A Review On Different Methods Development Approaches Of Micro Sponge's Drug Delivery System

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Abstract:
Microsponges delivery system is a apparent polymeric system consisting of porous microspheres. These are tiny sponge like spherical particles those consist of a myriad of interconnecting voids within a non-collapsible structure with a big porous surface through which active ingredients are released in a controlled manner. The size of the microsponges scale from 5 to 300 micrometer in diameter and a typical 25 micrometer sphere can have upto 2.5 lac pores and an internal pore structure equivalent to ten feet in length, providing a total pore volume of about 1milli litre per gram for extensive drug retention. This review gives all information regarding the methods available for preparation and development of Micro sponges.

Introduction:
In 1987 won was developed the microsponges technology and the original patents were assigned to advanced polymer system. A large number of variations of the technique has been developed by this company .This technique applied to the cosmetic as well as over the counter OTC and prescription pharmaceutical product. Now, this technology has licensed to cardinal Health inc, for use in topical products. These microsponges delivery system is a apparent polymeric system consisting of porous microspheres. These are tiny sponge like spherical particles those consist of a myriad of interconnecting voids within a non-collapsible structure with a big porous surface through which active ingredients are released in a controlled manner. The size of the microsponges scale from 5 to 300 micrometer in diameter and a typical 25 micrometer sphere can have upto 2.5 lac pores and an internal pore structure equivalent to ten feet in length, providing a total pore volume of about 1milli litre per gram for extensive drug retention. It has advantages over other technologies like liposomes and microencapsulation . microcapsules wouldn't control the release rate of actives. Once if the wall has broken then the actives contained within microcapsules would be released. Liposome suffers from lower payload, its tough for formulation, limited chemical stability and microbial instability.

A microsponge Delivery system is peculiar, highly cross-linked, porous, polymeric microspheres that can entrap wider range of actives and then release them with desired rate. This system is useful for the improvement of performance of relevant applied drug. It is a unique technology for the controlled release of relevant agents and consists of micro porous beads, normally 10 to 25 microns in diameter, loaded with active agent. Their high degree of cross-linking results in particles that are insoluble, inert and sufficient strength to stand up to the high shear generally used in manufacturing of creams, gels, lotions and powder. Their characteristics

feature is the adsorb or load a high degree of active materials into the particle and on to its surface. Therefore, they may increase stability, side effect and modify drug release favorably.

Microsponge technology has so many favorable characteristics, which make it a versatile drug delivery vehicle. Microsponge Drug delivery system could be provided increased effectiveness for topically actives agents with increased safety, extended product stability and improved aesthetic properties in an efficient manner. (1)

The scientist won in 1987 developed micro sponge technology, which again was further privileged as an advanced polymer that is useful for a prescription pharmaceutical product, cosmetics and over the counter product. These drug delivery system posses porous polymeric structure sponge-like sphere particle with interconnecting voids inside its non-flexible configuration and hefty porous surface, which the drug in a controlled manner. Various pharmaceutical formulation developed through possible headed integration of microsponge like gels, emulsions, tablets and capsules. The microsponges have following properties: the size range 5 to 300 micro meter in diameter, 1 micro meter sphere contains 10000 pores, pore volume 0.1 to 0.3cm^3 per gram and internal pore structure 10 ft in length**.** (2)

The different several systems were developed for systematic drugs under the class of trans-dermal delivery system using the skin as portal of entry. Contemporary drugs while applying having many problems such as ointments, which are often aesthetically unappealing, greasiness, stickiness etc. that often results into lack of patient compliance. Also gels, powders, lotion has low time of contact with skin therefore these vehicles require high concentrations of active agents for fruitful therapy because of their low efficiency of delivery system no longer drug can be absorb from skin. This issue could be recovered by the microsponges. Microsponges needed low drug content but having the longtime of contact with skin. Therefore no irritation and allergic reactions are observed in a patient. The MDS system is utilized for the improvement of performance of contemporary applied drugs. It is a distinctive technology for the controlled release of relevant agents and consists of micro porous beads, generally 10 to 25 microns in diameter, loaded with active agent. The high degree of cross-linking results in particles those insoluble, inert and of sufficient strength to stand up to the high shear commonly utilized in manufacturing of creams, gels, lotions and powders. Their characteristic feature is the capacity to adsorb or load a high degree of active materials into the particle and on to its surface. Microsponges are uniform, spherical having the cross linked polymeric system , non-collapsible structure consisting of porous void space for the huge entrapment of several active ingredients in the voids and it offers higher shear strength which are generally utilized in the area of creams, lotions, powders, having maximum payload of 50 to 60 percentage and inter connected void space of particle size range 5 to 500 micrometer. The loaded active compound would be shielded by microsponge formulation and diffuses long time. Its huge capacity for entrapment of actives, upto 3 times its weight, differentiates microsponge products from other types of dermatological delivery system. This sustained release of actives to skin over time is an especially valuable tool to extend the efficacy and lessen the irritation generally associated with powerful therapeutic agents like hydroxyl acids**.** Generally a Sertaconazole nitrate(SN) used in topical formulations to

treat several skin diseases like athelete"s foot, tineapedis. It is an imidazole derivative, which could be acted as a fungicidal, fungistatic, antibacterial, antitrichomonal, anti-inflammatory and antipruritic. It inhibits 14 alpha demethylase, which blocks ergosterol synthesis resulting in the prevention of fungal cell multiplication and hyphae growth. Contemporary antifungal preparations sometimes cause skin irritation, pruritis and sensitization. [2-3]

Microsponge preparation methods:

In microsponge drug delivery system loading of drug can be done by two ways, in one step process or by two step processed as discussed in liquid-liquid suspension polymerization and Quasi emulsion solvent diffusion method which are based upon the physiochemical properties of the drug that is loaded to be. If the drug is inert non-polar material, it will be created the porous structure and it is called porogen. Porogen drug , which either hinders the polymerization or becomes activated by it and stable to free radicals are catched with one step process. [4]

1) Liquid-liquid suspension polymerization:

Commonly, first the solution wills made by comprising of monomers and the functional or active ingredients, which are immiscible with water. This phase was then suspended with trouble in an aqueous phase, generally containing additives, like surfactants and dispersants, to promote suspension. If once the suspension was established with different droplets of the desired size, polymerization is effected by activating the monomers either by catalysis, increased temperature or irradiation. In the polymerization process it would be produced 1000 of microsponge cages which are spherical in structure and interconnected with each other its look like a grapes bunch. After completion of polymerization the produced solid particles were recovered from the suspension. Particles have been washed and dried for further use.

The different several steps in the preparation of microsponges are discussed as follows.

i)Choice of monomer or combination of the monomer.

ii)Development of chain monomer as polymerization begins.

iii)Development of monomer ladder as result of cross linkage between chain monomer.

iv)Folding of monomer stair to form spherical particles.

v)Collection of microsphere lead to formation of bunches of microsphere binding of bunches leads to formation of micro sponge.

Advantages: For drug loading one-step or two step methods can be changed .

Disadvantages: feasible trapping of unreacted monomers and solvent traces, monomers need long time to react to non-uniform structure, need two step methods for thermodynamic sensitive drugs need less drug loading capability. [5]

2)**Quasi-emulsion solvent diffusion**:

The micosponges can be prepared by quasi emulsion method. Mainly , in this method the internal phase consists of Eudragit RS100 which is dissolved in an organic solvent dichloromethane (DCM) after that Glycerol was added as plasticizer and followed by the addition of piroxicam under ultra-sonication at 35 C for 15 minutes. Then the internal phase can be poured into the external phase after one hour of stirring by mechanical stirrer (from Copley scientific, UK) at a rate of 500 rpm finally the micro sponges have been formed owing to the

removal of organic solvent from the system. The microsponges would be dried and filtered at 40 degrees centigrade for overnight. The prepared microsponge can be assessed for production yield, loading efficiency, particle size and FTIR, differential scanning calorimetry and scanning electron microscopy. [6-7]

In this method generally the preparation of oral and topical microsponges takesplace. Mainly two phases were prepared , one is inner phase that is organic and second is aqueous phase that is outer phase. The polymer was dissolved in ethyl alcohol that is in inner organic phase polymer and drug was dissolved in this solution by ultrasonication at room temperature. The outer phase consists PVA solution in water. The solution was stirred and filtered for future use. Both the phases inner and outer phases were mixed together by using mechanical stirrer dropwise. By stirring the Quasi-emulsion droplet was formed which may future evaporation of organic solvent produces the solid microsponge cages. The fabricated microsponges were filtered and dried in oven for 12 hr. loaded Eudragit RS-100 microsponges using acetone as dispersing solvent and liquid paraffin as the continuous medium. Choice of the organic solvent and external phase depend on the physicochemical properties of the drug and the polymer utilized for manufacture of microsponges. [8]

The various steps were discussed in the fabrication of microsponges by using quasi-emulsion solvent diffusion method. The internal phase in which the polymer containing such as eudragit RS-100 dissolved in ethyl alcohol. Slowly the drug is added to internal phase then dissolved under ultrasonication at 35^{o} C and added plasticizer such as triethylcitrate (TEC) in order to aid the plasticity. The polyvinyl alcohol which is containing in external phase dissolved in distilled water.The internal phase is poured into the external phase mixing together with continuous stirring for 2 hours. Again , separate the micro sponges after mixture filtered. Finally the microsponges was washed and dried in an air heated oven at 40^{o}C for 12 hr. [9-10]

Advantages: low solvent traces, High drug loading, no monomer entraoment, No exposure of drug to atmospheric condition, size of microsponges can be easily monitored by cotrolling the stirring , spherical particles.

Disadvantages: likely entrapment of unreacted monomers and solvent traces, unreliable structure, need a long time for the reaction of monomers, need two-step method for thermo sensitive drugs that has low drug-loading efficiency[11]

3)Multiple-emulsion Solvent Diffusion:

This technique has been developed to fabricate biodegradable porous microspheres. The internal aqueous phase containing an emulsifying agent like span, polyethyleneimine, and stearyl amine was diffused in organic polymeric solution. After that, this emulsion was again diffused in external aqueous phase containing PVA to form a double emulsion. In this method one advantage of entrapping both water-insoluble and water-soluble drugs. It can also be utilized for entrapping thermo labile materials like proteins. Some authors also explained the xanthan gum as an emulsifier to stabilize the internal emulsion. [12-13]

4) Addition of porogen: In this method porogen such as hydrogen peroxide or sodium bicarbonate have been introduced in place of internal multiple emulsions. For this purpose the

porogen was liquefied in the polymeric solution to form a single-phase system which was re-diffused in aqueous phase containing PVA. An initiator has been added to the multiple emulsion and the organic solvent was permitted to evaporate to leave the micro particles for producing microsponges. The effect of integrating hydrogen peroxide resulted in the formation of evenly distributed and interconnected pores with ranging from 5-20 micro meter of diameters. (14)

5)Oil in Oil Emulsion Solvent Diffusion: In the differences between w/o/w method, oil in oil emulsion was fabricated using volatile organic liquid as the internal phase that was permitted to evaporate gradually at a controlled rate with continuous stirring. As discussed in this technique dichloromethane used as a solvent for internal phase, polylactide glycolic acid as polymer and a mixture of fixed oil and dichloromethane containing span 85 as external phase. The internal phase has been mixed dropwise manner to the dispersion medium with continuous stirring to get the microsponges. This method was used for development of hydroxyzine HCl loaded Eudragit RS-100 microsponges utilizing acetone as dispersing solvent and liquid paraffin as the continuous medium. The choice of organic solvent and external phase depend on the physicochemical properties of the drug and the polymer utilized for preparation of microsponges. (15-16)

6) Vibrating Orifice Aerosol Generator Method: This method was earlier reported for the fabrication of lipid bilayered mesoporous silica particles. In this method synthesis of porous particles have been occurred by evaporation-driven surfactant templating in micro droplets by a VOAG method. In the preparation of core particle tetraethyl orthosilicate , ethanol, water and dilute hydrochloric acid were refluxed to fabrication of stock solution. The stock solution which was prepared diluted with the solvent containing surfactant and stirred to allow the formation of monodisperse droplets by utilizing this VOAG method. The microspheres produced has been encapsulated in the liposomes. These encapsulated particles can be used for targeted drug delivery of actives. (17)

7) Ultrasound-Assisted Production: This method has been established by modifying the liquid-liquid suspension polymerization. The microsponges were synthesized by using the monomer beta-cyclodextrin (BCD) and cross-linking agent diphenyl carbonate. Size control of the micro particles was carry out by heating and sonication of the reaction mixture. Then reaction mixture was permitted to cool, the product attained was milled to produce rough particles that were washed with distilled water and then by ethanol. The porous microparticles of cross-linked beta-CD can give out as carrier for efficient loading of drugs. This method has some limitation of entrapment of residues of the cross-linking agents that can be potentially toxic. (18-19)

s.no	Method	Advantages	Limitations	Excipient
1.	Liquid-liquid suspension polymerization	For drug loading one-step or two step methods can be	feasible trapping of unreacted monomers and solvent traces,	Surfactants like peroxides,benzoyl,t-butyl,diacetyl and lauroyl peroxides, and dispersants such as methyl and ethyl cellulose.

		changed	monomers need long time to react to non-uniform structure, need two step methods for thermodynamic sensitive drugs need less drug loading capability	
2.	Quasi-emulsion solvent diffusion	low solvent traces, High drug loading, no monomer entraoment, No exposure of drug to atmospheric condition, size of microsponges can be easily monitored by cotrolling the stirring , spherical particles	likely entrapment of unreacted monomers and solvent traces, unreliable structure, need a long time for the reaction of monomers, need two-step method for thermo sensitive drugs that has low drug-loading efficiency	Edugit RS-100, Dichloromethane, plasticizer, piroxicam, Triethylcitrate(TEC).
3.	Multiple-emulsion Solvent Diffusion	of entrapping both water-insoluble and water-soluble	The inversion of emulsion takesplace in	span, polyethylene imine, and stearyl amine, Xanthum gum.

		drugs	the presence of balanced emulsifying agent only	
4.	Addition of porogen	The effect of integrating hydrogen peroxide resulted in the formation of evenly distributed and interconnected pores with ranging from 5-20 micro meter of diameters.	-----	Hydrogen peroxide (or) sodium carbonate
6.	Vibrating Orifice Aerosol Generator Method	encapsulated particles can be used for targeted drug delivery of actives.	----	Tetraethyl orthosilicate and other surfactants
7.	Ultrasound-Assisted Production	The porous microparticles of cross-linked beta-CD can give out as carrier for efficient	This method has some limitation of entrapment of residues of the cross-linking agents that can	Beta-cyclodextrin (BCD), Diphenyl carbonate

		loading of drugs	be potentially toxic	

Table-1: Showing different methods of Micro sponge preparation with their limitations

Conclusion:

This review gives all in rank regarding the methods existing for preparation and development of Micro sponges. Some of the entrapment limitations have overcome with different new techniques in current scenario. These methods are used with toxin controlling with use of excipients.

References:

1. Shailesh Sharma, Anu Sharma and Chamanpreet Kaur, MICROSPONGES: AS A TOPICAL DRUG DELIVERY SYSTEM, IJPSR, 2020; Vol. 11(2): 524-534. E-ISSN: 0975-8232; P-ISSN: 2320-5148
2. Jagtap SC, Karale AA: Microsponge a novel topical drug delivery system. Journal of Drug Delivery Research 2014; 3(4).
3. Pawar A: Microspong: A novel strategy for drug delivery. International Journal of Pure and Applied Bioscience 2015; 3(1): 224-35.
4. Gupta NB, Sumbria R and Kumar K: Microsponges: topical preparations and its applications. World Journal of Pharmacy and Pharmaceutical Sciences 2017; 6(4): 629-42.
5. Kumari P and Mishra SK: A comprehensive review on novel microsponge drug delivery approach. Asian Journal of Pharmaceutical and Clinical Research 2016; 9(1).
6. Makwana R, Patel H and Patel V: Microsponge for drug delivery system. International Journal of Pharmacy and Technology 2014; 5(4): 2839-51.
7. Shrivastva S, Kumar D and Singh PS: A review: Microsponge- An effective drug delivery system. Asian Journal of Pharmaceutical Research and Development 2017; 5(2): 1-8.
8. Kar AK, Kar B and Parya H: A novel approach on microsponge: Multifunctional modern dosage form International Journal Pharmaceutical Sciences' Review and Research 2018; 51(2): 64-72.
9. Sagavkar SR and Mohit SK: Innovative and novel strategy: Microsponges drug delivery system. International Journal of Universal Pharmacy and Biosciences 2014; 3(4).
10. Rajurkar VG, Tambe AB and Deshmukh VK: Topical anti-inflammatory gels of naproxen entrapped in eudragit based microsponge delivery system. Journal of Advanced Chemical Engineering 2015; 5(2): 2-6.
11. Nawal A and Mohammad S: Formulation and in-vitro evaluation of piroxicam microsponge as a tablet. International Journal of Pharmacy and Pharmaceutical Sciences, 2016; 8(2): 104-11.

12. Charde MS, Ghanawat PB, Welankiwar AS, Kumar J and Chakole RD: Microsponge a novel new drug delivery system: A review. International Journal of Advances in Pharmaceutics 2013; 2(6).
13. S Patwekar, S Gattani, R Giri, A Bade, B Sangewar, V Raut , Review on nanoparticles used in cosmetics and dermal products, World J. Pharm. Pharm. Sci 3, 1407-1421
14. Vikrant K, Dolas RT, Somwanshi SB, Gaware VM, Kotade KB, Dhamak KB, Khadse AN and Kashid VA: Microparticles: a novel approach to enhance the drug delivery: A review. International J of Pharmaceutical Research and Development 2011; 3(8): 170-83.
15. Shah CN and Shah DP: Microsponges: A revolutionary path breaking modified drug delivery of topical drugs. International Journal of Pharmaceutical Research 2014; 6(2): 2-11.
16. Bamane GS, Kakade TB and Kulkarni LV: Microsponges: A novel drug delivery system. World Journal of Pharmacy and Pharmaceutical Science 2014; 3(3): 748-62.
17. Pentewar RA, Kazi S and Bharti R: MDS Technology: An approach for topical, oral controlled and cosmetic formulations. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2014; 5(3): 1170-90.
18. Deshwal S and Saxena AK: Microsponge delivery system: An overview. International Journal of Bio-pharmaceutics 2014; 5(1): 39-46.
19. Vishal Yadav, Prakash Jadhav, Shailaja Dombe , Anjali Bodhe, Pranali Salunkhe, Formulation And Evaluation Of Microsponge Gel For Topical Delivery Of Antifungal Drug, International Journal of Applied Pharmaceutics ISSN- 0975-7058 Vol 9, Issue 4, 2017
20. V. V. Pande, n. A. Kadnor, rupali n. Kadam and s. A. Upadhye, Fabrication and Characterization of Sertaconazole Nitrate Microsponge as a Topical Drug Delivery System, Indian Journal of Pharmaceutical Sciences, Indian J Pharm Sci 2015;77(6):675-680
21. Pawar Vitthal, Salunkhe Anuradha, A REVIEW ON MICROSPONGES DRUG DELIVERY SYSTEM, © 2020 IJRAR January 2020, Volume 7, Issue 1.
22. Rajnish Kumar, Sanjay K. Sharma, Manish Jaimini1, Nawaz Alam, Microsponge Drug Delivery Systems for Novel Topical Drug Delivery, International Journal of Pharmaceutical Sciences Letters 2014 Vol. 4 (3) 384- 390.
23. Kapoor D, Vays R, Lad C: A review on Microsponges Drug Delivey System, Journal of Drug Delivery and Therapeutics 2014, 4(5), 29-35
24. Patel B. U, Patel H. A review- Recent research on microsponges a novel drug delivery system. International of advances in pharmaceutics 2018: 07 (03): 10-16.