Review Article

Pharmaceutical and biotechnological applications of microsponges as novel nano technological drug delivery system

Shankar B. Kalbhare, Atish B. Velhal, Mandar J. Bhandwalkar, Rupali V. Jadhav, Akash S. Nalawade*

Department of Pharmaceutics, YSPM's, Yashoda Technical Campus, Satara, India 415003

Received: 19 January 2021

Revised: 13 July 2021

Accepted: 25 July 2021

Abstract

Microsponges drug delivery system composed of porous microsphere. They are tiny sponges-like spherical particles with a larger porous surface. Moreover they may enhance stability, reduce side effect and modify drug release favorably. Microsponges technology has many favorable characteristics, which make it a versatile drug delivery system. Microsponge system are based on microscopic, polymer-based microsphere that can suspend or entrap a wide variety of substance, and it can 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 substance out of the sphere. Microsponges are designated to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effect, and modify drug release.

Keywords: Controlled release, Healthcare system, Microsponges, Microsponges Delivery System

Introduction

One of the major challenges in pharmaceutical industry is to control the release of a drug at the specific organ in the body. Now days there are various systems are for targeting the delivery of a drug to a specific organ eg. transdermal delivery system (Kalbhare et al., 2020). But the transdermal system are not proven for the delivery of the drugs which target the skin. For gastric cancer, there are no systems available which give local effect along with the controlled release of drug. Therefore it is a challenging area for the research work. Microsponges is a type of drug delivery system that enables controlled release and transport of active ingredients too the target organ.

The microsphere drug delivery system was invented by Won in 1987, and the first patent was assigned to Advanced Polymer System. This industry formulated different types of procedures which are applied in the cosmetic and pharmaceutical industry (Jadhav et al., 2013). Microsphere drug delivery systems are

polymeric delivery systems composed of porous microspheres. They are small sponge like spherical structures that consist of a countless number of internally connected voids with a larger pores. It consists of non-collapsible structures. Moreover, they increase stability, reduce side effects and transform drug release. Because of the larger porous surface, the drug is released in specific manner. Microsponges have a number of favourable characteristics for targeted drug delivery. Microsphere drug delivery is based on polymeric microscopic spheres that can entrap and suspend wide variety of substances, and then they can be incorporated into a formulation such as a cream, gel, or powder. Microsphere drug delivery system can increase the efficacy, safety and product stability and improve the properties of the formulation in an effective manner (Jadhav et al., 2013; Kaity et al., 2010). Depending upon the size, pore length and pore volume, the microsphere drug delivery system releases the active ingredient. The release of the active ingredient depends on the rubbing, temperature and pH. Microsponges have the ability to absorb the load of polymers and active ingredients in the particles on their surface. Mostly microsphere systems are often used in the transdermal route (Mandava et al., 2012; Barkai et al., 1990)

*Address for Corresponding Author:

Akash Shivaji Nalawade
Department of Pharmaceutics,
YSPM's Yashoda Technical Campus,
Satara (India) 415003
Email: kirankal786@gmail.com

DOI: <https://doi.org/10.31024/apj.2021.6.4.1>

2456-1436/Copyright © 2021, N.S. Memorial Scientific Research and Education Society. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

The average size of the microsponges delivery system is in the range 5µm to 300µm in diameter size and a typical 25µm to 250000µm. The surface size of the microsponges varies 20 to 500 µm/g and pore volume range 0.1 to 0.3cm/g. This results in a large reservoir within each microsphere, which can be loaded with up to its own weight of active agent (Jadhav et al., 2013; Kaity et al., 2010; Embil et al., 1996). These pores can entrap large range of drug and other ingredients like emollients, fragrances, essential oils, sunscreens, anti-inflammatory agents. These formulations that can be applied into the targeted region and this entrapped material gets delivered to the skin and controls the release of the drug.

Potential characters of microsphere

Microsponges are stable at pH range from 1-11 and at high temperatures. Microsponges have good compatibility with different type of polymer and ingredients. They also have high entrapment efficiency up to 60-70%. The pore size of microsponges is small so that it prevents the penetration of bacteria. Microsponges do not require sterilization and the addition of preservatives. The system is cost effective and can be used for the long term treatment. The polymeric design of the microsponges is mainly utilized for the controlling the drug release for given period of time and also being used for targeting specific region.

Benefits of microsponges

The microsponges can enhance product performance and also extend the release of drug upto 12 hours. They reduce irritation, increase patient compliance and improve product elegance. Microsponges increase the physical, chemical, thermal stability of drugs and absorb the oil upto 6 times their weight. Because of flexibility of microsponges they can act as novel drug delivery systems. Microsponges are non-irritating, non-mutagenic, non-allergenic and non-toxic. Microsponges allow the incorporation of immiscible products. Microsponges can improve bioavailability of some drugs.

Method of preparation of microsphere

Preparation of Microsponges involves two steps which are liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques or w/o/w emulsion technique that can be based on physico chemical properties of drug.

Liquid-liquid suspension polymerization technique

The porous polymeric microspheres can be prepared by liquid-liquid suspension polymerization method. In this method, immiscible polymers are first dissolved with active moieties in a suitable solvent. The aqueous phase consists of additives like surfactant, suspending agents to form of suspension. The polymerization process is activated by increasing the

temperature. Following this process, the development of reservoir system contributes to the formation of the porous structure. The solvent is then removed and the spherical porous structured microspheres are formed. These formed microspheres are known as microsponges (Burton et al., 2002; Charde et al., 2013). If the drug is not suitable for the one step procedure mentioned above, then two-step process will be used for polymerization.

Quasi-emulsion solvent diffusion

By using quasi-emulsion solvent diffusion technique porous microsponges can be prepared. In this technique, the first phase is prepared by using eudragit and ethyl alcohol. Then, the active ingredient is added slowly in to the above phase and dissolved. The plasticizers like triethylcitrate (TEC) also added to impart plasticity. The internal phase is poured in the external phase which contains PVA and distilled water with continuous stirring for 2 hours. The product is washed and dried in a hot air oven at 40°C for 12 hr (Çomoğlu et al., 2003; Kumari et al., 2016).

w/o/w solvent diffusion

Microsponges can be prepared by double emulsion technique using sodium chloride as a porogenic solution. After that the solution of ethyl cellulose, eudragit and active ingredient in ethanol and dichloromethane is prepared. 1% (w/v) Aqueous solution is prepared using sufficient amount of Span. An aqueous polyvinyl alcohol solution and mucoadhesive polymer is prepared separately and previously prepared w/o emulsion is added to it. This w/o/w emulsion was stirred for 8 hr. The microsponges were obtained by filtration and dried at 60°C in the hot air oven and stored in desiccator till use. A compilation of the advantages and disadvantages of various methodologies used for preparation of microsponges (Table 1).

Drug release mechanism of microsponges

The active moieties are entrapped in porous microspheres. The microsponges consist of an open structure so that active ingredients are free to move through vehicle until equilibrium is attained and vehicle becomes saturated. This results in flow of the drug from the microsphere to the skin. The microsponges are then retained on the surface of the skin and will continue the drug release to the skin and provide a prolonged release for longer period of time. If the drug is freely soluble in the vehicle, the final product will not provide the desired drug release. Therefore, while formulating microsphere, it is important to choose a vehicle which has minimum solubilizing power of the active moieties.

Table 1. A compilation of the advantages and disadvantages of various methodologies used for preparation of microsponges

Method	Advantages	Disadvantages
Liquid-liquid suspension polymerization	Can be suitably modified to one step or two step methods for drug loading	Probable entrapment of unreacted monomers and solvent traces. Non-uniform structure. Requires long time for the reaction of monomers. Requires two-step method for thermosensitive drugs that has low drug loading efficiency
Quasi-emulsion solvent diffusion	No monomer entrapment. Low solvent traces. High drug loading. No exposure of drug to ambient condition. Size of microsponges can be easily controlled by controlling the stirring. Spherical particles	Cannot be used for the loading of water-soluble drugs. Requires long time for the reaction of monomers. Drug should be soluble in a volatile water-soluble solvent
w/o/w emulsion solvent diffusion	Efficient for loading water-insoluble drugs. Can be used to entrap proteins and peptides	Uses water-insoluble surfactants that can be present as residues in the resultant microsponges
Addition of porogen	Highly porous structure with nicely distributed and interconnected pores	May cause disruption in structure
o/o emulsion solvent diffusion	No presence of surfactant traces in microsponges	Requires vigorous washing to remove the traces of organic solvents
Lyophilization	Easy quick reproducible results	May lead to cracking or shrinkage of microparticle
VOAG method	Results in microsponges can be used for targeted drug delivery	Requires reflux conditions
Ultrasound-assisted production	No traces of solvents. Quick and reproducible results	Irregular structure.
Electrohydrodynamic atomization method	Quick reproducible and results	Require cross-linking agents that may be potentially toxic. May lead to the binding of drug molecule to the monomer. Control of size of particle and pores requires expertise.

Microsponges can release the given amount of drug over a period of time. The release is influenced by physicochemical factors like pressure, temperature change and solubility etc.

They are described as follows:

Temperature change

At certain temperature, few entrapped active ingredients become viscous and suddenly get released from microsponges. Increase in temperature of specific region also increases the flow rate and release (Of et al., 2015).

Pressure

When pressure is applied microsponges release the active ingredients at the targeted region (Of et al., 2015).

Solubility

Microsponges are filled with water soluble excipients and they release the drug with water. The release of drug that can be activated by diffusion technique.

pH

pH dependent drug release can be achieved by modifying the coating on the microsphere.

Evaluation of microsphere

Particle size determination

Particle size determination of loaded microsponges can be calculated by optical microscopy. In this sample that can be placed on the slide and mechanical stage. In that mean particle size is calculated by measuring more than 300 particles. For cumulative % drug release of microsponges will be determined by plotting particle size versus time. In the final topical formulation, particles of sizes between 1 nm and 25 µm are required to be used.

Determination of Production yield and Loading efficiency.

Loading efficiency it can be measured by following equation:

$$\text{Loading efficiency} = \frac{\text{Drug Content in Microsphere}}{\text{Drug Content in Microsphere}} \times 100$$

Production yield of microsponges can be calculated by the gravimetric method using following equation

$$\text{Production yield} = \frac{\text{M}_{\text{micro}}}{\text{MRM}}$$

In that,

M_{micro} = Weight of formulated Microsponges.

MRM = Weight of raw materials (Polymer and active ingredient)

All results can be calculated in the triplicates.

Characterization of pore structure

In this case, the volume of pore and diameter are very important in controlling the strength and duration of the effect of the drug. Pore diameter also affects the release of drug from the microsphere system through the vehicle in which all ingredients are distributed. By using mercury intrusion porosimetry the pore size of microspheres, percent porosity, the surface area of pore, percent porosity filled, pore diameters, shape and morphology of the pores, void volume, bulk, and apparent density can be determined.

In-vitro release studies

It is done by using dissolution test apparatus USP XXIII with a modified basket having 5µm mesh size. The dissolution rate can be measured at 37°C and 150 rpm. The dissolution media are chosen in order to maintain sink conditions and solubility of active ingredients. Sample aliquots are withdrawn from the dissolution medium and analyzed by a suitable analytical method (UV spectrophotometer) at regular intervals of time (Naga et al., 2019).

Polymer/Monomer composition

Various parameters such as spheres size, polymer composition, and drug loading govern the drug release from microspheres. The composition of polymer can also influence the partition coefficient of the trapped active ingredient between the microsphere system and the vehicle, thereby directly affecting the release rate of trapped substance. Drug release of microspheres of the different polymer compositions can be studied by the plotting the graph in-between average % drug release versus time. Polymers exhibiting varying degrees of hydrophobicity or lipophilicity or electrical charges may be prepared to impart flexibility to the release of active ingredients. A variety of probable excipient combinations can be screened for their compatibility with drugs by studying their drug release profile (Barkai et al., 1990).

Compatibility studies

Infra-red spectroscopy (IR) and thin-layer chromatography (TLC) is conducted to determine the compatibility of drug and excipient. Powder X-ray diffraction (XRD) and Differential scanning calorimetry (DSC) can determine the effect of polymerization or crystallinity of active ingredients. For DSC, approximately 5mg samples are weighed, sealed and heated at 15°C/min in nitrogen atmosphere (Shaha et al., 2010).

Resiliency

Viscoelastic properties (resiliency) of the microsphere system can be tailored to create beadlets which are soft, in accordance with the requirements of the final formulation. It increases cross-linking and slows down the release rate. Therefore, tests for

viscoelastic properties of microspheres are performed and optimized according to prerequisite, considering release as a feature of time of interconnection (Shaha et al., 2010).

Physicochemical characterization of microspheres

Scanning electron microscopy

For morphology and surface characteristics, The sample is coated in the gold-palladium at room temperature under an argon atmosphere, and the microsphere surface characteristics can be analysed by scanning electron microscopy (SEM).

Fourier transform infrared spectroscopy (FTIR)

Fourier transform infrared spectroscopy (FTIR) is performed for the pure drug, polymer and the drug-polymer physical mixture and microsphere formulations. The samples are incorporated in potassium bromide discs and are evaluated using the FTIR spectrometer. The peaks corresponding to the characteristic bands of the drug must be preserved in the spectra of the microspheres to indicate that no chemical interaction or changes have occurred during the preparation of the formulations.

Powder X-ray diffraction (XRD)

Powder X-ray diffraction (XRD) can be performed for both pure drug, polymer and microsphere formulation to investigate the effect of polymerization on the crystallinity of the drug. The disappearance of the characteristic peaks of the drug in the formulation could indicate that the drug is dispersed at a molecular level in the polymer matrix (Kilmer et al., 2010).

Safety Considerations

- Allergenicity in guinea pigs.
- Eye irritation study performed in rabbits
- Mutagenicity in bacteria
- Oral toxicity study in rats.
- Skin irritation studies in rabbits (Kiliçarslan et al., 2003; Sato et al., 1988).

Limitations

The use of organic solvents poses threats like toxicity and flammability. Traces of residual monomers in the bottom-up approach can be toxic and dangerous to health. But these shortcomings can be overcome by proper quality control measures along with optimization and standardization of procedures e. g, post-manufacture washing (Mandava et al., 2012; Srivastava et al., 2012).

Applications of microspheres

This system can be used to increase the effect, safety, and quality of prescription as well as over the counter products. Microsponge drug delivery system can be used in various applications. Microsponges drug delivery is mainly applicable to oral and topical applications. Several patents have been reported using different types excipients due to which microsponges exhibit high loading capacity and sustained release ability. These studies offer the formulator a scope to formulate a wide variety of products. Over the counter (OTC) products that contain microsponge drug delivery system and various sunscreens, specialized rejuvenated products, and moisturizers (Kilmer et al., 2010). Some more application of microsponges give (Table 2). Some examples of microsponge drug delivery with their formulations and uses (Table 3).

Marketed formulations

Microsponges Drug delivery System is ideal for skin and personal care and cosmetic products. They can take up the excess of skin oil while retaining an elegant feel on the surface of the skin. This technology is presently employed in a considerable number of products sold by leading cosmetic and toiletry companies worldwide. These products include oil control

lotions, moisturizers, conditioners, deodorants, lipsticks, skin cleansers, powders, makeup and eye shadows which offer various advantages. They are advantageous due to increased chemical and physical stability besides they show greater availability which reduces the skin irritation. The controlled release of the active ingredients and unique tactile qualities are other advantages of this system. Some marketed formulation of microsponges with their advantages (Table 4) with some filed patent related to the microsponges (Table 5).

Recent advances in microsponge drug delivery system

Various advances technology have been made by using different methods or techniques e.g. nanosponges, nanoferrosponges, mucoadhesivemicrosponges, and porous microbeads. β -CD nanosponges were also formulated and can be used for hydrophobic as well as hydrophilic drugs. This nanosponge can be developed by cross-linking the β -CD molecule by reacting the β -CD with diphenyl carbonate. Researchers also observed that incorporating cytotoxic substances in a nanosponge carrier system can increase the potency of the drug, these type of

Table 2. Applications of microspongesystem

Active agents	Applications
Anti-inflammatory e.g. hydrocortisone	Prolonged activity with lessened of skin allergic response and dermatoses.
Anti-dandruff e.g. zinc pyrithione, selenium sulfide	Reduced nasty odour with decreases irritation with increase in safety and efficacy.
Skin depigmenting agents e.g. hydroquinone	Improved stability against oxidation with increase in efficacy and aesthetic application.
Anti-fungals	Sustained release of active ingredients
Anti-acne e.g. Benzoyl peroxide	Reduced skin irritation and maintaining efficacy and sensitivity.
Antipruritics	Extended and improved activity.
Sunscreens	These are long lasting products having high efficacy with enhanced protection against Uv rays, and sunburns, sun related injuries at high concentration and with low irritation and sensitivity.

Table 3. Examples of microsponge drug delivery with their formulations

Microsponge Delivery Systems	Drug	Clinical Use
Gels	Terbinafine HCl	Anti-fungal
	Hydroxyzine HCl	Urticaria and atopic dermatitis
	Acyclovir	Viral infections
	Fluconazole	Inflammation
	Benzoyl peroxide	Anti-Acne Treatment
Lotions	Benzoyl peroxide	Anti-Acne Treatment
Creams	Hydroquinone and Retinol	Melanoma
Tablets	Indomethacin	Inflammation
	Paracetamol	Anti-pyretic
	Chlorpheniramine maleate	Hay Fever
	Ketoprofen	Musculoskeletal pain
	Paracetamol	Colon targeting
Implants	Poly (DL-lactic-co-glycolic acid)	Skin tissue engineering
Grafts	Poly (lactic-co glycolic acid)	Cardiovascular surgery
Injection	Basic fibroblast growth facto	Growth factor

Table 4. Marketed formulations of microsponges

Product name	Manufacturer	Advantages
Carac Cream	Dermik Laboratories, Inc. Berwyn, PA 19312 USA	Carac Cream contains 0.5% fluorouracil; it includes 0.35% incorporated in a porous microsphere consisted of methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone. Carac is a once-a-day topical application. For the treatment of actinic keratosis caused by over-exposure to the sun.
Retin-A-Micro	Ortho-McNeil Pharmaceutical, Inc.	Retin-A-Micro contains 0.1% and 0.04% tretinoin entrapped into a porous microsphere consisted of methyl methacrylatedimethacrylate cross-polymer to enable inclusion of the active ingredient, tretinoin, in an aqueous gel. Used for the topical treatment of acne vulgaris.
Salicylic Peel 20 & 30	Biophora	Salicylic acid 20% has been used in to it. Microspongesystem used for stimulat the skin for for faster results. Itimprove pigmentation, fine lines and acne. Salicylic acid passes easily through the pores.
Line Eliminator Dual Retinol Facial Treatment.	Avon	Retinol (Vitamin A) in MicrospongesDrug Delivery Systeem, for wrinkle-fighting action it release by two ways like immediate and timely release of drug. It clearly reduses appearance of lines and wrinkles.
Micro Peel Plus /Acne Peel	Biomedic	It stimulates the cell turnover so the application of salicylic acid in the form of microcrystals, These microcrystals target the specific areas of the skin. It is the chemical peels releases in to the skin of all dead cells while doing no damage to the skin.
Retinol cream, Retinol 15 Night cream	Biomedic, Sothys	Night cream. Microsponge technology it conatains pure retinol, Vitamin A. It diminishment of fine lines and wrinkles,
Lactrex™ Moisturizing Cream	SDR Pharmaceuticals, Inc., Andover, NJ, U.S.A. 07821	Natural humectant is used for soften and help to moisturizing the dryskin, cracked skin. It also contains 12% lactic acid as a neutral ammonium salt, ammonium lactate, water and glycerine.
Oil free matte block spf20	Dermalogica	Oil-free sunscreen protect the skin from damaging UV-rays while controlling the oil production and givesyou a healthy matte finish. That can be formulated with microsphere technology, Oil free matte block absorbs oil and prevents the shine without any powder esidue.
Sportscream RS and XS	Embil Pharmaceutical Co. Ltd.	Topicalpreparation It gives analgesic-anti-inflammatory and counterirritant actives for the management of musculoskeletal conditions.
Oil Control Lotion	Fountain Cosmetics	Microsponges that can absorb the oil from surface of skin, Eliminatethe shine for hours with this feature-weight lotion, formulated with oil-absorbing Microsponge technology. It can be mainly use for the Acne-Prone, oily skin conditions.s

carriers can be used mainly for the targeting the cancerous cells (Hu et al., 2007). Nanosponge, a novel approach constitutes the self-performing carriers having better penetration to the targeted site due to the external magnetic triggers which enforce the carriers to penetrate to the deeper tissues. Thereafter, the removal of magnetic material from the particles is effected leaving a porous system (Cavalli et al., 2006). The improved characteristics of porous microspheres, led to the development of a process to produce the porous microbeads. This method (High internal phase emulsion, HIPE) consisted of the monomer containing continuous oil phase, a cross-linking agent and

aqueous internal phase (Çomoğlu et al., 2007). They also observed increased stability of RNA and the relatively effective encapsulation process of siRNA. This approach may lead to novel therapeutic routes for siRNA delivery (Lee et al., 2012)

Future prospects

Microsponge drug delivery system holds a promising opportunity in various pharmaceutical applications and industry in the coming future as it has unique properties like enhanced the product performance and elegancy, extended the release of active moieties, improved drug release

Table 5. Patents Filed Related to Microsponges

Patent no	Inventors	Publication Date
US4690825	Won, Richard	1987
US4863856	Dean RC Jr et al.	1989
US5292512	Schaefer et al	1989
US5135740	Katz et al.	1992
US5679374	Fanchon; Chantal et al	1994
US5316774	Eury, Robert P et al.	1994
US5725869	Lo; Ray J. R.	1996
US6395300	Straub et al.	1999
US6211250	Tomlinson et al	2001
US20030232091	Shefer et al.	2002
US20040247632	Cattaneo, Maurizio	2004
US20050271702	Wright, Steven G et al.	2005
WO2008097429A1	Franklin Sadler Love	2007

profile, reduced irritation, improved physical, chemical, and thermal stability which makes it flexible to develop novel formulations. The real challenge in the future is the development of the delivery system for oral peptide delivery by changing ratios of polymers. The use of bioerodible and biodegradable polymers for drug delivery enables it for the safe delivery of the active material. These porous systems have also been studied for drug delivery through a pulmonary route, which shows that these systems can show effective drug release even in the scarce of the dissolution fluid. Therefore, colon is an effective site for targetted drug release. Development of carriers for alternative drug administration routes like parenteral and pulmonary route is necessary. These particles can also be used as cell culture media and thus can also be employed for stem cell culture and cellular regeneration in the body. These carrier systems have also found their application in cosmetics due to their elegance. These developments enabled researchers to utilize them for various purposes. These novelties in the formulation also a new way for drug delivery (Srivastava et al., 2012)

Conclusion

With the demand for innovative and highly efficient Pharmaceutical as well as Cosmetic products, the market holds considerable potential for Microsponge technology and the versatility they offer. Since the researchers have found the new and creative way to deliver actives moieties, they can realize that the full capability of these materials providing safety and stability. It also reduces side effects of the active moieties, enhances multi-functionality and also increases active ingredient compatibility with the excipients. Microsponge delivery system would be a winning and innovative strategy for future, in the Pharmaceutical and Cosmetic industry. Microsponges have a distinct advantage over the conventional topical dosage forms for the treatment of topical diseases; it is a new strategy or one of

a kind of technology for the controlled release of agents. It is advantageous over other products by because it is non-mutagenic, non-toxic & non-irritant. Thus the microsponge drug delivery system has got a lot of potential and is an emerging field which is essential to be explored for research in future.

Authors contribution

All the authors have contributed to the preparation and editing of this systematic review article.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No funding source.

Acknowledgment

Akash Shivaji Nalawade would like to thank the YSPM's Yashoda Technical Campus, Satara (India) and Dr. V. K. Redasani (Director, YSPM's Yashoda Technical Campus, Satara) for providing facilities and guidance to complete this review.

References

- Barkai A, Pathak YV, Benita S. 1990. Polyacrylate (Eudragit Retard) Microspheres for Oral Controlled Release of Nifedipine. I. Formulation Design and Process Optimization. Drug Development and Industrial Pharmacy, 16(13):2057–75.
- Burton S. 2002. Book Reviews 355:356(3):711–3.
- Cavalli R, Trotta F, Tumiatti W. 2006. Cyclodextrin-based nanosponges for drug delivery. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 56(1–2):209–13.
- Charde MS, Ghanawat PB, Welankiwar AS, Kumar J, Chakole RD. 2013. Microsponge A Novel New Drug Delivery System: A Review. International Journal of Advances in Pharmaceutical Sciences, 2(6):63–70.
- Chen G, Sato T, Ohgushi H, Ushida T, Tateishi T, Tanaka J. 2005. Culturing of skin fibroblasts in a thin PLGA-collagen hybrid mesh. Biomaterials, 26(15):2559–66.
- Çomoğlu T, Gönül N, Baykara T. 2003. Preparation and in vitro evaluation of modified release ketoprofen microsponges. Farmaco, 58(2):101–6.
- Çomoğlu T, Savaşer A, Özkan Y, Gönül N, Baykara T. 2007. Enhancement of ketoprofen bioavailability by formation of microsponge tablets. Pharmazie, 62(1):51–4.
- Development D, Pharmacy I. Of i i i f e d i p i n e . i . 1990;16(13):2057–75.

- Embil K, Nacht S. 1996. The Microsponge® Delivery System (MDS): A topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. *Journal of Microencapsulation*, 13(5):575–88.
- Grimes E, Pearl E. 2004. A Microsponge Formulation of in the Treatment of Melasma and Postinflammatory Hyperpigmentation. *Clinical Therapeutics*, 74(12):362–8.
- Hu SH, Liu TY, Liu DM, Chen SY. 2007. Nano-ferrosponges for controlled drug release. *Journal of Controlled Release*, 121(3):181–9.
- Jadhav N, Patel V, Mungekar S, Bhamare G, Karpe M, Kadams V. 2013. Microsponge Delivery System: An updated review, current status and future prospects. *Journal of Scientific and Innovative Research*, 2(26):1097–110.
- Kaity S, Maiti S, Ghosh AK, Pal D, Ghosh A, Banerjee S. 2010. Microsponges: A novel strategy for drug delivery system. Vol. 1, *Journal of Advanced Pharmaceutical Technology and Research*, 283–90.
- Kalbhare SB, Bhandwalkar MJ, Pawar RK, Sagre AR. 2020. Sodium Alginate cross-linked Polymeric Microbeads for oral Sustained drug delivery in Hypertension : Formulation and Evaluation, 10(3):153–7.
- Kiliçarslan M, Baykara T. 2003. The effect of the drug/polymer ratio on the properties of the verapamil HCl loaded microspheres. *International Journal of Pharmaceutics*, 252(1–2):99–109.
- Kilmer PD. 2010. Review Article: Review Article. *Journal Theory, Clinical Practice*, 11(3):369–73.
- Kumari P, Mishra SK. 2016. A comprehensive review on novel microsponges drug delivery approach. *Asian Journal of Pharmaceutical and Clinical Research*, 9:25–30.
- Lee JB, Hong J, Bonner DK, Poon Z, Hammond PT. 2012. Self-assembled RNA interference microsponges for efficient siRNA delivery. *Nature Materials*, 11(4):316–2224.
- Kashid V, nikam v, wagh v, chaudhari s. 2015. Nasal gel as promising mucosal drug delivery. *World Journal of Pharmaceutical Research*, 60.
- Mandava S, Thavva V. 2012. Novel Approach: Microsponge Drug Delivery System. *International Journal of Pharmaceutical Sciences and Research*, 3(04):967–80.
- Naga Jyothi K, Dinesh Kumar P, Arshad P, Karthik M, Panneerselvam T. 2019. Microsponges: A Promising Novel Drug Delivery System. *Journal of Drug Delivery and Therapeutics*, 9(5s):188–94.
- Of I, Material C, For SI, Conference NL. 2015. *International Journal of Pure and Applied Research in Engineering and Technology. Sustainable Technologies in Civil Engineering*, 3(8):515–34.
- Sato T, Kanke M, Schroeder HG, DeLuca PP. 1988. Porous Biodegradable Microspheres for Controlled Drug Delivery. I. Assessment of Processing Conditions and Solvent Removal Techniques. Vol. 5, *Pharmaceutical Research: An Official Journal of the American Association of Pharmaceutical Scientists*. p. 21–30.
- Shaha V, Jain H, Krishna J, Patel P. 2010. Microsponge drug delivery: A review. *International Journal of Research in Pharmaceutical Sciences*, 1(2):212–8.
- Srivastava R, Pathak K. 2012. Microsponges: A futuristic approach for oral drug delivery. *Expert Opinion on Drug Delivery*, 9(7):863–78.
- VG R. 2015. Topical Anti-Inflammatory Gels of Naproxen Entrapped in Eudragit Based Microsponge Delivery System. *Journal of Advanced Chemical Engineering*, 5(2).