Research Article

Formulation and Evaluation of Sustained Release Matrix Tablets of Ciprofloxacin HCL Using Gum Kondagogu and Chitosan as Matrix Forming Polymers

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ABSTRACT

The purpose of the present study was to design sustained release matrix tablets of Ciprofloxacin HCl with natural polymers (gum kondagogu and chitosan). Various formulations of Ciprofloxacin HCl, gum kondagogu (GK) and chitosan (CS) in different proportions were prepared by direct compression process. The pre-formulation studies such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio was evaluated for powdered blend, the formulated tablets were evaluated for thickness, weight variation, hardness, friability, drug content, swelling behaviour. All parameters were within the acceptable limits. IR spectral analysis showed there were no interactions between drug and polymer .The *in-vitro* dissolution study proved that as the polymer ratio is increased, then release of the drug is prolonged due to electrostatic interactions between carboxyl group of GK and amine group of CS. The drug release data obtained were extrapolated by Zero order, First order, Higuchi matrix, Hixson-Crowell's, Korsmeyer Peppa's equations. The *in-vitro* release profile of drug from CGC-1 to CGC-4 formulations could be best expressed by Zero order and Korsmeyer Peppa's equation as the plots showed highest linearity. It confers drug release is by diffusion.

Keywords: *In-vitro* dissolution study, Natural polymers, Sustained release tablets.

INTRODUCTION

Natural polymers are becoming very popular in formulating oral controlled-release tablets as they are bio compatible, biodegradable, non-toxic, cheap and easily available compare to synthetic polymers. In present study GK and CS has been selected as natural polymers.

GK is a naturally occurring polysaccharide derived as an exudate from the tree *Cochlospermum gossypium* and family Bixaceae. It is a polymer of arabinose, rhamnose, mannose, fructose, galactose, galacturonic acid, β -D-galactopyranose, glucuronic acid, α-D-glucose and β-D-glucose. A few works were reported on GK as mucoadhesive polymer,[1] polymer in gastro retentive systems and also proved it is a negative colloid can be used as food additive as it is non toxic.[2-4]

CS is a deacetylated form of chitin, CS is a linear cationic polysaccharide composed of glucosamine and N-acetyl glucosamine linked in a β -linkage. CS has been reported to possess immune stimulating properties such as promoting resistance to bacterial infection.[5]

Ciprofloxacin HCl is a broad spectrum flouroquinolone. It functions by inhibiting bacterial DNA gyrase necessary for its cell division, which is commonly prescribed drug for the treatment of patients suffering with urinary tract infection, acute uncomplicated cystitis, chronic bacterial prostatitis, lower respiratory tract infections, skin and structure infections etc. It is almost insoluble in water. The bioavailability, half life is 60-70%, 3-4 h respectively. These properties required the administration of 250-500 mg twice daily for 1-2 weeks. The fabrication of Ciprofloxacin HCl sustained release matrix tablets using GK and CS would be useful compared to the current dosage regimen.

The aim of the present study is to develop Ciprofloxacin HCl sustain release tablets using natural polymers (gum Kondagogu and chitosan) and to evaluate the *in-vitro* properties of the tablets.

MATERIALS AND METHODS

Chemicals

Ciprofloxacin HCl was obtained as a gift sample from Micro Lab Ltd., Bangalore. GK is procured from Girijan co-operative corporation, Vizag. CS is procured from Purex, Bangalore. Micro crystalline cellulose (Avicel) and magnesium stearate were procured from SD Fine Chemicals (Mumbai, India). All other chemicals used were of analytical grade and double distilled water was used throughout the experiments

Extraction of Gum

GK powder (1 g) was weighed accurately, and transferred into a clean glass beaker containing one litre of de-ionized water. Three volumes of this solution were mixed with one volume of 1M NaOH solution. The gum solution was kept at room temperature with gentle agitation on a magnetic stirrer for overnight and kept standstill for 12 h, one volume of 1M HCl was added to neutralize the solution. The gum solution was filtered through a sintered glass funnel #G-2 followed by#G-4 sintered funnel. The solution was freeze-dried and stored, until further use. All the chemicals used in the extraction process were of analytical grade.[6]

Characterization of Mucilage[7]

The mucilage was collected and was evaluated for various physicochemical characteristic parameters. The results are shown in Table 1.

Table 1: Characterization of GK

Parameters	GK
Description	white crystalline powder
Solubility (1% w/v)	soluble in water
Molecular weight	7.23±0.15 x 10^6
Swelling index in distilled water	4.7±0.329
Moisture content (g %)	15.25±1.289
pH (1% w/v in water)	5.0±0.1
% ash value (g)	6.1±0.78
Water binding capacity (ml/g)	34.1±0.55
Intrinsic Viscosity (1%w/v) poise	33.68±0.67
Specific rotation	+53.5
Angle of repose (^{o})	29.74±0.682
Loose Bulk Density (g/cm^3)	0.704±0.014
Tapped Bulk Density (g/cm^3)	0.846±0.010
% Carr's Compressibility Index	16.7±0.022
Hausner's ratio	1.201±0.032

**All values are mean ± SD, n=3.*

Drug-Excipient compatibility studies

Fourier Infrared (FT-IR) Spectroscopy

The physicochemical interaction between Ciprofloxacin HCl and polymers (GK and CS) were carried out using Bruker FT-IR spectrophotometer. The pellet preparation was carried out using about 4 mg of powder compressed with 100 mg of KBr. The scans were obtained at a resolution of 2 cm^{-1} from 4000 to 400 cm^{-1}.

Preparation of sustained release matrix tablets

Sustained release matrix tablets of Ciprofloxacin HCl with GK and CS were prepared by direct compression process using different drug: polymer ratios was shown in Table 2. GK and CS were used as matrix forming material while starch as a diluent and magnesium stearate as a lubricant. All ingredients except magnesium stearate were weighed, sifted through #40 sieve and blended in poly bag for 10 min. Magnesium stearate was passed through #80 mesh which was added to the above blend and lubricated for 5 min in polybag. From the final blend tablets were compressed using 8mm flat level edged round punches. These matrix tablets were evaluated for their physical properties as per I.P methods.

Evaluation of powder blend

Angle of Repose (Fixed Funnel Method) [8-10]

The angle of Repose was determined by passing powder blend through funnel fixed to a burette stand at a particular height. A graph was placed below the funnel on the table. The height and radius of the pile was determined by the following equation.

$$\Theta = \tan^{-1}(h / r)$$

h = height of the pile

r = radius of the pile

Table 2: Formulae of matrix tablets

Ingredients (mg)	CGC-1	CGC-2	CGC-3	CGC-4
Ciprofloxacin HCl	250	250	250	250
Gum Kondagogu (GK)	12.5	25	37.5	50
Chitosan (CS)	12.5	25	37.5	50
Starch	120	95	70	45
Magnesium stearate	5	5	5	5
Total weight of tablet	400	400	400	400

Bulk Density and Tapped Density

The powder sample was screened through sieve no: 18 and the sample equivalent to 25 g was weighed and filled into 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface form the height of 2.5 cm at 2 seconds intervals for 500 times. LBD and TBD were calculated using the following formulas.

LBD = weight of the powder / apparent unstirred volume

TBD = weight of the powder / tapped volume

Compressibility Index

The compressibility index of the powder blend was determined by Carr's compressibility index

Carr's index (%) = (TBD-LBD)/TBD X 100

Evaluation of Tablets

Thickness

The thickness of the tablets was determined using Digital micrometer. Ten individual tablets from each batch were used and average values were calculated.

Weight variation

Twenty tablets were randomly selected from each batch and weighed. The average weight and standard deviation were calculated. The test will be passed only if not more than two of the individual tablets weight deviate from the average weight more than the allowed percentage deviation and none deviate by more than twice the percentage shown.[11]

Hardness

The strength of the tablet is expressed as tensile strength (kg/cm^2). The tablet crushing load, which is the force required for breaking tablet by compression. It was measured using Pfizer hardness tester.

Friability

Ten tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min. Percentage friability was calculated by using following equation

% weight loss = {(Initial wt – Final wt) / Initial wt} X 100

Swelling behaviour of matrix tablets

The swelling behaviour of various formulations CGC-1, CGC-2, CGC-3 and CGC-4 were determined. The initial weight of each formulation was noted. One tablet from each formulation was placed in a petri dish containing phosphate buffer with a pH 7.4. At regular intervals of time (0, 2, 4, 8, 10 and 12 h) the tablet was taken and placed on the tissue paper and weighed. The % weight gain by the each tablet was calculated by using follow equation.[12]

$$S.I = \{(M_t - M_0) / M_0\} X 100$$

Where, S.I = Swelling Index, M = Weight of tablet at time't' and M_0 = Weight of of tablet at time 0.

***In-vitro* drug release studies**

In- vitro release of Ciprofloxacin HCl from the sustain release tablets were studied using USP II paddle method at 50 rpm in 900 ml of pH 7.4 buffer solution as dissolution medium. The dissolution medium was maintained 37° ± 0.5° C. A sample of Ciprofloxacin HCl matrix tablets equivalent to 250 mg was used in each test. 10 ml dissolution fluid were withdrawn every 60 min intervals for 12h the buffer solution was replaced to maintain constant volume throughout the experiment. The percentage of Ciprofloxacin HCl released from each formulation was measured at 278 nm using UV-Visible spectrophotometer (Shimadzu UV -1800, Asia Pacific). [13]

Drug Release Kinetics

The data obtained from *in-vitro* release studies were fitted in to various kinetic equations Zero order, First order, Higuchi matrix, Peppa's and Hixson Crowell to know the mechanism of drug release. The equation with high regression coefficient (r) and n values for formulation will be the best fit of release data. For Koresmeyer-Peppa's equation, if n is below 0.5 then the release is by fickian diffusion, 0.5<n<1 non-fickian diffusion and n=1 zero order release mechanism.[14]

Statistical analysis

Data were analysed by One- way analysis of variance. Difference between the means was calculated by student's t-test. P<0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Compatibility studies

IR spectrum of physical mixture containing Ciprofloxacin HCl, CS, GK shown in Fig. 1 were analysed, it was concluded that there were no changes in the peak shape and no shifts of peaks, so both the drug and excipients were compatible.

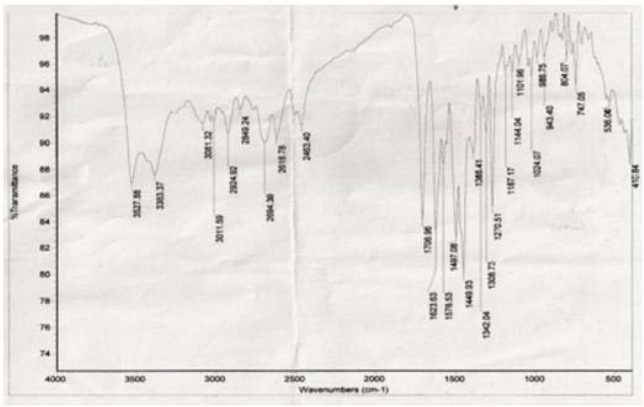

Figure 1: IR Spectrum of physical mixture of Ciprofloxacin HCl, GK and CS

Evaluation of granules and matrix tablet

The results of pre-compression and post-compression parameters of powder blend and matrix tablets shown in Table 3 revealed that the parameters of the prepared granules and matrix tablets were within the acceptable limits.

Swelling behaviour of matrix tablets

The better swelling behaviour studies were observed with CGC-5 formulation up to 12 h. The results are shown in Figure 2.

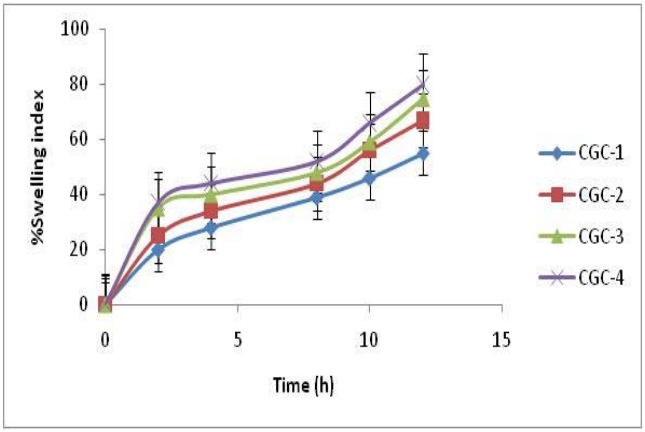

Figure 2: Swelling behaviour of formulated tablets

***In-vitro* drug release studies**

The results shown in Table 4 revealed that the *in-vitro* dissolution study drug release profile of Ciprofloxacin HCl from formulated matrix tablets was faster in CGC-1 and slower in CGC-4. The result shown that as the proportion of CS and GK was increased, the overall time of release of the drug from the matrix tablet was also increased**.**

Drug release Kinetics

The drug release data obtained were extrapolated by Zero order, First order, Higuchi matrix, Hixson-Crowell, Korsmeyer Peppa's equations to know the mechanism of drug release from these formulations. The results shown in Figure 3 and Figure 4 indicate that Zero order plots and

Korsmeyer Peppa's plots were linear for all formulations. The *in-vitro* release profile of drug from CGC-1 to CGC-4 formulations could be best expressed by Zero order equation as the plots showed highest linearity. It confers that the amount of drug release is independent of the concentration of dissolved species and prolonged pharmacological action can be obtained, the data was best fitted into Korsmeyer Peppa's equation, for all the the formulation showed good linearity indicating that anamolous diffusion was predominant mechanism of drug release.

Table 3: Evaluation of powder blend and matrix tablet

Evaluation of flow properties of powder blend					
F.Code	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio (HR)	Carr's index
CGC-1	31.05±1.00	0.426±0.006	0.454±0.02	1.06±0.055	6.16±0.94
CGC-2	31.78±0.60	0.456±0.009	0.511±0.01	1.12±0.001	10.76±0.88
CGC-3	32.50±0.19	0.467±0.009	0.488±0.06	1.04±0.011	4.30±0.85
CGC-4	32.05±1.00	0.478±0.005	0.495±0.05	1.03±0.02	3.40±1.71
Evaluation of Physical properties of formulated matrix tablets					
F.Code	Thickness (mm)	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
CGC-1	4.9±0.19	398±2.1	6.22±1.24	0.60±0.06	98.8±0.51
CGC-2	4.5±0.48	397±2.7	5.52±1.14	0.50±0.02	99.8±0.37
CGC-3	4.7±0.23	398±2.6	6.85±1.05	0.54±0.03	100.1±0.81
CGC-4	4.6±0.16	397±2.9	6.56±0.42	0.63±0.02	99.1±0.66

** All values are mean ± SD, n=3.*

Table 4: *In- vitro* dissolution profile of Ciprofloxacin HCl from formulation CGC-1 to CGC-4

Time (h)	% Drug release			
	CGC-1	CGC-2	CGC-3	CGC-4
1	13.46±0.26	12.50±0.32	11.60±0.30	7.5±1.01
2	19.94±0.18	17.94±0.24	16.24±0.14	11.6±0.22
3	23.42±0.10	21.42±0.16	19.21±0.24	13.79±0.45
4	28.03±0.51	27.06±0.14	25.22±0.31	19.96±0.54
5	37.16±0.42	35.21±0.40	33.13±0.32	25.03±0.36
6	45.60±0.32	43.16±0.31	39.85±0.45	30.16±0.76
7	62.41±0.24	57.13±0.46	50.17±0.31	39.46±0.85
8	75.16±0.70	66.19±0.42	64.16±0.54	48.42±1.23
9	86.12±0.82	76.14±0.51	74.81±0.70	59.16±0.87
10	99.72±1.01	91.6±1.03	87.02±1.04	71.16±1.14
11	-	99.45±1.12	92.5±0.79	84.33±1.32
12	-	-	99.47±1.31	91.64±0.89
13	-	-	-	99.67±0.92

**All values are mean ± SD, n=3.*

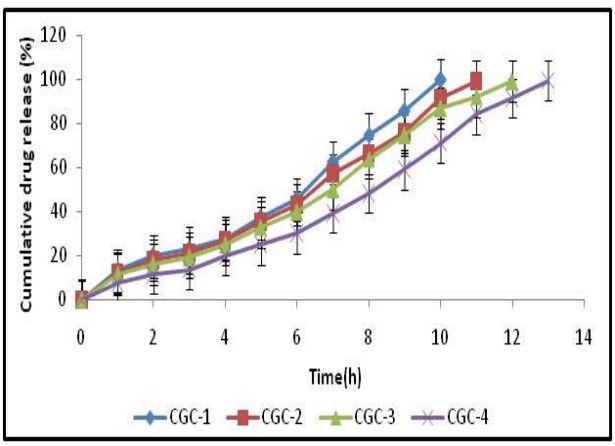

Figure 3: Zero order release Plots

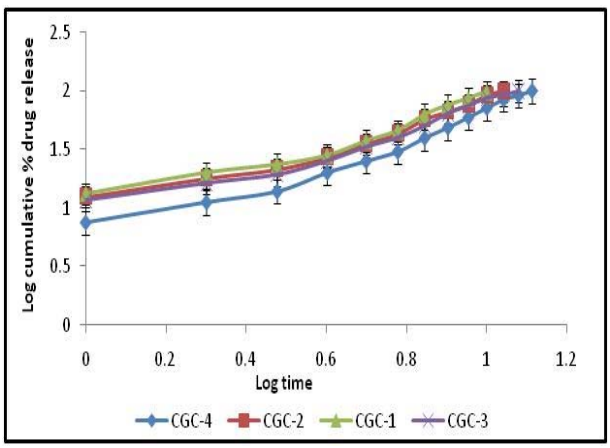

Figure 4: Korsmeyer Peppa's Plots

CONCLUSION

Fabrication of sustained release matrix tablets of Ciprofloxacin HCL using natural polymers (GK and CS) appears to be suitable for use as drug release retardants because formulated tablets gave satisfactory results for evaluation parameters such as swelling index, flow properties and *in-vitro* dissolution study. From the dissolution data obtained it was proved that as the concentration of polymer was increased the rate of drug release was prolonged and mechanism of drug release is by diffusion.

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