GEL AS A TOPICAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly achieve and to maintain the desired drug concentration. Delivery of drugs through the skin has been an attractive as well as challenging area for the research. Skin is one of the most extensive and readily accessible organs on human body for topical administration and is main route of topical drug delivery system. Topical application of drugs offers potential advantages of delivering the drug directly to the site of action and acting for an extended period of time. There are different semisolid dosage forms that are used for topical application among which gel formulations are becoming pre-eminent. A gel is colloid that is typically 99% by weight liquid, which is immobilized by surface tension between it and a macromolecular network of fibres built from a small amount of a gelatinous substance present. The basic network of gel is a combination of a gelling agent and a solvent in which the drug molecules are embedded or entwined evenly. Gels have better potential as a vehicle to administered drug topically in comparison to other topical dosage form because they are non-sticky requires low energy during the formation. This review highlights the basic advantages of gel formulations over other semisolid preparations as well as limitations of their use. Other aspects such as their classification, formulation, mechanism involved in the formation of gels and factors affecting their formulations have been included.

Keywords: Topical drug delivery, semisolid dosage form, gelling agents, topical gel

INTRODUCTION [1-4]

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders in order to produce pharmacological or other effect of the drug to the surface or within the skin. Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membrane. It can penetrate deeper into the skin and therefore gives better absorption. There are many advantages of topical application over the conventional dosage forms. In general, they are more effective and less toxic than conventional formulations due to the bilayer composition and structure. In the formulation of the topical dosage forms attempts are being make to utilize drug carriers that ensures adequate localization or penetration of the drug within or through the skin in order to enhance the local and minimize the systemic effects, or to ensure adequate percutaneous absorption. Topical preparation avoids the GI irritation, prevent the metabolism of drug in the liver and increase the bioavailability of the drug. Topical preparations gives its action directly at the site of action. Within the major group of semisolid preparations, the use of topical gels has expanded both in cosmetics and in pharmaceutical preparations.

ANATOMY OF SKIN [5-7]

Largest organ of body is skin, which form the outer most surrounding layers, protect the body from external environment, its function is essential for survival, as it is a complex organ, which interacts both physiological and pathological ways. Three components to skin:

1) Epidermis
2) Dermis
3) Subcutaneous tissue

Epidermis: it has five regions:

- Stratum germinativum
- Stratum spinosum
- Stratum granulosom
- Stratum lucidum
- Stratum corneum

Epidermis is most superficial layer of the skin and approximately 100µm thick. Its having keratinized stratified squamous epithelium and its main function is to protect the body from external environment and diminish fluid loss. Dermis forms the structural foundation of the skin supporting its superficial and deep layers. Its layer of connective tissue to which epidermis is attached and having thickness of 1-2 mm approx. The main function is thermoregulation and supports the vascular network to supply the epidermis with nutrients. The three layers of the skin form an effective barrier to the external environment, allow the transmission of sensory information, and serve a significant role in maintaining homeostasis. The dynamic epidermis continually produces a protective outer layer of corneocytes as cells undergo the process of keratinization and terminal differentiation. Collagen and elastic filaments of the dermal layer provide the underlying tensile strength of the skin, whereas the layer of subcutaneous fat provides a store of energy for the body. The high rate of cell proliferation in the epidermis and in epithelial tissue in general and the fact that this tissue is most frequently exposed to physical and chemical damage results in the exceedingly high rate of skin cancers

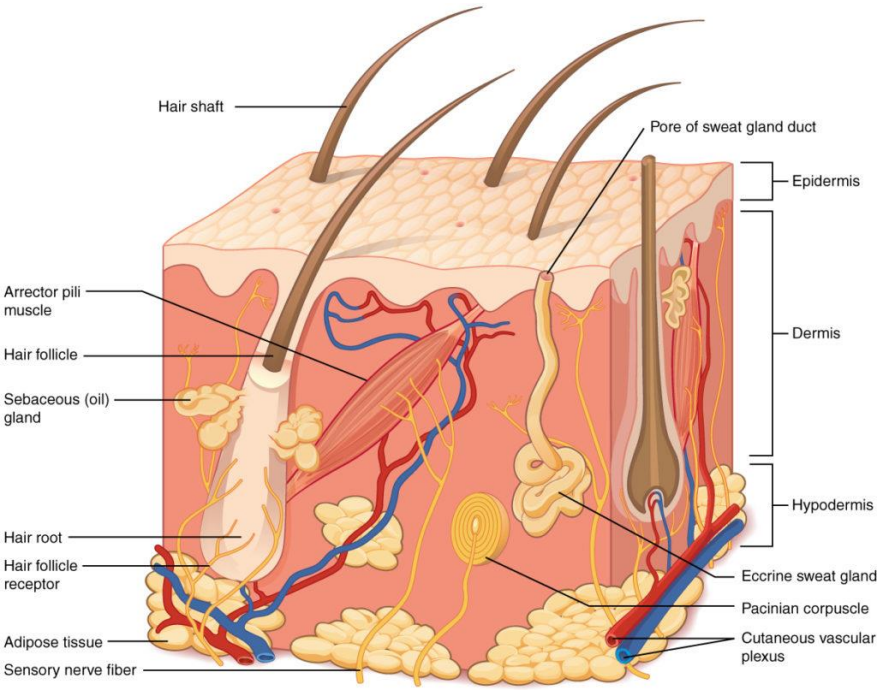
Subdivided into two zones:

- Papillary dermis
- Reticular layer

It mainly contains fibroblasts which are responsible for secreting collagen, elastin, glycosaminoglycans, proteoglycans, fibronectin and other extracellular matrix proteins that provide the support and elasticity to the skin.

Dermis- The dermis is an integrated system of fibrous, filamentous, and amorphous connective tissue that accommodates stimulus- induced entry by nerve and vascular networks, epidermally derived appendages, fibroblasts macrophages, and mast cells. The dermis comprises the bulk of the skin and provides its pliability, elasticity, and tensile strength. It protects the body from mechanical injury, binds water, aids in thermal regulation, and includes receptors of sensory stimuli. The dermis interacts with the epidermis in maintaining the properties of both tissues. The principal component of the dermis is collagen, a fibrous family of proteins with at least 15 genetically distinct types in human skin. Collagen is a major stress- resistant material of the skin. Elastic fibers, on the other hand, play a role in maintain elasticity but do very little to resist deformation and tearing of the skin.

Subcutaneous tissue- The subcutaneous tissue provides the body with buoyancy and functions as a storehouse of energy. Hormone conversion takes place in the panniculus, converting androstenedione into estrone by aromatase. Lipocytes produce leptin, a hormone that regulates body weight by way of the hypothalamus.



GEL[8-10]

Gels are defined as a semi rigid systems in which the movement of the dispersing medium is restricted by an interlacing three dimensional network of particles or solvated macromolecules of the dispersed phase. Gels are composed of two interpenetrating systems where the colloidal particles , also known as the gelator or gallant are uniformly distributed , a gelling agent (gelator) which could be natural, synthetic, or semi synthetic polymer or low molecular weight small molecules, into an organic, inorganic or aqueous solvent or solvent systems. The polymer in gels acts as the backbone of the gel matrix. The polymeric meshwork gives gel its structural strength, increased adherence to the surface throughout a dispersion medium or solvent forming a three dimensional matrix known as the gel. The gels are prepared by adding where applied and decreased permeation of the larger molecules hence making the retention possible. Gels may be either reversible or irreversible based on the type of bonding. The reversible gels are generally hydrogen bonded systems whereas irreversible gels are usually covalently bonded. The term gel was introduced in the late 1800 to name some semisolid material according to their physiological characteristics rather than molecular composition.

The USP defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid where the gel mass contains a network of small separate particles, the gel is classified as a two phase system. In a two phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes called a magma. Single- phase gels consist of organic macromolecules uniformly circulated throughout a liquid in such a way that no apparent boundaries occur between the dispersed macromolecules and the liquid.

STRUCTURE OF GEL[11-13]

A gel consists of a natural or synthetic polymer forming a three dimensional matrix throughout a dispersion medium or hydrophilic liquid after application the liquid evaporates leaving the drug entrapped in a thin film of the gel forming matrix physically covering the skin. The presence of a network formed by the interlocking of particles of the gelling agent gives rise to the rigidity of a gel. The nature of the particles and the type of form that is responsible for the linkage determines the structure of the network and property of the gel. The forces of attraction responsible for the linkage between gelling agent particles may range from strong primary

valencies, as in silic acid gels, to weaker hydrogen bond and wander wall forces. The weaker nature of these latter forces is indicated by the fact that a slight increase in temperature often causes liquefaction of gel.

PROPERTIES[14-15]

- Gel must be inert, safe and compatible with other additives of the formulation.
- It should be stable at storage condition.
- It should maintain all rheological properties
- It should not affect biological nature of the drug.
- It should possess suitable anti-microbial activity.

ADVANTAGES[14-15]

- It eliminate the parameters, which influences gastrointestinal absorption, drug absorption, difficulties causes by GI pH, enzymatic activity and drug interaction with food, drinks and other administered drugs.
- Patient acceptability is batter as this drug delivery system is non- invasive avoiding the inconvenience of parental therapy.
- It reduces the frequency of drug dosing.
- It produces sustainable and controlled level of drug in plasma so reduces the chance of over or under dosing.
- Gels have good adherence property to the site of application.
- Retention time of gels is higher than other topical dosage forms.

DISADVANTAGES[14-15]

- The route is not suitable for drugs that irritate or sensitize the skin.
- Topical drug delivery systems are relatively expensive compare to conventional dosage forms
- The effects of gels is comparatively slower and sustained.
- The water content may increase the chance of microbial or fungal attack in gels.
- Rheology of some gels may alter due to the effect of temperature, humidity and other environment factors.

CHARACTERSTICS [16-18]

A. Swelling

When a gelling agent is kept in contact with liquid that solvates it, then an appreciable amount of liquid is taken up by the agent and the volume increases. This process is referred to as swelling. This phenomenon occurs as the solvent penetrates the matrix. Gel- gel interactions are replaced by gel solvent interactions. The degree of swelling depends on the number of linkages between individual molecules of gelling agent and on the strength of these linkages.

B. Syneresis

Many gels often contract spontaneously on standing and exude some fluid medium. This effect is known as syneresis. The degree to which syneresis occurs, increases as the concentration of gelling agent decreases. The occurrence of syneresis indicates that the original gel was thermodynamically unstable. The mechanism of contraction has been related to the relaxation of elastic stress developed during the setting of the gels. As these stresses are relieved, the interstitial space available for the solvent is reduced, forcing the liquid out.

C. Ageing

Colloidal systems usually exhibit slow spontaneous aggregation. This process is referred to as ageing. In gels, ageing results in gradual formation of denser network of the gelling agent. In gels, ageing results in gradual formation of a denser network of the gelling agent. Theimer suggests that this process is similar to the original gelling process and continues after the initial gelation, since fluid medium is lost from the newly formed gel.

D. Structure

The rigidity of a gel arises from the presence of a network formed by the interlinking of particles gelling agent. The nature of the particles and the type of force that is responsible for the linkages, which determines the structure of the network and the properties of gel. The individual particles of hydrophilic colloid may consist of either spherical or an isometric aggregates of small molecules, or single macromolecules.

E. Rheology

Solutions of the gelling agents and dispersions of the flocculated solid are pseudo plastic i.e. exhibiting Non- Newtonian flow behaviour, characterized by a decrease in viscosity with increase in shear rate. The tenuous structure of inorganic particles dispersed in water is disrupted by gels, ageing results in gradual formation of a denser network of the gelling agent.

CLASSIFICATION[14,19]

Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties.

1. **Based on Colloidal phase**

a) **Inorganic (Two phase system)-** If the partition size of dispersed phase is relatively large and form the three- dimension structure throughout gel such a system consists of floccules of small particles rather than larger molecules and gel structure, in this system is not always stable. They must be thixotropic forming semisolid on standing and become liquid on agitation.

b) **Organic (single phase system)** - these consist of large molecules existing on the twisted strands dissolved in a continuous phase. This larger organic molecule either natural or synthetic polymers are referred as gel formers they tend to entangle with each other their random motion or bound together by Vander walls forces.

2. **Based on nature of solvent**

a) Hydro gels (water based) - they contain water as their continuous liquid phase.
E.g. - Gelatin, cellulose derivatives**.**

b) Organic gels (non-aqueous solvent)-they contain non- aqueous solvent on their continuous phase.
E.g. **-** Olag gel and dispersion of metallic stearate in oils.

c) Xerogels - solid gels with low solvent concentration.
E.g. - Tragacanth ribbons.

3. **Based on rheological properties**

Usually gels exhibit non- Newtonian properties.

a) **Plastic gels** - E.g. - Bingham Bodies, flocculated suspensions of Aluminium hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of the gels above which the elastic gel distorts and begins to flow.
b) **Pseudo plastic gels**- The viscosity of these gels decreases with increasing rate of shear, with no yield value. As the shearing stress is increased the disarranged molecules begin to align their long axis in the direction of flow with the release of solvent matrix
E.g. - Liquid dispersion of tragacanth, Na CMC.
c) **Thixotropic gels**- The bonds between particles in these gels are very weak and can be broken down by shaking. The resulting solution will revert back to gel due to the particle colliding and linking together again (the reversible isothermal gel-sol-gel transformation).
E.g. - Kaolin, bentonite, agar

4. **Based on physical nature**
   a) **Elastic gels-** the fibrous molecules in these gels are being linked at the point of junction by comparatively weak bonds like hydrogen bonds and dipole attraction. If the molecule possesses free COOH group then additional bonding takes place by a salt bridge of type –COO-X-COO between two adjacent strand networks.
   E.g. - Alginate and Carbopol

   b) **Rigid gels**- This can be formed from macromolecules in which the framework linked by primary valence bonds.
   E.g. - Silica gel

METHODS OF PREPARATION OF GELS[14,16]

Gels can be prepared by following methods

1. **Thermal changes-** Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reduced, the degree of hydration is decreased and gelation takes place. (Cooling of a concentrated hot solution will produce gel).
   E.g. - gelatin, agar sodium oleate, guar gummed and cellulose derivatives etc.
   In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method.

2. **Flocculation –** here gelation is produced by adding sufficient quantity of salt to precipitate to produce age- state but insufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentration of precipitant.E.g. Solution of ethyl cellulose, polystyrene in benzene can gelled by rapid mixing with suitable amounts of a non- solvent such as petroleum ether. The addition of salts to hydrophobic solution brings about coagulation and gelation is rarely observed. The gels formed by flocculation method are thixotropic in behaviour.

3. **Chemical reaction-** In this method gel is produced by chemical interaction between the solute and solvent.
   E.g. aluminium hydroxide gel can be prepared by interaction in aqueous solution of an aluminium salt and sodium carbonate an increased concentration of reactants will produce a gel structure**.**

MECHANISMS OF GEL FORMATION[4-20]

Gels can be formed via three types of cross linking which are described as follows:

a) **Chemical cross-linking**- sometimes dual or multifunctional monomers present in a polymer results in the formation of an unalterable chemical cross linking with massive molecular mass. These polymers are usually insoluble in the solvent but certain solvents, when incorporated, results in only swelling and hence forming a gel, E.g.-polyacrylamide gels. These gels are covalently bonded and are irreversible in nature.

b) **Physical cross linking**- In some cases, solution to gel transition can takes place by hydrogen bond formation, crystalline component solubilisation concentration variation, temperature variation transition or hydrophobic interactions. E.g.-dextran gels, cellulose gels.

c) **Ionic cross linking** -Cross linking can also be achieved by forming charges on polymers or other molecules that may attract each other to form a gel. Ionic bonds are formed as a result of the charges on such molecules. Ionic gelation can also be attained by altering the pH of the medium. Changing the pH of such mixtures results in gelation
E.g. – pectin forms gel when subjected to acidic pH in a suitable medium.

GEL FORMING AGENTS[21-22]

Polymers are used to give the structural network, which is essential for the preparation of gels. Gel forming polymers are classified as follows:

1. **Natural polymer:**
   a. Proteins –

      Collagen Gelatin

   b. Polysaccharides –
      Agar Alginic acid Tragacanth Pectin Guar gum Xanthin

2. **Semisynthetic Polymers:**
   a. Cellulose derivatives- Carboxymethyl cellulose hydroxypropyl cellulose
      Hydroxypropyl methylcellulose hydroxyethyl cellulose

3. **Synthetic polymers:**
   a) Carbomer- Carbopol 940, Carbopol 934, Carbopol 941
   b) Poloxamer
   c) Polyacrylamide
   d) Polyvinyl Alcohol
   e) Polyethylene and its copolymers

4. **Inorganic substances-** Aluminium hydroxide , bentonite

5. **Surfactants-** Cetosteryl alcohol, Brij- 96

➢ **Formulation considerations for pharmaceutical gels[14,23]**

- **The choice of vehicle/ solvent**
  Normally purified water is used as a solvent. To enhance the solubility of the therapeutic agent in the dosage form and/ or to improve drug permeation across the skin, co solvent may be used.
  E.g. alcohol, glycerol, PG, PEG400

- **Inclusion of buffers**
  Buffers may be involved in aqueous and hydroalcholic based gels to control the pH of the formulation. The solubility of buffer salts is reduced in hydroalcholic- based vehicles.E.g. Phosphate, citrate

- **Preservatives**
  Certain preservatives cooperate with the hydrophilic polymers used to prepare gels, thereby reducing the concentration of free (anti-microbial active) preservative in the preparation. Therefore, to compensate for this, the initial concentration of these preservatives should be improved.
  E.g. Parabens, phenolic

- **Antioxidants**
  It may be involved in the formulation to improve the chemical stability of therapeutic agents that are prone to oxidative degradation. Its choice is based on the nature of the vehicle used in the preparation of gel. Water soluble antioxidants are generally used as the majority of gels are aqueous- based.
  E.g. Sodium metabisulphite, sodium formaldehyde sulfoxylate**.**

- **Flavors/ Sweetening agents**
  Flavors and sweetening agents are only incorporated in gels that are designed for administration into the oral cavity.
  - **Sweeteners:** sucrose, liquid glucose, glycerol, sorbitol, saccharin sodium, aspartame.
  - **Flavors:** peach, apricot, mint, cherry, citrus flavors.

EVALUATION PARAMETERS OF THE FORMULATED GELS[3,24,25]

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

2. **Drug content-** 1g of the prepared gel was mixed with 100ml of suitable solvent. Aliquots of different concentration were prepared by suitable dilutions after filtering the stock solution and absorbance was measured. Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve.

3. **Viscosity study-** The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading was noted. The viscosity of the gel was obtained by multiplication of the dial reading with factor given in the Brookfield Viscometer catalogues.

4. **Spreadability-** It indicates the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic potency of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel which

is placed in between the slides under the direction of certain load. Lesser the time taken for the separation of two slides, better the spreadability. It is calculated by using the formula:

S=M.L/T

Where, M= wt. tied to upper slide
L= length of glass slides
T= time taken to separate the slides

5. **Extrudability study-** After the gels were set in the container, the formulations were filled in the collapsible tubes. The extrudability of the formulation was determined in terms of weight in grams requires to extrude a 0.5 cm ribbon of gel in 10 second.

6. **Skin irritation study-** Guinea pigs (400-500g) of either sex were used for testing of skin irritation. The animals were maintained on standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was shaved from back of guinea pigs and area of 4cm^2 was mark done both the sides, one side served as control while the other side was test. Gel was applied (500mg/ guinea pig0 twice a day for7 days and the site was observed for any sensitivity and the reaction, slight patchy erythema, slight but confluent or moderate but patchy erythema and severe erythema with or without edema, respectively.

7. **In vitro Diffusion studies-** The diffusion studies of the prepared gels can be carrying out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. Gel sample (0.5g) was taken in cellophane membrane and the diffusion studies were carried out at 37±1˚ using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. Five millilitres of each sample was withdrawn periodically at 1,2,3,4,5,6,7 and 8h and each sample was replaced with equal volume of fresh dissolution medium. Then the sample were analysed for the drug content by using phosphate buffer as blank.

8. **Stability-** The stability studies were carried out for all the gel formulation by freeze- thaw cycling. Here, by subjecting the product to a temperature of 4˚c for 1 month, then at 25˚C for 1 month and then at 40˚C for 1 month, then at 25˚C for 1 month and then at 40˚C for 1 month, syneresis was observed. After this, the gel is exposed to ambient room temperature and liquid exudate separating is noted.

9. **Homogeneity**- After the gels have been set in the container, all developed gels were tested for homogeneity by visual inspection. They are tested for their appearance and presence of any aggregates.

10. **Grittiness**- All the formulations were evaluated microscopically for the presence of any appreciable particulate matter which was seen under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness as desired for any topical preparations.

CONCLUSION

Gels are getting considerable amount of popularity because of it easy application controlled release of drug and are more stable. Conventional formulations for topical and dermatological administration of drugs have certain limitation like poor adherence to skin, poor permeability and compromised patient compliance. Gels overcome this problem and provide better site of disorder by allowing the accumulation of drug concentration within the tissue. The clinical evidence indicates the topical gel is a safe and effective treatment option for use in the management of skin related disease and used for local action to reduce the side effects associated with other conventional dosage form.

REFERENCES

1. Ashni Verma; Sukhdev Singh; Rupinder Kaur; Upendra K Jain. Topical Gels as Drug Delivery Systems: A Review.Int.J.Pharm. Sci.Rev.Res.23 (2), Nov-Dec 2013; n˚60,374-382.
2. Kamal Saroha; Sarabjeet Singh; Ajay Aggarwal and Sanju Nanda. Transdermal Gels- An Alternative Vehicle for Drug Delivery. IJPCBS2013, 3(3), 495-503.
3. Loveeleen Preet Kaur*; Tarun Kumar Guleri. Topical Gel: A Recent Approach for Novel Drug Delivery. Asian Journal of Biomedical and Pharmaceutical Sciences 3(17)2013, 1-5.
4. Syeda Ayesha Ahmed un Nabi; Muhammad Ali Sheraz*; Sofia Ahmed; Nafeesa Mustaan; Iqbal Ahmad. Pharmaceutical Gels: A Review. RADS-JPPS Vol 4(1), June 2016, 40-48.
5. Mackel RM, Clinical dermatology,5, Oxford University press Oxford,2002.
6. Nino M, Calabro G, Santoianni P, Topical delivery of active principles: the field of dermatological research, Dermatology online Journal,16(1), 2010,4.
7. Gawrodger DJ, Dermatology,3, Churchill Livingstone, Edinburh,2002,2-5.
8. Jain N.K. Pharmaceuticals product Development. CBS Publishers & Distributors Pvt. Ltd. 2006. First edition : 228-230.
9. Murdan S. Organogels in drug delivery. Expert OPin Drug Deliv. 2005,2:489-505.
10. Vintiloui A, Leroux JC, Orgnogels and their use in drug delivery: A reviw. J Control
11.
12. Release 2008;125,179-192.
13. Yasir EN, Khashab AL, Yasir MK, Hamadi SA, Al-Waiz MM, Formulation and evaluation of ciprofloxacin as a topical gel, Asian Journal of Phrr sci, 8 (2), 2010, 80-95
14. Uche DOV, Sol-gel technique: A veritable tool for crystal growth, Advances in applied science research, 4(1),2013,506-510
15. Carter SJ, Disperse system In: Cooper and Gunn's Tutorial Pharmacy,6, CBS Publishers and Distributors, New Delhi, 2000, 68-72.
16. Hemendrasingh J Rathod and Dhruti P Mehta. " A Review on Pharmaceutical Gel". International Journal of Pharmaceutical Sciences 1.1 (2015).
17. Labarre D, Ponchel G, Vauthier C. Biomedical and Pharmaceutical Polymers. Pharmaceutical press,London, UK,2010.
18. Roychowdhury Santanu*; Singh Deep Hussan; Gupta Rajesh; Masih Daljit. A Review on Pharmaceutical Gel. IJPRBS, 2012; Volume 1(5): 21-36.
19. Carter SJ, Disperse system In: Cooper and Gunn's Tutorial Pharmacy,6, CBS Publishers and Distributors, New Delhi, 2000, 68-72.
20. Lieberman HA, Reiger MM, Banker GS, Pharmaceutical dosage form: Disperse system, 2, Marcel Dekker, New York, 2005, 399-421.
21. Loyd VA,et al. " Ansel's pharmaceutical dosage forms and drug delivery systems. 9th edition.Philadelphia:Lippincott Williams& Will-dns;(2011).
22. Gad SC, Pharmaceutical, Manufacturing Handbook: Production and Processes. Wiley-Blackwell, Hoboken, USA, 2008.
23. Bhardwaj Sudhir, Gupta G.D. Sharma V.K. Topical Gel: A Novel approach for derug delivery. Journal of Chemical Biological and Physical Sciences 2012; Vol.2 (2):856-866.
24. Prateek Chittodiya*, rajesh Singh Tomar, Umesh Ramchandani, Dr. Nimita Manocha, Dr. Shikha Agrawal. International Journal Of Pharmaceutical & Biological Archives 2013; 4 (4):606-613.
25. Jones D."Pharmaceutical – Dosage Form and Design". 1st *ed. London: Pharmaceutical Press* (2008).
26. Goyal S.,et al. "Novel anti- Inflammatory Topical Herbal Gels Containing Withania somnifera and Boswellia serrate". International Journal of Pharmaceutical and Biological Archives 2.4 (2011):1087-1094
27. Summet Dwivedi and Shailesh Gupta. Formulation And Evaluation Of Herbal Gel Containing Sesbania Grandiflora(L.)Poir. Leaf Extract.Acta Chim. Pharm. Indica:2(1), 2012,54-59.