

## THE MICROSPONGE DRUG DELIVERY SYSTEM: AN OVERVIEW

**Vikrant K Nikam**\*<sup>1</sup>, Sachin B Somwanshi<sup>1</sup>, Ramdas T Dolas<sup>1</sup>, Vivekanand A Kashid<sup>1</sup>,  
Kiran B Dhamak<sup>2</sup>, Vinayak M Gaware<sup>2</sup>, Atul N Khadse<sup>2</sup> and Kiran B Kotade<sup>3</sup>

1- Department of Pharmaceutics, College of Pharmacy, Chincholi, Sinnar, Nashik, M.S, 422 101.

2-Department of Pharmaceutical Chemistry, College of Pharmacy, Chincholi, Sinnar, Nashik,  
M.S, 422 101.

3-Department of Pharmacology, College of Pharmacy, Chincholi, Sinnar, Nashik, M.S, 422 101.

### **Corresponding author\*:**

**Vikrant K Nikam**

Lecturer, Department of Pharmaceutics

College of Pharmacy, Chincholi, Sinnar, Nashik, M.S (422101)

E-mail: vikrantnikam82@rediffmail.com

### **Summary**

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge technology has many favorable characteristics, which make it a versatile drug delivery vehicle. Microsponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. The outer surface is typically porous, allowing a sustained flow of substances out of the sphere. Microsponges are porous, polymeric microspheres that are used mostly for topical use and have recently been used for oral administration. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release.

**Keywords:** Tran dermal delivery system, Micro sponge Delivery System, Suspension polymerization, Quasi-emulsion solvent diffusion, Controlled release.

### **Introduction**

The drug delivery technology landscape has become highly competitive and rapidly evolving. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy.<sup>1</sup> 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.<sup>2</sup> 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. Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant amounts is an area of research that has only recently been addressed with success. No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers and not beyond the epidermis. Application of topical drugs suffers many problems such as ointments, which 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. Thus the need exists for system to maximize amount of time that an active ingredient is present either on skin surface or with in the epidermis, while minimizing its transdermal penetration into the body. The microsponge delivery system fulfills these requirements.

A Microsponge Delivery System (MDS) 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.<sup>3</sup> It is a unique technology for the controlled release of topical agents and consists of microporous beads, typically 10-25 microns in diameter, loaded with active agent. When applied to the skin, the MDS releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc). MDS technology is being used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. Delivery system comprised of a polymeric bead having network of pores with an active ingredient held within was developed to provide controlled release of the active ingredients whose final target is skin itself.<sup>4</sup> The system was employed for the improvement of performance of topically applied drugs.<sup>5, 6, 7</sup> The common methods of formulation remains same; the incorporation of the active substance at its maximum thermodynamic activity in an optimized vehicle and the reduction of the resistance to the

diffusion of the stratum corneum. 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 microsphere system in contrast to the above systems are stable over range of pH 1 to 11, temperature up to 130°C; compatible with most vehicles and ingredients; self sterilizing as average pore size is 0.25µm where bacteria cannot penetrate; higher payload (50 to 60%), still free flowing and can be cost effective. Most liquid or soluble ingredients can be entrapped in the particles. Actives that can be entrapped in microspheres must meet following requirements,

- It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be water immiscible or at most only slightly soluble.
- It should be inert to monomers.
- It should be stable in contact with polymerization catalyst and conditions of polymerization

Release can be controlled through diffusion or other triggers such as moisture, pH, friction, or temperature. This release technology is available for absorbent materials or to enhance product aesthetics. Microsphere delivery system can be incorporated into conventional dosage forms such as creams, lotions, gels, ointments, and powder and share a broad package of benefits. Systems can and improve its formulation flexibility.

### **PREPARATION OF MICROSPONGES**

Drug loading in microspheres can take place in two ways, one-step process or by two-step process; based on physico-chemical properties of drug to be loaded. If the drug is typically an inert non-polar material, will create the porous structure it is called porogen. Porogen drug, which neither hinders the polymerization nor become activated by it and stable to free radicals is entrapped with one-step process.

- **Liquid-liquid suspension polymerization:**

Microspheres are conveniently prepared by *liquid-liquid suspension polymerization*. Polymerization of styrene or methyl methacrylate is carried out in round bottom flask. A solution of non-polar drug is made in the monomer, to which aqueous phase, usually containing surfactant and dispersant to promote suspension is added. Polymerization is effected, once suspension with the discrete droplets of the desired size is established; by activating the monomers either by catalysis or increased temperature.

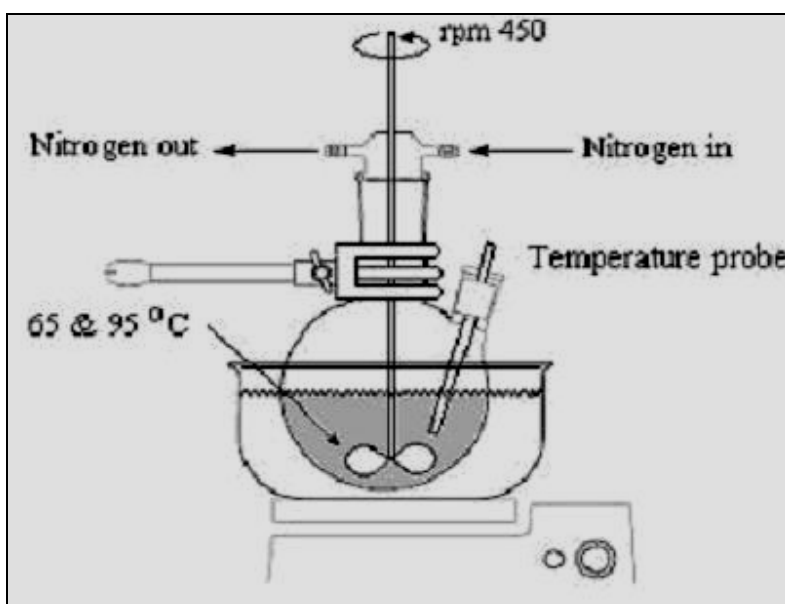


Figure 1: Reaction Vessel for Microsponge Preparation By Liquid-Liquid Suspension Polymerization

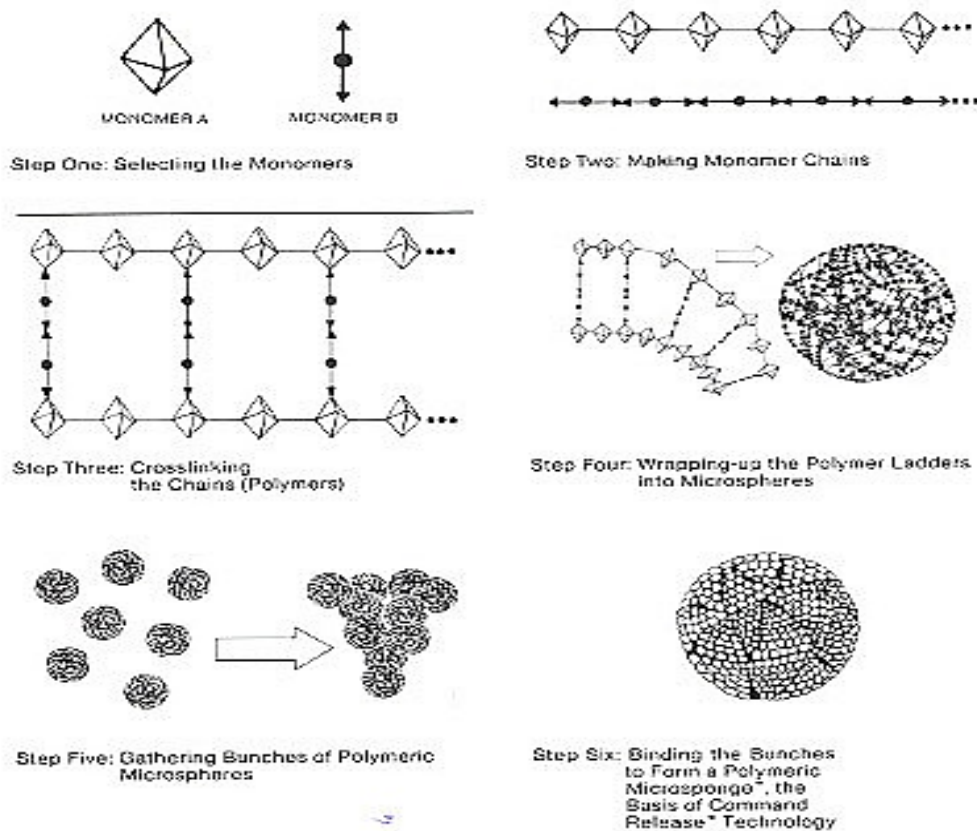


Figure no 2: Microsponges Synthesis by Suspension Polymerization

When the drug is sensitive to the polymerization conditions, two-step process is used. The polymerization is performed using substitute porogen and is replaced by the functional substance under mild experimental conditions<sup>8</sup>.

- **Quasi-emulsion solvent diffusion**

As explained in Figure 3 the microsponges can also be prepared by *quasi-emulsion solvent diffusion* method using the different polymer amounts. The processing flow chart is presented in Fig. 1a. To prepare the inner phase, Eudragit RS 100 was dissolved in ethyl alcohol. Then, drug can be then added to solution and dissolved under ultrasonication at 35 °C. The inner phase was poured into the PVA solution in water (outer phase). Following 60 min of stirring, the mixture is filtered to separate the microsponges. The microsponges are dried in an air-heated oven at 40 °C for 12 h and weighed to determine production yield (PY).<sup>9</sup>

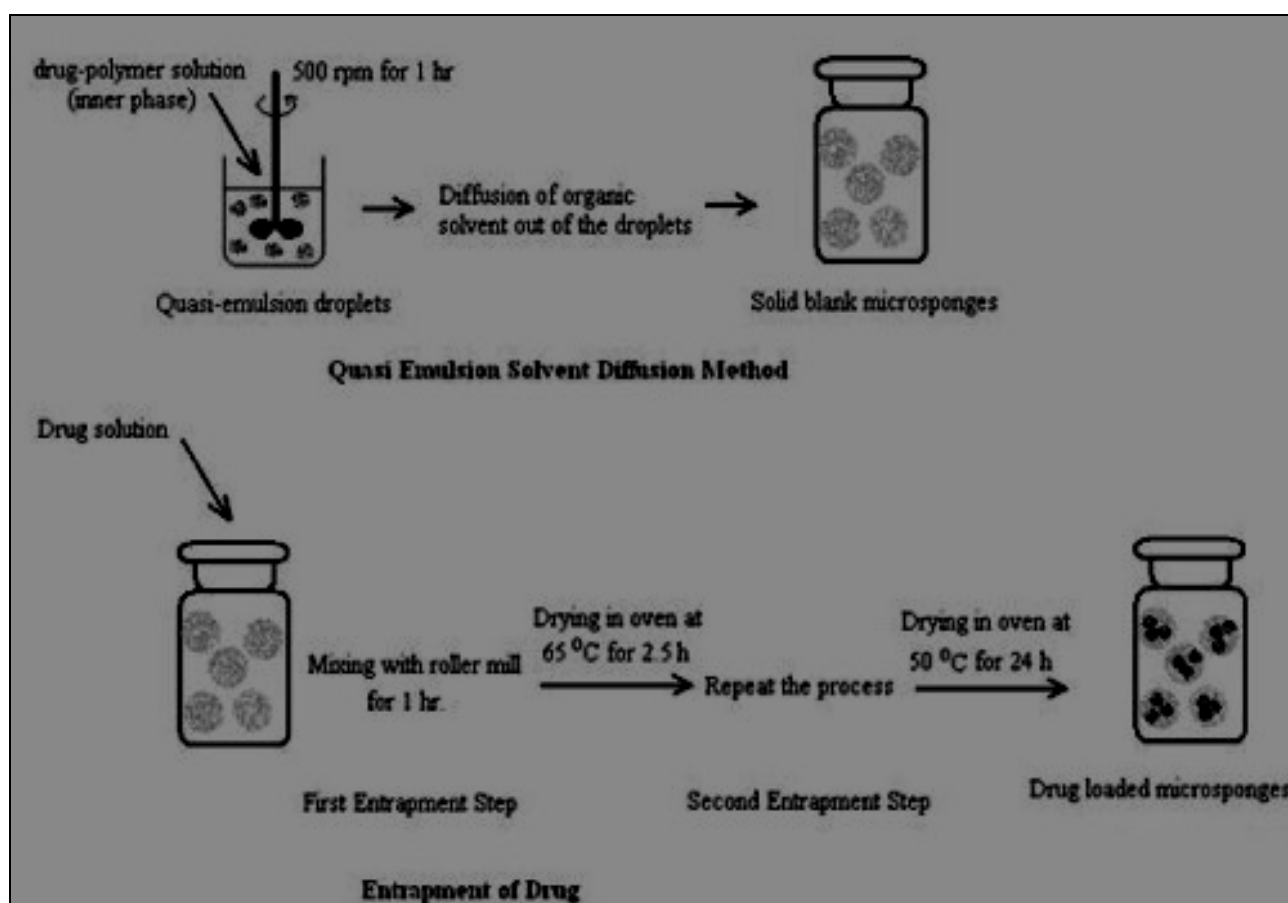


Figure 3: Preparation of Microsponges by Quasi Emulsion Solvent Diffusion Method

## PHYSICAL CHARACTERIZATION OF MICROSPONGES

- **Particle size determination**<sup>10</sup>

Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometry or any other suitable method. The values ( $d_{50}$ ) can be expressed for all formulations as mean size range. Cumulative percentage drug release from microsponges of different particle size will be plotted against time to study effect of particle size on drug release. Particles larger than 30  $\mu\text{m}$  can impart gritty feeling and hence particles of sizes between 10 and 25  $\mu\text{m}$  are preferred to use in final topical formulation.

- **Morphology and Surface topography of microsponges**

For morphology and surface topography, prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the microsponges can be studied by scanning electron microscopy (SEM). SEM of a fractured microsp sponge particle can also be taken to illustrate its ultrastructure<sup>11</sup>.

- **Determination of loading efficiency and production yield**

The loading efficiency (%) of the microsponges can be calculated according to the following equation:

$$\text{Loading efficiency} = \frac{\text{Actual Drug Content in Microsponges}}{\text{Theoretical Drug Content}} \times 100 \text{ — Eqn no. (1)}$$

The production yield of the microparticles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsp sponge obtained.<sup>12</sup>

$$\text{Production Yield (PY)} = \frac{\text{Practical Mass of Microsponges}}{\text{Theoretical Mass (polymer + drug)}} \times 100 \text{ — Eqn no. (2)}$$

- **Determination of true density**

The true density of microparticles and BPO was measured using an ultra-pycnometer under helium gas and was calculated from a mean of repeated determinations.

- **Characterization of pore structure**

Pore volume and diameter are vital in controlling the intensity and duration of effectiveness of the active ingredient. Pore diameter also affects the migration of active ingredients

from microsponges into the vehicle in which the material is dispersed. Mercury intrusion porosimetry can be employed to study effect of pore diameter and volume with rate of drug release from microsponges.<sup>13</sup>

Porosity parameters of microsponges such as intrusion–extrusion isotherms, pore size distribution, total pore surface area, average pore diameters, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry. Incremental intrusion volumes can be plotted against pore diameters that represented pore size distributions.

- **Compatibility studies**

Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC).<sup>16, 17, 18</sup> For DSC approximately 5 mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15°C/min over a temperature range 25–430°C in atmosphere of nitrogen.

- **Polymer/ Monomer composition**

Factors such as microsphere size, drug loading, and polymer composition govern the drug release from microspheres.<sup>19, 20</sup> Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsphere system and hence have direct influence on the release rate of entrapped drug. Release of drug from microsphere systems of different polymer compositions can be studied by plotting cumulative % drug release against time. Release rate and total amount of drug released from the system composed of methyl methacrylate/ ethylene glycol dimethacrylate is slower than styrene/ divinyl benzene system.

Selection of monomer is dictated both by characteristics of active ingredient ultimately to be entrapped and by the vehicle into which it will be dispersed.

- **Resiliency**

Resiliency (visco elastic properties) of microsponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release. Hence resiliency of microsponges will be studied and optimized as per the requirement by considering release as a function of cross-linking with time.

## **RELEASE EVALUATIONS**

- **Dissolution tests**

Dissolution profile of microsponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consisted of 5µm stainless steel mesh. The speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analysed by suitable analytical method at various intervals.

- **Release mechanisms**<sup>21</sup>

By proper manipulation of the aforementioned programmable parameters, microsponges can be designed to release given amount of active ingredients over time in response to one or more external triggers. 1. Pressure: Rubbing/ pressure applied can release active ingredient from microsponges onto skin.

2. Temperature change: Some entrapped actives can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased in skin temperature can result in an increased flow rate and hence release.

3. Solubility: Microsponges loaded with water-soluble ingredients like anti-prespirants and antiseptics will release the ingredient in the presence of water. The release can also be activated by diffusion taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system.

### **Safety considerations**<sup>22, 23</sup>

Safety substantiation of microsponges can be confirmed by skin irritation studies in rabbits; eye irritation studies in rabbits; oral toxicity studies in rats; mutagenicity in bacteria and allergenicity in guinea pigs.

## **FORMULATION CONSIDERATIONS**

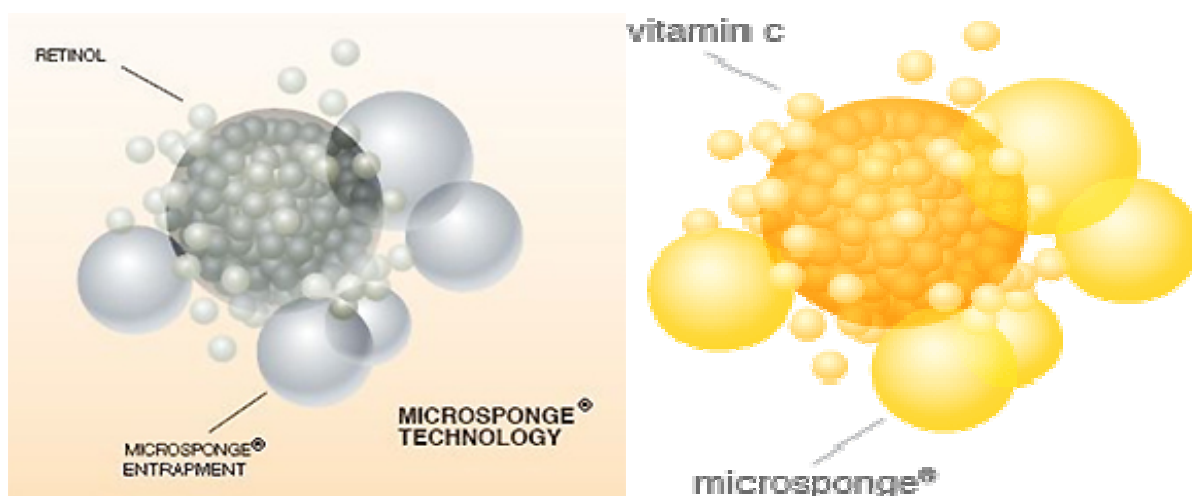
Actives entrapped in MDS can then be incorporated into many products such as creams, lotions, powders and soaps. When formulating the vehicle, certain considerations are taken into account in order to achieve desired product characteristics.

1. The solubility of actives in the vehicle must be limited. Otherwise the vehicle will deplete the microsponges before the application.
2. To avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle.



3. Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.

There remains equilibrium between micro sponge and vehicle and micro sponge releases drug in response to the depletion of drug concentration in the vehicle. Drug concentration in the vehicle is depleted by absorption of the drug into skin. Hence continuous and steady release of actives onto the skin is accomplished with this system. Drug release from the topical semisolid formulation can be studied by using Franz-type static diffusion cells.<sup>24</sup>



**Figure 4: Retinol & Vitamin C Microsponge**

### **APPLICATIONS OF MICROSPONGE SYSTEMS**

Microsponges are porous, polymeric micro spheres that are used mostly for topical and recently for oral administration. It offers the formulator a range of alternatives to develop drug and cosmetic products. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release.

The system can have following applications<sup>25</sup>,

Sr. No.	Active agents	Applications
1.	Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.
2.	Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
3.	Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
4.	Anti-fungals	Sustained release of actives.
5.	Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odour with lower irritation with extended safety and efficacy.
6.	Antipruritics	Extended and improved activity.
7.	Skin depigmenting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
8.	Rubefacients	Prolonged activity with reduce irritancy greasiness and odour.

**Table no: 1 Applications of microsponge drug delivery system**

### **MARKETED FORMULATION USING THE MDS**

Microsponge delivery systems are used to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter ("OTC") and personal care products. Products under development or in the marketplace utilize the Topical Microsponge systems in three primary ways;

- As reservoirs releasing active ingredients over an extended period of time,
- As receptacles for absorbing undesirable substances, such as excess skin oils, or
- As closed containers holding ingredients away from the skin for superficial action.

The resulting benefits include extended efficacy, reduced skin irritation, cosmetic elegance, formulation flexibility and improved product stability. The fundamental appeal of the Microsponge technology stems from the difficulty experienced with conventional topical formulations in releasing active ingredients over an extended period of time. Cosmetics and skin care preparations are intended to work only on the outer layers of the skin. Yet, the typical active ingredient in conventional products is present in a relatively high concentration and, when applied to the skin, may be rapidly absorbed. The common result is over-medication, followed by a period of under-medication until the next application. Rashes and more serious side effects can occur when the active ingredients rapidly penetrate below the skin's surface. Microsponge technology is designed to allow a prolonged rate of release of the active ingredients, thereby offering potential reduction in the side effects while maintaining the therapeutic efficacy. Marketed formulation using the MDS includes Dermatological products (APS defined ethical dermatology products as prescription and non-prescription drugs that are promoted primarily through the medical profession for the prevention and treatment of skin problems or diseases). Several ethical dermatology products approved by US FDA, OTC and personal care products are sold in the United States. Results from various human clinical studies reaffirmed that the technology offers the potential to reduce the drug side effects, maintain the therapeutic efficacy and potentially increase patient compliance with the treatment regimen.

### **Conclusion**

The MDS which was originally developed for topical delivery of drugs can also be used for controlled oral delivery of drugs using bioerodible polymers, especially for colon specific delivery. It provides a wide range of formulating advantages. Liquids can be transformed into free flowing powders. Formulations can be developed with otherwise incompatible ingredients with prolonged stability without use of preservatives. Safety of the irritating and sensitizing drugs can be increased and programmed release can control the amount of drug release to the targeted site.

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