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Research Article

FABRICATION OF STOMACH SPECIFIC MUCOADHESIVE DILTIAZEM HYDROCHLORIDE TABLETS

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ABSTRACT

The aim of present research work was development of stomach specific mucoadhesive sustained release diltiazem hydrochloride tablet formulations for increase gastric residence with natural polysaccharides. Tablet formulations were prepared by wet granulation technique and evaluated blend by FTIR, DSC for compatibility, hardness, and friability, swelling behavior, in-vitro drug release, gastric residence and mucoadhesive strength. The formulation D5 with drug-polymer ratio 1:1 containing 16% hibiscus polysaccharide (HEC) and 13 % xanthan gum (XNG) was found to be promising for mucoadhesion and sustained release characteristics. Formulation D5 exhibited the highest efficiency of mucoadhesion strength (29.8 gm) and mucoadhesion retention in 0.1 N HCL medium even at the end of 9.3 hours when compared with other formulations. The accelerated stability studies revealed that the tablets retain their characteristics even after stressed storage conditions.

Key words: *Diltiazem HCl (DLTH), Hibiscus esculentus mucilage (HEC), Xanthan gum (XNG), Matrix tablet*

INTRODUCTION

Stomach specific approach to increase the gastric residence time of drug delivery systems includes bioadhesive devices. Mucoadhesive drug delivery system utilize the property of bioadhesion where certain polymers become adhesive after hydration that can be used for targeting drug to a particular region of the body for extended period of time [1]. The hypothesis for this research study is that if drug can be delivered in a controlled manner to the duodenum at a rate that does not exceed the maximum rate of its absorption, then the oral bioavailability of drug could be improved.

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Based on this hypothesis, the bioadhesive tablets were designed in such a way that it should be retained in the stomach for a prolonged period of time, thus maximizing the exposure of this drug to its absorption site [2]. Oral sustained release formulations have drawbacks in respect to variation of gastric emptying time results in variable drug absorption. Too rapid gastrointestinal transit can lead to inadequate drug release from the dosage form above the absorption zone, resulting in diminished effectiveness of the given dose when the drug presents an absorption window.

Diltiazem hydrochloride, calcium channel blocker is a widely used cardiovascular drug for the treatment of angina, essential hypertension and flutter. When administered orally, frequent dosing is needed due to its short biological half-life. Diltiazem is an elimination half-life of 3 to 4.5 hours, an absorption zone from the upper intestinal

tract and requires multiple daily drug dosage to maintain adequate plasma concentrations in management of angina pectoris and hypertension [3]. Due to incomplete drug release from the device above the absorption zone, an efficacy of the administered dose may get reduced and mucoadhesive drug delivery systems that 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 gastrointestinal tract.

The mucoadhesive material of *Hibiscus Esculentus* polysaccharide (HEC) was extracted from the natural source by aqueous extraction and precipitating the addition of acetone. The isolated biomaterial shows promising inbuilt mucoadhesive properties [4]. Since this natural mucoadhesive agent is edible, easily biodegradable and may provide an alternative to conventional synthetic mucoadhesive agents. The mucoadhesiveness of HEC, mucoadhesive tablets are expected to remain in the upper GIT and release its drug content for a long period of time, thus providing sustained therapeutic effect [4]. The one of component, xanthan gum (XNG) has been a dominant hydrophilic material used in controlled release dosage forms due to its non-toxic nature, ease of compression, and capacity to accommodate high levels of drug loading. The most important characteristics is high swellability which exerts a significant influence on the release kinetics of an incorporated drug in it. Upon contact with water or biological fluid the latter diffuses into the device, resulting in polymer chain relaxation with volume expansion [5, 6]. In the present investigation, preliminary use of HEC and XNG natural polysaccharides in different proportion were retained residence property in favor of mucoadhesion to increase the gastric residence time, which helps predetermined release of diltiazem hydrochloride at or above the absorption window.

MATERIALS AND METHODS

Diltiazem hydrochloride was obtained as a gift by Zim Laboratories, Kalmeshwar, Nagpur (India). *Hibiscus esculentus* polysaccharide was isolated by simple maceration from *hibiscus esculentus* unripe fruits which were purchased from the local market, Amravati district Maharashtra. All excipients and chemicals were used of (analytical) USP grades.

Preparation diltiazem hydrochloride mucoadhesive matrix tablets

The tablets were prepared by a wet granulation method using 10 mm biconcave punches in rotary tablet punching machine (10 station rotary tablet compression machine Cadmach, Ahmadabad, India) [6]. The composition of the different formulations of DLTH tablets is listed in the table 1. All excipients except magnesium stearate and talc were accurately weighed and passed through # 80 meshes. The drug (DLTH), polymer (HEC, XNG) and filler dicalcium phosphate were mixed thoroughly. The four ratios drug: polymer, 1:0.5, 1:1, and 1:2 were established for each of the two polymers used for producing hydrophilic matrices. A sufficient volume of granulating agent of polyvinyl pyrrolidone solution was added slowly to achieve the granulation endpoint. After the enough cohesiveness obtained, passed through # 10 mesh, granules were dried at room temperature to evaporate the isopropyl alcohol and then were dried at 50°C for 30 min. The granules were collected and passed through # 12 mesh, lubricate with magnesium stearate and talc which were further compressed into matrix tablets.

Table 1: Composition of preliminary batches of DLTH

Formulation Code	H1	H2	H3	H4	H5	H6	D1	D2	D3	D4	D5	D6
Drug: polymer ratio	1:0.5	1:1	1:2	01:0.5	1:1	1:2	1:1	1:1	1:1	1:1	1:1	1:1
Diltiazem hydrochloride	90	90	90	90	90	90	90	90	90	90	90	90
Hibiscus esculentus polysaccharide	45	90	180	45	90	180	90	-	70	50	60	55
Xanthan gum	_	_	_	_		_	-	90	20	40	30	35
Microcrystalline Cellulose	159	114	24	_	_	_	_	_	_	_	_	_
Dicalcium Phosphate	_	_	_	159	114	24	109	109	109	109	109	109
Polyvinyl pyrrolidone K30	_	_	_	_	_	_	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	3	3	3	3	3	3
Talc	2	2	2	2	2	2	3	3	3	3	3	3

FTIR spectral and DSC analysis

FTIR spectrums were recorded on samples prepared in potassium bromide (KBr) disks using FTIR spectrophotometer (Model-1601 PC, Shimadzu Corporation, Japan). The scanning range was 400 to 4000 cm^{-1}. The FTIR spectrums of pure diltiazem, physical mixture and formulation blend were taken. The DSC curves diltiazem hydrochloride, physical mixture and formulation blend were obtained using differential scanning calorimeter (Shimadzu DSC-60, Shimadzu Limited, and Japan) at increasing heating rate at 10˚C/min and heated over a temperature range of 50˚C to 300˚C in an atmosphere of nitrogen (20ml/min). Accurately twelve mg of sample was taken in a hermetically sealed, flat bottom aluminium sealed pan and placed at sample stage and thermograms were recorded [7].

Pre-compression parameters

Before final compression of tablets, properties of the gastro retentive mucoadhesive granules were evaluated for bulk density, tapped density, angle of repose and compressibility as in-process characterization. All the experiments were done in triplicates and expressed as mean± SD.

Determination of bulk density and tapped density [8]

Weighed the granules (W), was poured into the graduated cylinder and the volume (V_0) was note. Then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume (V_f) was measured. The bulk density, tapped density was found out by using the formulae;

$$\text{Bulk density} = W/V_0$$

$$\text{Tapped density} = W/V_f$$

Angle of repose [8]

Angle of repose was determined using funnel method. The height of the funnel was adjusted in such a way that the tip of funnel just touches the heap of the blends. Accurately weighed blends are allowed to pass through the funnel freely on to the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation;

$$\tan \theta = h / r$$

Where, θ = Angle of repose, h = height of the pile, r = radius of plane surface occupy by the powder.

Post-compression parameters

Properties of the gastro retentive mucoadhesive tablets, such as appearance, thickness and diameter, surface pH, hardness, friability, weight variation and content uniformity were determined as per

procedures described in the Indian Pharmacopoeia.

Appearance, thickness, size and shape

The general appearance and elegance of tablet was identified visually, which include shape, color, presence or absence of an odor, taste, surface texture etc. The thickness and diameter of the tablets were determined by using vernier calipers (Mitutoyo, Japan). Three tablets were used from each batch and results were expressed in millimeter. Mean and SD values were also calculated.

Hardness [8]

Hardness of the tablets was evaluated using Monsanto hardness tester, which is expressed in kg/cm^2. The hardness of the tablets was measured during start and between the compressions.

Friability [8]

Friability of tablets was determined using Roche friabilator. Twenty tablets were weighed and placed in a chamber. According to guideline friabilator was operated at 100 revolutions (25 rpm for four minutes) and the tablets were subjected and the tablets were subjected for combined effect of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets were then dusted and reweighed and the percentage of friability was calculated by using the following formula,

$$\text{Friability} = \left(\frac{\text{weight loss}}{\text{weight of tablets before opereations}}\right) \times 100$$

Weight variation [8]

Weight variation test of tablets was performed according to guidelines of USP 2004, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The percentage deviation was calculated and checked for weight variation.

Content uniformity [8]

The amount of powder equivalent to 90 mg of the drug was weighed and dissolved in 100 ml of distilled water. After 10 minutes of centrifugation, aliquots of 1ml were taken from this solution and diluted to 100ml with 0.1 N HCl (10µg/ml). The absorbance of resulting solutions was measured in an UV spectrophotometer at 237 nm. Simultaneously, 10µg/ml of DLTH standard solution was prepared in the same medium and the absorbance was recorded. Drug content was calculated.

In-vitro drug dissolution study [6]

In-vitro dissolution of DLTH from mucoadhesive tablets (n=3) was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was carried out in 900 ml of 0.1 N HCl of pH 1.2 at a temperature of 37 ±0.5°C and a speed of 100 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 1 hour interval for 10 hour, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 237 nm using a UV/Vis spectrophotometer. The dissolution studies of all the batch formulations were performed in six replicates. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve. The drug in 0.1N HCl followed Beer-Lambert's law in the range of 2-20 µg/ml with correlation co-efficient of 0.999. Regression analysis was made for the slope, intercept and correlation coefficient values. The regression equations of calibration curves were y = 0.0511x + 0.001 (r^2 = 0.999) at 237 nm for diltiazem hydrochloride. The desirable drug release profile was optimized by analyzing the similarity with theoretical drug release profile.

In-vitro mucoadhesion strength studies [9, 10]

The mucoadhesive capacity of all formulations was determined by the modified physical balance method.

The apparatus consists of a modified double beam physical balance in which the right pan on lower end has been attached by a glass slide with copper wire. A glass vial of 3.8 cm diameter and 2 cm height was kept in a beaker filled with media 0.1N HCl of pH 1.2, which was then placed below right side of the balance. Goat stomach mucosa was used as a model membrane and media 0.1N HCl was used as moistening fluid. The goat stomach mucosa was obtained from local slaughter house. The underlying mucous membrane was separated using surgical blade and wash thoroughly with buffer media 0.1N HCl. The thickness of stomach mucosa employed in experiments ranged from 1.3 to 2.5 mm. It was then tied to a glass slide and this slide was fixed over the protrusion in the glass vial using a thread and two sided adhesives. The glass block was then kept in a glass beaker. The beaker was filled with 0.1N HCl up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments. The one side of the tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat mucosa and mucoadhesive tablet was established and additional weight, to make the right side weight equal with left side pan. A preload of 5 g was placed on the slide for 5 min (preload time) to establish adhesion bonding between mucoadhesive tablet and goat stomach mucosa. The preload and preload time were kept constant for all formulations. Next, water was dropped into the beaker at a speed of 2 ml·min^{-1} until the tablet and membrane were pulled apart by the gravity of water. The addition of water was stopped when mucoadhesive tablet was detached from the goat stomach mucosa. The beaker containing water was weighed and the minimum detachment force was calculated accordingly. The detachment force in gram (g) was transformed into Newton (N, force of adhesion) by using a conversion factor (1g=0.009806N). The test was performed at room temperature, and the mean of three measurements was used as the mucoadhesive strength of the tablets.

In-vitro gastro retention time

The *ex-vivo* mucoadhesion time studies were performed after application of tablets on freshly cut goat stomach mucosa. The mucosa was fixed on a glass slide using double sided adhesive and one side of glass slide was fixed to thread whose another end was fixed with the arm of tablet disintegration test apparatus [11]. A side of each tablet was wetted with 50µl dissolution fluid and was attached to the mucosa by applying a light force with a fingertip for 20 seconds. The beaker was filled with 900 ml of simulated gastric fluid and kept at 37˚C; after 2 minutes the slide was placed in a beaker and the apparatus was started. Care was taken that while up and down motion of the arm tablet should remain in a medium. The adhesion behavior and mucoadhesive retention time of tablets were monitored until a complete detachment or dissolution occurred.

Stability studies

The selected formulations were packed in blisters with PVC with aluminium foil. ICH specifies the length of study and storage conditions for accelerated testing**:** 40˚C ± 2˚C / 75 % RH ± 5 % for 3 months using REMI environmental chamber SGM-6S, Mumbai, India. At specified time intervals, of 0, 1, 2 and 3 months for accelerated testing condition, the samples were taken and evaluated for their drug content, hardness, friability, mucoadhesive strength and drug release characteristics and compared with the initial values before storage [12].

RESULTS AND DISCUSSION

The hypothesis of this research work is that if the drug can be delivered in a controlled manner in the stomach at a rate that does not exceed the maximum rate of its absorption, then the oral bioavailability of drug could be improved. Based on this hypothesis, the bioadhesive tablets were designed in such a

way that it should be retained in the stomach for a prolonged period of time, thus maximizing the exposure of this drug to its absorption site. Upon contact with water or biological fluid, the fluid diffuses into the device, resulting in polymer chain relaxation leading to volume expansion. The incorporated drug then diffuses out of the system. Studies of drug-excipients compatibility represent an important phase in the preformulation stage of the development of solid dosage forms. The occurring interactions between drug(s) and excipients are discovered and proved by IR spectroscopy with the following important characteristics: appearance of new IR absorption band(s), broadening of band(s), and alteration in intensity [13]. The IR spectra for pure diltiazem and its formulations with various polymers and other excipients are taken to establish the physical characterization of drug and its formulations (Fig.1).

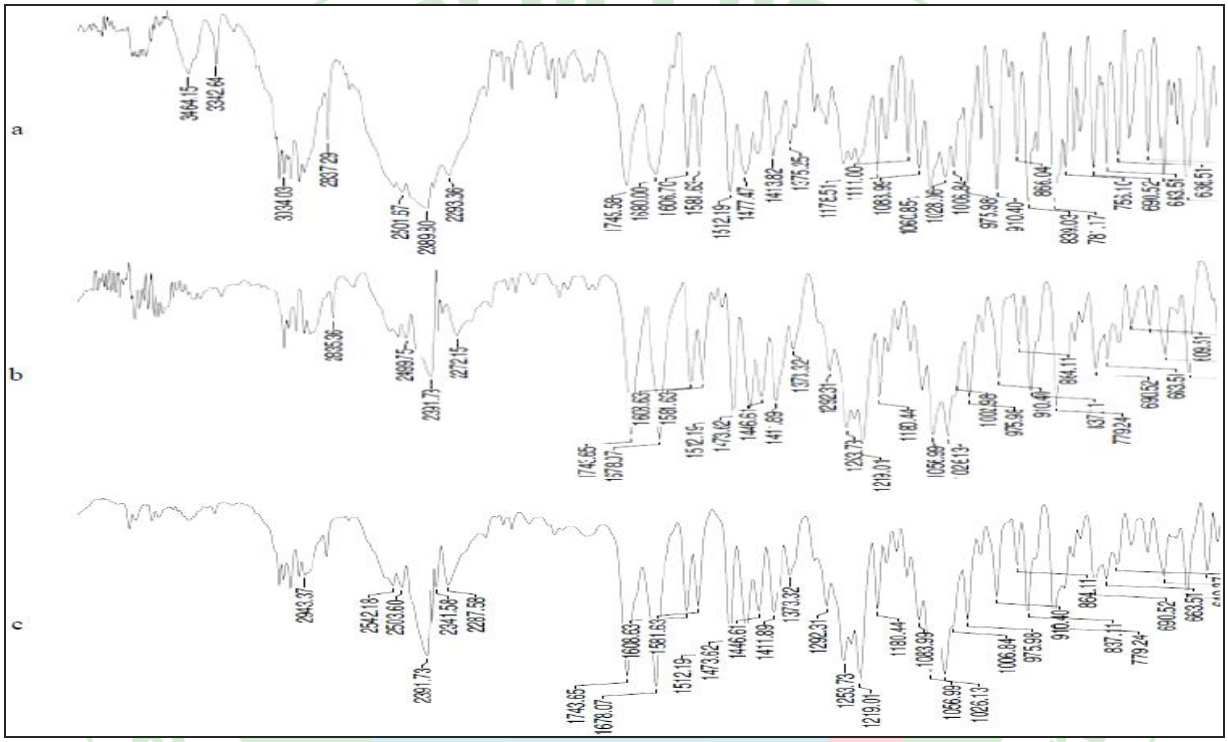

Figure 1: FTIR spectrum of DLTH, physical mixture and DLTH formulation blend

The IR spectrum of diltiazem hydrochloride contains two carbonyl groups, shows the values around 1680 (Amide) and 1745.58 cm^{-1} (Ester-C=0 Stretching). Infrared studies reveal that the characteristic band around 1680 and 1745.58, 1606 cm^{-1} (C=C-Benzene) due to the presence of ester, amide and functional group and aromatic ring in the structure of diltiazem HCl were present in the spectra. The FT-IR spectrum of the DLTH physical blend, indicated the presence of characteristic bands of the drug almost at the same wave numbers particularly for the bands observed at 1679 and 2393 cm^{-1}. These outcomes affirmed that, no interaction occurred between DLTH and polymers on mixing (Fig.1). From this it clearly indicates that, the drug was not interacted with the polymers used in the formulations. The peaks obtained in the spectra of all mixture correlates with the peaks of drug spectrum and were identical with the peaks of the pure drug and physical mixture of drug and HEC mucilage and the pure drug with all other excipients mixtures which ensured that there was no any chemical interaction between them. That there is no shift in the position of characteristic absorption bands of pure drug and its formulations. It means that the drug remains in the same normal form in its pure state and after its formulations. The fact that all characteristic bands for drug substance and excipients are present in the IR spectra of mixtures with varying contents of both

components signifies that no change occurred in the chemical structure of diltiazem hydrochloride. Thus, it may indicate the lack of interactions between the components of mixtures.

A sharp endotherm was observed for diltiazem hydrochloride at 217.49°. This melting endotherm was also observed at 211°, indicating absence of the drug to polymer interactions. Fig.6.2.11 shows the DSC thermo grams of DLTH, physical mixture and formulation. The thermo gram of hibiscus Esculentus showed an endothermic peak at 80.39°C. The DSC thermo gram of xanthan gum showed two endothermic peaks at 71.78 & 241°C and an exothermic one at 300°C at which the decomposition of xanthan gum occurred. The thermo gram of DLTH showed a single sharp endothermic peak at 215°C. The physical mixtures showed the characteristic endothermal peaks of the drug, while, the thermo gram of DTZ HCl physical mixture showed broad endothermic peaks only, with complete disappearance of the drug melting peak as a result of drug. These results agree with that of Sultana et al., 2009, who found that, the endothermic peak of DTZ HCl in alginate microspheres was not distinctive indicating that, the drug was no longer present in the crystalline form [14]. But not a significant change in the position of this peak or broadening of peak in the thermo gram of drug and excipients mixture was observed with respect to the thermo gram of pure drug. So, it can be concluded that the excipients and drug do not interact with each other.

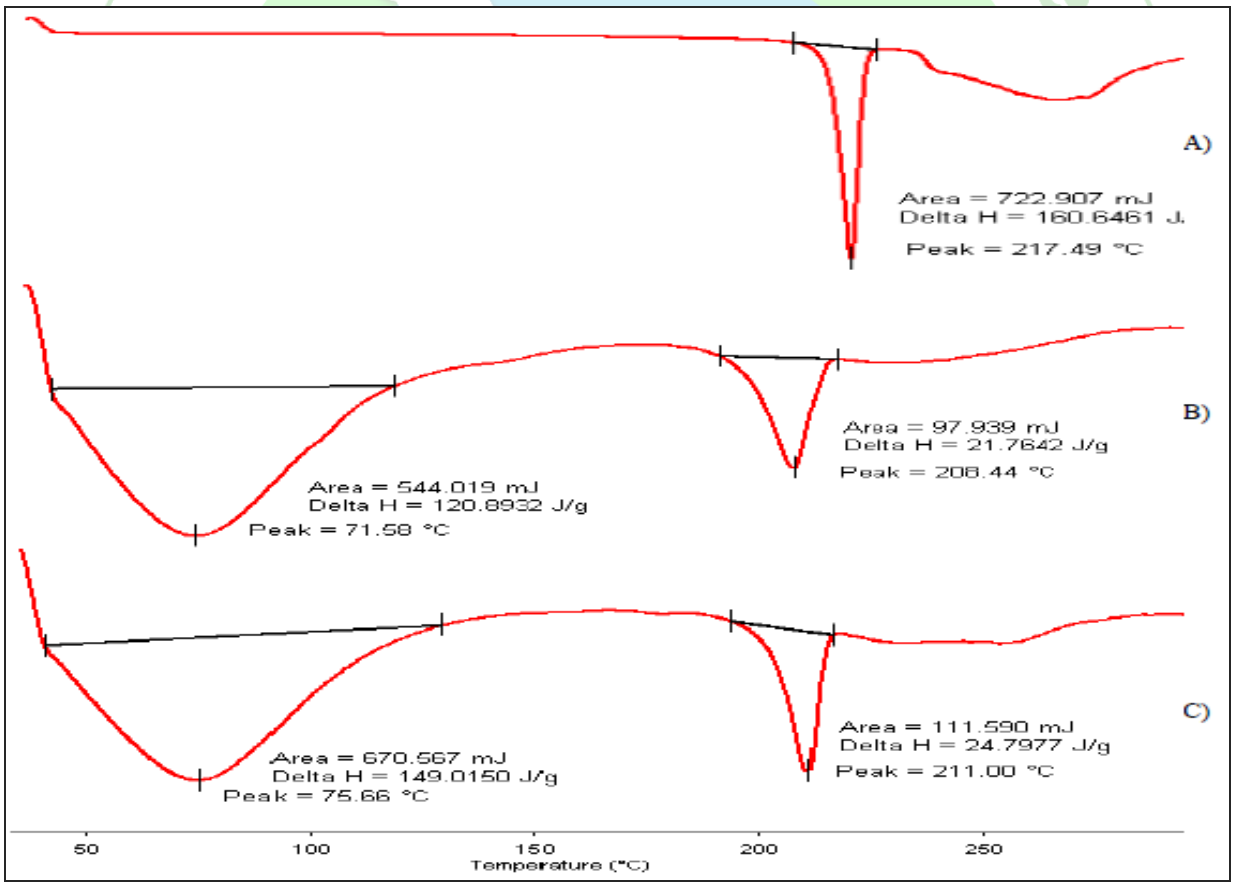

Figure 2: DSC of DLT, physical mixture and DLTH formulation blend

The granules evaluation is an investigation of physical properties of a drug along with excipients. It is the first step in the rational development of dosage forms. The results of precompression parameters and in-process quality control (IPQC) of batches are shown in table 2. The overall objective of the evaluation of granules was to generate useful information to the formulation in developing stable and bioavailable dosage form. The bulk and tapped density give an insight on the packaging and arrangement of the particles and the compaction profiles of the material. The bulk and tapped density of prepared granules were found to be in the range of 0.62 – 0.68 and 0.68 – 0.76 respectively.

Carr's compressibility index and hausner ratio are determined to be less than 14.69% and <1.17 for all formulations which indicates that the prepared granules of all the formulations have good free flow property .

Table 2: Precompression studies preliminary batches for DLTH

Batch	*Bulk density (gm/cc)*	*Tapped density (gm/cc)*	*Carr's index*	*Hauser's ratio*	*Angle of Repose (°) (mean ± SD)*
H1	0.67± 0.12	0.74± 0.24	9.46± 0.08	1.1± 0.03	25±0.12
H2	0.66± 0.11	0.69± 0.10	4.35± 0.05	1.05± 0.04	22±0.19
H3	0.69± 0.14	0.72± 0.04	4.17± 0.02	1.04± 0.10	26±0.14
H4	0.64± 0.05	0.68± 0.01	5.88± 0.12	1.06± 0.14	27±0.11
H5	0.62± 0.08	0.68± 0.12	8.82± 0.10	1.1± 0.04	25±0.18
H6	0.63± 0.03	0.71± 0.07	11.27± 0.13	1.13± 0.14	24±0.14
D1	0.67± 0.01	0.73± 0.12	8.22± 0.08	1.09± 0.12	27±0.08
D2	0.64± 0.12	0.71± 0.02	9.86± 0.11	1.11± 0.07	28±0.83
D3	0.64± 0.10	0.75 ± 0.13	14.67± 0.12	1.17± 0.02	30±0.23
D4	0.67± 0.04	0.73± 0.04	8.22± 0.09	1.09± 0.04	25±0.53
D5	0.67± 0.02	0.74± 0.08	9.46± 0.05	1.1± 0.01	26±0.13
D6	0.68± 0.04	0.76± 0.02	10.53± 0.06	1.12± 0.01	28±0.14

Average ± Standard deviation, n=3

The tablets were observed visually for their physical appearance such as color and texture. All the formulations are found good appearance, having white color and smooth surface texture. Thickness of all tablet formulations was found in between 3.13-3.72 mm and diameter of the tablets was found to be about 10.0 to 10.1 mm. The results of all these were in compliance with the specification of I.P are indicated in table 4. The pharmacopoeial limits of deviation for tablets of 280 mg are ± 10% for DLT. The value ranged for DLT HCL from 96.56-100.42% for preliminary batches. The average percentage deviation for all tablets formulation was found to be within the specified limits and hence all formulation complied with the test for uniformity of weight. Uniformity of the drug content was found within and among the different types of tablet formulation (table 3). Formulations containing HEC in combination with XNG were compared to explore the effect of polymers and the amount of the drug release. A formulation with an appropriate controlled release profile and 90% drug release over a 6–10 h period was desired for the purpose of this study. Formulations containing HEC in combination with XNG were compared to explore the effect of polymers and the amount of the drug release. Percent of the release of drug at the end of 10 hours for D1, D2, D4, D5 and D6 were 100.76±0.3%, 101.14±0.3%,100.09±0.3%,

82.19±0.3%,83.95±0.3 and 67.32±0.3% respectively, whereby more than 98 % drug release from H1 to H6 formulation (Fig. 3). Since preliminary studies confirmed that the polymers HECM and XNG had presented the problem of burst drug release, an attempt was made to study the drug release modulation by these polymers. It was evident from the dissolution profiles that while the drug release rate was controlled, more than 82% of DLTH were released with D1and D3 and D2, D4, D5 and D6 by the end of 6 and 10 hour respectively. XNG at both 16% and 13% concentrations retarded the drug release for a lesser duration compared to HEC which could be due to the difference in their viscosities.

Table 3: In process quality control (IPQC) test for preliminary batches of DLT

Batch	Diameter (mm) ± S.D	Thickness (mm) ± S.D	Hardness (Kg/cm^2) ± S.D	Friability (%)± S.D	Weight variation ± S.D	Content uniformity (%) ± S.D
H1	10.02± 0.06	3.13± 0.1	5.8± 0.12	0.87± 0.1	300.2± 0.18	97.5± 0.35
H2	10.02± 0.02	3.43± 0.09	5.2± 0.11	0.78± 0.13	300.15± 0.12	99.31± 2.10
H3	10.02± 0.06	3.43± 0.1	5.2± 0.06	0.78± 0.04	300± 0.65	100.42± 1.03
H4	10.03± 0.02	3.72± 0.02	5.97± 0.1	0.52± 0.03	301± 0.42	98.5± 1.15
H5	10.01± 0.03	3.6± 0.04	5.6± 0.12	0.65± 0.12	305± 0.6	99.12± 0.20
H6	10.03± 0.04	3.72± 0.1	5.6± 0.04	0.52± 0.07	302± 0.2	100.3± 1.2
D1	10.1± 0.14	3.41± 0.1	6± 0.14	0.51± 0.14	300± 0.14	98.6± 1.14
D2	10±0.09	3.83± 0.04	6± 0.24	0.45± 0.14	310± 0.17	99.23±1.10
D3	10± 0.1	3.72± 0.06	6± 0.14	0.5± 0.14	300± 0.15	96.56±0.18
D4	10.1± 0.04	3.71± 0.09	6± 0.15	0.38± 0.14	310± 0.12	99.46±1.04
D5	10± 0.08	3.48± 0.11	6± 0.14	0.32± 0.14	298± 0.91	98.89±0.94
D6	10± 0.14	3.56± 0.12	6± 0.14	0.26± 0.14	300± 0.18	99.6± 0.78

Average ± Standard deviation, n=3

The extended retardation of drug release observed with XNG may be attributed to the three dimensional gel network structure developed by complex formation between the drug and the polymer following penetration of dissolution medium into the tablet matrix. 18% HEC and 10% XNG presented unusual drug release blockade after 67% drug release indicating that these percentages are inappropriate for the complete release of DLTH from the formulation.

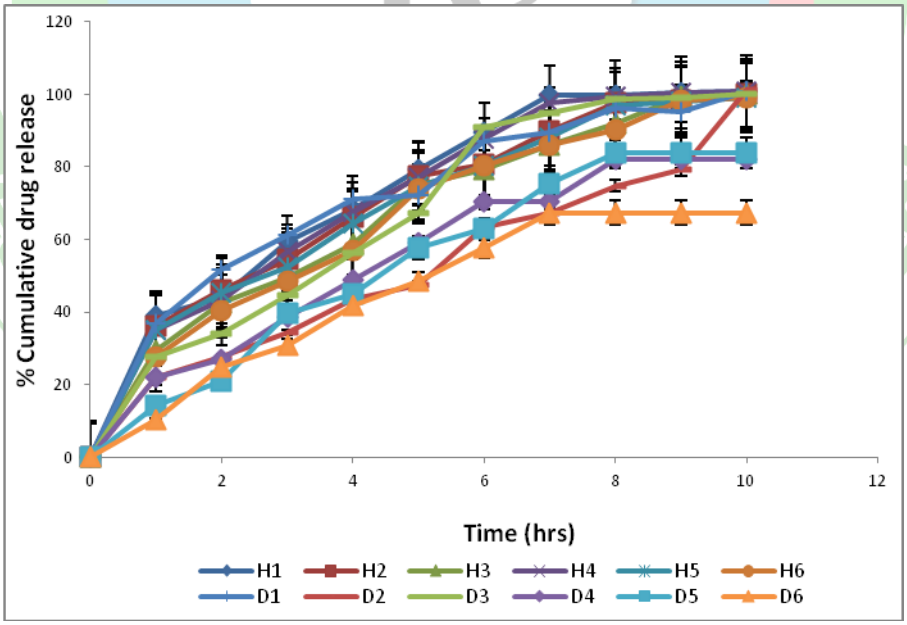

Figure 3: *In-vitro* drug release of diltiazem preliminary formulation

Therefore, for the purpose of this study, formulation with 16% HEC or 13 % XNG in combination, the extended mucoadhesive system was considered most suitable. Since the stomach mucosal pH is between 1 and 3, an acidic medium pH 1.2 was used for the dissolution studies. It was observed that for tablets prepared with combination of XNG and HEC (D1 to D6), as the concentration of XNG increased, drug release rate decreased due to greater viscosity imparted by XNG compared to HEC. An incorporation of XNG decreased the release rate of drug because the polymer absorbs water quickly and forms a

gelatinous barrier layer at the surface of the tablet matrix, unlike HEC which require lag time to form a gel layer. Thus, increasing the level of XNG in the tablet produced a stronger gel layer around the matrix resulting in decreased penetration of the solvent molecules into the matrix and outward diffusion of drug molecules in the dissolution medium. Usually, water diffusivity depends on the total concentration of viscosity-inducing agents in a system and this governs diffusion of water into matrix systems. The *in-vitro* mucoadhesive study was performed on modified physical balance and measures the mucoadhesive strength (g) requires to detachment the tablets. The results were shown in Fig.4.

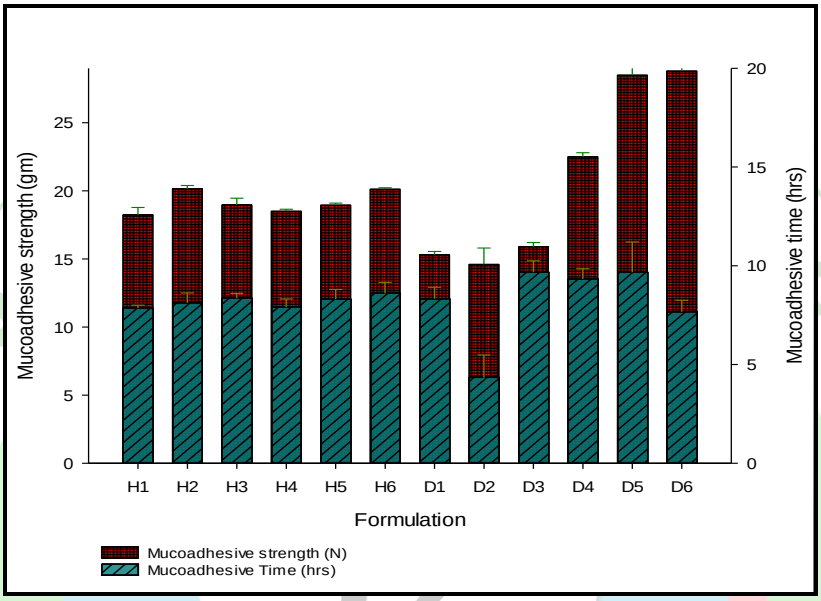

Figure 4: *Ex-vivo* mucoadhesive strength and mucoadhesive retention time of diltiazem formulation

The acidic environment favours the presence of excess uncharged COOH groups which form stronger hydrogen bonds with water and strengthen the mucoadhesive bond. The *in-vitro* mucoadhesive study was performed on modified physical balance and measures the mucoadhesive strength (g) requires to detach the tablet. Wash off test was performed for all the matrix tablet formulations (H1-H6 and D1-D6) of DLTH tablets. The results were graphically represented in Fig.4. Mucoadhesive force depends on the viscosity and concentration of polymer used. Formulation D3 exhibited lowest mucoadhesive strength. Batch D5 with 16% mucilage and 13 % gum shows greater mucoadhesive strength. Adhesion was reported to be affected by hydration. Hydration of the mucoadhesive polymer is essential to initiate the mucoadhesive bonding process. In case of tablets applied in the dehydrated state, which is most convenient, it is essential that sufficient water is available so that rapid hydration takes place, and a flexible rubbery state occurs. The capillary force arises when water from the space between the mucosa and the polymer was taken up by a dry system. The detachment time was found to be in the range of 4.33 to 5.67 hrs, suggesting that all the formulations have the sufficient mucoadhesive strength to remain intact with gastric mucosa for a long time to release the drug in a controlled manner. Formulation D5 exhibited the highest efficiency of mucoadhesion in 0.1 N HCL (16 and 13 % mucilage gum respectively) when compared with other formulations. The significantly greater mucoadhesive property of mucilage gum matrices may be due to the presence of a certain amount of unionized carboxyl groups within mucilage which forms a strong gel network with the mucus glycoprotein network of the intestinal mucosa. Students t-test paired was used to statistical analysis of the results, before and after conducting the

stability studies for 3 months [15]. No significant difference ($p > 0.05$) was observed in the tablet appearance, hardness or thickness. The drug dissolution was calculated for comparison of dissolution profile before and after stability studies. The optimized formulation (D5) values were found more than 50 (98. and 95.12 respectively after one and three months) that indicate a good similarity between both the dissolution profiles. Similarly, no significant difference was observed in the post formulation parameter. The periodic data of stability study is presented in table 4. The results of stability studies indicate that the developed formulation has good stability.

Table 4: Results of short term stability study

Parameter	***Study Period***		
	Initial	***1 month***	***3 month***
Hardness *(Kg/cm^2) ± S.D*	6.0± 0.14	6.1 ±0.02	6.0±0.01
Thickness *(mm) ± S.D*	3.48± 0.15	3.48±0.14	3.48±0.03
Friability *(%)± S.D*	0.32± 0.14	0.32±0.01	0.32±0.2
Drug Content *(%) ± S.D*	98.90±0.94	98.54±1.2	97.8±0.5
Dissolution Profile *(%) ± S.D*	83.95±0.3	85.15±1.3	86.95±0.8

All the values are represented in mean±SD (n=3)

CONCLUSION

The stomach specific adhesive tablet of diltiazem hydrochloride (D5) with *hibiscus esculentus* and xanthan polysaccharides showed good sustained release for longer time periods, mucoadhesive strength and *ex-vivo* mucoadhesion time than the other formulations and therefore it was considered as the optimized formulation. The results of stability studies for formulations D5 revealed no change in physical appearance, hardness and drug indicating the formulation was stable. The study reveals that effective natural pharmaceutical mucoadhesive, hibiscus esculentus polysaccharide along with xanthan gum could be used in the development of stable, and gastroadhesive sustained release matrix tablets of diltiazem hydrochloride.

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