ejpmr, 2021,8(8), 460-468.

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

MICROSPONGE: A NOVEL APPROACH FOR TOPICAL DRUG DELIVERY SYSTEM

Rakesh S. Pawara*, Nileshwari P. Chaudhari, S. A. Tadavi and S. P. Pawar

Department of Pharmaceutics, P. S. G. V. P. M's College of Pharmacy Shahada-425409, Dist- Nandurbar, Maharashtra, India.

***Corresponding Author: Rakesh S. Pawara**

Department of Pharmaceutics, P. S. G. V. P. M's College of Pharmacy Shahada-425409, Dist- Nandurbar, Maharashtra, India.

Article Received on 02/06/2021 **Article Revised on 23/06/2021** **Article Accepted on 13/07/2021**

ABSTRACT

Microsponge technology is a novel technique was introduced in topical drug delivery of formulation to facilitate the controlled release of active drug into the skin. Microsponges are similar to the polymeric porous microspheres. Microsponges are reduces the systemic exposure and minimize the local cutaneous reaction to active drug. The microsponges are 5-300 µm in diameter, spherical shape, large porous surface& tiny in structures. Nature of the microsponges is non-irritant, non-allergic, non-mutagenic and non-toxic. Most of the microsponge's formulation is used for topical drug delivery system as well as they are used in oral administration. Deliver the drug of microsponges in regular time of interval and response to the other stimulation. Advantages of the microsponges are mainly release of the drug and enhance the stability and effectively reduce the side effect of drug. Achieve the desired concentration of the drug in the blood is the main Aim of the formulation. microsponges are generally used in a topically the prevent of the accumulation of drug in dermis and epidermis Microsponges are easily entrapped or incorporated into formulated product such as creams, liquids, gels, powders, suspension.

KEYWORDS: Topical & oral administration, 5-300 µm, polymeric porous, stability.

INTRODUCTION

Microsponges drug delivery system are mainly control the drug release rate and drug target to the specific site of body in the healthcare system. Microsponges drug delivery therapy is a being an integrated to optimize the efficacy and cost effectiveness. The drug releaseand absorption is depends upon the characteristics of the drug. Therapeutic index and duration of action of the drug isaltering to the possible of the incorporation of drug into carrier system.[1] Microsponge drug delivery system is also called as solid phase porous microsphere in a micro-particulatesystem. Microsponges having a size range from 5-300 microns having in a diameter and it consist of typical 25 µm sphere having up to the 250000 pores and structure of the internal pore equivalent to 10 feet in the length.extensive drug retentionof the total pore volume having of 1 ml/g. Microsponges having in a surface varied from 20 to 500 m^2/g and 0.1 to 0.3 cm^3 /g of pore volume. Loaded of the microsponge in which up to the own weigh of the active agent.[2,3] Microsponges drug delivery system drug are release into the skin by various triggers such as rubbing, higher skin temperature, concentration gradient, application of the pressure etc. in the microsponge drug delivery system conventional formulation of the topical drug product are intended to be work on the outer layer of skin. This product are release into their active ingredient upon application of the product is producing a highly concentrated layer are rapidly absorbed of the active ingrediants. The microsponge drug delivery system can be prevent the excessive accumulation of the ingredients in within the dermis and epidermis. This system are significanty reduce their irritation effect of the drug in without reducing in their efficacy. Further the Formulation having porous microsphere with active ingredients should be incorporated into the formulation such as creams, powders, gels and lotions.[4,5]

History of Microsponges

The technique of microsponges discovered and developed by the scientist Won in 1987,and assigned to the original patents were advances in the polymer system, and his company developed in a number of the techniques and this technique are applied in the cosmetic as over the counter and the physician prescribed in the products.[6,7]

Properties of The Microsponges

Microsponges are employed in the skin. the bioactive agent are progressively release in the skin they having a predetermined the time mode and response of the stimuli such as temperature, rubbing, PH effect is the efficacy enhanced.

- It should be stable at the temprerature up to 1300^0c.
- It consist of the compatible with most of the excipient and vehicles.
- They have stable in the formulations over the range of pH 1-11.

- It should be self-sterilizing as their average of the pore size is about 0.2 µm, the bacteria are cannot be penetrate in the pores.
- It consist of the cost effective and free flowing.
- It should be appropriated size of the particles to be absorb into the skin.
- It consist of high entrapment up to 50-60 %.
- Formulation can be absorb oil up to 6 times of the its weight of without drying.
- It should be provide the continuous action up the 12 h. i.e.,extended release.
- It consist of the having superior formulation flexibility.[8,9,10]

Potential Feature of Microsponges Drug Delivery System.

- Microsponges drug delivery systems are affiliates with the excipients and vehicals.
- It should have increased the efficiency are trapping by the 50 to 60 %.
- It consists of the unbreakable range of the PH 1-11.
- Microsponges drug particles are mostly deployed by the shape of the skin absorbing.
- It should have freely flow and cost effective.
- They have more sense of the flexibility.
- It consist of due to self-sterility, and their its pore size is around the 0.25 µ, while the bacteria are cannot be infiltration in the pore size.
- Most of the microsponge shaving the microscopic in spheres they have able to the absorb skin secretion, and it should be reduce the oiliness and shine with skin.
- Formulation of the microsponges can be absorbed in 6 times in the weight of without oil drying.
- It consist of the non-allergic, it should be non-irritating, non-toxic and the non-metagenic in the nature.
- It should be provides 12 h of continuous action of drug,ie.in the extended release.[11,12,13]

Benefit of Microsponges Drug Delivery System.

- It should be improved the formulation flexibility.
- Improved the patient compliance and reduced the irritation.
- It consist of enhanced the product performance.
- It should be extended release.
- They have improved the patient compliance and reduced the irritation.
- It should be improved the product elegancy.
- It should be improvedthe oil control and absorb oil up to 6 times of its weight of without drying.
- It consist of improved the physical, thermal and chemical stability.
- Thise systems are non-toxic, non-allergenic, non-irritating and non-mutagenic.[14,15]

Characteristics of Materials Entrapped In Microsponges

In microsponges drug delivery system the active ingredientscan be entrapped into the microsponge can be incorporated into various product such as gels, creams, powders, lotions, soaps.

Requirements of the material are will be get entrapped in the microsponge such as.

- It should be stable of the polymerization in catalysts and conditions.
- They have only the lightly solublenot a water miscible or roughly.
- They have be inert to monomers.
- It consist during the formulation of product, it should not be raisethe viscosity of mixture.
- They have fully miscible with the monomer, it should not be miscible adding the small amount of water miscible solvent for the miscible.
- It should be stable polymerization catalysts and the conditions.
- Materials are entrapped in vehicle restricted the solubility to be avoid problems of the cosmetic preparations. Vehicle are consume in microsponges before of the application, solubility is not restricted.
- They having capacity of the microsponges and polymer are design for the materials are optimized for the desired release rate for certain period of the time.[15,16,17]

Polymer Used In The Preparation of Microsponge.

- ✓ Ethylcellulose
- ✓ Eudragit RL100
- ✓ Eudragit RS 100
- ✓ Polystyrene
- ✓ Acrylic polymer
- ✓ Carbapol 934
- ✓ Polyvinyl alcohol
- ✓ PHEMA (polyhydroxy ethyl methacrylate)

Drug Explored in Microsponge Delivery System.

- ✓ Benzoyl peroxide
- ✓ Aceclofenac
- ✓ Paracetamol (NSAID)
- ✓ Dicyclomine
- ✓ Fluconazole (Anti-fungal)
- ✓ Hydroquinone
- ✓ Ketoprofen (NSAID)
- ✓ Ibuprofen (NSAID)
- ✓ Retinol (vitamin-A)
- ✓ Acyclovir sodium (Anti-viral)
- ✓ Erythromycin (Anti-biotic)

Table 1: Optimum values for microsponge formulation.

Specification	Optimum values
Drug: polymer ratio	3:1, 4:1 and 5:1
Amount of drug (g)	2
PVA	30-70
Inner phase solvent	Ethyl alcohol
Amount of inner phase solvent (ml)	10 (ml)
Amount of water in outer phase (ml)	200 (ml)
Temp in inner phase (^{0}c)	37
Stirrer type	Three blade
Stirring rate (rpm)	500
Stirring time (min)	60

Method For Preparation of Microsponges

Preparation of microsponges using in various technique are following.

1. Liquid-liquid suspension polymerization technique.
2. Quasi-emulsion solvent diffusion technique.
3. Water in oil in water (W/O/W) emulsion technique.
4. Oil in oil emulsion solvent diffusion technique.
5. Lyophilization
6. Ultrasound assisted production method.
7. Addition of porogen techniques.
8. Electrohydrodynamic atomization method.
9. Vibrating orifice aerosol generator method.

1).liquid-liquid suspention polymerization technique,

Liquid-liquid suspention polymerization techniques are used in the preparation of the microsponges. Preparation of the microsponges by this technique two phase are prepared phase 1 and phase 2. In phase 1 contain the active pharmaceutical ingredients and monomers are mixing in the solvent, formation of the solution (non-polar). This phase are dispersed in the phase 2 contain the aqueous phase. The aqueous phase containing in surfactant and dispersing agent. Are the polymerizations then the activating the monomer either by the increasing temperatures r the irradiation. Continue the polymerization of lead to the formation of spherical structure. Then the polymerization are completed liquid will be the remove and microsponges are washed and dried for further use.[18,19]

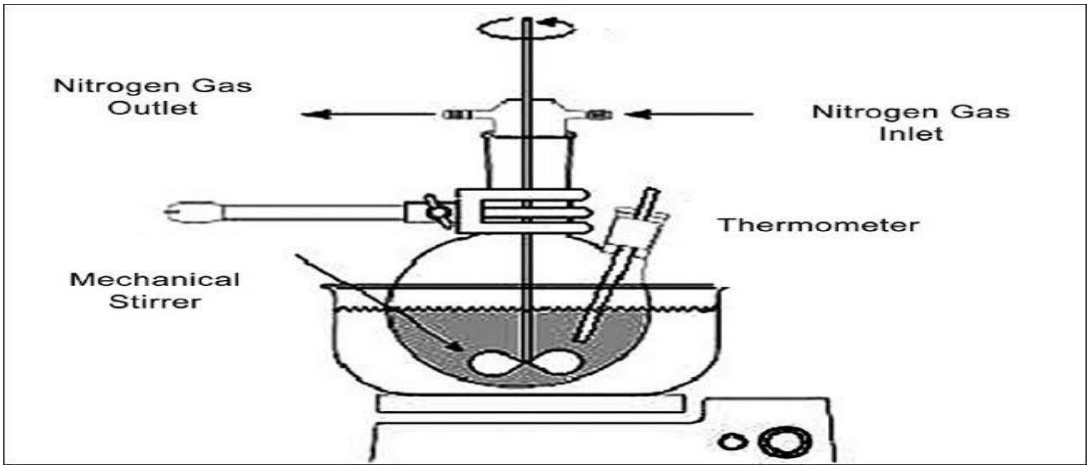

Fig.1: Liquid-liquid suspension polymerization.

2).Quasi-emulsion solvent diffusion method:

This method mainly used in preparation of the topical as well as oral microsponges. Preparation of the microsponges by the two phases one inner phase and another is outer phase. Inner phase is also called as organic phase and outer phase is also called as the aqueous phase. Inner organic phase containing polymer is dissolved in ethyl alcohol and drug are slowly added in the polymeric solution. then dissolved under the ultrasonication 500 rpm for 1 h. at 35^{0}c temperatures. Then added in mixture plasticizer such as triethylcitrate. Then the inner phase are poured in the outer phase. the external phase containing the polyvinyl alcohol and distilled water then continuous stirring the mixture for the 60 min. then the filtration of the mixture and isolated the microsponges. Obtain microsponges are washed and the dried under the vacuum oven at the 40^{0}c for 12 h.[20,21]

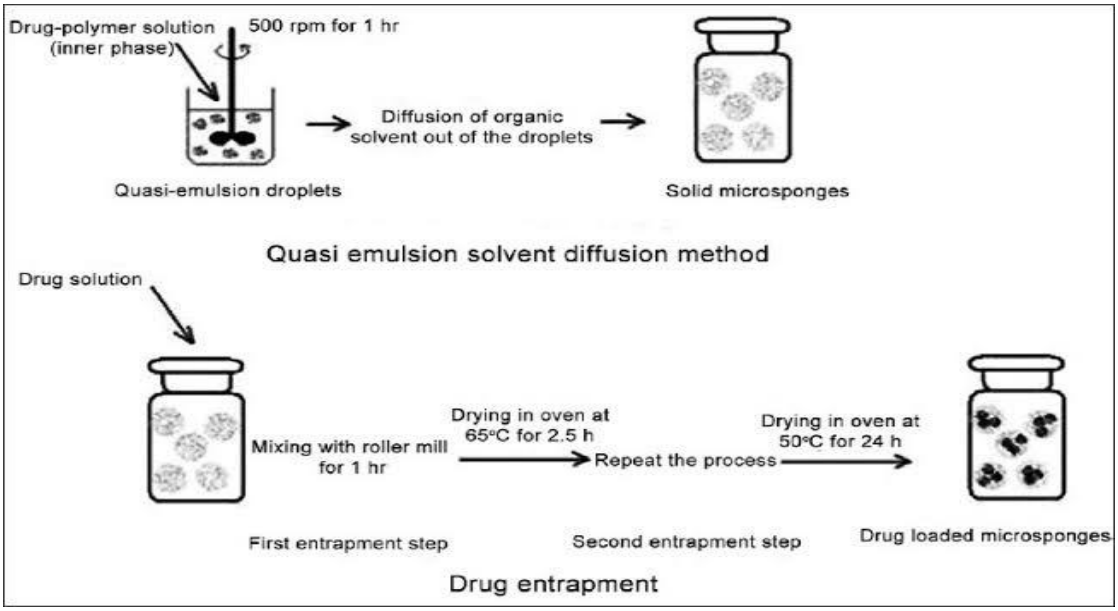

Fig. 2: Quasi-emulsion solvent diffusion method.

3).Water in oil in water emulsion technique

Waterin oil in water emulsion technique ismainlyused in preparation of biodegradable porous microspheres. Preparation of the microsponges in two phase. Internal aqueous phase contain emulsifying agent are use such as span, stearyl amine, polyethyleneimine are dispersed to the organic polymeric solution to be formation of w/o emulsion. Then emulsion are dispersed in the external phase. External phase contain PVA to be form of double emulsion. Water insoluble drug and water soluble drug both are entrapping mainly used in thermolabile material such as proteins. Some method preparation of the microsponges use in emulsifier such as xanthan gum to be stabilize of the internal w/o emulsion.[22,23]

4).Oil in oil emulsion solvent diffusion method:

Thise methods are used in the preparation of the microsponges. preparations of the internal phase contain polymer and drug and solvent. External phase contain emulsifier are used. then addition of the stabilizer for the reduction of particle aggregation. Then ultrasonic bath for 5 min. obtained in homogenous dispersion. Then mixture is added in the previously cooled liquid paraffin stirring magnetic stirrer o/o emulsion is formed. The mixture are stirring in different duration at different stirring speed. then the during period solvent are diffused into the liquid paraffin is evaporated then spherical porous particle are living, solidified the microsponges then the filtered and wash with the n-hexane in five time. Then dried at the room temperature for 12 h. microsponges are stored in the desiccator for the further investigations.[24]

5). Lyophilization

Lyophilization method are mainly used in the preparation of the microspheres are rapid and quickly. Prepared microsponges are converting the gelation technique to the porous microspheres.inthis method microspheres are incubated in solution of the chitosan hydrochloride then the lyophilized. Then the Lyophilization removal of solvent is quickly formation pores in the mcrosphrers. Major disadvantages of this method microspheres are crack and shrunken in du to quickly solvent are eliminate.[25]

6). Ultrasound assisted production technique

This method synthesis of microsponges by the monomer such as betacyclodextrin (BCD) and cross-linking agent such as diphenyl carbonate. Size of the microsponges are controlled the accomplished by the sonication or heating of the reaction mixture. Then cooling the mixture and obtained product are milled and give the rough particles. Then particle are washed with the distilled water and then again washed with ethanol. having the porous micro particles of the cross-linked β-CD can be sever to be efficient loading of drug. this techniques are developed by the modifying technique of liquid-liquid suspension polymerization.[26]

7). Addition of porogen technique

Addition of porogen method internal multiple emulsions is replaced by the porogen such as sodium bicarbonate and hydrogen peroxide. Porogen are dissolved in the polymeric solution and formation of single phase. then the redispersed aqueous phase contain PVA. Then the added of organic solvent and multiple emulsion then mixture are allowed to the evaporate and leave the microsponges.[27]

8). Electrohydrodynamic atomization method

This method are used to produce of the chitosan containing porous microsphere. Sonication of the chitosan solution and bubble are generate suspension and the bubble was drawn into syringe. Then steel capillary are perfused through the using a syringe pump and then subjected to the electrohydrodynamic atomization. then bubble suspension flow through chosen the capillary diameter. Then voltage are use in the concentration of

chitosan in the solution. Applied voltage and flow rate are resulted to be stable in cone-jet mode, highest concentration is used difficult the electrospray. Chitosan microspheres are cross-linked by the sodium hydroxide aqueous solution.[28]

9). Vibrating orifice aerosol generator method

This method is synthesis of porous particle by the evaporation driven of surfactant in microdroplets by the vibrating orifice aerosol generator method. core particle are prepared by tetraethylorthosilicate, ethanol, dilute hydrochloric acid, water were the prepared stock solution. Further the stock solution are diluted with the solvent contain surfactant and then stirrer then form the monodisperse droplet. Mcrosphrers are produce in encapsulated liposomes.[29]

Table 2: Marketed formulation based on microsponge drug delivery system.[30]

Name of product	Treatment	Manufacturer
Glycolic acid moisture w/SPF 15	Anti-wrinkles soothing	AMCOL Health and beauty solution
Retinol cream	Helps maintain healthy skin	Biomedic
Retinol 15 night cream	Anti-wrinkle	Sothys
Sports cream RS and XS	Anti-inflammatory embill	Pharmaceutical co.ltd
Retin A micro	Acne vulgaris	Ortho-McNell pharmaceutical, inc, Avon
EpiQuin Micro	Hyper pigmentation	Skin medicainc.
Line eliminator dual retinol facial	Anti-wrinkle	Avon
Salicylic peel 20	Excellent exfoliation	biophora
Ultra guard	Protects baby's skin	Scott paper company
Oil free matte block SPF 20	Sunscreen	dermalogica
Dermalogica oil control lotion	Skin protectant	John and ginger dermalogica skin
Lactrex^{TM}12% moisturizing cream	Moisturizer	SDR Pharmaceuticals, inc.
Carac cream, 0.5%	Treatment of actinic keratoses	Dermik laboratories, inc.
Oil control lotion	Tightness to promote healing, acne-prone, oily skin conditions	Fountain cosmetics

ADVANTAGES

- They are improved the product elegancy.
- Reduced the irritation of the product.
- This product is non-toxic, non-irritating, non-allergenic and non-mutagenic.
- It should be provides extended release up to 12 h.
- These are controls the oil.
- It should be permits the delivery system is incorporation of immiscible products.
- It should be permits the novel product form.
- Improved the product attractiveness.
- Better compliance in the product consumer acceptance.
- Physical and chemical stability enhanced.
- Liquid product is converted to the powder.
- It should be improved the effectiveness of the treatment.
- It should improve the bioavailability of the same drugs.[31,32]

Advantages of Microsponges Over Other Formulation

Advantages over conventional formulation.

- After application of the formulation contain active ingredient are producing the concentration of layer active ingredient are absorbed in great speed.
- Topical drug formulation is mainly design to working of the outer most layer of the skin.
- In this system are lower the side issue of drug parallel irritation without the reducing of its efficacy.
- Excessive ingredient is cumulating in the inside of the dermis and epidermis when compare to the microsponges drug delivery system are then prevented by the microsponges.[33]

Advantages over microencapsulation and liposome formulation.

- Formulation contain the rate of release of actives are generally cannot be control in the microcapsules.
- In this system in specific advantages on the other system like as liposomes and microencapsulation.
- They have narrow chemical stability or microbial.
- Microsponges drug delivery system is differs to liposomal drug delivery system because the system are study within range of PH 1-11 and temperature are up to 130^0c. which is compatible in the ingredients and instrument. And 0.25 µm of the pore size where bacteria cannot pierce.[34]

Advantages over ointment

- They have poor odor, the active ingredient areevaporation with uncontrolled or potential

inconsistency of the drug with vehicle is another disadvantages of the topical formulation.
- Ointment have a viscid, unpleasing, oily in nature, it is a patient compliance.
- Ointment having a low efficacy of the drug delivery system because they are required in highly concentration of the active ingredients for the effective and active treatment.[35]

LIMITATIONS

1. In the microsponges drug delivery system generally organic solvent are uses as porogen for the microsponge preparation method, because its shows the environmental hazard and highly inflammable and its showing the safe hazard.
2. Residual monomers arevery small amount which may be toxic and hazardous to life are monitored.[36]

DISADVANTAGES

- In this system loading of water soluble drug are cannot be used for the microsponges drug delivery system.
- This system is required for the long time of reaction in the monomers.
- In this system drug are soluble in volatile water soluble solvent.
- Microsponges are not uniform or irregular in structure.
- It may be causes disruption in the structure.
- It should be cracking and shrinkage of the microsponges.[37]

METHOD OF PREPARATION

Microsponges prepared by using Quasi-emulsion solvent diffusion method. External phase are prepared by containing 200 ml of distilled water and 40mg PVA (polyvinyl alcohol). Then internal phase are prepared, it consisted of tranexamic acid, polymer such as eudragit and ethyl alcohol. eudragit are dissolved in ethyl alcohol and then drug are slowly added the polymeric solution in dissolved under the ultrasonication at 35^0c. triethylcitrate (TEC) which was added in amount of the 20 % of purpose of facilitated theplasticity. Inner phase are prepared in the 60^0c and then added in the previously prepared external phase at room temperature. Then continuous stirring for 60 min. then mixture filtered and isolated the microsponges then the washed and dried in vacuum oven for the 40^0c for 1 h.[38]

RELEASE MECHANISM[39]

Mechanism of the drug release in microsponges are designed to release in the given amount of active ingredient are time in a response to the one or more external triggers such as pressure, solubility and temperature change.

1) Pressure

Formulation are applied into the skin in rubbing or pressure are applied can be release in their active ingredient from the microsponges to the skin.

2) Solubility

Solubility of the microsponges is loaded with the water soluble ingredients such as antiseptics and antiperspirants, ingredient will be release in the presence of water. They ingredients are releasing it should be activated in diffusion into the consideration of the partition coefficient of the ingredient between the outside system and microsponges.

3) Temperature change

Formulation contain the some entrapped in active ingredients can be viscous in form at the room temperature to the spontaneously flow from the microsponges into the skin. When the skin temperature is increased to the increased in the flow rate and hence release. Studied by the drug release into the topical semisolid dosage form are by using Franz-type static diffusion cells.

4) PH

Formulation having discharge the active ingredient are based on PH triggered system is an altering the coating of the microsponges .this system has several advantages and uses in the drug delivery system. The performance of the PH triggered study carry out by using the USP spindal dissolution apparatus.[40]

Evaluation of Microsponge

i) Particle size determination

In this process determination of the particle size analysis of loaded and unloaded microsponges performed by using the laser light diffractometry and other suitable method .it should be expressed in the values for all formulation mean size range. drug release cumulative percentage from the microsponges in different particle size are plotted against time to the study effect of particle size on the drug release. Size having larger than 30 µm of particle they can impart gritty felling and particle size having between the 10 µm - 25 µm use in the topical formulation.

ii) Morphology and surface topography.

This process prepared microsponges are coated with gold palladium under the orgon atmosphere in the room temperatures and then studied by using scanning electron microscopy (SEM) for the determination of surface morphology of the microsponges. Scanning electron microscopy determine by the fractured microsponge particle are illustrate of its ultra structure.

iii) Determination of loading efficiency and production yield.

Determination of the production yield of microsponges can be calculated accurately by the initial weight of the raw material and obtained last weight of the microsponges.

$$Production\ yield\ (PY) = \frac{Practical\ mass\ of\ microsponges}{Therotical\ mass\ (Polymer + Drug)} \times 100$$

Determination of the loading efficiency (%) of microsponges can be calculated by the using the following equation:

$$Loading\ efficiency = \frac{Actual\ drug\ content\ in\ microsponges}{Therotical\ drug\ content} \times 100$$

iv) Determination of true density

Measured by true density of the microsponges is using the ultra-pycnometer under the helium gas and calculated from the mean of repeated determination.

v) Determination of pore structure

Determination of diameter and volume of the pore are controlling the duration and intensity of effectiveness of the active ingredient. Diameter of the pore are affected the migration of active ingredient in from microsponges to the vehicle which the material is dispersed. Mercury instrusion porosimetry employed to the study effect of the pore volume or diameter in the rate of drug release from the microsponges. Parameters of the porosity in microsponges such as total pore surface area, shape and morphology of the pore, average pore diameter, intrusion- extrusion isotherm pore size distribution and apparent and bulk density determine by using the mercury intrusion porosimetry.

vi) Compatibility studies

Compatibility study of the drug reaction can be carried out by using thin layer chromatography (TLC), drug excipient interaction study are carry out by fourier transform infrared spectroscopy (FT-IR), study of the crystallinity of the drug using x-ray diffraction (XRD) and differential scanning colorimetry (DSC). Study of Differential scanning colorimetry carry out accurately weighted 5 mg of sample into the aluminum pan and sealed then the run for heating 15^0c/min. temperature range 25-430^0c in atmosphere of nitrogen.

vii) Polymer / monomer composition

Drug release from the microsponges some factors govern such as size of microsponge, drug loading, polymer composition. In microsponge drug delivery system of the polymer composition affected in partition coefficient of drug entrapped between the vehicle and microsponges delivery system and influence on release of entrapped drug. when the drug release from the microsponge different polymer composition are studied by plotting cumulative % drug release against time. Total amount of the drug release and release rate from system composed of ethylene glycol dimethacrylate or methyl methacrylate slower than styrene/divinyl benzene system.

viii) Resiliency

The formulation of the microsponges need of resiliency (viscoelastic properties) of microsponge can be modified to produce beadlets is softer and firmer. Cross-linking tends are increases when to slow down the rate release. Study and optimizing the resiliency of the microsponges will be required by considering release function of cross-linking with time.

ix) In-Vitro Dissolution study

Dissolution study of the microsponges can be carried out by the using dissolution apparatus USP XXIII with the modified basket consist of the 5 µm of stainless steel mesh. They have speed 150 rpm rotation. Dissolution medium are selected and fill while considering the solubility of active to ensure and maintain the sink condition. Different time of intervals sample is collected and analysis by the suitable analytic method.

x) Kinetics of release study

Determinationof kinetics release mechanism ofdrug release and to compare release profile differences of microsponges, used in amount of drug release versus time. Analyzed the release data in following the mathematical models:

$Q=K_1t^n$ OR Log $Q=\log k_1+n\log t$

Where,

Q - is amount of release at time (h),

n - is a diffusion exponent which indicates the release mechanism,

k_1 - is a constant characteristic of drug-polymer interaction.

From the slope and intercept of the plot of log Q versus log t, kinetic parameter n and k_1 is calculated.

For the purpose of comparison, data also subjected to equation, which may be consider simple, higuchi equation.

$Q=k_2 1^{0.5}+c$

Above equation release data are depend upon the square root of time, give in straight line release profile, k_2 presented as a root lime dissolution rate constant and C as a constant.[41,42]

CONCLUSION

This study presented the microsponge drug delivery system which were developed for the topical drug delivery system. which are mainly used in cosmetics, sunscreens, over –the-counter skincare and prescription products. Microsponge drug delivery system help in increasing the stability of the drug in formulation. In this system entrapment of its ingredient and contribute toward improved stability, reduced side effects and enhanced formulation flexibility, this technique are non-irritating, non- allergenic, non-mutagenic and non-toxic. this system is valuable drug delivery matrix substance for various therapeutic applications in the future.

ACKNOWLEGMENT: - My heartiest thanks to Asst. Prof S. A. Tadavi, and the management of P.S.G.V.P.M's College of Pharmacy, Shahada for providing there guidance, suggestion and support during study.

FUNDING: - Nil.

AUTHORS CONTRIBUTION: - All the authors have contributed equally.

CONFLICT OF INTEREST: - None.

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