# HYDROGEL: OVERVIEW AND RECENT ASPECTS

**Dr.P.K.BISWAL*1, Dr.B.Ray1, Dr.B.B.Panda1**

*1Associate Professor, Dr. Prasanta Kumar Biswal, Post Graduate Department Gayatri College of Pharmacy, Odissa, India*
*2Associate Professor, Dr. Biswaranjan Roy, Post Graduate Department Gayatri College of Pharmacy, Odissa, India*
*Associate Professor, Dr. Bipin Bihari Panda, Post Graduate Department Gayatri College of Pharmacy, Odissa, India*

---------------------------------------------------------------------***---------------------------------------------------------------------

**Abstract**

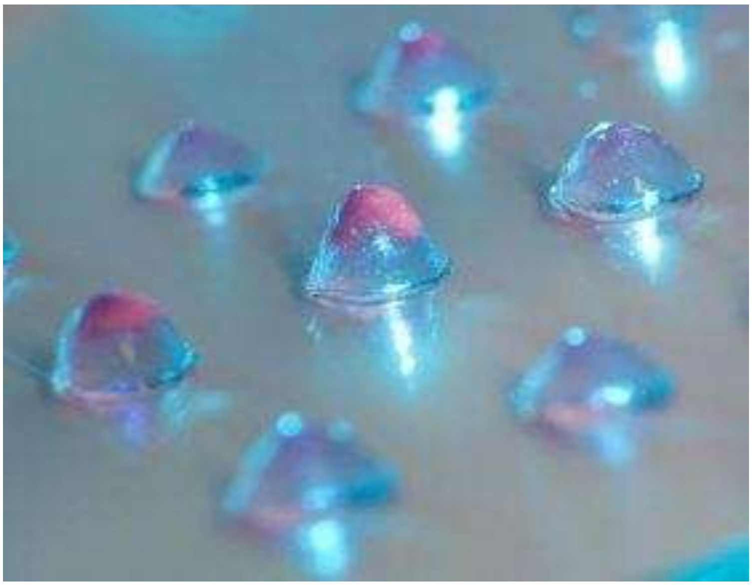
*The hydrogel means three –dimensional network structure obtained from either synthetic or natural polymers which can absorb and retain significant amount of water. The structure being created by the hydrophilic group or domains present in a polymeric network. The present review article delt with concept, aspect and application of hydrogel specially in the field of Pharmaceuticals.*

**Key Word: Hydrogel, Swelling, Macromolicules, Cross linking**

## 1. INTRODUCTION

For the past few decades, the pharmaceutical industry has experienced impressive growth year after year. Continuous introduction of life-saving drugs has propelled this growth. Beginning several years ago, however, the pharmaceutical industry has been experiencing difficulties in producing new drugs. The rate of introduction of new drugs is much less than the rate of blockbuster drugs coming off patent. There are many factors that contributed to the recent downturn in the pharmaceutical industry. The research and development of the pharmaceutical companies is not as productive as it used to be. In addition, the cost of new drug development is escalating every year, and one estimate indicates that the average cost of new drug development is $500 million. While there is no doubt that new drugs are the most important component in drug formulations, drug delivery technologies are also an important component in producing products on the market. Controlled-release technologies allow for effective use of existing drugs and successful development of new drug candidates.

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical companies to survive. This applies to all pharmaceutical companies, regardless of their size. In his book, Jurgen Drews has emphasized that the pharmaceutical industry must accomplish more than it has to date with more modest financial resources. One way of achieving this is to apply drug delivery technologies. Advances in drug delivery are occurring at a rapid pace, and it is important to keep up with innovations and applications of these technologies. **[1]**



### 1.1. HYDROGELS

The beginning of modern hydrogel research is considered to be the synthesis of poly(hydroxyethyl methacrylate) by Wichterle and Lim in 1960. Since then, considerable progresses have been made in the synthesis and applications of hydrogels. One of the areas that hydrogels have played a key role in is controlled drug delivery technology.

A hydrogel is a three-dimensional network of hydrophilic polymer chains that are cross linked through either chemical or physical bonding. Because of the hydrophilic nature of polymer chains, hydrogels absorb water to swell in the presence of abundant water. The swelling process is the same as the dissolution of non-cross linked hydrophilic polymers. By definition, water constitutes at least 10% of the total weight (or volume) of a hydrogel. When the content of water exceeds 95% of the total weight (or volume), the hydrogel is called a superabsorbent. Because measuring the weight of a swelling hydrogel is much easier than measuring the volume, the swelling ratio of hydrogels is usually expressed based on weights.

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. For this reason, there is no concept of molecular weight of hydrogels, and hydrogels are sometimes called infinitely large molecules or super macromolecules. One of the unique properties of hydrogels is their ability to maintain original shape during and after swelling due to isotropic swelling. Swelling only changed the size of the original hydrogel while maintaining the original shape. Hydrogels have been used widely in the development of biocompatible biomaterials, and this is mainly due to the low interfacial tension and low frictional surface by the presence of water on the surface. The dried hydrogels (also called xerogels) are usually clear, and swelling in water takes a long time. The slow swelling process is due to slow diffusion of water through the compact polymer chains. It is this slow swelling property that has been useful in controlled drug delivery. For a glassy hydrogel of a size equivalent to a stack of five pennies, it will take hours before the hydrogel showsappreciableswelling. [2]

## 2. PREPARATION OF HYDROGELS

### 2.1. TYPICAL PROCESS

- Polymerization of an acrylic acid monomer is carried out in the presence of PEGDA by radiation polymerization using a photochemical reactor. Solution polymerization is carried out in double distilled water. In Petri plates, weighed amounts of both PEGDA and acrylic acid up to a concentration range of total polymers of about 50% weight/volume (w/v) are dissolved in water and then exposed to ultraviolet radiations at wavelength of 365 nm for polymerization using a photochemical reactor. The hydrogel wafers then are dried and stored in a well-closed container until further use.

- The prepared hydrogels are purified by soaking the hydrogels in an excess amount of ethanol or ethanol and water mixture 12–24 hr to remove the soluble impurities. Spectral analysis of the washing medium confirmed the completion of washing.

- For easy handling and storage, the purified hydrogels are dried before drug loading. Drying is performed under a hot-air stream flowing over the hydrogel surface using a hot- air sterilizer oven at 60 °C for 2 hr followed by drying in a vacuum oven at 45 °C for 2 hr.

### 2.2. PREPARATION OF BIODEGRADABLE HYDROGELS

Biodegradable hydrogels can be prepared by following two methods:

**Method 1:**

Branched polymer of 1,6-linked D-glucopyranose residues with low % of 1,2- & 1,3- side chains is hydrolysed with Dextran polylactide cross-links.

Dextran can be functionalized with methacrylates & then cross-linked in the presence of small amount of monomer.

e.g. Dextran Hydrogel.

**Method 2:**

Coencapsulation of degradation catalyst.

Polymerization is carried out in the presence of protein to be delivered and bacterial dextranase.

e.g.Dextran Hydrogels encapsulating dextranase enzyme.

In this type degradation/protein release depends on amount of enzyme encapsulated.**[3**]

**2.3. PRODUCTION OF ELASTIC HYDROGEL**

Recently, superporous hydrogels with an elastic property are prepared. The elastic property is useful in making mechanically strong super porous hydrogels more resilient to compression and elongation. Figure demonstrates the elastic property of superporous hydrogels. The swollen hydrogel can be stretched to almost twice the original length without breaking. No previous hydrogels have shown such an elastic property. One way of making elastic superporous hydrogels is to form interpenetrating networks. **[4]**

**3. MATERIALS USED IN PREPARATION OF HYDROGELS**

**POLYMERS & THEIR USES [5]**

- **POLYMERS USED IN PREPARATION OF BLOOD COMPATIBLE HYDROGELS**
- Polyvinyl alcohol
- Polyacrylamide
- Poly(N-Propyl Pyrollidone)
- Poly(hydroxyethyl methacrylate)
- Polyethylene oxide
- Polyethylene glycol
- Poly(ethylene glycol)monomethyl ethyl cellulose
- **POLYMERS USED IN PREPARATION OF CONTACT LENSES**
- Polyhydroxy methacrylate co-polymerised with
- Methacrylic acid
- Butyl methacrylate
- Methyl methacrylate
- 3-Methoxy-2-hydroxy propyl methacrylate

**NETWORKS OBSERVED IN HYDROGELS [6]**

**1. Interpenetrating networks:**

Prepared by mixing swelling polymer with a temperature or PH responsive polymer to obtain networks that have a defined amount of swelling in response to changes in temperature or PH.

**2. Semi-interpenetrating networks:**

In this second component is entangled with first network but not cross-linked.

**4. METHOD TO INCREASE MECHANICAL STRENGTH OF HYDROGEL**

Hydrogels can be made to possess high mechanical strength even after swelling. The mechanical strength can be improved substantially by adding composite materials, e.g., Ac-Di-Sol, which is a hollow microparticle of a hydrophilic polymer. The presence of hollow microparticles results in physical entanglements of polymer chains around the microparticles. This essentially increases the effective crosslinking density without making the superporous hydrogels too brittle. Superporous hydrogel composites showed long-term gastric retention when tested in dogs, ranging from several hours to a day.

### 4.1 MODULUS OF HYDROGELS

The modulus of hydro gels is in the range of hundreds of KPa, which is very low. This is due to the small crosslinking density, which allows the large volume change but at the same time reduces the modulus of elasticity. In the past, people have tried different methods to increase the modulus of elasticity to the range of hundreds of MPa but were not very successful. Therefore, most of hydrogen applications are in the area where the mechanical propeties are not critical and small modulus is desired. For example, hydro gels have found applications in microfluidics, lens, cell encapsulation, drug delivery, etc.

## 5. NEW APPROACH TO MAKE HYDROGELS MORE ABSORBABLE

While the slow swelling property is the one that made hydrogels useful in controlled drug delivery, many applications required fast swelling (i.e., swelling in a matter of minutes rather than hours) of dried hydrogels. Fast swelling is usually done by making very small particles of dried hydrogels. The extremely short diffusion path length of microparticles makes it possible to complete swelling in a matter of minutes. Most hydrogels used in baby diapers are made of fine particles. Such a limitation in size poses a problem in certain applications. To make large dried hydrogels swell in a matter of minutes regardless of their size and shape, a new approach of preparing hydrogels was required.

One way of overcoming the slow absorption of water into glassy hydrogels by diffusion was to create pores that are interconnected to each other throughout the hydrogel matrix. The interconnected pores allow for fast absorption of water by capillary force. A simple method of making porous hydrogel is to produce gas bubbles during crosslinking polymerization of vinyl monomers. A monomer, initiator, and crosslinker are added to a test tube. The monomer solution is made slightly acidic to retard the polymerization process. To the monomer solution was added sodium bicarbonate to generate carbon dioxide bubbles, and generation of gas bubbles makes the foam rise. (The addition of sodium bicarbonate increases the pH, resulting in faster polymerization of vinyl monomers. Completion of polymerization while the foam is still stable results in formation of superporous hydrogels. Superporous hydrogels can be synthesized in any moulds, and thus, three-dimensional structure of any shape can be easily made. It shows a scanning electron microscopic picture of a porous hydrogel showing interconnected pores. The size of pores produced by the gas blowing (or foaming) method is in the order of 100 mm and larger. Because macroporous hydrogels are known to possess pores in the 100-nm to 10-mm range, the new porous hydrogels were named superporous hydrogels. If any portion of a superporous hydrogel is in contact with water, water is absorbed right away through the open channels to fill the whole space. This process makes the dried superporous hydrogels swell very quickly to very large sizes.**[7]**

## 6. EVALUATION OF HYDROGELS [8]

### 6.1. Physical appearance and texture:

Physical appearance is visually evaluated & inner morphology is studied using scanning electron microscopy. Samples are gold-coated and observed under an electron microscope under various magnifications.

Glass transition temperatures of the hydrogels are measured using a differential calorimeter. An aluminum crucible of 40-L capacity is used for this purpose. The samples are heated from 35 °C to 350 °C at a rate of 10 °C/min. Nitrogen gas is used as cooling (at 200 L/min) as well as the purging medium (at 80 L/min).

### 6.2. Water absorbing capacity:

The water-absorbing capacity of hydrogels is determined in terms of percent equilibrium water content (% EWC) or swelling ratio (SR). The dry hydrogels are weighed (W d) and then immersed in distilled water for 24 h at 37 ± 2 °C. The hydrogels then are reweighed (W s) after removing the excess water by lightly soaking the swollen hydrogels using filter paper. The swelling ratio of the hydrogels is determined using the formula:

$$\% \mathrm{EWC} = \left[\frac{w_s - w_d}{w_d}\right] \times 100 \qquad [1]$$

$$\mathrm{SR} = \frac{w_s}{w_d} \qquad [2]$$

### 6.3. Release kinetics and porosity:

Release studies are carried out in distilled water as receptor medium, maintained at 37 ± 2 °C. Sink condition is continuously maintained. The amount of drug released in the dissolution medium is determined spectrophotometric ally at 276 nm after every 1-h interval. The study is continued for 72 hr. The data of release profiles for each formulation are analyzed further by model fitting with the help of software PCP DissoV2.5.

## 7. ADVANTAGES OF HYDROGELS [9]

1. Currently used as scaffolds in tissue engineering. When used as scaffolds hydrogels may contain human cells in order to repair tissue.
2. Environmentally sensitive hydrogels have the ability to sense changes of ph, temperature, or the concentration of metabolite and release their load as result of such a change.
3. As sustained release delivery system.
4. Provide absorption, desloughing and debriding capacities of necrotic and fibrotic tissue.
5. Hydro gels that are responsive to specific molecules, such as glucose or antigens can be used as biosensors as well as in DDS.
6. In disposable diapers where they "capture" urine or in sanitary towels.
7. Contact lenses (silicone hydro gels, polyacrylamides)
8. Medical electrodes using hydro gels composed of cross linked polymers.
9. Breast implants.
10. Granules for holding soil moisture in arid areas.

## 8. DISADVANTAGES OF HYDROGELS

1. Fracture of hydro gels. Fracture is an important issue since most hydro gels are fragile. In some cases, the presence of a moving sharp front can cause hydro gels to break. In other cases, external mechanical constraints can break hydro gels.
2. Repeatability of swelling/shrinking behaviours or fatigue. In many hydrogen applications, it is expected that hydro gels can go through cyclic swelling and shrinking without damage. It is therefore important to understand the fatigue behaviour of hydro gels under cyclic swelling/shrinking.

Precise determination of mechanical properties at small scale. Major issues in determining mechanical properties of hydro gels are 1) low modulus and 2) the requirement to immerse hydro gels in solution.

## 9. APPLICATIONS OF HYDROGELS [10]

### 9.1. DEVELOPMENT OF GASTRIC RETENTION DEVICES

The idea is to make an oral formulation to swell fast to a size large enough to prevent them from passing through the pylorus. To avoid emptying into the intestine by the housekeeper waves of the stomach that occur about every 2 hours, the oral formulation has to swell as fast as possible. This is because it is difficult to know when the next housekeeper wave will come following administration of a super porous hydrogel formulation. The initial goal of fast swelling was to reach maximum swelling in about 20 minutes because water is known to remain in the stomach for about 30 minutes.

### 9.2. 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 per oral formulation has been developed to date. superporous hydrogels and their composites that increase their volume by about 200-fold. Such volume increase allowed the gels to mechanically stick to the intestinal gut wall and deliver the incorporated drug directly to the gut wall. The proper selection of functional groups of the superporous hydrogels, e.g., carboxyl groups, induced the extraction of calcium ions to induce opening of the tight junctions of the gut wall and deactivate the deleterious gut enzymes. After the peptide drugs have been delivered and absorbed across the gut wall, the superporous hydrogels become over hydrated, their structure is broken down by the peristaltic forces of the gut, and the remnants of the delivery systems are easily excreted together with the feces as miniparticulate systems.

### 9.3. 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 or gels in the stomach is expected to suppress the appetite.

For oral drug delivery as well as for diet control, superporous hydrogels can be modified to delay the swelling. Superporous hydrogels can be loaded inside hard gelatin capsules. In addition, the superporous hydrogels can be made to swell after a predetermined delay time. This will eliminate any concern on the premature swelling of superporous hydrogels for clinical applications.

### 9.4. DEVELOPMENT OF OCCLUSION DEVICES FOR ANEURYSUM TREATMENT [11]

The property of fast swelling to a large size of superporous hydrogels has been useful in the development of a new biomedical device for treating aneurysms. When the size and shape of an aneurysm site is predetermined by a non-invasive imaging method, a superporous hydrogel of the same shape (but smaller size) can be made. When a superporous hydrogel is deployed at the aneurysm site, it swells quickly to occupy the space and make the blood clot. Deposition of superporous hydrogels resulted in up to 95% aneurysm occlusion without any evidence of parent artery compromise and inflammatory response.[11] In similar application, superporous hydrogel particles can be used as an blood flow to solid tumors. One of the methods of treating solid tumors is to block the supply of nutrients and oxygen using an embolizing agent, and superporous hydrogel particles can be used for this purpose very effectively. A bioactive can be released from the superporous hydrogels either to enhance or to delay blood clotting.

### 9.5. APPLICATION OF HYDROGEL IN TISSUE CLOSURE

In urology, a partial nephrectomy (removal of part of a kidney) is performed for a kidney cancer in patients in whom a total nephrectomy would result in dialysis. Since 1992, kidneys have been removed using minimally invasive surgical techniques, namely laparoscopy, instead of large incisions. The advantage of this approach is not only in money saved resulting from a decreased stay in the hospital, but also more rapid healing for the patient and return to normal life. . However, cutting across the kidney results in severe bleeding that must be controlled. The hole through which the surgery is being performed is too small for the surgeon's hand to hold pressure. Traditional hemostatic methods (electrocautery, argon laser coagulation, fibrin glue, etc.) are not always effective. . Specifically, biodegradable hydrogen polymers, which have already received FDA approval for lung use, can be applied to the raw surface of the kidney and seal all of the blood vessels as well as the open urinary collecting system.

Advantages of using hydrogels in tissue closure are

- Perfect connectivity for cell migration.
- Improved nutrient transport.
- No dead volume.

### 9.6. APPLICATION IN SUPPORTING NERVE GROWTH

Hydrogels allows nerves to attach itself & grow through it. Nerve tissue is very soft, so, if the "bridge" material that is material joining two nerves is hard, the nerve won't be able to grow through it. This is also because nerve also needs structure to grow on to keep the nerve in place.

Hydrogels serves as "scaffolds". It binds proteins which controls adhesion, also it binds diffusion proteins which are necessary for nerve regeneration.

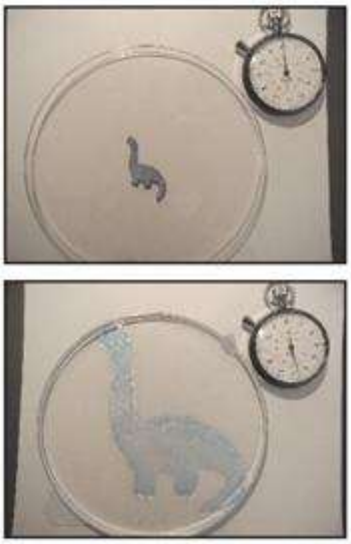
Hydrogels are useful in transplantation of autologus nerve, which comes from another part of the body, to bridge large nerve gap.

### 9.7. OTHER APPLICATIONS

Superporous hydrogels can be applied for the development of various non-pharmaceutical and non-biomedical products. As shown in Figure, superporous hydrogels swell extremely fast, and superporous hydrogels in many interesting shapes can be prepared. Superporous hydrogels can also be used as a tool in a science project for children. Children can enjoy the immediate swelling of superporous hydrogels in various shapes in front of their eyes. There are commercial toy products that are based on swelling several times of their original sizes, but the swelling takes 48 hours. Two days is too long for any child to wait and enjoy growing of an interesting object.[12]

FIGURE 4

Complete swelling of a superporous hydrogel (in a dinosaur shape) in less than 30 sec.



A superporous hydrogel can absorb more than several hundred-fold of its dried weight. This property can be used to prevent any accidental spilling of unwanted aqueous solution to the surroundings. The aqueous solution to be protected can be surrounded by superporous hydrogels, which can be prepared as one piece to fit the exact size and shape of the container, or as a particulate form. Superporous hydrogels can also be used to prevent water from sneaking into moisture-sensitive materials. They can be covered with superporous hydrogels so that any moisture passing through the superporous hydrogel layer can be trapped.

Hydrogels can be expand and contract in reaction to temperature, when fever raises the body temperature, tiny particles of hydrogen contract and squeeze out medication. When fever subside particles expand to hold medication in.

Applications of superporous hydrogels will increase as more people become aware of their properties and develop new ideas of applications. In addition to the fast swelling and large swelling properties, superporous hydrogels possess another unique property. While they absorb water and swell, they exert a significant force toward outside during swelling. This outward force of swelling superporous hydrogel is quite impressive. This outward force of swelling superporous hydrogels can be used in many applications. One of them is to use the force to trigger an alarm system where the invasion of water should be detected immediately. [13]

**Conclusions**:

Hydrogel has the capacity to hold water and medicament in them due to cross linked structure. This features support formulation of pharmaceutical products in the form of hydrogel. Due to the ability of holding water they can hold and retain wound exudates.

Gelatine and sodium alginate based hydrogels when applied have the ability to cover and protect the wound from bacterial infection

Hydrogel, A kind of revolutionary advancement since last few years in the field of Pharmaceutical and Biomedical products manufacturing. It supports as a tool for Novel drug delivery system in various system. Few limitations are there such as low mechanical strength

And difficulty in Sterilisation. Further researches necessitate overcoming such manufacturing variability which makes hydrogel more powerful supportive in the field of pharmaceutical, Biomedicals etc.

**Reference**

[1]. Peppas N.A., Huang Y, Torres-Lugo, M. Ward physicochemical foundations of hydrogels in medicines & biology 2;9-29.

[2]. Anseth, K.S. & Burdick, J.A. New directions in photopolymerizable biomaterials 27; 130-136.

[3]. Coviello, T., Matricardi, P., Marianecci, C. & Alhaique, F. (2007) Polysaccharide hydrogels for modified release formulations. Journal of Controlled Release 119, 5-24.

[4].Oyen,M.L(January2014)."Mechanicalcharacterisationofhydrogelmaterials". *InternationalMaterialsReviews*. **59** (1):4459. doi:10.1179/1743280413Y.0000000022. ISSN 0950-6608.

[5]. Joshi, J. and R.P. Patel, Role of biodegradable polymers in drug Materials Science and Engineering: C, 2013. 33(5): p. 2958-2966.

[6.] Das N. Preparation Methods and Properties of Hydrogel: A Review, International Journal ofPharmacyandPharmaceuticalSciences.2013; 5(3):1-2

[7]. Jen, A.C., Wake, M.C. & Mikos, A.G. Review, Hydrogels for cell immobilization, Biotechnology and Bioengineering 50,357-364.

[8]. Khullar P, Khar R K and Agarwal S P. Evaluation of hydrogel based controlled release Niacin tablets, Drug. Dev. Ind. Pharm, 24(5), 1998, 479-483

[9]. Hydrogels as Drug Delivery Systems; Pros and Cons, **June 2019 DOI: 10.30476/tips.2019.81604.1002**

[10].Kashyap N,Kumar N,Kumar M,Hydrogels for pharmaceutical and biomedical applied.Crit Rev Ther Drug carr Syst 2005;22:107-49.

[11].Stamatialis Dimitrios F,Papenburg Bernke J,Girones Miriam,Saiful Saiful,Bettahalli Srivastsa NM,Schmitmeier Stephanie,Wessling Matthias.Medical application of membrane drug delivery, artificial organs and tissue engineering, J Membr Sci 2008;(1-2):1-34.

[12]. El-said, I.A., Aboelwafa, A.A., Khalil, R.M. and ElGazayerly, O.N., Baclofen novel gastro retentive extended release gellan gum superporous hydrogel hybrid system: In vitro and in vivo evaluation. Drug delivery, 2016; 23(1): 101-112

[13]. Gupta, N.V. and Shivakumar, H.G., Preparation and characterization of superporous hydrogels as gastro retentive drug delivery system for rosiglitazone maleate. Daru, 2010; 18(3): 200-210