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FORMULATION AND CHARACTERIZATION OF DILTIAZEM HCL MATRIX TABLETS BY EMPLOYING ELECTROLYTES WITH GUM KONDAGOGU

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Keywords:

Diltiazem, electrolyte, Gum kondagogu, matrix, sustained release

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ABSTRACT: The objective of the present investigation is to prepare and evaluate the sustained release matrix tablets of Diltiazem HCl using a natural polymer Gum kondagogu. Diltiazem HCl was formulated as sustained release matrix tablet formulations with natural polymer by employing pharmaceutically acceptable electrolytes. Electrolytes such as Sodium carbonate, Magnesium carbonate and Calcium carbonate were used at specific concentration, in various formulations. Total twelve formulations (DG1-DG12) were prepared by using different proportions of drug and Gum kondagogu (1:0.5, 1:1, 1:1.5, 1:2) with the aid of granulating fluids such as distilled water, ethanol and isopropyl alcohol. From 12 formulations DG3, DG7 and DG11 were optimized based on results from physicochemical evaluation and drug release studies. These formulations have composition of 1:1.5 ratio of drug and Gum kondagogu & they have shown more than 95% drug release at 12 hours. Hence based on studies, formulation DG10 with drug and polymer with 1:1 ratio was selected for further studies by employing electrolytes in different concentrations. These electrolytes were employed to examine matrix swelling and gel properties. These were tested for release studies and to signify the influence of electrolytes type in sustaining the release of drug. Based on results the formulation DGE8 contains magnesium carbonate as electrolyte with 50 mg concentration was found to extend the drug release over extended period of time. The results signified that the drug released at a sustained rate, owing to differential swelling rate and matrix rigidity, and provides a uniform gel layer.

INTRODUCTION: Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages [1].

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Controlled release (CR) tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high potency drugs [2].

Controlled release products are designed to maintain constant therapeutic plasma concentration of the drug within the therapeutic range of the drug over prolonged periods [3]. Matrix is defined as a well mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers [4]. Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw

materials and dosage form and ease of scale-up and process validation [5].

Diltiazem hydrochloride is a widely used as a calcium channel blocking agent. It has a short biological half life of 3-4.5 hrs and it is rapidly eliminated from the body. Its effects last only for few hours and hence it needs to be administered 3 to 4 times a day. Diltiazem is completely absorbed in gastrointestinal tract but exhibits very low oral bioavailability due to extensive first pass metabolism in the liver by the enzyme CYP3A of cytochrome P450 enzyme group. Hence there is every need for formulating a sustained release dosage form for Diltiazem hydrochloride to improve its therapeutic efficacy and patient compliance [6-9].

The aim of the present investigation was to design and develop a novel oral monolithic, sustained release tablet dosage form of Diltiazem hydrochloride with Gum kondagogu as natural polymer along with pharmaceutically acceptable electrolytes which can induce in situ reactions between drug & electrolyte that alters drug release mechanism by matrix stiffening and changes in the gel would lead to extended drug release at a steady state manner has been elucidated.

MATERIALS AND METHODS:

Diltiazem HCl was obtained as a gift sample from Pellets Pharma Limited, Hyderabad. Gum kondagogu was purchased from Girijan co-operation society, Visakhapatnam. Avicel pH 102, Calcium carbonate, Sodium carbonate, Magnesium carbonate, Magnesium stearate, Talc and Isopropyl alcohol were procured from S.D Fine Chem. Ltd., Mumbai.

Preparation of Matrix Tablets:

Diltiazem HCl sustained release matrix tablets were prepared by wet granulation method [10, 11] using drug: polymer ratios 1:0.5, 1:1, 1:1.5, 1:2. Weighed drug, Gum kondagogu, Avicel pH 102 (Microcrystalline cellulose) & placed in motor then triturated well and then added distilled water, ethanol, isopropyl alcohol (granulating fluids) & prepared dough mass. Then dough mass was passed through sieve no. 14-16 for obtaining wet granules (wet screening). Then these wet granules were dried and they were passed through sieve no. 22 – 25 (dry screening). To dried granules added Magnesium stearate & Talc and mixed well. Tablets were prepared by using nine station tablet punching machine (Chamunda Pharma pvt Ltd, Ahmadabad), with use of punch sizes 8 mm for obtaining 350 mg of tablet weight.

Physical evaluation of tablets:

Tablet hardness was determined with a Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India). The individual hardness of 10 tablets randomly selected from each batch was measured and then mean and standard deviation taken. Whereas percentage friability of tablets was determined using a friabilator (Hoffmann-La Roche Ltd., Basel, Switzerland). The weight of ten tablets before and after the test, and the percent loss in weight recorded as friability [12, 13]. The drug content of the tablets was evaluated spectrophotometrically (Shimadzu, model 1700) at 237 nm.

Swelling Index:

The swelling behavior of a dosage form was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium distilled water at 37±0.5 ^{0}C. After 1, 2, 4, 6, 8 and 10 hours, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the formula.

$$\text{Swelling Index} = \frac{\text{Wet weight of tablet - Dry weight of tablet}}{\text{Dry weight of tablet}}$$

In vitro drug release studies:

In vitro drug release studies were carried out in distilled water for 12 hr using a USP XXII type 2 dissolution apparatus (Electrolab TDT-08L) at 100 rpm and 37 ± 0.5 °C. At predetermined interval, samples were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the amount of drug present in each sample was determined spectro photometrically at 237 nm.

Dissolution Parameters:
From the dissolution studies of various matrix tablets containing Diltiazem HCl the following *in-vitro* kinetics like Zero Order-Release Rate Constant, First Order-Release Rate Constant, Higuchi's Diffusion Constant, and Korsermeyer-Peppas Constant were evaluated.

Similarity factor:
The similarity factor *f*2 as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum square) difference of drug percent dissolved between the test and reference products. It is given by following equation:

$$f_2 = 50 \times \text{Log}\{[\sum_{n=1}^{\infty} Wt(Rt - Tt)^2]^{-0.5} \times 100\}$$

An *f*2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between release profiles increases. The similarity factor (S_d) is given as

$$S_d = \sum_{t=1}^{n=1} \frac{\left[Log\left(\frac{AUCR_{z_t}}{AUC_{T_t}}\right)\right]}{n-1}$$

For the test and reference formulations to be identical, the S_d value should be zero [14].

Characterization of Matrix Tablets:
Drug-excipients compatibility studies:
FT-IR studies:
By using dried KBr base line correction was taken. Weighed amount of the Diltiazem HCl was carefully mixed separately along with KBr (dried at 40°-50°C) after that entire mixture was compressed using 10 ton pressure in a hydraulic press to produce a pellet after that it was subjected for scanning from 4000–400cm^{-1} using FT-IR 410 PC spectrophotometer. In the same way the method was adopted for polymers and formulations. The obtained spectrum from FT-IR was compared with drug and polymer mixtures [15].

DSC studies:
The DSC thermal analysis of API, excipients and the mixtures of drug-polymers were studied in DSC analyzer model Universal V4.5A at a heating rate of 20^{0}C per min from 0 to 350^{0}C in a nitrogen environment. DSC is a thermal analytical method performed to examine the drug and excipient compatibility. In this together test and standard were warmed from 20-300^{0}C and same temperature maintained during observation. Individually API and excipients includes polymers were scanned[16].

SEM studies:
In scanning electron microscope as electrons are employed, a vacuum is maintained inside the microscope column to keep free of air molecules. Generally the column is maintained at a vacuum of about 10 torr. Now when a narrow beam of primary electrons are generated from the electron gun and hits the specimen surface then secondary electrons are emitted from the spot. The yield of the secondary electron depends on the angle between the direction of primary electrons and the specimen surface. A flat surface produces a minimum number of secondary electrons. If the beam is moved to another spot, there also the yields of secondary electrons would depend upon the topographical features of that region and maybe more or less than that of the first spot. Thus, continuous moving or scanning the electron beam over the specimen surface achieves a corresponding signal output. If the secondary electrons are also continuously collected and displayed on a cathode ray tube (CRT), an image appears which is comparable to the topographical detail of the specimen. The SEM study was carried out for matrix tablet to check the surface texture of the same. A smooth surface gives a uniform drug release whereas uneven or cracked surface gives an uncontrolled and non-uniform drug release.

Stability Studies:
Stability studies on the optimized matrix tablets (DGE8) were carried out as per ICH guidelines at 25^{0}C ±2^{0}C/60% ± 5% RH and 40^{0}C ±2^{0}C/75% ± 5% RH for 6 months by storing the samples in stability chamber. Further, the matrix tablets were evaluated for appearance, weight variation, hardness, drug content and for in vitro drug release profiles over a period of 6 months.

RESULTS & DISCUSSION:
The present work aimed to prepare and evaluate the sustained release matrix tablets of Diltiazem hydrochloride for extended period of time. The tablets were prepared by using Gum kondagogu

and pharmaceutically acceptable electrolytes by using wet granulation method [17]. Compositions of various formulations are given in **Table 1** and **2**. All prepared tablets with different electrolyte composition were within the weight range of 350 mg. Hardness of the matrix tablet formulations were constant for all batches maintained at 5 – 8 kg/cm^2. Friability loss for the formulations was negligible and was within the limits for all the batches. Drug content was uniform in all the batches of matrix tablet formulations. All the matrix tablets were prepared under identical conditions and were found to be stable. The results of physical parameters evaluated for various matrix tablets were given in **Table 3.**

TABLE 1: COMPOSITION OF DILTIAZEM HYDROCHLORIDE MATRIX TABLETS.

	DG1	DG2	DG3	DG 4	DG5	DG 6	DG 7	DG 8	DG9	DG10	DG 11	DG 12
Diltiazem HCl	90	90	90	90	90	90	90	90	90	90	90	90
Gum kondagogu	45	90	135	180	45	90	135	180	45	90	135	180
Avicel pH 102	208	163	118	73	208	163	118	73	208	163	118	73
Mg stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Water	q.s	q.s	q.s	q.s	--	--	--	--	--	--	--	--
ethanol	--	--	--	--	q.s	q.s	q.s	q.s	--	--	--	--
IPA	--	--	--	--	--	--	--	--	q.s	q.s	q.s	q.s
Total wt(mg)	350	350	350	350	350	350	350	350	350	350	350	350

TABLE 2: COMPOSITION OF DILTIAZEM HYDROCHLORIDE MATRIX TABLETS WITH ELECTROLYTES.

	DG E1	DG E2	DG E3	DG E4	DG E5	DG E6	DG E7	DG E8	DG E9
Diltiazem HCl	90	90	90	90	90	90	90	90	90
Gum kondagogu	90	90	90	90	90	90	90	90	90
Sodium carbonate	25	50	75	--	--	--	--	--	--
Calcium carbonate	--	--	--	25	50	75	--	--	--
Mg. carbonate	--	--	--	--	--	--	25	50	75
Avicel pH 102	138	113	88	138	113	88	138	113	88
Mg. stearaate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
IPA	qs	qs	qs	qs	qs	qs	qs	qs	q.s
Total Wt. (mg)	350	350	350	350	350	350	350	350	350

TABLE 3: PHYSICAL EVALUATION PARAMETERS OF DILTIAZEM HCL MATRIX TABLETS WITH ELECTROLYTES.

Formulation code	Weight variation (%)	Friability (%)	Hardness (Kg/cm^2)	Drug content (mg)
DGE1	1.25± 0.14	0.36± 0.041	5.1± 0.11	98.75± 0.32
DGE2	1.43± 0.15	0.64± 0.016	5.3± 0.22	99.99± 0.24
DGE3	1.34± 0.15	0.53± 0.013	5.3± 0.21	98.12± 0.21
DGE4	1.58± 0.21	0.97± 0.043	5.5± 0.21	98.76± 0.23
DGE5	1.46± 0.14	0.65± 0.018	5.1± 0.20	99.81± 0.23
DGE6	1.45± 0.04	0.38± 0.012	5.3± 0.26	98.69± 0.17
DGE7	1.52± 0.12	0.61± 0.043	5.6± 0.31	96.14± 0.13
DGE8	1.48± 0.14	0.56± 0.044	6.0± 0.20	99.95± 0.92
DGE9	1.39± 0.04	0.44± 0.011	5.3± 0.15	99.82± 0.20

The physicochemical compatibility between drug and polymers was determined by FT-IR analysis. In spectra, additional peaks were observed due to polymers, apart from that, the spectra indicating no chemical interaction in Diltiazem HCl and polymer mixtures. FT-IR spectrums of pure drug, combination of drug with excipients and excipients spectra's were attained; the spectras were shown in **Fig.1** and **2**. In DSC analysis the Tg value of complexes (117.14 ^{0}C) were similar that of the Tg value of Diltiazem HCl and confirming that there was no significant interaction between the drug and polymers. The DSC thermo grams of pure drug and mixture of drug and polymers were shown in the **Fig. 3** and **4**. In SEM images, it showed intact surface only swells without any perforations, channels, or troughs. After dissolution, the solvent front enters the matrix and moves slowly toward the center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium.

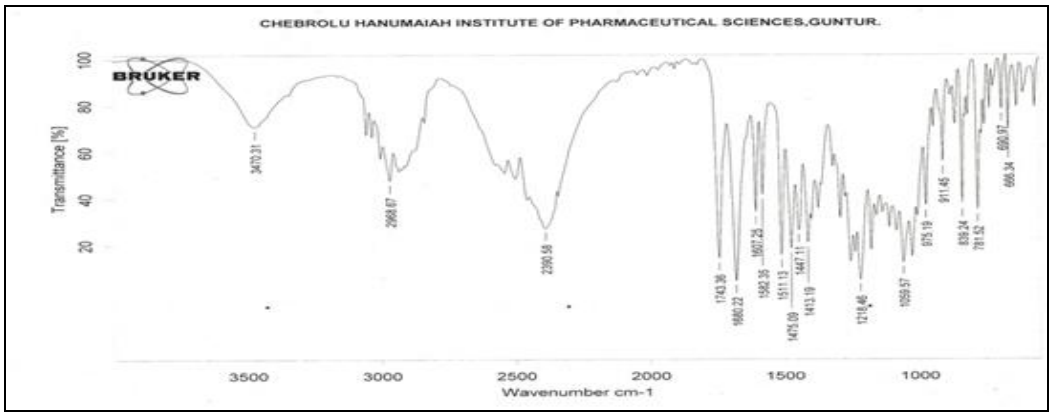

FIG. 1: FT-IR INTERPRETATION IMAGE OF DILTIAZEM HYDROCHLORIDE PURE DRUG

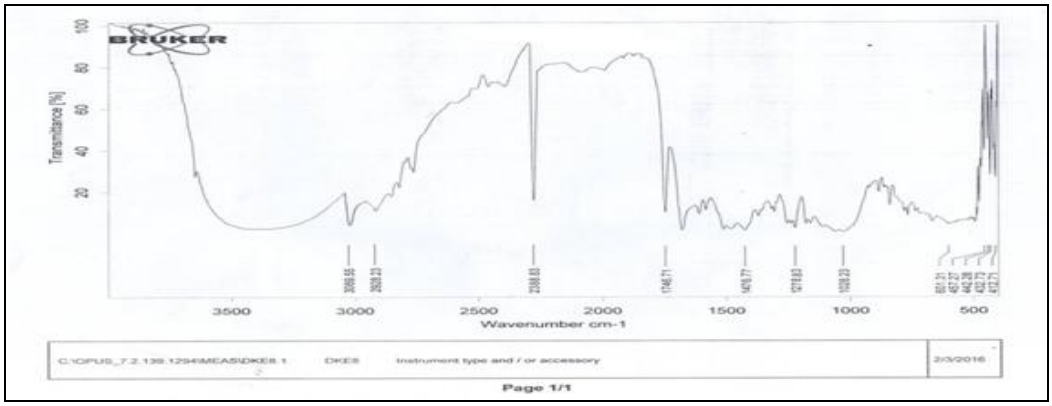

FIG. 2: FT-IR INTERPRETATION IMAGE OF DILTIAZEM HYDROCHLORIDE OPTIMIZED FORMULATION DG3.

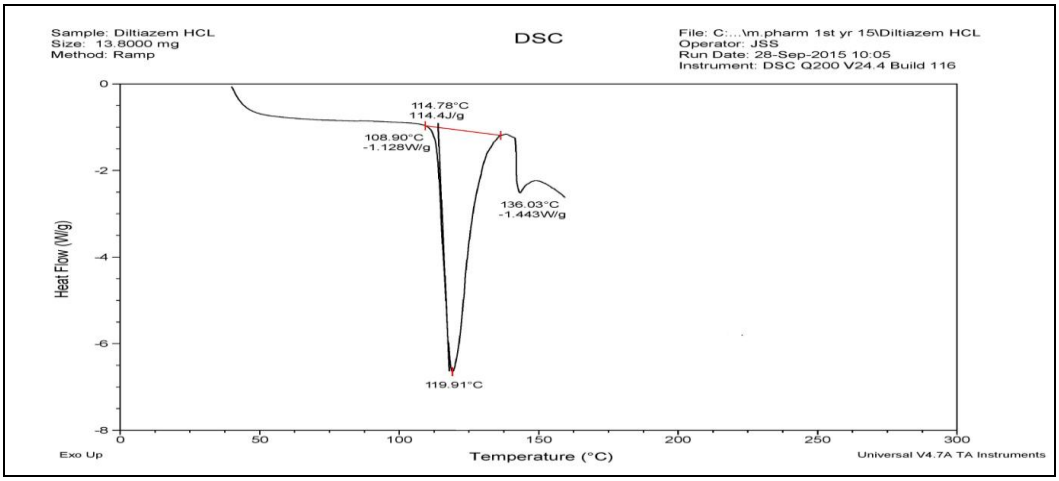

FIG. 3: DSC IMAGE OF DILTIAZEM HYDROCHLORIDE PURE DRUG.

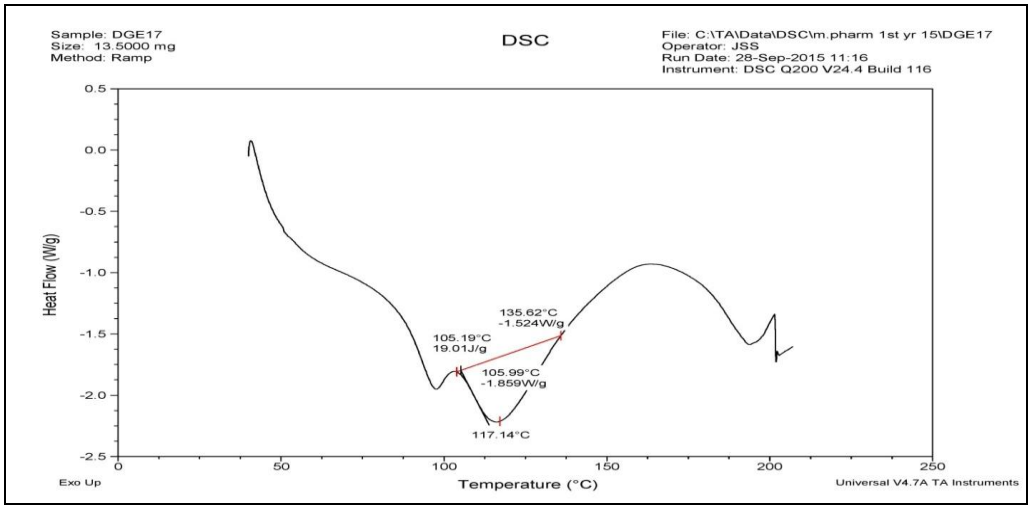

FIG. 4: DSC IMAGE OF DILTIAZEM HYDROCHLORIDE OPTIMIZED FORMULATION DGE8.

The images of the tablet showed a network in the swollen polymer through which the drug diffused to the surrounding medium. Thus, it was concluded that the drug was released from matrix by diffusion mechanism. During in-vitro dissolution study, the polymer swells as the dissolution media enter into the polymer matrix. The surface becomes smooth and uniform which results in a slower and controlled drug release. SEM study of matrix tablets further confirmed both diffusion and erosion mechanisms. SEM images were shown in **Fig. 5** and **6**.

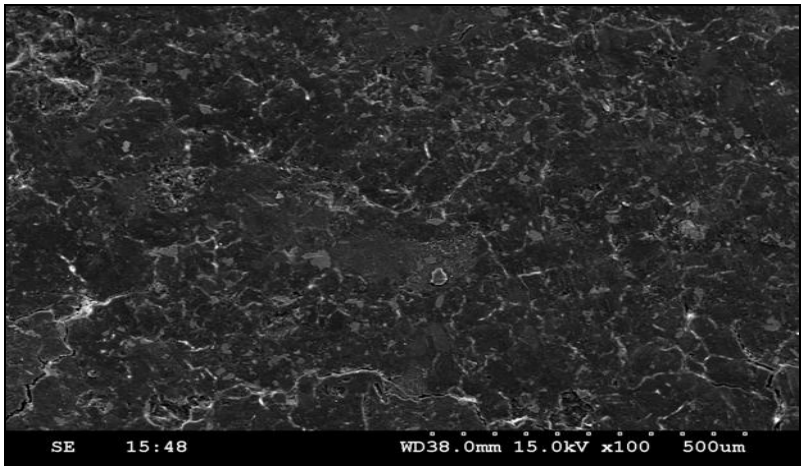

FIG. 5: SEM IMAGE OF DILTIAZEM HYDROCHLORIDE OPTIMIZED FORMULATION DGE8 100X BMP BEFORE DISSOLUTION.

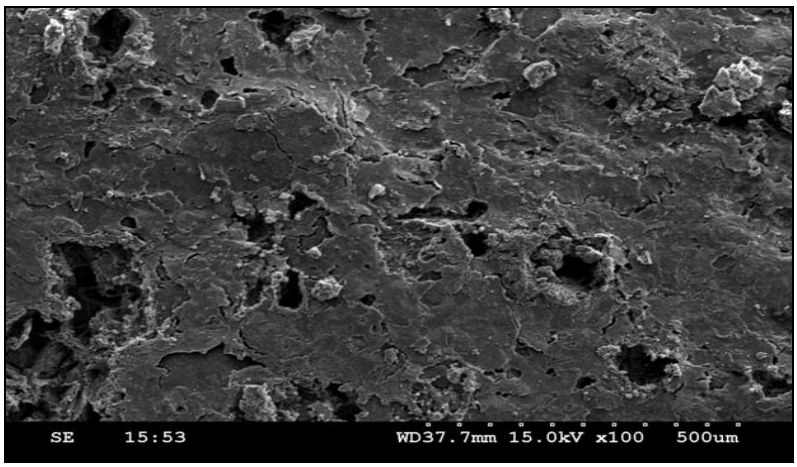

FIG. 6: SEM IMAGE OF DILTIAZEM HYDROCHLORIDE OPTIMIZED FORMULATION DGE8 100X BMP AFTER DISSOLUTION.

The swelling studies on some optimized matrix tablet formulations showed that, the rate of swelling of matrix tablets containing Magnesium carbonate as electrolyte was higher than that of matrix tablets containing Sodium carbonate and calcium carbonate as electrolytes [18]. Initial swelling rate was little low in all three formulations DGE2, DGE5 and DGE8 when compared to formulations DG3 and DG7 and DG11 (matrix tablets without electrolytes) for the first 2-4 hrs and later the rate of swelling was gradually increased due to competition in uptake of media by the drug and electrolytes. The swelling index values for selected formulations were given in **Table 4**.

TABLE 4: SWELLING CHARACTERISTICS OF VARIOUS MATRIX TABLETS WITH ELECTROLYTES FORMULATIONS.

Time	Percentage Swelling Index								
(hrs)	DGE1	DGE2	DGE3	DGE4	DGE5	DGE6	DGE7	DGE8	DGE9
1	52.46	50.59	67.92	55.62	54.59	48.55	60.44	57.64	61.75
2	72.15	71.39	88.79	81.42	75.98	71.39	82.71	81.42	84.79
4	103.64	98.49	121.03	113.36	106.69	98.49	115.08	113.36	113.67
6	121.37	115.69	141.74	128.49	121.39	115.69	131.94	128.49	130.89
8	144.63	138.94	160.14	154.26	145.67	138.94	156.46	154.26	152.79
10	152.34	149.89	174.25	158.56	155.98	148.89	164.29	159.99	164.46

The percentage drug content for different tablets formulations were varied from 96.14% to 99.99% indicating the uniformity in drug content. It was also observed that increase in the concentration of gum, the drug release was extended. This is due the hydrophilic nature of the gum. These tablets showed greater water uptake which resulted in the formation of highly viscous gel layer around the tablet [19]. The formed gel layer resulted in the longer diffusional path length, there by retarding the drug diffusion. The critical value of 'n' calculated for these formulations indicated non-fickian diffusion i.e., the drug release is by diffusion from the hydrated matrix and by polymer erosion.

The dissolution studies of all the prepared matrix tablet formulations were carried out in distilled water as medium. From the dissolution studies it was observed that as the proportion of the polymer was increased, the release of drug was decreased to certain extent. Good linear relationship was observed between polymer concentration and drug release to certain extent. The electrolyte employed has significant influence on drug release of Diltiazem HCl from the matrix tablet composed of natural polymer. The electrolytes employed in the study are Calcium carbonate, Magnesium carbonate, and Sodium carbonate. The rate of release from these matrix tablets prepared with different electrolytes in each case was found to be first order and controlled by both diffusion and dissolution mechanisms. The influence of each and individual electrolyte on drug release were given below;

Electrolytes has high influence on drug release from the matrix tablets of Diltiazem HCl. Good linear relationship was observed between all electrolytes concentration and drug release from the matrix tablets. The drug release was slow and extended for prolonged period as the concentration of electrolyte was increased. Electrolytes at higher concentration (75mg/tablet) exhibited greater inhibition in drug release from matrix & at lower concentration (50mg/tablet) showed controlled release of the drug. The concentration of electrolyte at 50 mg per tablet concentration was found to produce ideal drug release from the matrix tablets. The influence of retardation of drug release by various electrolytes was in the order of Sodium carbonate > Calcium carbonate > Magnesium carbonate.

The inclusion of electrolytes within a swollen matrix for controlling the release rate of Diltiazem may lead to the formation of free base of Diltiazem and fundamental structural changes in gel boundary, thus inducing the textural variations in the swollen matrix. It appears that electrolyte induced buffer threshold within the matrix place an essential role in effective interaction with drug and textural changes. An inverse relationship was observed between concentration of polymer and release rate of Diltiazem from the matrix tablets [20]. Upon model fitting analysis of matrix tablets, it was found that the release of Diltiazem from matrix tablet follow zero order kinetics with anomalous diffusion. Peppa's model with 'n' values and the correlation coefficient 'r' values were shown in

Table 5. The drug release profile from the developed formulations manufactured in this study was compared to the marketed product and results were shown in **Table 6.** It was found that the *in-vitro* dissolution profile of drug from test product containing natural polymer is almost similar with that of the marketed product. The results of this study indicated that the release of drug from the marketed as well as test product followed Zero order of release kinetics via anomalous (non-fickian) diffusion.

The similarity and the dissimilarity factors depict that the drug release from the prepared batches were significantly different from the release of drug from the marketed tablet. The significance of using similarity factor was to compare the solubility and release profile of the prepared tablets with that of the marketed tablets. The f2 value was found to vary from 13 to 57. The f1 value ranged from 13 to 88. **Table 7** represents the similarity and the dissimilarity factors for the various batches. The similarity and the dissimilarity factors indicate that the sustained release formulations are quite different from the marketed tablet, and more sustained than the marketed tablet. It may thus be concluded that the sustained release formulation can be achieved using hydrophilic polymers, which can also maintain the sustained release profile over an extended period of time.

TABLE 5: RELEASE KINETICS OF VARIOUS MATRIX TABLETS WITH ELECTROLYTES FORMULATIONS.

Formulation code	Zero order		First order		Higuchi's		Koresmayer & Peppas	
	K	R^2	K (hr^{-1})	R^2	K ($m.g.h^{1/2}$)	R^2	N	R^2
DGE1	5.14	0.843	0.231	0.936	11.34	0.946	0.425	0.945
DGE2	6.25	0.736	0.134	0.934	12.64	0.975	0.565	0.965
DGE3	5.35	0.975	0.237	0.967	14.36	0.935	0.426	0.975
DGE4	5.26	0.825	0.178	0.935	12.76	0.975	0.535	0.965
DGE5	6.35	0.935	0.136	0.978	11.78	0.936	0.465	0.925
DGE6	5.26	0.876	0.215	0.946	11.13	0.975	0.553	0.965
DGE7	5.85	0.7945	0.146	0.934	8.16	0.925	0.415	0.932
DGE8	5.37	0.986	0.266	0.986	9.97	0.975	0.534	0.915
DGE9	4.73	0.845	0.135	0.846	16.78	0.915	0.542	0.940

TABLE 6: DISSOLUTION DATA FOR OPTIMIZED AND MARKETED FORMULATIONS.

Time (hours)	Optimized Formulation	Marketed Formulation
0	0	0
1	7.65	14.29
2	15.28	20.45
3	22.45	28.56
4	29.89	38.79
5	37.47	45.94
6	45.65	54.82
7	55.39	60.82
8	62.39	66.98
9	70.15	73.08
10	81.28	80.49
11	92.39	88.79
12	97.85	95.79

TABLE 7: SIMILARITY FACTOR FOR OPTIMIZED MATRIX TABLET WITH ELECTROLYTE FORMULATION (DGE8) IN COMPARISON WITH MARKETED FORMULATION.

Similarity factor f2	52
Difference factor f1	16

The stability studies on optimized formulations (DGE8) were carried out for 6 months as per ICH guidelines. No significant changes in the physicochemical properties viz., weight of the tablet, hardness, friability and drug content of Diltiazem HCl matrix tablets were observed. The result of stability tests suggested that Diltiazem HCl release properties from the prepared tablets were stable under the above storage conditions and no significant changes in their physical attribute was observed.

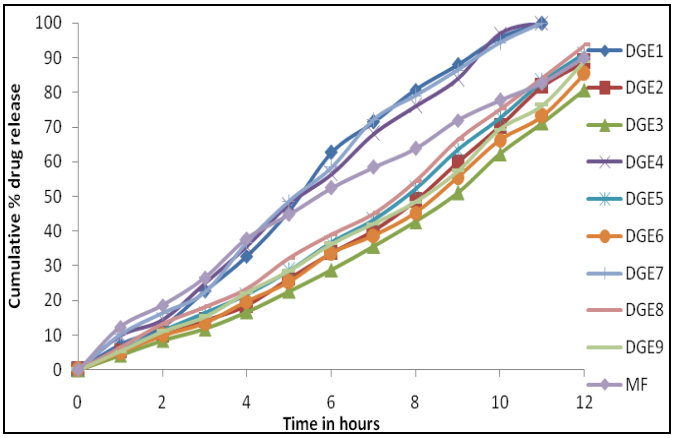

FIG. 7: DRUG RELEASE PROFILES OF VARIOUS SUSTAINED RELEASE FORMULATIONS OF DILTIAZEM HYDROCHLORIDE WITH ELECTROLYTES IN COMPARISON WITH MARKETED FORMULATION.

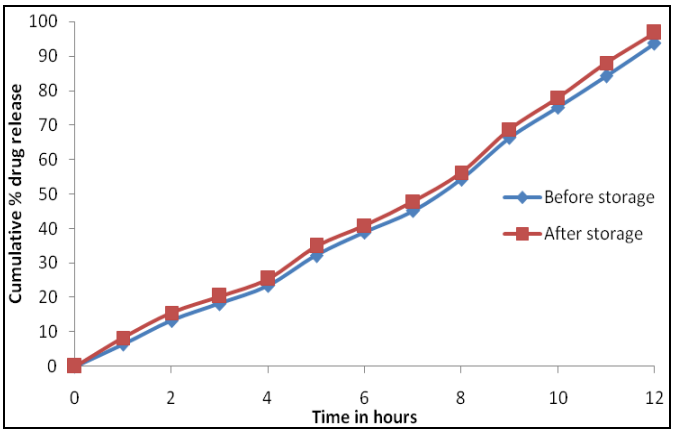

FIG. 8: STABILITY PROFILE OF OPTIMIZED FORMULATION (DGE8) BEFORE AND AFTER STORAGE.

CONCLUSION: Diltiazem HCl sustained release matrix tablets were successfully formulated using the combinations of natural gum such as Gum kondagogu with electrolytes for delivery of drug over an extended period of time. Previous studies have shown that natural gums like xanthan gum, guar gum, karaya gum and sodium alginate alone in the tablets cannot efficiently control the drug release for prolonged period of time. This study demonstrates that the combination of hydrophilic natural gum and electrolytes with optimum concentrations led to prolonged release of the drug up to 12 hrs. An important feature of this system is the potential for generating constant drug release.

The physical parameters were satisfactory and obtained within IP specified limits. The FT-IR studies revealed the absence of drug-polymer interaction. The optimized formulation DGE8 was able to control the drug release up to 12 hours. The formulated sustained release tablets can decrease, the frequency of drug administration and it can decrease the plasma drug fluctuation and it can improve the patient compliance. In this study it was also found that the concentration of polymer have also a tremendous effect on drug release rates, by increasing the amount of polymer, drug release rate can be reduced to a high value. The tablets showed good stability and physicochemical characteristics.

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