Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6 suppl 2, 2014

Research Article

FORMULATION AND EVALUATION OFRANITIDINE HYDROCHLORIDEAS FLOATING IN SITU GEL

MILAD JAWAD HASAN, BALKIS AHMED KAMAL

College of pharmacy, University of Baghdad, Iraq. Email: melloda@yahoo.com

Received: 27 Nov 2013, Revised and Accepted: 03 Feb 2014

ABSTRACT

Gastro retentive floating in situ gel of ranitidine hydrochloride were formulated to increase the residence time in stomach and to sustain the release behavior of the drug that lead to increase drug bioavailability. Different formulations were prepared of sodium alginate alone and in combination with HPMC as a floating polymers besides to sodium bicarbonates gas generating agents. Sodium alginate-based in-situ gelling systems were prepared by dissolving various concentrations of sodium alginate in deionized water, to which varying concentrations of drug and sodium bicarbonate were added The results showed that the formulas which containing a combination of the polymers (sodiumalginate and HPMC) shows more retardation in drug release than formulas based only with sodium alginate at the same percentage. on the other hand increasing gas generating agent sodium bi carbonate (0.5, 1 ,1.5and 2%w/v) reduces floating lag time gelling integrity and increase floating duration .Mean while Sorbitol 2%w/v was added to the selected formula as sweetening agent, appear to decrease the viscosity of the gel with no significant effect on drug release. A stomach specific in-situ gel of Ranitidine hydrochloride could be prepared using floating mechanism to increase the residence time of the drug in stomach and thereby increase the absorption.

Keywords: Ranitidine hydrochloride, Gastric floating in situ gel, Sodium alginate, HPMC , NaHCO3

INTRODUCTION

In situ gel formulations offers an interesting alternative for achieving systemic drug effects of parenteral routes which can be in convenient or oral routs, which can result in unacceptable low bioavailability and passes the hepatic first pass metabolism , in particular of proteins and peptides[1].

Oral in situ gel forming system also known as stomach specific or raft forming systems have provided a suitable way of providing the controlled drug delivery within stomach with enhanced gastro-retention [2].

In this technique, a solution of low viscosity is used which on coming in contact with the gastric fluids, undergo change in polymeric conformation and a viscous gel of density lower than the gastric fluids is produced. This low density gel formation called as raft not only provide the much desired gastro retention to prolong the contact time, but also produce the continuous and slow drug release[3].

The sol-gel transition process is induced by the presence of divalent ions. Gelation was delayed until the orally administered solution reached the stomach by complexing the calcium with sodium citrate, then acidic environment of the stomach causes break down of the complex releasing free calcium ions and causing instantaneous gelation[4]Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system [5].

Floating in- situ gelling system is a promising potential in developing drug delivery system that prolongs the residence time of the formulation[6].

Ranitidine hydrochloride ishistamine H2-receptor antagonist that inhibits stomach production. It is commonly used in treatment of peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD)[7]. Ranitidine is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis[8]. The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of ranitidine 4 times a day. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 hours but not up to 10 hours. An alternative dose of 300 mg leads to plasma fluctuations; thus, a sustained-release dosage form of Ranitidine HCl is desirable [9].

The short biological half-life of the drug (~2.5-3 hours) also favors development of a sustained-release formulation[10]. A traditional oral sustained release formulation releases most of the drug at the colon; thus, the drug should have an absorption window either in the colon or throughout the gastrointestinal tract.

Ranitidine is absorbed in only the initial part of the small intestine and has 50% absolute bioavailability[11]. Moreover, colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon[12]. These properties of Ranitidine HCl do not favor the traditional approach to sustained-release delivery. Hence, clinically acceptable sustained release dosage forms of Ranitidine HCl prepared with conventional technology may not be successful.

The gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract.

MATERIALS AND METHODS

Ranitidinehydrochloride, sodium bi carbonate(Samara's drug industry-Iraq supplier).Sodium alginate, HPMC(Provizer pharma-India) Hydrochloric acid (Gainland chemical company (GCC). U.K.) Calcium chloride, sodium citrate, sorbitol(HI media lab- India),

Preparation of in situ gel:

Sodium alginate solution (table 1) of concentrations 1, 2, 3 and 4 % (w/v)prepared by adding the polymer to distilled water containing 0.5% (w/v) sodium citrate and 0.15% (w/v) calcium chloride,0.8%(w/v) HPMC and heating to 60^{o}C for sodium alginate .Then various amount of sodium bi carbonate and Ranitidine equivalent to 1.5% (w/v) was then dispersed in the resulting solution after cooling to below 40^{o}C [13, 14].

Gelation Property

Instantaneous gelation was checked by addition of the sols dropwise to simulated gastric fluid pH 1.2[15].Gelation was observed by visual examination.

The Effect of Different Concentrations of Calcium Chloride and Sodium Citrate on the Gelling Properties

F1-F9was selected to determine the optimum quantities of calcium chloride and sodium citrate that maintained fluidity of the formulation before administration and resulted in gelation when the formulation was added to simulated gastric fluid, in which sodium alginate sols 3%, (w/v) containing sodium citrate concentrations of 0.125, 0.25 and 0.50% (w/v) and calcium chloride

Table 1: The Composition of the Ranitidine HCL formulas

No.	Content					
	Ranitidine HCL	CACL2	Na Citrate	NaHCO3	Sodium alginate	HPMC
F1	1.5	0.075	0.125	0.5	3	0.8
F2	1.5	0.075	0.25	0.5	3	0.8
F3	1.5	0.075	0.5	0.5	3	0.8
F4	1.5	0.1	0.125	0.5	3	0.8
F5	1.5	0.1	0.25	0.5	3	0.8
F6	1.5	0.1	0.5	0.5	3	0.8
F7	1.5	0.15	0.125	0.5	3	0.8
F8	1.5	0.15	0.25	0.5	3	0.8
F9	1.5	0.15	0.5	0.5	3	0.8
F10	1.5	0.15	0.5	1	3	0.8
F11	1.5	0.15	0.5	1.5	3	0.8
F12	1.5	0.15	0.5	2	3	0.8
F13	1.5	0.15	0.5	0.5	1	0.0
F14	1.5	0.15	0.5	0.5	2	0.0
F15	1.5	0.15	0.5	0.5	3	0.0
F16	1.5	0.15	0.5	0.5	1	0.8
F17	1.5	0.15	0.5	0.5	2	0.8
F18	1.5	0.15	0.5	0.5	4	0.8

All the formulas contents are represented by(g/ml) concentrations of 0.075, 0.1 and 0.15 % (w/v) were added drop wise to 50 ml simulated gastric fluid (pH 1.2).

***In-vitro* buoyancy**

The *in-vitro* buoyancy study was performed using the USP dissolution apparatus II with 500 mL of simulated gastric fluid (pH = 1.2). The medium temperature was kept at 37° C . A 10 mL sample of the prepared solution (in-situ gelling formulation) was drawn up with the help of a disposable syringe and placed into a Petri dish. Then, the Petri dish was placed in the dissolution vessel containing the medium.

The time for the gel to come to surface (floating lag time) and the time the gel remained floated on the medium surface (floating time) were recorded[3, 16].in this study F9-F12 were selected to study the effect of different concentration of effervescent agent on floating lag time, floating duration.

Drug release tests

Drug release tests were done in 0.1N HCl to measure the rate and extent of RHCL release. The Paddle method was used in studying the release pattern of RHCL, and each experiment was done in triplicate. At predetermined time point, a sample of 5ml was withdrawn and immediately replaced with 5ml of dissolution medium to maintain a constant volume of 900ml, then the samples were filtered using a 0.45 mm filter and assayed for the amount of RHCL released up to 8hr at 315 nm using a spectrophotometer [17]

a) Effect of sodium alginate and its concentrations

Formulas, F13, F14, F15 and were used to study the effect of using sodium alginate polymer on release behavior of ranitidine hydrochloride.

b) Effect of combination of polymers (effect of using HPMC and sodium alginate) Formulas F9, F16, F17 and F18 were selected to study the effect of combination of HPMC with different concentration of sodium alginates on release profile of ranitidine hydrochloride.

RESULTS AND DISCUSSION

Gelling Property

In this study Ca^{+2}ions were included in all formulations for induction of gelation[18, 19]. However, for ease of administration the prepared formula must be introduced in a fluid (sol) state. This was achieved by addition ofsufficient sodium citrate to the formulation to form a complex with all of the Ca^{+2}ions present in the formulation and hence to effectively remove them from solution. Then, in the acidic environment of the stomach thecomplex is broken down and the Ca^{+2}ions released cause gelation to occur[20].Instantaneous gelation was observed by addition of the sols of sodium alginate and drop wise to simulated gastric fluid maintained at pH 1.2.

The Effect of Different Concentrations of Calcium Chloride and Sodium Citrate on the Gelling Properties

The results indicated that the minimum concentration that maintained fluidity of the sol before administration and caused gelation of sols in the gastric fluids was 0.5% (w/v) sodium citrate and 0.15% (w/v) calcium Chloride (F9). Moreover, gelation occurred without exposure to simulated gastric fluid pH 1.2 in formulations containing 0.075, 0.1 or 0.15% (w/v) CaCl2 and sodium citrate concentration of 0.125%(F1,F4and F7) (w/v) as shown in table(2).

In vitro Buoyancy study

Sodium bicarbonate was used as a gas-generating agent in order to float the gel [21].the sodium bicarbonate induces CO2 in the presence of acidic dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the formed gel below 1 gm/ml.

Effect of Different concentration of NaHCO3

The floating ability of prepared formulation was studied in simulated gastric fluid (pH 1.2)where the floating lag time and floating duration shown in(table 3) From the results of floating behavior studies, it was found that as the concentration of effervescent mixture increase, the floating lag time and gel integrity decreased, floating duration increase and vice versa. all the solutions were found to gel spontaneously oncontact with the 0.1 N HCl,for NaHCO3 concentrations 0.5%(F9) , the formedformed gels remained intact leaving a clear test medium,at1% NaHCO3(F10)the formed gels are soft, but still leaving a clear test medium.

At NaHCO3 concentrations 1.5% (F11), the formed gels floated immediately but they were divided due to the high concentration of the CO2 produced, leaving turbid solutions below. Such weak gels are not suitable as oral liquid formulations, as they will be removed earlier from the stomach by peristaltic movements. increase the concentration more than 2%(F12) no significant results were observed. Thus, 0.5% was selected as the optimum NaHCO3 concentration for forming gel with sodium alginate polymer.

a) Effect of sodium alginate and its concentrations:

in vitro release profile of different concentration of sodium alginate sols loaded with1.5% RHCL are shown in(figure 1) the results showrapid release from alginate solutions at concentaration 1%, with almost 100%of the drug released within 5hr. In acidic medium, sodium alginate converts rapidly to insoluble alginic acid, which swells upon hydration. some dissolution of the polymer occur due to a temporary rise in pH within the hydrating polymer as a result of the intrinsic buffering capacity of sodium alginate. This results in an intact but relatively porous, rubbery texture [22]. This porous structure enables solute egress and explains the rapid release of the drug. As sodium alginate amountincrease from 1%w/v to2%w/v and then to 3%w/v a change decrease in the rate and extent of drug release was observed with the increase in polymer concentration and is attributed to increase in the density of the polymer matrix and also an increase in the diffusional path length which the drug molecules have to traverse

Table 2: The effect of different concentrations of sodium citrate and calcium chloride on the gelationproperties of sodium alginate 3% (w/v) sols before and after addition to gastric fluid.

No. of formula	Cacl2 g/100ml	Na citrateg/100ml	Gel property
F1	0.075	0.125	Gel before administration
F2	0.075	0.25	Sol before administration &weak gel after administration
F3	0.075	0.5	Sol before administration &weak gel after administration
F4	0.10	0.125	Gel before administration
F5	0.10	0.25	Sol before administration low gel strength after administration
F6	0.10	0.5	Sol before administration low gel strength after administration
F7	0.15	0.125	Gel before administration
F8	0.15	0.25	Gel before administration
F9	0.15	0.5	Sol before administration& optimum gel strength after administration(stiff gel)

Table 3: effect of sodium bicarbonate concentration on the some of physical properties of Ranitidine HCL floating in situ gel

No. of formula	NaHCO3 (g/100ml)	Buoyancy Lag Time	Total Floating time	Gel property
F9	0.5	1-2min.	>12hr	Intact gels
F10	1.0	<1min	>12hr	softgels
F11	1.5	0 time	>24hr	dividedgels
F12	2.0	0 time	>24hr	dividedgels

Dissolution Behavior of ranitidine HCL from insitu gel (in vitro release)

b) Effect of combination polymer

The effect of combination polymers on RHCL release are shown in (figure2and 3). sustained release over a long period cannot be expected from hydro gels because the release from hydro gels is generally diffusion-controlled, with rapid passage through hydro gels due to their loose network structure; therefore a combination with another polymer was used to improve the formula characteristics[23] .in this study HPMC add to all formulation to further sustain release of drug ,HPMC act as a release retardant[24] and as viscosity enhancing agent[25].it was observed that the formulations containing combination of polymers shows more retardation in drug release at same concentration compared to sodium alginate alone. This indicates that combinations of polymers are more efficient in formulating the sustained release dosage form.

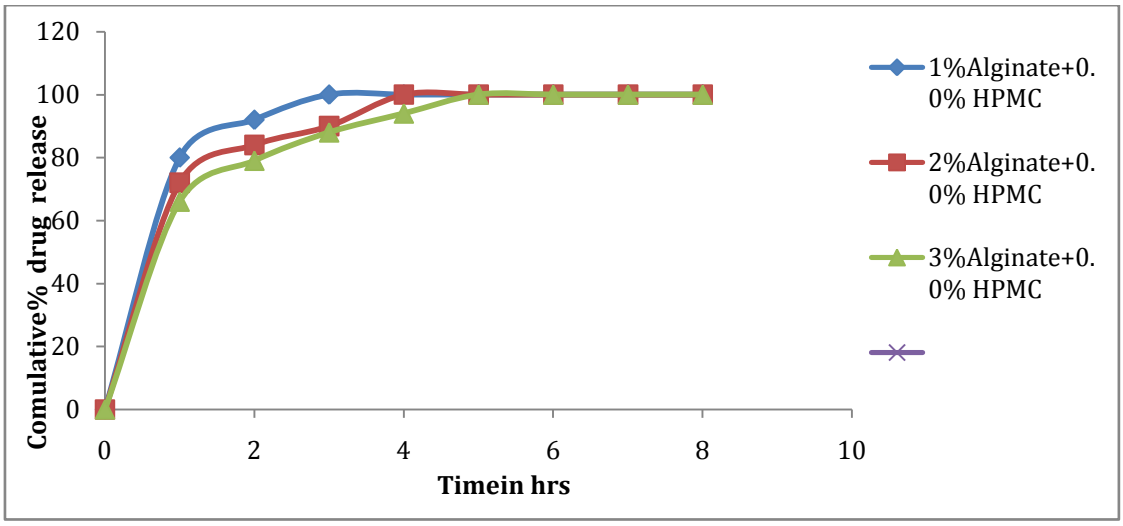

Fig. 1: *In vitro* dissolution profile of RHCL from various concentration alginate floating in situ gel.

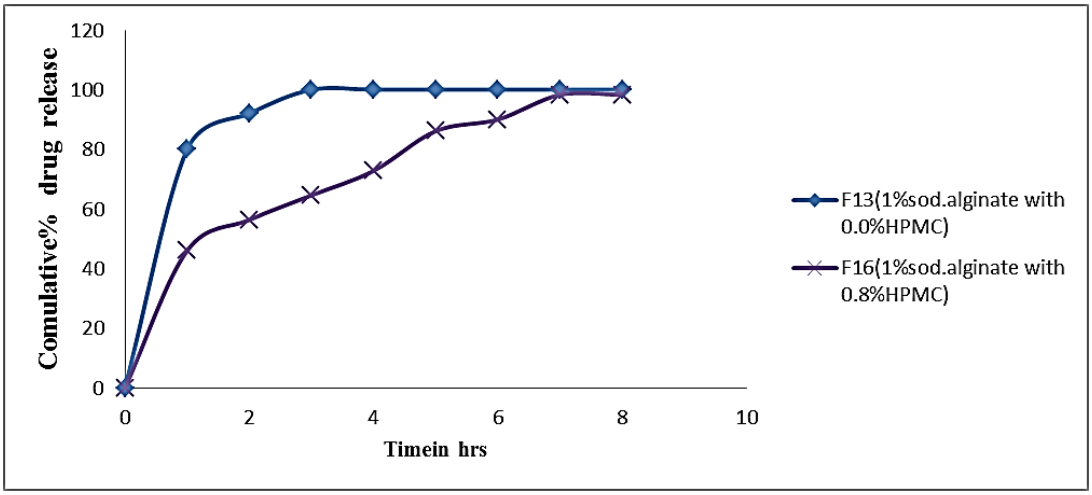

Fig. 2: Effect of combination of 1% sodium alginate with 0.8% HPMC

From above result formula that contain 4% sodium alginate and 0.8% HPMC(F18) show less cumulative percent drug release and so selected as best formula for further study. To selected formula 2%w/v) sorbitol added for improvement of the taste and stability of formulation[26] And it was found that the viscosity of selected formula change(reduced) with no significant effect in drug release this could be due to hydrogen bonding of sorbitol with polymer chain [27],the change in viscosity resulting from sorbitol addition at all shear rate, since it is hygroscopic and may withdraw water from gel structure that decrease viscosity and so improving the ease of swelling of sols[28].

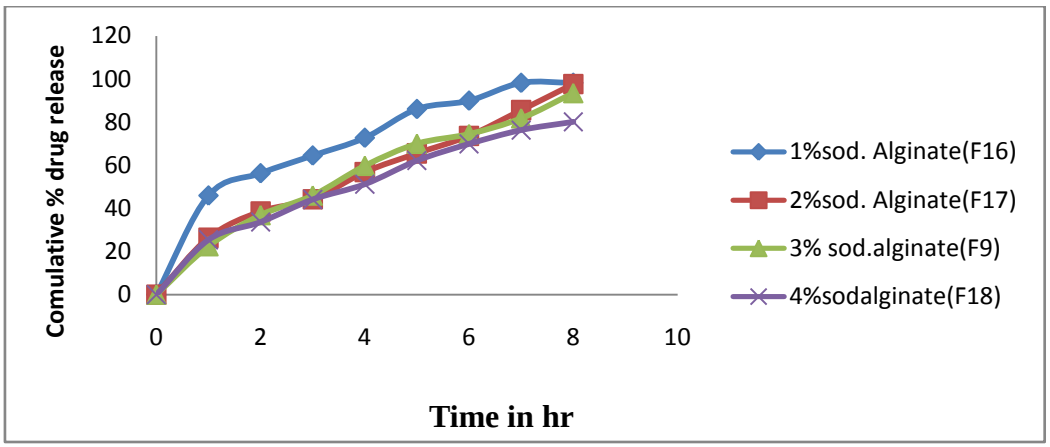

Fig. 3: Effect of adding HPMC with different concentration of sodium alginate on dissolution profile

CONCLUSION

- Based on the results obtained, the optimum concentration of calcium chloride was 0.15% (w/v) and sodium citrate was 0.5% (w/v) for in situ gelling formulations of ranitidine hydrochloride.
- Sodium bicarbonate was used as gas generating agent,the optimum concentration of Sodium bicarbonate that maintain good gelling property and short lag time and long floating duration was 0.5%w/v
- HPMC add to all formulation to further sustain release of drug ,act as a release retardantand as viscosity enhancing agent.
- The formulated in situ gel for Ranitidine HCl was found to be easier and simpler, to produce stable in situ gel. It was found to have better floating efficacy and in vitro release profile characteristics. Hence it may represent as a new alternative, natural easier and formulation of Ranitidine which may improve the patient compliance.

REFERENCES

1. Liu, Z., et al., Study of An Alginate/HPMC-based in situ Gelling Ophthalmic Delivery System for Gatifloxacin. International Journal of Pharmaceutics, 2006. **315**(1–2): p. 12-17.
2. Kishor K. Bhalerao , M.S.K., Pravin P. Aute, Sandeep M. Dange, Rohini P. Chavan, Krunal K. Vaidya, Sanket B. Munot, Pravin D. Chaudhari., A short Review on Stomach Specific Floating in-situ gel. Journal of Biomedical and Pharmaceutical Research 2012. **1**(3): p. 01-04.
3. Jayvadan K. Patel , J.R.C., Moin K. Modasiya, Floating In Situ Gel based on Alginate s Carrier for Stomach-Spesific Drug Delivery of Famotidine. international Journal of Pharmaceutical Sciences and Nanotechnology, 2010. **3**(3): p. 1092-1104.
4. Tang, J., M.A. Tung, and Y. Zeng, Gelling Properties of Gellan Solutions Containing Monovalent and Divalent Cations. Journal of Food Science, 1997. **62**(4): p. 688-712.
5. Sharma, N., D. Agarwal, M.K. Gupta andM.P. Khinchi, A Comprehensive Review on Floating Drug Delivery System. international Journal of Research in Pharmaceutical and Biomedical Sciences, 2011. **2**(2): p. 428-441.
6. Rajinikanth PS, B.J.a.M.B.f.e.o.H.p., Development and Evaluation of A Novel in-situ gelling System of Amoxicillin. Int. J. Pharm, (2007). **335**: p. 114-122.
7. R Shireesh Kiran, B.C.S., B Nagendra Babu, Ranitidine HCl Gastroretentive Floating Tablets based on Hydrophilic Polymers. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2010. **1**(4): p. 964- 976.

8. Brijesh S. Dave, A.F.A., and Madhabhai M. Patel, Gastroretentive Drug Delivery System of Ranitidine Hydrochloride:Formulation and In Vitro Evaluation. AAPS PharmSciTech, 2004. **5**(2): p. 1-6.
9. Dumpeti Janardhan, M.L., Chinnala Krishna Mohan and Vobalaboina Venkateswarlu, Formulation and In vitru Evaluation of Gastroretentive Drug Delivery System For Rhanitidine Hydrochloide. Intenational journal of pharmaceutical science and nanotechnology, 2008. **1**: p. 3.
10. Kumar Darapu B.N , K.S.a.T.V., Formulation and in-vitro Evaluation of Gastroretentive Floating Microspheres of Rantidine Hydrochloride. An International Journal of Advances In Pharmaceutical Sciences, 2010. **1**(2): p. 298-306.
11. V. S. Patil , P.D.G., V. H. Bankar and S. P. Pawar Formulation and Evaluation of Floating Matrix Tablet of Locally Acting H2-Antagonist. International Journal Of Pharmacy&Technolog y 2010. **2**(3): p. 528-540
12. J. A. Raval, J.K.P., Naihong Li, M. M. Patel, Ranitidine hydrochloride Floating Matrix Tablets based on Low Density Powder: Effects of Formulation and Processing Parameters on Drug Release. Asian Journal of Pharmaceutical Sciences 2007. **2**(4): p. 130-142
13. Miyazaki, S., et al., Comparison of in situ gelling Formulations for the Oral Delivery of Cimetidine. International Journal of Pharmaceutics, 2001. **220**(1–2): p. 161-168.
14. Miyazaki, S., W. Kubo, and D. Attwood, Oral Sustained Delivery of Theophylline Using in-situ gelation of Sodium Alginate. Journal of Controlled Release, 2000. **67**(2–3): p. 275-280.
15. Kubo W, M.S., Dairaku M, Togashi M, Mikami R, Attwood D., Oral Sustained Delivery of Ambroxol From in situ-gelling Pectin Formulations. Int J Pharm, 2004. **271.**(1-2): p. 233-240.
16. Vinay Wamorkar, M.M.V., Manjunath SY, Formulation and Evaluation of Stomach Specific In-Situ Gel of Metoclopramide Using Natural, Bio-Degradable Polymers. International Journal of Research in Pharmaceutical and Biomedical Sciences 2011. **2**(1): p. 193-201.
17. Rajinikanth, P.S., J. Balasubramaniam, and B. Mishra, Development and Evaluation of A Novel Floating in situ gelling System of Amoxicillin for Eradication of Helicobacter pylori. International Journal of Pharmaceutics, 2007. **335**(1–2): p. 114-122.
18. Michel Audebrand, C.G., Max Kolb, Monique A.V. Axelos, Gelation of Pectin-Alginate Mixture :Ultrastructure and Rheological Properties. International Symposium on Food Rheology and Structure: p. 517-518.
19. Durand, D., et al., Calcium-induced Gelation of Low Methoxy Pectin Solutions — Thermodynamic and Rheological Considerations. International Journal of Biological Macromolecules, 1990. **12**(1): p. 14-18.
20. Rishad R. Jivania, C.N.P., Dashrath M. Patelb and Nurudin P. Jivani, Development of a Novel Floating In-situ Gelling System for Stomach Specific Drug Delivery of the Narrow Absorption Window Drug Baclofen. Iranian Journal of Pharmaceutical Research, 2010. **9** (4): p. 359-368.
21. Baumgarter, S., Kristl, J., Vrecer, F., Vodopivec, P., Zorko, B.,, Optimisation of Floating Matrix Tablets and Evaluation of Their Gastric Residence Time. International Journal of Pharmaceutics, 2000. **195**(1–2): p. 125-135.
22. Hodsdon, A.C., et al., Structure and Behaviour in Hydrophilic Matrix Sustained Release Dosage Forms: 3. The Influence of pH on the Sustained-release Performance and Internal Gel Structure of Sodium Alginate Matrices. Journal of Controlled Release, 1995. **33**(1): p. 143-152.
23. Ikada Y, T.Y., Protein Release From Gelatin Matrices. Adv Drug Deliv Rev. , 1988. **31**(3): p. 287-301.
24. Rakesh P. Patel, R.L., Binal Dadhaniya and B. G. Prajapati, In situ gel Delivery Systems for Chlordiazapoxide using. Int. J. Pharm. Health Sci.,. **Vol 1** (1): p. 10-22.
25. Basavaraj K. Nanjwade , M.A.S. and Y.D.P. Murthy R.S.Rb, A novel pH-triggered in-situ gel for Sustained Ophthalmic Delivery of Ketorolac tromethamine. Asian Journal of Pharmaceutical Sciences, 2009. **4**(3): p. 189-199.
26. osmond J.D Cruz, P.S., and Faith M .Uckun, Conceival A Novel Non Contracepptive Vaginal Vehical for Lipophilic Microbicides. AAPS PharmSciTech, 2004. **6**(1): p. 1-9 Artical 11.
27. Miyazaki, S., et al., The Effect of Taste Masking Agents on in situ gelling Pectin Formulations For oral Sustained Delivery of Paracetamol and Ambroxol. International Journal of Pharmaceutics, 2005. **297**(1–2): p. 38-49.
28. Sweetman, S.C. and F. BPharm, The Complete Drug Reference. Thirty-sixth ed. Vol. 1 p1965. 2009.