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# Floating Oral *In-Situ* Gel: A Review

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## ABSTRACT

The drugs having a narrow absorption window in the gastrointestinal tract (GIT) when administered by oral route are often limited by poor bioavailability due to incomplete drug release and short residence time at the site of absorption. Novel drug delivery systems in the form of gastroretentive systems such as floating systems, mucoadhesive, high-density, expandable have been developed as they provide controlled delivery of drugs with prolonged gastric residence time. Liquid orals are more prone to low bioavailability because they are eliminated quickly from the stomach since they are subjected to faster transit from the stomach/ duodenum. The problems of immediate release and short gastrointestinal residence of liquids are eliminated by formulating as oral in situ gels as they provide the best means to overcome these problems The *in situ* gel dosage form is a liquid before administration and after it comes in contact with gastric contents due to one or more mechanisms gets converted to gel which floats on gastric contents. This achieves increased residence as well as sustained release. This approach is useful for systemic as well as local effect of drugs administered. This review gives a brief idea about floating oral in-situ gel formation and research done by various scientists on a number of drugs and polymers.

**Keywords:** Floating drug delivery, gastric retention time, *In-situ* gel.

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## INTRODUCTION

Floating Drug Delivery System is one of the novel system of drug delivery. Various dosage forms are formulated in the form gastro retentive floating systems such as microspheres, micro beads, tablets, capsules, films etc. In-situ gelling system is a new trend in floating DDS. In-situ gelling system have its application in different routes of administration like oral, nasal, ophthalmic, peroral, rectal, vaginal and also parenteral route. In situ forming polymeric drug delivery systems has many advantages such as ease of administration, increased local bioavailability, reduced dose frequency, improved patient compliance and has less complex method of production and so is cost effective. Gastro retentive FDDS have bulk density lower than gastric fluid and hence remain buoyant in stomach without affecting the gastric emptying rate for a long period of time. When the gel so formed float on gastric fluid the drug get released slowly at desired rate from the floating gel. After drug is released from floating system, the residual part is emptied from stomach. This may increase GRT and also control the fluctuations in plasma drug concentration (PCD). Floating system are the controlled or sustained release dosage form and have properties similar to hydrophilic matrices and so called as hydrodynamically balanced system (HBS) as they form a low density polymeric gel barrier at outer surface. Drug is slowly released from the matrices same as that in case of conventional hydrophilic matrices. This form may remain buoyant (8-10 hours) on gastric contents without affecting the rate of gastric emptying. Different polymer systems are used in floating drug delivering dosage forms. Among those some are polysaccharides, polymethacrylates, hydrocolloids etc. in this cellulose ether polymers are most popular, especially HPMC. The formulation of floating in situ gelling solution may sustain and prolong drug action, improve patient compliance and reduce frequency of administration of the drug in comparison to conventional drug delivery system[1-9]. Floating drug delivery system (FDDS) was first described by Davis in 1968. FDDS is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. Floating drug delivery systems meant for gastric retention, float on the surface of the gastric fluids, due to their low density and produce prolonged effect by showing the controlled release. This type of delivery system is of great value for drugs which get absorbed from upper part of the stomach i.e. their absorption window resides in upper part of stomach. It is also useful for drugs which are inserting at alkaline pH of intestine and remains unabsorbed or causes side effects due to insolubility. The FDDS are particularly

useful for drugs required for their local effect in stomach. Though, immediate floating of the delivery system can only be achieved if the density of the delivery system is on lower side. Delivery system with higher density, initially settle down in stomach and then absorb water, swell and then float due to decrease in density of the system. But, with such system, there may be a possibility of gastric emptying of system, before the floating starts. Low density of system, which leads to floating, rendered either by incorporation of low density excipients or by providing a mechanism which leads to air entrapment within the system may have their own certain limitations.

## CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of Floating Drug Delivery Systems[10-14].

### 1. Effervescent systems

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the carbon dioxide produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed.

### 2. Non-effervescent systems

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxyl propyl methylcellulose(HPMC) polyacrylates, polyvinyl acetate, carbopol, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates

**Factors affecting the floating drug delivery system**

a. **Density:** gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.

b. **Size and Shape:** Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kiloponds per square inch (KSI) are reported to have better GIT for 90 to 100% retention at 24 hours compared with other shapes[15].

c. **Fed or Unfed State:** Under fasting conditions, the gastro intestinal motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer[16].

d. **Nature of the meal:** Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release[17].

e. **Caloric Content:** GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

f. **Frequency of feed:** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC[18].

g. **Gender:** Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

h. **Age:** Elderly people, especially those over 70 years have a significantly longer GRT[19-20].

i. **Posture:** GRT can vary between supine and upright ambulatory states of the patients[21].

j. **Concomitant drug administration:** Anticholinergic drugs like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

## NEED OF FLOATING DRUG DELIVERY SYSTEM

Oral dosage forms pose low bioavailability problems due to their rapid gastric transition from stomach, especially in case of drugs which are less soluble at alkaline pH of intestine. Similarly, drugs which produce their local action in stomach get rapidly emptied and do not get enough residence time in stomach. So, frequency of dose administration in such cases is increased. To avoid this problem floating drug delivery system has been developed. 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. The tablet/capsule floating dosage forms are stable as compare to liquids but the problem with them is that they are needed to swallow as whole unit. In case of dosage adjustment these cannot be broken in halves as these are also designed for controlled release and floating ability also depends on dimensions of tablets. Elderly patients, children some adult persons and patient with certain conditions suffer from dysphasia, so it becomes difficult for them to swallow tablet/capsule dosage forms. Also in case of dosage adjustments these floating solid dosage forms are needed to be available in different strengths. Where an environment specific gel forming solution, on conversion to gel, floats on the surface of the gastric fluids (due to less density than gastric contents). 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[22-23].

## *IN SITU* GELLING SYSTEM

This novel drug delivery system promotes importantly ease and convenience of administration, deliverance of accurate

dose as well as to prolong residence time of drug in contact with mucosa that problems generally encountered in semisolid dosage forms.

*In situ* gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered. From the early 1970's natural and synthetic polymers began to be investigated for controlled release formulations. The advantages of using biodegradable polymers in clinical applications are apparent. Various natural and synthetic polymers are used for formulation development of in situ forming drug delivery systems.

**Mechanism of floating oral *in situ* gel[24]**

In order to increase the retention time of dosage form in the stomach various attempts have been made and these include floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids so they remain floating in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (given in the Figure 1 (a)), the drug is released slowly at the desired rate from the system. After release of drug from the system, the residual system is emptied from the stomach which results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably floating on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Figure 1(b)). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy Capability variations.

F = F buoyancy - F gravity

= (Df - Ds) gv

Where, F= total vertical force, Df = fluid density,

Ds = object density, v = volume and

g = acceleration due to gravity.

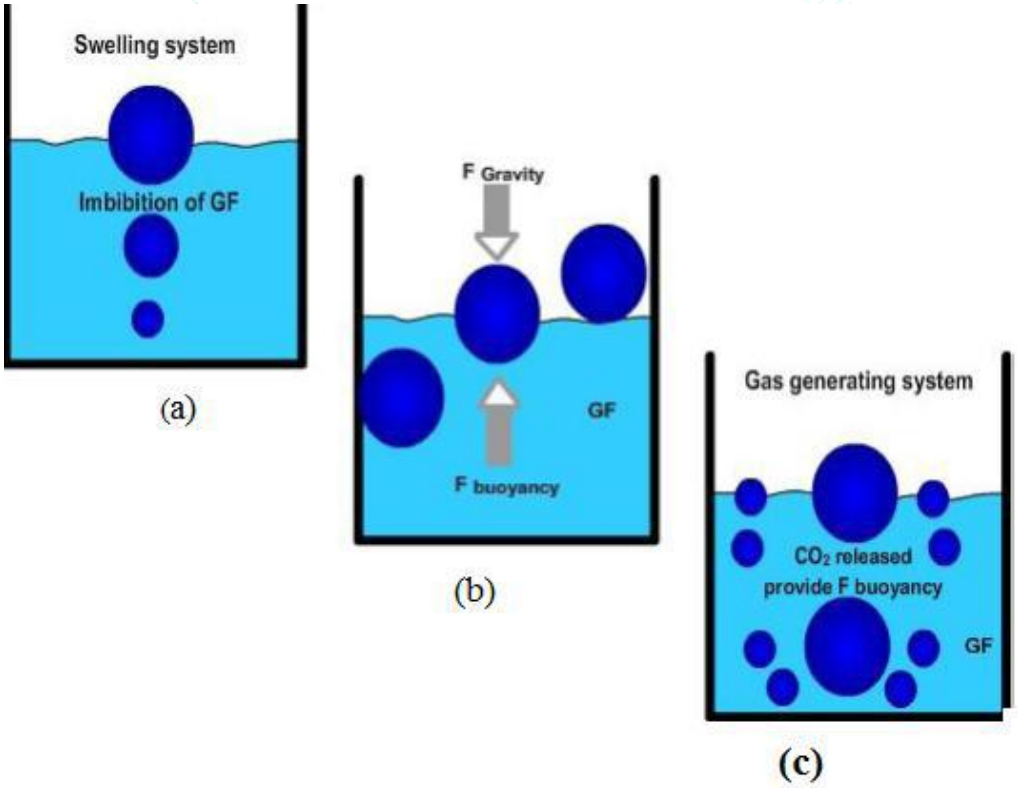


**Figure 1: Mechanism of floating systems[25]**

**GF= Gastric fluid**.

**Approaches of *In- Situ* Gel Drug Delivery**

Different approaches and mechanisms utilized or involved in producing the *in situ* gel formation are as follows:

**1. Physiological stimuli**

A. Temperature

B. pH

**2. Physical changes in biomaterials**

A. Solvent exchange

B. Swelling

**3. Chemical reactions**

A. Enzymatic

B. Chemical

C. Photo-initiated polymerization.

***In situ* formation based on physiological stimuli**

❖ **Thermally triggered system**[26-28]

Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. The use of a biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach in-situ formation.

The ideal critical temperature range for such system is ambient and physiologic temperature, such that clinical manipulation is facilitated and no external source of heat other than that of body is required for trigger gelation. A useful system should be tolerable to account for small differences in local temperature, such as might be encountered in appendages at the surface of skin or in the oral cavity.

Three main strategies exist in engineering of thermoresponsive sol-gel polymeric system. For convenience, temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive, and thermally reversible gels (1, 3). Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST) and contract upon heating above the LCST. Polymers with low critical temperature (LCST) transition between ambient and physiologic temperature is used for this purpose. One of the most extensively investigated polymers that exhibit useful LCST transition is poly(N-isopropyl acrylamide) (PNIPAAm). PNIPAAm is a water soluble polymer at its low LCST, but hydrophobic above LCST, which result on precipitation of PNIPAAm from the solution at the LCST. Pluronics are poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPOPEO) triblock co- polymer that are fluid at low temperature, but forms thermo responsible gel when heated as a consequences of a disorder-order transition in micelle packing which makes these polymers suitable for in situ gelation. A positive temperature sensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST. Polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acrylamide-co-butyl methacrylate) have positive temperature dependence of swelling. The most commonly used thermoreversible gels are these prepared from poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (Pluronics, Tetronics, poloxamer). Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature. Novel "protein polymers" called as ProLastins, which undergo an irreversible sol gel transition, when injected as a solution into the body, the material forms a firm, stable gel within minutes. It remains at the site of injection providing absorption times from less than one week to many months. Such a system would be easy to administer into desired body cavity.

❖ **pH triggered systems**[29-33]

Another formation of in situ gel based on physiologic stimuli is formation of gel is induced by pH changes. All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. The most of anionic pH- sensitive polymers are based on PAA (Carbopol®, carbomer) or its derivatives. Likewise poly vinyl acetal diethyl amino acetate (AEA) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition. Drug formulated in liquid solutions have several limitations including limited bioavailability and propensity to be easily removed. To minimize these factors and maximize this drug delivery by making a poly(acrylic acid) (PAA) solution that would be gel at pH 7.4, by that we found that at concentrations high enough to cause gelation, however, the low pH of PAA solution would cause damage to surface of eye before being neutralized by the lacrimal fluid. This problem was solved by partially by combining PAA with HPMC, a viscous enhancing polymer, which resulted in pH responsive polymer mixtures that was solution at pH 4 and gel at pH 7.4. Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) also has been used as a pH sensitive system to achieve gelation.

***In situ* formation based on physical mechanism**

❖ **Swelling**[34-36]

In situ formation may also occur when material absorbs water from surrounding environment and expand to occupy desired space. One such substance is myverol 18-99 (glycerol mono-oleate), which is polar 1400 lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded in vivo by enzymatic action.

❖ **Diffusion** [37-38]

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N- methyl-pyrrolidone (NMP) has been shown to be useful solvent for such system.

***In situ* formation based on chemical reactions**

Chemical reactions that results in situ gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

❖ **Ionic cross linking**[39-44]

Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones .While k-carrageenan forms rigid, brittle gels in reply of small amount of K+, i- carrageenan forms elastic gels mainly in the presence of Ca2+. Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca2+, Mg2+, K+ and Na. Gelation of the low-methoxypectins can be caused by divalent cations, especially Ca2+. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e. g. Ca2+ due to the interaction with glucuronic acid block in alginate chains. In situ formation catalysed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators. Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Adjusting the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows the

mixtures to be injected before gel formation.

❖ **Enzymatic cross-linking**[45-47]

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❖ **Photo Polymerisation**[48-51]

Photo-polymerisation is commonly used for in situ formation of biomaterials. A solution of monomers or reactive macromer and initiator can be injected into a tissues site and the application of electromagnetic radiation used to form gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromers because they rapidly undergo photo- polymerisation in the presence of suitable photoinitiator. Typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet is not used often because it has limited penetration of tissue and biologically harmful. A ketone, such as 2,2- dimethoxy-2-phenyl acetophenone, is often used as the initiator for ultraviolet photo- polymerization, where as camphorquinone and ethyl eosin initiators are often used in visible light systems. These systems can be designed readily to be degraded by chemical or by enzymatic processes or can be designed for long term persistence *in-vivo.* Photo polymerizable systems when introduced to the desired site via injection get photocured *in situ* gel with the help of fiber optic cables and then release the drug for prolonged period of time. The photo-reactions provide rapid polymerization rates at physiological temperature. Furthermore, the systems are easily placed in complex shaped volumes to an implant formation.

**Table 1: Commercial Formulations of In Situ Polymeric Systems**[51-53]

| Dosage Form | Drugs | Brand Name | Company Country |
|---|---|---|---|
| Opthalmic | Timolol maleate | Timoptic-XE | Merck and Co |
| Regel:depot-technology | Paclitaxel | Oncogel | Macromed's drug delivery |
| Injectable depot formulation | Interleukin -2 | Cytoryn | Macromed's drug delivery |
| Ophthalmic | Lidocaine HCl | Akten | |
| Ophthalmic solution | Azithromycin | Azasite | Insite Vision |

**Table 2: Marketed Products of FDDS**

| Dosage Form | Drugs | Brand Name | Company;Country |
|---|---|---|---|
| Floatingk Controlled Release Capsule | Levodopa, Benserazide | MODAPAR | Roche Products,USA |
| Floating Capsule | Diazepam | VALRELEASE | Hoffmann-LaRoche,USA |
| Effervescent Floating Liquid alginate Preparation | Aluminium hydroxide, Magnesium carbonate | LIQUID GAVISON | Glaxo Smith Kline,INDIA |
| Floating Liquid alginate Preparation | Aluminium - Magnesium antacid | TOPALKAN | Pierre Fabre Drug,FRANCE |
| Colloidal gel forming FDDS | Ferrous sulphate | CONVIRON | Ranbaxy,INDIA |
| G;2as-generating floating Tablets | Ciprofloxacin | CIFRAN OD | Ranbaxy,INDIA |
| Bilayer floating Capsule | Misoprostil | CYTOTEC | Pharmacia,USA |

## RECENT ADVANCES

One of the challenges facing today's pharmaceutical industry centers on coming up with efficient treatment options that are readily acceptable to physicians and patients. Delivery systems must also contribute to a better therapeutic outcome if they are going to provide viable alternatives to pharmaceuticals currently delivered by other routes. *In situ* gel formulations are one of the challenging drug delivery systems.

Various biodegradable polymers are used for formulation of *in situ* gels, but there are fabrication problems, difficult in processing, use of organic solvents for their preparation (especially for synthetic polymer based systems), burst effect and irreproducible drug release kinetics. Natural polymers satisfy the characteristics of an ideal polymer but batch to batch reproducibility is difficult therefore synthetic polymers are used.

Poly(ether-ester) based biodegradable block copolymers are available such as poly(ethylene oxide)-poly(lactic acid) i.e. (PEO-PLA) copolymer, poly(ethyleneoxide)-poly(caprolactone) i.e. (PEO-PCL), poly(ethyleneglycol)-poly(lactide-co-glycolide)-poly(ethylene glycol) i.e. (PEG-PLGA-PEG) copolymer may also be used for formation of *in situ* injectable hydrogels showing improved biocompatibility, biodegradability, reduced burst effect, better mechanical strength and processability

The recent advancement of biotechnologies has led to the development of labile macromolecular therapeutic agents that require complex formulations for their efficient administration. *N*-stearoyl L-alanine(m)ethyl esters when mixed with a vegetable oil and a biocompatible hydrophilic solvent led to the formation of injectable, *in situ*-forming organogel. Following subcutaneous injection, leuprolide-

loaded organogel degraded and gradually released leuprolide for 14 to 25d.

## FUTURE PROSPECTS

Herbal drug delivery is the emerging field in the pharmacy. The use of floating drug delivery system for herbal medicament is the novel approach for the better delivery of drugs. For this purpose there is a great opportunity to work on GI transit profiles. This has given rise to new products with substantial benefits to the patients. Now with the advent of FDDS the products have been designed which could release drug for upto 24 hrs. Some herbals that can be delivered as floating drug delivery systems are:

### Black Myrobalan

The aqueous extract of black myrobalan (familiar with Terminalia chebula Retz) has been shown to have uniform antibacterial activity against ten clinical strains of H. pylori.

### Ginger

Ginger root (familiar with Zingiber officinale Rosc.) has been used traditionally for the treatment of gastrointestinal ailments such as motion sickness, dyspepsia and hyperemesis gravidarum, and is also reported to have chemo preventative activity in animal models.

### Turmeric

Curcumin, a polyphenolic chemical constituent derived from turmeric (familiar with Curcuma longa L.), has been shown to prevent gastric and colon cancers in rodents .various mechanisms had been proposed for the chemo preventative effects, although the effect of curcumin on the growth of H. pylori has not been reported.

### Licorice

In a recent study at the Institute of Medical Microbiology and Virology, Germany, researchers found that licorice extract produced a potent effect against strains of H. pylori that are resistant against clarithromycin, one of the antibiotics typically used in the three antibiotic treatment regimens.

## CONCLUSION

In conclusion, the primary requirement of a successful controlled release product focuses on increasing patient compliance which the *in situ* gels offer. Exploitation of polymeric in- situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the *in situ* gel dosage forms very reliable. Use of biodegradable and water soluble polymers for the *in situ* gel formulations can make them more acceptable and excellent drug delivery systems. In-situ drug delivery provides a great potential for development of liquid orals for their sustained drug release. This floating in-situ gel approach is suitable for drugs having narrow absorption window in stomach or drugs showing local effect in stomach. These types of drugs which are currently present in market as their solid dosage forms (tablets or capsules) will be available as their floating in-situ gels.

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