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PREPARATION AND EVALUATION OF DILTIAZEM SUTAINED RELEASE TABLETS BY USING WET GRANULATION TECHNIQUE

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ABSTRACT

Sustained releases tablets of Diltiazem hydrochloride were prepared by employing hydroxypropyl methylcellulose (HPMC K100 M) and the sustained release behavior of the fabricated tablets was investigated. Sustained release tablets containing 120 mg Diltiazem hydrochloride were developed using different drug: polymer (HPMC K100 M) ratios. Tablets were prepared by wet granulation technique. Formulation was optimized on the basis of acceptable tablet properties and in vitro drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and low friability. All tablets but one exhibited gradual and near-complete sustained release for Diltiazem hydrochloride (90-100%) at the end of 24 h. The results of dissolution studies indicated that formulation F-5 (drug to polymer 1:1.25) was found to be most successful as it exhibits drug release pattern very close to theoretical release profile.

KEYWORDS: Diltiazem hydrochloride, hydroxypropyl methylcellulose (HPMC K100 M), Sustained releases Tablets, and wet granulation technique.

INTRODUCTION:

Diltiazem is a non-dihydropyridine (non-DHP) member of the class of drugs known as calcium channel blockers, used in the treatment of hypertension, angina pectoris, and some types of arrhythmia. It is also an effective preventive medication for migraine. Diltiazem is a potent vasodilator, increasing blood flow and variably decreasing the heart rate via strong depression of A-V node conduction. Its pharmacological activity is somewhat similar to Verapamil**.**

Wet granulation method was adopted for the preparation of tablets using different retardant polymer excipients namely; hydroxypropyl methyl cellulose H100M, ethyl cellulose, Lactose (Monohydrate), Isopropyl Alcohol, Magnesium Stearate, Talcum**.**

The conventional dosage forms have some drawbacks. Multiple daily dosing is inconvenient to the patient and can result in missed doses, made up doses and patient incompliance with the therapeutic regimen. When conventional immediate release dosage forms are taken on schedule and more than once daily, there are sequential therapeutically blood peaks and valley associated with taking each dose. It should be emphasized that the plasma level of a drug should be maintained within the safe margin and effective range. Drug need to be given at different time interval by conventional dosage form. To achieve and maintain the concentration of administered drug within therapeutically effective range, it is often necessary to take drug dosage several times and this result in a fluctuating drug level in plasma. A simple dosing scheme with a once- or twice daily administration of the antihypertensive agent is known to increase patient compliance For this reason, the pharmaceutical industry is intensively searching for longer-acting antihypertensive drugs, either by the development of novel agents with a longer elimination half-life, or by the improvement of the dosage form of existing shorter-acting compounds, so that plasma concentrations compatible with a blood-pressure-lowering activity are maintained during the whole day. The present research endeavor was directed towards the development of a sustained release tablet formulation containing Diltiazem hydrochloride tablet taken once rather than two or three times a day. The aim of present project work was to design, process optimization and evaluation of sustained-release tablet of poorly soluble drug diltiazem.[11, 12]

MATERIALS AND EQUIPMENTS:

Diltiazem HCl was gift sample from Lincoln pharmaceutical, Khatraj, kalol. Lactose monohydrate was gift sample Paxmy speciality chemicals, Chennai. HPMC K100M [13, 14, 15], Talcum powder and Ethyl cellulose were gift samples from Loba Chemie Pvt. Ltd, Mumbai. Magnesium stearate and Isopropyl alcohol was gift samples from S.d. Fine Chemical Pvt. Ltd; Mumbai. All the other chemicals used were of analytical reagent grade.[10]

METHOD OF PREPARATION

Weigh accurately all the ingredients and pass the materials (Diltiazem HCl and HPMC K100 M) through 40 # sieve and transferred into RMG (Rapid mixer and granulator) and mix for 10 min. Now add previously prepared solution of ethyl cellulose in IPA (Isopropyl Alcohol) slowly with appropriate speed of impellor and chopper to obtained granules. Now transferred material into fluid bed drier and operate at inlet temperature 60 ^{0}C and outlet at 40 ^{o}C to achieve % L.O.D (loss of drying) between 1.5 - 2.0 % then pass the dried granules through 20 # sieve. Weight accurately talcum powder, magnesium stearate and pass through 40 # sieve and mix it with above granules in octagonal blander (Gansons) for 5 min. Now compressed the tablet on 16 station tablet compression machine (Cadmach, India) by using 13/32 mm SC plain punches.[1]

S.no	Composition	F-1	F-2	F-3	F-4	F-5
1	**Diltiazem Hydrochloride**	120mg	120mg	120mg	120mg	120mg
2	**HPMC K-100M**	100mg	120mg	130mg	140mg	150mg
3	**Lactose (monohydrate)**	69mg	49mg	39mg	29mg	19mg
4	**Ethyl cellulose**	25mg	25mg	25mg	25mg	25mg
5	**Isopropyl Alcohol**	150mg	150mg	150mg	150mg	150mg
6	**Magnesium Stearate**	3mg	3mg	3mg	3mg	3mg
7	**Talcum**	3mg	3mg	3mg	3mg	3mg

EVALUATION PARAMETERS:

Prepared tablets were evaluated for certain physical properties like Loss of drying, Weight variation of Tablet, Hardness, Friability, Thickness, Assay method and In-vitro dissolution study etc.[1,2]

1. LOSS ON DRYING

Loss on drying is the loss in weight in % w/w resulting from water and volatile matter of any kind that can be driven off under specific conditions. The rest is carried out on a well-mixed sample of substance.

Mix and weigh accurately 1 to 2 gm of the substance. If the substance is the form of large crystals, reduce the particle size to about 2mm by quickly crushing Tare a glass-stoppage shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination, Put the test specimen in the bottle, replace the cover and accurately weigh the bottle and the contents. Distribute the test specimen as evenly as practicable to a depth of about 5mm generally and not more than 10mm in the case of bulky materials Place the loaded bottle in the drying chamber (LOD Oven) by removing the stopper and leaving it also in the chamber. Dry the test specimen at the temperature of 85^0C.

Calculation:

$$\% \text{ Loss on drying} = \frac{W_2 - W_3}{W_2 - W_1} \times 100$$

Where,

W_1 = Weight of the empty bottle in grams.

W_2 = Weight of the bottle with sample in gram (Before drying).

W_3 = Weight of the bottle with sample in grams (After drying) – As time specified.

Weight variation of tablets: Every individual tablet in a batch should be in uniform weight and weight variation within permissible limits. Weight control is based on a sample of 20 tablets. Twenty tablets were randomly selected and accurately weighed using an electronic balance (Ax, Shimadzu-Corporation, Japan). The results are expressed as mean values of 20 determinations.[4]

Calculation

$$\% \text{ Loss on drying} = \frac{\text{Individual wt} - \text{Average wt}}{\text{Average wt}} \times 100$$

The percentage deviation shown in table and none deviated by more than twice the percentage In house specification limit of Percentage deviation of fabricated tablets The results are tabulated in the following table.

S.no.	Average weight of tablet	Percentage
1.	80 mg or less	+ 10 %
2.	More than 80 mg and less than 250 mg	+ 7.5%
3.	250 mg or more	+ 5 %

3. Hardness Test: The hardness of the tablets was determined using a Hardness testing apparatus (Pfizer hardness tester).[5]

S.no	Formulation of tablet	Normal Value
1.	Un-coated tablet	4 kg
2.	Coated tablet	10-20 kg
3.	Chewable tablet	3kg

4. Thickness or dimension Test: Control of physical dimension of the tablets such as thickness, width and length is essential for consumer acceptance and to maintain tablet to tablet uniformity. The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each formulation and their thickness was measured by using vernier caliper (MitutoyoCorps, Japan). Thickness values were reported in millimeters.[3]

5. Friability Test: The friability of the tablets was measured in a Roche friabilator (Model: ED-2, Electro Lab, ET-2, India). Tablets of a known weight (W0) or a sample of 10 tablets are deducted in a drum for a

fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 % w/w.

% Friability = (W0 - W)/W0 X 100

6. In vitro dissolution study: Dissolution tests were performed in a USP Dissolution Tester Apparatus II (paddle method) (TDT-08 L, Electro lab, Mumbai, India.) at 37 ± 2°C. The paddle was rotated at a speed of 100 rpm. The prepared tablets were placed in the cylinder with 900 ml distilled water. 10 ml samples were withdrawn at time intervals of 1, 4, 8, 12, 16, 20, and 24 hrs and replace with fresh dissolution media. Samples were analyzed on UV-spectrophotometer at 237nm. [3, 5, 7, 8, 9]

RESULT AND DISCUSSION:

1. Physical properties of diltiazem tablet:

S.no	Formulation	Thickness (mm)	Friability (%)	Hardness (Kg)
1	**F-1**	3.59±0.25	0.14	10.71 ± 0.9
2	**F-2**	3.47±0.26	0.20	11.35 ± 0.5
3	**F-3**	3.62±0.30	0.25	11.96 ± 0.7
4	**F-4**	3.49±0.18	0.18	12.32 ± 0.55
5	**F-5**	3.64±0.31	0.21	12.84 ± 0.32

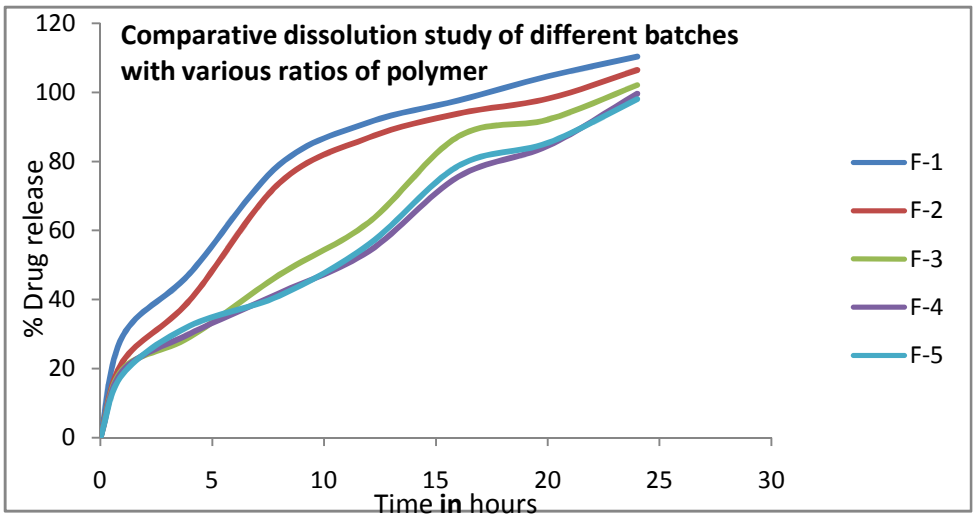
2. Physical properties of directly compressible powder mixture:

S.no	Formulation	Bulk Density g/cm^3	Tapped Density g/cm^3	Compressibility Index (%)	Hausner's Ratio	Angle of Repose, θ
1	**F-1**	0.4132	0.4797	13.68	1.132	31º
2	**F-2**	0.4216	0.5224	15.46	1.157	32º
3	**F-3**	0.4510	0.5781	15.37	1.160	33º
4	**F-4**	0.4329	0.5146	18.75	1.274	29º
5	**F-5**	0.4452	0.5120	14.43	1.194	30º

3. IN-VITRO RELEASE STUDY:

Comparative dissolution study of different batches with various ratios of polymer

S.no	TIME(in hours)	% OF DRUG RELEASE				
		F-1	F-2	F-3	F-4	F-5
1	0	0.000	0.000	0.000	0.000	0.000
2	1	29.44	22.04	19.89	19.36	18.40
3	4	47.59	39.83	29.13	30.10	32.40
4	8	79.02	73.73	47.14	41.84	41.10
5	12	91.30	86.91	62.36	53.98	56.00
6	16	97.64	93.86	87.18	75.52	78.7
7	20	104.63	98.16	92.07	84.48	85.37
8	24	110.35	106.46	102.07	99.56	98.04



CONCLUSION:

The present study concludes that combination of hydrophilic polymer such as hydroxy propyl methyl cellulose k-100M and hydrophobic polymer such as Ethyl cellulose can be utilized for designing and development of sustained release solid dosage form. Using selected polymers the developed sustained release tablet of diltiazem HCL drug was found to be equivalent with regard to dissolution profile with marketed product. The best formulation (F-5) has shown a drug release NLT 80% in 20hr was in accordance with the USP

dissolution criteria for extended release diltiazem hydrochloride formulation. There was an excellent agreement for the dissolution profile of the formulation F-5 and marketed product (DILTIME-SR).In conclusion, in the present research, sustained release tablet formulations of diltiazem hydrochloride were successfully prepared for a once daily administration.

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