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Superporous Hydrogels: An Adroit to Drug Delivery System

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ABSTRACT

Development of new drug delivery system has become the requirement of today's pharmaceutical industry. As the number of off-patent drugs and cost of new drug development increases, pharmaceutical companies are managing the life cycles of their products (from product launch to their withdrawal from the market) by adopting new and innovative delivery systems. This gives the pharmaceutical industry another chance to make the most of their current products. Oral route is the most preferred route for administration of drugs as the administration is easy and economic. But the problem is the loss of their functions due to the short residence in the body. About 80% of the administered drugs are excreted without being absorbed. This article comprehensively explains need of hydrogels and its modifications to prolong the residence time of drugs in the body, with brief introduction of associated other drug delivery systems.

Keywords: Superporous Hydrogels, Absorption Window, Stomach Specific Drug Delivery System

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INTRODUCTION

Hydrogels are one of the upcoming classes of polymer-based controlled-release drug delivery systems. Hydrogels are polymeric networks that absorb large quantities of water while remaining insoluble in aqueous solution due to chemical or physical cross-linking of individual polymer chains[1]. The first part of the article explains why there is a need to have a gastroretentive device. The second part tells what the challenges in developing the devices are and how one can deal with them? The third part comprehensively explains the concept of hydrogels.

Why gastroretentive devices?

To tailor and evaluate a drug to a specific organ or even a part of organ, the relevant anatomical and physiological parameters should be considered in the development of gastric retentive dosage forms.

Relevant Factors Affecting Absorption of Drugs & Drug Delivery System via Stomach

The stomach anatomy and physiology constrains the parameters to be considered in the development of gastric retentive dosage forms.

Gastric motility and emptying of food from the stomach:

There are two modes of motility patterns in the stomach and consequently in the intestine. The FASTED STATE PATTERN (commonly called Migrating Motor Complex, MMC) is organized into alternating cycles of activity and quiescence and can be roughly subdivided into three phases: I (basal), II (pre burst), and III (burst)[2]. Phase I lasts 45-60 min, is quiescent, with rare low amplitude contractions; phase II with a length of 30-45 min, has intermediate amplitude contractions[3] and involves bile secretion[4]; phase III is also termed 'housekeeping wave' and extends for 5-15 min. it is initiated in the stomach in most cases (71%), or in the duodenum[5]. Very high amplitude contractions, with a frequency of 4-5 per min[6], and maximal pyloric opening[7], characterize this phase. This enables efficient evacuation of the stomach contents, phase IV has a length of less than 5 min and connects between the maximal amplitude contractions to the basal phase[3]. In general, it takes about 2 h for the activity wave to migrate from the stomach to ileocecal junction[8]. The FED STATE PATTERN consists of continuous motor activity which is induced 5-10 min after ingestion of the meal and persists as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2-6 h, and more typically, 3-4 h. its phasic contractions are similar to those seen during phase II of the IMMC. The stomach churns food while suspended fine particles, typically in a size of less than 1 mm[5], are emptied every 20 s to the duodenum[9].

Emptying of Dosage Form from the stomach:

Size of dosage form is especially important in designing indigestible solid dosage forms (single unit systems). The human pyloric sphincter diameter is 12±7 mm[10]. It has been stated that particles with diameter <7 mm are efficiently evacuated, and it is generally accepted that a diameter >15 mm is necessary for useful prolongation of retention especially during the fasting state.

Density determines the location of the system in the stomach. Systems with density lower than gastric contents can float to the surface, while high-density systems sink to the bottom of the stomach. Both positions may isolate the dosage form from pylorus.

The transit time in the duodenum is relatively short, less than 1 min[11].

Nutritional Factors:

Passage of liquids through Stomach follows first order kinetics[12, 13] whereas food particles are handled differently according to their dimensions. The flow of digestive chow into duodenum depends on (a) the magnitude of antral constriction, (b) the degree of pyloric relaxation, (c) the receptive relaxation of duodenum, and (d) the type of duodenal contractions[14] and on calorific content of food. It has been suggested that stimulation of three types of duodenal receptors regulates the rate of gastric emptying[15]: hydrogen ion receptors, carbohydrates and proteins osmotic pressure receptor, and fat products receptors. In general, emptying of liquid nutrients has a rate of 200 kcal/h, regardless of whether the calories are from fats, carbohydrates or proteins. It has been stated that higher the energy density of gastric contents, the lower the transfer rate of digesta into duodenum. On molar basis, fat causes the greatest delay, followed by protein. The delay by fatty acid appears to increase with chain length[16]. Non-nutrient liquids empty rapidly, with a time to 50% emptying of 8-18 min. solids empty much more slowly than liquids. Digestible nonfat solids are first ground for upto I h, and then emptied in zero order kinetics. Solids and semisolid fats, after being consumed and warmed to body temperature in the stomach, are converted into a liquid. In cases, where the stomach contractions during food digestion and in the second phase of IMMC activity are unable to empty undigested matter, including nondisintegrating DFs, through the relaxed pyloric sphincter, a retropulsion reflex is activated to deliver the material from the pylorus and distal antrum to the proximal antrum and stomach body[17-19].

It has been found in human studies that non-disintegrating tablets ranging from 3 to 11 mm do not differ significantly in their gastric emptying times when administered after rest meals. Profound delay was observed only for 13 mm tablets discharged from the fed stomach[20-21]. There is no exact cut off size for smaller particles and their emptying from the fed stomach may be uncertain and highly variable[22]. Particles smaller than 1 mm size disperse in the liquid content of the stomach and empty as a fluid (square root of the retained volume kinetics)[23].

Non-nutritional Factors:

Stress and aggression increase gastric motility and cause acceleration of gastric emptying rate. Vigorous exercise reduces gastric emptying[24]. The effect of body posture is known to influence gastric emptying and may alter significantly the oral bioavailability of drugs.

pH gradient:

The pH of the resting stomach is acidic, ranging between 1.7 in young people and 1.3 in the elderly, but there are short periods of 7+_6 min characterized by higher values[25]. Immediately after meal ingestion the pH in the stomach increases sharply (to values of 5-6) and decreases again slowly when gastric acid secretion overrides the buffering capacity of the food[26]. This decline lasts between 2 (young people) and 4 (elderly people) h, after which the pH values return to the basal levels of the empty stomach. In fasted humans the duodenal pH is around 6.4. After a meal, the pH of proximal duodenum drops because the influx of acidic chime. The bicarbonate secretion then rapidly buffers the chime as it moves distally.

Diffusional path in mucus layers and possible drug interactions:

The thickness of the mucus layer in the human stomach is about 570 µm[27], whereas in the human colon the thickness is about 100-150 µm[28]. For a solute to reach the lateral surfaces for absorption, an additional barrier needs to be transversed. Apart from being diffusional barrier, mucin can also interact with drugs to decrease their bioavailability. On the other hand, studies in rats have shown that binding of some water soluble drugs to intestinal mucus was essential for their absorption. The acidic mucus is essential for lipid absorption and could be important for the diffusion of lipophilic drugs. In addition to the longitudinal pH gradient, there is a pH gradient starting with the lumen to the absorbing surface[29-30].

Gastric Mucosa:

The epithelial cells of the stomach are characterized by abrupt transition from stratified squamous epithelium extended from the esophagus to a columnar epithelium dedicated to secretion. The surface of gastric epithelium is flat with numerous cavities, being the opening of gastric pits, which extend into the mucosa to form the gastric secretion glands. The unique structure of the gastric mucus together with thick mucus lining practically prevents significant drug absorption from the organ[31].

Molecular Weight and lipophllicity of active ingredient, depending on its ionization state are also important parameter[32].

Molecular weight and lipophillicity of the active agent, depending on its ionization state are also important parameters. Gastric secretion is an aqueous isotonic solution containing H^+, Na^+, K^+, Cl^-, $HCO3^-$, mucus, intrinsic factor, pepsinogen and gastric lipase. The gastro-duodenal lumen pH approaches 2, while the layer immediately adjacent to the epithelium is almost neutral[33-36]. This pH gradient, which helps protect the mucus membrane from digestion by acid dependent pepsin, is maintained by the secretions of HCO_3^- and mucus[37]. Gastric mucus is an approx. 5% aqueous solution of glycoproteins with molecular weight $>10^6$ Da[38]. Its electrical charge is determined by the presence of sailic acid ($pk_a \sim 2.6$)[39-40]. The layer of mucus varies in thickness between 100 µm and 200 µm according to gastric location. Mucus ensures lubrication of solid particles, and its gelatinous consistency enable retention of water and bicarbonate ions close to the epithelium. Diffusion of drugs through the mucus to epithelium is dependent on their size. Shah et al showed that gastric mucus is more permeable to metronidazole (171Da) than ampicillin (365.4 Da).

What Is Absorption Window

The Biopharmaceutical Classification System, introduced by FDA in 1995, has categorized drugs in terms of their solubility and permeability. Class I compounds are well absorbed orally whereas Class II-IV suffer from low solubility, low permeability or both, and will present challenges to the development of products with acceptable oral bioavailability. An increasing number of new chemical entities are to be found in Class II-IV and many of these display variable absorption in different regions of human GIT[41]. Polar compounds and those that rely on some form of facilitated transport process generally display good absorption from upper GIT (stomach and deuodenum). As discussed in the previous section, many factors affect the bioavailability of such drugs. So, the delivery site has to be controlled in order to control the absorption.

Challenges Ahead

Researchers and drug developers face many challenges while developing the dosage forms that will release the medicament at absorption site with optimum size.

POTENTIAL CHALLENGES IN EXPLORATION OF ORAL CONTROLLED RELEASE OF DRUG ADMINISTRATION

Development of Drug Delivery System:

To develop a viable oral controlled-release drug delivery system capable of delivering a dug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.

Modulation of Gastric Transit Time (Absorption Window):

To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of drug dose in the desired absorption window.

Minimization Of Hepatic First Pass Elimination:

If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measured should be devised to either bypass or minimize the extent of hepatic metabolic effect.

It is the intention of this article to review potential developments and new approaches that have been recently explored to meet first two challenges in upper GI window.

FACING THE CHALLENGES:

Development of Drug Delivery Systems:

A recent development of several novel drug delivery systems can be utilized for the controlled delivery of drugs in the alimentary canal. Few of them are discussed below[42]:

Osmotic Pressure Controlled GI Delivery Systems:

The osmotically active drug core is encapsulated in a semipermeable membrane made from rigid biocompatible polymer, e.g. cellulose acetate. A delivery orifice with a controlled diameter is drilled, using a laser beam through the coating membrane for the controlled release of drug solutes. Because of semi permeable characteristics of membrane, it is permeable to influx of water in GIT; on the other hand, it is impermeable to drugs solutes. When in use, water is continuously absorbed into the drug reservoir compartment through the semipermeable membrane to dissolve the osmotically active drug and/or salt.

Hydrodynamic Pressure Controlled GI Delivery Systems(Hydrogels):

A collapsible drug compartment is enclosed inside a rigid shape-retaining housing. The space between the drug compartment and external housing contains a laminate of swellable, hydrophilic cross-linked polymer, e.g., polyhydroxyalkyl methacrylate, which absorbs the gastrointestinal fluid through the annular opening in the bottom surface of housing. This absorption causes the laminate to swell and expand which generates hydrodynamic pressure in the system and forces the drug compartment to reduce in volume and induce the delivery of a liquid drug formulation through the delivery orifice.

Membrane Permeation Controlled GI Delivery Systems:

This approach has successfully applied to the development of controlled-release drug delivery systems for the transdermal controlled delivery of nitroglycerine, estradiol, scopolamine and clonidine through the intact skin for systemic medication for site-specific administration. The membrane permeation has also been utilized in the development of oral controlled release drug delivery systems in which the microporous membranes are produced, during the course of transit in the GIT, directly from a nonporous polymer coating.

Gel Diffusion Controlled GI Delivery Systems:

It is prepared by first dispersing the therapeutic dose in layers of water-soluble polymer, sandwiching the drug loaded polymer layers between layers of cross-linked polymer (water insoluble but water swellable) and then compressing these layers to form a multi laminate device. This device can be further coated with a polymer coating material to form a gastrointestinal device. Furthermore, with incorporation of a sealing layer two incompatible drugs can be formulated in the same device.

pH Controlled GI Delivery Systems:

This design is suitable for controlled release of acidic (or basic) drugs in GIT at a rate independent of the variation in gastrointestinal pH. It is prepared by first blending an acidic (or basic) drugs with one or more buffering agents, granulating with appropriate pharmaceutical excipients to form small granules, and then coating the granules with GI fluid-permeable film-forming polymer.

Ion Exchange Controlled GI Delivery Systems:

This design is suitable to provide the controlled release of ionic (or ionizable) drug for intragastric delivery. It is prepared by first absorbing an ionized drug onto the ion-exchange resin granules and then, after filtration from the alcoholic medium, coating the drug-resin complex granules with a water-permeable polymer and then spray drying the coated granules to produce the polymer-coated-resin preparation.

Modulation of Gastric Emptying Time:

By using adapted formulations, it is possible to target three different parts of GIT, namely stomach, the small intestine and the colon. In this review, an attempt has been made to understand all the relevant parameters to target stomach.

The delivery of drugs to the stomach takes advantage of several features of this organ, particularly the ones related to its physiology like the low pH, motility or gastric emptying time. By affecting the physiology, formulation variables including concomitant administration of other materials, such as food, one can retain a dosage form in the stomach or improve its displacement to the duodenum. In order to retain dosage form in the stomach and, for this purpose different strategies can be suggested: changes in the density of the dosage forms (e.g., high porosity, swelling or expansion, superporous hydrogels) after administration, bioadhesion and changes in geometry of dosage forms[43]. Floating, magnetic retention or geometry changes of the dosage form can be achieved with the aim of increasing the bioavailability of the carrying drug by prolonging the gastric residence time.

The modified release drug delivery system with prolonged residence time in stomach is applicable for drugs i) that are locally acting in stomach ii) that have narrow absorption window which are mostly associated with improved absorption at the jejunum and ileum (due to their enhanced absorption properties e.g. large surface area, in comparison to the Colon) (iii) that are unstable in distal intestinal or colonic environment (iv) that have low solubility at high pH values i.e. which have enhanced solubility in the stomach as opposed to more distal parts of the gastrointestinal tract**.**

The devices which are used as platforms for gastric retention are- Intragastric Floating Systems (low density systems), Mucoadhesive Systems, High density (Sinking) Systems, Magnetic Systems, Unfoldable, Expandable (Swellable) Systems, Superporous Hydrogels (SPH)[44-46].

High Density Systems:

Gastric contents have a density close to water (~1.004 gcm^{-3}). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand peristaltic waves of the stomach. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on diameter of the pellets, although many conflicting reports stating otherwise also abound in literature[47]. A density close to 2.5 g cm^{-3} seems necessary for significant prolongation of gastric residence time[48]. No such system has still been marketed.

Intra-Floating Systems (Low Density System):

These have bulk density lower than gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug & eventually, the residual system is emptied from the stomach.

The three approaches used in designing floating systems are: Hydrodynamically balanced systems (HBS™), Gas Generating Systems and Raft- Forming Systems.

Hydrodynamically balanced systems are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. The polymer is mixed with drug and is usually administered in a gelatin capsule. The capsule readily dissolves in gastric fluid, and hydration and swelling of the surface polymers produce a floating mass. Madopar LP®, based on this system, was marketed by Roche during 1980s[49-51]. The main drawback is the passivity of the operation. It depends on the air sealed in the dry mass center following hydration of the gelatinous surface layer and hence characteristics and amount of polymer[52].

Gas Generating Systems are formulated by incorporating carbonates and bicarbonates in the formulation, Carbon Dioxide is generated in situ when excipients react with acid-either gastric acid or co-formulated as citric or tartaric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate is reported to be 0.76:1[53]. An alternative is to incorporate a matrix with entrapped liquid, which forms a gas at body temperature[54-56]. The approach has been used for single and multiple unit systems.

Raft-forming Systems, a gel-forming solution swells and forms a viscous cohesive gel containing entrapped carbon dioxide bubbles on contact with gastric fluid. They form a layer on the top of gastric fluids typically containing antacids such as aluminium hydroxide, calcium carbonate etc. These are often used for gastroesophageal reflux treatment[57-59].

Drugs reported to be used in the formulation of floating dosage forms are floating microspheres (aspirin, griseofulvin, p-nitroaniline, ibuprofen, terfinadine and tranilast), floating granules (diclofenac sodium, indomethacin and prednisolone), films (cinnarizine), floating capsules (chlordiazepoxide hydrogen chloride, diazepam, furosemide, misoprostol, L-Dopa, benserazide, ursodeoxycholic acid and pepstatin) and floating tablets and pills (acetaminophen, acetylsalicylic acid, ampicillin, amoxycillin trihydrate, atenolol, diltiazem, fluorouracil, isosorbide mononitrate, para- aminobenzoic acid, piretamide, theophylline and verapimil hydrochloride, etc.). Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol®, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. Some of the marketed formulations are listed as follows:

- Valrelease® – floating capsule of diazepam;
- Madopar® – benserazide and L-Dopa combination formulation;
- Liquid Gaviscon® – floating liquid alginate preparations;
- Topalkan® – aluminium – magnesium antacid preparation; and
- Almagate Flot-Coat® – antacid preparation[47].

Expandable Systems:

A dosage form in stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required: a small configuration for oral intake, an expanded Gastroretentive form and a final small form enabling evacuation following drug release[32]. The swelling can be achieved by swelling or by unfolding in the stomach.

Unfoldable systems are made of biodegradable polymers. The concept is to make a carrier, such as capsule, incorporating a compresses system which extends in the stomach due to mechanical shape memory.

Swellable systems are small enough to be swallowed, swells in gastric fluid due to osmotic absorption of water. They are retained because of their mechanical properties. The bulk enables gastric retention and maintains the stomach in the fed state, suppressing housekeeping waves.

Superporous Hydrogels:

Although they are swellable systems, they differ sufficiently from the conventional types to warrant separate classification. With pore size ranging between 10nm and 10 µm, absorption of water by conventional hydrogels is very slow process and several hours may be needed to reach an equilibrium state[52] during which premature evacuation of dosage form may occur. Superporous hydrogels, average pore size >100µm, swell to equilibrium size within a minute due to rapid intake of water by capillary wetting through numerous interconnected open pores[60]. Moreover, they swell to large size (swelling ratio~ 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction.

Mucoadhesive or bioadhesive systems:

These systems are used to localize a delivery device within the lumen to enhance drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach.

Magnetic Systems:

The dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of stomach. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance[52].

Co-administration of Gastric-emptying Delaying Drugs:

This concept of simultaneous administration of a drug to delay gastric emptying together with a therapeutic drug has not received the favour of clinicians and regulatory agencies because of the questionable benefit-to-risk ratio associated with these devices.

What are superporous hydrogels?

Hydrogels are polymeric networks that absorb large quantities of water while remaining insoluble due to chemical and physical cross-linking of individual polymer chains which make them float in the stomach & remain there for a longer period of time. The swelling of (nonporous) hydrogels is determined by the collective diffusion of the polymer network in the water[61]. The diffusion process in plain hydrogels is very slow leading to slow swelling. To make dried hydrogels swell faster, macroporous hydrogels were prepared. Macroporous hydrogels are hydrogels that contains pores in the micrometer range. But their swelling kinetics is not very fast because their pores are not interconnected to each other. The lack of interconnected channels leads to slow swelling[62].

Therefore, a new generation of hydrogels i.e. Superporous hydrogels have been developed. These are the hydrogels having interconnected pores of few hundred µm which swell to equilibrium size in a short period of time i.e. less than 20 minutes, to make them useful as gastroretentive device. The interconnected pores lead to the formation of open capillary channels and fast swelling is achieved via capillary wetting of interconnected pores i.e. water is rapidly absorbed by capillary attractive forces within the pores (Table 1).

Table 1: Comparison of the differences among conventional hydrogels, macroporous hydrogels and superporous hydrogels[64].

	Hydrogels	**Macroporous Hydrogels**	**Superporous Hydrogel**
Pore Size	Nonporous	<10 µm	> 100 µ
Pore connection	-	Lack of interconnected channels	Rich in interconnected channels
Swelling Kinetics	Very Slow	Fast (minutes to hours)	Extremely fast (< 2 min)
Preparation	1. Bulk, Solution, Emulsion, or Suspension Polymerization 2. Physical interaction	1. Crosslinking in the phase sepaated state 2. Freeze-drying of nonporous hydrogels.	1. Crosslinking polymerization in the presence of gas bubbles

Salient Features Of SPHs

Swelling:

- Superporous hydrogels achieve full swelling in 20 min. or less to avoid premature emptying via housekeeper waves as to act as gastroretentive device. It is determined either gravimetrically or volumetrically.
- Swelling is measured in terms of change in weight, volume and dimensions at different time intervals. Two swelling parameters mainly equilibrium swelling time and equilibrium swelling ratio are determined[63].The third swelling parameter is T_{core} which denotes transition from opaqueness in dried form to transparency in swollen form[64].
- The swelling properties are influenced by the type and nature of swelling media (pH, ionic strength).

- The swelling of hydrogels is also affected by different postsynthesis treatments like method of drying and the use of wetting agent.

Mechanical Strength:

- Superporous hydrogels are required to be sufficiently mechanically strong to withstand gastric pressure associated with different contractions.
- Various mechanical testers like bench comparator have been used to measure the mechanical strength in terms of swelling height under 100 cm water pressure and ultimate compression pressure (UCP)[65]. Another device reported is the use of gastric simulator to evaluate SPHs. This applies controlled amount of different type of stresses on the hydrogel (to be tested) immersed in testing fluid to simulate stress conditions in GI fluids. It measures the energy absorbed by the sample until it fails under the stresses applied[64].
- Different post synthesis treatments like acidification, drying and slipperiness affect the mechanical strength
- The slippery property of hydrogel surface helps in smooth migration of peristaltic waves over the surface of hydrogel, which is a requirement for gastric retention. Mucin from porcine stomach provides the slippery nature to the hydrogel surface.

CLASSIFICATION OF HYDROGELS

Polymer Based Classification: Hydrogels can be prepared from natural or synthetic polymers[66] as :

Natural Polymer: Chitosan, Alginate, Fibrin, Collagen, Gelatin, Hyaluronic acid and Dextran.

Synthetic Monomer: Hydroxyethyl methacrylate (HEMA), N-(2-hydroxypropyl) methacrylate (HPMA), N-vinyl-2-pyrrolidone (NVP), N-isopropyl acrylamide (NIPAAm), Vinyl Acetate Acrylic acid, Methacrylic acid, Polyethylene glycol acrylate/ methacrylate (PEGA/ PEGMA), Polyethylene glycol diacrylate/ dimethacrylate (PEGA/ PEGMA) [67,68].

Although hydrogels made from natural polymers may not provide sufficient mechanical properties and may contain pathogens or evoke immune/ inflammatory responses, they do offer several advantageous properties such as inherent biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities and usually nontoxic. Synthetic hydrogels on the other hand, do not possess these inherent bioactive properties. Fortunately, synthetic polymers usually have well-defined structures that may lead to hydrogels with well-defined and fine-tunable degradation kinetic as well as mechanical properties.

Classification Based on their behavior in Physiological Environment (Stimuli Sensitive SPHs)/ SMART HYDROGELS**:** An ideal drug delivery system should respond to physiological requirements, sense the changes and alter the drug release pattern. Hydrogels are said to be smart or intelligent in the sense that they can perceive the prevailing stimuli and respond by exhibiting changes in their physical or chemical behavior resulting in controlled release of drug entrapped[69]. A number of stimuli (external/ internal) exist to control structural changes in polymer network:

Temperature Sensitive Hydrogels:

The common characteristic of temperature-sensitive polymers is the presence of hydrophobic groups, such as methyl, ethyl and propyl groups. Of the many temperature-sensitive polymers, poly(*N*-isopropylacrylamide) (PNIPAAm) is probably the most extensively used. Poly(*N*,*N*-diethylacrylamide (PDEAAm) is also widely used because of its lower critical solution temperature (LCST) in the range of 25–32^{0}C, close to the body temperature. Certain types of block copolymers made of poly (ethylene oxide) (PEO) and poly(propylene oxide) (PPO) also possess an inverse temperature sensitive property. A large number of PEO–PPO block copolymers are commercially available under the names of Pluronics®(or Poloxamers®) and Tetronics®.

Many temperature sensitive hydrogels shows stimuli sensitivity because of polymer's responsive phase transition property. Polymers with LCST, however, decrease their water-solubility as the temperature increases. Hydrogels made of LCST polymers shrink as the temperature increases above the LCST. This type of swelling behavior is known as the inverse (or negative) temperature-dependence. The inverse temperature-dependent hydrogels are made of polymer chains that either possess moderately hydrophobic groups (if too hydrophobic, the polymer chains would not dissolve in water at all) or contain a mixture of hydrophilic and hydrophobic segments. At lower temperatures, hydrogen bonding between hydrophilic segments of the polymer chain and water molecules are dominates, leading to enhanced dissolution in water.

If the polymer chains in hydrogels are not covalently crosslinked, temperature-sensitive hydrogels may undergo sol–gel phase transitions, instead of swelling–shrinking transitions. The thermally reversible gels with inverse temperature dependence become sol at higher temperatures. Polymers that show this type of behavior are block copolymers of PEO and PPO.

Clinical applications of thermosensitive hydrogels based on NIPAAm and its derivatives have limitations. The monomers and crosslinkers used in the synthesis of the hydrogels are not known to be biocompatible, i.e. they may be toxic, carcinogenic or teratogenic. In addition, the polymers of NIPAAm and its derivatives are not biodegradable. The observation that acrylamide-based polymers activate platelets upon contact with blood, together with the unclear metabolism of poly (NIPAAm), requires extensive toxicity studies before clinical applications can emerge[70].

pH- Sensitive Hydrogels:

All the pH-sensitive polymers contain pendant acidic (e.g. carboxylic and sulfonic acids) or basic (e.g. ammonium salts) groups that either accept or release protons in response to changes in environmental pH. Poly (acrylic acid) (PAA) becomes ionized at high pH, while poly(*N*,*N* -diethylaminoethyl methacrylate) (PDEAEM) becomes ionized at low pH. Cationic polyelectrolytes, such as PDEAEM, dissolve more, or swell more if cross linked, at low pH due to ionization. On the other hand, polyanions, such as PAA, dissolve more at high pH.

The pendant acidic or basic groups on polyelectrolytes undergo ionization just like acidic or basic groups of monoacids or monobases. Ionization on polyelectrolytes, however, is more difficult due to electrostatic effects exerted by other adjacent ionized groups. This tends to make the apparent dissociation constant (K) different from that of the corresponding monoacid or became ionized[71].

Since the swelling of polyelectrolyte hydrogels is mainly due to the electrostatic repulsion among charges present on the polymer chain, the extent of swelling is influenced by any condition that reduce electrostatic repulsion, such as pH, ionic strength, and type of counterions[72].

The swelling and pH-responsiveness of poly-electrolyte hydrogels can be adjusted by using neutral comonomers, such as 2-hydroxyethyl methacrylate, methyl methacrylate and maleic anhydride[73-76].

pH-sensitive hydrogels have been most frequently used to develop controlled release formulations for oral administration. pH-sensitive hydrogels have also been used in making biosensors and permeation switches[77].

One of the inherent limitations of synthetic pH sensitive polymers is their non-biodegradability. For this reason, hydrogels made of non-biodegradable polymers have to be removed from the body after use. The non-biodegradability is not a problem in certain applications, such as in oral drug delivery, it becomes a serious limitation in other applications, such as the development of implantable drug delivery agents or implantable biosensors.

Glucose Sensitive Hydrogels:

Insulin has to be delivered in an exact amount at the exact time of need. Self-regulated insulin delivery systems require the glucose sensing ability and an automatic shut-off mechanism. Many hydrogel systems have been developed for modulating insulin delivery, and all of them have a glucose sensor built into the system. pH-sensitive membrane systems, Con A-immobilized systems and Sol–gel phase reversible hydrogel systems are few of them.

Electrical-Signal Sensitive Hydrogels:

Hydrogels sensitive to electric current are usually made of polyelectrolytes, as are pH-sensitive hydrogels. Electro-sensitive hydrogels undergo shrinking or swelling in the presence of an applied electric field.

Sometimes, the hydrogels show swelling on one side and deswelling on the other side, resulting in bending of the hydrogels. The hydrogel shape change (including swelling, shrinking and bending) depends on a number of conditions.

If the surface of hydrogel is in contact with the electrode, the result of applying electric field to the hydrogel may be different from systems where the hydrogel is placed in water (or acetone–water mixture) without touching the electrode. The result will be different yet if the aqueous phase contains electrolytes.

Partially hydrolyzed polyacrylamide hydrogels which are in contact with both the anode and cathode electrodes undergo volume collapse by an infinitesimal change in electric potential across the gel. It should be noted that the hydrogels do not contain any salts. When the potential is applied, hydrated H^+ ions migrate toward the cathode resulting in loss of water at the anode side. At the same time, electrostatic attraction of negatively charged acrylic acid groups toward the anode surface creates a uniaxial stress along the gel axis, mostly at the anode side. The two simultaneous events lead to shrinking of the hydrogel at the anode side[78,79].

When microspherical hydrogel particles are placed in water without any salts, application of an electric field results in the shrinkage of the hydrogels due to electroosmosis (migration of water) and electrophoresis (migration of charged ions) from the hydrogel cathode[80]. This property has been used for modulated drug delivery by 'on–off' of the electric field.

Hydrogels made of poly(2-acrylamido-2-methylpropane sulfonic acid–co-*n*-butylmethacrylate) were able to release edrophonium chloride and hydrocortisone in a pulsatile manner using electric current[81]. Control of 'on–off' drug release was achieved by varying the intensity of electric stimulation in distilled–deionized water.

Chemo mechanical shrinking and swelling of PMA hydrogels under an electric field was used for the pulsatile delivery of pilocarpine and raffinose. In addition to hydrogel swelling and contraction, electric fields have also been used to control the erosion of hydrogels made of poly(ethyloxazoline)– PMA complex in a saline solution[82].

Additionally, Electro-sensitive hydrogels, which are basically pH-sensitive hydrogels, are able to convert chemical energy to mechanical energy[83]. Those systems can serve as actuators or artificial muscles in many applications. All living organisms move by the isothermal conversion of chemical energy into mechanical work, e.g. muscular contraction, and flagellar and ciliary movement.

Light- Sensitive Hydrogels:

Light-sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices. Since the light stimulus can be imposed instantly and delivered in specific amounts with high accuracy, light-sensitive hydrogels may possess special advantages over others. For example, the sensitivity of temperature- sensitive hydrogels is rate limited by thermal diffusion, while pH-sensitive hydrogels can be limited by hydrogen ion diffusion. The capacity for instantaneous delivery of the sol–gel stimulus makes the development of light-sensitive hydrogels important for various applications in both engineering and biochemical fields.

Light-sensitive hydrogels can be separated into UV-sensitive and visible light-sensitive hydrogels. The UV-sensitive hydrogels were synthesized by introducing a leuco derivative molecule, bis(4-di-methylamino)phenylmethyl leucocyanide, into the polymer network[84]. Visible light-sensitive hydrogels were prepared by introducing a light-sensitive chromophore (e.g. trisodium salt of copper chlorophyllin) to poly(*N*-iso-Light-sensitive hydrogels have potential applica- propylacrylamide) hydrogels[85].

Light-sensitive hydrogels can be used in the development of photo-responsive artificial muscles, switches and memory devices. The potential application of visible light-responsive hydrogels for temporal drug delivery was also proposed, based on the response of crosslinked hyaluronic acid hydrogels that undergo photosensitized degradation in the presence of methylene blue[86].

Novel Engineering of Hydrogels for Drug Delivery

Biodegradable Hydrogels

For most biomedical applications, biodegradable hydrogels are favored over non-degradable gels since they degrade in clinically relevant time-scales under relatively mild conditions. The fabrication and modeling of hydrolytically degradable hydrogels are well-developed. For example, West and Hubbell fabricated PLA-b-PEG-b-PLA hydrogels composed of poly(lactic acid) (PLA) and poly(ethylene glycol) (PEG) block copolymers for protein release applications[87].

In addition to hydrolytically degradable hydrogels, synthetic gels incorporating biological moieties that can be degraded enzymatically are also under intensive investigation.

One way to fabricate this type of hydrogel is that the polymers that can be naturally degraded by enzymes (e.g. polycaprolactone can be degraded by lipase) can be copolymerized with PEG to form enzymatically degradable gels[88].

Biomimetic Hydrogels

One drawback of using synthetic and some natural hydrogels for in vivo applications is that they do not possess biological recognition sites for supporting cellular activities. For this reason, relatively inert polymer chains can be tailored with select biological moieties to yield bioactive hydrogels for tissue engineering applications. The Arginine–Glycine–Aspartic acid (RGD) tri-peptide derived from fibronectin is the most commonly used biological moiety in this regard as it mediates the adhesion of many cell types through integrin-binding without the need for protein adsorption on a hydrogel surface[89-92].

The controlled incorporation and presentation of biological cues within hydrogel matrices has also played a role in the development of novel controlled delivery devices. For example, in vivo observations of the sequestering and protection of proteins by the extracellular matrix (ECM) have inspired the design of novel biomimetic hydrogels with specific and reversible protein-binding capabilities[93-95]. This approach is especially useful in controlled release of growth factors for tissue regeneration as it mimics the mechanism and temporal profiles of endogenously produced growth factors.

Other Characteristics

Pressure Sensitive Hydrogels:

The concept that hydrogels may undergo pressure induced volume phase transition came from thermodynamic calculations based on uncharged hydrogel theory. According to the theory, hydrogels which are collapsed at low pressure would expand at higher pressure.

Specific Ion Specific Hydrogels:

Little or no effect of salt concentration on swelling behavior is expected for neutral hydrogels. A nonionic poly(*N*-isopropylacrylamide) hydrogel, however, showed a sharp volume phase transition at a critical concentration of sodium chloride in aqueous solution[96]. Below the LCST, the water content of the hydrogel is a strong function of the sodium chloride concentration. The gel collapses sharply at a critical sodium chloride concentration; this concentration was also found to be temperature dependent. Increasing temperatures leads to a corresponding decrease in the critical concentration of sodium chloride. Other salts tested show no such behavior outside the salting-out regime. Sodium ions were common to all of the salts tested, suggesting that chloride ions played a major role in this phase transition.

Specific Antigen Responsive Hydrogels:

Sol–gel phase-reversible hydrogels were prepared based on atantigen–antibody interactions. The concept is the same as that used in glucose-sensitive phase-reversible hydrogels. A semi-interpenetrating network hydrogel was prepared by grafting an antigen and a corresponding antibody to different polymer networks[96]. The gel is formed by crosslinking interactions that occur upon antigen–antibody binding. Hydrogel swelling is triggered in the presence of free antigens that compete with the polymer-bound antigen, leading to a reduction in the crosslinking density.

Thrombin Induced Infection-Responsive Hydrogels:

For release of antibiotics at the site and time of infection, PVA hydrogels loaded with grafted gentamycin were made. Gentamycin was chemically attached to the polymer backbone through peptide linkers that can be enzymatically degraded by thrombin[97]. This approach was based on the observation that exudates from the dorsal pouch of rats infected by *Pseudomonas aeruginosa* showed sufficiently higher thrombin-like enzymatic activity, toward a certain peptide sequence than exudates from non-infected wounds.

Different Generations of SPHs

The fact that SPHs absorb water very fast even in large sizes make them useful in the development of gastrointestinal platform. To distinguish SPHs with different properties, SPHs are divided into three different generations[98]:

First generation **(Conventional Superporous Hydrogels (CSPH)):**

They are characterized by fast swelling kinetics, high swelling ratio and weak mechanical properties. Dried SPHs are hard and brittle while swollen forms were soft and flexible due to moisture induced plasticization. Regardless of their size in dry state, these swell to large sizes which is few hundred times of its own volume in dried state. These show repeated and rapid swelling and shrinking characteristics at different pH values (1.2-7.5). . Swollen forms are fragile against bending or stress and get easily fall apart or break under light loading due to lack of sufficient mechanical strength[61]. Commonly used monomers are highly hydrophilic vinyl monomers like Acrylamide, ionic monomers like salts of acrylic acid, sulfopropylacrylate potassium etc

Second generation **(Superporous Hydrogels Composites (SPHC)):**

These are characterized by fast swelling, medium swelling ratio and improved mechanical propertyes. A composite agent or matrix swelling additive was incorporated into the same monomer system (as with CSPH). A composite is said to be a matrix of continuous phase in which second phase is dispersed. The composite agent or swellable filler is a cross linked water absorbent hydrophilic polymer that can absorb the solution of monomer including other ingredients. These swollen filler particles act as individual reactor in crosslinking polymerization and as polymerization proceeds throughout the solution, these individual swollen partices are connected together through extended polymeric chains. Upon polymerization, the composite agent acts as local point for physical crosslinking of formed polymeric chains. Upon drying, there is formation of heterogenous interpenetrating networks which are non-integrated. The most widely used composite agent is Crosslinked Sodium Carboxymethylcellulose (Ac-Di-Sol). Other composite agents used are Crosslinked Sodium Starch Glycolate (Primojel) and Crosslinked Polyvinylpyrrolidone (Crosspovidone). These are also used as superdisintegrants in tablets. PVA, PEI, Carbopols are also used as strengthening agents to improve the mechanical strength of SPHs. Though, this modification leads to polymeric networks with improved mechanical strength in swollen state but still these are prone to breakdown under high tensile stress.

Third generation **(Superporous Hydrogels Interpenetrating Networks (SPH IPNs) and Superporous Hybrid Hydrogels (SPHHs)):**

Unlike SPH composites wherein a pre-cross-linked matrix-swelling additive is added. SPH hybrids are prepared by adding a hybrid agent that can be cross-linked after SPH is formed. The hybrid agent is a water-soluble or water-dispersible polymer that can form cross-linked structure through chemical or physical cross-linking. For example, Sodium alginate/ polyacrylamide SPHH can resist high compression up to 25 N whereas SPHC of same polymer system break even under 2N compression force. Various hybrid agents have been used and specific treatment has been applied to get integrated IPN Hydrogels e.g. natural hydrocolloids like sodium alginate, chitosan, sodium CMC, Pectin and synthetic water soluble PVA. Natural hydrocolloids show ionotropic gelation via treatment with metal ion like Calcium, iron etc. (e.g. Sodium Alginate with Ca^{2+} ions, Chitosan with phosphates).

METHOD OF PREPARATION OF SPHS:

Methods of Preparation

Porosigen Technique Porous hydrogels are prepared in the presence of dispersed water soluble porosigens e.g. micronized cellulose, sodium chloride, PEG etc. these create meshworks and can be removed by washing with water. The pore size of hydrogels depends on the size of porosigens[99].

Phase separation technique This method is applicable for limited type of porous hydrogels e.g. HEMA, NIPAM. However, there is not much control over porosity of prepared hydrogels[100].

Gas blowing technique: In this method, superporous hydrogels are prepared by crosslinking polymerization of monomers in the presence of gas bubbles. Different ingredients like monomer, crosslinker, foam stabilizer, polymerization initiator, initiation catalyst (if any) and foaming agent are added sequentially in a test tube of specific dimensions. Initially and before addition of foaming agent, the pH of monomer solution is maintained at 5 to 6, because low pH favors foaming process. The addition of foaming agent leads to formation of bubbles followed by increase in pH of solution. The increased pH accelerates the polymerization process. Thus, simultaneous foaming and gelation lead to the formation of homogenous porous hydrogels i.e. Superporous hydrogels[63]. After synthesis, SPHs are subjected to washing, drying using different methods which influence the swelling and mechanical behavior of resulting hydrogels. This is the most widely used method for the preparation of superporous hydrogels.

Following is the list of basic ingredients which are used in synthesis of SPHs and its different generations.

Monomer- Acrylic Acid, Acrylamide, SPAK, HEMA, NIPAM etc.

Crosslinking Agent- N, N'-methylenebisacrylamide (Bis) is used most widely in blowing technique. Glutarldehyde (chemical crosslinker), metal ions like calcium, iron and phophorus, are used in ionotropic crosslinking of hydrocolloids.

Foam Stabilizer- Pluronic F127, Pluronic P105, Silwet L7605, Span, Tween etc.

Polymerization initiator pair: APS/TEMED (Ammonium Persulfate/ N,N,N,N-tetramethylethylenediamine, KPS/Sodium Metabisufite, APS/Sodium metabisufite, Azo-initiator (V545)etc.

Foaming Agent: Sodium Bicarbonate ($NaHCO_3$)

Composite agent: Various Superdisintegrants like Crosslinked Sodium Carboxymethylcellulose (Ac-Di-Sol), Crosslinked Sodium Starch Glycolate (Primojel), Crosslinked Polyvinylpyrrolidone (crosspovidone) and Ac-Di-Sol is mostly used.

Hybrid agent: Natural polymers like Sodium Alginate, Sodium Carboxymethylcellulose, Chitosan based on ionogelation and synthetic polymers like Poly Vinyl Alcohol (PVA) based on cryogelation.

Hydrogels intended for drug delivery are required to have acceptable biodegradability which necessitates the development of novel synthesis and crosslinking methods to design the desired products; here crosslinking plays an important role. A great variety of crossinking approaches have been developed to develop desired hydrogels for each particular application[101]. Novel Cross-linking methods are (Figure 1):

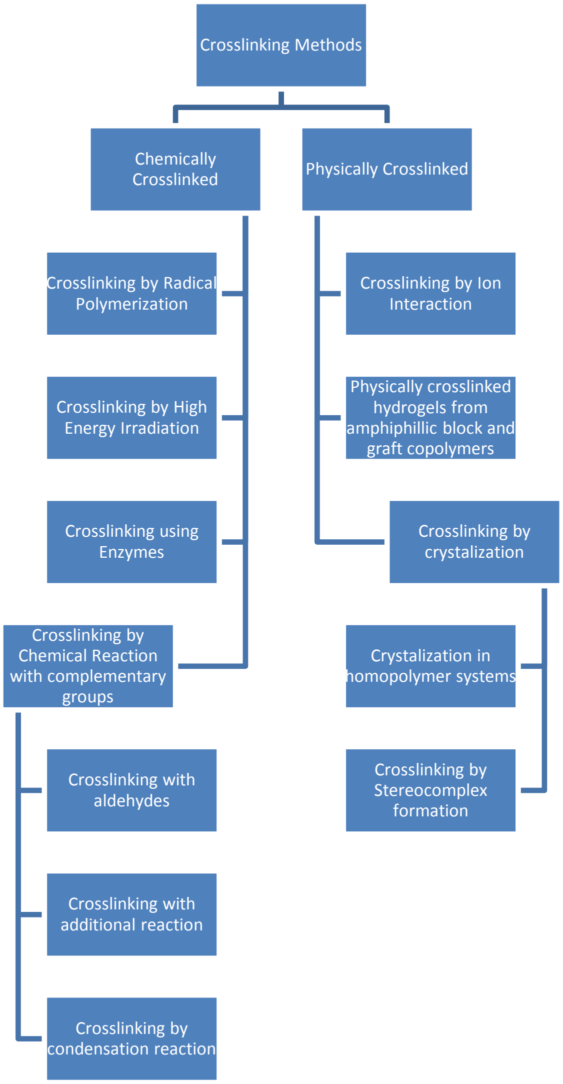

Figure 1: Novel Crosslinking Methods Used In Hydrogels[102]

General Requirements for Superporous Hydrogel Preparation by Gas Blowing Technique

During the synthesis of SPHs via gas blowing technique, gelation and foaming processes lead to formation of porous SPHs. The following points should be considered for better synchronization between these two processes to get homogenous porous product[63]:

- The monomer should be used as aqueous solution form to prevent excess rise of temperature (due to high heat of polymerization) which may lead to heterogeneity in the structure.
- Since acid dependant foaming agent ($NaHCO_3$) is used as foaming agent, the glacial acetic acid or acrylic acid should be added to interact with bicarbonate ions for generation of gas bubbles. The addition of acid also maintains the pH of the monomer solution between 5 to 6, which favors foaming but polymerization is slow at this pH. The reason is that in monomer

solution at this pH (5-6), TEMED catalyzed free radical generation of APS was inhibited due to protonation of TEMED, resulting in very slow polymerization.

- Addition of bicarbonate also increases the pH of the monomer solution to 7-8 which favors polymerization. At this pH, TEMED in its free base form, catalyze free radial generation from APS and accelerate polymerization. Excess of $NaHCO_3$ (100-120mg) is used to increase the final pH of monomer solution above neutral and act as a trigger for accelerated polymerization.
- Thus, foaming and gelation are two processes which are required to occur simultaneously to get homogenous porous hydrogels. For this, the timing of addition of foaming agent and the onset of gelling are controlled carefully. If foaming starts too early or polymerization occurs too slowly then the foam get raised and subsided before onset of gelling, resulting in formation of poorly or nonporous hydrogels. If foaming starts too late, the solution becomes too viscous for even distribution of gas bubbles, resulting in formation of porous nonhomogenous hydrogels
- Gelling or crosslinking polymerization Process is also governed by careful selection of monomer (type and concentration), initiator pair, (type and concentration), temperature, solvent system etc[63]. For Example, AA, AM, SPAK, NIPAM monomers in more than 10%concentration, show fast gelling (1-2 min) in aqueous solution with APS/TEMED initiator pair (1-2%). HEMA, HPMA, VP show fast gelling at high temp. (60^0C -80^0C) with APS/TEMED pair. Vinylpyrrolidone (VP), Acrylic acid monomers show effective gelling with Azo-initiator (V545).
- Foaming process is governed by control on timing for addition of foaming agent and start of gelling process. Gelling should start in stabilized foam to get homogenous porous hydrogel. The foam stabilizer like Pluronic F127 (0.5-1.0%) produce adequate and prolonged foam stability with acrylate monomers and a combination of Pluronic F127, Pluronic P105 and Silwet L7605 has been used with hydrophobic monomers like NIPAM and HEMA. Also the foam size is controlled by amount of acid present in the monomer solution[63].

Release Mechanism

As discussed in the previous sections, hydrogels have a unique combination of characteristics that make them useful in drug delivery applications. Due to their hydrophilicity, hydrogels can imbibe large amounts of water (90 wt. %). Therefore, the molecule release mechanisms from hydrogels are very different from hydrophobic polymers. Both simple and sophisticated models have been previously developed to predict the release of an active agent from a hydrogel device as a function of time. These models are based on the rate-limiting step for controlled release and are therefore categorized as follows:

1. Diffusion-controlled
2. Swelling-controlled
3. Chemically-controlled.

Diffusion-controlled is the most widely applicable mechanism for describing drug release from hydrogels. Fick's law of diffusion with either constant or variable diffusion coefficients is commonly used in modeling diffusion-controlled release. Drug diffusivities are generally determined empirically or estimated a priori using free volume, hydrodynamic, or obstruction-based theories[103].

Swelling-controlled release occurs when diffusion of drug is faster than hydrogel swelling. The modeling of this mechanism usually involves moving boundary conditions where molecules are released at the interface of rubbery and glassy phases of swollen hydrogels. The release of many small molecule drugs from hydroxypropyl methylcellulose (HPMC) hydrogel tablets is commonly modeled using this mechanism[104-105].

Chemically-controlled release is used to describe molecule release determined by reactions occurring within a delivery matrix. The most common reactions that occur within hydrogel delivery systems are cleavage of polymer chains via hydrolytic or enzymatic degradation or reversible or irreversible reactions occurring between the polymer network and releasable drug. Under certain conditions the surface or bulk erosion of hydrogels will control the rate of drug release. Alternatively, if drug-binding moieties are incorporated in the hydrogels, the binding equilibrium may determine the drug release rate. Chemically-controlled release can be further categorized according to the type of chemical reaction occurring during drug release[103,106,107].

HYDROGELS ARE SUITABLE FOR WHICH CATEGORY OF DRUGS?

- Most drugs are not significantly absorbed in stomach, due to a combination of short retention time e.g. in comparison to the colonic transit time of dozens of hours[108], and small surface area of 3.5 m[109]. Exceptions are furosemide[110] and salbutamol[111].
- Identifying drugs or drug candidates which may benefit from compounding into GRDFs involves various considerations. Such drugs should be stable in gastric milieu and have either a narrow absorption window, or be used for gastro–duodenal local therapy. The following pharmacodynamic aspects may further substantiate the potential benefits from such compounding[112-113]
- Reduced fluctuations in drug effects: continuous input of the drug following GRDF dministration narrows the range of blood drug concentrations.Thus, fluctuations in drug

effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for narrow therapeutic index drugs.

- Improved selectivity in receptor activation: minimization of fluctuations in the drug concentration enables certain selectivity in the elicited pharmacodynamic effects of drugs that activate different types of receptors at various concentrations.
- Reduced counter-activity of the body: in many cases the pharmacodynamic response, which intervenes with the natural physiologic processes, provokes a rebound activity of the body that minimizes drug action i.e. causes tolerance. Slow input of the drug e.g. furosemide, from a GRDF into the body has been shown to minimize the counteractivity[114].
- Extended time over critical (effective) concentration: for certain drugs that have nonconcentration dependent pharmacodynamics e.g. b-lactam antibiotics, the clinical response is not associated with peak concentration, but rather, with the time span where drug levels are over a critical therapeutic concentration. GRDF may extend the duration of time over an effective concentration and thus improve therapy.
- Minimized adverse activity at the colon: prolonged GRT of DF minimizes the amount of drug that reaches the colon. Thus, undesirable activities in the colon may be prevented. For example, this pharmacodynamic aspect provides an additional rationale for GRDF of b-lactam antibiotics that are absorbed only from the small intestine, as their presence in the colon leads to the development of microorganisms' resistance.

I. METHODS OF MONITORING ABSORPTION SITE OF DRUGS INGI SYSTEMS

The drug absorption site through GIT can be monitored either by in situ or by in vivo methods.

The *in situ* methods include open loop techniques such as single-pass perfusion, recirculating perfusion and oscillating perfusion as well as closed loop techniques[114]. A drug solution is placed or perfused in the predetermined GI site of an animal model. The amount of drug or metabolite is measured either in the blood stream or in the loop. There is appreciable membrane storage in the case of highly lipophilic drugs during gastrointestinal absorption which may destroy the direct correlation between drug absorption and luminal disappearance[115]. Furthermore, in order to measure in the loop, a non-absorbable marker such as PEG 4000, phenol red or inulin, is often added to the drug solution to assess the net intestinal water transport[116].

The *in vivo* methods include: a. Perfusion Technique, b. Local Instillation, c. High-frequency capsule, and d. Pharmacoscintigraphy and deconnvolution methods. In **Perfusion Technique**, a multiluminal tube is placed in a predetermined site of the gastrointestinal tract. This tube is used to introduce the drug in solution or in a homogenized meal. The disappearance of the drug is measured in the site using non-absorbable markers[117]. During **Local Instillation**, the drug is placed via a catheter at different sites of the gastrointestinal tract which are localized by endoscopy, by fluoroscopy or by pH monitoring. Blood samples are then collected at various time intervals. The drug absorption is excluded from parts distal to the administration site. The effect of the pH solution or meal may be determined in order to assess a possible degradation in the stomach as well as to assess the influence of food intake on drug absorption[118-119]. In **High-frequency capsule,** the transit of a capsule along the gut is traced by X-ray. In **Pharmacoscintigraphy and deconvolution methods,** the position of a controlled-release system within the gastrointestinal tract during the pharmacokinetic study is determined by gammascintigraphy[120]. The very small amount of tracer needed has no influence on the properties of the preparation[121]. As opposed to methods where the drug is administered in solution, this method has the advantage of determining, under normal physiological conditions[122].

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