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As Review on Microsponge Gel as Topical Drug Delivery System

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Abstract

Microsponges are drug delivery systems composed of porous microspheres. They are little sponge – like spherical particles with an outside surface porous surface. Moreover, they will enhance stability, scale back aspect effect and modify drug unharness favourably. Microsponge technology has several favorable characteristics that make it a flexible drug delivery vehicle. Microsponge system square measure supported microscopic, chemical compound based mostly microspheres that may suspend or entrap a good type of substances, and might may be incorporated into a developed product like a gel, cream, liquid, powder. The outer surface is often porous, permeating a sustained flow of drugs out of sphere. Microsponges square measure porous, compound microspheres that square measure used principally for typical use and have recently been used for oral administration. microsponge square measure designed to deliver a pharmaceutical active ingredient with efficiency at the minimum dose and additionally to reinforce solubility, scale back aspect effects and modify drug unharness.

Kyewords: Controlled release, drug delivery, care systems, microponges.

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INTRODUCTION:

In recent years, there has been right smart stress given to the event of novel microsponge base drug delivery systems, so as to change and management the discharge behavior of medication. By incorporation into a carrier system, it's doable to change the therapeutics index and length of the activity of medication. The ever-increasing interest among shoppers with relevance skin care and skin treatment merchandise has been fostered by the widespread use of ingredients like α-chemical group acid and vitamins in topical merchandise, which might induce perceivable and demonstrable edges- particularly in aging or image broken skin. Though quite helpful, in several instances, these ingredients might turn out irritancy; such irritancy is perceived as burning, stinging or redness and notably happens in people with sensitive skin. Recognizing this drawback, the formulators have tried to traumatize drawback in one in all two stratergies . They need reduced the concentration of such ingredients, however within the method, sacrified effectuality. They need additionally changed the vehicles so as to create the merchandise additional emplients or skin- compatible. [1] But this approach, in several cases, additionally reduces the useful effects of ultimate product. The increasing arena of rising medicine, magnified sensitivity to clinical outcomes, and care prices are driving the requirement for different drug delivery strategies and devices. Drug delivery systems that may exactly management the discharge rates or target medicine to a selected body website have had a vast impact on the care system. Many predictable and reliable systems been developed for general medicine underneath the heading of percutaneous drug delivery systems (TDS) mistreatment the skin as a portal of entry.[2] it's improved the effectuality and safety of the many medicine that will be higher administered through skin. However, TDS isn't sensible for delivery of materials whose final target is that the skin itself. Controlled unharness of drug onto stratum with associate assurance that the drug remains primarily localized and doesn't enter the circulation in important amounts, is a locality of analysis that has solely recently been addressed successfully. No economical vehicles are developed for controlled and localized delivery of medication into horny layer and underlying skin layer and not on the far side the stratum. Moreover, the applying of topical medicine has several issues, such as, ointments that are typically esthetically unappealing, greasiness, stickiness, and so on, that always leads to lack of patient compliance. These vehicles need a high concentration of active agents for effective medical aid owing to their low potency of delivery system, leading to

irritation and hypersensitivity in important users. Different drawbacks of topical formulations and uncontrolled evaporation of active ingredient, unpleasant odor, and also the potential incompatibility of the medicine with the vehicles. Typical formulations of medicine are meant to figure on the outer layers of the skin. Typically, such merchandise unharness their active ingredients upon application, manufacturing extremely targeted layer of active ingredients that's apace absorbed. Therefore the requirement exists for a system to maximize the quantity of your time that an energetic ingredients is gift either on the skin surface or inside the stratum, whereas minimizing its percutaneous penetration into the body. Microsponges are microscopic spheres capable of engrossing skin secretions, therefor reducing oiliness and shine from the skin. Spherical particles composed of clusters of even tinier sphere are capable of holding fourfold their weight in skin secretions. Microsponge particles are very little, inert, indestructible spheres that don't meet up with the skin. Rather, they collect within the small nooks and crannies of the skin and slowly unhaeness the entrapped drug, because the skin desires it. The microsponge system will stop excessive accumulation of ingredients inside the stratum and also the stratum. Doubtless, the microsponge system will considerably scale back the irritation of effective drug while not reducing their effectuality. The empty spheres are then washed away with subsequent cleansing. The microsponge system fulfills these needs and has resulted in new generation of terribly well-tolerated and extremely efficacious, novel merchandise. These merchandise are usually conferred to the patron in typical forms like creams, gel or lotions and that they contain a comparatively high concentration of active ingredients. Microsponge area unit proprietary compound delivery systems consisting of porous microsphere which will entrap a good vary of active ingredients like emollients, fragrances, volatile oil, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents.[3] sort of a true sponge, every microsphere consists of a myriad of inter connecting voids among a non-collapsible structure, with an outsized porous surface. The microsponge technology was developed by won in 1987, and also the original patents were allotted to advanced chemical compound systems, Inc.[4] This company developed an outsized variety of variations of the technique and applied those to the cosmetic still as over-the-counter [OTC] and prescription pharmaceutical product. At this time, this attention grabbing technology has been accredited to cardinal health, Inc., to be used in topical product the scale of microsponges may be varied, typically from 5-300µm in diameter, relying upon the degree of smoothness or after-feel needed for the top formula. Though the microsponge size could vary, a typical 25µm sphere will have upto 250000 pores associate degreed an internal pore structure such as ten foot long, providing a complete pore volume of regarding 1ml/g. this leads to an outsized reservoir among every microsponge, which may be loaded with up to its own weight of chemical agent. The microsponge particles themselves live large to be absorbed into the skin and this adds a measure of safety to those microsponge materials. Another safety concern is that the potential microorganism contamination of the materials entrapped within the microsponge. Because the size of the pore diameter is smaller, the microorganism starting from 0.007to 0.2µm cannot penetrate into the tunnel structure of the microsponges.

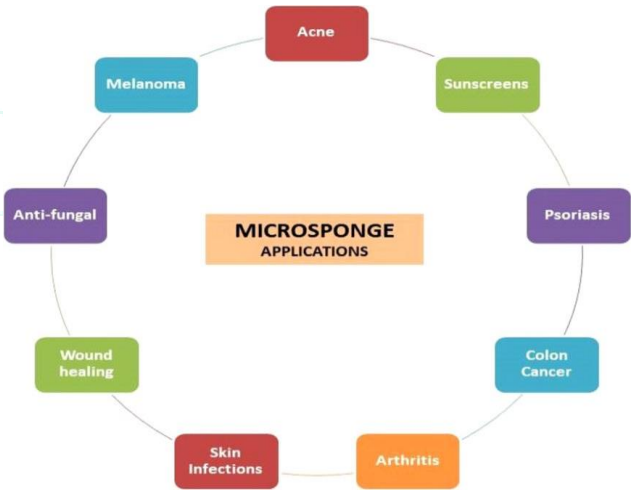
ADVANTAGES OF MICROSPONGE

- Microsponge systems are non- irritating, non-mutagenic, non-allergenic and non-toxic.
- Improved formulation flexibility.
- Extended release of drug continuous up to 12 hours.
- Reduce irritation and improve patient compliance.
- Microsponge drug delivery can improve bioavailability of drug.
- They have better thermal, physical and chemical stability.
- Allows incorporation of immiscible product.
- Advance oil control.
- Easy to formulate.

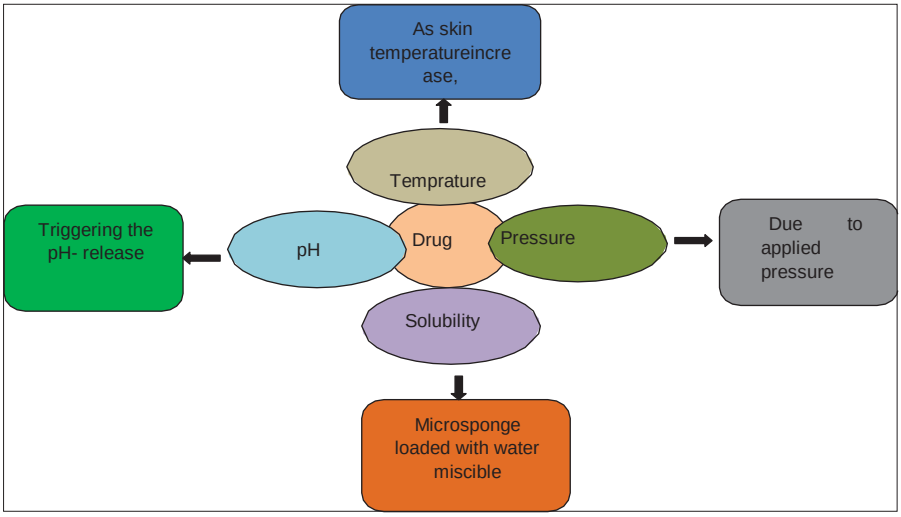
LIMITATION OF MICROSPONGE

- The preparation methods usually use organic solvents as paragons, which pose an environmental hazard, as some may be highly inflammable, posing a safety hazard.
- In some cases, the traces of residual monomer have been observed, which may be toxic and hazardous to health.

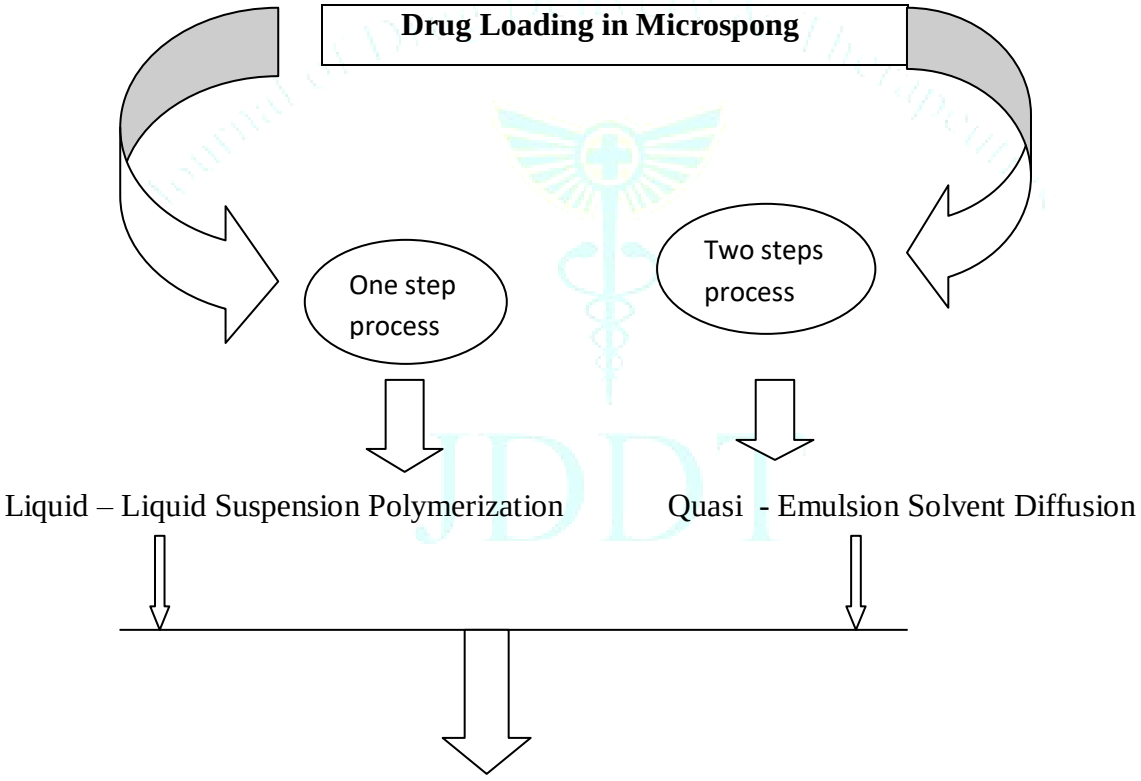
APPLICATION OF MICROSPONGE



RELEASE MECHANISM OF MICROSPONGES:-



METHOD OF PREPARATION:



Based on Physico-Chemical Properties of Drug to be loaded

Liquid-Liquid suspension chemical process [24-26]

In this vehicle of chemical process, the monomers area unit dissolved beside the active ingredients, i.e., water in appropriate solvent followed by addition of additives, suspending agent area unit additional to the formation of suspension. The chemical process is like initiated by adding catalyst porous. Once the chemical {process| chemical change| chemical action} process the solvent is removed deed the spherical porous structure microsponge.

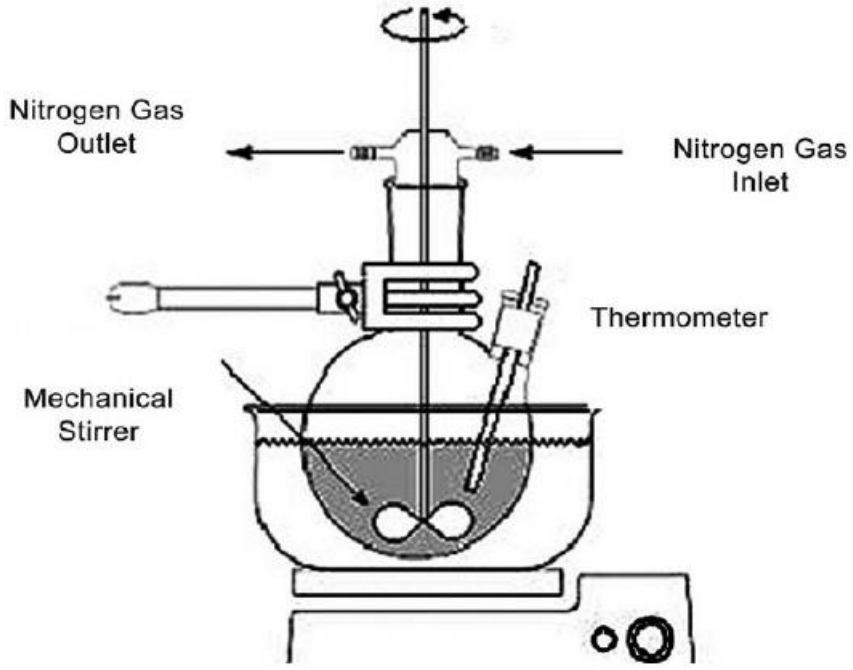


Figure 1: Liquid – Liquid Suspension Chemical Method.

Quasi-emulsion solvent diffusion [27-29]

Microsponge may be ready by quasi-emulsion solvent diffusion methodology exploitation the various compound amounts to arrange the inner organic part, compound dissolved in appropriate solvent followed by addition drug dissolved beneath ultra - sonication at 35ºC This resolution created inner part. The inner part is poured into the outer part (polyvinyl alcohol resolution in water). Once stirring, the mixture is filtered to separate the developed microsponges. The microsponges area unit dried in associate air heated kitchen appliance at a temperature that is compatible for compound.

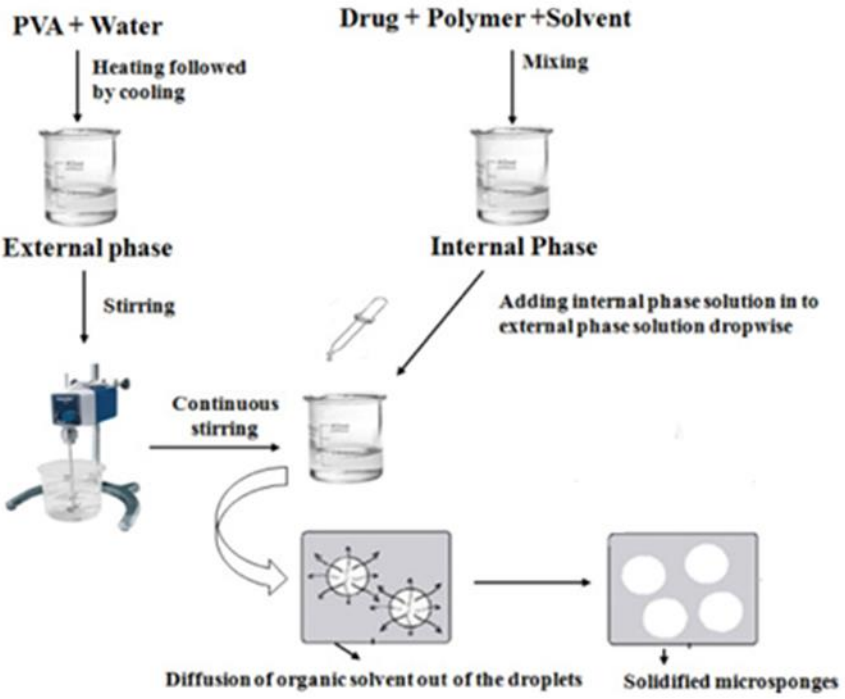


Figure 2: Quasi – Emulsion Solvent Diffusion Method

List of instruments

Sr. no.	Instruments	Manufacturer
1	Single pan electronic balance	Schimadzu crp. Model (ATX224)
2	Infrared spectrophotometer	FTIR- schimadzu
3	Ultrasonicator	Wensar electronics Pvt. Ltd. ,Mumbai
4	Mechanical stirrer	Remi equipments ltd., Mumbai
5	Magnetic stirrer	Remi equipments ltd., Mumbai
6	UV Spectrophotometer.	Dynamica model :halo DB20
7	Differential scanning calorimeter	Mettle- Toledo DSC 82 le, Switzerland.
8	Brook field viscometer	LVDV-E Brook fieid viscometer, Eng. Lab, USA.
9	Diffusion cell digital	Fabricated apparatus
10	Digital potentiometer motic digital microscope	Equiptronics model (EQ-601)
11	Motic digital microscope	B1 Advanced series.
12	Hot air oven	Biotechnics india.
13	Dissolution test apparatus	Electrolab (TDT)-08LUSP Type I

EVALUATION OF MICROSPONGE

Preformulation Study

Preformulation parameters area unit designed to spot those chemical science properties, freezing point, and excipients that will have an effect on the formulation style, methodology of manufacture, pharmacokinetics and biopharmaceutical properties. Organoleptic property as a chemical state, taste, odor and color of the drug area unit studied out [37]

Identification and drug – chemical compound compatibility

Differential scanning measuring system (DSC) analysis DSC analysis area unit meted out to verify compatibility and thermal behavior of medication, physical mixture of medication, chemical compound and their formulation.

Fourier remodel infrared spectroscopic analysis (FTIR)

Identification of purposeful teams gift in pure drug, physical mixture of drug, and chemical compound area unit interpretated by FTIR prism spectroscope. The result showed that no chemical interaction or changes manifest itself throughout the preparation of formulation, and also the drug was found to be stable[39]

Particle size analysis of microsponge

Particle sizes of the microsponge area unit meted out by optical maser light-weight diffractometry, optical research the other applicable methodology.

Analysis of morphology and surface topography of microsponges. The presence of pores is an important feature of microponges, its internal and external morphology and surface topography will be obtained by mistreatment SEM and transmission microscopy (TEM). The particle size, form and surface morphology examined by SEM and TEM found porous, spherical form in μm size [41].

Analysis of pore structure

The rate of drug unharness from microsponges will impact by diameter of microsponges. Many consistence parameters of microsponges like total extent, intrusion-extrusion isotherms, pore size, distribute, average pore size diameters, form and morphology of the pores, bulk and apparent density also are be analyzed [42].

Determination of loading efficiency and production yield [43]

The loading efficiency (%) is calculated using the following equation:

$$\text{Loading efficiency} = \frac{\text{Actual drug content in microsponges}}{\text{Theoretical dug content}} \times 100$$

The production of microparticles will analyzed by calculative accurately the initial weight of the raw material and also the final weight of microsponge obtained.

Production Yield:

$$\text{Production yield} = \frac{\text{Particle mass of microsponges}}{\text{Theoretical mass [polymer a drug]}} \times 100$$

In vitro dissolution analysis:

Dissolution profile of microsponges square measure studied by dissolution equipment USPXXIII with a changed basket consisted of five chrome steel mesh and therefore the speed of rotation 100rpm and temperature of 37±0.5ºC was maintained throughout the experiment. Whereas considering solubility of active guarantee sink conditions. At mounted intervals, aliquots were withdrawn and replaced with contemporary dissolution medium. Samples from the dissolution medium will be analyzed by actinic radiation photometer at numerous nm at numerous intervals. The concentrations of drug free at totally different time intervals make up my mind by measurement absorbance [45]

Motic Digital Resaerch

For morphology and surface topography, ready microsponges will be placed on a glass slide at temperature so the surface morphology of the microsponges will be studied by motic digital research (B1 advanced series). Motic digital research of a broken microsponge particle also can be taken as an example its ultrastructure. [11]

Analysis of True Density

Ultrapycnometer is employed for determination of true density of microsponges [46].

PATENTS FILED ASSOCIATED WITH MICROSPONGES APPROCHES [66]

Intellectual property quality (patents) is that the core of the many organization and transaction associated with technology. Licenses and assignments of belonging rights square measure common operations within the technology markets, still as providing loan security. Few patents square measure mentioned in following table associated with microsponges approach in pharmaceutical science.

Patents field related to microsponge approaches:-

Sr. no.	Inventors	Publication data	Patent number
1	Won	1987	US4690825
2	Dean et al.	1989	US4863856
3	Schaefer et al.	1989	US5292512
4	Katz et al.	1992	US5135740
5	Chantal et al.	1994	US5679374
6	Robert et al.	1994	US5316774
7	Ray	1996	US5725869
8	Straub et al.	1999	US63953000
9	Tomlinson et al.	2001	US6211250
10	Shefer et al.	2002	US20030232091
11	Singh	2003	US20030008851
12	Maurizio	2004	US20040247632
13	Steven et el.	2005	US20050271702
14	Malek	2007	US20070141004
15	Halliday	2008	US20080160065
16	Karyion Inc.	2009	US7604814
17	Sara Vargas	2010	US7740886
18	Celmatrix Corporation	2011	US7749489
19	Karykion Corporation	2012	US8323672
20	Ferring B.V	2013	US8361273
21	Stiefel Research Australia Pty Ltd.	2014	US8758728
22	Galderma Research and Development	2015	US8936800

Preparation of Microsponge Loaded Gel:

The optimized microsponge formulation was incorporated in compound base to gels. At first needed quality of compound base further to water and unbroken long for complete association of compound chains. Microsponge dispersion was further to the hydrous compound resolution to get final concentration of drug. The ready gel was used for drug deposition study.

Viscosity Measuring

The consistency of the various gel formulation was firm employing a Brookfield viscometer. The consistency of the optimized formulation was firm while not dilution victimization Brookfield viscometer (Model-LVDV-E). Brookfield viscometer consist of a cup, that is stationary and a spindle that is rotating totally different sized rotating spindles square measure used and immersed within the check material. For liquids with low consistency, giant size spindles (large diameter and surface square measure) square measure used whereas for higher consistency liquid little spindles (small diameter and surface area) are used. Rotate the spindle within the microsponge gel until we tend to get a continuing dial reading on the show of the viscometer. This procedure is continual 3 times for duplicable results [15-16]

pH Determination

this is determined for the hydrogen ion concentration of microsponge of non-steroidal anti- inflammatory drug gel hydrogen ion concentration half-dozen. 2±0.2 by victimization digital hydrogen ion concentration meter and therefore the reading taken for a median of three times et al., 2014, were optimized hydrogen ion concentration of microsponge of antifungal agent nitrate loaded gel was firm victimization digital hydrogen ion concentration meter result was needed by formulation hydrogen ion concentration half dozen. 7±0.06, 6.8±0.06.

Stability Test:

Stability studies of microsponge square measure studied out of varied formulation at totally different temperature and ratio. Om storing microsponge gel was evaluated 15,30, and 45 days. Non-steroidal anti-inflammatory drug gel as per ICH pointers, on keeping at 40ºC with RH 45% for the amount of 90-days.

Rheological Charaterization:

The microsponge gel showed creep recovery. Creep recovery check, it's shown higher creep recovery that was useful for promising gelling with higher snap. This property helps in dilution of the gel fraught with higher adherence time on the skin.

Skin Irritation Test:

Skin irritation check of optimized loaded microsponge gel was compared with the marketed and placebo gel. The microsponge is simply too giant to submit to the horny layer and it might expected to stay on the skin surface, bit by bit cathartic its contents over time. This reduces the upper exposure to the skin and make contact with amount. This was useful to scale back the irritation and toxicity of drug.

In vitro drug release kinetic study

To determine the drug unleash mechanism and to see the discharge profile variations among microsponge gel formulations, the knowledge obtained from the drug discharge amount and time were used. The drug unleash dynamics was analyzed with mathematical model like Zero

order, First order, Higuchi model, Hixson Crowell and Korsmeyer-Peppas model. Projected to elucidate the discharge characteristics od a drug from matrix. The three parameters were accustomed study the discharge mechanism i.e. unharness rate Constant(k), correlation and unharness exponent (n) and confirm the simplest work model for optimized formulation [17].

The discharge the knowledge was analyzed with subsequent methamatical model:-

Zero Order Kinetics:

Drug dissolution from pharmaceutical indefinite quantity forms that don't disaggregate and unharness the drug alowly (presumptuous that space doesn't amendment and no equilibrium conditions square measure obtained) will be best by the subsequent equation :

$$Q = K0t$$

Where Q letter is that the quantity of drug discharged at time t, K0 is that the zero order rate constant expressed inunit of concentration/time and t is the time in hours. The pharmaceutical indefinite quantity forms following profile, unharness an equivalent quantity of drug by a unit of your time. This model represents a perfect unharness profile so as to realize the prolonged medicine action[17].

First Order Kinetics;

This model was conjointly been accustomed described absorption and / or elimination of some drug, through its tough to gestate this mechanism on a theoretical basis;

$$Q1 = Q0\ e\text{-}K1t$$

Wherever Q1 is that the quantity of drug discharged in time t, Q0 is that the initial quantity of drug within the answer and K1 is that the initial order constant. The pharmaceutical indefinite quantity type following this profile, like water soluble medication in porous matrices release the drug in such some way that's proportional to the number of drug remaining in its interior, in such some way that the number of drug discharged by a unit of your time diminishes[17].

Higuchi Matrix Model:

This model is employed to check the discharge of water soluble and low soluble medication incorporated in solid and/or solid matrices. Mathematical expressions were obtained for drug particles spread in a very uniform matrix behaving because the diffusion media. It describes drug unharness as a diffusion method supported the Fick's law, root time dependent [17].

$$Q = KH\ t1/2$$

Where Q is that the quantity of drug unharnesses in time t, KH is that the Higuchi dissolution constant.

Korsmeyer –Peppas Model:

Korsmeyer developed a straight forward, empirical model, relating exponentially the drug unharness to the match on time(t).

$$Ft = a.\ tn$$

Where a is constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism and function of t is Mt/M∞ (fractional release of drug) [17].

Hixson – Crowell Model:

Hixson and Crowell (1931) recognized that the particle regular space is proportional to the root of its volume. They derived the equation :

$$W01/3 - Wt\ 1/3 = kt$$

Where W0 is that the initial quantity of drug within the pharamceuitical indefinite quantity type, Wt. is that the remaining quantity of drug within the pharmaceutical indefinite quantity type at time t and k (kappa) could be a constant incorporating the surface volume relation. The equation describes the discharge from system wherever there's a amendment in expanse diameter of particles or tablets. To check the discharge dynamics, knowledge obtained from in vitro drug unharness studies were premeditated because the root of drug share remaining matrix versus time [17]

Spreadability Studies:

One of the standards for a gel to fulfil the best qualities is that it ought to prossess sensible spredability. It's the term expressed to denote the extent of the world to that gel apace spread on application to the skin or affected half. The medical speciality effectualness of a formulation conjointly depends upon its spredability worth. Spredability is expressed in terms of your time in second taken by two slides to slide aloof from gel placed in between the slides beneath the direction of sure load. Lesser the time is taken for separation of two slides, higher the spredability. Spredability determined by glass slides and a engraving, that was provided by an easy machine at one end. By this method, spredability was measured on the premise of slip and drag characteristics of gels. A ground glass slide was fixed on this block. Associate way more than gel (about 1gm) of varied formulations was placed on very cheap slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide. Way more taken for separation of two slides. The very best plate was then subjected to drug of 20gm , lesser spredability was then calculated by the following formula:-

$$S = M \times L/T$$

Where S is that the spredability, M is the burden among the pan (tied to the upper slide), L is that the length tormented by the glass slide, T represents the time taken to separate the slide absolutely from each other [11,15].

Application of Microsponge Gel

Active agents	Applications
Anti-acne eg. Benzyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
Anti-inflammatory eg. Hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatomes.
Antifungal eg. Fluconazole	Sustained release of actives
Antidandruff eg zinc pyrithione, selenium sulphide	Reduced unpleasant odor with lowered irritation with extended safety and efficacy.
Antipruitics	Extended and improved activity.
Skin de-pigmenting agents eg. Hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
Rubefacients	Prolonged activity with reduced irritancy greasiness and odor.

MARKETED PRODUCT USING MICROSPONGE DELIVERY SYSTEM:

Product	Advantages	Manufacturer
Retin-A-Micro	Around 0.1% and 0.04% tretinoin entrapped in microsponge drug delivery for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/ glycol dimethacrylate cross-polymer porous microspheres (MICROSPONGE® System) to enable inclusion of the actives, tretinoin, in an aqueous gel.	Ortho-McNeil Pharmaceutical, Inc.
Carac Cream, 0.5%	It consist of fluorouracil up-to 0.5 %, with 0.35% being inclusive into a patented microsponge that is composed of methylmethacrylateorglycol dimethacrylatecross-polymeranddimethicone.Itisatopicalprescription product for the treatment of actinickeratoses(AK)andusedonce-a-day, a common pre-cancerous skin condition caused byover-exposure to the sun	Dermik Laboratories, Inc.
Retinol cream	The retinol molecule is kept in the microsponge system to protect the potency of the vitamin A. This helps to enhance retinol dosage mean while decreasing the possibility of irritation. Retinol is a topical vitamin A derivative which helps to maintain the healthy skin, hair andmucous membranes.	Biomedic, Inc.
Biomedic, Inc.	The Microsponge ® system uses the microscopic reservoirs that trap HQ and retinol. This confers the skin with continuous exposure to hydroquinone and retinol over time, which may reduce skin irritation.	Skin Medica Inc
Line Eliminator DualRetinolFacial Treatment	Lightweight cream with a retinol in microsponge drug delivery system, it delivers both immediate and time released of drug and having wrinkle-fighting action.	Avon
Retinol 15 Nightcream	When we use Retinol 15 continuously in night will results in the visible Diminishment of fine lines and wrinkles, observable improvement in the skin discolorations due to aging and enhanced skin smoothness.	Sothys
EpiQuin Micro	This confers the skin with continuous exposure to hydroquinone and retinol over time, which may reduce skin irritation.	Skin medica inc.
Sports cream RS and XS	Topical analgesic-anti-inflammatory and counterirritant actives used for the management of musculoskeletal conditions in a Microsponge® Delivery System.	Embil pharmaceutical co.Ltd.

CONCLUSION:

Microsponge drug delivery holds sizable potential every in pharmaceutical additionally as cosmetics field. This strategies square measure engaging and create some ways to release bioactive agents with full efficiency, safety, improved stability, provided reduced aspect effects. Microsponges to boot provide nice advantages over different formulation with relevance agent and irritancy of drug. So contain various potential for developing novel formulations for the topical malady. Microsponge gel may give benefits of reduced facet effects, multiplied magnificence, increased formulation flexibility, and modify drug release. These microsponge gel square measure penetrate through skin by controlled release manner. Microsponges gel give patient compliance. This is often the benefit of the microsponge gel.

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