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Formulation, Development and Evaluation of Sustained Release Matrix Tablet of Antihypertensive Drugs

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Abstract

The current study was focus on to the formulation of sustain release tablet of Diltiazem. Diltiazem is calcium channel blocker was used for the treatment and management of high blood pressure, chronic stable angina. Diltiazem having the short half-life i.e., 3.0 to 4.5 hours and it is also having low bioavailability so that need to develops the controlled release tablet. The aim of this study was to provide sustained action, reduce the frequency of dose administration and increase bioavailability, reduce the dose dumping and increase patient compliance. Dry granulation method was used to the preparation of the matrix sustain release tablet. By using different polymers, the drug release extended up to the 24 hours. The drug-excipient compatibility study was done by using the FTIR studies. The evaluation of tablets was done by using various parameters like bulk density, tapped density, Angle of repose, Hauner's ratio, Carr's index, thickness, weight variation, friability, Disintegration and dissolution studies. The formulation F9 gives better result it release drug up to 24 hours.

Keywords: Matrix tablets; Sustain release; Dry granulation; Diltiazem; Bulk density; Tapped density; Weight variation; Friability; Compatibility study; FTIR studies

Introduction

Present days novel medication conveyance frameworks are critical for transportation of the medicine to the human body. Presently the customary frameworks are recuperated by the novel medication conveyance frameworks [1,2]. In present day pharmaceutical innovation, the continued and controlled medication exchange frameworks are the more celebrated frameworks. Presentation of framework measurements structure as Supported Release (SR) has given another breakthrough for novel dynamic substance move framework within the field of pharmaceutical innovation [3,4]. Diltiazem was generally indicated for the management of chronic stable angina. The Sustained Release (SR) sort of the drug has been found to end in better compliance, reducing the frequency of dosage and within the end, the foremost important thing, maintaining a consistent drug concentration within the body [5,6]. Calcium Channel Blockers (CCBs) are generally used to treat high blood pressure, angina and certain cardiac rhythm abnormalities [7]. CCBs are a category of medicine that ought to not be prescribed as initial or first-line treatment in people with high blood pressure who haven't any other form of heart condition. They're often used as a second or third drug to assist lower blood pressure when other drugs haven't been successful in bringing down the level. However, CCBs could also be considered as initial treatment (usually together with other drugs) for people that have high blood pressure plus angina and/or a high risk of stroke. CCBs shouldn't be given to people with heart failure (often called congestive heart failure). Coronary artery disease has been documented to be one among the most causes of morbidity and mortality in chronic hemodialysis patients with End-Stage Renal Disease (ESRD) [8,9]. It's well established that Heart Rate (HR) lowering, both at rest and during exercise, has beneficial effects in patients with angina. Hypertension has been recognized as a serious public health issue.

Materials and Methods

Materials

Diltiazam, Microcrystalline cellulose 101 (MCC), Ethyl Cellulose, HPMC K4M, Polyvinylpyrrolidone (PVP), Magnesium Stearate, Talc.

Methods

The dry granulation method used for the formulation development of matrix tablets of Diltiazam.

Dispensing: Accurate quantity of drug and chosen excipients are weighed.

Sieving: The dispensed quantity of drug and excipients are sieved through 40 number sieve.

Mixing: The sieved drug and excipients are undergone for manual mixing. The talc and mg stearate added lastly.

Dump mass: After mixing the dump mass is formed by adding IPA to mixed blend. The dump mass is formed.

Size reduction: After preparation of dump mass undergone for size reduction by using sieve number 12. The granules are obtained.

Drying: After size reduction the granules are dried in oven for 30 mins.

Compression: After drying the granules undergo for compression in multipunch compression machine using 10 mm diameter **(Table 1).**

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem HCL	180	180	180	180	180	180	180	180	180
Microcrystallin cellulose 101	237	237	217	217	177	177	207	157	77
Ethyl cellulose	-	40	-	60	-	100	40	60	100
HPMCK$_4$M	40	-	60	-	100	-	40	60	100
Polyvinylpyr--rolidpne (PVP)	20	20	20	20	20	20	20	20	20
Mgstearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1
Table weight	480	480	480	480	480	480	480	480	480

Table 1: Formulation table for diltiazem matrix tablets.

Characterization of tablets

Bulk density: The bulk density is measured as the accurately weighed powder blend is transferred in to the measuring cylinder. First the initial weight of the sample is calculated [10,11].

Tapped density: The tap density is measured as the transferred powder in the cylinder is kept and fix to the tap density apparatus and the tapping is performed about (100).

Percentage compressibility (or) Carr's index (%): The compressibility index is defined as it comes from the standards of the loose thickness and tap thickness. The compressibility index is calculated.

Hausner's ratio: It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.

Angle of repose: The point of rest is performed by the pipe technique. Some amount of the powder is taken in a pipe by shutting the hole of the channel. Under the pipe one paper is kept. By opening hole, the powder frames a load like heap. The heap flat width is taken by the scale by the perimeter drawn on the paper. The edge of rest is for the most part for the assurance of the stream property of the powder. Edge of rest is determined by the accompanying recipe,

$$\text{Angle of repose} = \tan^{-1}(h/r)$$

Where, h=height r=radius

Evaluation of tablets

Physical appearance: The readied tablets are under kept for the perception of the colour, size and shape. For observing of parcel to-part consistency and tablet-to-tablet consistency.

Thickness: The readied tablets are then under kept for watching the thickness of the tablets. The thickness of the tablets are completed by the smaller scale meter or by the vernier calipers. The tablets thickness ought to screen inside the ± 5% variety of standard esteem.

Weight variation: The readied tablets are kept for the weight variety test. The weight variety is performed by the weighing of the individual tablet and all the tablets. Initial weight is taken after that gathering of tablets weight is taken. The weight variety is finished by the accompanying recipe.

% Weight variation=initial weight of the tablet/final weight × 100

Drug content: The drug content was determined by taking ten tablets. It is poured into the motor and pestle and crushed finely. An accurately weighted amount of the powder equal to 10 mg of the diltiazem HCL is taken. From the crushed powder 10 mg of the powder is taken in to the 100 ml of the volumetric flask with 7.4 ph. buffer solution. It is mechanically stirred thorough for 1 hr. The stirred powder solution is filtered through the whatsman filter paper. The absorbance was measured at 237 nm against blank solution.

Friability: Friability is finished through using the Roche friabilator. About 10 tablets are taken for performing the method. First take initial weight of tablets and transfer them into friabilator, the apparatus where they are exposed to the rolling and repeated shocks as they fall from 6 inches in each turn within the apparatus. The tablets revolutions are about 100 per minute. The tablets final weight is compared with the initial weight of the tablets. Aimed at decisive the asset of the tablets the following formula is used; the percentage friability was determined by the formula:

$$\% \text{ friability} = (W1-W2)/W1 \times 100$$

Where, W1=Weight of tablets before test; W2=Weight of tablets after test

***In-vitro* drug release study**: The prepared tablets are the under kept for the *In-vitro* drug release educations. For *in vitro* drug release educations, the USP-II apparatus is used. It is paddle method. The dissolution volume is up to 900 ml [12,13]. It is maintained up to the temperature 37 ± 1°C. The rpm is about 50. The dissolution education is accepted obtainable for 10 hours. The sink conditions are maintained. First start with acid buffer for 2 hrs after that the process is continued in the buffer solution that is 7.4 pH buffer solution. 5 ml of sample is withdrawn in different time intervals and it is replaced with same volume with the buffer solution while the sink conditions

are maintained. The withdrawn sample is diluted with the buffer solution and it is under kept for the U.V for knowing of the absorbance of the sample spectrophotometrically at 237 nm.

Results and Discussion

FTIR Studies: IR Spectral investigation diltiazem (medicate) demonstrated the crests at wave quantities of 2317(C-N) 2990(C-H Alkane) 1732(N-H Bending) 1240 (OCH3-extending) 2478(C=C) affirming the virtue of the medication with the standard separately. In physical blend of diltiazem with HPMC K4M and ethyl cellulose real pinnacles of diltiazem were 2318(C-N) 2998(C-H Alkane) 1750 (N-H Bending) 1268 (OCH3-extending) 2567 (C=C) wave numbers. Anyway, the extra pinnacles were seen in physical blends which could be because of the nearness of excipients and it tends to be said that there was no concoction cooperation between the medication and excipients from the spectra **(Figures 1-3 and Tables 2-4).**

Drug content: The drug content was determined by taking ten tablets. It is poured into the motor and pestle and crushed finely. An accurately weighted amount of the powder equal to 10 mg of the diltiazem HCL is taken. From the crushed powder 10 mg of the powder is taken in to the 100 ml of the volumetric flask with 7.4 ph. buffer solution. It is mechanically stirred thorough for 1 hr. The stirred powder solution is filtered through the whatsman filter paper. The absorbance was measured at 237 nm against blank solution.

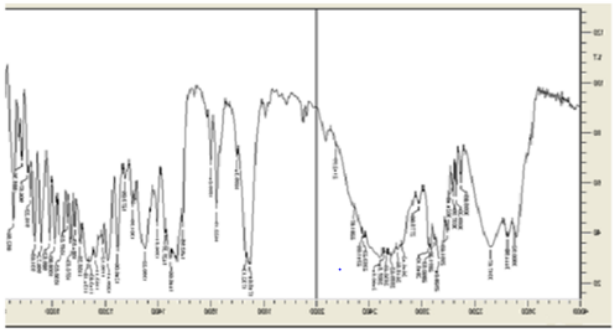

Figure 1: FTIR graph of pure API (Drug).

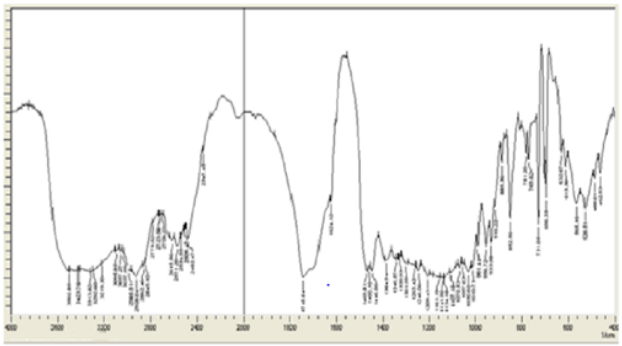

Figure 2: FTIR graphs of drug+polymers.

Formulation	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	28.53	3.40 ± 0.01	4.4 ± 0.06	0.612	95.24 ± 0.22
F2	28.26	3.55 ± 0.00	4.5 ± 0.06	0.646	94.57 ± 0.42
F3	26.59	3.6 ± 0.01	4.4 ± 0.00	0.686	96.43 ± 0.13
F4	28.54	3.48 ± 0.01	4.70 ± 0.06	0.526	96.83 ± 0.42
F5	26.05	3.32 ± 0.01	4.60 ± 0.10	0.546	97.86 ± 0.32
F6	29.52	3.40 ± 0.01	4.40 ± 0.06	0.612	95.24 ± 0.22
F7	32.52	3.55 ± 0.00	4.50 ± 0.06	0.646	96.57 ± 0.42
F8	31.45	3.60 ± 0.01	4.40 ± 0.00	0.686	94.43 ± 0.13
F9	35.25	3.48 ± 0.01	4.70 ± 0.06	0.53	96.83 ± 0.42

Table 2: Pre-compression results of the diltiazam matrix tablets.

Thickness: The readied tablets are then under kept for watching the thickness of the tablets. The thickness of the tablets are completed by the smaller scale meter or by the vernier calipers. The tablets thickness ought to screen inside the ± 5% variety of standard esteem.

All the formulations (F1-F9) Angle of repose, bulk density, tapped density, hansures ratio, compressability all are within the limits.

Formulation	Weight variation	Thickness (mm)	Hardness (Kg/ cm^2)	Friability (%)	Drug content (%)	Disintigration (min)
F1	399.23 ± 0.001	3.51 ± 0.01	4.7 ± 0.06	0.258	98.25 ± 0.2	25
F2	399.8 ± 0.01	3.52 ± 0.00	4.5 ± 0.06	0.41	99.23 ± 0.1	26
F3	399.44 ± 0.01	3.49 ± 0.01	4.5 ± 0.00	0.235	99.52 ± 0.1	26
F4	400 ± 0.00	3.54 ± 0.01	4.7 ± 0.06	0.42	98.52 ± 0.2	25
F5	399.58 ± 0.01	3.50 ± 0.01	4.5 ± 0.10	0.52	99.55 ± 0.1	24
F6	398.85 ± 0.02	3.48 ± 0.01	4.6 ± 0.06	0.4	100.12 ± 0.01	27

F7	399.2 ± 0.01	3.63 ± 0.00	4.5 ± 0.06	0.243	99.80 ± 0.1	28
F8	399.5 ± 0.01	3.62 ± 0.01	4.6 ± 0.00	0.402	98.90 ± 0.1	28
F9	399.2 ± 0.01	3.59 ± 0.01	4.7 ± 0.06	0.421	99.32 ± 0.1	29

Table 3: Post-compression results of the diltiazam matrix tablets.

Time (Hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	25.63	24.65	24.25	23.87	20.14	19.86	18.52	18.46	19.52
2	40.23	38.25	41.23	44.23	39.55	38.43	29.3	29.3	29.3
4	50.54	49.55	55.43	65.54	49.82	48.23	41.52	40.2	39.2
6	64.25	66.35	70.52	64.25	62.54	60.48	52.2	51.52	45.52
8	76	80.5	81.52	76	73.56	72.65	64.24	63.1	53.1
10	89.5	94.56	94.2	89.5	84.2	82.45	74.54	74.2	61.2
12	98.58	100.02	99.65	99.52	96.52	93.59	81.36	83.85	70.85
14	98.86	100.02	99.72	99.54	99.68	100	92.52	91.56	78.56
16	98.86	100.02	99.72	99.54	99.69	100	97.52	99.7	85.7
20	98.86	100.02	99.72	99.54	99.69	100	98.14	99.81	90.8
24	98.86	100.02	99.72	99.54	99.69	100	98.32	99.85	99.62

Table 4: *In –vitro* drug release profile of all formulation.

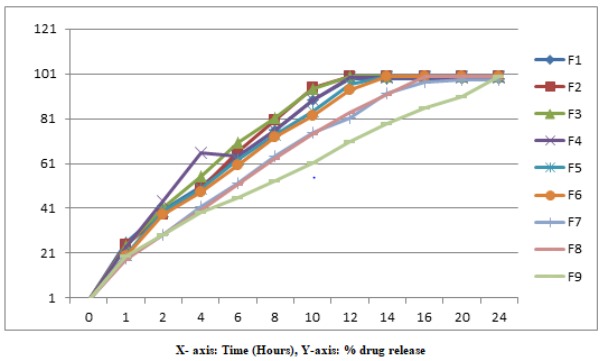

Figure 3: *In –vitro* drug release profile of all formulation.

Conclusion

Diltiazem HCL tablet was prepared by using different types of excipients and controlled release polymer (HPMC K4M, Ethyl Cellulose). The tablet was formulated by using dry granulation method. The use of the combination of controlled release polymer is extends the release of the drug up to the 24 hours. The *in vitro* drug release study was done by using USP-II apparatus, the Phosphate Buffer pH 6.8 was used. The optimized formulation F9 shows sustained-release of the drug diltiazem by controlled manner up to the 24 hours.

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