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Research Article

Development and Optimization of Gastro-retentive Mucoadhesive Formulation of Hydralazine HCl

Himanshu A. Acharya[1*], Rakesh P. Patel[2]

[1]*Faculty of Pharmacy, Ganpat University, Kherva, Mahesana, Gujarat, India.*
[2]*Shree S. K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva, Mahesana, Gujarat, India.*

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ABSTRACT

The present study was focused to develop and optimize a gastro retentive drug delivery system (GRDDS) dosage form suitable for controlled drug release. Gastroretention results from unfolding and swelling of the film and its bioadhesion to the gastric mucosa. Hydralazine hydrochloride (HZH) is very short and thus it requires frequency of dosing several times a day. Hence, in order to avoid frequent administrations, a long acting mucoadhesive oral dosage forms can be given which can keep on delivering the drug at controlled rate for a specified period of time. A mucoadhesive drug delivery systems is an optimum system that interacts with the mucus layer covering the mucosal epithelial surface and increase the residence time of the dosage form at the absorption site. A sustained release mucoadhesive gastro-retentive with reduced dosing frequency and increased drug bioavailability is developed. Inclusion of different polymers like hydroxy propyl methyl cellulose K4M (HPMC K4M), carbopol 940 and sodium alginate at different concentration were used in order to study and get desired results. The results indicate the dosage form is gastroretentive and can provide controlled release of drugs with a release drug profile upto 24 hours. The above said formulation was further optimized using box-behnken factorial design.

INTRODUCTION

The development of controlled release formulations has had a tremendous impact on the drug delivery field particularly for drugs with a narrow absorption window. However, typical controlled release formulations are limited by insufficient retention in the stomach. To extend the residence time of dosage forms in the stomach, a number of strategies have been developed,[1] including (a) reducing the density to promote floating in the gastric contents, (b) increasing the density to promote retention in the lower part of the stomach, (c) introducing mucoadhesive properties and (d) producing a formulation that swells or unfolds in the stomach to hinder its escape through the pyloric sphincter. Each of these approaches has its advantages and disadvantages.

An alternative strategy is to combine bioadhesion with the ability to expand by unfolding and swelling. This paper describes the design of a controlled release formulation which after ingestion, would remain in stomach and/or upper part of glass and instrument technology, (GIT) for prolonged period of time in view to maximize the drug release in the upper part of GIT resulting in its increased retention.[2,3] The concept of a gastroretentive drug loaded polymeric films has been previously reported and the effects of shape, folding pattern and polymer characteristics on performance of gastroretention has been studied.

Although this type of dosage form has various advantages such as the convenience of a hard gelatin capsule and the ability to modify drug release through using a

***Corresponding Author:** Mr. Himanshu A. Acharya

Address: Faculty of Pharmacy, Ganpat University, Kherva, Mahesana, Gujarat, India.

Email ✉**:** himans90@gmail.com

Tel.: +91 9898646007

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multilayer design, there remain a number of issues. These include the difficulty in formulating a drug loaded polymeric film and the selection of a polymer with the desired ability to unfold and expand in the stomach. This paper focuses on practical aspects of designing such a dosage form and the difficulties encountered in its development.[4]

Hydralazine hydrochloride (HZH) is a direct acting smooth muscle relaxant that is used to treat hypertension by acting as a vasodilator primarily in arteries and arterioles, it act's by relaxing vascular smooth muscle, vasodilators act to decrease peripheral resistance, thereby lowering blood pressure and decreasing afterload. It has a low biological half-life of 2–3 hours. The patient dosing starts with 10 mg four times daily for the first 2 to 4 days, increase to 25 mg four times daily for the balance of the first week. For the second and subsequent weeks, increase dosage to 50 mg four times daily. The low bioavailability and short half-life of following drug oral administration favour a development of a sustained release formulation. The gastro retentive drug delivery system (GRDDS) can be retained in the stomach and assist in improving the oral sustained delivery of drugs.[5] The specific objective of research includes: formulation of GRDDS containing HZH, which would remain in stomach and/or upper part of GIT for prolonged period of time in view to maximize the drug release in the upper part of GIT.[6] Employment of box-behnken design for optimization of formulation. Evaluation of the formulation for their hardness, friability, drug content, mucoadhesive lag time, total mucoadhesive time, *in-vitro* dissolution study and stability study.

The GRDDS can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Local delivery also increases the stomach wall receptor site bioavailability and increases efficacy of drugs to reduce acid secretion. Hence this principle may be applied for improving systemic as well as local delivery of hydralazine, which would efficiently reduce gastric acid secretion.

The advantage of this type of drug delivery is in oral drug delivery, the drug absorption is limited by the GI transit time of dosage forms.[7] Since many drugs are absorbed only from upper small intestine, localizing oral drug delivery systems in the stomach or in the duodenum would significantly improve the extent of drug absorption.

Mucoadhesive drug delivery system has three distinct advantages when compared to conventional dosage forms. Firstly, the mucoadhesive systems, which are readily localized in the region applied to, can improve and enhance the bioavailability of drugs, for example, a greater bioavailability of some drugs was observed from mucoadhesive dosage systems. Secondly, these dosage forms can facilitate the intimate contact with underlying absorption surface resulting in a better absorption. Lastly, they can prolong residence time at the site of application to permit once or twice a day dosing.

Materials And Methods

Drug and Chemicals

The active pharmaceutical ingredient was procured from Sun Pharma Ltd, Vadodara, India and were British Pharmacopeia grade. The excipients were gifted by SD fine chemical, Vadodara, India and were United Pharmacopeia grade.

Instruments

Melting points of active pharmaceutical ingredient were determined in open capillaries using Veego melting point apparatus, Model VMP-D (Veego India ltd., Mumbai, India) and were uncorrected. Infrared spectra were recorded using potassium bromide (KBr) pellets on SHIMADZU-FTIR 8400S instrument. Mass spectra were recorded on PerkinElmer LC–MS PE Sciex API/65 Spectrophotometer. SHIMADZU dissolution apparatus was used to study drug release profile. Pfizer tester was used for hardness evaluation. Sartorius LoD instrument for measuring Loss on drying (LoD).

Methods

Formulation of Hydralazine Hydrochloride Mucoadhesive Tablets

The gastro-retentive mucoadhesive tablets was prepared by mixing drug along with the different excipients and applied for evaluation of suitability, critical quality attributes and the behavior of the drug material and excipients used for the formulation development. Pure HZH and release-retarding polymers (HPMC K4M, sodium alginate and carbopol 940) were accurately weighed and were collected in a mortar and pestle. The blend was prepared mixing all ingredients and this was subjected to granulation. The binding paste was prepared by mixing starch in water. The blend was well mixed in 2 L rapid mixing granulator (RMG) for 5 minutes in order to achieve uniform mixing, after uniform mixing was achieved the binder was added at constant rate, the end point was decided by visual granule formation. On achieving granule, the granulated blend was discharged from RMG and this wet blend was passed through 30# sieve in order to get uniform size granule, this was subjected to drying. The dried blend was further pass through 40# sieve and was subjected to lubrication. Lubricating material was then passed through 40# and 60# sieve and added to blend. This blend was subjected to geometrical mixing in order to get uniform mixing. The blend was further evaluated prior to compression. The results are showed in Table 1. This blend was compressed using 9.0 mm standard punches plain on both sides. In-process quality control tests were performed

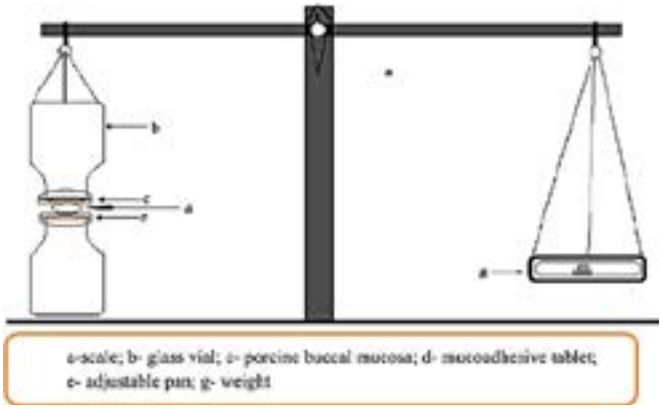

Figure 1: General lay out of modified pan balance used for the determination of mucoadhesion force of newly formulated tablets.

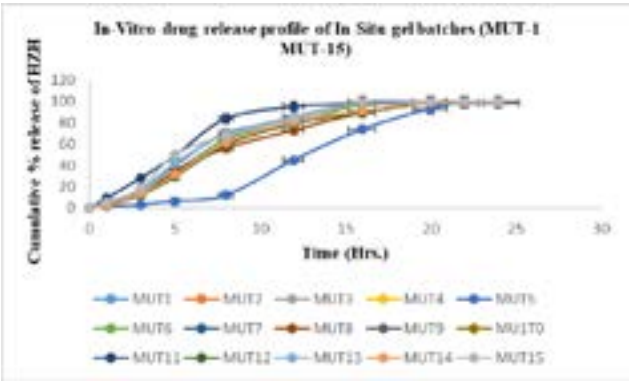

Figure 2: *In-vitro* dissolution profile of batches (MUT-1-MUT-15).

on the compressed tablets such as disintegration time, thickness, hardness and weight variation.

Evaluation of the Formulation

Different quality control parameters of all the batches of mucoadhesive HZH tablets were analyzed by adopting the method described in Indian Pharmacopeia 2018.

Weight Variation

Twenty tablets (n = 20) from each batch were weighed using electronic balance and their average weight was calculated.

Friability

Twenty tablets (n = 20) of each batch were weighed and put into the friabilator drum. After 100 revolutions of friabilator, tablets were recovered. The tablets were then freed from dust and weighed.

Hardness

Twenty tablets (n ¼ 20) were taken for the hardness test using a hardness tester. The tablet was placed between the two probes, of which, one is a movable probe and another is an immovable probe of the hardness tester. Then the force was applied from the movable probe. The force to break the tablet was recorded, which was taken as the hardness of the tablet.

Drug Content

Aliquots of 5 mL sample were withdrawn filtered and analyzed for quantitative determination of HZH by UV-spectroscopy after each hour for 12 hours. The mobile phase was prepared by mixing acetonitrile and methanol in the ratio of 27:30, respectively. The filtered mobile phase components were pumped and the eluent was detected by a UV detector at λ_{max} 278 nm.

Table 1: Evaluation of powder blend ready for compression.

Batch no.	*Angle of repose*	*Bulk density (g/cm^3)*	*Tapped density (g/cm^3)*	*%compressibility*
MUT-1	24.83 ± 1.34	0.27 ± 0.04	0.32 ± 0.04	15.62
MUT-2	26.20 ± 1.24	0.28 ± 0.02	0.32 ± 0.05	12.50
MUT-3	27.36 ± 1.44	0.27 ± 0.04	0.33 ± 0.03	12.12
MUT-4	26.25 ± 1.23	0.27 ± 0.03	0.31 ± 0.03	12.90
MUT-5	25.45 ± 1.56	0.28 ± 0.04	0.32 ± 0.02	15.15
MUT-6	26.71 ± 1.33	0.27 ± 0.03	0.33 ± 0.02	15.62
MUT-7	25.92 ± 1.55	0.26 ± 0.03	0.31 ± 0.03	13.12
MUT-8	25.81 ± 1.48	0.27 ± 0.02	0.32 ± 0.04	15.62
MUT-9	26.14 ± 1.62	0.28 ± 0.03	0.34 ± 0.04	15.64
MUT-10	26.55 ± 1.25	0.29 ± 0.02	0.34 ± 0.2	14.70
MUT-11	24.96 ± 1.34	0.27 ± 0.04	0.32 ± 0.2	12.50
MUT-12	25.12 ± 1.45	0.28 ± 0.03	0.32 ± 0.3	15.15
MUT-13	25.48 ± 1.38	0.27 ± 0.03	0.32 ± 0.3	15.91
MUT-14	25.98 ± 1.56	0.28 ± 0.04	0.33 ± 0.2	15.15
MUT-15	25.81 ± 1.72	0.27 ± 0.04	0.32 ± 0.2	15.62

(n = 3, mean ± SD)

Table 2: Results of post compression properties of mucoadhesive tablets.

Batch code	*Thickness (mm)*	*Hardness (kg/cm^2) n = 3*	*Weight variation (mg)*	*Friability (%)*	*Drug content (%)*
MUT-1	3.1 ± 0.1	5.1 ± 0.21	280 ± 2	0.852 ± 0.005	98.99 ± 1.89
MUT-2	3.1 ± 0.1	5.1 ± 0.20	280 ± 4	0.852 ± 0.008	99.12 ± 1.27
MUT-3	3.2 ± 0.1	5.0 ± 0.20	280 ± 3	0.852 ± 0.003	98.67 ± 1.72
MUT-4	3.1 ± 0.1	5.2 ± 0.21	280 ± 2	0.852 ± 0.004	100.22 ± 1.21
MUT-5	3.1 ± 0.1	5.1 ± 0.19	280 ± 1	0.852 ± 0.006	101.03 ± 0.82
MUT-6	3.1 ± 0.1	5.2 ± 0.21	280 ± 4	0.852 ± 0.006	98.90 ± 1.85
MUT-7	3.2 ± 0.1	5.1 ± 0.19	280 ± 3	0.852 ± 0.007	99.67 ± 1.65
MUT-8	3.2 ± 0.1	5.2 ± 0.18	280 ± 3	0.852 ± 0.008	99.19 ± 1.34
MUT-9	3.1 ± 0.1	5.1 ± 0.19	280 ± 4	0.852 ± 0.004	98.90 ± 1.98
MUT-10	3.2 ± 0.1	5.0 ± 0.20	280 ± 3	0.852 ± 0.008	99.88 ± 1.16
MUT-11	3.1 ± 0.1	5.1 ± 0.18	280 ± 2	0.852 ± 0.006	99.73 ± 1.76
MUT-12	3.1 ± 0.1	4.9 ± 0.22	280 ± 4	0.852 ± 0.007	98.90 ± 1.88
MUT-13	3.2 ± 0.1	5.1 ± 0.21	280 ± 3	0.852 ± 0.005	100.12 ± 1.12
MUT-14	3.1 ± 0.1	5.0 ± 0.20	280 ± 4	0.852 ± 0.008	98.17 ± 1.82
MUT-15	3.1 ± 0.1	5.1 ± 0.21	280 ± 2	0.852 ± 0.007	99.23 ± 1.23

In-vitro Drug Dissolution Study

In-vitro dissolution technique is one of the best quality control tools to assess batch to batch release performance of the drug, formulation development and to monitor the manufacturing process. Drug dissolution test was performed by using USP type II apparatus with 900 mL of 0.1 N HCl as the dissolution medium at 45 RPM and 37°C.

Differential Scanning Calorimetry (DSC)

The thermal behavior of HZH formulation was estimated in terms of their melting endotherms using a pyris 6 instrument (Perkin elmer) with 3 mg samples in standard aluminium pans. The samples were heated from 30.1°C to 250°C at a constant rate of 5°C/min under nitrogen.

Fourier Transform Infrared Study (FTIR)

FTIR Spectra of samples were obtained by mixing about 2–3 mg of samples with dried potassium bromide of equal weight and compressed to form a KBr disc and finally, the sample was scanned from 500 to 5000 cm^{-1} wave number for all of the formulations giving interactions between the drug and various polymers.

Mucoadhesion Test

Porcine buccal mucosa was used as a model mucosal surface for bioadhesion test. Immediately after slaughter, the buccal mucosa was removed from the pig and transported to the laboratory in tyrode solution and kept at room temperature. Mucoadhesive forces of the tablets (n = 3) were determined utilizing modified balance using strips of the porcine buccal mucosa washed with tyrode solution.

The mucoadhesive forces of the tablets were determined by the modified pan balance as shown in Fig. 1. The porcine buccal mucosa was cut into the appropriate size pieces and washed with tyrode solution. During the test, a section of buccal mucosa (a) was fitted on the upper glass vial (b) using a rubber band. The exposed mucosa had a diameter of 1-cm. The vial with buccal mucosa (c) was stored in the tyrode solution for 10 minutes at room 37°C. Then, the vial with buccal mucosa (d) and another vial (e) were fixed on adjusted height which was equal to the thickness of the tablet. To the lower vial, the tablet was placed with the help of bilayer adhesive tape. The position of both vials was adjusted so that the adhesive tape and the buccal mucosa get attached. A constant force was applied to the upper vial to get the tablets attached to buccal mucosa uniformly for 2 minutes, and then the upper vial was connected to the balance. Then the weight on the right pan was slowly increased by 0.5 g until two vials get detached from each other. The total weight (g), to detach was recorded as the measure of mucoadhesive strength.

Optimization of Formulation

3^2 Factorial Design and Multiple Regression Analysis

Factorial design was used to find out the best polymer for mucoadhesive layer and for that three independent factors i.e, HPMC K4M (X_1), sodium alginate (X_2) and carbopol 940 (X_3) were selected at 3 levels such as for HPMC K4M (X_1) upper 100 mg, middle 90 mg and lower 80 mg, whereas for sodium alginate (X_2) upper 50 mg, middle 45 mg and lower 40 mg, whereas for carbopol 940 (X_3) upper 60 mg, middle 50 mg and lower 40 mg. Based on these values 15 factorial batches were prepared. A backward regression analysis technique that was used to generate the best fit models for the analyzed responses and final equation contains only

Table 3: *In-vitro* drug release data of MUT-1- MUT-15 batches (n = 3, mean ± SD)

TIME (hours)	*MUT-1*	*MUT-2*	*MUT-3*	*MUT-4*	*MUT-5*	*MUT-6*	*MUT-7*	*MUT-8*	*MUT-9*	*MUT-10*	*MUT-11*	*MUT-12*	*MUT-13*	*MUT-14*	*MUT-15*
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	1.23 ± 0.11	1.23 ± 0.14	3.95 ± 0.2	2.3 ± 0.11	1.23 ± 0.12	4.01 ± 0.31	5.68 ± 0.15	2.9 ± 0.21	2.3 ± 0.13	2.3 ± 0.11	8.2 ± 0.12	2.3 ± 0.2	5.68 ± 0.12	6.1 ± 0.12	5.01 ± 0.15
3	3.12 ± 0.14	3.12 ± 0.15	15.1 ± 0.11	6.5 ± 0.15	3.12 ± 0.14	12.66 ± 0.21	16.75 ± 0.12	7.2 ± 0.11	12.55 ± 0.12	12.55 ± 0.15	14.33 ± 0.14	12.55 ± 0.13	16.75 ± 0.13	10.22 ± 0.15	18.65 ± 0.13
5	6.45 ± 0.21	6.45 ± 0.16	35.21 ± 0.12	16.44 ± 0.16	6.45 ± 0.12	29.21 ± 0.11	40.21 ± 0.11	18.2 ± 0.15	29.88 ± 0.11	29.88 ± 0.15	19.22 ± 0.13	29.88 ± 0.13	42.11 ± 0.13	27.11 ± 0.12	49.99 ± 0.15
8	12.01 ± 0.18	12.01 ± 0.13	63.98 ± 0.12	27.44 ± 0.14	12.01 ± 0.11	65.18 ± 0.13	70.11 ± 0.15	28.9 ± 0.15	59.68 ± 0.13	59.68 ± 0.12	27.32 ± 0.12	59.68 ± 0.11	69.1 ± 0.15	38.12 ± 0.11	67.82 ± 0.12
12	45.11 ± 0.13	45.11 ± 0.14	86.01 ± 0.12	44.23 ± 0.11	45.11 ± 0.15	79.21 ± 0.11	83.15 ± 0.15	42.1 ± 0.13	79.8 ± 0.12	79.8 ± 0.11	45.1 ± 0.11	79.8 ± 0.12	86.01 ± 0.2	49.21 ± 0.15	83.11 ± 0.14
16	73.65 ± 0.11	73.65 ± 0.18	96.12 ± 0.11	69.22 ± 0.14	73.65 ± 0.11	97.13 ± 0.15	99.12 ± 0.13	70.1 ± 0.17	90.06 ± 0.13	90.06 ± 0.15	71.22 ± 0.15	90.06 ± 0.14	99.31 ± 0.4	79.22 ± 0.11	99.66 ± 0.13
20	93.15 ± 0.12	93.15 ± 0.16	96.11 ± 0.15	84.22 ± 0.12	93.15 ± 0.21	98.65 ± 0.14	99.36 ± 0.15	89.2 ± 0.14	99.21 ± 0.11	99.21 ± 0.15	90.11 ± 0.12	99.21 ± 0.15	99.3 ± 0.4	92.17 ± 0.16	99.66 ± 0.13
22	99.01 ± 0.15	99.01 ± 0.15	96.15 ± 0.13	97.22 ± 0.11	99.01 ± 0.22	98.68 ± 0.13	99.36 ± 0.15	98.1 ± 0.16	99.21 ± 0.14	99.21 ± 0.17	98.12 ± 0.11	99.21 ± 0.17	99.3 ± 0.4	99.12 ± 0.13	99.66 ± 0.15
24	99.01 ± 0.15	99.01 ± 0.15	96.15 ± 0.13	99.21 ± 0.11	99.01 ± 0.22	98.67 ± 0.13	99.36 ± 0.15	99.9 ± 0.14	99.21 ± 0.12	99.21 ± 0.17	99.91 ± 0.11	99.21 ± 0.14	99.3 ± 0.4	101.22 ± 0.11	99.66 ± 0.11

the significant factor terms corresponding to the response obtained from coded and actual values of factors.

Results And Discussion

The mucoadhesive tablets were prepared, with simple, easy, cost effective and extensively used method. HPMC K4M, sodium alginate and carbopol were used as different polymer. The drug and polymer were taken in different ratios to formulate 15 batches coded as MUT-1 to MUT-15 formulations. The formulations were prepared to reduce the dosing frequency thereby improving the effectiveness of the drug.

Evaluation of MUT-1-MUT-15 Batches

Tablet powder blend was subjected to various pre-compression parameters Table 1. The bulk density of all the formulations was found to be in the range of 0.421 to 0.457 (gm/mL) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.31 to 0.34 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 12.12 to 15.91 which shows that the powder has good flow properties. All the formulations have shown the Hauser's ratio ranging between 1.230 to 1.247 indicating the powder has good flow properties.

The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 2. All the tablets of different batches complied with the official requirements of uniformity of weight. The hardness of the tablets ranged from 4.9 ± 0.2 to 5.2 ± 0.1 kg/cm^2 and the friability values were less than 0.9% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 3.1 ± 0.1 mm to 3.2 ± 0.1 mm. All the formulations satisfied the content of the drug as they contained 98.69 ± 0.32 to 101.56 ± 0.45% of drug and good uniformity in drug content was observed.

Weight Variation, Friability, Hardness, Thickness of the Tablets

Numerical values of all the quality control parameters, investigated for 12 different batches are depicted in Table 2. In the weight variation study, the weight of the tablet varied between 280 ± 7.5% which was within the Indian Pharmacopeia limit i.e. 259–301 mg (7.5% deviation).

Tablet thickness was almost uniform in all the batches and found to be between 3.8 ± 0.01 to 4.05 ± 0.05 mm. Also, the diameter was found to be uniform (9 mm) in all batches. Similarly, the friability of tablets ranged from 0.04 to 0.2%, which was within the acceptable range as mentioned in IP i.e, below 1%, indicating that the tablets of all batches are having good compactness and showing enough resistance to mechanical shock and abrasion. In the hardness test, the harnesses for different batches

Table 4: Release kinetics data for MUT-1-MUT-15 formulation.

Batch no.	*Higuchi kinetics R^2*	*Zero order kinetic R^2*	*First order kinetic R^2*	*Hixon crowell*	*Krosmeyer peppas*	
				R^2	*R^2*	*n*
MUT-1	0.890	0.996	0.755	0.088	0.609	0.5865
MUT-2	0.890	0.996	0.755	0.066	0.444	0.7486
MUT-3	0.993	0.979	0.759	0.072	0.475	0.8284
MUT-4	0.925	0.994	0.771	0.065	0.448	0.9108
MUT-5	0.995	0.976	0.770	0.074	0.423	0.6240
MUT-6	0.978	0.982	0.771	0.078	0.415	0.6914
MUT-7	0.980	0.974	0.848	0.065	0.448	0.5947
MUT-8	0.985	0.988	0.891	0.086	0.454	0.6801
MUT-9	0.959	0.994	0.848	0.065	0.448	0.6364
MUT-10	0.961	0.994	0.807	0.065	0.448	0.7750
MUT-11	0.989	0.986	0.868	0.083	0.474	0.6045
MUT-12	0.977	0.994	0.825	0.065	0.448	0.7402
MUT-13	0.989	0.987	0.830	0.080	0.485	0.6391
MUT-14	0.999	0.972	0.804	0.077	0.478	0.6390
MUT-15	0.989	0.933	0.832	0.072	0.475	0.6388

Table 5: Summary of results of regression analysis for responses Y1, Y2, Y3 and Y4 for fitting to quadratic model.

Quadratic model	*R^2*	*Adjusted R^2*	*Predicted R^2*	*SD*	*%CV*
Response (Y1)	0.9103	0.7489	-0.3491	116.70	10.38
Response (Y2)	0.9758	0.9324	0.6135	38.40	10.44
Response (Y3)	0.9532	0.8689	0.2511	0.513	13.61
Response (Y4)	0.9351	0.8183	-0.0385	4.58	14.56

Table 6: Optimization batches of MUT-CP1.

Batch no.	*Hydralazine HCl (mg)*	*HPMC K4M (mg)*	*Carbopol 940 (mg)*	*Sodium bicarbonate (mg)*
MUT-CP1	50	70	50	60

Table 7: Cumulative percentange release of batch optimized batches (n = 3, mean ± SD).

Time (hours)	*MUT-CP1*
0	0
1	2.3 ± 0.35
3	6.5 ± 0.43
5	16.44 ± 1.05
8	27.44 ± 1.10
12	44.23 ± 1.15
16	69.22 ± 1.22
20	84.22 ± 1.45
22	97.22 ± 1.05
24	99.21 ± 1.32

were found to be between 8.32 ± 1.36 to 11.56 ± 1.36 kg that indicates the hardness of the tablets was within the pharmacopoeia limit i.e, above 5 kg.

Drug Content

As shown in Table 2, the drug content varied between 98.17 to 101.03% which reflects good uniformity in drug content among different batches. *In-vitro* drug release of MUT-1- MUT-15 batches was carried out and the results are showed in Table 3.

Mucoadhesion Test on Tissue

The *in-vitro* mucoadhesive strength study was performed and results were noted. On the modified pan balance, the force required to detach the tablet from the porcine buccal mucosa was recorded. The mucoadhesive properties were reported to be influenced by the nature and amount of bioadhesive polymers used in the formulation. In this study, the mucoadhesive strength of the formulations was reported to be prominently influenced by the concentration of polymer. The lowest value was reported in MUT- 4 in which the lowest proportion of polymer was incorporated. Similarly, highest value was reported in

MUT- 8 which has the highest amount of polymer, among other batches.

Effect of Variables on Buoyancy and Release Profile

To explore the effect of polymer composition and proportion in drug release behavior, the *in-vitro* dissolution study of formulated batches of mucoadhesive tablets was carried out and the results are presented in Fig. 2. The highest and lowest drug release was observed in MUT-14 (106.14%) and MUT-3 (96.12%), respectively. In the case of batches with carbopol 934 and sodium alginate, the drug release was found to be relatively fast upto 20 hours, i.e, 99.21, 99.11 and 99.66%, respectively. Similarly, the better drug release patterns were shown by the combination of carbopol 934 and HPMC, where the drug release was constant reported to be 99.82, 101.22 and 98.67%, respectively upto 24 hours. Furthermore, an almost similar drug release pattern was observed in the batches having the combination of all three polymers (MUT-4–MUT-8). In batches MUT-3 and MUT-7, the drug release was found to be 99.11, 99.36%, respectively in 20 hours and MUT-4 and the drug release of batch MUT-8 was constant and showed a good release profile upto 24 hours.

Determination of Release Kinetics

The data obtained from *in-vitro* dissolution studies were fitted into mathematical models. The R^2 and n values for zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models were illustrated in Table 4. In the kinetics study, the order of drug release from all the batches was studied by plotting the log percentage cumulative retained versus time curve. Observation of higher R^2 values for zero-order and first order indicated that MUT-4 and MUT-8 seems to fit better with first order kinetics whereas the release pattern of all other batches seem to be suitable with zero order kinetics. From Table 4, it is confirmed that the batches MUT-1, MUT-2, and MUT-4 follow Hixson-Crowell kinetic model i.e, they release by erosion mechanism. The remaining batches follow Korsmeyer-Peppas models i.e their drug release mechanism cannot be described exactly or more than one type of release is involved.

Fitting of Data to the Model

A three-factor, three-level box–behnken statistical experimental design as the RSM requires 15 experiments. All the responses observed for 15 formulations prepared was simultaneously fitted to quadratic model using design expert 7.1.6. It was observed that the best fit model was quadratic model and the comparative values of R^2, SD, and %CV are given in Table 5 along with the regression equation generated in Table 5 for each response. A positive value represents an effect that favors the optimization, while a negative value indicates an inverse relationship between the factor and the response. It is evident that all the three independent variables, viz., the concentration of HPMC K4M (X_1), carbopol 940 (X_2) and sodium alginate (X_3) have positive effects on the two responses.

Discussion

An ideal mucoadhesive tablet should ensure immediate and sustained drug release, to exhibit an instantaneous but prolonged pharmacological effect as well as it must have sufficient residence time in the GIT. To achieve these requirements, HZH mucoadhesive tablets were formulated and investigated for different physicochemical characters. The tablets of all the batches were smooth, flat-faced, white, and circular with no visible cracks. The variation in weight, hardness, friability, and diameters of the entire batch was within pharmacopeial limit, ensuring formulated tablets were of standard quality. Hardness was reported to be increased with an increased proportion of carbopol 934. The drug content of the batches was found to be in the range of 98.16 to 101.22%, which falls within the prescribed limit of the pharmacopeia.

Mucoadhesive strength signifies the extent of adherence between the epithelial surface and/or mucus and a polymeric substance present in the formulation. Three major stages in the mucoadhesion process are wetting of polymer, interpenetration, and mechanical interconnection between polymer and mucus. Strength of mucoadhesion is highly affected by residence time with mucus, type of biological membrane used, swelling behavior of the polymer, average molecular weight, concentration, and composition of the polymer being used. In our study, all the formulated batches exhibited satisfactory mucoadhesive strength ranging from 40 gm to 50.5 gm.

The statistical analysis suggested that there was a significant difference ($p < 0.05$) in mucoadhesive strength, among most of the batches. In this study, an increased amount of carbopol 934 and sodium alginate has led to the increased mucoadhesive force proportionally, in all the batches. Also, high-density polymeric chains present in it can result in greater entanglement and interpenetration at the interfacial region of mucosa. This might be a possible reason for its maximum mucoadhesive effect. While analysing the effect of HPMC K4M, mucoadhesive strength was decreased with its increased amount. The tendency of HPMC K4M to disintegrate in the water might be the possible reason for this effect. Besides that, polymeric groups required for bioadhesion process are occupied by the water molecules and higher swelling of this polymer creates a strain of hydrogen bond and other forces. However, sodium alginate has a better mucoadhesive effect than HPMC K4M due to its higher viscosity. Therefore, the combination of carbopol 934 and sodium alginate resulted in more bioadhesive strength as compare to the combination of carbopol 934 and HPMC K4M. The surface pH of the tablets was in the range of 3.4–5.4, which was almost similar to the pH of the GIT. Therefore, all the

batches do not produce mucosal irritation and discomfort and improve patient compliance.

Swelling of the mucoadhesive tablet to the optimum extent is very crucial to ensure the prolonged and steady release of the drug with successful mucoadhesion. In this study, the swelling index of all the batches was improved with the increase in time. This is due to the gradual absorption of water by the hydrophilic polymers used. The swelling index for the batches containing carbopol 934 was found to be a maximum. Additionally, the swelling behavior of all the batches was improved by increasing the proportion of carbopol 934.

The *in-vitro* drug release studies revealed that the release of HZH drug depends upon the nature and proportion of polymers used. In the case of the batches containing carbopol 934 and HPMC K4M, the percentage of drug release was comparatively fast even after 8 hours. It has been reported that the drug release profile is decreased with increasing the proportion of HPMC K4M. Slowly hydrating nature and comparatively low viscosity of the HPMC may lower the rate of dissolution. Similarly, the rate of drug release is inversely proportional to the amount of carbopol 934 present in the formulation. When carbopol 934 comes in contact with water, it swells well and its viscosity becomes very high which ultimately hinders the drug release. Also, in the case of the batches containing carbopol 934 and sodium alginate the percentage of drug release was very proportionate even within 20 hours. This can be credited to the higher extent of swelling of polymer. This result was further proved by the swelling studies results, where the maximum swelling behaviour was also shown by the batches having a high dissolution profile. Interestingly, we reported that there was a gradual decrease in dissolution rate from MUT-4 to MUT-8, as the proportion of HPMC K4M was gradually reduced.

This signifies that the drug release profile is mainly influenced by the concentration of HPMC K4M. It is expected that the property of HPMC K4M to uptake a higher amount of water may result in significant swelling of the polymer matrix, enabling the drug to release out rapidly. Batch MUT-8 showed a linear release meeting the hypothesis of the study.

Check-point Batch of Mucoadhesive Tablet

The optimum formulation was selected based upon trading of various response variables and comprehensive evaluation of feasibility search and exhaustive grid search, the two formulation batches as shown in Table 6 (MUT-CP1) was found to fulfill the maximum requisite of an optimum formulation because of optimum T90, T20%, Q1, considering the applied constraints on other.

In summary, the mucoadhesive strength of the optimized batches tablet was mainly attributed to the amount of carbopol 940 present. Moreover, the dissolution profile met the criterial of the research. The results are showed in Table 7.

Conclusion

The study was conducted to formulate, evaluate and optimized the mucoadhesive tablets of HZH with a sustained release property, to achieve patient compliance for the management of different types of pain. Among 15 different batches, MUT-8 showed sustained and effective drug release with good mucoadhesive strengths. Its physicochemical properties also complied with the pharmacopoeial standards. The results also demonstrate that polymers have a major role to increase the mucoadhesive strength. The swelling behavior of the formulation can be optimized by changing the proportion of carbopol and HPMC K4M. Moreover, the formulation of an HZH mucoadhesive tablet can be an effective alternative route to prevent the first-pass effect and to improve the bioavailability of drug. It can also enhance better patient compliance by fascinating extended release of the drug and it is cost effective.

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