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FORMULATION AND EVALUATION OF DILTIAZEM SUTAINED RELEASE TABLETS

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ABSTRACT

Sustained releases tablets of Diltiazem hydrochloride were formulated by employing hydroxypropyl methylcellulose (HPMC K100 M) and the sustained release behaviour of the fabricated tablets was investigated. Sustained release matrix 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 (96-100%) at the end of 24 h. The results of dissolution studies indicated that formulation B5 (drug to polymer 1:1.25) was found to be most successful as it exhibits drug release pattern very close to theoretical release profile. A decrease in release kinetics of the drug was observed on increasing polymer ratio.

KEYWORDS

Sustained releases Tablets , Diltiazem hydrochloride, hydroxypropyl methylcellulose (HPMC K100 M)

INTRODUCTION

For decades an acute or chronic illness is being clinically treated through delivery of drugs to the patients in form of some pharmaceutical dosage forms like tablets, capsules, liquids, creams, pills, aerosols, injectables, and suppositories. However, these 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 with in the safe margin and effective range. For this proper and calculated doses of the

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 results 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.

Greater attention has been focused on development of sustained or controlled release drug delivery systems with concomitant recognition of the therapeutic advantages of controlled drug delivery. Controlled drug delivery systems have been introduced to overwhelm the drawback of fluctuating drug levels associated with conventional dosage forms.

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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.

MATERIALS AND METHODS

Diltiazem HCl was gift sample from Lincoln pharmaceutical, Khatraj, kalol. HPMC K100M, Lactose monohydrate, Talcum powder were gift samples from Colorcon Asia Pvt ltd. Ethyl cellulose and magnesium stearate were gift samples from Signet Chemical Corporation Pvt. Ltd. All the other chemicals used were of analytical reagent grade.

Method for preparation of sustained release tablet of Diltiazem HCl

Acurately weigh 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 slowly with appropriate speed of impellor and chopper to obtained granules. Now transferred material into fluid bed drier and operate at inlet temperature 60^{o} C and outlet at 40^{o} C to achieve % L.O.D 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 for 5 min. Now compressed the tablet on 16 station tablet compression machine by using 13/32 mm SC plain punches.

FORMULATION BATCHES FOR B1-B5

Sr. No.	Item Name	B1 Mg/tab	B2 Mg/tab	B3 Mg/tab	B4 Mg/tab	B5 Mg/tab
			MIXING			
1	Diltiazem Hydrochloride IP	120.00	120.00	120.00	120.00	120.00
2	HPMC K-100M	100.00	120.00	130.00	150.00	150.00
3	Lactose (monohydrate)	69.00	49.00	39.00	19.00	19.00
			BINDING			
6	Ethyl cellulose	25.00	25.00	25.00	25.00	25.00
7	Isopropyl alcohol	150.00	150.00	150.00	150.00	150.00
			LUBRICATION			
10	Magnesium Stearate	3.00	3.00	3.00	3.00	3.00
11	Talcum	3.00	3.00	3.00	3.00	3.00
12	Total	320.00	320.00	320.00	320.00	320.00

DRUG-EXCIPIENTS COMPATIBILITY STUDY[4]

Compatibility study of Active Pharmaceutical Ingredient (API) with exicipients was carried out by performing Accelerated Stability Studies.

The test was performed by keeping API(s) and adjuvant mixed with 5%w/w water in sealed containers for 6 months at 40 ℃ ±2 ℃, 75% ± 5% RH. The concentration of all was kept as per the final formulation.

Experiment (I)

API:
Diltiazem hydrochloride

Experiment (II)

API:
Diltiazem hydrochloride
EXCIPIENTS:
Lactose(monohydrate)
Ethyl cellulose
HPMC K-100M
Talcum
Magnesium stearate

Experiment (III)

API:
Diltiazem hydrochloride
EXCIPIENTS:
Lactose(monohydrate)
Ethyl cellulose

Experiment (IV)

API:
Diltiazem hydrochloride
EXCIPIENTS:
HPMC K-100M

After 1, 2, 3 and 6 Months, Samples were withdrawn and Compatibility of Active ingredients with excipients was examined.

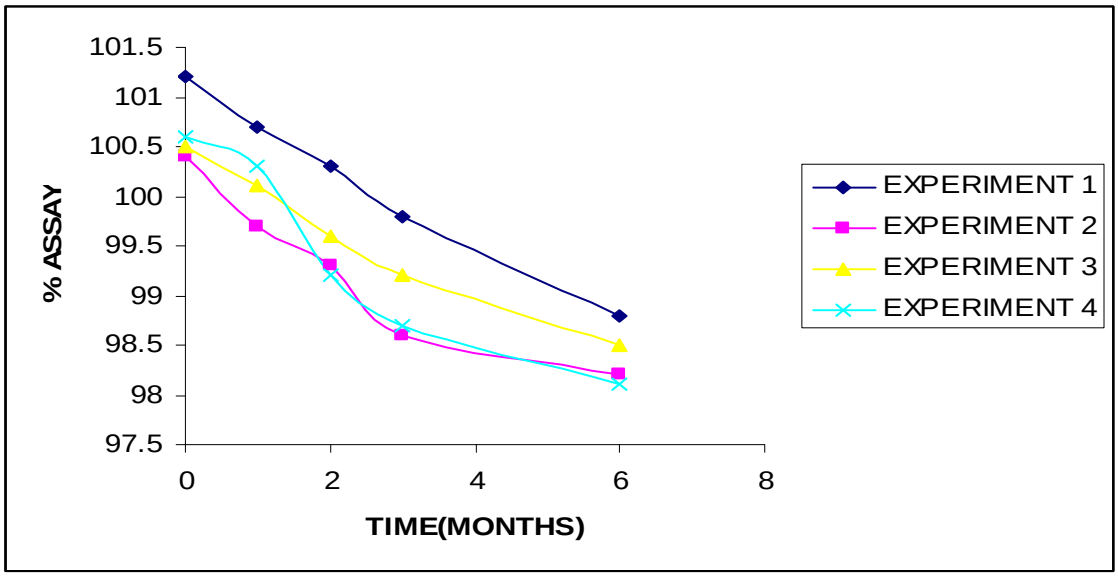

Figure 1.
Chart showing compatibility study of API with chosen inactive ingredients.

DESCRIPTION

It remained same in experiments till 6 months.

CONCLUSION

a . Diltiazem hydrochloride was found to be compatible with fillers, i.e. Lactose (monohydrate).
b.Diltiazem hydrochloride was found to be compatible with selected hydrophobic binding agent i.e., ethyl cellulose.
c.Diltiazem hydrochloride was found to be compatible with blend of filler (Lactose monohydrate), selected hydrophobic binder, (ethyl cellulose), rate-controlling polymer (HPMC K-100M), glidant (talcum) and lubricant (magnesium stearate).

EVALUATION PARAMETERS OF DILTIAZEM HCL SR TABLET[3]

Prepared tablets were evaluated for certain physical properties like Tablet wt. variation, Assay, hardness, friability, dissolution study etc.

1. Tablet weight variation: 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 (Metteler Toledo electronic balance: Model P G 03-S). The results are expressed as mean values of 20 determinations.[4]

2. Hardness: The hardness of the tablets was determined using a Hardness testing apparatus (Batch top Tablet Tester, Model: 5y, tablet tester, Dr. Schleuniger P harmatron).[5]

3. Thickness : 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 form each formulation and their thickness was

measured by using vernier caliper. Thickness values were reported in millimeters.[3]

4. Friability: The friability of the tablets was measured in a Roche friabilator (Model:ED-2, Electrolab). Tablets of a known weight (W_0) or a sample of 10 tablets are dedusted 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.

$$\% \text{ Friability} = (W_0 - W)/W_0 \times 100$$

5. In vitro dissolution study: Dissolution tests were performed in a USP Dissolution Tester Apparatus II (paddle method) (TDT-08 L, Electrolab, Mumbai, India.) at 37 ± 0.5℃. The paddle were 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 237 nm.[3,5,7,8,9]

CALCULATION FOR RELEASE PROFILE

Standard weight = ---------- *Standard absorbance* = ----------

$$\text{Formula} = \frac{\text{Sample abs}}{\text{Std.abs}} \times \frac{\text{Std.abs}}{200\text{ml}} \times \frac{10}{100} \times \frac{900}{120\text{mg}} \times \frac{100}{10} \times \text{Std.Potency.}$$

6. Stability study : Compressed tablets were packed in alu-alu blister by packaging machine (RCS Engineering Works, Ahmedabad), labeled them and stored in stability chamber (Thermolab stability chamber, Mumbai, India) at 30 ± 2℃ / 65 ± 5% RH, 40 ± 2℃ / 75 ± 5% RH for the period of 1 month. Change" occurs at any time during 6 months' testing at the accelerated storage condition should be conducted and evaluated against significant change criteria. The Initial application should include a minimum of 6 months' data from a 12- months study at intermediate storage condition.

"Significant Change" for a drug product is defined as

1. A 5% change in assay from its initial value;
2. Any degradation product's exceeding its acceptance criteria;
3. Failure to meet acceptance criteria for appearance, physical attributes and functionality test (eg. Color, phase separation, hardness, dose delivery per actuation);
4. Failure to meet the acceptance criteria for pH;
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

To develop a sustained release tablets of Diltiazem which is stable and gives in vitro drug release according to **Theoretical Release Profile.**

Time(hours)	%CPR of Diltiazem	Range
1	17.24	15-25%
2	20.94	
3	24.53	
4	28.12	20-35%
5	31.78	
6	35.31	
7	38.90	
8	42.5	35-50%
9	46.09	
10	49.68	
11	53.28	
12	56.87	45-65%
13	60.48	
14	64.06	
15	67.65	
16	71.25	65-80%
17	74.84	
18	78.43	
19	82.03	
20	85.62	NLT 80%
21	89.21	
22	92.81	
23	96.4	
24	99.98	

7. *COMPARISON OF OPTIMIZED FORMULATION WITH MARKETED FORMULATION*

The dissolution profile of optimized diltiazem hydrochloride formulation (B4) was compared with that of marketed diltiazem hydrochloride SR tablet (DILTIME SR) for $t_{50\%}$ (time for 50% drug release), regression coefficient (r^2 fitted to various models) and f2 (similarity factor). The in vitro drug release for 24 hr of marketed formulation was shown in table. The $t_{50\%}$ of marketed formulation was found to be 9.65 hours which is close to that of optimized formulation.

In vitro release form marketed formulation was fitted into different kinetic equation (zero order, first order and Higuchi equation).The *in vitro* drug release showed the highest regression coefficient values (r^2 = 0.9790) for Higuchi's model, indicating diffusion to be the predominant mechanism of drug release.

8.*Cummulative % drug release of marketed Formulation DILTIME SR TABLET*[10]

Sr. No.	Time (Hrs)	Cumulative % Drug Release
1.	0	0
2.	1	16.25
3.	4	30.28
4.	8	43.2
5.	12	58.65
6.	16	73.28
7.	20	86.43
8.	24	99.12

RESULT AND DISCUSSION

1.Physical properties of diltiazem tablet, in Mean ± S.D.

Formulation	Thickness (mm)	Friability (%)	Hardness (Kg)
B1	3.51±0.25	0.15	6.71 ± 0.9
B2	3.42±0.26	0.21	6.95 ± 0.5
B3	3.67±0.30	0.26	7.33 ± 0.7
B4	3.59±0.18	0.19	6.68 ± 0.55
B5	3.61±0.31	0.22	6.84 ± 0.32

2.Physical properties of directly compressible powder mixture

Formulation code	Bulk Density g/cm^3	Tapped Density g/cm^3	Compressibility Index (%)	Hausner's Ratio	Angle of Repose, θ
B1	0.4212	0.4897	13.98	1.162	30º
B2	0.4316	0.5124	15.76	1.187	32º
B3	0.4813	0.5681	15.27	1.180	33º
B4	0.4128	0.5056	18.35	1.224	29º
B5	0.4352	0.5110	14.83	1.174	30º

3. In-vitro release study of sustained release diltiazem tablet (B_1-B_5)

Time (hour)	Batch B1-B5				
	B1	B2	B3	B4	B5
1	29.44	22.04	19.89	19.36	18.40
4	47.59	39.83	29.13	30.10	32.40
8	79.02	73.73	47.14	41.84	41.1
12	91.30	86.91	62.36	53.98	56.00
16		93.86	87.18	75.52	78.7
20(NLT 80%)			92.07	84.48	85.37
24				96.96	98.04

DISCUSSION[11]

The present study concludes that combination of hydrophilic polymer such as Hydroxy propyl methyl cellulose k 100 M and hydrophobic polymer such as Ethyl cellulose can be utilized for designing and development of controlled release solid dosage form. Using selected polymers the developed controlled release table of diltiazem HCL drug was found to be equivalent with regard to dissolution profile with marketed product.

The best formulation (B5) 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 B5 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.

Comparison of optimized formulation with marketed formulation

The dissolution profile of optimized diltiazem hydrochloride formulation (B5) was compared with that of marketed diltiazem hydrochloride SR tablet (DILTIME SR) for $t_{50\%}$ (time for 50% drug release), regression coefficient (r^2 fitted to various models) and f2 (similarity factor). The in vitro drug release for 24 hr of marketed formulation was shown in above table. The Invitro-release profile of formulation (B5) was similar to that of marketed product DILTIME SR TABLETS.

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REFERENCES

1) Brannon PL., L. Med. Plast. & Biomater, Med. Plast. & Biomater; 1998; 199(6); 34-46.
2) Lee TW., Robinson JR., In Remington: The science and practice of pharmacy; Gennaro, Ed.; Lippincott Williams and Wilkins: Baltimore; 2000; (2); 903- 929.
3) L. Lachman, H.A. Liberman, J.L. Kanig. Theory and practice of industrial pharmacy. 3rd Edn, Varghese Publishing House, Mumbai: 296 – 302, (1991).
4) Tripathi K.D, Essentials of medical pharmacology, 5th eds, New Delhi: Jaypee brothers medical publishers; 2003: 493-496.
5) Barar FSK. Essentials of pharmacotherapeutics. New Delhi: S. chand & company; 2004: 271-274
6) Moffat AC., Osselton MD. and Widdap B. Clarke's analysis of drug and poison. 3rd ed. vol. 2. .London (UK): Pharmaceutical press; 2004: 925-926
7) Indian pharmacopoeia. Vol 1. Delhi: Published by the controller of publication; 1996: 256-257.
8) The united states of pharmacopoeia 26/ National formulary 21, The united states pharmacopoeial convention,Inc., Rockville, MD; 1995: 625-628
9) Britain Harry G., Analytical profiles of drug substances and excipients, vol-23,Elsevier: 53-98
10) www.cimsasia.com
11) Ozturk AG., Ozturk SS., Palsson BO. *et. al*. Mechanism of release from pellets coated with an ethyl cellulose-based film. *J Control Release.* 1990; 14(3): 203–213.