

GASTRORETENTIVE DRUG DELIVERY SYSTEMS AS A POTENTIAL TOOL FOR ENHANCING THE EFFICACY OF ANTIBIOTICS: A REVIEW

N.H. FODA^{*1} AND S.M. ALI¹

Department of Pharmaceutics, Faculty of Pharmacy, King AbdulAziz University



N.H. FODA

Department of Pharmaceutics, Faculty of Pharmacy, King AbdulAziz University,

ABSTRACT

An optimum GRDF system can be defined as a system which retains in the stomach for a sufficient time interval against all the physiological barriers, releases active moiety in a controlled manner, and finally is easily metabolized in the body. This in turn improves bioavailability, reduces drug wastage, improves solubility of drugs that are less soluble at high pH environment. They also help in achieving local delivery of drug to the stomach and proximal small intestine, thus they were found to be suitable for formulating drugs with narrow therapeutic indices. Antibiotics belonging to different classes were proven to be good candidates for the formulation of GRDDS, therefore, the purpose of this paper is to review the recent literature and current technology used in the development of gastroretentive dosage form of various antibiotics.

KEY WORDS

Gastroretentive, Drug Delivery System, Antibiotics, Narrow Absorption Window

INTRODUCTION

The increased interest in developing oral controlled release dosage forms can be attributed to their ability to maintain an effective drug concentration in the systemic circulation for a long time and offering improved therapeutic advantages such as ease of dosing administration, patient compliance, flexibility in formulation. However, the short gastric retention time and unpredictable rapid gastric rate can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to decreased therapeutic efficacy of administered dose².

This limitation has led to the development of oral gastro-retentive dosage forms. Several gastroretentive drug delivery approaches being designed and developed, including: high density sinking systems that is retained in the bottom of the stomach³, low density floating systems that causes buoyancy in gastric fluid⁴, mucoadhesive systems that causes bioadhesion to stomach mucosa⁵, swellable, expandable or unfoldable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach⁶, superporous hydrogel systems⁷, and magnetic systems⁸.

Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substances. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract², and the drugs that are less soluble or are degraded by the alkaline pH may benefit from the prolong gastric retention^{9,10}. In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of the dose size^{11,12}.

However, there are certain situations where gastric retention is not desirable. These situations include drugs that may irritate the stomach lining e.g. aspirin and nonsteroidal anti-inflammatory agents, or those that are unstable in the acidic environment of the stomach e.g. erythromycin. Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system¹³.

Generally, drugs that are considered to be good candidates for stomach specific drug delivery systems include¹⁴:

1. Drugs that are locally active in the stomach.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT).
3. Drugs that are unstable in the intestinal or colonic environment.
4. Drugs that are primarily absorbed in the stomach.
5. Drugs that exhibit low solubility at high pH values.

Antibiotics belonging to different classes have been found to be good candidates for formulation into gastroretentive drug delivery systems. The current review deals with the gastroretentive drug delivery systems that have been developed to improve the therapeutic efficacy of such drugs.

GASTRORETENTIVE SYSTEMS OF FLOUROQUINOLONE ANTIBIOTICS

Ciprofloxacin, Norfloxacin and Ofloxacin are flouroquinolone, broad spectrum antibiotic used in the treatment of urinary tract infections, prostatitis and gonorrhoea. These drugs have



narrow absorption window¹⁵. Ciprofloxacin is mainly absorbed in the proximal areas of GIT¹⁶. Norfloxacin is least absorbed from the lower part of the gastrointestinal tract and is better absorbed from the stomach. This drug has a repetitive dose schedule (400 mg twice daily)¹⁷, short biological half-life of 3–4 hours¹⁸ and reduced bioavailability (30–40 %)¹⁹. In addition, Ofloxacin exhibits pH dependant solubility, where the drug is readily soluble in the acidic environment of the stomach; however, in the intestine, where neutral to slightly alkaline pH prevail, precipitation of the active compound occurs, which adversely affects absorption in the lower sections of the intestine²⁰. Therefore, these drugs have been found to be good candidates for the development of a gastroretentive drug delivery system aiming to increase their bioavailability.

Sa Hoo *et al.*²¹ developed floating microspheres of ciprofloxacin hydrochloride by simple dripping method using a polymer mixture of sodium alginate and hydroxyl propyl methyl cellulose. Sodium bicarbonate was used as a gas forming agent. The prepared floating microspheres were evaluated for particle size distribution, floating behavior, drug content and *in-vitro* release. The prepared microspheres showed enhanced buoyancy and controlled release of the drug.

Varshosaz *et al.*¹⁶ formulated floating-bioadhesive effervescent tablets using sodium carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose (HPMC), polyacrylic acid (AA), polymetacrylic acid (MAA), citric acid, and sodium bicarbonate. Tablets with 5% effervescent base had longer lag time than 10%. The type of polymer had no significant effect on the floating lag time. All tablets showed floating times for 23-24 hr. All formulations showed a Higuchi, non-Fickian release mechanism. Tablets with 10% effervescent base, 80% CMC/20% HPMC, or 80% AA /20% MAA showed desirable lengthening of the stay of drug in its absorption area.

Ciprofloxacin loaded multi-unit floating alginate beads were prepared by Srinatha and Pandit²² using simultaneous external and internal gelation. The effect of blending of alginate with gellan, hydroxypropyl methylcellulose, starch, and chitosan on the bead properties was evaluated. Beads were spherical and exhibited buoyancy over a period of 7-24 hr based on the formulation variables. *In-vitro* drug release was studied in simulated gastric fluid (SGF). The release of the drug from the beads was influenced significantly by the properties and concentration of additives. Among the polymers incorporated into alginate beads, hydroxy propyl methylcellulose (HPMC) provided an extended release over 7 hr. The drug release predominately followed Higuchi's square root model.

Arza *et al.*¹⁵ developed swellable, floating sustained release tablets of ciprofloxacin hydrochloride by wet granulation method using a combination of hydrophilic polymer (different grades of hydroxypropyl methylcellulose), different swelling agents (crospovidone, sodium starch glycolate, and croscarmellose sodium) and gas generating agent (sodium bicarbonate). Formulations were evaluated for hardness, friability, weight variation, thickness, percentage swelling, *in vitro* drug release, floating lag time, total duration of floating, and mean residence time (MRT) in the stomach. The optimized formula containing a combination of HPMC K100M, crospovidone, and sodium carbonate showed better swelling, drug release, and floating characters than the marketed product CIFRAN OD[®]. *In-vivo* studies conducted on healthy volunteers supported prolonging of the gastric residence time, where the mean gastric retention is found to be 320±48.99 min (n=6). This result indicates increase in MRT of the ciprofloxacin HCl in the stomach.

Controlled-release floating matrix tablets of ciprofloxacin hydrochloride have been successfully formulated by Tadros²³ using the efferevescent technique. Hydroxy propyl methyl cellulose (HPMC K15M) and/or sodium alginate (Na alginate) were used as release-retarding polymer(s), sodium bicarbonate or calcium carbonate were used as gas forming agents. Swelling ability, floating behaviour, adhesion period and drug release studies were conducted in 0.1 N HCl (pH 1.2). Tablets containing HPMC K15M (21.42%, w/w), Na alginate (7.14%, w/w) and CaCO₃ (20%, w/w) showed satisfactory results with respect to floating lag time, total floating duration, swelling ability, adhesion retention period, sustained drug release and acceptable physical stability

when stored at 40° C under 75% RH for 3 months. The mean gastric retention period of this optimum formula loaded with barium sulfate, in six healthy human volunteers was 5.50 ± 0.77 h.

Bomma *et al.*²⁴ developed floating matrix tablets of norfloxacin by the wet granulation technique, using three different polymers, namely; hydroxypropyl methylcellulose (HPMC K4M, HPMC K100M) and xanthan gum. Tablets were evaluated for hardness, thickness, friability, and weight variation, drug content, *in-vitro* buoyancy and drug release. Optimized formulations with HPMC floated with a lag time less than that exhibited by formulations with xanthan gum. The prepared tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium. The best formula selected on the basis of *in-vitro* evaluation was subjected to *in-vivo* radiographic studies by incorporating barium sulfate. These studies revealed that the tablets remained in the stomach for 180 ± 30 min in fasting human volunteers indicating prolongation of gastric residence time.

Chavanpatil *et al.*²⁰ have developed a gastroretentive drug delivery system (GRDDS) with floating and swelling features for ofloxacin using different polymers such as psyllium husk, HPMC K100M, croscopovidone and their combinations. They aimed to get the desired sustained release profile over a period of 24 h. Various formulations were evaluated for buoyancy lag time, duration of buoyancy, dimensional stability, drug content and *in-vitro* drug release profile. Psyllium husk and HPMCK100M were found to increase the dimensional stability of the formulations. It was also found that *in-vitro* drug release rate increases with increasing amount of croscopovidone due to the increased water uptake, and hence increased driving force for drug release. The optimized formulation was found to be stable at different temperature and humidity conditions as per ICH guidelines. *In-vivo* studies carried out for the optimized formulation in 24 healthy human volunteers showed percent relative bioavailability of 97.55% compared to the marketed product Zanicin[®]. In another study, Chavanpatil *et al.*²⁵ evaluated the swelling and bioadhesive properties of the developed formulations. Swelling studies indicated that water uptake was significant, contributed in drug release and could be significant in gastroretention. The developed formulation also showed significant bioadhesion as compared to that of the polymers alone.

Gastroretentive drug delivery systems of ofloxacin were developed by Ali *et al.*²⁶. The formulation was optimized regarding *in-vitro* buoyancy and *in-vitro* release in citrate phosphate buffer (pH 3). Hydrodynamically balanced capsules were prepared by physical mixing of various grades of HPMC and poly(ethylene oxide) (PEO) alone as well as in combinations. Release modifiers were used so as to maintain release of drug over a period of 12 h. The optimized capsule formulation regarding the *in-vitro* release was that prepared with PEOWSR 60K and drug coated with 2.5% ethyl. A combination of various grades of Eudragit and PEO and two different solvents were used in combination for formulating floating microspheres using solvent diffusion technique for preparation of multiple unit system. The *in-vitro* release of the optimized floating capsules and microspheres was found to be 96.02% and 95.83% in 12 h, respectively. The release of the drug from both dosage forms followed Higuchi model and exhibited non-Fickian diffusion mechanism.

Janardhan *et al.*²⁷ formulated gastroretentive tablets of ofloxacin by wet granulation technique. Different formulations were prepared using various concentrations of HPMC K4M (rate retarding polymer), HPMC 5cps (promotes floating), sodium carboxymethyl cellulose (channeling agent), sodium bicarbonate and citric acid anhydrous (effervescent agents). The formulations were evaluated for quality control tests and subjected to *in-vitro* buoyancy and dissolution studies compared to the marketed formulation. The floating lag time was below 15 seconds for all the formulations except F1 and F2. The optimized formulation was found to follow zero order kinetics and showed no significant change in the dissolution profile after storage for 3 months at 25°C/60%RH and 40°C/75%RH. It was found that the system using sodium carboxy methyl cellulose along with sodium bicarbonate and citric acid added in equal quantities before granulation and during lubrication significantly increased the drug release from the formulation. It was also evident



that sodium bicarbonate levels had a considerable effect on the drug release profile along with the hardness levels as well.

Amoxicillin (α -aminohydroxybenzylpenicillin) is a semisynthetic antibiotic, belonging to the β -Lactam family, which is effective for bacterial infection treatment, especially for *Helicobacter pylori* infection²⁸. It is associated with the development of serious gastro duodenal disease including peptic ulcers, gastric lymphoma and acute chronic gastritis²⁹. *H. pylori* reside mainly in the gastric mucosa or at the interface between the mucous layer and the epithelial cells of the antral region of the stomach³⁰. Thus, the concentration and residence time of amoxicillin in stomach should be effective for complete eradication of *Helicobacter pylori*. Therefore, many attempts have been made to formulate the drug in the form of gastroretentive drug delivery systems.

Nagahara *et al.*³¹ formulated amoxicillin in the form of mucoadhesive microspheres by spray chilling method, which have the ability to reside in the gastrointestinal tract for an extended period. The microspheres contained the antimicrobial agent and carboxyvinyl and curdlan as adhesive polymers dispersed in melted hydrogenated castor oil. The prepared microspheres were compared to 0.5% methylcellulose amoxicillin suspension in infected Mongolian gerbils under feeding conditions. The percentage of amoxicillin remaining in the stomach both 2 and 4 h after oral administration of the mucoadhesive microspheres was about three times higher than that after administration in the form of a 0.5% methylcellulose suspension. Both formulations showed anti-*H. pylori* effects, with effective reduction of the required dose of amoxicillin by a factor of 10 when the mucoadhesive microspheres were used.

Modified positively charged biodegradable mucoadhesive microspheres of amoxicillin were prepared by Wang *et al.*³². The microspheres were prepared using aminated gelatin by surfactant-free emulsification in olive oil, followed by a cross-linking reaction with glutaraldehyde. The influence of glutaraldehyde concentration, cross-linking reaction time, drug-loading patterns, and type of release media on the *in vitro* release characteristics of amoxicillin from the microspheres was investigated. Amoxicillin release rate from the modified gelatin microspheres was significantly reduced compared with that from gelatin microspheres. Furthermore, the release was decreased with the increase of glutaraldehyde concentration and/or cross-linking time. On the other hand, a faster release was observed in a lower pH release medium and/or using a lower pH solution for amoxicillin loading. The gastric mucoadhesion of the modified gelatin microspheres was markedly improved in an isolated rat stomach compared with that of gelatin microspheres. Thus, the authors concluded that the modified gelatin microsphere is a possible candidate delivery system for the effective eradication of *H. pylori*.

Whitehead *et al.*³³ have developed floating alginate beads from alginate solutions containing either dissolved or suspended amoxycillin. The beads were produced by the dropwise addition of the alginate into calcium chloride solution, followed by removal of the gel beads and freeze drying. The beads prepared with the drug in solution yielded sustained release dissolution that can be further improved by adding amylose. The beads retained their buoyancy when amylose and amoxycillin were incorporated. The beads prepared from alginate solutions containing amoxycillin in suspension showed increase in drug loadings, but exhibited faster release and lower buoyancy than that prepared from solutions containing the dissolved drug.

Microparticles of amoxycillin-loaded ion-exchange resin encapsulated in polycarbophil and Carbopol 934 as mucoadhesive polymers were prepared by Cuna *et al.*³⁴. A modified oil-in-oil solvent evaporation technique was applied to obtain microparticles containing multiple amoxycillin-resin cores. The prepared microspheres were evaluated for morphology and size, drug release, drug content and gastric transit time in rats. Polycarbophil microparticles were spherical, while carbopol 934 microparticles were irregular. *In vitro* release of amoxycillin was rapid with or without a polymer coating. However, the gastrointestinal transit time was longer, and the distribution of the particles on the mucosa apparently better, without any polymer coating. Therefore, the authors

concluded that microencapsulation of ion-exchange resin particles in the mucoadhesive polymers polycarbophil and Carbopol 934 failed to prolong their residence in the stomach of rats to a significant extent and appeared to favour the aggregation of the particles thereby making the distribution of particles in the stomach more difficult.

Chuña *et al.*³⁵ using the interpolymer complexation of poly(acrylic acid) (PAA) with poly(vinyl pyrrolidone) (PVP) and solvent diffusion method. The prepared microspheres were evaluated for loading efficiency, morphology and dissolution. *In-vitro* release of antimicrobial agents was also studied at different pH values. The loading efficiency of clarithromycin in the complex microspheres was higher than that of amoxicillin due to the stronger interaction of clarithromycin with the PAA. The microspheres were spherical in shape. The dissolution rate of the complex microspheres was significantly slower than that of the PVP microspheres, particularly at pH 2.0. The amoxicillin release was mainly by diffusion with similar release rates at different pH values, while clarithromycin release was mainly through dissolution exhibiting pH-dependent release rates. The drug release rate from the complex microspheres was significantly lower than that from the PVP microspheres.

Liu *et al.*³⁶ prepared mucoadhesive microspheres containing amoxicillin. The microspheres were prepared by emulsification/evaporation method, using ethylcellulose as matrix and carbopol 934P as a mucoadhesive polymer. Stability studies of amoxicillin in pH 1.0 HCl medium showed that the drug exhibited some degradation in the acidic medium. However, it was found that amoxicillin entrapped within the microspheres could be kept stable. *In-vitro* release test of the drug showed that amoxicillin released faster in pH 1.0 hydrochloric acid (HCl) than in pH 7.8 phosphate buffer, where about 90% was released in the acidic medium within 4 h. In addition, *in-vivo* evaluation of mucoadhesiveness showed that, during the same time 63.6T21.9% of the microspheres remained in the rat stomach. Also, the amoxicillin concentration in gastric tissue of rats after oral administration of mucoadhesive microspheres was found to be higher than amoxicillin powder at the same dose. Furthermore, *in-vivo* H. pylori clearance tests performed in H. pylori infectious BALB/c mice under fed conditions revealed that, in single-dosage administration, the mucoadhesive microspheres had a better effectiveness compared to amoxicillin powder. Also, in a multidosage administration regimen, the microspheres showed a complete eradication of H. pylori in five of six rat stomachs, whereas amoxicillin powder showed four times less effectiveness.

Patel and Patel³⁷ also formulated mucoadhesive microspheres of amoxicillin. The microspheres were prepared by simple emulsification phase separation technique using the mucoadhesive polymer chitosan cross linked with glutaraldehyde. The results of the preliminary trial batches showed that the percentage mucoadhesion, drug entrapment efficiency, and characteristics of the microspheres were affected by the volume of cross-linking agent (glutaraldehyde), time for cross-linking, and stirring speed. Microspheres were discrete, spherical, free flowing showing high percentage drug entrapment efficiency and strong adherence to the gastric mucous layer. On the basis of the preliminary trials a full 3² full factorial design was employed to optimize the mucoadhesive formulation. The results revealed that both the independent variables; polymer-to-drug ratio and stirring speed significantly affected the dependent variables; % mucoadhesion, the time required for 80 % drug dissolution, drug entrapment efficiency, particle size and swelling index. However, the polymer-to-drug ratio had a more significant effect on the dependent variables. The microspheres of the best batch exhibited a high % mucoadhesion of 79 % after 1 h, 70 % drug entrapment efficiency and swelling index of 1.42. The drug release was also sustained for more than 12 hours. The morphological characteristics of the mucoadhesive microspheres were studied using scanning electron microscopy. Finally, the authors performed *in-vivo* H. pylori clearance tests in H. pylori infectious Wistar rats under fed conditions at single dose or multiple dose(s) oral administration, where the



results showed that amoxicillin mucoadhesive microspheres had a better clearance effect than amoxicillin powder.

Gellan based floating in situ gelling system for controlled delivery of amoxicillin was developed by Rajinikanth *et al.*³⁸. the systems were prepared by dissolving varying concentrations of gellan gum in deionized water containing sodium citrate, to which varying concentrations of drug and calcium carbonate, as gas-forming agent, was added and dissolved by stirring. The in situ gelling solutions were subjected to viscosity measurements, *in-vitro* gelation, floating and drug release studies in 0.1 N HCl (pH 1.2). the authors found that the formulation variables; concentration of gellan gum and calcium carbonate significantly affected the in vitro drug release from the prepared formulations. The *in-vivo* H. pylori clearance efficacy of prepared amoxycillin floating in situ gelling system (AFIG) was studied in H. pylori infected Mongolian gerbils following repeated oral administration by polymerase chain reaction (PCR) technique and by a microbial culture method in comparison to amoxicillin suspension. The AFIG showed a significant anti-H. pylori, where the required amount of amoxicillin for eradication of H. pylori was 10 times less than that from the corresponding amoxicillin suspension.

Kerč and Opara³⁹ developed a new peroral amoxicillin/clavulanate therapeutic system composed of immediate release tablet and controlled release floating capsule. Amoxicillin/clavulanate is a widely prescribed combination of beta-lactam antibiotic and beta-lactamase inhibitor for the treatment of a wide range of bacterial infections, including upper and lower respiratory tract infections and infections of the skin and soft-tissue structures. The new pharmacokinetically enhanced formulations were developed to expand the time over MIC of amoxicillin in vivo in relation to a regular IR amoxicillin/ clavulanate formulation in the form of a coated tablet, thus providing more effective therapy against organisms with increasing resistance to amoxicillin, notably *Streptococcus pneumoniae*. The prepared systems were evaluated for *in-vitro* floating, dissolution and *in-vivo* bioavailability. The bioavailability study confirmed enhanced pharmacokinetic parameters of a newly developed therapeutic system containing 1500 mg of amoxicillin and 125 mg of clavulanic acid. Prolonged time over MIC of amoxicillin in relation to a regular immediate release amoxicillin/clavulanate formulation was also confirmed.

Patel and Chavda⁴⁰ developed mucoadhesive amoxicillin microspheres for anti-*Helicobacter pylori* therapy using emulsion-solvent evaporation technique. They used carbopol-934P as mucoadhesive polymer and ethyl cellulose as carrier polymer. Preliminary trials indicated that quantity of emulsifying agent, time of stirring, drug-to-polymers ratio and speed of rotation affected the characteristics of microspheres. The morphological characteristics of the mucoadhesive microspheres were studied under a scanning electron microscope. Microspheres were discrete, spherical, free flowing showing a good percentage of drug entrapment efficiency and adhered strongly to the gastric mucous layer and could retain in the gastrointestinal tract for an extended period of time. A 3² full factorial design was employed to study the effect of independent variables; drug-to-polymer-to-polymer ratio and stirring speed on percentage mucoadhesion, drug entrapment efficiency, particle size and time for 80% dissolution. The best batch exhibited a high drug entrapment efficiency of 56%; mucoadhesion percentage of 80% after 1 h particle size of 109 µm. A sustained drug release was obtained for more than 12 h. In vitro release test showed that amoxicillin released slightly faster in pH 1.2 hydrochloric acid than in pH 7.8 phosphate buffer. In-vivo H. pylori clearance tests carried out by administering in H. pylori infectious Wistar rats under fed conditions at single dose or multiple oral dose(s) showed that amoxicillin mucoadhesive microspheres had a better clearance effect than amoxicillin powder.

A novel hydrogel nanoparticles (NPs) containing amoxicillin were synthesized by Moogooee *et al.*⁴¹. The drug loaded hydrogel nanoparticles were prepared using the mucoadhesive polymer cross-linked N-isopropylacrylamide-acrylic acid-hydroxyethyl methacrylate. The prepared nanoparticles were characterized for their entrapment efficiency (EE%), mean diameter, morphology and *in-vitro* release in both pH 1.0 and 7.4 media. It was found that about 88.5% of



amoxicillin entrapped in the nanoparticles was released in 4 h in the pH 1.0 medium, whereas in phosphate buffer at pH 7.4 no more than 45% was released after 4 hours incubation at 37 °C. *In-vivo* studies were performed to determine the drug concentration in rats' gastric tissues. The studies revealed that the hydrogel nanoparticles enhance drug concentration at topical site than powder amoxicillin. Thus, the authors concluded that the developed hydrogel nanoparticle formulation may provide therapeutic concentration at a much lower dose that may reduce the adverse effects of amoxicillin in high doses.

Narkar *et al.*⁴² developed amoxicillin-loaded mucoadhesive gellan beads. The beads were prepared by the cation-induced ionotropic gelation method using acidic and alkaline cross-linking media. The authors used a 3² randomized factorial design to evaluate the effect of the two variables; concentration of gellan gum (X1) and quantity of drug (X2) on both yield and entrapment efficiency. Each factor was used at three different levels. The results revealed a positive effect for the polymer concentration and a negative effect for the drug quantity. In addition, the beads prepared in alkaline cross-linking medium showed higher yield entrapment efficiency than the acidic cross-linking medium. Therefore, batches with lowest, medium, and highest drug entrapment obtained using alkaline crosslinking medium were selected to be coated with chitosan in order to obtain controlled drug release. The prepared beads were also evaluated for micromeritic properties, scanning electron microscopy (SEM), thermal properties, swelling behavior, *in vitro* drug release, *in-vivo* and *in-vitro* mucoadhesive properties, and *in-vitro* growth inhibition study. Chitosan-coated gellan beads exhibited *in-vitro* drug release up to 7 hours in a controlled manner. They also showed good mucoadhesivity and complete growth inhibition of *H. pylori*.

Mucoadhesive and floating chitosan-coated alginate beads of amoxicillin were also formulated and evaluated by Sahasathian *et al.*⁴³ The authors found that amoxicillin-loaded alginate beads coated with 0.5% (w/v) chitosan exhibited excellent floating ability, high encapsulation efficiency, high drug loading capacity, and a strong *in-vitro* mucoadhesion to the gastric mucosal layer. Moreover, the coated beads exhibited sustained *in-vitro* drug release of amoxicillin for over six hours in simulated gastric fluid.

Pandit *et al.*²⁸ prepared and evaluated floating non effervescent mini tablets of amoxicillin by wet granulation technique. Different hydrophilic polymers were evaluated for buoyancy and matrix integrity. Maximum buoyancy was observed in formulations containing various grades of hydroxypropyl methyl cellulose; HPMC K4M and HPMC (15cps), alone or in combination with other tablet ingredients. Thus, they were used to achieve controlled release of the drug. The prepared tablets were evaluated for weight variation, hardness, friability, drug content, buoyancy and *in-vitro* dissolution studies. Optimized formulation of amoxicillin was found to have prolonged drug release and increased gastric residence.

Clarithromycin is a macrolide antibiotic that can be used in a combination of a gastric protector as a first line therapy for *H. pylori* eradication. Therefore, its formulation as a gastroretentive system can maintain higher levels of the drug for longer periods of time, allowing complete and effective eradication of the bacteria. Go´mez-Burgaz *et al.*⁴⁴ developed a controlled-release gastro-retentive system of clarithromycin by the novel method "tablets-in-capsule". Mini-matrices containing clarithromycin and composed of chitosan (CS) and carboxymethyl cellulose (CMC) in different proportions were prepared. The authors investigated the influence of the molecular weight of chitosan and the proportion CS/CMC on physical properties and drug release. Swelling was found to be dependent on CS molecular weight., medium pH and proportion CS/CMC. The drug release rates have shown to be dependent on pH and on polymer proportion. Based on these results, the authors concluded that the controlled-release gastro-retentive system obtained by the "tablets-in-capsule" method, where mini-matrices containing clarithromycin and composed of CS and CMC in the proportion 80:[75:25] (w/w) have demonstrated to have suitable swelling properties and the most suitable drug release profile.

REFERENCES

1. Iannucelli V, Coppi G, Bernabei MT, Camerorni R, Air compartment multiple-unit system for prolonged gastric residence. Part-I. Formulation study, *Int J Pharm*, 174 (1-2): 47-54, (1998).
2. Rouge N, Buri P, Doelker E, Drug absorption sites in the gastrointestinal tract and dosage form for site-specific delivery, *Int J Pharm*, 136: 117-139, (1996).
3. Rouge N, Allemann E, Gex-Fabry M, Balant L, Cole ET, Buri P, Doelker E, Comparative pharmacokinetic study of a floating multiple-unit capsule, a high density multipleunit capsule and an immediate-release tablet containing 25 mg atenolol. *Pharm Acta Helv*, 73(2): 81-87, (1998).
4. Sauzet C, Claeys-Brunob M, Nicolasc M, Kister J, Piccerelle P, Prinderrea P., An innovative floating gastro retentive dosage system: Formulation and in vitro evaluation, *Int J Pharm*, 378: 23-29, (2009).
5. Dhaliwal S, Jain S, Singh HP, and Tiwary AK, Mucoadhesive microspheres for gastroretentive delivery of acyclovir: *in vitro* and *in vivo* evaluation, *AAPS J*, 10(2): 322-330, (2008).
6. Klausner EA, Lavy E, Stepensky D, Friedman M, Hoffman A, Novel gastroretentive dosage forms: evaluation of gastroretentivity and its effect on riboflavin absorption in dogs, *Pharm Res*, 19(10), 1516–1523, (2002).
7. Gupta NV, Shivakumar HG, Development of a Gastroretentive Drug Delivery System based on Superporous Hydrogel, *Trop J Pharm Res*, 9(3): 257-264, (2010).
8. Fujimori J, Machida Y, Nagai T, Preparation of a magnetically-responsive tablet and configuration of its gastric residence in beagle dogs, *STP Pharma Sci*, 4: 425-30, (1994).
9. Mathura RS, Sangahavi NM, Novel drug delivery systems for captopril, *Drug. Dev Ind Pharm*, 18: 1567-1574, (1992)
10. Fell JT, Whitehead L, Collet H, Prolonged gastric retention using floating dosage forms, *Pharm Technol* 24(3): 82-90, (2000).
11. Despande AA, Rhodes CT, Shah NH, Malick AW, Controlled release drug delivery systems for prolong gastric residence: an overview, *Drug Dev Ind Pharm*, 22(6): 531-539, (1996).
12. Baumgartners S, Kristal J, Vrecer F, Vodopivec P, Zorco B, Optimization of floating matrix tablets and evaluation of their gastric residence time, *Int J Pharm*, 195(1-2): 125-135, (2000).
13. Gutierrez-Rocca J, Omidian H, Shahk, Progresses in gastroretentive drug delivery systems, *Business Briefing: Pharm Tech*, 152-156 (2003).
14. Nayak AK, Maji R, Das B, gastroretentive drug delivery systems: A review. *Asian J Pharm Res*, 3(1): 2-9, (2010).
15. Arza RAK, Gonugunta CSR, and Veerareddy PR, Formulation and Evaluation of Swellable and Floating Gastroretentive Ciprofloxacin Hydrochloride Tablets, *AAPS PharmSciTech*, 10(1): 220-226, (2009).
16. Varshosaz J, Tavakoli N, Roozbahani F, Formulation and in vitro characterization of ciprofloxacin floating and bioadhesive extended-release tablets, *Drug Deliv*, 13 (4): 277-285, (2006).
17. K.M. Gerald. Norfloxacin. In *AHFS Drug Information*, The American Society of Health System Pharmacists, Bethesda, 2004, pp. 396–402.
18. Thomson PDR, Noroxin tablets. In: *Physician Desk Reference*, 61st ed., Montvale: 2032-2038, (2007).
19. C. Mazuel. Norfloxacin. In: K. Florey (ed.), *Analytical Profiles of Drug Substances*, Vol. 20, Academic Press, San Diego, 1991, pp. 557–600.



20. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P, Development of sustained release gastroretentive drug delivery system of ofloxacin: In vitro and In vivo evaluation, *Int J Pharm*, 304:178-184, (2005).
21. Sahoo SK, Mohapatra S, Dhal SK., Behera BC, Barik BB, Formulation of floating microspheres of ciprofloxacin hydrochloride by crosslinking technique, *The Indian Pharmacist*, 6:65-68 (2007).
22. Srinatha A, Pandit JK, Multi-Unit Floating Alginate System: Effect of Additives on Ciprofloxacin Release, *Drug Deliv*, 15:471-476 (2008).
23. Tadros MI, Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitro–in vivo evaluation in healthy human volunteers, *Eur J Pharm Biopharm*, 74:332-339 (2010).
24. Bomma R, Naidu RAS, Yamsani MR, Veerabrahma K, Development and evaluation of gastroretentive norfloxacin floating tablets, *Acta pharm*, 59:211-211 (2009).
25. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P, Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin, *Int J Pharm*, 316:86-92 (2005).
26. Ali J, Hasan S, Ali M, Formulation and development of Gastroretentive drug delivery system for ofloxacin, *Methods Find Exp Clin Pharmacol*, 28:433 (2006).
27. Janardhan D, Sreekanth J, Bharat V, Subramaniyan PR, Formulation and Evaluation of Gastro Retentive Drug Delivery System for Ofloxacin, *Int J Pharm Sci Nano*, 2:428-434 (2009).
28. Pandit V, Suresh S, Joshi H, Gastroretentive drug delivery system of amoxicillin: Formulation and in vitro evaluation, *Int J Pharma Bio Sci*, 1(2): 1-10 (2010).
29. Crescenzi V, Dentini M, Coviello T, 1990. Solution and gelling properties of polysaccharide of industrial interest, the case of gellan. In: E.A. (ed.), *Novel biodegradable microbial Polymers*, Klumer Academic Publishers, The Netherlands, 1990, pp. 227–284.
30. Peterson WL, Helicobacter pylori and peptic ulcer disease, *N Engl J Med*, 324: 1043–1048, (1991).
31. Nagahara N, Akiyama Y, Nakao M, Tada M, Kitano M, Ogawa Y, Mucoadhesive microspheres containing amoxicillin for clearance of Helicobacter pylori, *Antimicrob Agents Chemother*, 42(10): 2492-2494, (1998).
32. Wang J, Tauchi Y, Deguchi Y, Morimoto K, Tabata Y, Ikada Y, Positively charged gelatin microspheres as gastric mucoadhesive drug delivery system for eradication of H. pylori, *Drug Deliv*, 7(4):237-243, (2000).
33. Whitehead L, Collett JH, Fell JT, Amoxicillin release from a floating dosage form based on alginates, *Int J Pharm*, 210: 45-49, (2000).
34. Cuna M, Alonso MJ, Torres D, Preparation and in vivo evaluation of mucoadhesive microparticles containing amoxicillin-resin complexes for drug delivery to the gastric mucosa, *Eur J Pharm Biopharm*, 51(3):199-205, (2001).
35. Chuñ MK, Sah H, Choi HK, Preparation of mucoadhesive microspheres containing antimicrobial agents for eradication of H. pylori, *Int J Pharm*, 297(1-2):172-179, (2005).
36. Liu Z, Lu W, Qian L, Zhang X, Zeng P, Pan J, In vitro and in vivo studies on mucoadhesive microspheres of amoxicillin, *J. Control. Release*, 102(1): 135-144, (2005).
37. Patel JK, Patel MM, Stomach specific anti-helicobacter pylori therapy: preparation and evaluation of amoxicillin-loaded chitosan mucoadhesive microspheres, *Curr Drug Deliv*, 4(1):41-50, (2007).
38. Rajinikanth PS, Balasubramaniam J, Mishra B, Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of Helicobacter pylori, *Int J Pharm*, 335:114-122, (2007).



39. Kerč J, Opara J, A new amoxicillin/clavulanate therapeutic system: Preparation, in vitro and pharmacokinetic evaluation, *Int J Pharm* 335: 106-113, (2007).
40. Patel JK, Chavda JR, Formulation and evaluation of stomach-specific amoxicillin-loaded carbopol-934P mucoadhesive microspheres for anti-*Helicobacter pylori* therapy, *J Microencapsul*, 1-12, (2008).
41. Moogooee M, Ramezanzadeh H, Jasoori S, Omid Y, Davaran S, Synthesis and in vitro studies of cross-linked hydrogel nanoparticles containing amoxicillin, *J Pharm Sci*, 2010 Nov 4. [Epub ahead of print].
42. Narkar M, Sher P, Pawar A, Stomach-specific controlled release gellan beads of acid-soluble drug prepared by ionotropic gelation method, *AAPS PharmSciTech*, 11(1):267-77, (2010).
43. Sahasathian T, Praphairaksit N, Muangsin N, Mucoadhesive and floating chitosan-coated alginate beads for the controlled gastric release of amoxicillin, *Arch Pharm Res*, 33(6):889-99 (2010).
44. Go´mez-Burgaz M, Garcı´a-Ochoa B, Torrado-Santiago S, Chitosan–carboxymethylcellulose interpolymer complexes for gastric-specific delivery of clarithromycin, *Int J Pharm* 359: 135-143 (2008).