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FORMULATION AND CHARACTERIZATION OF DILTIAZEM HYDROCHLORIDE MATRIX TABLETS BY USING NATURAL POLYMERS

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Keywords:

Diltiazem Hydrochloride, Gum karaya, Gum kondagogu

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ABSTRACT: The purpose of present study was to design and evaluate matrix tablets of Matrix tablets of Diltiazem hydrochloride were prepared by using natural polymers like Gum karaya and Gum kondagogu. The pre formulation study was performed on combination of drug with polymers by FTIR suggested that drug and polymers were compatable. The matrix tablets were prepared by using by wet granulation method. All the prepared tablets were evaluated for weight variation, hardness, friability, drug content uniformity and in vitro drug release characteristics. The formulation F4 shows the 99.75% of drug release up to 12 h when compared with all other formulations. Formulation containing diltiazem hydrochloride with gum karaya shows best and maximum drug release of 99.75% up to 12hrs.

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 within the safe margin and effective range.

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For this proper and calculated doses of the drug need to be given at different time interval by conventional dosage form.[1-3]

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.[4-7]

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. 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.[8-13]

The purpose of this research was to design and developments of diltiazem hydrochloride were prepared by using natural polymers like Gum karaya and Gum kondagogu.

MATERIALS AND METHOD:

Diltiazem HCL was gift sample from s gift sample from M/S. NATCO Pharmaceuticals Ltd, Hyderabad, India, Gum kondagogu and Gum karaya is from Girijana co-oparative corporation society, Tirupathi, MCC and Magnesium sterate was gift samples from S D. Fin chem Ltd, Mumbai, Talc is from Drugs India, Hyderabad. All the other chemicals used were of analytical reagent grade.

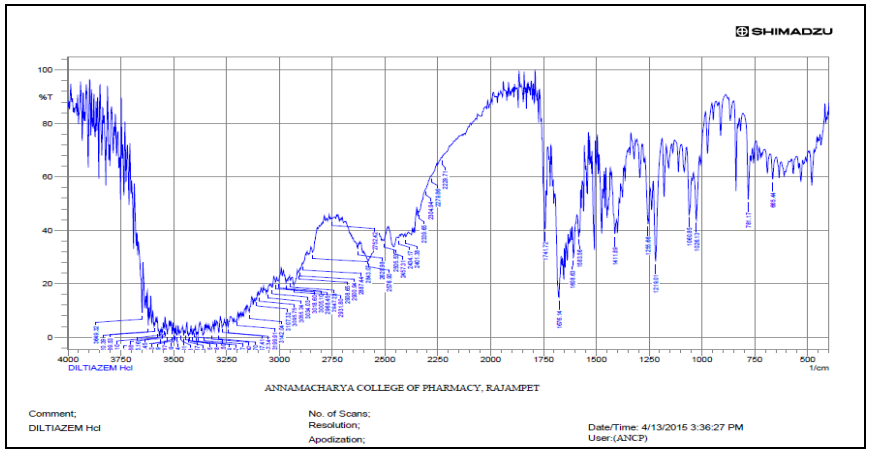

FIG.1: FTIR SPECTRAL STUDIES OF DILTIAZEM

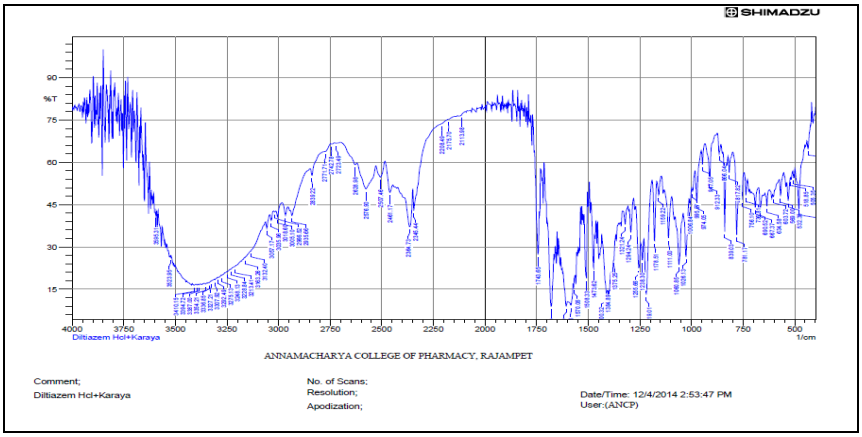

FIG.2: FTIR SPECTRAL STUDIES OF DILTIAZEM WITH GUM KARAYA

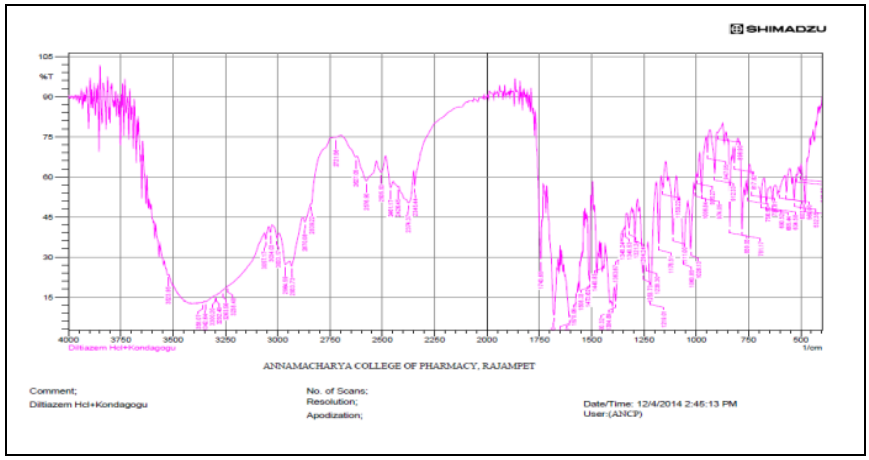

FIG.3: FTIR SPECTRAL STUDIES OF DILTIAZEM WITH GUM KONDAGOGU

Drug-excipient interaction studies:

Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers, binders and lubricants used in case tablet formulations. Positive interactions sometimes have a beneficial effect as far as desired release parameters are concerned. FTIR studies were shown in **Fig.1-3**.

Preparation of Diltiazem matrix tablets:

Sustained release Matrix tablets of Diltiazem hydrochloride were prepared using wet granulation method. [14-15] Required amounts of ingredients were weighed accurately such as Diltiazem Hydrochloride, gum karaya, gum kondagogu and MCC.

The weighed quantities were transferred into mortar and pestle, Triturated well with the addition of sufficient Quantity of ethanol as a solvent. The resulted granular mass was screened through the sieve number 16. The sieved granules dried in hot air oven for 10 min at 40^0c to 50^0c. Finally Talc and Magnesium sterate were added. Then the granules are undergoes compression using tablet compression machine. (**Table 1**)

TABLE 1: COMPOSION OF POLYMERS FOR DILTIAZEM HCL SR MATRIX TABLETS

S.no	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Diltiazem Hcl	90	90	90	90	90	90	90	90
2	Gum kondagogu	-	-	-	-	45	90	135	180
3	Gum karaya	45	90	135	180	-	-	-	-
4	Micro crystalline cellulose	208	163	118	73	208	163	118	73
5	Magnesium sterate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
6	Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
	Total weight (mg)	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

3. Evaluation of tablets:

All the batches were evaluated for weight uniformity, hardness, friability and drug content uniformity as per USP XXIV monograph (**Table 2**)

a. **Weight variation test:** To study weight variation twenty tablets of the formulation were weighed using an Essae electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

b. **Drug content:** Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 276 nm after suitable dilution using a UV- Vis double beam spectrophotometer Shimadzu 1800, Japan

c. **Hardness:** Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the Tablets

was determined using Pfizer hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

d. Thickness: The thickness of the tablets was determined by using Vernier calipers. Five tablets were used, and average values were calculated.

e. Friability: The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The % friability was then calculated by, % F =1-(loss in weight/ initial weight) 100 % Friability of tablets less than 1% are considered acceptable.

f. *In vitro* dissolution studies: The studies were done using the USP XXIII dissolution rate test apparatus (type II) fitted with six rotating paddle type (Model Electrolab, India). All the batches of tablets were evaluated (3 runs for each batch) using 900 ml of sequential gastrointestinal release medium, i.e. 0.1N hydrochloric acid (pH 1.2) for first two hrs and then pH 7.4 phosphate buffer for next 6 hr, maintained at 37 ± 0.5°C and stirred at 100 rpm. 5 ml of aliquots were withdrawn at different time intervals and an equivalent volume of medium (pre warmed at 37°C) was added to maintain constant volume. Withdrawn samples were analyzed spectrophotometrically at 237 nm using an Elico double beam UV-Visible Spectrophotometer. (**Table 3** and **Fig.4**)

Stability studies: The stability studies were done by storing the optimized formulation F4 tablets in Screw capped container in stability chamber for 3 months at 40^0C ± 2ºC and 75 ± 5% RH. The samples were withdrawn after 3 months and analyzed for drug release study and various physical tests.

TABLE 2: PHYSICOCHEMICAL PROPERTIES OF FORMULATION F1-F8

Formulation Code	Weight Variation (mg)	Thickness	Hardness	Friability	% Drug Content
F1	348±0.13	3.70±0.03	5.06±0.11	0.76±0.04	98.44±0.36
F2	349 ±0.18	3.64±0.31	5.04±0.07	0.69±0.02	99.74±0.51
F3	348±0.16	3.53±0.23	6.98±0.14	0.87±0.05	99.66±0.46
F4	351±0.21	3.62±0.08	5.00±0.16	0.74±0.01	99.86±0.65
F5	348±0.17	3.43±0.16	5.02±0.04	0.84±0.03	99.57±0.30
F6	349±0.32	3.46±0.12	6.03±0.12	0.89±0.04	98.45±0.55
F7	347±0.25	3.55±0.15	5.99±0.16	0.80±0.05	98.35±0.45
F8	348±0.15	3.72±0.10	6.09±0.15	*0.79±0.03*	99.85±0.25

TABLE 3: *IN-VITRO* DISSOLUTION DATA OF PREPARED DILTIAZEM SR MATRIX TABLETS FORMULATIONS

S.no	Time (h)	F1	F2	F3	F4	F5	F6	F7	F8
1	0	0	0	0	0	0	0	0	0
2	1	10.28±0.12	11.93±0.23	9.88±0.32	11.78±0.21	9.24±0.15	9.88±0.12	8.28±0.25	10.68±0.2
3	2	19.27±0.21	21.57±0.14	13.56±0.30	16.67±0.12	17.32±0.25	18.92±0.13	12.36±0.25	15.47±0.25
4	3	32.42±0.11	31.57±0.16	22.66±0.24	25.65±0.14	31.36±0.26	33.27±0.18	21.26±0.34	23.55±0.31
5	4	47.16±0.13	38.74±0.18	29.24±0.35	38.72±0.15	45.62±0.17	48.36±0.28	27.65±0.23	33.54±0.34
6	5	65.48±0.15	44.74±0.10	38.33±0.26	41.22±0.17	63.49±0.26	65.42±0.30	32.44±0. 25	37.13±0.16
7	6	83.54±0.23	58.86±0.15	48.61±0.28	49.55±0.25	82.41±0.16	77.14±0.35	40.56±0.32	43.52±0.12
8	7	96.27±0.24	70.27±0.17	59.28±0.31	55.42±0.23	95.61±0.19	83.42±0.32	55.58±0.19	55.51±0.19
9	8	-	83.48±0.13	65.24±0.23	69.37±0.24	-	90.17±0.27	67.49±0.27	62.68±0.20
10	9	-	97.12±016	72.77±0.12	81..15±0.25	-	96.21±0.20	76.56±0.20	77.68±0.22
11	10	-	-	88.82±0.15	87.34±0.24	-	-	86.54±0.23	84.29±0.15
12	11	-	-	98.62±0.16	95.33±0.27	-	-	97.44±0.27	91.14±0.23
13	12	-	-	-	**99.75±0.28**	-	-	-	98.12±0.25

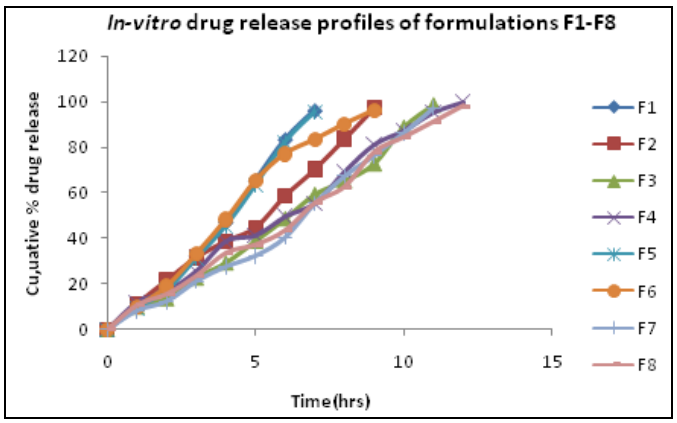

FIG. 4: *IN-VITRO* DISSOLUTION DATA OF PREPARED DILTIAZEM SR MATRIX TABLETS FORMULATIONS

RESULTS AND DISCUSSION: In the present study an attempt has been made to formulate matrix tablets of Diltiazem hydrochloride using gum karaya and gum kondagogu as matrix material. Over the last few years a large number of naturally obtained gums were evaluated as release retardants. The pre formulation study was performed on combination of drug with polymers by FTIR studies suggested that drug and polymers were compatable. The hardness of tablets was found to in the ranges of 5 to 6.98 kg/cm2. The average weight of tablets was found to be 350 mg for all batches and % deviation within specified limits (of 347±0.25 and 349 ±0.18). Overall the all prepared formulation was good quality with regard to drug content.

The percent of weight loss in friability test was found to be less than 1% (0.69 to 0.89%) indicate tablets can withstand the mechanical shock or during handling. Good uniformity in drug content was found among different batches of tablets and percentage of drug content was more than 99 %. Hence it complies with official specification. In formulation f4 the drug content was found to be 99.86% which indicate better drug content uniformity among all formulation *In-vitro* dissolution data of formulation (F1 to F8) reported in (**Fig.4**).

When matrices containing swellable polymers are exposed to dissolution medium, tablet surface becomes wet and hydrated to form a gel layer. The initial release of drug from these matrices occurs by the drug dissolution in the water penetrated into the matrix. The overall drug release from these matrices is governed by hydration, gel layer formation and drug diffusion into the gel layer and to the dissolution media Polymer erosion also plays a major role in releasing drug from these matrices. These considerations indicate that hydrophilic polymers have the potential to sustain the release of drug from matrix tablets. The release of drug is regarded as concentration of gum increases in all formulation. In order to investigate the effect of polymer type and percentage on drug release profile, different formulations containing various percentages of gum kondagogu and gum karaya with Diltiazem. The formulation (F1 to F8) containing Gum kondagogu and gum karaya were able to sustain the drug release up to 12 hrs with percentage drug release as (96.27%, 97.12%, 98.62%, 99.75%, 95.61%, 96.21%, 97.44%, 98.12%) respectively.

To investigate the mechanism of drug release the *In vitro* data were plotted as cumulative drug release verses square root of time as described by higuchi, for all matrix formulations were found to be linear, indicating the diffusion mechanism of drug release. The stability studies showed that there was no significant change in dissolution profile after 3 months for storage.

CONCLUSION: It was also concluded that the drug release was greatly influenced by the nature of the polymer incorporated in the formulations. Finally to achieve a sustained release formulation of diltiazem hydrochloride matrix tablets by using gum karaya and gum kondagogu matrix tablets were developed to be capable to provide prolonged release patterns over 12hrs. Formulation containing diltiazem hydrochloride with gum karaya shows best and maximum drug release of 99.75% up to 12hrs.

CONFLICT OF INTEREST: Authors declare no conflict of interest.

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