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Design, Development and Evaluation of Tetracycline Controlled Release Microspheres

Surita Basu, Baishali Ghosh, Sudipta Das*, Biswajit Ghosh, Sanjoy Nag

Department of Pharmaceutics, Netaji Subhas Chandra Bose Instiitute of Pharmacy, Chakdaha, Nadia, West Bengal, India

A B S T R A C T

Microsphere drug delivery methods have been used to boost efficacy, reduce toxicity, and improve patient compliance. Additional benefits of using microspheres to deliver medications include controlled drug release, improved bioavailability, and targeted drug delivery to the desired location. In order to achieve the required therapeutic effect, hydroxypropyl methyl cellulose K4M and sodium alginate are used as a polymer in microsphere delivery system and different concentration of aluminium chloride is used as cross linking agent. The advantage of microsphere formulations over traditional tablet or capsule formulations is that they increase the surface area exposed to the absorption site, boosting medication absorption and reducing drug dose frequency. Tetracycline is a broad-spectrum antibiotic that is frequently used to treat illnesses like pneumonia and respiratory tract infections. The encapsulation effectiveness, particle size, *in -vitro* release analysis and release kinetics of the microsphere formulations was assessed.

Key Words: Microspheres, Cross-linking agent, Controlled release, Encapsulation.

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*Address for Correspondence:
Sudipta Das, Department of Pharmaceutics, Netaji Subhas Chandra Bose Instiitute of Pharmacy, Chakdaha, Nadia, West Bengal, India

INTRODUCTION:

CRDDS (control release drug delivery system) have been introduced to eliminate many of the challenges and complications associated with conventional medication administration systems. Liposomes, hydrogels, polymer-based disks, rods, pallets, and microspheres are being used in CRDDS to encapsulate the drug and release it at a controlled rate over a longer period of time, ranging from days to months.

CRDDS offer great advantages over conventional drug delivery systems. Firstly, drug release rates can be customizing to the need of a specific application. For example, some diseases treated most effectively maintaining a relatively constant drug concentration within a certain therapeutic range, which may require a constant rate of drug delivery. In the case of administration of antibiotics and vaccinations, require bursts of drug at the specified time interval. Secondly, CRDDS gives protection of drugs that are otherwise rapidly destroyed by the body. Finally, the controlled release system provides good patient compliance.

The drug has to be taken for a longer period of time and simultaneously many medicines have to take in case of a chronic patient. Patient's compliance decreases due to frequent administration of the drug when those have a shorter half-life. To address these issues, a variety of controlled release dosage forms are produced and modified, resulting in increased patient compliance due to the longer effect. [1]

One of the most effective methods is to use microspheres as drug carriers. Microspheres are characteristically polymer coating freely flowing powder which is bio-degradable and ideally particle size range between 1 to 1000 µm. [2]

Microspheres are prepared by some methods like Emulsion solvent evaporation technique, Emulsion cross-linking method, Coacervation method, Spray drying technique, Emulsion solvent diffusion technique, Multiple emulsion method and Ionic gelation method.

For decades, oral drug delivery has been recognised as the most extensively used route of administration among all the ways that have been investigated for systemic drug delivery

via multiple pharmaceutical products in various dose forms. Currently, the majority of pharmaceutical scientists are working on producing an ultimate DDS. This system would benefit from a single dose for the time taken of the treatment and deliver the medicine to a specified location. Scientists have developed a system that is as close to an appropriate system as possible, which pushes scientists to design such system.

The major purpose of an oral CRDDS should be to improve predictability and repeatability in drug release, drug concentration in target tissue, and optimization of a medication's therapeutic efficacy by managing drug release in the body with lower and fewer frequent doses.

For the preparation of microspheres, emulsion solvent, phase-separation method and spray drying method have been widely used. Many parameters influence the performance of any micro-encapsulation process, including drug solubility, partition co-efficient, polymer composition, and molecular weight. Separation of organic solvent from dispersing oil droplets containing both polymer-drug by the solvent evaporation technique produce the micro particles. Traditional drug therapy comprises the administration of a medicinal substance on a regular basis in order to assure its stability, activity, and bioavailability. For the most part, traditional formulation procedures are quite effective. Some medications, on the other hand, are unstable and poisonous, have a limited therapeutic range, have extreme solubility issues, must be localised to a specific place in the body, or require rigorous compliance or long-term use. [3]

In such instances, a continuous drug administration approach is preferable to maintain constant plasma drug levels. By localizing the medication at the site of action, lowering the dose necessary, or delivering uniform drug administration, the purpose of constructing controlled or controlled delivery systems is to reduce the frequency of dosing or to maximize the effectiveness of the medicine. A control-release (CR) dosage form is one that delivers one or more drugs over time in a controllable manner, either systemically or to a specific target organ.

To achieve optimum therapeutic efficacy, the agent must be delivered to the target area in the correct amount and at the proper time, resulting in minimal toxicity and adverse effects. There are various methods for delivering a medicinal chemical to the target region in a regulated and controlled manner. One method is to use microspheres as medication carriers.[4]

Advantages of microspheres of Tetracycline are increasing the solubility of a poorly soluble medication by reducing the particle size, ensuring a consistent and long-lasting therapeutic impact, increasing patient compliance by maintaining a steady drug concentration in the blood, Protects the medication against enzymatic and photolytic cleavage, making it perfect for protein drug delivery, Controlled-release administration Biodegradable microspheres are utilised to regulate drug release rates, reducing hazardous side effects and eliminating the hassle of many injections.[5]

MATERIALS AND METHODS:

Materials:

Tetracycline from Yarrow chem. Pvt. Ltd., Sodium Alginate and HPMC K30 from Loba Chemie Pvt. Ltd., Aluminium Chloride from Nice Chemicals, Cochinwere used without further purification. All the chemicals were of analytical grade.

Methods:

An accurately weighed quantity of sodium alginate was taken and dissolved in 10 ml of distilled water. Then precise amount of Tetracycline drug was added to it and stirring for 20 mins. In another beaker accurate amount of hydroxypropyl methylcellulose (HPMC) was dissolved in 10 ml of distilled water. Then HPMC solution was added to the previous mixture under continuous stirring in magnetic stirrer. After completely dissolve, the drug-polymer mixture was added drop wise in the aluminium chloride solution of different concentration with continuous stirring in magnetic stirrer. Then the beads are collected and dried by using hot air oven at a temperature of 50°C. Then dried microspheres are collected and weighed.[6]

Table 1: Composition of Tetracycline microspheres

Formulations	Sodium alginate (mg)	HPMC (mg)	Drug(mg)	Aluminium Chloride
F1	500	500	100	1%
F2	500	500	100	2%
F3	500	500	100	3%

Evaluation of Tetracycline Microsphere:

Particle Size and Shape:

Particle size of the beads was determined by optical microscopy. The study employed an average of 100 beads, and the mean particle size (arithmetic mean diameter) was used to select the optimum formulation conditions for each variable parameter investigated.[7] Shape of microspheres was observed by visual observation.

Drug Entrapment Efficiency of the microsphere:

The actual amount of Tetracycline present into the different formulation was estimated by weight of drug loaded microspheres were placed in fixed amount of buffer medium and kept overnight followed by sonication for 15 min in water bath sonicator. Then absorbance was measured in 368 nm in UV spectrophotometer.[8] Drug entrapment efficiency is calculated using this formula:

$$\%\text{Drug Entapment Efficiency (DEE)} = \frac{Experimentaldrugcontent}{Theoriticaldrugcontent} \times 100\ \%$$

In-vitro drug release study:

The *in-vitro* drug release from the micro particles was investigated in distilled water. These experiments were performed using a U.S.P-II rotating paddle type dissolution test apparatus under the sink condition. A weighed quantity of each formulation was added in dissolution media and at regular time interval 5ml aliquots were withdrawn and replace by an equal volume of fresh stocksolution. The amount of the drug release was analysed by using a UV Spectrophotometer at a wavelength of 368 nm. These studies were performed for each sample to achieve a reproducible result. To analyse the pattern of drug release, the cumulative percentage release of the drug is calculated and plotted against the function of time based on these investigations.[9]

Drug release Kinetic:

The data obtained from the *in vitro* release study were analyzed using linear regression method according to the following equations:

Zero Order

$$Qt = K0t$$

Where, Q= Amount of drug release in time t

K0 = Zero order rate constant expressed in unit ofconcentration/time

t = Release time

First Order

$$Log\ Q = Log\ Q0 - Kt/2.303$$

Where, Q0= is the initial concentration of drug

k= is the first order rate constant

t = release time

Higuchi Model

$$Q = Kt1/2$$

Where, k= Release rate constant, t = release time

Hixon-Crowell Model

$$W01/3 - Wt1/3 = \text{Kt}$$

Where, W0 = initial amount of drug in the pharmaceutical dosage form

Wt = remaining amount of drug in the pharmaceutical dosageform at time t and K = rate constant incorporating the surfacevolume relation

Korsemeyer- Peppas model

$$\frac{Mt}{M\infty} = Kt\ n$$

Where, Mt = amount of drug released at time t

M∞ = amount of drug released after infinite time

Mt/M∞ = fraction solute release

t = release time, K = kinetic constant incorporating structuraland geometric characteristics of the polymer system, n =diffusion exponent that characterizes the mechanism of therelease of traces[10].

The results are shown in the table 4 and figs 2 -6.

RESULTS AND DISCUSSIONS:

Sodium alginate and hydroxypropyl methylcellulose (HPMC) microparticles are prepared by using tetracycline as a model drug. Sodium alginate is a linear polyamine containing a number of free hydroxyl groups that are readily available for cross-linking. Sodium alginate is soluble in water. The formation of micro particles was cross linked by using aluminiumchloride.

Particle Size of Microsphere:

The particle size of sodium alginate and hydroxypropyl methylcellulose (HPMC) containing micro particles was analysed by using optical microscope.

Drug Entrapment Efficiency:

In this study the drug entrapment efficiency (DEE) of the formulations are found to be 85.84±0.01 %, 81.59±0.19 %and 78.19± 0.08 % respectively .The percent encapsulation efficiency decreases with increasing content of cross-linking agent aluminium chloride.F-1 was selected as the best batch due to higher Drug entrapment efficiency.

Table 2: Properties of Tetracycline Microsphere

Formulation No	% Drug Entrapment Efficiency	Mean Particle Diameter (µm)
F1	85.84±0.01	90 ± 1.271
F2	81.59±0.19	77 ± 1.112
F3	78.19±0.08	63 ± 1.162

(Mean±SD, n=6)

In-vitro Release Study:

In- vitro release experiments is carried out for a time period of 5 hrs. Initially a burst effect was observed within 60 mins and remaining amount of drug releases in a controlled manner. Initial burst release was due to associated drug present close to the particle surface which diffuses rapidly during *in-vitro* drug release studies. At the end of 5 hr % of drug release from F1, F2 and F3 were 83.678, 75.628 and 60.781 respectively. % of drug release is decreased with amount of % of aluminium chloride is increased.

The percent of Tetracycline released over a 5-hour period from produced microsphere formulations with the same initial drug concentration is discussed utilising various concentration of aluminium chloride.

3% Aluminium chloride containing microspheres have the lowest percentage of Tetracycline release. As we requires sustain release dosage form, in comparison to the other batches, the F3 batch has a sustainable release.

Various kinetic models, such as zero order, first order, Higuchi model and Hixon-Crowell model and Korsemeyer model were used to analyse the release data, as shown in figure 2 -6. In table 3, the R2 value was tabulated.

Table 3: Kinetic study of *in-vitro* release data of prepared tetracycline microspheres

Formulation code	**F1**	**F2**	**F3**
Corelation Coefficient (R^2)			
Zero order	0.46	0.53	0.673
First order	0.688	0.708	0.796
Higuchi	0.705	0.771	0.878
Hixon croweel	0.61	0.649	0.757
Korsemeyer	0.961	0.976	0.977

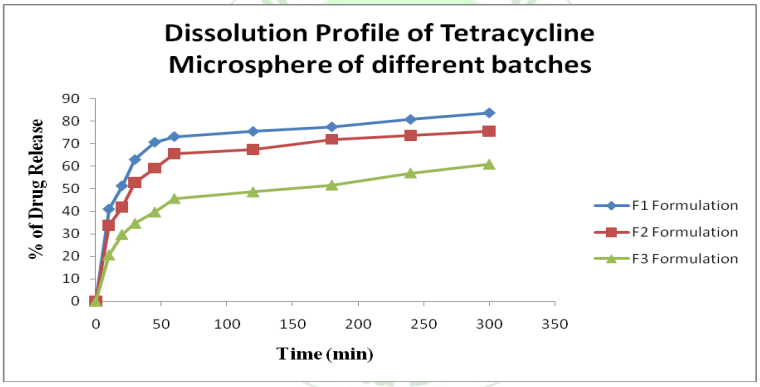

Figure 1: *In-vitro* dissolution Profile of Tetracycline microspheres

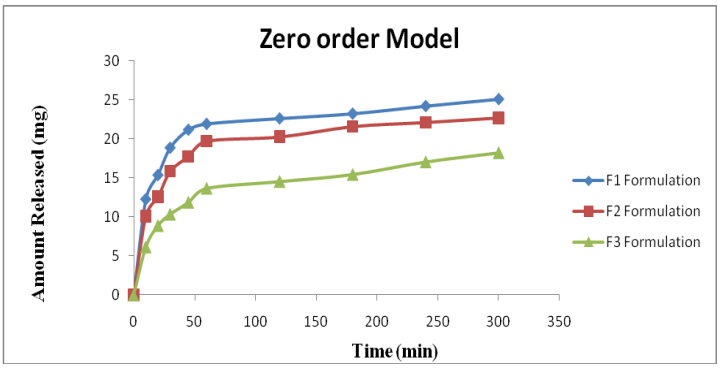

Figure 2: Zero order release plot for prepared Tetracycline microspheres

Figure 3: First order release plot for prepared Tetracycline microspheres

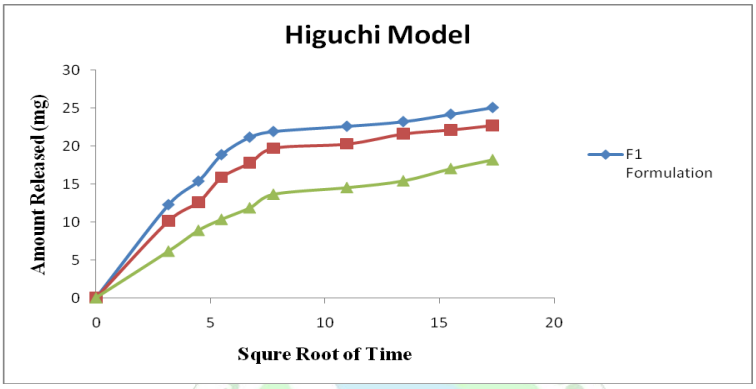

Figure 4: Higuchi release plot for prepared Tetracycline microspheres

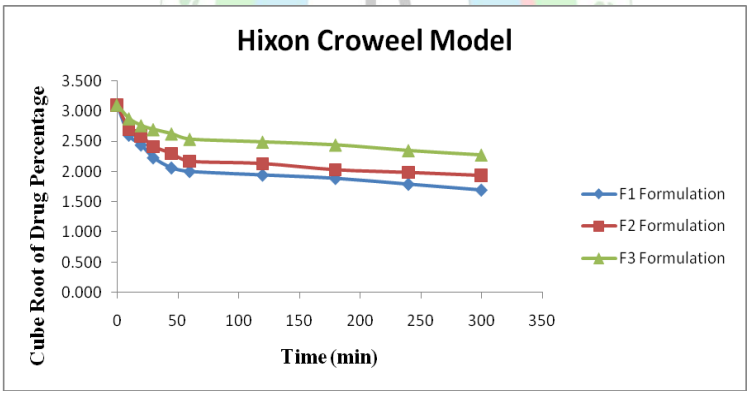

Figure 5: Hixon Croweel release plot for prepared Tetracycline microspheres

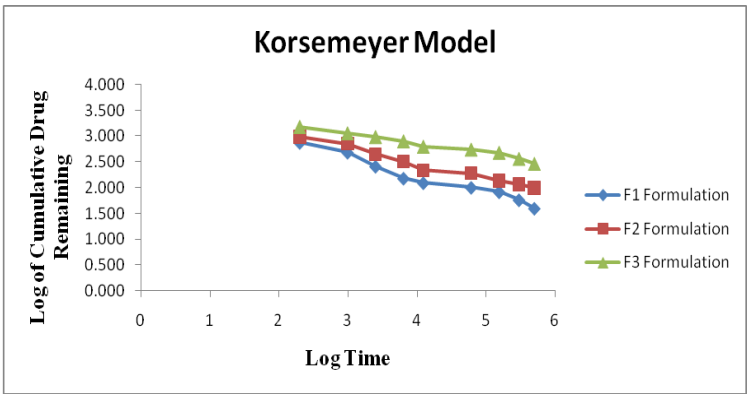

Figure 6: Korsemeyer release plot for prepared Tetracycline microspheres

CONCLUSION:

From the above study, it was concluded that tetracycline loaded sustain release microspheres were prepared by using sodium alginate and hydroxypropyl methylcellulose (HPMC) polymer complex, it showed that better sustain release pattern of the drug over a period of 5 hours. The size of microspheres, drug content, and polymer concentrations could determine the rate and release pattern of the drug. It can be seen that by using two polymers, the rate of drug release from the microspheres increases gradually.

As a result, we may conclude that the current study demonstrates the effectiveness of microspheres in delaying the release of drug. The frequency of dose may be reduced, improving patient compliance. As a result, the F3 batch is regarded as the most optimized. Though, long term stability study is required for future development of these formulations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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