Formulation And Evaluation of Sustained Release Matrix Tablet of Diltiazem HCL

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Abstract- *Controlled release and sustained release drug delivery has become the standards in the modern pharmaceutical design and intensive research for achieving better drug product effectiveness, reliability and safety. Oral sustained release drug delivery (OSRDD) medication will continue to account for the largest share (up to 80%) of drug delivery systems. The matrix tablet preparation appears to be most attractive approach for the process development and scale-up point of view. A calcium channel blocker, Diltiazem hydrochloride has found its applicability in cardiovascular diseases advised to take the long term treatment of cardiovascular medicaments like anti-anginals, anti-hypertensives, etc. The calcium channel blockers are utilized as the potential agents for the treatment of these diseases. They are considered as a slow calcium channel blockers. The direct compression method was adopted for the preparation of sustained release matrix tablets with the 10mm punches and targeted weight of 450mg. The % drug release studies for combined hypromellose and xanthan gum matrices confirmed the batch H2X2 (at the end of 12 hours) as per USP criteria Test 2, which give the 93.78% drug release. Hence, this formulation was optimized and subjected to release kinetic study and accelerated stability studies.*

Keywords- Calcium channel blocker, Diltiazem hydrochloride, Matrix tablet, Sustain release, Control releas

I. INTRODUCTION

SUSTAINEDRELEASESYSTEM

The goals of sustained drug delivery are to conserve and maintain effective drug concentration, to improve compliance and to decrease side effects. Oral sustained release formulations aim at releasing drug at zero order rate of release. Physicochemical nature of drug generally decides pharmacokinetic profile of drug. Sustain release drug delivery system are formulated by decreasing rate of absorption or modifying the structure of drug.

Advantages

1. Improved therpy
2. Patient Convenience/ improved patient compliance
3. Economy

Disadvantages

- Dose Dumping
- Less flexibility in a cute dose adjustment
- Poor in vitro-in vivo correlation
- Patient variation
- Sustained Release dosage forms are expensive

II. EXPERIMENTAL WORK

1. Determinationofmelting point:
   Melting points of Diltiazem Hydrochloride and Metoprolol Succinate were determined by capillary method.
2. Solubility:
   The solubility of Diltiazem Hydrochloride and Metoprolol Succinatein various media was observed.
3. FTIR Spectroscopy
   The FT-IR spectrum for the obtained gift sample of pure drug was obtained by KBr method and compared with the standard FT-IR spectra.
4. Compatibility studies:
   FT-IR spectroscopic studies were performed to check the compatibility between the drug and polymer in formulation and in final dosage form.The FT-IR spectra of drug alone and with formulation polymers were obtained by KBr method and compared with the standard FT-IR spectrum of the pure drug.
5. Determination of λmax:
   From the stock solution, a suitable concentration of Diltiazem Hydrochloride (10 µg/ ml) was prepared in distilled water and UV scan was taken for the above stock solutions between the wavelengths of 200- 400 nm. The absorption maximum was found to be 237 nm and this wavelength was selected and utilized for further studies

COMPOSITION OF MATRIXTABLETS

TableNo: Composition of Diltiazem Hydrochloride

Ingredients (mg)	**Allbatchesquantityinmg/tablet**				
	FD1	**FD2**	**FD3**	**FD4**	**FD5**
DiltiazemHydrochloride	90	90	90	90	90
HPMCK100LV	45	90	180	270	-
EudragitL100-55	-	-	-	-	45
Microcrystallinecellulose	155.25	132.75	87.75	42.75	155.25
Lactose	155.25	132.75	87.75	42.75	155.25
MagnesiumStearate	4.5	4.5	4.5	4.5	4.5
Totalweight	450	450	450	450	450

PREPRATION OF MATRIX TABLETS

The corresponding amounts of active ingredient(drug-Diltiazem hydrochloride), HPMC, Eudragit, microcrystalline cellulose and lactose were accurately weighed. The powders were sieved using screen #25. The screened powder was then transferred into the turbula mixer jar and mixed for 10 minutes. Magnesium stearate was accurately weighed ,sieved through screen#25andaddedtotheturbulajar and mixed for an additional 2 minutes. The powder mix was then compressed into tablets using the instrumented tablet press, using a 7 mm round punch. Tablets were collected during compression for in-process testing (weight and hardness).

III. EVALUATION OF MATRIX TABLETS

Pre-compressional Studies[95]

Mixed powder were evaluated for various properties like bulk density, tapped density, compressibility index, Hausner ratio, flow properties (angle of repose) by using standard procedures. All studies were carried out in triplicate (n=3) and average values are reported with respective standard deviation.

1. Bulk Density and Tapped Density:

Both loose bulk density (LBD) and tapped bulk density (TBD) of prepared granules were determined. A quantity of 10 gm of blend from each formula, previously shaken to break any agglomerates formed was introduced in to 50ml measuring cylinder. The initial volume was noted, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2.5 cm by using bulk densito meter. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following equations. (According to the USP-NF Guidelines 100 gm of sample was taken. I fit is not possible to use 100 gm, the amount of the test sample and the volume of cylinder may be modified). LBD=Weight of the Granules/Untapped Volume of the packing TBD=Weight of the Granules/Tapped Volume of the packing

2. Compressibility Index:

The Compressibility Index of the blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it is packed down. The formula for Carr's Index is as below:

Carr's Index(%) =[(TBD-LBD)x100]/TB

3. Hausner's Ratio:

Hausner's Ratio was determined by Following Equation Hausner's Ratio = Tapped Density / Bulk Density

4. Angle of repose:

Angle of repose was determined by measuring the height and radius of the heap of the granules. A funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the plane. Granules were placed in funnel and allowed to flow freely and the height and radius of the heap of granules was measured. Similar studies were carried out after incorporating lubricants / glidants calculated using the equation.

POST-COMPRESSIONALSTUDIES

1. Hardness test:

It indicates the ability of a tablet to with stand mechanical shocks while handling. Hardness of tablets was determined using a validated Monsanto hardness tester. It is expressed in kg/cm^2.SixtabletsaccordingtoUSP Guide lines werer an domly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated.

2. Weight variation test:

According to USP-NF twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

3. Friability test:

Roche friabilator was used for friability test. According to IP guidelines Pre weighed tablet(WInitial) sample (20 tablets) were placed inthe friabilator apparatus and rotated at 25 rpm for a period of 4 min.Tablets were again weighed (Wfinal) and the percentage weight loss in tablet was determined using formula. The %Friability of tablets less than1% are considered acceptable.

DRUG CONTENT:

Diltiazem Hydrochloride

1. Standard Solution:

100 mg of pure drug was weighed accurately and dissolved in 5 ml of distilled water. A sufficient quantity of distilled water was added to produce 100 ml and mixed well. From this 1 ml taken and distilled water was added to produce 100 ml.

2. Sample Solution:

20 tablets were weighed accurately and finely powdered. To powder equivalent to 100 mg of Diltiazem hydrochloride, 15 ml of distilled water was added and dispersed with the aid of shaker for 15 minutes. Sufficient quantity of distilled water was added to produce 100 ml, mixed well and filtered. To 1 ml of the filtrate distilled water was added to produce 100 ml and mixed well. The absorbance of the resulting solution was measured at the 237 nm using blank in the reference cell. The total content of diltiazem hydrochloride in the solution was calculated using the absorbance of a standard solution. The above test was done in triplicate.

Drug content was determined by crushing the tablet in a glass mortar and pestle and extracting the drug in phosphate buffer pH 7.4 with continuous shaking on a rotary shaker (Remi instruments Ltd, Mumbai, India) for 24 h. The drug content in extracted fluid was analyzed using a UV-Spectrophotometer (UV- 1601, Shimadzu, Japan) at 237nm against

INVITRO DISSOLUTION STUDY

Dissolution Studies

To understand the release profiles of the drug from the tablets, dissolution experiments were performed in simulated gastric (0.1 N HCl, i.e., pH 1.2) and intestinal (pH 7.4) conditions. The release of Diltiazem hydrochloride from the tablet was studied using USP XXIII paddle apparatus (Electrolab). Drug release profile was carried out in 750 ml of 0.1NHCl for 2 hand then in 900ml of phosphate buffer solution(PBS)Ph 7.4 maintained at 37 ± 0.5˚C and 100 rpm. Ten ml of samples were withdrawn at predetermined time intervals of every 1 h up to 12 h. The samples were replaced by its equivalent volume of dissolution medium and were filtered through 0.45µm whatman filter paper and assayed at 237 nm by UV spectrophotometer (Evolution201,UV-visible spectrophotometer, Thermo Fisher Scientfic, USA).

IV. RESULTS AND DISCUSSION

ANALYSISOFDRUG

Description:

Drug	Description
Diltiazem Hydrochloride	A white, odorless, crystalline powder and has a bitter taste

Determination of melting point:

Melting point of Diltiazem Hydrochloride and Metoprolol Succinate were determined by capillary method.

Drug	Melting point
Diltiazem Hydrochloride	212^0C

Solubility:

Diltiazem hydrochloride was found to be soluble in water, formic acid, methanol & chloroform. It was slightly soluble in ethanol.

Fourier Transformed Infrared(FT-IR)Spectroscopic Analysis:

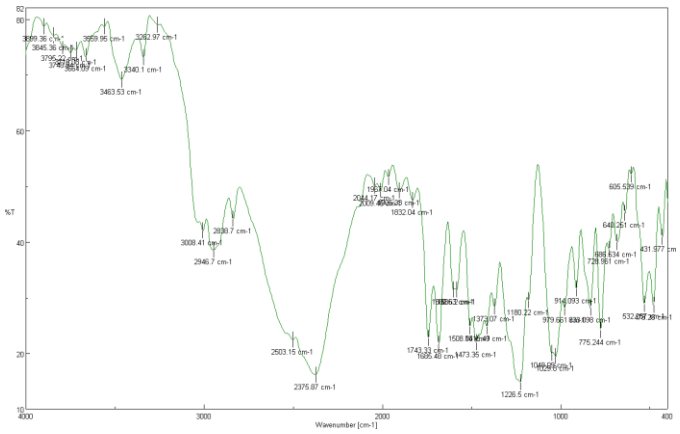

Figure: IR spectra of pure diltiazem hydrochloride

DETERMINATION OF λmax : Determination of λmax of Diltiazem Hydrochloride

The absorption maximum Diltiazem Hydrochloride was found to be 237 nm and this wavelength was selected and utilized for further studies.

PREPARATION OF CALIBRATION CURVE

Table: Absorbance values of Diltiazem Hydrochloride in 0.1NHCl

Sr.No.	Concentration in mcg/ml	Absorbance mean ±SD*(237nm)
1	0	0
2	2	0.116±0.002
3	4	0.224±0.003
4	6	0.332±0.004
5	8	0.434±0.001
6	10	0.536±0.001

Standard deviationn=3

EVALUATION OF MATRIX TABLETS:

Evaluation of pre-compression parameters

Formu l-ation	Bulk Density* (g/Cm^3)	Tapped Density* (g/Cm^3)	Compressi b- ility Index*(%)	Hausne r Ratio*	Angle of Repose*(^{O})
FD1	0.517±0.0 04	0.564±0.0 04	8.33±0.021	1.09±0.0 8	23.62±0.1 2
FD2	0.510±0.0 03	0.555±0.0 02	8.10±0.022	1.08±0.0 7	23.89±0.2 6
FD3	0.513±0.0 06	0.564±0.0 07	7.62±0.020	1.08±0.0 6	25.64±0.2 0
FD4	0.521±0.0 06	0.564±0.0 04	7.62±0.020	1.08±0.0 7	25.64±0.2 1
FD5	0.500±0.0 02	0.553±0.0 02	9.58±0.024	1.10±0.1 0	21.58±0.1 5

*mean(n=3)

POST-COMPRESSIONAL STUDIES

Formulation	Hardness* (kg/cm^2)	Weight Variation*(mg)	Friability* %	Content Uniformity(%)
FD1	5.0±0.04	449±2.57	0.80 ±0.02	98.6 ±0.05
FD2	5.2±0.05	449±2.28	0.51 ±0.03	99.5 ±0.03
FD3	5.2±0.08	448±3.57	0.43 ±0.02	99.5 ±0.02
FD4	5.4±0.04	446±2.39	0.42 ±0.03	97.7 ±0.03
FD5	4.6±0.04	439±2.13	0.38 ±0.01	98.5 ±0.03

DISSOLUTION STUDIES OF MATRIX TABLET:

.Time (HRS)	Mean Cumulative % Drug Release of all Formulation (Mean±SD,n=3)				
	Formulation				
	FD1	FD2	FD3	FD4	FD5
1	96.4±0.46	52.2±0.28	20.22±0.80	16.23±0.78	98.1±0.45
2	98.4±0.79	82.2±0.90	30.12±0.10	22.26±0.36	98.1±0.64
3	98.4±0.40	90.2±0.85	38.21±0.19	31.63±0.16	98.1±0.64
4	98.4±0.40	94.6±0.92	50.14±0.69	39.67±0.92	98.1±0.64
5	9.4±0.40	97.1±0.66	60.23±0.03	44. ±0.3576	98.1±0.64

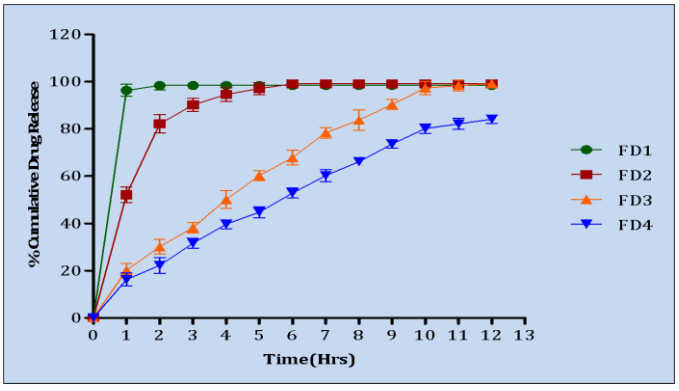

Figure : diltiazem hydrochloride release from SR matrix table

V. CONCLUSION

From the complete study, it is concluded that, HPMC K100LV & Eudragit® L100-55 at a concentration of20% respectively produced sustained release Diltiazem hydrochloride/ matrix tablets that are similar to the markete dproduct (DilzemSR) in-vitro according to the f2 similarity factor.

PVAP & dibasic calcium phosphate at a concentration of 39.5% respectively, produced sustained release Diltiazem hydrochloride matrix tablets that are similar to the marketedproduct (Dilzem SR) in vitro according the f2 similarity factor.

Optimized sustained release Diltiazem hydrochloride Metoprolol Succinate matrix tablets, showed square root of time dependent kinetics of drug release indicating a dissolution and diffusion controlled release mechanism.
Selected polymers and their concentrations are also capable of sustaining the release of drug Diltiazem hydrochloride beside drug concentration.

The in-vivo X-ray study of selected sustained release HPMC and Eudragit and PVAP Diltiazem hydrochloride matrix Tablets proved that the polymerutilized for the optimization of the formulation showed the sustaining activity in-vivo in rabbit by sticking to various sites in the GIT. Under long term storage conditions at 25ºC and 60% RH, stability testing performed on the selected HPMC/Eudragit and PVAP tablets showed no significant change in the dissolution rates. Based on this finding, the recommended storage conditions are 25ºC and 60% RH.Based on the above, it is concluded that sustained release Diltiazem hydrochloride/Metoprolol Succinate matrix tablets was developed using HPMC and Eudragit combination and PVAP as the release sustaining excipients. In vitro testing indicated that sustained release Diltiazem hydrochlorid etec matrix tablets had similar dissolution behavior to the marketed product according to the model independentFDA guideline (f2 factor).

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