A Review of Process Validation of Hydrogel Formulation

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ABSTRACT

Hydrogels are a class of polymeric materials characterized by a hydrophilic structure that enables them to entrap substantial amounts of water in their 3D networks. Eventually, synthetic hydrogels superseded natural ones due to their superior water-absorbing capacity, longer product life, and greater availability of raw materials resources. Variations in the manufacturing process that occur are likely to have a substantial impact on the final product's characteristics. The conclusion drawn from such a comprehensive study of hydrogel in-process shortfalls offers a clearer and more realistic perspective when designing and developing new formulations. The primary goal of this review article is to provide a comprehensive literature review of the technologies used in hydrogel production, including the implications for process design and optimal conditions for preparation and process validation. As per a review of the literature, hydrogels can adhere to an application surface for lengthy periods before being washed away. This property extends the duration of drug delivery at the application site. Due to their water-washable bases, innovative hydrogels are non-greasy. Therefore, they are superior to conventional hydrogel forms and cause less skin irritation. In addition to this review article, Process validation is an ongoing program, an essential part of GMP, and by aligning process validation operations with the product lifecycle, the pharmaceutical industry ensures that its processes are reliable and consistent over the whole duration of their commercialization.

Key Words: *Hydrogel, GMP, Process validation, Product life cycle, Commercialization*

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INTRODUCTION

Hydrogel

Hydrogels are an extraordinary type of cross-linked 3D polymeric network that retains a large number of watery liquids and organic liquids. The incorporation of hydrophilic groups into the polymeric chains, like amino, carboxyl, and hydrogel groups, helps the water retention capacity of the hydrogel. These polymeric materials are stable in water under physiological conditions of temperature and pH but fully expand in an aqueous configuration. Poly (vinyl alcohol), poly (ethylene glycol), and poly (propylene glycol) are some models (acrylic corrosive) [1].

Classifications

Hydrogels are classified as per the following:

Classification as indicated by source

1. Normal source
2. Manufactured source [2]

Classification dependent on the polymeric structure

a. Hydrogels made of Homopolymeric polymers

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Homopolymers have a cross-connected skeletal design that changes relying upon the monomer's starting point and polymerization strategy [3].

b. Hydrogels made of copolymeric polymers

These are comprised of at least two monomer species having something like one hydrophilic part that are coordinated in an arbitrary, block, or rotating design along the polymer organization's chain [4].

c. Multipolymer

Polymeric hydrogel with interpenetrating properties This is a typical sort of hydrogel that comprises two cross-connected engineered and additionally normal polymer parts held together in an organization structure. A cross-linked polymer and a non-cross-linked polymer form the two components of a semi-IPN hydrogel [5, 6].

Classifications as per arrangement

The order of hydrogels relies upon their actual design and synthetic organization.

1. Amorphous or non-translucent
2. Semi-translucent: contains a combination of formless and translucent stages.
3. Crystalline

Classification dependent on a sort of cross-connecting

Hydrogels are partitioned into two classifications dependent on the actual nature of the cross-interface intersections. Synthetic cross-links are permanent connections between polymer chains, while physical cross-links are temporary connections that result from either polymer chain entanglements or physical interactions such as ionic bonds, H-bonds, or hydrophobic interactions [6].

The classification depends on physical appearance

The shape of hydrogels as matrix, film, or microsphere depends on the polymerization method used in the preparation process.

Classification indicated by network electrical charge

The cross-linked chains of hydrogels can be classified into four groups based on whether they have electrical charges or not.

1. Non-ionic.
2. Ionic (counting anion or cation).
3. Ampholytic (an electrolyte that has both basic and acidic groups is called amphoteric).
4. Zwitterionic (have both negative and positive groups in each basic repeating unit) [7].

Advantages of hydrogels [8]

1. They are very flexible and similar to natural tissue because of their high water content.
2. They can respond to changes in temperature, pH, or metabolite concentration and release their cargo accordingly.
3. They are biocompatible, biodegradable, and injectable.
4. They can trap microbial cells inside hydrogel beads with low toxicity.
5. They can control the release of growth factors and other nutrients for proper tissue growth.
6. They have good transport properties.

Limitations of hydrogels [9]

1. They have low mechanical strength and are expensive.
2. They are not adhesive and may require additional dressing
3. They might create an uproar like what is felt by the development of worms.
4. They can be difficult to handle.
5. Trouble stacking with drugs/supplements can be capable.

The primary goal of this review article is to provide a comprehensive literature review of the technologies used in hydrogel production, including the implications for process design and optimal conditions for preparation and process validation.

RESULTS AND DISCUSSION

Applications of hydrogel

Delivery of drug in the oral cavity

The mouth can be treated locally for various diseases, such as gum disease, inflammation, fungal and viral infections, and oral cancer, by delivering drugs to the oral cavity. For instance, a product called X is a bio-adhesive tablet that has two layers: one layer that sticks to the mouth and is made of hydroxypropyl cellulose and poly (acrylic acid), and another layer that does not stick and is made of lactose. This product releases triamcinolone acetonide, a drug that helps heal ulcers in the mouth**.**

Delivery of drug in the GI tract

Patients prefer to take drugs through the GI tract because it is easy and it has a large area for the drugs to enter the body. However, different methods are needed to deliver drugs effectively in the GI tract. They made positive hydrogels that can swell and release drugs depending on the pH level for treating infections in the stomach, which is acidic.

Delivery of drug through the rectal path

The rectum is mainly used for treating diseases related to it, such as hemorrhoids. This route is more accepted because it avoids first-pass metabolism and drugs from the lower rectum go directly into the blood. Earlier, conventional suppositories were used, but they had a problem of releasing drugs in an uncontrolled way. So, now, people prefer to use modified and sustained-release products like implants, hydrogels, etc.

Ocular delivery

Conventional ophthalmic preparations such as eye drops are quickly removed from the eye, have limited absorption and retention, and need to be applied often to work well for a long time. To solve these problems, suspensions and ointments were used, but some patients may feel uncomfortable. This leads to the development of hydrogel formulation, which may be more pleasant and less gritty because of its elastic properties.

Hydrogels for wound healing activity

Hydrogel formulations can hold water and drugs in them; they can absorb and keep wound fluids. Hydrogels made of gelatine and sodium alginate can protect the wound from germs by covering it [10].

Drug delivery through transdermal pathway

Hydrogels can release drugs steadily through the skin, avoiding liver metabolism. Hydrogels are similar to living tissues and can be easily taken off, like patches and ointments. Novel hydrogels made of poloxamer 407 with gentamycin can treat skin infections better, while gentamycin injection can cause serious problems [11].

Evaluation parameters of hydrogel

Hydrogels have many applications in biomedical and pharmaceutical fields. Some of the evaluation parameters of hydrogels are described in **Table 1**.

Table 1. Details description of evaluation parameters of hydrogels

S/N	Parameters	Descriptions
1.	Appearance	The physical appearance of hydrogel formulations will be visually checked, and observations should be reported.
2.	Homogeneity	The hydrogels will be analyzed for their physical properties like tone, lucidity, and stage division by visual assessment.
3.	Grittiness	The hydrogels will be checked to find out whether any visible particles are present in the prepared formulation batches or not.
4.	Washability	The hydrogels that are made need to be tested on the skin, and how easily and how much they can be washed off with water needs to be checked by hand.
5.	Extrudability	The hydrogels will be put into metal or aluminum tubes that can be squeezed. The material needs to be squeezed out of the tubes, and the ease of squeezing the formulation needs to be checked.
6.	pH	A digital pH meter can measure the pH of the hydrogel formulations. The pH meter needs to show a steady reading after dissolving 1 g of hydrogel in 25 ml of pure water. The measurement needs to be recorded.
7.	Viscosity	A Brookfield Digital Viscometer was used to measure the viscosity of the hydrogel. The spindle no.6 rotated at 10 rpm, and the temperature was 25 °C when the viscosity was measured.
8.	Spreadability	Spreadability is how easily the gel covers a large area when applied. It is measured by how long it takes for two slides with the gel between them to slide apart under a certain weight. The faster the slides separate, the better the spreadability.
	Stability	The stability studies for the formulations will be carried out. It should be stored in a wide-mouth container and kept in the stability chamber at a maintained temperature of 40 ± 2 °C; relative humidity was 75 ± 5% for 2 months.

Determining the spreadability parameter

To measure the spreadability of the hydrogel, two glass slides (7 × 2) were used. The hydrogel was put on one slide, and the other slide was placed on top of it, making a thin layer of the hydrogel between them along a 7 cm length of the slide. The extra hydrogel on the slides was removed, and a 100 g weight was put on the upper slide. The lower slide was fixed to a board, and the upper slide was attached to a string with a 20 g weight that could pull it 50 times using a simple pulley. The time for the upper slide to move 7 cm and separate from the lower slide was recorded.

$$\text{Spreadability} = m \times l / t \quad (1)$$

Where m = weight on the upper slide, l = length of a glass slide, and t = time in seconds.

Process validation

It is generally agreed that Pharmaceutical Process validation is the single most critical cGMP parameter. Validation is testing not only medical devices but also testing computer systems, labeling, process

control, and analytical methods for drug quality. Validation should be part of cGMP, which is the basic and necessary practice for making drugs, rather than separate from it because it follows the regulatory standards but is not required by them [12].

The Food and Drug Administration (FDA) suggests several steps, from selecting a quality process to conducting in-process and final product testing, as a means to guarantee a product's quality [13].

The three stages of making sure that a process is validated are designing the process, testing the process, and checking the process continuously. Making drugs needs a lot of following the cGMP, which are the rules for making drugs well. Process validation operations with the product lifecycle **(Figure 1)**, the pharmaceutical industry ensures that its processes are reliable and consistent over the whole duration of their commercialization.

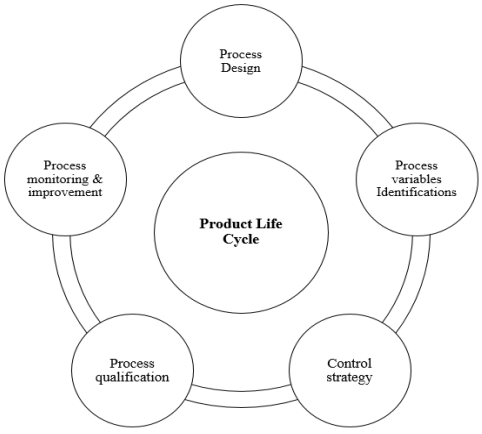

Figure 1. Product life cycle

Validation is making sure with written proof that a certain process can always make a product that meets its quality and standards.

Benefits of process validation [14]:

- It improves knowledge of the process, minimizes the potential for error, and prevents potential impediments. Defect costs are reduced as a result.
- Noncompliance with regulations is less likely as a result.
- There might be less need for quality assurance testing and control measures all along the production line if the process has been fully validated.

Process validation of hydrogels

They are mainly prepared for external applications. Generally, the hydrogels lie between the solid and liquid, where the matrix holds more water in the molecule, and there is a challenge in the preparation for manufacturers [15].

QTPP for hydrogel formulation

QTPP is the goal of making a drug that is safe and effective. QTPP is a tool that the USFDA uses for new drug development.

CMA and CPPs affect CQA by the Ishikawa diagram **(Figure 2)** in which the main branch represents the problem or effect, and several sub-branches represent the categories of causes. The sub-branches can have further sub-branches for more specific causes.

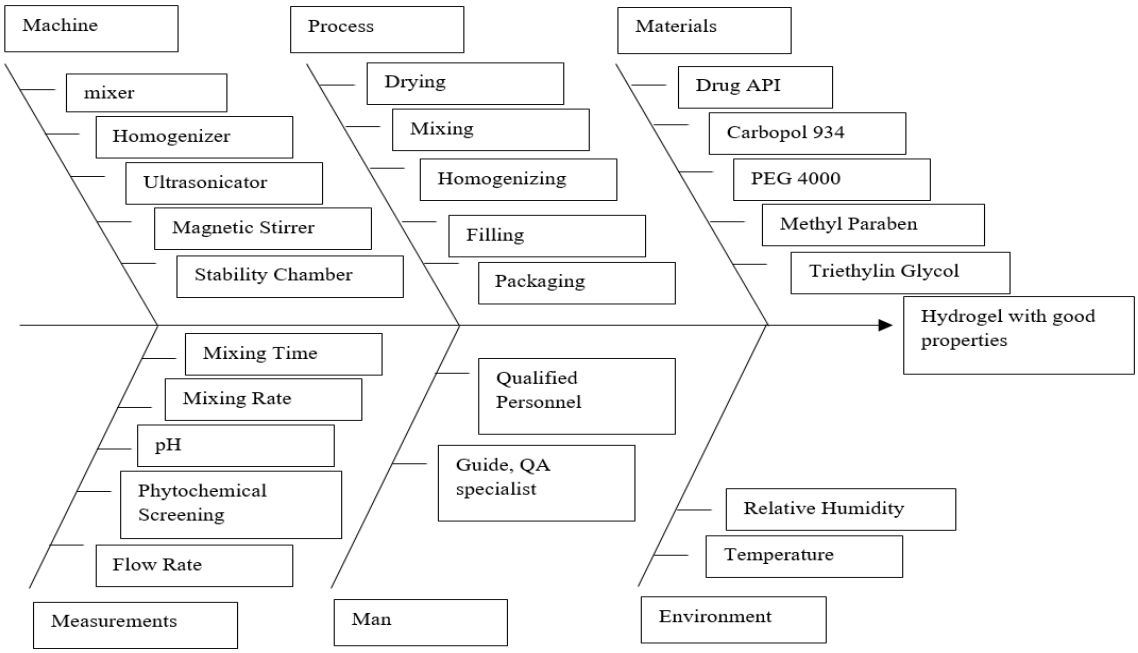

Figure 2. Ishikawa diagram

Validation of critical process parameters

Temperature

The product must be processed at the optimal temperature to avoid any adverse effects on its chemical and physical properties. For instance, too much heat can cause degradation of the ingredients, while too little heat can result in batch failures. Moreover, rapid cooling can lead to precipitation or crystallization of some components [16].

Heating and cooling rates

The heating and cooling rates also affect the product characteristics, especially for ointments [17]. For example,

a. Slow heating can cause evaporation and reduce the yield of the product.
b. Excessive heating can cause scorching or burning of the ingredients near the heating surface, which can impair the quality of the product.
c. Rapid cooling can increase the viscosity or cause phase separation of the product.

Mixing methods and speeds

The product must be mixed with the appropriate shear and speed to achieve the desired dispersion and homogeneity. Different types of products may require different mixing methods and speeds. For example, emulsions usually need high shear or homogenization to obtain a uniform droplet size and distribution, while hydrogels may need low shear to maintain their viscosity and other physical properties. The mixing speeds must also be adjusted for different batch sizes and phases. For instance, the proper hydration of polymers depends on the initial shear applied to disperse them in the medium. If the shear is too low, the polymers may not be fully dispersed and hydrated, resulting in a low-viscosity product that does not meet the specifications. Alternatively, equipment such as a recirculation loop can be used to improve the uniformity of the product without changing the mixing speed or time.

Mixing times

The mixing time must be optimized to ensure that all the ingredients are dissolved and dispersed adequately but not overmixed to cause product degradation or failure. For example, excessive mixing, especially high shear, can damage the structure of polymeric gels based on acrylic acid and reduce their viscosity. Similarly, overmixing an emulsion can cause phase separation and viscosity loss [18].

Flow rates

The flow rate must be optimized to provide the required shear or throughput for the product. Different types of products may have different flow rate requirements. For example, a water-in-oil emulsion may need a slower addition rate than an oil-in-water emulsion, and the flow rate must be adjusted accordingly. The flow rate also affects the performance of pumps and other equipment used in the process. If the flow rate is too high, overheating may occur, which can affect the product quality. If the flow rate is too low, the product may be exposed to excessive shear in an in-line homogenizer, which can also affect its quality [18].

Incorporation of polymers and gums

Polymers (Carbomers) and gums (Xanthan) require careful addition to a batch if they are not pre-dispersed.

The following processes in pharmaceutical manufacturing need validation

- Cleaning
- Sanitizing
- Fumigating
- Depyrogenating and sterilizing the equipment and environment
- Filling sterile products
- Producing bulk products through fermentation and purification
- Filling, capping, and sealing the products
- Lyophilizing the products [19]

Validation protocol

- A written plan that describes the process to be validated and the production equipment involved
- The method and procedure of conducting the validation
- The objective test parameter and the product characteristics to be measured
- The predetermined specification and the acceptable result criteria
- The factors that may affect the outcome of the validation

Protocol for validation of manufacturing process

- A presentation of the whole process and its sub-processes, with flow diagrams and critical step analyses
- Approval of the validation protocol
- Product qualification test data from pre-validation batches
- Installation and operation qualification of the equipment
- Qualification reports that include the method, procedure, release criteria, calibration of test equipment, test data, and result summaries from formal validation batches
- Sampling strategy - how, when, and where samples will be taken

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- Analysis of test results and conclusion
- Any requirement for revalidation and requalification
- Certification and approval of the validation
- A summary report of findings and conclusion
- Product stability copies

Components included in cGMP process validation that require validation.

- Facility
- Environment
- People
- Analytical laboratory
- Raw materials
- Equipment
- Procedures
- Process

Five unit operations for the hydrogel system

There are generally five types of unit operation for formulating the hydrogel. All the operations and the specific equipment used for the operations are mentioned in **Table 2**.

Table 2. Equipment used for unit operations

Sl no	Operation	Equipment
1.	Mixing of liquid	Kettle and tank fitted with agitator
2.	Mixing of solid	Blade mixture and tumbler
3.	Mixing of API	Blade mixture and kinder
4.	Dispersing	Homogenizers or ultrasonic device
5.	Milling and size reduction of solid and hydrogel	Micronizer

Filling and packaging operation

The following critical aspects must be controlled and evaluated during large-scale validation and manufacturing runs.

- Maintaining product temperature to ensure product flow and consistency before and during filling and packaging operations.
- Agitating the product in holding tanks and filling the order to keep product uniformity and homogeneity during filling and packaging operation.
- Using air pressure and inert atmosphere to achieve product performance and stability in the primary container. Consistency before and during filling and packaging operations.

Product testing

- Validation testing of bulk and finished products must be based on standard release criteria and in-process testing criteria.
- QC release testing should be done on a routine sample.
- These samples should be separate from the validation samples. Validation sampling and testing typically involves 3-6 samples, including the usual QC sampling.

Validation batch: bulk sampling

- Take 10 samples from the mixture, tank, or during product transfer to the storage/filling vessel.
- The samples must cover the top, middle, and bottom of the vessel.
- If sampling from the mixture/tank using specific equipment, samples should be taken near blades, baffles, and shafts where product movement during mixing may be limited.
- If possible, the bottom of the tank and any potential dead spots should be sampled and checked for unmixed material.

Sampling plan

- Samples must be representative of each filling nozzle.
- For single-filling size.
- Take at least 3 fill containers from each of the beginning, middle, and end of the filling run.
- The total number of samples must be at least 10.
- Test all samples.
- Multiple filling sizes.
- Take at least 3 samples each at the beginning and end of the filling size.

CONCLUSION

Hydrogels can be formulated in various ways but require careful control of the in-process problems that may arise in different steps. To produce a successful product batch, extensive studies and testing should be conducted. Readers of this review article will be helpful about the challenges faced during the manufacturing of hydrogel and, after manufacturing, how to store it in a particular condition as it is a very sensitive product. Future research studies should aim for more precise and accurate products.

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