ISSN: 0974-2115
www.jchps.com Journal of Chemical and Pharmaceutical Sciences

FORMULATION AND EVALUATION OF DILTIAZEM HYDROCHLORIDE TABLETS FOR COLON TARGETTING

M. VASAVI CHANDRIKA*, M. KISHORE BABU, D.V.D.MURTHY, D. MOHAN KRISHNA, T.DURGA PRAVEEN

Department of Pharmaceutics, Bapatla College of Pharmacy, Bapatla-522101, India

***Corresponding author: E.Mail: chandrika.vasavi@gmail.com**

ABSTRACT

The present aim of this wok was o formulate Diltiazem hydrochloride colon targeting tablets with a view to provide better absorption of diltiazem hydrochloride. The Preformulation studies performed with diltiazem hydrochloride and Gum kondagogu were found to be satisfactory. Rheological studies on Gum kondagogu indicated that the gum exhibited Non-Newtonian, Pseudoplastic behavior at the concentration of 0.6%, 0.8% and 1% w/v dispersions. Diltiazem hydrochloride colonic tablets containing Gum kondagogu were formulated by direct compression technique. When subjected to physical evaluation the weight variation was found within the limits. The hardness of the tablets ranged from 7.7±0.01 to 7.9±0.03 kg/cm^2. Thickness of the tablets was found to be 2.3±0.02 to 2.9±0.04 mm. the percent friability of the prepared tablets were found to be less than 1. The percent drug content in all the formulated tablets were in the range of 97.4±0.03 to 99.8±0.05% ensuring the uniformity of the drug content in all the formulations. The formulated tablets ascertained zero order kinetics and followed peppas mechanism. Among all the colonic tablets 'F_2' produced better release 94.1% at the end of 18 hrs when compared to the other formulations in the simulated colonic fluid.

KEY WORDS: Diltiazem hydrochloride, Gum kondagogu, HPMC (3000 cps), Colon targetting

1. INTRODUCTION

Colon targeted drug delivery system (CDDS) is used mainly for the treatment of colonic diseases, for drugs like proteins and peptides, for the treatment of diseases sensitive to circadian rhythms such as Asthma, Angina and Rheumatoid arthritis and for delivery of steroids, which absorbable in colon (Michael J, 2006) The advent of slow release technologies increase the chances for a drug to be released in the colon and thus this organ has an important role to play in drug absorption from oral sustained release formulations (Edith Mathiowitz,1999)

The site-specific delivery of the drugs to the target receptor sites has the potential to reduce the side effects and improve the physiological response (Anil K. Philip, 2010). However, for successful colonic drug delivery, many physiological barriers must be overcome, the major one being absorption of the active drug in the upper part of the G I tract. The disease state can also potentially alter the delivery and absorption characteristics of drug from the colon (N. K Jain, 2003; Sateesh Kumar Vemula, 2009; Vyas and Khar). The specific release in the colon also affects a time delay between administration and onset of action, which can be useful for diseases with various degrees of severity, such as asthma and arthritis. Further, drug targeting to colon would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of diseases that have peak symptoms in the early morning such as nocturnal asthma, angina or arthritis (Charles R.Craig, 2004).

2. MATERIALS AND METHODS

Diltiazem hydrochloride (Ranbaxy gorgon, Delhi) gum kondagogu (Girijana cooperative society, Tirupathi) hpmc (3000 cps) (Natco Pharma Ltd, Hyderabad), microcrystalline cellulose (Natco Pharma Ltd, Hyderabad), magnesium stearate (S.D. Fine chem Ltd, Mumbai), talc (S.D. Fine chem Ltd, Mumbai)

2.1. Preformulation studies:

2.1.1. Characterization of Drug and Excipients: Compatibility study of Diltiazem hydrochloride, gum kondagogu, by IR spectroscopy: The physicochemical compatibility between Diltiazem hydrochloride, gum kondagogu used in the research were carried out by IR Spectral studies using Perkin Elmer Fourier transform infrared spectrophotometer, Bruker, Germany, in the wavelength region between 4000cm^{-1} to 400cm^{-1}. The spectra obtained for Diltiazem hydrochloride, gum kondagogu were compared.

2.1.2. Preparation of diltiazem hydrochloride colon targeted tablets (KishoreBabu M, 2006; Rowe RC, 2006; Prushottamarao K, 2003; Samia Omar, 2007; Kishore Sahebrao Salunkhe, 2008; Asha Patel, 2011) **:** Diltiazem hydrochloride colon targeted tablets were formulated by direct compression technique the composition used in manufacturing if tablets are listed in the table. For formulation purpose all the ingredients were passed through sieve no.60 and mixed homogenously in a mortar. Finally calculated quantities of talc and magnesium stearate

were added and mixed. The resultant mixture was compressed into tablets by using cadmach 16 station tablet machine with convex faced punches (9mm diameter).

2.3. Evaluation of tablets: The formulated tablets were assessed for its general appearance.

2.3.1. Thickness: The thickness of the formulated tablets was measured by using Vernier calipers. An average of these readings was taken.

2.3.2. Weight variation: Formulated matrix tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.

% Weight Variation = Average Weight – Individual Weight / Average Weight ×100

2.3.3. Hardness: Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

2.3.4. Friability: The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.

2.3.5. Drug Content: Twenty tablets of each formulation were collected and powdered. Powder equivalent to 100 mg of Diltiazem Hydrochloride was weighed. 100 ml of pH 6.8 phosphate buffer was added and sonicated until complete solution is affected. Diluted to a suitable volume with pH 7.4 phosphate buffer and the absorbance were measured by using Shimadzu Double Beam Spectrophotometer (UV- 1700) at 237 nm.

2.3.6. Sterilization studies on gum kondagogu (Kulkarni R, 2011; Vinod V.T.R**,** 2007)**:** 100mg of the gum samples were aseptically mixed with 9ml of sterile normal saline and the pH was adjusted to 7 with p^H meter. From this, 1 ml of each dispersion was mixed with 20 ml of sterile lactose broth and placed separately in petridish. All the plates were incubated at 37 ± 1^0c for 24 hrs and observed for the presence of microbial flora.

2.3.7. ***In vitro*** **dissolution studies:** Dissolution studies were carried out using USP dissolution testing apparatus II (paddle type). The stirring speed was maintained at 100 rpm. The tablets were placed in simulated gastric fluid (SGF- pH 1.2) for 2 hrs, simulated intestinal fluid (SIF- pH 7.4) for 3 hrs and simulated colonic fluid (SCF- pH 6.8) for 13 hrs. Samplings were done at predetermined time intervals and the samples were estimated for drug content after suitable dilution by UV method.

2.3.8. ***In vivo*** **evaluation of diltiazem hydrochloride colon targeted tablets** (Janaki.B, 2000):

2.3.8.1. Gamma-Scintigraphic Studies: Gamma-scintigraphic studies were carried out in healthy Wistar rats with technetium-99m-DTPA (^{99m}Tc-DTPA) as a tracer in colonic tablets with Gum Kondagogu to find their in vivo behavior. The tablet was administered to the overnight fasted healthy Wistar rats weighing 290 mg, via polyethylene under light ether anesthesia condition. During the study the rat was allowed to free access to water. Imaging of the fabricated tablet device, in the GIT was performed using a latest generation SPECT Gamma Camera connected to computer.

The scintiscans were taken immediately after first dosing and were carried out for 6 hours. The acquisition was taken for 60 seconds. Before every acquisition, the sedated rat was immobilized on a mounting chamber in supine position.

3. RESULTS & DISCUSSIONS

The rheological studies indicated that the 1% w/v Gum dispersion of Gum Kondagogu behaved like a gel. 0.6 % w/v & 0.8 % w/v of Gum dispersion were found to be translucent with thinner consistency and 0.2 % w/v & 0.4 % w/v dispersion were appeared to be like a colloidal dispersion. The gum exhibited Non-Newtonian, pseudo plastic behavior at the concentration of 0.6% w/v, 0.8% w/v and 1 % w/v dispersions. The viscosity decreased with increasing the pH of the buffers. Further, results with respect to the rate of shear as the viscosity of the gums suggested that there was a slight decrease in the viscosity with the raise in the rate of shear.

Direct compression technique was adopted for the formulation as it was easy to fabricate and all the excipients complied with this technique. The formulated colonic tablets were subjected to physical evaluation.

The weight variation observed was well within the accepted limits. The hardness of the tablets ranged from 7.7±0.01 to 7.9±0.03 kg/cm^2. The thicknesses of the tablets were found in between 2.3±0.02 to 2.9±0.04mm. The hardness and thickness results indicated the mechanical strength of the tablets. The percent friability of the prepared tablets was found to be < 1 indicating the physical integrity of the tablets. The percent drug content in all the formulated tablets were in the range of 97.4±0.03 to 99.8±0.05% ensuring the uniformity of the drug content in all the formulations.

In-vitro dissolution studies revealed that all the formulated tablets ascertained zero order kinetics and followed peppas mechanism. Based on the exponential constant 'n' value considering the slope it was observed that the release pattern was of non- fickian type except F5 and F6 which showed fickian release pattern. Of all the formulated colonic tablets the formulation 'F2' produced better release (92.1%) at the end of 18 hrs when compared with the other formulations. Further it was observed that there was a slight increase in release (94.9%) of the formulation 'F2' in the simulated colonic fluid at the end of 18 hrs. The results obtained were found to be satisfactory well being in the acceptable limits.

According to *In-vivo* gamma scintigraphic studies, the images obtained in the form of scintiscans in male wistar rats are categorized. Image (A) was taken immediately after administration of the tablet. Image (B) was after 2 hours. Image (C) at the 5th hour. Image (D) after the 5th hour of the administration. (A) and (B) indicated the intactness of the tablet where as in the image 'C' the movement can be clearly noticed. Image 'D' is crucial since it suggests that the drug release may be in the lower part of GIT which might be colon (Figure.13).

Figure.1. IR Spectra of Diltiazem Hydrochloride

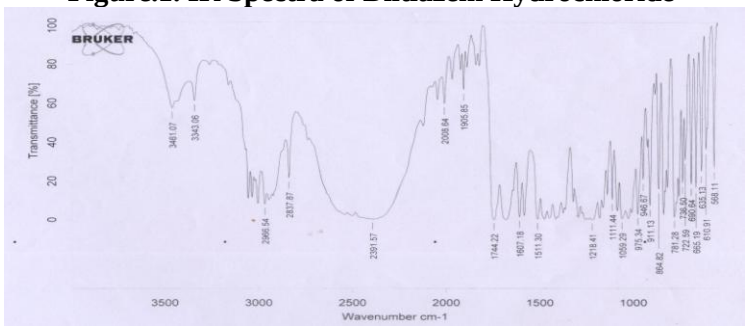


Figure.2. IR Spectra of Gum kondagogu

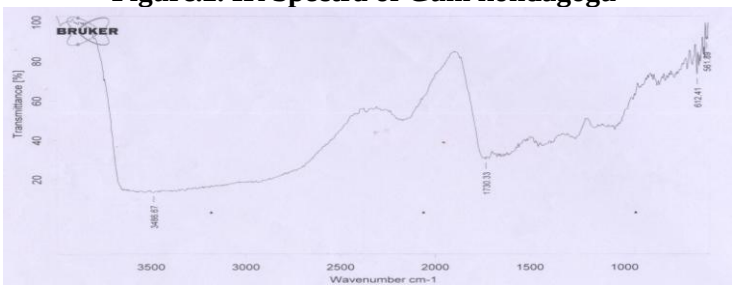


Figure.3. IR Spectra Physical Mixture of Diltiazem Hydrochloride and Gum Kondagogu

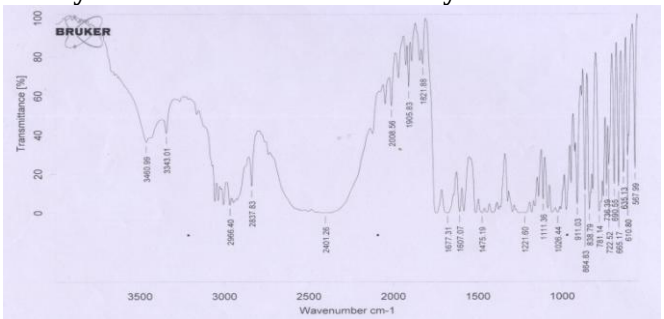


Fig.4. Photographs to confirm the sterility of Gum Kondagogu after 24 hours (Nutrient agar medium)

Control

Gum kondagogu inoculated sample

Table 1: Composition of Diltiazem hydrochloride colon targeted tablets

Ingredients (mg)	F_1	F_2	F3	F4	F5	F6	F7	F8	F9
Diltiazem HCl	90	90	90	90	90	90	90	90	90
Gum Kondagogu	180	180	180	180	180	180	180	178	175
HPMC (3000 cps)	20	20	20	20	20	20	20	20	17
Lactose	120	-	-	-	-	-	-	-	-
Micro Crystalline Cellulose	-	120	-	-	-	-	-	-	-
Pre gelatinized starch	-	-	180	200	250	220	250	220	220
Talc	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1

Table 2: Rheological studies on Gum Kondagogu

Viscosity(cps)	Dispersion	Speed(rpm)	% Torque	Shear stress (D/cm^2)	Shear rate (1/sec)
187.76	0.2%	5	31.3	12.39	6.60
193.16	0.4%	5	32.3	12.75	6.60
223.15	0.6%	5	37.2	14.73	6.60
244.15	0.8%	5	40.7	16.11	6.60
293.94	1%	5	49	19.4	6.60

Table.3.Physical properties of Diltiazem hydrochloride colon targeted tablets

Formulations	Weight Variation (%)	Hardness (kg/cm^2)	Friability (%)	Drug Content %	Thickness (mm)
F1	2.56±0.03	7.7±0.01	0.68±0.02	98.1±0.02	2.7±0.05
F2	2.78±0.02	7.9±0.03	0.65±0.01	99.8±0.05	2.9±0.04
F3	2.32±0.01	7.8±0.02	0.67±0.03	98.2±0.03	2.4±0.04
F4	2.64±0.02	7.9±0.03	0.70±0.02	99.3±0.01	2.65±0.07
F5	3.01±0.03	7.8±0.01	0.69±0.01	97.4±0.03	2.3±0.02
F6	2.87±0.04	7.8±0.01	0.72±0.02	98.6±0.02	2.6±0.01
F7	2.73±0.02	7.9±0.03	0.67±0.03	99.2±0.03	2.7±0.05
F8	2.64±0.02	7.8±0.01	0.70±0.02	98.4±0.01	2.6±0.01
F9	2.56±0.03	7.9±0.03	0.68±0.02	97.6±0.02	2.8±0.02

Table.4.*In-vitro* release data of colon targeted tablets of Diltiazem hydrochloride formulated with gum kondagogu

Dissolution	Time (hr)	Percentage of drug released				
		F1	F2	F3	F4	F5
	0	0	0	0	0	0
Simulated gastric fluid	0.5	10.7	6.4	5.89	4.26	8.3
	1	12.6	8.3	8.24	8.43	12.83
	1.5	14.4	12.4	11.8	10.96	17.97
	2	20.3	13.6	16.9	15.26	22.9
Simulated intestinal fluid	3	22.9	21.5	17.36	16.65	28.41
	4	28.6	23.7	21.3	20.89	32.24
	5	32.1	24.4	28.9	27.67	37.4
Simulated colonic fluid	6	36	38.1	30.4	29.42	42.46
	7	40.7	42.1	32.8	30.96	47.7
	8	42.2	44.2	35.1	34.98	51.24
	9	44.5	48.2	38.6	36.4	53.4
	10	48.9	52	41.4	39.1	57.9
	11	59.7	58.7	44.75	41.94	64.41
	12	64	64.1	47.3	44.75	69.9
	13	69.1	70.2	50.7	47.3	72.8
	14	72.3	76.4	53.2	50.7	73.12
	15	74.8	78.4	57.9	53.2	
	16	77.1	81.4	61.32	57.9	77.4
	17	79.1	89.23	70.43	61.32	81.2
	18	81.2	92.1	73.12	70.43	87.9

Table.5.*In-vitro* release data of colon targeted tablets of Diltiazem hydrochloride formulated with gum kondagogu

Dissolution	Time (hr)	Percentage of drug released			
		F6	F7	F8	F9
	0	0	0	0	0
Simulated gastric fluid	0.5	16.3	14.2	9.27	9.27
	1	20.4	18.4	13.5	13.5
	1.5	22.7	20.5	16.8	16.8
	2	24.2	22.8	18.4	18.4
Simulated intestinal fluid	3	27.6	26.3	20.6	20.6
	4	30.9	28.7	22.97	21.9
	5	33.5	30.3	26.84	25.9
Simulated colonic fluid	6	36.9	37.9	27.43	33.8
	7	37.65	39.3	28.8	38.4
	8	41.7	44.6	30.6	45.5
	9	44.7	48.3	33	48.2
	10	48.9	51.2	36.7	50.9
	11	52.1	53.1	40.9	54.87
	12	58.6	55.7	43.48	61.4
	13	62.1	59.4	46.7	63.6
	14	65.9	64.2	53.9	67.42
	15	69	66.8	56.7	71.2
	16	72.45	67.1	59.1	73.7
	17	74.5	74.7	62	76.3
	18	77.9	78.2	65.43	80.1

Table.6.*In vitro* drug release kinetics of colon targeted tablets of Diltiazem Hydrochloride formulated with gum kondagogu

Formulation	Correlation coefficient				Release rate			
	Zero order	First order	Higuchi	Peppas	T_{50}	T_{90}	K	Exponential coefficient
F1	0.983	0.971	0.941	0.981	10.373	18.672	4.338	0.631
F2	0.977	0.893	0.877	0.988	8.409	15.137	5.351	0.827
F3	0.990	0.952	0.952	0.991	12.352	22.234	3.643	0.716
F4	0.991	0.940	0.940	0.984	11.630	20.935	3.869	0.709
F5	0.984	0.949	0.949	0.994	9.083	16.350	4.954	0.676
F6	0.972	0.964	0.964	0.979	12.349	22.228	3.644	0.407
F7	0.974	0.969	0.969	0.971	11.996	21.594	3.751	0.447
F8	0.975	0.956	0.911	0.924	14.446	26.003	3.115	0.477
F9	0.987	0.979	0.979	0.948	10.693	19.249	4.208	0.580

Table.7.Comparision of *In Vitro* release data of Diltiazem Hydrochloride colon targeted tablets of F2 best formulation with and without simulated colonic fluid

Dissolution	Time (hr)	Percentage of drug released	
		F2	F2 + Silmulated colonic fluid
Simulated gastric fluid	0	0	0
	0.5	6.4	5
	1	8.3	9.4
	1.5	12.4	13.4
	2	13.6	18.3
Simulated intestinal fluid	3	21.5	24.6
	4	23.7	28.3
	5	24.4	32.6
Simulated colonic fluid	6	38.1	38.4
	7	42.1	43.7
	8	44.2	52.4
	9	48.2	61.5
	10	52	68.7
	11	58.7	73.2
	12	64.1	80.4
	13	70.2	81.5
	14	76.4	83
	15	78.4	84.5
	16	81.4	89.9
	17	89.23	93.6
	18	92.1	94.9

Table.8.Comparision of *In vitro* release kinetics of Diltiazem Hydrochloride colon targeted tablets of F2 best formulation with and without Simulated colonic fluid

Formulation	Correlation coefficient				Release rate			
	Zero order	First order	Higuchi	Peppas	T_{50}	T_{90}	K	Exponential coefficient
F2	0.977	0.893	0.877	0.988	8.409	15.137	5.351	0.827
F2 + Simulated colonic fluid	0.967	0.896	0.871	0.975	9.019	16.235	4.989	0.826

Figure.5.Comparative dissolution profile of Diltiazem HCl tablet formulations F1 to F5

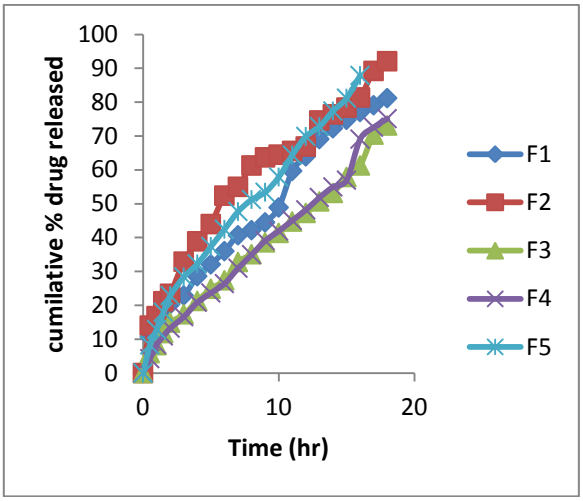


Figure.6.Comparative dissolution profile of Diltiazem HCL tablet formulations F6 to F9

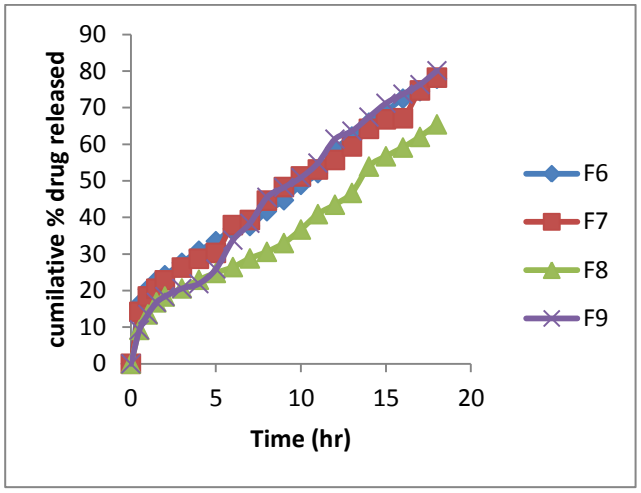


Figure.7. Zero order comparative plots of Diltiazem HCl formulations F1 to F5

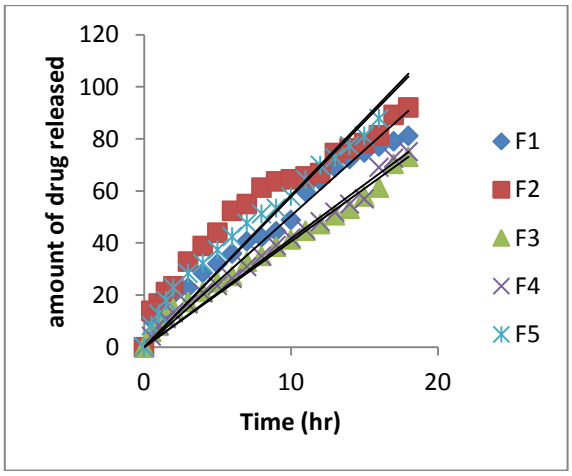


Figure.8. Zero order comparative plots of Diltiazem HCl formulations F6 to F9

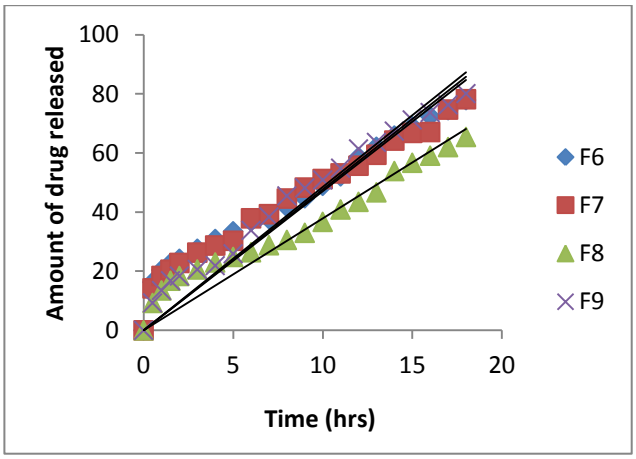


Figure.9. Peppas comparative plots of Diltiazem HCl formulations F1 to F5

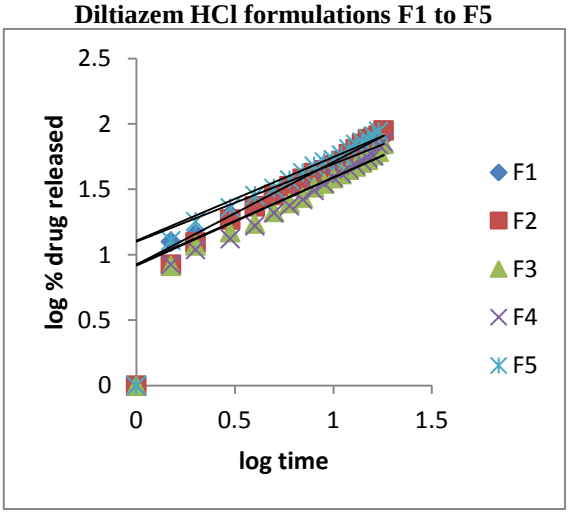


Figure.10. Peppas comparative plots of Diltiazem HCl formulations F6 to F9

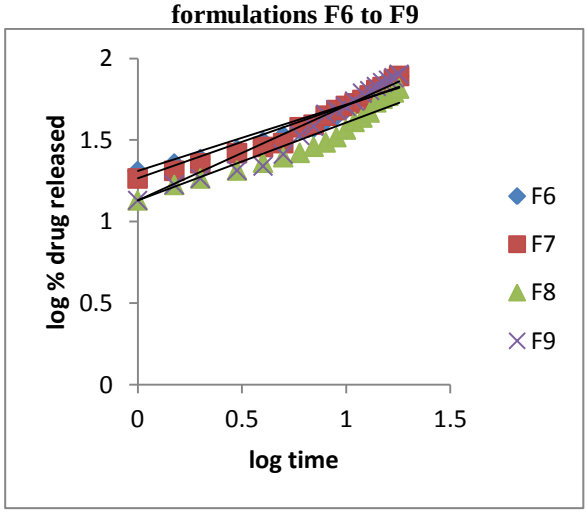


Figure.11. Comparative dissolution profile of Diltiazem HCl tablets of F2 best formulation with and without simulated colonic fluid

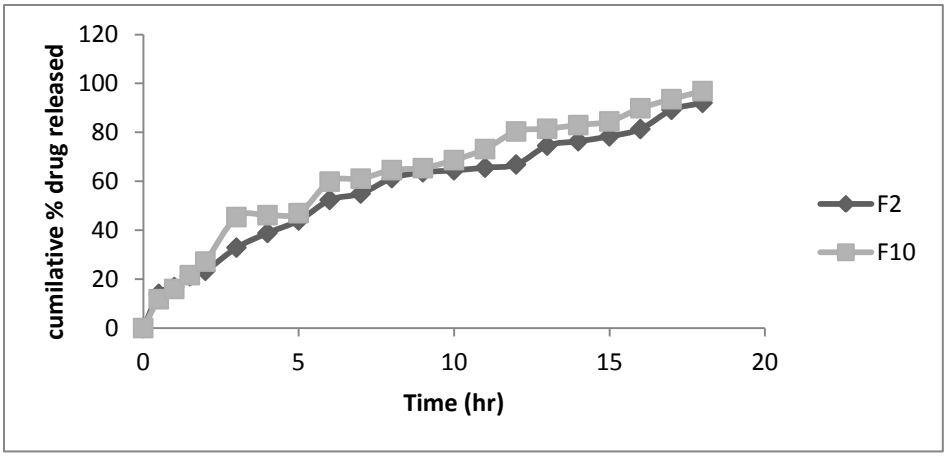


Figure.12. Zero order comparative plots of Diltiazem HCl tablets of F2 (best formulation without simulated colonic fluid) and F10 (best formulation with simulated colonic fluid)

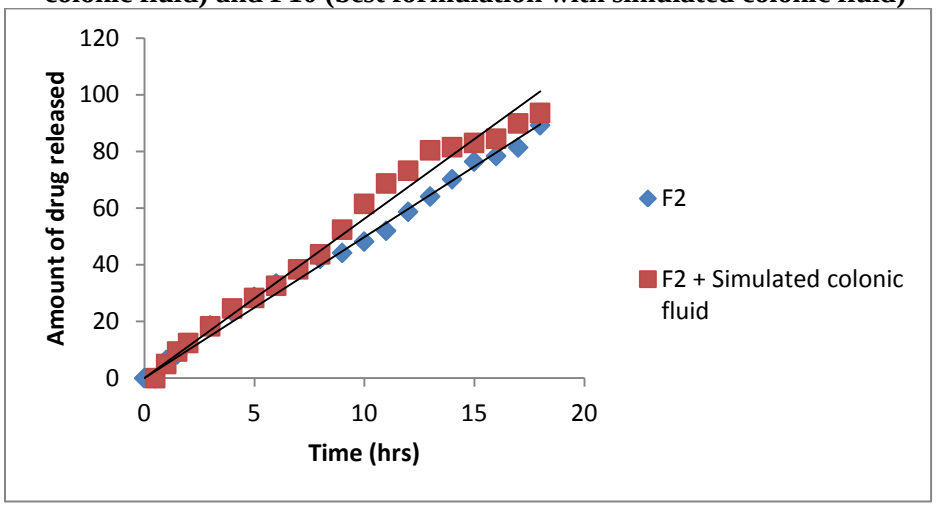
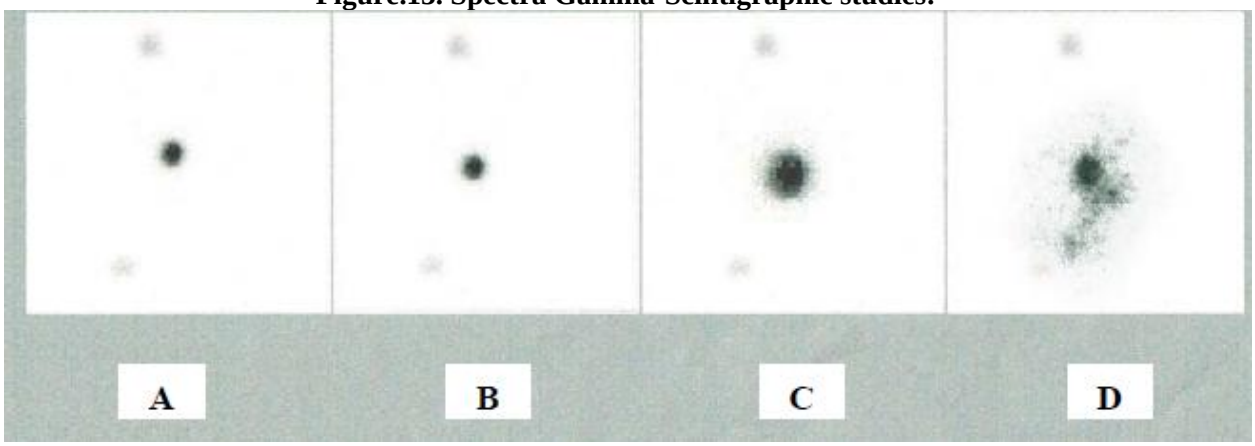


Figure.13. Spectra Gamma-Scintigraphic studies:



CONCLUSION

The aim of present study is to formulate a colonic tablet of Diltiazem hydrochloride with a view to provide time dependent release which effectively acts in the morning suppressing the higher intensity of angina pectoris and also to increase the bioavailability by targeting to colon. For this purpose gum Kondagogu was selected as a release rate retardant the additional advantage being the suitable material the simulated colonic fluid.

Various formulations of colon targeted tablets of Diltiazem hydrochloride were prepared using Gum Kondagogu, HPMC and Microcrystalline Cellulose as key excipients. The evaluation of the tablets such as weight variation, Friability, hardness, thickness and drug content were found to be satisfactory and well within the confined limits. All the formulated tablets ascertained zero-order and followed peppas mechanism. All the formulations showed non- fickian release pattern where as F5 and F6 showed fickian release pattern. Of all the formulations, the formulation F2 was found to produce better release profile of 92.1% in 18 hrs confirming the release rate limits of colon tablets when compared to the colon tablets formulated with other proportions. Further it was observed that there was not much difference of the formulation 'F2' in the simulated colonic fluid (94.9%) at the end of 18 hrs. The in vivo gamma-scintigraphic studies suggested that the drug release may be in the lower part of GIT which might be colon.

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