Advancements in Treatment of Laceration by Chitosan Coated Flexible Liposomes of Mupirocin: A Current Prospective.

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***Abstract*— In present era, research work has the continuous focus on the formulation development of chitosan coated flexible liposomes (chitosomes) of Mupirocin that has persistent mitigation of laceration. Skin injuries also known as Lacerations that need proper management to avoid serious consequences in terms of morbidity, disability and quality of life. Currently, the focus of wound management is to maintain the water balance of the wound bed and prevent the invasion of pathogens. Wound dressings in the form of flexible liposomes containing antimicrobial agents (mupirocin) can be used to control skin infections. The drug in the flexible liposome can also extend the contact time between the drug and the wound area, thus reducing the need for frequent use of wound dressings. Human skin is the largest organ in the human body, with a surface area of 100 cm2.can effectively use for the drug delivery. Our project aims to develop the chitosomes of Mupirocin using soya lecithin and edge activator. Mupirocin was analyzed through physio-chemical and analytical parameters like pre-formulation studies, melting point, solubility, calibration curve, FTIR. The drug excipient compatibility study was also conducted. The chitosomes were prepared by Rota evaporator technique with a dose 100mg per 50 ml. The chitosan coated flexible liposomes were evaluated by various parameters like particle size, polydispersity index, percentage yield, encapsulation efficiency, %dug content and *in vitro* drug release studies. The stability study for all formulations were conducted for 2 months and found to be satisfactory as per requirement.**

***Index Terms*—Chitosan coated flexible liposomes, Laceration, Mupirocin, Wound healing.**

I. Introduction

Laceration is commonly known as wound. Skin wounds are the basic tissue in which the skin is cut, punctured or torn. When injury shows up within the frame of a burn wound, it can influence a few skin layers. Various objects can cause wounds in different ways, whether they are blunt, sharp, or projectiles. They are divided into several categories according to the cause and injury: cuts, lacerations, scrapes, punctures, avulsions, and amputations. Separate burn wounds can be a colossally difficult errand to treat in burn units as they incorporate expanded hazard of fluid loss, hypothermia, infections and impeded scarring. Burn injury to the skin makes a nearby immune compromised zone, leading to possibly life-threatening microbial contaminations. In spite of the progresses in treatment of laceration, wound diseases are still the major cause of wound related morbidity and mortality. Effective burn treatment represents a particular challenge in regard to therapeutic outcome, terrifying, utilitarian and corrective results. A few promising lines in advancement of burn treatment were proposed, among which flexible liposome show up to fulfil numerous of the criteria for perfect wound dressing. The perfect dressing ought to accomplish lasting skin recovery, have great utilitarian and tasteful characteristics, ideal mechanical properties, be bio-adhesive and conceivably give controlled discharge of active ingredients. Chitosan may be a natural biodegradable polymer with wound healing properties on it possess. Chitosan coated flexible liposome give a sodden environment at wound location and show bio adhesive properties. In arrange to guarantee controlled release of active ingredient, flexible liposome bearing mupirocin were consolidated in chitosan coat. Mupirocin was chosen as antimicrobial drug due to its action against different microbes, commonly infecting injured regions of skin. Its extra advantage is the fact that it appears low activity against microorganisms within the normal skin flora. This could be seen as an advantage due to the skin's typical resistances against pathogens, will not be interfered by the chosen medicate. **[1-3]**

II. Transdermal Drug Delivery System

A transdermal drug delivery system is a dosage form designed to deliver a therapeutically effective amount of a drug through the skin of a patient. By improving patient compliance, especially avoiding first-pass metabolism, transdermal administration offers numerous advantages over injection and oral routes. Compared to oral drug delivery, transdermal delivery is a pleasant option, and it is also ready to deliver another to subcutaneous infusion. The main transdermal system, Transdermal SCOP, was approved by the FDA in 1979 to prevent nausea and vomiting associated with the disease, especially at sea. **[4-5]**

This also prevents extracutaneous administration of high molecular weight therapy and can also be used as non-invasive transdermal immunity. However, the skin, especially the stratum corneum, is a considerable obstacle to restricting the effective and transdermal bioavailability of drugs in this way. Furthermore, the transdermal system is non-invasive and can be self-administered. Perhaps the greatest challenge of transdermal administration is that only a limited number of drugs are suitable for administration by this route. **[6-7]**

Using current delivery technologies, effective transdermal drugs have molecular masses of several hundred Daltons, exhibit an octanol-water partition coefficient that strongly favors lipids, and require a daily dose of milligrams or less. **[8]**

A. The Benefits of Transdermal Delivery over Other Delivery Systems

From the changes in plasma drug levels, applicants use drugs with short half-life and low therapeutic index. Cancel the drug administration in case of poisoning. The drug is continuously infused for a long period of time. With a little leeway, it is conceivable that the contribution of transdermal drugs can trigger similar useful effects, while the portion of daily drugs is lower than the necessary portion, for example, if the drug is administered orally. **[9-10]**

B. Limitation of Transdermal Delivery Systems

The drug must have some attractive physicochemical properties to penetrate through the stratum corneum. If the dose of drug required to restore the value exceeds 10 mg / day, if it is really feasible, transdermal administration will be very problematic. Clinical requirements are another area that must be carefully examined before opting to build a transdermal project. **[11]**

III. Laceration (Wounds)

Laceration, are wounds to the underlying tissue in which the skin is cut, penetrated or torn. Skin wounds can be partitioned into two classes dependent on their appearance and capacity to recuperate, as intense or ongoing injuries, individually. An intense injury is tissue injury that mends inside 8-12 weeks. The meaning of an ongoing injury is the harmed tissue that has a debilitated capacity to mend up.

The underlying conditions for a persistent injury might be because of chemotherapy, steroid use, diseases, blood vessel inadequacy, diabetes mellitus, radiation, pressure and venous deficiency. Ongoing injuries can display complex microbiological consistency that can influence the recuperating interaction without giving any indications of underlying disease. Frankel et al explored ongoing injuries and their seven microbial verdure and found a high level of methicillin-resistant S. The microbial investigation affirmed that injuries are inclined to diseases and that joining of antimicrobial specialists in injury dressings is hence suggested. Consume wounds can be separated into a few classes relying upon the skin layers influenced by the injury. **[12]**

Mending of the skin ordinarily takes five to seven days. Recuperating of the skin generally requires fourteen days.

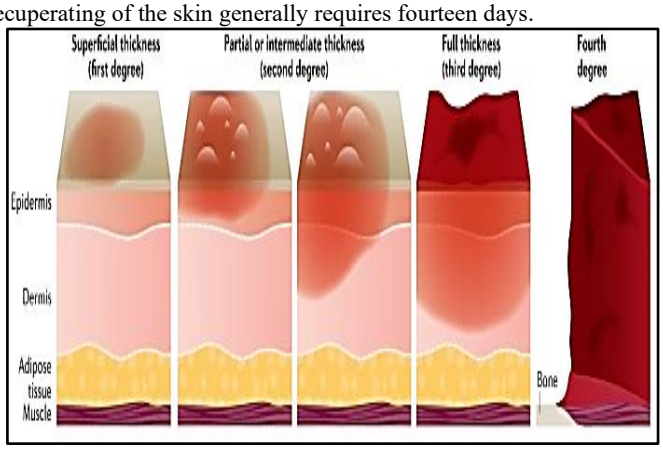

Fig. 1. Classification of laceration**[13]**

A. Epidemiology of laceration

Pressure ulcers are a common condition in acute hospitalized patients and long-term hospitalized patients. It is estimated that they occur in approximately 9% of hospitalized patients, usually within the first 2 weeks of hospitalization. A study found that even with the use of decompression beds and early nutritional support, 3% of patients in the surgical intensive care unit participating in the study still had pressure ulcers. The annual risk of pressure ulcers in patients with neurological impairment is 58%, the lifetime risk is approximately 85%, and the mortality rate is 8%. **[14]**

The incidence of pressure ulcers in the heel was determined in 150 orthopedic patients. The cohort consisted of patients admitted to an emergency hospital for elective orthopedic surgery or treatment of hip fractures. The incidence of pressure ulcers in the heel in all patients was 13.3% and the incidence of hip fractures was higher than that of elective surgery patients. However, hip fracture patients who use pillows and rolled sheets to relieve heel pressure have significantly lower ulcer rates than other hip fracture patients. **[15]**

When all patients in the study are considered, the presence of respiratory disease is the only factor significantly associated with the development of pressure ulcers. According to reports, the prevalence of pressure ulcers among patients living in long-term care facilities ranges from 2.328% and has become an increasingly common cause of litigation. This means that 12% of people with diabetic foot ulcers need to have their limbs amputated at some point. **[16]**

IV. Wound Healing

Hemostasis happens among a number of minutes when a tissue is dislocated. The disruption of blood vessels and therefore the ensuing leak of blood into the wound square measure followed by protoplasm activation and aggregation. This can then result in the formation of a protein clot that causes the hemorrhage to prevent and plugs the defect and seals off the exposed tissue. This part consists of attraction of neutrophils and monocytes from the current blood to the wounded space resulting in cleansing and elimination of germs and trash. **[17]**

The proliferative part of the wounded skin starts 45 days when injury and lasts for concerning twothree days. The latter is meted out by formation of recent blood vessels, embryonic cell proliferation and formation of animate thing matrix like scleroprotein. Wound contraction is achieved by the differentiation nine of fibroblasts to myofibroblasts that have the power to increase and retract, and therefore the attachment of fibroblasts to scleroprotein resulting in the inspiration of a connective tissue. Remodelling of wounds is associate equilibrium between formation of recent cellular animal tissue and its degradation by proteases. **[18]**

This stage, which can continue for months, is characterised by modification of the structural integrity of the tissue with the aim of restoring traditional design of the skin. Counting on the regulation of this maturation method the ultimate result could either be a scar that`s indistinguishable from the healthy skin that is that the goal, or connective tissue that elevates on top of the encircling uninjured skin, indicating a deficient regulation of the method. **[19]**

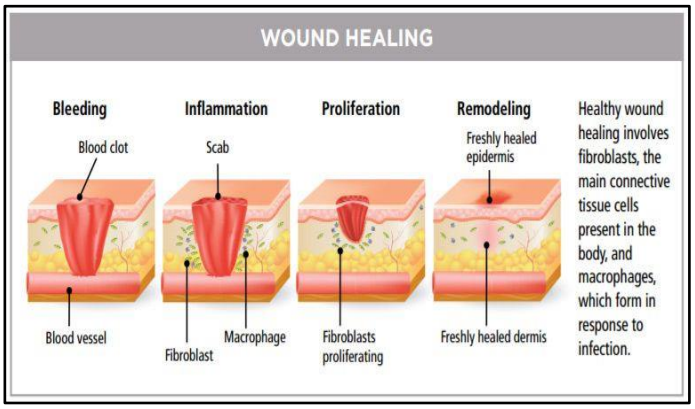

Fig. 2. Phases of wound healing.

V. Transfersomes (Flexible Liposomes)

In broadest sense, a Transfersome may be an extremely all-mains and stress responsive, complicated mixture. Its most popular kind is associate ultra-deformable cyst possessing associate liquid core encircled by the complicated lipoid bilayer. The reciprocity of natural ingredients and double-layer shape leads to self-activation and optimization of the cyst. This enables Transfersome to effectively traverse various transport barriers, thereby serving as a drug carrier for

non-invasive targeted drug delivery and sustained release of therapeutic drugs. **[21]**

The elasticity of these cyst metastases is many orders of magnitude higher than that of high-quality liposomes, so they are suitable for skin penetration. Metastases overcome the problem of skin penetration by compressing the protective lipids in the cells of the stratum. This is foreseeable, due to the high deformability of the cyst, allowing it to enter in an adaptive manner through mechanical closing forces. The flexibility of the transfer body membrane is achieved by mixing the appropriate active parts in the correct ratio. **[22]**

The resulting flexibility of the transfer body membrane minimizes the risk of complete rupture of the cyst in the skin and allows the transfer body to follow the natural water gradient of the entire stratum corneum after application under non-occlusive conditions. The transfer body will spontaneously penetrate the entire layer in two pathways within the intracellular lipid, which have different opinions on the properties of the bilayer.

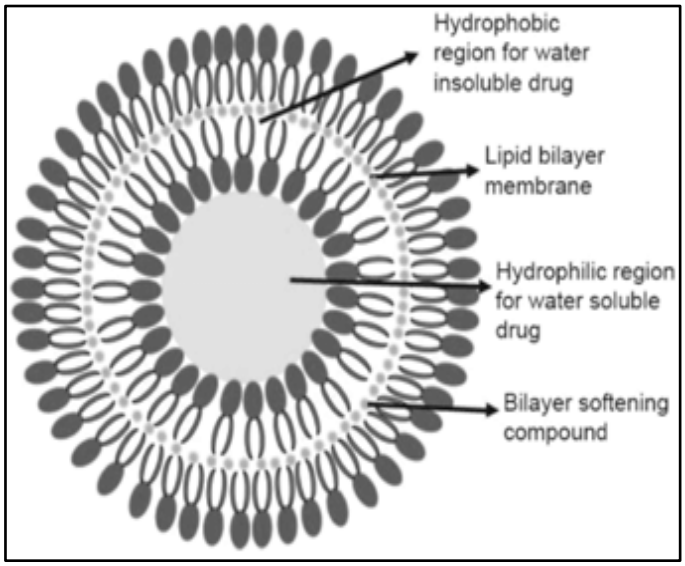

Fig. 3. Structure of transfersomes. **[23]**

A. Mechanism of penetration of transfersomes

All polar lipids attract some water, which is generally due to the beneficial energetic interaction between the deliquescent lipid residue and its proximal water. Therefore, all lipid vesicles composed of polar lipid vesicles move from a relatively dry position to a position with a sufficiently high water concentration.

Therefore, once the lipid suspension is placed on the surface of the skin, that part will become dehydrated due to the loss of water through evaporation, so the lipid vesicles will feel this "osmotic gradient" and move in this gradient to avoid complete drying. They can only achieve this if they have sufficient deformability to taste the elongated pores of the skin, because the transfer body composed of surfactants has appropriate additional associative and rheological properties, not because they have conventional vesicle liposomes with higher deformability and not easy to deform. They are limited to the surface of the skin, no matter where they are completely dehydrated and fused, their penetration force is less than that of the transfer body.

In this sense, Transfersomes have been optimized, thus obtaining maximum flexibility to take full advantage of the transepidermal diffusion gradient. The carrier combination consists of at least one amphiphilic substance, which self-assembles into a lipid bilayer in a liquid solvent, and the lipid bilayer is closed into a single lipid capsule. By adding at least one bilayer softening element, the flexibility and porosity of the lipid bilayer are greatly accumulated.

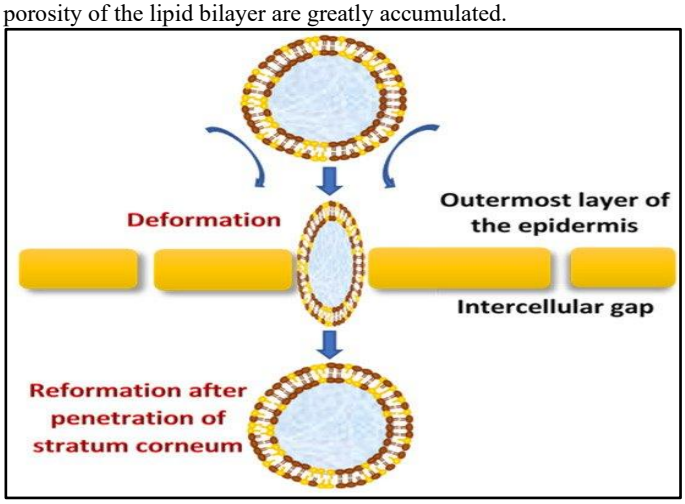

Fig. 4. Mechanism of penetration of transfersomes.

B. Salient Features of Transfersomes

They will serve as carriers for low and high molecular weight drugs. They need high defense power, only when lipophilic drugs are close to ninety.They will be used for each general moreover as topical delivery of drug.

C. Method of preparation of Transfersomes

- Film method: Here the transfersomes are ready by dissolving the lipid in organic solvent that is then removed underneath the vacuum. Once the organic solvent is gaseous, the film fashioned is then hydrous with liquid medium. Following hydrating and swelling, the liposomes are going to be fashioned.

D. Characterization of Transfersomes

- *Particle Size And Polydispersity Index*

The average particle size and polydispersity index of chitosan were measured by photon correlation spectroscopy using Malvern Zetasizer.

- *Encapsulation Efficiency*

1ml of chitosomes was taken and diluted with pH 7.4 phosphate buffer which was sonicated in bath sonicator for 20 min. and further the solution was centrifuged at 14000rpm for 30 minutes. The concentration of free mupirocin was determined in the supernatant by measuring the UV absorbance.

$$EE\ (\%) = \frac{\text{Total drug added} - \text{Unentrapped drug}}{\text{Total drug added}} \times 100$$

- *Percentage Drug Content*

1ml of chitosomes was taken and diluted with pH 7.4 phosphate buffer. The solution was centrifuged at 14000rpm for 40 minutes. Further the solution was diluted to 25ml with methanol. Then drug concentration was determined UV-Vis spectrophotometer.

- *In Vitro Drug Release Studies*

Chitosomes equivalents to 100mg of drug was accurately weighed and placed in a sac of semi-permeable membrane which was transferred into a glass beaker containing phosphate buffer of pH 7.4. The temperature was maintained at 37ºC stirred at 140 rpm. Sampling is performed at predetermined time intervals. The concentration is determined by spectrophotometry.

VI. MUPIROCIN

Mupirocin could be a metallic element salt of the antibiotic created by bacteria genus fluorescens. Mupirocin expresses a broad activity

against numerous microorganisms. Mupirocin is additionally used nasally in infection-control programs to eradicate nasal colonisation by MRSA. This will be seen as a plus thanks to the skin traditional defenses against pathogens that remains unaffected by mupirocin. **[25]**

The potent medicine activity of MHz is any increased in an acidic atmosphere, and might therefore be a plus in relevance the acidic hydrogen ion concentration related to the skin and its surroundings. Once skin is battle-scarred or traumatized in any type, mupirocin will probably penetrate to deeper layers. This can be additionally true once occlusive dressings square measure used, leading to higher permeation. Patients tormented by burn injury square measure at high risk of attracting pathogens and developing infections. **[26]**

Burn wounds colonisation with *S. Aureus* vary to an excellent extent, similarly like the severity of the burn wound, the patients age, the patient's own nasal and tubular cavity *S. Aureus* colonisation, the health care staff and also the sort of care given by the health care skilled at the center of treatment. Aureus are related to a delay within the wound healing method, an exaggerated demand for surgery, and an extended hospital residence. Thirty administering nasal mupirocin to patients with high risk of developing the infections could contribute to reduced risk of wound colonisation with *S. Aureus.*

Polyethylene glycol is often used to extend the circulation time of liposomes. Heparosan is used to coat flexible liposomes. By analogy, the drug-loaded liposome coating with HEP should be able to disguise the MPS delivery vehicle, prolong circulation time and possibly prevent immune-mediated clearance. Chitosan has the ability to increase vesicle stability, encapsulation efficiency and mucosal adhesion properties.

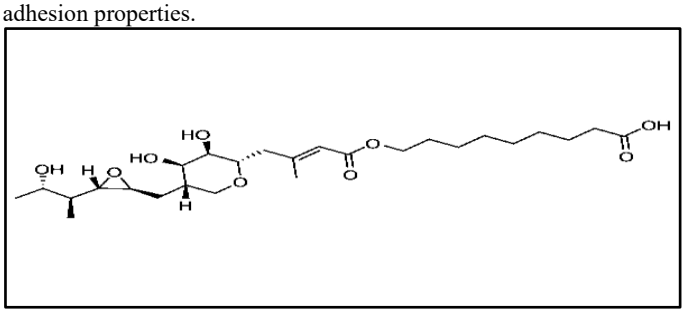

Fig. 5. Structure of Mupirocin

VII. Chitosan

Chitosan is widely used as an adhesive coating polymer for flexible liposomal drug delivery systems due to its adhesive properties to the mucus layer. The coating mechanism or the interaction between the chitosan and the liposome or mucin depends mainly on the electrostatic force. Chitosan can be used to prevent or treat burn wounds and infections, not only because of its inherent antibacterial properties, but also because it can deliver external antibacterial agents to wounds and burns. It can also be used as a sustained-release drug vehicle for growth factors to enhance wound healing.

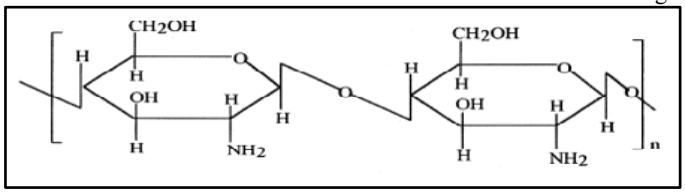

Fig. 6. Structure of Chitosan

Chitosan is a deacetylated chitin, a natural carbohydrate found in the bones of insects, crustaceans, and some fungi. The main parameters that affect the square properties of chitosan measure its relative molecular mass and degree of acylation and represent the proportion of deacetylated units. These parameters are combined with the conditions used throughout the chitosan preparation process, but can also change in later stages. The completely different degree of deacetylation and the different relative molecular mass of chitosan show many advantages as a gelling polymer, which is related to its biological properties. **[29-30]**

These properties embrace physiological condition, stimulation of wound healing, potential to function tissue engineering scaffolds, and potential in drug delivery, particularly controlled drug delivery. Chitosan possesses charged amino teams and, as a result, chitosan is according to possess antimicrobial properties in addition. Moreover, chitosan exhibits bio adhesiveness at web site the location the positioning} of application leading to exaggerated retention time at the administration site, because of the charge at physiological ph. scale. There's conjointly chance of numerous redox depolymerisation and atom degradation. **[31-33]**

The environment of the channel can also have an effect on the degradation. Once administering chitosan via the oral route, and also the subsequent absorption, the tissue distribution is, for the foremost half, suffering from the mw. It's reportable that increasing the mw of chitosan, ends up in a remittent plasma concentration. Aureus. **[34-36]**

This can be additionally an extra advantage once applying chitosan drug delivery systems in skin injuries and burns. However, one should take into account the factors that will have an effect on the chitosan toxicity, like its purity, source, the salt type and polydispersity. Because of its supply of origin, chitosan might not be counselled orally to those who square measure allergic to shellfish. . **[37-38]**

VIII. Conclusion

Vesicle drug delivery systems have been studied extensively for drug delivery, drug targeting, and controlled release phenomena. However, the poor stability and poor retention of the drug have been the main problems that limit its application.. To resolve these problems variety of approaches have been studied. But novel approach of coating of vesicles with biodegradable polymer, chitosan seems to be very effective one. Chitosan coated vesicles are a new type of drug delivery system, especially with reference to their preparation, characterization and application. This system takes advantage of vesicles as a carrier and chitosan as a polymer because it has useful physicochemical properties for drug delivery. Chitosomes may prove a drug delivery of choice in near future.

IX. Acknowledgement

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References

[1] T. M. Allen, "Liposomal drug formulation-Rationale for development and what we can expect for the future," *Drugs*, vol. 56, pp. 747-756, 1998.

[2] I. A. Alsarra, "Chitosan topical gel formulation in the management of burn wounds," *International Journal of Biological Macromolecules*, vol. 45, pp. 16-21, 2009.

[3] S. Amselem, A. Gabizon and Y. Barenholz, "Evaluation of a new extrusion device for the production of stable oligo lamellar

liposomes in a liter scale," *Journal of Liposome Research*, vol. 1, pp. 287-301, 1989.
[4] M. E. Aulton, "Aulton's Pharmaceutics: The Design and Manufacture of Medicines," *Edinburgh, Churchill Livingstone, Elsevier*, vol. 1, pp. 661-665, 2007.
[5] P. Basnet, H. Hussain, I. Tho, and N. Skalko-Basnet, "Liposomal delivery system enhances anti-inflammatory properties of curcumin," *Journal of Pharmaceutical Sciences*, vol. 101; pp. 598-609, 2012.
[6] O.A. Berg, "Advanced delivery system for skin and burns therapy: mupirocin as an antibacterial model drug," *University of Tromso*, Norway, vol. 57, pp. 9037, 2011.
[7] N. Bhogal, C. Grindon, and M. Balls, "Toxicity testing: creating a revolution based on new technologies," *Trends in Biotechnology*, vol. 23, pp. 299-307, 2005.
[8] J. S. Boateng, K. H. Matthews, H. N. E. Stevens, and G. M. Eccleston G. M., "Wound healing dressings and drug delivery systems: a review," *Journal of Pharmaceutical Sciences*, vol. 97, pp. 2892-2923, 2013.
[9] P. A. Botham, L. K. Earl, J. H. Fentem, R. Roguet, and J. J. M. Van De Sandt, "Alternative methods for skin irritation testing: the current status," *Alternatives to Laboratory Animals*, vol. 26, pp. 195-212, 1998.
[10] P. Boukamp, R. Petrussevska, D. Breitkreutz, J. Hornung, A. Markham, and N. E. Fusenig, "Normal keratinization in a spontaneously immortalized a neuploid human keratinocyte cell line,"*The Journal of Cell Biology*, vol. 106, pp. 761-771, 1988.
[11] P. G. Bowler, "Wound pathophysiology, infection and herapeutic options," *Annals of Medicine*, vol. 34, pp. 419-427, 2002.
[12] P. G. Bowler, B. I. Duerden, and D. G. Armstrong, "Wound microbiology and associated approaches to wound management," *Clinical Microbiology Reviews*, vol. 14, pp. 244-269, 2001.
[13] M. Brandl, "Liposomes as drug carriers: a technological approach," *Biotechnology Annual Review*, vol. 7, pp. 59-85, 2001
[14] D. W. Brett, (2006), "Impact on exudate management, maintenance of a moist wound environment, and prevention of infection," *Journal of Wound Ostomy & Continence Nursing*, vol. 33, pp. 9-14, 2006.
[15] Z. Cao, R. J. Gilbert, and W. He, "Simple agarose-chitosan gel composite system for enhanced neuronal growth in three dimensions," *Bio macromolecules*, vol. 10, pp. 2954-2959, 2009.
[16] E. Casals, A. M. Galan, G. Escolar, M. Gallardo, and J. Estelrich, "Physical stability of liposomes bearing haemostatic activity", *Chemistry and Physics of Lipids*, vol. 125, pp. 139- 146, 2001.
[17] K. F. Cutting, "Wound dressings: 21st century performance requirements," *Journal of Wound Care*, vol. 19, pp. 4-9, 2010.
[18] T. Dai, G. P. Tegos, M. Burkatovskaya, A. P. Castano, and M. R. Hamblim, "Chitosan acetate bandage as a topical antimicrobial dressing for infected burns," *Antimicrobial Agents and Chemotherapy*, vol. 53, pp. 393-400, 2009.
[19] M. Dash, F. Chiellini, R. Ottenbrite, and E. Chiellini, "Chitosan-A versatile semisynthetic polymer in biomedical applications," *Progress in Polymer Science*, vol. 36, pp. 981- 1014, 2011.
[20] S. Diehr, A. Hamp, B. Jamieson, and M. Mendoza, "Do topical antibiotics improve wound healing," *Journal of Family Practice*, vol. 56, pp.140-144, 2007.
[21] G. Dow, A. Browne, and R. Sibbald, "Infection in chronic wounds: controversies in diagnosis and treatment," *Ostomy Wound Management*, vol. 45, pp. 23, 1999.
[22] L. Echevarria, M. Blanco-Prieto, M. Campanero, S. Santoyo, and P. Ygartua, "Development and validation of a liquid chromatographic method for in vitro mupirocin quantification in both skin layers and percutaneous penetration studies," *Journal of Chromatography B*, vol. 796, pp. 233-241, 2003.
[23] R. Edwards, and K. G. Harding, "Bacteria and wound healing," *Current Opinion in Infectious Diseases*, vol. 17, pp. 91-96, 2004.
[24] G. Eisenbrand, B. Pool-Zobel, V. Baker, M. Balls, B. Blaauboer, A. Boobis, A. Carere, S. Kevekordes, J. C. Lhuguenot, and R. Pieter, "Methods of in vitro toxicology," *Food and Chemical Toxicology*, vol. 40, pp. 193-236, 2002.
[25] European Pharmacopoeia online database 7th Edition (7.3).
[26] K. Fan, J. Tang, J. Escandon, and R. S. Kirsner, "State of the art in topical wound healing products," *Plastic and Reconstructive Surgery*, vol. 127, pp. S44-S59, 2011.
[27] M. A. Fonder, G. S. Lazarus, D. A. Cowan, B. Aronson-Cook, A. R. Kohli, and A. J. Mamelak, "Treating the chronic wound: A practical approach to the care of non-healing wounds and wound care dressings," *Journal of the American Academy of Dermatology*, vol. 58; pp.185-206, 2008.
[28] M. Grit, and D. J. Crommelin, "Chemical stability of liposomes: implications for their physical stability," *Chemistry and Physics of Lipids*, vol. 64, pp. 3-18, 1993.
[29] H. Hagerstrom, M. Paulsson, and K. Edsman, "Evaluation of mucoadhesion for two polyelectrolyte gels in simulated physiological conditions using a rheological method," *European Journal of Pharmaceutical Sciences*, vol. 9, pp. 301-309, 2001.
[30] K. G. Harding, V. Jones, and P. Price, "Topical treatment: which dressing to choose," *Diabetes/Metabolism Research and Reviews*, vol. 16, pp. 47-50, 2002.
[31] M. C. Heng, "Wound healing in adult skin: aiming for perfect regeneration," *International Journal of Dermatology*, vol. 50, pp. 1058-1066, 2011.
[32] M. Hernandez, J. Pellicer, J. Delegido, and M. Dolz, "Rheological characterization of easy-to-disperse (ETD) Carbopol hydrogels," *Journal of dispersion science and technology*, vol. 19, pp. 31-42, 1998.
[33] S. Hupfeld, A. M. Holsaeter, M. Skar, C. B. Frantzen, and M. Brandl, "Liposome size analysis by dynamic/static light scattering upon size exclusion-/field flow fractionation," *Journal of Nanoscience and Nanotechnology*, vol. 6, pp. 3025-3031, 2006.
[34] Hurler J., Engesland A., Kermany B. P. and Skalko-Basnet, N., (2012), Improved texture analysis for hydrogel characterization: Gel cohesiveness, adhesiveness, and hardness, Journal of Applied Polymer Science, 125; 180-188.
[35] J. J. Hutchinson, and J. C. Lawrence, "Wound infection under occlusive dressings," *Journal of Hospital Infection*, vol. 17, pp. 83-94, 1991.
[36] G. A. James, E. Swogger, R. Wolcott, E. Pulcini, P. Secor, J. Sestrich, J. W. Costerton, and P. S. Stewart, "Biofilms in chronic wounds," *Wound Repair and Regeneration,* vol. 16, pp. 37-44, 2008.
[37] R. Jayakumar, M. Prabaharan, P. T. Sudheesh Kumar, S. V. Nair, and H. Tamura, "Biomaterials based on chitin and chitosan in wound dressing applications," *Biotechnology Advances*, vol. 29, pp. 322-337, 2011.
[38] E. T. Kaye, "Topical antibacterial agents," *Infectious Disease Clinics of North America*, vol. 14, pp. 321-339, 2000.