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Formulation and Evaluation of Cefixime Loaded Grafted Gellan Gum Tablet

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Abstract

The objective of the present work is to design sustained release tablets of cefixime by incorporating drug with polymer using microwave assisted graft co-polymerization method. In the present study, Gellan gum was used as a polysaccharide and grafted with acrylamide to make a sustained release formulation of cefixime which can solve mainly problem associated with multiple dose frequency and it can also increase patient compliance. The effect of combination of polymers on parameters like release pattern, release mechanism of the drug were studied. Preparation of total Seven formulation A1, A2, A3, A4, A5, A6 and A7 each containing gellan gum and acrylamide. The characterization of optimized formulation A6 was evaluated for Average time (75 sec) , weight of grafted gum (3.029 gm), % yield (84.138%) ,% Grafting (202.9%) and % Grafting Efficiency (57.971%). Cefixime matrix tablets were formulated successfully by changing the excipient amount in four batches A6a, A6b, A6c, A6d and evaluated for the various parameters as per Indian Pharmacopoeia like Thickness (**3.37±0.588 mm**), Weight Variation (**405±2.36 mg**), Hardness **(6.3Kg/cm^2)**, Friability (0.44% weight loss), Disintegration Time (**4.25±0.110 min**), and Uniformity of content (**96.022±0.113 %**). In vitro release profiles of all batches were carried out in simulated gastric fluid pH 1.2 and simulated intestinal fluid pH 7.2 for upto 10 hr. From in vitro release studies, it was found that 81% drug was released in A6c in 10 h. From the result it was confirmed that grafting formed gives sustain drug delivery system.

Keywords
cefixime, sustained release, polymer, acrylamide

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INTRODUCTION:

Infectious diseases are most common in developing countries. The infectious bacterial classes are both Gram positive and Gram negative hence, the treatment is necessary with an agent, which have broad spectrum of activity. Cephalosporins possess a wide range of activity against Gram positive and Gram negative bacteria; these are act by inhibiting bacterial cell wall synthesis. Cefixime is an orally active third generation cephalosporins

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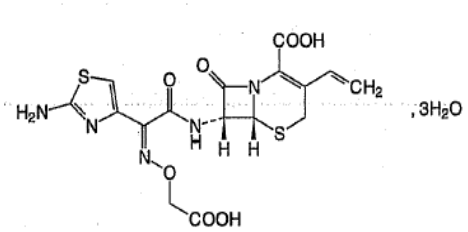


Figure 1: Cefixime

The objectives of the present work are to design, formulate and evaluate matrix tablets of cefixime for sustained release dosage form. As the effect of sustained release dosage form is relatively more, incorporating the drug in the matrix tablet will prolong the drug release. These are prepared by direct compression method.

A polymer is a macromolecule which is poised of repeating structural units i.e. monomer and this structural unit are connected to each other via covalent bonds. Polysaccharides are the polymers comprising of monosaccharides connected to each other via glycoside linkage.

Grafted co-polymer includes a previously formed polymer backbone onto which the other species of polymer chains, which are of varying chemical natures, are attached at different sites of the polymeric backbone. The connected side chains may be comprises of a monomeric unit or of a binate mix. The one which is having one monomer only is easier to synthesize and generally happens in a solitary step, nevertheless grafting in the case of binate blend requires to be done in continuous and stepwise addition of the monomers.

The Gellan Gum is one of the anionic polysaccharides that have a linear structure composed of a tetrasaccharide-repeating sequence that comprises one α-L-rhamnose, one β-D-glucuronate and two residues of β-D-glucose. Gellan Gum naturally exits in acylated form, yet its deacylation can be formed by alkaline hydrolysis.

MATERIAL AND METHODS:

Chemical and Reagents

Cefixime was purchased from KAPL., Bengaluru, India, Acrylamide were purchased from Sisco research laboratories Pvt Ltd, Mumbai, India. Gellan Gum was purchased from Qualikem, Mumbai, India. HCl and methanol were purchased from SD Fine-chem. Ltd, Mumbai.

Identification of Pure Drug and Polymers

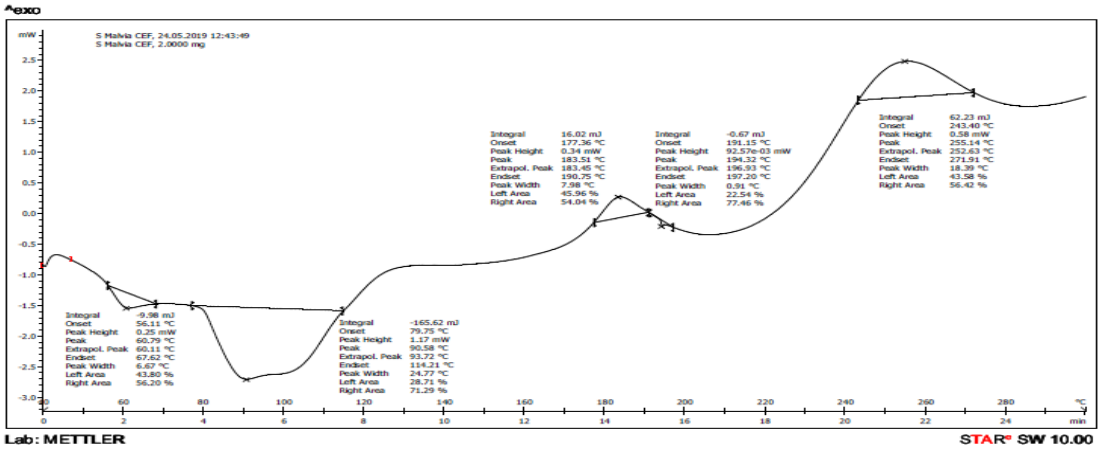


Figure 2: DSC of Cefixime

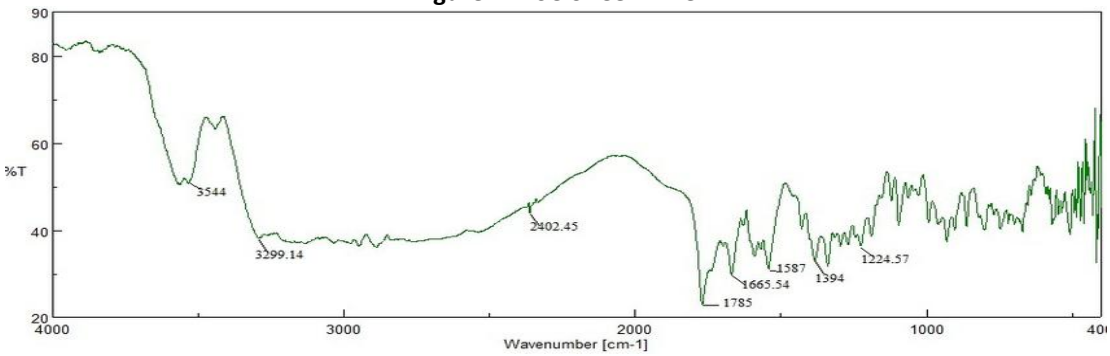
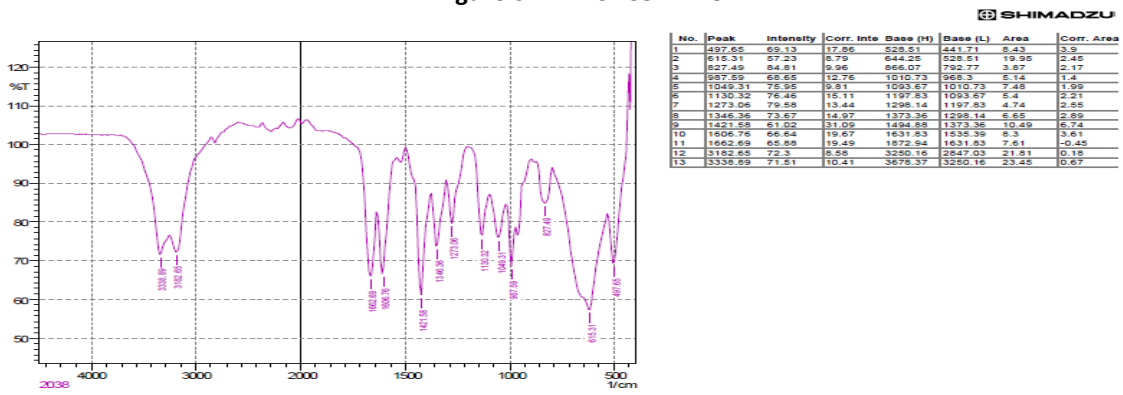


Figure 3: FTIR of Cefixime



No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Area
1	497.65	69.13	17.86	528.51	441.71	8.43	3.9
2	615.31	57.23	8.79	644.26	528.51	19.95	2.45
3	827.49	84.81	9.96	866.07	792.77	3.87	2.17
4	987.59	68.65	12.76	1010.73	968.3	5.14	1.4
5	1049.31	76.95	9.51	1093.67	1010.73	7.48	1.99
6	1130.32	76.46	15.11	1197.83	1093.67	5.4	2.21
7	1273.06	79.58	13.44	1298.14	1197.83	4.74	2.55
8	1346.36	73.67	14.97	1373.36	1298.14	6.65	2.89
9	1421.58	61.02	31.09	1494.88	1373.36	10.49	6.74
10	1606.76	66.64	19.67	1631.83	1535.39	8.3	3.61
11	1662.69	65.88	19.49	1672.94	1631.83	7.61	-0.45
12	3182.65	72.3	8.58	3250.16	2647.03	21.81	0.18
13	3338.89	71.51	10.41	3678.37	3250.16	23.45	0.67

Figure 4: FTIR of Acrylamide

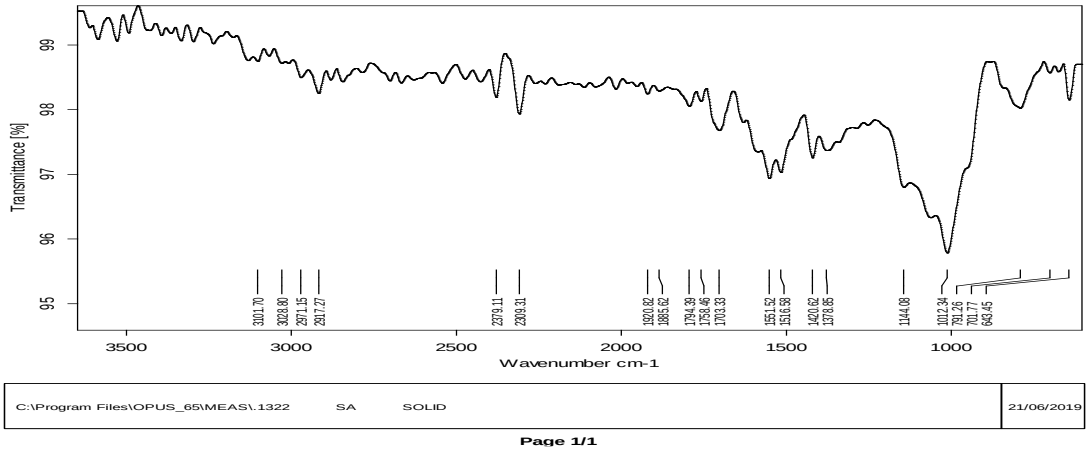


Figure 5: FTIR of Gellan Gum

Preparation of Grafted gum

Gallen gum (2 g) was slowly dispersed in 100 ml water in a three-necked round bottom flask and allowed to hydrate for 4 h with continuous purging of a slow stream of nitrogen gas. Acrylamide (2-3 g) and potassium persulfate (0.05-0.150 gm) were added to solution and irradiated to microwaves at 440 W under different time (60-90seconds) to carry out the polymerization reaction. The resulting co-polymer was allowed to cool to ambient temperature and then poured into 400 ml acetone. The product was filtered and washed with excess amount of aqueous methanol (30% v/v) to remove the homo-polymer of Acrylamide. The co-polymer was then dried overnight at 50°C to constant weight. Finally the product was stored in vacuum desiccators until use as given in Table 1.The percentages yield, grafting and grafting efficiency were calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Weight of Grafted Gum}}{\text{Theoretical weight}} \text{X100} \qquad (1)$$

$$\%\text{Grafting} = \frac{W_1 - W_0}{W_0} \text{X100} \qquad (2)$$

$$\% \text{ Grafting Efficiency} = \frac{W_1}{W_0 + W_1} \text{X100} \qquad (3)$$

Where W_0, W_1 and W_2 denote the weights of gallen, graft co-polymer and Aam, respectively

Table 1: Grafting parameters from various batches of microwave-assisted grafting.

S.No	Formulation code	Gum weight (gm)	Acrylamide weight (gm)	Amount of initiator (gm)	Power (Watt)	Time (sec)
1	A1	1	2.5	0.05	440	60
2	A2	1	2.5	0.1	440	60
3	A3	1	2.5	0.15	440	60
4	A4	1	2	0.1	440	60
5	A5	1	3	0.1	440	60
6	A6	1	2.5	0.1	440	75

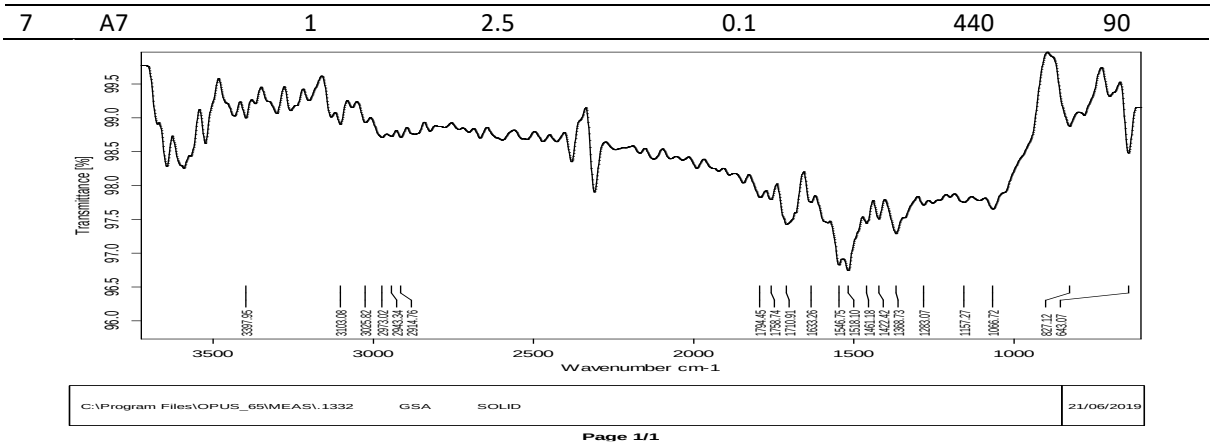


Figure 6: FTIR interpretation data of A6 gellan-gum and Acrylamide

RESULT AND DISCUSSION:

Preparation Gellan Gum Acrylamide matrix tablets of Cefixime

Matrix tablets of cefixime were prepared employing graft copolymer as the matrix. The required quantity of cefixime was blended with grafted gallen gum and acrylamide in different proportions along with magnesium stearate as lubricant, Talc and Microcrystalline cellulose. The dry blend so obtained was directly compressed using 8 mm biconvex punches and dies in a single station hand-operated, tablet punching machine (R&D model, Konark Instruments, Ambala, India).

Table2: Composition of grafted tablets of Cefixime

S.No	Formulation code	Drug (mg)	Grafted Gum (mg)	Microcrystalline cellulose (mg)	Talc (mg)	Magnesium stearate (mg)	Total weight (mg)
1	A6a	200	100	60	20	20	400
2	A6b	200	125	35	20	20	400
3	A6c	200	150	10	20	20	400
4	A6d	200	175	5	10	10	400

Evaluation of tablets

The matrix tablets of cefixime were evaluated for thickness, weight variation, hardness, friability, content uniformity and in vitro release as per Indian Pharmacopoeia 2010.

Table 3: Values of physical parameters of Cefixime tablets containing gellan gum Acrylamide

S.No	Batch code	Thickness (mm)	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (% weight loss)	Disintegration Time (minutes)	Uniformity of content (%)
1	A6a	3.26±0.872	401±1.61	5.6	0.48%	3.30±0.102	90.416±0.065
2	A6b	3.35±0.567	404±2.03	6.6	0.39%	5.42±0.007	92.159±0.113
3	**A6c**	**3.37±0.588**	**405±2.36**	**6.3**	**0.44%**	**4.25±0.110**	**96.022±0.113**
4	A6d	3.40±0.921	405±2.44	6.8	0.36%	5.50±0.101	93.712±0.065

In-Vitro Drug Release Studies

The optimized batch of grafted gallen-g-Aam was carried for in vitro drug release studies. The in vitro drug release study of A6c matrix tablet and UN-SA matrix tablet was carried out for 10 hours in simulated gastric fluid (SGF) pH 1.2 for the 2 h, followed by simulated intestinal fluid (SIF) pH 7.2. A6c matrix tablet has provided sustained release of the drug from tablet as compared to the tablet prepared from ungrafted gum. Drug released from the A6c tablet was in controlled manner as compared to the ungraftedUN-gallen tablet. The drug content in each sample was analyzed by UV-VIS spectrophotometer at 288 nm. It was observed from the results that the matrix tablet of A6c released the maximum drug within 8 hours as compared to UN-gallen. A6c compressed tablets was able to sustain

the drug release up to 10 hours so this may be the suitable polymer for sustain drug delivery.

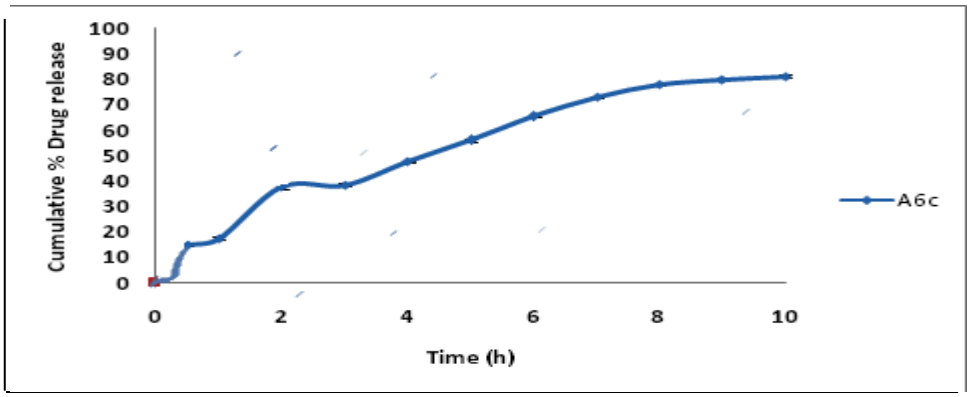


Figure 7: In vitro cumulative % release of drug between A6c

Table 4: In vitro cumulative % drug release of A6c

S.No	Time (hour)	Cumulative % Release of A6c formulation (Mean±S.D) n=3
1	0.25	7.158±0.090
2	0.5	14.676±0.285
3	1	17.470±0.636
4	2	37.705±0.734
5	3	38.411±0.713
6	4	47.764±0.269
7	5	56±0.619
8	6	65.294±0.176
9	7	73±0.269
10	8	78±0.305
11	9	79.941±0.176
12	10	81.176±0.529

Drug release kinetics

To explore and explain the mechanism of drug released from the matrix tablets, formulations were subjected to the modelling and release kinetic studies such as zero order, first order, Higuchi model and Korsmeyer–Peppas model.

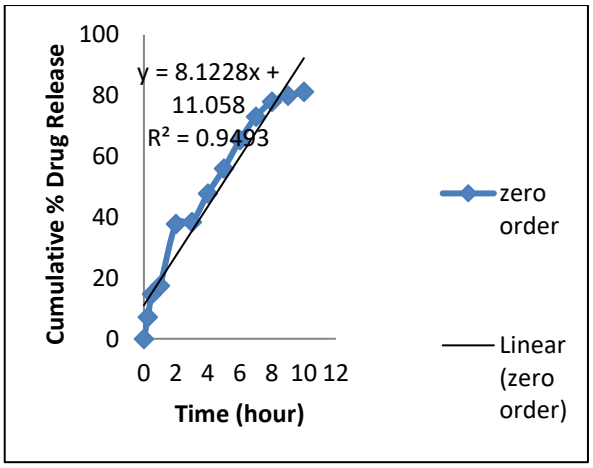


Figure 8: Zero order release kinetics of A6c

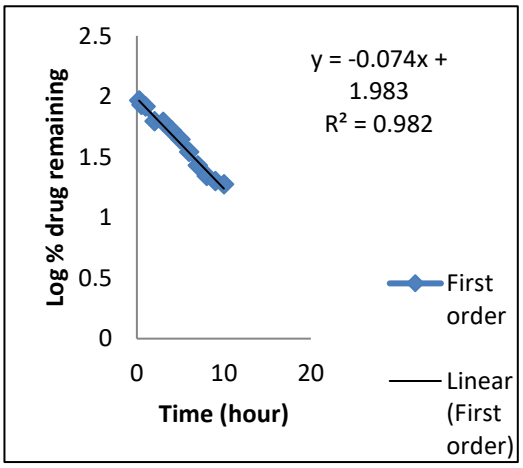


Figure 9: First order release kinetics of A6c

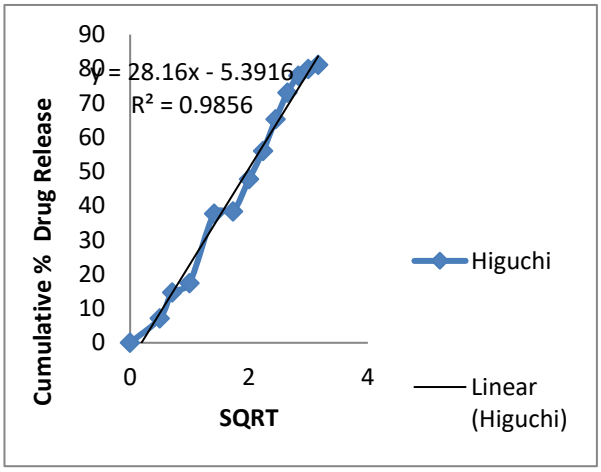


Figure 10: Higuchi model release kinetics of A6c

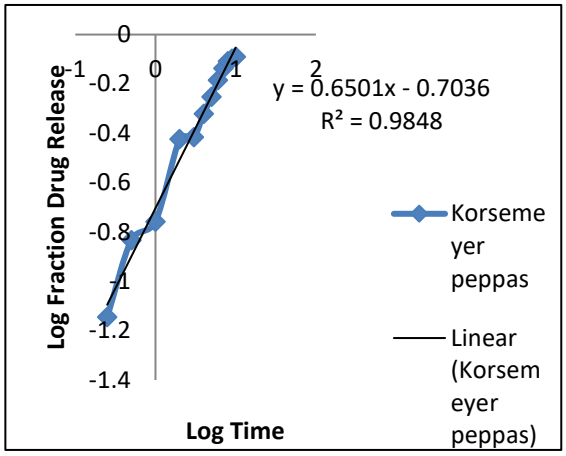


Figure 11: Korsmeyer-Peppas model release kinetics of A6c

Table 5: Kinetic equation parameter of A6c formulation

Formulation Name	Zero order		First order		Higuchi		Korsymer-peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
A6c	0.949	8.122	0.982	-0.170	0.985	28.16	0.984	1.496

The values of regression coefficient (R^2) from the different drug release kinetic models are tabulated in **table**. The results of the modelling study revealed that release of drug from the matrix tablets of A6c tablet of cefixime fitted best into Higuchi model with the maximum values of R^2 while the value of n characterizes the release mechanism of drug. For the case of matrix tablets, 0.45 ≤ n corresponds to fickian diffusion mechanism, 0.45 < n < 0.89 to non-fickian transport,n = 0.89 to case II (relaxational) transport, and n > 0.89 to super case II transport [102].The n values for the tablet A6c is more than 1, it revealed that the mechanism of drug release was a super case-II transport indicating the drug release rate does not change over time and the release is characterized by zero order.

SUMMARY AND CONCLUSION:

A graft co-polymer is a macromolecular chain with one or more polymer attached to the main chain. Therefore, it may be described as, having the general structure, where the main polymer backbone, commonly referred to as the trunk polymer, having branches of another polymeric chain. Graft co-polymerization of natural polysaccharide backbone is one of the best ways to use polysaccharide for controlled drug delivery. Microwave assisted graft co-polymerization is an efficient method.

Cefixime was selected as the drug candidate for the present study for its immense potential as an antibiotic. Further, its short half-life (3-4 hr) of administration, feasible analytical methodology for its in vitro studies and high physicochemical stability makes it an ideal drug for oral sustain release dosage form. FT-IR spectrum, UV-VIS spectrum and melting point studies confirmed the identity and purity of obtained sample of Cefixime. Solubility profile was analyzed and log P confirmed its hydrophillic nature. Gellan gum was selected as a natural polymer for grafting with acrylamide which is a natural polymer and gellan gum Acrylamide was prepared by Microwave assisted method. Different formulations were prepared using the various amount of acrylamide and microwave time of exposure formulation with highest percentage grafting efficiency was considered as optimized formulation.

The matrix tablets of Cefixime were prepared by using drug, polymer, diluents and lubricant blended in pestle mortar followed by direct compression in a single punching machine.

The matrix tablets of to check for weight variation, hardness, friability, disintegration time and drug content as per I.P. and were found to be within the specified limits.

In vitro release profiles of all batches and marketed formulation were carried out in simulated gastric fluid pH 1.2 and simulated intestinal fluid pH 7.2 for upto 10 hr. From in vitro release studies, it was found that 81% drug was released in A6c in 10 h. From the result it was confirmed that grafting formed gives sustained drug delivery system.

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