



EFFECT OF NATURAL GUMS ON FORMULATION OF ORAL SUSTAINED RELEASE MATRIX TABLETS OF CHLORZOXAZONE

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Article Received on: 17/01/12 Revised on: 29/03/12 Approved for publication: 06/04/12

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ABSTRACT

The aim of the study was to prepare and evaluate the Chlorzoxazone sustained release tablets by using natural gums in order to reduce the dose frequency and to improve the patient compliance. The tablets were prepared by direct compression method using natural gums such as Acacia (F₁, F₂ and F₃), Guar gum (F₄, F₅ and F₆) and Tragacanth (F₇, F₈ and F₉) at different concentrations. The tablets were evaluated for weight variation, hardness, friability, thickness, drug content uniformity and *in-vitro* drug release. All the formulations have passed in physical characterization as per the standard limits in average weight, hardness, thickness, friability and drug content. FT-IR studies, reveals that the drug was compatible with excipients. Based on the *in-vitro* drug release F₃, F₆ and F₉ showed sustained release effect up to 12 hours (98.2%, 86.4% and 91.6%). Optimized formulation F₆ was subjected to stability studies for two months at 28°C and 45°C with 75±5% RH as per ICH guidelines and result does not shows any changes in physical parameters and *in-vitro* release studies.

KeyWords: Chlorzoxazone, Acacia, Guar gum, Tragacanth, Sustained release

INTRODUCTION

Sustained drug delivery systems are aimed to control the rate of drug release and to maintain desire drug level in the blood which is therapeutically effective for an extended period of time. Thus the reduction of both total dose of drug administered and the incidence of adverse side effects better patient compliance can be achieved^{1, 2}. The most commonly used method for modulating the drug release is to include it in a matrix system². Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules in slowly disintegrating or inert porous materials. It is also called as controlled release delivery systems³.

Chlorzoxazone (5-chloro-2,3-dihydro-1,3-benzoxazol-2-one) is a centrally acting muscle relaxant used to treat muscle spasm and the resulting pain and discomfort⁴. Chlorzoxazone may act by inhibiting calcium and potassium influx which would lead to neuronal inhibition and muscle relaxation. It is having a shorter half life (1.1hour) with the dose administration of 3-4 times a day leads to decreased patient compliance^{4, 5}. In order to decrease the frequency of drug administration and for improving better patient compliance a sustained-release formulation of Chlorzoxazone is desirable. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of sustained release dosage form⁶. Guar gum a polysaccharide derivative with glycoside linkage, produced from the guar plant seeds (cyampopis tetragonolobus) have been used as matrix former for controlled release⁷. Gum acacia is the dried gummy excaudate obtained from the stems and branches of acacia. It is available as a yellowish or white colored angular fragments⁸. Tragacanth is a naturally occurring dried gum obtained from Astragalus gummifer Labillardiere and other species of Astragalus. The gum consists of a mixture of water-insoluble and water-soluble poly-saccharides. Tragacanth gum is used as an emulsifying and suspending agent in a variety of pharmaceutical formulations⁹. Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in designing a sustained release system¹⁰.

The aim of the present work was to prepare sustained release matrix tablets of Chlorzoxazone by using natural polymers such as Guar gum, Acacia, Tragacanth in varying proportions by direct compression method.

MATERIALS AND METHODS

Materials

Chlorzoxazone was received as a gift sample from Panacea Biotech (Mohali). Guar gum, Acacia, Tragacanth, lactose and magnesium stearate were purchased from Loba Chemicals, Mumbai. Talc was purchased from Micro fine chemicals, India. All other solvent and reagents were of analytical grade.

Preparation of Chlorzoxazone SR tablets⁹

Sustained release tablets each containing 200mg Chlorzoxazone were prepared by direct compression technique. The active ingredient and polymers at various concentrations (45, 60, 75mg) were accurately weighed and passed through sieve no. 45. The content was mixed thoroughly in a mixer for 10 minutes. The lubricant and glidants were added to the above mixture and again mixed for 5 minutes. Then the mixture was directly compressed on a Rotary Tablet Machine (Single punch, Inco) equipped with an 8 mm standard flat faced punch and die set. The compositions of different tablet formulations are shown in Table-1.

Drug-excipient Interaction studies¹¹

Preformulation studies are very important for the successful formulation of any dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were performed by using Shimadzu FTIR spectrometer, which helps in the prediction of interaction of the drug with polymers, diluents and lubricants used in case tablet formulations.

PHYSICOCHEMICAL CHARACTERIZATION

Thickness¹²

Thickness of tablets was important for uniformity of tablet size. The thickness of the tablet was measured by using digital vernier caliper, twenty tablets from each batch were randomly selected and thickness was measured.

Weight variation¹²

Twenty tablets were randomly selected from each batch individually weigh, the average weight and standard deviation of 20 tablet calculated.

Hardness¹²

Hardness was measured using Pfizer hardness tester, for each batch three tablets were tested.

Friability¹²

Twenty tablets were weighed and placed in the Roche Friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted weight.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablet}} \times 100$$

Drug content uniformity¹²

From each batch of prepared tablets, ten tablets were collected randomly and powdered. The powder equivalent to 10 mg of Chlorzoxazone was transferred in to 10 ml of volumetric flask to this 5 ml of methanol was added and then the solution was subjected to sonication for about 10 min. The solution was made up to the mark with methanol. The solution was filtered and suitable dilutions were prepared with pH 7.4 buffer. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 280.5 nm by using UV-Visible spectrophotometer.

In vitro dissolution studies¹³

The dissolution studies were performed in triplicate for all the batches in a USP XXIII dissolution rate test apparatus (Campbell electronics, DR-6) employing the paddle stirrer. The release studies were performed at 75 rpm in 900 ml of phosphate buffer pH 7.4 at $37 \pm 0.5^\circ\text{C}$. Five milliliters aliquots were withdrawn at predefined intervals, and the volume of the dissolution medium was maintained by adding the same volume of fresh pre warmed dissolution medium. The absorbance of the withdrawn samples was measured spectro photometrically at 280.5 nm.

Drug release kinetics^{14, 15}

To analyze the mechanism of drug release rate kinetics, the results of *In vitro* release profile were plotted in various kinetic models like zero order, first order, Higuchi and Krosmeier-peppas model. The methods were adopted for deciding the most appropriate model.

1. Cumulative percent drug released versus time (Zero order kinetic model)
2. Log cumulative percent drug remaining versus time (First order kinetic model)
3. Cumulative percent drug released versus square root of time (Higuchi's model).

Zero order:

In many of the modified release dosage forms, particularly sustained or controlled release dosage forms is zero order kinetic. The plot of cumulative percent drug released versus time is the linear.

$$Q = K_0 t$$

Where, Q is the amount of drug release at time, t and K_0 is the release rate constant.

First order

Most conventional dosage forms exhibits this dissolution mechanism. Some modified release preparation, particularly prolonged release formulations, adheres to this type of dissolution pattern. It assumes that the drug molecules, diffuses out through a gel like layer formed around the drug during the dissolution process. A plot of log cumulative percent drug remaining versus time is the linear.

$$\log Q = K_1 t$$

Where Q is the percent of drug release at time, t and K_1 is the release rate constant

Higuchi model

A large number of modified release dosage form contain some sort of matrix system. In such instances, the drug dissolves from the matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled). In Higuchi model, a plot of cumulative percent drug released versus square root of time is linear.

$$Q = K_2 t^{1/2}$$

Where, Q is the percentage of drug release at time t and K_2 is the diffusion rate constant

Peppas Equation

$$Q = K t^n$$

Where, Q is the percent of drug release at time, t and K is the diffusion rate constant and n is diffusional exponent. If n is equal to one the release is zero order. If n is equal to 0.5 the release is best explained by fickian diffusion and if $0.5 < n < 1$ then the release is through anomalous diffusion or case II diffusion in this model a plot of % drug released versus log time is linear.

Stability Studies

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess the drug and formulation stability, stability studies were done according to ICH guidelines. The stability studies were carried out of the most satisfactory formulation as per ICH guidelines. The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at $30 \pm 2^\circ\text{C} / 65 \pm 5\%$ RH for two months. At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution sustained behavior.

RESULTS AND DISCUSSION**Evaluation of Physical characterization**

Tablets of all formulations were subjected to various physicochemical evaluation parameters such as weight variation, thickness, diameter, hardness, friability, and drug content. The results of these studies were also found to be within limits and were uniform given in Table-2.

Compatibility Studies

The FTIR studies proved chemical and physical compatibility of drug with excipients which is shown in the Figure 1.

In vitro Drug Dissolution Study

The results of dissolution studies showed that as the concentration of polymer increases in the release of drug also retarding. The $t_{50\%}$ of the formulation F₁, F₄ and F₇ is with in 4 hours where as for the formulation F₂, F₅ and F₈ showed nearly six hours. The polymers in high concentration showed $t_{50\%}$ more than six hours. The formulations with high concentration F₃, F₆, F₉ shows the sustained release of the drug up to 12 hrs which are found to be F₃ (98.2%), F₆ (86.4%), F₉ (96.6%). Among the nine formulations F₆ formulation showed good sustained activity. *In vitro* release study results revealed that the release of drug was retarded with the proportional increase of the polymer concentration. It was observed that the amount of polymer influences the drug release which is shown in Figure 2-5.

Drug Release Kinetics

The release data was fitted to various mathematical models to evaluate the kinetics and the mechanism of drug release. The data was analyzed for the optimized formulations F₃, F₆ and F₉ and the r^2 values are tabulated in Table-3. Among the models, zero order, Higuchi, Hixson-crowell and Krosmeier peppas the above three formulation F₃, F₆ and F₉ were best fitted in Krosmeier-peppas and its r^2 values were found to be

0.9926 (F_3), 0.9954 (F_6) and 0.9856 (F_9) which indicates diffusion is the mechanism of drug release.

Stability Studies

The optimized formulation (F_6) was further evaluated for stability studies as per ICH guidelines mention earlier. It was suggested that there was no significant changes in physical parameters like hardness, thickness, weight variation, content uniformity. *In-vitro* release profile of optimized batch (F_6) was shown in Figure 6. Thus formulation was stable at given condition of temperature and humidity for 2 month period of time.

CONCLUSION

From the above study it may be concluded that at higher concentration of Guar gum and Tragacanth were retarded the release of Chlorzoxazone. As the concentration of polymer increases the release of drug was retarded. Thus the polymer concentrations were optimized for producing the oral SR tablets of Chlorzoxazone. The mechanism of drug release observed to be following may be Korsmeyer-Peppas model which depicts diffusion is the mechanism of drug release.

ACKNOWLEDGEMENT

The authors are thankful to Faculty of Pharmacy, PRIST University, Thanjavur, for providing laboratory facilities.

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TABLE NO 1: FORMULATION OF CHLORZAXONE TABLETS

Ingredients	Weight in (mg)								
	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉
Chlorzoxazone	10	10	10	10	10	10	10	10	10
Acacia	45	60	75	---	---	---	---	---	---
Guar gum	---	---	---	45	60	75	---	---	---
Tragacanth	---	---	---	---	---	---	45	60	75
Lactose	141	126	111	141	126	111	141	126	111
Talc	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200

TABLE NO 2: PHYSICAL CHARACTERISTICS OF CHLORZOXAZONE TABLETS

Formulations	Weight variation(mg)	Fraibility (%)	Hardness (kg/cm ²)	Thickness (mm)	Diameter (mm)	Drug content (%)
F ₁	197.560±1.078	0.58±0.028	5.2±0.141	2.5±0.141	8±0.01	96.15±0.212
F ₂	197.000±1.412	0.48±0.038	5.65±0.070	2.20±0.141	8±0.01	101.10±1.202
F ₃	196.990±1.127	0.49±0.028	5.65±0.212	2.35±0.141	8±0.01	95.60±0.282
F ₄	197.730±1.441	0.33±0.049	5.10±0.282	2.15±0.141	8±0.03	96.75±0.353
F ₅	196.960±1.286	0.72±0.035	5.10±0.282	2.45±0.141	8±0.01	97.75±0.494
F ₆	196.945±1.265	0.29±0.021	5.15±0.353	2.20±0.141	8±0.02	98.10±0.282
F ₇	197.180±1.401	0.32±0.035	5.15±0.212	2.20±0.141	8±0.01	98.25±0.212
F ₈	196.930±1.313	0.55±0.014	5.70±0.141	2.30±0.141	8±0.02	99.65±0.070
F ₉	197.500±1.231	0.34±0.007	5.60±0.282	2.25±0.141	8±0.01	98.60±0.424

*above values shows Mean ± S.D

TABLE NO 3: KINETIC RELEASE DATA FOR THE OPTIMIZED FORMULATIONS

MODEL	R ² VALUE		
	F ₃	F ₆	F ₉
Zero order	0.9631	0.9961	0.9769
First order	0.8543	0.8519	----
Higuchi	0.9421	0.9742	0.9553
Krosmeyer peppas	0.9926	0.9954	0.9856

TABLE NO 4: STABILITY STUDIES: DRUG CONTENT

Formulation	Initial Amount	30 ± 2 °C / 65 ± 5 % RH after 1 month	30 ± 2 °C / 65 ± 5 % RH after 2 nd month
F ₆	98.10±0.282	97.50±0.212	97.46±0.201

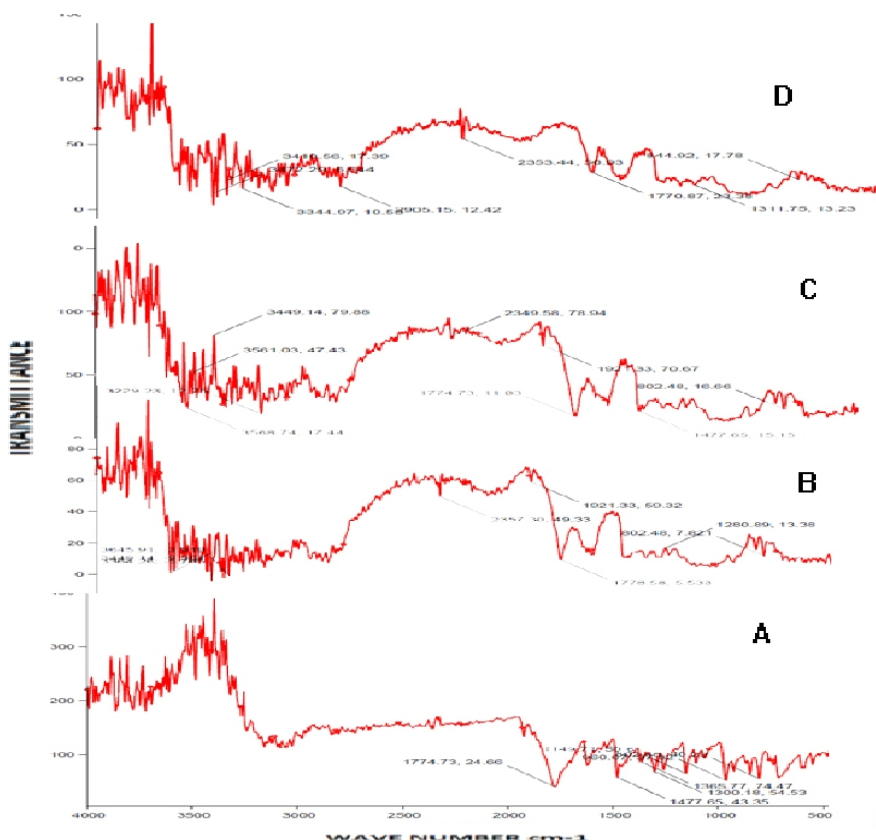


Figure 1: FTIR Spectrum of Chlorzoxazone (A), FTIR Spectrum of Acacia (B), FTIR Spectrum of Guar Gum (C), FTIR Spectrum of Tragacanth (D).

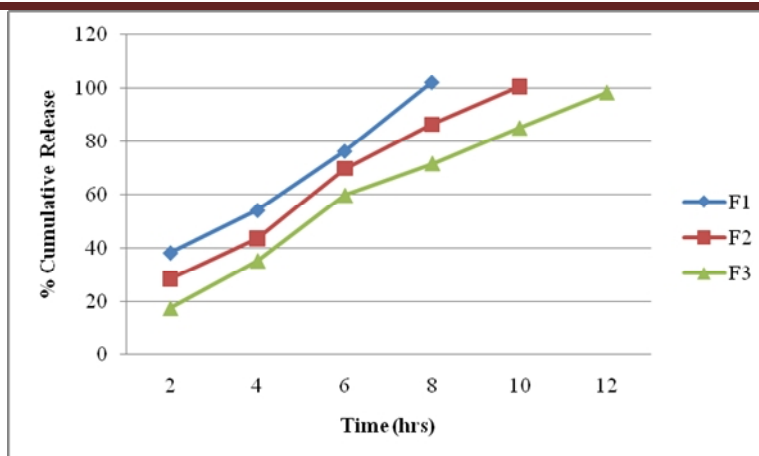


Figure 2: Comparative *in vitro* drug release profile of formulations F₁-F₃

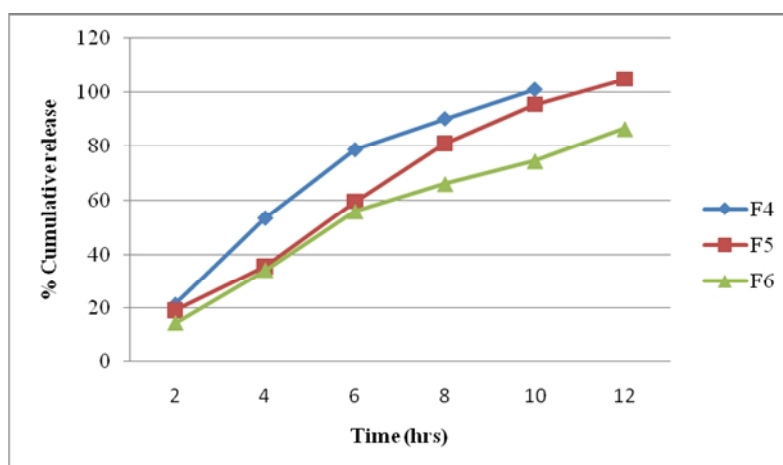


Figure 3: Comparative *in vitro* drug release profile of formulations F₄-F₆

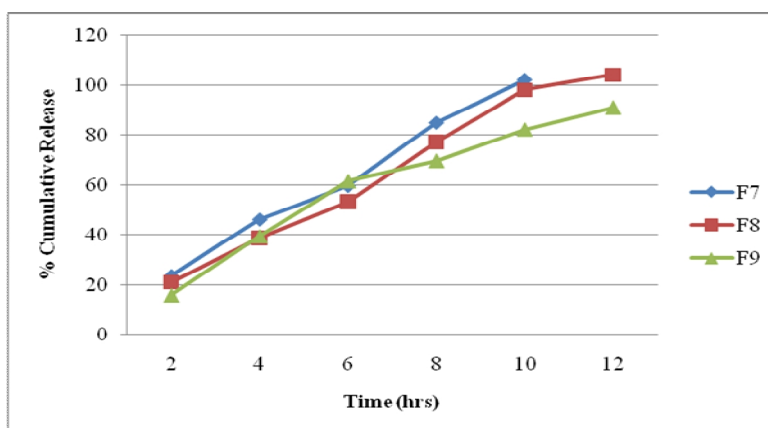


Figure 4: Comparative *in vitro* drug release profile of formulations F₇-F₉

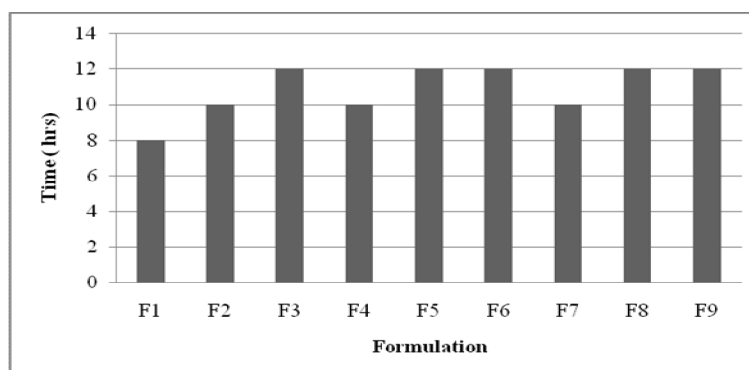


Figure 5: Comparative percentage cumulative release of Chlorzoxazone formulation indicates the maximum time taken for the drug release

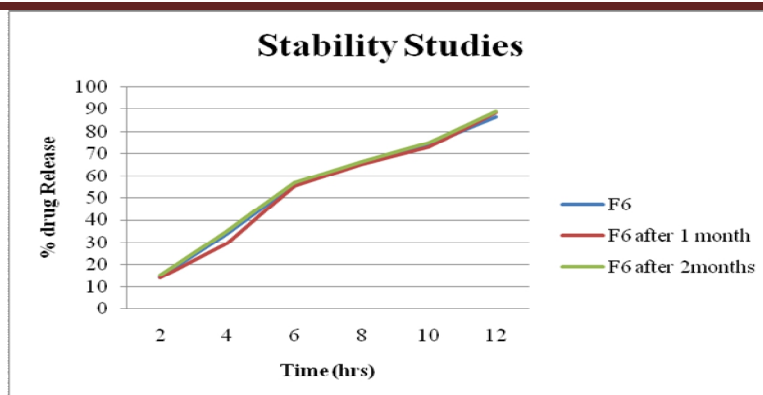


Figure 6: Comparative Stability dissolution studies of formulations F₆

Source of support: Nil, Conflict of interest: None Declared