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DESIGN AND EVALUATION OF CONTROLLED RELEASE BUOYANT FORMULATIONS OF SUMATRIPTAN BASED ON SUPER POROUS HYDROGEL COMPOSITES

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ABSTRACT

Formulation of potent drug molecules as dosage form still draws continuous interest and challenges against its optimization towards pharmacokinetics parameters like absorption, bioavailability, onset of action, duration of action etc. The consistent maintenance of plasma drug concentration within the therapeutic level for prolonged periods of time has been persisting as a challenge to the pharmaceutical field. The conventional dosage forms are designed to be consumed by the patients two, three or even four times a day, which ultimately results in non compliance by the patient. The principal aim of an oral controlled release drug delivery system is to achieve better bioavailability and release of the drug from the system, in a predictable and reproducible manner. A number of controlled drug delivery systems have developed to prolong and control the release of drugs for a period of times in order to enhance their curing efficiencies. The main objectives are

1) The present research work aims to design and evaluate hydro dynamically balanced buoyant formulations of Sumatriptan based on Superporous hydrogels.
2) To carry out the drug-excipient compatibility studies.
3) To evaluate the drug release in developed formulations by in-vitro studies.

The drugs with low biological half life and unstable in the small intestine are good candidates for Gastro retentive dosage forms.

KEYWORDS: Pharmacokinetics, conventional dosage forms, Sumatriptan, Superporous hydrogels.

INTRODUCTION

Hydrogels are crosslinked hydrophilic polymer chains with a network structure consisting of acidic, basic, or neutral monomers and are able to imbibe large amount of water. The hydrogel swelling properties are mainly relates to the elasticity of the network, the extent of crosslinking, the presence of hydrophilic functional groups (such as -OH, -COOH, -CONH2, -SO3H) in the polymer chains, porosity of the polymer[1], manufacturing process and materials used[2] and their swelling takes more time.[3] Japanese researchers have created a rapidly self-healing hydrogel material, forming a gel in seconds and useful in regenerative medicine and green chemistry.[4]

Nowadays the applications require fast swelling, for that purpose super porous hydrogels were developed. In a chemical hydrogel, all polymer chains are cross linked to each other by covalent bonds and thus, the hyrogel is one molecular 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 supermacromolecules.One of the unique properties of hydrogels is their ability to maintain original shape during and after swelling due to isotropic swelling. Figure 1.1 shows a hydrogel in the dried state and the same hydrogel after swelling. Swelling only changed the size of the original hydrogel while maintaining the original shape.

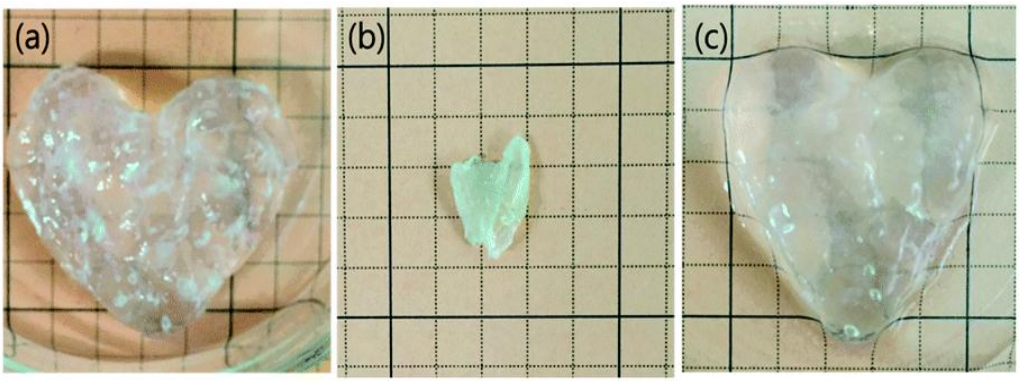

Figure: 1.1 Swelling of a dried hydrogel

SUPER POROUS HYDROGELS

A super porous hydrogel(SPH)is a three dimensional network of a hydrophilic polymer chains and their complete swelling occurs in less than 30 sec as shown in figure 1.2. The formulation of super porous hydrogels involves components like cross linking agents, intiators for initiation of polymerization, foaming agents like inorganic carbonates such as

Na_2Co_3 and $NaHCO_3$. These inorganic carbonates are safely used as a gas -forming ingredient in effervescent tablets for antacids. They are safe, cheap, and easy to Use.[5]

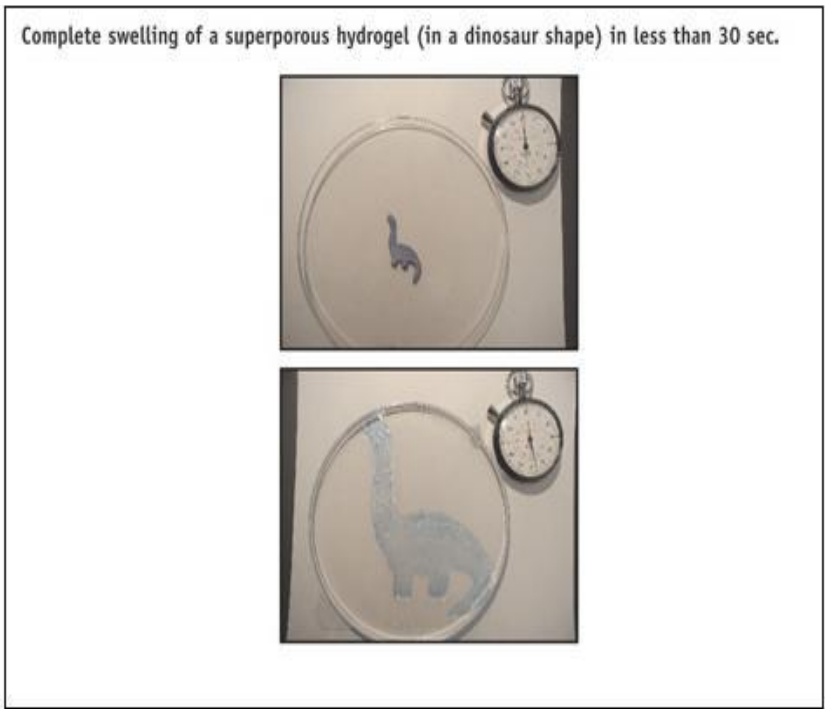

Figure-1.2: Complete swelling of a super porous hydrogel

There are different ways to improve swelling behaviour of SPHs

1. Some of the vinyl monomers having poor swelling characterstics, so to improve the swelling characterstics of strong poly hydroxyl ethyl methacrylate, different poly(HEMA-coacrylic acid) hydrogels were polymerized and crosslinked, followed by treating with divalent calcium and trivalent aluminium cations[6]

2. The swelling power of PEG-grafted SPHs were 3.6 times faster than the control SPHs and they were prepared by copolymerization of acrylic acid and acrylamide monomers in the presence of PEG acrylate followed by a gas blowing foaming process to create super porous structures.[7]

There are different ways to improve the Mechanical strength.

1. To improve the mechanical strength, several super disintegrants like Ac-Di_sol, Primojel, Explotab and Cross povidone was generally added.[8]
2. Swelling and mechanical properties of super porous hydrogels of poly(acrylamide-co-acrylic acid)/polyethylenimine interpenetrating polymer networks were established.[9] If the super porous hydrogels are very pure they have outstanding swelling properties.

Omidian, Hossein et al studied that very-pure super porous hydrogels having outstanding swelling properties.

GENERATIONS OF SPH's

There are three generations of super porous hydrogels: conventional super porous hydrogels, super porous hydrogel composites, super porous hydrogel hybrids.

First generation SPH (conventional SPHs, CSPHs)

Polymerization and crosslinking of different vinyl monomers in the presence of a foaming agent, a foam stabilizer and a foaming aid resulting in the formation of conventional SPHs having fast swelling kinetics and superabsorbent properties. They are very difficult to handle as they are very rigid and brittle in the dry state. The swelling rate of conventional SPHs was controlled by coating with a poly (acrylamide-co-acrylic acid) SPH with an ethanolic solution of an amphiphilic block copolymer of ethylene glycol and tetramethylene oxide (PEGTMO).

Second generation SPH (SPH composite, SPHCs)

SPH composites involves monomer, crosslinker and initiating system, water-soluble foaming additives but additionally a swellable filler act as an isolated individual reactor, in which polymerization and crosslinking could occur simultaneously. The swollen particles would then be connected to each other through the extended polymeric chains. Upon drying, an interpenetrated network structure (IPN) would be formed.6 Super porous hydrogel composites (SPHCs) based on, carbopol and o-carboxymethyl chitosan, as the second generation of SPHs, resulted in improvement of the properties of SPH.[10]

MATERIALS & EQUIPMENTS

Preformulation studies

5.1 Solubility Studies

5.1.1 Determination of Sumatriptan Solubility

Solubility study of the Sumatriptan was investigated in four different media as follows:

1) Purified water

2) 0.1 N hydrochloric Acid (HCl), (pH 1.1 4) USP

3) Acetate buffer pH 4.5, USP

4) Phosphate buffer pH 6.8, USP

Required quantity of above media was transferred in to a volumetric flask and heated up to 37 ±0.5oC using magnetic stirrer provided with heat. Previously weighed quantity of Sumatriptan was added to the above volumetric flask until the saturation point occurs. The total quantity of Sumatriptan added was recorded. Stirring was continued up to 5 hours at 37 ±0.5oC. The sample was filtered through 0.45 µm membrane filter (MILLIPORE). A measured quantity of filtered sample was transferred in to another volumetric flask and made further dilutions. The absorbance was measured using UV visible spectrophotometer at respective λmax of 282 nm.

5.2 Synthesis of Various SPH Composites

For the synthesis of poly (AM-co-AA), the following method was used. All the ingredients namely 300µl of Acrylamide(AM) 50%w/v; 200µlAcrylic acid (AA) 50%v/v; 70µl N,N1 Methylene-bis-acrylamide(BIS)2.5%w/v;30µl span 80, 10%v/v; 25µl ammonium persulfate(APS) 20%w/v; 25µl N,N,N1,N1,tetra methylethylenediamine(TEMED) 20%v/v; 400µl chitosan aqueous solution 6%w/v and were subsequently added into a test tube at 250c with vigorous shaking. The required amount of Chitosan/ Ac-Di-Sol/ was selected based on primary studies. SPH was prepared using double distilled water.

200mg of sodium bicarbonate was added very quickly to the solution and mixed with a spatula.

 Polymerization was allowed to continue for approximately 10 min.

 Synthesized SPHC was removed with a forceps, allowed to dry in an oven at 600c or air dried for 48 hrs and cut into pieces of required size.

 The SPHC was submerged in an organic solvent overnight. This treatment dehydrated the SPHCs followed by drying.

 Finally drying of SPHC was done in an oven at 600c for 48 hrs and stored in an air tight container.

SUMMARY AND CONCLUSION

Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. Controlled/sustained release preparations using alternating routes have also been formulated but oral route still remains preferable. In recent years, per oral dosage forms for gastric retention have attracted more and more attention for their theoretical advantage in gaining control over the time and the site of drug release. This would be particularly valuable for

drugs that exhibit an absorption window in the upper part of the small intestine. Sumatriptan has shown highest solubility in 0.1N HCl. The solubility of Sumatriptan in water, pH 4.5 Acetate buffer and pH 6.8 phosphate buffer was almost similar which is in the range of 76-83 mg/ml, indicating the high solubility of the drug in the pH range of 1 to 7. SPH‘s synthesized employing various composite agents viz., Chitosan, Ac-Di-Sol, Carbopol were subjected to density and Swelling property(Swelling Time, Swelling Ratio) characterization. SPH-Ac-Di-Sol has shown best results, it was optimized for further characterization. Through water retention studies it was observed that lower the concentration of the crosslinking agent, the faster was the loss of water from the superporous hydrogel. As composite agent is responsible for maintaining the capillary structure required for fast swelling of SPH, the effect of optimized Composite on mechanical characters and swelling behavior of SPH was assessed. Ac-Di-Sol conc. was increased from 50 mg to 175 mg in 2D-1 to 2D-6 SPH‘s. As the Composite (Ac-Di-Sol) conc. increased, there was an extensive variation in swelling properties. Swelling time was gradually decreased from 38 min to 12 min. As the amount of Ac-Di-Sol increases the mechanical strength increases due to increased cross linking density of the Superporous Hydrogel.

The gelation kinetics gives good information determining the introduction time of blowing agent (sodium bicarbonate). In order to produce large and uniform pores, the blowing agent must be introduced when the reactant system has appropriate viscosity. Bubbles cannot maintain their shapes by completion of reaction when blowing agent is introduced too early, and they cannot even be formed when introduced too late. The Sol-gel transition time for various formulations was between 18-22 seconds. This clearly indicated that the blowing agent must be introduced immediately after the adjustment of pH to 5.0 with sodium hydroxide solution. Sumatriptan –SPHCP formulation had successfully retarded the drug release upto 8 hours. The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model dependent approach, the dissolution data was fitted to five popular release models.

SEM photograph clearly reveals the presence of the swollen pores on the surface of the Superporous hydrogel composite drug delivery systems.

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