International Journal of Current Trends in Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ijctpr

RESEARCH ARTICLE

Formulation and Evaluation of Repaglinide Insitugel

G. Uma Rani[1*], R. Nagaraju[2]

[1]*RBVRR Women's college of pharmacy, Hyderabad.*
[2]*Instituite of Pharmaceutical technology, Sri padmavathi mahila university, Tirupathi.*

ABSTRACT

The present research was focused to develop the formulation to release the drug Repaglinide for an extended period of time and buoyant, thus prolong the residence time of formulation in the stomach. Sodium alginat, Chitosan, Carbopol934P are used as polymers. sodium citrate and calcium carbonate are the main ingredients for the formation of gelling solution. In the present study calcium ions released from calcium carbonate complexes with citrate ions. The conversion of complexed calcium into free calcium causes gelation of Alginate. In order to release the drug from the formulation the gelled material floats upwards with a potential in the stomach. Based on the concentration of polymer the drug release was varied. Totally 18 formulations were prepared with sodium alginate, Chitosan and Caropol 934P in various combinations. *Invitro* evaluation study was conducted in USP- Type II apparatus. In all the formulations, MIG-4 and MIG-9 are optimized for 8 hrs. The viscosities of the samples were measured by Brookfield Viscometer. The porosity of gel was evaluated by using scanning electron microscope. The floating *in-situ* gels can be formulated by using polymers like Chitosan,Carbopol 934P and natural polymers like Xanthu Gum.This formulation enhances the residencetime. The *in-situ* gel formulations were developed for improve patient complence. **Keywords:** Formulations, MIG-4 and MIG-9, Chitosan, Carbopol 934P.

ARTICLE INFO
Corresponding Author
G.Uma Rani
Department of Pharmaceutics,
RBVRR Women's college of Pharmacy,
Hyderabad, India
MS-ID: IJCTPR3683

PAPER QR-CODE

Article History: Received 21 March 2018, **Accepted** 27 April 2018, **Available Online** 15 May 2018

Citation: G. Uma Rani, *et al.* Formulation and Evaluation of Repaglinide Insitugel. *Int. J. Curnt. Tren. Pharm, Res., Res*., 2018, 6(3): 82-89.

CONTENTS

1. Introduction

The development of In situ gel systems has received considerable attention over the past few years. In situ gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner and maintain plasma concentration in a stable manner [1]. At room temperature,

these gels are liquid in nature and when in contact with body fluids or undergoes change in pH they show gelation. pH dependence, temperature dependence and cation induced gelation are their characteristic properties. In situ forming drug delivery systems possess potential advantages when compared to conventional controlled release formulations [2].

They can be easily applied in liquid form to the site of drug absorption, In contrast to very strong gels. They swell to form a strong gel that is capable of prolonging the residence time of the active substance at the site of drug absorption. in situ gels can be produced by using both natural and synthetic polymers. One or a combination of different stimuli like pH change, temperature modulation and ionic cross- linking forms in situ gels. So, In situ gels are administered by oral, ocular, rectal, vaginal, parentral and intra-peritoneal routes. Recent advances in in situ gels have made it possible to exploit the changes in physiological uniqueness in different regions of the GI tract for the improved drug absorption as well as patient's convenience and compliance. In the present research formulation of floating in situ gels, these reside specifically in stomach. Moxifloxacin HCl (Fig:1) is a Group 4 fluoro quinolone with activity against a broad spectrum of gram positive, gram negative and anaerobic bacterial pathogens. It acts by inhibiting the Topoisomerase II (DNA gyrase) and Topoisomerase IV. Moxifloxacin HCl was novel anti-biotic having anti-ulcer property. The ulcer treatment done by inhibiting the H.pylori infection (as antimicrobial agent) [3].

Ionic crosslinking:

Some ion sensitive polysaccharides like carragenan, gellan gum (Gel rite), pectin, sodium alginate undergo phase transition (sol to gel) in the presence of various ions like K+ , Ca2+, Mg2+, Na+. All These polysaccharides come under the class of ion-sensitive polymers. For example, Alginic acid undergoes gelation in the presence of divalent/polyvalent cations like Ca^{2+}. Some of the polymers used as In situ gelling agents are: Sodium alginate, gellan gum, alginic acid, pluronic F127, xyloglucan, pectin, xanthum gum and chitosan etc.

2. Materials and Methods

Repaglinide was obtained from Bioplus Pvt. Ltd. Bangalore, sodium alginate and pectin were obtained from Loba Chemie Pvt. Ltd. Mumbai, calcium carbonate and sodium citrate were obtained from Qualigens Fine Chemicals, HCl was obtained from S.D Fine Chem. Limited, Mumbai.

Methods

Calibration curve of Repaglinide :

Calibration curve of Repaglinide was constructed by preparing a stock solution of 100mg of drug in 100 ml of o.1N Hcl. From this 1 ml was diluted to 100 ml with 0.1N HCl.From the secondary stock samples of concentratons 2,4,6,8,10were removed and were tested in a uv-Visible spectrophotometer at 291nm.

Procedure:

Drug and Polymers were made lumpfree following powder and distilled water was boiled for sufficient period inorder to protect solutions from microbial contamination and degradation.Both polymers were stirred thoroughly for 10-15mins.Preweighed quantity of calcium carbonate dispersion was added with continuos stirring,Then the solution so formed was sonicated for 10 mins inorder to find the most suitable combination of gelling polymer in combination with xanthum gum and calcium carbonate.

Characterization of gastro retentive In-situ gels:

Compatibility Studies:

(a)Fourier Transformed Infrared (FTIR) Spectroscopy:

The FTIR spectra of samples were done by KBr pellet method. 1 mg of the substance was triturated with approximately 100 mg of dry, finely powdered potassium bromide IR as directed. The mixture was grinded thoroughly, spread it uniformly in a suitable die and compress under vacuum at a pressure of about 800 MPa. Mount the resultant disc in a suitable holder in the spectrophotometer. These were analyzed by Bruker FTIR Alpha model, to study the polymer and drug interaction. The integrity and compatibility of the pure drug and polymer were evaluated with the help of IR spectra of the pure drug and polymer. The major functional group's revealed particular wavelength, these have not changed in physical mixture of pure drug and polymer.

b) Gel strength: Gel strength was calculated by using the gel strength apparatus. It contains two tubes; upper tube is attached with pan through thread in which weights are added. Two surfaces were tightly covered with egg membranes.1 gm of gel was kept between the two surfaces then the weights are added into pan. The weight at which the two surfaces detached was noted and the gel strength was calculated by using formula. Gel strength=M.g/a (M: weight at which the two surfaces detached g: gravitational force a: area of surfaces)

c)Viscosity: Viscosity of the samples was determined using Brookfield Digital Viscometer (Model: LV DV-E). Spindle no.LV-4 64 was used in cup and bob model of Brookfield Digital Viscometer for determination of viscosity of the fixed volume of formulation. Viscosities were determined at 20 rpm and room temperature. [5]

d)Gelling time: The in-vitro gelling capacity of prepared formulations was measured by placing 10ml of the formulation in 100ml of 0.1N HCl. As the medium comes in contact with the formulation, immediately it was converted into stiff gel like structure. The gelling capacity of formulation was evaluated and graded on the basis of stiffness of formed gel, The gelling time was noted by observing the time gap between addition of formulation and formation of gel. [7]

e) Floating ability: The in-vitro floating study was carried out using 0.1N HCl (pH 1.2) at 37± 0.5°C.10 ml of formulation was introduced into the dissolution vessel containing medium without much disturbance. The time, the gel form of formulation took to emerge on the surface of medium (floating lag time) and the duration of time the formulation constantly floated on surface of the dissolution medium (floating ability)

f) In-vitro drug release study: The in -vitro release of Repaglinide from in-situ gels was carried out with 0.1N HCl as dissolution medium using USP dissolution

apparatus type II (paddle method) at a rotating speed of 50rpm for 12hrs. Samples were collected at specific time intervals and were analyzed using single beam UV spectrophotometer at 291 nm.

g) Drug content:

10 ml of in-situ gel was measured and transferred to 100 ml of volumetric flask. 50-70 ml of 0.1N HCl was added to this and shaken on mechanical shaker for 30 min, followed by sonication for 15 min to ensure complete dispersion of contents and filtered using 0.45 µ membrane filter. 10 ml of sample was withdrawn from this solution and diluted to 100 ml with 0.1NHCl. Then % of Repaglinide was determined spectrophotmeterically at 318 nm using double beam UV-Visible spectrophotometer. [8]

Floating behavior:

Floating Behaviour The buoyancy lag time varied with the formulation variables. Irrespective of formulation variables, buoyancy duration was > 12 hours.

In-vitro gelling capacity : To evaluate the formulations for their in-vitro gelling capacity by visual method, solutions of in situ gel forming drug delivery system were prepared. The in-vitro gelling capacity of prepare formulations was measured by placing 5 ml of the gelation solution (0.1N HCL, pH 1.2) in a 15 ml borosilicate glass test tube and maintained at 37±1ºC temperature. One ml of formulation solution was added with the help of pipette. The formulation was transferred in such a way that places the pipette at surface of fluid in test tube and formulation was slowly released from the pipette. As the solution comes in contact with gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity of solution was evaluated onthe basis of stiffness of formed gel and time period for which the formed gel remains as such. The in-vitro gelling capacity was graded in three categories on the basis of gelation time and time period for which the formed gel remains.

(+) Gels after few minutes, dispersed rapidly

(++) Gelation immediate remains for 12 hours

(+++) Gelation immediate remains for more than 12 hours

Physical Appearance and pH: All the prepared sodium alginate based in situ solution of Repaglinide were checked for their clarity and the type of the solution. After administration of the prepared solution in (0.1N HCL, pH 1.2) also checked the time required for gel formation and type of gel formed. The pH was measured in each of the solution of sodium alginate based in situ solution of Repaglinide, using a calibrated digital pH meter. The measurement of pH of data were in triplicate and the Average values given.

3. Results and Discussion

18 formulaitons were formulated with varying concentrations of sodium alginate, Chitosan, Carbopl 934 P in combination with xanthum gum by ionisation technique.The charecterization of the formulations were done for Gel strength,Viscosity,Gelling time,Drug content,Floating time, Gelling Capacity and Invitro drug release studies. The Gel strength for all the formulaitons were performed and and were found tobe within the range of 63.25 to 138.52.The viscosity was calculated using a broofield viscometer and was observed ot be in the range of 2856 to 14568 cps. The gelling time for all the formulaitons were observed to e in the range of 10 to 8secs. The drug content of all the formulaitons were osered to be within the range of 98.12 to 98.92% which was found to be within the prescribed limits. The floating lag time was observed to be within a range of 62 to 34 secs for all the formulaitons. The floating log time was observed to be within the range of >12 hrs for all the formulations . The gelling capacity of all the formulations were apt with minimum of 12 hours and stable gels were formed.Th pH range for all the formulations were observed to be within the iological limits of 6.8 to 7.4.

The invitro dissolution studies were performed in 0.1N Hcl at a pH of 1.2 and the sustainability of drug release ranged from 4-9 hours with varing concentration(100-300 mg) of sodium alginate respectively. drug release ranged from 5-11 hours with varing concentration(100-300 mg) of Chitosan respectively. drug release ranged from 6 to 12 hours with varing concentration(100-300 mg) of Carbopol934P respectiely.The dissolution graphs are depicted below.

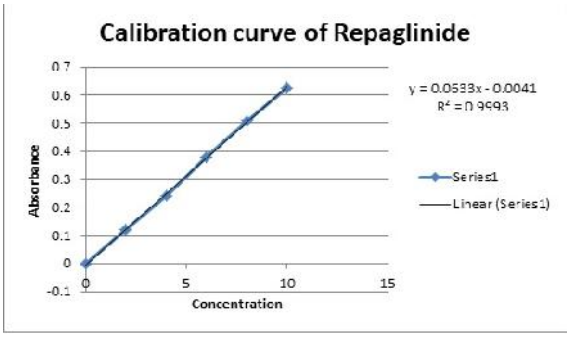

Figure 1: Calibration curve of Repaglinide

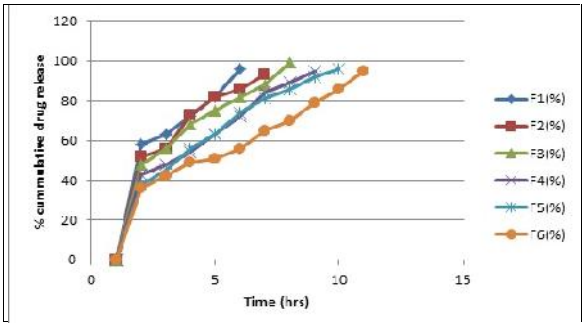

Figure 2: Drug release profile of repaglinide Insitu gels with varying concentration of sodium alginate

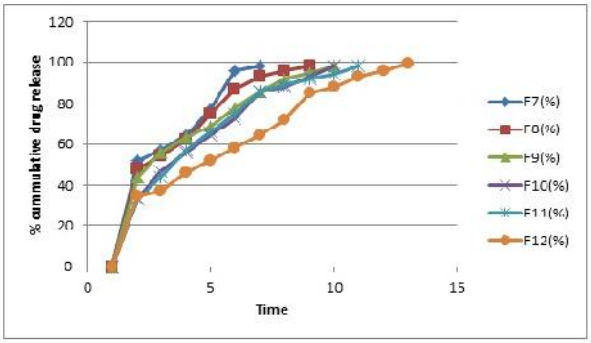

Figure 3: Drug release profile of repaglinide Insitu gels with varying concentration of Chitosan

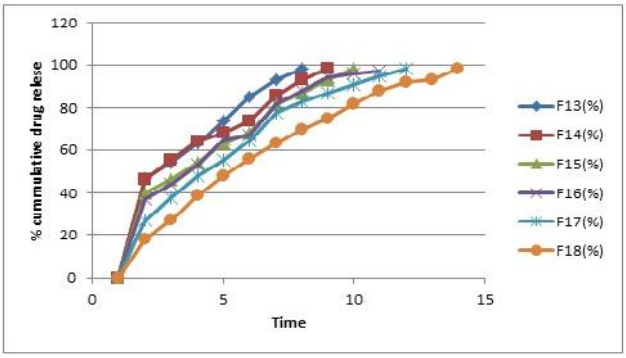

Figure 4: Drug release profile of repaglinide Insitu gels with varying concentration of Carbopol 934P

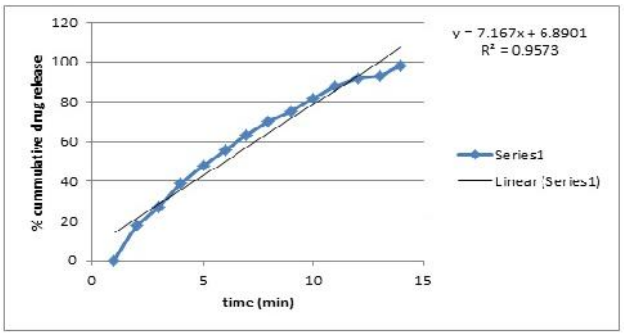

Figure 5: Zero order F graph for F18 Formulation

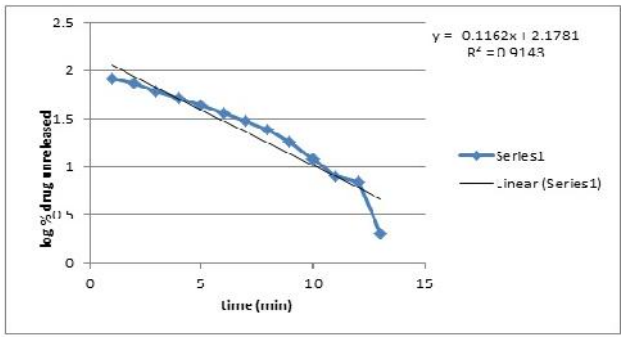

Figure 6: First Order Plot for F18 Formulaiton

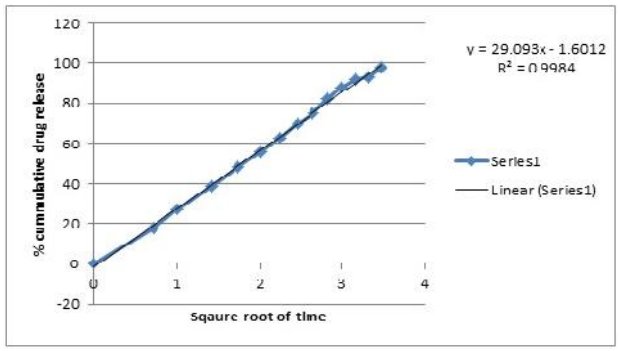

Figure 7: Higuchi Graph for F18 Formulation

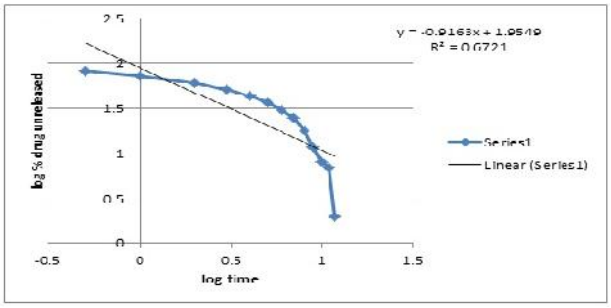

Figure 8: Kosmeyer Peppas plot For F18 Formulation

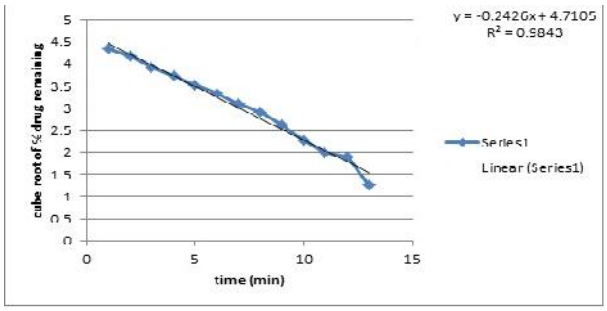

Figure 9: Hixon Crowell Plot For F18 Formulation

4. Conclusion

In the present work, floating microspheres of Cyclobenzaprine using sodium alginate along with HPMC K100M, HPMC K15M, and HPMC K4M as copolymers and sodium bicarbonate as floating polymer were formulated to deliver Cyclobenzaprine via oral route. The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Cyclobenzaprine microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. Other methods utilize larger volume of organic solvents, which are costly and hazardous because of the possible explosion, air pollution, toxicity and difficult to remove traces of organic solvent completely. Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion. The in-vitro mucoadhesive study demonstrated that microspheres of Cyclobenzaprine using sodium alginate along with HPMC K100M as copolymer adhered to the mucus to a greater extent than the microspheres of Cyclobenzaprine using sodium alginate along with HPMC K15M and HPMC K4M as copolymers.The in-vitro drug release decreased with increase in the polymer and copolymer concentration. Based on the results of evaluation tests formulation coded T4 was concluded as best formulation.

Table 1: Calibration plot for Repaglinide

S.no	Concentration(µg/ml)	Absorbance
1.	2	0.12
2.	4	0.24
3.	6	0.38

4.	8	0.51
5.	10	0.624

Table 2: Preparation of Formulations

Formulation coe/Chemicals	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)	F9(mg)	F10 (mg)	F11 (mg)	F12 (mg)	F13 (mg)	F14 (mg)	F15 (mg)	F16 (mg)	F17 (mg)	F18 (mg)
Repaglinide	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Sodium alginate	100	125	150	200	250	300												
Chitosan							100	125	150	200	250	300						
Carbopol 934P													100	125	150	200	250	300
Xanthumgum	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700	700
Methyl paraben	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120
Propyl Paraben	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70
Sodium citrate	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Calcium carbonate	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500
Sodium bicarbonate	350	350	350	350	350	350	350	350	350	350	350	350	350	350	350	350	350	350
Distilled water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 3: Results of different parameters of all formulations

Sl. No	Formulation code	Gel strength (N/m^2)	Viscosity (cp)	Gelling time(sec)	Drug content(%)
1	F1	63.25	2856	10	98.24
2.	F2	72.65	3492	11	96.54
3	F3	83.17	4936	9	97.21
4	F4	89.24	6871	9	98.26
5	F5	96.140	8924	8	98.34
6	F6	98.64	9356	12	98.12
7	F7	102.95	3598	8	97.14

8	F8	111.63	4368	11	97.23
9	F9	12278	5874	7	98.14
10	F10	136.52	8962	6	99.14
11	F11	73.47	10471	10	98.23
12	F12	86.24	12685	12	99.14
13	F13	93.45	4258	10	99.30
14	F14	97.18	5987	9	100.28
15	F15	105.61	8631	9	97.51
16	F16	115.73	10681	10	97.43
17	F17	122.63	12987	11	97.19
18	F18	138.52	14568	8	98.92

Table 4: Floating behavior

Formulation code	Floating lag time(secs)	Floationg log time (hrs)
F1	62	>12
F2	58	>12
F3	55	>12
F4	50	>12
F5	48	>12
F6	44	>12
F7	58	>12
F8	51	>12
F9	47	>12
F10	41	>12
F11	38	>12
F12	36	>12
F13	55	>12
F14	52	>12
F15	48	>12
F16	43	>12
F17	39	>12
F18	34	>12

Table 5: In-vitro gelling capacity

Formulation code	Gelling Capacity
F1	++
F2	++
F3	+++
F4	+++
F5	+++
F6	+++
F7	++
F8	++
F9	+++
F10	+++
F11	+++
F12	+++
F13	++
F14	++
F15	+++
F16	+++
F17	+++
F18	+++

Table 6: Physical Appearance and pH

Formulation code	pH
F1	**7.2**
F2	**7.3**

F3	**7.2**
F4	**6.8**
F5	**7.1**
F6	**7.2**
F7	**6.9**
F8	**7.0**
F9	**7.1**
F10	**7.2**
F11	**7.2**
F12	**7.1**
F13	**7.3**
F14	**7.2**
F15	**7.2**
F16	**7.4**
F17	**7.3**
F18	**7.2**

Table 7: Invitro drug release studies of Repaglinide formulations

Formulation code/Parameter	**F1(%)**	**F2(%)**	**F3(%)**	**F4(%)**	**F5(%)**	**F6(%)**	**F7(%)**	**F8(%)**	**F9(%)**	**F10(%)**	**F11(%)**
0.5 hr	58.24	52.34	48.25	43.96	38.25	36.22	52.62	48.17	44.10	34.32	33.36
1 hr	63.63	56.25	56.62	48.24	45.09	42.14	57.94	54.92	56.17	47.55	44.48
2 hr	72.21	73.64	68.55	54.17	56.10	49.71	64.63	62.17	63.15	56.24	57.62
3 hr	82.65	82.93	75.14	63.24	63.21	51.22	77.21	75.22	69.36	64.36	66.35
4 hr	96.64	86.25	82.36	72.55	74.55	56.14	96.56	87.14	78.66	73.26	75.17
5 hr		93.94	88.47	84.32	81.62	65.55	98.24	93.33	86.14	86.24	86.21
6 hr			99.17	89.17	86.17	70.01		96.22	92.63	88.22	89.88
7 hr				95.22	92.22	79.33		98.45	95.24	93.63	92.27
8 hr					96.17	86.07			98.56	98.45	94.61
9 hr						95.00					98.18
10 hr											
11 hr											
12 hr											

Formulation code/Parameter	**F12(%)**	**F13(%)**	**F14(%)**	**F15(%)**	**F16(%)**	**F17(%)**	**F18(%)**
0.5 hr	35.26	47.21	46.14	40.34	37.22	27.17	18.27
1hr	37.94	54.22	55.26	46.18	44.37	38.64	27.48
2 hr	46.55	63.63	64.61	54.17	53.61	48.26	39.22
3 hr	52.17	74.51	68.27	63.66	65.23	55.78	48.28
4 hr	58.27	85.14	74.10	68.19	67.57	64.94	56.54
5 hr	64.33	93.23	86.19	82.16	82.19	78.64	63.39
6 hr	72.22	98.27	93.47	87.14	88.95	83.22	70.67
7 hr	85.17		98.56	93.56	94.64	87.18	75.29
8 hr	88.16			98.18	96.37	91.26	82.17
9 hr	93.24				97.22	95.27	88.89
10 hr	96.18					98.56	92.36
11 hr	99.10						93
12 hr							98

5. References

[1] Rani K, Garg V, Sankar Goswami D: Formulation and evaluation of stomach specific in-situ gel of Ofloxacin using natural,synthetic polymers. World Journal of Pharmaceutical Research 2013, 2(3):631-645.

[2] Rajalakshmi R, Sireesha A, Subhash KV, Pavani P: Development and evaluation of a novel floating in-situ gelling system ofLevofloxacin hemihydrates. International Journal of Innovative Pharmaceutical Research 2011, 2(1):102-108.

[3] Dinesh MD, Shirkhedkar AA, Sanjay JS: Quantitative determination of Moxifloxacin HCl in bulk and ophthalmicsolution byUV-spectrophotometry and first order Derivative using

area under curve: Der Pharmacia Lettre 2011, 3(3):453-456.

[4] Sahu SK, Afzal Azamb Md, Sahu D, Banarjee M: Spectrophotometric Estimation of Moxifloxacin in Bulk and its PharmaceuticalFormulations. Pharmacology online 2011, 2:491-502.

[5] Kavin G, Joshi P, Shah M, Ramkishan A, Patel J: Formulation and evaluation of periodontal in-situ gel. International Journal ofPharmaceutical Investigation 2013, 3(1):29-41.

[6] Basavaraj K, Nanjwade, Manjappa AS, Murthy RSR, Yuvaraj DP: A Novel pH-Triggered *In situ* gel for sustained ophthalmic delivery of Ketorolac tromethamine. Asian Journal of Pharmaceutical Sciences 2009, 4(3):189-199.

[7] Sarrof R, Shikh A, Pawar Y, Kumbhar S: Sodium alginate based oral *In situ* floating gel of metformin HCl. Res J Pharm Bio Chem Sci 2012, 3(1): 890-897.

[8] Shashank NN, Bharani SS, Thakur RS: Formulation and evaluation of pH triggered In situ ophthalmic gel of Moxifloxacin HCl, Int J Pharm Sci, 4(2):452-459.

[9] Patel RP, Ladani R, Dadhaniya B, Prajapati BG: *In situ gel* delivery systems for chlordiazepoxide using artificial neural network. Int J Pharm Health Sci 2009, 1(1):10-22.

[10] Higuchi I: Analysis of data on the medicament release from ointments. J. Pharm.sci 1962, 51:802-4.

[11] Korsmeyer R, Gurny R, Doelker E, Buri P, Peppas N: Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm 1983, 15:25-35.

[12] Lemoine D, Wauters F, Bouchend S, Preat V, preparation and characterization of alginate microspheres containing a model antigen. J. Pharm. Sci 1998, 176:9-19.