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Preparation and Evaluation of Diltiazem Hydrochloride Controlled Release Matrix Tablets Employing *Aegle marmelos* Gum: A Novel Natural Controlled Release Polymer

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ABSTRACT

Oral Drug Delivery is considered as the holy grail of drug delivery due to its convenience which resulted in high patient compliance. Of all the drug delivery systems that have been explored, oral drug delivery is the most preferred option for systemic delivery of drug via various pharmaceutical products of different dosage forms. The advantage of administering a single dose of drug which is released over an extended period of time, instead of administering numerous doses, is now a day's area of interest for formulation scientists in the pharmaceutical industry. For this reason, the conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst these, the controlled release dosage forms have gradually gained medical acceptance and became extremely popular in modern therapeutics. The aim of the present work is to isolate *Aegle marmelos* gum and use it as a controlled release polymer in the formulation of diltiazem hydrochloride controlled release tablets.

Keywords: Isolation, Controlled release, *Aegle marmelos* Gum.

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INTRODUCTION

Several approaches are currently used to retain the dosage form in the gastro-intestinal tract. The principle of the controlled release tablets is simple and practically approached to obtain prolonged release of drug. Controlled release tablets design needs a strong release retarding polymer. *Aegle marmelos* gum, a novel naturally isolated polymer was tried as 'release retarding' polymer in the design of controlled release tablets.

MATERIALS AND METHODS

Materials

1) Diltiazem Hydrochloride (Yarrow Chemicals, Mumbai)
2) *Aegle marmelos* gum (Isolated in the Laboratory)
3) Lactose (Yarrow Chemicals, Mumbai)
4) Talc (Molychem, Mumbai)
5) Magnesium stearate (Molychem, Mumbai)

Isolation of Gum from *Aegle Marmelos* Fruits:

The edible pulp of *Aegle marmelos* fruit was collected and soaked in double distilled water. After soaking, it was boiled for 5 hours in a water bath until slurry was formed. Thus formed slurry was cooled and refrigerated over-night so that most of the undissolved portion was settled out. The upper clear solution was decanted off and centrifuged at 500 rpm for 20 minutes. The supernatant was allowed to concentrate at 60° C on a water bath until the volume reduced to one-third of its original volume. Solution was cooled to room temperature and was poured into acetone (three times the volume of slurry) with continuous stirring to form precipitate. Thus formed precipitate was separated, washed repeatedly with acetone and dried under vacuum at 50°C in an oven. The completely dried gum was powdered and was passed through sieve #100, packed in a tightly closed container and stored in a dessicator for further usages.

Methods

Preparation of Diltiazem Hydrochloride Controlled Release Matrix Tablets Employing

Aegle marmelos Gum

Oral controlled release matrix tablets each containing 90mg of Diltiazem hydrochloride were prepared by wet granulation method using different drug: gum ratios viz. 1:0.25, 1:0.5, 1:1 and 1:1.25 for various formulations containing *Aegle marmelos* gum. The composition of different formulations of Diltiazem Controlled Release tablets is shown in Table 2. All the ingredients of the formulation were accurately weighed and the coherent mass was formed using distilled water as granulating fluid. The coherent mass was passed through mesh No. 12 and the granules obtained were air dried. The lubricants talc (2%) and magnesium stearate (2%) were passed through mesh No. 60 onto the dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on an 8 – station tablet punching machine (Shakthi Pharmatech Pvt Ltd., Ahmedabad) to a hardness of 5 – 6 kg/sqcm. The compressed tablets were stored in a closed container.

Evaluation of Diltiazem Hydrochloride Controlled Release Tablets

The prepared formulations were evaluated for the following parameters:

1. Pre-compression Evaluation

i. Angle of Repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed (10gms) granules were taken in the funnel. The granules were allowed to flow freely through the funnel on to the surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation:

$$\theta = \tan^{-1}\frac{h}{r} \quad \text{(or)} \quad \tan\theta = \frac{h}{r}$$

Where, θ = angle of repose,

h = height of the cone, and

r = radius of the cone base [1]

ii. Bulk Density:

Bulk density (D_b) was determined by measuring the volume (V_b) of known weighed quantity (W) of granules using bulk density apparatus and can be calculated by using the formula:

$$\text{Bulk density } (D_b) = \frac{\text{Bulk volume of powder } (V_b)}{\text{Mass of powder } (W)}$$

iii. Tapped Density:

Tapped density (D_t) was determined by measuring the volume (V_t) of known weighed quantity (W) of granules after desired mechanical tapping using tapped density tester and can be calculated by using the formula:

$$\text{Tapped density } (D_t) = \frac{\text{Mass of powder } (W)}{\text{Tapped volume of powder } (V_t)}$$

iv. Hausner's Ratio:

The Hausner's ratio was obtained by dividing the tapped density by the bulk density of the granules.

$$\text{Hausner's ratio} = \frac{\text{Tapped density of powder } (D_t)}{\text{Bulk density of powder } (D_b)}$$

v. Carr's Index:

The Carr's index (% compressibility) of the granules was calculated from the difference between the tapped and bulk densities divided by the tapped density and the ratio is expressed as a percentage [1].

$$\text{Carr's index (\%)} = \frac{\text{Tapped density } (D_t) - \text{Poured density } (D_b)}{\text{Tapped density } (D_t)} \times 100$$

The results of Pre-compression Evaluation are tabulated in table in Table 3.

2. Post-compression Evaluation

i. Tablet Thickness:

The thickness of the tablets was determined by using vernier caliper. Five tablets were used, and average values were calculated [2].

ii. Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined [2].

iii. Weight Variation:

To study weight variation twenty tablets of the formulation were weighed using a digital balance and the test was performed according to the official method. The specification for weight variation of tablets as per USP. Twenty tablets were selected randomly and weighed individually to check for weight variation [2].

iv. 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 25 rpm for 4 minutes. The tablets were weighed again. The % friability was then calculated by:

$$\%\ \text{Friability} = \frac{\text{Initial weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

% Friability of tablets less than 1% are considered acceptable [2].

v. Content Uniformity:

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in methanol and then the methanolic extract was filtered and collected into 100 ml volumetric flasks. The solution was then made up to volume with methanol. After suitable dilution, the drug content was then determined by measuring the absorbance at 240 nm using Elico SL210 UV-Visible double beam spectrophotometer. The drug content was estimated from the standard curve of

Diltiazem hydrochloride. Four samples of tablet powder were analyzed in each case [2].

vi. Disintegration Time:

Disintegration time test was carried out according to USP specification. 6 tablets were placed in a disintegration tester filled with distilled water at 37±0.20C. The tablets were considered completely disintegrated when all the particles passed through the wire mesh. Disintegration times recorded are mean of two determinations [2].

vii. *In-vitro* Dissolution Studies

Release of Diltiazem hydrochloride from the matrix tablets was studied using an eight basket USP dissolution apparatus taking 900 mL of 0.1 N HCl (pH 1.2) solution for first 2 hrs and phosphate buffer (pH 7.2) for next 22 hrs. The dissolution media were maintained at a temperature of 37°± 0.5°C. The speed of rotation of basket was maintained at 50 rpm. Aliquot equal to 5 ml sample was withdrawn at specific time intervals and the dissolution media volume was complimented with fresh and equal volume of phosphate buffer. The samples were filtered and suitably scanned with appropriate dilution and amount of Diltiazem hydrochloride released from the tablet samples was determined spectrophotometrically at a wavelength of 240 nm by comparing with the standard calibration curve [2].

viii. Kinetic Modelling of Drug Release

The dissolution profiles of all the batches was fitted to various models like zero-order, first order, Korsmeyer and Peppas, and Higuchi models to ascertain the kinetic modeling of drug release.

1. Zero Order Kinetics:

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_0 - Q_t = K_0 t \quad — \quad (1)$$

Rearrangement of equation (1) yields:

$$Q_t = Q_0 + K_0 t \quad — \quad (2)$$

Where Q_t is the amount of drug dissolved in time *t*, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released *versus* time.

2. First Order Kinetics:

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis . The release of the drug which followed first order kinetics can be expressed by the equation:

$$\frac{dx}{dt} = -Kc \quad — \quad (3)$$

Where *K* is first order rate constant expressed in units of time^{-1}.

Equation (3) can be expressed as:

$$\text{Log } C = \log C_0 - K_t / 2.303 \quad — \quad (4)$$

Where C_0 is the initial concentration of drug, k is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining *vs*. time which would yield a straight line with a slope of -K/2.303.

3. Higuchi Model:

This model is based on the hypotheses that —

(i) Initial drug concentration in the matrix is much higher than drug solubility.

(ii) Drug diffusion takes place only in one dimension (edge effect must be negligible).

(iii) Drug particles are much smaller than system thickness.

(iv) Matrix swelling and dissolution are negligible.

(v) Drug diffusivity is constant and

(vi) Perfect sink conditions are always attained in the release environment.

Accordingly, model expression is given by the equation:

$$f_t = Q = A\sqrt{D(2C - C_s)\,C_s\,t} \quad — \quad (5)$$

Where Q is the amount of drug released in time t per unit area A,

C is the drug initial concentration,

Cs is the drug solubility in the matrix media and

D is the diffusivity of the drug molecules (diffusion coefficient) in the matrix substance.

The data obtained were plotted as cumulative percentage drug release versus square root of time [3].

4. Korsmeyer-Peppas Model:

To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model

Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system equation:

$$M_t / M_\infty = Kt^n \quad — \quad (6)$$

Where M_t/M_∞ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices.

Table 1: Interpretation of diffusional release mechanisms from polymeric systems

Release Exponent (n)	Drug Transport Mechanism	Rate as a Function of time
0.5	Fickian Diffusion	$t^{-0.5}$
0.45 < n < 0.89	Non-Fickian Diffusion	t^{n-1}
0.89	Case II Transport	Zero order release
Higher than 0.89	Super Case II Transport	t^{n-1}

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release *versus* log time [4,5].

Table 2: Formulae of Diltiazem Hydrochloride Controlled Release Tablets Prepared Employing Aegle marmelos Gum

Ingredients (mg)	F1	F2	F3	F4	F5
Diltiazem hydrochloride	90	90	90	90	90
Aegle marmelos gum	22.5	45	67.5	90	112.5
Lactose	175.5	153	130.5	108	85.5
Talc	6	6	6	6	6
Magnesium stearate	6	6	6	6	6
Total Weight of Tablet (mg)	300	300	300	300	300

Table 3: Characteristics of Diltiazem Hydrochloride Granules Prepared with Different Concentrations of *Aegle marmelos gum*

Formulation	Bulk Density (g/cc)	Tapped Density (g/cc)	Angle of Repose (°)	Carr's Index (%)	Hausner's Ratio
F1	0.357 ± 0.020	0.400 ± 0.143	20.44 ± 0.210	10.75 ± 0.03	1.120 ± 0.06
F2	0.370 ± 0.121	0.434 ± 0.129	24.91 ± 0.036	14.70 ± 0.19	1.172 ± 0.123
F3	0.384 ± 0.062	0.454 ± 0.017	27.19 ± 0.261	15.40 ± 0.05	1.183 ± 0.151
F4	0.416 ± 0.085	0.476 ± 0.065	26.56 ± 0.091	12.66 ± 0.15	1.144 ± 0.103
F5	0.396 ± 0.062	0.466 ± 0.089	22.32 ± 0.191	15.96 ± 0.12	1.156 ± 0.050

Table 4: Physical Properties: Thickness, Hardness, Friability, Weight Variation, Drug Content of Diltiazem Hydrochloride Controlled Release Tablets Prepared Employing *Aegle marmelos* Gum

Formulation	Thickness (mm)	Hardness (Kg/cm²) ± S.D	Friability (%) ± S.D	Weight Variation (mg)	Drug Content (mg/tab)±S.D
F1	4.65 ± 0.21	5.2 ± 0.86	0.24 ± 0.02	299.45 ± 0.26	88.45 ± 0.36
F2	4.82 ± 0.10	5.2 ± 0.58	0.23 ± 0.04	299.61 ± 0.11	88.56 ± 0.25
F3	4.74 ± 0.35	5.2 ± 0.64	0.23 ± 0.02	299.17 ± 0.02	89.23 ± 0.11
F4	4.88 ± 0.26	5.3 ± 0.75	0.2 ± 0.03	300.06 ± 0.19	90.0 ± 0.16
F5	4.91 ± 0.30	5.4 ± 0.62	0.19 ± 0.05	300.02 ± 0.06	89.97 ± 0.32

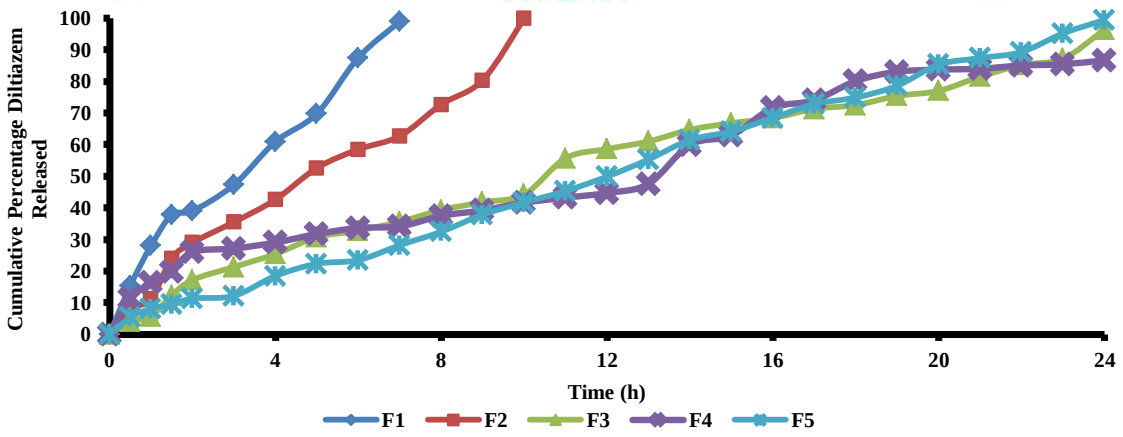

Fig 1: Release Profiles of Diltiazem HCl Controlled Release Tablets Prepared Employing *Aegle marmelos* Gum

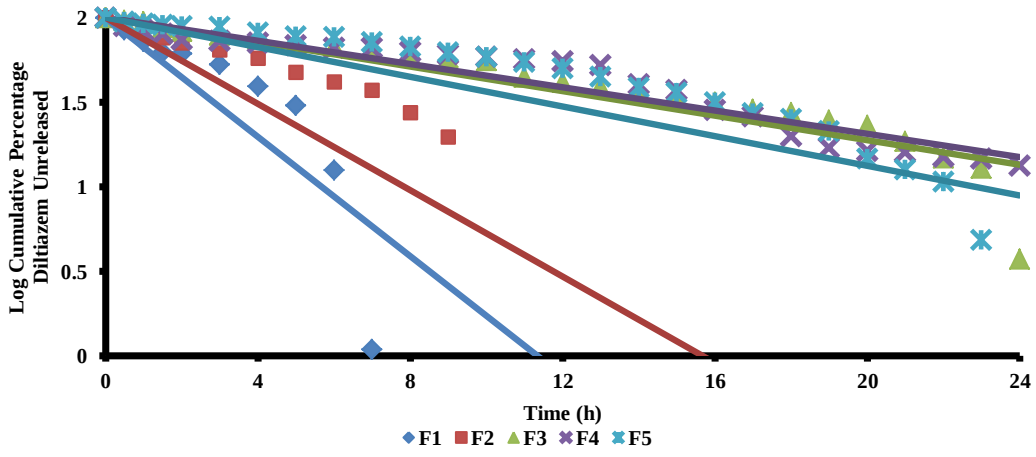

Fig 2: Time Vs Log Cumulative Percent Drug Remaining Plots of Diltiazem HCl Controlled Release Tablets Prepared Employing *Aegle marmelos* Gum

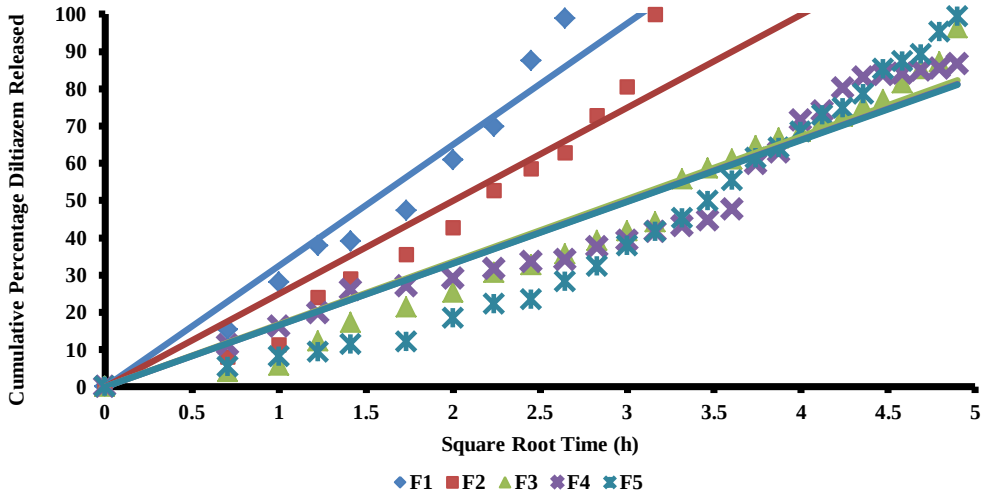

Fig 3: Square Root Time Vs Cumulative Percent Drug Released Plots of Diltiazem HCl Controlled Release Tablets Prepared Employing *Aegle marmelos* Gum

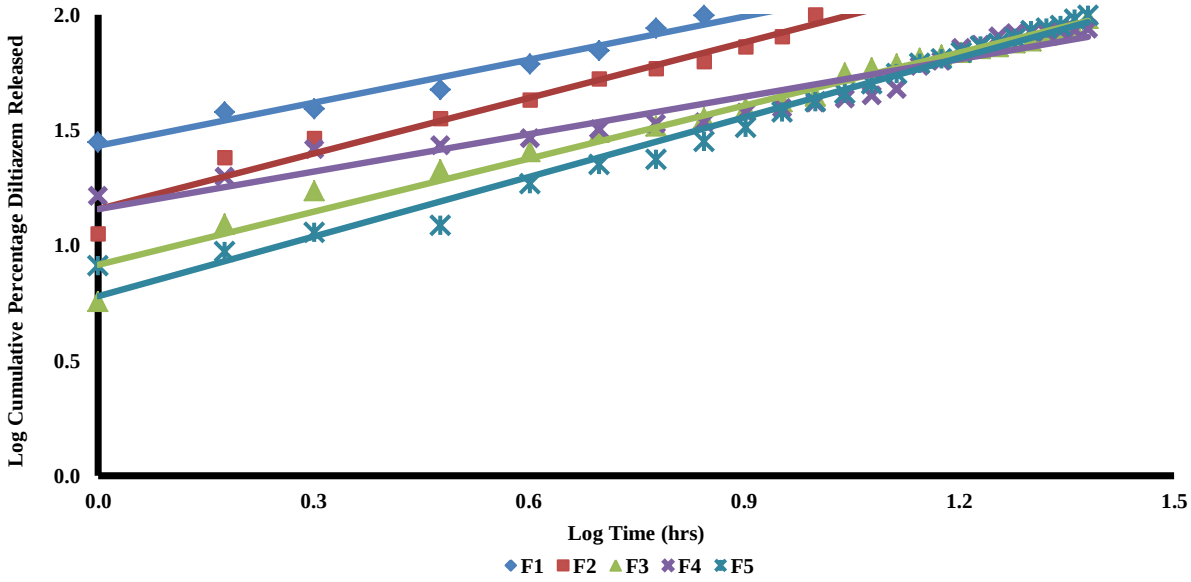

Fig 4: Log Time Vs Log Cumulative Percent Drug Released Plots of Diltiazem HCl Controlled Release Tablets Prepared Employing *Aegle marmelos* Gum

Table 5: Correlation Coefficient (R^2) Values in the Analysis of Release Data as per Zero order, First order, Higuchi and Peppas Equation Models

Formulation	Zero Order Model	First Order Model	Higuchi Model	Peppas Equation
F1	0.9733	0.7507	0.9623	0.9677
F2	0.9798	0.9748	0.9474	0.9646
F3	0.9791	0.8691	0.9775	0.9787
F4	0.9625	0.9252	0.9292	0.9220
F5	0.9976	0.7184	0.9381	0.9816

Table 6: Release Characteristics of Diltiazem Hydrochloride Controlled Release Tablets Prepared Employing *Aegle marmelos* Gum

Formulation	% Release in 24 h ± S.D	T_{50} (hr)	K_o (mg/hr)	K_1 (h^{-1})	'n' in Peppas Equation
F1	98.91 ± 0.44	3.2	11.459	0.4833	0.6233
F2	99.89 ± 0.2	4.7	7.9338	0.1640	0.8041
F3	96.29 ± 0.38	10.5	3.2846	0.0924	0.7657
F4	86.66 ± 0.6	13.2	3.058	0.0835	0.5415
F5	99.45 ± 0.22	12.0	3.6736	0.1271	0.8610

RESULTS AND DISCUSSION

Aegle marmelos gum obtained after extraction from its fresh fruit pulp was an amorphous, free flowing powder, with yellow color, sweet in taste and with characteristic sweetish odor. Controlled release tablets each containing 90mg of Diltiazem hydrochloride could be prepared employing *Aegle marmelos* gum as controlled release matrix polymer and release retardant by wet granulation technique.

Hardness of tablets was in range of 5.2 - 5.4 kg/sqcm. Weight loss in the friability test was less than 0.24 % in all the cases. All the matrix tablets prepared contained Diltiazem hydrochloride within 100 ± 5% of the labeled claim. All the tablets were found to be non-disintegrating in water and aqueous acidic (pH fluids) fluids. As such the prepared controlled release tablets were of good quality with regard to the drug content, hardness, and friability (Table 4).

Diltiazem hydrochloride release profiles of the controlled release tablets are shown in Fig 1 - 4. Diltiazem hydrochloride release from controlled release tablets was spread over 24h depending on the concentration of *Aegle marmelos* gum.

The dissolution data of tablets F1 to F5 was fitted to zero order, first order, Korsmeyer and Peppas and Higuchi models. The results of correlation coefficient (R^2) were used to select the most appropriate model. The release profiles of formulations F1-F5 fitted the best to zero order model (Table 1). Thus, it may be concluded that drug release from the controlled release Diltiazem hydrochloride tablets is best explained by zero order model. Percent drug released versus square root time were found to be linear. This indicates that the drug release from the prepared controlled release tablets was diffusion controlled. The release data was also analyzed by the Korsmeyer and Peppas equation shown below in order to assess the release mechanism.

$$M_t / M_\infty = K\, t^n$$

$$\text{Log } (M_t / M_\infty) = \log K + n \log t$$

In the above equation, M_t / M_∞ is the fractional release of the drug, t is the release time, 'k' is the constant for incorporating structural and geometric characteristics of the relative device and n is the release exponent that could be used to characterize the different release mechanisms as n=0.5 (fickian diffusion), 0.5 < n < 1 non-fickian (anomalous transport), n = 1 (case II transport i.e., Zero order release) and n>1 (super class II transport). The release exponent 'n' was in range 0.5415 - 0.8610 with all the controlled release tablets prepared, indicating drug release from all these formulations was by non-fickian (anomalous) diffusion.

CONCLUSION

Aegle marmelos gum is an efficient release retarding polymer for controlled release tablets. Drug release from the prepared tablets was slowed over more 24h and depended on the composition of *Aegle marmelos* gum. Diltiazem hydrochloride release was diffusion controlled and followed zero order kinetics. Non-fickian diffusion was the drug release mechanism exhibited by the prepared Diltiazem hydrochloride controlled release tablets.

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