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Research Article

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Observation of the release of aspirin from gelatin-sodium alginate polymeric implant

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ABSTRACT

Implantation technology is currently the most utilized route for studying sustained drug release potential. Present investigation explores the scope of sustaining the release of drug by using Gelatin-Sodium Alginate combination biodegradable implants. Implants were formulated in varied ratios of Gelatin and Sodium alginate, i.e. 70:30, 80:20 and 90:10 % w/w by heating and congealing method. They were then exposed to formaldehyde for different time periods, (3 Hrs, 6 Hrs, 12 Hrs and 24 Hrs) for hardening. Aspirin was chosen as the model drug because it plays an important role in treating many long term conditions like rheumatoid arthritis, myocardial infarction, stroke and cancer. The implants were evaluated for thickness, weight variation, presence of free formaldehyde and in-vitro release studies over a period of 96 hours (4 days). The implant formulated with 80:20 Gelatin-Sodium Alginate ratio and hardened for 12 hours with formaldehyde were found to produce the maximum sustained action for 96 hours (4 days). Tests for free formaldehyde revealed that none of the implants contained free formaldehyde. The results of in-vitro dissolution study were fitted to different kinetic models to evaluate the kinetic data. The kinetic data was determined by finding the best fit of the release data to these models. Implants were found to follow the Higuchi model of kinetics the best. Also good correlations were obtained with Korsmeyer-Peppas model. Therefore, 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.

Keywords: Biodegradable Implant, Gelatin, Sodium Alginate, Aspirin

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INTRODUCTION

Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. In the recent years, focus on the development of controlled release drug delivery systems has increased. The basic rationale of controlled release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of the drug in such a way that its utility is maximized, side effects are reduced and cure or control of the condition is achieved. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance, due to less frequent drug administration, reduction of fluctuations in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug and reduction of healthcare costs through improved therapy [1]. The purpose of the research was to fabricate Gelatin-Sodium Alginate combination biodegradable implants for sustained release. The active ingredient chosen was Aspirin, an NSAID. The main challenge of the work was to sustain the release of the drug from the implants since the polymers used (Gelatin and Sodium

Alginate) dissolves rather rapidly in aqueous environment, thus limiting its use in the production of long term drug delivery system. This adverse aspect required the use of crosslinking procedures by formaldehyde, reducing gelatin dissolution and drug release at body temperature by the formation of non-soluble networks [2]. Although a few studies on novel delivery system of Aspirin have been carried out, no studies have been reported so far on biodegradable implants. The research is aimed towards patients, who require taking Aspirin orally for prolonged periods of time for treating chronic conditions like rheumatoid arthritis[3], [4], [5], myocardial infarction[6], stroke [6] and cancer[7], [8]. 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.

EXPERIMENTAL SECTION

Materials:
Aspirin was obtained as a gift sample from Incepta Pharmaceuticals Limited, Bangladesh. Purified Gelatin was purchased from Merck Specialties Pvt. Ltd, Mumbai. Sodium Alginate was purchased from Loba Chemie Pvt. Ltd, Mumbai. Other chemicals used were of analytical grade.

Preparation of Implants:
Biodegradable implants of the drug Aspirin were prepared by the use of two biodegradable polymers Gelatin and Sodium Alginate by heating and congealing method. The implants were prepared using 10% Drug Load and at 3 different polymer ratios (70:30, 80:20, 90:10).

Weighed quantity of Gelatin was sprinkled on surface of water and kept aside for 30 minutes to hydrate. Sodium alginate was added in hydrated gelatin. Glycerin was added as a plasticizing agent with continuous stirring and the solution was heated in a water bath at 60°C until gelatin was dissolved. Aspirin was dissolved separately in a small quantity of acetone and added to the Gelatin and Sodium Alginate solution. The solution was poured in a glass petridish upto 1mm height and allowed to gel by placing the petridish on ice for 30 minutes. Then they were allowed to set by placing in a refirigerator for 3 days. After 3 days, the implants were placed in formaldehyde for hardening [9], [10], [11].

Hardening of Implants:
A petri-dish containing Formaldehyde solution (37% v/v) was placed in an empty glass dessicator. Four petri-dishes containing the implants were kept on top of a perforated plate above the petridish containing the formaldehyde solution, and the dessicator was closed immediately. The implants were made to react with formaldehyde vapors for different time intervals such as 3, 6, 12 and 24 hours. Then they were removed from the dessicator and air dried for 72 hours, so that the reaction between formaldehyde and gelatin was complete. Afterwards the implants were kept in an open atmosphere in aseptic conditions for a week to make sure that the residual formaldehyde gets evaporated. The same procedure was employed for the implants containing 70:30%, 80:20%, 90:10% w/w gelatin and sodium alginate. The implants were then cut into square shapes of 1cm length and 1 cm width with a specially designed stainless steel cutter [9], [10], [11].

Characterization of Implants:
Photographic Imaging
Photographs of drug loaded implants were taken using digital camera (SONY CYBERSHOT, DSC –S650, 7.2 Mega Pixels). Surface morphology greatly influences the release kinetics of implants [12]. The kinetics of drug release is greatly dependent on the morphological characters of implants. Figure 1 displays randomly selected digital images of Gelatin-Sodium Alginate polymeric implants.

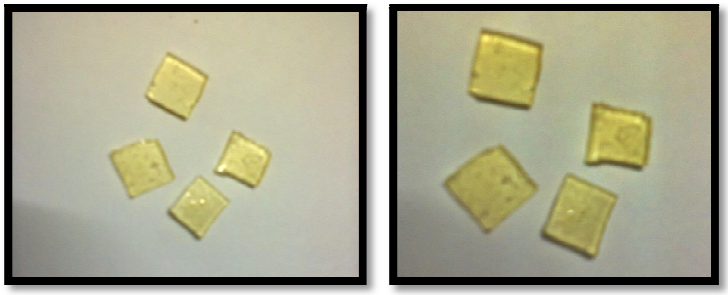

Figure 1: Digital Images of Gelatin-Sodium Alginate Combination Implants

Measurement of Implant Thickness

The thickness of the implants was measured by picking three samples of implants for a particular formulation and exposure time, and measuring their thickness with slide calipers [13]. Table 1 shows the average thickness of implants (80:20) hardened with formaldehyde.

Weight Variation of Implants

Weight variation of implants was checked by weighing a minimum of three implants of a particular formulation and exposure time individually [14]. Table 1 shows the average weight of the prepared implants (80:20) hardened with formaldehyde.

Table 1: Various Experimental Parameters of Prepared Implants (80:20) Hardened with Formaldehyde

Sl. No.	Hardening Time (Hrs)	Thickness of Implants (mm) ± S.D.	Weight of Implants (mg) ± S.D.
1	3	1.00 ± 0.01	105.3 ± 0.52
2	6	1.01 ±0.01	105.13 ± 0.23
3	12	1.01 ± 0.01	105.07 ± 0.12
4	24	1.01 ± 0.01	105.23 ± 0.25

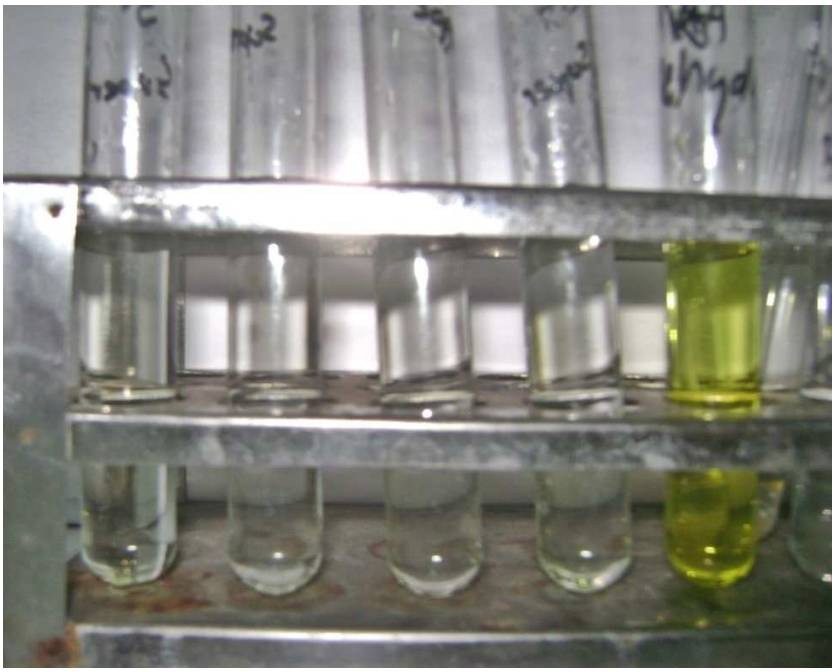

Figure 2: Test for Free Formaldehyde at Different Hardening Times of Prepared Implants (80:20)

Test for Free Formaldehyde
Formaldehyde was used to harden the implants. Since formaldehyde is toxic in nature, it was important to ensure that the implants did not contain any residual formaldehyde. To ascertain the absence of free formaldehyde, the implants were subjected to pharmacopoeial test for free formaldehyde [15]. Any color change was observed. Figure 2 shows the result for free formaldehyde with polymer ratio 80:20.

In Figure 2, the bright yellow colored solution is the Standard Formaldehyde solution. The implants, after being subjected to the pharmacopoeial test for free formaldehyde, were observed for color changes against the standard solution. The intense the yellow color of the solution of the samples, the greater the amount of free formaldehyde. The figure reflects that the color of the sample solutions were colorless. This indicates that these implants did not retain any free formaldehyde.

In-vitro Dissolution Studies
After formulation of implants, *in-vitro* dissolution studies of the implants were carried out in static conditions in order to observe the drug release profile for Aspirin implants. A minimum of 3 implants from each formulation and exposure time were taken, and their weight recorded. They were then transferred to rubber capped glass vessels containing 100 ml of Phosphate Buffer, pH 7.4. At predetermined time intervals, 10 ml of sample is withdrawn from the dissolution vessels using 10 ml conventional disposable syringe, after mild stirring of the dissolution vessel for a few seconds to ensure uniform distribution of drug throughout the dissolution medium. 10 ml of fresh medium (phosphate buffer, pH 7.4) 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 drugs by UV spectrophotometer at 237 nm (λ_{max} of Aspirin 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 [16], [17].

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. *In-vitro* release studies were performed under the same conditions for each implant system. 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

In-vitro Drug Release Studies
Sustained release of drugs from biodegradable matrices is accepted to occur by three mechanisms: diffusion through the polymer continuum, liberation from the matrix via polymer degradation, or a combination of drug diffusion and polymer degradation [18]. The drug release studies of Aspirin in phosphate buffer pH 7.4 indicated 100% of drug release in 96 hours (Figure 3).

To analyze the *in-vitro* release data, various kinetic models were used to describe the release kinetics [19], [20], [21], [22]. The kinetics of Aspirin from 80:20 Gelatin-Sodium Alginate polymer ratio with different hardening times were fitted to Higuchi, Korsmeyer-Peppas, Zero Order and First Order plots. The zero order rate equation describes the systems where the drug release rate is independent of its concentration. The first order rate equation describes the release from the system where release rate is concentration dependent. Higuchi describes the release of drugs from insoluble matrix as a square root of time dependent process based on the Fickian diffusion. The Kormeyer-Peppas equation describes the mode of release of drugs from swellable matrices [23]. As observed, the Higuchi fits for 80:20 Gelatin-Sodium Alginate implants showed the highest R^2 values among all models (R^2 values in Table 2). Good correlations were also obtained with Kormeyer-Peppas model. According to these models, Aspirin release from the 80:20 Gelatin-Sodium Alginate Implants is diffusion controlled where the drug leaving the matrix through pores and channels formed by the entry of dissolution medium.

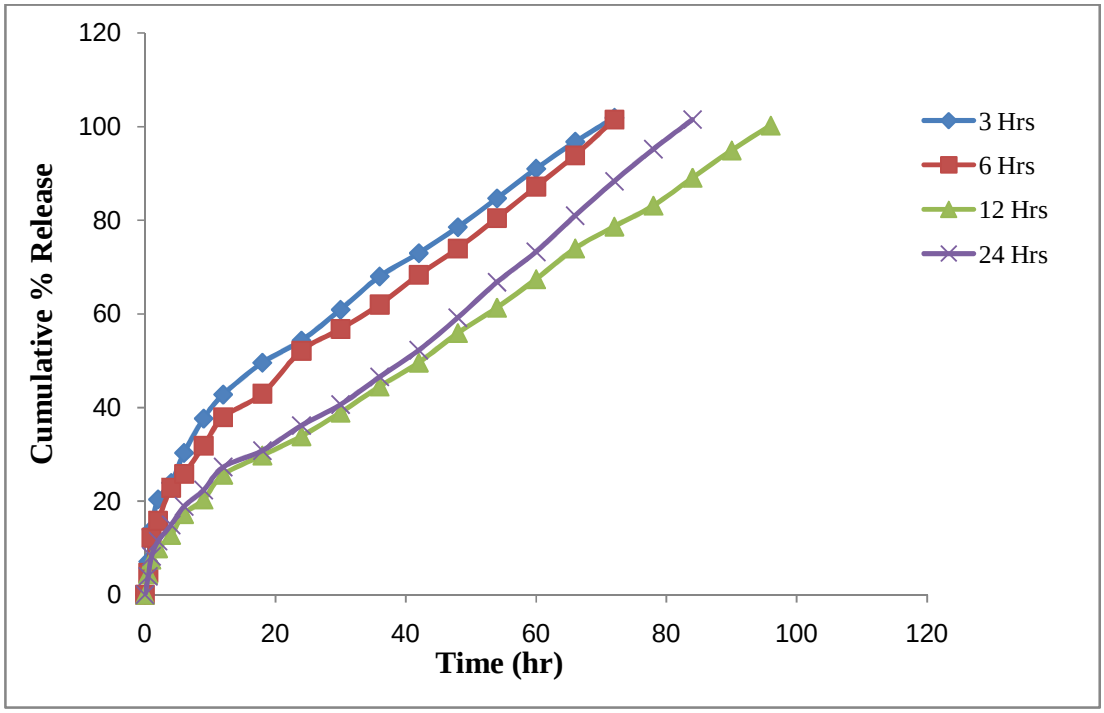

Figure 3: Drug Release Profile of Implants Formulated with 80:20 Gelatin-Sodium Alginate Polymer At Different Hardening Times.

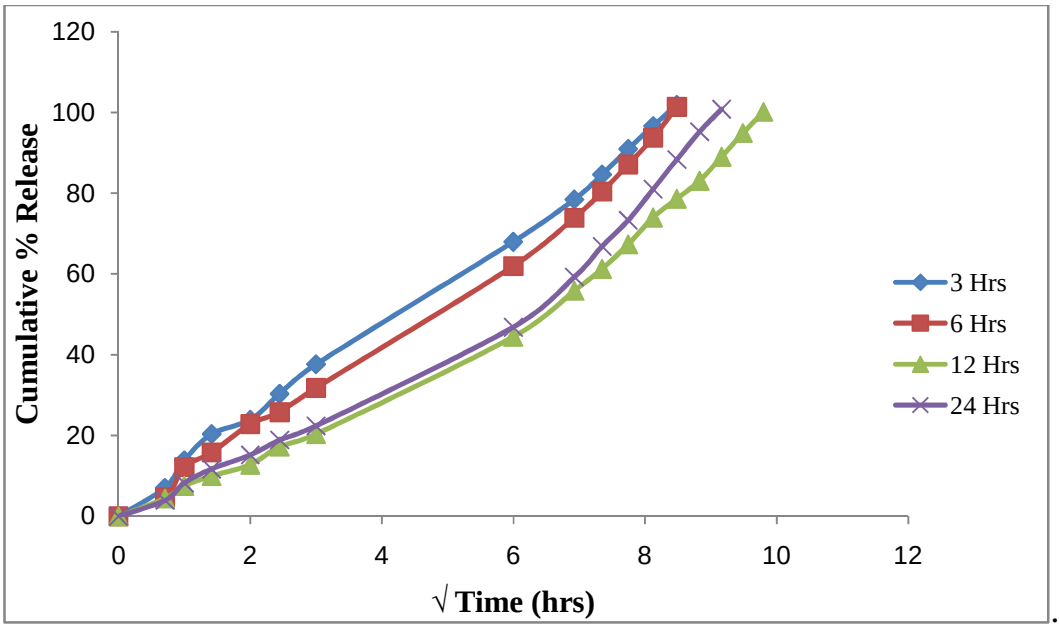

Figure 4: Higuchi Plot of Implants Formulated with 80:20 Gelatin-Sodium Alginate Polymer At Different Hardening Times

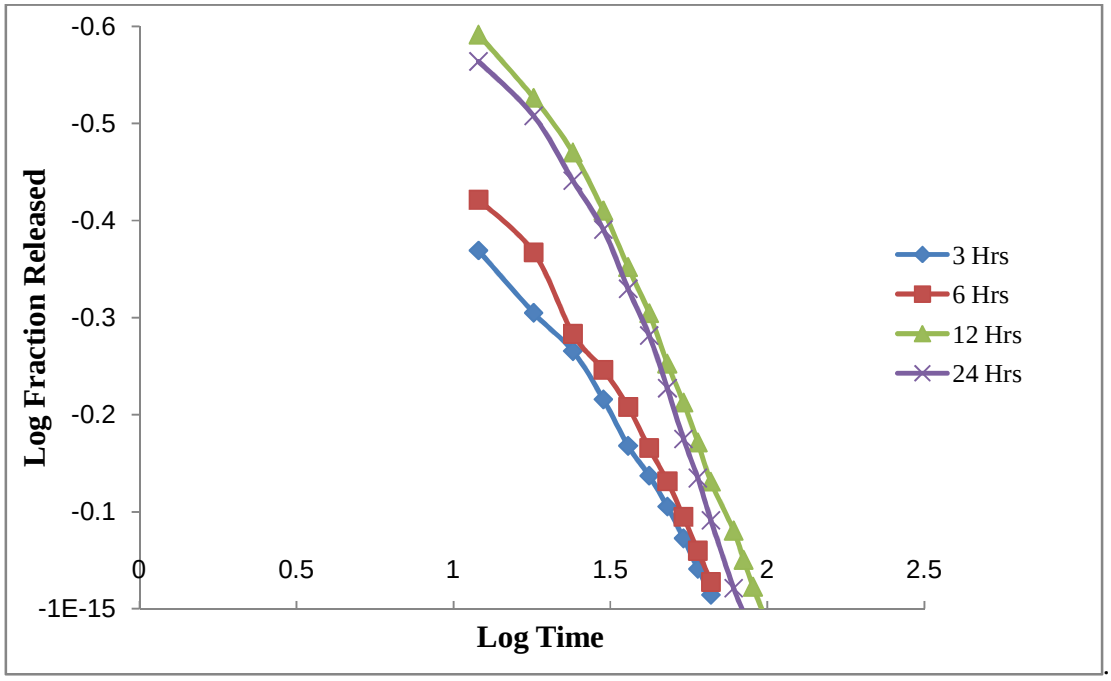

Figure 5: Korsmeyer Plot of Implants Formulated with 80:20 Gelatin-Sodium Alginate Polymer At Different Hardening Times

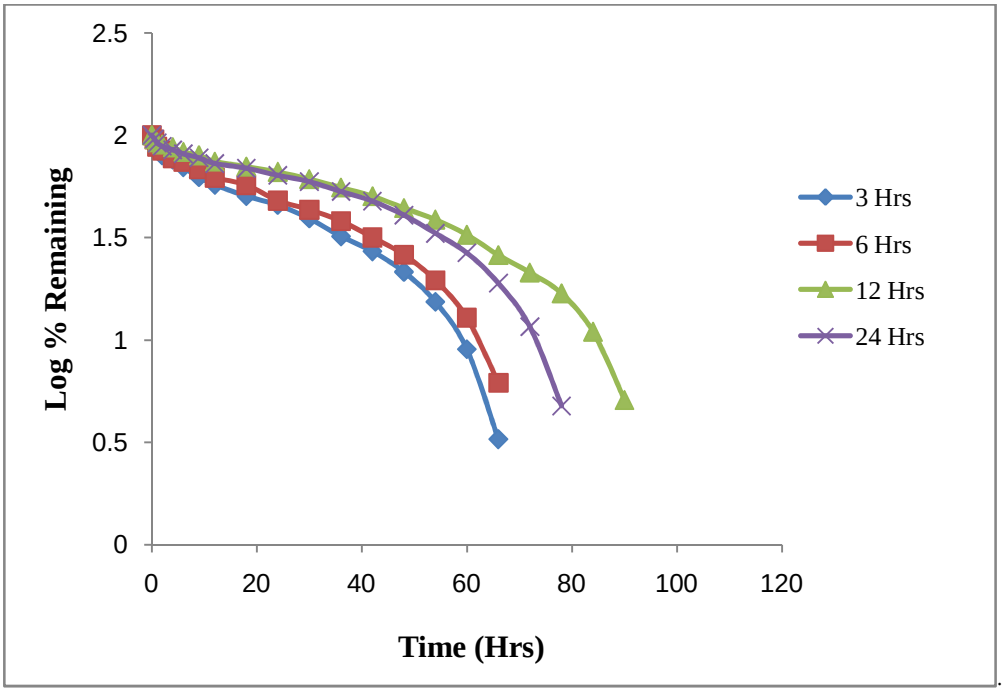

Figure 6: First Order Plot of Implants Formulated with 80:20 Gelatin-Sodium Alginate Polymer At Different Hardening Times

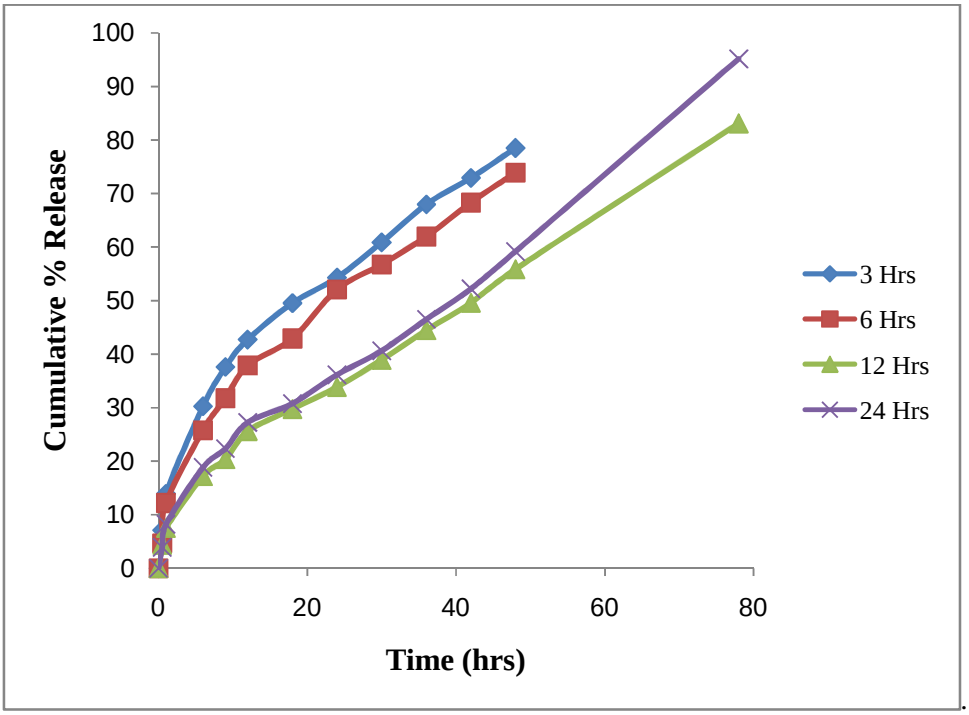

Figure 7: Zero Order Plot of Implants Formulated with 80:20 Gelatin-Sodium Alginate Polymer At Different Hardening Times

Table 2: Fitting Comparison of Equations of Higuchi, Korsmeyer-Peppas, Zero Order and First Order for Describing Release Profiles of Aspirin from 80:20 Gelatin-Sodium Alginate Implant

Kinetic Model		Hardening Time (Hrs)			
		3	6	12	24
Higuchi	Rate constant (% release /√hr)	11.562	11.42	10.525	9.9
	R^2	0.9973	0.9937	0.9806	0.9752
Korsmeyer	Rate constant (log fraction release/ log hr	0.4852	0.5367	0.707	0.6955
	R^2	0.9854	0.986	0.9804	0.9674
First Order	Rate constant (log % remaining/ hr)	-0.0168	-0.0142	-0.0122	-0.0107
	R^2	0.91	0.9327	0.8961	0.8597
Zero Order	Rate Constant (% Release/hr)	1.4645	1.4105	1.1112	0.9951
	R^2	0.9078	0.9281	0.9748	0.9748

CONCLUSION

Implants have been developed to avoid daily injections and improve patient compliance. However their administration and withdrawal require surgical intervention which is a compliance problem. To address this problem, use of biodegradable polymers has increased in recent studies. Biodegradable polymers are highly desirable in these situations because they degrade in the body to biologically inert and compatible molecules. By incorporating drug into biodegradable polymers, dosage forms that release the drug over a prolonged length of time can be prepared in a variety of shapes and sizes. No secondary surgical procedures are needed after completion of the dosing regimen since the remaining polymer dosage form will be degraded and cleared by the body. As a result, biodegradable polymers offer a novel approach for sustained release drug delivery systems that are simple and convenient to the patient [24]. Gelatin-Sodium Alginate based implants of Aspirin having uniform character can be prepared with minimum batch to batch variation. Gelatin-Sodium Alginate combination biodegradable implants exhibited long term drug release under *in-vitro* conditions. The implants containing 80:20 % w/w Gelatin: Sodium Alginate and hardened for 12 hours were found to produce the most satisfactory drug release. Since the drug of choice has found its use in many long term conditions, this system shows sufficient promise as a candidate for further development.

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