OBSERVATION OF METOPROLOL TARTARATE RELEASE FROM BIODEGRADABLE POLYMERIC IMPLANTS

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ABSTRACT

Objective: Implantable drug delivery systems (IDDS) are developed to optimize the therapeutic properties of the drug and to transmit the drug and fluid into the bloodstream without the repeated insertion of needles. Due to the fat rich area, with poor haemoperfusion and nerve area of areolar connective tissue, subcutaneous implantation became an ideal route of drug delivery. In this investigation, Metoprolol Tartarate, a cardioselective $beta_1$ adrenoceptor blocking agent, widely used to treat hypertension, angina pectoris and myocardial infarction, has been chosen to develop a gelatin-sodium alginate biodegradable implant. Methods: Implants were prepared by heating and congealing methods in different ratios of gelatin-sodium alginate (70:30, 80:20 and 90:10), hardened for cross linking with formaldehyde for 3 hrs, 6 hrs, 12 hrs and 24 hrs. Glycerin was used as a plasticizer and water as vehicle. At ambient temperature, the prepared Metoprolol Tartarate implants were evaluated for weight variation, thickness and *in-vitro* drug release. The drug release kinetics of the implants was obtained and fitted to different kinetics models. To ensure absence of formaldehyde, free formaldehyde test was carried out. Results: Implants containing 70:30 % w/w Gelatin-Sodium Alginate and hardened with formaldehyde for 24 hrs were found to produce most satisfactory drug release over a period of 6 days (144 hours). The release pattern mostly followed the Higuchi kinetic model. Good correlations were also found with Korsmeyer-Peppas suggesting drug release from the biodegradable implants by diffusion.

Keywords: Biodegradable Implant, Gelatin, Sodium Alginate, Metoprolol Tartarate.

INTRODUCTION

Hypertension (HT), heart diseases like angina pectoris, myocardial infarction etc represents significant and growing global health issues. Carotid body hyperactivity increases central sympathetic drive and thus contributes to hypertension through direct increases in renal neurogenic sodium avidity and increases in renal secretion of renin, as well as neurogenically mediated increases in vascular resistance [1], [2], [3]. Angina pectoris (also referred to as angina) is a chest pain or pressure that occurs when the blood and oxygen supply to the heart muscle cannot keep up with the needs of the muscle. When coronary arteries are narrowed by more than 50 to 70 percent, the arteries may not be able to increase the supply of blood to the heart muscle during exercise or other periods of high demand for oxygen. An insufficient supply of oxygen to the heart muscle causes angina [4], [5], [6]. Myocardial infarction is the technical name for a heart attack. A heart attack occurs when an artery leading to the heart becomes completely blocked and the heart does not get enough blood or oxygen, causing cells in that area of the heart to die called an infarct [7], [8]. The treatment of these diseases needs long term medication, so the sustained therapeutic effects of Metoprolol Tartarate subcutaneous implantable system can be the best choice of treatment. Metoprolol Tartarate is a $beta_1$ adrenoceptor blocking agent and has a preferential effect on beta adrenoceptors chiefly located in the cardiac muscle. Metoprolol Tartarate implant can be a choice of drug delivery system, where drug is delivered from the implant and absorbed into the blood circulation. This system reduces the dosing frequency of drugs, increases patient compliance with minimum risk factors. The aim of this investigation was to introduce Metoprolol Tartarate subcutaneous implants and to assess the *in vitro* release of Metoprolol Tartarate from the implant, and its sustainability. Gelatin and sodium alginate were used to prepare the implant. The implants are believed to reduce the frequency of taking medicines by mouth, thus reducing dosing frequency and increasing patient compliance, while producing its therapeutic effect. Thus, fabricating a biodegradable implant with a combination of Gelatin and Sodium Alginate to sustain drug release, and loading the implant with a drug which has found its applications in treating many chronic conditions makes it a potential candidate for research.

MATERIALS AND METHODS

Materials

The active ingredient Metoprolol Tartarate was obtained as a gift sample from Incepta Pharmaceuticals Limited, Dhaka, Bangladesh. Sodium Alginate was purchased from Loba Chemie Pvt. Ltd, Mumbai, India and Purified Gelatin was purchased from Merck Specialties Pvt. Ltd, Mumbai, India. Other chemicals used were of analytical grade.

Preparation of Implant

Metoprolol Tartarate implants were prepared by using gelatin and sodium alginate, which are the biodegradable polymers, in three different ratios 70:30, 80:20 and 90:10 respectively. Heating and congealing methods were used to prepare the implants with 10% drug load for each formulation. In this preparation water was used as vehicle and glycerin as plasticizer. The method employed to prepare the Gelatin-Sodium Alginate implants loaded with Metoprolol Tartarate was similar to those adopted by Islam et al [9], Purushotham et al. [10] and Gupta et al. [11], [12] with some modifications. Formulations varied with respect to Gelatin-Sodium Alginate polymer ratios.

Hardening of Implants

The method employed to harden the prepared implants under formaldehyde vapor was similar to those adopted by Islam et al [9], Purushotham et al. [10] and Gupta et al. [11], [12] with little modifications.

Physical Characterization of Implants

Digital Photographic Imaging

Digital photograph of the finally prepared square-shaped implants was taken with the help of digital camera (SONY CYBER-SHOT, DSC-WX7, 16.2 MEGA PIXELS). Figure 1 shows some randomly selected digital images of the implants.

Measurements of Implant Thickness

All the implants of three different ratios were measured with the help of slide calipers for determination of thickness [9], [13].

Measurement of weight variation

Weight variation of implants was checked by weighing a minimum of three implants of a particular formulation and exposure time individually [9,14].

Test for Free Formaldehyde

To ascertain the absence of free formaldehyde, the implants were subjected to pharmacopoeial test for free formaldehyde. During the test the color of 1 ml of 1 in dilution of implant preparation was compared with the color of 1 ml of standard formaldehyde solution [9], [15].

Procedure

After preparing the standard and sample solutions individually according to pharmacopoeial test, they were taken in two different volumetric flasks and treated with hot water in a water bath at 40ºC for 40 minutes. Any visible color changes in them were observed [9], [16].

In-Vitro Drug Release Studies

For *in- vitro* drug release studies, a minimum of three samples of implants containing Metoprolol Tartarate were taken from each formulation (70:30, 80:20 and 90:10) and exposure time (3hrs, 6hrs, 12 hrs and 24 hrs). Rubber capped glass vessels containing 100 ml of phosphate buffer (pH 7.4) were used to transfer the implants. With the help of 5 ml conventional disposable syringe, 5 ml of sample is withdrawn from the glass vessels containing the dissolution medium at predetermined time intervals. To replace the withdrawn sample to maintain the sink condition, 5 ml of fresh medium of phosphate buffer (pH 7.4) was added to the vessels [9]. The drug concentration was analyzed spectrophotometrically at 280 nm (λ_{max} of Metoprolol Tartarate in phosphate buffer, pH 7.4). The withdrawn samples were then analyzed for determining the percentage of release of drugs by UV spectrophotometer at 280 nm (λ_{max} of Metoprolol Tartarate in Phosphate Buffer, pH 7.4), after subsequent dilution of the samples. All data were used in statistical analysis for the determination of mean, standard deviation and release kinetics [9], [16], [17], [18]

Statistical Analysis

Results were expressed as mean + S.D. Statistical analysis was performed by linear regression analysis. Coefficients of determination (R^2) were utilized for comparison [19].

RESULTS

Metoprolol Tartarate biodegradable implants were prepared with the biodegradable polymers such as gelatin and sodium alginate. Implants were hardened by exposing them to formaldehyde for different time intervals (3hrs, 6hrs, 12hrs and 24 hrs). Different physico-chemical tests such as thickness, weight variation; drug content uniformity and *in-vitro* drug release were carried out. The *in-vitro* release patterns of the formulations were pleasantly controlled in behavior. The release pattern mostly followed the Higuchi model.

Fig. 1: It Shows the Photographic Image of Metoprolol Tartarate Implants

Digital Photographic Imaging

The drug release kinetics is strongly related with morphological characters of implants [20]. Therefore, implant shapes were investigated for thorough characterization. Figure 1 shows the digital photographic images of Metoprolol Tartarate implants.

Measurements of Implant Thickness

All the implants were measured with the help of slide calipers for determining the thickness [9], [13]. Table 1 shows the variations in thickness of 70:30% Gelatin-Sodium Alginate implants at different formaldehyde exposures (3 hrs, 6 hrs, 12 hrs and 24 hrs).

Measurement of weight variation

Weight variation of implants was checked by weighing a minimum of three implants of a particular formulation and exposure time individually [9], [14]. Table 1 shows the variations in weight of 70:30% Gelatin-Sodium Alginate implants at different formaldehyde exposure times.

Table 1: It Shows Various Experimental Parameters of Gelatin-Sodium Alginate Implants (70:30) At Different Formaldehyde Exposures.

S. No.	Hardening time (hrs)	Thickness of Implants (mm) ± S. D.	Weight of Implants (mg) ± S. D.
1	3hrs	1.02 ± 0.01	0.255 ± 0.0015
2	6 hrs	1.03 ± 0.00	0.288 ± 0.0006
3	12hrs	1.00 ± 0.01	0.305 ± 0.0047
4	24hrs	1.02 ± 0.01	0.296 ± 0.001

Test for Free Formaldehyde

The Metoprolol Tartarate implants were hardened by exposing them to formaldehyde. Therefore, tests for free formaldehyde are necessary to ensure that the final sample of the formulations were free from any residual formaldehyde. To ascertain the absence of free formaldehyde, the implants were subjected to pharmacopoeial test for free formaldehyde. Any color change was observed. Figure 2 shows the result for free formaldehyde with 70:30 polymer ratio. The comparison shows the standard solution with an intense yellow color, when treated with the reagent, indicating the presence of formaldehyde. On the other hand, the sample solution shows a faint yellow color with the reagent, which is indicative of having a very little or no formaldehyde residue.

Fig. 2: It Shows the Test for Free Formaldehyde of Prepared Implants (70:30)

In Vitro Drug Release Studies

The drug release mechanism from the matrix is a consequence of concomitant process such as diffusion of the active ingredient

through the polymer matrix along a concentration gradient, erosion of biodegradable polymers by hydrolysis or combination of drug diffusion and polymer degradation [20] .The drug release rate from a polymeric matrix is also dependent on interactions between the active ingredients and polymer. Figure 3 shows the drug release profile of 70:30 Gelatin-Sodium Alginate implants, and implants hardened for 24 hours indicated almost 100% release at 144 hrs.
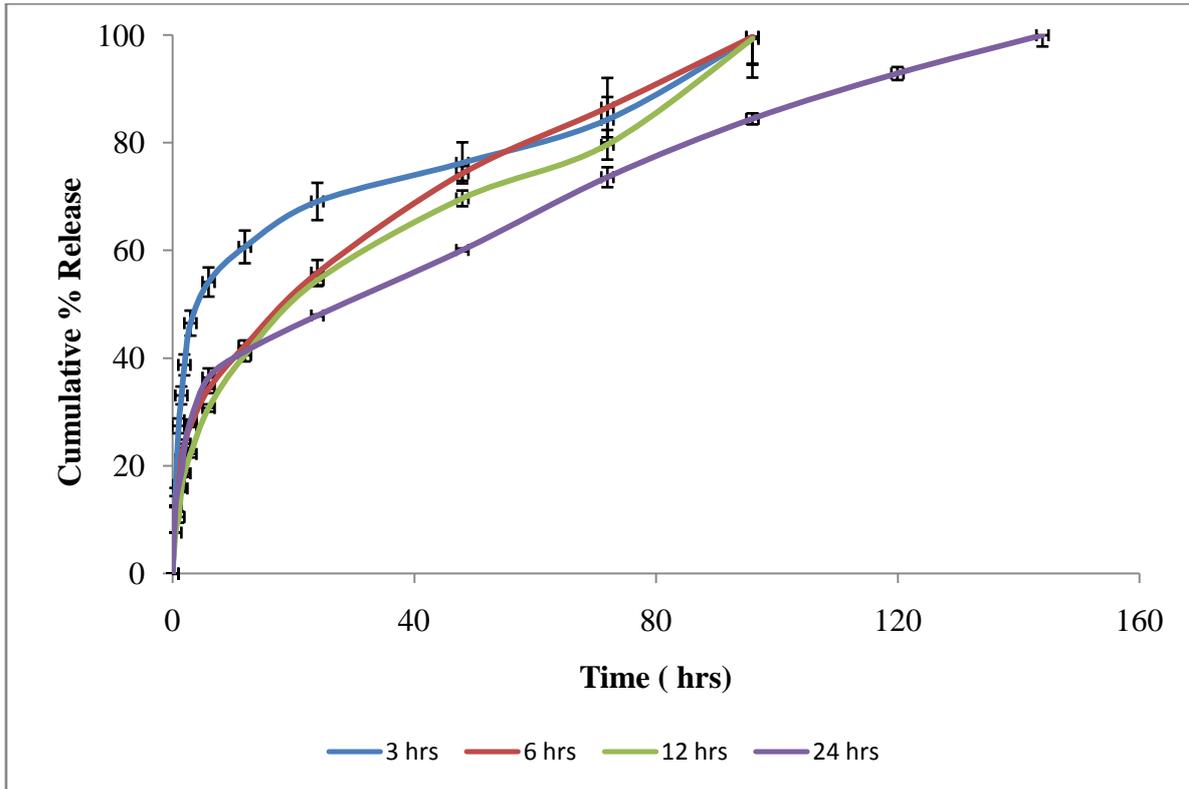

Fig. 3: It Shows the Drug Release Profile of 70:30 (Gelatin: Sodium Alginate) Implants At Different Hardening Times in pH 7.4 Phosphate Buffer at 37ºC.

The release kinetics of Metoprolol Tartarate from Gelatin-Sodium Alginate implants with different polymer ratio were determined by finding the best fit of the linear portion of release data to Higuchi, Korsmeyer-Peppas, Zero order and Firsts order plots [21], [22], [23]. The graphical representation reveals that the Higuchi fits for 70:30% Gelatin-Sodium Alginate implants showed the highest R^2 value (0.999) among all models (R^2 values in Table-2). In the present study, almost as good correlations were also obtained with Korsmeyer-Peppas model where the highest value of R^2 is 0.996 (Table-2). Figures 4, 5, 6 and 7 show the Higuchi, Korsmeyer-Peppas, Zero order and Firsts order plots for 70:30 Gelatin-Sodium Alginate implants respectively.
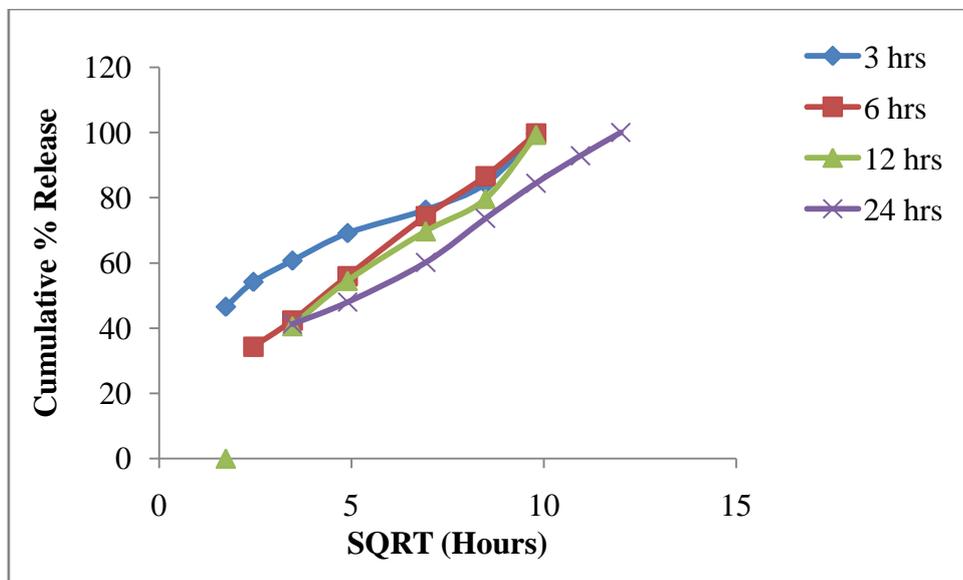

Fig. 4: It Shows Higuchi plots of Metoprolol Tartarate Steady State Release Profiles from 70:30 (Gelatin-Sodium Alginate) Implants with Different Exposure Times.
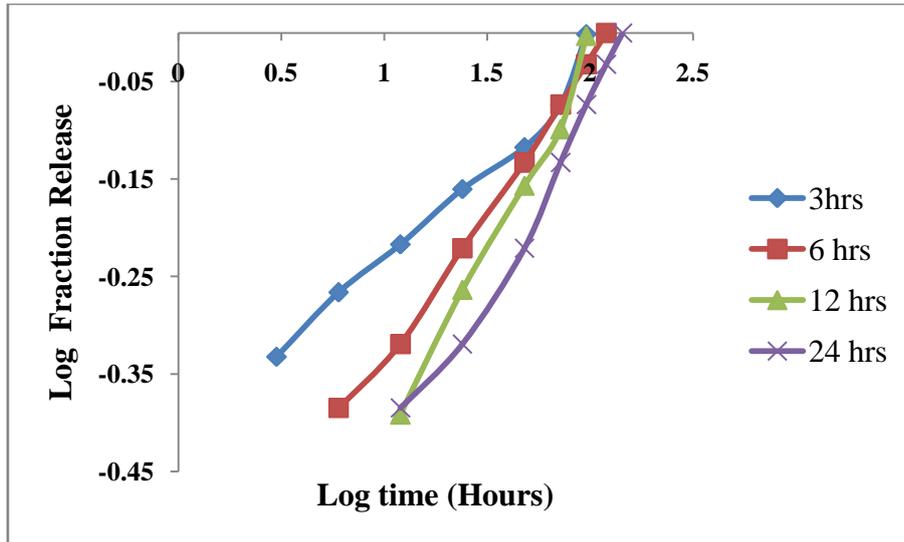
Fig. 5: It Shows Korsmeyer-Peppas Plots of Metoprolol Tartarate Steady State Release Profiles from 70:30 (Gelatin-Sodium Alginate) Implants with Different Exposure Times.
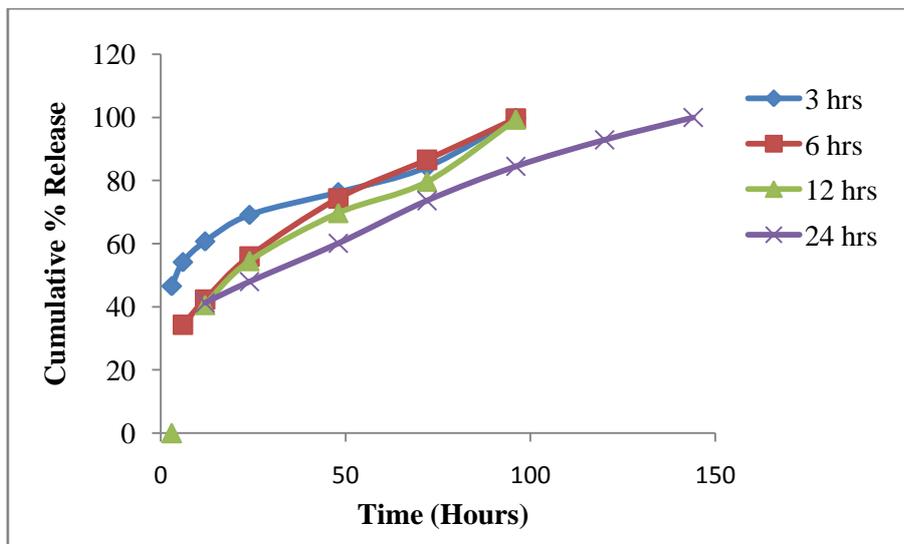

Fig. 6: It Shows Zero Order Plots of Metoprolol Tartarate Steady State Release Profiles from 70:30 (Gelatin-Sodium Alginate) Implants with Different Exposure Times.
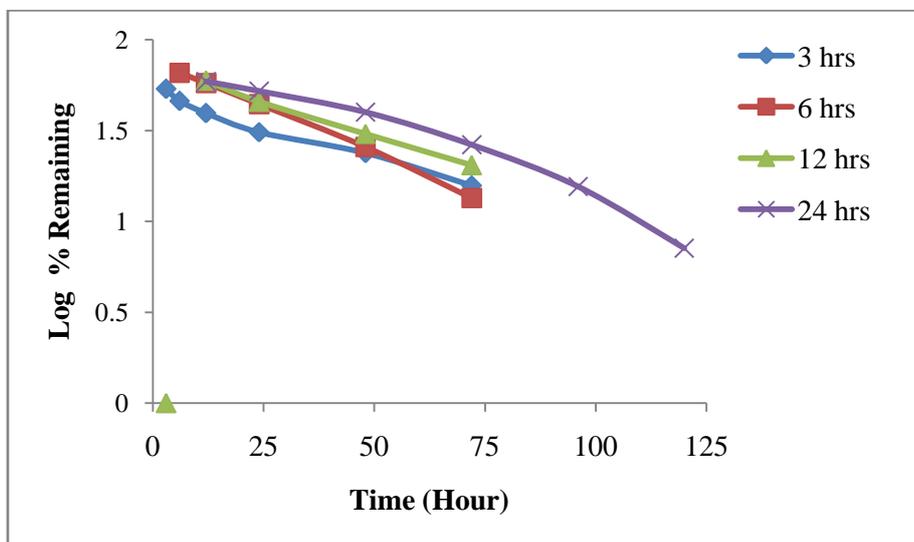

Fig. 7: It Shows First Order Plots for Metoprolol Tartarate Steady State Release Profiles from 70:30 (Gelatin-Sodium Alginate) Implants with Different Exposure Times.

Table 2: It shows the Fitting Comparison of Equations of Higuchi, Korsmeyer-Peppas, Zero Order and First Order for Describing Release Profiles of Metoprolol Tartarate from 70:30 Gelatin-Sodium Alginate Implant.

Kinetic Model		Hardening Time (Hrs)			
		3	6	12	24
Higuchi	Rate constant (% release /$\sqrt{hr}$)	5.851	8.877	8.703	6.958
	R^2	0.9974	0.999	0.981	0.9998
Korsmeyer	Rate constant (log fraction release/ log hr)	0.199	0.300	0.400	0.369
	R^2	0.974	0.996	0.987	0.981
First Order	Rate constant (log % remaining/ hr)	-0.018	-0.021	-0.007	-0.002
	R^2	0.737	0.805	0.888	0.620
Zero Order	Rate Constant (% Release/hr)	0.369	0.611	0.652	0.455
	R^2	0.983	0.996	0.982	0.988

DISCUSSION

The implants were evaluated for thickness, weight variation, presence of free formaldehyde and *in-vitro* release studies over a period of 144 hours (6 days). It was observed that drug release from the implants Gelatin-Sodium Alginate in the ratio 70:30 showed optimum sustained effect. Also, hardening the implants with formaldehyde sustained drug release, with the optimum hardening time being 24 hours. The implants formulated with 70:30 Gelatin-Sodium Alginate ratio and hardened for 24 hours with formaldehyde were found to produce the maximum sustained action for 144 hours (6 days).

It was found that Gelatin-Sodium Alginate implants can be prepared with minimum batch to batch variation. Since formaldehyde is toxic in nature, it was important to ensure that the implants did not retain any residual formaldehyde. For this reason, the implants were subjected to pharmacopoeial test for free formaldehyde. Tests for the presence of free formaldehyde revealed that none of the implants contained free formaldehyde.

The results of the *in-vitro* dissolution study were fitted to Higuchi, Korsmeyer-Peppas, First Order and Zero Order kinetics to evaluate the kinetic data. The kinetic data was determined by finding the best fit of the release data to these models. The release rate constants (calculated from the slopes of the best-fit lines) and the coefficients of determination, R^2 values, were also used to calculate the accuracy of the fit. Implants were found to follow the Higuchi model of kinetics the best. Also good correlations were obtained with Korsmeyer-Peppas model. According to these models, the drug release from the implants was diffusion-controlled, where the drug was found to leave the matrix through pores and channels formed by the entry of dissolution medium [20].

CONCLUSION

Implantable drug delivery system (IDDS) has created a new era in the field of modern drug delivery system. The development of the IDDS has received extensive attention over the past few decades. This interest has been fostered by the potential advantages these technology may provide including decrease of overall drug dose, associated with possible reduction or local or systemic side effects, as well as prolonged delivery period at desired releasing rate. The minimization of dosing frequency enhances patient compliance and comfort. IDDS capable of releasing an active ingredient in a controlled manner for a designed period are therefore a high priority. These formulations give sustained therapeutic effects over a long period of time for about 6 days through continuous dissolution in phosphate buffer pH 7.4. Besides these, this technology has several other attractive features such as simplicity of concept, ease of manufacturing, less chances of side effects, better compatibility as well as using of FDA approved polymers. Since it is convenient to the patient with minimum risk factor (except the burst release in some cases) and removal of the implant with surgery can be avoided, this can be an attractive candidate for further future development.

ACKNOWLEDGEMENT

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