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EFFECT OF EXCIPIENTS ON THE RELEASE OF TRIMETAZIDINE DIHYDROCHLORIDE FROM BIODEGRADABLE POLYMERIC IMPLANTS

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ABSTRACT

The purpose of this research was to evaluate the prospect of fabrication of biodegradable implants with Trimetazidine dihydrochloride which plays an important role in prophylactic treatment of angina pectoris, ischemia, tinnitus and Meniere's disease to achieve prolonged release of the drug in order to reduce the dosing frequency as compared to the conventional dosage form. Drug loaded implants with Chitosan and Sodium Alginate were prepared in two varying ratios of 60:40 and 70:30. As the 70:30 Chitosan-Sodium Alginate implants with 25 mg drug load produced the maximum sustained action, this formulation was explored for further development using different excipients. The implants were evaluated for loading efficiency and *in-vitro* drug release profiles. The results of *in-vitro* dissolution study were fitted into Zero order, First order, Higuchi and Korsmeyer-Peppas kinetics to elucidate the drug release mechanism. Implants were found to follow Korsmeyer-Peppas model. Also good correlations were obtained with Higuchi model. According to these models, the drug release from the implants was diffusion controlled, where the drug leaving the matrix through pores and channels formed by the entry of dissolution medium.

KEYWORDS: Biodegradable Polymeric Implant, Chitosan, Sodium Alginate, Trimetazidine dihydrochloride.

INTRODUCTION

Implantable drug delivery system (IDDS) originated in the 1960s was recognized as a mode of delivery that could eradicate the problems associated with oral administration of specific therapies.[1] Subcutaneous implant based on natural biodegradable polymers allows for slow and uniform release of drug and also systemic side effects associated with this route of administration would be minimal as compared to oral route.[2-3]

Controlled drug delivery systems are one of the most common areas in which biodegradable polymers are applied. Biodegradable polymers have long been used in controlled release technology because of their long-term drug delivery applications and reabsorbing ability by the body.[4] As no surgical procedures are needed after completion of dosage regime since the remaining polymer will degrade and get cleared by the body, biodegradable polymers offer a novel approach for developing sustained release drug delivery systems that are simple and convenient to patients.[5]

Chitosan, mainly derived from the exoskeletons of crustaceans, insects, mollusks and the cell wall of microorganisms, is the second most abundant biopolymer found in nature.[6] Due to its antimicrobial, functional, renewable, nontoxic, biocompatible and mucoadhesive properties, Chitosan has been extensively studied for a number of biomedical and pharmaceutical applications, including prolonged or controlled release drug delivery systems.[7-8] Moreover, Chitosan is metabolized by certain human enzymes, such as lysozyme and it is biodegradable.[9]

Alginate molecules are playing vital role in the fields of pharmacy and medicine. It is mainly used as gelling and viscosifying agent because of its ability to retain water. Alginates can be used in controlled drug delivery systems where the rate of drug release depends on the type and molecular weight of alginates.[10] Sodium Alginate, a polysaccharide from natural sources is available abundantly and is used extensively in the preparation of sustained release preparations.[11]

Trimetazidine dihydrochloride used in the prophylaxis and management of angina pectoris, ischemia of neurosensorial tissues and also in Meniere's disease is freely soluble in water, rapidly absorbed and its half-life is relatively short ($t_{1/2}$ = 6.0 ± 1.4 h).[12, 13] Trimetazidine dihydrochloride, available as both immediate release and modified release tablets, needs repeated administration which leads to poor compliance for angina pectoris patients who need a long term therapy. Therefore, the aim of the research was to explore the scope of sustaining the release of Trimetazidine dihydrochloride by Chitosan-Sodium Alginate biodegradable polymeric

implants to maintain their therapeutically effective concentrations in systemic circulation for prolonged periods of time and to decrease the number of daily administrations, minimise local and systemic side effects and improve patient compliance.[14]

MATERIALS AND METHODS

Materials

All the chemicals and reagents used in this study were of analytical grade. Trimetazidine dihydrochloride was obtained as a gift from Eskayef Bangladesh Ltd. Purified Chitosan and Sodium Alginate were purchased from Haihang Industry Co., Ltd. China and Loba Chemie Pvt. Ltd, Mumbai. Suitable storage conditions were maintained to store the working chemicals and reagents.

Methods

Preparation of implants

Biodegradable implants of Trimetazidine dihydrochloride were prepared by using two biodegradable polymers, Chitosan and Sodium Alginate. Implants were prepared using 25 mg drug with two different polymer ratios (60:40 and 70:30) as well as 25 mg drug load using 70:30 ratio and different excipients. 100 ml of 1% acetic acid solution was prepared to dissolve 4.167 g of Chitosan. The solution was stirred until no large chunks remained and then blended until it was homogenous. 100 ml of distilled water was used to dissolve 4.167 g of Sodium Alginate. The solution was stirred until no large chunks were remaining and then it was added to the blended Chitosan solution.[15] Drug Trimetazidine dihydrochloride was then dispersed to the Chitosan and Sodium Alginate solution. After being mixed with ultrasonic mixer, the mixture was poured into petri dish. Then it was placed in a refrigerator at -32˚C for 1 day. After 1 day, implants were cut into 1 cm width and 1 cm length square shape by NT cutter. **Figure 1** shows photographic image of Chitosan-Sodium Alginate polymeric implants.

Figure 1: Photographic image of Chitosan-Sodium Alginate polymeric implants.

Cross linking and hardening of implants

The plentiful amino groups (-NH2) and hydroxyl groups (-OH) along the Chitosan chains can be used as cross-linkable functional groups to react with cross-linking agents.[16] Implants were placed into a crosslinking solution of Glutaraldehyde for hardening. The contact time of cross linking was 15 minutes for different formulations. After hardening they were kept in aseptic cabinet for air drying for few minutes. **Table 1** and **2** show formulations of implants that had been prepared.

Table 1: Formulation chart of implant.

Name of Formulations	Drug Loading	Polymer Ratio
F1	25 mg	60:40
F2	25 mg	70:30

Table 2: Formulation chart of implant with different excipients.

Name of Formulations	Drug Loading	Excipient Loading	Polymer Ratio	Excipients
F3	25 mg	25 mg	70:30	Glyceryl Monostearate
F4	25 mg	25 mg	70:30	Cetostearyl Alcohol
F5	25 mg	25 mg	70:30	Stearic Acid
F6	25 mg	25 mg	70:30	Eudragit RSPO
F7	25 mg	25 mg	70:30	Cetyl Alcohol
F8	25 mg	25 mg	70:30	Methocel K 100M

Analysis of drug loading efficiency

The amount of drug that was actually loaded in implants during fabrication process was determined by spectrophotometric analysis. For determining the drug content of Trimetazidine dihydrochloride loaded implant, first the implant was weighted and then crushed in a mortar and pestle. Then it was dissolved in 2 ml acetic acid by vigorous ultrasonication. 2 ml acetronitrile, 4 ml hot buffer (pH 7.4) and 2 ml acetic acid were then added for precipitating the polymer and extracting the drug in solvent. The total volume of acetic acid, acetronitrile and phosphate buffer ratio was 40:20:40. Then it was centrifuged at 4000 RPM for 15 minutes to separate the solid material. Clear supernatant was withdrawn and it was analyzed at 270 nm in UV spectrophotometer. The percentage of loading efficiency (% LE) of implants was determined with the formula.

% LE= (LD/AD) x 100.

Where,

LD is the amount of loaded drug in the implant and

AD is the amount of added drug in the formulation.[17]

SEM (Scanning Electron Microscope)

SEM was used to observe interior surface morphology of implants. An in depth understanding of the structure of the surface and the internal morphology were analyzed by scanning electron microscope (SEM Philips XL30, Netherlands). Electronic devices were used to detect and amplify the signals which were digitally captured. They were then displayed on a computer monitor.

***In-Vitro* dissolution study**

After formulation of implants, *in-vitro* dissolution studies were carried out in static condition in order to observe the drug release profile for Trimetazidine dihydrochloride implants. Three implants from each formulation were taken, and their weigh were recorded. They were then transferred into rubber capped glass vessels containing 100 ml phosphate buffer (pH 7.4). At predetermined time interval, 3 ml of sample was withdrawn from the dissolution vessels using 5 ml conventional disposable syringe, after mild stirring of the dissolution vessels for few seconds to ensure uniform distribution of drug throughout the dissolution medium. 3 ml of fresh buffer was then added to the dissolution vessels to replace the withdrawn sample to maintain the sink condition. The withdrawn samples were then analyzed for determining the percentage of release of drug by UV spectrophotometer at 270 nm (**λ**max of Trimetazidine dihydrochloride in phosphate buffer, pH 7.4). Obtained data were then used in statistical analysis for the determination of mean, standard deviation and release kinetics.

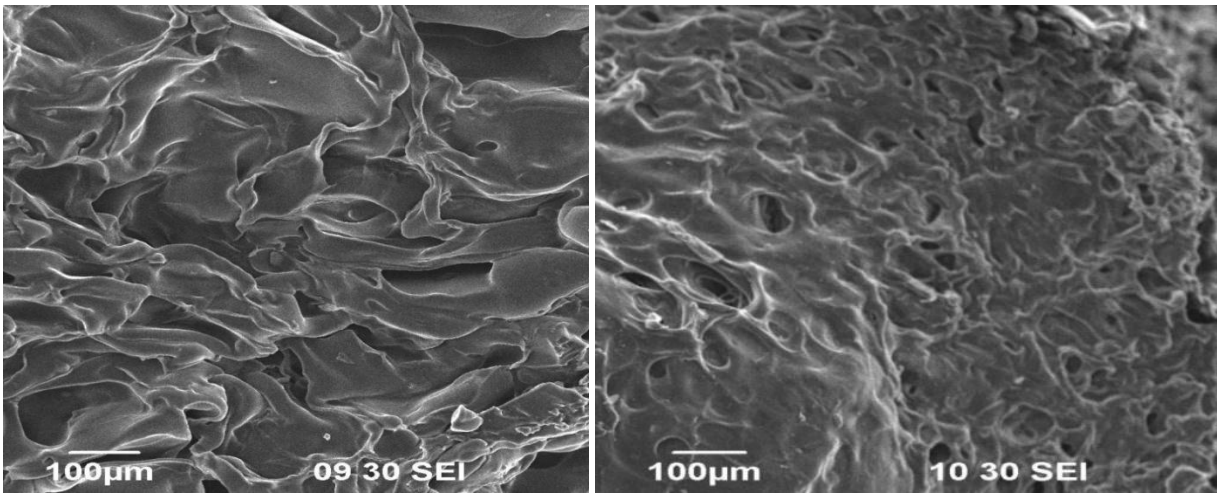
Statistical analysis

Results were expressed as mean ± S.D. Statistical analysis was performed by linear regression analysis. Co-efficient of determination (R^2) was utilized for comparison. The means and standard deviations were calculated at each time interval. The means were graphed for each release profile with the standard deviations included as error bars. Linear regression was performed on cumulative drug release as a function of time and also on fitted curves to different kinetic models.

RESULTS AND DISCUSSION

Scanning Electron Microscope

SEM micrograph of Trimetazidine dihydrochloride loaded biodegradable polymeric implant surface before and after drug release is shown in **Figure 2**.



A **B**

Figure 2: Scanning Electron Microscope of Trimetazidine dihydrochloride loaded biodegradable polymeric implant surface (100 times magnification) before drug release (A) and after drug release (B).

Figure 2 shows that SEM micrograph of Trimetazidine dihydrochloride loaded polymeric implant surface before drug release is found to be non porous and smooth while the implant surface after drug release contains large pores and roughness.

Effect of excipients on the loading efficiency of chitosan-sodium alginate polymeric implant

The loading efficiency of different excipients with 25 mg load of Trimetazidine dihydrochloride is presented in the **Table 3**.

Table 3: Effect of excipients on loading efficiency of Trimetazidine dihydrochloride Chitosan-Sodium Alginate polymeric implants.

Formulations	Loading Efficiency (%)
F2 (Drug only)	77.62
F3 (Glyceryl Monostearate)	89.68
F4 (Cetostearyl Alcohol)	86.09
F5 (Stearic acid)	80.14
F6 (Eudragit RSPO)	76.57
F7 (Cetyl Alcohol)	66.62
F8 (Methocel K 100M)	79.31

Loading efficiency was found in the range from 66.62% to 89.68% from different formulations. The highest loading efficiency was observed with Glyceryl Monostearate (89.68%) and the lowest with Cetyl Alcohol (66.62%).

The loading efficiency was found to decrease in the following sequence.

Glyceryl Monostearate > Cetostearyl Alcohol > Stearic Acid > Methocell K100M > Drug only > Eudragit RSPO > Cetyl Alcohol.

Drug release pattern of implants with different polymer ratios

A comparison of drug release of the implants with different polymer ratios was made to analyze the drug release pattern changing with the ratio of Chitosan and Sodium Alginate polymers. Comparison of drug release pattern of implants in combination of Chitosan and Sodium Alginate ratios of 60:40(F1) and 70:30(F2) is shown in **Figure 3**.

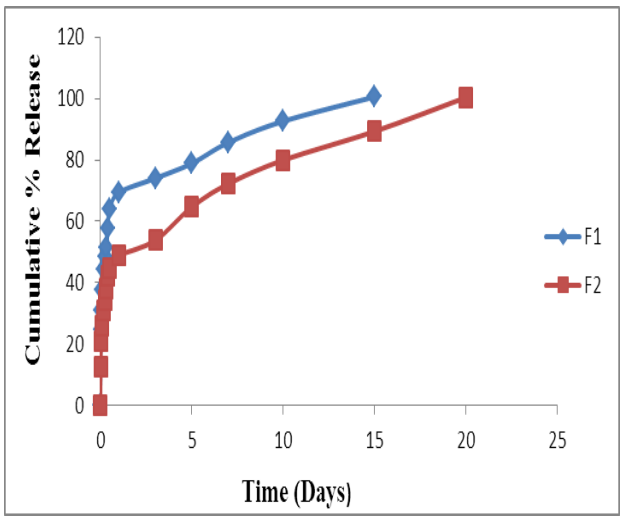


Figure 3: Comparison of drug release pattern of Trimetazidine dihydrochloride from 60:40 (F1) and 70:30 (F2) formulations.

From Figure 3, we can see that formulation 70:30 (F2) shows better sustained release action than formulation 60:40 (F1).

Drug release pattern from Chitosan-Sodium Alginate polymeric implants with different excipients

Biodegradable polymeric implants of Trimetazidine dihydrochloride containing different excipients were studied for 30 days. Comparison of drug release profile of implants containing different excipients with F2 (70:30) is graphically represented in **Figure 4 and 5**.

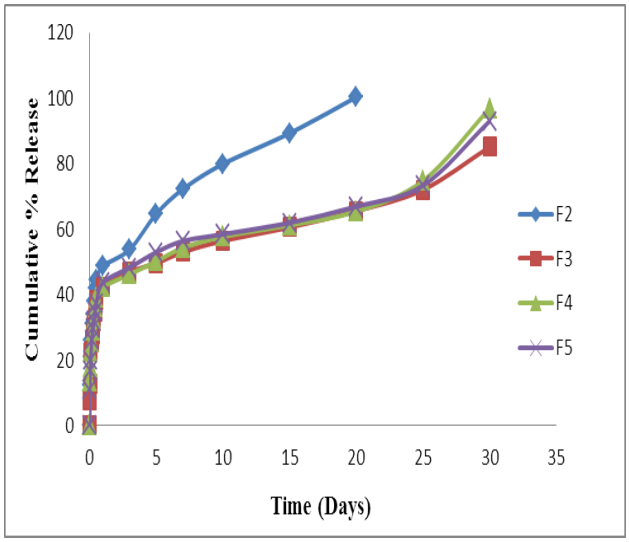


Figure 4: Comparison of Trimetazidine dihydrochloride release from F2 (Drug only), F3 (Glyceryl Monostearate), F4 (Cetostearyl Alcohol) and F5 Stearic Acid.

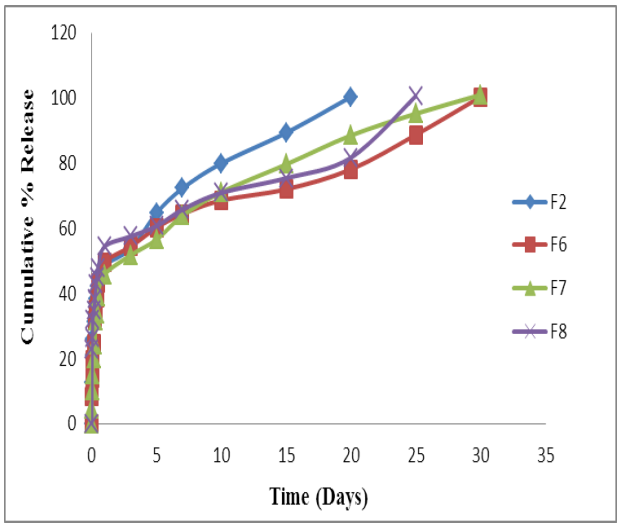


Figure 5: Comparison of Trimetazidine dihydrochloride release from F2 (Drug only), F6 (Eudragit RSPO), F7 (Cetyl Alcohol) and F8 (Methocel K 100M).

From **Figure 4 and 5**, it is observed that all formulations exhibited good sustained release action. The maximum sustained release effect was obtained with implants containing Glyceryl Monostearate (F3) and implants containing Methocel K 100M (F8) showed minimum sustained release action. Amount of drug released from different formulations (%) which were studied for 30 days is displayed in **Table 4**.

Table 4: Amount of drug released from different formulations (%) which were studied for 30 days

Formulation with Different Excipients	Amount of Drug released (%)	Time Taken for Drug Release
F2 (Drug only)	100	20
F3 (Glyceryl Monostearate)	85	30
F4 (Cetostearyl Alcohol)	97	30
F5 (Stearic acid)	93	30
F6 (Eudragit RSPO)	100	30
F7 (Cetyl Alcohol)	100	30
F8 (Methocel K 100M)	100	25

Kinetics of drug release

The qualitative and quantitative changes in a formulation may alter drug release and *in-vivo* performance. Therefore, the values that are obtained from the dissolution studies can be quantitatively analyzed by using different mathematical models that can facilitate product development by reducing the necessity of bio-studies.[18] The kinetics of Trimetazidine dihydrochloride from Chitosan-Sodium Alginate Polymeric implants containing different excipients were determined by finding the best fit of the release data to Zero order, First order, Higuchi and Korsmeyer-Peppas plots. The implants mostly followed Korsmeyer-Peppas kinetic model.

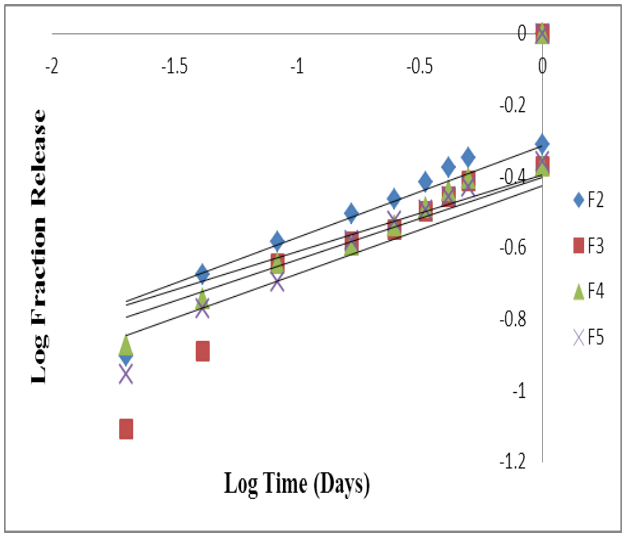


Figure 6: Korsmeyer-Peppas plots of F2, F3, F4 and F5 formulations.

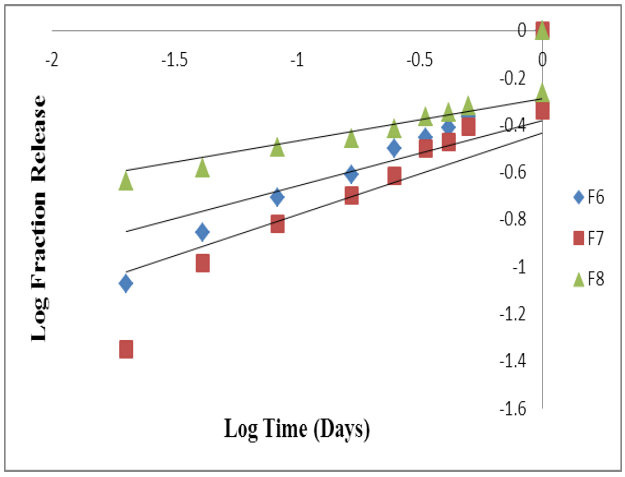


Figure 7: Korsmeyer-Peppas plots of F6, F7 and F8 formulations.

CONCLUSION

Biodegradable polymeric implants offer certain benefits that can eradicate the complications associated with oral route of administrations. The effects of different polymer ratios and excipients were studied on loading efficiency and drug release profile of Chitosan-Sodium Alginate polymeric implants of Trimetazidine dihydrochloride which is used in the prophylaxis and management of angina pectoris, ischemia and Meniere's disease. The implants produced long term drug release with all of the excipients under *in-vitro* conditions. The biodegradable polymeric implants of Trimetazidine dihydrochloride are convenient to the patients as the implants exhibit slow and uniform drug release, minimise dosing frequency, reduce side effects and eliminate the need of surgical procedures.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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