Journal of Advanced Zoology
ISSN: 0253-7214
Volume 44 Issue 05 Year 2023 Page 618:628

Overview Of In-Situ Gelling System For Diabetic Wound

Raj B Patel[1*], Dr. Neha Tiwari[2], Dr. Pragnesh Patani[3]

[1*,2,3]*Khyati College of Pharmacy, Palodia, Ahmedabad*

***Corresponding Author:** Raj B Patel*
Khyati College of Pharmacy, Palodia, Ahmedabad, Email: praj59298@gmail.com

Article History

Received: 1 Nov 2023
Revised: 25 Nov 2023
Accepted: 20 Dec 2023

Abstract

The "in situ gel" system has become one of the best innovative drug delivery methods; thanks to its unique property of "Sol to Gel" transition, it aids in the prolonged and regulated release of the pharmaceuticals. An in situ gelling system is a formulation that, before entering the body, is in solution form but transforms into a gel under different physiological circumstances. Different polymers can potentially be utilized for different drug administration routes and go through in situ gel formation. In situ gelling systems have a variety of uses and benefits in modern society. The introduction to in situ gel, its mechanism, the numerous polymers utilized, and its applications are the primary topics of this paper.
Through a challenging biological process known as wound healing, damaged tissues are rebuilt and skin integrity is recovered. Insulin, a crucial component in wound healing, has been proven in numerous studies to speed up the healing of a variety of wounds in both people and animals. Despite the fact that several research have looked at how systemic insulin can treat burn wounds, relatively few have looked at how well topical insulin works. Therefore, the objective of this study was to review the information on the effects of topical insulin on both diabetic and non-diabetic wound healing. Topical insulin improves quicker wound healing through a variety of mechanisms without causing any harmful side effects, according to published animal and clinical experiments. Additionally, a number of wound dressings that deliver bioactive insulin gradually and regularly hasten the healing process. Therefore, topical insulin has been valued in the field of wound healing, and additional research is required to better understand the role of insulin in the healing of different types of wounds.

Keywords: In-Situ Gel, Novel Drug Delivery System, Polymers, Wound healing, Insulin therapy, Review

1. Introduction

One of the greatest innovative drug delivery technologies is the "in situ gel" technology, which aids in the prolonged and regulated release of drugs. Enhanced patient compliance, medication release, and comfort [(1)] by the 'Sol to Gel' transition, which is a unique trait. An in situ gelling system is a formulation that, before entering the body, is in solution form but transforms into a gel under different physiological circumstances. The sol-to-gel transition is influenced by a number of variables, including temperature, pH change, solvent exchange, UV light, and the presence of certain molecules or ions. The creation of sustained delivery vehicles for bioactive compounds can make extensive use of drug delivery systems with the aforementioned "sol to gel transition" features. The "in situ gelling system" has a number of benefits, including simplified dosage administration, a

reduction in the frequency of administration, and even protection of the drug against changes in the environment. It is possible to administer medications by oral, ophthalmic, transdermal, buccal, intraperitonial, parenteral, injectable, rectal, or vaginal routes using a variety of natural and synthetic polymers that go through in situ gel formation. Utilizing the changes in physiological individuality has been made possible by recent developments in in situ gels.[2,3,4] promotes enhanced drug absorption as well as patient convenience and compliance, in various areas of the digestive tract. Natural polymers utilized for in situ gelling systems include pectin, gellan gum, chitosan, alginic aicd, guar gum, carbopal, xyloglucan, xantham gum, HPMC, and poloxamer. Several applications are available. [5]

With 29.3 million adult patients and over $320 billion in annual healthcare costs, diabetes mellitus has emerged as one of the most difficult healthcare issues in the United States.Diabetes patients are particularly prone to decubiti and chronic leg and foot ulcers.[6,7] One of the most prevalent metabolic diseases, diabetes will impact 439 million people worldwide by 2030.[8] A considerable health hazard and financial burden are created by the delayed wound closure in the lower extremities of around 15–25% of this population .[9,10] Acute wounds, such surgery and burn wounds, and chronic wounds, like diabetic foot ulcers and pressure ulcers, are two common categories for wound classification. One of the main causes of persistent and non-healing wounds is diabetes mellitus. About 6.5 million Americans suffer with chronic wounds, and about $25 billion is spent on their care each year in the United States. [11] So, the need to address wound healing as a public health issue is growing. Although stem cells and growth hormones have demonstrated effectiveness in aiding wound healing, [12,13,14] These treatments are very expensive, and it is still unknown how safe they are. Therefore, safe and inexpensive methods to speed up wound healing will be very beneficial for society and the economy.

An earlier investigation revealed that insulin is essential for wound healing.[15] Insulin is a growth factor and peptide hormone that helps repair injured skin.[16,17] Additionally, the inclusion of insulin in wound dressings can be a desirable treatment to hasten healing due to its low cost.[18] In fact, systemic insulin therapy lowers surgical site infections in diabetic patients and speeds up the healing of pressure ulcers. [19] however, this therapy has the disadvantage of causing hypoglycemia and hypokalemia. In contrast, topical insulin promotes wound healing in both diabetic and non-diabetic patients without altering blood glucose levels.[20] Hrynyk et al. have examined preliminary data regarding the impact of insulin on burn wound healing.[21] Only a few research have looked into the effectiveness of topical insulin, despite the fact that many have addressed the healing effect of systemic insulin on burn wounds. Therefore, the purpose of this study was to review the data regarding the impact of topical insulin on the healing of wounds, both diabetes and non-diabetic wounds.

2. In Situ Gelling Systems

The viscous, polymer-based liquids known as in situ gel forming systems go through a sol-to-gel phase transition when a certain physico-chemical parameter changes. Gelation results from the cross linking of polymer chains through the production of covalent or non-covalent bonds.

Advantages of in situ gels:

It shows various advantages like

- Ease of administration.
- Improved patient compliance.
- Reduced dosing frequency.
- Site specificity and local action.

3. Approaches of In Situ Gel Drug Delivery

- Physiological stimuli sensitive in situ gels systems.
  - Temperature induced in situ gel systems
  - pH induced in situ gel systems
- Physically induced in situ gel systems.
- Chemically induced in situ gel systems.
  - Enzymatic cross linking
  - Ionic cross linking
  - Photo-initiated polymerization.

3.1 Thermally Triggered System

The temperature-sensitive gelling process starts working as the temperature changes. The use of biomaterials whose transitions from sol-gel are dictated by rise in temperature is an intriguing way to approach in-situ production. The ideal critical temperature range for such a system is ambient. Physiologic temperature, making it simpler to manage clinical cases, and there is no external source of Heat other than body heat must cause gelation. A useful system needs to be flexible to considering minute changes in local temperature, such as those that could happen in appendages at the mouth or the surface of the skin. Thermosensitive hydrogels come in a variety of forms. Positively and negatively thermosensitive gels that are thermally reversible. [22]

3.2 PH Triggered Systems

As the pH fluctuates in this system, gel forms. The polymers used in this technique are pH responsive or pH sensitive. PH sensitive polymers have attached acidic or basic groups that can take in or release protons in response to variations in the pH of the surroundings. Polyelectrolytes are polymers with many ionizable group compositions. The formulation's polyelectrolytes induce the external pH to rise, which causes the hydrogel to expand and produce in-situ gel. When the external pH rises, hydrogel swelling increases for weakly acidic (anionic) groups, but it decreases for weakly basic (cationic) groups. The majority of anionic pH-sensitive polymers (such as Carbopol®, carbomer) and for pH-triggered systems, pH-responsive polymers are appropriate. Being a natural anion. For pH-sensitive in situ gels, the polymers cellulose acetate phthalate (CAP), carbomer and its derivatives, polyethylene glycol (PEG), pseudo latexes, and polyethylene are used. Such as methylcarbamate (PMC). [23]

4. Polymers Used as In Situ Gelling Agents

4.1 Pectin

A family of polysaccharides known as pectins, the polymer of which is primarily made up of residues of (1-4)--D galacturonic acid. Low methoxy pectins (degree of esterification 50%) easily form gels in aqueous solution when free calcium ions are present. These gels crosslink the galacturonic acid chains in a way that is consistent with the egg-box hypothesis. Pectin will gel when H+ ions are present, hence a supply of divalent ions—typically calcium ions—is needed to create the gels that are appropriate for use as drug delivery vehicles. Pectin is primarily employed in these formulations because it is water soluble, eliminating the need for organic solvents. When pectin is taken orally.[24] divalent cations in the stomach cause it to change from a liquid state to a gel state.

4.2 Guar Gum

Properties

Guar gum, which is a naturally occurring gum made from the endosperm of the seed, is also known as guaran.Guar gum is soluble in water but insoluble in hydrocarbons, lipids, esters, alcohols, and ketones. These demonstrate its ability to dissolve in both hot and cold water and create a colloidal solution at low concentrations. Guar gum derivatives are utilized to create coated matrix systems, nano-microparticles, and hydrogels, which are all forms of targeted delivery systems. Guar gum also has derivatives that are good at targeting the colon, such as graft polymers like polyacrylamide grafted guar gums. In matrix tablets with controlled release, it can also be employed as a polymer.[25]

4.3 Carbopol

Properties

A polymer made of polyacrylic acid (PAA), carbopol transformed into a gel when the pH was increased from 4.0 to 7.4. Carbopol does not change from its solution state in an alkaline pH environment to a low viscosity gel. In order to increase the viscosity of the carbopol solution and lessen its acidity, HPMC is employed in conjunction with carbopol. Comparing various forms of poly (acrylic acid) (Carbopol 940, 934, 941 and 910), 47 came to the conclusion that Carbopol 940 displayed superior clarity and appearance.[26]

4.4 Xyloglucan

Properties

The polysaccharide xyloglucan, often known as tamarind gum, is extracted from the seed's endosperm.The three distinct oligomers that make up xylogulcan—heptasaccharide, octasaccharide, and nonsaccharide—differ in the number of galactose side chains. Due to its non-toxic, biodegradable, and biocompatible qualities, it is

mostly employed in oral, rectal, and ocular medication delivery. Similar to poloxamer, when heated to refrigerator temperature or cooled from a higher temperature, it displays gelation. [27]

4.5 Alginic acid

Properties

It is a linear block copolymer polysaccharide made up of 1,4-glycosidic links connecting D-mannuronic acid and L-glucuronic acid residues. Depending on the algae source, there are differences in each block and the way the blocks are arranged along the molecule. On addition of divalent and trivalent metal ions, diluted aqueous solutions of alginates form solid gels through a cooperative mechanism involving successive glucuronic residues in the -L glucuronic acid blocks of the alginate chain.[28] Alginic acid is employed as a carrier for ocular formulations because it has advantageous biological characteristics including being biodegradable and non-toxic[29].

4.6 Chitosan

Properties

Chitosan gels as a result of two changes, including temperature change and pH responsive change. A naturally occurring substance found in shrimp and crab shells, chitosan is a biodegradable, thermosensitive, polycationic polymer made from chitin that has undergone alkaline deacetylation. Chitosan is a cationic polymer that is pH dependant and biocompatible. It may dissolve in aqueous solutions up to a pH of 6.2. When chitosan aqueous solution is neutralized to a pH higher than 6.2, a hydrated gel precipitates as a result.[30,31]

4.7 HPMC

Properties

The glucan chain that makes up cellulose has repeated (1, 4)-D-glucopyranose units. Some naturally occurring polymers, including MC, HPMC, and EC, show temperature-sensitive sol-gel phase transition. The viscosity of cellulose material increases with decreasing temperature, whereas the viscosity of its derivatives, such as HPMC and MC, increases with increasing temperature. An alternative methyl substitution group has been added to the chain of native cellulose to create the natural polymer known as MC. The solution is liquid at low temperatures (under 300 C), but as the temperature rises (between 40 and 500 C), gelation takes place.[32]

5. PHYSICAL MECHANISM

5.1Swelling

In situ production can also occur when a substance takes up water from its surroundings and then expands to fill the necessary space. One example of such a molecule is Myverol 18-99 (glycerol mono-oleate), a polar lipid that expands in water to produce lyotropic liquid crystalline phase structures. It has some bioadhesive properties can be destroyed in vivo by enzymatic activity.

5.2Diffusion

With this technique, the solvent from the polymer solution diffuses into the tissue around it, precipitating or solidifying the polymer matrix. It has been demonstrated that a good solvent for such a system is N-methyl pyrrolidone (NMP). [33]

5.3Ionic Cross-Linking

In the presence of different ions, polymers may transition into another phase. When the cation existing in the biological fluid comes into touch with the ion sensitive polymers, it transforms into gel. This is due to the negatively charged helices being cross-linked by monovalent or divalent cations like Na+, Ca+, etc. Ion-sensitive polysaccharides are a subset of the polysaccharides.I-carrageenan forms elastic gels primarily in the presence of Ca2+, whereas k-carrageenan forms rigid, brittle gels in response to tiny amounts of K+.[34]

5.4Enzymatic Cross-Linking

Although in situ gel formation, which is aided by natural enzymes, has not received much research, it appears to have certain advantages over chemical and photochemical methods. An enzymatic process, for instance, functions effectively in physiologic settings without the requirement for potentially hazardous chemicals like monomers and initiators.

5.5Photo-Polymerization

Photo-polymerization is commonly used to create biomaterials on-site. A solution of monomers or reactive macromers plus an initiator can be injected into a tissue site to create gel. Acrylate or equivalent polymerizable functional groups are used as the polymerizable groups on the macromers, which quickly photopolymerize the individual monomers and macromers in the presence of a suitable photo initiator. As photo initiators, UV visible wavelengths with long wavelengths are widely used. Since short wave ultraviolet radiation has a low penetration and harms living things, it is not employed very often.[35]

6. Applications of In Situ Polymeric Drug Delivery System [36,37]

6.1 Oral Drug Delivery System

The pH-sensitive hydro gels may be used for site-specific medication administration to particular parts of the GI tract. Preparing silicone microspheres that create prednisolone in the gastric media or exhibit gastro protecting properties was made possible by hydrogels made of various ratios of cross-linked PEG and PAA derivatives. Other polysaccharides such amidaded pectin's, inulin, and guar gum were studied in order to improve a prospective colon-specific drug delivery method. Cross-linked dextran hydro gels had a faster swelling under high pH circumstances. Both sodium alginate and gellan formulations comprise a complexed calcium ion that goes through a process of gelation by releasing these ions in the stomach's acidic environment.

6.2 Ocular Drug Delivery System

In ocular delivery systems, natural polymers including alginic acid, inulin, and xyloglucan are widely used. To reduce intra ocular tension in glaucoma, a variety of chemicals, including autonomic medications, anti-inflammatory drugs, and antibacterial agents, are used for local ophthalmic delivery. Ophthalmic in-situ gel was created to deal with the bioavailability problem because traditional administration methods typically produce subpar availability & therapeutic response due to quick tear fluid turn over & dynamics, which causes rapid clearance of the medication from the eye. Carboxy Methyl Cellulose, Hydroxy Propyl Methyl Cellulose, Carbomers, and Poly Vinyl Alcohol are examples of viscosity enhancers that are used to increase formulation viscosity in order to increase formulation bioavailability and prolong precorneal residence time. To develop corneal medication penetration, penetration enhancers such preservatives, chelating agents, and surfactants are employed.

6.3 Nasal Drug Delivery System

Xanthan gum and gallan gum are employed in nasal in-situ gel systems as in-situ gel-forming polymers, and momethasone furoate is tested for its effectiveness in treating allergic rhinitis. An animal model of allergic rhinitis was used in the investigation, and the effect of in-situ gel on antigen-induced nasal symptoms in sensitized rats was noted. When compared to the commercially available product nosonex (Momethasone furoate suspension 0.05%), in-situ gel was proven to reduce the occurrence of nasal symptoms.

6.4 Rectal and Vaginal Drug Delivery System

Many different types of medications that are manufactured as liquid, semisolid (ointments, creams, and foams), and solid dose forms (suppositories) may be administered via the rectal route. Acetaminophen, an anti-inflammatory medication, was created as a rectal in situ gel by using polycarbophil, poloxamer F188, and poloxamer 407 as synthetic polymers to create an in situ gelling liquid suppository. This formulation is thought to be an effective method that increases bioavailability.

6.5 Injectable Drug Delivery System

Since no surgical procedure is necessary and patient compliance is also improved, in situ gels have been developed for use in this medication delivery system over the past ten years. Injectable in situ gel is made primarily of synthetic polymers and block copolymers. Bupivacaine is one example of an anti-inflammatory medication. It is designed as an injectable in situ gel employing poly (D.L-lactide), poly (D,L-lactide coglycolide), and PLGA as a polymer that prolongs the activity of the medication in gel environments.

6.6 Dermal and Transedermal Drug Delivery

The effectiveness of Pluronic F127 in thermally reversible gel as a delivery system for indomethacin was examined. In-vivo research indicates that 20% w/w Aqueous gel can serve as a useful basis for topical. the process of giving a medicine. combining both of The use of chemical enhancers and iontophoresis led to improvement of insulin penetration through synergy.

7. Wound Healing Mechanism

7.1 Normal Wound Healing

For the complicated, dynamic, and systematic process of repairing and reconstructing skin damage, wound healing is a crucial step. [38,39] Hemostasis, inflammation, hyperplasia, and remodeling are the four overlapping stages of the wound healing process.[40,41]

A thrombus forms when wound exudate that contains coagulation factors coagulates after an injury and subsequent bleeding. The first thrombus acts as a framework for platelet aggregation and cell migration. The subsequent inflammatory phase, which lasts for about 3 to 7 days and is accompanied by an inflammatory reaction that causes vasodilation and increased capillary permeability, continues. The wound develops a significant amount of plasma exudate along with the migration of inflammatory cells, macrophages, monocytes, and lymphocytes. In the early stages of inflammation, neutrophils and invasive bacteria that could cause infection are primarily responsible for the release of numerous inflammatory mediators in wounds. These mediators also remove damaged and inactive components of the cell matrix, resulting in the first cleaning of the wound. Macrophages engulf the tissue cell fragments and other wound-damaging agents, digest them, and neutralize them to stop further wound damage. Several cellular kinases and growth factors that macrophages can create and release simultaneously can be used to dissolve debris and promote angiogenesis to rebuild the tissue's vascular structure, creating the ideal environment for the development of granulation tissue. Immune cell death and the proliferative phase begin once the inflammation has subsided. This stage's primary characteristics are the development of new blood vessels and granulation tissue, in which fibroblasts move to the location of the injury and serve as the seed for the development of granulation tissue. The remodeling stage, which lasts for two years or longer, is the last stage of the healing process. During this time, connective tissue forms and the granulation tissue is strengthened further to form scars and continue to heal.[42,43]

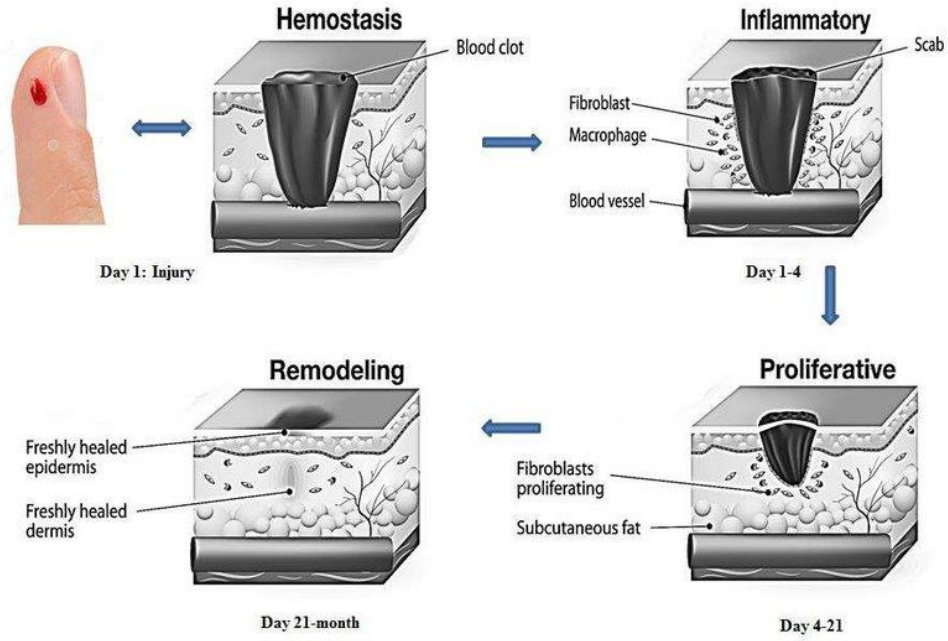

Figure 1: (1–4) The four overlapping stages of wound healing: (1) hemostasis, (2) inflammation, (3) hyperplasia (4) and remodeling. Hemostasis occurs following wound bleeding, and wound exudate combined with coagulation factors generates thrombus. Inflammatory cells, macrophages, monocytes, and lymphocytes also migrate to the site in order to accomplish the goal of debridement. Inflammation decreases as immune cell apoptosis gets going. Fibroblasts move to the wounded area at this stage to serve as the seed cells for the development of granulation tissue. The granulation tissue becomes stronger and forms scars as it keeps healing. With permission from Wiley and copyright 2019, a reproduction of the reference Advances and Impact of Antioxidant Hydrogel in Chronic Wound Healing.

7.2 Chronic Wound Healing

It is challenging to complete the typical wound healing process on chronic wounds in a timely manner and with organization. They are primarily characterized by abnormalities in the control of pro-inflammatory factors, an abundance of reactive oxygen species (ROS), senescent cells, and protease synthesis, as well as problems

reacting to relapses in dermal or epidermal cells. Persistent infections may also be present. We are all aware that one of the key factors in the transformation of wounds from the inflammatory stage to the proliferative stage is the alteration of inflammatory cells dominated by macrophages.[44,45] In the early stages of wound healing, pathogen-activated macrophages exhibit phagocytic activity and are called upon to produce inflammatory mediators and sterilize the wound. Pro-inflammatory macrophages (M1) change into anti-inflammatory macrophages (M2) in the later stages of inflammation, which encourages the release of anti-inflammatory molecules and the creation of an ECM, opening the door for the proliferation and remodeling of the wound.[46]

8. NORMAL WOUND VERSUS DW HEALING

Injury-induced wound healing is a sophisticated biological process that replaces dead tissue with living tissue (Richmond et al., 2013). According to several factors, including age and physical condition of the patient, healing period, the location of the wound, origin or severity of the damage, and associated disorders such diabetes or renal insufficiency, wounds are typically classified as acute (normal wound) or chronic (DW) (Lazarus et al., 1994). Hemostasis, inflammation, proliferation (granulation and epithelization), and tissue remodeling are the four stages that make up the wound healing cascade (Tarnuzzer et al., 1997).The inflammatory process in DWs, however, will be hampered, delaying subsequent phases and delaying recovery (Singer & Clark, 1999).

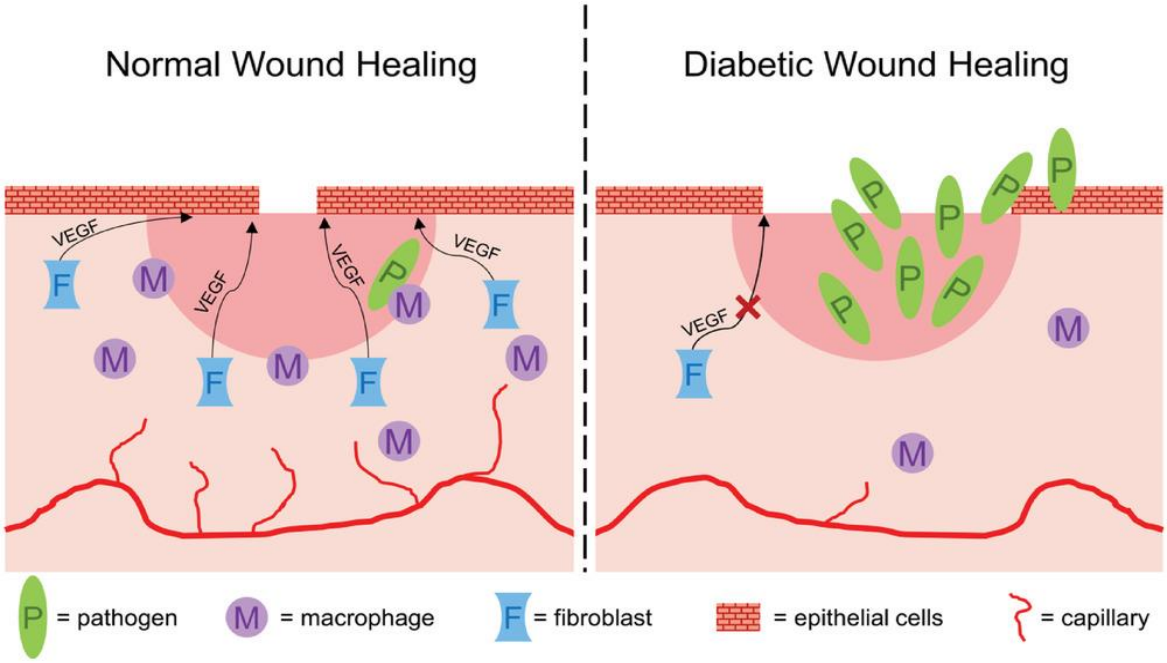

Figure 2: NORMAL WOUND VERSUS DW HEALING

9. CURRENT TREATMENTS

9.1 Patient Enlightenment

It informs people about how to properly care for themselves with regard to diabetes, its complications such DWs, the significance of monitoring foot health, pressure offloading through limited walking and wearing appropriate footwear, and managing blood sugar levels. Total contact casting (TCC) is the most widely used and effective unloading method for treating most DWs. For DWs, it is regarded as the "gold standard" for lowering ulcer pressure. (Wu et al., 2008). (47)

9.2 Wound Debridement

Without disturbing the healthy tissue, wound debridement removes the necrotic tissue or damaged dead tissue from the wound. This procedure aids in lowering wound exudate and odor while promoting a healthy granulation of the wound bed. There are five important methods for debriding wounds: mechanical, enzymatic, autolytical, biological, and surgical.[48] Biological debridement is a maggot therapy that involves applying green bottle fly larvae or maggots to a site to eliminate necrotic tissue.[49] .Autolytic debridement removes nonviable

tissue from a wound using a person's bodily fluids and an endogenous enzyme. Manuka honey, hypertonic saline, hydrocolloids, and other substances are examples.[50] Commercially produced enzymes are used in enzymatic debridement to eliminate necrotic tissue. Abrasive force is used in mechanical debridement to eliminate unhealthy tissue. Examples include gauze, soft fiber, and wound irrigation. Scalpel or scissors are used during surgery to debride wounds of necrotic tissues.[51]

9.3 Wound Dressing

In addition to absorbing wound exudate, wound dressings also offer a moist environment at the wound site, fight off infections, and speed up the healing process. Traditional wound dressings include bandages, saline, gauze, and other materials.[52] Since standard dressings cannot moisten the wounds, they use more advanced formulations in place of advanced dressings. Sponge, films, foams, microfibers, nanofibers, hydrogels, hydrocolloids, silver dressing, and alginates are a few examples of cutting-edge skin dressings.[53]

9.4 Infection Control

Ertapenem, Imipenem, Piperacillintazobactam, Tigecycline, and other commercially available antibiotics for DW are a few examples.leads to infections, which further delays wound leading. Antibioticsare used to control bacterial infections. Some of the commerciallyavailable antibiotics for DW are Ertapenem, Imipenem, Piperacillin tazobactam, tigecycline, and so forth.

9.5 Multidisciplinary Care

Nurses, orthopedic, plastic, vascular, nutrition, and endocrinology departments make up the multidisciplinary team that provides care to lower the frequency of foot/limb amputations.

9.6 Advanced Therapies

It entails the use of electrical simulations, negative pressure wound therapy, bioengineered skin, and topical growth factor injection.

1. Hyperbaric oxygen therapy
2. Negative pressure wound therapy
3. Bioengineered skin substituents (soft tissue substituents)
4. Growth factors

10. Advantages of In Situ Gelling System [54-57]

The principle of HBS can be used for any particular medicament or class of medicament.

A) The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.

B) The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.

C) The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.

D) Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolve drug available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.

E) When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

F) Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

G) Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.

H) Certain types of drugs can benefit from using gastro retentive devices. These include:

- Drugs acting locally in the stomach;

- Drugs those are primarily absorbed in the stomach;
- Drugs those are poorly soluble at an alkaline pH;
- Drugs with a narrow window of absorption;

11. Disadvantages of In Situ Gelling

- Systems for in-situ gel formation are more vulnerable to stability issues due to chemical or biological degradation.
- Change in pH may prompt to degradation

12. CONCLUSION

The current review comes to the conclusion that the "in situ gel" system has become one of the best innovative drug delivery methods. The in situ gelling system aids in the controlled and sustained release of the medications, as well as increased patient comfort. It is possible to administer medications by oral, ophthalmic, transdermal, buccal, intraperotonial, parenteral, injectable, rectal, or vaginal routes using a variety of natural and synthetic polymers that go through in situ gel formation. In situ gel system research has a lot of potential for developing cutting-edge drug delivery strategies.

Reference

1. Nisha Patel, Gajanan Shinde and Rajesh KS. "*Ophthalmic In situ gel*", A genesis journal Pharmagene, 2(4), **2014**, 29-33.
2. F. Suisha, N. Kawasaki, S. Miyazaki, M. Shirakawa, K.Yamatoya, M. Sasaki, D. Attwood, Xyloglucan gels as sustained release vehicles for the intraperitoneal administration of mitomycin C. Int. J. Pharm., 172**, 1998**, 27–32.
3. Miyazaki S, Endo K, Kawasaki N, Kubo W, Watanabe H, Attwood D. "*Oral sustained delivery of paracetamol from in situ gelling xyloglucan formulations*". Drug Dev Ind. Pharm., 29(2), **2003**, 113-9.
4. Nerkar Tushar, Gujarathi Nayan A, Rane Bhushan R, Bakliwal Sunil R, Pawar S.P. "*In situ gel: Novel Approch in sustained and controlled drug delivery system*". International Journal of Pharmaceutical sciences, 4(4), **2013**, 1-18.
5. Saraswat R.1, Bhan C. S., Gaur A. "*A Review on Polymers Used In In-Situ Gel Drug Delivery Systems*", 1(2), **2011**.
6. [1] IDF Diabetes Atlas 2015, 7th ed, "*International Diabetes Federation*"**,2015**, www.diabetesatlas.org, ISBN: 978-2-930229-81-2.
7. F. L. Bowling, S. T. Rashid, A. J. M. Boulton, Nat. Rev. Endocrinol.**2015**, 11, 606; b) S. A. Eming, P. Martin, M. Tomic-Canic, Sci. Transl.Med. **2014**, 6, 265sr6.
8. J.E. Shaw, R.A. Sicree, P.Z. Zimmet, "*Global estimates of the prevalence of diabetes*" for **2010** and **2030**, Diabetes Res. Clin. Pract. 87 (2010) 4–14.
9. D.G. Armstrong, A.J.M. Boulton, S.A. Bus, "*Diabetic foot ulcers and their recurrence*", N. Engl. J. Med. 376 **(2017)** 2367–2375.
10. W.J. Jeffcoate, L. Vileikyte, E.J. Boyko, D.G. Armstrong, A.J.M. Boulton, "*Current challenges and opportunities in the prevention and management of diabetic foot ulcers*", Diabetes Care 41 **(2018)** 645–652.
11. Sen CK, Gordillo GM, Roy S, et al. "*Human skin wounds: a major and snowballing threat to public health and the economy*". Wound Repair Regener. **2009;17**(6):763–771.
12. Hassan WU, Greiser U, Wang W. *"Role of adipose-derived stem cells in wound healing*". Wound Repair Regener. **2014;**22(3):313–325.
13. Barrientos S, Brem H, Stojadinovic O, Tomic-canic M. "*Clinical application of growth factors and cytokines in wound healing.Wound Repair Regener*". **2014**;22(5):569–578.
14. Nie C, Yang D, Xu J, Si Z, Jin X, Zhang J. "*Locally administered adipose-derived stem cells accelerate wound healing through differentiation and vasculogenesis*". Cell Transplant. **2011**;20(2):205–216.
15. Oryan A, Alemzadeh E. "*Effects of insulin on wound healing: a review of animal and human evidences*". Life Sci. **2017**;174:59–67.
16. Wang L, Yang B, Jiang H, et al. "*The molecular mechanism study of insulin in promoting wound healing under high-glucose conditions*". J Cell Biochem. **2019**;120(9):16244–16253.
17. Kakanj P, Moussian B, Gronke S, et al. "*Insulin and TOR signal in parallel through FOXO and S6K to promote epithelial wound healing*". Nat Commun. **2016**;7:12972.

18. Zhao L, Niu L, Liang H, Tan H, Liu C, Zhu F. *"pH and glucose dual-responsive injectable hydrogels with insulin and fibroblasts as bioactive dressings for diabetic wound healing*". ACS Appl Mater Interfaces. **2017**;9(43):37563–37574.
19. Vatankhah N, Jahangiri Y, Landry GJ, Moneta GL, Azarbal AF. "*Effect of systemic insulin treatment on diabetic wound healing*". Wound Repair Regener. **2017**;25(2):288–291.
20. Sridharan K, Sivaramakrishnan G. "*Efficacy of topical insulin in wound healing: a preliminary systematic review and meta-analysis of randomized controlled trials*". Wound Repair Regener. **2017**;25(2):279–287.
21. Hrynyk M, Neufeld RJ. "*Insulin and wound healing. Burns*". **2014**;40 (8):1433–1446.
22. Goole J, Vanderbist F, Aruighi K. "*Development and Evaluation of new multiple-unit- Levodopa sustained release floating dosage forms*". Int J Pharm **2007**:334:35-41.
23. Sharma S, Pawar A. "*Low density multiparticulate system for pulasatile release of Meloxicam*". Int J.Pharm **2006**:313:150-58.
24. Miyazaki S, Kawasaki N. "*Comparison of in situ gelling formulations for the oral delivery of cimetidine*". Int J Pharm, 220, **2001**, 161-8.
25. Kokate C.K., Purohit A. P., Gokhale S.B. "*Pharmacognocy. 14th Ed. Published by Nirali Prakashan*", 137**, 2008**,141,146,152.
26. Davies N.M., Farr S.J., Hadgraft J., Kellaway L.W. "*Evaluation of mucoadhesive polymers in ocular drug delivery*". I. Viscous solutions, Pharm. Res., 8(8), **1991**, 1039–1043.
27. Shastri DH, Patel LD, "*Novel alternative to ocular drug delivery system*": Hydrogel, Ind J Pharma Res, **2010**; 2: 1-13.
28. Miyazaki S, Suisha F, Kawasaki N, Shirakawa M, Yamatoya K, Attwood K, "*Thermally reversible xyloglucan gels as vehicles for rectal drug delivery*", J Control Rel, 56, **1998**, 75-83.
29. Sechoy O, Tissie G, Sebastian C, Maurin F, Driot JY, Trinquand C. "*A new long acting ophthalmic formulation of carteolol containing Alginic acid*". Int J Pharm, 207, **2000**,109-16.
30. Grant G.T., Morris E.R., Rees D.A., Smith P.J.C., Thom D. "*Biological interactions between polysaccharides and divalent cations*": The egg box model. FEBS Lett., 32, **1973**,195-198.
31. Al-Shamklani A, Bhakoo M, Tuboku MA, Duncan R. "*Evaluation of the biological properties of alginates and gellan and xanthan gum. Proc Int Symp Control Release Bioact Mater*", 18, **1991**, 213-4.
32. Chenite A, Chaput C, Wang D, Combes C, Buschmann MD, Hoemann CD et al. *"Novel injectable solution of chitosan form biodegradable gels in situ*". Biomaterials, 21, **2000**,2155-61.
33. Nirmal H.B, Bakliwal S.R., Pawar S.P, "*In-Situ gel: New trends in Controlled and Sustained Drug Delivery System*". Int J Pharm Tech Research, **2010**;2(2), 1398-408.
34. Thakur RR, Sharma M. "*An insight to ophthalmic in situ gel an overview*". Int Res J Pharm,**2012**; 3(3):16-21
35. Available from *"http:www.slideshare.net/shreeraj9183/in situ-gel-delivery system"*. [Last accessed on January **2016** 25 1].
36. Sterile ophthalmic gel forming solution, Timoptic- XE;, 0.25% and 0.5%, (Timolol maleate ophthalmic gel forming solution), Merck and Company Inc. NJ08889: Whitehouse Station, USA.
37. 40. Ramesh CR, Zentner GM, Jeong B. Macro med, Inc. "*Biodegradable low molecular weight triblock poly (lactideco- glycolide) polyethylene glycolcopolymers having reverse thermal gelation properties*". US patent 6201072. **2001**.
38. B. Farhdihosseinabadi, M. Salimi, B. Kazemi, H. Ghanbarian, M. Mozafari and H. Niknejad, "*Med.Hypotheses*", **2020**, 134, 109389.
39. Z. Xu, S. Han, Z. Gu and J. Wu, Adv. "*Healthcare Mater*"**.,2020**, 9, 1901502.
40. S. A. Eming, P. Martin and M. Tomic-Canic, Sci. Transl. Med., 2014, 6, 265sr266 265sr266.
41. B. K. Sun, Z. Siprashvili and P. A. Khavari, Science, **2014**,346, 941–945.
42. S. A. Shah, M. Sohail, S. Khan, M. U. Minhas, M. de Matas, V. Sikstone, Z. Hussain, M. Abbasi and M. Kousar,Int. J. Biol. Macromol., **2019**, 139, 975–993.
43. M. Otero-Viñas and V. Falanga, "*in The Diabetic Foot, Springe*"r, **2018**, pp. 257–264.
44. V. Falanga, Lancet, **2005**, 366, 1736–1743.
45. D. Skuratovskaia, M. Vulf, O. Khaziakhmatova, V. Malashchenko, A. Komar, E. Shunkin, V. Shupletsova,A. Goncharov, O. Urazova and L. Litvinova, Biomedicines,**2020**, 8(10), 400.
46. T. A. Wynn and K. M. "*Vannella, Immunity*", **2016**, 44, 450–462.
47. Wu, S. C., Jensen, J. L., Weber, A. K., Robinson, D. E., & Armstrong, D. G.**(2008)**. "*Use of pressure offloading devices in diabetic foot ulcers*": Do we practice what we preach? Diabetes Care, 31(11), 2118–2119.

48. Mosti, G., Iabichella, M. L., Picerni, P., Magliaro, A., & Mattaliano, V**. (2005)**."*The debridement of hard to heal leg ulcers by means of a new device based on Fluidjet technology*". International Wound Journal, 2(4),307–314.
49. Sherman, R. A. "*Mechanisms of maggot-induced wound healing:What do we know, and where do we go from here?*" Evidence-based Complementary and Alternative Medicine**, 2014**, 1–13.
50. Enoch, S., & Harding, K. **(2003).** "*Wound bed preparation: The science behind the removal of barriers to healing. Wounds*", 15(7), 213–229.
51. Liu, W.-L., Jiang, Y.-L., Wang, Y.-Q., Li, Y.-X., & Liu, Y.-X. **(2017)**. "*Combined debridement in chronic wounds*": A literature review. Chinese Nursing Research, 4(1), 5–8.
52. Boateng, J. S., Matthews, K. H., Stevens, H. N., & Eccleston, G. M. **(2008)**. "*Wound healing dressings and drug delivery systems*": A review. Journal of Pharmaceutical Sciences, 97(8), 2892–2923.
53. Rivera, A. E., & Spencer, J. M. **(2007)**. "*Clinical aspects of full-thickness wound healing*". Clinics in Dermatology, 25(1), 39–48.
54. S. Cohen, E. Lobel, A. Trevgoda, Y. Peled. "*A novel in situ-forming ophthalmic drug delivery system from alginates undergoing gelation in the eye*". J. Control, Release. **1997**;44 201-208.
55. B. Srividya, R.M. Cardoza, P.D. Amin. *"Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system*". J. Control Release. **2001**;73: 205-211.
56. S. Miyazaki, N. Kawasaki, K. Endo, D. Attwood "*Oral sustained delivery of theophylline from thermally reversible xyloglucan gels in rabbits*". J. Pharm. Pharmacol. **2001**; 53: 1185-1191.
57. S. Miyazaki, S.Suzuki, N. Kawasaki, K. Endo, Takahashi, D. Attwood. "*In situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride*".Int. J. Pharm. **2001**; 229: 29-36.
58. Hoffman A., Stepensky D. **(1999)** "*Pharmacodynamic aspects of modes of drug administration for optimization of drug therapy*". Crit. Rev. Ther. Drug carrier Syst. 16:571-639.