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REVIEW ON MICROSPONGE LEADING MICROPOROUS PARTICULATE TECHNOLOGY WITH CONTROLLED RELEASE, IMPROVE STABILITY TO PROVIDE OPTIMUM SKIN DISORDERS MANAGEMENT ENVIRONMENT FOR THERAPEUTIC APPLICATION

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Keywords:

Controlled release, Drug delivery, Microsponges, Stability, Validation

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ABSTRACT: Although serious systemic and cutaneous side effects need a novel delivery system that provides prolonged and controlled drug release, minimum systemic drug absorption with reduced side effects. Microsponge, a drug delivery system, possesses the versatility to load a wide range of active ingredients to facilitate the controlled release of active ingredients to reduce systemic exposure and to reduce side effects. Microsponges are polymeric sponges that consist of interconnecting voids with a non-flexible structure with a porous surface. Microsponge delivery technique provides extended product stability, enhanced safety, enhanced formulation flexibility, enhanced product efficacy, enhanced aesthetic appeal with reduced side effects. Therefore, this review provides an overview of microsponge technology with its methodology, mechanism, programmable release, and characterization of the microsponge delivery system. Review compiled recent data regarding marketed formulation, their applications, and the list of patents. This review also contains validation, stability guidelines, and examples of drug release profiles from microsponges. Microsponges are frequently used for topical use but recently used for oral use.

INTRODUCTION: Deceive a privileged drug concentration due to the microsponge drug delivery system which contains interconnecting networks and pores leads to control release rate, and target drugs to a particular body site comprise [1]. Won in 1987 developed microsponge technology, which was further patented as an advanced polymer that is useful for a prescription pharmaceutical product, cosmetics and over the counter product [2].

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These delivery systems contain porous polymeric structure sponge-like sphere particle with interconnecting voids inside its non-flexible configuration and hefty porous surface, which releases the drug in a controlled manner [3]. Various pharmaceutical formulation developed through possible headed integration of microsponge like; gels, emulsions, tablets, and capsules. The micro-sponges have subsequent properties: size range - 5-300 µm in diameter, 1µm sphere contains 10000 pores, pore volume – 0.1 – 0.3cm^3/g, and internal-pore structure - 10 ft. in length (20 to 500m^2/g).

Microsponge application, as a controlled topical delivery system needed to be developed for the following reason, which is shown in **Fig. 1**.

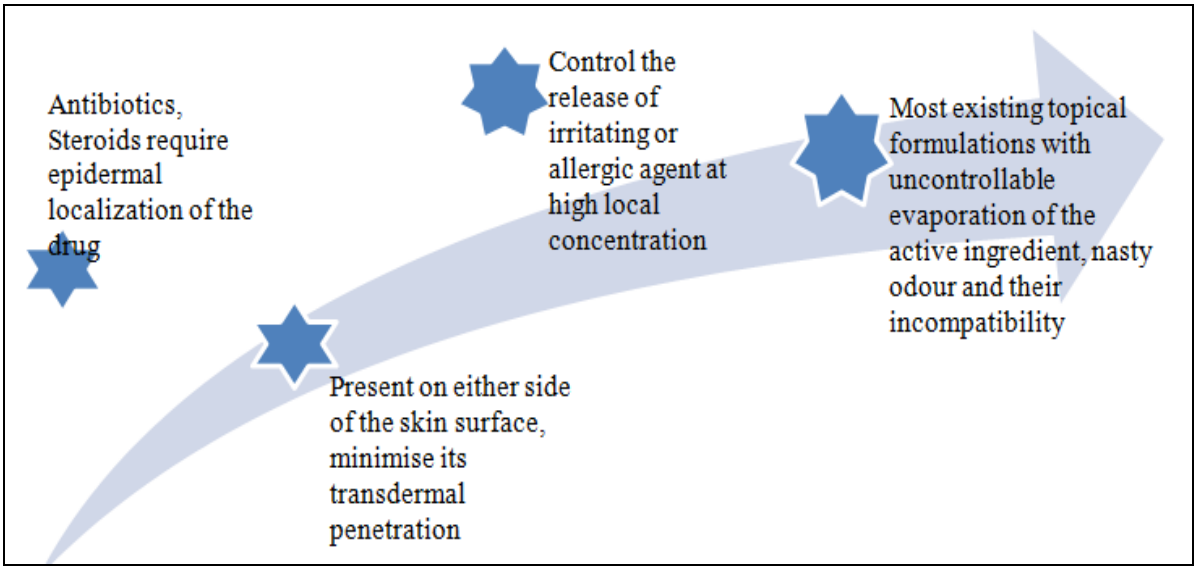

FIG. 1: CONTROL RELEASE OF MICROSPONGES IS REQUIRED IN THE ABOVE MENTIONED CONDITIONS

The objectives of microsponges formulation are to grasp drug ingredients in a circumscribed atmosphere. Endow with controlled deliverance of oral medication to the lower gastrointestinal (GI) tract. Improve the solubility of feebly water-soluble drugs through entrapment in the microsponge system pores. Boost the dissolution of the drug. Lessen the irritation at the site of the application.

The active ingredient to be entrapped into microsponge should have the following properties, as shown in **Fig. 2** [6-8].

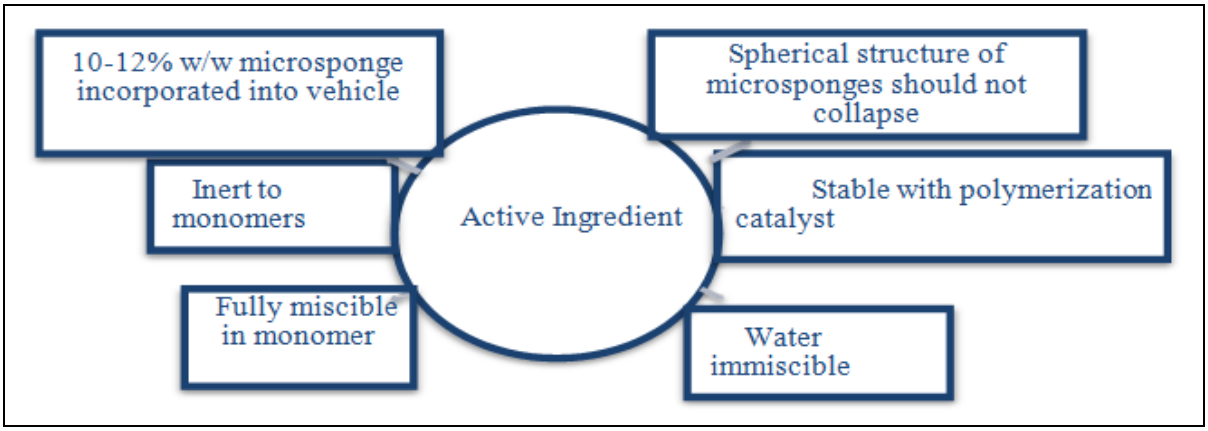

FIG. 2: DRUG PROPERTIES TO ENTRAP IN MICROSPONGES

Microsponges strategy with following potential advantage over other delivery systems as listed in **Fig. 3**. [7-11]

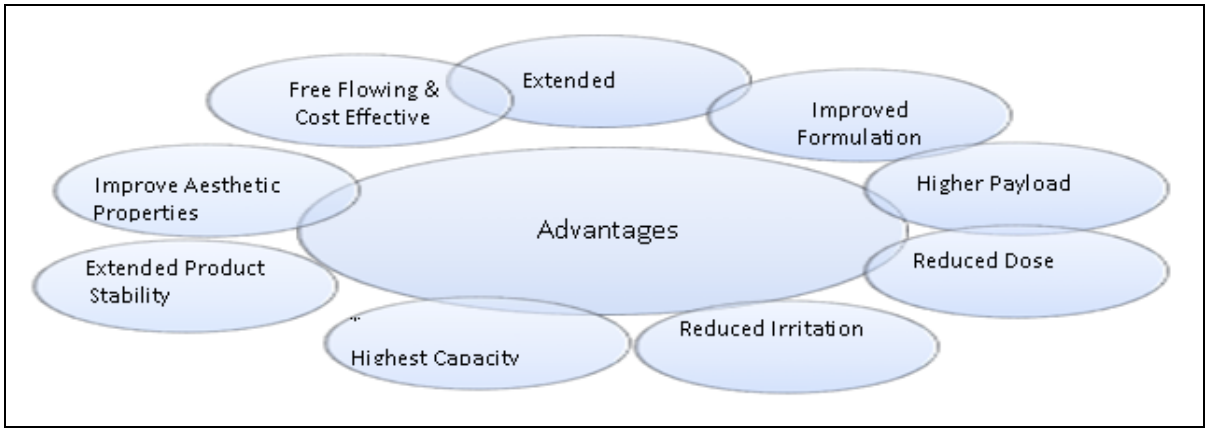

FIG. 3: ADVANTAGES OF MICROSPONGES DRUG DELIVERY SYSTEM

1. Method of Preparation of Microsponges: Entrapment of drug substance into microsponge particles mostly done by two methods namely (one-step process or by two-step process): Quasi-Emulsion Solvent Diffusion method and Liquid-Liquid Suspension Polymerization method

1.1. Quasi-Emulsion Solvent Diffusion Method: In this method, the former two phases (external and internal phase) is prepared. The external phase consists of organic solvents and distilled water containing surfactants and internal phase containing drug, polymer, solvent, and plasticizer. The Quasi-Emulsion Solvent Diffusion is a two-step process, as shown in **Fig. 4.** [11-14]

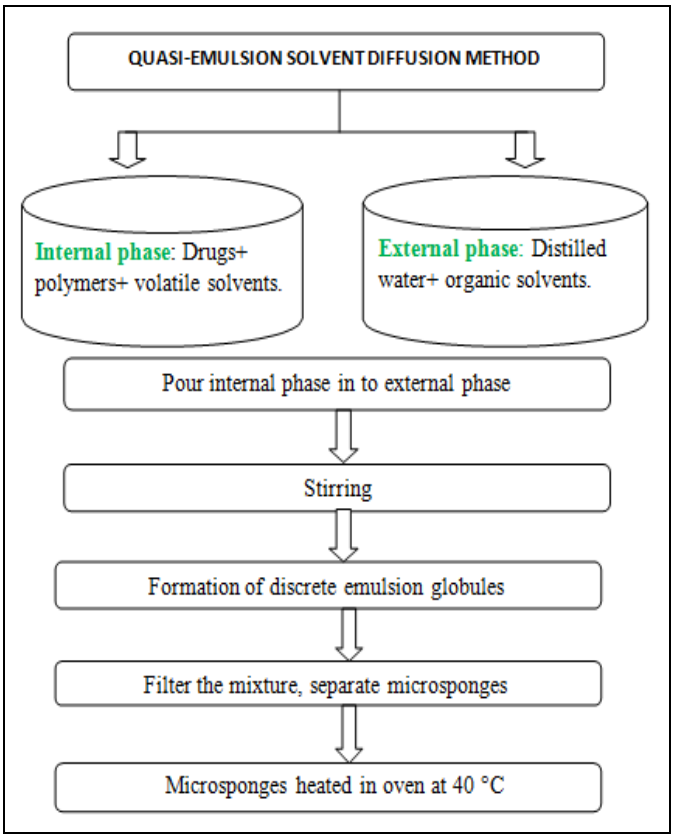

FIG. 4: QUASI-EMULSION SOLVENT DIFFUSION

1.2. Liquid-Liquid Suspension Polymerization Method: Microsponges is primed by liquid-liquid suspension polymerization method; in this procedure, initially, the monomer and active ingredient assorted into an appropriate solvent subsequent to that the muddle solution is dispersed in the aqueous phase containing (surfactants) with the agitation. Throughout the polymerization progression, the solvent is distant, and spherical porous microsponges are formed, which is shown in **Fig. 5** as follows [12-16].

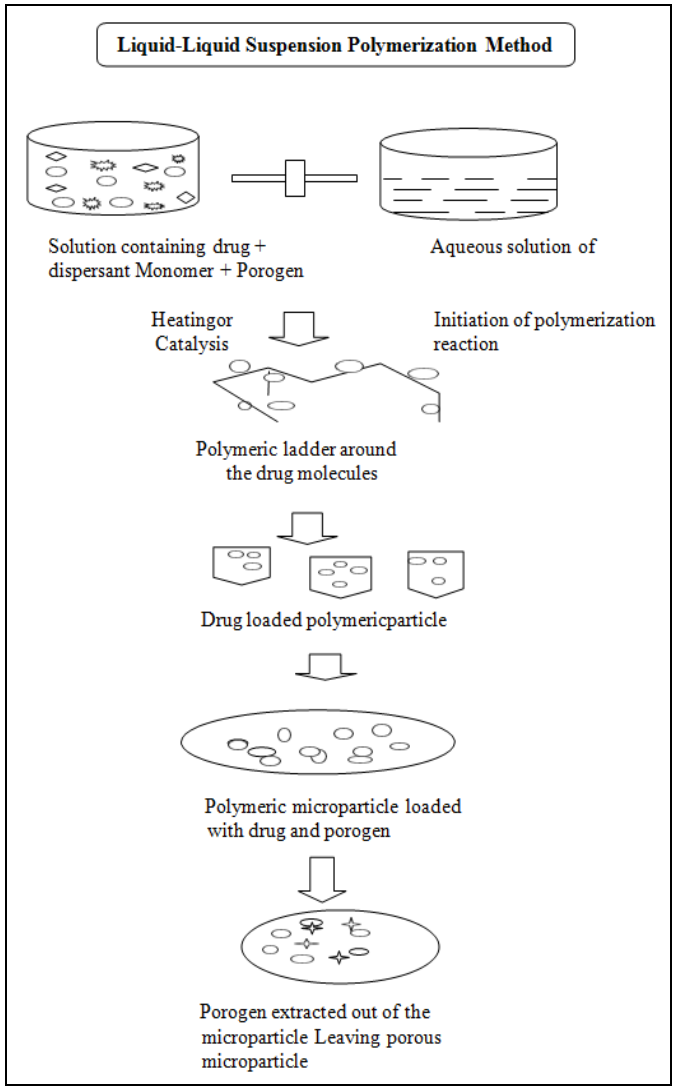

FIG. 5: LIQUID-LIQUID SUSPENSION POLYMERIZATION METHOD

2. Mechanism: Drugs should not be too much soluble in the preferred vehicle, so it is important that formulating vehicles for the proposed mechanism throughout compounding of refined products should less to endow benefits of control steady release. Alternatively addition of drugs in solvent in liberated form and device solvents which has nominal solubilizing power for microsponge entrapment. Release mechanism triggered by a shift in equilibrium from microsponge polymer to carrier vehicle provides an initial loading dose of the drug before releasing in microsponge entrapment. The drug release rate depends on the partition coefficient between polymer and solvent, surface area, mean pore diameter, moisture, pH, temperature, and pressure [16-17].

The details of the mechanism of action showed in **Fig. 6** and **7** as follows:

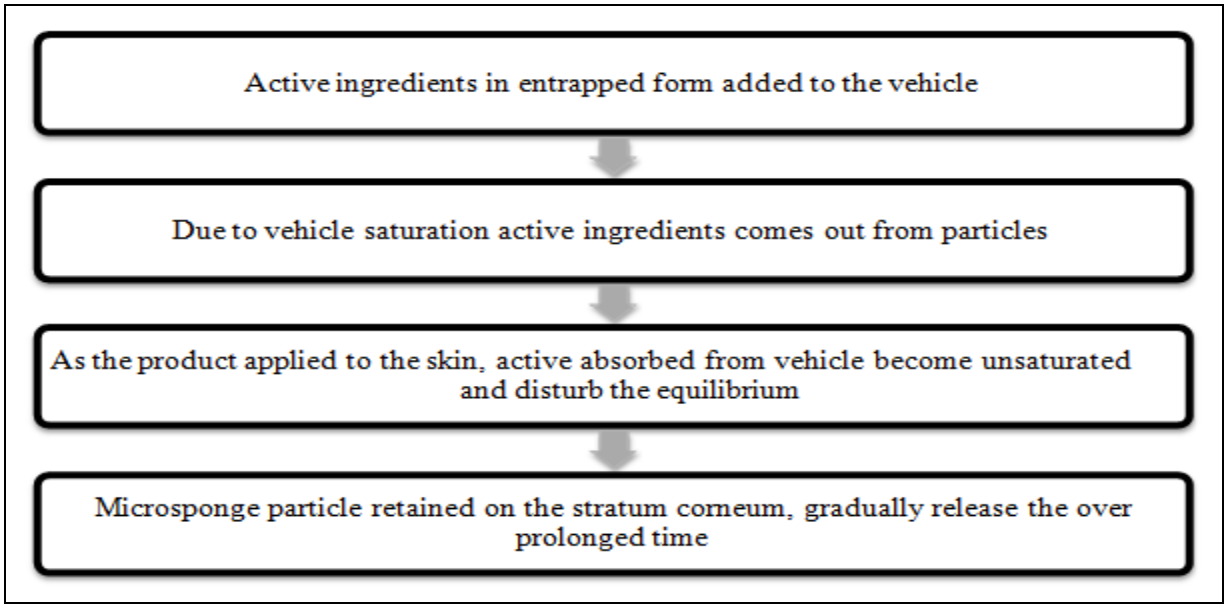

FIG. 6: MECHANISM OF ACTION OF MICROSPONGE FORMED

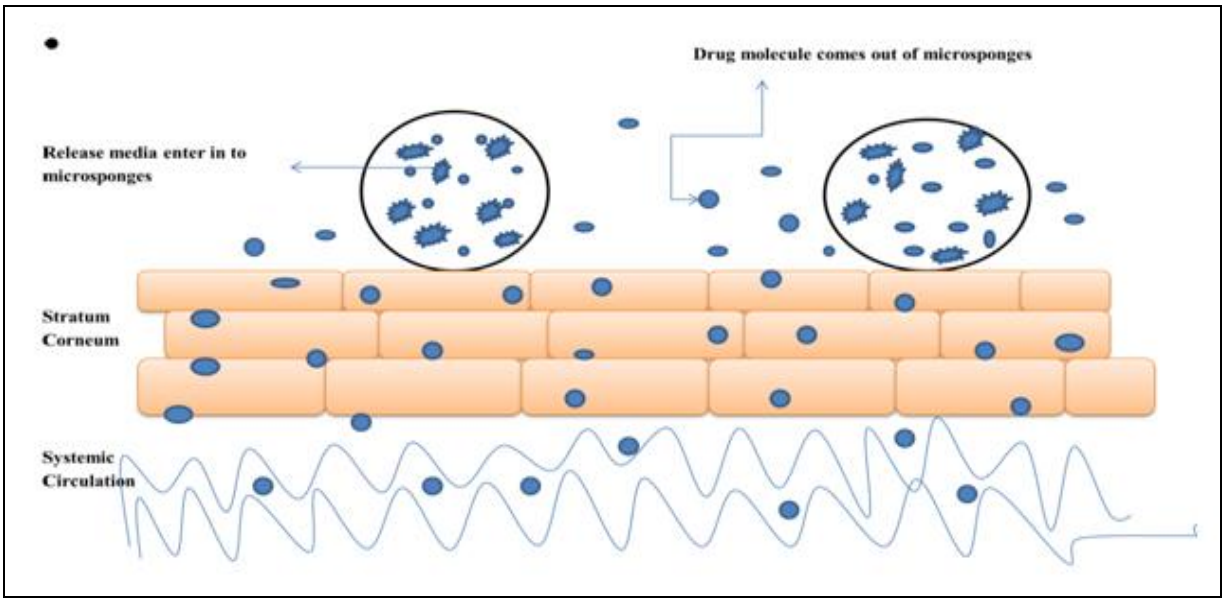

FIG. 7: DRUG SUBSTANCE RELEASE FROM MICROSPONGE AT THE SITE OF ACTION

2.1 Factors Affecting Release Mechanism:

2.1.1 Pressure Triggered Systems: When microsponge formulation rubbed on-site release its entrapped material. The pressure trigger system depends on characteristics of sponge formed, nature of material entrapped, process, and formulation variables.

2.1.2 Temperature Triggered Systems: By increasing the temperature flow rate of active ingredient encumbered in microsponge can be enhanced especially when excessively tacky material entrapped. Feasibility increase in temperature can increase in the release of active from microsponge.

2.1.3 pH Triggered Systems Formulation pH depends on the site of the same application pH triggers the release rate of active ingredient this can be achieved by modifying coating of microsponge.

2.1.4 Solubility Triggered System: Microsponge encumbered with hydrophilic ingredients that deliver active ingredients in the existence of water. This release rate depends on the capability of the external medium to suspend the active, the concentration gradient, or the capability to puff up the microspore network [8-9, 17-19].

The increased release of entrapped drug with several factors shown in **Fig. 8**.

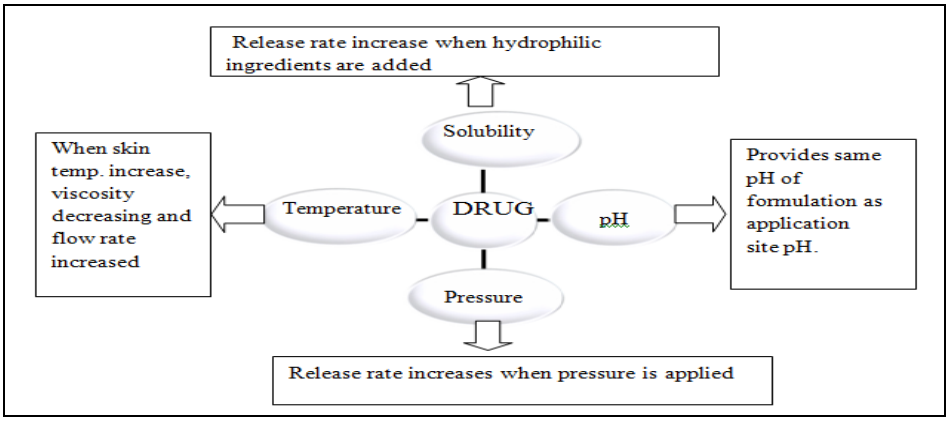

FIG. 8: FACTORS AFFECTING RELEASE OF DRUG FROM MICROSPONGE FORMULATION

3. Methods of Drug Release: The methods for analyzing drug release from microsponges and permeation through the skin are divided into three categories, as shown in **Fig. 9** [20-21].

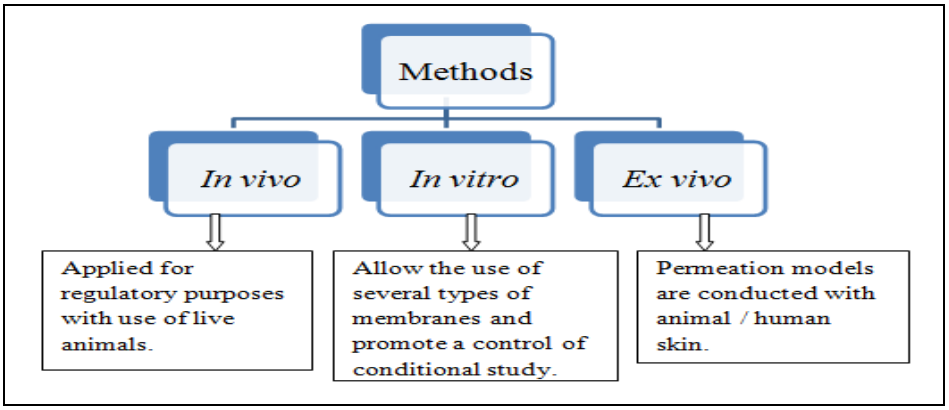

FIG. 9: METHOD ADOPTED FOR STUDY OF DRUG RELEASE FROM MICROSPONGE FORMULATION

4. Research on Prepared Microsponges: Recent research on microsponge delivery technique summarized in **Table 1,** which contains drugs, polymers, solvent, method of preparation with results as shown below:

TABLE 1: SUMMARY OF RECENT RESEARCH ON MICROSPONGES DRUG DELIVERY SYSTEM

Author	Drug used	Polymer used	Solvent used	Method of preparation	Result
Rekha *et al.*, (2011)	Mometasone furoate	Eudragit RS-100	Dichloromethane and Ethanol	Quasi emulsion solvent diffusion	Increasing the ratio of the drug: polymer will decrease the release rate of the drug from microsponges [22]
Swetha *et al.*, (2011)	Etodolac	Ethylcellulose, Eudragit RS100	Dichloromethane and Ethanol	Quasi emulsion solvent diffusion	Formulation of Etodolac with Ethylcellulose give the maximum drug release 99.3% within 8 h [23]
Maiti S *et al.*, (2011)	Diclofenac sodium	Ethylcellulose	Dichloromethane	Quasi emulsion solvent diffusion	Increasing the drug and polymer ratio will increase their release rate followed Higuchi diffusion kinetic [24]
Yerram Chandramouli *et al.*, (2012)	Acyclovir sodium	Ethylcellulose	Dichloromethane	Emulsion solvent diffusion method	Optimized F1 released 50.85% drug at 8 and Ficks law of diffusion not followed [25]
Karthika R *et al.*, (2013)	Lornoxicam	Eudragit RS 100	Ethyl alcohol	Quasi- emulsion solvent diffusion	Drug releases follow First-Order kinetic and mechanism followed Hixson- Crowell model [26]
Sonali *et al.*, (2014)	Prednisolone	Eudragit RS 100	Ethyl alcohol	Quasi- emulsion solvent diffusion	Cumulative release of microsponges 48-87% at 8 h [27]
Hamid Hussain *et al.*, (2014)	Diclofenac sodium	Ethylcellulose	Dichloromethane	Quasi emulsion technique	The drug content of different formulations was found from 19.07 to 33.09. [28]

Riyaz Ali M. Osmani *et al*., (2015)	Domperidone	Eudragit RS100	Dichloromethane	Quasi- emulsion solvent diffusion	Drug- Polymer ratio of 1:2 more efficient and 76.38% drug releases at 8 h [29]
Rajurkar VG *et al*., (2015)	Naproxen	Eudragit RS100	Dichloromethane and Ethanol	Quasi- emulsion solvent diffusion	Increase in the ratio of the drug: polymer resulted in control release rate of naproxen from microsponges [30]
Atmaram P *et al*., (2015)	Oxybenzone	Ethylcellulose	Dichloromethane	Quasi- emulsion solvent diffusion	Controlled release of drug from microsponges promote the retention of drug with reduced permeation activity [31]
Pande VV *et al*., (2015)	Sertaconazole nitrate	Eudragit RS-100	Dichloromethane	Quasi- emulsion solvent diffusion	Batch F5 releases 69.38%drug at 8 hrs. that followed Zero-Order kinetics [32]
Moin A *et al*., (2016)	Fluconazole	Eudragit S-100	Ethanol and Dichloromethane	Quasi- emulsion solvent diffusion	Microsponges loaded gel releases 85.38%drug at 8 h [33]
Charagonda S *et al*., (2016)	Famotidine	Eudragit RS-100	Dichloromethane	Quasi- emulsion solvent diffusion	% Entrapment efficiency was 88.83% and % cumulative release 86.9% for F6formulation [34]
Shapali A *et al*., (2016)	Bifonazole	Propylene Glycol	Dichloromethane & Polyvinyl alcohol	Quasi- emulsion solvent diffusion	80.71%drug release of an optimized batch at the end of 24 h [35]
Bhandare CR *et al*., (2016)	Risperidone	Ethylcellulose and Eudragit RS 100	Ethyl alcohol	Quasi- emulsion solvent diffusion	Ethylcellulose and Eudragit gave better drug release and encapsulation efficiency as compared to their single-use [36]
Mohanty D *et al*., Q(2016)	Betamethasone	Eudragit RS 100	Ethanol and Dichloromethane	Quasi- emulsion solvent diffusion	a pH of microsponges gel was6.8 and 73% drug release [37]
Naji GH *et al*., (2017)	Piroxicam	Eudragit RS, RL, S -100	Dichloromethane and Ethanol	Quasi- emulsion solvent diffusion	Piroxicam micro sponge carbopol 934 gel produced a significant ($p<0.05$) improvement of the *in-vitro* release than pure piroxicam gel [38]
Selvapriya A *et al*., (2017)	Nateglinide	Eudragit RS 100	Dichloromethane	Quasi- emulsion solvent diffusion	Microsponge with drug-polymerr ratio 1:3 was more proficient to give controlled release at the end of 12 h [39]
Othman MF *et al*., (2018)	5-Fluorouracil	Eudragit RS 100	Acetone	Oil in oil emulsion solvent diffusion	MS loaded 5-FU was more effective than 5-FU itself [40]
Patil N *et al*., (2018)	Ritonavir	Ethylcellulose	Dichloromethane	Quasi- emulsion solvent diffusion	Drug release of 50.32% at the end of 10 h [41]

5. Characterization of Microsponges: Various methods are used for the characterization of microsponges.

5.1 Preformulation Studies: Preformulation is an assemblage of studies to predict physicochemical properties of a new drug substance that variable drug performance and important parameters for the development of a dosage form and formulation aspects. The Group of studies before formulation development is stated in **Fig. 10** [42-44].

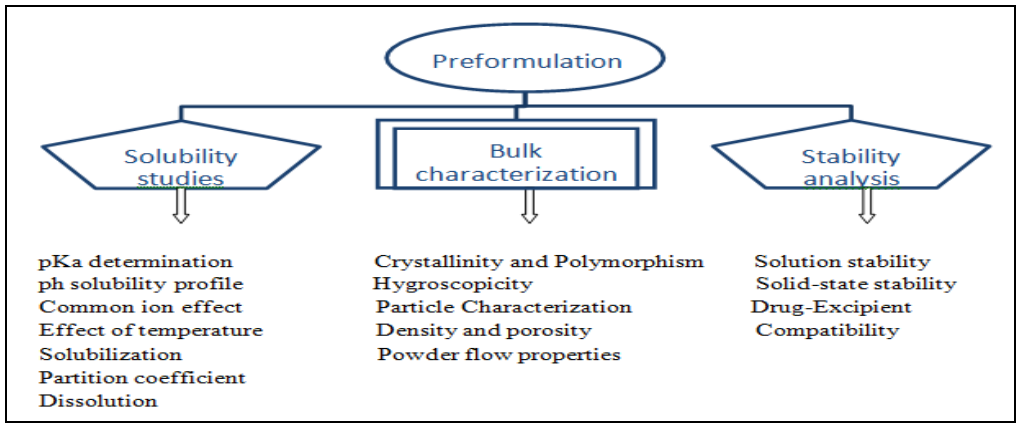

FIG. 10: BRIEF SUMMARY OF PREFORMULATION STUDIES

5.1.1 Particle Size and Size Distribution: Particle size distribution testing done by using laser diffraction, microfluidic resistive pulse sensing, electro zone, single-particle optical sensing, sieve analysis, dynamic light scattering, air permeability diameter and nanoparticle tracking analysis. Particle size analysis designed to evaluate and report information about the size and range of a set of particles that affect the texture of formulation, predict material representation. Controlling particle size distribution attributes free-flowing properties of the powder and decreases agglomerates or polymerization at most important handling, packing, research quality control, and product development. Particle size analysis of loaded and unloaded microsponge can be performed by laser light diffractometry, mean size range, cumulative percentage drug release of microsponge of different particle size can be performed [45-51].

5.1.2 Compatibility Studies: Compatibility studies of drug-excipients are carried out to ensure that a finished dosage form does not show any unplanned reaction. Compatibility studies testing done by differential scanning calorimetry, powder X-ray diffraction, isothermal microcalorimetry, differential thermal analysis, isothermal stress testing, Fourier transform infrared spectroscopy, scanning electron microscopy, hot stage microscopy, thin layer chromatography, high-performance thin layer chromatography and solid-state nuclear magnetic resonance spectroscopy [45-52].

5.1.3 Morphology and Surface Topography of SPM: Available techniques for morphology and surface topography of microsponges are photon correlation spectroscopy (PCS), Scanning electron microscopy (SEM), transmission electron microscopy (TEM). Microsponges are encrusted by gold-palladium at 25°C - 27°C in an argon atmosphere, so surface morphology of microsponges is evaluated [45-54].

5.1.4 Determination of Loading Efficiency and Production Yield: Loading efficiency means quantity of drug encumbered per unit weight of microsponges. The loading efficiency of the microsponges can be done by using the following equation [45-51].

Loading efficiency = Actual drug content in microsponges / theoretical drug content

For calculating % loading efficiency, the above equation should be multiplied by 100.

The production yield of microsponges are determined by using the following equation:

% Production yield = Production yield / theoretical mass (polymer + drug) × 100

5.1.5 Polymer / Monomer Composition: Microsponge releases active constituents depends on particle size, drug loading, and polymer composition. The release rate of microsponges exaggerated by polymer composition due to change in partition coefficient between polymer and vehicle.

By intrigues, a graph of cumulative % release of the drug against time, the release rate of microsponges can be determined. Appropriateness of monomer combination with a drug will be screened for studying drug release profile [45-51].

5.1.6 Resiliency: Visco-elastic properties of microsponges should be optimized as per the requirement of the finished dosage form. The release rate of microsponges will be slower due to greater cross-linking. Release rate can be calculated by plotting graph of drug release against time [45-51].

5.1.7 Bulk and Tapped Density, Hausner's Ratio, Carr's Index, Angle of Repose: The tapping method is used for calculating the tapped density and % compressibility index. Angle of repose (θ) of the micro microsponges is determined by fixed funnel method, tilting box method, and rotating cylindrical method and other parameters are calculated by using following equation [55]:

- Bulk density = Mass of Microsponges / Volume of microsponges before tapping
- Tapped density = Mass of Microsponges / Volume of microsponges after tapping
- Hausner's ratio = Tapped density / Bulk density
- Carr's index = (Tapped density- Bulk density) / Tapped density × 100
- Angle of repose (θ) = $\tan^{-1}$ (h/r)

  Where, h = Height of the powder cone and r = Radius of powder cone.

5.1.8 Determination of Encapsulation Efficacy: The encapsulation efficacy of microsponges means %age of active constituents entrapped into microsponges, which is calculated by following equation [45-51].

Encapsulation efficacy = Actual drug content/ Theoretical drug content × 100

5.1.9 Diffusion Test: Franz diffusion cell is used for measuring drug release from microsponges. Membrane from animal skin (rat abdominal skin, mouse skin, and mucin) and artificial membranes (cellulose acetate and silastic) are used for determining dug release and permeation profile. Microsponge formulation is applied on membranes in donor compartment, and diffusion studies are studied by using phosphate buffer as a dissolution medium in receptor compartment at 37 ± 1 °C [58-59].

5.1.10 Stability Studies: Stability studies of micro-sponge in order to predict and ensure shelf life for acceptance and approval of microsponge based formulation over different time periods, temperature and humidity conditions.

Types of Stability: Chemical stability, physical stability, microbiological stability, therapeutical stability and toxicologic stability. Stress testing includes effects of temperature, humidity, photo-lysis and oxidation on drug substances. Photo-stability is also a part of stress testing. The selection of batches includes three primary batches; these batches should be manufactured to a minimum pilot scale by the same procedure involved in the final production batch. The specification contains a list of tests, reference to analytical procedures, and proposed acceptance criteria. Stability studies include testing of those attributes of the drug substance that are susceptible to change during storage and possibly to influence quality, safety and/or efficacy.

Frequency of testing for drug substances with a planned re-test period of at least 12 months, the frequency of testing for long term storage condition should be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period. Four ICH stability climatic zones are described for the purpose of assessment of stability worldwide as follows in **Tables 2, 3, 4,** and **5** [56-57].

TABLE 2: WORLDWIDE TEMPERATURE ZONE WITH TEMPERATURE AND HUMIDITY CONDITION

S. no.	Zone	Climate	Temperature Condition
T	Zone I	Temperate zone	21 °C ± 2 °C
2.	Zone II	Mediterranean zone	25 °C ± 2 °C
3.	Zone III	Hot and dry zone	30 °C ± 2 °C
4.	Zone IV	Hot and humid zone	30 °C ± 2 °C
5.	Zone IVb	ASEAN testing condition hot/higher humidity	30 °C ± 2 °C

TABLE 3: STORAGE CONDITION IN GENERAL CASE

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C/ 60% RH ± 5% RH Or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C/ 65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

TABLE 4: DRUG SUBSTANCES INTENDED FOR STORAGE IN A REFRIGERATOR

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

TABLE 5: DRUG SUBSTANCES INTENDED FOR STORAGE IN A FREEZER

Study	Storage condition	Minimum time period covered by data at Submission
Long term	- 20°C ± 5°C	12 months

5.1.11 Statistical Analysis: The records be prevalent from all testing were subjected to statistical examination by Student t-test and one-way analysis of variance (ANOVA) via Graph Pad Instate software [45-51].

6. Drug Delivery from Microsponges:

6.1 Methodologies Applied: Methodology reliant on the drug and the dosage form. The drug influences the predilection of the receiver medium, whereas the dosage form does the temp. of analysis and equipment to be used.

The control of the temperature is extensive to stimulate the application site of dosage forms. Oral and suppository dosage form should be evaluated at 37 °C to mimic the body temperature. Topical formulations usually evaluated at 32 °C, the temp.

of the skin. The stirring speed generates a flux which alters the liquid/solid interface stuck between solvent and drug. In order to maintain a reproducible laminar flow, the stirring should be maintained at a moderately low rate.

Most frequently used apparatuses are static and used to inspect the drug release profile from microsponges are:

- USP apparatus 1
- USP apparatus 2
- Vertical diffusion cell
- Modified Rossett-Rice cell [1, 60-6]

6.2. Kinetic Models: To figure out the control mechanism of drug release, *in-vitro* data of release profile have been used to authenticate the integrity of the kinetic equation.

6.2.1. Zero-Order Kinetics: Defines a system in which the release of drugs is a function of time only. The process is autonomous of active concentration and proceeds at a constant rate.

$$Q_t = Q_0 + k_0.t$$

Where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug, k_0 is the zero-order constant.

First-order defines a system that alteration relies on concentration gradient with time. A straight line will be obtained as a result with a slope of $k_t/2.303$ and intercept at t = 0 of log Q_0.

$$\text{Log } Q_t = \log Q_0 + k_1.t/2.303$$

6.2.2 The Higuchi Model: Describes a system in which amount of drug release and the square root of time is proportional to each other

$$Q_t / Q_\infty = k.t1/2$$

Where Q_∞ is the cumulative amount of drug released at the infinite, k_1 is the first-order constant.

6.2.3 Korsmeyer and Peppas Model: Defines a system that is helpful in the case of multiple phenomena.

$$M_t / M_\infty = k.tn$$

Where M_t and M_∞ are cumulative quantity of drug release at time t and infinite time, k is the constant incorporating structural and geometrical characteristics of cumulative release device, n is a diffusion release exponent investigative of the mechanism of drug release for drug dissolution. Examples of the drug showing different kinetics are as shown in **Fig. 11** [1, 62-63].

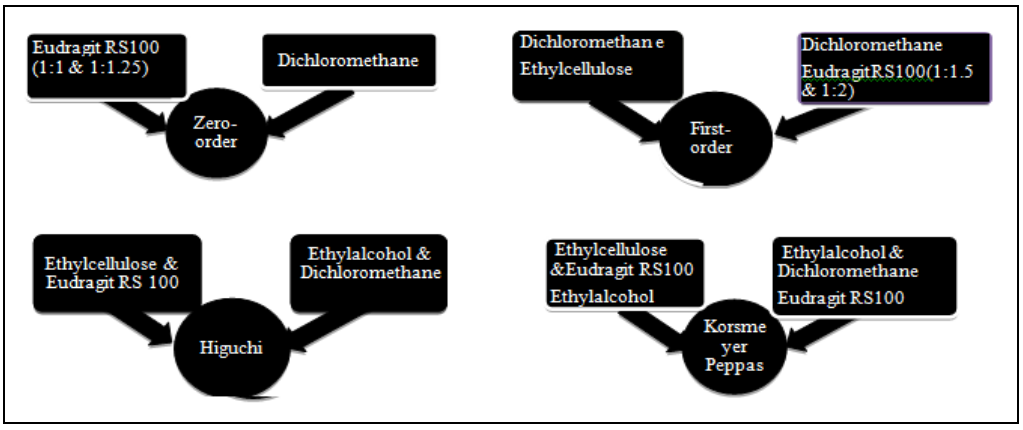

FIG. 11: DRUG SHOWING DIFFERENT KINETICS

It is possible to set up a classification of realistic behavior, according to n-value. Thus, n <0.5 designates the release that is governed with Fickian diffusion, in which the diffusion is superior to the progression of polymeric sequence relaxation.

n = 1 designate the release that is controlled merely *via* respite of polymeric chains and notorious as swelling (transport case II).

Values between 0.5 and 1.0 designate an unexpected transport (non-Fickian kinetics), subsequent to the phenomenon of both diffusion and swelling processes.

Kinetics of super case II characterized by n values more than 1, the effect of n values on the release mechanism of microsponges as shown in **Fig. 12** [64-66].

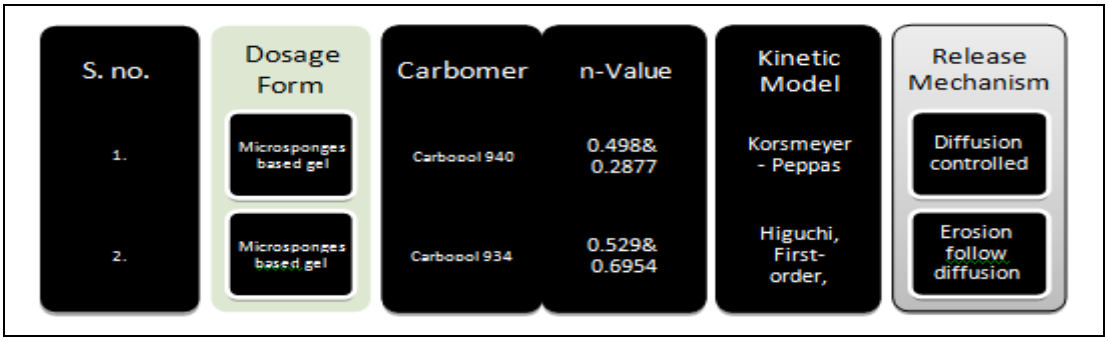

FIG. 12: EFFECT OF CARBOMERS AND N-VALUES ON RELEASE MECHANISM OF MICROSPONGES

5.15. Drug Release Studies: Microsponge releases active constituents in a précised amount in a specified time period due to the presence of interrelated channels. The relationship among the microsponge physical properties and the polymers are used for preparing microsponges, which influence the size and number of interrelated channels in microsponge, which ultimately influence the release rate of microsponges as shown below in **Fig. 13** & **14** [67-68, 36, 66, 69].

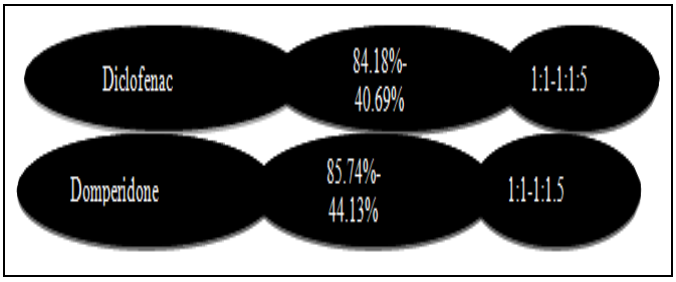

FIG. 13: EFFECT OF POLYMER RATIO ON RELEASE RATE OF MICROSPONGES

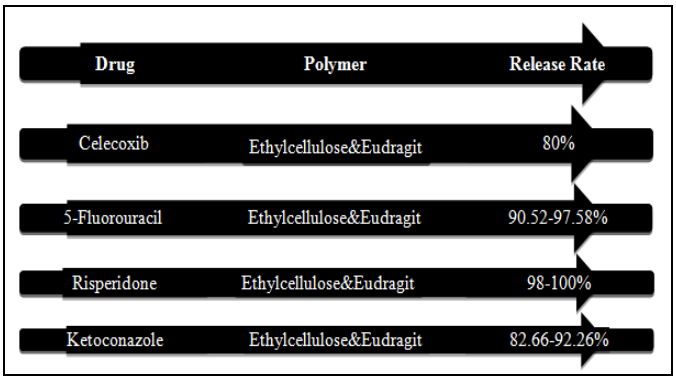

FIG. 14: EFFECT OF POLYMERS ON RELEASE RATE OF MICROSPONGES

7. Preclinical Studies: Preclinical studies include *in-vivo* animal models to identify microsponge based formulation initial safe dose and safety parameters. Type of preclinical testing includes short term animal study (acute) and long term animal studies (chronic). Acute studies to determine pharmacological action and toxicity and whereas chronic studies look for potential side effects and for reproductive effect. Preclinical trials are required for the regulatory body and also check for a kinetic profile of drug and selection of administration route.

8. Skin Irritation Study: The study protocol of skin irritation study approved from Institutional review board of India through institutional animal ethics committee other regulation like Declaration of Helsinki, the guidance of good clinical practice, ICH of the technical requirement for registration of pharmaceutical for humans and EMEA, CPMP/ICH/135/95JULY2002 give guidance for skin irritation studies.

Test microsponge based formulation has to be applied to an area of approximately 6cm^2 of skin and covered with gauze patch for 1 h. After 1 h, gauze is removed, and response is recorded. Same observation make under the application of controls.

The mean erythemal scores are recorded according to Draize in which 0 means no erythema, 1 means slighter erythema, 2 means moderate erythema, 3 means moderate to severe erythema, 4 means severe erythema.

9. Anti-inflammatory Activity by Ear Edema Measurement: After approval of the Animal Ethical Committee in accordance with CPCSEA guidelines. The anti-inflammatory activities are conducted with the use of male Swiss mice (25-35g), which is housed at 22 ± 2 °C under 12 h light and 12 h dark cycle. Induced edema in right ear with microsponge formulation of the amount per ear of cotton oil dissolved in 20 ml acetone. Measure thickness before and after 6 h of induction of inflammation by use of digital Vernier caliper and prepare result report documents [70-71].

10. Validation of Microsponges: The perception of validation was introduced in order to improve the eminence of pharmaceuticals. Process validation is stated as troup and analysis of data from the process design stage during the production. Process validation confirms that a process produces a product of a determined standard and quality characteristics.

10.1. Process Validation Reports Contains: Product name, generic name, label claim, shelf life, batch size, no. of batches selected for study, batch no., batch manufacturing record no. and master formula record no.

10.2. Contents for Process Validation: Content should contain title, objective, scope, responsebility, references, batch selected for study, list of equipment, sampling plan, sampling detail, standard batch formulation, raw material details, flow diagram for manufacturing and packing, operation, cleaning, line clearance, area clearance, equipment clearance, environmental monitoring, preparation, filling, evaluation, crimping and coding, packing, summary and conclusion, approval, the preliminary approval, final approval.

10.3. Title and Objective: Process validation of microsponge formulation and determination of process by continually running the system and record all significant information and data.

10.4. Scope: To be performed when there is a change in Mfg. process or formula, equipment used, Mfg. site/location.

10.5 Batch Selected for Study: Firstly, three batches will be selected and maintain a record with manufacturing date, expiry date, and batch size.

10.6 List of Equipment: Electronic weighing balance, Stirrer, Homogenizer, Hot air oven, UV-Spectrophotometer, Zetasizer, Differential scanning Calorimetry (DSC), X-ray diffraction (XRD), Scanning electron microscopy (SEM), Transmission electron microscopy (TEM), Fourier-transform infrared spectroscopy (FTIR) and pH meter.

10.7 Area Clearance: Cleanliness of the area, cleanliness of process control equipment.

10.8 Equipment Clearance: Physically check clearance of equipment, check wash water report, sterilization of equipment.

10.9 Environment Monitoring: Environmental condition should be maintained during the processing of microsponges as follows: Temperature - 25 ± 2 °C, Pressure - 6-15 Pascal, Relative Humidity - 50 ± 5%.

10.10 Evaluation: Preformulation studies, Particle size and size distribution, Compatibility studies, Morphology and Surface topography of SPM, Determination of loading efficiency and production yield, Polymer / Monomer composition, Resiliency, Bulk and tapped density, Haussner's ratio, Carr's index, Angle of repose, Dissolution tests, Determination of encapsulation efficacy, Stability studies, Statistical analysis and safety considerations- Skin irritation studies in rabbits, anti-inflammatory activity by ear edema measurement.

10.11. Summary and Conclusion: Process validations of 3 batches should be completed successfully. All the data should be reviewed and concluded that.

10.12 Cleaning Stage: Data from the cleaning stage indicates that all the parameters and analytical results are lies well within specification. Hence the stage will be validated.

10.13. Bulk Manufacturing Stage: Data from the manufacturing stage indicates that all the parameters and analytical results are lies well within specification. Hence, the stage will be validated [72].

11. Marketed Formulation: Microsponge delivery technique at the moment employed in a huge number of products vend by various cosmetic and toiletry companies.

Table 5 summarizes the marketed formulation with their brand name, drug, treatment, advantages, and manufacturer, as shown as follows [25, 73].

12. Intellectual Prospect of Microsponge Drug Delivery System: A number of patents were documented on the microsponge drug delivery system none of them deals with oral drug delivery. Patented MDS was used by advanced polymer systems for enhancing the safety, efficacy, and visual eminence of various products such as Tretinoin, Dimethicone, Salicylic acid, *etc*.

A patent on collagen microsponges was disclosed by Dean *et al*., in 1989 for immobilizing micro-sponges. Another patent includes microsponge impregnating non-wovel towel invented by Love *et al.,* in 2008, biodegradable photocatalytic nano-composite microsponges of Polylactic acid by Eugenia *et al*., in 2017, *etc*.

Proprietary technology was developed by AP Pharma using porous alginate microspheres with macromolecules like (vaccines and peptides) for oral controlled delivery. The company is conducting clinical trials for these carriers as a vehicle to deliver agents to lower G.I.T. by developing a composite tablet design with active ingredients loaded in microsponges [76].

13. Recent Advancement in Microsponge Drug Delivery System: Diverse advances in micro-sponge drug delivery systems were prepared by modifying the methods to make nanosponges, nanoferrosponges, porous microspheres, and porous microbeads. Nanosponges were used for passive targeting of cosmetic agents and incorporation of hydrophobic and hydrophilic drugs for example β-cyclodextrin nanosponge. By increasing drug-polymer ratio, particle size will be reduced. The pore size in β-cyclodextrin nanosponge modulated by CD-PMA molar ratio.

Nanoferrosponges were prepared by co-precipitation of polymer and magnetite. Nanoferro-sponge have improved penetration at a specific site due to the outer magnetic trigger. The magnetic trigger penetrates carriers into deeper tissues and then the exclusion of magnetic substances from the particle parting the porous structure.

Polymerization and cross-linking were activated by heating in the High internal phase emulsion method for producing porous microbeads [7-18, 73-75].

TABLE 6: VARIOUS MARKETED FORMULATION BASED ON MICROSPONGES DELIVERY TECHNIQUE

S. no.	Microsponge Delivery System	Name of Product	Drug	Treatment	Advantages	Manufacturer
1	Cream	Retin-A- Micro	Tretinoin	*Acne vulgaris*	0.17 & 0.04% tretinoin entrapped into a microsponges containing methylmethacrylate/ glycol & dimethylacrylate polymers	Ortho-McNeil Pharmaceuticals, Inc.
2	Cream	Carac Cream, 0.5%	Fluorouracil	Actinic keratoses	0.5% Fluorouracil incorporated into a microsponge composed of glycoldimethacrylate / methyl methacrylate and dimethicone	Dermik Laboratories Inc.
3	Cream	Line eliminator dual retinol facial treatment	Retinol	Anti-wrinkle	Light weight cream delivers both immediate and time-released wrinkle fighting action	Avon
4	Cream	Retinol 15 Night cream	Retinol	Anti-wrinkle	Retinol 15 Nightcream result in the visibled iminishment offine lines and wrinkles, improve skin discoloration.	Biomedic, Sothys
5	Sunscreen	Oils freematte block spf-20	Green Tea	Sunscreen	Oil free formula containing green tea with cornstarch and vinyl dimethicone	Dermalogica
6	Cream	EpiQuin micro	Hydroquinone & Retinol	Hyper pigmentation	Microsponges release active ingredients into the skin gradually throughout the day which minimize skin irritation	Skin MedicaInc
7	Gel	Salicylic peel 20 & 30	Salicylic acid	Excellent Exfoliation	Excellent exfoliation and stimulation of the skin which improve fine lines, pigmentation & acne concerns	Biomedic
8	Moisturizing Cream	Lactrex™ 12% Moisturizing Cream	Lactic acid & Ammonium lactate	Moisturizer	Moisturize dry, flaky, cracked skin	SDR Pharmaceuticals, Inc.
9	Lotion	Oil control lotion	Natural antibiotics	Tightness to promote healing, acne- prone, oily skin conditions	Absorb oil on the skin surface	Fountain Cosmetics
10	Spray	*Aramis Fragrances*		Antiperspirant spray gives sustained release of fragrance	Ultra light powder absorb fragrant oil easily	Aramis Inc.
11	Lotion impregnated Wipes	Ultra Guard	Dimethicone	Protects babies skin	Dimethicone that helps to protect babies skin from a diaper rash	Scott Paper
12	Cream	NeoBenz	Benzyl Peroxide	Anti-acne treatment	Reduce the amount of acne-causing bacteria by causing the skin to dry	Skin Media, Inc.

14. Patents List on Microsponge: Patents number, inventors, and publication shown in **Table 7** [73].

TABLE 7: INVENTORY OF SEVERAL PATENTS FILED IN MICROSPONGES DRUG DELIVERY SYSTEM

S. no.	Patent number	Inventors	Publication date
1	US4997753	Dean RC *et al.*	1991
2	US5135740	Katz *et al.*	1992
3	US5100783	Robert *et al.*	1992
4	US5679374	Fanchon *et al.*	1994
5	US5316774	Robert P *et al.*	1994
6	US5725869	Ray JR *et al.*	1996
7	US5851538	Forix M. *et al.*	1998
8	US6395300	Straub *et al.*	1999
9	US6211250	Tomlinson *et al.*	2001
10	US20030232091	Shefer *et al.*	2002
11	US20030008851	Singh	2003
12	US20040247632	Cattaneo & Maurizio	2004
13	US20050271702	Steven G *et al.*	2005
14	US7098315	Schaufler A *et al.*	2006
15	US20070141004	Malek	2007
16	US20080160065	Halliday	2008
17	US7426776	Franklin SL *et al.*	2008
18	US7604814	Kariyon Inc.	2009
19	US7740886	Sara Vargas	2010
20	US7749489	Celmatrix Corporation	2011
21	US8323672	Karykion Corporation	2012
22	US8361273	Ferring BV *et al.*	2013
23	US8758728	Stiefel Research Australia Pty Ltd.	2014
24	US8936800	Galderma Research & Development	2015
25	US9764316	Eugenia P *et al.*	2017

15. Microsponge Approach in Future Prospective: As a novel drug delivery system besides use as topical delivery of drugs, micro-sponge can also use in controlled oral peptide delivery, tissue engineering in cell culture media (stem cell culture and cellular regeneration) and transdermal delivery system.

Developed formulation with prolonged stability, without the use of preservatives, extended-release, reduce irritation. Microsponge technology act as carrier system in cosmetics, toothpaste or mouthwash, long lasting colored cosmetics, lipsticks and covering powder.

We can develop for alternative drug administration route like parenteral and pulmonary route[1-2, 4-11, 18, 73-75].

16. Application of Microsponge: Application of microsponge drug delivery system from topical route and oral route as shown in **Table 8** and **9** [6-14, 25, 73-75].

TABLE 8: TOPICAL DRUG DELIVERY USING MICROSPONGE TECHNOLOGY

Category	Drugs	Applications
Antifungal	Fluconazole, Miconazole, Clotrimazole, Econazole	Give sustained release of drugs.
Antidandruff	Selenium Disulfide, Zinc Pyrithione	Enhanced safety and efficacy of drugs with reduced irritation and odor
Anti-acne	Tretinoin, Benzoyl Peroxide	Reduce skin irritation and sensitization.
Anti-wrinkle	Retinol	Time-released delivery into the skin
Anti-inflammatory	Piroxicam, Hydro-cortisone	Extended drug release with reduced dermatoses and allergy
Anti-actinic Keratoses	5-Fluorouracil	Treat actinic keratoses with the reduced dosage form.
Skin depigmentation	Hydroquinone	Improve aesthetic appeal with reducing oxidation.
Moisturizer	Lactic acid and ammonium lactate	Moisturize dry, cracked and flaky skin

TABLE 9: ORAL DRUG DELIVERY USING MICROSPONGE TECHNOLOGY

Category	Drugs	Applications
Anti-inflammatory	Indomethacin	Reducing side effects like G.I. irritation with modified release
Anti-pyretic	Paracetamol	Time-release dosage form with a pH-dependent polymer coating
Anticholinergic	Dicyclomine	Effective local action with prolonged drug release
Colon targeting	Paracetamol	Time-release dosage form with a pH-dependent polymer coating
Musculoskeletal pain	Ketoprofen	Provided modified-release wit reducing the severity of side-effects

CONCLUSION: The Microsponge, drug delivery system, is a flexible approach complemented by novel dosage form development approach in pharmaceutical, cosmeceutical, and biopharmaceutical products. Interconnecting pores in microsponge responsible for the release of active constituents in a controlled manner. The Microsponge, drug delivery system, perks up the stability of incompatible constituents devoid of using any preservatives. For cosmetics perspective, microsponge delivery technique is advanced among other delivery techniques due to the porous nature of microsponge, which offers oil controlling property. So, a micro-sponge delivery system offers various advantages; therefore, MDS is a promising meadow that needs to be scrutinized for further research.

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