1. INTRODUCTION

1.1. Introduction Topical Route of Drug Administration:

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. Among the topical formulations a wide choice for the treatment from solid dosage to semisolid doses forms and to liquid dosage formulation. Topical gels have widely accepted in both cosmetics and pharmaceuticals.

1.2. Introduction to Topical Gel:

Gel formulation provides better application property and stability in comparison to cream and ointment. 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. Topical gels are intended for skin application or to certain mucosal surfaces for local action or percutaneous penetration of medicament or for their emollient or protective action. Gels are evaluated by following parameters such as pH, homogeneity, grittiness drug content, viscosity, spreadability, extrudability, skin irritation studies, in-vitro release, in Stability.

1.3. Introduction to Microsponges Drug Delivery System:

Microsponge can be effectively incorporated into topical drug delivery system for retention of dosage form on skin, and also use for oral delivery of drugs using bioerodible polymers, especially for colon specific delivery and controlled release drug delivery system thus improving patient compliance by providing site specific drug delivery system and prolonging dosage intervals. Microsponge drug delivery systems offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, reduces systemic exposure and minimize local cutaneous reactions, increased elegance, and enhanced formulation flexibility. Topical preparations have some disadvantages like unpleasant odour, greasiness and skin irritation and fail to reach the systemic circulation this problem is overcome by microsponge delivery system. Microsponge formulations are stable over range of PH 1 to 11; Microsponge formulations are stable at the temperature up to 1300C; compatible with most vehicles and ingredients. The present review introduces Microsponge technology along with its synthesis, characterization, programmable parameters and release mechanism of MDS.
The microsponge technology was developed by Won in 1987 and the original patents were assigned to advanced polymer system, Inc 1. This company developed a large number of variations of the technique and applied to the cosmetic as well as over the counter (OTC) and prescription pharmaceutical products. Microsponge Delivery System MDS is a unique technology for controlled delivery of drug. MDS technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce the systemic exposure and minimize local cutaneous reactions to active drugs. A Microsponge delivery system is patented, highly cross-linked, porous, polymeric microspheres polymeric system consisting of porous microspheres that can entrap wide range of actives and then release them onto the skin over a time and in response to trigger. To control the delivery rate of active agents to a predetermined site in human body has been one of the biggest challenges faced by drug industry.\(^4\) Several predictable and reliable systems were developed for systemic drugs under the heading of transdermal delivery system (TDS) using the skin as portal of entry. It has improved the efficacy and safety of many drugs that may be better administered through skin. But TDS is not practical for delivery of materials whose final target is skin itself. Further, these porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders. Release of drug into the skin is initiated by a variety of triggers, including rubbing and higher than ambient skin temperature. Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Typically, such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. Moreover, the application of topical drugs has many problems like greasiness, stickiness associated with the ointments and so on, that often result in lack of patient compliance. The fundamental appeal of the Microsponge technology overcomes these difficulties experienced with conventional formulations in releasing active ingredients over an extended period of time. Microsponge can be used to deliver active agents to the skin, with improved localization and prolonged residence of the drug at site of action.\(^5\)

**Characteristics of microsponges**\(^6\)

1) Microsponge formulations are stable over range of PH 1 to 11
2) Microsponge formulations are stable at the temperature up to 1300\(^0\)C
3) Microsponge formulations are compatible with most vehicles and ingredients
4) Microsponge formulations are self sterilizing as their average pore size is 0.25 μm where bacteria cannot penetrate
5) Microsponge formulations have higher payload (50 to 60%), still free flowing and can be cost effective

**Advantages**

- Advanced oil control, absorb up to 6 times its weight without drying
- Improved product elegance.
- MDS allows the incorporation of immiscible products.
- Extended release
- Reduced irritation formulas
- Allows novel product form
- These are non-irritating, non-mutagenic, non-allergenic and non-toxic.
- Improved product aesthetics
- Extended release, continuous action up to 12 hours
- Reduced irritation, better tolerance means broader consumer acceptance
- Improved product aesthetics, gives product an elegant feel
- Improves stability, thermal, physical and chemical stability
- Allows incorporation of immiscible products.
- Improves material processing e.g. liquid can be converted to powders
- Improves efficacy in treatment.
- Cure or control confirm more promptly.
- Improve control of condition
- Improve bioavailability of same drugs

**Advantages over conventional formulation**

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. When compared to the Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the Microsponge system can reduce significantly the irritation of effective drugs without reducing their efficacy. For example, by delivering the active
ingredient gradually to the skin like MDS Benzoyl peroxide formulations have excellent
efficacy with minimal irritation.

**Advantages over microencapsulation and liposomes**\(^{19,20}\)
The MDS has advantages over other technologies like microencapsulation and liposomes.
Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured the
actives contained within microcapsules will be released. Liposomes suffer from lower
payload, difficult formulation, limited chemical stability and microbial instability. While
microsponge system in contrast to the above systems are stable over range of pH 1 to 11,
temperature up to 1300°C; compatible with most vehicles and ingredients; self sterilizing as
average pore size is 0.25 μm where bacteria cannot penetrate; higher payload (50 to 60%),
still free flowing and can be cost effective.

**Advantages over ointments**\(^{21,22}\)
Ointments are often aesthetically unappealing, greasiness; stickiness etc. That often results
into lack of patient compliance. These vehicles require high concentrations of active agents
for effective therapy because of their low efficiency of delivery system, resulting into
irritation and allergic reactions in significant users. Other drawbacks of topical formulations
are uncontrolled evaporation of active ingredient, unpleasant odour and potential
incompatibility of drugs with the vehicles, when microsponge system maximize amount of
time that an active ingredient is present either on skin surface or within the epidermis, while
minimizing its transdermal penetration into the body.

**1.4. Introduction to Quality by Design:**
Quality by design is an essential part of the modern approach to pharmaceutical quality.\(^{23}\)
There is much confusion among pharmaceutical scientists in generic drug industry about the
appropriate element and terminology of quality by design. Process parameters and quality
attributes were identified for each unit operation.\(^{24}\) The use of QbD was contrasted with the
evaluation of product quality by testing alone. The QbD is a systemic approach to
pharmaceutical development. It means designing and developing formulations and
manufacturing processes to ensure predefined product quality.\(^{25}\) Some of the QbD elements
include: Defining target product quality profile, Designing product and manufacturing
processes, Identifying critical quality attributes, process parameters, and sources of variability
and controlling manufacturing processes to produce consistent quality over time. Using QbD,
pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables. Product testing confirms the product quality. Implementation of QbD will enable transformation of the chemistry, manufacturing, and controls (CMC) review of abbreviated new drug applications (ANDAs) into a science-based pharmaceutical quality assessment. The pharmaceutical industry works hard to develop, manufacture, and bring to market new drugs—and to comply with regulatory requirements to demonstrate that the drugs are safe and effective. A new approach to drug development could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product’s life cycle. The work also clarifies the risk based distinctions governing the assignment of criticality to provide consistency and facilitate the adoption and implementation of Quality by Design (QbD) principles in the development of pharmaceutical manufacturing processes. The application of the concept of quality by design (QbD) presented in this paper aligns with the principles of ICH Q8, Q9 and Q10 guidelines.

1.5. Introduction to Experimental Design:

Factorial design is a useful tool in order to characterize multivariable process. It gives the possibility to separate the important factors from these which are not identifying any possible interactions between them. Traditionally pharmaceutical formulations are developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to evolve an ideal formulation using this classical technique since the joint effect of independent variables is not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial designs. Desirability function was used for the optimization process finally. The application of the desirability function combines all the responses in one measurement and gives the possibility to predict the optimum levels for the independent variables. The combination of the responses in one desirability function requires the calculation of the individual desirability function.