ISSN 0975-6299 Vol 2/Issue 1/ Jan-Mar 2011

International Journal of Pharma and Bio Sciences

REVIEW ARTICLE

NOVEL DRUG DELIVERY SYSTEM

SOLID POROUS MICROSPHERE: EMERGING TREND IN PHARMACEUTICAL TECHNOLOGY

Corresponding Author

KIRTI DESHMUKH

Prin. K. M. Kundnani College of Pharmacy, Cuffe Parade, Colaba, Mumbai 400 005, India.

Co Authors

SUSHILKUMAR S. PODDAR

Prin. K. M. Kundnani College of Pharmacy, Cuffe Parade, Colaba, Mumbai 400 005, India.

ABSTRACT

SPMs are at the forefront of the rapidly developing field of novel drug delivery technology and tissue engineering technology. This technology holds a great promise for reaching the goal of controlled and site-specific drug delivery and hence, have attracted wide attention of researchers. This review presents a broad treatment of SPMs delivery system discussing the principles and preparation methods. Appropriate analytical techniques for characterization of SPMs like Particle size and its distribution, surface morphology, porosity, density etc are covered. Advantages, limitations and their possible remedies of the MDS are also mentioned. The aspect of route of administration and release mechanisms are also touched upon. If appropriately investigated, SPMs may navigate into new vistas in the therapy of complex diseases and also new opportunities for biomaterial designs for bone related repair, vascular grafts and implants.

KEY WORDS

Solid porous microspheres, topical, oral, grafts

INTRODUCTION

The area of drug delivery technology is evolving rapidly and becoming highly competitive day by day. The developments in the delivery systems are being utilized to optimize the efficacy and the cost effectiveness of the therapy. The challenges faced by drug development industry are:

- Sustained release technology for reducing irritation of a wide range of APIs and other skin care actives thereby increasing patient/client compliance and results
- Enhanced formulation stability ensuring long term product efficacy and extended shelf life.
- Superior skin feel and exceptional product esthetics.

Carrier technology is the potential solution to these challenges. These include nanoparticles, liposomes, microspheres etc which modulate absorption and release characteristics of the drug. Liposomes suffer from lower payload, difficult formulation, limited chemical stability and microbial instability so the addition of preservatives is required. Microspheres cannot usually control the release rate of actives. Once the wall is ruptured the actives contained within microspheres will be released. SLNs are one of the newer colloidal drug delivery systems and may offer benefits in almost all areas of topical drug delivery. But nanomaterials can gain access to the blood stream following inhalation or ingestion, and possibly also via skin absorption, especially if the skin is damaged. Once in the blood stream, nanomaterials can be transported around the body and are taken up by organs and tissues including the brain, heart, liver, kidneys, spleen, bone marrow and nervous system. Nanoparticles may modify the way cells behave[1]. In contrast to these solid porous microspheres(SPMs) have higher payload, compatibility with most of the vehicles and ingredients, stability up to temperature of 130^0C & over a range of pH 1 to 11, self sterilizibility as average pore size is 0.25µ. in addition it has well characterized toxicologic profile and has been accepted amongst regulatory authorities[2]. Their use is also being investigated for oral products.

This article provides a brief introduction to the various aspects of the structure, development, applications and future of SPMs. It is not intended to be exhaustive, but rather only introductory to the vast amount of research that has been done and the large number of opportunities that exist in the field of SPMs.

WHAT IS SPM

SPMs are solid porous microspheres of particle size range 3-300µm having myriad of intraparticulate voids. A polymeric particle less than 50 microns in diameter is not palpable and thus makes for increased compliance with the use of the product. By contrast, if the particle size is 200 microns or more, the product can give a scrubbing action resulting in gentle exfoliation[3]. The particles used in the current crop of commercial prescription products range from approximately 5 to 50 micron. SPMs consisting of non-collapsible structures with porous surface through which active ingredients are released in a controlled manner[2]. Depending upon the size, the total pore length may range up to 10 ft and pore

density up to 1 ml/g for extensive drug retention.

PREPARATION METHODS

Various polymers can form SPMs. These include Ethyl Cellulose, Eudragit RS100, Polystyrene and PHEMA. In addition to actives, some SPMs contain plasticizers that help stabilize their structure [4, 5, 6, 7].

Examples of SPM based delivery systems includes incorporation of various actives such as Benzoyl Peroxide[4], Ketoprofen[5], Retinol[3], Fluconazole[8], Ibuprofen[9], Tretinoin[10], Flurbiprofen[11], Mupirocin[12], Dicyclomine[13] and Fluocinolone Acetonide[14]. Most liquid or soluble ingredients can be entrapped in the particles.

1. Preparation of SPMs

Drug loading in SPMs can take place in two ways, one-step process or by two-step process; based on physico-chemical properties of drug to be loaded.

1. Bottom up approach (One step process)
2. Top down approach (Two step process)

If the drug is typically an inert non-polar material, will create the porous structure. It is called porogen. It should have following properties:

1. It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
2. It should be water immiscible or at most only slightly soluble.
3. It should be inert to monomers.
4. It should be stable in contact with polymerization catalyst and conditions of polymerization [15].

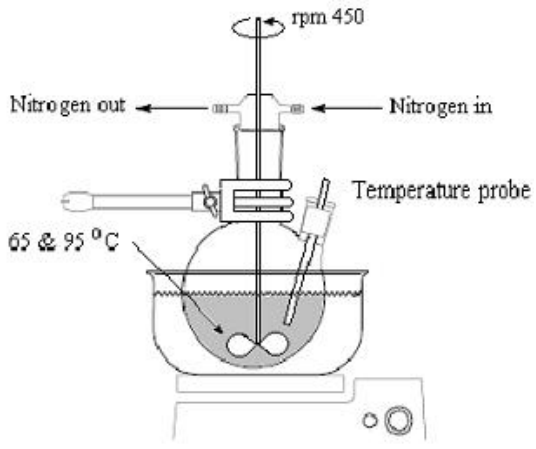
1.1 Bottom-up approach: starting with monomer

SPMs are conveniently prepared by liquid-liquid suspension polymerization.

Suspension polymerization assembly

Figure 1

Suspension polymerization assembly used for the preparation of SPMs



In this approach, the monomer is polymerized into microparticles in the presence of a porogen either by a free radical suspension polymerization or by concentrated emulsion polymerization. Typically, an emulsified bi-phasic system consisting of a dispersed phase is set-up, which includes the monomer and a continuous phase. The polymerization is initiated using free radicals or irradiation. Finally, the porogenic liquid is removed and highly porous particles are formed. Porogen drug, which neither hinders the polymerization nor become activated by it and which is stable to free radicals is entrapped with one-step process. When the material is sensitive to the polymerization conditions, polymerization is performed using substitute porogen. The porogen is then removed and replaced by contact absorption assisted by solvents to enhance absorption rate [16, 17].

The various steps in the preparation of SPMs are summarized as:

1. Selection of monomer or combination of monomers
2. Formation of chain monomers as polymerization begins
3. Formation of ladders as a result of cross linking between chain monomers
4. Folding of monomer ladder to form spherical particles
5. Agglomeration of microspheres, which give rise to formation of bunches of microspheres
6. Binding of bunches to form SPMs

The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores. In some cases an inert liquid immiscible with water but completely miscible with monomer is used during the polymerization to form the pore net-work. After the polymerization the liquid is removed leaving the porous microspheres. Some-times solvent may be used for faster and efficient in-corporation of the active substances [18].

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.

1.2 Top-down approach: starting with preformed polymer

This is a two-step process wherein the polymer along with the active, plasticizer and diffusible substance (*Porogen*) is poured into an external aqueous phase, which typically consists of a stabilizer such as polyvinyl alcohol. This system is continuously stirred and maintained at a high temperature if required. Diffusion of the porogen into the external medium results in highly porous microparticles called 'SPMs'. To prepare the inner phase, Eudragit RS 100 is dissolved in ethyl alcohol. Then, drug is added to solution and dissolved under ultrasonication at 35^{o}C. Triethylcitrate (TEC), which was added at an amount of 20% of the polymer in order to facilitate the plasticity [19]. The inner phase is poured into the PVA (Polyvinyl alcohol) solution in water (outer phase) [20]. Following 60 min of stirring, the mixture is filtered to separate the SPMs. The SPMs are dried in an air-heated oven at 40^{o}C for 12 h and weighed to determine production yield (PY). In this addition of the drug–polymer–ethanol phase to the aqueous medium resulted in the immediate formation of discrete coacervate-like oil droplets of the ethanol solution. The droplets solidified to form well-shaped, rigid microspheres on diffusion of the ethanol from the droplets. Ethanol and water counter-diffuse out of and into the oil droplets,

respectively. The diffused water within the droplets may decrease the drug and polymer solubilities. Both components co-precipitate and continued ethanol diffusion results in further solidification, producing matrix-type microspheres.

Similarly ethyl cellulose is dissolved in dichloromethane and poured into the PVA solution in water. After stirring for 6hrs SPMs are formed and filtered through Millipore.

In another method, drug loading is done after the formation of SPMs. In this method, blank SPMs and drug solution in ethanol is added. Bottles are arranged on roller mill and mixed for 1hr. The mixture is dried in an oven at 65 °C for 2.5 h. This process is repeated for a second entrapment step and the drying process is held at 50 °C for 24 h.

CHARACTERIZATION

1. ***Particle size and size distribution***

Particle size and size distribution are evaluated using either an optical microscope or an electron microscope. This is an extremely crucial step, as the size of the particles greatly affects the texture of the formulation and its stability. 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 SPMs 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 SPMs of different particle size will be plotted against time to study effect of particle size on drug release [21].

Figure 2

2. ***Morphology and Surface topography of SPMs***

For morphology and surface topography, various techniques have been used like photon correlation spectroscopy (PCS), Scanning electron microscopy (SEM), transmission electron microscopy (TEM) etc. SEM is used widely for which prepared SPMs are coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the SPMs is studied [22].

3. ***Determination of loading efficiency and production yield***

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

$$\text{Loading Efficiency} = \frac{\text{Actual drug content in SPMs}}{\text{Theoretical drug content}} \times 100 \quad \text{Eqn. No. 1}$$

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 SPM obtained [23].

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

4. ***Determination of true density***

The true density of SPMs can be measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations.

5. ***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 SPMs 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 SPMs [24].

Porosity parameters of SPMs 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. The pore diameter of SPMs can be calculated by using Washburn equation [25].

$$D = \frac{-4\gamma\cos\theta}{P} \qquad \text{(Eqn. no. 3)}$$

Where D is the pore diameter (μm); γ the surface tension of mercury (485 dyn cm^{-1}); θ the contact angle (130°); and P is the pressure (psia).

Total pore area (A_{tot}) was calculated by using equation,

$$A_{tot} = \frac{1}{\gamma\cos\theta}\int_0^{V_{tot}} P.dV \qquad \text{(Eqn. no. 4)}$$

Where P is the pressure (psia); V the intrusion volume (mL g^{-1}); V_{tot} is the total specific intrusion volume (mL g^{-1}).

The average pore diameter (Dm) was calculated by using equation,

$$D_m = \frac{4V_{tot}}{A_{tot}} \qquad \text{(Eqn. no.5)}$$

Envelope (bulk) density (ρ_{se}) of the SPMs was calculated by using equation,

$$\rho_{se} = \frac{W_s}{V_p - V_{Hg}} \qquad \text{(Eqn. no. 6)}$$

Where Ws is the weight of the SPM sample (g); V_p the empty penetrometer (mL); V_{Hg} is the volume of mercury (mL).

Absolute (skeletal) density (ρ_{sa}) of SPMs was calculated by using equation,

$$\rho_{sa} = \frac{W_s}{V_{se} - V_{tot}} \qquad \text{(Eqn. no.7)}$$

Where V_{se} is the volume of the penetrometer minus the volume of the mercury (mL).

Finally, the percent porosity of the sample was found from equation,

$$\text{Porosity (\%)} = \left(1 - \frac{\rho_{se}}{\rho_{sa}}\right) X\ 100 \qquad \text{(Eqn. no. 8)}$$

Pore morphology can be characterized from the intrusion–extrusion profiles of mercury in the SPMs as described by Orr [26].

6. *Compatibility studies*

The drug-excipient compatibility studies are carried out in order to ensure that there is no inadvertent reaction between the two when formulated into a dosage form. These studies are commonly carried out by recording the differential scanning calorimetry (DSC) of both the chemicals viz., API and excipient individually and also together and checking for any addition or deletion of any peaks or troughs. 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. Infrared (IR) spectroscopy can also reveal the incompatibilities between the chemical moieties. Compatibility of drug with reaction adjuncts can also be studied by thin layer chromatography (TLC). Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC) [27, 28, 29].

7. *Polymer/ Monomer composition*

Factors such as particle size, drug loading, and polymer composition govern the drug release from SPMs[30, 31]. Polymer composition of the SPM Drug Delivery system can affect partition coefficient of the entrapped drug between the vehicle and the

SPM system and hence have direct influence on the release rate of entrapped drug. Release of drug from SPM 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. Polymers with varying electrical charges or degrees of hydrophobicity or lipophilicity may be prepared to provide flexibility in the release of active ingredients. Various monomer combinations will be screened for their suitability with the drugs by studying their drug release profile.

8. *Resiliency*

Resiliency (viscoelastic properties) of SPMs 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 SPMs is studied and optimized as per the requirement by considering release as a function of cross-linking with time.

9. *Drug Release*

Dissolution profile of SPMs 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.

9.1Release mechanisms

By proper manipulation of the aforementioned programmable parameters, SPMs can be designed to release given amount of active ingredients over time in response to one or more external triggers.

(i) Pressure

Rubbing/ pressure applied can release active ingredient from SPMs onto skin. SPM system releases the entrapped material when pressurized; the amount released depends upon various characteristics of the sponge. By varying the type of material and different process variables, the SPM best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing SPMs showed much more softening effect. The duration of emolliency was also much more for the SPM systems.

(ii) Temperature change

Some entrapped actives can be too viscous at room temperature to flow spontaneously from SPMs onto the skin. Increased in skin temperature can result in an increased flow rate and hence release. So it is possible to modulate the release of substances from the SPM by modulation of temperature. For example, viscous sunscreens were found to show a higher release from SPMs when exposed to higher temperatures; thus a sunscreen would be released from a SPM only upon exposure to the heat from the sun.

(iii) Solubility

SPMs 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 SPMs and the outside system and the ability to swell the microspore network [32].

SAFETY

Most polymers used in the formulation are inert and the SPMs' inability to pass through the stratum corneum enhances their safety. Furthermore, it reduces the irritation of various actives, and thereby demonstrates its harmlessness[33, 34].

LIMITATIONS

Use of organic solvents poses threats, such as toxicity and flammability. Traces of residual monomers in bottom- up approach can be toxic and dangerous to health. But these limitations can be overcome by proper quality control measures coupled with optimization and standardization of procedures e.g, post manufacture washing.

APPLICATIONS

SPMs can be utilized in variety of applications. Several patents have reported that it can be used as an exipient due to its high loading capacity and sustained release ability. It is used mostly for topical and recently for oral administration. It offers the formulator a range of alternatives to develop drug and cosmetic products. SPMs 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[35, 59]. Over-the-counter products that incorporate MDS include numerous moisturizers, specialized rejuvenative products, and sunscreens. Currently, prescription products employing this technology include Retin-A Micro[R], Neobenz Micro[R], Carac[R], and Epiquin Micro[R]. The indications for these drugs include acne vulgaris, actinic keratoses (AK), and pigmentary changes.

1. Topical drug delivery

1.1 Sunscreens

Genetically engineered melanin is incorporated in SPMs, melanosponge-α to spread it evenly hence give protection against UV-A and UV-B radiation[36].

1.2 Anti-acne

Irritation is the common side effect of many anti-acne actives. Controlled release of actives would help to overcome it. Part of the irritation in tretinoin products is attributable to the organic solvents required to dissolve the active ingredient into the vehicle cream or gel. Perhaps more importantly, the biologic effects of retinoids result in cutaneous changes known as retinoid dermatitis. Separating retinoid dermatitis from clinical efficacy against acne lesions has been the focus of much work [37]. 0.1% and 0.04% tretinoin is entrapped in MDS for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/ glycol dimethacrylate cross-polymer porous microspheres to enable inclusion of the active ingredient, tretinoin, in an aqueous gel. It has been marketed as Retin-A-Micro by Ortho-Mcneil pharmaceutical [38]. In a 21 day cumulative irritancy study and a split face study, SPM formulation showed a reduced level of systemic absorption of tretinoin ranging from 25% - 40% reduction helping to explain the improved tolerability. Numerous studies have been conducted and published comparing the tolerability of various retinoids : tazarotene, Adapalene [39, 40, 41, 42, 43].

Degree of irritancy due to Benzyl Peroxide is thought to be related to its concentration in the skin, hence Benzyl Peroxide was one of the earlier topical products incorporated into MDS. Animal and human irritancy studies verify that the use of MDS with

Benzyl Peroxide reduce the irritation profile through more prolonged release into and reduced permeation through the skin. Ultimately, a commercial Benzyl Peroxide formulation was developed using methylacrylate MDS (NeoBenz Micro, SkinMedica, Carlsbad, CA). To demonstrate the efficacy and tolerability of this new formulation, a comparison study was conducted using a 5.5% Benzyl Peroxide formulation incorporating MDS and a traditional, commercially popular 6% Benzyl peroxide gel. The tolerability data favored SPM formulation with 38% of the subjects rating their satisfaction as excellent in the MDS group [44]. Reports by other workers have also supported reduction in irritancy of Benzyl Peroxide by way of MDS [45, 46, 47, 58].

1.3 Anti-fungals

els containing fluconazole SPMs showed extended drug release and reduced irritation as compared to conventional fluconazole gels.

2. Oral Delivery

A SPM system offers the potential to hold active ingredients in a protected environment and provide controlled delivery of oral medication to the lower gastrointestinal (GI) tract, where it will be released upon exposure to specific enzymes in the colon. In oral applications, the SPM system has been shown to increase the rate of solubilization of poorly water-soluble drugs by entrapping such drugs in the SPM system's pores. Because these pores are very small, the drug is in effect reduced to microscopic particles and the significantly increased surface area thus greatly increases the rate of solubilization. Also the time taken by the SPMs to traverse the large and small intestine is also increased, therefore the amount of the drug that is absorbed is also increased.

In SPMs prepared using ethanol to dissolve drug and polymer, variation in the ratios of drug and polymer gave the control over porosity of the particle and drug release properties are fitted to Higuchi model [48].

Ketoprofen and flurbiprofen SPMs produce mechanically strong tablets due to plastic deformation of sponge-like structure.

3. Grafts and implants

Biodegradable materials with autologous cell seeding have attracted much interest as potential cardiovascular grafts. However, pretreatment of these materials requires a complicated and invasive procedure that carries the risk of infection. To avoid these problems, biodegradable graft material containing collagen SPM was developed that would permit the regeneration of autologous vessel tissue. Poly (lactic-co-glycolic acid) as a biodegradable scaffold was compounded with collagen SPM to form a vascular patch material. It showed good histologic findings and durability with and without pre-cellularization. This patch shows promise as a bioengineered material for promoting in situ cellularization and the regeneration of autologous tissue in cardiovascular surgery [49, 55].

A thin biodegradable hybrid mesh of synthetic poly (DL-lactic-co-glycolic acid) (PLGA) and naturally derived collagen was used for three-dimensional culture of human skin fibroblasts. The hybrid mesh was constructed by forming web-like collagen SPMs in the openings of a PLGA knitted mesh. The behaviors of the fibroblasts on the hybrid mesh and PLGA knitted mesh were compared. The efficiency of cell seeding was much higher and the cells grew more quickly in the hybrid mesh than in the PLGA mesh. The fibroblasts in the

PLGA mesh grew from the peripheral PLGA fibers toward the centers of the openings, while those in the hybrid mesh also grew from the collagen SPMs in the openings of the mesh resulting in a more homogenous growth. The proliferated cells and secreted extracellular matrices were more uniformly distributed in the hybrid mesh than in the PLGA mesh. Histological staining of in vitro cultured fibroblast/mesh implants indicated that the fibroblasts were distributed throughout the hybrid mesh and formed a uniform layer of dermal tissue having almost the same thickness as that of the hybrid mesh. However, the tissue formed in the PLGA mesh was thick adjacent to the PLGA fibers and thin in the center of the openings. Fibroblasts cultured in the hybrid mesh were implanted in the back of nude mouse. Dermal tissues were formed after 2 weeks and became epithelialized after 4 weeks. The results indicate that the web-like collagen SPMs formed in the openings of the PLGA knitted mesh increased the efficiency of cell seeding, improved cell distribution, and therefore facilitated rapid formation of dermal tissue having a uniform thickness. PLGA–collagen hybrid mesh may be useful for skin tissue engineering. Human skin fibroblasts were cultured in a thin biodegradable mesh having a hybrid structure with web-like collagen SPMs formed in the openings of a PLGA knitted mesh. More fibroblasts adhered and proliferated more quickly in the hybrid mesh than in the PLGA knitted mesh. The collagen SPMs in the hybrid mesh facilitated cell seeding, uniform cell distribution and, therefore, the formation of homogenous dermis tissue. The PLGA knitted mesh served as a skeleton, reinforced the hybrid mesh, maintained the integrity of the forming tissue, and resulted in easy handling. PLGA–collagen hybrid mesh could be a useful candidate as a porous scaffold for skin tissue engineering [50, 51, 53].

4. Bone substitutes

Bone-substitute compounds were obtained by mixing pre-polymerised powders of polymethylmethacrylate and liquid methylmethacrylate monomer with two aqueous dispersions of a-tricalcium phosphate (a-TCP) grains and calcium-deficient hydroxyapatite (CDHA) powders. The final composites appeared to be porous. Osteoconductivity and osteoinductivity of the final composites were tested in vivo by implantation in rabbits. Formation of new trabecular bone was observed inside the pores where the inorganic powders had been placed. The material produced shows a good level of biocompatibility, good osteointegration rate and osteogenetic properties[52].

FUTURE PERSPECTIVE

Today, as we realize the immense advantages offered by the nano-size, the micro sized products are likely to be outdated. The nanosized particles have a very high surface area to size ratio and a greater potential to modulate the release of actives compared to micro-sized particles. While inorganic nanosponges have many applications in electronics, the first pharmaceutical nanosponges based on cross linked cyclodextrins have been reported by Roberta Cavalli et al.[60] and Swaminathan et al.[61] These are nanosized, highly porous materials composed of beta-cyclodextrins cross linked with carbonate bonds.

SPMs have opened a new vista in the field of cosmetics. Colours are entrapped in SPMs and are used in lipsticks, rouge, etc. SPMs also possess oil absorbing ability. Incorporating them in talcum powders & compacts, absorbs excess surface oil, prevents shine without any powdery residue and gives all day matte effect to skin.

CONCLUSION

In Conclusion, the use of SPMs has improved the drug delivery of active ingredients for several prescription products in dermatology. Depending upon the active ingredient involved, the benefits include reduced irritation, improved performance, reduced drug consumption, and decreased dosing frequency. Further improvements in formulations and drug delivery by these mechanisms, may explore the new frontiers in giving us better tools to care for patients.

REFERENCES

1. Georgia Miller, Cosmetics, nanotoxicity and skin penetration – a brief summary of the toxicological and skin penetration literature, Friends of the Earth, October 2006, pp 1-8.
2. Nacht S, Katz M. The Microsponge: A novel topical programmable delivery system. Topical Drug Delivery Formulations. New York, NY: Marcel Dekker: 229-325(1990).
3. DiSapio AJ. Microporous entrapment polymers offer new options for formulators. Global Cosmetic Industry, Sept. (1999).
4. M. Jelvegiri, A. Nokhodchi et al., The microsponge delivery system of benzoyl peroxide: Preparation, characterization and release studies, Int. J. Pharm, 308:124-132(2006)
5. C. Tansel, T. Baykara et al., The effects of pressure and direct compression on tabletting of microsponges, Int. J. Pharmaceutics, 242:191-195(2002)
6. E. Ruckenstein, L. Hong, Chem. Mater., 4:1032-1037(1992)
7. V. Chadawar, J. Shaji, Current Drug Delivery, 4, 123-129 (2007).
8. J. D'Souza, H. More et al., Proceedings of the 1st Indo-Japanese International Conference on Advances in pharmaceutical Research and Technology, Book of Abstracts, 94(2005)
9. Y. Kawashima, Y. Ito et al., Control of prolonged drug release and compression properties of ibuprofen microsponges with acrylic polymer, Eudragit RS, by changing their interparticle porosity, Chem. Pharm. Bull.,40:196-201(1992)
10. J. Nyirady, M. Bennett, Advancement of tretinoin through the microsphere technology, Cosmet. Dermatol, 14:22-24(2001).
11. M. Orlu, A. Araman et al., Design and evaluation of colon specific drug delivery system containing flurbiprofen microsponges, Int. J. Pharm., 318:103-117(2006)
12. Netal Amrutiya, Amrita Bajaj and Madhu Madan (2009). Development of Microsponges for Topical Delivery of Mupirocin, AAPS PharmSciTech, 10(2): 402-409.
13. Vikas Jain, Ranjit Singh. Dicyclomine-loaded Eudragit based Microsponge with Potential for Colonic Delivery: Preparation and Charactrization. Tropical Journal of Pharmaceutical Research, 9(1):67-72(2010).
14. John I D'souza, Harinath N More. Topical Anti-Inflammatory Gels of Fluocinolone Acetonide Entrapped in Eudragit Based Microsponge Delivery System. Research Journal of Pharm. And Tech, 1(4):502-506(2008).
15. Aritomi H, Yamasaki Y, Yamada K, Honda H and Koshi M. Development of sustained release formulation of chlorpheniramine maleate using powder coated microsponges prepared by dry

impact blending method. Journal of Pharmaceutical Sciences and Technology,56(1): 49-56(1996).
16. Won, Richard (Palo Alto, CA) United States Patent 5145675, Two step method for preparation of con-trolled release formulations (1992).
17. Won, Richard, United States Patent 4690825, Method for delivering an active ingredient by controlled time release utilizing a novel delivery vehicle which can be prepared by a process utilizing the active ingredient as a porogen, (1987).
18. Vyas SP, Khar RK, Targeted and Controlled Drug Deli-very-Novel Carrier System: New Delhi, CBS Publication, 453(2002)
19. Y. Kawashima, T. Iwamoto, T. Niwa, H. Takeuchi, T. Hino, Role of the solvent-diffusion rate modifier in a new emulsion solvent diffusion method for preparation of ketoprofen microspheres. Microencapsulation, 10:329-340(1993).
20. Tansel C¸ omog˘lu, Nurs¸ in Go¨nu¨ l, Tamer Bayka-ra, Preparation and in vitro evaluation of modified release ketoprofen Microsponges, Il Farmaco, 58:101-106(2003).
21. Martin A., Swarbrick J. & Cammarrata A., In: Physical Pharmacy- Physical Chemical Principles in Pharma-ceutical Sciences. 3rd Ed., .527(1991).
22. Emanuele A. D., Dinarvand R., Preparation, Characterization and Drug Release from Thermo responsive Microspheres. Int. J. Pharm, 237-242(1995).
23. Kilicarslan, M., Baykara, T. The effect of the drug/polymer ratio on the properties of Verapamil HCl loaded microspheres. Int. J. Pharm, 252:99–109(2003).
24. Poresizer Model No. 9310, Micromeritics Instrument Corp., Nor-cross , Georgia .
25. Washburn, E.W., Note on a method of determining the distribution of pore sizes in a porous material. Proc. Natl. Acad. Sci. U.S.A.7:115–116(1921).
26. Orr Jr., C., Application of mercury penetration to material analysis. Powder Technol.3:117–123(1969).
27. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y, Furuyama S. Characterization of polymorphs of tranilast anhydrate and tranilast monohydrate when crystallized by two solvent change spherical crystallization techniques. J. Pharm. Sci. 81:472-478(1991).
28. Bodmeier R, Chen H. Preparation and characterization of microspheres containing the anti-inflammatory agents, indomethacin, ibu-profen, and ketoprofen. J. Control. Release, 10:167-175(1989).
29. Jones DS, Pearce KJ. Investigation of the effects of some process variables on, microencapsulation of propranolol HCl by solvent evaporation method. Int. J. Pharm, 118: 99-205(1995).
30. Wakiyama N, Juni K, Nakano M. Preparation and evaluation in vitro of polylactic acid microspheres containing local anesthetic. Chem. Pharm. Bull. (Tokyo), 29:3363-3368(1981).
31. Barkai A, Pathak V, Benita S. Polyacrylate (Eudragit retard) microspheres for oral controlled release of nifedipine. I. Formulation design and process optimization. Drug Dev. Ind. Pharm, 16:2057-2075(1990).
32. Shah V.P., Determination of In-vitro Release from Hydrocortisone Creams. Int. J.Pharm., 53: 53-59(1989).
33. Sato T, Kanke M, Schroeder G, Deluca P. Porous biodegradable microspheres for controlled drug delivery. I: Assessment of processing conditions and solvent removal techniques. Pharm Res., 5:21 - 30(1988).
34. Draize J.H., Woodard J & Calvary H.O., Methods for the Study of Irritation &

Toxicity of Substances Applied Topically to the Skin & Mucous Membranes. Journal of Pharmacology & Experimental Therapeutics., 82: 377-389(1944).
35. Khopade A. J., Jain Sanjay, Jain N.K. The Microsponge. Eastern Pharmacist. March 1996; 49-53.
36. V.B. Patravale, S.D. Mandawgade. Novel cosmetic delivery systems: an application update. Int.J.Cosmetic Sci., 30:19-33(2008).
37. Leyden J, Grove G, Zerweck C. Facial tolerability of topical retinoid therapy. J Drugs Dermatol.,3:641-651(2004).
38. Summary Basis of Approval Retin-A Micro 0.1%. Available at: www.accessdata.FDA.com. Accessed April 5, 2006.
39. Leyden JJ, Tanghetti EA, Miller B, Ung M, Berson D, Lee J. Once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.1% microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. Cutis.,69(suppl):12-19(2002).
40. Cunliffe WJ, Danby FW, Dunlap F, Gold MH, Gratton D, Greenspan A. Randomised, controlled trial of the efficacy and safety of adapalene gel 0.1% and tretinoin cream 0.05% in patients with acne vulgaris. Eur J Dermatol.,12:350-354(2002).
41. Egan N, Loesche MC, Baker MM. Randomized, controlled, bilateral (split-face) comparison trial of the tolerability and patient preference of adapalene gel 0.1% and tretinoin microsphere gel 0.1% for the treatment of acne vulgaris. Cutis.,68(suppl):20-24(2001).
42. Thiboutot D, Gold MH, Jarratt MT, et al. Randomized controlled trial of the tolerability, safety, and efficacy of adapalene gel 0.1% and tretinoin microsphere gel 0.1% for the treatment of acne vulgaris. Cutis.,68(suppl):10-19(2001).
43. Kakita L. Tazarotene versus tretinoin or adapalene in the treatment of acne vulgaris. J Am Acad Dermatol.,43:S51-54(2000).
44. Smith S, Kempers S. Multicenter, randomized, evaluator-blinded, parallel group comparison study of the safety and efficacy of microentrapped benzoyl peroxide cream vs. benzoyl peroxide gel in mild to moderate acne vulgaris. Presented as a poster at: The 64th Annual Meeting of the American Academy of Dermatology 2006
45. Yazici, E.; Kas, H. S.; Hincal, A. A. Microsponges. Farmasotik Bilimler Dergisi (Turkey), 19,3:121-128(1994).
46. Wester R., Patel R., Natch S., Leyden J., Melendres J., Maibach H. Controlled release of benzoyl peroxide from a porous microsphere polymeric system can reduce topical irritancy. J. Am. Acad. Derm., 24:720-726(1991).
47. John I. D'souza, Jagdish K. Saboji, Suresh G. Killedar, Harinath N. More "Design and Evaluation of Benzoyl Peroxide Microsponges to Enhance Therapeutic Efficacy in Acne Treatment", Accepted for presentation in 20th FAPA Congress, Bangkok , Thailand , Nov 30-Dec 3, 2004 .
48. Kawashima Y., Niwa T., Takeuchi H., Hino T., Itoh Y. Control of Prolonged Drug Release and Compression Properties of Ibuprofen Microsponges with Acrylic Polymer, Eudragit RS, by changing their Intraparticle Density., Chem. Pharm. Bull., 40(1):196-201(1992).
49. Shigemitsu Iwai MD, Yoshiki Sawa MD, Hajime Ichikawa MD, Satoshi Taketani MD, Eiichiro Uchimura PhD, Guoping Chen PhD, Masayuki Hara PhD, Jun MiyakePhD and Hikaru Matsuda MD. Biodegradable polymer with collagen microsponge serves as a new

bioengineered cardiovascular prosthesis. Journal of Thoracic and Cardiovascular Surgery,128(3):472-479(2004).
50. Guoping Chen, Takashi Sato, Hajime Ohgushi, Takashi Ushida, Tetsuya Tateishi, Junzo Tanaka. Culturing of skin fibroblasts in a thin PLGA–collagen hybrid mesh, Biomaterials, 26:2559–2566(2005).
51. Chen G, Ushida T, Tateishi T. A Biodegradable Hybrid Sponge Nested With Collagen Microsponges. J Biomed Mater Res., 51:273–9(2000).
52. Dario T. Berutoa, Rodolfo Bottera, Milena Fini. The effect of water in inorganic microsponges of calcium phosphates on the porosity and permeability of composites made with polymethylmethacrylate. Biomaterials, 23:2509–2517(2002).
53. Akihiro Kanematsua,b, Akira Maruic, Shingo Yamamotob, Makoto Ozekia, Yoshiaki Hiranod, Masaya Yamamotoa, Osamu Ogawab, Masashi Komedac, Yasuhiko Tabata, Type I collagen can function as a reservoir of basic fibroblast growth factor, Journal of Controlled Release, 99:281–292(2004).
54. Koral Embil V. P., OTC External Analgesic Cream / Topical Analgesic-Anti-inflammatory, Counterirritant utilizing the Microsponge Delivery System (MDS) for controlled release of actives, UK Patent Application No: 0101058.6 dated 15 Jan 2000 .
55. Shigemitsu Iwai, Yoshiki Sawa, Satoshi Taketani, Kei Torikai, Koichiro Hirakawa, and Hikaru Matsuda. Novel Tissue-Engineered Biodegradable Material for Reconstruction of Vascular Wall. Ann Thorac Surg, 80:1821–8(2005).
56. A.A. Date, B. Naik, M.S. Nagarsenker. Novel Drug Delivery Systems: Potential in Improving Topical Delivery of Antiacne Agents. Skin Pharmacology and Physiology,19:2-16(2006).
57. Newton D. W. Biotechnology Frontier: Targeted Drug Delivery. US Pharmacist,16:38-39, 43-44, 46-48, 50-51(1991).
58. D'souza J. I. et al, In-vitro Antibacterial and Skin Irritation Studies of Microsponges of Benzoyl Peroxide, Indian Drugs,38:7(2001).
59. L. Delattre and I. Delneuville. Biopharmaceutical aspects of the formulation of dermatological vehicles. Journal of the European Academy of Dermatology and Venereology. October,5:S70(1995).
60. R. Cavalli, W. Tumiatii et al. J.Inclusion Phenomena and Macrocyclic Chemistry, 56:209-213(2006).
61. S. Swaminathan, S. Torne etal.J.Inclusion Phenomena and Macrocyclic Chemistry, 2007;57:89-94.