IJPSR (2014), Volume 5, Issue 9 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 March 2014; received in revised form, 25 April 2014; accepted, 07 June 2014; published 01 September 2014

EFFECT OF EXCIPIENTS ON THE RELEASE OF TRAMADOL HYDROCHLORIDE FROM BIODEGRADABLE POLYMERIC IMPLANTS

Mukta Saha [1], Arnab Debnath [2], Farjana Afrose [1] and Swarnali Islam [*1]

Department of Pharmacy [1], University of Asia Pacific, Dhaka - 1209, Bangladesh.
Infusions Unit [2], Beximco Pharmaceuticals Ltd. Dhaka - 1711, Bangladesh.

Keywords:

Biodegradable Implant, Gelatin, Sodium Alginate, SEM, Tramadol Hydrochloride, *In- vitro* Release

Correspondence to Author:
Swarnali Islam

Department of Pharmacy,
University of Asia Pacific,
Building 73, Road 5A, Dhanmondi,
Dhaka-1209, Bangladesh.

E-mail: swarnali@uap-bd.edu

ABSTRACT: Subcutaneous implantation of the drug is known to be the first medical approach aiming to achieve prolonged and continuous administration of drugs. The purpose of the research was to achieve sustained delivery of Tramadol Hydrochloride from biodegradable Gelatin-Sodium Alginate polymeric implant. Implants were prepared by using Gelatin-Sodium Alginate polymer in two ratios 70:30 & 80:20% w/w by heating and congealing method and then exposed to formaldehyde vapor for different periods (3, 6, 12 & 24 h) for hardening. Implants formulated with 80:20 Gelatin-Sodium Alginate ratio and hardened for 12 h were chosen for further studies based on drug loading and release performance. Effects of different excipients were studied on drug loading efficiency and drug release profile. Morphology of implant matrices, as studied by SEM, supported the experimental results. The release kinetics of drug was evaluated by fitting the data in four different kinetic models, namely, Zero order, First order, Higuchi and Korsmeyer-Peppas. Implants were found to follow Korsmeyer Peppas Model the best in most cases. Good correlations were obtained with the Higuchi model as well. According to these models, the drug release mechanism was diffusion controlled.

INTRODUCTION: When considering new options for drug delivery, the most direct approach is usually parenteral administration as innovative pharmaceutical treatments require innovative methods of administration. The development of sustained-release dosage forms is more likely to succeed commercially such as implants providing controlled, local release of active substances are of interest in different medical applications, assuming that they provide the desired efficacy and safety.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(9).3802-09

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(9).3802-09

The plethora of drug therapies and types demand different formulations, fabrications conditions, and release kinetics. No single polymer can satisfy all the requirements. Therefore there have been tremendous advances in the area of biodegradable polymers over the last 30 years [1].

Present investigation explores the scope to formulate and evaluate sustaining the release of drug by using Gelatin-Sodium Alginate combination biodegradable implants. Tramadol Hydrochloride was chosen as a model drug because it is centrally acting analgesic with a low affinity for opioid receptors and is used treat many long term conditions like rheumatoid arthritis, restless legs syndrome, motor neuron disease, fibromyalgia [2].

Its limiting side effects in the treatment of acute and chronic pain are reported to be less intense and less frequent than other opioids. The drug has a good bioavailability and elimination half-life (5–6 h). It is prescribed 3–4 times a day and therefore is a good candidate to be formulated in sustained release dosage form [3]. The goal in designing sustained delivery systems is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery [4].

MATERIALS AND METHODS:

Materials: Tramadol Hydrochloride was obtained as a gift sample from Beximco Pharmaceuticals Ltd, Bangladesh. Gelatin was purchased from Merck Specialties Pvt. Ltd, Mumbai. Sodium Alginate was purchased from Loba Chemie Pvt. Ltd, Mumbai. Other chemicals were of analytical grade.

Preparation of Implant: Tramadol Hydrochloride implants were prepared by using biodegradable polymers Gelatin and Sodium Alginate in two different ratios 70:30 and 80:20, respectively. Implants with 10% drug load for each formulation were prepared using heating and congealing method. Gelatin was weighed & sprinkled with water for 30 min. Then Sodium Alginate was added to hydrated gelatin at 60 °C with continuous stirring until gelatin was dissolved and then glycerin (plasticizing agent) was added into it.

Tramadol Hydrochloride was dissolved with acetone and added to the previous mixture. After homogenous mixing of all ingredients, the solution was poured in a glass Petri dish and kept in an ice bath for 1 hr. Then it was allowed to set by placing in the refrigerator for 3 days and hardened with Formaldehyde [5, 6, 7]. After that, the implants were dried at room temperature for 3 days and cut into thin films.

Hardening of Implants: In an empty glass desiccator, a Petri dish containing 37% v/v formaldehyde solution was placed below the perforated plate. Petri dishes containing the implants were kept on top of a perforated plate, and the desiccator was closed immediately. Then implants were removed from the desiccator after 3, 6, 12, and 24-hour intervals, respectively, which allowed the implants to react with formaldehyde vapor for the said hours. After that, they were dried at room temperature for 3 days to make sure that the residual formaldehyde gets evaporated [5, 6, 7, 8].

Morphological Characterization of Implants:

Digital Photographic Imaging: Photograph of the drug-loaded implants was taken with the help of digital camera Canon Ixus, 10.0 Mega Pixel. **Fig. 1(B)** shows some randomly selected digital images of the implants.

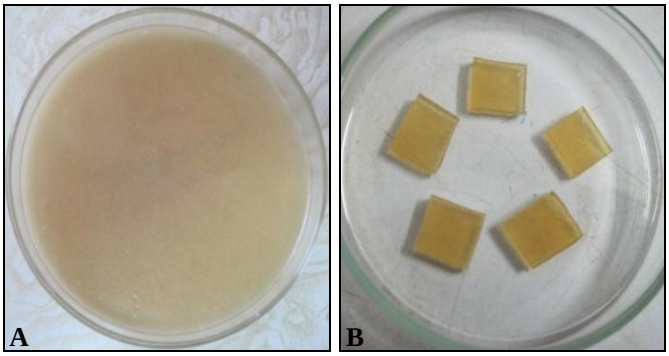

FIG. 1: IMAGES OF GELATIN- SODIUM ALGINATE IMPLANTS (A) AFTER POURING INTO PETRI DISH (B) AFTER CUTTING

Scanning Electron Microscope (SEM): Scanning electron microscope (Philips XL 30, The Netherlands) was used to observe the surface morphology of implants. The Au layer was coated to make the implant surface conductive to electrons in the SEM. Surface morphology greatly influences the release kinetics of implants [9]. The kinetics of drug release is greatly dependent on the morphological characters of implants.

The SEM micrograph of Mg Stearate incorporated drug-loaded implant surface before drug release found porous. Thereby probably entrapping of the drug is relatively lower compared to 100% entrapping capability, and it also correlates with loading efficiency found from drug content analysis. The loading efficiency was found 72.363% when Mg Stearate was incorporated in the implant. In **Fig. 2(A)** represented no porous surface, then loading efficiency would 100%. But loading efficiency 72.363% which comply with the figure. **Fig. 2(B)** being more porous and rough we can say that a very low amount of drug was remaining after drug release.

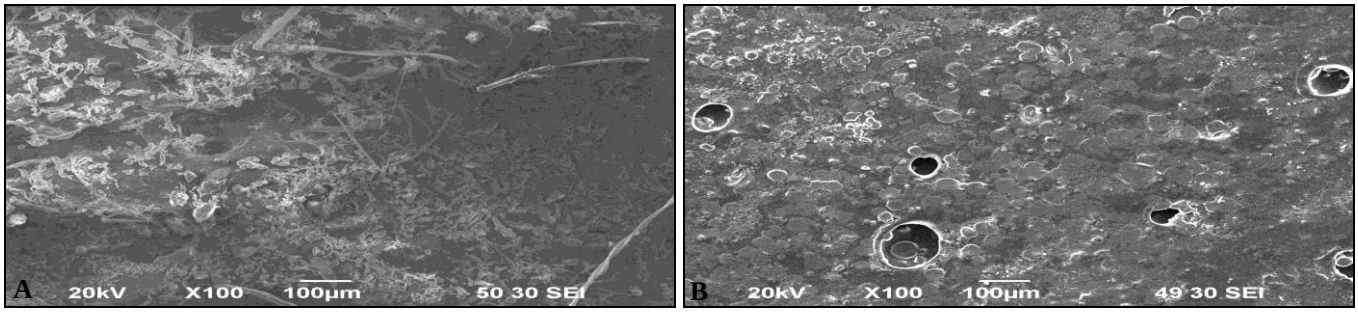

FIG. 2: SEM MICROGRAPH OF TRAMADOL HYDROCHLORIDE IMPLANT WITH Mg STEARATE (A) BEFORE DRUG RELEASE (B) AFTER DRUG RELEASE

Physical Parameters of Implants:

Weight Variation of Implants: Weight variation of implants was checked by weighing three implants of a particular formulation and exposure time individually [10]. **Fig. 3(A)** shows the average weight of the implants for 70:30 and 80:20 formulations and hardening times of 3 h, 6 h, 12 h, and 24 h are similar with little deviations. Thus it can say that the implants of various polymer ratios with different hardening time did not affect the average weight of the implants.

Thickness of Implants: The thickness of implants was checked by taking 3 implants from each batch of formulations and measured their thickness individually by using slide calipers [11]. **Fig. 3(A)** denotes variations in the thickness of the implants with different polymer ratios including 70:30 and 80:20 which were gone for 3hrs, 6 hrs, 12 hrs, and 24 h exposure time for their hardening. From **Fig. 3(B)** it can say that the average thickness of the implants of formulations 70:30 and 80:20 with their different hardening times (3, 6, 12 and 24 h) remain relatively similar with little deviations. Thus it can say that the implants of various polymer ratios with different hardening times did not affect the average thickness of the implants.

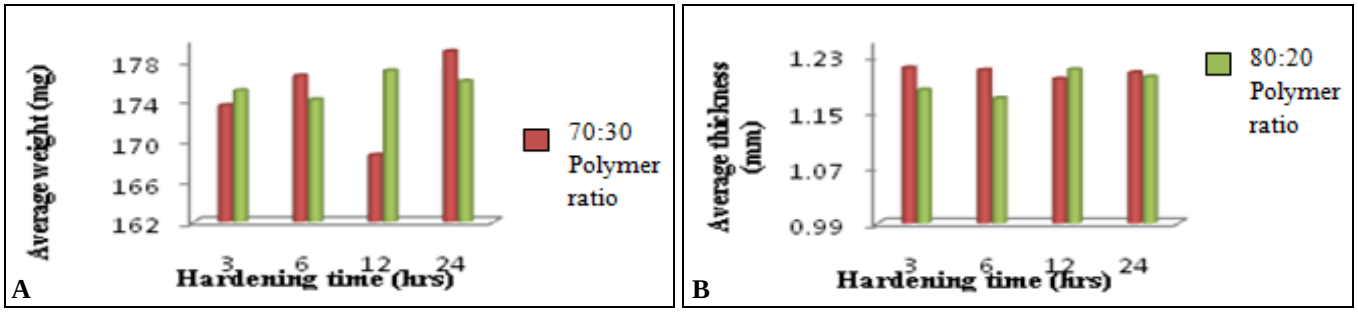

FIG. 3: COMPARISON OF 70:30 AND 80:20 GELATIN-SODIUM ALGINATE IMPLANT (A) AVERAGE WEIGHT (IN MG) (B) AVERAGE THICKNESS (IN mm)

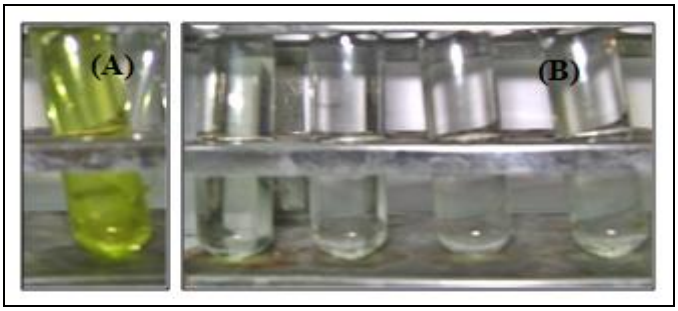

FIG. 4: FREE FORMALDEHYDE TEST (A) STANDARD FORMALDEHYDE SOLUTION (B) COLORLESS SAMPLE SOLUTIONS

Test for Free Formaldehyde: Implants were subjected to a pharmacopoeial test to detect the absence of free formaldehyde [12]. **Fig. 4** shows the comparison of the sample solution and the standard solution with each other according to visual color change. The intense the yellow color, the greater the amount of free formaldehyde. **Fig. 4(B)** reflect that the color of the sample solutions was colorless. So, from this observation, we may be sure that these implants did not retain any free formaldehyde.

Determination of Drug Content (Loading Dose): The amount of drug that was loaded in implants during the fabrication process was determined by spectrophotometric analysis. First, the implants were weighed and then crushed **Fig. 5** in a mortar and pestle. Then it was dissolved in 1 ml hot buffer

by vigorous ultrasonication. For precipitating the polymer and extracting the drug, 9 ml of phosphate buffer (pH 7.4) was added. Then it was centrifuged at 3000 rpm for 15 min to separate the solid material. The supernatant from the solution was collected, and it was analyzed at 271 nm with UV spectrophotometer with phosphate buffer (pH 7.4) as blank.

FIG. 5: IMAGE OF CRUSHED IMPLANT

***In-vitro* Drug Release Studies:** For *in-vitro* dissolution of Tramadol Hydrochloride implants at least 3 samples were taken from each formulation and transferred to 50 & 100 ml rubber capped glass vial containing Phosphate Buffer (pH 7.4) in order to observe the drug release profile **Fig. 6**. Then they were kept in static condition for certain time period and after predetermined time intervals with mild stirring of the dissolution vessel 10 ml of sample was withdrawn using conventional disposable syringe (10 ml). To replace the withdrawn sample, 10 ml of fresh phosphate buffer was added to the vessels. The withdrawn samples were analyzed for determining the percentage release of drugs by UV spectrophotometer at 271 nm (λmax of Tramadol Hydrochloride). All data were used in statistical analysis for the determination of mean, standard deviation and release kinetics [13, 14].

FIG. 6: *IN-VITRO* DISSOLUTION OF IMPLANTS

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 [15].

RESULTS AND DISCUSSION:

The Drug Loading Efficiency of Implants: The loading dose has a significant effect on resulting release kinetics along with drug solubility. In case of freely water-soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. The loading efficiency of the implant is dependent on several factors related to the drug, polymer, and solvent properties. Implants were analyzed for actual Tramadol Hydrochloride content against theoretical drug content. The percentage of loading efficiency (%LE) of implants was determined with the formula:

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

Where LD is the amount of drug that was loaded in the implant, and AD is the amount of drug originally added in the formulation [16].

Effect of Excipients on Loading Efficiency of Implants: The effect of incorporation of different excipients on loading efficiency of Tramadol Hydrochloride was studied for 10% drug load. The changes in the loading efficiency were probably caused by the respective excipients. The data for different excipients are represented in **Table 1.**

TABLE 1: EFFECTS OF EXCIPIENTS ON LOADING EFFICIENCY (%)

Excipients	Actual drug content Mean ± SD	Loading efficiency (%)
Drug only	12.354 ± 0.129	65.65
GMS	11.283 ± 0.077	66.46
Stearic Acid	11.981 ± 0.413	76.006 (max)
Stearyl Alcohol	11.267 ± 0.282	70.77
Cetyl Alcohol	11.315 ± 0.088	73.25
Cetostearyl Alcohol	9.296 ± 0.019	63.38
Arachis Oil	9.243 ± 0.037	48.62 (min)
Cremophore RH 40	15.932 ± 0.130	69.67
Xanthan Gum	13.416 ± 0.099	67.96
Magnesium Stearate	13.761 ± 0.267	72.36

Loading efficiency was found in the range between 48.62% to 76.00% from different formulations. The highest loading efficiency was found with Stearic Acid (76.00%) and the lowest with Arachis Oil (48.62%). **Fig. 7** represents a graphical comparison of the drug loading efficiency of different excipient

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

Stearic Acid > Cetyl Alcohol > Mg Stearate > Stearyl Alcohol > Cremophore RH 40 > Xanthan Gum > GMS > Drug Only > Cetostearyl Alcohol > Arachis Oil

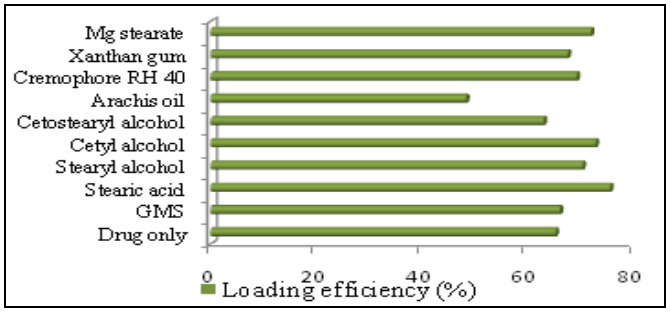

FIG. 7: EFFECTS OF EXCIPIENTS ON DRUG LOADING EFFICIENCY

***In-vitro* Drug Release Studies for 70:30 and 80:20 Ratio:** The profile and kinetics of drug release are important because they correlate the *in-vitro*, *in-vivo* drug responses by comparing results of pharmacokinetics and dissolution profile patterns [17, 18, 19]. The drug release mechanism from the matrix is a consequence of concomitant processes 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 [16]. The formulation containing Gelatin-Sodium Alginate in the ratio 80:20 and hardened for 12 h showed maximum sustained action of drug release **Table 2** and **Fig. 8**.

TABLE 2: TIME TAKEN FOR DRUG TO BE RELEASED FROM IMPLANTS

Gelatin- Sodium Alginate polymer ratio	Time (days) taken for drug release to be completed from implants			
	3 h	6 h	12 h	24 h
70:30	7	8	9	7
80:20	9	10	13 (max)	11

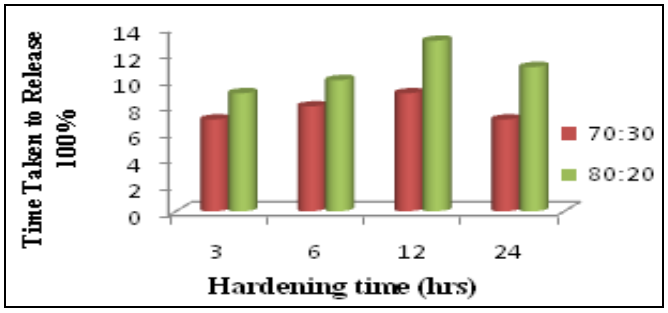

FIG. 8: TIME TAKEN FOR DRUG TO RELEASED

TABLE 3: OVERVIEW OF CALCULATED TIME

Excipients	Time (days) for drug release
GMS	16
Stearic Acid	16
Stearyl Alcohol	15
Drug only	13
Cetyl Alcohol	13
Arachis Oil	13
Cremophore RH 40	13
Cetostearyl Alcohol	12
Xanthan Gum	12
Mg Stearate	10

Drug Release Profile from 80:20 Gelatin-Sodium Alginate Polymer Ratio with 12 h Exposure Time: Effect of Excipients: Excipients have various effects on drug release profile. The rate and extent of drug release can be controlled by the use of excipients in the formulation. These agents can act as rate modifier by increasing or retarding the rate of release depending upon the nature of the agent. They probably extend their effects by influencing the way of formulation formed and therefore on the release characteristics of the sustained release implants. Result of *in-vitro* release are summarized in **Table 3** and also graphically represented in **Fig. 9** as compared to the drug only implant.

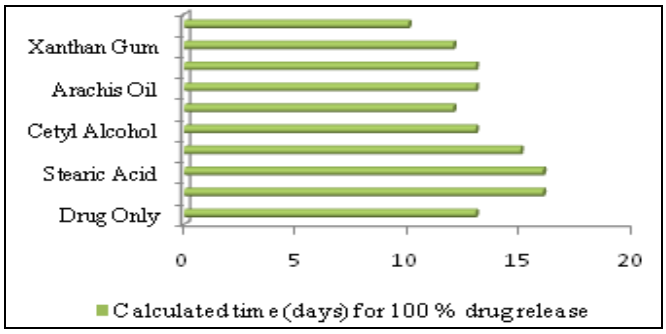

FIG. 9: GRAPHICAL REPRESENTATION OF % RELEASE FOR DIFFERENT EXCIPIENT INCORPORATED IMPLANT

The *in-vitro* release data of Tramadol Hydrochloride were analyzed using Higuchi, Korsmeyer Peppas, First order, and Zero order model to identify drug release characteristics for implants [20, 21, 22]. R^2 values in **Table 4** show the Korsmeyer-Peppas model to be the best fit. Good correlations were also obtained with the Higuchi model. The Korsmeyer-Peppas equation describes the mode of release of drugs from swellable matrices and Higuchi describes the release of drugs

from the insoluble matrix as a square root of time-dependent process based on the Fickian diffusion [23]. According to these models, Tramadol Hydrochloride release from implants is diffusion controlled where the drug is leaving the matrix through pores and channels formed by the entry of dissolution medium.

TABLE 4: FITTING COMPARISON OF EQUATION OF KINETIC MODELS

Formulations	Kinetic Model							
	Higuchi		Korsmeyer-Peppas		First order		Zero order	
	Rate constant	R^2	Rate constant	R^2	Rate constant	R^2	Rate constant	R^2
Drug Only	17.99	0.92	0.19	0.91	-0.05	0.91	3.97	0.92
GMS	19.46	0.95	0.16	0.96	-0.06	0.90	4.76	0.90
Stearic Acid	17.34	0.87	0.17	0.91	-0.04	0.87	4.15	0.79
Stearyl Alcohol	21.41	0.95	0.20	0.96	-0.07	0.94	5.33	0.86
Cetyl Alcohol	20.33	0.92	0.16	0.98	-0.08	0.88	5.30	0.83
Cetostearyl Alcohol	21.31	0.91	0.17	0.91	-0.05	0.87	5.69	0.80
Arachis Oil	19.54	0.90	0.17	0.91	-0.05	0.89	5.16	0.83
Cremophore RH 40	19.87	0.90	0.17	0.91	-0.07	0.81	5.29	0.85
Xanthan Gum	22.04	0.93	0.18	0.95	-0.08	0.88	6.07	0.87
Mg Stearate	23.54	0.89	0.15	0.94	-0.10	0.92	7.00	0.79

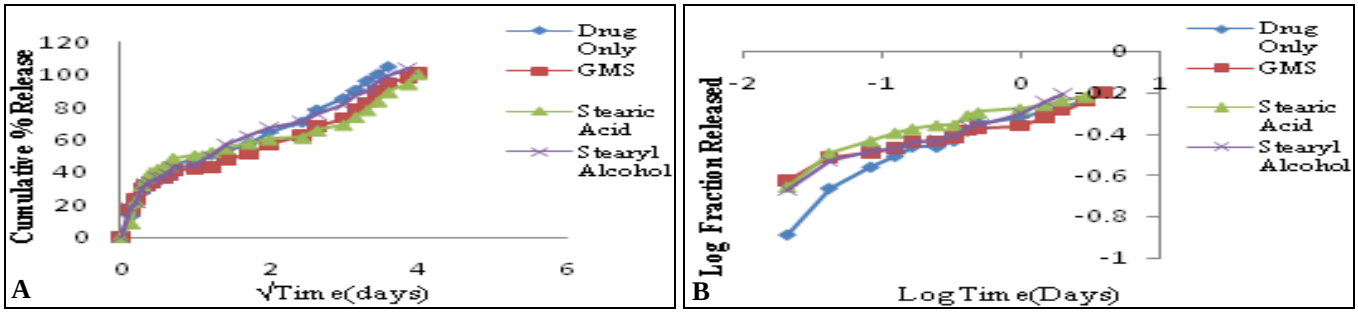

FIG. 10: TRAMADOL HYDROCHLORIDE RELEASE FROM IMPLANTS WITH GMS, STEARIC ACID AND STEARYL ALCOHOL: (A) HIGUCHI (B) KORSMEYER-PEPPAS

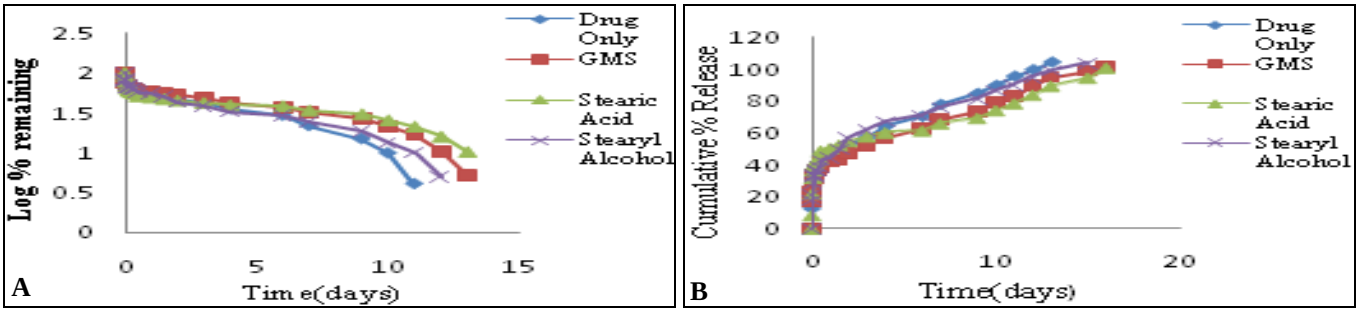

FIG. 11: TRAMADOL HYDROCHLORIDE RELEASE FROM IMPLANTS WITH GMS, STEARIC ACID AND STEARYL ALCOHOL: (A) FIRST ORDER (B) ZERO ORDER

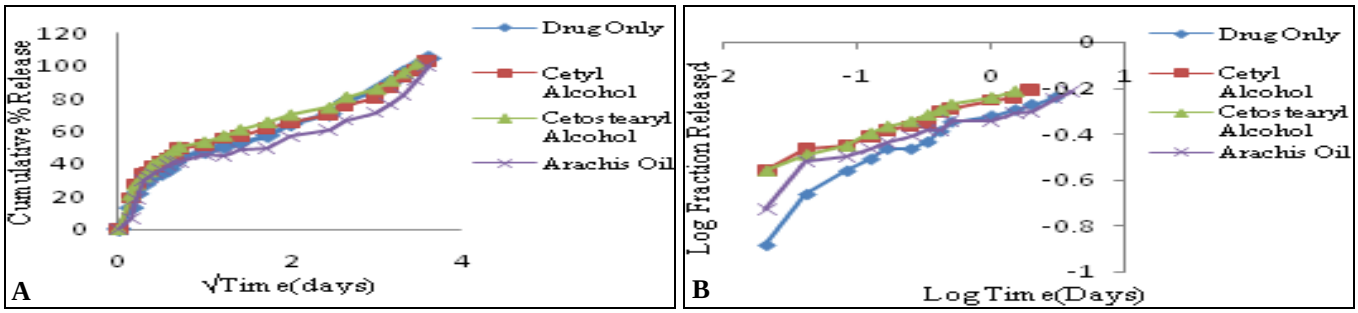

FIG. 12: TRAMADOL HYDROCHLORIDE RELEASE FROM IMPLANTS WITH CETYL ALCOHOL, CETOSTEARYL ALCOHOL, AND ARACHIS OIL: (A) HIGUCHI (B) KORSMEYER-PEPPAS

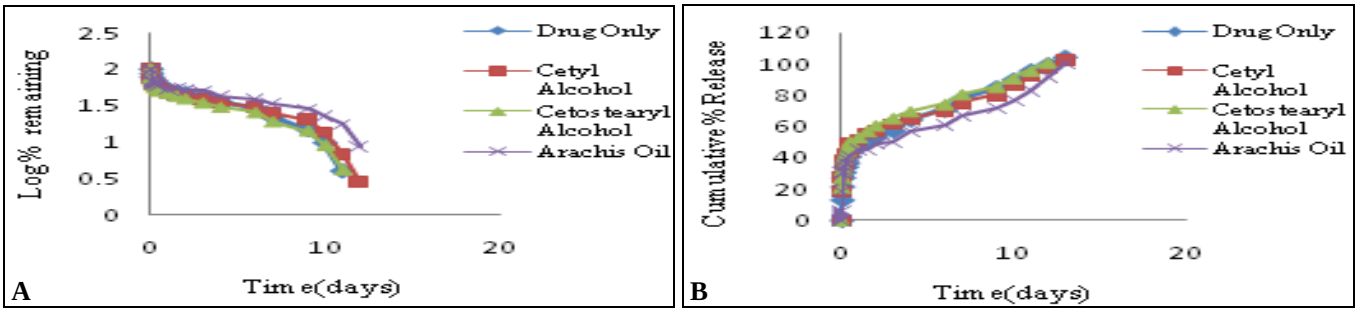

FIG. 13: TRAMADOL HYDROCHLORIDE RELEASE FROM IMPLANTS WITH CETYL ALCOHOL, CETOSTEARYL ALCOHOL, AND ARACHIS OIL: (A) FIRST ORDER (B) ZERO ORDER

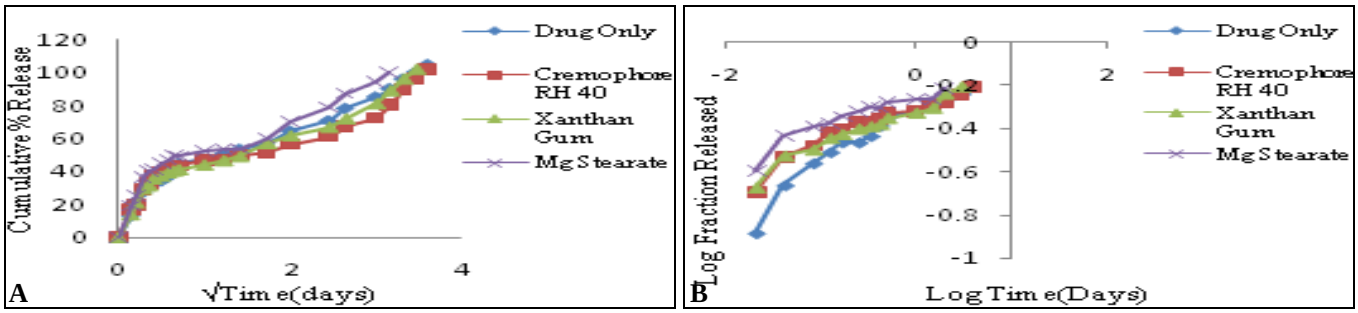

FIG. 14: TRAMADOL HYDROCHLORIDE RELEASE FROM IMPLANTS WITH CREMOPHORE RH 40, XANTHAN GUM AND MG STEARATE: (A) HIGUCHI (B) KORSMEYER-PEPPAS

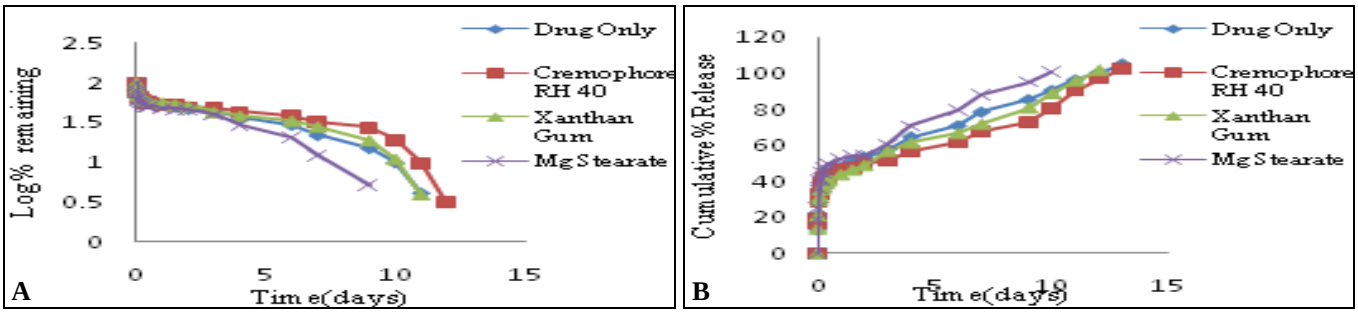

FIG. 15: TRAMADOL HYDROCHLORIDE RELEASE FROM IMPLANTS WITH CREMOPHORE RH 40, XANTHAN GUM AND MG STEARATE: (A) FIRST ORDER (B) ZERO ORDER

CONCLUSION: Polymeric drug delivery systems are attractive alternatives to control the release of drug to obtain defined blood levels over a specified time. The patients suffering from some disease conditions often benefit from such long-term drug delivery systems [24]. This interest has been fostered by the potential advantages provided by these technologies, including a decrease of overall drug dose and possible reduction of local or systemic side effects. Biodegradable polymers are highly desirable in these situations because they degrade in the body to biologically inert and compatible molecules, and no surgical retrieval is required.

As a result, biodegradable polymers offer a novel approach for sustained release drug delivery systems that are simple and convenient to the patient [1]. Tramadol Hydrochloride release from Gelatin–Sodium Alginate implants sustained up to 16 days through the drug is highly water soluble. The polymer content had a significant influence on drug loading efficiency. Variation in polymer ratio and inclusion of different excipients affected the drug release characteristics. Since this delivery system has been found to provide sustained drug release, it can be an attractive candidate for further development.

ACKNOWLEDGEMENT: The authors are thankful to Beximco Pharmaceuticals Ltd., Bangladesh, for providing support with the active ingredient.

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Kotwal VB, Saifee M, Inamdar N and Bhise K: Biodegradable polymers: Which, when and why? Review of

Article. Indian Journal of Pharmaceutical Sciences 2007; 69(5): 616-25.
2. Sagarbechara, Padmavathi PP, Subrahmanyam EVS, Jignesh JK, Sumit S and Shabaraya AR: Development of New Analytical Method and Its Validation for the Determination of Tramadol Hydrochloride in Bulk and Marketed Formulations. Asian Journal of Biomedical and Pharmaceutical Sciences 2013; 3(23): 53-56.
3. Scott LJ and Perry CM: Tramadol: a review of its use in perioperative pain. Drugs 2000; 60(1): 139-76.
4. Kumar V, Prajapati SK, Soni GC, Singh M and Kumar N: Sustained release matrix-type drug delivery system: a review. World Journal of Pharmacy and Pharmaceutical Sciences 2012; 1(3): 934-60.
5. Purushotham RK, Jaybhaye SJ, Kamble R, Bhandari A and Pratima S: Designing of Diclofenac Sodium Biodegradable Implant for Speedy Fracture Healing. Journal of Chemical and Pharmaceutical Research 2010; 3(1): 330-37.
6. Gupta LS, Rao KP, Choudhary KPR and Pratima S: Designing of Biodegradable Drug Implants of Nimesulide. Journal of pharma and bio sciences 2010; 2(2): 1-4.
7. Gupta LS, Rao KP, Choudhary KPR and Pratima S: Preformulation Studies of Biodegradable Drug Implants of Meloxicam for Orthopedic Patient Care. Journal of Pharmaceutical Science and Technology 2011; 3(1): 494-98.
8. Islam S, Islam S and Urmi AB: Observation of the release of aspirin from gelatin-sodium alginate polymeric implant. J Chem Pharm Res 2012; 4(12): 5149-56.
9. Joób-Fancsaly A and Divinyi T: Electron Microscopic Examination of the Surface Morphology of Dental Implants. Fogorvosi Szemle 2001; 94(6): 239-45.
10. Roohullah ZI, Khan JA and Daud SMA: Preparation of Paracetamol Tablets using PVP- K30 and K-90 as Binders. Acta Pharm Tur 2003; 45: 137-45.
11. Saparia B, Murthy RSR and Solanki A: Preparation and Evaluation of Chloroquine Phosphate Microspheres using Cross-Linked Gelatin for Long Term Drug Delivery. Ind J Pharm Sci 2002; 64: 48-52.
12. The European Pharmacopoeia 7.0. 7th edition. Europe: EDQM Publication 2010; 1: 118.
13. Tayade PT and Kale RD: Encapsulation of water-insoluble drug by a cross-linking technique: effect of process formulation variables on encapsulation efficiency, particle size, and *in-vitro* dissolution rate. AAPS Pharm Sci Tech 2004; 6: 112-19.
14. Islam S: Lipophilic and hydrophilic drug loaded PLA/PLGA *in-situ* implants: studies on thermal behavior of drug & polymer and observation of parameters influencing drug burst release with corresponding effects on loading efficiency & morphology of implants. Int J Pharm Pharm Sci 2011; 3(3): 181-88.
15. Gokhan E, Mine O, Ercument K, Mesut A and Tamer G: *In-vitro* programmable implants for constant drug release. Acta Pharm Tur 2005; 47: 243-56.
16. Rahman MA and Islam S: Study of Metoprolol Tartrate delivery from biodegradable polymeric in situ implants for parenteral administration. International Journal of Pharmacy and Pharmaceutical Sciences 2011; 3(4).
17. Rajamma AJ, Yogesha HN and Sateesha SB: Natural gums as sustained release carriers: development of gastroretentive drug delivery system of ziprasidone HCl. Daru J Pharmaceu Sci 2012; 20(1): 58.
18. Faith A, Chaibva, Sandile MM, Khamanga and Roderick BW: Swelling, erosion and drug release characteristics of Salbutamol sulfate from Hydroxypropyl methylcellulose-based matrix tablets. Drug Dev Ind Pharm 2010; 36(12): 1497-10.
19. Sateesha SB, Rajamma AJ, Narode MK and Vyas BD: Influence of organic acids on diltiazem HCl release kinetics from hydroxypropyl methyl cellulose matrix tablets. J Young Pharm 2010; 2(3): 229-33.
20. Prabhushankar GL, Gopalkrishnan, Manjunatha B and Girisha KM: International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2(1): 162-68.
21. Prabhushankar GL, Gopalkrishna B, Manjunatha KM and Girisha CH: Formulation and Evaluation of Levofloxacin Dental Films for Periodontics. Int J Pharm Pharm Sci 2010; 2(1): 162-68.
22. Brazel CS and Peppas NA: Modeling of Drug Release from Swellable Polymers. Eur J Pharm Biophrarm 2000; 49(1): 47-58.
23. Young CR, Dietzsch C, Cerea M, Farrell T, Fegely KA, Siahboomi AR and McGinity JW: Physicochemical characterization and mechanisms of release of theophylline from melt-extruded dosage forms based on a methacrylic acid copolymer. Int J Pharm 2005; 301(1): 112-20.
24. Umadevi S, Rohini B, Nithyapriya and Sasidharan: Formulation and evaluation of ciprofloxacin dental films for periodontitis. J Chem and Pharmaceu Res 2012; 4(6): 2964-71.

How to cite this article:
Saha M, Debnath A, Afrose F and Islam S: Effect of excipients on the release of tramadol hydrochloride from biodegradable polymeric implants. Int J Pharm Sci & Res 2014; 5(9): 3802-09. doi: 10.13040/IJPSR.0975-8232.5(9).3802-09.