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Swelling agents and devices in oral drug delivery

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Swelling agents are hydrophilic crosslinked polymers, which swell from 10 to 1,000 times their own weight when placed in an aqueous medium. Depending on their swelling properties, these materials have been exploited in developing three different classes of materials in pharmaceutical industries, i.e. swellable matrices, superdisintegrants and swelling devices. Since their development, these pharmaceutical excipients have found significant applications in drug delivery area. This review examines the properties of swelling agents and devices with the focus on drug delivery applications.

Key words: Swelling agent – Swelling device – Drug delivery – Pharmaceutical industry.

All products, including pharmaceutical products, have certain life cycles which last from their launch to their withdrawal from the market. As the number of off-patent drugs and the cost of new drug development increases, pharmaceutical companies are managing the life cycles of their products by adopting new and innovative delivery systems. This gives the pharmaceutical industry another chance to make the most of their current products. While there is no doubt that new compounds are the most important component in drug formulations, drug delivery technologies are now considered an equivalent component in drug development. Controlled-release technologies allow for effective use of existing drugs and successful development of new drug candidates. Therefore, developing new drug delivery technologies and utilizing them in product development is crucial for pharmaceutical companies to compete and survive.

I. SWELLING AGENTS

A swelling agent is a three-dimensional network of hydrophilic polymer chains that are chemically or physically cross-linked. Depending on their structure, swelling agents can absorb aqueous or organic solutions. If the former is the case, a swelling agent is called a hydrogel. Since most swelling agents are hydrophilic in nature, they can absorb significant amounts of gaseous (moisture) or liquid water. The driving force for the absorption or swelling process is generally a balance of three forces of osmotic, electrostatic and entropy-favored dissolution of polymer in water. Elastic forces are tailor-made into the hydrogel structure to control the entropy of the dissolution process. In other words, the densities of cross-links in the hydrogel structure will prevent the hydrogel from infinite dissolution in water.

Swelling agents can be divided into chemical and physical hydrogels. In a chemical hydrogel, all polymer chains are cross-linked to each other by covalent bonds, and thus, the hydrogel is one molecule regardless of its size. In the synthesis of chemical hydrogels, a multifunctional cross-linker is used to link the hydrogel chains. For addition polymers, the multifunctional cross-linker contains more than one double bond. For condensation polymers, the multifunctional cross-linker should normally have multiple functional groups. With physical hydrogels, the precursor hydrophilic polymer will be treated physically with active agents. Polymers should therefore contain functional groups capable of reacting with ions, or other functional groups like aldehydes.

The presence of water at the surface of hydrogels results in low frictional surface forces, which is a desirable property in developing biocompatible materials. Swellable hydrogels can swell at different rates depending on many factors; among these, the cross-link density is the most important factor. The cross-links prevent the chains from collapsing onto each other, thereby decreasing the inter-chain intermolecular forces. This will facilitate the intrusion of water into the hydrogel structure or more accurately the diffusion of polymer chains into the water phase. As a result, highly cross-linked hydrogel networks display faster swelling compared to their lightly-cross-linked counterparts. Controlled release drug delivery may take advantage of tailor-made swelling kinetics, which can be provided by different means including a change in cross-link density.

II. SWELLING PROCESS

Three major elements control the swelling process of a hydrogel: the cross-link content, the ionic content and the hydrophilic content.

Cross-link content: Thermodynamically speaking, different states of matter may be assigned to the hydrogel molecules in water. For a non-cross-linked hydrogel, hydrogel molecules will eventually dissolve in water and occupy the whole volume, which is already occupied by water. In this way, non-cross-linked hydrogel chains behave like typical liquid molecules as they reach high entropy states by occupying the entire space. Most hydrocolloids display a pseudo-swelling behavior, in which no real physical swelling occurs. Instead, the hydrocolloid chains will start making a gel phase in the presence of water. At a low ratio of water to hydrogel and in the short period of contact time, the gelling process resembles the swelling process of the cross-linked hydrogels. At a very high ratio of water to hydrogel and in the long period of contact time, the hydrogel chains are significantly hydrated and eventually dissolved. Pseudo-swelling behavior is the major mechanism of controlled drug delivery in tablet matrices. As the cross-link density increases, hydrogel molecules behave similar to semi-solid molecules with less entropy. At the extreme, when cross-link density is high, the hydrogel molecules behave like a solid with minimum entropy, which enables them to swell to minimum extent. Since entropy of the hydrogel molecules increases in water, the swelling of the hydrogel will be spontaneous if hydrogel molecules have sufficient mobility, which is dependent on the hydrogel cross-link density. *Figure 1* displays the important difference in entropy between non-cross-linked and cross-linked hydrogels when they are placed in an aqueous medium.

Ionic content of the system and the surrounding: Structurally speaking, swellable hydrogels can be divided into two major groups:

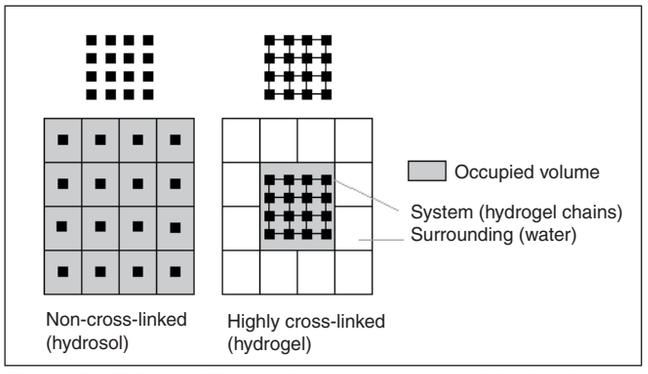


Figure 1 - Entropy difference between non-cross-linked and cross-linked hydrogels.

ionic and non-ionic. At a given amount of elastic forces, swelling of the ionic hydrogels will be a more entropy-favored process as opposed to their non-ionic counterparts. As the number of ions within the hydrogel structure increases, more and more osmotic and electrostatic forces will be created within the hydrogel structure. This forces a typical hydrogel to behave thermodynamically like a liquid as it occupies more space of the surroundings. On the other hand, changing the nature of the surroundings, which is water, can control the entropy-driven swelling process of the ionic hydrogel. Adding ions to the surroundings limits the swelling capacity of an ionic hydrogel and changes its state of matter. In other words, ionic hydrogel chains behave generally like solid and semi-solid molecules in the high and low ionic strength aqueous solutions, respectively.

Hydrophilic content: With no doubt, the hydrophilic content of the hydrogel will affect the intermolecular forces responsible for diffusion and swelling. As hydrophilicity of the hydrogel increases, the interaction between water and hydrogel will increase too; this facilitates water diffusion and leads to greater swelling.

III. SWELLING MECHANISM

When a hydrogel matrix is exposed to the aqueous medium, water will be absorbed by the hydrogel. At any point in time after exposure to water, three regions will generally be distinguishable within the hydrogel matrix. The first region is highly swollen with water and is mechanically weak. This hydrogel layer will act as a diffusional barrier for the remaining water; as such, the second region will be characterized as moderately swollen and is relatively strong. The third region is yet to get wet with water and will remain almost in its glassy state for a longer period of time. Therefore, water diffusion into the hydrogel matrix will differentiate the whole matrix into three distinct regions: "glass" (mostly hydrogel), "tough rubber" (significant proportion of water and hydrogel) and "soft rubber" (mostly water) regions. Across the matrix, water content of the hydrogel increases from the core to the surface as hydrogel content decreases. This is the basic mechanism that affects drug release. Although drug release is generally affected by the size of the drug and polymer, drug solubility, type of polymer, drug/ polymer interaction, and a few other minor factors, the glass-rubber transition of the hydrogel particles will remain the major factor in drug release. Two different subjects may be distinguished, i.e., water penetration into the hydrogel matrix and the drug release from the hydrogel matrix. For a hydrogel matrix in the absence of drug, water penetration will depend on how fast polymer chains will relax. Therefore, water penetration will be controlled by diffusion and relaxation depending on the water content of the hydrogel matrix in the different regions. Regardless of drug solubility, whether water-soluble or water-insoluble, the extent of swelling in different layers and the corresponding mechanical strengths of the layers will generally dictate the rate at which the drug is released. Apparently, as swelling increases, drug release will be more diffusion-controlled

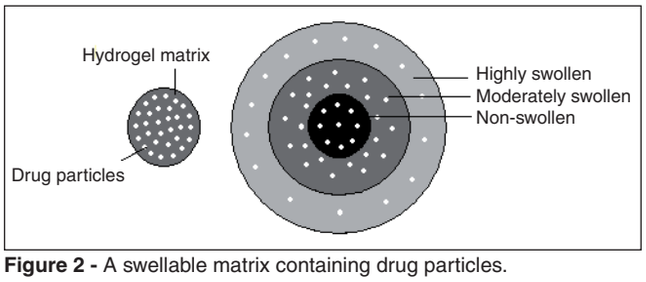


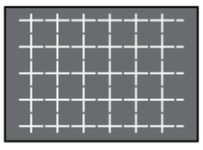
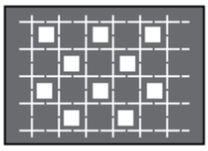
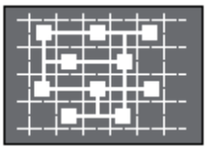
Figure 2 - A swellable matrix containing drug particles.

or erosion-controlled for water-soluble and water-insoluble drugs, respectively (*Figure 2*).

Initially, a swellable hydrogel is in its glassy state. When water comes into contact with the hydrogel, swelling will begin as water penetrates between the chains. The process is self-accelerating and a sheath of the swollen polymer is formed. Water then travels through the sheath to reach the interior of the hydrogel. In general, Fick's laws of diffusion govern permeation, while the degree of water absorption is proportional to the square root of time, which is known as Case I sorption. In some cases, however, the amount of absorption is directly proportional to time and Case II sorption occurs. With Case I, the rate of advance of permeant (water in this case) is determined by the rate of water diffusion and with Case II the rate of advance is determined by the rate of expansion of the material (polymer relaxation). Experimental data demonstrates that the overall swelling behavior of the swellable hydrogel changes progressively from Case II (relaxation controlled) in the early stages of swelling to Case I (diffusion controlled) in the later stages [1]. Major parameters affecting the rate of expansion or relaxation of polymer chains at the early stages of swelling are the type of polymer (affects inter-chain interactions), functional group (water-polymer interaction), drying, cross-linking and porosity. Events during the early stages are fundamentally important in designing fast swelling hydrogels including superdisintegrants, superporous hydrogels and modified generations of superabsorbent polymers. For instance, the principal action of pores and cross-link joins is to decrease the intermolecular forces and to increase the wicking action. These two factors to a great extent can contribute in tailoring the kinetics and thermodynamics of the swelling process. General features of different hydrogel structures are shown in *Table I*.

Kim *et al*. [2] used anionic hydrogels as oral protein delivery carriers because of their pH-responsive swelling behavior. The dynamic swelling behavior of poly(methacrylic acid-co-methacryloxyethyl glucoside) and poly(methacrylic acid-g-ethylene glycol) hydrogels was investigated to determine the mechanism of water transport through these anionic hydrogels. The water transport was significantly affected by the pH of the swelling medium and became more relaxation-controlled in a swelling medium of pH 7.0. Bussemer *et al*. [3] investigated the swelling behavior of various swellable polymers for pulsatile drug delivery applications. They found that various swellable excipients have different swelling energy or force; the order is croscarmellose sodium (Ac-Di-Sol) > low-substituted hydroxypropyl cellulose (L-HPC) > sodium starch glycolate (Explotab) > crospovidone (Kollidon-CL) > hydroxypropyl methylcellulose (Methocel K100M). Analysis of the time-dependent swelling force data confirmed a diffusion-controlled swelling force development, predominantly controlled by the penetration rate of the swelling medium. Kosmidis *et al*. [4] discussed the mechanism of drug transport in axial and radial directions from a cylindrical dosage form. Vlachou *et al*. [5] discussed the fronts created by the swelling process, their movement and the effect of drug solubility on release mechanisms. They prepared tablets comprising hydroxypropyl methylcellulose (HPMC), HPMC with sodium diclofenac (relatively soluble in the given buffer solution) and HPMC with furosemide (insoluble in the given buffer solution). The results showed that the rate and mechanism of drug release from swellable matrices

Table I - Comparison between different types of hydrogel networks.

				
Hydrogel type	Non-cross-linked	Poreless cross-linked	Porous cross-linked	Superporous cross-linked
Porosity	Poreless	Nanoporous	Macroporous	Interconnected macroporous
Intermolecular forces	High	Low	Lower	Lowest
Chain packing	Tight	Loose	Looser	Loosest
Water diffusion	Slow	Fast	Very fast	Ultra-fast
Timed Swelling capacity	Low	High	High	High
Resistance to water permeation	High	Low	Low	Very low
Swelling rate	Slow	Fast	Very fast	Ultra-fast

depend on the dissolution, the diffusion of the drug, the translocation of undissolved drug particles in the gel layer, and the solubility of the drugs used. Wu *et al*. [6] developed a mathematical model to describe the transport phenomena of a water-soluble drug (caffeine) from highly swellable polyethylene oxide (PEO) cylindrical tablets. The overall drug release process was found to be highly dependent on the matrix swelling, drug and water diffusion, polymer dissolution and initial dimensions of the tablets. Isik *et al*. [7] prepared random copolymers of acrylamide and N-vinylimidazole using redox system. The influence of pH, temperature, and ionic strength on the swelling behavior of the copolymer hydrogels was investigated. The hydrogels exhibited the highest equilibrium swelling in basic medium at high temperature. Swelling kinetics of the hydrogels was found to be non-Fickian at an ordinary temperature of 25°C. The process tended to be Fickian at a higher pH and temperature. Krusic *et al*. [8] studied the swelling behavior of copolymer hydrogels of N-isopropylacrylamide (NIPAM) and itaconic acid (IA) in response to temperature and pH of the swelling medium. The equilibrium degree of swelling for PNIPAM and PNIPAM/IA copolymers was greater at lower temperatures. A swelling-deswelling study showed that the deswelling process of the hydrogels was faster than the swelling process. Authors found that the diffusion exponent and the diffusion coefficient both increase with the acid content. Lee *et al*. [9] synthesized porous thermoreversible hydrogels from N-isopropylacrylamide and poly(ethylene glycol) methylether acrylate. The influence of pore volume in the gel on the physical properties, swelling kinetics, and solute permeation from these porous gels was investigated. The results show that the surface areas, pore volumes, and equilibrium swelling ratios for the porous gels increased with increasing MW of PEG, but the shear moduli and effective cross-linking densities decreased with increasing MW of PEG. The results from the dynamic swelling kinetics show that the transport mechanism was non-Fickian. The diffusion coefficients of water penetrating into the gels increased with increasing pore volume of the gels. Jamzad *et al*. [10] developed a new monolithic matrix system based on swellable hydroxypropylmethylcellulose (HPMC) or erodible polyethylene oxide (PEO) to deliver glipizide. Glucotrol XL push-pull osmotic pump (PPOP) was used as the reference. The interrelationship between matrix hydration, erosion and textural properties were determined and analyzed under the dissolution test conditions. Results indicate that in the case of low dose/low soluble drug, the total drug release in a zero order manner greatly depends on the synchronization of erosion and swelling fronts during the entire dissolution study.

IV. ISOTROPIC SWELLING

As a result of isotropic swelling, swellable hydrogels can generally keep their original shape after swelling. In other words, a gel system usually swells isotropically in all directions. Hydrogels will swell isotropically if no internal stress is applied to the gel during their synthesis. In other words, if the synthesis is isotropic, swelling will occur isotropically too. The origin of internal stresses can be mechanical, physical or thermal. Like thermoplastics, when they are extended in one direction, they will behave heterotropically under stress. A known example of heterotropic products is tissue paper, which displays different deformational behavior under tearing or tensile stress. Superporous hydrogels are made porous and the shape of the pore will determine the extent to which swelling occurs isotropically. The swelling will be lower in the direction where pores are elongated (oval shape). On the other hand, circular pores will favor isotropic swelling. This fact is shown in *Figure 3*.

A pore can be characterized by its dimensions, x and y. When hydrogels swell to their equilibrium, dimensions will be changed respectively to x' and y'. In the case of a circular pore for which x and y are similar, swelling will occur isotropically, so that x' and y' will be similar too. If the pore is elongated along the x-axis, x will be assigned as the major radius of the ellipse. In this case, hydrogel chains are elongated along the major radius and build up a pseudo-crystalline region. Since chains are elongated, the inter-chain interactions will be stronger and swelling will be delayed significantly. For a reasonable period of swelling time, the swelling in the direction perpendicular to the elongated direction will therefore be higher [11].

Anisotropic swelling behavior can be induced into swellable matrices like tablets. Tablets are generally manufactured under compression. A hydrogel polymer which is used in the tablet formulation will behave differently along the axis which is compressed. In the presence of water, the compressed hydrogel chains will swell to a greater extent in axial than in radial directions. This behavior is generally observed in sustained release tablets where hydroxypropyl methylcellulose is used as a swelling agent [12]. An anisotropic swelling with scleroglucan/borax [13] and xanthan gum [14] tablets have also been reported. As discussed by Pallechi *et al*. [15], the compressed matrix elongates essentially in its axial direction, while radial swelling is almost negligible.

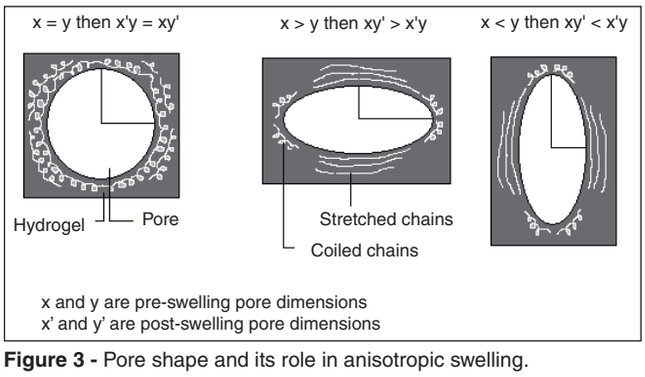


Figure 3 - Pore shape and its role in anisotropic swelling.

1. Pharmaceutical applications of swellable hydrogels

Swelling agents or swellants are structurally cross-linked hydrophilic polymers, which absorb significant amounts of water or aqueous fluids in relatively short periods of time. Depending on the origin of the material (natural or synthetic) and the manufacturing process, swellants offer a vast range of swelling properties as far as the kinetics and thermodynamics of swelling are concerned. Natural polymers are normally high molecular weight materials and generally swell slowly to their equilibrium. On the other hand, swelling properties of the synthetic swellants can be tailor-made using different formulation and processing conditions. Semi-synthetic swellants have been increasingly studied as the properties of natural swellants are modified using chemical approaches.

2. Swelling agents as controlled release matrix

There are two ways in which swellable hydrogels can help control the drug release. The hydrogel can be mixed with the drug and other excipients and compressed into a tablet or a tablet containing a drug and other excipients may be coated with the swellable hydrogel. Both approaches can be used with either water-soluble or water-insoluble drugs. The drug will be released from a swellable hydrogel through diffusion, degradation or both depending on the level of swelling and the solubility of the drug. If the drug is water-soluble, diffusion will be the primary approach. On the other hand, degradation will be a primary mechanism for the release of water-insoluble drugs. If swelling is not excessive, drug release through degradation will be less likely to occur or occurs as a secondary mechanism.

3. Important factors in drug release

Mechanical properties of the gel: Mechanical properties are a fundamental factor in determining the onset of erosion for the non-biodegradable swellable polymers. A swellable matrix will start to erode when hydration is severe (highly swollen) because the inter-chain intermolecular forces will no longer be able to resist any external forces. Once hydrogel erodes, it breaks up into smaller and smaller particles, more surfaces will be exposed to the fresh swelling medium and hence more drugs will be released. For a swellable matrix as shown in *Figure 4*, mechanical properties of different gel layers would be different depending on the rate at which water or the aqueous fluid would be absorbed into the hydrogel structure. If the kinetics of swelling is fast, the three gel layers will be less distinguishable as water content across the hydrogel will be almost the same. Therefore, mechanical properties of the gel across the hydrogel layers will be similar and erosion becomes significant at any point in time. This indicates that a fast swellable hydrogel could release a water-insoluble drug to a great extent. On the other hand, for a hydrogel with slow kinetics of swelling, three layers of glass, tough rubber and soft rubber will be more and more distinguishable and erosion will occur at a much slower pace and to a different extent.

Ratio of swelling agent to the swelling medium: The same discussion as above can be applied here. Whether fast or slow swelling, the hydrogel needs water to swell. The maximum amount of water a swellable hydrogel can absorb is called the equilibrium swelling capacity, which depends on many factors including hydrogel structure, cross-link density, ionic content, and hydrophilic content. As discussed above, the presence of a sufficient swelling medium allows both fast and slow swelling gels to function in a way they are supposed to. However, if the swelling medium is not enough, the swelling medium will be fully absorbed to the hydrogel structure and there will be no water left to extract and to help release the drug. The gel will be unsaturated. This is shown in *Figure 5*. In the case of a water-soluble drug, extra swelling medium will extract the drug from the swollen matrix as a result of diffusion. For water-insoluble drugs, extra swelling medium will transfer the mechanical forces of the stomach to break

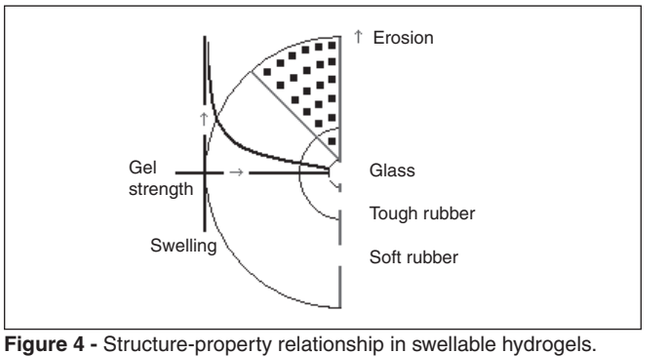


Figure 4 - Structure-property relationship in swellable hydrogels.

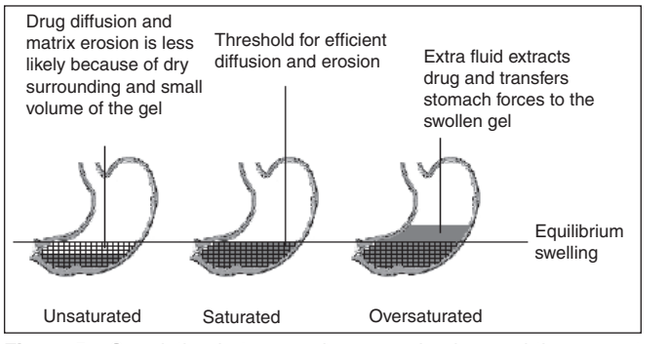


Figure 5 - Correlation between release mechanism and the amount of swelling medium.

the swollen gel; unless the swollen gel is large enough to receive the forces directly.

Although there has been a large volume of research on the swelling agents and devices over the last decade, the most recent activities are included in this review. The swelling agents can be categorized as either natural polysaccharides or (semi) synthetic polymers. With the former, research has been focused on dietary fibers, alginic acids (alginate), amylose, arabinogalactans, chitosan, chondroitin sulfate, cyclodextrin, dextran, galactomannans, gellan, konjac, guar gum, inulin, karaya gum, laminarin, locust bean gum, pectins, pullulan, rice bran, scleroglucan, tragacanth, wheat starch, and xanthan. With the latter, cross-linked polyacrylic acid, polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethylcellulose, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene oxide, cellulose, starch, superporous hydrogels, polyacrylamide, polyisopropyl acrylamide, cross-linked starch, cross-linked hyaluronic have been studied to a great extent. Campan *et al*. [16] performed photochemical graft polymerization of mono and di-functional alkyl acrylates (butyl, 2-ethylhexyl, lauryl and hexanediol diacrylate) onto the cross-linked poly(hydroxyethyl methacrylate) in order to reduce the hydrophilicity of the swellable network. The grafting yield was shown to depend primarily on PHEMA swelling in the ethanol/monomer mixture. The authors established a correlation between the hardness and equilibrium water content of the water-swollen gels. Acosta *et al*. [17] prepared and studied alginate-chitosan microcapsules to control the release of Tramadol-HCl. Microcapsules prepared by the addition of alginate to the chitosan solution in the presence of two-valent cations were spherical in shape and swelled greater in high pH medium than in the low pH medium. Drug release was studied in SGF and SIF solutions and different release behavior were observed. Cilurzo *et al*. [18] developed low swelling buccal mucoadhesive dosage forms based on sodium and potassium salts of methacrylic copolymers Eudragit L100 and Eudragit S100. The adhesion properties of these materials, measured by texture analyzer, were similar to Carbopol 934P. Based on an *in vivo* bioadhesion test, the methacrylic salts are claimed to be promising

for buccal tablets and patches with good patient compliance due to their low swelling properties. Huang *et al*. [19] studied the burst release of proxyphilline from swellable hydrogels of cross-linked poly(vinyl alcohol). They studied a few structural factors and concluded that high drug loading and low cross-linking ratio of the polymer would lead to more pronounced bursts. Lee *et al*. [20] prepared thermosensitive copolymeric hydrogels based on N-isopropylacrylamide (NIPAAm) and poly(ethylene glycol) methylether acrylate (PEGMEA) and studied the effect of the chain length of oxyethylene in PEGMEA, and the amount of the PEGMEA in the gels. Results showed that the swelling ratio for the present copolymeric gels increased with increasing chain length of oxyethylene in PEGMEA and the amount of PEGMEA in the copolymer gels. However, the gel strength and effective cross-linking density of these gels decreased with an increase in swelling ratio. De la Torre *et al*. [21] prepared polyionic complexes of chitosan (CS) and poly(acrylic acid) (PAA) and studied the release of amoxicillin trihydrate and amoxicillin sodium. The diffusion of amoxicillin trihydrate was controlled only by the swelling/eroding ratio of the polyionic complexes. The swelling degree of amoxicillin sodium hydrogels was more extensive compared to the amoxicillin trihydrate formulations. It was concluded that the water uptake was mainly governed by the degree of ionization and the diffusion of amoxicillin sodium could be restricted by polymer/ionized-drug interaction. Buonocore *et al*. [22] prepared cross-linked PVOH films to release antimicrobial agents (lysozyme, nisin and sodium benzoate) for food applications and studied the release kinetics using mathematical models. Buonocore *et al*. [23] evaluated the suitability of antimicrobial release films made from highly swellable polymers for use in food packaging. Results indicate that the release kinetics of both lysozyme and nisin can be modulated through the matrix cross-link density, whereas multilayer structures need to be used to control the release kinetics of sodium benzoate. All the active compounds released from the investigated active films were shown to be effective in inhibiting microbial growth. Papadokostaki *et al*. [24, 25] studied the performance of a model monolithic controlled release device, consisting of a swellable polymeric matrix loaded with a simple osmotic agent (NaCl) and activated by water. Bravo *et al*. [26] evaluated the release behavior of sodium diclofenac from a swellable matrix tablet containing hydroxypropyl methylcellulose (HPMC) and Carbopol made by wet granulation. Drug release was studied in terms of polymer content, polymer ratio, and pH. Carbopol tends to increase the rate of release at a higher polymer concentration. The overall release was found to be pH dependent and almost at zero order. While a low pH swelling medium prevents the carbopol from playing any role in the release, its contribution increases as pH increases. Chern *et al*. [27] prepared non-ionic, cationic, and anionic NIPAAm-based hydrogels by free radical polymerization method and studied the release kinetics of caffeine. The maximum caffeine absorption capacity increased significantly with the swelling ratio in the case of the nonionic and cationic hydrogels, while it decreased slightly with the swelling ratio for the anionic hydrogels. Thombre *et al*. [28] studied a swellable-core technology (SCT) formulation, which exploits the osmotic pressure and polymer swelling to deliver drugs to the GI tract in a reliable and reproducible manner. The formulations consisted of a core tablet containing the drug (tenidap and sildenafil), a water-swellable component, and one or more delivery ports. Alvarez *et al*. [29] developed a colon-targeting delivery system using swellable hydroxyethylcellulose (HEC), insoluble ethylcellulose (EC), microcrystalline cellulose (MCC) and theophylline as a model drug. A methacrylic acid copolymer was used as a pH-sensitive enteric coating. The system assured an adequate lag time for the intended colon targeting and a controlled release mechanism afterwards. While coating is the primary factor in controlling the lag time, matrix composition dictates the release rate. Missaghi *et al*. [30] evaluated the effect of various hydrodynamic conditions on drug release from an eroding and gel-forming matrix. They formulated dimenhydrinate hydroxypropyl methylcellulose and polyethylene oxide into matrix tablets. They highlighted the significance of hydrodynamics and the choice of a dissolution method and their respective effect on overall release profiles when erodible and swellable matrix systems are involved. Choi *et al*. [31] developed hydrogels based on HEMA and N-vinyl pyrrolidone using photoinitiators (2,2-dimethoxy-2-phenyl-acetophenone), cross-linkers (polyethylene glycol dimethacrylate) and swelling agents, and claimed they can be used potentially to solve the problem of acoustic feedback in hearing aids. The tensile modulus, strength, hardness and durability of the hydrogels in dry and wet conditions were evaluated. Lee *et al*. [32] synthesized poly(ethylene glycol) methylether acrylate (PEGMEA) and tetraethylene glycol diacrylate (TEGDA). The thermosensitive hydrogels were then prepared from N-isopropylacrylamide (NIPAAm), PEGMEA, and three cross-linkers N, N'-methylene-bis-acrylamide (MBA), TEGDA, and poly(ethylene glycol) dimethacrylate (PEGDMA). The results indicated that the swelling ratios for the copolymeric gels decrease with an increase in temperature. In addition, the higher swelling ratios observed for the gels prepared from TEGDA were due to the larger space between the gel networks. Drug release from these networks was also studied. Dashevsky *et al*. [33] developed and evaluated a pulsatile multiparticulate drug delivery system coated with an aqueous dispersion Aquacoat ECD. The system consists of a drug core, a swelling layer, comprising a superdisintegrant and a binder, and an insoluble, water-permeable polymeric coating. Theophylline release from this system was studied. Goole *et al*. [34] prepared a sustained-release floating minitablet. Formulations were made of a meltable binder, a swellable hydrocolloid and combined progens. Riboflavin release from this system was studied. Floating and non-floating formulations were studied in nine healthy volunteers in fasted and fed states. Pharmacokinetic urine data indicates floating formulations enhance the drug release. Chen *et al*. [35] prepared mini matrix-based multiple-unit drug delivery systems by loading conventional and cross-linked chitosan into hard gelatin capsules. Mini matrices manufactured by direct compression of chitosan powder (not cross-linked), cross-linked chitosan microparticles or cross-linked chitosan granules and were characterized in terms of hardness, friability, dimensions as well as their swelling and dissolution characteristics. The mini-matrices were film coated with Eudragit L100, S100 and L100-55 polymers to allow the drug release at desirable pHs. Bajpai *et al*. [36] used w/o emulsion technique to prepare nanoparticles of type A gelatin loaded with an anticancer drug cytarabine. IR, SEM and particle size analysis were used to characterize the nanoparticles (100-300 nm). The drug release was evaluated in terms of the drug loading, pH, temperature and ionic strength of the release medium. An optical microscope was used for the swelling studies and a correlation was made between the drug released and the swelling of the nanoparticles. Baloglu *et al*. [37] developed a bioadhesive vaginal tablet formulation of ornidazole, prepared using Carbopol 934, pectin, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and guar gum. Bioadhesive properties, swelling capacity, release studies, and histological studies of the formulations were carried out. The bioadhesive strength between bovine vagina and surface of the tablets was found to be dependent on carbopol content. Baranovskii *et al*. [38] prepared water-swellable networks of poly(acrylic acid) and various macrodiisocyanates. They assumed that the presence of hydrophobic and hydrophilic regions and the difference in their local dynamics presumably affects the pharmacokinetics of the drugs immobilized in these hydrogels. Bajpai *et al*. [39] prepared and characterized microparticles of cross-linked starch to release heparin "anticoagulant". Heparin loading, composition of microspheres and pH of the release medium were evaluated for this typical delivery system. Conti *et al*. [40] investigated the swelling behavior of matrix systems comprising HPMC and NaCMC with a soluble model drug to find the correlation between the mor-

phological behavior and the drug release performance. Lu *et al*. [41] reported the swelling properties and release kinetics of two model drugs with different water solubility (i.e. diltiazem and ibuprofen) from monolithic matrix tablets consisting of chitosan and polycarbophil. Matrix tablets consisting of this polymeric complex showed extremely high swelling properties that are completely reversible upon drying. The drug release from matrix systems with different formulations depended on the concentration of the chitosan-polycarbophil interpolyelectrolyte complex and approached zero order release kinetics for both model drugs. The chitosan-polycarbophil complex has demonstrated a high potential as an excipient for the production of swellable matrix systems with controlled drug release properties. Rane *et al*. [42] used a full factorial design to study the dissolution efficiency and the ability of forming solid dispersion with swellable polymers associated with carbamazepine. Polymers including sodium carboxymethyl cellulose, sodium starch glycolate, pregelatinized starch, and hydroxypropylmethyl cellulose were studied. Psyllium, a medicinally active natural polysaccharide has been recently modified, with acrylamide [43], N-hydroxymethylacrylamide [44] and methacrylamide [45] to develop novel drug delivery hydrogels. To evaluate drug release and diffusion mechanism, iriodel drugs (salicylic acid and tetracycline hydrochloride) were used as a model. Youn *et al*. [46] prepared an osmotic pellet consisting of a water swellable seed layer, drug layer, and membrane layer. With this study, the effect of Eudragit RL and RS on the release behavior of nifedipine was evaluated. It was found that the drug release from osmotic pellets was dependent on the composition ratio and thickness of the coating layer.

Bajpai *et al*. [47] prepared an IPN of poly(ethylene glycol), poly(vinyl alcohol) and poly(acrylamide) to release diastase, a digestive enzyme. Release dynamics of the enzyme were studied by changing IPN composition, enzyme loading, pH and temperature of the swelling medium and molecular weight of the PEG component. The interpenetrating networks of polyvinyl alcohol (PVA) and poly(acrylamide-co-acrylic acid) were also prepared and studied by Bajpai *et al*. [48]. Network and swelling parameters of the IPNs were studied in relation to change in IPN composition, pH, temperature and ionic strength of the swelling medium. With another study, Bajpai *et al*. [49] prepared a semi IPN of carboxymethyl cellulose and crosslinked polyacrylic acid and studied the water sorption capacity in terms of IPN structure, pH and temperature of the swelling medium, ionic strength and biological content of the swelling medium. Mohan *et al*. [50] synthesized semi-IPNs composed of poly [(acrylamide)-co-(sodium acrylate)] with poly [(vinylsulfonic acid), sodium salt]. The swelling behavior of these IPNs was studied in distilled water/physiological solutions/buffer solutions/salt solutions. As the amount of poly [(vinylsulfonic acid), sodium salt] increased in the network, the swelling capacity of the semi-IPNs increased considerably. The semi-IPN hydrogels followed non-Fickian diffusion behavior in water and physiological fluids, whereas Fickian behavior was observed in buffer solutions. The swelling of the semi-IPNs decreased markedly with an increase in salt concentration of the solutions. Mohammadnia *et al*. [51] synthesized IPN beads of carrageenan-sodium alginate to release betamethasone acetate, a water-soluble drug model. Loading efficiency of the system was found to be dependent on the pH and temperature.

4. Superdisintegrants

Despite the increasing demand and interest in controlled release systems, a significant portion of solid dosage forms require fast disintegration and dissolution after administration. For years this requirement has been met using superdisintegrants. Superdisintegrants are another version of superabsorbing materials with tailor-made swelling properties. These materials are not intended to absorb significant amounts of water or aqueous fluids, but intended to swell very fast. Superdisintegrants are used as a structural weakener for the disintegrable solid dosage forms. They are physically dispersed within the matrix of the dosage form and will expand when the dosage form is exposed to the wet environment. Swelling pressure and isotropic swelling of the particles create stress concentrated areas where a gradient of mechanical properties will exist. In fact, a mild explosion occurs at the stress-concentrated area by which the whole structure will break apart. The overall breakdown mechanism is shown in *Figure 6*.

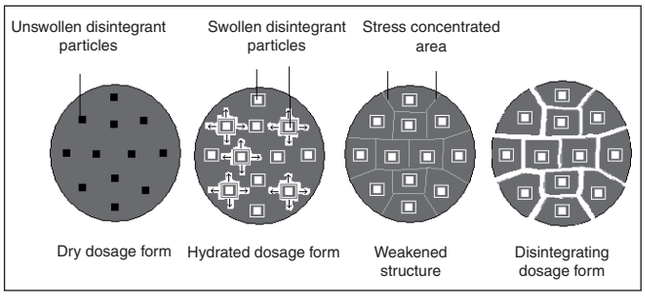


Figure 6 - Disintegration mechanism of superdisintegrant materials.

To assure that the tablet or solid dosage form will break apart at a desirable rate, the disintegrant should be evenly distributed within the matrix and should swell very fast to a size of about 10-40 g/g. In other words, one gram of superdisintegrant absorbs 10-40 g of water or aqueous medium. It should also be compatible with the other excipients and have desirable tableting properties.

In recent years, there has been considerable growth in the number of orally dissolving and chewable tablet products on the market. These tablets rapidly disintegrate in contact with saliva, thus eliminating the need for water and the difficulties children and the elderly have with swallowing the whole tablet. Orally dissolving tablets is also known as mouth dissolving, orodisperse, fast dissolving, fast melting, rapidly dissolving, quick dissolving or orally-disintegrating tablets. These products have increased in popularity because they are convenient and increase compliance among pediatric and geriatric patients. In addition, they allow for effective life-cycle management. Since superdisintegrant is used as an excipient in the tablet formulation, it has to meet certain criteria other than its swelling properties. These include mouth-feel, compressibility and good flow properties. Although some are better than others, the currently marketed superdisintegrants exhibit an optimum combination of properties. Their particles are generally small and porous, which allow for rapid tablet disintegration in the mouth without an undesirable mouth-feel from either large particles or gelling. The particles are also compressible which improves tablet hardness and its friability.

Freeze-drying and direct compression are utilized to make fast-melting tablets. The former produces tablets that dissolve in the mouth in about 5-15 s, but the technology is relatively expensive and tablets are not mechanically strong. One way of making fast-dissolving tablets by the direct compression method is to add fine particles of a swellable hydrogel to the granulation or powder formulation. The hydrogel microparticles within the tablet core expedite water absorption by an increased wicking mechanism. Tablets prepared by direct compression in the presence of hydrogel microparticles disintegrate in less than 10 s. Alebiowu [52] prepared a powder from the natural sponge *Luffa aegyptica* Mill family Cucurbitaceae and studied its disintegrant activity with corn starch as the standard. The powder showed promising results in terms of weight uniformity, friability, tensile strength and disintegration time of tablets prepared for evaluation. Di Martino *et al*. [53] studied superdisintegration properties of the marketed products by looking at the concentration of the disintegrant and compression force in tableting. They measured these properties against disintegration time, tensile strength and porosity. Freeman *et al*. [54] evaluated the subchronic and developmental toxicity of

Ac-Di-Sol (croscarmellose sodium). In the subchronic study, groups of rats (20/sex/group) received 0 (control), 10,000, or 50,000 ppm Ac-Di-Sol in the diet for 90 consecutive days. No mortality, clinical signs of toxicity, or adverse toxicological effects on hematology or serum chemistry parameters, feed consumption, or ophthalmologic examinations were noted in any treatment group. Fukami *et al*. [55] prepared a rapid disintegration tablet using glycine as a disintegrant. The effect of this disintegrant on the disintegration behavior of the tablet in the oral cavity was evaluated. The authors highlighted the fact that certain tablet excipients like ascorbic acid could prolong the disintegration time. They suggested that a tablet of water-insoluble drugs like ethenzamide can efficiently be disintegrated using a disintegrant hybrid of carboxymethylcellulose and glycine. Hipasava *et al*. [56] prepared a tablet formulation containing nilvadipine using crospovidone and methylcellulose. Several grades were studied in terms of their effect on tablet properties including hardness, disintegration, dissolution and chemical stability. Drug solubility and its dissolution rate, as well as tablet hardness, were found to be dependent on the povidone size and viscosity of cellulose polymer. Medeiros *et al*. [57] compared technical quality parameters of the superdisintegrants using different analytical techniques. They evaluated the water-disintegrant interaction using a differential scanning calorimeter and found it a valuable technique for quality control of disintegrants. Odeku *et al*. [58] investigated disintegration properties of native and modified forms of millet starch, obtained from a tropical cereal plant, *Pennisetum glaucum*, in a chloroquine tablet formulation. The mechanical properties of the tablets were assessed using the crushing strength and friability tests, while the drug release properties of the tablets were assessed using disintegration and dissolution times. Compared to cornstarch, the modified forms of millet starch showed significantly ($p < 0.01$) lower values of disintegration and dissolution times. Sinha *et al*. [59] formulated a fast release enteric-coated tablet for colon delivery. In one approach they used crospovidone in the tablet. The amount of superdisintegrant (cross-linked PVP) in the tablet and the coat weight were varied to formulate a suitable time-controlled release system. Souto *et al*. [60] evaluated the application of superdisintegrants (croscarmellose sodium or sodium starch glycolate) in microcrystalline cellulose extrusion-spheronization pellets to increase the dissolution rate of poorly water-soluble drugs. The model drug was hydrochlorothiazide, with water or water/ethanol as wetting agent for pellet preparation. Although pellet morphology, flow properties and disintegration were not affected by superdisintegrant, drug dissolution rate was increased to a certain extent as a result of increased pellet micropore volume. Takeuchi *et al*. [61] prepared a rapidly dissolving tablet of indomethacine using partially gelatinized starch as disintegrant. Xiao *et al*. [62] isolated linear pachyman from the sclerotium of Poria cocos. They synthesized hydroxypropyl and carboxymethyl derivatives of the compound and used them in ampicillin and probenecid dispersible tablets. Detailed characterization of the tablets indicates a great potential for the synthesized derivatives to be used as pharmaceutical disintegrant. Yang *et al*. [63] exploited the unique wicking properties of superporous hydrogels in making fast-disintegrating tablets. They used microparticles of polyacrylic acid-based superporous hydrogels for this purpose. Young *et al*. [64] used the dynamic vapor sorption (DVS) technique to determine the moisture sorption properties of sodium starch glycolates. They compared the results with the results from potato starch, pregelatinized starch, microcrystalline cellulose (MCC), and crystalline lactose. Compared to others, sodium starch glycolate was found to be more effective in moisture absorption. Zhao *et al*. [65] developed a discriminatory disintegration test and compared the disintegration efficiency of sodium carboxymethylcellulose (Ac-Di-Sol), sodium starch glycolate (Primojel) and cross-linked polyvinyl pyrrolidone (polyplasdone). They used a digital video camera to monitor the disintegration process of aspirin tablets containing the same weight amounts of disintegrants. Ac-Di-Sol was found to rapidly disintegrate tablets into primary particles. A slower disintegration to primary particles was observed with Primojel. Polyplasdone XL10 disintegrated tablets rapidly but into larger masses of aggregated particles. This observation shows that the type of disintegrant in the formulation will definitely affect the drug dissolution rate. Zhao *et al*. [66] investigated factors influencing croscarmellose sodium functionality with special emphasis on developing a discriminating model tablet formulation to evaluate the brand-to-brand variability of the product. The particle size distribution, water uptake, and swelling properties of five brands of croscarmellose sodium were studied in either neutral water or 0.1 N HCl. The tablet disintegration times were inversely proportional to the swelling ability of superdisintegrant in the testing medium regardless of medium temperature and disintegrant concentration. In conclusion, the particle size, total degree of substitution, and the ratio of basic to acidic substituent are important factors that should be considered during product optimization. Zhao *et al*. [67] identified the causes of efficiency loss of superdisintegrants following granulation or reworking. Two processes, pre-compression and pre-wetting, were proposed to simulate the processes during dry and wet granulation, respectively. The disintegration efficiency of the resulting disintegrant granules was tested in model formulations composed of dicalcium phosphate and lactose with the unprocessed disintegrants as controls. No significant difference was shown in the intrinsic swelling and the water uptake abilities of all superdisintegrants following dry granulation. However, for both Primojel and Polyplasdone XL10, the rate of water absorption into the tablet matrix significantly decreased following the wet granulation process.

5. Swelling devices

Orally administrable swelling devices are products designed to swell in the GI tract. The extent to which a swelling device can swell will depend on the desirable swelling and mechanical properties. For instance, if a swelling device is intended for gastric (stomach) application, it has to be mechanically strong in its fully swollen state to be able to resist excessive gastric pressures. It needs to be compatible with drugs and foods, tolerable to dynamic gastric changes (pH, contraction/expansion forces, temperature, water content, food content) and should also have reasonable swelling size. A swelling device can be a swellable material by itself or it may contain swelling agents. Swelling devices containing swelling agents are much more popular and have long been a focus for many research activities in academia and industry. As far as the manufacturing is concerned, a swelling device containing a swelling agent can be prepared as granules, tablets and capsules. All tableting techniques can be used potentially to make a swelling tablet, a tablet matrix, multilayer tablets, mini-matrix in tablet and coated tablet. Swelling devices have frequently been used as a diet aid, as sustained and controlled release platform for local treatment in the stomach, as sustained and controlled release platform in the GI tract, colon-specific delivery, pulsed and triggered drug delivery systems and recently as targeted gastroretentive device.

Development of swellable devices for pharmaceutical and highly regulated industries will be a major challenge as the FDA demand for a safe and efficient product needs to be met. Swellable devices are normally based on synthetic monomers and polymers and major challenges will remain the purity, safety, and non-toxicity of the final product as well as its efficacy. Depending on the final application, a swellable device may be formulated into a very complex structure that adds another barrier in formulation and development. Most importantly, pharmaceutical companies need to outsource the scale up and manufacturing phases of the development as they normally lack the required infrastructure. A typical complex design of a swellable gastroretentive platform is shown in *Figure 7* [68]. The platform is based on superporous hydrogel hybrids with the ability of fast swelling to a medium size. The structure is mechanically strong but will weaken after a certain time depending on the polymer and the severity of the service condition and also the

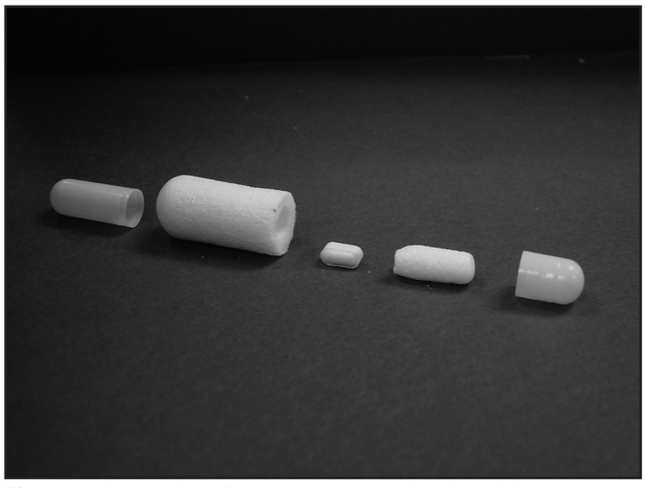


Figure 7 - A typical swellable device containing drug delivery system.

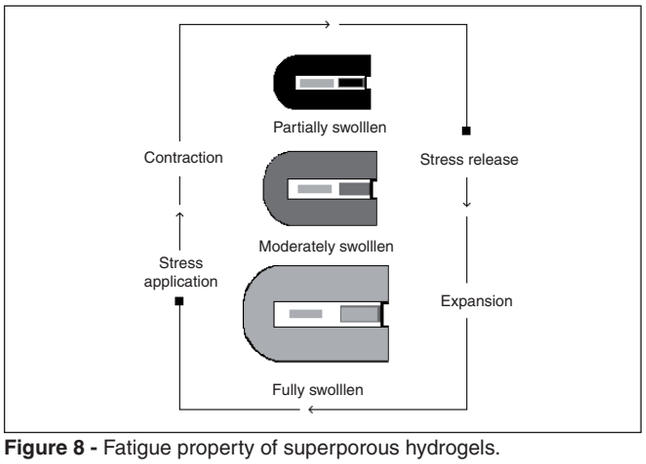


Figure 8 - Fatigue property of superporous hydrogels.

diet status (fasted or fed). In order to be feasible as a gastroretentive device, the superporous hydrogel (SPH) will house the drug or drug delivery system as tablet, wax, semi-solid, microparticle or any other applicable dosage forms [69, 70]. The assembly is made of an SPH body, SPH plug, a drug delivery system and an orally administrable capsule. The SPH is flexible and squeezable into a smaller size, so that it can be encapsulated into an orally administrable capsule. When the capsule is taken, it will enter the stomach area, which is considered a constantly changing service environment. The pH will be very low, around 1, in the fasted state and in the absence of food. The pH will then change to a higher value after introducing foods. The food may contain ingredients, which may react with the SPH and change its properties. Cold water or hot drink may change the temperature of the gastric content, which may also affect the SPH performance. In the real gastric condition as schematically shown in *Figure 8*, a water hammer effect [71, 72], results in partial de-swelling of the swollen SPH, which results in SPH contraction. After stress is released, the shrunken SPH will swell again in the presence of the swelling fluid. The dynamic cycle of expansion and contraction will be repeated up to a point where the SPH will start to disintegrate and empty from the stomach. This process resembles the fatigue properties of rubber products for which durability of a rubber compound is measured under timed loading/ unloading conditions. The life cycle of superporous hydrogel from swelling to disintegration will determine the gastric retention properties of these typical and novel swellable platforms. Swelling devices made of different swellable materials are compared in *Table II*. Conway [73] reviewed and discussed different gastroretentive delivery systems with regard to *Helicobacter pylori*, which is one of the most common pathogenic bacterial infections. Drug delivery to the site of residence in the gastric mucosa may improve efficacy of the current and emerging treatments. Gastric retentive delivery systems including swellable ones potentially allow increased penetration of the mucus layer and therefore increased drug concentration at the site of action. De la Torre *et al*. [74] developed a stomach-specific drug delivery system to increase the efficacy of amoxicillin against the Helicobacter pylori. Polyacrylic acid, chitosan, and amoxicillin were employed to obtain a floatable gastric retention device. The *in vivo* study was performed on healthy volunteers, using the octanoic acid breath test. The proposed hydrogel showed a prolonged gastric retention time of up to 3 h. The preliminary results from this study suggest that amoxicillin polyionic complexes have a potential for improving local antibiotic therapy against *H. pylori*. Chavanpatil *et al*. [75] developed a gastroretentive sustained release delivery system with floating, swellable and bioadhesive properties. Various release-retarding polymers like psyllium husk, HPMC K100M and a swelling agent were tried and optimized to obtain a 24-h release profile. The *in vitro* ofloxacin

Table II - Comparison between different swellable products.

	Swellable matrices	Superdisintegrants	Swellable devices
Commonly used materials	Cellulose derivatives including HPMC, MC; hydrocolloids including alginate, chitosan, pectin, poly (ethylene oxide), carbopol, poly (vinyl alcohol)	Sodium carboxymethylcellulose, Sodium starch glycolate, cross-linked poly (vinyl pyrrolidone)	Acrylamide, acrylic acid, salts and esters of acrylic acid including sodium and sulfopropyl acrylates, 2-hydroxyethyl methacrylate
Structure	Generally non-porous, non-cross-linked (PEO) and cross-linked (carbopol)	Medium porous, highly cross-linked	Interconnected open cells, highly cross-linked
Final product	Solid powder, emulsion	Particle	Any shape including particle, sheet, film, rod
Water absorption mechanisms	Mostly diffusion	Capillary and diffusion	Mostly capillary
Type of absorbed water	Mostly bound	Semi-bound	Mostly free
Free swelling capacity	5-20 g/g	10-40 g/g	5-40 g/g
Applications	Where slow and low swelling required	Where medium but fast swelling as well as size-dependent swelling required	Where medium very fast swelling as well as size-independent swelling required
Service environment	Simulated gastric fluid and simulated intestinal fluid	Simulated gastric fluid and simulated intestinal fluid	Simulated gastric fluid and simulated intestinal fluid

release was found to be non-Fickian. The swelling properties were enhanced with increased concentration of the swelling agent. Ahmed *et al*. [76] prepared a gastroretentive device made of natural polymers and used riboflavin as a model drug. Dogs in fasted state were used for gastric retention studies. The bioavailability of riboflavin, a drug with a narrow absorption window was studied in fasted healthy humans and compared to an immediate release formulation. Results indicated that the bioavailability from using a gastroretentive device is dependent on the water content, size and shape of the device.

*

In this review, swelling agents and devices are discussed with the focus on swelling process, materials and their pharmaceutical applications. Swelling agents differ in terms of their swelling behavior, kinetics and thermodynamics. Some show pseudo-swelling behavior and have found applications in tablet matrix for controlled drug delivery. Some display very fast swelling kinetics with moderate swelling capacity and were included in the important class of pharmaceutical excipients named superdisintegrants. The last groups of swelling agents are those that swell by themselves and are used as a platform for controlled delivery. For this group, properties other than swelling are more desirable. These include mechanical properties, fatigue properties, safety, non-toxicity and efficacy.

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