

STUDY OF METOPROLOL TARTRATE DELIVERY FROM BIODEGRADABLE POLYMERIC *IN SITU* IMPLANTS FOR PARENTERAL ADMINISTRATION

MOHAMMAD ASHIKUR RAHMAN AND SWARNALI ISLAM*

Department of Pharmacy, The University of Asia Pacific, Dhaka, Bangladesh. Email: swarnali_islam@yahoo.com

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ABSTRACT

Two step surgery processes during administration and withdrawal of conventional implants and also the initial burst effect leading to poor drug loading have been considered as major complaints associated with *in situ* drug implants. The objective of this research was to develop *in situ* forming implant with highly water soluble drug Metoprolol Tartrate and biodegradable polymer DL-PLA to minimize these problems. Formulations were attempted to be developed with the incorporation of six different hydrophobic excipients namely, Arachis oil, Glycerol monostearate, Stearic acid, Magnesium stearate, Cetostearyl alcohol and Stearyl alcohol. Effects of drug : polymer ratio and presence of hydrophobic excipients in formulations were observed on extent of drug burst, implant loading efficiency, duration of drug release and possible drug release mechanism. Loading efficiency of 5% theoretically drug loaded implant was found to be more than that with 10%. The lower drug loaded formulation more efficiently controlled the extent of drug burst while also extending the duration of drug release for a longer period of time. While addition of Arachis oil, Glycerol monostearate, Stearic acid, Magnesium stearate in 5% theoretically drug loaded formulations improved drug loading efficiency as compared to implants without excipients, Cetostearyl alcohol and Stearyl alcohol did not exert any such effects. Extent of burst was reduced as well as duration of drug release extended for Arachis oil, Glycerol monostearate and Stearic acid incorporated implants. Even though improved loading efficiency was observed with Magnesium stearate, an insignificant raise in burst and no change in duration of release were also observed. While with Cetostearyl alcohol and Stearyl alcohol the duration of release remained the same, the former increased the burst and the later reduced the same as compared to drug only implants. The release profile exhibited biphasic behavior in all the cases, an initial burst release phase followed by steady state drug release. The kinetics was evaluated for the both phases by fitting the data in four different kinetic models, namely, Zero order, First order, Higuchi and Korsmeyer-Peppas. While the burst phase fitted best with Zero order kinetics the steady-state phase complied more with Higuchi model.

Keywords: Metoprolol tartrate, *In situ* implants, Loading efficiency, Drug release mechanism, Drug/polymer ratio.

INTRODUCTION

The efficiency of any drug therapy can be described by achieving desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period. This goal can be achieved on the basis of proper design of the dosage regimen¹. Polymeric *in situ* implants have potential to deliver drug in a controlled fashion. Therefore significant research interest in the development of subcutaneously implantable polymeric devices for long term maintenance of therapeutic drug levels coincides with the increased medical and public acceptance of such systems².

The ability to inject a drug incorporated into a polymer to a localized site and have the polymer form a semi-solid drug depot has a number of advantages. Among these advantages is ease of application and localized, prolonged drug delivery. For these reasons a large number of *in situ* setting polymeric delivery systems have been developed and investigated for use in delivering a wide variety of drugs³. As time progressed, there was a need for delivery systems that could maintain a steady release of drug to the specific site of action. Therefore, drug delivery systems were developed to optimize the therapeutic properties of drug products and render them more safe, effective and reliable. Implantable drug delivery systems are an example of such systems available for therapeutic use⁴. In the past decades, implants based on biodegradable polymers have become commercially available to improve the efficacy and prolong the activity of pharmaceutical agents of a wide variety of types⁵. The application of biodegradable polymers as matrix for injectable drug delivery systems has caught more and more attention over the world. These polymers have been proven to be safe, effective and controllable and already been used in clinical practice. Over the past decades, most of commercial products were prepared with PLA and various copolymers of PLGA⁶.

In the biodegradable polymeric *in situ* implant formulation, a biodegradable and biocompatible polymer is used. Therefore, DL-PLA has been used in the present work which undergoes biodegradation resulting in production of CO₂ and H₂O or excreted by normal physiological procedure⁷. Therefore no surgery is needed

again to remove the polymer from the body after once the formulation is injected which is very common with conventional implants. However burst release is a common problem which still remains to be solved, it can be reduced by using suitable hydrophobic excipients in the formulation of high molecular weight drugs with hydrophobic polymer matrix⁸.

In this research work DL-PLA was used as biodegradable polymer and different hydrophobic excipients were used aiming to retard the drug release and also to reduce the burst release effect. Metoprolol Tartrate was chosen as the model drug due to its high water solubility and proven application in extended release matrix tablet with its use in a wide variety of indications including hypertension, angina, dysrhythmias⁹ etc. Therefore, entrapping it in sustained release *in situ* implant would certainly be a piece of work with great challenge. The prospect of *in situ* formed Metoprolol Tartrate preparation and drug release retardation for prolonged period was explored in this research work.

MATERIALS AND METHODS

Materials

The drug Metoprolol Tartrate was provided by Incepta Pharmaceuticals Ltd, Dhaka, Bangladesh. Its purity was 99.99%. Biodegradable polymer, Poly (DL-lactide) designated as DL-PLA was purchased from Boehringer Ingelheim, Ingelheim, Germany. Solvents used in the present work were Dimethyl sulfoxide (DMSO) (Gaylord Chemical Corporation, USA) and Acetonitrile (HPLC grade) (Fisher Scientific, UK). Excipients used in this study were Glycerol monostearate (GMS), Magnesium stearate, Stearic acid, Cetostearyl alcohol, Stearyl alcohol (BDH Chemicals Ltd, England) and Arachis oil (Merck, India).

Preparation of Biodegradable Polymeric *in situ* Implant

The preparation method of Metoprolol Tartrate loaded biodegradable polymeric *in situ* implants was similar to those adopted by Shah et al.¹⁰ and Shively et al.¹¹ with some modifications. The formulations are presented in Table 1.

Required amount of DMSO was accurately measured by pipette into glass vial. Weighed amount of DL-PLA (polymer/solvent ratio 1: 2) was incrementally added to DMSO and dissolved over a period of time by means of heating at 50°C with a heating magnetic stirrer. After complete dissolution of the polymer, the polymer solution was cooled under ambient condition and required amount of Metoprolol Tartrate incrementally added. The drug was thoroughly mixed with the polymer solution and final weight of the formulation taken. Formulations were taken up into a 1 ml syringe and injected into pH 7.4 phosphate buffer contained in glass vials through 21 G

hypodermic needles. When injected, the formulation came into contact with phosphate buffer and as a result the polymer precipitated and formed an implant (solidified) entrapping the drug having spherical shape (Fig.1). Formulations were prepared with respect to two different drug loadings, 5% and 10%. Excipient incorporated implants were prepared the same way with 5% drug load. The only exception was that the excipient was triturated with the drug before mixing with the polymer solution. The excipient load (5%) was the same as the drug load.

Table 1: Composition of different *in situ* implant formulations

Batch No	Drug load (%)	Excipient	Amount % w/w*		
			Drug	Polymer	Excipient
F-A	5	-	0.5	9.5	0
F-B	10	-	1	9	0
F-C	5	Arachis Oil	0.5	9	0.5
F-D	5	Glyceryl Monostearate	0.5	9	0.5
F-E	5	Stearic Acid	0.5	9	0.5
F-F	5	Mg Stearate	0.5	9	0.5
F-G	5	Cetostearyl Alcohol	0.5	9	0.5
F-H	5	Stearyl Alcohol	0.5	9	0.5

* Amount of solvent was double of the amount of polymer used in each formulation.

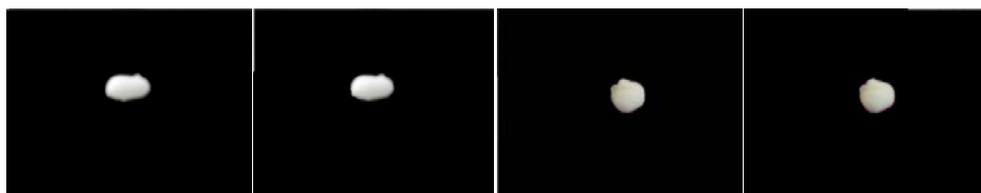


Fig. 1: Digital images of *in situ* implants

Implant Analysis

The amount of drug that was actually loaded in implants during the fabrication process was determined by spectrophotometric analysis (UV-VIS Spectrophotometer: UV-1601, Shimadzu, Japan). Implant was crushed, weighed portion taken, and dissolved in 1 ml Acetonitrile by vigorous ultrasonication. For precipitating the polymer and extracting the drug, 9 ml of phosphate buffer, pH 7.4 was added. Centrifugation at 3000 rpm for 15 minutes separated the solid material. The supernatant form the solution was collected and it was analyzed at 273.5 nm with UV spectrophotometer (UV-1601, Shimadzu Corporation) with the phosphate buffer (pH 7.4) as blank.

In vitro Drug Release Studies

After formation of implants, in vitro dissolution studies of implants were carried out in static condition at 37°C in an incubator in order to observe the drug release profile. Implants were prepared spontaneously upon injection of drug containing liquid polymeric solution inside rubber-capped glass vials containing 100 ml phosphate buffer (pH 7.4) and kept in incubator at 37°C without agitation. At predetermined time intervals, 5 ml of solutions was withdrawn using syringe after shaking the vials. The volume was replaced with fresh 5 ml of phosphate buffer (pH 7.4). The withdrawn sample was analyzed for release by UV spectrophotometer at 273.5 nm. The dissolution study was carried out till over the period of days 100% drug was released.

RESULTS

The objective of this study was to prepare biodegradable polymeric *in situ* implants that could retard drug release for an extended period of time. The implants prepared were studied for drug loading efficiency, drug release profile including any possible burst effect and drug release kinetics.

Results were expressed as mean \pm S.D. Statistical analysis was performed by linear regression analysis. Coefficients of determination (R^2) were utilized for comparison.

Loading Efficiency

In situ biodegradable polymeric implants were analyzed for actual Metoprolol Tartrate content. Based on the experimentally determined drug load, the percentage of loading efficiency (% LE) of implants was determined with the formula:

$$\% \text{ LE} = (\text{LD}/\text{AD}) \times 100$$

where LD is the amount of drug that was actually loaded in the implant and AD is the amount of drug originally added in the formulation.

Loading efficiency was found in the range between 50.73% to 90.71% from different formulations. The highest loading efficiency was found with Arachis Oil incorporated 5% drug loaded implants (F-C) and lowest with 10% drug loaded implants without any excipients (F-B). Table 2 shows the loading efficiency of different formulations of the present study. Figure 2 presents a graphical comparison of loading efficiencies of different formulations.

Table 2: Loading efficiency of *in situ* implants with different formulations

Formulation	Actual Drug Load (% w/w)	Loading Efficiency (%)
	Mean \pm SD	
F-A	6.25 \pm 1.06	79.83
F-B	7.62 \pm 0.53	50.73
F-C	6.50 \pm 0.35	90.71
F-D	6.62 \pm 0.88	87.08
F-E	6.12 \pm 0.17	87.08
F-F	5.62 \pm 0.17	83.45
F-G	5.62 \pm 0.17	79.83
F-H	6.12 \pm 0.88	79.83

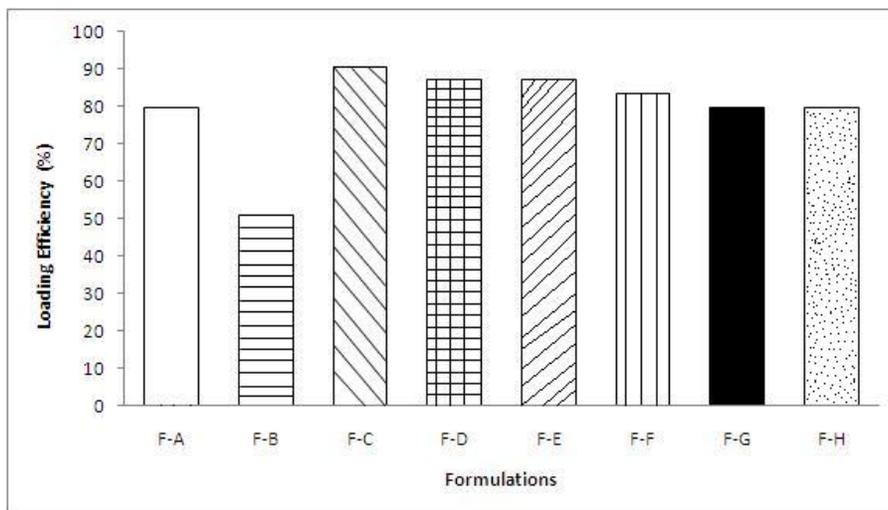


Fig. 2: Effects of variation in drug load and excipient addition on Metoprolol Tartrate loading efficiency of *in situ* implants

Drug Release Profile

Drug release profile was studied in phosphate buffer (pH 7.4) at 37°C. Implants with 5% drug load (F-A) retarded the drug release for 7 days whereas the release was extended only for 3 days for 10% drug loaded implants (F-B). Incorporation of Glyceryl Monostearate, Stearic Acid and Arachis Oil in the implant was found to retard the drug release for 4 more days than that of the drug only implant. In case of Cetostearyl Alcohol, Stearyl Alcohol and Mg Stearate

incorporated implants retardation of drug release was the same as the drug only implant.

The initial burst release extended for a period of one hour in all the cases. The data are presented in Table 3. Incorporation of Glyceryl Monostearate, Stearic Acid, Arachis Oil and Stearyl Alcohol in the formulation reduced % release of drug from the implant in the initial burst phase. Figures 3, 4 and 5 graphically show the drug release profiles from different *in situ* implants.

Table 3: Drug Release Profile from *in situ* implants of different formulations

Formulation	Burst Release (%)	Correlation equation*	Correlation Coefficient	Duration (d)
F-A	25.93	$y = 26.73x + 22.68$	0.988	7
F-B	36.09	$y = 38.64x + 33.09$	0.970	3
F-C	21.87	$y = 22.17x + 20.23$	0.950	10
F-D	18.59	$y = 27.12x + 14.89$	0.996	10
F-E	19.35	$y = 22.68x + 21.24$	0.949	10
F-F	27.41	$y = 25.14x + 25.78$	0.974	7
F-G	27.57	$y = 27.19x + 25.74$	0.980	7
F-H	24.56	$y = 26.42x + 27.41$	0.976	7

*The correlation equations are of steady state release phase using Higuchi kinetic model

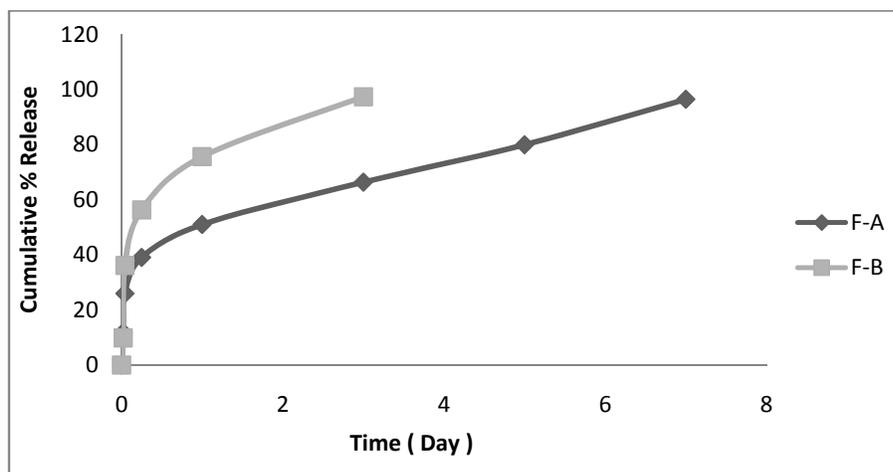


Fig. 3: Drug Release Patterns of 5% and 10% drug loaded implants (F-A and F-B)

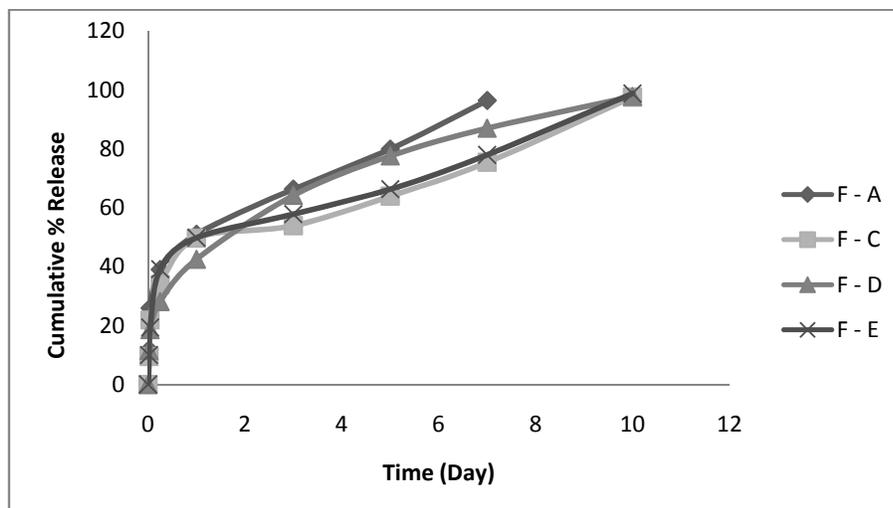


Fig. 4: Effect of Excipients on Drug Release Patterns of different implants (F-A, F-C, F-D and F-E)

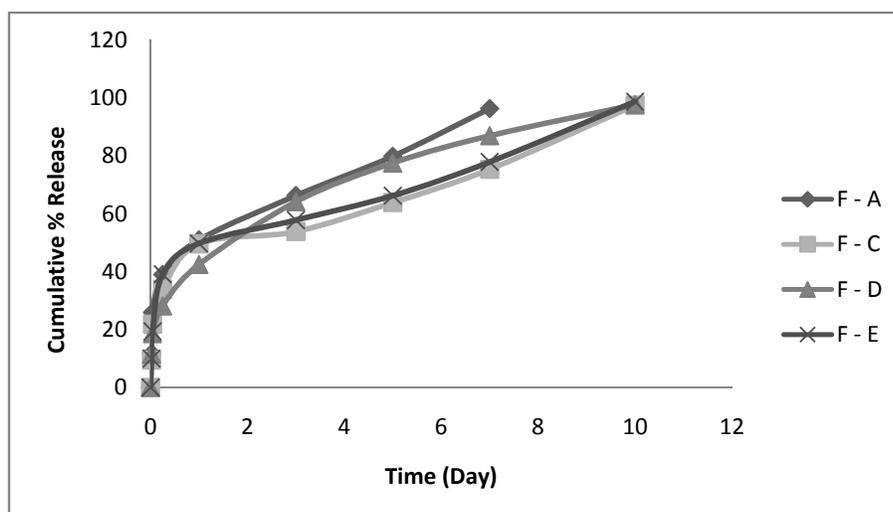


Fig. 5: Effect of Excipients on Drug Release Patterns of different implants (F-A, F-F, F-G and F-H)

Drug Release Kinetics

The release of drug from the implants showed biphasic behavior. Both the phases were fitted in different kinetic models and regression analysis was performed on the fitted curves. The burst release phase best fitted to Zero order kinetic model and regression analysis was performed on the fitted curves. The Zero order release of Metoprolol Tartrate for two drug loads in burst phase was approximately linear, $R^2 = 0.997, 0.935$ for 5% and 10% drug load respectively.

The steady state release phase best fitted to Higuchi kinetic model and regression analysis was performed on the fitted curves. The Higuchi release of Metoprolol Tartrate for two drug loads in steady state phase was approximately linear, $R^2 = 0.988, 0.970$ for 5% and 10% drug load respectively.

All excipients best fitted to Zero order kinetic model in the burst phase, except Glycerol Monostearate which best fitted the Higuchi model with R^2 value 0.991.

DISCUSSION

The polymer content has a significant influence on drug loading efficiency¹². Ideally the more polymers in the implant, the more is

entrapment of drug. As the polymer content decreased with the increased drug content, higher loading efficiency was probably observed with formulation A than B.

In case of excipient incorporated implants the highest drug loading efficiency was found with formulation C and the lowest formulations G and H. The loading efficiency was found to decrease in the following sequence:

$C > D \approx E > F > G \approx H$

Most recently Arachis Oil has been used as a part of controlled release injectables¹³. As Arachis Oil is an organic material, it is insoluble in aqueous media. Therefore it might have arrested the drug particles and helped to entrap them in the polymer resulting in decreased drug loss in aqueous buffer and increased drug loading efficiency. As this excipient is oily in nature it probably resulted in rapid phase separation. Any condition leading to rapid phase separation is likely to increase drug loading by decreasing drug loss in non solvent¹⁴.

Glycerol Monostearate has a HLB value 3.8¹⁵, which indicate its hydrophobic nature.¹⁶ It is also practically insoluble in water¹⁵. Therefore, it probably decreased the dispersibility of the drug.

Stearic Acid has a lower acid value: 200-212¹⁵, indicating its hydrophobic nature¹⁷. Stearic Acid and Mg Stearate are practically insoluble in water¹⁵ for which they may dissolve in DMSO and decrease the passage for hydrophilic drug which may result in increased drug loading efficiency.

Different research articles been published in which Cetostearyl Alcohol has been used to slow the dissolution of water soluble drugs^{18,19,20,21} and Stearyl Alcohol has been used in controlled release tablets^{22,23} for their hydrophobic property. Therefore loading efficiency is found higher with these excipients.

In case of drug release profile observation excipient incorporated implants retarded the release of drug for 7 to 10 days as well as reduced the burst release immediately after injection to buffer media. These may be due their strong hydrophobic behavior as mentioned above.

The release profile exhibited biphasic behavior; therefore the kinetics was evaluated for the both phases, the initial burst release phase and the steady state release phase. In order to determine the possible drug release mechanism the release data were fitted in four different kinetic models, namely, Zero order, First order, Higuchi and Korsmeyer-Peppas model.

CONCLUSION

The DL-PLA *in situ* implant of Metoprolol Tartrate delayed the drug release up to a period of 3 to 10 days though it is a highly water soluble drug. Moreover decreasing drug content and increasing polymer content in the implant exhibited increasing loading efficiency as well as decreasing drug release in many cases. Inclusion of suitable excipient also increased loading efficiency with retarding the drug release more than that of the drug only implant. As no surgery is needed for this type of drug delivery system, *in situ* implants with Metoprolol Tartrate may be a very attractive candidate for further future development.

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