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Formulation and Evaluation of Sustained Release Matrix Tablets of an Antibiotic Agent Using Synthetic and Natural Polymers

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ABSTRACT

Cefixime is a 3rd generation cephalosporin derivative which is widely used in the treatment of bacterial infection. The tablets were prepared by wet granulation method using different natural polymers such as karaya gum, locust bean gum. Selection of natural gum is due to their non toxicity and patient's compliance. The compatibility studies of drug and excipients were performed by FT-IR spectroscopy. After examining the flow properties of the granules the results are found to be within prescribed limits and indicated good flow property, then granules were subjected to tablet compression. The tablets were evaluated for pre-compression parameter like angle of repose, bulk density, tapped density, Carr's index, all the results were found within the prescribed limit. Post-compression parameters like weight variation, hardness, thickness, friability, drug content uniformity and *in-vitro* dissolution study. *In-vitro* dissolution studies were conducted for 12hrs. The best *in-vitro* drug release was obtained from formulation F7 (95.24%) and F8 (97.02%) at the end of 12hrs. From the above results, it indicates that formulation F7 and F8 showed a maximum amount of drug release within 12 hrs using natural gums in combination. Both the formulations were containing equal concentration of different polymers in combination. When combination polymer concentration increased in the formulation, the rate of drug release was also increased as compared to individual polymer concentration. Stability studies were carried out which indicate that selected formulation (F7, F8) were found to be stable.

INTRODUCTION

Oral route is the most commonly employed route of drug administration. Although different routes of administration are used for the delivery of the drug, oral route remains the preferred mode. The popularity of the oral route is attributed patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method and generally improved shelf-life product[1].

Oral drug delivery continues to rise in popularity as formulation scientists look for ways to control drug release and improve patient convenience. However, developing oral controlled release tablets for water soluble drugs with constant release rate has always been a challenge to the pharmaceuticals technologist. Most of these water-soluble drugs, if not formulated properly may readily release the drug at a faster rate and produce a toxic concentration of the drug on oral administration[2].

Sustained release drug delivery system, which is mainly, consists of two parts: an immediately available dose and a sustaining part. The immediately available dose is normally directly added to the sustaining part of the tablet or alternatively is incorporated in the tablet coating with the sustaining portion in the core of the tablet i.e., apportion (initial priming dose) of the drug is released immediately in order to achieve the desired therapeutic response promptly. The remaining dose of the drug (maintenance dose) is then released slowly thereby remaining in therapeutic drug/tissue level, which is a prolonged but not maintained constant[3].

Sustained release systems include any drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue. It is considered as a controlled release system. If it is unsuccessful of this day nevertheless extends the duration of action over that achieved by conventional delivery. It is considered as a prolonged released system[4].

Cefixime is a white yellowish crystalline powder having melting point 218^0C-220^0C. It is insoluble in water and soluble in methanol and ethanol. Cefixime is a third generation cephalosporin antibiotic having bactericidal activity and used in the treatment of uncomplicated UTI, otitis media, pharyngitis, acute bronchitis and acute exacerbation of chronic bronchitis, uncomplicated gonorrhea. The mechanism action of cefixime is the bactericidal action of cephalosporin is due to the inhibition of cell wall synthesis. It binds to one of the penicillin

binding proteins (PBPs) which inhibits the final transpeptidation step of the peptidoglycan synthesis in the bacterial cell wall, thus inhibiting biosynthesis and arresting cell wall assembly resulting in bacterial cell death. It is available in 50mg, 100mg, 200mg and can be used in the dose range of 200mg/twice a day[5].

Hence, the aim of present work is to develop, formulate and evaluate Sustained release matrix tablets of an antibiotic agent using synthetic and natural polymers.

MATERIALS AND METHODS

Materials

Cefixime gift sample were obtained from Karnataka Antibiotic & Pharmaceuticals Limited, Bengaluru. Karaya gum, locust bean gum were obtained from S.D fine chemicals limited, Mumbai, India. MCC, PVP, Magnesium stearate, Talc and Aerosil were obtained from Karnataka Antibiotic & Pharmaceuticals Limited, Bengaluru.

Methods

The compatibility studies of drug and excipients were determined by FTIR studies. Both pure drug and excipients were individually analysed and further the physical mixture and formulations were also studied.

Preparation of Sustained release matrix tablets of Cefixime by wet granulation method[6]

Different tablets formulations were prepared by wet granulation technique. All the ingredients, polymers and drug weighed accurately and were passed through 40mesh. Shifted ingredients, polymers and drug mixed thoroughly in a motor pestle for 10 min. For preparation of binder, add weighed quantity of PVP in 2ml of water, mix to form a paste, warm if necessary. This granulating fluid is added to the mixture and triturated to form a Dump granules. Prepared granules dried at 50^0 C for 1hr in hot air oven and then this dried granules were further sieved for 20mesh and transferred into poly bag and finally weighed quantity of magnesium stearate, talc, and aerosol were shifted through sieve No. 60 and mixed with dry granules in a poly bag for 15min. Before compression, hardness was adjusted and compressed into 400mg each tablets using tablet compression machine equipped with 11mm flat concave punches on 23 station

rotary tablet machine and same hardness was used for the required number of tablets. The formulations are shown in Table 1.

Pre-Compression Parameters

Pre-compression parameters. The various Pre-compression parameters like Angle of repose, Bulk density, Tapped density, compressibility index, Hausner's ratio and Carr's index were studied[7, 8].

Angle of Repose: The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\text{Tan } \theta = h/r$$

Where h and r are the height and radius of the powder cone.

Bulk Density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$Db = \text{Mass powder}/\text{Volume}$$

Tapped density (Dt): It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gram/ml and is given by

$$Dt = M/Vt$$

Where, M - Mass of the powder

V t – Tapped volume of the powder.

Compressibility index (I) and Hausner's ratio: Carr's index and Hausner's ratio measure the propensity of granule to be compressed and the flow ability of granule. Carr's index and Hausner's ratio were calculated using following formula.

$$C.I = (Dt - Db)100/Dt$$

Where, Dt – Tapped density of the powder

Db – Bulk density of the powder

Post-Compression Parameters

The prepared Cefixime tablets were evaluated for the following various post-compression parameters.

Organoleptic Characters

Organoleptic characters properties such as colour, odour, taste, were evaluated. Tablets from each batch were randomly selected and tested for taste, colour visually compared and odour checked.

Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The weight variation test is done by selecting 20 tablets randomly from each formulation after compression, weighed individually using an "Electronic weighing balance" and average weight was determined. The individual weights are compared with the average weight for the determination weight variation[7].

Tablet hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using "Monsanto hardness tester". The hardness was measured in terms of kg/cm^2.

Friability

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. The friability was determined by using Roche friabilator[8].

Tablet thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using "Vernier Callipers". It was determined by checking the thickness of ten tablets of each formulation[8].

Drug content uniformity

Accurately weighed quantity of the powdered tablet equivalent to 40mg of the drug and 20mg of tablet powder was transferred to 100ml volumetric flask separately. 50ml of buffer solution of pH 7.2 was added. And then the volume was made up to 100ml with the same buffer solution, mixed solution was filtered through the membrane filter. 5ml of the filtrate was diluted to 50ml with same buffer solution and examined under U.V Spectrophotometry at 290nm[8].

***In-vitro* Dissolution studies**

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type 2 (Electrolab, Mumbai, India). Dissolution studies were carried out using acid buffer 0.1N HCl as a dissolution medium for first 2 hrs at 37 + 0.5^0C and 50 rpm. 5ml sample was withdrawn at regular time intervals and replaced with freshly prepared pH 7.2 phosphate buffer. The sample withdrawn was filtered through Whatman filter paper and after suitable dilution. The drug release at different time intervals was measured using an UV spectrophotometer (Labindia, Mumbai, India) at 290nm. The study was performed in triplicate[8].

Details of Dissolution Test

Dissolution test apparatus	: USP type II
Speed	: 50 rpm
Stirrer	: Paddle type
Volume of medium	: 900 ml
Volume withdrawn	: 5 ml every 1 hr
Medium used	: phosphate buffer pH 7.2
Temperature	: 37±0.5ºC
Duration of study	: 12 hours
λ_{max}	:290nm

Stability Studies

Stability can be defined as the capacity of drug product to remain within specifications established to ensure its identity, strength, quality, and purity. The formulations were subjected to short term stability studies. The formulations were packed in aluminium foil in tightly closed container. They were then stored at 30ºC 65% RH and 40ºC / 75% RH for two months and evaluated for their post-compression studies[6].

RESULTS AND DISCUSSION

The compatibility studies revealed both drugs and excipients were compatible after FTIR studies, the results shown in Figure 1.

Pre-compression evaluation parameters

For each type of formulation blends of active pharmaceutical ingredients and excipients were prepared and evaluated for various parameters as explained earlier. Bulk density was found in the range of 0.533-0.576 g/cm^3 and the tapped density between 0.592 - 0.665 g/cm^3. Using the above two density data, Carr's compressibility index were calculated. The compressibility index was found between 9.81-10.76% and the compressibility and flow ability data indicated good flow properties of all powder blends. The better flow property of all powder blends was also evident from angle of repose. The angle of repose was range of 24.76°-30.22°. Angle of repose below 30º indicates good flow property. In the present study all powder blends showed good flow property. The results are shown in Table 2.

Post- Compression evaluation parameters

Organoleptic characters

Various organoleptic properties viz. taste, colour and odour performed on all the formulations, the results found that all the formulations were bitter in taste, yellowish-white in colour and odour less.

Thickness

Thickness of all the formulations was evaluated as per the procedure and the average values was ranges between minimum of 4.16mm to maximum of 4.32mm and found to be within the allowed limit. Results are shown in Table 3.

Hardness

All the tablet formulations were evaluated for their hardness as per procedure and the results were shown in Table 3. All the formulations have an average hardness in between 7.6 to 9.4kg/cm2 which was found to be acceptable.

Friability

All the Sustained release matrix tablets were evaluated for their percentage friability as per the procedure and the results are shown in Table 3. The average percentage friability for all the formulations were found between 0.299% to 0.473%, which is observed to be within the limit as per the standard (i.e. maximum 1%).

Weight Variation

All the Sustained release matrix tablet formulations were evaluated for their uniformity of weight according to the procedure and the results were shown in Table 3. The maximum weight of 402.6 mg for F1 and the minimum weight of 398.6 mg for F6 formulations were observed. The maximum allowed percentage weight variation for tablets 400mg by Indian pharmacopoeia is 7.5%, and no formulations were exceeded the limit. Thus all the formulations were found to be complying with the standards given in IP.

Drug Content

All the Sustained release matrix tablet formulation was evaluated for their uniformity of drug content according to the procedure and results were shown in Table 3. The percentage drug content of all formulations was found in the range of 95.00 to 99.15% w/w. The maximum drug content of 99.01% w/w for F8 and the minimum of 95.10% w/w for F5 formulations were observed.

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

Dissolution studies on all the eight formulations of Sustained release matrix tablets of Cefixime were carried out using a USP type II (paddle type) dissolution test apparatus in phosphate buffer pH 7.2 was used as the dissolution medium. The *in-vitro* drug release data of different formulations are shown in **Figure 2.** The amount of drug released from formulations F1 to F8 at the end of 12hrs were 64.60%, 84.09%, 73.72%, 88.54%, 76.47%, 91.50%, 95.24% & 97.02%

respectively. The maximum drug release of 97.02% was obtained from formulation F8, and minimum drug release of 64.60% shown by F1. Results showed that when combination polymer concentration increased in the formulation, the rate of drug release was also increased as compared to individual polymer concentration. Formulation F7 and F8 shows fast drug release compared to all formulations. The formulation F7 and F8 containing equal ratio of karaya gum: locust bean gum: (1:1) at increasing polymers concentration. The release data was fitted to various mathematical models such as zero order, first order, Higuchi, Korsmeyer-peppas and it was found that the drug release follows first order kinetics.

Stability studies results

The formulations subjected to the stability studies and the evaluation parameters performed after the study period was shown no significant changes with respect to the initial observations. Further results were compared and all the formulations found to be stable during the study period.

CONCLUSION

Sustained release matrix tablets of Cefixime were prepared using different types of natural polymers such as Karaya gum, Locust bean gum by wet granulation method, using PVP as a binder. A total of eight formulations were prepared. The powder properties like angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index of all the formulations were found to be within the standard limits. All the post-compression characteristics of the formulations like thickness, weight variation, hardness, friability, drug content and drug release were found to be well within the limits of official standards. The formulations containing an individual polymer has a less amount of drug release when compared to combined polymers formulations. Overall formulation contains 20 to 30% of polymers, both in individual and in combination. We observed that combination of the polymer at the higher concentration found to have the higher percentage of drug release by dissolution studies. All the formulations subjected for the stability studies showed there were no significant changes in the parameters even after the period of 60 days. From these results it was concluded that, the cefixime is suitable to develop into Sustained release matrix tablets, further clinical trials and commercial exploitation is needed for the better usefulness in the intended therapeutic treatment.

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Table 1: Formulation development of Sustained release tablets of Cefixime

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Drug	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**
Karaya gum	**80**	**100**	**120**	**-**	**-**	**-**	**40**	**50**
Locust bean gum	**-**	**-**	**-**	**80**	**100**	**120**	**40**	**50**
MCC	**86**	**66**	**46**	**86**	**66**	**46**	**86**	**66**
PVP	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Magnesium stearate	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Talc	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Aerosil	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Total	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

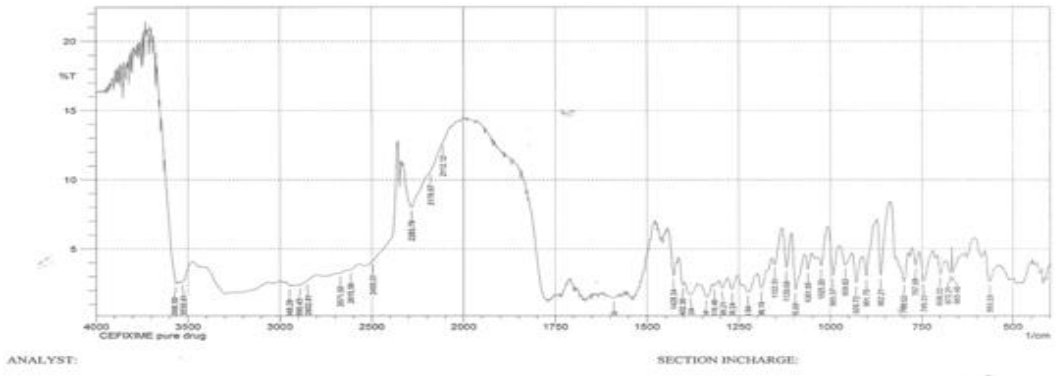
All quantities are in milligrams (mg).

Table 2: Pre-compression parameter

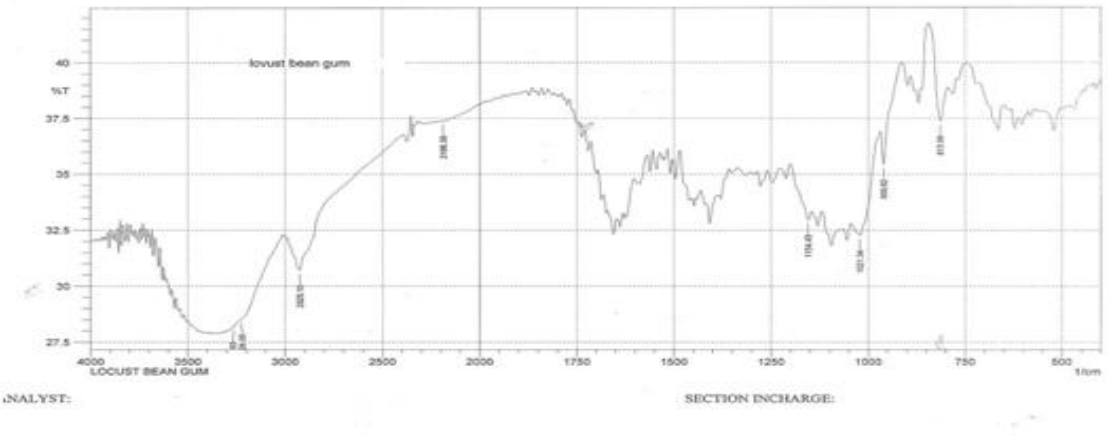
Formulation	Bulk Density (G/CC)	Tapped Density (G/CC)	Carr's Compressibility Index (%)	Hausner's Ratio	Angle of Repose (Ɵ)
F1	0.533±0.012	0.592±0.014	9.96±0.216	1.110±0.055	24.77±0.503
F2	0.597±0.014	0.630±0.011	10.47±0.848	1.117±0.025	25.25±0.708
F3	0.554±0.005	0.615±0.015	9.91±0.886	1.110±0.029	24.76±0.601
F4	0.588±0.015	0.653±0.023	9.95±0.714	1.110±0.015	25.91±0.466
F5	0.580±0.011	0.650±0.011	10.76±0.346	1.120±0.026	29.21±0.367
F6	0.579±0.020	0.641±0.020	9.81±0.585	1.108±0.037	30.22±0.385
F7	0.589±0.011	0.665±0.015	10.76±0.973	1.112±0.012	28.82±0.434
F8	0.585±0.015	0.644±0.026	9.87±0.812	1.100±0.014	28.00±0.421

Table 3: Post- compression parameter

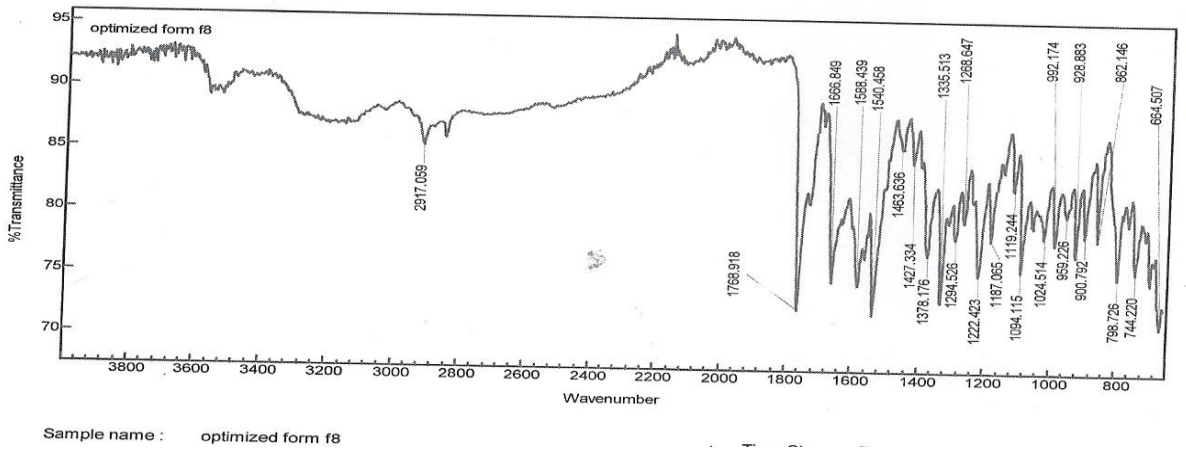
Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	402.6±0.45	7.8±0.20	4.32±0.02	0.337±0.027	98.28±0.76
F2	401.7±0.58	9.0±0.15	4.31±0.01	0.473±0.030	97.74±0.63
F3	401.7±0.75	8.5±0.15	4.31±0.02	0.465±0.046	98.02±0.60
F4	399.7±0.35	8.1±0.11	4.26±0.06	0.299±0.037	97.63±0.80
F5	400.1±0.66	7.6±0.05	4.29±0.05	0.359±0.041	95.10±0.48
F6	398.6±0.70	8.5±0.15	4.30±0.02	0.369±0.055	96.85±0.52
F7	402.1±0.87	9.4±0.15	4.16±0.06	0.344±0.039	98.72±0.57
F8	401.2±0.85	8.6±0.23	4.19±0.03	0.386±0.028	99.01±0.45



A. Pure Drug Cefixime



B. Locust bean gum



C. Optimized formulation F8

Figure 1: FTIR studies of pure drug, polymer and formulation

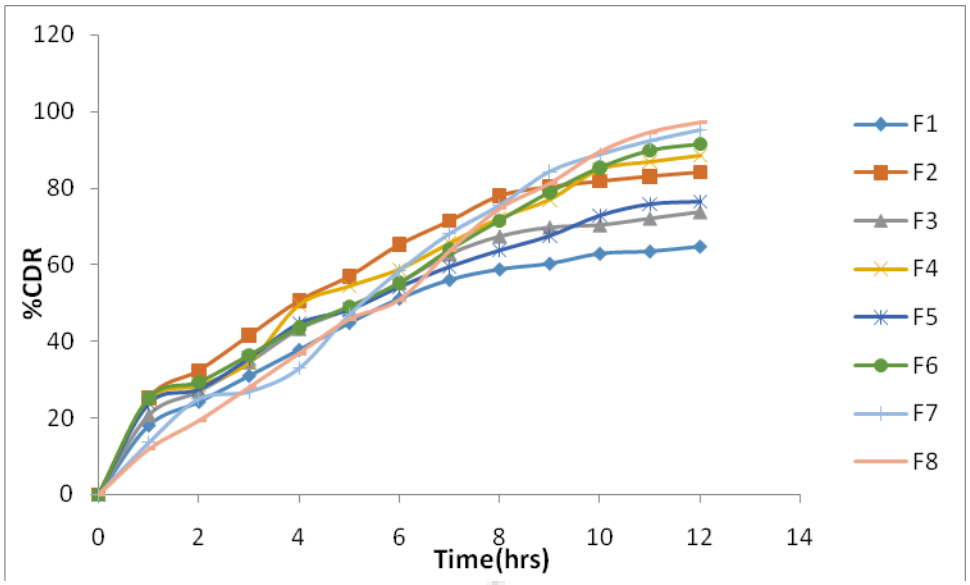


Figure 2: *In-vitro* drug release studies of Sustained release matrix tablet of Cefixime (Formulation F1 to F8)