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ORIGINAL RESEARCH

Formulation and evaluation of bilayer tablets of diltiazem HCl

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Abstract

The present investigation concerns development of bilayer floating tablets of Diltiazem HCl is class I drug, though its reported bioavailability is only 40 %. It is having very short half life of 3 to 4 hr. Hence many sustained release formulations were developed for diltiazem HCl. But they take lag time to start the action. Hence a new approach is tried that gives one immediate release dose and a sustained release dose in single dosage form call bilayer tablets. Immediate release layer delivers the initial dose, it contains superdisintegrant which increase drug release rate whereas sustained release layer float due to gas generating agent and releases drug at sustained manner for prolonged period. A direct compression method was used to formulate 9 batches. Superdisintegrants like sodium croscarmellose, crospovidone was used for immediate release layer and HPMC K4 M, HPMC K 15 M, PVP K30 like polymers were used in floating layer. A simple visible spectrophotometric method was employed for the estimation of diltiazem at 236 nm and Beer's law is obeyed in the concentration range of 5-25 µg/ml. Preformulation studies were carried out to optimize the ratios required for various grades of polymers. The prepared floating tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, buoyancy lag time, total floating time, water uptake (swelling index), and *in vitro* dissolution studies. Successful formulation was developed having floating lag time as low as 30 sec and drug release was sustained up to 12 hrs. A biphasic drug release can be obtained by using bilayer tabletting technology which involved compression of immediate and sustained release layer together. Bilayered floating tablets with release characteristics offer critical advantages such as, site specificity with improved absorption and efficacy. This technology can be inculcated to various medicaments which have stomach as the major site of absorption.

Keywords: Bilayer floating tablets, Diltiazem HCl, Biphasic drug release, HPMC K 15 M

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Introduction

Narrow absorption window is one of the major problems in bioavailability of the drugs. Hence irrespective of higher solubility in GI tract some drugs like Diltiazem HCl shows poor bioavailability. Oral route is considered as the most promising route for drug delivery [1]. Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract [2]. The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time [3]. One of the novel approaches in the area of oral sustained release drug delivery is gastro retentive drug delivery system [4]. 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 gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability [5]. Extended-release dosage forms with prolonged residence time in the stomach are highly desirable for drugs with i) narrow absorption windows, ii) stability problems in the intestinal or colonic environment, iii) local action in the stomach and iv) low solubility at high pH values [6]. The biphasic system is used mostly when maximum relief needs to be achieved quickly and it is followed by a sustained release phase. It also avoids repeated administration of drug. Coronary vasodilator, antihypertensive, antihistaminic, analgesic, antipyretics and antiallergenic agents are mainly used for this system. Bilayer tablet is new era for developing a combination of two or more active pharmaceutical ingredient in single dosage form, Promoting patient convenience and compliance. Dual release tablet is a unit compressed tablet dosage form intended for oral application. It contains two layers in which one layer having conventional or immediate release part of single or multiple actives; another layer is sustained or controlled release part of single or multiple actives. They are also called as multi-layer matrix tablet. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose [7]. Diltiazem HCl is calcium channel blocker and used in the treatment of angina pectoris and hypertension. It is mainly

absorbed from stomach and upper part of intestinal track; it has low bioavailability of 40%. It has biological half-life 3-4 h. More over with 60mg sustained dosage form time required to reach peak plasma concentration is about 3.9 h. So an administration of the loading dose also becomes beneficial to reach peak plasma concentration rapidly [8]. Diltiazem undergoes an extensive biotransformation, mainly through the cytochrome p-450 CYP3A [9], which results in less than 4% of its oral dose being excreted unchanged in urine [10]. The present work concern with the formulation and evaluation of bilayer floating tablets of diltiazem hydrochloride having immediate and floating sustain release layer. These tablets showed the biphasic drug release means an immediate release layer releases the drug immediately as loading dose. Floating sustained release layer releases the drug for prolonged period of time as maintenance dose.

Materials and methods

Diltiazem hydrochloride was received as a gift sample from Pharmaceutical Company. HPMC K4M, K15M, PVP K 30 was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Sodium bicarbonate, citric acid, magnesium stearate and talc were obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Drug excipient compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Brukers Alpha Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks.

FORMULATION DEVELOPMENT

Formulation of immediate release (IR) layer

The immediate release granules were prepared by blending the drug with different concentration of superdisintegrants like sodium starch glycolate, crospovidone, croscarmellose sodium and other excipients like microcrystalline cellulose by direct compression method. The powder blend was lubricated with magnesium stearate and talc. A weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 8 mm flat faced punch

of 16 station Rimek mini press rotary compression machine to get IR layer. Nine formulation batches with different super superdisintegrants were made in order to achieve desired disintegration time and drug release. The composition of diltiazem HCl immediate release tablets were shown in Table 1.

Formulation of floating sustained release (SR) layer

The floating sustained release granules were prepared by direct compression technique. Required quantity of diltiazem HCl and polymers like HPMC K4M, HPMC K15M, PVP K30, alkalizing agent sodium bicarbonate and acidifying agent citric acid were weighed and passed through sieve with mesh #40 and were mixed homogeneously in a poly-bag for about 5-10 min and was taken in a mort. The powder mass was passed through mesh #14. Finally the powder was lubricated with lactose and talc Table 2.

Formulation of bilayer tablet

Optimized formulation IF-8 of immediate release layer and optimized formulation of F-8 for sustained release used for formulation of Bi-layer tablet.

Evaluation of Precompression Parameter

Angle of Repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation.

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

Where, h and r are the height and radius of the powder cone respectively.

Bulk Density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula [11-13].

Hausner's ratio = Tapped density/Bulk density.

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Evaluation of post compression Parameter

General appearance

Morphological characters like shape and texture was determined visually.

Thickness

The thickness of the prepared tablets was tested using dial-caliper (Mitutoyo, Japan).. The test was done in triplicate and average was determined.

Hardness

Hardness of prepared tablets was determined using Pfizer hardness tester and measured in terms of kg/cm^2.

Weight variation

The weight variation test was performed as per the U.S guidelines. Twenty randomly taken tablets were weighed together and the average weight was determined. Each tablet was then weighed individually and deviation from average weight was calculated.

Friability

A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche friabilator. The friabilator was operated for 4 min at a speed of 25 rpm. The tablets were removed from the friabilator, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,

%Friability= (Loss in weight/ Initial weight) x 100.

Drug content

Ten tablets for each batch was taken and triturated. Powder equivalent to 100mg of drug was weighed and was transferred to breaker and 0.1N HCl was added and it was then shaken for 5 minutes and finally 0.1N HCl was added to make the volume up to 100ml and solution was then sonicated for 15 minutes and filtered through Whatmann filter paper. Finally a solution was diluted suitably and the absorbance of resultant solution was measured to determine the drug content spectrophotometrically at 236 nm using UV/Visible spectrophotometer against 0.1N HCl blank.

Buoyancy lag time determination & total floating time

The in vitro buoyancy was determined by the floating lag time. The tablet was placed in a 250 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the buoyancy lag time and further total floating time of all tablets was determined by visual observation

***In vitro* disintegration time of immediate release tablets**

The disintegration time for all immediate release formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The medium, water was maintained at a temperature of 37° ± 2°C

and time taken for the entire tablet to disintegrate completely was noted.

***In vitro* dissolution studies**

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50c and rpm of 75. One Diltiazem HCl tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^0C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCL and take the absorbance at 236 nm using spectroscopy.

Stability studies

The stability of Diltiazem HCl bilayer floating tablets to assess their stability with respect to their physical appearance, drug content and release characteristics after storing at 25°C/60% RH and 40°C/75% RH in properly closed HDPE bottles along with 1 g desiccant for 3 months.

Results and discussion

Infrared spectrum of any compound given information about the functional group present in particular compound. IR spectrum of Diltiazem HCl and with all excipient was taken using KBr pellet method. Various peaks in IR spectrum were interpreted for presence of different group in the structure of drug. The spectra of FTIR indicate that the sample used was Diltiazem HCl.

The powdered blends of different formulations of immediate release tablets and sustained release floating tablets were evaluated for angle of repose, bulk density (BD), tapped density (TBD) and compressibility index. The results of SR floating tablets of BD and TBD ranged from 0.570 to 0.585 and 0.728 to 0.792, respectively. The range of angle of repose and compressibility index was found to be 27.82 to 30.69 and 16.24 to 19.30 respectively. The results of angle of repose (<35) indicate good flow properties of the powdered blend. The formulation of immediate release tablet prepared by using the superdisintegrants exhibited the LBD, TBD, angle of repose, compressibility index and Hausner's ratio of within the range, which shows good flow properties of the powdered blend.

The prepared tablets were evaluated for different physico-chemical properties and the results are summarized in Table. The tablets were white, circular in shape and were found to be uniform with respect to weight variation, hardness; thickness, friability and content uniformity of different batch of tablets were found

within acceptable range. Where the distribution of drug in all the formulations was uniform.

The prepared bilayer tablets were evaluated for different physico-chemical properties. The tablets were found to be uniform with respect to weight variation and hardness (6.12 kg/cm^2). The thickness (6.15mm) and friability (0.698%) of optimized batch of tablets were found within acceptable range. Content uniformity of formulations was found to be 99.89 %, where the distribution of drug in all the formulations was uniform. The Instant layer of Diltiazem HCl release Approx 99.89percent drug within 15 minutes and control floating layer Diltiazem HCl shows release up to 12 Hours Approx 95.56percent of Drug release in 12 hours

Conclusion

In the present investigation, several formulations were prepared by using different polymers for immediate layer and sustained layer separately. Based on the evaluation parameters for immediate layer, IF8 was found to be optimized formulation upon its disintegration time i.e., 30 sec. For Sustained release tablet, F8 was decided as optimized formulation, because the lag time, buoyancy period and in vitro drug release was better than other formulations. This is due to the good sustained release properties of HPMC and other polymers. The release pattern of bilayer tablet was best fitted to First order and Higuchi kinetic model suggested that the drug is released from bilayer sustain dosage form by Fickian diffusion mechanism. From FT-IR spectra, there was no evidence of interactions between Diltiazem HCl and the used excipients. From the results, it can conclude that the systemic concentration of the Diltiazem HCl was high after administration to attain immediate action due to the immediate release layer, from sustained release layer the drug was released in controlled manner from bilayer floating tablet by increasing the gastric residence time for prolonged period of 12 h.

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Table 1: Formulation of immediate release layer

Excipients (mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Diltiazem HCl	20	20	20	20	20	20	20	20	20
Sodium Starch glycolate	5	7.5	10	_	_	_	_	_	_
Croscarmellose sodium	_	_	_	5	7.5	10	_	_	_
Crospovidone	_	_	_	_	_	_	5	7.5	10
Microcrystalline cellulose	155	161.5	159	155	161.5	159	155	161.5	159
Talc	10	5	5	5	5	5	5	5	5
Magnesium stearate	10	6	6	6	6	6	6	6	6
Total weight	200	200	200	200	200	200	200	200	200

Table 2: Formulation of sustained release floating layer

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem HCl	40	40	40	40	40	40	40	40	40
HPMC K 15	_	_	_	160	170	180	80	85	90
HPMC K 4	160	170	180	_	_	_	80	85	90
PVP K30	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	80	70	60	80	70	60	80	70	60
Total Weight	300	300	300	300	300	300	300	300	300