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FUTURE OF STIMULUS RESPONSIVE HYDROGEL AS DERMATOLOGICAL FORMULATION, PREPARATION AND EVALUATION - A REVIEW

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Abstract:

Hydrogels have similarities in the case of tunable soft porous microarchitecture, biomimetic structure to the extracellular matrix of natural living tissues, proper biocompatibility, superb biomechanical properties, etc. Hydrogel resemble skin on application on skin surface, and provide moisturizing effect even if applied as placebo. Hydrogels have very high levels of hydrophilicity structure and biocompatibility because of their unique network, as hydrogels exhibit the soft physical properties associated with living tissue which makes them ideal biomaterials. In recent years, stimulus-response hydrogel is becoming a hot topic in research. Stimulus-responsive hydrogels are particularly effective as they can respond to the external environment which includes temperature, pH, electricity, light, etc., so, conducting and controlling material properties. As such Stimulus Responsive Hydogel can be used in various skin condition and improve the patient compliance toward medication

Key words: Stimulus responsive hydrogel, skin, tissue, external environment, method of preparation.

Introduction:

Hydrogel can be described as a 3D (three-dimensional) network of polymers with hydrophilic nature that can swell in aqua (water) and hold a large amount of aqueous content (water) by chemical or physical cross-linking for maintaining the structure due to of individual polymer chains [1], [2]. As per defined, water must be component of at least 10% of the whole volume (or weight) for a hydrogel's material. Hydrogels are very similar to natural tissue as they possess degree of flexibility due to their significant aqueous (water) content and shows high potential to be used as a dermatological formulation for external use or filling in cavities or made in-situ. The presence of hydrophilic groups such as -NH2, -COOH, -OH, -CONH2, - CONH -, and -SO3H imparts hydrophilicity of the network. In response to certain physical and chemical stimuli a significant gel-sol phase transition or volume phase can be underwent in Hydrogels [3].

Stimulus Responsive Hydrogel:

These are Hydrogels which shows higher response to environmental stimulus like change in pH, Temperature, Wavelength of light, etc. of surrounding to impart controlled release of drug at targeted site for its optimal action and to minimize wastage of drug and increase its efficacy. The biochemical or chemical stimuli include pH, ions, and specific chemical compositions while magnetic fields electric and temperature, solvent composition, light intensity, and pressure are included as physical stimuli. Conformational transitions as such are reversible in many of cases; so, no sooner than the trigger is removed, the hydrogels return to their initial state afterwards.

Impact of stimulus-responsive hydrogels have been especially high, in response to external cues it allowed very high levels of control over material properties. in healthcare this enhanced control has enabled enormous advances, effective treatment of a vast array of diseases is allowed because of such and for tissue engineering and wound healing has more improved approaches [4].

Numerous properties possessed by hydrogels that make them ideal biomaterials candidates for use, in the fields of drug delivery it found significant use, implants, tissue engineering, and more. When they are used as "smart" materials hydrogels become especially useful that can respond to changes in their environment [4].

Classification of Stimulus Responsive Hydrogel:

Environment stimulus responsive hydrogels are classified based on external stimuli type as, *light, pressure, and ionic-strength*, as well as sensitive to *thermo-sensitive, pH sensitive, electro-sensitive*. More attention is attracted for reducing the risks of surgical implantation such as scarring and infection by Hydrogels which are formed de novo in physiological conditions [5].

The types can be understood better by

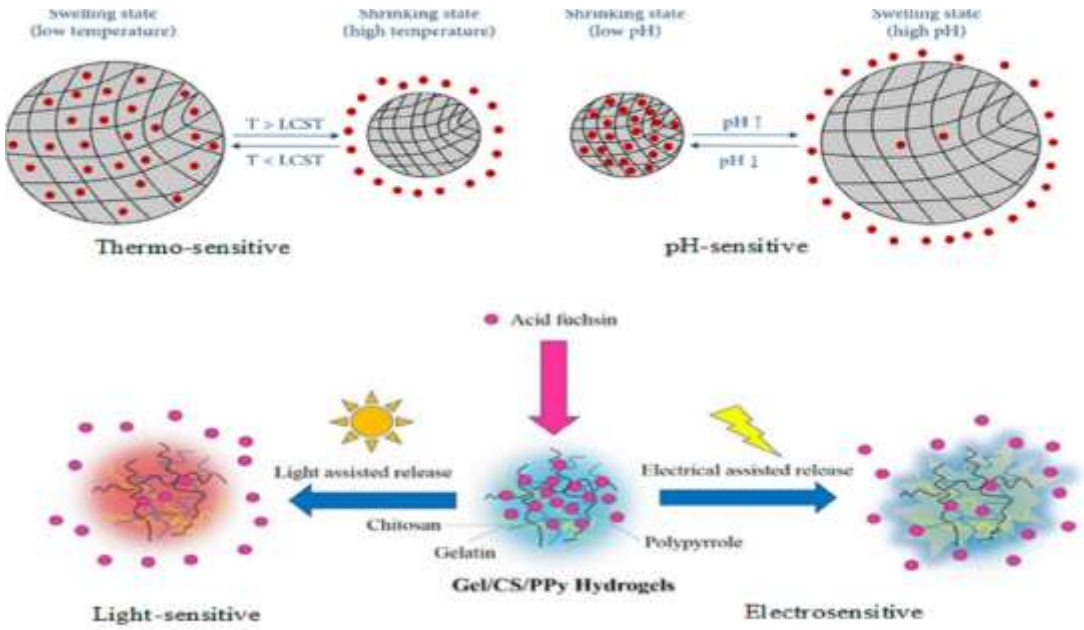

Fig no. 1 - Types of stimulus responsive hydrogels and effect of various stimulus [6], [7]

I. *Thermo-sensitive Hydrogel*:

As delivery system thermo-sensitive gels have many advantages. First pass metabolism can be avoided as the temperature-sensitive properties gift the hydrogel injectability for local administration, but in case of traditional hydrogels need to be surgically implanted[5]. The temperature-sensitive gel responds to temperature, and the temperature-induced sol-gel transition is safer in the body and as temperature-sensitive gel does not require any denaturing cross-linking agent these are more suitable for injectable systems [6]. The uniform dispersion of therapeutic agent in hydrogels is allowed by encapsulation in a flowing state, and initial burst release of the therapeutic agents is avoided at body temperature with the help of rapid solution-to-gel transition, as such making the release behavior being controlled in a controlled manner.
At last, the flowable state of administration imparts the hydrogel shape controllability [7].

1) Negatively sensitive hydrogels:
It contains polymers like mentioned below-
i) N-Isopropyl acrylamide-based system
ii) Polysaccharides
iii) PEO/PPO based system
iv) PEG/PLGA based system [5], [8], [9], [10]

2) Positively temperature sensitive hydrogels:
i) amylose,
ii) gelatin,
iii) amylopectin,
iv) agarose, and
v) Some thermo-reversible gel phase forming cellulose derivatives(acts by lowering the temperature [5], [11], [12].

II. *pH-sensitive hydrogels*:

pH-sensitive polymer structurally contains basic (e.g., ammonium salts) or acidic (e.g., carboxylic and sulfonic-acids) groups that respond to the pH changes in environment of them by loss or gain of protons[3],[13]. Poly-electrolytes are polymers which are having a large number of such ionizable groups [14]. Amphiphilic hydrogels contain both basic and acidic moieties; so, rather than in neutral media, in both acidic and basic environments they exhibit two-phase transitions. Polymer backbone can be made by incorporating

hydrophobic moieties or by selecting the ionizable moiety with a pKa matching with the desired pH range for the phase transition pH range that can be modulated [15].

By using different monomers different degrees of swelling and pH-sensitive behaviors can be achieved.

Ionic polymers which are studied for pH-responsive behavior include

i) Poly (acrylamide) (PAAm),
ii) PAA, poly (methacrylic acid) (PMAA),
iii) Poly (diethyl-aminoethyl methacrylate) (PDEAEMA),
iv) Poly (dimethyl-aminoethyl methacrylate) (PDMAEMA).
v) Polymers containing phosphoric acid derivatives have also been reported.

III. *Electro-sensitive hydrogels*:

In the presence of an applied electric field, electro-sensitive hydrogels can undergo swelling or shrinking [3], [16]. Poly-electrolytes is main component of which they are usually composed of, as like pH-sensitive hydrogels. A force on immobile and counter ions charged groups is produced in the network, and that is in presence of electric field, by which mobile ions get attracted to the electrodes. As such, the hydrogel shows shrinking and swelling regionally at the anode and cathode, in accordance with charge present on them[17].Electro-responsive hydrogels have promising applications in sensing, controlled drug delivery, biomechanics, sound dampening, tissue engineering, chemical separations, and energy transduction as it can transform mechanical energy from electrical energy[18].
The most commonly studied electro-sensitive polymers are

i) acrylamide
ii) carboxylic acid derivatives (e.g., PAA)

IV. *Light-responsive hydrogels*:
When applied with light of the appropriate wavelength photo-responsive hydrogels undergo a change in their properties[3],[19]. Typically, specific functional groups along the polymer backbone or side chains show light-induced structural transformations. When provided exposure with ultraviolet (UV) or visible light, light-sensitive hydrogels can contract and expand. Ease of manipulation, wide availability, clean operation, and low cost are some of many advantages over UV light of Visible light. Visible light-induced volume change's mechanism of hydrogels is based on the induction of changes of temperature by incorporating a chromophore (photo-responsive functional group) into the polymer network[20].The chromophore absorbs light which is then dissipated locally as heat when exposure of a specific wavelength is given and increasing the temperature of the hydrogel at that location. Hydrogel belonging to these types can be induced to swell by increasing the pH and can be induced to shrink by visible light. By introducing a leuco-derivative molecule into the polymer network, the UV-sensitive hydrogels can be synthesized. Upon UV exposure, Leuco-derivatives which are normally neutral get dissociate into ion pairs. In response to UV irradiation, the hydrogels discontinuously swelled but when the UV light was removed showed shrinking, at a fixed temperature [21].
The most commonly studied Light-sensitive polymers are [22], [23]:

i) Alginate
ii) Collagen
iii) Gelatin
iv) Silk

Advantage:

1) Increased biocompatibility,
2) Tunable biodegradability,
3) Properly mechanical strength,
4) Porous structure [24], [26]

Disadvantage:

1) The main disadvantage of hydrogels is expensive.
2) Hydrogel are non-adherent and need to be secured by a seconder dressing and the sensation felt by movement of the maggots [24], [26].

Application:

1) Hydrogels for Three-Dimensional Cell Culture
2) Hydrogels for Self-Healing
3) Hydrogels for Drug Delivery [25].

Methods of preparation of Hydrogels:

I. *Process optimization and Preparation of hydrogel by solution polymerization technique*:

The process is as per the flow chart in figures which are made by completion of data provided by many research papers.

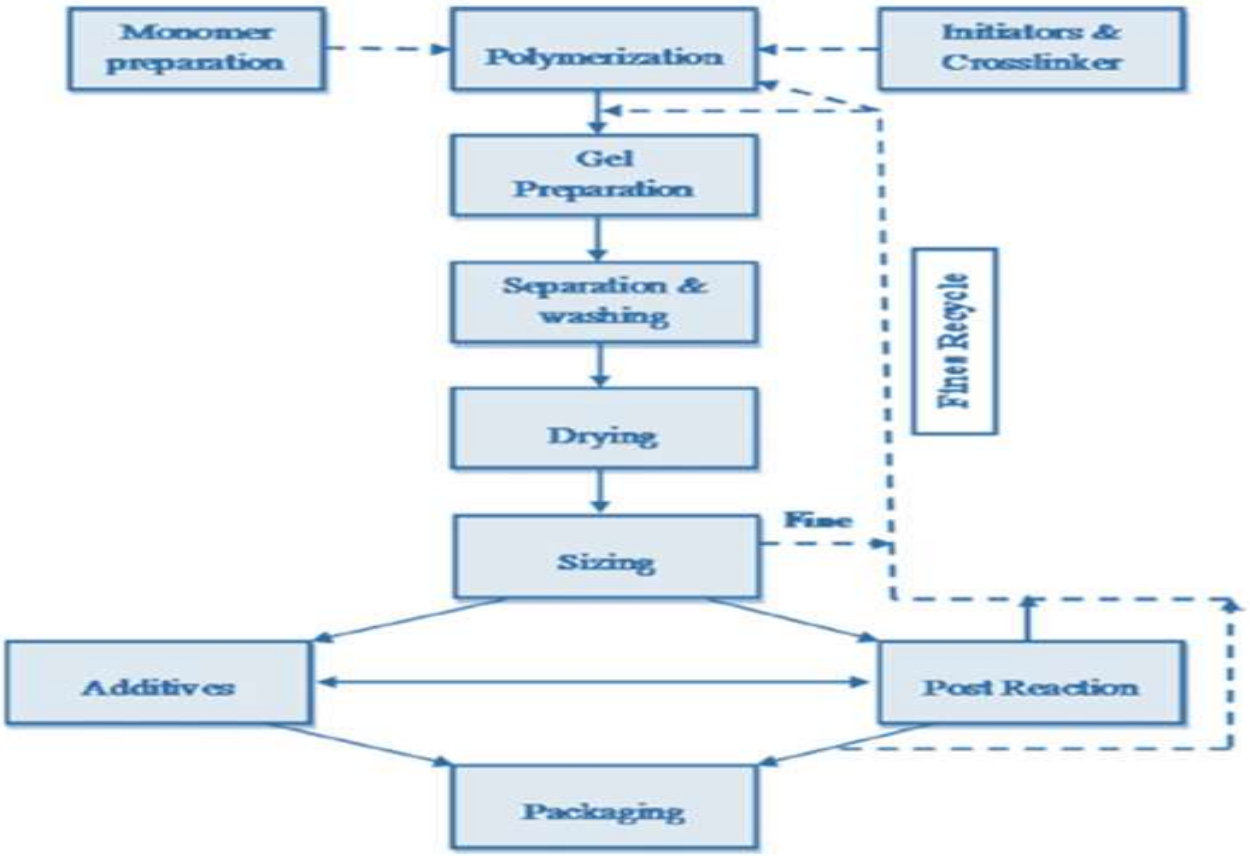

Fig. no. 2 - Hydrogel preparation block diagram (solution polymerization/ cross-linking procedure) [26], [27], [28], [29], [30], [31], [32], [33]

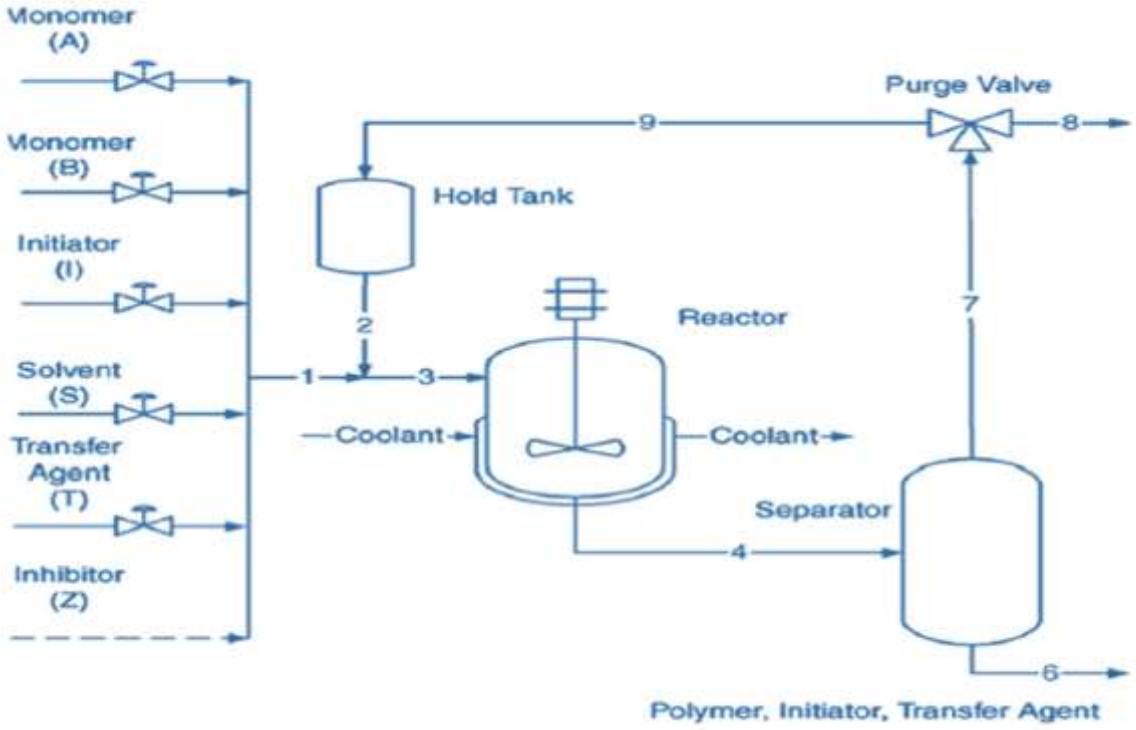

Fig. no. 3 - Solution polymerization with recycle loop [26]

II. *Preparation and process optimization of hydrogel beads using a suspension polymerization technique*:

The process is as per shown in figures which are made by completion of data provided by many research papers.

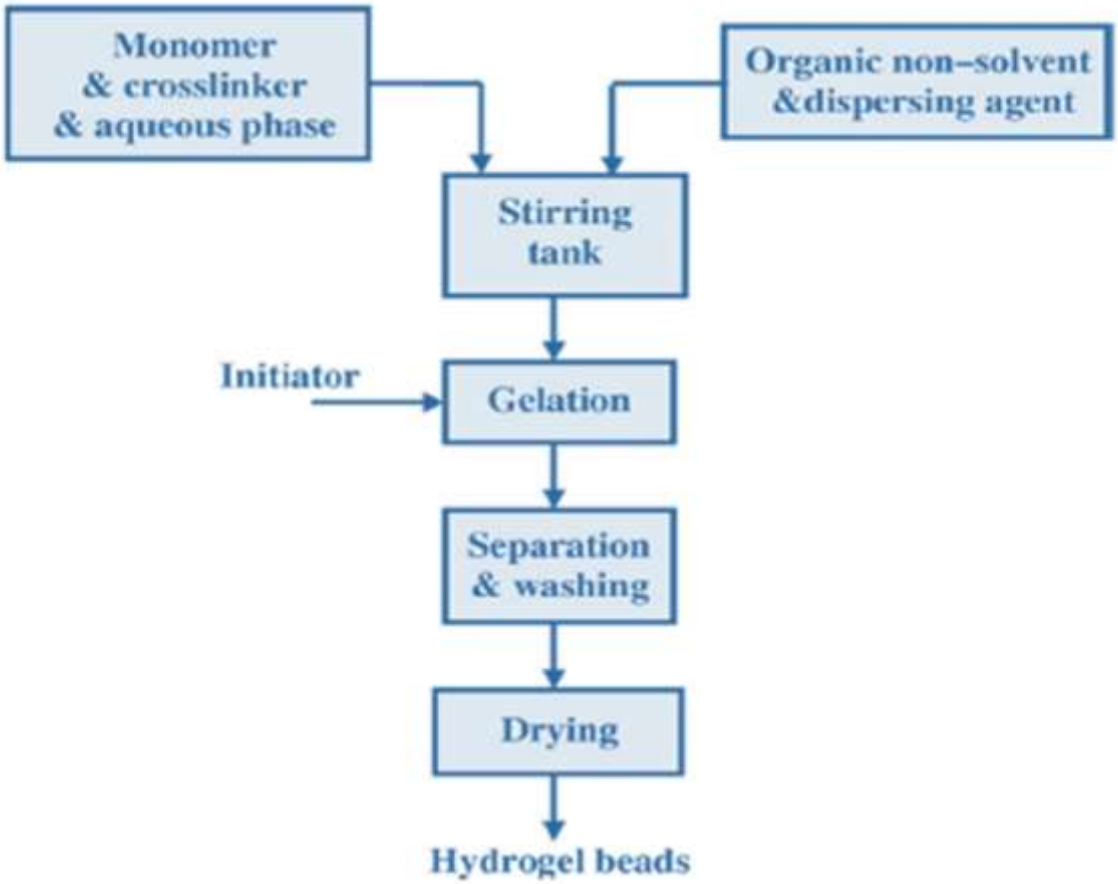

Fig. no. 4 - Block diagram of suspension polymerization process [27],[34],[35],[36]

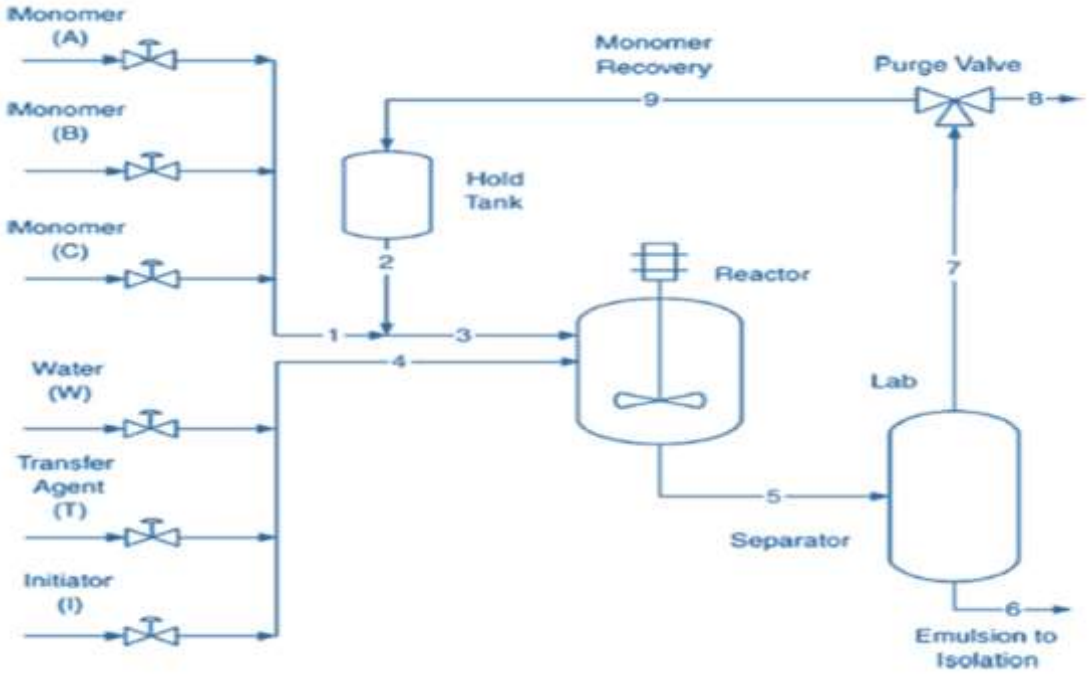

Fig. no. 5 - Suspension Ter-polymerization process with recycle loop [26]

III. Preparation and process optimization of hydrogel based on grafted starch

This is as per illustration of figures which are made by completion of data provided by many research papers.

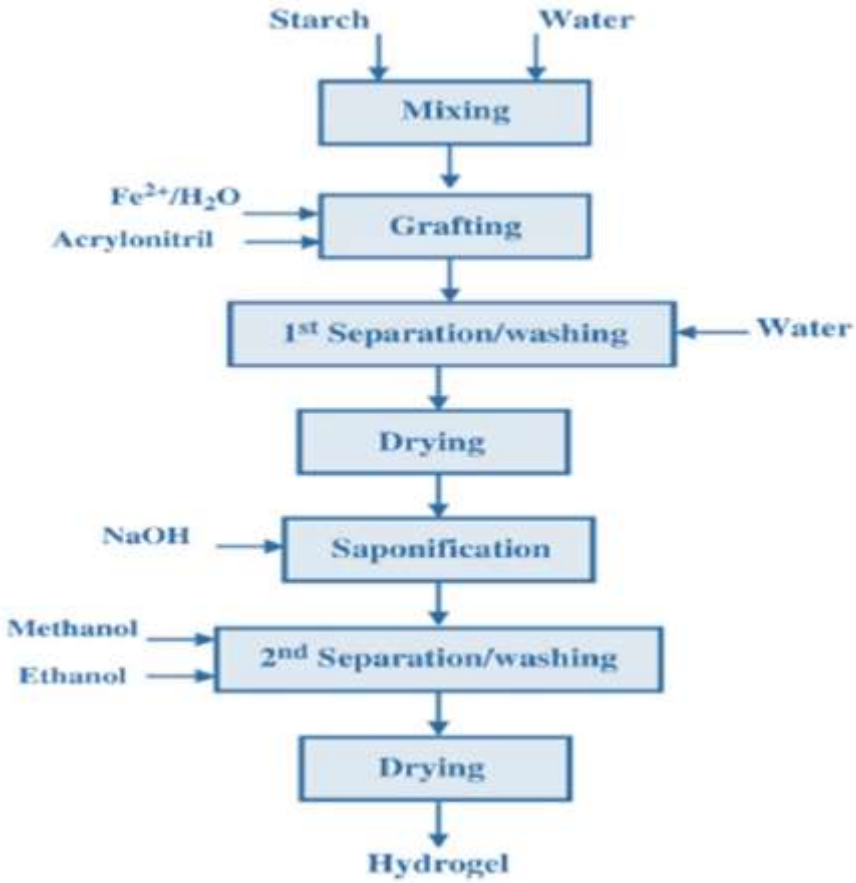

Fig. No. 6 - block diagram for the preparation of the high swelling hydrogel [27], [37], [38], [39], [40], [41]

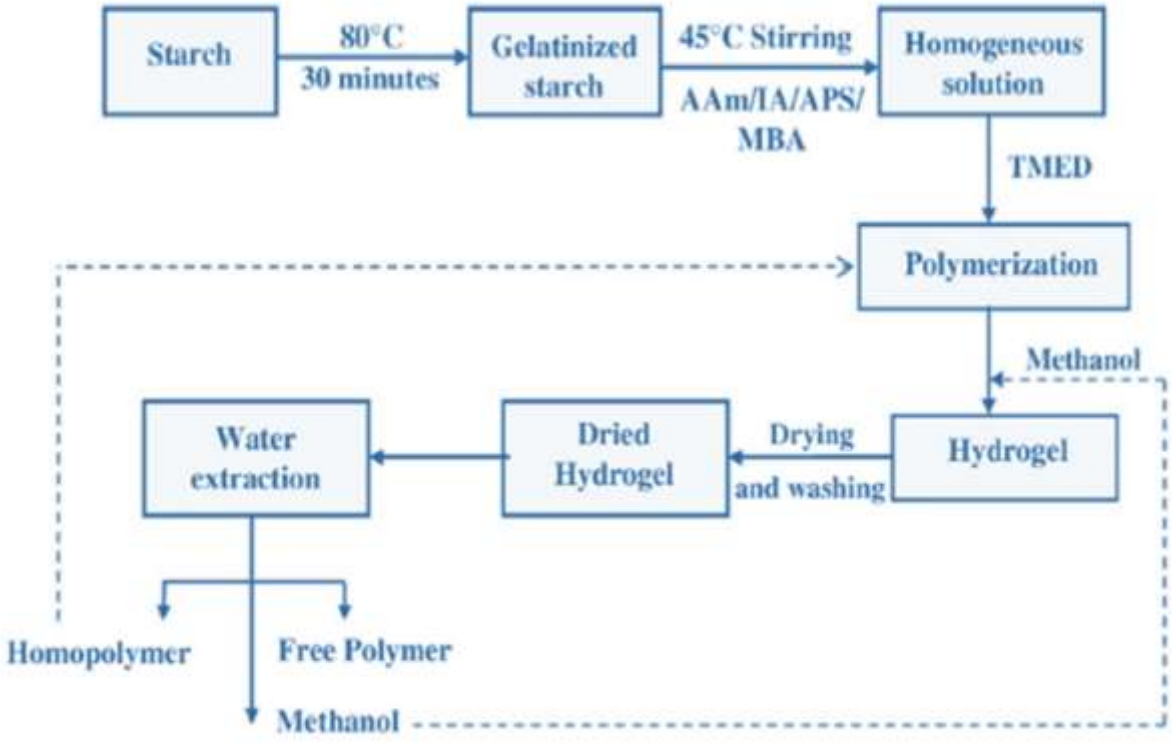

Fig. no. 7 - Preparative flowchart for grafted starch and P(AM-co-IA) hydrogel [26]

IV. Preparation of super-absorbent and super-porous hydrogels

The process is as per shown in the fig. which is made by completion of data provided by many research papers.

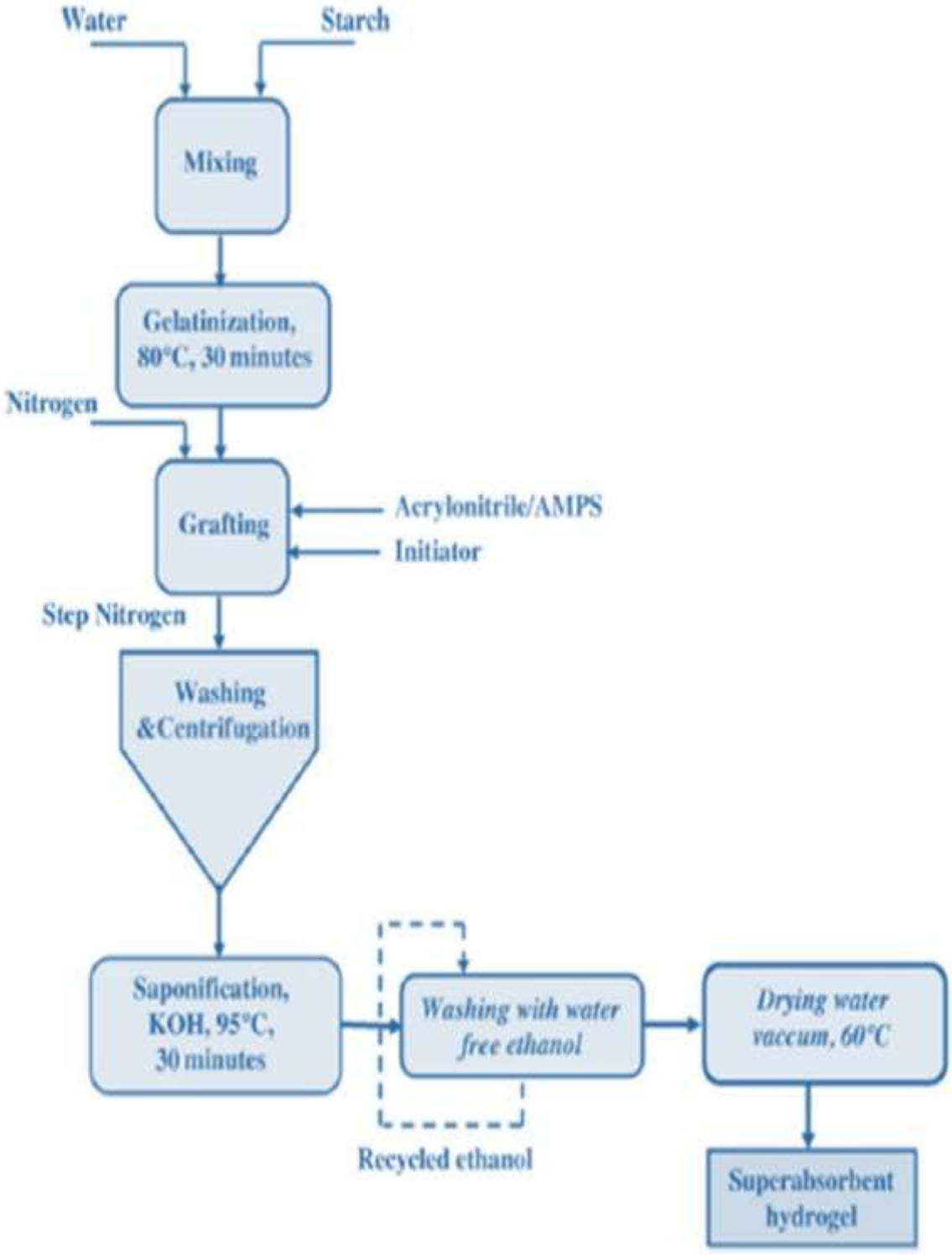

Fig. no. 8 - Block diagram of the rapid preparation process of superabsorbent hydrogel [27],[42],[43],[44]

General Features of SAPS and SPHS are given in table below;

Table No. 1: GENERAL FEATURES OF SUPERABSORBENT (SAPS) AND SUPER-POROUS (SPHS) HYDROGELS [26], [45].

Sr. No.	Point of comparison	SAPs	SPHs
1.	Commonly used monomer	Acrylamide, acrylic acid, salts of acrylic acid including sodium and potassium acrylates	Acrylamide, acrylic acid, salts of acrylic acid including sodium and sulfopropyl acrylates, 2-hydroxyethyl methacrylate
2.	Method of synthesis	Bulk, solution, inverse-suspension	Mostly aqueous solution
3.	Initiating system	Thermal, redox	Mostly redox
	Porous structure	Random closed to semi open cells	Interconnected open cells
4.	Final product	Particles	Any shape including particles, sheet, film, rod.
5.	Applications	Where high swelling, fast-medium rate of swelling is required	Where size-independent high and very fast swelling is required

Aspects of designing batch polymerization reactor:

It is shown as per figures which are made by completion of data provided by many research papers.

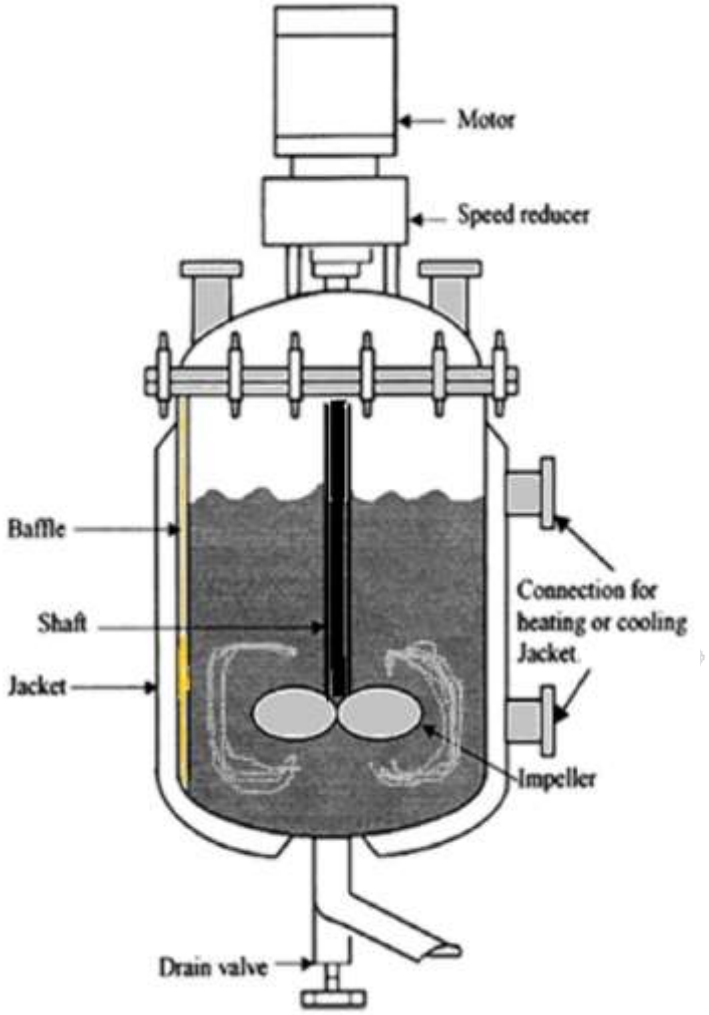

Fig. no. 9 - Schematic diagram of batch reactor [27],[46],[47],[48]

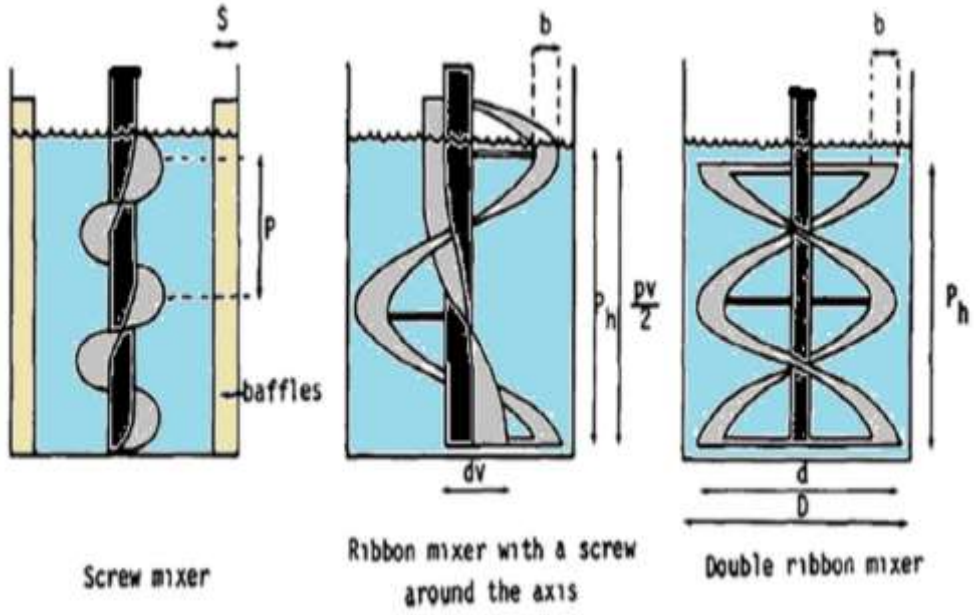

Fig. no. 10 - Schematic diagram of impellers used in high viscosity range [26],[49]

Evaluation Parameters

I. Homogeneity

The gels were examined for their physical properties like color, clarity and phase separation by visual inspection. They are tested for the presence of any aggregates.

II. Grittiness

Presence of any particulate matter in the formulations was observed microscopically.

III. pH measurement

The pH of gel formulations was determined by using digital pH meter. 1gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation is done in triplicate and average values are calculated and reported.

IV. Swelling study

This study is done by using phosphate buffer pH 7.4. A known quantity (~0.2 g) of hydrogel films were immersed in the swelling medium (10 ml) at room temperature. The swollen samples were removed at predetermined time intervals for 24 h, excess medium was blotted using tissue paper and the swollen hydrogel were weighed. The swelling index was calculated using the following

Eqn., swelling ratio (g/g) = (WT–W0)/WT,

where, WT is the weight of swollen hydrogel at time T, and W0 is the weight of dry hydrogel films before start of the study. All measurements are done in triplicate[50],[51].

V. Spreadability

Concentric circles of different radius were drawn on graph paper and a glass plate were fixed onto it. 5gms of gel was placed on the center of the lower plate. Another glass plate of 100±5 gm was placed gently on the gel and the spread diameter was recorded after 1 minute of each addition.

VI. Extrudability

The gel formulations were filled in collapsible tubes. After being set in the containers, the extrudability of gel formulations was determined in terms of weight required in grams to extrude 0.5 cm.

VII. Drug content

Gel is to be dissolved in 100 ml of phosphate buffer pH5.8. Suitable dilutions were made using phosphate buffer pH5.8. Absorbance was measured at 282 λ-max nm using UV spectrophotometer.

VIII. Viscosity and Rheological properties:

The rheological analysis of the experimental gels or hydrogel was performed using a Brookfield viscometer pro D II + apparatus [52].

IX. In-vitro - drug diffusion study

In-vitro drug release studies were carried out using Franz diffusion cell. 0.5 g of gel was applied on cellophane membrane as donor compartment. Phosphate buffer pH 5.8 was placed in the receptor compartment as the dissolution medium. The whole assembly was place on magnetic stirrer with thermostat maintained at 37° C. samples were collected regular time interval and sink conditions were maintained by replacing with new buffer solution. Collected samples are analyzed at 282 λ-max nm using UV spectrophotometer.

X. Skin adhesion test

The modified Patel et al (2007) method can be used to measure the bio-adhesive strength of prepared hydrogel with excised pig ear skin[53].

Bio-adhesive Strength = Weight required (in g) / Area (cm2)

XI. In-vivo - Skin irritation test

Skin irritation test was conducted on ten healthy male and female volunteers. 100 mg of gel was applied on area of 2 cm and observed for any lesions or irritation/redness[54]

OR

The irritation potential of gel or hydrogel in comparison with gel or hydrogel can be evaluated by carrying out the Draize patch test on rabbits[55].

Illustration is shown in fig. given below;

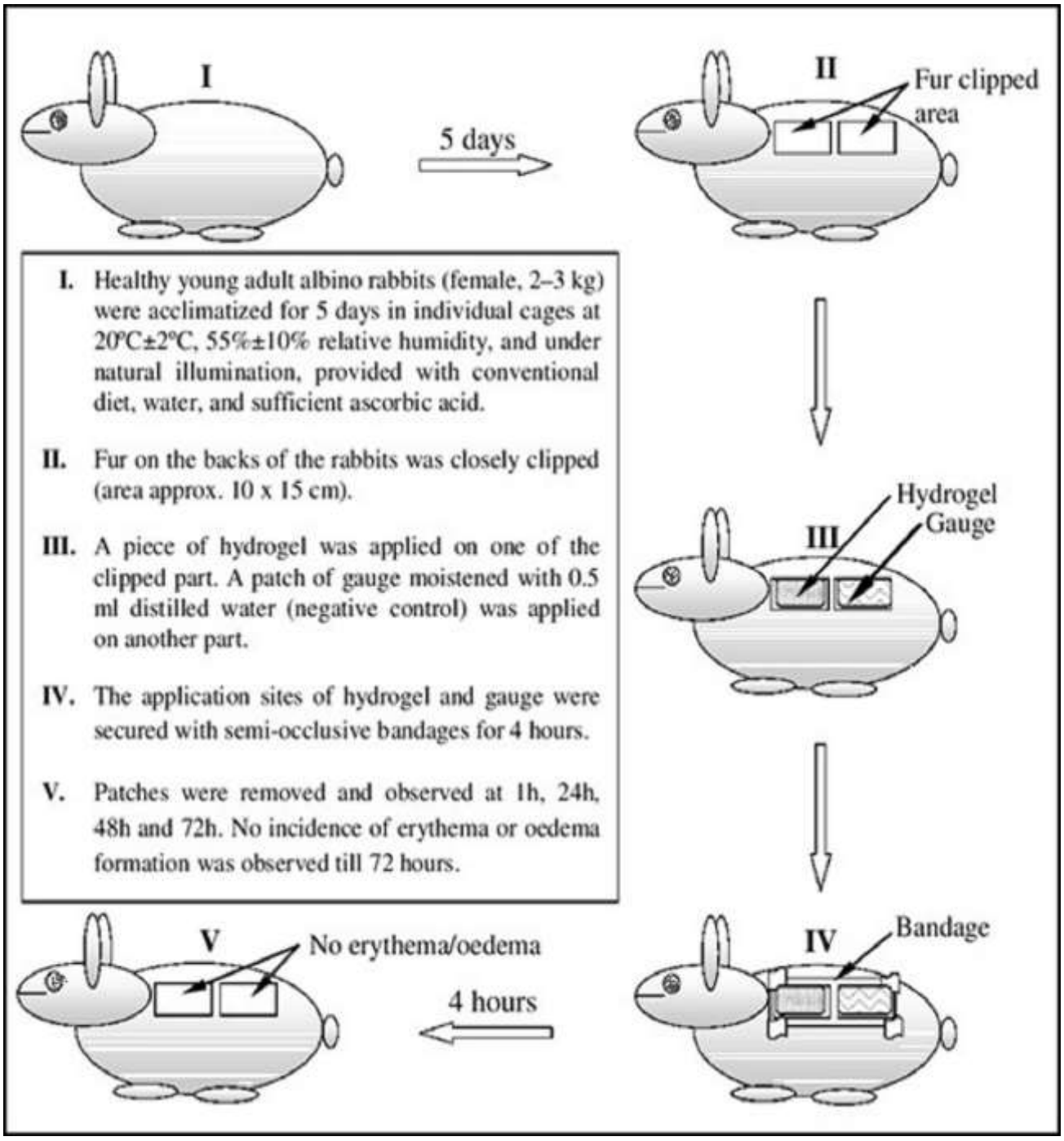

Fig. no. 11: In-vivo process for testing of irritability of hydrogel[56]

Examples of Stimulus Responsive Hydrogels in research paper:

These are given in table given below;

Table no. 2: Examples of stimulus responsive hydrogel in research papers.

Sr. No.	Name of Research paper/ Formulation	Reference no.
1.	Stimulus Responsive Ocular Gentamycin-Ferrying Chitosan Nanoparticles Hydrogel	[57]
2.	Thermosensitive hydrogels for sustained-release of sorafenib and selenium nanoparticles for localized synergistic chemoradiotherapy	[58]
3.	A stimulus-responsive, in situ-forming, nanoparticle-laden hydrogel for ocular drug delivery	[59]
4.	pH-responsive hydrogel loaded with insulin as a bioactive dressing for enhancing diabetic wound healing	[60]
5.	pH and glucose dual-responsive injectable hydrogels with insulin and fibroblasts as bioactive dressings for diabetic wound healing	[61]
6.	Hydrogel Dressings for Chronic Wound Healing in Diabetes: Beyond Hydration	[62]
7.	Thermosensitive Chitosan-Based Injectable Hydrogel as an Efficient Anticancer Drug Carrier	[63]
8.	Formulation of Thermosensitive Hydrogel Containing Cyclodextrin for Controlled Drug Delivery of Camptothecin	[64]
9.	A Near-Infrared Light-Responsive Hybrid Hydrogel Based on UCST Triblock Copolymer and Gold Nanorods	[65]
10.	Synthesis and Analysis of Electrically Sensitive Hydrogels Incorporated with Cancer Drugs	[66]

References:

1. O. Wichterle, D. Lím, Hydrophilic Gels for Biological Use, Nature 1960.
2. C. S. Satish, K. P. Satish and H. G. Shivakumar*. Hydrogels as controlled drug delivery systems: Synthesis, crosslinking, water and drug transport mechanism – Review article. Indian Journal of Pharmaceutical Science. 2006, 68 (2): 133-140
3. Morteza Bahram, Naimeh Mohseni and Mehdi Moghtader. An Introduction to Hydrogels and Some Recent Applications. Intech Open, publisher of Open Access books Built by scientists, for scientists 2016
4. Michael C. Koetting, Jonathan T. Peters, Stephanie D. Steichen, and Nicholas A. Peppas. Stimulus-responsive hydrogels: Theory, modern advances, and applications. Mater Sci Eng R Rep. 2015 Jul. Published online 2015 May 16

5. Haiqin Huang, Xiaole Qi, Yanhua Chen. Thermo-sensitive hydrogels for delivering biotherapeutic molecules: A review. Saudi Pharmaceutical Journal Volume 27, Issue 7. November 2019.
6. Y.Y. Liu, Y.H. Shao, L. Jian. Preparation, properties and controlled release behaviors of pH-induced thermosensitive amphiphilic gels. Biomaterials, 27. 2006.
7. N. Masamichi, O. Teruo, M. Takanari, K. Fukashi, S. Kiyotaka, Y. Masayuki. Molecular design of biodegradable polymeric micelles for temperature-responsive drug release. J. Control Release, 115. 2006.
8. D.C. Coughlan, F.P. Quilty, O.I. Corrigan. Effect of drug physico-chemical properties on swelling/deswelling kinetics and pulsatile drug release from thermo-responsive poly (N -isopropylacrylamide) hydrogels. J. Controll. Release Off. J. Controll. Release Soc., 98. 2004.
9. L. Li, H. Shan, C.Y. Yue, Y.C. Lam, K.C. Tam, X. Hu. Thermally induced association and dissociation of methylcellulose in aqueous solutions. Langmuir, 18 (2002).
10. W. Liu, B. Zhang, W.W. Lu, X. Li, D. Zhu, K. De Yao, Q. Wang, C. Zhao, C. Wang. A rapid temperature-responsive sol-gel reversible poly(N-isopropylacrylamide)-g-methylcellulose copolymer hydrogel. Biomaterials, 25. 2004.
11. A. Richter, G. Paschew, S. Klatt, J. Lienig, K.F. Arndt, H.J.P. Adler, Review on Hydrogel based pH Sensors and microsensors, Sensors. 2008.
12. K. Na, K.H. Lee, Y.H. Bae, pH-sensitivity and pH-dependent Interior Structural Change of Self-assembled Hydrogel Nanoparticles of Pullulan Acatate/Oligo-sulfonamide Conjugate, J. Controlled Release. 2004.
13. A.K. Bajpai, J. Bajpai, R. Saini, R. Gupta, Responsive Polymers in Biology and Tech-nology, Polym. Rev. 2001.
14. Y. Qiu, K. Park, Environment-sensitive Hydrogels for Drug Delivery, Adv. Drug Deliv. Rev. 2001.
15. T. Tanaka, I. Nishio, S. T. Sun, S. Ueno-Nishio, Collapse of Gels in an Electric Field, Science. 1982.
16. M. Doi, M. Matsumoto, Y. Hirose, Deformation of Ionic Gels by Electric Field, Macro- molecules. 1992.
17. T. Shiga, T. Kurauchi, Deformation of Polyelectrolyte Gels under the Influence of Electric Field, J. Appl. Polym. Sci. 1990.
18. A. Mamada, T. Tanaka, D. Kungwachakun, M. Irie, Photoinduced Phase Transition of Gels, Macromolecules. 1990.
19. A. Suzuki, T. Ishii, Y. Maruyama, Optical Switching in Polymer Gels, J. Appl. Phys. 1996.
20. J. Ter Schiphorst, S. Coleman, J.E. Stumpel, A.B. Azouz, D. Diamond, A.P.H.J. Schenning, Molecular Design of Light-responsive Hydrogels, for In Situ Generation of Fast and Reversible Valves for Microfluidic Applications, Chem. Mater. 2015.
21. Lixian Li, Yongpeng He, Xiaodong Zheng, Lin Yi, Weiqi Nian. Review Article Progress on Preparation of pH/Temperature-Sensitive Intelligent Hydrogels and Applications in Target Transport and Controlled Release of Drugs. Hindawi International Journal of Polymer Science Volume - 2021.
22. Jianyu Xing, Bin Yang, Wenwen Dang, Jingchang Li, Bo Bai. Preparation of Photo/Electro Sensitive Hydrogel and Its Adsorption/Desorption Behavior to Acid Fuchsine. 6 may 2020.
23. Hadi Samadian, Hassan Maleki, Zahra Allahyari, Mehdi Jaymand. Review- Natural polymers-based light-induced hydrogels: Promising biomaterials for biomedical applications. Coordination Chemistry Reviews. 2020.
24. Nayan M. Dr. Shrikant P. Development and Chacterisatization of Hydrogel using Antifungal agent. Department of P.G. and Research, Vidyabharti College of Pharmacy, Camp, Amravati. (M. S.) 444602. Sant Gadge Baba Amravati University, Amravati. 2019-2020.
25. Garima Singh, Alka Lohani, Shiv Sankar Bhattacharya. Hydrogel as a novel drug delivery system: a review. Journal of Fundamental Pharmaceutical Research. 2014.
26. Enas M. Ahmed. Review - Hydrogel: Preparation, characterization, And applications. Cairo University Journal of Advanced Research. 2013.
27. Don T., Huang M., Chiu A., Kuo K., Chiu W., Chiu L.; Preparation of thermoresponsive acrylic hydrogels useful for the application in transdermal drug delivery systems. Mater Chem Phys. 2008.
28. Zohuriaan-Mehr M. J, K. Kourosh; Superabsorbent polymer materials: a review. Iran Polym J. 2008.
29. Pourjavadi A, Kurdtabar M, Mahdavinia GR, Hosseinzadeh; Synthesis and super-swelling behavior of a novel protein-based superabsorbent hydrogel. Polym Bull 2006.
30. Wampler FM; Formation of diacrylic acid during acrylic acid storage. Plant/Operation Prog. 1988.
31. A. Javad, B. S. Hasan, R. Zahra. Application of hydrogels in drying operation. Petrol Coal. 2005.
32. BenAmor S, Doyle FJ, McFarlane R. Polymer grade transition control using advanced real-time optimization software. J Process Control. 2004.
33. Bindlish R, Rawlings JB. Target linearization and model predictive control of polymerization processes. AIChE J. 2003.
34. Hong J., Lee J., Rhym Y., Kim D., Shim Sang Eun. Polyelectrolyte-assisted synthesis of polystyrene microspheres by dispersion polymerization and the subsequent formation of silica shell. J Colloid Interface Sci. 2010.
35. Turakhiya J. M., Savani H. D., Patel J. M, Akbari B. V., Prajapati N. G., Shah V. S; A review super porous hydrogel (SPH) – an approach for controlled drug delivery. Univ J Pharm. 2013.
36. Ma Y, Lee P. Investigation of suspension polymerization of hydrogel beads for drug delivery. Iran Polym J. 2009.
37. Talaat HA, Sorour MH, Abouln our AG, Shaalan HF, Ahmed Enas M, Awad AM, Ahmed MA. Development of a multicomponent fertilizing hydrogel with relevant techno-economic indicators. Am-Euras J Agric Environ Sci. 2008.
38. Raju KM, Raju MP. Synthesis of novel super absorbing copolymers for agricultural and horticultural applications. Polym Int. 2001.
39. Talaat HA, Sorour MH, Aboulnour AG, Shaalan HF, Ahmed Enas M, Awad AM, Ahmed MA. Development of a multicomponent fertilizing hydrogel with relevant techno-economic indicators. Am-Euras J Agric Environ Sci. 2008.

40. Q. Tong, G. Zhang. Rapid synthesis of a superabsorbent from a saponified starch and acrylonitrile/ AMPS graft copolymers. Carbohydr Polym. 2005.
41. Lanthong P, Nuisin R, Kiatkamjornwong S. Graft copolymerization characterization and degradation of cassava starch-g-acrylamide/itaconic acid super absorbents. Carbohydr Polym. 2006.
42. O. Hossein, R. Jose G, P. Kinam. Advances in super porous hydrogels. J Pharm Pharmacol. 2007.
43. N. Argyrios, D. Dionysios, B. Nikolaos. In vitro release of bovine serum albumin from alginate/HPMC hydrogel beads. Carbohydr Polym. 2008.
44. Chen J, Park H, Park K. Synthesis of super porous hydrogels: hydrogels with fast swelling and superabsorbent properties. J Biomed Mater Res. 1999.
45. Park K, Chen J, Park H. Hydrogel composites and super porous hydrogel composites having fast swelling, high mechanical strength, and superabsorbent properties. US patent no. 6271278. 2001.
46. Polnok A, Verhoef JC, Borchard G, Sarisuta N, Junginger HE. In vitro evaluation of intestinal absorption of desmopressin using drug-delivery systems based on super porous hydrogels. Int J Pharm. 2004.
47. Dorkoosh FA, Verhoef JC, Borchard G, Rafiee-Tehrani M, Verheijden JHM, Junginger HE. Intestinal absorption of human insulin in pigs using delivery systems based on super porous hydrogel polymers. Int J Pharm. 2002.
48. Dorkoosh FA, Verhoef JC, Verheijden JHM, Rafiee-Tehrani M, Borchard G, Junginger HE. Peroral absorption of octreotide in pigs formulated in delivery systems on the basis of superporous hydrogel polymers. Pharm Res. 2002.
49. Le Cardinal G, Germain E, Gelus M, Guillon B. The design of stirred batch polymerization reactor. Chem Eng Sci 1980.
50. K. K. Mali*, S. C. Dhawale, R. J. Dias, N. S. Dhane and V. S. Ghorpade. Citric Acid Crosslinked Carboxymethyl Cellulose-based Composite Hydrogel Films for Drug Delivery. Indian Journal of Pharmaceutical Science 2018;80(4): 657-667
51. N Vishal Gupta, CS Satish, HG Shivakumar. Preparation and characterization of gelatin-poly (methacrylic acid) interpenetrating polymeric network hydrogels as a pH-sensitive delivery system for glipizide. Indian J. Pharm Sci., 2007, 69 (1): 64-68
52. M. Kurakula, C. Srinivas, N. Kasturi, P. V. Diwan. Formulation and Evaluation of Prednisolone Proliposomal Gel for Effective Topical Pharmacotherapy. International Journal of Pharmaceutical Sciences and Drug Research 2012.
53. Pawan Kumar, Shailendra Kumar Singh, Deepak Kumar Jindal, Vandana Handa, Jyoti Bilonia. Formulation and Evaluation of Minoxidil Gel Using Acrylamide/Sodium Acryloyl-dimethyl taurate copolymer for Alopecia areata. International Journal of Pharmaceutical Sciences and Drug Research 2018.
54. T. P. Kumar, M. C. Eswaraiah. Formulation and evaluation of topical hydrogel containing antifungal drug. MedCave - Pharmacy & Pharmacology International Journal. Volume 8 Issue 4. 2020.
55. Rajkumar Aland, M. Ganesan, P. Rajeswara Rao. In vivo Evaluation of Tazarotene Solid Lipid Nanoparticles Gel for Topical Delivery. International Journal of Pharmaceutical Sciences and Drug Research 2019.
56. Niladri R., Nabanita S., Petr H., Petr S. Permeability and Biocompatibility of Novel Medicated Hydrogel Wound Dressings. November 2010.
57. N. K. Alruwaili, A. Zafar, S. S. Imam, K. S. Alharbi, N. H. Alotaibi, S. Alshehri, N. A. Alhakamy, A. I. Alzarea, M. Afzal, M. Elmowafy. Stimulus Responsive Ocular Gentamycin-Ferrying Chitosan Nanoparticles Hydrogel: Formulation Optimization, Ocular Safety and Antibacterial Assessment. International Journal of Nanomedicine. 2020; 15: 4717–4737.
58. Lan Zheng, Chang'e Li, Xiaoting Huang, Xueran Lin, Weiqiang Lin, Fang Yang, Tianfeng Chen. Thermosensitive hydrogels for sustained-release of sorafenib and selenium nanoparticles for localized synergistic chemoradiotherapy.Biomaterials2019.
59. M. Kabiri & S. H. Kamal & S. V. Pawar & P.R. Roy & M. Derakhshandeh & U. Kumar & S. G. Hatzikiriakos & S. Hossain & V. G. Yadav. A stimulus-responsive, in situ-forming, nanoparticle-laden hydrogel for ocular drug delivery. Drug Delivery and Translational Research. 2018.
60. Zuhao Li, Yue Zhao, He Liu, Ming Ren, Zhonghan Wang, Xianggang Wang, Hou Liu,Yubin Feng, Quan Lin, Chenyu Wangc, Jincheng Wanga. pH-responsive hydrogel loaded with insulin as a bioactive dressing for enhancing diabetic wound healing. Materials & Design. 2021.
61. Lingling Zhao, Lijing Niu, Hongze Liang, Hui Tan, Chaozong Liu, and Feiyan Zhu. pH and glucose dual-responsive injectable hydrogels with insulin and fibroblasts as bioactive dressings for diabetic wound healing. ASC Applied Material and Interfaces. 2017.
62. Paul R Hartmeier, Ngoc B Pham, Ketki Y Velankar, Fadi Issa, Nick Giannoukakis, and Wilson S Meng. Hydrogel Dressings for Chronic Wound Healing in Diabetes: Beyond Hydration. Journal of Pharmaceutics & Drug Delivery Research. 2021.
63. Anam Ahsan, Muhammad Asim Farooq, and Amna Parveen. Thermosensitive Chitosan-Based Injectable Hydrogel as an Efficient Anticancer Drug Carrier. ACS Omega. 2020.
64. S. K. Singh Kushwaha, A. K. Rai and S. Singh. Formulation of Thermosensitive Hydrogel Containing Cyclodextrin for Controlled Drug Delivery of Camptothecin. Tropical Journal of Pharmaceutical Research. 2014; 13 (7): 1007-1012.
65. Hu Zhang, Shengwei Guo, Shangyi Fu and Yue Zhao. A Near-Infrared Light-Responsive Hybrid Hydrogel Based on UCST Triblock Copolymer and Gold Nanorods. Polymers – MDPI. 2017.
66. Aybala Usta and Ramazan Asmatulu. Synthesis and Analysis of Electrically Sensitive Hydrogels Incorporated with Cancer Drugs. Journal of Pharmaceutics & Drug Delivery Research. 2016.