2. Literature Review:

Jadhav Ravindra et al., (2011), developed a semisolid preparation (ointment, gel, cream) of Thiocolchicoside which is a centrally acting skeletal muscle relaxant for the effective treatment of muscle spasm. Thiocolchicoside is available in market in the form of capsules & In-jection. The major problem associated with Thiocolchicoside is its bioavailability which is very low i.e. 25% only so in order to minimize drug loss due to first pass metabolism, and overcome problem associated with low bioavailability drug there is need to formulate semisolid preparation.

M Artusi et al., (2003) carried out in vitro permeation studies through porcine oral mucosa and in vivo buccal transports in humans were investigated. Results from in vitro studies demonstrated that thiocolchicoside is quite permeable across porcine buccal mucosa and that permeation enhancers, such as sodium taurocholate and sodium taurodeoxycholate, were not able to increase its flux. The in vivo thiocolchicoside absorption experiments, in which the drug loss from oral cavity was measured, indicated that both formulations could be useful for therapeutic application. The fast dissolving (sublingual) form resulted in a quick uptake of 0.5 mg of thiocolchicoside within 15 min whereas with the adhesive buccal form the same dose can be absorbed over an extended period of time.

Shailesh et al., (2008) elaborated the advantage of topical delivery system to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time are other advantage of topical preparations. Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use. The topical drug delivery system is generally used where the others system of drug administration fails or it is mainly used in pain management, contraception, and urinary incontinence. This review describes the various formulation aspects, various excipients, evaluation tests, challenges and drugs explored in the field of topical drug delivery.
**Selcan Türker et al., (2004)** concentrated on Nasal drug administration, used as an alternative route for the systemic availability of drugs restricted to intravenous administration. This is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism, and ready accessibility. The article highlights the importance and advantages of the drug delivery systems applied via the nasal route, which have bioadhesive properties. Bioadhesive, or more appropriately, mucoadhesive systems have been prepared for both oral and peroral administration in the past. The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. It must be emphasized that many drugs can be absorbed well if the contact time between formulation and the nasal mucosa is optimized.

**Charlier C et al., (2006)** judged that fluconazole is one of the well established as a leading drug in the setting of prevention and treatment of mucosal and invasive candidiasis. The aim of this review is to summarize the main available data on the position of fluconazole in the prophylaxis or curative treatment of invasive Candida spp. infections. Fluconazole is still a major drug for antifungal prophylaxis in the setting of transplantation (solid organ and bone marrow), intensive care unit, and in neutropenic patients. Prophylactic fluconazole still has a place in HIV-positive patients in viro-immunological failure with recurrent mucosal candidiasis.

**Garg S et al., (2002)** emphasized on the development of vaginal formulations ('microbicides') that prevent sexual acquisition of acquired immunodeficiency syndrome (AIDS) and other sexually transmitted diseases. The primary objective of this study was to survey vaginal preparations available in the Indian market to determine the types of products that are most frequently used by Indian women. In addition, this survey provides information about the active ingredients and dosage forms of these products.

**Acarturk, Fusun et al., (2009)** reviewed vaginal drug delivery and consider it’s an important route of drug administration for both local and systemic diseases. The traditional commercial preparations, such as creams, foams, gels, irrigations and tablets, are known to reside in the vaginal cavity for a relatively short period of time owing to the self-cleaning action of the vaginal tract, and often require multiple daily doses to ensure the desired therapeutic effect. The vaginal route appears to be highly appropriate for bioadhesive drug delivery systems in order to retain drugs for treating largely local conditions, or for use in contraception. In particular, protection against sexually-transmitted diseases is critical. To prolong the residence time in the
vaginal cavity, bioadhesive therapeutic systems have been developed in the form of semi-solid and solid dosage forms.

**Jennifer Merabet et al., (2005)** represented newly launched Site Release Vaginal Drug delivery technology for the treatment of Bacterial vaginosis and vulvovaginal candidiasis which are the two most common forms of vaginitis in female patients. Although a variety of effective treatments have been available to eradicate these infections, limitations have lessened the utility of previously available products.

**Kim Knuth et al., (1993)** reviewed a Hydrophilic polymeric gels (hydrogels) which exhibit a range of physical, chemical, and biological properties which makes them attractive as drug delivery systems. Such systems are biocompatible and can be formulated to give controlled, pulsed, and triggered drug release profiles in a variety of tissues. This review will focus on delivery to the vaginal and oral areas including the oral cavity, stomach, small intestine, colon and rectum. Careful attention to the unique physiology of each area allows the development of drug formulations capable of providing the desired release profile, minimum irritation, and fewest side effects.

**Gupta H et al., (2009)** explained the different ways to deliver drugs into the body, viz oral (through swallowing), sub mucosal (through buccal and sublingual mucosa), parenteral (through injection), transdermal (through skin), pulmonary (through inhalation) etc. This paper reviews recent patents, technologies and products with their importance, manufacturing and novel approaches implemented till date to overcome the challenges in oral drug delivery systems.

**Himanshu Gupta et al., (2009)** developed and optimized a bioadhesive chitosan and gellan gum based in situ gel system of clindamycin for vaginal application. The optimized gel was evaluated for various physicochemical properties, in vitro drug release, bioadhesive force, retention time, microbial efficacy, irritation test, and stability studies.

**E.V.S Subrahmanyam et al., (2009)** formulated and evaluated pH triggered system using carbopol and ion triggered using gellan gum, which release clotrimazole locally in the buccal cavity for the treatment of oropharyngeal candidiasis. A combination of carbopol-
hydroxypropylmethylcellulose (HPMC) and gellan gum-HPMC were investigated as vehicle for the formulation.

**Joachim Brouwers et al., (2008)** focused on the concept of Supersaturating Drug Delivery Systems in the gastrointestinal tract as a strategy to enhance the intestinal absorption of poorly water-soluble drugs. Discussed the principles behind precipitation or crystallization delay or inhibited by excipients. Also, discussed the approach of both generating and maintaining supersaturation and illustrate this with examples of supersaturating drug delivery systems.

**Tamaki Miyazaki et al., (2004)** inhibited crystallization of amorphous acetaminophen (ACTA) by polyvinylpyrrolidone (PVP) and polyacrylic acid (PAA) using amorphous solid dispersions prepared by melt quenching. Co-melting with PVP and PAA decreased the average molecular mobility, as indicated by increases in glass transition temperature and enthalpy relaxation time. The ACTA/PAA dispersion exhibited much slower crystallization than the ACTA/PVP dispersion with a similar glass transition temperature value, indicating that interaction between ACTA and polymers also contributed to the stabilizing effect of these polymers.

**Karine Khougaz et al., (2000)** investigated the effects of polyvinyl pyrrolidone (PVP) molecular weight, composition, and content on the crystallization of a model amorphous drug, MK-0591 (Form I). Solid dispersions of crystalline MK-0591 with PVP homopolymers of different molecular weights and with a copolymer containing poly(vinyl acetate) (PVA), were prepared by the solvent method. The extent of crystallization inhibition increased with PVP molecular weight and, for a comparable PVP molecular weight, the homopolymer was more effective in the crystallization inhibition of the drug than the copolymer.

**Robert H Levin et al, (1997)** disclosed a topical composition comprising LYCD together with known topically active useful medicinal agents such as anti-wrinkling, antibiotic, anticancer, antifungal, antiinflammatory such as anti-acne, antiviral, wound healing, and hair-growing agents. The LYCD works together with the other active agents to achieve a synergistic result more effective than can be obtained from the topical agents individually, and more effective than could be predicted from the mere addition of the known efficacies of the individual ingredients.
Zook, Gerald P. et al, (1995) disclosed drug delivery system for the topical administration of medication which utilizes a viscoelastic gel pad having a liquid fraction, wherein the medication is incorporated within the liquid fraction, the viscoelastic gel pad being partially encapsulated between two layers of liquid fraction impermeable material which are joined together to form a seal about the periphery of the gel pad so as to control migration of the pad, and the medicating skin contact of the pad is limited to a drug delivery aperture formed in the skin-contacting layer of liquid fraction impermeable material. The aperture-containing layer, which contacts a wearer's skin, may be provided with a pressure sensitive adhesive. The invention is exemplified in a topical anesthetic delivery system wherein a viscoelastic gel pad, partially encapsulated by transparent alcohol and water impermeable layers, has an alcohol and water liquid fraction in which is dissolved lidocaine base.

Gilman, Marvin S, et al., (2000) disclosed drug delivery system for the topical administration of medication or other therapeutic material wherein the prior art peripheral layer of adhesive surrounding the active drug delivery area of the system is replaced by a bandage wrap.

Drizen et al., (2002) disclosed in invention relates to the formation of a stable, sterile gelled composition and its use in treating acute or chronic conditions. More particularly, this invention relates to a stable, sterilized composition, optionally containing a therapeutic drug, which comprises: a polymer matrix composed of a highly negative charged polymer material which may be selected from the group consisting of polysulfated glucosoglycans, glycosaminoglycans, mucopolysaccharides and mixtures thereof, and a nonionic polymer which may be selected from the group consisting of carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, and mixtures thereof.

Reed Jr., et al, (1999) invented transdermal drug delivery device includes a plurality of adhesive laminae containing the drug to be transdermally administered which laminae are separated by alternating interlaminar layers within the device and extending in stacked configuration from a contact adhesive for adhering the device to the epidermis of a user. Modulated migration of molecules of the drug serially from and through the interlaminar layers to and through the contact adhesive results from the continous physical equilibration of the drug between the multiple alternating interlaminar layers and adhesive lamine which, when stacked,
provide a relatively constant rate of dermal diffusion to the skin surface (dermis) for an extended period.

**Unger et al, (1996)** introduced therapeutic drug delivery systems comprising gas-filled microspheres comprising a therapeutic are described. Methods for employing such microspheres in therapeutic drug delivery applications are also provided. Drug delivery systems comprising gas-filled liposomes having encapsulated therein a drug are preferred. Methods of and apparatus for preparing such liposomes and methods for employing such liposomes in drug delivery applications are also disclosed.

**Staniforth et al, (2010)** disclosed invention is directed to a pharmaceutical formulation for topical administration on a mammal, comprising a unit dose of a therapeutically effective amount of a therapeutic agent and a pharmaceutically acceptable carrier medium therefor, said formulation being solid at ambient temperature and having a softening point of not higher than 35° C., such that when the formulation is placed in continuous contact with the skin of a mammalian patient, it is softened to a consistency to effect substantial application of the unit dose of said therapeutic agent onto a desired skin area of the mammalian patient within a time period of less than 10 minutes.

**Rajni Gulabdas et al., (2011)** disclosed herein is liquid oral spray composition comprising Thiocolchicoside in combination with at least one anti-inflammatory agent in unique blend of solvents along with pharmaceutically acceptable excipients useful for pain management in arthritis, rheumatoid arthritis, acute nonspecific low back pain, osteoporosis and osteoarthritis.

**Umit Cifter et al, (2008)** invented a novel controlled release (CR) flurbiprofen and muscle relaxant combinations for oral administration with anti-inflammatory, analgesic, myorelaxant activity and methods of its manufacture. The pharmaceutical composition of the present invention is administered orally in tablet, multilayer tablet, multicoated tablet and capsule form.

**Fatih Cakir et al., (2010)** invented topical pharmaceutical formulation made up of nimesulide or a pharmaceutically acceptable derivative of nimesulide, together with thiocolchicoside or a pharmaceutically acceptable derivative of thiocolchicoside. The present invention more particularly relates to pharmaceutical combinations of nimesulide and thiocolchicoside, in the
form of topical gels, ointments, cream, sprays, or lotions with anti-inflammatory, analgesic, and myorelaxant activities.

Amar Lulla, et al., (2009) disclosed the use of at least one immunosuppressant, or a pharmaceutically acceptable salt, solvate of physiologically functional derivative thereof, in the treatment of topical immune disorders of the scalp, and scalp conditions, and compositions suitable for such use.

Wilson Trafton, et al., (1999) disclosed a process and composition for moisturizing and rejuvenating keratinous tissues including skin, hair, fingernails, and toenails of humans and animals, and also hooves and horns of animals. More particularly, the present invention relates to topically applying the composition disclosed herein in order to treat the affected keratinous tissue.

Patrick M. Hughes et al, (2005) reviewed on posterior segments of the eye are exquisitely protected from the external environment. This poses unique and fairly challenging hurdles for drug delivery. It is somewhat dogmatic that topical ocular delivery is insufficient to achieve therapeutic drug levels in the posterior segments. However, some drugs are currently challenging this dogma. In this review we investigate the constraints and challenges of drug delivery to the posterior segment. Additionally, we outline several potential absorption pathways that may potentially be exploited to deliver drug to the back of the eye. Data on several compounds that achieve therapeutic posterior segment concentrations after topical dosing is presented. Finally, the issues surrounding systemic delivery to the posterior segment are reviewed.

Ranjit Singh et al, (1995) developed liposomal reservoir system bearing the local anesthetic, benzocaine, was developed for controlled and localized delivery via topical route. The liposomal suspension was incorporated into an ointment and gel base. The developed systems were studied for various physical and kinetic attributes in vitro.

Huabing Chen et al, (2006) constructed microemulsion-base hydrogel formulation for topical delivery of ibuprofen. Ethyl oleate (EO) was screened as the oil phase of microemulsions, due to a good solubilizing capacity of the microemulsion systems and excellent skin permeation rate of
ibuprofen. The pseudo-ternary phase diagrams for microemulsion regions were constructed using ethyl oleate as the oil, Tween 80 as the surfactant, propylene glycol as the cosurfactant. Various microemulsion formulations were prepared and the abilities of various microemulsions to deliver ibuprofen through the skin were evaluated in vitro using Franz diffusion cells fitted with porcine skins. The in vitro permeation data showed that microemulsions increased the permeation rate of ibuprofen 5.72–30.0 times over the saturated solution.

Yi-Hung Tsai, et al (2010) formulated an optimal microemulsion formulation by in vitro permeation study for hesperetin topical dosage form and determine its topical photoprotective effect and skin irritation by in vivo study. The hesperetin-loaded microemulsion showed an enhanced in vitro permeation compared to the aqueous and isopropyl myristate (IPM) suspension dosage form of hesperetin. In comparison, the effect of co-surfactant on the drug permeation capacity, propylene glycol showed highest permeation rate, followed by ethanol, glycerol and polyethylene glycol (PEG 400). Sunscreen agent padimate O, as a transdermal enhancer could increase the permeation rate of hesperetin. In case of in vivo study, the hesperetin-loaded microemulsion showed significant topical whitening effect and diminished skin irritation when compared with the non-treatment group, indicating that the hesperetin microemulsion could be used as an effective whitening agent.

Huabing Chen et al.,(2007) worked out on a hydrogel-thickened microemulsion (HTM) for delivering an extremely low concentration of drug molecule. The powerful permeation enhancing ability of HTM with a suitable viscosity makes it promising alternative carrier for transdermal administration of drug molecule at an extremely low concentration.

Amnon C Sintov, et al., (2004) improved skin bioavailability of lidocaine were designed and explored for some characteristics by preparing the microemulsion. Two principal factors were found to govern the transdermal penetration of lidocaine from the microemulsion: water content and the CoS/S ratio. By analyzing skin layers (epidermis and dermis) for lidocaine content, significantly higher concentrations were found after rats were treated in vivo with liquid microemulsions (CoS/S=1.8, 30 wt.% water) or patches compared to those measured after application of EMLA cream. It has been suggested, therefore, that these microemulsions loaded with lidocaine would provide adequate analgesia in relatively shorter periods of time.