World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 7.409

FORMULATION AND EVALUATION OF LORNOXICAM MICROSPONGE-BASED GEL AS A TRANSDERMAL DRUG DELIVERY SYSTEMS

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Article Received on 23/03/2025 **Article Revised on 13/04/2025** **Article Accepted on 03/05/2025**

ABSTRACT
Microsponges are porous microspheres ranging in size from 5 to 300 micrometers used in a polymeric delivery system. Microsponge may reduce undesired side effects and increase drug stability by boosting drug release. Multiparticulate drug delivery systems are important because they are simple to build and can control drug release in various ways, such as rate control, site control, or both. Drug-entrapped microsponge can be used to make a variety of formulations, including tablets, gels, capsules, powders, lotions, and creams. This microsponge drug delivery technique provides enhanced drug entrapment and stability, allowing for greater formulation flexibility and a significant reduction in unwanted side effects. Lornoxicam (chlortenoxicam), a new nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties, is available in oral and parenteral formulations. It differs from other oxicam compounds in its potent inhibition of prostaglandin biosynthesis, a property that explains the particularly pronounced efficacy of the drug. It is a strong analgesic and anti-inflammatory NSAID as compared to other NSAIDs**.** The objective of present study was to formulate and evaluate Lornoxicam microsponges using quasi emulsion solvent diffusion technique and Microsponge-Based Gel by using Carbopol and to enhance the release and release of Lornoxicam which is the limitation for preparation in topical forms Also skin delivery (TDDS) is an alternative administration for Lornoxicam that can minimize gastrointestinal (GI) side effects and improve patient compliance. The effects of drug to excipients and physical characteristics of Lornoxicam were investigated. Microsponge-Based Gel containing Lornoxicam and Eudragit® (S100, RS100, E100, L100) were prepared by quasi emulsion solvent diffusion method. The internal phase consisting Eudragit®and glycerol dissolved in dichloromethane, drug is slowly added to polymer solution with continuous stirring for 1h, and then mixture was filtered to separate the microsponges. Production yield, particle size analysis, surface morphology and in-vitro release from the Microsponge-Based Gel was also investigated. In-vitro release study showed that the release rate of the drug has been modified. The formulations were prepared as Microsponge-Based Gel in 0.5%w/w Carbopol and studied physical parameters of Microsponge-Based Gel and evaluated of pH. Microsponge-Based Gel formulation F1 (EudragitE100+Drug) show controlled drug release therefore it can be used to formulation a Microsponge-Based Gel with controlled release profile and it can cover the need of patient of therapeutic concentration all over the day.

KEYWORDS: Lornoxicam, Formulation, Microsponge, Microsponge-Based Gel, Transdermal Drug Delivery Systems.

INTRODUCTION
Microsponge-Based gel[1-100]
The main goal of any drug delivery system is to achieve desired concentration of the drug in blood or tissue, which is therapeutically effective and non-toxic for a prolonged period. The pointing of the goal is towards the two main aspects regarding drug delivery, namely spatial placement and temporal delivery of a drug. Spatial placement means targeting a drug to a specific organ or a tissue while temporal delivery refers to controlling the rate of drug delivery to that specific organ or a tissue. Frequent administration of drug is necessary when those have shorter half-life and all these leads to decrease in patient's compliance. In order to overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect, adverse effect decreases by lowering peak plasma concentration.

The controlled release dosage form maintaining relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time. one of those system is Transdermal drug delivery system (TDDS) which is a dosage form designed to deliver drug through skin by topical route of administration to the systemic circulation or for local treatment. However, they are commonly used as a carrier strategy because their non-collapsible structures and porous surfaces can entrap various active pharmaceutical compounds and allow for controlled release. Drug-entrapped Microsponge can be used to make a variety of formulations, including tablets, gels, creams, ointments, capsules, powders and emulsions. The TDDS can enhance drug stability, decrease side effects, improve bioavailability and also Microsponge as carriers of drug become an approach of controlled release dosage form in novel drug delivery system. Microsponge drug delivery system is an exclusive technology that has been used for the controlled release of topically and systemically active agents. Microsponges are porous microspheres ranging in size from 5 to 300 micrometers used in a polymeric delivery system. Microsponge may reduce undesired side effects and increase drug stability by boosting drug release. When it is applied, microsponges releases the active substance based on its time mode and in response to other stimuli like temperature and pH. It offers entrapment of ingredients and increased stability, elegance, flexibility in formulation and reduced side effects. Thus, in current research work an attempt was made to develop Microsponge-Based Gel TDDS of Lornoxicam in order to supply local medication to the affected tissues (painful joints), avoid its gastrointestinal side effects and to improve patient compliance by supplying sustained release of Microsponge-Based Gel TDDS. Microsponges are also the most explored carrier particles due to their numerous advantages over other microparticulate systems, such as ease of manufacture, improved drug loading, and rate control.

Structure and Function of the skin

The skin could be mistakenly viewed as a simple cover to contain the body and internal organs. Conversely, skin is a metabolically active, complex tissue that serves as a 2-way barrier between the body and the external hostile environment. As the largest organ in the body, the skin is an excellent target for drug delivery purposes. Transdermal drug delivery has several distinct advantages over other common drug delivery routes (oral and intravenous), including avoidance of first-pass metabolism, allowing for a constant zero-order delivery profile for up to 7 days from one dose, and ease of application that enhances patient compliance. Despite these advantages, the unique structure and barrier of the skin presents significant challenges for the passive diffusion of most drug molecules, except for those drug molecules that possess a very specific combination of physicochemical characteristics that permit penetration through the outer layers of the skin.

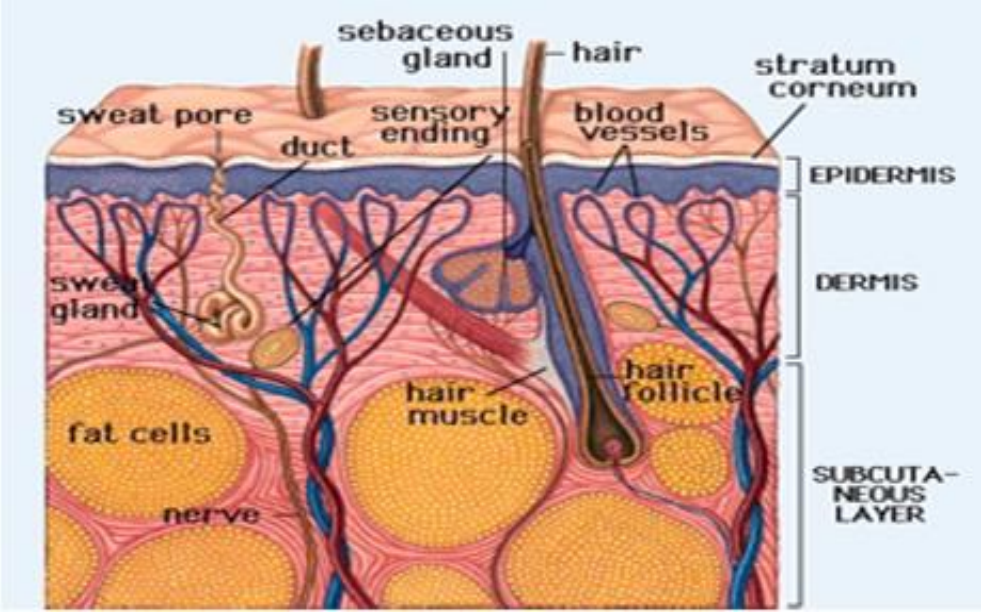

Fig. 1: Structure of the Skin.

The skin is the largest organ in the human body, and serves a multitude of functions. It represents the body's first defense against a hostile external environment, and as such it provides defenses against noxious chemical and microbial external insults and UV radiation. In addition, it provides critical homeostatic functions through the regulation of body temperature, blood pressure, and preventing excessive water loss. The skin is composed of multiple layers, each with distinct characteristics that contribute to the overall function of this intricate organ. From the outside in, the layers of the skin include the stratum corneum (the outermost layer of the epidermis), viable epidermis, and the dermis as shown in Figure 1.

Stratum corneum

The true interface between the body and the hostile external environment is the outermost layer of the skin, known as the stratum corneum (SC), or horny layer. It was believed to be a metabolically inactive tissue, similar to a plastic film, until the mid-1970s. It is now known to be a biosensor with limited metabolic activities that can respond to external cues and insults. The SC is a multicellular layer that is approximately 10 to 15 μm thick over most of the body, though it is much thicker on the friction surfaces of the skin (palms and soles). This outermost layer of the skin serves many critical functions, as it prevents excessive water loss to the outside environment while protecting the body from external xenobiotics and microbes. Structurally, the SC has been described as a "brick and mortal" model, composed of fully differentiated keratinocytes ("bricks") embedded in a continuous lipid matrix ("mortar"). Mechanical strength of the barrier is provided by the keratinocytes, while the lipids serve as the barrier to water and electrolyte movement. This layer of the skin is structurally distinct from all other layers, imparting its unique barrier properties to the skin as a whole.

The mechanical strength of the SC is provided by the keratinocytes(corneocytes). Over most parts of the body, the SC is composed of approximately 10 –15 layers of flattened keratinocytes (each with a mean thickness of about 1 μm). The individual keratinocytes are composed of keratin that fills up the cell, and a substance known as natural moisturizing factor, a mixture of amino acids and their derivatives, that helps to maintain the normal hydration of the SC (approximately 20% water under normal conditions). Natural moisturizing factor acts as a humectant by absorbing atmospheric water, thus allowing the SC to remain hydrated and not lose its moisture to the outside environment; maintaining this free water helps facilitate biochemical events within the SC. The keratinocytes in the SC are encapsulated by a cornified envelope (CE) that is composed of insoluble proline-rich proteins (loricrin and involucrin). The CEs of neighboring keratinocytes are linked together by intercellular protein structures called corneodesmosomes. These structures must be enzymatically degraded in order for the outermost layer of cells to be shed, in a process known as desquamation. The entire SC is replaced and turned over every2 weeks in healthy adults.

The intercellular lipid matrix makes up approximately 15 - 20% of the SC volume, and provides the barrier to water and electrolyte movement. These lipids are notably different from other biological membranes, in that there is very little phospholipid present. The composition of the lipid species found in the SC is always in an equimolar ratio as follows: ceramides (50% by mass), cholesterol (25% by mass), and free fatty acids (10 - 20% by mass). These lipids are secreted as lamellar bodies from the keratinocytes. Lamellar bodies are unique to the epidermis (first seen in the stratum spinosum layer), and are membrane bilayer-encircled secretory organelles. These lamellar bodies contain the lipids that serve as precursors to the SC extracellular lipids, and after secretion, these lipids are metabolized by enzymes that are also secreted in the lamellar bodies. This sequence of events is known as "lipid processing" and is a critical step for the formation of a normal permeability barrier.

The extracellular processing of lipids has important effects with regard to the barrier function of the SC (in fact, many of the key functions of the SC are somewhat derived from the extracellular processing of lipids). For example, maintenance of the SC hydration is partly maintained by the glycerol formed by the breakdown of phospholipids. Free fatty acids contribute to the acidic pH of the SC (the pH of the skin surface ranges from ~5 to 5.5 in humans and animals), and this acidity is very important for regulating activity of many of the SC enzymes. If the pH is increased, the lipid processing is impaired, thereby decreasing the permeability barrier function.

Viable epidermis

The viable epidermis (often simply referred to as the 'epidermis', which includes the SC) is contained between the SC and the underlying dermis (it deserves note that the epidermis is often described as two distinct layers: the viable epidermis and the SC). The epidermis is approximately 50 – 100 μm thick and is completely avascular. From the perspective of drug delivery this section of the skin is viewed as one single diffusional field, though under microscopic evaluation it can be seen that multiple strata make up the epidermis (representing progressive differentiation of the cells towards the external skin surface). From outward in, the layers of the epidermis consist of the stratum corneum, stratum granulosum, stratum spinosum, and stratum basale.

The cells of the basement layer of the epidermis (stratum basale) give rise to the cells that eventually comprise the SC; for this reason, the stratum basale is often referred to as the germinative layer. The cells flatten and begin to internally synthesize lipids and proteins that will ultimately characterize a fully differentiated SC layer. Several distinct cell types are found within the epidermis, though the primary cells are keratinocytes. Langerhans cells serve as the primary antigen presenting cells; melanocytes synthesize the pigment that gives unique colorations across different human races and these cells also produce the suntanning effect in response to ultraviolet radiation. Additional cell types include lymphocytes and migrant macrophages, which are especially evident following skin trauma.

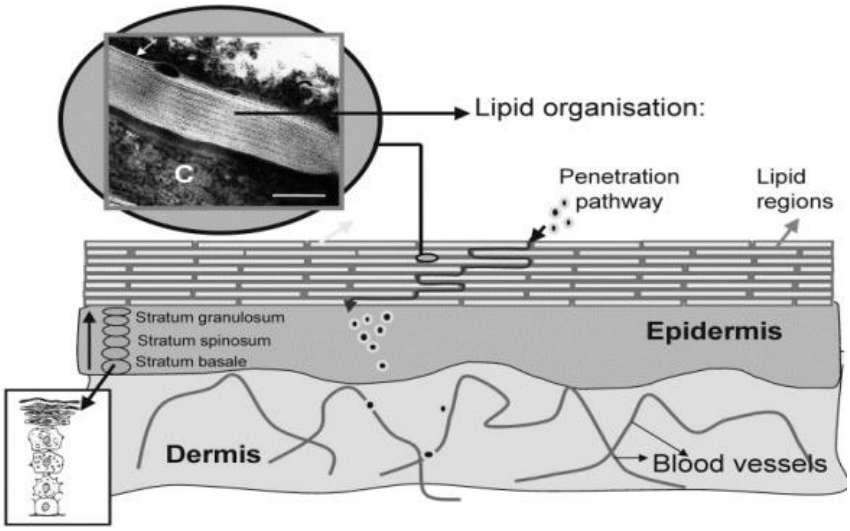

Fig. 2: Cross-Section of the Skin Depicting the Various Layers of the Epidermis and Dermis and the Intercellular Pathway of Penetration.

Dermis and Microvasculature

The dermis lies sandwiched between the epidermis and the underlying subcutaneous tissue and is approximately 1 – 2 mm thick. This layer of the skin is quite complex and it provides the mechanical support of the skin structure. The structure of the epidermis is comprised of multiple components including collagen (75%), elastin (4%), reticulin (0.4%), and ground substance (20%, made of mucopolysaccharide gel), all woven into a mesh with structural fibers. Various cell types are found in the dermis, including: nerve cells and endings (sensors of the skin); endothelial cells that form the vessels of the vasculature; blood cells; fibroblasts that produce the structure fiber network; and mast cells responsible for production of ground substance and release of histamine following aggravation. The appendages of the skin arise in the dermis, including sebaceous glands, hair follicles, eccrine and apocrine sweat glands of particular importance, the dermis is highly vascularized, providing the circulation that serves all of the skin. The first point of entry for a drug into the systemic circulation occurs within the papillary plexus (a delicate capillary structure in the upper dermis). A rich lymphatic system is also present, in addition to a network of sensory nerves for pain, pressure, and temperature.

Routes of skin penetration

With passive delivery techniques, there are 3 steps that must occur for a drug to be successfully delivered from the vehicle and through the skin. First, the drug must diffuse out of the vehicle and reach the vehicle-SC interface. Following this, the drug must partition into and diffuse through the SC to reach the viable epidermis below. The final step is the diffusion of the drug through the dermis and then into the microcirculation.[6] Based on the general structure of the skin, there are 3 major diffusion pathways that a drug molecule can take through the skin: Through the continuous lipid matrix in the SC (intercellular route), directly through the keratinocytes (transcellular route); or appendageal route (hair follicles and sweat glands). The various routes of skin penetration are displayed in Figure 2.

Intercellular

The lipid matrix of the SC in which the keratinocytes are embedded provides the only continuous phase throughout the SC, and this is thought to be the primary pathway of percutaneous delivery for most compounds. This creates a very tortuous route through the skin, and as such, generally only low molecular weight and moderately lipophilic drug compounds can transverse this environment successfully.

Transcellular

The transcellular path of delivery would include delivery through the keratinocytes, requiring that a drug compound transverse through the keratin-filled corneocytes as well as the intercellular lipid matrix, with several transfers between the corneocytes and the lipid matrix between them. As such, it is thought that this pathway would be generally unfavorable and would not likely contribute substantially to the overall delivery of most drug compounds through the SC.

Appendageal

The appendageal route of transport simply refers to the pathway of hair follicles and sweat ducts, which can be seen as a mean of bypassing the permeability barrier of the SC. For this reason, appendageal transport is often known as a "shunt pathway", as it provides a pathway of lesser resistance as compared to the tortuous lipid pathway of the SC. However, the area available for appendageal transport is very small (about 0.1%), and thus this route typically can be considered negligible in its contribution to drug flux at steady state, as shown in Figure 3.

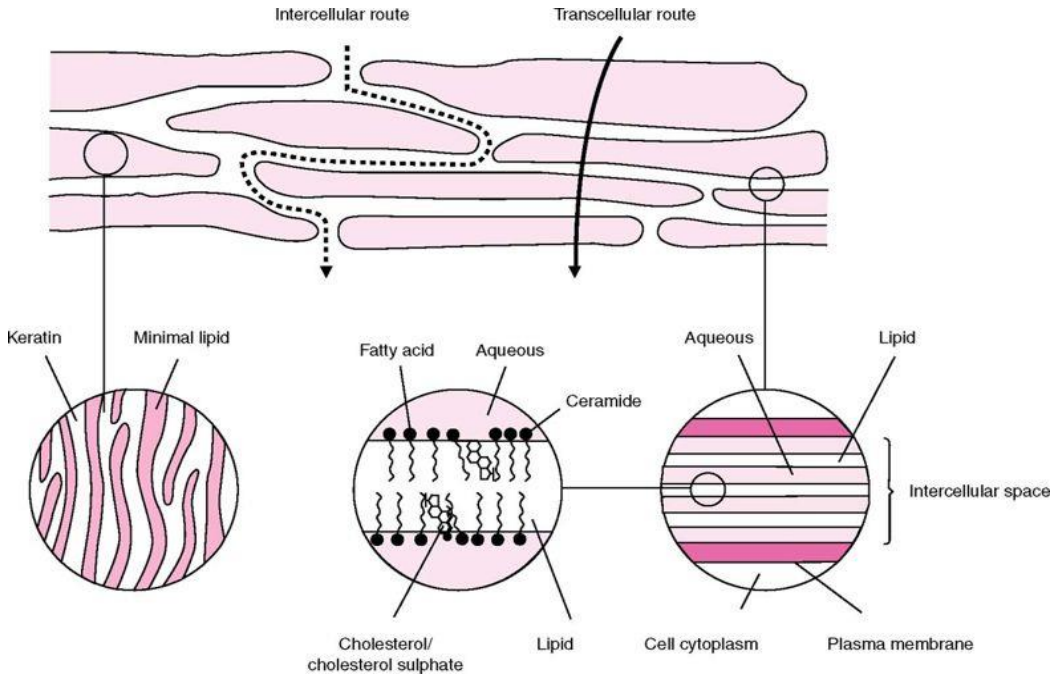

Fig. 3: Depiction of the Intercellular and Transcellular Routes of Penetration Through the Skin.

Microsponge-Based an effective drug delivery system

The microsponge-based drug delivery system is a unique technology for controlled release and enhanced drug deposition in the skin while minimizing transdermal penetration of topically active agents. Drug loaded microsponge consist of microporous beads, typically 10-25 µm in diameter as shown in Figure 4. Microsponge delivery system (MDS) can provide increased efficacy for topically active agents with enhanced safety, extended product stability, enhanced formulation flexibility, reduced side effects and improved aesthetic properties in an efficient and novel manner. In addition these are non-irritating, non-allergenic, non-mutagenic, and non-toxic. The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems. This Company developed a large number of variations of the procedures and those are applied to the cosmetic as well as over-the-counter (OTC) and prescription pharmaceutical products. At the current time, this interesting technology has been licensed to Cardinal Health, Inc., for use in topical products.

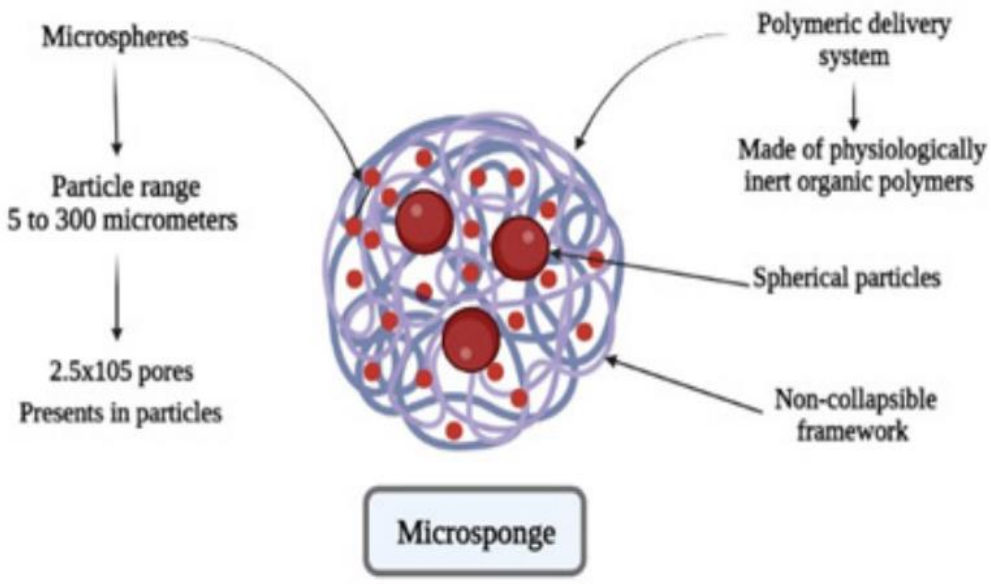

Fig. 4: Diagram of Microsponge.

Future perospectives of microsponges drug delivery systems

Microsponges drug delivery systems have a promising future in the pharmaceutical industry due to its unique properties, which include enhanced product performance and refinement, extended release, less irritation, increased physical, chemical, and thermal stability, and the abildeliver topical antifungal, anti-inflammatory, and anti-dandruff medications. The list of granted patents for the microsponge industry, which spans the years 1985 to 2021, includes a vast array of innovations.

In the early time, the microsponges used in Transdermal drug delivery system was benzyl peroxide microsponges in 1991. And later, the Retin-A microsponges (0.1% or 0.04% tretinoin) and Carnac microsponges (0.5% 5-flurouracil) for acne and actinic keratoses respectively were approved by Food and Drug Administration (FDA). Afterward, microsponges for topical skin-target drug delivery are widely developed and utilized in topical drug delivery system, such as mupirocin microsponge, hydroxyzine hydrochloride microsponge, paeonol microsponge and so on. Micro-sized delivery systems are now obsolete, and the search for nanosized carriers is currently intensifying. Micron-sized particles have a much lower ratio of specific surface area to size and a lower capacity to alter active release than nano-sized particles. Although inorganic nanosponges have numerous applications in electronics, more research is required before they can be utilized effectively in medicine. Nanosponges will undoubtedly continue to be popular in the future.

Use of drug delivery system relying on microsponges

The active ingredient is added to the vehicle in an entrapped form. As the Microsponge particles have an open structure (i.e., they do not have a continuous membrane surrounding them), the active is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. Once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium This will start a flow of the active from the Microsponge particle into the vehicle, and from it to the skin, until the vehicle is either dried or absorbed. Even after that the Microsponge particles retained on the surface of the stratum corneas will continue to gradually release the active to the skin, providing prolonged release over time. This proposed mechanism of action highlights the importance of formulating vehicles for use with Microsponge entrapments. If the active is too soluble in the desired vehicle during compounding of the finished products, the products will not provide the desired benefits of gradual release. Instead, they will behave as if the active was added to the vehicle in a free form. Therefore, while formulating microsponge entrapments, it is important to design a vehicle that has minimal solubilizing power for the actives.

In recent years, there has been more interest in making medicines that can be given to specific parts of the body. Microsponges are flexible polymeric delivery systems that contain porous microspheres. They can contain a wide range of active chemicals, such as emollients, perfumes, essential oils, sunscreens, anti-infectives, anti-fungal, anti-inflammatory agents, the role of Microsponges in the delivery of anticancer drugs, Microsponge used in the topical administration, oral drug delivery system Microsponges, Microsponges as a bone replacement technique, cardiovascular system treating microsponges, Microsponge for sustained release drug delivery, diagnostic agent delivery using Microsponges, as vehicles for diabetes treatment, anti-allergic and anti-inflammatory drug delivery via Microsponge, antimicrobial drug entrapment Microsponge, Microspheres, nanoparticles, Microsponges, and liposomes may be used to better disperse active medicines. The pharmaceutical industry's biggest issue is regulating active medicine distribution to a specific body area. The microsponge delivery system is easyto build and may regulate drug release through rate, location, or both. It also has a lot of benefits, such as better control over drug loading and rate, uniform distribution, and easy production.

Advantages of microsponge drug delivery systems

1. Microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures (up to130°C).
2. Microsponges exhibit good compatibility with various vehicles and ingredients.
3. Microsponges have high entrapment efficiency up to 50 to 60%.
4. Microsponges are characterized by free flowing properties.
5. The average pore size of microsponges is small (0.25 μm) in a way to prevent the penetration of bacteria, thus they do not need sterilization or addition of preservatives.
6. Microsponges are non-allergenic, non-irritating, nonmutagenic and non-toxic.
7. Microsponges can absorb oil up to 6 times their weight without drying
8. Microsponges offer better control of drug release than microcapsules. Microcapsules cannot usually control the release rate of the active pharmaceutical ingredients (API). Once the wall is ruptured, the API contained within the microcapsules will be released.
9. Microsponges show better chemical stability, higher payload and easier formulation compared with liposomes.
10. In contrast to ointments, microsponges have the ability to absorb skin secretions, therefore, reducing greasiness and shine from the skin. Ointments are often aesthetically unappealing, greasy and sticky, resulting in lack of patient compliance.

Characters of drugs to be entrapped in the microsponges

There are certain requirements that should be fulfilled (or considered) when active ingredients are entrapped into microsponge

1. It Should exhibit complete miscibility in monomer or have the ability to be miscible using the least amount of a water immiscible solvent.
2. Must be inert to monomers and do not increase the viscosity of the preparation during formulation.
3. It should be water immiscible or almost slightly soluble.
4. The solubility of active ingredients in the vehicle should be minimum; otherwise, the microsponge will be diminished by the vehicle before application.
5. It should maintain (preserve) the spherical structure of microsponge.
6. It should be stable in polymerization conditions.
7. Only 10 to 12% w/w microsponge can be incorporated into the vehicle to eliminate cosmetic delinquent.
8. Payload and polymer design of the microsponges for the active must be adjusted to obtain the desired release rate of a given period of time.

Techniques of microsponges preparation

Some of the methods used to develop microsponge-based drug delivery systems include liquid-liquid suspension polymerization, quasi-emulsion solvent diffusion, water-in-oil-in-water (w/o/w) emulsion solvent diffusion, oil-in-oil emulsion solvent diffusion, the addition of porogen method, vibrating orifice aerosol generator method, electro-hydrodynamic atomization method, and ultrasound-assisted production method.

Preparation of microsponge can take place in a one-step or two-step process based on the physicochemical properties of drug to be loaded. If the drug is porogen, (that is an inert non-polar substance which will generate the porous structure), it will not deter the polymerization process or become activated by it and also is stable to free radicals. A porogen drug can be entrapped with one step process (liquid-liquid suspension polymerization). Microsponges are prepared by the following methods:

Liquid-Liquid Suspension Polymerization

Suspension polymerization process in liquid-liquid systems is utilized for the preparation of microsponges in a one step process. At first, the monomers are dissolved with the active ingredients (non-polar drug) in a proper solvent. The prepared solution is then dispersed in the aqueous phase containing surfactants and dispersants to facilitate the formation of suspension.

Once the suspension is formed with droplets of the required size, then polymerization is initiated by the addition of catalyst, increasing temperature, or irradiation. As the polymerization process continues, a spherical structure is produced containing thousands of microsponges bunched together. During the polymerization process, an inert water-immiscible liquid but completely miscible with monomer is used to form the pore network in some cases, which is then removed once the process is complete. The particles are then washed and processed until they are substantially ready for use.

Quasi-Emulsion solvent diffusion method

Microsponges can be prepared by quasi-emulsion solvent diffusion method. In this method, an internal phase is used containing polymer such as Eudragit RS 100 or ethyl cellulose dissolved in organic solvent. The drug is then dissolved into the polymer solution under ultrasonication. The inner phase is then poured into external phase containing polyvinyl alcohol and distilled water with continuous stirring for adequate period of time Microsponges are then separated by filtration. Finally, the microsponges are washed and dried in an air heated oven at 40°C for 12 h.

Characterization of microsponges

Measurement of particle size

Various formulation and process variables can greatly affect the particle size of microsponge formulations. Measurement of particle size of loaded and unloaded microsponges can be performed using laser light diffractometry or using the optical microscope fitted with an ocular micrometer and stage micrometer or any other suitable method. Results can be expressed in terms of mean size range. Cumulative (%) drug release from microsponges of different particle sizes should be plotted against time to study the effect of particle size on drug release. Particles larger than 30 μm can impart grittiness and hence particles of sizes between 10 and 25 μm are preferred to be used in topical formulations.

Production Yield and Entrapment efficiency

Percentage yield can be calculated using the equation. Percentage yield (PY) = (Final obtained mass of microsponges / initial mass of polymer and drug) × 100.

The entrapment efficiency of the microsponges can be computed using the equation: Entrapment Efficiency (EE%) = (Actual drug content / Theoretical drug content) × 100.

In vitro Release Studies, Release Kinetics and Mechanism

In vitro release studies can be performed using United States Pharmacopeial (USP) dissolution apparatus. The release medium is selected according to the type of formulation that is, topical or oral, while considering solubility of active ingredients to ensure sink conditions. Sample aliquots are withdrawn from the medium and analyzed by suitable analytical method at regular intervals of time. The drug release from topical preparations (for example, creams, lotions and emulgels) containing microsponges can be carried out using Franz diffusion cells. Dialysis membrane is fitted into place between the two chambers of the cell. A predetermined amount of formulation is mounted on the donor side of Franz cell. The receptor medium is continuously stirred

at and thermostated with a circulating jacket. Samples are withdrawn at different time intervals and analyzed using suitable method of assay. To determine the drug release kinetics and investigate its mechanism from microsponges, the release data are fitted to different kinetic models. The kinetic models used are; first order, zero order, Higuchi and Korsmeyer- Peppas models. The goodness of fit was evaluated using the determination coefficient (R2) values.

Factors affecting the release of drug from microsponge

In the design and manufacture of these multifunctional microcarriers, the physicochemical characterization of the microsponge is a crucial step. Several complementary techniques, such as HPLC, FTIR, DSC, PXRD, and SEM, are used to study the morphological features and porosity of microsponges. When using microsponge entrapment, it is highly recommended that the active chemicals be sufficiently soluble in the vehicle so that the vehicle can deliver the final loading dose of the substances before releasing them from the microsponge. This is possible by altering the equilibrium between the polymer and the carrier. Producing the microsponge polymer with both free and trapped active ingredients, resulting in a pre-saturated vehicle, is another strategy for minimizing the unintended leaching of the active components. In addition to the partition coefficient between the polymer and the vehicle, diffusion or other stimuli, such as steam, pH, friction, or temperature, may influence the release rate. Depicts a variety of factors that may influence the drug release from the microsponge include the:

Temperature

Some encapsulated active substances may be too viscous to transfer rapidly from microsponges to the skin at normal temperatures. Enhanced release is a result of the higher flow rate generated by a rise in skin temperature.

Pressure

By rubbing or applying pressure on microsponges, the active chemical may be released onto the skin. The strength of the microsponge determines the amount of release.

Solubility

Microsponges that contain untargeted substances such as antiseptics and deodorants release their contents upon contact with water. The release may also be initiated via diffusion, but the partition coefficient between the microsponges and the external system must be considered.

pH triggered systems

Microsponges that contain untargeted substances such as antiseptics and deodorants release their contents upon contact with water. The release may also be initiated via diffusion, but the partition coefficient between the microsponges and the external system must be considered.

Lornoxicam: A newest oxicam member

Lornoxicam (chlortenoxicam), a new nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties, is available in oral and parenteral formulations. It is distinguished from established oxicams by a relatively short elimination half-life (3 to 5 hours), It is a strong analgesic and anti-inflammatory NSAID as compared to other NSAIDs. Its analgesic activity is comparable to that of opioids. Studies have shown that it is more effective than 10 mg morphine when used at doses > or = 8 mg to control pain after oral surgery. Lornoxicam combines the high therapeutic potency of oxicams with an improved gastrointestinal toxicity profile as compared to naproxen which is probably due to the short half-life of lornoxicam as compared to the other oxicams. Clinical investigations have established it as a potent analgesic with excellent anti-inflammatory properties in a range of painful and/or inflammatory conditions, including postoperative pain and RA [38,39]. Like all NSAIDs, Lornoxicam acts by inhibiting the metabolites of COX branch of arachidonic acid pathway. It inhibits both isoforms in the same proportion, a perfectly balanced inhibition of COX-1 and COX-2 is achieved. As Prostaglandins play an important role in gastrointestinal mucosal protection by strengthening the mucosal barrier for acid and in inhibiting gastric acid secretion. Thus inhibition of prostaglandin synthesis leads to adverse effects. The gastric side effects range from mild dyspepsia and heartburn to ulceration and hemorrhage.

Chemical structure of lornoxicam

The active drug substance is 6-chloro-4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno-[2,3-e]-1,2-thiazine-3-carboxamide-1,1-dioxide (Fig. 5). It is a yellow crystalline solid with a pKa of 4.7. It is highly ionized at physiological pH and has relatively low lipophilicity thereby preventing distribution to fatty tissues. It has a molecular weight of 371.82 Da.

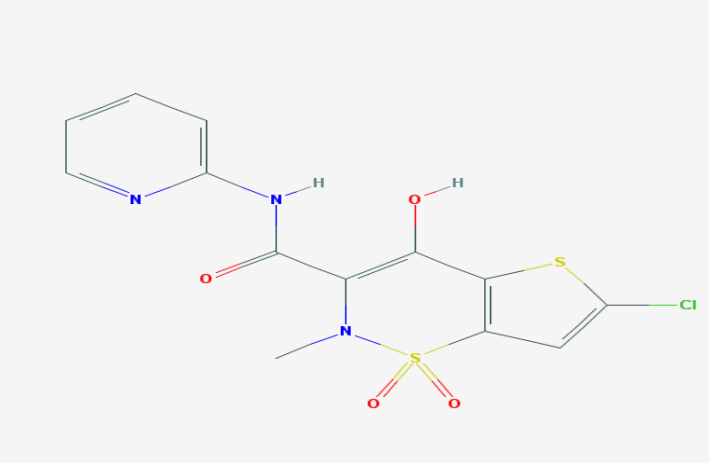

Fig. 5: Chemical structure of lornoxicam.

Mechanism of action

Like all NSAIDs, it acts by inhibiting the metabolites of COX branch of arachidonic acid pathway. It inhibits both isoforms in the same concentration range i.e. COX-1/ COX-2 = 1. Thus, a perfectly balanced inhibition of COX-1 and COX-2 is achieved. COX-1 is a constitutive enzyme expressed in many cells as a house keeping enzyme and provides homeostatic prostaglandins. COX-2 is an inducible enzyme, which is expressed at the onset of inflammation in many cell types involved in inflammatory responses. It differs from other oxicam compounds in its potent inhibition of prostaglandin biosynthesis, a property that explains the particularly pronounced efficacy of the drug. Prostaglandins are involved in all phases of inflammatory events including fever, pain reactions and physiological functions like intestinal motility, vascular tone, renal function, gastric acid secretion etc. The inducing events include phorbol esters, cytokines and endotoxins. It might produce the peripheral analgesic effects by NO-cGMP pathway and the opening of K+ channels. It also acts by inhibition of spinal nociceptive processing's, elevation of plasma levels of dynorphin and ß endorphin following IV administration. *In vitro* tests have shown that lornoxicam also inhibited the formation of nitric oxide. It has also shown marked inhibitory activity on endotoxin induced IL-6 formation in THP 1 monocytes with less activity on TNF alpha and IL-1â**.**

In the present study, it was proposed to formulation and evaluation study of Lornoxicam Microsponge-Based Gel TDDS.

MATERIALS AND METHODS

As shown in Table 1.

Table 1: List of materials used.

NO	Materials
1	Lornoxicam
2	Eudragit® (RS100, S100, L100, E100)
3	Polyvinyl alcohol (PVA)
4	Glycerol
5	Methyl Paraben
6	Carbopol 940
7	Phosphate buffer
8	Triethanolamine
9	Dichloromethane
All materials were purchase from the local market and China market.	

Formulation and Evaluation of Lornoxicam Microsponge-Based Gel Transdermal Drug Delivery Systems [50-196]

Preparation of lornoxicam microsponges

Lornoxicam microsponges were prepared by quasi-emulsion solvent diffusion method. The organic internal phase was consisted of Eudragit RS 100, Eudragit S100, Eudragit L100 or Eudragit E100 and glycerol (1ml) dissolved in dichloromethane. Glycerol was used as plasticizer. Then, Lornoxicam was added to solution and dissolved under magnetic stirrer at 35◦C for 15 minutes. The resulting solution was then poured into PVA solution in water (external phase of 200 ml volume). The mixture was stirred at 500 rpm for 1hr room temperature to remove dichloromethane from the reaction flask. The formed microsponges were filtered and dried for 12hr and stored for further investigations. The composition of various microsponge formulations is give in Table 2.

Table 2: The composition of microsponges formulations.

Materials		Formulation Code			
		F1	F2	F3	F4
Lornoxicam		0.25%	0.25%	0.25%	0.25%
Type of Eudragit Polymer	Internal Phase	E100	S100	RS100	L100
Polymer (g)		1%	1%	1%	1%
Dichloromethane (ml)		25	25	25	25
Purified Water (ml)	External Phase	200	200	200	200
PVA (g)		0.5%	2%	1.5%	1%
Stirring Rate (rpm)		500	500	500	500
Stirring Time (hr)		1	1	1	1

***In-vitro* drug release studies of microsponge formulations**

In vitro release study was performed using USP dissolution test apparatus-II. The release was performed in 900 ml of phosphate buffer solution (pH 7.4) as a release medium and maintained at 37 ± 0.5°C and 100 rpm for optimum Lornoxicam microsponge formulations. A sample of microsponges equivalent to 15mg of Lornoxicam was used in each test. Samples of release fluid (10 ml) were withdrawn at different time intervals and immediately replaced with 10 ml of the fresh release medium to maintain a sink condition. The samples were filtered through a syringe filter suitably diluted and analyzed 376 nm using a UV-visible spectrophotometer and the release was calculated.

Preparation of lornoxicam microsponge gel

0.5% w/w Carbopol 940 gel was prepared. methyl paraben was dissolved in a sufficient quantity of water pre-warmed to 40°C. The Carbopol 940 was then added in small amount with vigorous stirring. The dispersion was homogenized using a magnetic stirrer for 1hr and then left for 24 hr for complete swelling. After that, the triethanolamine was added drop by drop with continuous mixing and the final weight was completed to 100 g with water. the final concentration of Lornoxicam microsponge is 1% w/w in the final gel formulation.

Physical characterization of microsponge loaded gel

The visual examination

The examination considered a series of visual characteristics (consistency, color, and homogeneity).

pH Determination

The pH of the prepared gel was measured using pH – meter by putting the tip of the electrode into the gel and after 2 minutes the result was recorded.

Spreadability

A sample of 0.1g of gel was pressed between 2 slides with 500g weights and left for about 5 min where no more spreading was expected. Diameters of spread circles were measured in cm and were taken as comparative values for spreadability (diameter of the spread circle – initial diameter).

RESULTS AND DISCUSSION

In-vitro drug release studies of microsponge formulations

The release profiles obtained for the microsponge are presented in Figure 6.

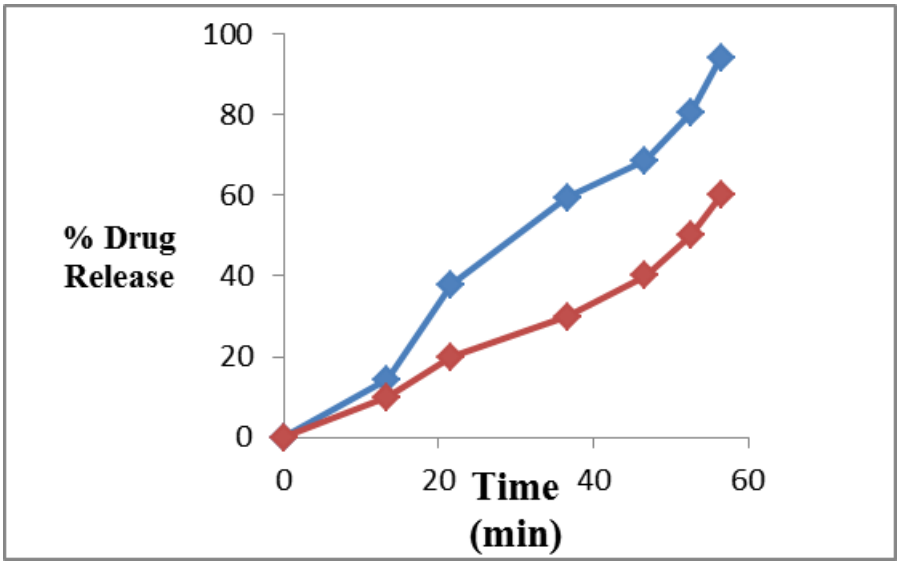

Fig. 6: Release study of various microsponge formulations.

Cumulative release for the microsponges after 50-minute ranged from 54-95%. Drug release from the formulations increase depend on the type of polymer.

Physical characteristics of lornoxicam microsponge loaded carbapol gel

For preparation of Lornoxicam loaded microsponge carbapol gel, we select only the formulation F1 and the obvious reason was its stability in all pervious examination.

The visual examination

The observed formulation indicates non-transparent yellowish gel, no phase separation, with smooth texture and of good homogeneity without lumps.

pH Determination

The result of pH for obtained Carbopol gel is 7.3±0.02 due to neutralization the formulation by triethanolamine.

Spreadability

The efficacy of a topical therapy depends on the patient spreading the drug formulation in an even layer to administer a standard dose. Spreadability is therefore an important characteristic of these formulations and is responsible for correct dosage transfer to the target site and ease of application on the substrate. The Spreadability of Lornoxicam microsponge loaded gel was 25 g.cm/sec.

CONCLUSION

Microsponges are porous microspheres ranging in size from 5 to 300 micrometers used in a polymeric delivery system. Microsponge may reduce undesired side effects and increase drug stability by boosting drug release. In the present study a new approach for the preparation of modified Lornoxicam Microsponge-Based Gel with prolonged release and immediate release characteristics depend on the type of the polymer used. By considering the solubility study of the drug and polymer, the internal phase suitable for the preparation of Microsponge-Based Gel to be dichloromethane and the external phase was found to be water. The minimum concentration of an emulsifier PVA required to produce Microsponge-Based Gel was found to be 500 mg/200 ml. The drug release studies from the Microsponge-Based Gel formulations F1 and F4, it can be concluded that the quasi-emulsion solvent diffusion method used for the preparation of the Microsponge-Based Gel was simple, reproducible, and rapid. Microsponge-Based Gel formulation F1 (EudragitE100+Drug) show controlled drug release therefore it can be used to formulation a Microsponge-Based Gel with controlled release profile and it can cover the need of patient of therapeutic concentration all over the day.

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