Formulation code	Diameter (mm) MEAN±S.D	Thickness (mm) MEAN±S.D	Hardness (Kg/cm^2) MEAN±S.D	Friability (%) MEAN±S.D	Average Weight (mg) MEAN±S.D
F1	11.08±0.11	4.68±0.03	5.3±0.4	0.31±0.02	351.0±0.3
F2	11.13±0.10	4.64±0.02	5.5±0.1	0.18±0.03	350.5±0.3
F3	11.09±0.10	4.66±0.03	5.4±0.4	0.27±0.03	352.1±0.1
F4	11.01±0.13	4.67±0.01	5.45±0.2	0.23±0.06	350.1±0.4
F5	11.00±0.12	4.69±0.02	5.2±0.3	0.30±0.02	349.8±0.3
F6	11.08±0.14	4.65±0.04	5.5±0.2	0.15±0.04	352.2±0.1
F7	11.06±0.12	4.67±0.02	5.35±0.2	0.12±0.02	349.1±0.2
F8	11.02±0.16	4.7±0.01	5.6±0.2	0.26±0.03	349.5±0.4
F9	11.01±0.17	4.66±0.04	5.4±0.3	0.26±0.06	350.2±0.3

F1 to F9 represent the various formulations of Nizatidine S.D denotes Standard Deviation

Table 3: Drug content, Surface pH, Swelling Index and Bioadhesive strength of Mucoadhesive Tablets

Formulation Code	% Drug Content MEAN±S.D	Swelling Index MEAN±S.D	Bioadhesive Strength MEAN ±S.D
F1	100.01±0.63	1.631	15.950
F2	99.94±0.56	1.688	19.203
F3	99.28±0.32	1.710	23.349
F4	99.71±0.37	1.595	22.882
F5	99.54±0.65	1.937	23.952
F6	98.97±0.32	1.940	28.225
F7	99.99±0.78	2.207	14.653
F8	98.91 ±0.27	2.891	19.231
F9	98.71±0.34	3.266	24.944

F1 to F9 represent the various formulations of Nizatidine; S.D denotes Standard Deviation

Table 4: *In vitro* release and *In vitro* diffusion data of Mucoadhesive Tablets

Formulation Code	*In vitro* release		*In vitro* diffusion	
	Drug release (%)	Time (hrs)	Cumulative amount released (mg)	Flux (mcg/cm^2/hr)
F1	99.051	11	107.37	71.58
F2	99.863	12	84.42	56.28
F3	97.649	12	72.38	48.25
F4	99.657	12	94.87	63.24
F5	96.509	12	65.81	41.88
F6	93.339	12	73.08	48.72
F7	100.033	10	94.59	63.06
F8	99.769	11	64.29	42.86
F9	99.384	12	59.87	39.91

F1 to F9 represent the various formulations of Nizatidine

Table 5: Release Kinetic Treatment of Mucoadhesive Tablets of Nizatidine

Formulation code	Zero Order Plot		First Order Plot		Higuchi's Plot	
	R^2	K	R^2	K	R^2	K
F1	0.9402	38.535	0.9132	0.3724	0.9894	28.039
F2	0.8996	41.102	0.8596	0.4613	0.9710	27.244
F3	0.9475	38.599	0.9293	0.2764	0.9882	25.344
F4	0.9555	37.287	0.8589	0.4118	0.9926	27.300
F5	0.9551	35.669	0.9473	0.2713	0.9916	27.122
F6	0.9705	29.992	0.9659	0.1948	0.9983	26.186
F7	0.9728	36.436	0.9208	0.3293	0.9992	29.607
F8	0.9576	35.989	0.8290	0.4687	0.9954	29.296
F9	0.9521	39.400	0.8752	0.3613	0.9947	26.171

F1 to F9 represent the various formulations of Nizatidine; R^2 is correlation coefficient, K is release rate constant

The result for physical, physical properties are illustrated in Table 2 shows mean of the three determinations along with standard deviation.

Table 6: Release Kinetic Treatment of Mucoadhesive Tablets of Nizatidine

Formulation code	Koserm eyer's Peppa's Plot		
	R^2	K	n
F1	0.9941	35.8179	0.5402
F2	0.9773	35.1965	0.5501
F3	0.9760	36.1743	0.5233
F4	0.9938	34.2295	0.5435
F5	0.9876	32.6287	0.5496
F6	0.9987	28.3400	0.5788
F7	0.9994	36.4838	0.5403
F8	0.9983	34.2847	0.5598
F9	0.9980	36.0413	0.5188

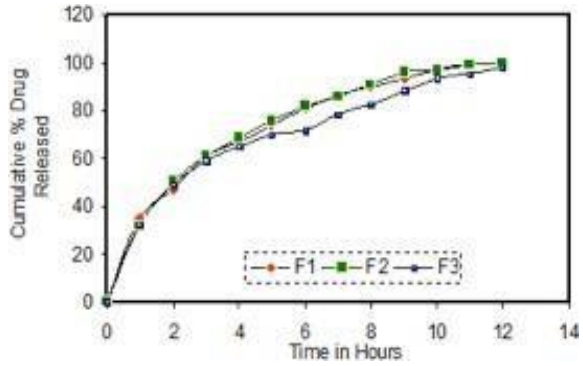
F1 to F9 represent the various formulations of Nizatidine; R^2 is correlation coefficient, K is release rate constant; n is diffusional exponent based on the mechanism of release

Bioadhesive strength

The mucoadhesive tablet must maintain intimate contact with mucus layer overlying the epithelial tissue. This parameter is very critical for successful utilization of these dosage forms.

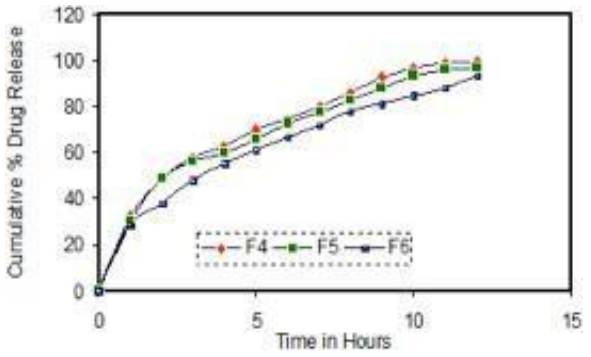
In the present study, the bioadhesive strength of the matrix tablet was found to be the function of nature and concentration of polymer (Table 3 and Figure 5) and shows an increasing trend of bioadhesive strength with the increase in the amount of Carbopol 934P and controlled release polymers.

The average bioadhesive strength varied between 14.653-28.225gm. The tablet formulations containing Polyox WSR 303 (F4 to F6) required the maximum force in grams to break the bond between the mucoadhering tablet and the mucosal surface followed by formulations containing HPMC K4M and Xanthan Gum.



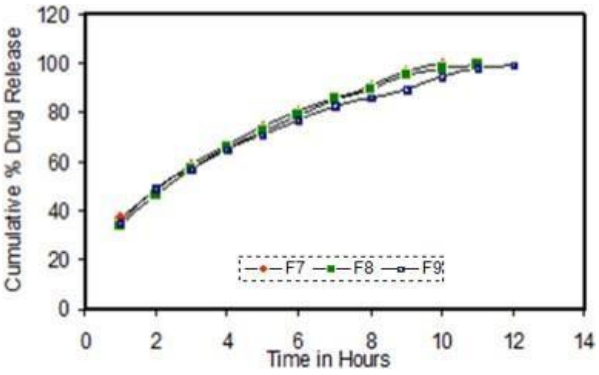
F1, F2, F3 represent the formulations of Nizatidine.

Figure 2: The in vitro release profile of Nizatidine from F1, F2, F3



F4, F5, F6 represent the formulations of Nizatidine.

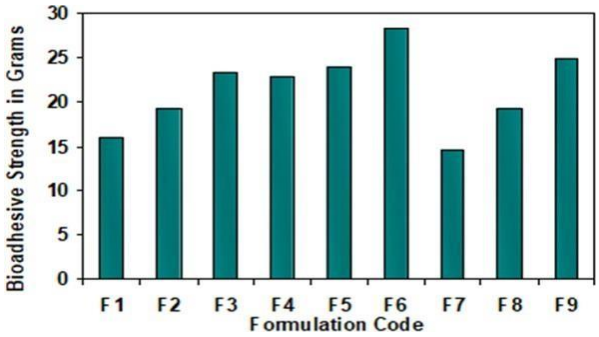
Figure 3: The in vitro release profile of Nizatidine from F4, F5, F6



F7, F8, F9 represent the formulations of Nizatidine

Figure 4: The in vitro release profile of Nizatidine from F7, F8, F9

Although formulations containing Xanthan Gum (F7 to F9) contained the highest concentration of Carbopol 934P among all the 9 formulations, the bioadhesive strength of formulations containing HPMC K4M (F1 to F3) was comparable with that of formulations containing Xanthan Gum (F7 to F9). This is because of the higher additive bioadhesion property of formulations containing HPMC K4M in combination with Carbopol 934P as compared to formulations containing Xanthan Gum. This showed that natural polymer Xanthan Gum has much weaker bioadhesive strength as compared to HPMC.



F1 - F9 represent the formulations of Nizatidine

Figure 5: Bar graph indicating Bioadhesive strength

Although the maximum value of bioadhesive strength was attained at the highest levels of both the polymers, yet the effect of Carbopol 934P is more pronounced.

Hydrocolloids are believed to adhere to mucus upon hydration as the polymer molecules become more freely mobile and are able to orient adhesive sites favourably with those of the substrate. As they hydrate, the glass transition temperature reduces resulting in uncoiling of the polymer chains becoming rubbery. This plasticization results in large adhesive surface facilitating maximum contact with the mucin. Increase in polymer concentration provides more adhesive sites thus increasing the bioadhesive strength.

Swelling Index: Swelling index of all formulation batches is given in Table 3. Swelling index was determined by measuring the weight of the tablet upto 8 hrs. As the time increased, the swelling index was increased, because the weight gain by tablet was increased proportionately with the rate of hydration upto 8 hrs. The direct relationship was observed between the swelling index and polymer concentration. The results indicate that the formulations F7 to F9 show a greater degree of swelling as compared to formulations F1 to F6.

In-vitro release kinetics

An in-vitro dissolution study was performed using simulated gastric fluid [pH 1.2] using USP-II apparatus for 12 hrs.

Cumulative percent drug release for formulations F1 and F8 was found to be 99.051% and 99.769% respectively at the end of 11 hours. While formulation F7 released the whole drug at the end of the 10th hour. However, formulations F2, F4, F9 were significant in retarding the drug release upto 12 hours with the release of 99.863%, 99.657%, 99.384% respectively. The release data for all formulations are shown in Table 4.

Overall release data indicates that the hydrophilic polymers used were effective in retarding drug release for 12 hours in different concentrations. The release rate was shown to be more prolonged with the increase in the polymer concentration.

In-vitro release data was fitted in 4 kinetic models viz; Zero order, First order, Higuchi and Peppa's plot. The data of plots were subjected to linear regression analysis. The models that best fit the data were evaluated by the correlation coefficient (R) as shown in Table 5 & 6. The R values for zero order plots were significantly higher as compared to first order plots which indicated that the all the formulations best fitted in zero order kinetics and poorly fitted in first order kinetics.

Similarly, the data treated according to Higuchi's diffusion equation shows that the best fit with higher correlation was found with the Higuchi's equation for most of the formulations with the highest correlation coefficient (R^2 = 0.9992). The result indicated that all formulations exhibited a diffusion mechanism in drug release.

An ideal matrix system is that in which the drug released constantly from the beginning to the end, in a zero-order kinetic model. Drug release from matrix tablets, in general, become progressively slower with time, like Higuchi's model, in which the amount of drug released is proportional to square root of time.

Further, the data was subjected to Peppa's model where R-value revealed that the Peppa's model best fitted in all dissolution profiles. The values of 'n' as derived from Peppa's model ranges between 0.5-1. Hence, it was concluded that drug release occurred via Non-Fickian diffusion, which shows that the hydrophilic glassy polymers that swell when added to the medium show anomalous diffusion.

Thus, the drug release from mucoadhesive tablets was *Diffusion Controlled* and followed *Zero order kinetics*.

In-vitro diffusion study

The cumulative amount of drug permeated across the sheep stomach mucosa varied between 59.87 – 107.37 mg per square centimetre of membrane. Most formulations showed a declining trend with the increase in polymer content (Table 4). Among

all the formulations, F1 and F9 which contained the lowest and highest concentration of polymers respectively showed the highest and lowest amount of drug diffusion through mucosa respectively in 12 hours.

Optimized formulation

Based on the analysis and comparison of the results of all the evaluation tests of all nine formulations, an ideal optimized formulation was selected which gave satisfactory results for all the evaluation tests which are a pre-requisite for successful utilization of this drug delivery system. F4 was selected as an optimized formulation.

Stability study

Selected optimized formulation (F4) was subjected to an accelerated stability study at 40±2^{0}C/75±5%RH for 1 month. Results of the stability study showed no significant changes in hardness, drug content, weight variation, bioadhesive strength of the tablet. The results are tabulated in Table 7.

The study attempted the preparation of mucoadhesive gastro-retentive tablets of Nizatidine. The mucoadhesive based formulation is a promising approach in retaining the drug in the upper part of GIT, thus enhancing the drug efficacy.

It was concluded by the results of an evaluation that formulation containing 20.83% Carbopol 934P and 11.11% Polyox WSR303 was an ideal optimized formulation. The approach for delivering Nizatidine as the gastroretentive mucoadhesive tablet was observed to be successful. The results and observation of this study conclude that the mucoadhesive tablets established to be an ideal formulation for controlled drug delivery through gastric retention, thus providing a more efficient mode for successful therapy.

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