A Review On: Topical Gel Formulation

Vikram Namdev Kerle[1], Shubham Suresh Gaike[2], Dr.Ashok Bhosale[3]
[1]Dept of Quality Assurance
[2]Dept of Pharmaceutics
[1, 2, 3] PDEA'S ShankarraoUrsal College of Pharmaceutical Sciences and Research Center,Kharadi Pune-14

Abstract- *The purpose of the article is to review potential advancements of gel formulation in topical drug delivery applications. Skin drug movement systems integrate a tremendous variety of medication portion structures like semisolids, liquid preparation, sprinkles and solid powders. Most great and comprehensively elaborate semisolid foundation for skin drug movement consolidates gels, creams and medicine. Creams, ointments and lotions have a characteristic disadvantage of active sticky nature on the skin when compared to the gels. Gels are considered to be more rigid due to their covalent crosslinks. A combination of antibiotic agent and diuretic agent into a gel formulation for treatment of Angioedema is done.*

I. INTRODUCTION

The idea behind the present innovation is to formulate the suitable gel formulation containing the antibiotic and diuretic agent in combination form. The gel formulation may be formulated by using suitable additives/excipients. The present invented gel can be used in the treatment of angioedema topically.

Angioedema is the quick oedema, or enlarging, of the region underneath the skin or mucosa. It is ordinarily an unfavourably susceptible response, yet it can likewise be innate. The enlarging happens on the grounds that liquid amasses. It will in general influence regions with free areas of tissue, particularly the face and throat, as well as the appendages and privates. It can likewise be compelling in hives or urticaria. Hives is a common skin rash set off by various things, including explicit food assortments, medication and stress. There are various incidental effects consolidate aggravated, raised, red or skin-concealed welts on the skin's surface.

The normal side effects of angioedema incorporate, a hot or agonizing sensation in the enlarged regions likewise the expanding of within the throat, the windpipe and the tongue, making breathing troublesome. The present combination of antibiotic and diuretic agent can able to reduce the symptoms of angioedema and urticaria along with the common symptoms to get the relief.

The antibiotic agent helps to act against bacteria at the site of infection to avoid further spread of infection. Whereas the diuretic agent acts by its water retention property to control the swelling at the site of infection. There are certain gel formulations that are available for the treatment, but the present combination canprovide uniqueness by providing booster effect in the treatment of angioedema or hives or urticaria.

The USP characterizes gels as semisolid frameworks containing either suspensions comprised of little inorganic particles, or huge natural atoms interpenetrated by a fluid. Gels contains a gelling agent stabilizer, preservative, and other excipients. The concentration of the gelling agent is usually less than 10% usually 0.5 to 2.5% in range.The powers of fascination answerable for the linkage between gelling specialist particles might go from solid essential valences to more vulnerable hydrogen bonds and Vander Waals powers. The more vulnerable nature of these last option powers is demonstrated by the way that a slight expansion in temperature frequently causes liquefaction of gels.

Ideal properties: (1-4)

1. The gel should convey a sensible solid like nature at the hour of limit which is conveniently broken when introduced to shear powers made by pounding the chamber, shaking the holder or at the hour of successful application.
2. It ought to have appropriate enemy of microbial specialist.
3. The effective gel should not be tacky.
4. The effective gel should be sterile.
5. They show the mechanical attributes of the strong state.
6. Each part is ceaseless all through the framework.
7. Gel effectively gets spread and retained on the skin surface.
8. This effective gel detailing applied on the skin can likewise be effortlessly taken out by washing with cleanser and water.
9. Its antimicrobial properties help to stay away from the development of microbes on the skin.

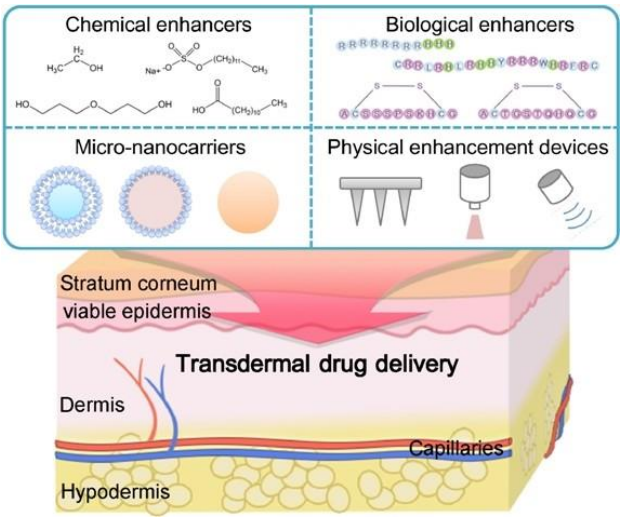

Figure: Drug Penetration in skin

Salient Features:

In effective applications the complete amount of dynamic fixing retained changes significantly founded on many variables including application region size, the recurrence and power of utilization and the consistency or thickness of the applied vehicle. Different variables impacting drug retention are application site, age and state of the skin. Non-keratinized dermis is all the more effortlessly infiltrated by a functioning fixing. In the ideal skin plans, the medication dispersion through skin is constrained by guaranteeing that the medication is sufficiently solvent in the vehicle to empower drug discharge at the ideal rate. This is accomplished by guaranteeing that the whole medication is in arrangement.

Structure of gels: (5)

- Gels comprise of a strong three-layered network that traverses the volume of a fluid medium and catches it through surface pressure impacts.
- Design of gel emerges from the linkage of the particles of the gelling specialist.
- The force responsible for the linkage between the particles of the gelling agent may vary depending upon the valences. Weaker valency bonds such as hydrogen bond and Vander Waal's forces and stronger bonds are formed by single valency or primary valency.
- Weaker bonds in gels can be determined by the fact that slight increase in temperature causes liquefaction of gels.
- These particles may consist of either spherical or and isometric aggregate of small molecule.
- Depending on the type of linkage between the molecules of the gelling agent, API and the solvent the gel network is determined. Various molecules form a linkage with the water molecules to form an aggregated structure of the gel.

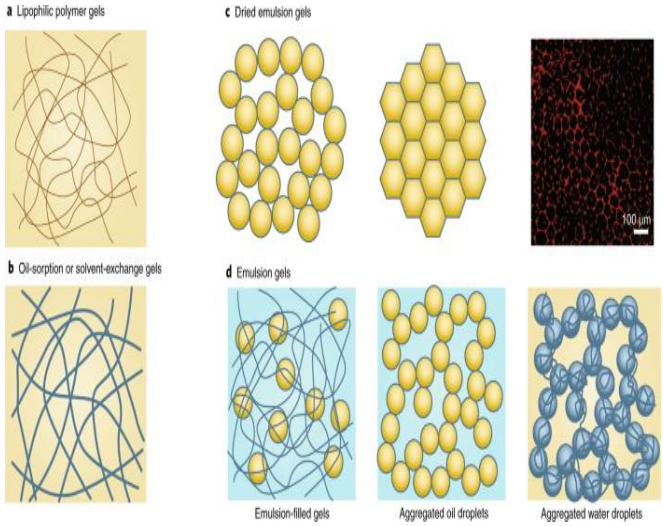

Figure: Various Structure of Gels

Types of gels: (1,6,7)

There are mainly four types of gels as mentioned below:

1. Hydrogels
2. Organogels
3. Xerogels
4. Non-composite hydrogels

1. Hydrogels:

- A hydrogel is a network of polymer chains that are hydrophilic, sometimes found as a colloidal gel in which water is the dispersion medium. A three-dimensional solid result from the hydrophilic polymer chains being held together by cross-links.
- In view of the inborn cross-connects, the underlying honesty of the hydrogel network doesn't break up from the high grouping of water. Hydrogels are exceptionally permeable (they can contain more than 90% water) normal or engineered polymeric organizations.
- Hydrogels likewise have a level of adaptability basically the same as regular tissue, because of their huge water content. As responsive "brilliant materials hydrogels can epitomize substance frameworks which upon feeling by outside elements, for example, a difference in pH might cause explicit mixtures, for example, glucose to be freed to the climate, generally speaking by a gel-sol change to the fluid state

2.Organogels :

- An organogel is a non-glasslike, non-lustrous thermoreversible (thermoplastic) strong material made out of a fluid natural stage ensnared in a three-correspondingly cross-connected network.
- The dissolvability and molecule aspects of the structurant are significant attributes for the versatile properties and solidness of the organogel.
- Frequently, these frameworks depend on self-gathering of the structurant atoms. An illustration of development of an undesired thermoreversible organization is the event of wax crystallization in petrol.
- Organogels have potential for use in various applications, for example, in drugs, beauty care products, workmanship preservation, and food.

3.Xerogels:

- A xerogel might be a strong formed from a gel by drying with intemperate shrinkage. Xerogels at times hold high permeability (15-half) and huge field (150-900 m2/g), along the edge of appallingly small pore size (1-10 nm).
- When dissolvable evacuation occurs under basic circumstances, the organization doesn't recoil and a very permeable, low-thickness material called associate in nursing aerogel is made.
- Heat treatment of a xerogel at raised temperature produces gooey sintering (shrinkage of the xerogel thanks to a little amount of thick stream) which closes in a really denser and extra durable strong, the thickness and permeability accomplished depend upon the sintering conditions.

4.Nano composite:

- A xerogel might be a strong formed from a gel by drying with intemperate shrinkage. Xerogels at times hold high permeability (15-half) and huge field (150-900 m2/g), along the edge of appallingly small pore size (1-10 nm).
- When dissolvable evacuation occurs under basic circumstances, the organization doesn't recoil and a very permeable, low-thickness material called associate in nursing aerogel is made.
- Heat treatment of a xerogel at raised temperature produces gooey sintering (shrinkage of the xerogel thanks to a little amount of thick stream) which closes in a really denser and extra durable strong, the thickness and permeability accomplished depend upon the sintering conditions.

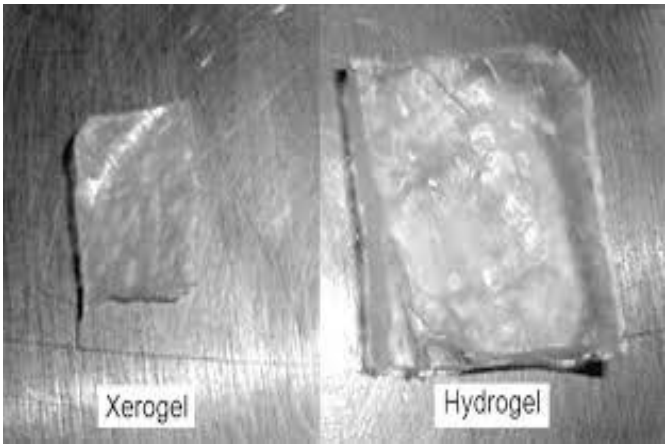

Figure: Types of gels

Advantages:

- Gels square measure acclimated win ideal body covering and body covering drug conveyance.
- they will fill in for oral organization of drug once the course is unsatisfactory.
- They have confined sway with least aspect impacts.
- Effective gel definitions square measure less oily and might be essentially taken out.
- It is extra conservative sort of medication organization because of its objective based application.
- Steadiness after some time is a significant issue.
- It forestalls undesirable feature impacts through bypassing the stomach related tube (GIT)
- A cooling sway is also hard on the skin.

Disadvantages

- Some drugs aren't absorbed easily through the skin.
- There's a possibility of an allergic reaction.
- The effect of gels initiates slowly.
- Effectiveness may be impacted by temperature, humidity, and other environmental factors.

Preservatives:

The parabens region unit among the substances unexceptionally utilized as additives. Additives work with to keep away from the debasement of the gel detailing. It moreover keeps up with the relentlessness of the gel detailing. alkyl bunch paraben, synthetic gathering paraben, and so forth region unit in the fundamental utilized as additives. they help

to stay away from any microorganism tainting inside the gel definition. Gelling agent

Gelling specialists square measure the gel-framing specialists once broke up during a fluid area as a blend combination shapes a dilapidated strong interior design. they're natural hydrocolloids or hydrophilic inorganic substances.

Carbomers square measure in the primary utilized as gelling specialists inside the creating of gels. generally gelling specialists embrace normal gums, starch, gelatin, agar and gelatin.

Solubilizing agent:

A solubilizing specialist goes about as a surfactant and increment the dissolvability of one specialist in another. Solubilization is a peculiarity wherein conglomerations, for example, micelles, which structure in surfactant solvents are utilized to solubilize substances that in any case don't solubilize into these solvents. This assistance to plan a steady gel definition.

Gelling agent:

Gelling agents are the gel-forming agents when dissolved in a liquid phase as a colloidal mixture forms a weakly cohesive internal structure. They are organic hydrocolloids or hydrophilic inorganic substances.

Carbomers are mainly used as gelling agents in the manufacturing of gels. Typically, gelling agents include natural gums, starch, pectin, agar agar and gelatin.

Gelling Agents	Subtypes	Examples	Remark
Polymeric gelling agents	Acrylic acid–based	Carbomers (carbomer 934P, carbomer 940, carbomer 941)	pH range of 2.8–3.2
	Acrylic acid polymers	Pemulen1 polymeric emulsifiers	
Cellulose-based gelling agents	–	Hydroxypropyl cellulose (HPC), carboxymethylcellulose, and hydroxyethyl cellulose (HEC)	–
Natural gelling agents	–	Xanthan gum, gellan gum, guar gum, pectin, and gelatin	–
Polymeric gelling agents	Acrylic acid–based	Carbomers (carbomer 934P, carbomer 940, and carbomer 941)	pH range of 2.8–3.2
	Acrylic acid polymers	Pemulen1 polymeric emulsifiers	
Cellulose-based gelling agents	–	Hydroxypropyl cellulose (HPC), carboxymethylcellulose, and hydroxyethyl cellulose (HEC)	–
Natural gelling agents	–	Xanthan gum, gellan gum, guar gum, pectin, and gelatin	–

Method of preparation: (5)

- Next step involves addition of API with continuous stirring. Active pharmaceutical ingredients used should contain a antimicrobial agent or antibiotic in combination form with other necessary drugs for treatment of the specific diseases.
- Finally, the addition of excipients is done such as solubilizing agent and preservatives.
- Water or other vehicle is used to increase the consistency of the formulation and to make the volume to required quantity.
- During all the processes, continuous stirring of the formulation is required to avoid formation of water bubbles which may mess with the consistency of the formulation.
- The gel formulation then prepared is kept still for 30 mins to check whether it solidifies or not.
- Then the formulation is subjected to various analytical procedures and tests for confirming the consistency of the formulation.

Figure: Preparation of gel with the help of mortar and pestle.

Applications: (1-4)

- Gels are utilized to accomplish ideal cutaneous and percutaneous medication conveyance.
- They can keep away from gastrointestinal medication ingestion troubles brought about by gastrointestinal ph.
- Gels have a property to stay away from enzymatic action and medication cooperation with food and beverages.
- They stay away from fundamental and gateway dissemination following gastrointestinal assimilation.
- Gels are not deactivated by liver compounds on the grounds that the liver is skirted.

- Gels have additionally been applied in drug store to some thick suspension for oral use for instance Aluminium hydroxide gel.
- They have confined impact with least aftereffects.

Storage Containers: (5)

- These containers protect the gel formulation from any contamination or spoilage.
- Gel is stored in such containers and transported to various places for its marketing and sales.
- These containers have the following information on them:
  I. Date of manufacture of the gel formulation.
  II. Date of expiry.
  III. Ingredients.
  IV. Maximum retail price.
  V. Name of the manufacturing industry.
  VI. Storage conditions.
  VII. Directions for use.

Figure: Containers for Gels

Evaluation Tests: (11)

- Appearance:Color is important for patient compliance. The prepared gels were inspected visually for clarity, color and presence of any particle.

- pH**:** One gram each of the gel formulations and the reference was accurately weighed and dispersed in 10 ml of purified water. The PH of the dispersions was measured with a digital pH meter.

- Spreadability: Sample was placed between two glass slides and 100 g weight was placed on the glass slide for 5 minutes to compress the sample to a uniform thickness. The time in seconds required to separate the two slides was taken as a measure of spreadability.

- Zeta potential: It explains the physical property which is exhibited by any particle in suspension, macromolecule or material surface. It is measured by adding a solution to a cell that contains two gold electrodes. When a voltage is applied to the electrode, the particle will move towards the electrode with the opposite charge. A doppler technique is used to measure the particle velocity as a function of voltage.

- Conductivity: voltage is applied between two electrodes in a probe immersed in the sample water. The drop in voltage caused by the resistance of the water is used to calculate the conductivity per centimetre. It is used to determine how well a sample can conduct an electrical current.

- % Of drug content: Formula for determination of percentage of release of drugs from in vitro dissolution technique.

Concentration of drug (µg/ml) = (slope × absorbance) ± intercept. Amount of drug = Concentration × Dissolution bath volume × dilution factor.

- Extrudability: It can be defined as the ability of a material to be extruded through the nozzle of 3D printer with minimal energy needed.

EXTRUDABILITY is the power required to push or force something out of something. A compression-extrusion test consists of applying force to a product until it flows through an outlet (or number of outlets) that may be in the form of one or more slots or holes that are in the test cell.

- Particle size: Particle size analysis is used to characterise the size distribution of particles in a

given sample. Particle size analysis can be applied to solid materials, suspensions, emulsions, gels and even aerosols. There are many different methods employed to measure particle size.

- Viscosity: Viscosity can also be measured by applying oscillating vibrations to the sample and monitoring the damping effects of the fluid. These can be assessed by monitoring power input, the decay time of oscillations, or changes in the resonated frequency.

- Skin irritation study:The Skin Irritation Test (SIT) is an in vitro, non-animal test designed to identify those chemicals and mixtures capable of inducing moderate skin irritation. Formulated gel should not cause irritation on the surface of skin.so, to test this gel is applied on skin to a specific limited area for test purpose mainly on the hand. Skin irritation is observed and if found the formulation is changed to avoid the chemical or the combination causing the irritation on the skin.

Mechanism of action of gel on skin: (12-14,21-30)

The gel acts by topical delivery which involves application of the formulation to the superficial areas such as skin for its absorption in the body for the treatment of the diseases. (12-14) The process involves various steps including the following:

a. Application on skin.
b. Drug absorption into the skin.
c. Drug reaches the deepest layer of the skin and then it gets absorbed into the blood stream.
d. Drug action on the site of infection to reduce the infection and minimize the symptoms of the disease.
e. Drug metabolism into the body.
f. Drug removal by the body through various processes.

The gel formed gets absorbed into the body through the skin into the deep layers named dermis. The absorbed gel gets in the blood through the skin blood barrier. The drug reaches the site of the infection and acts by antibiotic and anti-bacterial action for the treatment of disease.

The diuretic action drug acts on the nephron in the kidney to cause water reabsorption from the site of infection to decrease the swelling. Gel formulations mainly contain the anti-microbial agent from the treatment of the diseases.

Cooling effect:

The gel when applied on the skin provides a cooling effect at the site of application. This cooling effect helps to cure any irritation or heat sensation at the site of infection. Some of the excipients used in the also provide a soothing effect at the site of infection.

Hydration effect:

This effect of the gel on the skin is also a property of gel. It also helps to moisturize the skin and helps the skin from dryness. The dryness of the skin happens due to the disruption of the homeostatic balance between skin lipids and the moisture content of the skin. (21-25)

Disease treatment:

Diseases such as angioedema, redness, swelling due to injury, infection on the skin these are treated by topical administration of drugs by gels. The active pharmaceutical drug used in the formulation provide an antibiotic and diuretic effect to treat the swelling and infection at the site of injury. (25_30)

REFERENCES

[1] Loyd VA., et al. “Ansel’s pharmaceutical dosage forms and drug delivery systems. 9th ed. Philadelphia: Lippincott Williams & Will- dns; (2011).
[2] Ofner CM., et al. “Encyclopedia of Pharmaceutical Technology”. Informa Healthcare (2007): 1875-1890
[3] “The United States Pharmacopoeia 32, the National Formulary 27. Maryland: The United States Pharmacopoeial Convention”. (2009): 667.
[4] Cooper and Gunn. “Disperse systems. In: Carter SJ, editor. Tutorial Pharmacy”. CBS Publishers and Distributors (2000): 68-72.
[5] http://en.wikipedia.org [Internet]. Gel [updated 2014 December 13]. Available from: http://en.wikipedia.org/wiki/gel.
[6] Niyaz BB., et al. “Formulation and evaluation of Gel containing Fluconazole-Antifungal agent”. International Journal of Drug Development and Research 3.4 (2011): 109-128.
[7] Warren DS, Sutherland SP, Kao JY, Weal GR, Mackay SM (2017-04-20). "The Preparation and Simple Analysis of a Clay Nanoparticle Composite Hydrogel". *Journal of Chemical Education*. **94** (11): 1772–1779.
[8] Terech P. (1997) "Low-molecular weight organogelators ", pp. 208–268 in: Robb I.D. (ed.) *Specialist surfactants*.
[9] Van Esch J, Schoonbeek F, De Loos M, Veen EM, Kellogg RM, Feringa BL (1999). "Low molecular weight

gelators for organic solvents". In Ungaro R, Dalcanale E (eds.). *Supramolecular science: where it is and where it is going*. Kluwer Academic Publishers. pp. 233–259.

[10] Visintin RF, Lapasin R, Vignati E, D'Antona P, Lockhart TP (July 2005). "Rheological behavior and structural interpretation of waxy crude oil gels". *Langmuir*. **21** (14): 6240–9.

[11] Kumar R, Katare OP (October 2005). Lecithin organogels as a potential phospholipid-structured system for topical drug delivery: a review *AAPS Pharm SciTech*. **6** (2): E298-310.

[12] Gaharwar AK, Peppas NA, Khademhosseini A (March 2014). Nanocomposite hydrogels for biomedical applications. *Biotechnology and Bioengineering*. **111** (3): 441–53.

[13] Kutvonen A, Rossi G, Puisto SR, Rostedt NK, Ala-Nissila T (December 2012). "Influence of nanoparticle size, loading, and shape on the mechanical properties of polymer nanocomposites". *The Journal of Chemical Physics*. **137** (21): 214901.

[14] Zatz JL., et al. "Pharmaceutical dosage form: Disperse system". Marcel Dekker (2005): 399-421.

[15] Goyal S., et al. "Novel Anti-Inflammatory Topical Herbal Gels Containing Withaniasomnifera and Boswellia serrata". International Journal of Pharmaceutical and Biological Archives 2.4 (2011): 1087-1094.

[16] Attwood D. "Disperse systems. In: Aulton ME, editor. Pharmaceutics-The Science of Dosage Form Design". London: Churchill Liv- ingstone (2002): 83-85 85-91, 528-529.

[17] Kaur LP., et al. "Development and evaluation of topical gel of minoxidil from different polymer bases in application of alopecia". International Journal of Pharmacy and Pharmaceutical Sciences 2.3 (2010): 43-47.

[18] Chen HY, Fang JY. Therapeutic patents for topical and transdermal drug delivery systems. Expert Opinion on Therapeutic Patents 2000; 10:1035-43

[19] Tripathi KD. Essentials of Medical Pharmacology. JP Medical Ltd., 2013

[20] Mycek MJ, Harvey RA, Champe RC. Lippincott's Illustrated Reviews Pharmacology. Philadelphia: Lippincott-Raven, 2009.

[21] Harding C, Long S, Richardson J, et al. The cornified cell envelope: An important marker of stratum corneum maturation in healthy and dry skin. Int J Cosmet Sci 2003; 25(4): 157-167

[22] Scott IR and Harding CR. Filaggrin breakdown to water binding compounds during development of the rat stratum corneum is controlled by the water activity of the environment. Dev Biol 1986; 115(1): 84-92.

[23] Saraf S. Formulating moisturizers using natural raw materials, in Treatment of Dry Skin Syndrome. 2012; Springer. p. 379-397

[24] Carville K, Leslie G, Osseiran-Moisson R, et al. The effectiveness of a twice-daily skin-moisturising regimen for reducing the incidence of skin tears. Int Wound J 2014; 11(4): 446-453.

[25] Kapoor S and Saraf S. Assessment of viscoelasticity and hydration effect of herbal moisturizers using bioengineering techniques. Pharmacognosy Mag 2010; 6(24): 298.

[26] Visuthikosol V, Chowchuen B, Sukwanarat Y, Sriurairatana S, Boonpucknavig V. Effect of Aloe vera gel to healing of burn wound– a clinical and histologic study. *J Med Assoc Thai.* 1995; 78:403–9.

[27] Miller MB, Koltai PJ. Treatment of experimental frostbite with pentoxifylline and aloe vera cream. *Arch Otolaryngol Head Neck Surg.* 1995; 121:678–80. [Pubmed] [Google scholar]

[28] Heggers JP, Pelley RP, Robson MC. Beneficial effects of Aloe in wound healing. *Phytotherapy Res.* 1993;7: S48–52. [Google scholar]

[29] Rajan RG, Kumar MV, Rao CV, Shirwaikar A, Mehrotra S, Pushpangadan P. Healing potential of Anogeissus latifolia for dermal wounds in rats. *Acta Pharm.* 2004; 54:331–8. [Pubmed] [Google scholar]

[30] Singer AJ, Clark RA. Cutaneous wound healing. *N Engl J Med.* 1999; 341:738–46. [Pubmed] [Google scholar]

[31] Subramanian S, Kumar DS, Arulselvan P. Wound healing potential of Aloe vera leaf gel studied in experimental rats. *Asian J Biochem.* 2006; 1:178–85. [Google scholar]

[32] Davis RH, Donato JJ, Hartman GM, Haas RC. Anti-inflammatory and wound healing activity of a growth substance in Aloe vera. *J Am Podiatr Med Assoc*. 1994; 84:77–81. [Pubmed] [Google scholar]