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Research Article

FEASIBILITY OF KONDAGOGU GUM AS A CARRIER FOR COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT
The present study has been undertaken to develop colon targeted drug delivery system for metoprolol succinate using kondagogu gum as a polymer. Matrix tablets of metoprolol were prepared using PVP K-30 as binder and kondagogu gum as a rate controlling polymer. The prepared tablets were evaluated for properties such as hardness, thickness, friability etc. The prepared tablets were coated with shellac as an enteric coat polymer and evaluated for enteric coat test. *In vitro* release studies of were carried out for 2 hrs in pH 1.2 HCl buffer, 3 hrs in pH 6.8 phosphate buffer and 7 hrs in the presence of 200 ml of simulated colonic fluid (SCF). In addition, kinetics of drug release from the matrices and stability of the tablet formulations were also investigated. Mathematical analysis of the release kinetics was done using PCP-V02 disso software and it showed that the nature of drug release from the matrix tablets has followed super case II transport which means drug release fro this system is by both diffusion and relaxation of polymer chain. FTIR and DSC studies have shown that no chemical interaction occurred between the drug and polymers used. The optimized formulation (F9) showed negligible difference in release mechanism as well as release kinetics when stability study was done for three months at 40±2^0 C and 75±5% RH.
Key words: metoprolol succinate, kondagogu gum, matrix tablets, colon targeting

INTRODUCTION

Oral delivery is still the preferred route of drug administration, especially for chronic therapies where repetitive administration is required. Oral administration assures less pain, higher likelihood of compliance, greater convenience and reduced risk of cross-infection and needle stick injuries[1, 2, 3]. Thus, formulations of oral drug delivery continue to take over more than half of the drug delivery market share[4].

Apart from this, oral route is not favorable for the administration of most protein and polypeptide drugs available today, due to their high susceptibility to digestive enzymes in the gastrointestinal (GI) tract, poor absorption, and their restricted ability to transport across the intestinal epithelial barrier. As a consequence, new strategies of drug delivery have been developed to surmount the obstacles encountered by oral delivery. Amongst these strategies, colon-specific delivery has been studied thoroughly for the last two decades. GI tract is essentially tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine(consisting of duodenum, jejunum and ileum) and large intestine (consisting of cecum, appendix colon and rectum)[5].

The colon has conferred the importance as a target for drug delivery because of the therapeutic benefits to be gained for the treatment of local disorders such as inflammatory bowel disease, irritable bowel disease and carcinoma. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. The colon has also been anticipated as a more favourable target site for systemic absorption of therapeutic peptides due to its lower peptidase activity, as well as for other drugs that would otherwise be inactivated in the upper gastrointestinal regions. The inherent lag time in mouth to colon transit can also be exploited to achieve delayed drug release in the therapy of conditions that display a diurnal rhythm such as nocturnal asthma and arthritis[6]. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. As the large intestine is relatively free of peptidases such special delivery systems will have a fair chance to get their drug sufficiently absorbed after peroral administration[7].

Various systems have been developed for colon-specific drug delivery. These include coating with pH-sensitive polymers, covalent linkage of a drug with a carrier, time dependent release systems, and enzymatically controlled

delivery systems. Enteric coated systems are the most commonly used for colonic drug delivery, but the drawback of this system is that the pH difference between small intestine and colon is not being very distinct and they donot give reproducible drug release. Whereas the time-dependent release system is not able to sense any variation in the upper gastro-intestinal tract transit time, any variation in gastric emptying time may lead to drug release in small intestine before arrival to colon. Apparently, the most appropriate approach for site-specific drug delivery to colon is enzymatically controlled delivery systems. No drug release can occur unless the system arrives to the colon . To improve the specificity of drug release, certain types of polysaccharides (e.g., pectin, chitosan, dextran, guar gum, inulin) can be used to create the enzymatically controlled delivery systems[8].

New formulations which make use of different delivery vehicles from synthetic and natural polymers, which are either hydrophilic or hydrophobic, have been tested for this purpose. The challenge is to device or design the oral drug delivery vehicles which effectively carry drugs to the colon site. Initially, they need to remain intact when it is passing through the upper GI tract and then relese the drug after reaching the colon. Moreover, the released drugs need to be absorbed at an efficient rate in the GI tract in order to be therapeutically effective. Several carbohydrate polymers are able to satisfy these requirements to some extent, having demonstrated their potential as starting materials for the construction of oral drug delivery vehicles[5].

Kondagogu gum (KG) is a dried exudates obtained from tree *Cochlospermum gossypium* which belongs to the family Bixaceae. It is a high molecular weight complex acetylated polysaccharide consisting mainly of D-galacturonic acid, D-galactose and L-rhamnose[9 - 11]. Since a major restriction in the design of KG matrices for drug delivery is its high swelling characteristics (a property which requires high compression forces at production to avoid premature burst release), a chemical modification of KG to reduce its enormous swelling properties is a practical alternative solution, especially for orally administered colon-specific drug delivery systems. In this study trisodium trimetaphosphate (STMP) was used to reduce KG swelling properties. STMP is a non toxic crosslinker, used to crosslink starch in the food industry[12,13].

Metoprolol (MTL), which is a β_1-selective adrenergic blocking agent is prescribed widely in diverse cardiovascular diseases such as hypertension, angina pectoris, arrhythmias, and congestive heart failures was selected as model drug. Administration of conventional tablets of MTL has exhibited fluctuations in the plasma drug levels finally resulting either in the manifestation of side effects or reduction in drug concentration at the receptor site. MTL undergoes extensive first-pass metabolism in the liver, which leads to the low oral bioavailability, which is about 40 - 50% in humans and has a short biological half-life of 4 hrs. In order to avoid these disadvantages, several formulations like tablet, buccal sprays and capsules, CR dosage forms, osmotic pumps CR solid dispersions dosage forms hydrophilic matrices have been developed[14-18].

The objective of the present study is to develop a colon targeted matrix tablet of metoprolol and to study the dissolution of metoprolol succinate from kondagogu gum based formulations.

MATERIALS AND METHODS

Materials

Metoprolol succinate was obtained as gift sample from Dr. Reddy's laboratories, Hyderabad; Kondagogu gum was procured from Girijan Co-operative Society, Hyderabad; Directly compressable lactose (DCL) was obtained as gift sample from Strides Arcolab Ltd., Bangalore; All other chemicals used were of analytical grade and purchased from Loba Chemie, Mumbai.

Purification of kondagogu gum

Kondagogu gum was procured from Girijan Co-operative Society. First the foreign extraneous matter like bark etc was separated.Then the gum was powdered by using mortar and pestle. Further fine powder of gum was obtained using mixer grinder. The powdered gum was passed through sieve # 65 and used for further studies .The powdered gum is dispersed in distilled water to get a 1% solution. The solution was sonicated for 10 min ans ethanol was added in the ratio of (2:1 v/v) to give precipitate of the gum. Precipitated polymer is dried in an oven kept in an oven, powdered, passed through sieve # 80 and used for further studies.

Cross linking of kondagogu gum

A solution of kondagogu gum was prepared by dissolving 1 g of gum in a beaker which containing 5 ml of a 0.5 M sodium hydroxide (NaOH) aqueous solution. Solution of tri sodium tri meta phosphate (STMP) was prepared by dissolving STMP in a beaker containing 50 ml of deionized water. The aqueous phase was obtained by mixing the gum solution and STMP solution and stirring the mixture for 45 min. The solution was then dried overnight in an oven at 45 ^{0}C and the dried gum was powdered and used for further study.

Preparation of tablets

Accurately weighed quantities of drug, polymer (cross linked kondagogu gum) and binder (PVP K-30, 4% w/w) were physically mixed with a mortar and pestle.

Required quantity of the solvent (ethanol) was added and the same was mixed thoroughly to form a mass suitable for preparation of granules. The dough mass was passed through sieve # 22 to form granules which were dried in an oven at 50^0C. The granules were mixed with required quantities of diluent (DCL), lubricant (talc, 3% w/w) and were compressed to form tablets in a 10 station rotary tablet machine (Rimek, Ahmedabad, India) at 10 rpm and using 9 mm round concave punches at an optimum pressure. Ten formulations were prepared by varying the amount of pure kondagogu gum and cross linked KG viz., 30, 40, 50, 60 and 70% w/w of the tablet and coded as F1, F2, F3, F4, F5 F6, F7, F8, F9 and F10 respectively. The composition of various formulations is shown in Table 1.

Coating of the prepared tablets

For the purpose of enteric coating, a solution of shellac (10% w/v) in ethanol was used along with PEG 6000 (4% w/w of shellac) as plasticizer. The coating solution was passed through a 0.3 mm sieve prior to coating. The prepared matrix tablets were coated with shellac solution till a weight gain of 2.5% w/w over the tablets was obtained. Coating of the tablets was carried out in a conventional coating pan (Ram Scientific Suppliers, Bangalore, India) at an inlet temperature of 55^0C, pan rotation speed of 15 rpm, spray pressure of 4 kg/cm^2 and a spray rate of 1 ml/min. A omega type spray gun (Type 79) fitted with a 1 mm atomizing nozzle was used to spray the solution. The coated tablets were evaluated for hardness and drug content.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the pure kondagogu gum and cross linked KG, pure metoprolol succinate and the optimized formulation were recorded using a Fourier transform infrared spectrophotometer (FTIR 8400 Shimadzu, Japan)[19]. Samples were prepared as KBr disks using a hydraulic pellet press and scanned from 4000 to 400 cm^{-1}.

Evaluation of prepared tablets

The prepared tablets were evaluated for weight variation, friability (Electrolab EF-2 friabilator, Mumbai, India), thickness (Mitotoya screw guage), and hardness (Inweka hardness tester IHT 100). Evaluation data for the prepared formulations were shown in the Table 2[20].

Content Uniformity

Twenty tablets of metoprolol succinate were weighed and powdered. Crushed tablet powder equivalent to 0.15 gm of drug was weighed and dissolved in pH 6.8 Phosphate buffer. The solution was filtered, diluted and drug content was analyzed spectrophotometrically at 222 nm.

***In vitro* drug release study**

Release studies were carried out using USP XXII dissolution apparatus, basket type at 100 rpm and 37 ± 1˚ C. The formulations were tested to account for individual variability by subjecting the formulation to prolong dissolution studies based on conditions mimicking from mouth to colon and GI transit time. The release studies were carried out for tablets coated with shellac.

The tablets were tested for drug release for 2 hrs in 1.2 pH HCl buffer (900 ml), as the average gastric emptying time is about 2 hrs. Then the dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) and tested for drug release for 3 hrs. Later the studies were conducted in 200 ml of simulated colonic fluids.

In case of control conditions, the extent of drug release in absence of colonic contents was examined. Here the dissolution for the prepared formulations was carried out for the first 5 hrs as above. Later the dissolution medium was replaced with 900 ml of pH 7 saline phosphate buffer. The dissolution was further carried out for 7 hrs. The results obtained were compared in order to find out the drug release in presence and absence of ceacal contents.A 10-ml aliquot of the dissolution solution was withdrawn at regular interval of time and analyzed for drug released using a UV– visible spectrophotometer at λ_{max} of 222 nm. A 10-ml of the same solution maintained at 37.5˚C was replaced back to the dissolution vessel so as to maintain the sink conditions.

Preparation of simulated colonic fluid

To evaluate the performance of colon specific delivery systems triggered by colon specific bacteria, animal cecal contents of rats, rabbits and pigs have been utilized as alternative dissolution medium. Because of the similarity of human and rodent colonic microflora, predominantly comprising *Bifidobacteria*, *Bacteroides* and *Lactobacillus*, rat cecal contents were used for dissolution studies. Rat cecal contents have been collected and immediately suspended in saline phosphate buffer of pH 7, which was previously aerated with carbon dioxide to maintain anaerobic condition. The above solution was kept in an incubator for 24 hrs to ensure that the bacteria present multiplies and sufficient enzymes will be produced. Later the suspension is filtered through Whatmann no. 42 filter paper and 4 % w/v solution of ceacal contents was prepared. This solution was used for dissolution studies as simulated colonic fluid (SCF). Incubation of the prepared solution was carried out in order to induce the enzyme concentration. This is to simulate the conditions of human colon wherein large amount of cecal contents will be present. During all the processes, the solution was kept bubbled with carbon dioxide to maintain anaerobic

condition as the bacteria present in cecal contents are predominantly anaerobic. Dissolution studies were carried out in both incubated and un incubated SCF to check the effect of incubation over drug release.

Mechanism of drug release

The kinetics of metoprolol succinate release from tablets formulations were determined by from release data to Korsmeyer-Peppas plot.

Korsmeyer-Peppas model is one of the mathematical expressions to evaluate the mechanism of drug delivery. The Korsmeyer-Peppas equation is as follows;

$$M_t/ M_\infty = 1- A (exp^{-kt}) \quad (1)$$

$$\log (1 - M_t/M_\infty) = \log A – kt/2.303 \quad (2)$$

where, M_t/M_∞ is the fractional amount of drug released and t is the time in hrs. In this study, the release constant, k and constant, A were calculated from the slopes and intercepts of the plot of In $(1- M_t/M_\infty)$ versus time t respectively where, M_t is the amount of drug release at time t; M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release. To find out the release exponent, the log value of percentage drug dissolved was plotted against log time for each batch according to the above equation. If value of n is equivalent to 0.5 it indicates Fickian (case I) release; if n is greater than 0.5 but less than 1 for non-Fickian (anomalous) release and n is greater than 1 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain, and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release[21].

Stability studies

Stability studies of the optimized formulations of metoprolol succinate tablets was carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 40 ºC/75% RH for 3 months (Thermolab, Mumbai, India).The formulation was analyzed at every 15 days interval for its hardness and % drug content.

Differential scanning calorimetry (DSC)

DSC thermograms were recorded for pure metoprolol succinate drug and the optimized formulation using a differential scanning calorimeter. Accurately weighed samples were placed on aluminum plates, sealed with aluminum lids, and heated at a constant rate of 5 °C/min over a temperature range of 0–400 °C. All dynamic DSC studies were carried out using DuPont thermal analyzer with 2010 DSC module[19].

RESULTS AND DISCUSSION

The prepared tablets were having an average diameter of 9 mm. Percentage weight variation, percent friability and content of active ingredient for all the formulations were found to be well within United States Pharmacopoeia (USP) limits. From table 2 it is clear that the hardness of the core tablets increased as the amount of polymer concentration in the tablet increased. Formulations containing 70% w/w of polymer showed maximum hardness among the various ratios selected (30%, 40 %, 50 %, 60 % and 70 % w/w). The percentage of drug content lies in the range 98.1- 100.4 %.

The tablets were evaluated for parameters such as average weight, hardness and drug content before and after coating. The results indicated that the hardness increased slightly after coating and it was observed that the weight increased upto 15 mg per tablet (table 3).

At basic pH a complex of di-polymer phosphate ester is formed from KG and STMP. The expected low-swelling product could potentially be used as an improved platform for colon-specific delivery of drugs

Kondagogu gum and modified gum (cross linked with STMP) were subjected for FTIR spectroscopic analysis for compatibility studies and to ascertain whether cross linking has occurred. There is a significant decrease in the intensity of the characteristic IR absorption peaks at 3428 (NH, OH stretching) and 1412 (C=O stretching vibrations). Absence of peaks at 2925.5 (C-O, C-H stretching), 1732.13 (C= O acetyl group) and1253.7 cm^{-1} (C-O acetyl group) confirms that cross linking has occurred. Appearance of new peaks at1103.12, 997.65 and 752.32 cm^{-1} further confirms that cross linking has occurred. As such, the P=O and P–O–C peaks could not be detected by the FTIR spectroscopy The IR spectra of pure kondagogu gum and cross linked kondagogu gum is presented in fig 1 and the data is tabulated in table 4.

Metoprolol succinate pure drug and the optimized formulation were subjected for FTIR spectroscopic analysis for compatibility studies and to ascertain whether there was any interaction between the drug and the polymers used. The IR spectra of metoprolol succinate and optimized formulation F9 were found to be identical and presented Fig 2 and table 5 The characteristic IR absorption peaks of metoprolol succinate at 3600-2300 (NH_2, OH - aliphatic and aromatic OH), 1580 (carboxylic acid salt), 1580 & 1515 (aromatic ring), 1250, 1015 (aromatic ether), 1180 (isopropyl group) and 1100 cm^{-1} (aliphatic ether, secondary alcohol) 820 1,4 (disubstituted benzene) were present in both pure drug and the formulation. FTIR spectra of the optimized formulation F9 showed all the metoprolol succinate characteristic absorption bands with

minor fluctuations suggesting the absence of interaction between the drug and the other components of the formulation.

The dissolution studies were carried out for 2 hrs in pH 1.2 HCl buffer, 3 hrs in pH 6.8 phosphate buffer and 6 hrs in SCF simulating stomach small intestinal and colonic transit times respectively. Results showed that there were no signs of cracking, peeling or disintegration of the tablets in pH 1.2 HCl buffer i.e., the tablets remained intact in pH 1.2HCl buffer. The data obtained is shown graphically in fig. 3-6 and tabulated in tables 6-9. From the data, it is clear that the tablets coated with shellac have prevented the drug release till the tablets reach small intestine.

For purified kondagogu gum: *In vitro* studies revealed that the formulations containing 30 (F1) and 40 % (F2) w/w of polymer (kondagogu gum) did not show sustained release whereas, the formulations containing 60% (F4) showed sustained drug release from the coated tablets over a period of time. Formulations F1 and F2 (30% and 40% w/w of polymer) exhibited burst release and released almost entire drug within 8 hrs of dissolution. Formulation containing 30% (F1) w/w showed almost 85.63% of the drug release within 6 hours whereas the formulation containing 70% (F5) w/w showed 49.63 % of the drug release in the same time. On the other hand tablets containing 70% w/w of kondagogu gum (F5) showed about 99.96 drug release at the end of 12 hrs of dissolution. Hence the order of drug delivery from the coated tablets with reference to polymer (kondagogu gum) concentration is; 30 >40 > 50 >60> 70%.

For crosslinked kondagogu gum (with STMP): *In vitro* studies revealed that the formulations containing 30% and 40% w/w of polymer viz., F6 & F7, released almost entire drug within 12 hrs of dissolution . Formulation containing 30 % (F6) w/w showed almost 53.65% of the drug release within 6 hours. On the other hand tablets containing 60% and 70% w/w of modified gum showed only about 88.61 and 81.52% of drug release at the end of 12 hrs of dissolution. Hence the order of drug delivery from the coated tablets with reference to percent of polymer (modified gum) concentration is as follows 30 >40 > 50 >60> 70 %. It can be stated that the retardation of drug release increased with increase in the concentration of modified polymer.

The data obtained from *in vitro* release studies was fitted into Peppas model. The various parameters the diffusion exponent 'n', the release constant 'k' and regression coefficient 'R' were calculated. The release mechanism was studied using Koresmeyer Peppas equation. For the formulations F1, F2, F3, F6, F7 'n' value was between 0.5 and 0.8 indicating the release followed non-Fickian diffusion, whereas for the formulations F4, F5, F8, F9 and F10 the values were above 1 indicating the release followed more than one mechanism i.e., super case II transport which implies that the release is by diffusion and relaxation of polymer chains. The interpretation of diffusional release mechanisms can be obtained by the data given in table 10 and the corresponding results were tabulated in table 11.

Stability studies of the drug formulations are performed to ascertain whether the drug undergoes any degradation during its shelf life. In the present study depending on hardness, drug content and *in vitro* drug release, formulation F9 was selected as optimized formulation. The stability studies for F9 were carried out at 40ºC/ 75%RH for 90 days. The metoprolol succinate content in the formulation at accelerated conditions along with 95% confidence limit was plotted using sigmaplot software 10.0. The observations of conditions are shown in table 12 and fig 7.

A 40^{o}C and 75 % RH the tablets showed good physical stability as the color remained about the same as that of the tablets before the stability study. The hardness of the tablets did not show much variation before and after the stability study. It was found to be about 6.4 kg. The assay values did not show much variation before and after the stability study. The % drug content of F9 was 99.2% and 97.98 % before and after the stability studies respectively.

In order to study any possible interactions between the drug and polymers, DSC studies were carried out. The DSC thermograms obtained are reported in the fig.3. From the thermograms it was observed that, metoprolol succinate displayed a single sharp peak at 138.49 ^{0}C corresponding to its melting point and peak at the same temperature was observed in the formulation. Hence it can be observed that there was no significant interaction between the drug and the polymers used even after keeping for 3 months of stability testing

CONCLUSION

The results obtained indicate that kondagogu gum as such cannot be useful for colon targeting but the modified kondagogu gum could be useful as matrix system for colon targeted drug delivery. The 12 hrs drug release study indicated that the optimized formulation is ideal for colonic release. Enteric coating and the rate of swelling has favored the colonic release of the drug from the formulation. The final product is expected to have the advantage of being biodegradable and pH dependant. Hence it can be stated that colon specific drug release can be obtained using modified kondagogu gum, a

naturally available, environmental friendly, non-toxic and biodegradable gum as carrier.

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Table 1: Formulation chart of metoprolol succinate matrix tablets

Formulation code	Avg. Wt. (mg)	% weight variation*	Thickness (mm)	Hardness (kg)	Friability (%)	% Drug content*
F1	302	-2.4 to +3.9	4.97±0.15	5.4±0.63	0.88±0.92	99.9±0.41
F2	299	-2.0 to +2.2	4.92±0.12	5.5±0.71	0.84±0.71	98.1±0.83
F3	300	-3.5 to +2.2	5.05±0.16	5.8±0.48	0.71±0.51	99.1±0.77
F4	298	-2.4 to +3.2	4.89±0.15	5.9±0.96	0.71±0.51	99.2±0.41
F5	301	-2.6 to +3.2	4.93±0.13	5.9±0.71	0.78±0.41	100.4±0.11
F6	298	-2.6 to +3.5	4.95±0.18	5.7±0.62	0.78±0.41	98.9±0.77
F7	300	-2.7 to +3.1	4.94±0.13	5.8±0.55	0.86±0.35	100.4±0.11
F8	299	-2.6 to +2.9	4.95±0.18	6.1±0.74	0.82±0.64	98.9±0.77
F9	297	-2.4 to +3.5	4.82±0.11	6.3±0.67	0.76±0.57	99.2±0.24
F10	302	-2.3 to +2.9	4.92±0.18	6.3±0.52	0.65±0.49	98.6±0.39

*mean ± SD, n = 3

Table 2: Evaluation data of prepared metoprolol succinate tablets

Formulation	Metoprolol succinate (mg)	Polymer (kondagogu gum) (mg)	Cross linked polymer (mg)	Diluent (Lactose) (mg)	Binder PVP (mg)	Talc(mg)
F1	50	90	----	139	12	9
F2	50	120	----	109	12	9
F3	50	150	----	79	12	9
F4	50	180	----	49	12	9
F5	50	210	----	19	12	9
F6	50	----	90	139	12	9
F7	50	----	120	109	12	9
F8	50	----	150	79	12	9
F9	50	----	180	49	12	9
F10	50	----	210	19	12	9

Table 3: Evaluation data of coated tablets

Formulations	Avg wt (mg)*	Hardness (Kg)*	% Drug content*
F1	316.9±1.9	5.5±0.96	97.7±0.71
F2	315.5±1.45	5.7±0.63	97.8±0.46
F3	316±1.8	5.9±0.71	98.1±0.25
F4	316.4±2.38	6.1±0.48	99.06±0.41
F5	317.1±2.47	6.1±0.71	98.3±0.28
F6	315.3±1.35	5.9.±0.48	97.7±0.46
F7	316.1±1.5	6.0±0.35	97.0±0.45
F8	316.8±1.25	6.2±0.56	97.5±0.37
F9	315.9±2.43	6.3±0.84	98.7±0.73
F10	317.2±1.86	6.3±0.64	99.12±0.82

*mean ± SD, n = 3

Table 4: FTIR spectral data of pure kondagogu gum and cross linked kondagogu gum

Groups	Peak positions in kondagogu gum (cm^{-1})	Peak positions in cross linked kondagogu gum (cm^{-1})
OH, NH streching	3430.6	3429.8(low intensity)
C-O, C-H streching	2925.5	---------
C= O acetyl group	1732.13	---------
C-N, COO^- stretching	1417.12	1412.2(low intensity)
C-O acetyl group	1253.7	---------
P-O-C vibrations	---------	1103.12,997.65,752,32

Table 5: FTIR spectral data of pure drug and optimized formulation F4

Groups	Peak positions in pure drug (cm^{-1})	Peak positions in F9(cm^{-1})
3600-2300 NH_2, OH, aliphatic OH	3149.96 2943.47 2875.96 2847.03	3146.97 2943.47 2876.69 2829.67
1580 carboxylicacid salt	1560.20	1561.71
1515 aromatic ring	1516.10	1517.21
1250 aromatic ether	1242.24	1243.47
1180 isoproppyl ether, secondary alcohol	1186.26	1184.58
820 (1,4 disubstituted benzene)	842.92	846.65

Table 6 :*In vitro* release data of prepared metoprolol succinate tablets in the absence of rat cecal contents for the formulations F1 – F5

Time (hr)	Cumulative % drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
2	0	0	0	0	0
4	49.96 ± 3.45	49.14 ± 2.29	43.80 ± 2.68	29.56 ± 2.83	28.19 ± 1.28
5	60.28 ± 2.19	55.19 ± 1.83	47.93 ± 3.19	37.21 ± 3.29	33.19 ± 2.73
6	75.59 ± 2.24	59.30 ± 1.52	50.45 ± 3.14	43.75 ± 3.75	39.66 ± 2.24
8	82.75 ± 2.36	76.29 ± 3.45	59.53 ± 1.36	54.73 ± 1.34	51.26 ± 3.69
10	99.49 ± 1.14	83.89 ± 2.76	76.29 ± 2.73	67.87 ± 3.59	59.80 ± 1.48
12	----	99.64 ± 1.84	83.71 ± 3.57	79.16 ± 2.12	77.27 ± 2.19

Table 7 :*In vitro* release data of prepared metoprolol succinate tablets in the absence of rat cecal contents for the formulations F6 – F10

Time (hr)	Cumulative % drug release				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
2	0	0	0	0	0
4	39.84 ± 3.52	27.69 ± 1.29	25.33 ± 1.64	19.11 ± 2.32	17.13 ± 1.46
5	44.98 ± 2.49	36.39 ± 2.18	33.29 ± 2.82	28.97 ± 1.98	23.18 ± 1.72
6	47.60 ± 2.71	39.77 ± 2.86	38.26 ± 2.88	34.23 ± 1.28	29.48 ± 2.69
8	51.97 ± 1.46	50.71 ± 3.49	48.30 ± 3.73	43.46 ± 3.54	35.19 ± 3.25
10	71.84 ± 2.59	63.74 ± 3.83	63.24 ± 2.92	55.15 ± 2.82	48.06 ± 2.37
12	83.07 ± 3.48	78.84 ± 1.38	73.05 ± 1.59	64.17 ± 2.39	58.59 ± 1.29

Table 8 :*In vitro* release data of prepared metoprolol succinate tablets in the presence of rat cecal contents for the formulations F1 – F5

Time (hr)	Cumulative % drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
2	0	0	0	0	0
4	50.02 ± 1.34	49.74 ± 2.84	45.16 ± 1.24	33.22 ± 1.74	28.19 ± 1.36
5	67.43 ± 1.29	62.29 ± 2.57	53.39 ± 1.76	44.62 ± 1.87	41.29 ± 2.71
6	85.63 ± 2.76	80.90 ± 2.37	75.02 ± 2.39	71.24 ± 2.37	49.63 ± 2.54
8	98.91 ± 1.53	94.75 ± 2.56	84.85 ± 2.72	82.29 ± 2.51	81.12 ± 2.78
10	----	----	95.96 ± 1.93	94.38 ± 2.47	91.14 ± 1.16
12	----	----	----	----	99.96 ± 1.94

Table 9 :*In vitro* release data of prepared metoprolol succinate tablets in the presence of rat cecal contents for the formulations F6 – F10

Time (hr)	Cumulative % drug release				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
2	0	0	0	0	0
4	43.80 ± 1.72	35.17 ± 3.18	30.18 ± 1.21	19.88 ± 1.36	18.18 ± 1.15
5	49.21 ± 1.92	42.12 ± 2.98	34.18 ± 1.46	25.76 ± 1.98	24.21 ± 3.27
6	53.65 ± 1.64	53.69 ± 3.36	48.16 ± 2.38	40.29 ± 2.22	37.55 ± 2.28
8	71.92 ± 2.47	68.44 ± 2.52	64.61 ± 1.58	59.20 ± 3.48	55.66 ± 2.34
10	83.21 ± 2.32	80.41 ± 1.68	79.44 ± 2.65	73.60 ± 1.92	69.14 ± 3.46
12	97.75 ± 1.24	94.12 ± 2.72	91.25 ± 3.79	88.61 ± 1.76	81.52 ± 3.58

Table 10: Interpretation of diffusional release mechanisms

Value of constant, n	Drug transport mechanism
<0.5	Fickian diffusion
>0.5<1.0	Non-fickian diffusion
Higher than 1.0	Super case II transport

Table 11 : Data obtained from peppas model fitting for the formulations

Formulation code	R	K	n
F1	0.9068	24.687	0.5995
F2	0.9776	22.0939	0.6427
F3	0.9973	19.4329	0.6427
F4	0.9944	7.6039	1.0287
F5	0.9924	7.3312	1.0115
F6	0.9992	15.8985	0.7250
F7	0.9967	7.829	0.9768
F8	0.9977	4.6329	1.1855
F9	0.9935	3.7043	1.2697
F10	0.9788	3.7114	1.2340

R= Regresion coefficient, K= Release constant, n= Diffusion exponent for peppas.

Table 12: Stability studies of optimized formulation F9

Sampling Interval (days)	% Drug content	Hardness (N)
0	99.12 ± 1.36	6.4 ± 0.84
15	99.18 ± 1.45	6.4 ± 0.76
30	98.87 ± 1.48	6.4 ± 0.78
45	98.91 ± 0.92	6.4 ± 0.29
60	97.95 ± 1.27	6.3 ±0.53
90	97.98 ± 1.68	6.4 ± 0.82

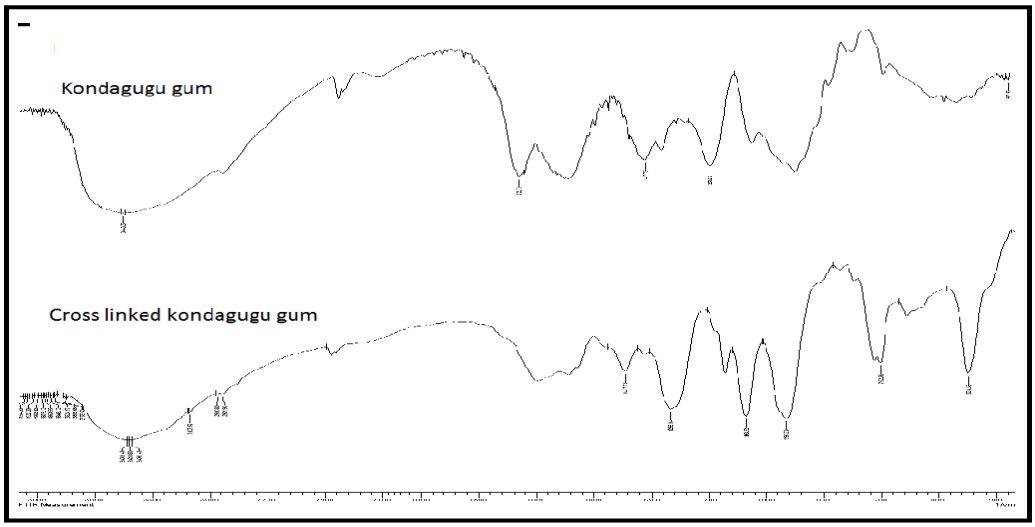

Fig 1. FTIR spectra of pure gum(kondagogu gum) and cross linked gum

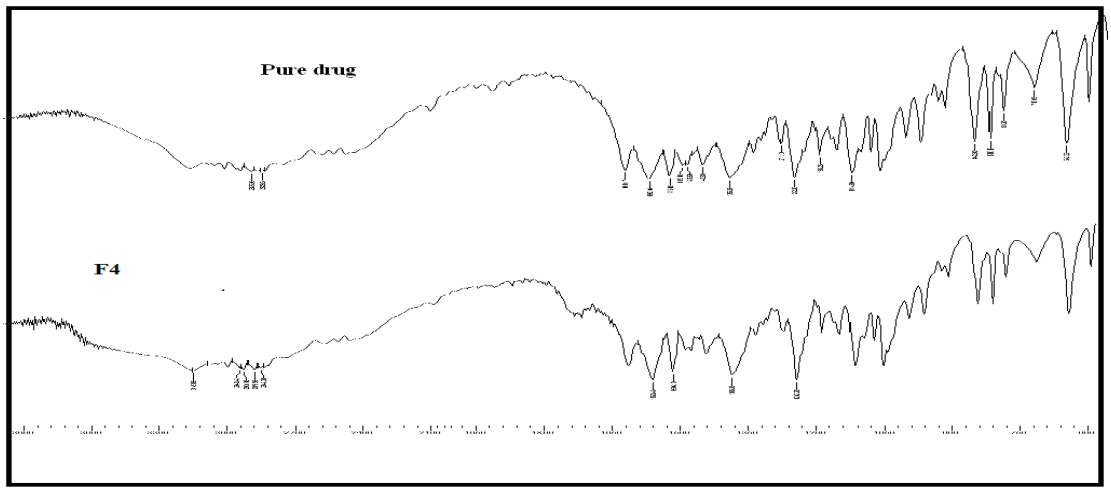

Fig 2: FTIR spectra of pure drug and optimized formulation F9

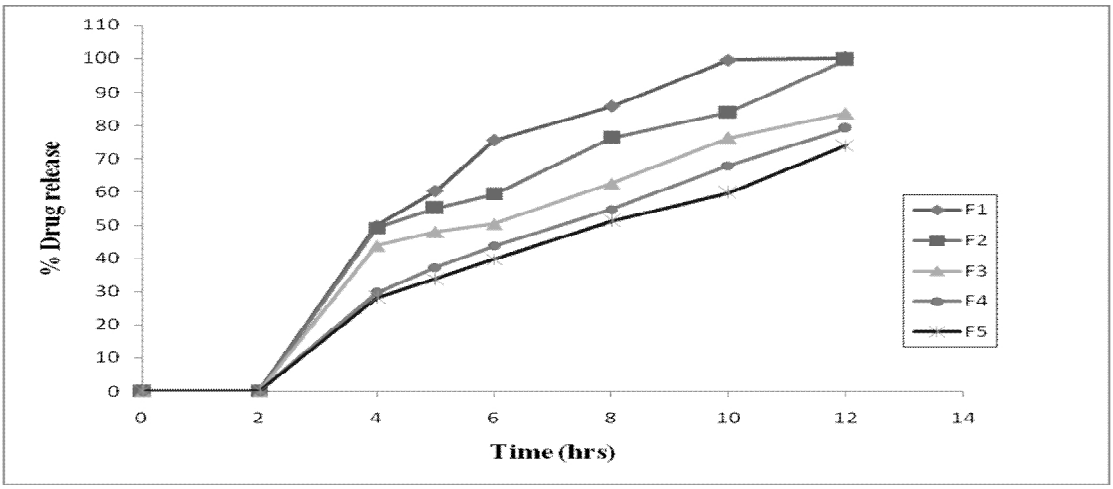

Figure 3: *In vitro* release pattern for the formulations F1-F5 in the absence of rat cecal contents

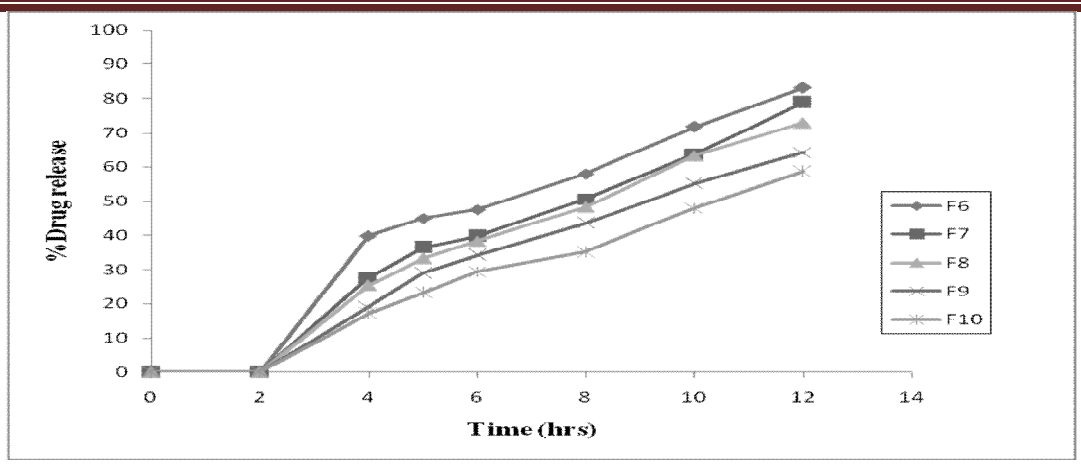

Fig. 4: ***In vitro*** **release pattern for the prepared formulations F1-F5 in the absence of rat cecal contents**

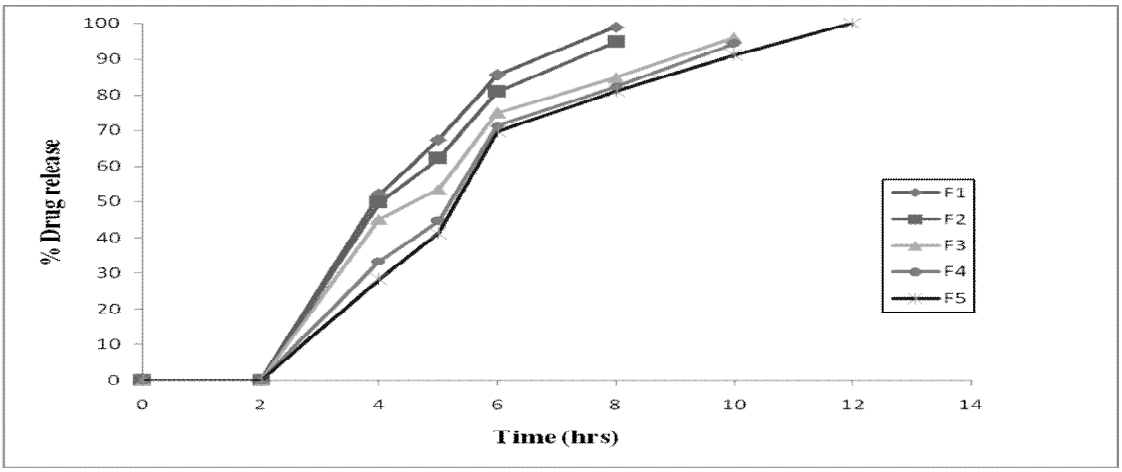

Fig 5*: In vitro* release pattern for the prepared formulations F1-F5 in the presence of rat cecal contents

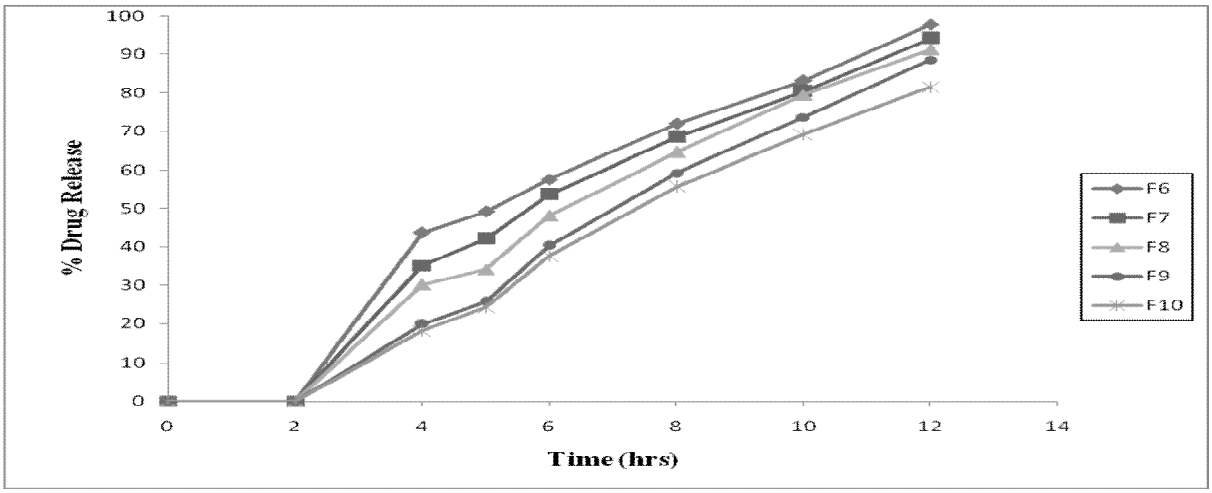

Fig. 6: ***In vitro*** **release pattern for the prepared formulations F6-F10 in the presence of rat cecal contents**

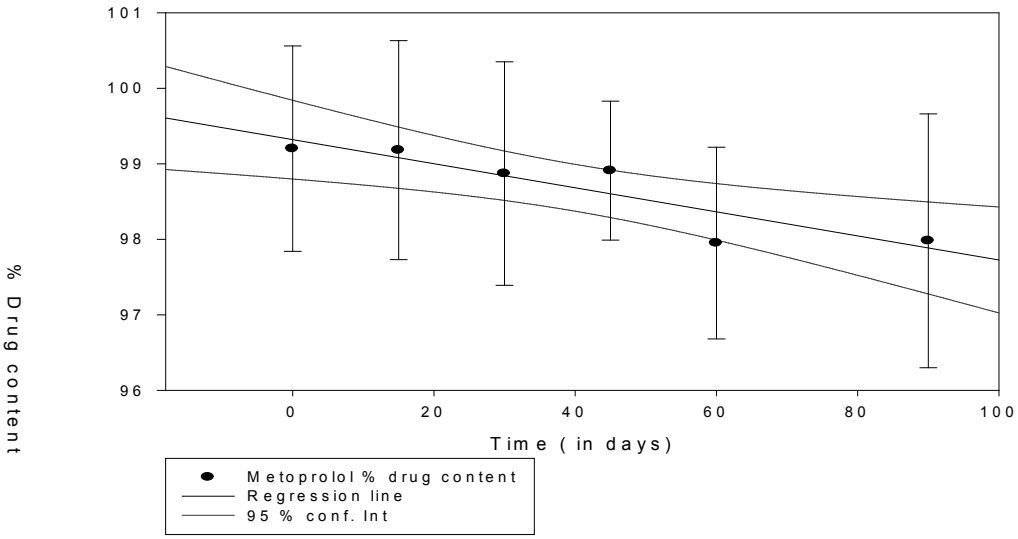

Fig.7: Metoprolol succinate content in F9 when stored at 40ºC/ 75%RH for 90 days

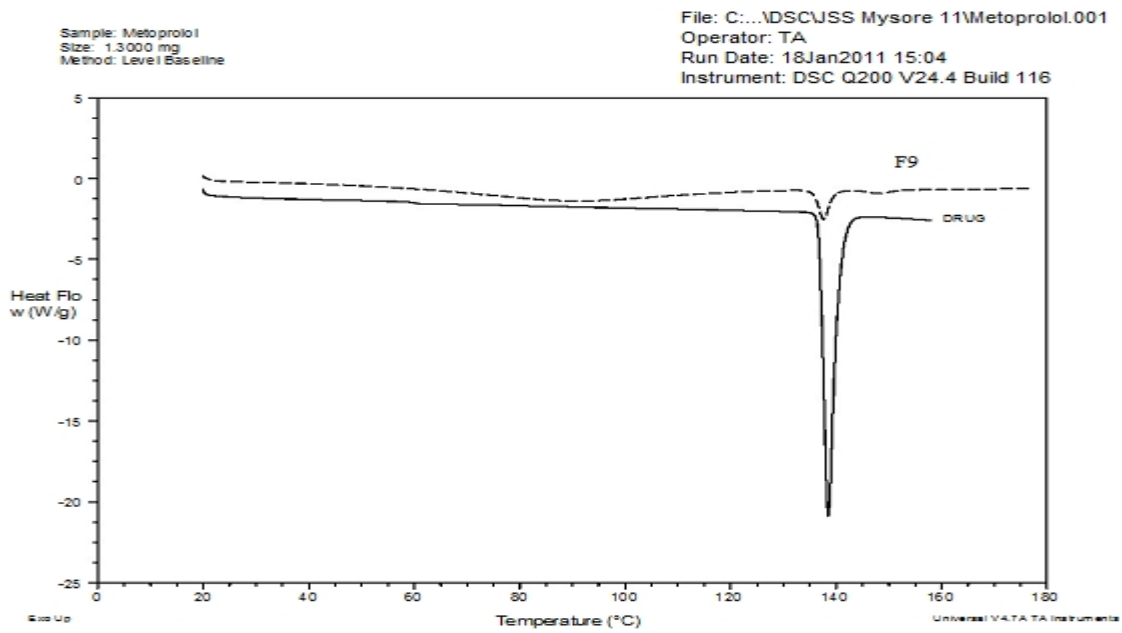

Fig 8: DSC thermogram of pure drug and optimized formulation F9

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