

# **Techniques For the Preparation of Porous Hydrogels and Its Applications**

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## **Abstract**

Porous Hydrogels are generally characterized by their swelling and mechanical properties in different media. The swelling properties are measured by weight, volume and dimension at regular time intervals or at equilibrium. Superporous Hydrogels (SPHs) are mostly based on hydrophilic and ionic monomers, their swelling and mechanical properties are generally sensitive to the type and nature of the swelling medium such as ionic strength, pH, salts, organic solvents and pressure are the most important factors. Mechanical Quantifying the SPH mechanical properties has been challenging. The SPHs in their swollen state are generally weak, contain inter connected pores of different sizes and their overall microstructure is very complex. Regular mechanical testers and texture analyzers are commonly used to evaluate SPH mechanical properties. Gastric simulator generally pores inside the SPH vary from 100 to 1000  $\mu\text{m}$  in size. Under homogeneous loading, pores of different sizes resist deformation differently. The SPHs mass will break apart from its weakest point, which cannot be monitored by using regular mechanical testers. Safety/Toxicity, the safety and non-toxicity of synthetic superporous hydrogels must be known before these delivery systems can be pharmaceutically acceptable.

**Keywords: Porous hydrogels, Techniques, properties.**

## **Introduction:**

SPHs absorb a large volume of environmental fluids, which expand their volume considerably over a very short period of time, their sheer bulkness hinders their transport to the next organ through the narrow pylorus. This unique swelling property allows them to be used as gastric retention carriers, providing sustained release through long residence in the stomach. One of the drawbacks are its unsatisfactory mechanical properties in the highly swollen state, which limits its successful applications to gastric retention devices. To enhance these mechanical properties, synthesis of interpenetrating polymer network (IPN) type hydrogels composed of chitosan polymer & other polymeric materials called strengtheners like carbopol, PVA, PVP etc. Chitosan is a natural polysaccharide, biocompatible, biodegradable, non-toxic material and has abundant amine groups within polymer chain, it dissolves in acidic solution and forms a gel with dialdehyde such as glutaraldehyde and glyoxal (crosslinking agents). Thus, in low pH solution, chitosan hydrogels swells due to the presence of the positive charges in the network. To distinguish SPHs with different properties, SPHs are divided into three different generations: The conventional (i.e., the first generation) SPH is characterized by fast swelling, high swelling and weak mechanical properties. The other hand, the second-generation SPHs (SPH composites) are characterized by fast swelling, medium swelling and improved mechanical properties. The third-generation SPH hybrids (SPHHs) possess elastic properties that can be highly useful in the development of gastrointestinal devices, as well as in other pharmaceutical and biomedical applications.

## **Methods for preparation of superporous hydrogels (SPHS)**

**Porosigen Technique:** This technique involves the preparation of porous hydrogels in the presence of dispersed water soluble porosigens. eg. Micronized cellulose, sodium chloride, PEG etc which forms like meshworks that can be removed by washing with water.

**Phase separation technique:** This method is applicable for limited type of porous hydrogels eg. Hydroxy ethyl methyl cellulose, N-isopropyl acrylamide. However, there is not much control over porosity of prepared hydrogels.

**Cross linking technique:** Crosslinking of individual hydrogel leads to the formation of aggregates of particles. The pores in such structures are present between hydrogel particles. The size of pores is smaller than the size of particles. This technique is limited to absorbent particles with chemically active functional groups on the surface.

**Gas blowing technique:** This is the most widely used method for the preparation of superporous hydrogels, where, SPHTs are prepared by crosslinking polymerization of monomers in the presence of gas bubbles. Different ingredients like monomer, crosslinker, foam stabilizer, polymerization initiator, initiation catalyst and foaming agent are added sequentially in a test tube of specific dimensions. Before addition of foaming agent, the pH of monomer solution should be maintained at 5 to 6 pH, since 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. After synthesis, SPHTs are washed and dried which influence the swelling and mechanical behavior of hydrogels.

### **Properties of SPHTs:**

**Swelling:** SPHTs are generally characterized by their swelling and mechanical properties in different media. The swelling properties are measured by weight, volume and dimension at regular time intervals or at equilibrium. Since SPHTs are mostly based on hydrophilic and ionic monomers, their swelling and mechanical properties are generally sensitive to the type and nature of the swelling medium such as ionic strength, pH, salts, organic solvents and pressure are the most important factors.

**Mechanical:** Quantifying the SPHT mechanical properties has been challenging. The SPHTs in their swollen state are generally weak, contain inter connected pores of different sizes and their overall microstructure is very complex. Regular mechanical testers and texture analyzers are commonly used to evaluate SPHT mechanical properties.

**Gastric simulator:** Generally pores inside the SPHT vary from 100 to 1000  $\mu\text{m}$  in size. Under homogeneous loading, pores of different sizes resist deformation differently. The SPHTs mass will break apart from its weakest point, which cannot be monitored by using regular mechanical testers.

**Safety/toxicity:** The safety and non-toxicity of synthetic superporous hydrogels must be known before these delivery systems can be pharmaceutically acceptable. One study have been investigated on the safety of novel gastroretentive SPHT platforms in a swine emesis model.

### **APPLICATIONS OF SPHTS<sup>1</sup>**

**Development of gastric retention devices:** SPHTs were initially developed to make gastric retention devices. The concept was to make an oral formulation to swell fast to a size i.e. large enough to prevent them from entering into the pylorus. To avoid emptying into the intestine by the housekeeper waves of the stomach that occur about every 2 h, the oral formulation has to swell as fast as possible because it is difficult to know when the next housekeeper wave will come following administration of a superporous hydrogel formulation. The primary goal of fast swelling was to reach maximum swelling in about 20 mins because water is known to remain in the stomach for about 30 mins.

**Gastroretentive tablets:** The processes of dry blending and direct compression have been used to make gastroretentive tablets. The SPH particles of acrylic acid/sulfopropyl acrylate copolymers were blended with gelatin and tannic acid, and then tableted by direct compression. Hydrogen bonding between gelatin and the tannic acid, as well as the carboxyl groups on the polymeric carrier, create an integrated matrix, which was shown to be stable after swelling. In a 40 min period, the gastroretentive tablet could swell up to 30 times of its own volume while maintaining its original shape. Further, the swollen tablet could withstand up to 16 KPa compression force before breaking apart.

**Development of peroral peptide delivery systems:** Superporous hydrogels are also used in the development of peptide delivery systems via oral administration. Peptide drugs have been administered mostly by the parenteral route, and no peroral formulation has been developed to date. Superporous hydrogels and their composites increase their volume by about 200-fold. Such volume increased, allowed the gels to mechanically adhere to the intestinal gut wall and deliver the drug directly to the gut wall.

**Development of fast dissolving tablets:** have been used to develop a large number of successful commercial products. The main advantage of the fast dissolving tablet technologies is that the dosage forms can be administered easily in the absence of water and without the need of swallowing. This feature is especially beneficial to children and the elderly patients.

**Chemoembolization and occlusion devices:** Chemoembolization is a combined method of embolization and chemotherapy. Embolization has been used for cancer treatment by restricting the oxygen supply to the growing tumors. This method could be combined with chemotherapeutic agents to achieve local delivery and low systemic toxicity. SPHs containing a chemotherapeutic agent and an anti-angiogenic agent could be loaded for chemoembolization therapy. The strong SPHs would likely be better candidates for this application as they fit better in the blood vessels and provide better blocking. SPHs can also be used to develop biomedical devices for treating aneurysms.

**Development of diet aid:** Controlling body weight is an important aspect in maintaining a healthy body. Diet soft drinks, meal replacement shakes, diet drugs, and even surgical methods have been used for lowering the body weight. Because the main goal of these approaches is simply to reduce the amount of food intake, one alternative approach would be administering superporous hydrogel tablets so that the swollen superporous hydrogels can occupy a significant portion of the stomach space, leaving less space for food. Taking superporous hydrogel tablets can be compared to taking Jello before a meal. The presence of a bulky gel in the stomach suppress the appetite.

**Other applications:** SPHs can be used in industries other than pharmaceutical and biomedical, where rapid and extensive swelling in an aqueous medium is major requirements. As seen with the superabsorbent polymers, children can enjoy the immediate swelling of SPHs and learn the associated science and knowledge. The SPHs can be colored and may find decorative applications. SPHs quickly absorb moisture from the surrounding environment and may be a suitable substitute for silica gel.

**Pellets :** In the pharmaceutical industry, the word pellets can be defined as agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically ranging from about 0.5 mm to 1.5 mm, and are intended for oral administration.<sup>2-5</sup>

These multiple unit dosage forms are usually formulated in the form of suspensions, capsules or disintegrating tablets, having a number of advantages over the single unit dosage system.<sup>5-8</sup> multiple unit

systems, the total drug dose is divided over several units. Failure of a few units of dose may not be as serious as failure of a single unit dosage form.<sup>2,8</sup>

Their small size also enables them to be well distributed along the GIT, thereby improving absorption and reducing the irritant effect that a single unit dosage form may cause to the mucosal lining, especially for a prolonged period at a particular site.<sup>10</sup>

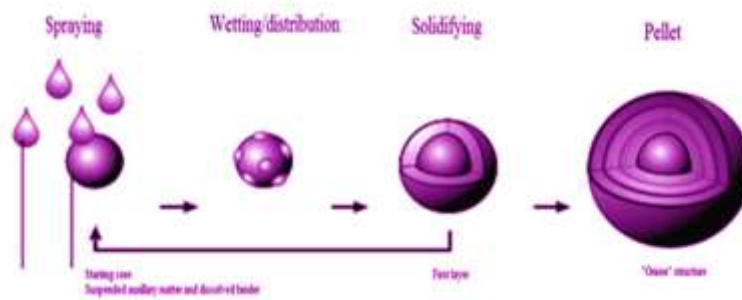
Pellets are free flowing and pack easily without any difficulties, resulting in uniform and reproducible fill weight of capsules and tablets.<sup>11-14</sup> Successful film coatings can be applied onto pellets due to their spherical shape.<sup>7</sup> Pellets composed of different drugs can be formulated in a single dosage form.

Variety of techniques is available for manufacturing of pellets. Layering processes have been used from many years and have some limitations such as non uniformity in the size of the pellets and less drug loading. In recent year's extrusion-spheronization, cryopelletization, freeze pelletization and hot melt extrusion have been widely used to produce spherical pellets.

**Layering:** Layering process is the most old as the well as controlled and straight forward pelletization techniques. The layering process comprises the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be granules of the same material. They are classified into two categories: solution/suspension layering and powder layering.<sup>2,15</sup>

Solution/suspension layering (Figure 1), drug particles and other components are dissolved or suspended in the particular medium. The droplets impinge on the cores and spread uniformly as the solution or suspension is

cores. drying, this the dissolved crystallize and bridges cores and the drug and successive layers of drug or polymer.<sup>2,5</sup>

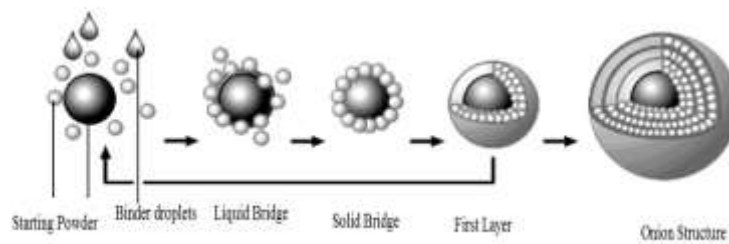


sprayed on the Followed by phase allows material to form solid between the initial layer of among the

**Figure 1: Principle of solution and suspension layering**

In powder layering, the binding liquid helps in the deposition of successive layers of dry powder of drug and other components on starting cores. In this technique, the drug particles are bound to the cores and subsequently to the

with the help of from the sprayed These liquid replaced by solid either from a liquid medium or material.



forming pellets liquid bridges binding liquid. bridges are bridges derived binder in the from any Successive

layering of the drug and binder solution continues until the required pellet size is obtained.<sup>2,7,16,17</sup>

**Figure 2: Principle of powder layering process.**

The most commonly used equipments for layering are the coating pans and fluidized bed granulators (bottom spray, top spray and tangential spray). Conventional pan coaters have been used from the very beginning of drug layering pelletisation. But, however the use of conventional pan coaters is not very economic due to the high labour costs, time consumption, and less percentage yield. The disadvantage of pan coater is the shortage of process control.<sup>2,14</sup> More recently modified forms of pan coater have been developed.

**Cryopelletization :** This technology was initially developed for the nutrition industry to lyophilize viscous bacterial suspension, and can also be used to produce drug loaded pellets. In cryopelletization, the pellets can be produced by allowing droplets of liquid formulation such as solution, suspension or emulsion to come in contact with liquid nitrogen at  $-160^{\circ}\text{C}$  in which liquid nitrogen acts as solidifying medium. The procedure permits rapid and even freezing of the material being processed due to the rapid heat transfer that occurs between the droplets and the liquid nitrogen. The pellets are dried in conventional freeze dryers to remove water or organic solvents.<sup>17</sup>

The equipment consists of a container with perforated plate below which a reservoir of liquid nitrogen in which a conveyer belt along with baffles is immersed. The speed of conveyer belt provides the required residence time necessary for freezing of the pellets. The frozen pellets are moved into storage container at  $-60^{\circ}\text{C}$  and then dried in freeze dryer. Droplet formation is a very critical step in cryopelletization and is influenced by formulation related variables such as equipment design and the corresponding processing variables such as viscosity, surface tension and solids content.

**Freeze pelletization:** Freeze pelletization is a novel technique for formulating spherical pellets containing active ingredients. In this technique, a solid carrier along with an active ingredient is introduced as droplets into an inert, immiscible column of liquid. This method has several advantages over other pelletization techniques, in terms of quality of pellets and process cost. The pellets produced by this technique are spherical in shape with narrow size distribution. Since the pellets are solid at room temperature, they do not require drying. Carrier may be hydrophilic or hydrophobic in nature and are melted at temperature  $5-10^{\circ}\text{C}$  higher than the melting point of the carrier solids.

**Extrusion and spheronization:** The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniform sized spheroids.<sup>2</sup>

#### **Advantages of spheronization**

- The packing of small spheres into containers, such as hard gelatin capsules, or larger packages is more convenient than other dry forms such as powders or granules etc.
- Spheres are usually dense material and provide the lowest surface area to volume ratio and thus pharmaceutical active ingredient can be coated with a minimum coating material.
- Coating can provide controlled and targeted release at different locations within the body.
- Spheres will reduce production of fines and dust during transportation, handling and packaging.
- Depending on adhesive forces and surface characteristics, spheronization increases the hardness and reduces friability of granules.

Extrusion-spheronization is a multi step compaction process consisting of

**Dry mixing:** Dry mixing of ingredients is done to get homogeneous powder dispersion using different types of mixers like twin shell blender, high shear mixer, tumbler mixer and planetary mixer.<sup>2</sup>

**Wet massing:** Wet massing of powder dispersion is done to produce a plastic mass for extrusion. This granulation is similar to conventional wet granulation with the exception of the granulation endpoint. The granulation endpoint is determined by the behavior of the wetted mass during the extrusion operation. The most commonly used granulator is planetary mixer or sigma blade mixer or high shear mixer and Hobart mixer. Typically, planetary mixer is used for both blending and granulation operation. High shear mixer introduces a high amount of energy into the wet mass, which is transformed into heat and induces evaporation of granulation fluid. This changes the behavior of the wet mass.

**Extrusion:** This is the third step in the process. The extrusion operation can be considered to be a specialized wet granulation spheronization process. Extrusion is a method of applying pressure to a mass until it flows through an opening, is a technique that determines two dimensions of an agglomeration of particles. Because the cross sectional geometry is defined by the orifice, extrudate length is usually the only dimensional variable. This operation is the major contributing factor in the final particle size of the pellets. The diameter of the extruder screen opening directly controls the diameter of the extrudate.

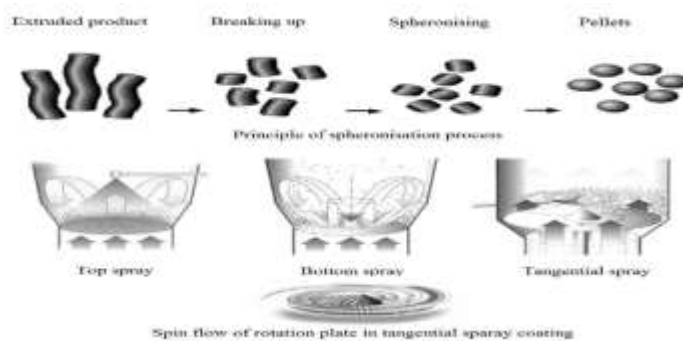
In this process the wet mass is passed through the extruder to form rod shaped particles of uniform diameter. The extrudate must have enough plasticity to deform but not so much that the extrudate particles adheres to other particles when rolled during spheronization process. The granulation solvent serves as the binding agent to form the granules and as a lubricant during the extrusion operation.

**Spheronization:** The spheronization technology was introduced by Nakahara in 1964. The formation of pellets during the spheronization operation depends on the formulation of extrudates. The extruded granulation must have the characteristics of cohesiveness, firmness and plasticity. This operation has been divided into three stages such as breaking of the extrudate, agglomeration of the broken segments and smoothing of the particles. Breaking of the cylindrical segments occurs due to the interaction of the extrudate with the rotating plate, stationary wall and other extrudate particles. Agglomeration occurs when the small fragments produced during the breaking stage are picked up by the larger granules during smoothing. Spherical particles are created during smoothing stage by generating rotational motion of each granule about its axis in constantly changing planes.

**Extrusion and spheronizing equipment**

Extruders have been generally classified as screw, sieve and basket, roll and ram extruders. Screw extruders are the only continuous extrusion devices, since product can exit in a smooth continuous flow. The remainder of the extrusion devices produce surge of material. Based on the type of feed mechanism used to transport the mass, they have been classified as screw, gravity or piston-type extruders.

Screw fed extruders have screws that rotates along the horizontal axis that transport the material horizontally, they may be axial or radial. Die plate type extruder. In placed axially in axial radial extruder, the radially through around the horizontal Gravity fed extruder rotary cylinder and extruders, which vary design of the two radial. Die plate type extruder. In mass is extruded screens mounted axis of the screw. consists of the rotary gear mainly in the counter rotating





cylinders. In the rotary cylinder extruder one of the two counter rotating cylinders is hollow and perforated, whereas the other cylinder acts as a pressure roller. Rotary gear extruders consist of two hollow counter rotating gear cylinders with counter bored holes.

In ram extruders, a piston displaces and forces the material through a die at the end. Ram extruders are used in the development phase because they can also be used to measure the rheological properties of formulations.

### **Figure 3: Principle of spheronisation process**

A spheronizer consists of a vertical hollow cylinder with a horizontal rotating disk (friction plate) where the extrudate is broken up into smaller segments by contact with friction plate or other particle or with wall. The friction plate is responsible for providing the energy necessary to produce desired pellets and for controlling the extent of pellet growth.

The friction plate, a rotating disk with a characteristic grooved surface to increase the frictional forces is the most important component of the equipment. Two geometric patterns are basically used. A cross hatched pattern with grooved surface running at right angle to one another and a radial pattern with grooved surface running radial from the center of the disc.

In air assisted spheronizer, small amount of dry air allows the granules to slide across each other more easily and induces fluidization. The friction plate looks rather similar to a plate a standard merumerizer, except for what appears to be a propeller like device that is mounted on top. The base is perforated so that air can be distributed throughout the product.

Recently, different types of fluidised bed rotary processors have been developed more successfully for preparing compaction-type pellets such as the extrusion spheronization process in a one-step process. This technique has solved many problems related to the multi-step extrusion and spheronization process; it consumes less time, requires lower labour costs and less space.

To get desired moisture content in pellets a drying stage is required. The pellets can be dried at room temperature or at elevated temperature in a tray dryer/ oven or in a fluidized bed dryer.

### **Hot melt extrusion**

Hot-melt extrusion is one of the most widely used processing technologies in the plastic, rubber and food industry. Presently, half of all plastic products, including plastic bags, plastic sheets and plastic pipes are manufactured by this process. Melt extrusion has found its place in the pharmaceutical manufacturing operations. This process is currently applied in the pharmaceutical for the manufacture of variety of dosage forms and formulation to modify drug release such as immediate and sustained release pellets, granules and tablets.

### **Conclusion:**

Gastric simulator generally pores inside the SPH vary from 100 to 1000  $\mu\text{m}$  in size. Under homogeneous loading, pores of different sizes resist deformation differently. The SPHs mass will break apart from its weakest point, which cannot be monitored by using regular mechanical testers. Safety/Toxicity, the safety and non-toxicity of synthetic superporous hydrogels must be known before these delivery systems can be pharmaceutically acceptable.

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