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Research Article

FORMULATION AND EVALUATION OF DILTIAZEM HYDROCHLORIDE COLON TARGETED TABLETS

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ABSTRACT

The present study deals with formulation of controlled release tablet of Diltiazem hydrochloride for colon targeting tablets using gum kondagogu. The drug excipient interaction studies were carried out by FTIR, DSC, and XRD studies. The prepared matrixes showed controlled delivery for over 18hrs. Studies were also carried out in presence of 4% w/v RCC. In vitro drug release studies showed that F6 released 92%, 94% in stimulated colonic fluid and 98% in stimulated colonic fluid in presence of rat cecal content in a controlled manner over a period of 18 hours. Formulation F6 was optimized and put for Stability studies. Stability studies revealed that matrix tablets were stable over a period of 6 months. All the formulation followed zero order release kinetics and fit into peppas model of drug release.

Keywords: Matrix tablets, Diltiazem hydrochloride, Gum kondagogu, release kinetic, peppas model.

INTRODUCTION

A novel oral colon-specific drug delivery system (CDDS) has been developing as one of the site-specific drug delivery systems. This delivery system, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the gastrointestinal (GI) tract, but rapidly releases drug in the colon following oral administration. CDDS is convenient for treating localized colonic diseases, i.e. ulcerative colitis, Crohn's disease and constipation *etc*, CDDS, also selectively deliver drug to the colon, but not to the upper GI tract. Colon is referred to as the optimal absorption site for protein and polypeptide after oral administration, because of the existence relatively low proteolytic enzyme activities and quite long transit time in the colon[1].

Matrix tablet has given new break through for novel drug delivery system in the field of pharmaceutical technology. In colon release matrix formulations the drug release from the dosage form is mainly controlled by type and proportion of polymers used in the preparation. Controlled release can be achieved by formulating drugs as matrix devices [2].

There are several ways in which colon-specific drug delivery has been attempted. Prodrugs coating with pH dependent polymers, design of timed-release dosage forms and the use of carriers that are degraded exclusively by colonic bacteria are an array of such attempts. The targeting of orally administered drugs to the colon is accomplished by:

1. Coating with pH dependent polymers.
2. Timed release dosage forms.
3. Delivery systems based on the metabolic activity of colonic bacteria[3].

MATERIALS AND METHODS

MATERIALS

Diltiazem hydrochloride was gratis sample from Ranbaxy Ltd, Guorgan, Gum Kondagogu was gift sample from Girijana cooperative society, Tirupathi, HPMC (3000cps) and Micro crystalline cellulose was gift sample from Natco Pharma Ltd, Hyderabad, Talc and Magnesium stearate were from S.D. Fine chem Ltd, Mumbai.

METHODS

Matrix tablets of diltizem hydrochloride were prepared by direct compression method by using different concentration of release retardant polymer gum kondagogu . All ingredients except magnesium stearate and talc were blended in glass mortar uniformly. After the sufficient mixing of drug as well as other components, magnesium stearate and talc were added and mixed for additional 2-3 minutes and finally, compressed by using multistation tablet compression machine.

Evaluation of physical properties:

The blended powders were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, Hausner's Ratio and drug content etc. The prepared tablets were subjected to thickness, weight variation test, hardness, friability, drug content[4, 5, 6, 7, 8, 9, 10].

FT-IR spectra of the Diltiazem hydrochloride

FT-IR spectra of prepared formulations were taken and compared with the spectrum of pure drug. The Characteristics peak of drug was checked in the best formulation spectra.

In-vitro release study

In-vitro release studies of Diltiazem hydrochloride matrix tablets were carried out in USP Type II (Paddle Type) apparatus by using 0.1N HCl and 6.8 pH phosphate buffer as a dissolution media. Rotated at 50 rpm and temperature maintained at 37 ± 0.5˚C. Sample was withdrawn up to 18 hrs and analyzed by UV-spectrophotometer at 237 nm. Due to similarity of human intestinal microflora with the rat cecal contents, the drug release studies were carried out in presence of rat cecal contents to assess the susceptibility of kondagogu gum to colonic bacteria. The rat caecal content 4% w/v was prepared. The drug release studies were carried out using USP dissolution test apparatus I at 50 rpm and 37 °C. The experiments were carried out initially in the same manner in 0.1M HCl and pH 6.8 phosphate buffer. After this testing the dissolution medium was replaced with 500 ml beaker containing 200 ml of 4% w/v rat caecal contents which is kept in water batch of dissolution test apparatus. The experiment was carried with continuous CO_2 supply into beakers to simulate anaerobic environment of caecum. At different time intervals, 1 ml of the sample was withdrawn and replaced with 1 ml of fresh phosphate buffer bubbled with CO_2 and the experiment or drug release studies were carried out for 18hours since the usual colonic transit time is 18−30 hours. The volumes of samples were finally made up to 10 ml and centrifuged. The supernatant was filtered through a bacteria proof filter and the filtrate was analyzed for Diltiazem hydrochloride content at 237nm.

Stability study

The selected formulation was subjected to stability studies for 180 days at 40^{0}C in 75% RH, *in- vitro* permeation study was performed on every 3 months.

RESULTS AND DISCUSSION

IR of the Diltiazem hydrochloride was determined by FTIR spectra as mentioned the Physical mixture of drug and polymer was characterized by FTIR spectral analysis. From the results, it was concluded that there was no interference of the functional group as the principle peaks of diltizem hydrochloride were found to be unaltered in the drug- polymer physical mixtures, indicating they were compatible chemically for the best formulation. The studies were also supported DSC and XRD studies shown in Fig 1, 2, 3, 4, 5, 6, 7.

Pre- compression parameter

Flow properties of the granules were evaluated by determining the bulk density 0.46±0.04 to 0.63±0.06, tapped density 0.54±0.01 to 0.72±0.03, angle of repose17.21±0.06 to 22.01 ±0.04, compressibility index 11.09±0.01 to 16.36 ±0.02 and Hausner's ratio 1.12±0.08 to1.19±0.08 shown in table no 1.

Post- compression parameter

The % weight variation was within pharmacopoeia limits of ±5% of weight. The weights variations range from 2.32±0.01to 2.78±0.02. Hence all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets of each batch ranged between 7.8±0.02 and 7.9±0.03 Kg/cm^2. This ensures good handling characteristics of all batches. The values of friability test were tabulated in table no 2. The friability was in the range 0.65±0.01 to 0.72±0.02, so, less than 1% in all formulations ensuring that the tablets were mechanically stable and the drug content was in the range 98.1±.02 to 99.8 ± 0.05 shown in table no 2.
The present study reveals to control the drug release by increasing the concentration of as a retarding agent.

Stability study

The selected formulation was subjected to stability studies for 180 days at 40ºC in 75%

RH, *in- vitro* permeation study was performed on every 3 months and showed negligible change in permeation profile. The formulation subjected for stability studies was found to have no change in the physical appearance and drug content shown in table no 7.

CONCLUSION

From the drug release study it was concluded that the formula of matrix tablets was given the desired release profile by showing a minimal release during the lag period of 5 hours and complete release by the end of 18 hrs. For the optimized formula showed minimal release in the lag period of 5 hrs about 24% and 92% of the drug was released at the end of the 18hrs as shown in table no 4 and 6. Matrix tablets formulated by employing 44% gum kondagogu are the best used for colon targeting of Diltiazem hydrochloride. The results of *in- vitro* dissolution study indicated that the drug release was in controlled fashion. To analyze the mechanism of drug release from the matrices, the *in-vitro* drug release data were fitted to Zero order, First order. It was observed that the release of drug followed non-Fickian diffusion mechanism and followed zero order kinetics and fit into peppas model shown in table no 5.

Table 1: Formulation of Diltiazem hydrochloride colon targeted tablets using gum kondagogu

Ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)
Diltiazem HCl	90	90	90	90	90	90
Gum Kondagogu	175	178	180	180	180	180
HPMC (3000 cps)	20	20	20	20	20	20
Pre gelatinised starch	180	200	220	250	-	-
Lactose	-	-	-	-	120	-
Micro Crystalline Cellulose	-	-	-	-	-	120
Talc	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1

Table 2: Micromeritic properties of the physical mixtures of the formulations

Formulations	Bulk density (g/cc)	Tapped density (g/cc)	Hausner's ratio	Compressibility Index (%)	Angle of repose (^{o})
F1	0.56±0.02	0.63±0.03	1.12±0.08	11.09±0.01	17.21±0.06
F2	0.46±0.04	0.54±0.01	1.16±0.07	14.41±0.02	21.22±0.05
F3	0.51±0.02	0.61±0.03	1.19±0.08	16.36±0.02	20.54±0.02
F4	0.53±0.04	0.62±0.05	1.16±0.05	14.30±0.06	21.56±0.05
F5	0.61±0.03	0.71±0.04	1.16±0.02	14.22±0.05	22.87±0.01
F6	0.63±0.06	0.72±0.03	1.14±0.03	12.32±0.04	21.03±0.04

Table 3: Physico-chemical evaluation of Diltiazem hydrochloride colon tablets formulated with gum kondagogu

Formulations	Weight Variation (%)	Hardness (kg/cm^2)	Friability (%)	Drug Content %	Thickness (mm)
F1	2.32±0.01	7.8±0.02	0.67±0.03	98.2±0.03	2.4±0.04
F2	2.64±0.02	7.9±0.03	0.70±0.02	99.3±0.01	2.65±0.07
F3	2.87±0.04	7.8±0.01	0.72±0.02	98.6±0.02	2.6±0.01
F4	2.73±0.02	7.9±0.03	0.67±0.03	99.2±0.03	2.7±0.05
F5	2.56±0.03	7.7±0.01	0.68±0.02	98.1±0.02	2.7±0.05
F6	2.78±0.02	7.9±0.03	0.65±0.01	99.8±0.05	2.9±0.04

Table 4: Invitro release data of F1 to F6 formulations

Dissolution	Time (hr)	Percentage of drug released					
		F1	F2	F3	F4	F5	F6
Simulated gastric fluid	0	0	0	0±	0	**0**	**0**
	0.5	5.89±0.33	4.26±0.32	16.30±0.12	14.20±0.23	10.70±0.12	6.40±0.26
	1	8.24±0.09	8.43±0.45	20.40±0.24	18.40±0.15	12.60±0.15	8.30±0.24
	1.5	11.80±0.05	10.96±0.12	22.70±0.24	20.50±0.35	14.40±0.23	12.40±0.12
	2	16.90±0.44	15.26±0.32	24.20±0.21	22.80±0.45	20.30±0.26	13.60±0.26
Simulated intestinal fluid	3	17.36±0.66	16.65±0.25	27.60±0.26	26.30±0.51	22.90±0.25	21.50±0.12
	4	21.30±0.31	20.89±0.24	30.90±0.35	28.70±0.26	28.60±0.24	23.70±0.35

	5	28.90±0.28	27.67±0.15	33.50±0.28	30.30±0.12	32.10±0.26	24.40±0.15
Simulated colonic fluid	6	30.40±0.17	29.42±0.24	36.90±0.29	37.90±0.45	36.01±0.35	38.10±0.24
	7	32.80±0.25	30.96±0.26	37.65±0.32	39.30±0.35	40.70±0.24	42.10±0.36
	8	35.10±0.12	34.98±0.32	41.70±0.13	44.60±0.54	42.20±0.15	44.20±0.15
	9	38.60±0.45	36.40±0.25	44.70±0.34	48.30±0.12	44.50±0.15	48.20±0.45
	10	41.40±0.12	39.10±0.26	48.90±0.26	51.20±0.45	48.90±0.42	52.01±0.52
	11	44.75±0.25	41.94±0.35	52.10±0.15	53.10±0.02	59.70±0.52	58.70±0.36
	12	47.30±0.14	44.75±0.45	58.60±0.27	55.70±0.23	64.01±0.36	64.10±0.21
	13	50.70±0.41	47.30±0.27	62.10±0.38	59.40±0.12	69.10±0.41	70.20±0.15
	14	53.20±0.25	50.70±0.29	65.90±0.45	64.20±0.12	72.30±0.25	76.40±0.45
	15	57.90±0.46	53.20±0.37	69.01±0.51	66.80±0.12	74.80±0.35	78.40±0.25
	16	61.32±0.21	57.90±0.36	72.45±0.21	67.10±0.15	77.10±0.23	81.40±0.51
	17	70.43±0.36	61.32±0.45	74.50±0.45	74.70±0.12	79.10±0.15	89.23±0.23
	18	73.12±0.45	70.43±0.51	77.90±0.14	78.20±0.25	81.20±0.24	92.10±0.36

Table 5: *In-vitro* release kinetics of Diltiazem hydrochloride colon tablets

Formulation	Correlation coefficient				Release rate			
	Zero order	First order	Higuchi	Peppas	T_{50}	T_{90}	K	Exponential coefficient
F1	0.990	0.952	0.952	0.991	12.352	22.234	3.643	0.716
F2	0.991	0.940	0.940	0.984	11.630	20.935	3.869	0.709
F3	0.972	0.964	0.964	0.979	12.349	22.228	3.644	0.407
F4	0.974	0.969	0.969	0.971	11.996	21.594	3.751	0.447
F5	0.983	0.971	0.941	0.981	10.373	18.672	4.338	0.631
F6	0.977	0.893	0.877	0.988	8.409	15.137	5.351	0.827

Table 6: Comparison of In-Vitro release data of Diltiazem Hydrochloride colon targeted tablets of F6 best formulation with, without simulated colonic fluid and in presence of cecal content

Dissolution	Time (hr)	Percentage of drug released		
		F6	F6 + Simulated colonic fluid	F6 + Simulated colonic fluid with 4%w/v cecal content
Simulated gastric fluid	0	0	0	0
	0.5	6.40±0.26	5.01±0.12	6.20±.15
	1	8.30±0.24	9.40±0.35	10.20±0.24
	1.5	12.40±0.12	13.40±0.26	14.50±0.35
	2	13.60±0.26	18.30±0.41	19.60±0.35
Simulated intestinal fluid	3	21.50±0.12	24.60±0.52	25.90±0.35
	4	23.70±0.35	28.30±0.35	30.10±0.15
	5	24.40±0.15	32.60±0.25	33.70±0.24
Simulated colonic fluid	6	38.10±0.24	38.40±0.15	39.60±0.25
	7	42.10±0.36	43.70±0.42	45.20±0.26
	8	44.20±0.15	52.40±0.51	55.20±0.28
	9	48.20±0.45	61.50±0.19	65.40±0.24
	10	52.01±0.52	68.70±0.18	70.20±0.35
	11	58.70±0.36	73.20±0.28	73.21±0.38
	12	64.10±0.21	80.40±0.27	82.45±0.26
	13	70.20±0.15	81.50±0.38	83.21±0.35
	14	76.40±0.45	83.01±0.39	85.63±0.15
	15	78.40±0.25	84.50±0.26	89.23±0.24
	16	81.40±0.51	89.90±0.18	93.20±0.15
	17	89.23±0.23	93.60±0.27	96.35±0.26
	18	92.10±0.36	94.9±0.21	98.23±0.35

Table 7: Release Data of Diltiazem hydrochloride colon tablet (F6) formulated With Gum Kondagogu Kept At 40° C ± 2°C/75 % RH ± 5% RH

Time (h)	Avg % released (X± s.d)		
	Initial	90 daya	180 days
0	0.00	0.00	0.00
0.5	30.215±0.04	32.321±0.05	34.046±0.04
1	45.850±0.05	33.691±0.04	41.862±0.08
1.5	49.033±0.06	50.550±0.08	46.924±0.09
2	52.884±0.07	54.013±0.06	48.707±0.05
3	56.754±0.05	58.910±0.04	50.245±0.06
4	59.342±0.06	64.185±0.08	52.044±0.04

5	63.244±0.04	68.427±0.09	54.614±0.05
6	71.398±0.03	70.568±0.07	56.942±0.06
7	73.736±0.05	72.012±0.04	60.553±0.05
8	77.388±0.05	77.352±0.06	63.166±0.04
9	79.430±0.04	81.166±0.03	68.333±0.05
10	83.759±0.05	83.258±0.02	72.765±0.06
11	86.808±0.09	85.321±0.06	77.220±0.07
12	88.896±0.08	87.123±0.05	80.171±0.08
13	90.666±0.07	89.258±0.05	81.866±0.09
14	92.119±0.04	91.236±0.04	83.821±0.05
15	93.251±0.05	92.354±0.08	85.277±0.06
16	94.230±0.03	93.123±0.09	89.123±0.04
17	95.231±0.06	94.154±0.08	90.152±0.07
18	96.123±0.05	95.123±0.04	92.123±0.08

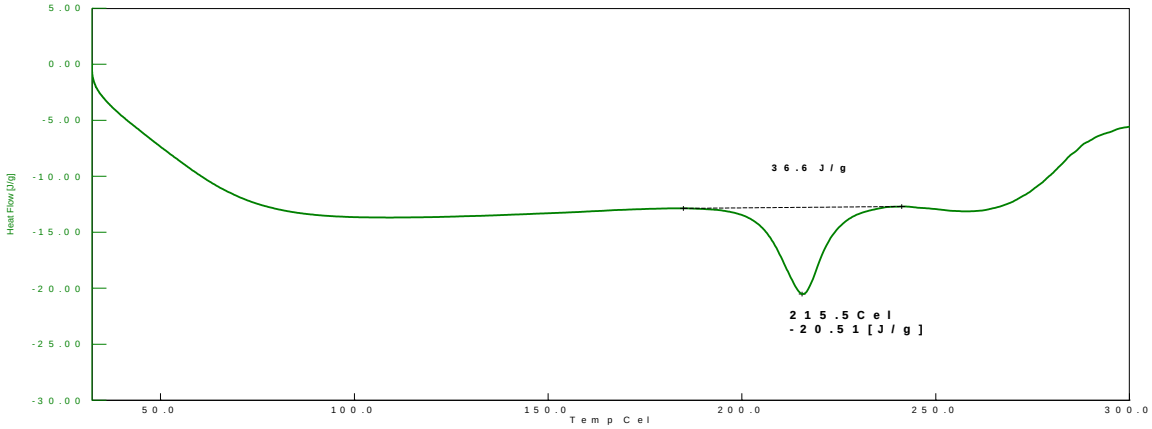

Fig. 1: DSC thermogram of Diltiazem hydrochloride

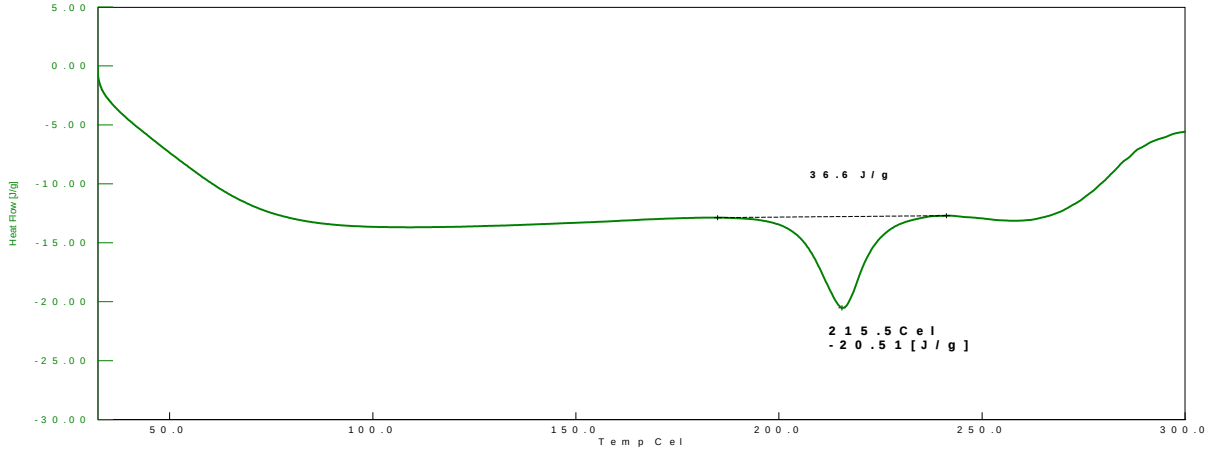

Fig. 2: DSC thermogram of Diltiazem hydrochloride and gum kondagogu

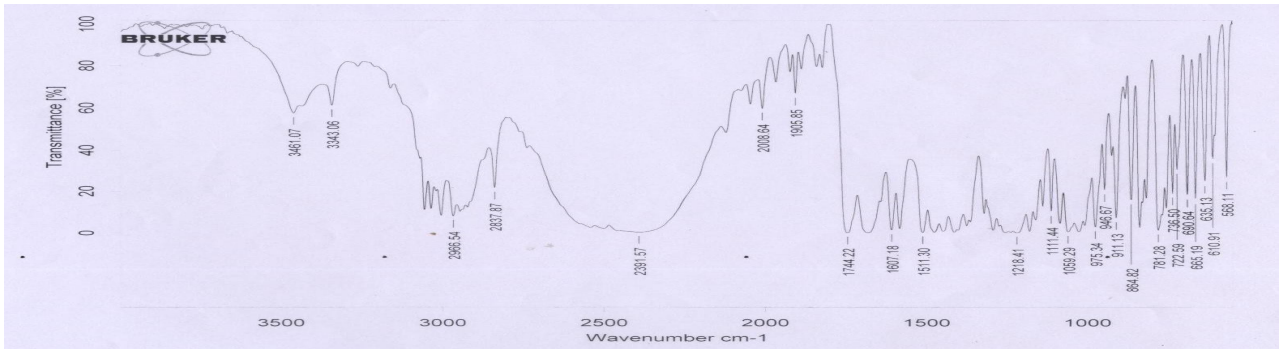

Fig. 3: IR Spectra of Diltiazem Hydrochloride

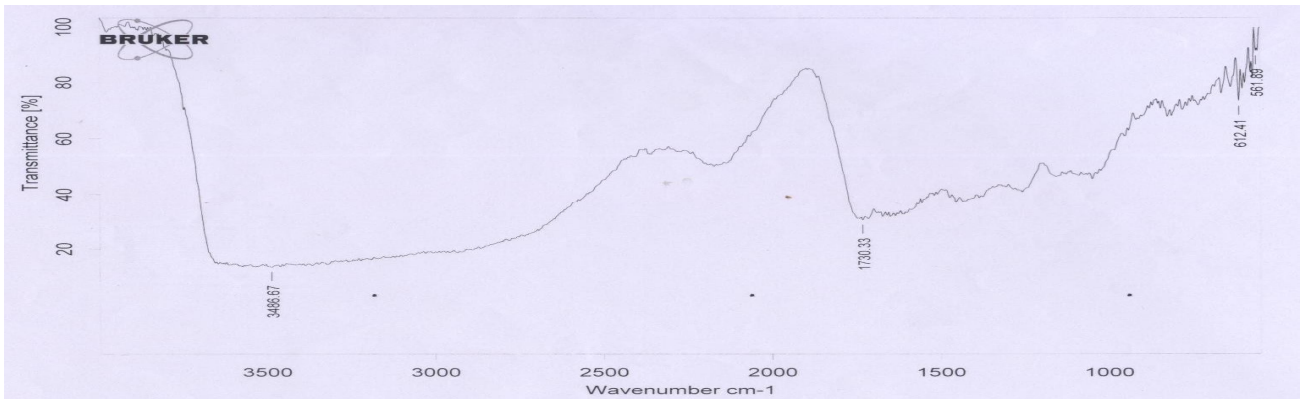

Fig no:4 IR Spectra of Gum kondagogu

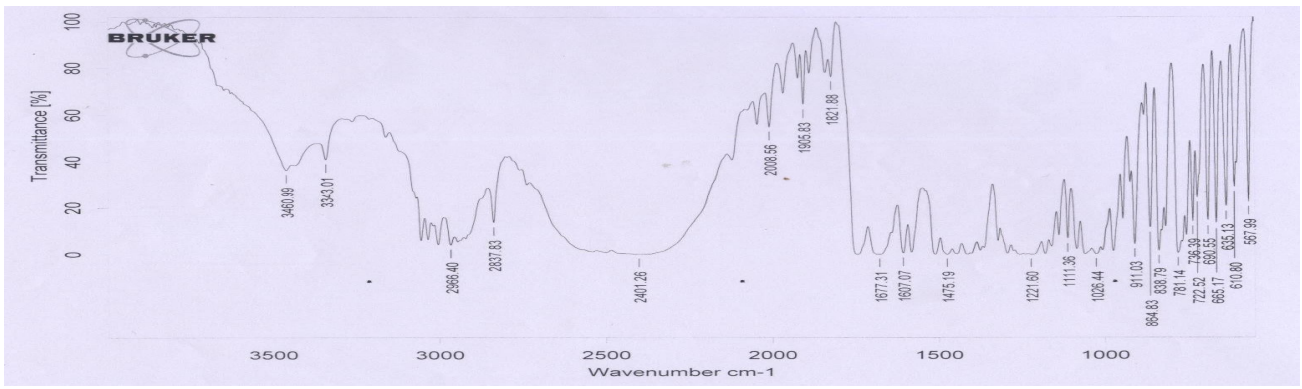

Fig 5: IR Spectra Physical Mixture of Diltiazem Hydrochloride and Gum Kondagogu

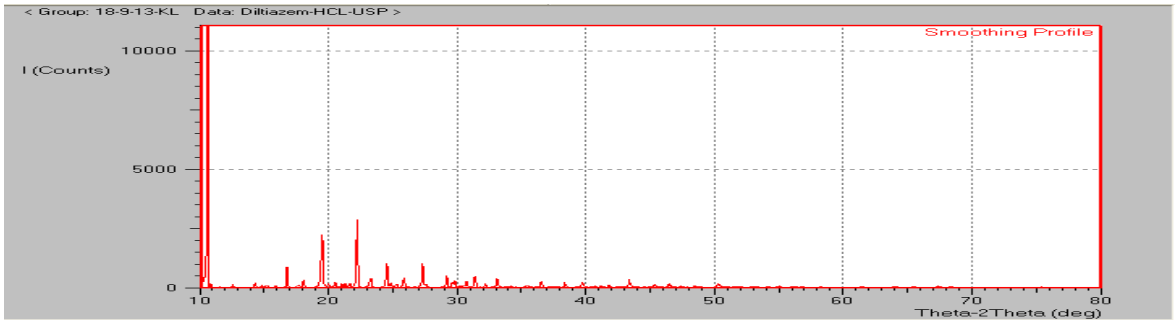

Fig. 6: XRD spectra of Diltiazem hydrochloride tablet

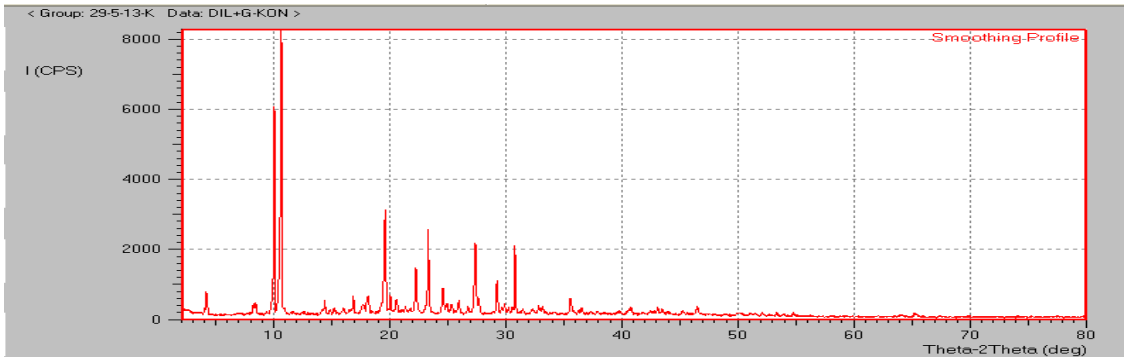

Fig. 7: XRD spectra of Diltiazem hydrochloride and Gum Kondagogu tablet

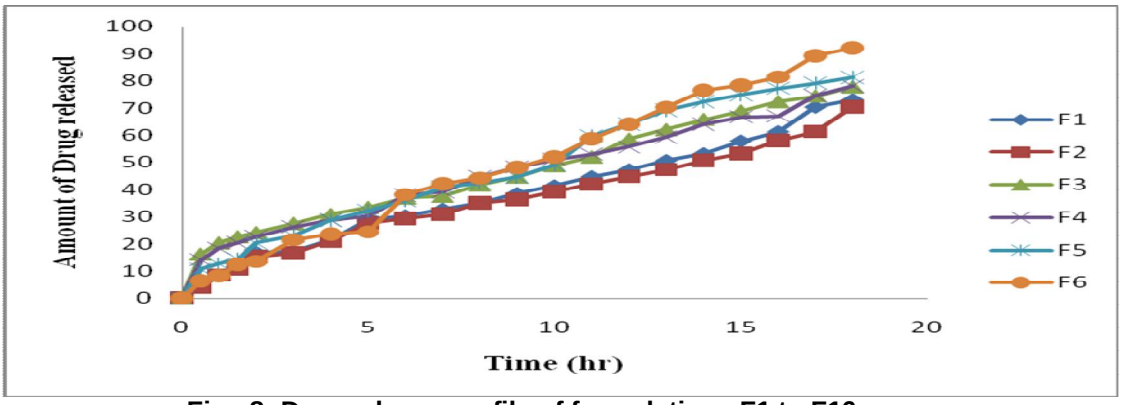

Fig . 8: Drug release profile of formulations F1 to F16

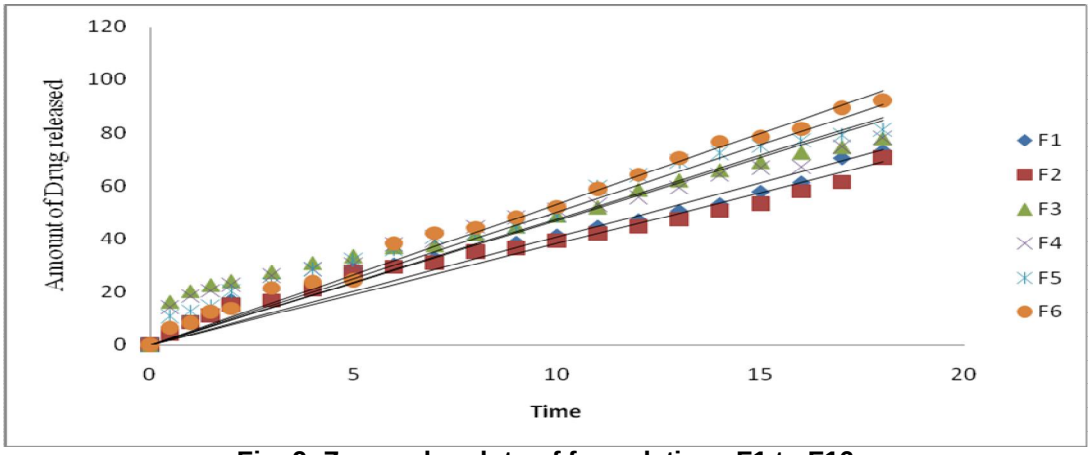

Fig. 9: Zero order plots of formulations F1 to F16

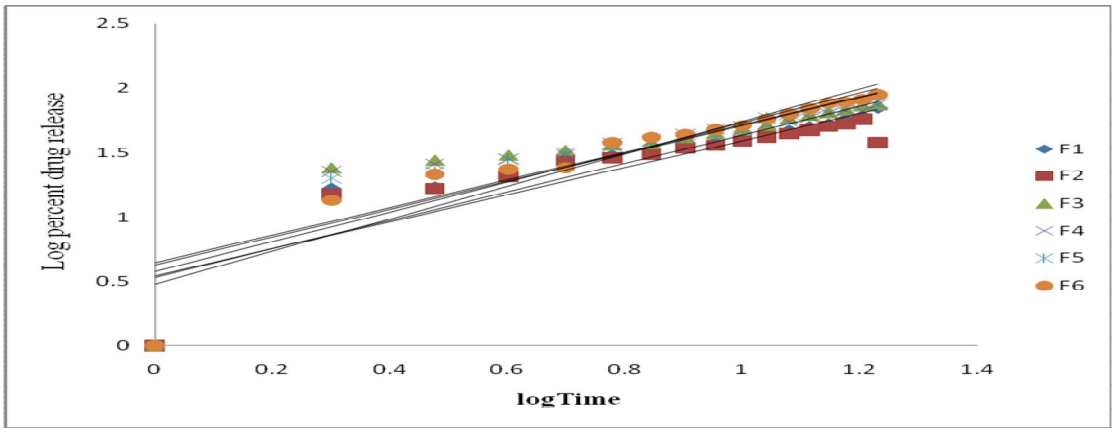

Fig. 10: Peppas plots of formulations F1 to F16

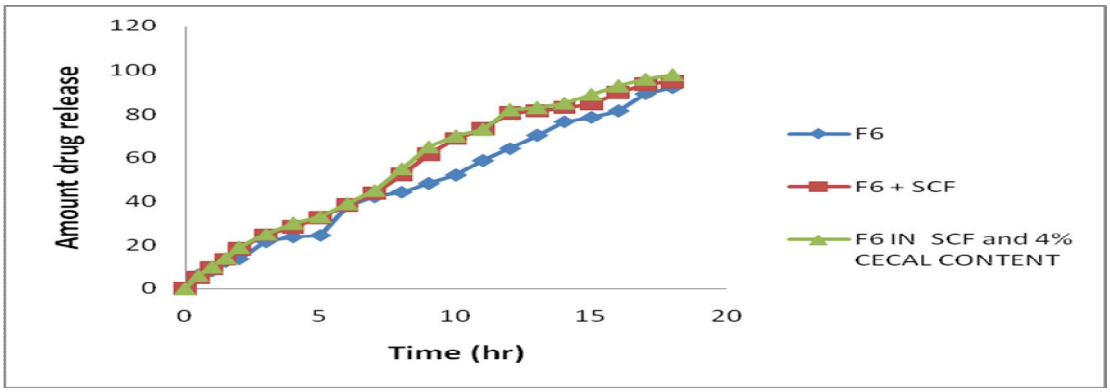

Fig. 11: Comparative dissolution profiles of Diltiazem hydrochloride tablet F6 (Best formulation) with and without simulated colonic fluid and in presence of cecal content

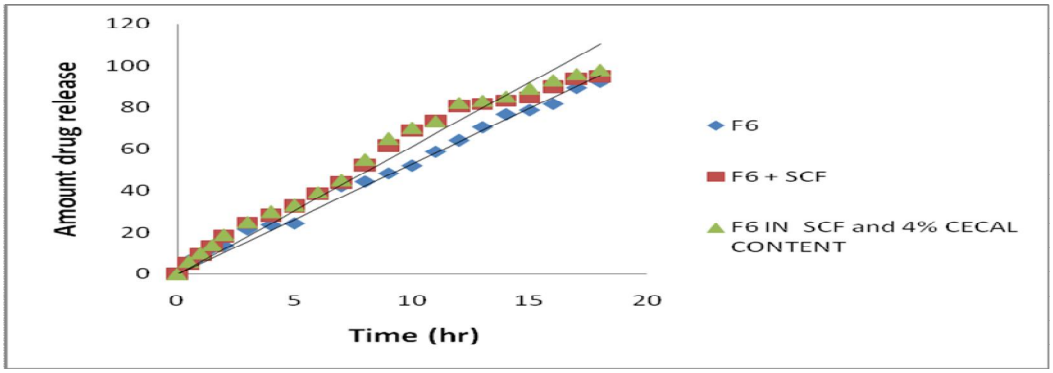

Fig. 12: Zero order comparative plots of Diltiazem HCl tablet of F6 (best formulation) without simulated colonic fluid and F6 (best formulation) with simulated colonic fluid and in presence of cecal content

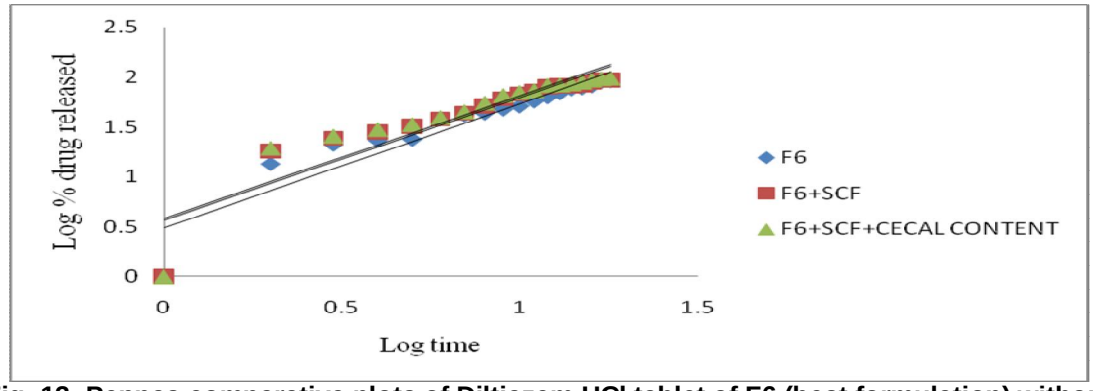

Fig. 13: Peppas comparative plots of Diltiazem HCl tablet of F6 (best formulation) without simulated colonic fluid and F6 (best formulation) with simulated colonic fluid and in presence of cecal content

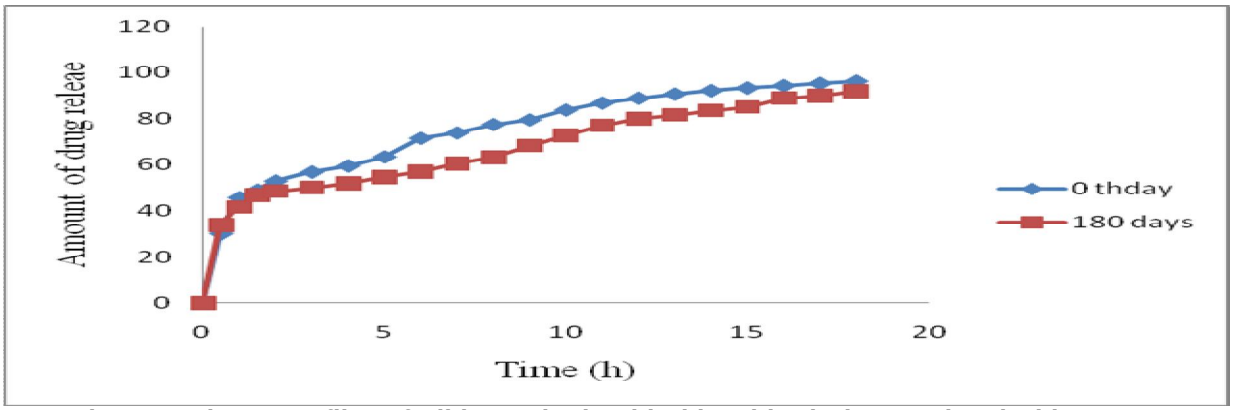

Fig. 14: Release profiles of Diltiazem hydrochloride tablet (F6) Formulated with Gum Kondagogu kept at 40±2ºC/75±5% RH

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