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Original Article

MODIFIED KONDAGOGU GUM AS MATRIX FORMING MATERIAL FOR SUSTAINED-RELEASE

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ABSTRACT

Objective: To develop sustained release matrix tablets of Tizanidine HCl using modified kondagogu gum.

Methods: Modified kondagogu gum was prepared by cross-linking kondagogu gum with sodium chloride, barium chloride, calcium chloride and sodium tripolyphosphate which was used as a crosslinker. Matrix tablets of Tizanidine HCl were prepared using unmodified kondagogu gum and modified kondagogu gum. The matrix tablets were evaluated for pharmacy technical properties and *in vitro* release.

Results: Tablets formulated with modified kondagogu gum showed higher mean dissolution time (MDT) and lower dissolution efficiency than those prepared with kondagogu gum. Percentage weight variation, percent friability and content of active ingredient for the prepared colon targeting tablets were found to be well within limits. *In vitro* release studies for prepared sustained release tablets were carried out for 2 h in pH 1.2 HCl buffer and 6 h in pH 7.4 phosphate buffer. A series of kondagogu gum based tablets were prepared for sustained release. FTIR studies confirmed that there was no chemical interaction between the drug and the polymers in modified kondagogu gum formulation.

Conclusion: The results of the study demonstrate that modified kondagogu gum is a potential matrix material for formulating suitable sustained-release matrix tablets of Tizanidine HCl.

Keywords: kondagogu gum, Tizanidine HCl, Sodium tripolyphosphate, Matrix tablets Sustained release

INTRODUCTION

Natural polymers and their derivatives are widely used to prepare various pharmaceutical dosage forms and drug delivery systems. Natural polymers are being modified to have tailor-made materials for developing novel drug delivery systems and thus can compete with synthetic polymeric materials which are widely used in the present market [1]. Oral sustained release drug delivery systems are being developed for the past several decades due to their considerable therapeutic advantages over the immediate release and conventional drug delivery systems [2, 3]. Natural polysaccharides hold several distinct advantages over synthetic polymeric materials as they are non-toxic, biodegradable, less expensive and easily available.

Kondagugu gum [KG] is the dried exudates obtained from tree Cochlospermum gossypium which belongs to the family Bixaceae [4].

KG is a high molecular weight complex acetylated polysaccharide consisting mainly of D-galacturonic acid, D-galactose, and L-rhamnose [5]. KG has aroused lot of interest in the preparation of hydrophilic matrix tablets because of its high water swellability, nontoxicity, and low cost. Unlike other water-soluble gums, it does not dissolve in water but absorbs it to form a viscous colloidal solution [6]. Powdered KG swells in cold water to an extent that a 3% to 4% sol will produce a gel of uniform smoothness and texture. Kondagogu gum has also been used for biosorption of nickel and total chromium from aqueous solutions [7].

Gum kondagogu modified magnetic nano adsorbent has also been prepared for removing toxic metal ions [8]. It was also used as a carrier in preparing floating drug delivery system [9]. And a polyelectrolyte complex in combination with chitosan [10]. Even though kondagogu gum is an important forest product, its commercial exploitation was limited due to non-availability of scientific information, especially in relation to its application in pharmaceutical preparations. In the present study, an attempt was made to develop polymeric blend beads of sodium alginate and kondagogu gum containing GAL as a model drug. The overall objective of the present investigation is to investigate the utility of kondagogu gum, a natural and biodegradable gum in pharmaceutical preparations as a carrier in formulating sustained drug delivery systems different formulations were prepared by varying the concentration of gums and the prepared beads were evaluated for particle size, scanning electron microscopy (SEM), percent yield, entrapment efficiency, differential calorimetry (DSC), Fourier transform infrared spectrophotometer (FTIR), *in vitro* drug release studies, diffusion coefficient (n) and stability studies.

A matrix may be defined as a uniform dispersion of a drug in a solid, which is less soluble than the drug in the depot fluid and which, as the continuous external phase of the drug from the matrix to the depot fluid.

The external phase in a matrix is usually hydrophobic material. Variables that are important in obtaining the desired action from a hydrophobic matrix are the concentration of the drug, the hydrophobicity of the external phase, the pore size and distribution thereof, and the pore length. The solubility of a drug in a depot fluid, to a considerable extent, determines which hydrophobic material and manufacturing technique can be selected. Hydrophilic materials such as polymers can also be used to provide a matrix for the drug particles.

MATERIALS AND METHODS

Materials

Tizanidine hydrochloride was purchased from Endoc pharma, Rajkot (Gujarat). Kondagogu gum (natural polymer) was purchased from Girijan corporative society, Govt. of Andhra Pradesh, Hyderabad. Sodium chloride, Calcium chloride. Barium chloride was purchased from Reachem Lab, Chennai. Polyvinylpyrrolidone K-30, Shellac were purchased from Loba chemie, Mumbai. Purification of gum

Methods

Procedure for the purification of kondagogu gum

First, gum was powdered by using mortar and pestle. Further fine powder of gum was obtained using mixer grinder. Gum was dispersed in distilled water to get a 1% solution. The solution was kept in a sonicator for 10 min until it was clear. After that, ethanol was added in the ratio of (2:1 v/v) to give precipitation of gum. The precipitated polymer is kept in an oven for drying and then powdered.

Preparation of cross-linked polymers using various cross linking agents like NACl, $CACl_2$, $BACl_2$, NATPP

Purified gum (1% solution) was prepared in distilled water. It was stirred using a magnetic stirrer until a solution is clear various cross-linking agents like sodium chloride, barium chloride, calcium chloride and sodium tripolyphosphate were added to the solution in desired quantities independently so as to get 5% and 10% cross-linked polymers. The solution was kept in oven for drying and then powdered

Formulation

Procedure for the preparation of tizanidine HCL sustained release tablets

Tablets intended for sustained release were prepared in three steps.

1. Preparation of granules.

2. Compression of granules into core tablet.

3. Coating of prepared tablets with shellac

All the process parameters were maintained constant in the preparation of tizanidine tablets. The formulation chart is shown in table 1.

Preparation of granules

The drug and excipients were passed through 80-mesh screen prior to the preparation of dosage form. The sieved drug, polymer, lactose and PVP K-30 were weighed separately and mixed thoroughly. The above blend was granulated using ethanol as a wetting agent. The resulting dough mass was passed through a 16-mesh sieve. The sieved fraction was dried in an oven at 50 ˚C until the LOD complied with the desired limits and then passed through a 22-mesh sieve.

Compression of granules into core tablets

The dried granules were mixed with talc as a lubricant and punched into 9 mm tablets, using a Rimek mini press tablet punching machine. The core tablet weight was adjusted to 300 mg.

Enteric coating of the tablets

Prepared tablets of all the formulations were coated with shellac, an enteric coating polymer. It was done to prevent drug loss from the tablets in the acidic environment of the stomach. Shellac solution (5 % w/v in ethanol) was used as a coating solution. PEG-400 (2 % of shellac) was used as a plasticizer. Coating parameters maintained were 20 RPM, at a spray rate of 2 ml/min and inlet temperature of 55˚ C. Coating was continued till the tablets gained over 2 % w/w of the tablet. These tablets were further tested for enteric coating.

Table 1: Formulation chart of Tizanidine HCl sustained release tablets

Formulation	Tizanidine HCl (mg)	Polymer (Cross-linked) (mg)	Diluent (Lactose) (mg)	Binder PVP (mg)	Talc(mg)
F1 (5 % NaCl)	4	210	65	12	9
F2 (10% NaCl)	4	210	65	12	9
F3 (5 % $CaCl_2$)	4	210	65	12	9
F4(10% $CaCl_2$)	4	210	65	12	9
F5 (5 % $BaCl_2$)	4	210	65	12	9
F6(10% $BaCl_2$)	4	210	65	12	9
F7(5% NaTPP)	4	210	65	12	9
F8(10 % NaTPP)	4	210	65	12	9
F9 *	4	210	65	12	9

Total weight of Tablet = 300 mg, *Formulation prepared using non-cross-linked polymer

RESULTS AND DISCUSSION

Calibration curve using 0.1 N HCL (PH 1.2)

Tizanidine Hydrochloride has the λmax at 320 nm. A standard graph of tizanidine hydrochloride in 1.2 pH and phosphate buffer pH 7.4 dissolution medium was plotted and a good correlation was obtained with R^2value of 0.9990.

Determination of absorption maximum (λ MAX)

Determination of tizanidine hydrochloride was done in 1.2 pH and phosphate buffer pH 7.4 dissolution medium for accurate quantitative assessment of drug dissolution rate. The λ max was found to be 320 nm.

Table 2: Calibration curve data of tizanidine hydrochloride in pH 1.2 HCl buffer

S. No.	Concentration (µg/ml)	Absorbance±SD.*
1	0	0
2	2	0.1279±0.057
3	4	0.2347±0.018
4	6	0.3398±0.084
5	8	0.4487±0.052
6	10	0.5504±0.046

*Standard deviation, mean n = 3

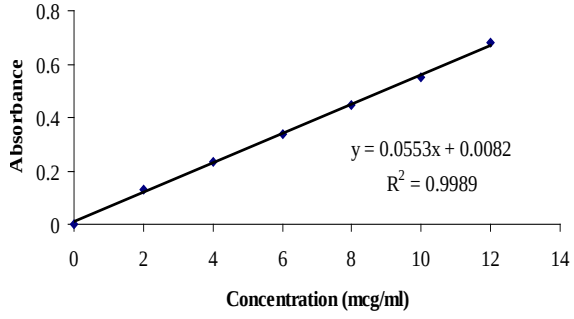


Fig. 1: Calibration curve of tizanidine hydrochloride in pH 1.2 buffer

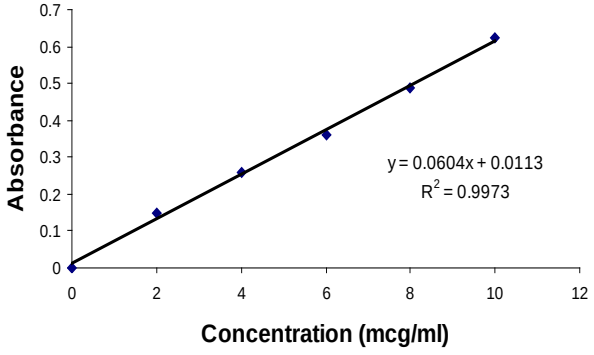


Fig. 2: Calibration curve of tizanidine hydrochloride in pH 7.4 phosphate buffer

Table 3: Calibration curve data of tizanidine hydrochloride in pH 7.4 phosphate buffer

S. No.	Conc (µg/ml)	Absorbance±SD.*
1	0	0
2	2	0.1488±0.061
3	4	0.2596±0.048
4	6	0.3617±0.051
5	8	0.4868±0.062
6	10	0.6217±0.048

*Standard deviation, mean n = 3

Flow properties of tablet blend

Angle of repose (θ)

The values obtained for the drug and polymer under investigation are shown in table 9. The results indicated that the polymer and drug have poor flow property. Hence wet granulation method was employed.

Bulk density (CARR'S INDEX)

The values obtained for Carr's index are shown in table 4. From the results obtained it is clear that the polymer and drug are having poorly compressible properties. Hence wet granulation method was employed for the preparation of tablets.

Drug excipient compatibility [11]

Compatibility between the drug, polymer and other excipients used were studied by using FT-IR spectroscopy. The drug tizanidine hydrochloride have exhibited general characteristic peaks. The position of peaks in FT-IR spectra of pure drugs are compared with those in FT-IR spectra of the formulations prepared. The spectra of pure drug tizanidine HCl are shown in fig. 3 and the spectra of prepared formulations F2, F4, F6, F8 and F9 are shown in fig. 4.

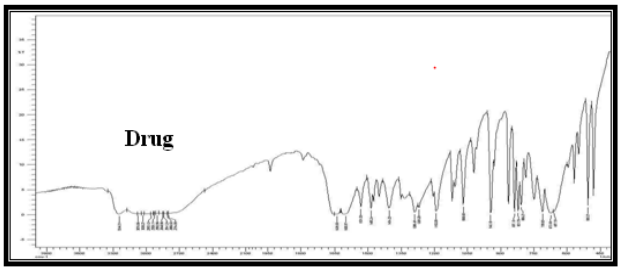
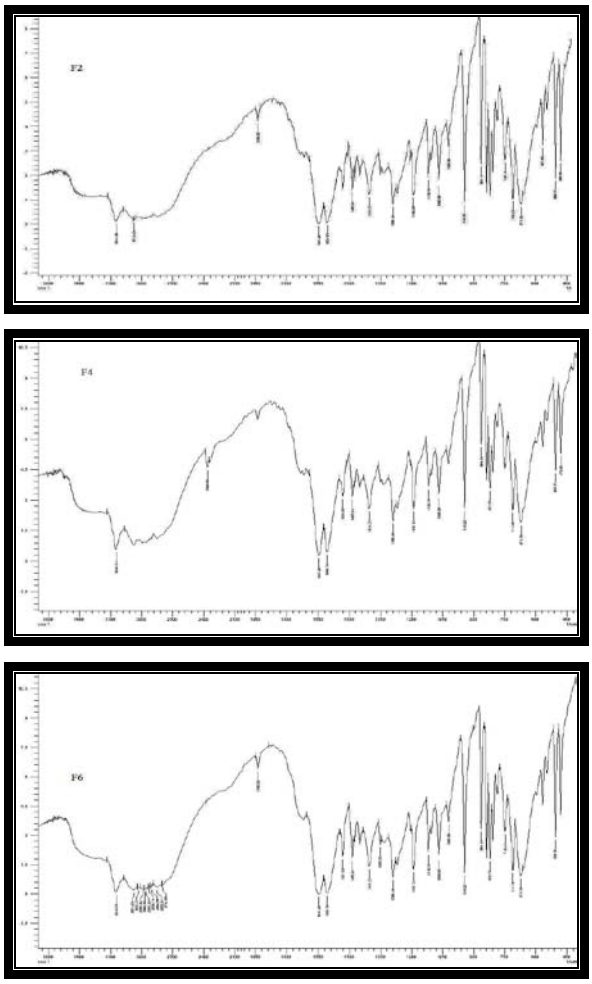


Fig. 3: FTIR data of pure drug

Table 4: Angle of repose and carr's index data obtained

S. No.	Material	Angle of repose (θ)*	Carr's index*
1	Tizanidine hydrochloride	33.35+0.50	34.65+2.5
2	Kondagogu gum	38.78+0.41	38.29+0.92

*Mean+SD., n=3



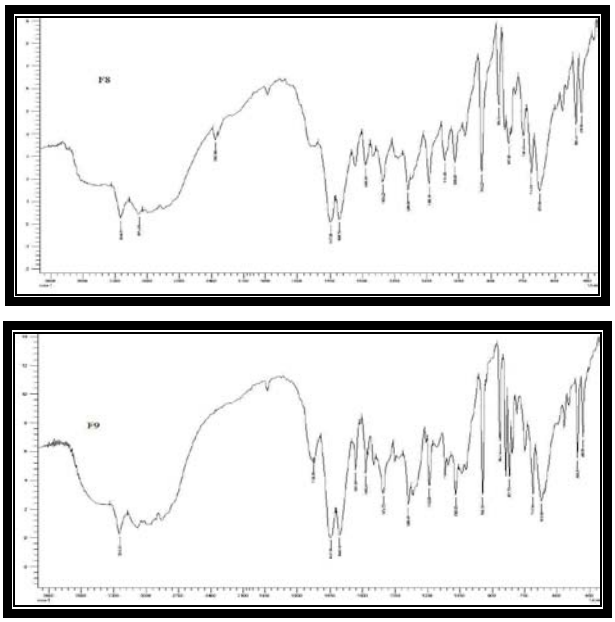


Fig. 4: FTIR spectra of formulations F2, F4, F6, F8 and F9

From the FT-IR spectra, it was observed that similar characteristic peaks appear with minor differences for the drugs and the formulations. Hence, it may be confirmed that no chemical interaction has taken place between the drugs and the polymers used.

Evaluation of prepared matrix tablets (Uncoated tablets)

The matrix tablets prepared were evaluated for various tests and the results obtained are given in table 5. Thickness, diameter, average weights, hardness, percentage friability of prepared tablets were found to be satisfactory. Percentage weight variation, percent friability and content of active ingredient were found to be well within IP limits. The tablets were having an average diameter of 9 mm.

Table 5: Evaluation data of prepared tizanidine HCl sustained release tablets

Formulation code	Avg. Wt. (mg)	% weight variation*	Thickness (mm)	Hardness (kg/cm²)	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	5.9±0.96	0.84±0.71	98.1±0.83
F3	300	-3.5 to+2.2	5.05±0.16	6.5±0.71	0.71±0.51	99.1±0.77
F4	298	-2.4 to+3.2	4.89±0.15	5.5±0.71	0.71±0.51	99.2±0.41
F5	301	-2.6 to+3.2	4.93±0.13	5.8±0.48	0.78±0.41	100.4±0.11
F6	298	-2.6 to+3.5	4.95±0.18	6.1±0.67	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	5.7±0.62	0.76±0.57	99.2±0.24

*mean±SD, n = 10

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 the weight increased up to 15 mg per tablet.

Assay (Tizanidine HCL)

10 tablets of each formulation were crushed in a mortor and pestle. A quantity of powder equivalent to 4 mg of tizanidine hydrochloride was taken in a 100 ml volumetric flask to which 10 ml of water was added and allowed to stand for 10 min, swirling occasionally. Later sufficient amount of water was added to produce 100 ml and the solution was filtered. 10 ml of the above solution was pipetted out into another 100 ml volumetric flask and the volume was made up to the mark using distilled water. 1 ml of the above solution was diluted to 10 ml using distilled water. The absorbance of the resulting solution was measured at 320 nm and the content of tizanidine present was calculated.

Enteric coating test

The enteric coated tablets were suspended in a beaker of disintegration apparatus containing 900 ml of 0.1 M HCl and operated for 120 min. The HCl in the beaker was replaced with pH 7.4 phosphate buffer and operated for further 60 min. The coated tablets were also evaluated for the tablet properties such as, hardness, thickness, weight variation and drug content (assay).

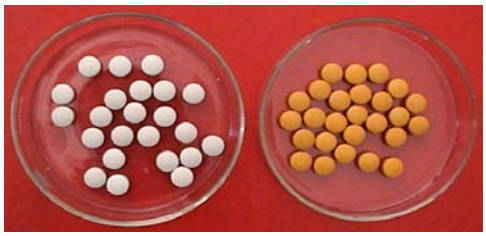


Fig. 5: Uncoated and coated tablets

***In vitro* drug release studies of tizanidine HCl sustained-release tablets**

Release studies were carried out using USP XXII dissolution apparatus, basket type at 100 rpm and 37±1° C. The formulations were tested under extreme conditions of gastrointestinal tract 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 separately.

The tablets were tested for drug release for 2 h in 1.2 pH HCl buffer (900 ml), as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 ml) and tested for drug release for 12 h

Table 6: Evaluation data of coated tablets

Formulations	Avg wt (mg)*	Hardness (Kg/cm²)*	% Drug content*
F1	316.9±1.9	6.1±0.96	97.7±0.71
F2	315.5±1.45	6.0±0.63	97.8±0.46
F3	316±1.8	6.8±0.71	98.1±0.25
F4	316.4±2.38	6.2±0.48	99.06±0.41
F5	317.1±2.47	5.9±0.71	98.3±0.28
F6	315.3±1.35	6.6±0.48	97.7±0.46
F7	316.1±1.5	6.5±0.35	97.0±0.45
F8	316.8±1.25	6.4±0.56	97.5±0.37
F9	315.9±2.43	6.0±0.84	98.7±0.73

*mean±SD, n = 10

Table 7: *In vitro* release data of prepared Tizanidine HCl sustained-release tablets

Time (h)	Cumulative % drug release*								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0
3	42.8±0.84	27.5±0.79	45.9±1.48	29.3±0.34	47.9±0.81	27.5±0.94	29.1±0.67	25.4±0.94	43.6±0.67
4	61.5±1.06	40.7±1.47	59.4±1.38	42.3±0.84	65.6±1.28	40.8±1.76	41.4±1.38	32.1±0.88	65.2±0.58
5	76.5±0.94	65.0±1.08	73.1±1.08	62.6±1.64	71.6±0.67	59.7±1.03	58.5±0.57	43.1±0.60	79.3±1.5
6	81.5±1.68	70.5±1.06	83.5±0.79	74.9±0.94	85.2±0.58	70.3±0.88	67.0±0.46	54.1±0.49	85.9±0.94
8	90.9±1.46	81.9±0.94	88.3±0.94	85.1±1.0	88.3±1.5	81.4±0.58	75.3±0.61	65.4±1.35	94.4±1.06
10	94.3±0.67	85.4±1.74	93.2±1.81	88.2±1.81	94.9±0.91	85.8±1.64	79.9±1.64	72.5±1.37	98.5±0.83
12	98.9±1.28	89±1.57	96.2±0.74	91.5±1.07	95.8±1.27	88.9±1.28	86.1±0.58	80.7±0.76	100±1.28

*mean±SD, n = 3,

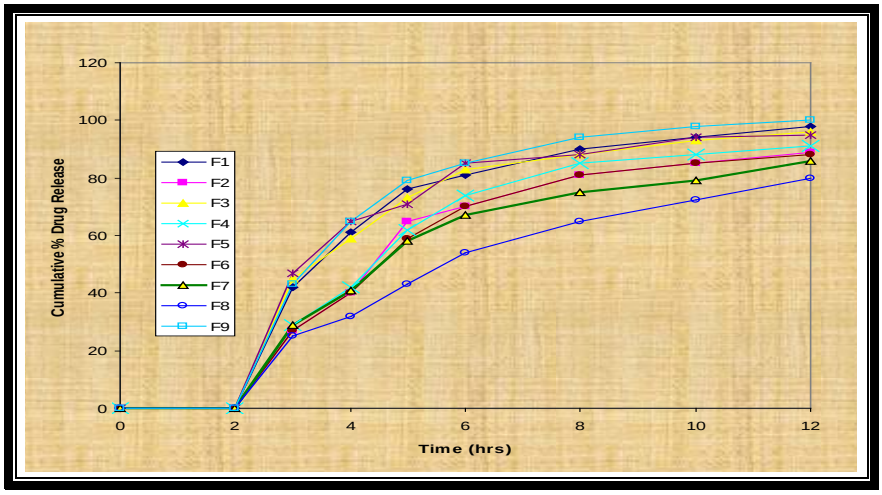


Fig. 6: *In vitro* release pattern for the prepared formulations

From the graph, it is clear that the tablets coated with shellac have limited the drug release till the tablets reach the small intestine.

Stability studies [12]

Stability studies of the drug formulations are performed to ascertain whether the drug undergoes any physical/chemical change or degradation during its shelf life. In the present study, the formulations F8 for sustained release dosage form were selected for stability studies. The stability studies were carried out by exposing the tablets kept in a glassed vial at 40 ± 1°C and at 75% RH for 6 w. After the end of each week, 3 tablets were taken and the total drug content was estimated spectrophotometrically. The obtained results of the stability studies are given in table 11. From the stability study data, it was concluded that the formulations were stable for the study period.

Table 11: Stability study data of optimized formulations F8 and FF7

Time in weeks	Drug content in F8 mean ± SD* at 40 ± 1°C and 75% RH
Initial	99 ± 0.65
1	100 ± 0.49
2	98 ± 0.78
3	99 ± 0.91
4	100 ± 0.98
5	98 ± 0.84
6	99 ± 0.82

*Standard deviation n=3

Peppas model fitting [13]

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

$Mt/M\infty = 1-A (exp-kt)$

$\log (1-Mt/M\infty) = \log A - kt/2.303$

Where, $Mt/M\infty$ 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 $(1-Mt/M\infty)$ versus time t respectively where Mt is the amount of drug release at time t; $M\infty$ is the amount of drug release after infinite time;

k is a release rate constant incorporating structural and geometric characteristics of the tablet; and Ais the diffusional exponent indicative of the mechanism of drug release.

The data obtained from *in vitro* release studies was fit into Peppas model. The various parameters the intercept, A, the release constant K and regression coefficient, R^2 obtained are given in table 9.

Table 9: The data obtained for peppas model fitting

Parameter	F8
K	-0.0296
A	1.1959
R^2	0.9871

In all the cases the value of intercept, A were found to be more that 1. This indicates that the release of drug from all the formulations was found to be super case-II transport, i. e release by more than one mechanism (drug release by diffusion and relaxation of the polymer chain).

Summary

In the present study, the feasibility of preparing sustained release formulation using polymer in the form of matrix tablets and coating them with shellac has been carried out. Pre-formulation studies carried out yielded satisfactory results. From the FT-IR spectra, it was observed that characteristic peaks appear with minor differences for both the drug and its formulations. Hence, it was confirmed that no chemical interaction has taken place between the drug and the polymers used.

The tablets were prepared using Rimek 10 station rotary tablet machine. The tablets were evaluated for parameters such as hardness, thickness, friability, weight variation and content uniformity. *In vitro* dissolution studies indicated that tablets without shellac coat were unable to restrict the drug release till small intestine. From the dissolution data, it was clear that shellac protected drug release from the tablets in the stomach environment and limited the drug release in the small intestine.

CONCLUSION

From the study it can be concluded that modified kondagogu gum is a potential matrix material for formulating suitable sustained-release matrix tablets of Tizanidine HCl.

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