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Development and Physicochemical Characterization of Tramadol Hydrochloride Matrix Tablet Based on Gum Odina

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ABSTRACT

Gum odina, a natural polymer of carbohydrate moiety, has already been shown its potential as pharmaceutical excipient as a binder in tablet dosage form and also as an emulsifying agent but very little data are available regarding the use of it as controlled release polymer. In the present study the objective was to investigate the potential use of gum odina as natural release retarding material in sustained release drug delivery system (matrix tablet) using tramadol hydrochloride as a model drug. Tablet containing tramadol hydrochloride was prepared using gum odina and further coated with Eudragit L 100 to prevent its release in stomach. The prepared tablets were evaluated for physical characterization and in-vitro drug release. The results of this study has proven the suitability of using gum odina as an alternative to existing natural polymer in the field of controlled delivery of drug with a significant effect on drug release and desired release rate of drug from tablets.

Keywords: Gum odina, matrix tablet, tramadol, sustained release.

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INTRODUCTION

Hydrophilic matrix tablet has received major attention in the field of drug delivery because of their ready availability, simple technique, low cost of manufacture and ease of administration. Hydrophilic swellable polymer is the main excipient present in these tablets. When this system is placed in aqueous environment, it absorbs water and swells to form a gel layer surrounding the tablet. Drug release from matrix tablet varies from polymer to polymer depending on the nature of this gel layer, viscosity of the polymer and polymer swelling. Therefore correct choice of hydrophilic polymer, its quantity in matrix formulation, erosion and swelling property are very important factors to formulate matrix tablet. The natural materials that have been extensively used in the field of drug delivery are hydroxy propyl methyl cellulose^{1, 2}, sodium alginate³, gum karaya⁴, chitosan³, xanthan gum etc.⁵. However fast release of drug in the stomach and small intestine is the major drawback associated with these types of natural polymer. It appears that each and every polymeric materials have its merits and demerits and none of them is an absolutely suitable carrier system for oral sustained drug delivery⁶. Gum odina, a natural polymer of carbohydrate moiety, is the natural or induced exudation from the bark of *Lannea Woodier* (also called *Odina woodier Roxb*), family *Anacardiaceae*, locally known as *Jingan*, *Kamlai tree*, which is common in deciduous forests of India. Previously, some work was done about its structural elucidation, its biodegradation property and toxicity by *Bhattacharyya et al*^{7, 8}. It is a negatively charged polyelectrolyte where the carbohydrate moiety composed of D-galactose (63.7%), L-arabinose (19.5%) and two types of uronic acids (11.5%-17%)-galactouronic acid and aldobiouronic acid also known as, 3-0-(D-galactopyranosyluronic acid)-D-galactopyranose. The composition analysis of the gum reveals the presence of a core 1, 6 linked s-D-galactopyranosyl residues. The side chains are composed of single-branched galactopyranose units, which are linked through C1, C3 and C6, while those which are doubly branched are linked through C1, C3, C4, and C6 in the main chain with single unit side chain of the uronic acid (galactouronic and aldobiouronic acid) linked to C3 of this galactose residue. The branched arabinose units forming from the main chain are, however, linked through C1, C3, and C5. The majority of the glycosidic linkages are of β -type determined by the negative rotation of the degraded gum as well as its methylated derivative⁹. We first explored the *Woodier* gum (gum odina) as natural pharmaceutical excipients¹⁰, Initially gum odina was used as pharmaceutical excipients such as tablet binder in tablet dosage form¹⁰ and also on emulsifying agent⁹. However, its use as controlled release polymer has not been explored adequately though limited data are available as its use as

polyelectrolyte complex coacervate in colon targeted drug delivery system¹¹ and tablet containing tramadol HCl¹². The objective of the present study is to investigate the potential use of gum odina as natural release retarding material in sustained release drug delivery system using tramadol hydrochloride as a model drug. Tramadol is mainly used in severe pain without causing serious cardiovascular or respiratory side effects¹³. Half-life of tramadol is 5.5 hours which makes it a suitable candidate for development of sustained release formulation. Tablet containing tramadol hydrochloride was prepared using gum odina and further coated with Eudragit L 100 to prevent its release in stomach. The prepared tablets were evaluated for physical characterization and in-vitro drug release.

MATERIALS AND METHOD

Tramadol HCl and Microcrystalline cellulose (MCC) were obtained as gift samples from Ajanta Pharma, Mumbai, India. Eudragit L-100 was obtained from Mepro labs, Ahmedabad, India. Magnesium stearate was procured from Loba. Chemie. Pvt. Ltd, Mumbai, India.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of finely powdered pure tramadol hydrochloride, pure gum and crushed powder of drug loaded tablet were recorded in Perkin Elmer FTIR spectrometer (Spectrux RX 1, UK) from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1} using KBr pellets. The pellets were made by applying a pressure of 10 ton for 15 min in a hydraulic pellet press (Type-KP, Kimaya Engineers, Mumbai, India).

Differential Scanning Calorimetry (DSC)

The DSC analysis of the gum, and the physical mixture of gum and the drug were carried out using a Differential Scanning Calorimeter (Shimadzu DSC 60, Koyto, Japan) to evaluate any possible drug-polymer interaction. Sample (2mg) were heated in a hermetically sealed aluminum pans in the temperature range of 25°C-300°C at heating rate of 10°C /min under nitrogen flow of 30ml/min.

Preparation of matrix tablet

Gum odina (**Table 1**) was ground with a clean glass mortar and pestle. Ground gum was triturated with a small quantity of water. After that the required amount of microcrystalline cellulose, which was previously passed through 120 mesh, was added and triturated along with a small quantity of water to mix the excipient properly with the gum. Then the required amount of tramadol (sieved through 120 mesh) was added with water and mixed with it. The mixture was passed through sieve No.6 to make the granules. The granules were dried in hot air oven for 3 h at 40°C and the dried

granules were passed through sieve No.44. Then the Magnesium stearate was added and mixed. The granules were compressed to form a tablet using a single punch machine (Cadmach -DMS-25, Ahmedabad, India).

Table 1: Composition of Tablets

Formulation code	Ratio at which Drug and excipients were used (Drug: Gum odina: Microcrystalline cellulose: Magnesium stearate)
T ₁	1:1:4:0.008
T ₂	2:3:7:0.008
T ₃	1:2:3:0.008
T ₄	2:5:5:0.008
T ₄ *	2:5:5:0.008

*T₄ is a tablet coated with Eudragit L100.

Evaluation of tablets

The prepared matrix tablets were evaluated for hardness, thickness, friability, weight variation test and drug content. Hardness of tablets was measured by Monsanto hardness tester (Biomate India Pvt. Ltd Delhi, India) and friability of the tablets was measured by Roche friabilator (Electro Lab EFL Friabilator, Mumbai, India). Vernier caliper (Bombay Tools Center, Bombay, India) was used to measure the thickness of tablets. For measurement of drug content¹⁴, twenty tablets were weighed accurately and powdered. Powder equivalent to 50 mg of tramadol hydrochloride was shaken with 100 ml 0.1N HCl for 10 minutes to ensure complete solubility of drug. Then the mixture was centrifuged and 10 ml of the supernatant liquid was taken and the absorbance was determined spectrophotometrically at 272 nm using calibration curve.

In vitro drug release studies:

Matrix tablets were prepared and undergone in-vitro dissolution in USP type 1 paddle basket type apparatus (Electrolab, model TDT-06P (USP), Mumbai, India). Drug dissolution study was conducted at two different pH (i.e. pH 1.2 and 6.8) at 37± 0.5°C at 50 rpm. At pH 1.2 the drug dissolution was investigated for 2 hrs and for the next 6 hrs the study was carried out at pH 6.8. At definite time intervals, 5 ml of samples in each case was withdrawn and the same volume of fresh media was incorporated in the dissolution basket. After filtration and appropriate dilution, the samples were analyzed at 271 nm for tramadol hydrochloride against blank using UV visible spectrophotometer (Thermospectro, UV-1, UK) and the respective concentrations were determined from the calibration curve.

Release Kinetics

Data obtained from drug release studies were fitted to different kinetic equations such as Zero order (eq 1), First order equation (eq 2) which describes concentration dependent drug release, Higuchi equation (eq 3) and Korsmeyer Peppas equation (eq 4)¹⁵

$$C = K_0t \quad (1)$$

Where K_0 is the zero-order rate constant and t is time (min).

$$\text{Log}C = \text{Log}C_0 - kt / 2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and k is first order constant

$$Q = Kt^{1/2} \quad (3)$$

Where Q is the amount released in time t , K is the kinetic constant and t is time.

$$M_t / M_\infty = Kt^n \quad (4)$$

M_t / M_∞ is fraction of drug released at time t . 'K' and 'n' are the drug release rate constant and release exponent respectively.

Drug release data were tested for different kinetic models by plotting them graphically. For zero order kinetics plots were drawn concentration vs. time, for first order kinetics log cumulative of % drug remaining vs. time, for Higuchi model cumulative % drug release vs. square root of time and for Korsmeyer Peppas model log cumulative % drug release vs. log time. Regression coefficients (r^2), rate constant (K) and release component (n) (for Korsmeyer Peppas model) were determined.

RESULTS AND DISCUSSION

In the present study, the drug release retardant activity of gum odina from matrix tablet dosage form was explored. Gum odina is a water soluble anionic polysaccharide with pH dependent swelling ability. Swelling index varies from 4.6% to 6.1% depending on the pH of the external medium. Gum odina swells more in acidic pH (swelling index 6.1% in pH 1.2) than in pH 6.8 (swelling index 4.6)¹⁶. It forms a viscous gel in presence of water and this hydrated swollen gel is responsible for the release retardant property of the gum. Its swelling ability has encouraged us to develop sustained release matrix tablet with it. Drug polymer interactions were studied by FTIR spectroscopy. In the FTIR spectral analysis (Figure 1) of pure tramadol HCl, broad band at 3306.67 cm^{-1} was attributed to O-H stretching mode, whereas bands at 1243.20 cm^{-1} , 1289.47 cm^{-1} , 1356.36 cm^{-1} , 1481.38 cm^{-1} were attributed to O-H bending mode. Two sharp peaks at 1578.87 cm^{-1} and 1607.73 cm^{-1} were due to N-H bending. The bands at 3066.50 cm^{-1} , 3005.12 cm^{-1} , 2930.48 cm^{-1} and 2861.75 cm^{-1} were attributed to both aromatic and aliphatic (C-H) stretching vibrations. The bands at 1074.05 cm^{-1} and 1045.44 cm^{-1} were due to C-O stretching vibrations. The peaks from 703.11 to 866.75 were due to N-H rocking vibrations. The peak at 647.70 was due to

C-Cl stretching. These bands were also observed in drug loaded tablets with very minor differences in frequencies.

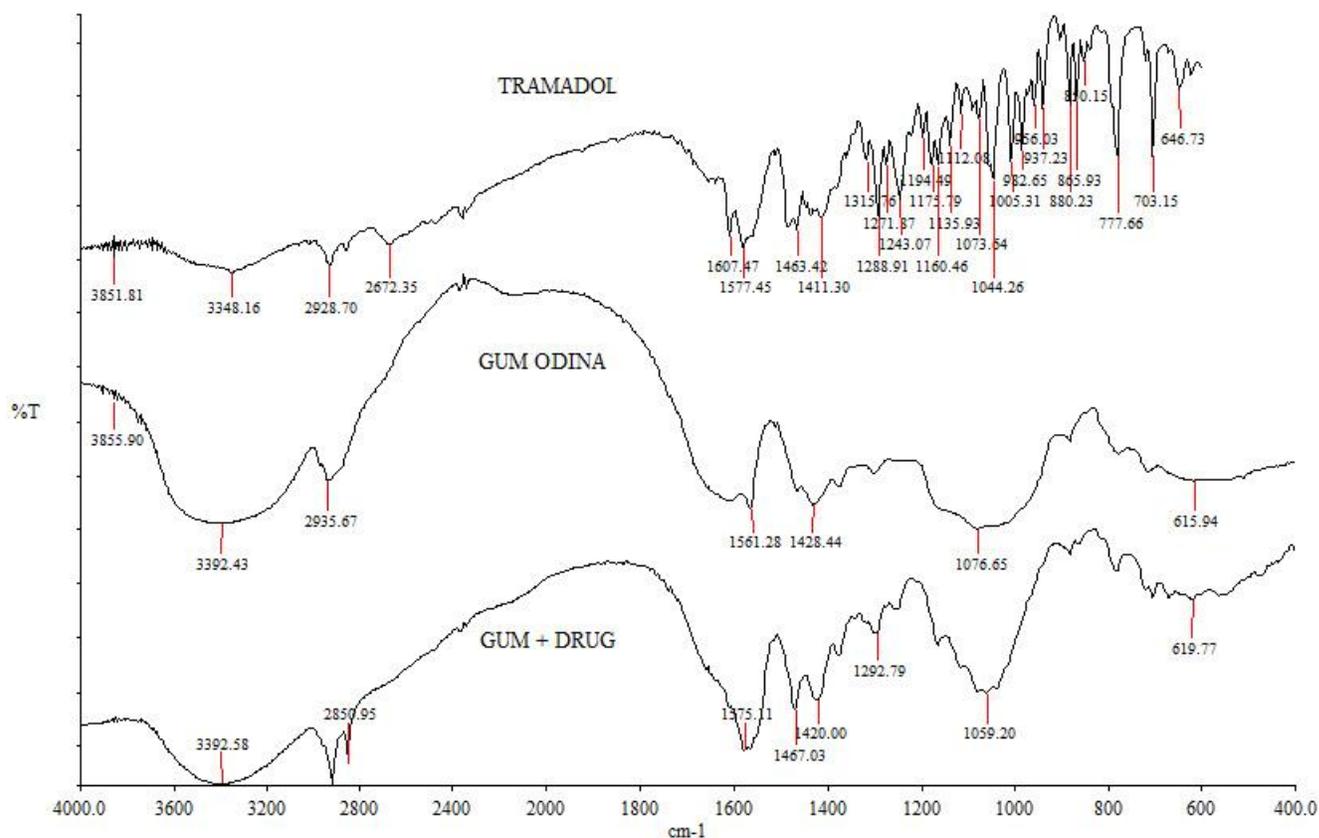


Figure 1: Fourier transform infrared spectroscopy (FTIR) spectra of Tramadol, Gum odina, Physical mixture of Gum odina and drug (Tramadol)

The FTIR data suggests that there is no interaction exists between the drug and the excipients mixture which has been further substantiated by DSC analysis of the gum and their formulation (Figure 2). The DSC and DTA thermograms of the Woodier gum and the drug loaded formulations show the transitions associated with loss of water owing to the hydrophilic nature of the natural polymer¹². Enhancement of temperatures showed steady eventual loss of initial moisture content and the gradual drying of the gum. In the DSC thermogram of formulation, there is a peak near 180°C, which corresponds the drug, tramadol in the formulation, which suggests the absence of any physical or chemical interaction between the components.

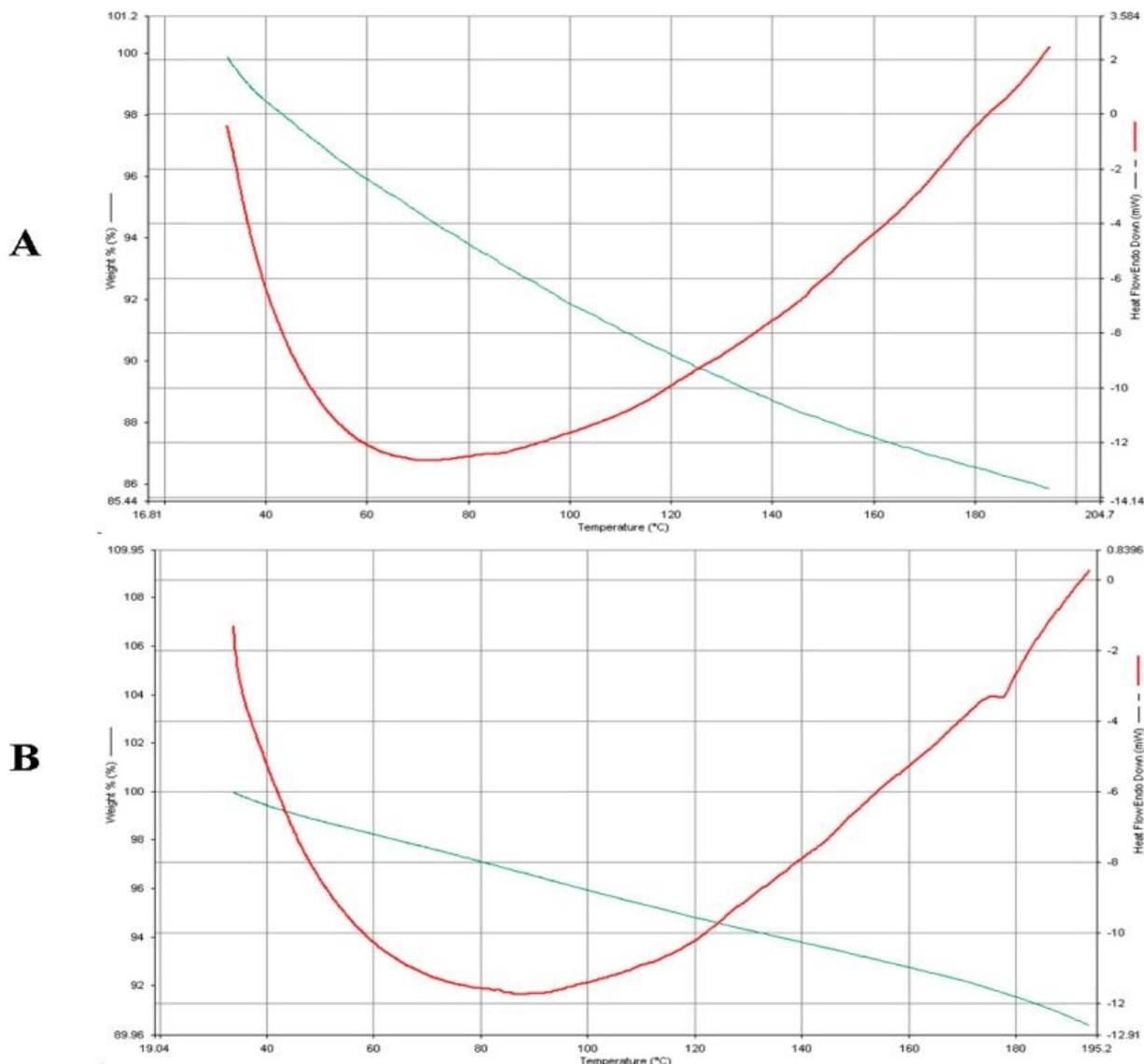


Figure 2: DSC image of A) Gum odina B) Tablet formulation

Four different formulations were prepared varying the concentration of gum in the matrix tablet. Results obtained for Friability, Thickness, Weight variations and drug content of the experimental tablets were given in table 2. The average diameter and thickness of the tablets were found to be 8.58 ± 0.3 mm. Friability was $>0.5\%$ which was within the pharmacopeia permissible limits¹⁷. Hardness of the tablets varied between 4.44 ± 0.05 to 4.54 ± 0.3 and the percentage drug content varied between $97.20 \pm 0.65\%$ to $98.65 \pm 0.41\%$. The above data indicate the experimental matrix tablets passed pharmacopeia permissible hardness and drug content. The higher drug release was observed in pH 1.2 than that in pH 6.8 (Figure 3 and 4). Increasing amount of gum decreased the drug release both at pH 1.2 & 6.8. A direct relationship was observed between the amount of gum in the tablets and release of the drug from it. However, drug release was found to increase at pH

1.2 than at pH 6.8 with the decreasing polymer concentration in the tablets. The amount of drug released after 6 h at pH 6.8 was 73.4% and 62 % from formulation T₃ and T₄ respectively, whereas after 2 h 79.2% and 72.9 % of drug were released at pH 1.2 from the respective formulations. To compare release profile of drug from different formulations, time point approach was adopted. Significant difference ($p < 0.5$) is present between $t_{50\%}$ values (time for 50% drug release) of different formulations at pH 1.2 and 6.8. The $t_{50\%}$ values clearly indicate that gum concentration and pH of external medium have significant impact on the release profile of drug. Faster release of drug at pH 1.2 could be correlated to higher swelling rate of gum at pH 1.2 than at pH 6.8. Although initial burst release was observed from all the formulations in both pH 1.2 and 6.8, only 62% drug was released in pH 6.8 after 6 h from T₄ which contained highest amount of gum odina. Release retardation at higher concentration of gel can be explained by the phenomenon of formation of stiffer gel with high degree of tortuosity due polymeric bond entanglement leading to slow diffusion of drug from the polymer matrix¹⁸. At low polymer level, the rate of advancement of swelling was less and the attrition of the rubbery state of gum polymer may have been insufficient to retard the drug release from the gum efficiently, resulting in an enhanced diffusion for the drug until the entire drug was released from the tablets¹⁹.

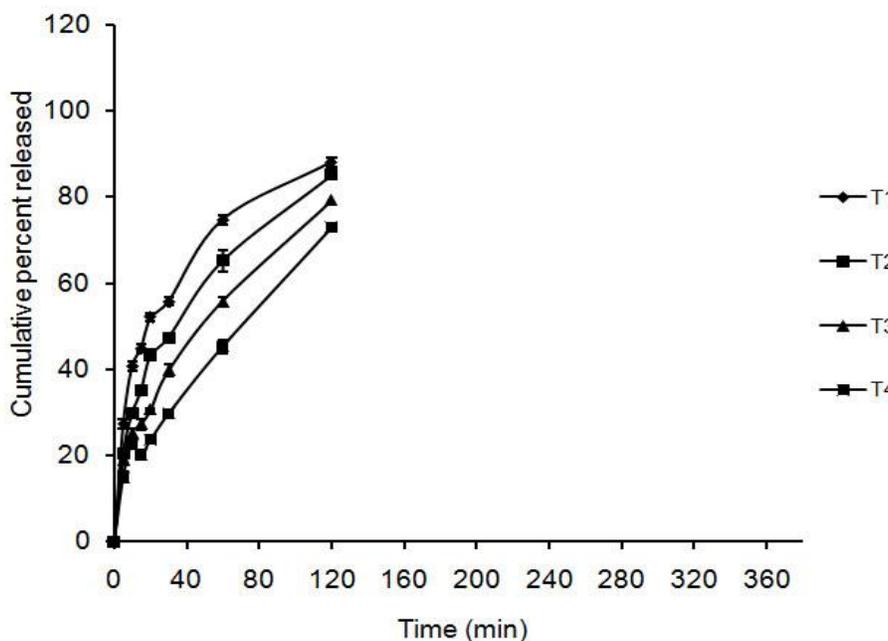
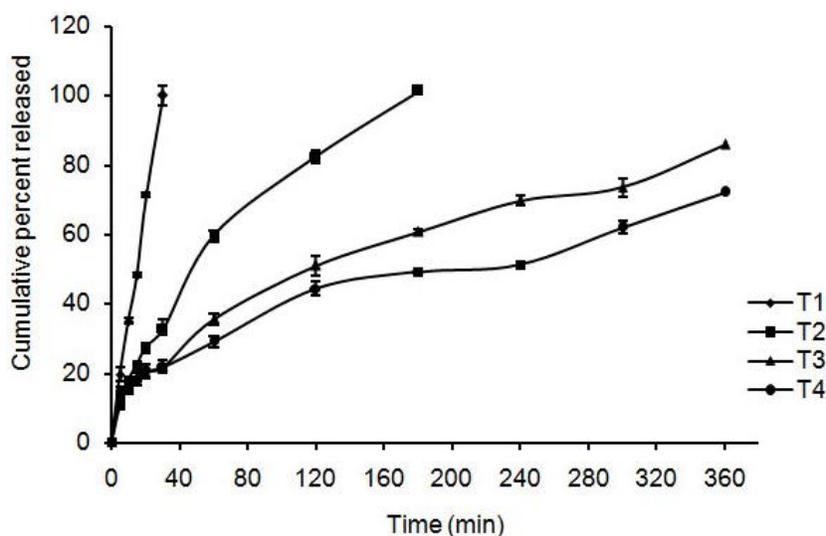
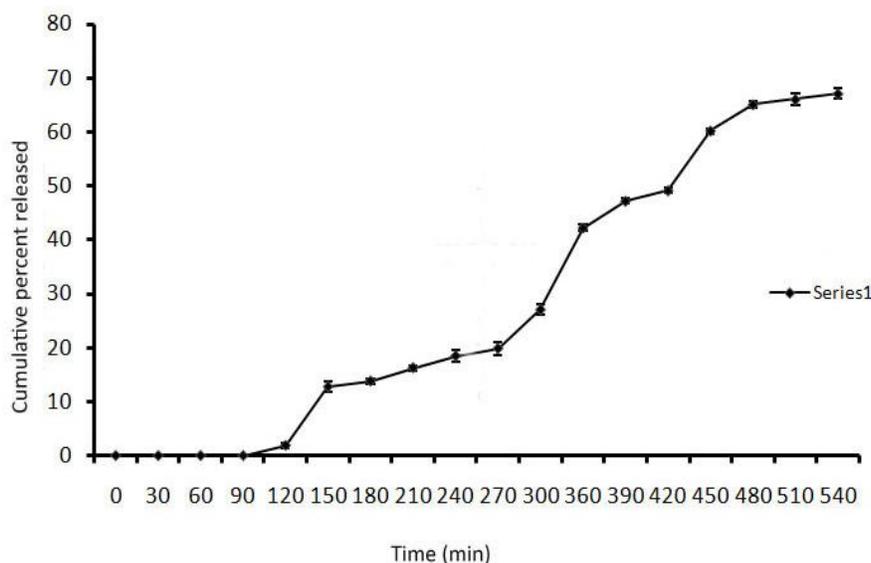


Figure 3: Release profile of Tramadol from matrix tablet formulation in pH 1.2

Table 2: Physical Parameters of the Formulated Tablets

Formula tion code	Diameter (mm)	Thickness (mm)	Weight (mg)	Hardness (kg/cm ²)	% Friability (n=10)	% drug content	T _{50%} (min)	
							pH 1.2	pH 6.8
T ₁	8.58±0.01	3.48±0.02	239.35±0.72	4.54±0.3	>0.5	98.20±0.12	18	21
T ₂	8.58±0.02	3.47±0.01	238.54±0.60	4.50±0.0	>0.5	98.50±0.10	34	46
T ₃	8.58±0.01	3.47±0.07	242.50±0.12	4.53±0.12	>0.5	97.20±0.65	48	116
T ₄	8.58±0.03	3.47±0.04	241.45±0.0.5	4.44±0.05	>0.5	98.65±0.41	70	220

**Figure 4: Release profile of Tramadol from matrix tablet formulation in pH 6.8****Figure 5: Release profile of Tramadol from the coated matrix tablet formulation**

To prevent the release of drug in acidic pH, tablet T4 was found to be coated successfully with eudragit L100. Drug release profile from the coated formulation at pH 6.8 had satisfactory drug

diffusion profile (Figure 5). Hence gum odina may be a suitable option for the preparation of tablet matrix for prolonging drug release at the intestinal pH.

To explain drug release mechanism, release data were fitted to different rate equations (Table 3). The r^2 values suggest that all the matrices showed best fit to the Korsmeyer Peppas equation (Ritger and Peppas). The “n” values of T₁, T₂, T₃, T₄ were found to be between 0.4987 to 0.6259 which suggest anomalous transport mechanism i.e combination of Fickian diffusion and polymer relaxation. It is interesting to note that at low gum concentration, “n” value of Korsmeyer Peppas model shifted to 0.9189 which indicates super case II transport, i.e., drug release occurred due to polymer relaxation. The tablet T₁ containing the least amount of gum odina among the experimental formulations when placed in drug release medium, polymer began to swell more due to the formation of less stiffer gel compared to T₂, T₃, and T₄, which ultimately leads to the relaxation of polymer side chain more.

Table 3. Release Kinetics of Matrix Tablet Prepared Using Different Concentration of Gum odina

Formulation code	Zero Order		1st Order		Higuchi		Korsmeyer peppas	
	r^2	k	r^2	k	r^2	k	r^2	n
T1	0.99	3.33	0.9061	0.22	0.879	15.09	0.9935	0.9189
T2	0.94	0.53	0.7262	0.187	0.975	7.2	0.9951	0.6259
T3	0.9254	0.228	0.803	-0.167	0.9843	4.468	0.9806	0.4987
T4	0.92	0.1656	0.887	0.1336	0.971	3.709	0.9706	0.4987
Coated tablet	0.782	0.186	0.978	0.138	0.655	2.72	0.982	0.4987

CONCLUSION

From the results it can be concluded that being a natural, nontoxic, hydrophilic gum with excellent swelling ability, gum odina can serve as a suitable alternative to the existing natural polymers in the field of controlled delivery of drug. Though initial burst release was observed in acidic pH, it can be prevented by coating the tablet with eudragit or other enteric coated materials. Gum concentration had significant effect on drug release and desired drug release rate can be achieved by modulating the concentration of gum in the matrix.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest in this work.

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