

IN-SITU GELLING SYSTEM – POTENTIAL TOOL FOR IMPROVING THERAPEUTIC EFFECTS OF DRUGS

RAMYA DEVI D*, ABHIRAMI M, BRINDHA R, GOMATHI S AND VEDHA HARI B N

Department of Pharmaceutical Technology, School of Chemical and Biotechnology, SASTRA University, Thanjavur-613 401. Tamil Nadu, India.
Email: *ramya@scbt.sastra.edu

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ABSTRACT

In-situ forming polymeric gelling systems has become prominent among novel drug delivery system (NDDS) in recent years due to advantages such as sustained and prolonged drug action, improved patient compliance and reduced frequency of administration of the drug in comparison to conventional drug delivery system (DDS). This is a type of mucoadhesive DDS where the polymeric formulation is in sol form before administration and once comes in contact with body fluids; it undergoes gelation to form a gel. Use of various natural, biocompatible, biodegradable as well as water soluble polymers such as chitosan, glycolic acid, poly-caprolactone, gellan gum, xyloglucan, poly-D,L-lactic acid, pluronic F127, carbopol, poly-D, L-lactide-co-glycolide and pectin makes this DDS more acceptable. *In-situ* gels can be fabricated by various methods in combination with different drugs and polymers for both local and systemic therapy where each drug shows its own therapeutic effects at the targeted site of action. This review presents the current developments and importance of various drugs formulated as *in-situ* polymeric gelling systems and its corresponding improvement in therapeutic effects.

Keywords: *In-situ* gel, Pluronic, Carbopol, β -cyclodextrin, Celecoxib.

INTRODUCTION

In-situ is a Latin word which means 'In its original place or in position'. There are many mechanisms which triggers the formulation of *in-situ* gels such as solvent exchange, ultra violet irradiation, ionic cross linkage, temperature modification, pH change and ionization. Studies are performed through various routes like oral, rectal, ocular, injectable, vaginal, nasal, parental and intraperitoneal. With the increased demand in techniques and recent developments in the field of polymer sciences various stimuli sensitive hydrogels like pH and temperature sensitive hydrogels are developed, which are used as chemotherapeutic agents to tumour regions. Prolonged and sustained release of the drug, reproducible, excellent stability, biocompatible and accurate quantities of administration makes the *in-situ* gel system more reliable. *In-situ* gel formulation applied for targeted delivery via ophthalmic, rectal, vaginal, nasal mucosa avoids the hepatic first-pass metabolism, especially for the proteins and peptides [1].

Enormous research works are being carried out for various category of drug, to prove the significance of *in-situ* gelling systems. This review paper highlights on the contribution of various researchers worked on the different *in-situ* gelling polymers, to improve the therapeutic effect of drugs. The categories of drugs discussed here includes anti-microbial, anti-tumour, anti-glaucoma, anti-asthma, anti-ulcer, anti-diabetic and drugs used for CNS disorders.

Anti-microbial effects

A range of the drugs with antimicrobial effects such as Ciproflaxin, Amoxillin, Linezolid, etc., have been investigated by various scientists through different routes of *in-situ* gelling action, employing various biodegradable polymers. These systems were identified with improved drug targeting, sustained drug release and enhanced bioavailability. The polymers used and their significant results are shown in table 1.

Table 1: List of Anti-microbial drugs developed as *in-situ* gel drug delivery system

S. No.	Drugs	Polymer	Route	Result
1.	Ciproflaxin	Carbopol 940P, pluronicF-127, gellan gum, 1.5% HPMC	Ophthalmic	Drug release for about 6 h [2]
2.	Amoxillin	Sodium alginate, calcium chloride, sodium bicarbonate, sodium citrate, HPMC-K100	Incorporated directly to stomach	Drug release was found to be 6 to 10 h [3]
3.	Linezolid	Hydroxyl propyl guar, hydroxy ethyl cellulose, carbopol, sodium alginate, xanthum	Ocular	Sustained release over a period of about 6 h [4]
4.	Itraconazole	Poloxamer 407, 188, HPMC	Vaginal	Improved treatment of vaginal candidiasis [5]
5.	Gatifloxacin	Sodium alginate, HPMC	Ocular	Sustained drug release of about 8 h [6]
6.	Clotrimazole	Carbopol 934P, gellan gum, HPMC	Oral	Zero order release kinetics with the sustained release for 8 h [7]
7.	Doxycycline hyclate	Poloxamer 188, gellan gum, HPMC, sodium alginate	Ocular	Controlled release for about 24 h [8]
8.	Moxifloxacin hydrochloride	HPMC, sodium alginate	Ocular	Drug release for about 10 h [9]
9.	Metronidazole	Pluronic F68, F127	Vaginal	Treats bacterial vaginosis [10]
10.	Sesbania grandiflora	Pluronic F127, chitosan	—	An increase in the viscosity at a temperature of about 37°C to form gel and provide sustained release [11]
11.	Ofloxacin	Carbopol, HPMC	Ophthalmic	Sustained release for a period for 8 h [12]
12.	Levofloxacin	Gelrite	Ophthalmic	Drug release of about 90.2% [13]

Anti-tumour effect

An ophthalmic *in-situ* gelling formulation of 5-Fluorouracil with the polymers sodium alginate and poly lactic acid (PLA) made as nanoparticles for the treatment of conjunctival squamous cell carcinoma. The Nanoparticles with gel matrix-embedded drug showed increased retention time due to the higher 5-Fluorouracil level in aqueous humour [14]. An injectable mucoadhesive *in-situ* gel of Paclitaxel was designed with chitosan and glycerol monooleate. This formulation resulted in a sustained drug delivery and drug targeting [15].

In-situ gel for rectal administration of Oxaliptalin with Pluronic-poly(acrylic acid)(PAA) polymer was formulated for treating colorectal cancer where pluronic and PAA were proved to be non-

toxic. The formulation showed increased C_{max} and higher AUC (0 to 12 h) than the orally administered dosage form [16]. Anti-tumour efficacy and sustained release behaviour was obtained when Doxorubicin hydrochloride was encapsulated with graphene oxide [17]. An ophthalmic delivery of Matrine with alginate, gelrite, gelrite/ alginate was formulated which was found to have enhanced ocular retention [18].

Anti-inflammatory effects

Certain anti-inflammatory drugs like Radix bupleri, Diclofenac sodium, Curcumin, etc., were used in formulating *in-situ* gels by various methods. Different routes has been chosen for delivery of these drugs to show the improvement in their activity and bioavailability which are shown in table 2.

Table 2: Anti-inflammatory drugs formulated as *in-situ* gelling system

S. No.	Drug	Polymer	Route	Result
1.	Radix bupleri	Gellan gum	Nasal	The <i>in-situ</i> gel had a greater effect (longer anti pyretic effect) than the <i>in-situ</i> solution [19].
2.	Diclofenac sodium	Carbopol, sodium alginate, HPMC	Ophthalmic	Drug release prolonged for 8 h [20].
3.	Curcumin	Capryol 90, solutol HS15, transcitol HP	Nasal	Direct drug transport of nose-to-brain is better in nasal route than intravenous route [21].
4.	Bupivacaine hydrochloride	Poly(D,Llactide), poly(D,L-lactide-co-glycolide)(PLGA)	Parenteral	Prolonged analgesic effect of the drug in gel condition [22].
5.	Ketorolac tromethamine	Methyl cellulose	Ophthalmic	Gelation tempature at 32°C and sustained drug release upto 9 h [23].
6.	Acetomenophen	Polycarbophil, polaxamer F188, 407	Rectal	<i>In-situ</i> gelling liquid suppository and mucoadhesive gels found to be more effective and convenient method for rectal delivery [24].
7.	Indomethacine	Gelrite	Ocular	Drug release upto 8 h [25].
8.	Nimesulide	Sodium alginate, polaxamer, Poly Ethylene Glycol , HPMC	Rectal	Addition of PEG resulted in satisfactory drug release rate and rectal retention [26].
9.	Paracetamol	Xyloglucan	Oral	Over a period of 6 h diffusion-controlled drug release was found [27].

Anti-glaucoma effect

Ocular delivery of Timolol maleate with carbopol and chitosan showed sustained release behaviour over period of 24 h [28]. For treating glaucoma an ophthalmic administration system of S(-)-Satriptene along with formic acid, acetonitrile and phemotolamine was developed. After instillation, within 1 h the bio availability of S(-)-Satriptene in aqueous humor increased to the maximum level with C_{max} of $1.508 \pm 0.297 \text{ gml}^{-1}$. This *in-situ* gel formulation exhibited 3.2 fold greater C_{max} and 2.2 fold greater $AUC_{0-3 \text{ h}}$ ($p < 0.05$) [29].

Pilocarpine, used in the treatment of glaucoma, formulated with xyloglucan and pluronic F127 showed a sustained drug release of about 6 h. Here, the ratio of xyloglucan to pluronic was about 1.5%:25% (w/w) [30]. *In-vitro* release study of Forskolin, an anti-glaucoma agent with poloxamer showed efficient release of drug for more than the period of 5 h when administered ocularly. *In-vivo* results indicated that intra-ocular pressure lowering efficacy of the gel was about 31% for 12 h where as only 18% observed in eye suspension [31]. For treating precorneal loss, an ophthalmic administration of Dexamethasone with gellan gum was used which resulted in the sustained drug release upto 7 h [32].

Drugs for chronic diseases

In-situ gel for rectal administration of Meveberine hydrochloride was formulated with hydroxyl propyl methylcellulose (HPMC), methyl cellulose, polyvinyl pyrrolidone and poloxamer188/407 for treating irritable bowel syndrome. *Ex-vivo* antispasmodic activity was studied and compared with the conventional drug. Sustained release of drug for 8 h is observed for the gels [33]. Nasal administration of *in-situ* gel of Scopolamine hydrobromide along with gellan gum was used to treat motion sickness. The symptoms of motion sickness were decreased by nasal administration of 100 µg/kg of Scopolamine hydrobromide [34].

Drugs for CNS disorder

Central Nervous System disorders are categorized into various types which include alzheimers disease, cerebral malaria, schizophrenia, migrane, etc., and they are treated with drugs obtained from natural and synthetic sources. The detailed description of different *in-situ* gelling formulations of drugs using novel polymers for treating various disorders is shown in table 3.

Table 3: Drugs for CNS disorders formulated as *in-situ* gelling system

S. No.	Drug	Polymer	Diseases	Result
1.	Rivastigmine	N-stearoyl L-alanine methyl ester (SAM)	Alzheimers disease	Drug with SAM showed a prolonged therapeutic efficacy for 11 days [35].
2.	Artemether	Pluronic, hydroxyl propyl β-cyclodextrin, HPMC	Cerebral malaria	Better stability for 90 days [36].
3.	Huperazine A	Triethanol amine and chloral hydrate	Alzheimers disease	The AUC brain 0 to 6 h/AUC plasma 0 to 6 h was found to be ($p < 0.05$) 96.5% [37]
4.	Midazolam hydrochloride	Pluronic F127, carbopol 934P and HPMC	Epileptic seizure	Increased bioavailability of the drug is obtained in the <i>in-situ</i> formulation [38]
5.	Eletriptan hydrobromide	Poloxamer 407(17%), carbopol 934 (0.3%)	Migraine and head ache	Increased bioavailability of about 86.27% was obtained and permeation rate was found to be more (480 min) [39]
6.	Sumatriptan succinate	Pluronic F127, carbopol 974	Headache and migraine.	Controlled drug release with higher permeability rate of 250 min [40]

Anti-ulcer drugs

Oral administration of Famotidine was formulated with calcium chloride and sodium alginate resulted in extraordinary formation of gel in stomach region and sustained the release of drug [41]. Similarly, oral administration of the drug Cimetidine with gellan gum, sodium alginate and xyloglucan was also used for treating ulcer. In release studies each formulation followed time dependent drug release kinetics for a period of 6 h [42].

Anti-diabetic drugs

To treat diabetes and to remove toxins, *in-situ* gel of Paracetamol and Ambroxol was formulated with pectin. The bioavailabilities of these drugs when released from gels formulated at the two pH limits didn't show any notable difference. This signifies that in the fasting state the normal variations of gastric acidity did not affect the bioavailability of these drugs. An ocular delivery of Ambroxol *in-situ* gel was formulated with the polymers pectin, sorbital, polyhydric acid. Sustained release was obtained with pectin (1 or 1.5%) and sorbitol (10%) [43].

Drugs to treat asthma

An oral administration of Theophylline *in-situ* gel was formulated with sodium alginate and 2-1% w/v concentration of alginate to treat asthma. When administered in rats, it showed increased bioavailability of the drug [44]. Salbutamol sulphate *in-situ* gel was formulated with carbopol 934P, HPMC to treat chronic diseases. The optimized formulation containing 0.25% Salbutamol sulphate, 0.4% carbopol, 1% HPMC, 0.9% NaCl, 0.02% benzalkonium chloride, 0.1% sodium metabisulphate showed a sustained drug release for 8 h [45].

Other category of drugs

Ocular administration of the anti-hypertensive drug Diltiazem hydrochloride as floating *in-situ* gel was formulated with HPMC, sodium alginate, calcium chloride, sodium methyl paraben. Formulation containing Diltiazem HCl-300 mg, HPMC-0.5%w/v, sodium alginate-2.5% w/v, calcium carbonate-2%w/v and sodium methyl paraben-180 mg showed significant floating efficacy. Thus, the optimized formulation *in-situ* gel proved to be an alternate for conventional dosage form [46].

Prilocaine hydrochloride, which is used as an anaesthetic for dental administration, was formulated as *in-situ* gel with the polymers chitosan and HPMC. This formulation showed good gelation at pH 7.4 [47]. Metoclopramide hydrochloride *in-situ* gel was formulated with polymers guar gum, sodium alginate and calcium carbonate which produced a better anti-emetic effect in the stomach. Release of drug content from this formulation was observed upto 8 h which showed that guar gum is responsible for controlled release of drug for longer period than sodium alginate due to its viscous nature [48].

An *in-situ* oral formulation of the drug Dexomethorphan, an anti-tussive agent was formulated along with sodium citrate, calcium chloride, sodium alginate and chitosan. The release pattern of this formulation in both the intestinal and gastric condition showed sustained release [49]. Ophthalmic *in-situ* gelling system of the drug Peurarin, an anti-angiogenic agent with the polymers Polaxamer 407,188 and carbopol was formulated which showed diffusion-controlled *in-vitro* drug release for about 8 h [50]. More recently, the fourth generation fluoroquinolone antibiotic Moxifloxacin was successfully developed as ophthalmic *in-situ* gel for commercial applications, to overcome the drawbacks associated with its eye drops. [51] The specific relevance of *in-situ* gelling system for ophthalmic delivery of various drugs has been extensively studied in this field [52].

CONCLUSION

Each drug having its own therapeutic effects can be administered through various routes as *in-situ* gels. These gels are more capable of sustained release and hence used widely nowadays. *In-situ* gelling systems have transformed as conventional drug delivery systems because of its controlled delivery and convenient application. *In-situ* gel dosage forms are very reliable due to sustained and prolonged

drug release and good stability. The contact time of the drug in the target should be longer to increase the efficacy of the drug which will lengthen the residence time of the gel along with improved systemic absorption and trim down the need for frequent administration leading to enhanced patient compliance.

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REFERENCES

1. Nirmal HB, Bakliwal S, Pawar SP. In-Situ gel: New trends in Controlled and Sustained Drug Delivery System. Int J Pharm Tech Res 2010; 2: 1398-1408
2. Eaga CM, Jagan MK, Venkatesham A. Preparation and evaluation of *in-situ* gels for ocular drug delivery. J Pharm Res 2009; 2: 1089-1094.
3. Dasharath MP, Divyesh KP, Chhagan NP. Formulation and evaluation of floating oral *in-situ* gelling. International Scholarly Research Network, 2011.
4. Shivanand SP, Fatima SD, Abidabegum N, Vilas GJ, Jameel SM, Sreenivas SA, et al. Formulation and evaluation of a novel *in-situ* gum based ophthalmic drug delivery system of Linezolid. Scientia Pharmaceutia 2008; 76: 515-532.
5. Sinem YK, Seda R, Zeynep AS, Esra B. A new *in-situ* gel formulation of Itraconazole for vaginal administration. J Pharm Pharmacol 2012; 3: 417-426
6. Doijad RC, Manvi FV, Malleswaran Rao VSN, Prajakta A. Sustained ophthalmic delivery of Gatifloxacin from *in-situ* gelling system. Indian J Pharm Sci 2006; 68: 814-818.
7. Harish NM, Prabhu P, Charlu RN, Subramanyam EVS. Formulation and evaluation of *in-situ* gel containing Clotrimazole for oral candidiasis, J Pharm Sci 2012; 4: 1885-1889.
8. Rahul N, Venkatakrisnakiran P, Dhanalakshmi P, Prasannaraju Y. Formulation and evaluation of *in-situ* gelling systems for ocular delivery of Doxycycline hyclate. Journal of Innovative Trends of Pharmaceutical Science 2012; 3: 1-7.
9. Sonjoy KM, Thimmasetty GL, Prabhu S, Geetha MS. Formulation and evaluation of an *in-situ* gel forming ophthalmic formulation of Moxifloxacin hydrochloride. Int J Pharma Investig 2012; 2: 2.
10. El-sayed AI, Sayed I, Gihan F, Omar S, Khaled H, Noura HA. Development and characterization of thermosensitive pluronic-based Metronidazole *in-situ* gelling formulations for vaginal application. Acta Pharm 2012; 62: 59-70.
11. Wagh VD, Deshmukh KH, Wagh KV. Formulation and evaluation of *in-situ* gel drug delivery system of Sesbania grandiflora flower extract for the treatment of bacterial conjunctivitis. J Pharm Res 2012; 4: 1880-1884.
12. Srividya B, Cardoza RM, Amin. Sustained ophthalmic delivery of Ofloxacin from a pH triggered *in-situ* gelling system. J controlled release 2001; 73: 205-211.
13. Kavitha K, Rajas NJ. Sustained ophthalmic delivery of Levofloxacin hemihydrate from an ion activated *in-situ* gelling system. Int J Pharm Tech Res 2011; 3: 702-706.
14. Ramesh CN, Rakesh K, Dhanawat M, Pandit JK. Modified PLA nano *in-situ* gel: A potential ophthalmic drug delivery system. Colloids and Surfaces B: Biointerfaces 2011; 86: 28-34.
15. Saurabh J, Alekha KD. A Mucoadhesive *in-situ* gel delivery system for Paclitaxel. AAPS Pharm SciTech 2006; 7: 2.
16. Lin HR, Tseng CC, Lin YJ, Ling MH. A novel *in-situ* gelling liquid suppository for site-targeting delivery of anti-colorectal cancer drugs. J Biomater Sci Polym Ed 2012; 23: 807-822.
17. Dong M, Jiantao L, Yuyun C, Wei X, Li-Ming Z. *In-situ* gelation and sustained release of an antitumor drug by graphene oxide nanosheets. Carbon 2012; 50: 3001-3007.
18. Yuejiang L, Jinpeng L, Xiaolin Z, Ruodan Z, Yongliang H, Chunjie Wu. *In-situ* gelling gelrite/alginate formulations as vehicles for ophthalmic drug delivery. AAPS Pharm Sci Tech 2012; 11: 2.
19. Shi-Lei C, En C, Qi-Zhi Z, Xin-Guo J. A novel nasal delivery system of a chinese traditional medicine, Radix Bupleuri, based on the concept of ion-activated *in-situ* gel. Arch Pharm Res 2007; 30: 8.

20. Padma PJ, Karthika K, Rekha NR, Khalid E. Formulation and evaluation of *in-situ* ophthalmic gels of Diclofenac sodium. J Chem Pharm Res 2010; 2: 528-535.
21. Wang S, Chen P, Zhang L, Yang C, Zhai G. Formulation and evaluation of microemulsion-based *in-situ* ion-sensitive gelling systems for intranasal administration of Curcumin. J Drug Targeting 2012; 20: 831-840.
22. Heiko K, Erol Y, Gayle AB, Roland B. *In-vitro* and *in-vivo* drug release from a novel *in-situ* forming drug delivery system. Pharm Res 2008; 25: 6.
23. Bain MK, Bhowmik M, Ghosh SN, Chattopadhyay D. *In-situ* fast gelling formulation of methyl cellulose for *in-vitro* ophthalmic controlled delivery of Ketorolac Tromethamine. J Appl Polym Sci 2009; 113: 1241-1246.
24. Choi HG, Oh YK, Kim CK. *In-situ* gelling and mucoadhesive liquid suppository containing Acetaminophen: Enhanced bioavailability. Int J Pharm 1998; 165: 23-32.
25. Thilek KM, Bharathi D, Balasubramaniam J, Kant S, Pandit JK. PH-induced *in-situ* gelling systems of Indomethacin for sustained ocular delivery. Indian J Pharm Sci 2005; 67: 327-333.
26. Yuan Y, Cui Y, Zhang L, Zhu HP, Guo YS, Zhong B, et al. Thermosensitive and mucoadhesive *in-situ* gel based on poloxamer as new carrier for rectal administration of Nimesulide. Int J Pharm 2012; 430: 114-119.
27. Miyazaki S, Endo K, Kawasaki N, Kubo W, Watanabe H, Attwood D. Oral sustained delivery of Paracetamol from *in-situ* gelling xyloglucan formulations. Drug Dev Ind Pharm 2003; 29: 113-119.
28. Swati G, Suresh PV. Carbopol/Chitosan based pH triggered *in-situ* gelling system for ocular delivery of Timolol Maleate. Scientia Pharmaceutia 2010; 78: 959-976.
29. Jun F, Xuemei F, Haihong Y, Liming Y, Xiaodong K, Zheng X, et al. Study of ocular pharmacokinetics of *in-situ* gel system for S(-)-sartropane evaluated by microdialysis. J Pharm Biomed Anal 2008; 48: 840-843.
30. Miyazaki S, Suzuki S, Kawasaki N, Endo K, Takahashi A, Attwood D. *In-situ* gelling xyloglucan formulations for sustained release ocular delivery of Pilocarpine hydrochloride. Int J Pharm 2001; 229: 29-36.
31. Saurabh G, Malay KS, Ashok MR. Dual-drug delivery system based on *in-situ* gel forming nanosuspension of Forskolin to enhance antiglaucoma efficacy. AAPS Pharm Sci Tech 2010; 11: 1.
32. Nagesh C, Patil M, Chandrashekhara S, Sutar R. A novel *in-situ* gel for sustained ophthalmic delivery of Ciprofloxacin hydrochloride and Dexamethasone- design and characterization. Der Pharmacia Lettre 2012; 4: 821-827.
33. Seham S, Abd E, Nahed DM, Gehanne ASA, Noha MZ, Ragia AT. Development of *in-situ* gelling and mucoadhesive Mebeverine hydrochloride solution for rectal administration. Saudi Pharmaceutical Journal 2003; 11: 159-171.
34. Shi-lei CAO, Qi-zhi Z, Xin-guo J. Preparation of ion-activated *in-situ* gel systems of Scopalamine hydrobromide and evaluation of its antimotion sickness efficacy. Acta Pharmacol Sin 2007; 28: 584-590.
35. Anda V, Michel L, Guillaume B, Jean-Christophe L. *In-situ*-forming oleogel implant for Rivastigmine delivery. Pharm Res 2008; 25: 4.
36. Hitendra SM, Saurabh KS, Sanjay J, Surana J. Nasal *in-situ* gel containing hydroxy propyl β -cyclodextrin inclusion complex of Artemether: Development and *in-vitro* evaluation. Incl Phenom Macrocycl Chem 2011; 70: 49.
37. Yan Z, Peng Y, Tao T, Qing-hua C. Drug brain distribution following intranasal administration of Huperzine A *in-situ* gel in rats. Acta Pharmacol Sin 2007; 28: 273-278.
38. Shyamoshree B, Amalkumar B. Development and characterization of mucoadhesive *in-situ* nasal gel of Midazolam prepared with Ficus Carica mucilage, AAPS Pharm Sci Tech 2011; 11: 3.
39. Avinash BA, Pranit R, Ashwini B, Nitin M, Sanjay C. Formulation and evaluation of Eletriptan hydrobromide thermoreversible nasal *in-situ* gel. Int J Pharm Res Dev 2012; 4: 264-275.
40. Shyam DB, Manish AS, Dhananjay RN, Ritesh RK, Tupkar SV, Barhate SD. Formulation and evaluation of Sumatriptan succinate nasal *in-situ* gel using fulvic acid as novel permeation enhancer. Int J of Pharm Res Dev 2007; 2 :8.
41. Moink M, Bhupendrag P, Vishnum P, Jayvadan KP. Sodium alginate based *in-situ* gelling system of Famotidine: Preparation and *in-vivo* characterizations. e-journal of Science and Technology 2010; 5: 1.
42. Miyazaki S, Kawasaki N, Kubo W, Endo K, Attwood D. Comparison of *in-situ* gelling formulations for the oral delivery of Cimetidine. Int J Pharm 2011; 220: 161-168.
43. Miyazaki S, Kubo W, Itoh K, Konno Y, Fujiwara M, Dairaku M, et al. The effect of taste masking agents on *in-situ* gelling pectin formulations for oral sustained delivery of Paracetamol and Ambroxol. Int J Pharm 2005; 297: 38-49.
44. Miyazaki S, Kubo W, Attwood D. Oral sustained delivery of Theophylline using *in-situ* gelation of sodium alginate. J Controlled Release 2000; 67: 275-280.
45. Tanagi N, Rahul T, Nitin J, Pradip D, Vivek C, Nitin H. Formulation and evaluation of pH induced nasal *in-situ* gel of Salbutamol sulphate. International Journal of Pharmaceutical Science and Nanotechnology 2008; 1: 2.
46. Prathiba P, Deepak C, Gaurav J, Shoerey RV. Formulation and evaluation of oral *in-situ* gel of Diltiazem HCl. International Journal of Novel Drug Delivery 2011; 2: 1.
47. Gupta H, Singh RM, Singh GN, Kaushik D, Sharma A. pH-induced *in-situ* gel for Prilocarpine anaesthesia. Indian J Pharm Sci 2008; 70: 776-778.
48. Vinay W, Mohan VM, 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 Science, 2011; 2: 2.
49. El Maghraby GM, Elzayat EM, Alanazi FK. Development of modified *in-situ* gelling oral liquid sustained release formulation of Dextromethorphan, Drug Dev. Ind. Pharm, 2012; 38: 971-978.
50. Qi H, Chen W, Huang C, Li L, Chen C, Li W. Development of a poloxamer analogs/carbopol-based *in-situ* gelling and mucoadhesive ophthalmic delivery system for puerarin. Int J Pharm 2007; 337: 178-187.
51. Shashank Nayak N, Bharani S Sogali, R S Thakur, Formulation And Evaluation Of pH Triggered In Situ Ophthalmic Gel Of Moxifloxacin Hydrochloride. Int J Pharm Pharm Sci, 2012; 4(2): 452-459.
52. Rathore KS. Insitu gelling ophthalmic drug delivery system: An overview Int J Pharm Pharm Sci, 2010; 2: 30-34.