Microsponge as a Strategy for Effective Drug Delivery System

Nora Zawar. Yousif*, Zeina D Salman*
Department of Pharmaceutics, college of Pharmacy, Mustansiriyah University, Baghdad, Iraq

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Corresponding Author email:
Email: pharm.nora.zawar@uomustansiriyah.edu.iq
Orcid: https://orcid.org/0000-0002-6025-506X

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Abstract:

The technology of drug delivery has become massively competitive and quickly growing. Enhancing efficacy is the primary objective of delivery system development, and hence cost-effectiveness of the treatment. Nevertheless, controlling the rate of delivery of active pharmaceutical moieties to a target site within the body has been one of the major obstacles confronted by the drug industry. Microsponge represents a delivery system considered a promising innovation that overcomes the different challenges, since, this dosage form provides the delivery of active pharmaceutical moieties in a timely manner, in addition to responding to different stimuli (pressure, temperature, pH). Microsponge drug delivery technology proposed capturing of active moieties into tiny spongy spheres thus, donating towards reducing side effects, improving stability, increasing elegance, and enhancing formulation flexibility. The goal behind this contribution is to cover microsponge as a successful innovation, summarizing the characteristics, advantages, and limitations with certain insight into the mechanism and factors triggering the release. Furthermore, shed light on the methodology of preparation.

Keywords: Microsponge, characteristics, hypothetical mechanism, monomer, bottom to top, top to bottom, porogen.

مايكروسبونج كاستراتيجية لنظام فعال في توصيل الأدوية

م. نورا زاوار يوسف *, م. زينة داود سلمان*
قسم الصيدلانيات، كلية الصيدلة، جامعة المستنصرية، بغداد، العراق

الخلاصة:

أصبحت تقنية توصيل الأدوية تنافسية للغاية وتنمو بسرعة ان .الهدف الرئيسي لتطور أنظمة التوصيل هو زيادة كفاءة العلاج و وتحسين الكلفة ومع ذلك ، فإن التحكم في معدل تسليم الدواء الفعال إلى موقع محدد داخل الجسم يعتبر أحد العقبات الرئيسية التي تواجه صناعة الادوية ,يعتبر المايكروسبونج نظام توصيل مبتكر وواعد يتغلب على التحديات المختلفة التي تواجه صناعة الأدوية , نظرًا لأن شكل هذه الصيغه الدوائيه توفر توصيل الادويه الصيدلانية بطريقة زمنية ، بالإضافة إلى الاستجابة للمحفزات المختلفة (الضغط ودرجة الحرارة ودرجة الحموضة). اقترحت تقنية توصيل الأدوية المايكروسبونج التقاط الدواء في كرات اسفنجيه صغيره وبالتالي التقليل من الاثار الجانبية وتحسين الاستقرارية وزياده الاناقه ومرونة الصياغة . الغرض من مراجعة المقال هو تغطية موضوع المايكروسبونج باعتباره ابتكارا ناجحا من ناحية المزايا والقيود مع نظرة ثاقبة للالية والعوامل التى تؤدي الى اطلاق التحرر علاوة على ذلك ، تسليط الضوء على منهجية التحضير.

الكلمات المفتاحية: مايكروسبونج ، الخصائص ، الآلية الافتراضية ، المونومر ، من الأسفل إلى الأعلى ، من أعلى إلى أسفل ، بوروجين

Introduction

The foremost helpful and frequently utilized route is the oral route. The effortlessly absorbed active pharmaceutical molecules from the gastrointestinal tract and their rapid elimination from the systemic circulation due to their short half-life are both desirable characteristics [1,2]. Controlling, compelling and customized drug delivery systems have been a dream for decades, however it has been to a great extent disappointed by the multifaceted nature that is included within the formulation innovation of new drug delivery systems [3,4]. Drug delivery systems that control the release rate and target to a particular location of the body has a tremendous effect on the health care system [5,6].

Different drug delivery systems are being adopted to optimize the efficacy and cost-effectiveness of the treatment, especially with expanding competition and need for patient friendly dosage forms. In current time, enormous efforts are given to improve microsponges constructed drug delivery systems, thus, alter and regulated the release behavior of the drugs. Capturing drug by carrier system will provide a convenient optimization of therapeutic index and duration of action [7]. The microsponge innovation was created by Won in 1987, and thus the first patents were allotted to progressed Polymer Systems, Incorporation, this association created a huge quantity of varieties of the strategy and connected it to the cosmetic besides to the over-the-counter products. Recently, this innovation has been authorized to Cardinal wellbeing, Incorporation, to be utilized in topical products [8]. Microsponges are tiny sponge-like spherical particles that include a myriad of interconnection voids inside a structure that is non collapsible with massive spongy surface [9]. Besides, microsponges may improve stability, diminish side effects, and boost drug release as well [10]. The empty polymeric spheres change in diameter from 5 to 300 μm. A sphere of 25 μm average size can have pore length up to 3000 mm, given that an over-all pore volume at approximately of about 1 ml/g. Particles, depending on their size, these tiny empty polymeric spheres can be subdivided into microporous micro-structured beads (particle size less than 50 μm) and microporous large-scale beads (particle size extend of 100-200 μm) [11]. Microsponges deliver their API (active pharmaceutical ingredient) when applied, producing a profoundly concentrated layer of API which is rapidly absorbed. A significant number of topical drugs endures different drawbacks like greasiness, stickiness related with the treatments, which frequently result in consumer inconvenience [12]. Nowadays microsponges broadly considered as a driving innovation for overcoming skin conditions like acne, hyperpigmentation, keratosis, aging and photodamage [13]. The aim of this presented review is to introduce microsponge as a successful innovation summarizing the characteristics, advantages and limitation of this technology with certain insight for mechanism and factors triggering the release. furthermore, shed the light on the most common methodology of preparation.

Engineering of Microsponge Dug Delivery System

Microsponge polymers can capture active pharmacological substances through synthesis or, if the substrate is highly sensitive to polymerization conditions, through post loading after the construction of the sponge structure. Since many common cosmetic components and a significant fraction of pharmaceutical chemicals may decompose at polymerization temperatures, post-loading is the most significantly predicted. When the polymer is placed in proximity to the skin, such microscopic structures can then be constantly released after being loaded

by diffusion in a manner similar to that of a sponge. [14]

Characteristics of Microsponge Drug Delivery Systems:

Improves materials processing as fluid changes into solid state. Also, A large acid stability and thermal resistance from a pH scale of 1 to 11 and up to 130 °C respectively. Higher payload microsponges formulation (50 to 60%) can be cost-effective. According to several studies no allergy, irritation, toxicity, and malignancy were noticed. Microsponges either possess the ability to be fully mixed with monomer or possess the capability to be miscible by adding a little quantity of a water-immiscible solvent. Microsponge neither elevates the mixture viscosity of monomer nor reacts with the monomer or is inert. A microsponge capable of absorbing oil up to 6 times its original mass with no drying impact. [15-23]

Prerequisites of Materials Entrapped in Microsponge Delivery Systems:

Generally fluid or dissolvable materials can be entrapped within the microsized particles. Materials that can be entangled within microsponges have to meet the prerequisites as follows: the API components must have a restricted solubility in the vehicle. It must have limited water-immiscibility. Designing and loading the microsponges with polymers must be improved for the specified release rate for a certain period of time. It needs to be resistant to polymerization catalysts and a wide range of polymerization conditions. [24-26]

Advantages of Microsponge Drug Delivery System:

Microsponges provide entrapment of various ingredients and are widely accepted dosage forms due to formulation elegance and flexibility. Microsponges are characterized by thermal, physical, and chemical stability as well offer compatibility with a large number of vehicles and ingredients. Microsponge is considered as a successful barrier for microscopic organisms' (bacteria) that their size (0.007 to 0.2 μm) as the average particle size is estimated to be 0.25 μm, thus, it may possess the property of self-sterilizing. Microspone provides modified release and site targeting drug delivery systems for improved treatment. Moreover, microsponge promotes precise delivery of small amounts of effective therapeutics and diminishes therapeutics concertation at a location apart from the intended target. In addition, microsponge gives continuous steady release for up to 12 hr, improving bioavailability. The medicate delivers from microsponges by exterior boosts like pressure, temperature, and rubbing [27-30].

Microsponge Over Ordinary and Progressive Formulation:

The existing predominated formulations within the market are characterized as having adverse impacts. Ordinary dosage forms of topical drugs are designed to be applied to the topmost layers of the skin. When administered, certain products deliver their active pharmaceutical components. While microsponge systems can anticipate over-the-top aggregation ingredients inside the epidermal and dermal layers. Possibly, the microsponge dosage form can diminish the medication's irritation without diminishing its effectiveness. [10,31-32] The microsponge has many points of interest above other recent technological innovations such as microencapsulation and liposomes. Microcapsules are characterized by lacking the control of the therapeutic release rate as the outside shell of the capsule is torn, and the therapeutic entrapped within the microsponge will undergo burst and uncontrolled release. Liposomes have several drawbacks: loading insufficiency, formulation difficulties, and inadequate chemical and bacterial stability. [33] Whereas the microsponge drug delivery system is dissimilar to the previously mentioned technologies and provides pH stabilizing and thermal stabilizing effects.

Compatibility with the majority of ingredients and vehicles, improved payload (50 to 60%), followability and can be considered an economic approach in comparison to others. [34-35]

Limitations of Microsponge Drug Delivery System :The essential restriction of microsponge innovation is the utilization of several organic solvents in formulations. The utilize of organic solvents postures risks such as toxicity of preparation and flammability. Moreover, the remaining monomers within the bottom-up approach can be harmful and unsafe for health. However, the restriction can be defeated by quality control measures, optimization, and standardization of preparation methods e.g., post-manufacture washing. [36,37]

Drugs Explored in The Microsponge Delivery System :Diverse studies supported that many of API has been formulated in effective dosage forms as microsponges delivery system, table 1 listed variant API incorporated as microsponges in different dosage formulations.

Table 1: Instances for microsponge technology applications for various medication and dosage forms

Medications	Application	Microsponge Technology
Nicorandil [٣٨] Indomethacin[٣٩] Paracetamol[٤٠] Piroxicam[٤١]	Cardiovascular Inflammation Anti-pyretic Rheumatoid arthritis	**Tablets**
Oxybenzone [4٢] Acyclovir[٤٣] Diclofenac sodium[4٤] Tazarotene, Tretinoin[٤٥] Nebivolol[٤٦] Fluconazole[4٧] Terbinafine[٤٨] Mupirocin [٤٩] Silver sulfadiazine [٥٠]	Sunscreen agent Viral infections Inflammation Facial acne vulgaris Diabetic rash Inflammation Antibacterial activity Anti-fungal Antibacterial Burn wounds	**Gels**
Hydroquinone and Retinol [51]	Hyperpigmentation	**Creams**
Babchi oil[52] Benzyl peroxide[53]	Antimicrobial Anti-Acne	**Oils** **Lotions**
5-fluorouracil [54] Calcium Phosphate [55]	Colorectal cancer Bone substitute	**Capsule** **Powder**
Polylacticglycolic acid [56] Fibroblast growth	Cardiovascular uses	**Grafts**

factor [°7] DL Polylactic-co-glycolic Acid [°8] Ketorolac Tromethamine[59]	Growth factors Tissue engineering Inflammation	**Injection** **Implants** **Implants**

Polymers Utilized in Microsponge Delivery System:

Microsponges are made from a variety of polymers, including Eudragit RS 100, Eudragit RL 100, ethylcellulose, carbopol 934, polystyrene acrylic polymer. (38,60) Because of its adaptability, researchers have been studying Eudragit RS-100 polymer to use in a wide variety of applications. In addition to increasing the drug's solubility, Eudragit RS PO formed a solid dispersion-like structure that allowed for controlled drug release. There was some research on the efficacy of polylactide-co-glycolic acid and polylactic acid in transporting the proteins and peptides. Polymers like Eudragit RS-100, polylactide-co-glycolic acid, and Eudragit RS PO can be used to create floating microsponge. This is because these polymers are hydrophobic, preventing the particles from becoming wet under aquatic situations. Some microspong formulations also included a plasticizer, like triethyl citrate, for the active moiety and polymers, which aids in microsponge structural stability (61).

Considerations in the Formulation Process :

Micro sponge-based drug delivery actives can be included in various products such as gels, creams, powders, lotions, and soaps, or compacted into tablets. Certain aspects should be considered when designing the vehicle to get the required product qualities, to avoid cosmetic problems; less than 10 to 12% w/w microsponges must be incorporated into the vehicle, and the solubility of active ingredients must be restricted inside the vehicle. Instead, the vehicle's microsponges will be depleted prior to the application, the polymer design and payload of the active microsponges must be tailored to achieve the desired rate of release for a given amount.(62)

Methodology for Preparation of Microsponges

The solubility characteristics of polymer and drug consider as the main determents for choosing the specific encapsulation method. For water-insoluble drug and polymer, the solvent diffusion is the most convenient method for the encapsulation of drug; however, the chosen method must meet the following requirements: Capability to switch *in vitro* release pattern through manipulating process parameters results in microparticles with optimal *in vivo* release properties. The core material is highly encapsulated. The release profile from batch to batch is reproducible. Also, high production yields of microparticles, besides no extensive agglomeration, should be formed. (10)

Bottom-up Approach: Free Radical Suspension Polymerization:

Starting with the monomer, the bottom-up strategy is adopted. Micro sponges were created in an emulsified liquid-liquid environment using a radical suspension polymerization approach. Mainly there are two-phase systems for preparing polymerization mixtures, the monomer phase or called the dispersed phase and polymerization medium which is mainly refers to the immiscible liquid phase

containing the dispersed or soluble monomer. A pore network can be achieved by adding another liquid which is characterize by miscibility with the monomer while immiscibly with the polymerization medium. This liquid element is referred as monomer diluent or porogen, when added to the polymerization mixture, this inert non-polar organic solvent results in formulation of porous structure and that's why the term microsponge is referred, as these structures appear as sponge when morphological examination is done. The temperature has an impact for successful preparations. It has a role in rate of decomposition, free radicals' formation and rate of polymerization. (63)

As the suspension forms distinct droplets of specific size, the process of polymerization is subjected to certain effects through triggering the monomer by for instance catalyst system, increase temperature and irradiation. As a result, a multiple polymer ladder covering around each other hence, forming a solidified microsphere as the process of polymerization lasts a huge number of microspheres attached together like groups forming a spherical structure and resulting in the formation of interrelating reservoirs. As the porogen is captured, active ingredients are released through opening on the surface of the sphere which they triggered. The resulted particles are washed and processed for further use. (64,65) Figure 2 summarize the methodology for free radical suspension polymerization (bottom-up approach)

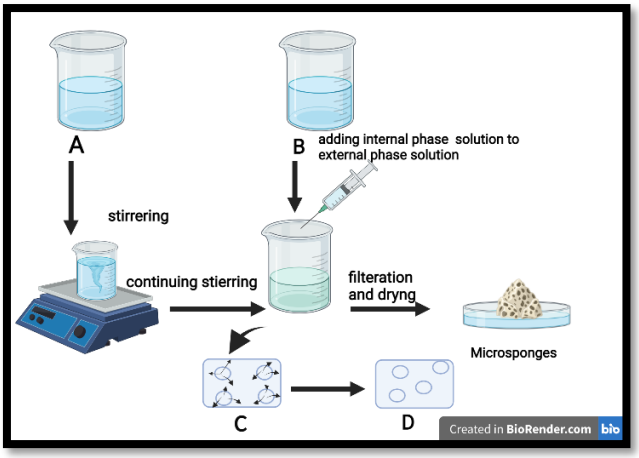

Figure 2: Methodology for free radical suspension polymerization (bottom-up approach), A: Monomer dispersed phase + cross linker+ diluent+ active ingredient, B: Aqueous continuous phase, C: Recovery of crosslinked Microphage

Merits and Demerits of Free Radical Suspension Polymerization Methodology

Merits:

ease of modification of drug loading methods

Demerits:

the possibility to trap unreacted monomers and solvent residues; monomers take a long time to react to form their non-uniform structure; two-step techniques are required for thermodynamically affected pharmaceuticals that demand lower drug entrapment capacity. (64,65)

Top-Down Approach: Quasi-Emulsion Solvent Diffusion Methodology:

Unlike the first method, the starting point of this method is the polymer, this is the top to down process. The strategy involves the formulation of a quasi-emulsion of dual variable phases, the internal phase and external phase as analogous to the emulsion dosage form. The drug-polymer of highly volatile solution (internal phase) (for instance, acetone, ethanol dichloromethane) is added to the external phase mainly composed of polyvinyl alcohol (PVA) polymeric solution with vigorous stirring. [66] An adequate amount of triethyl citrate (TEC) is added to enhance plasticity. The continuous stirring is likely to result in the production of discrete emulsion droplets named quasi-emulsion droplets. Eventually, insoluble rigid microparticles will be produced, after extraction of the solvent from the droplets. This rigid microparticles are called (microsponge). The mixture is subjected to filtration to get isolated microparticles. The final microsponge is dried in a heated air-oven. The counter diffusion of volatile organic solvent and water out of and into the droplets, consequently the dispersed droplets of polymeric drug solution led to solidification of the droplets. Reducing drug-polymer solubility as a result of emulsion of the aqueous phase into the droplets will lead to their co-precipitation of them. [67] Meanwhile, the organic phase is subjected to continuous diffusion leading to intensifying solidification, thus producing microspheres of matrix-porous type. In contrast, this approach provides the virtues of low exposure to the medication in ambient conditions as for the liquid-liquid suspension polymerization. In addition, there are few solvent residues within the final formulation due to the extraction of solvent as a result of drug aqueous solubility or for its volatile character. [68]

The drug loading is initiated after microsponge creation. This approach entails adding dummy (blank) microsponges and ethanol-medicated solutions. The bottles were organized and mixed in a roller mill for 1 hour. In the oven at 65°C, the mixture is dried for 2.5 hours. This is accomplished for a second level of trapping and the drying process is consequently maintained at 50 °C for 24 hours. [69] The quasi-emulsion solvent diffusion approach methodology can be summarized in Figure 3: (Approach to Top-Down)

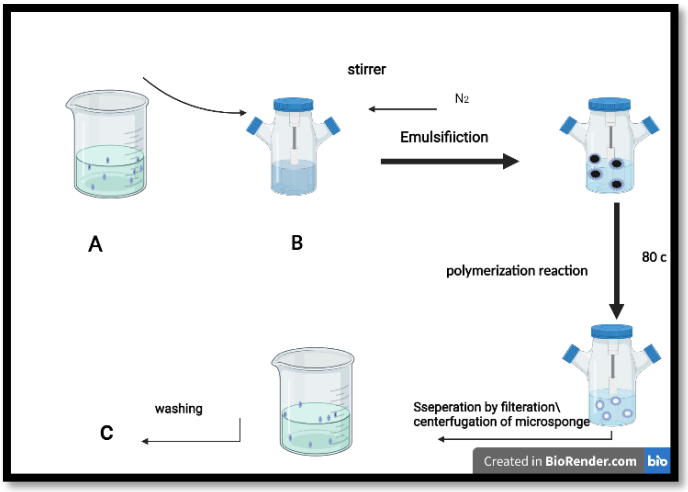

Figure 3: Quasi-Emulsion Solvent Diffusion Methodology (Top to Down approach) A: PVA+ water (external phase), B: Drug +polymer + solvent (internal phase), C: Diffusion of organic solvent out of droplets, D: Solidified micro sponge.

Merits and Demerits of the Quasi-Emulsion Solvent Diffusion Method

Merits: Do not include monomer trap, low solvent remnants, or excellent capacity to load medicines. Moreover, it is an essential approach for protecting the medicinal exposure to environmental conditions, micro sponge size, and the spherical particles can be regulated simply by manipulating stirring**.**

Demerits: Probably trapping non-uniform structures of unreacted monomers and solvent traces, involving considerable periods for the reaction of monomers, necessitates a two-step thermosensitivity method. [70]

Lyophilization

Lyophilization is an innovative technique used for modifying ordinarily formed microparticles into porous microspheres. This technology involves immersing the microparticles in chitosan HCl solution and then subjecting them to lyophilization. The pores within microparticles are formed in response to the rapid evaporation of the solvent. The characteristics of this method are rapidity and quickness. However, the disadvantage of this technology is the shrunken or broken microparticles that are produced due to momentous evaporation of the solvent. [71,72]

Water in Oil in Water (W/O/W) Emulsion Solvent Diffusion

To organize biodegradable porous microparticles, another innovative method called w/o/w emulsion solvent diffusion has been devised. An internal water phase is distributed by this procedure into an organic polymer solution. The inner phase comprises a span, stearlamine and polyethyleneimine emulsifying agent. This w/o emulsion was subsequently redistributed to an external aqueous phase containing PVA for double emulsion preparation. Having both water-soluble and water-insoluble drug entrapment is the major benefit of this technique. [73,74]

Hypothetical Mechanism of Action of Micro sponges : In a micro sponge, the microstructure particles are characterized by being free from a continuous encompassing membrane and thus the active ingredient moves unreservedly inside and outside the microstructures and into the vehicle till equilibrium is attained. Once the product is administered topically to the skin for instance, the therapeutic active moiety will be retained in the skin, thus the vehicle that holds the therapeutic will be depleted, leading to unsaturated state achievement, as a consequence, a sharp flow of active moieties from microstructure particles into the vehicle, and from the vehicle to the skin until the vehicle become either dehydrated or absorbed. Subsequently, the micro sponge particles proceed to have on the stratum corneum surface and proceed to steadily discharge the API thus, providing an extended discharge. [75] This anticipated mechanism of activity emphasizes the significance of certain vehicles that are utilized for micro sponge entrapments. If the API is exceptionally dissolvable within the favored vehicle; the product will not offer the favored merits of continuous release. In contrast, the active moiety will be included in the vehicle as a free form. Hence, whereas designing micro sponge entrapments, it is firmly requested not to use a vehicle that has adequate solubilizing effect for the actives. This rule is inverse to the ordinary formulation principles that is wildly utilized to the topical items, a rule prescribed for ordinary formulation it is to enhance the solubilization of the API within the vehicle.[76] However, when utilizing micro sponge entrapments, a couple of the API with the same solubility in the vehicle is desirable, since the vehicle can deliver the primary load dose of the API until discharge from the microsponge is actuated by the shunt equilibrium into the carrier from the polymer. Additional strategy to bypass the unwanted untimely leaching of API from the polymer is to prepare the formulation with a few free

and few captured moieties, thus maintaining the pre-saturated state of the vehicle. The rate of API release will not majorly rely on the partition coefficient of the API fixing between the vehicle (or the skin) and the polymer, but moreover on many of the parameters that characterize the micro sponge. These indicate surface area and pore diameter. (77)

Release Mechanism of Micro sponge Delivery System

Micro sponges are engineered to gradually release a predetermined dose of active ingredients in response to one or more external stimuli. Generally, microsponges delay drug release. Various researchers declared a faster rate of release by cumulative the active/polymer ratio and decrease in the polymer boundary thickness; nevertheless, these findings have not been verified by other studies. Consequently, there are many other contributors influencing drug's release from the micro sponges. Regulation of drug release claimed to pore diameter and general porosity (involving the diameter of the pore) and therefore the number of pores. (78)

Factors Contribute to the Release of Active ingredient: -

Temperature-triggered systems

At ambient temperature, only a few amounts of captured active ingredients can leave the microsponge into the skin, while while rising the thermal state of the skin, the chance of flow of captured API will be enhanced, thus the release will be enhanced. (79,80)

Solubility

Microsponge enriched with water soluble ingredients, the presence of water will enhance their active moieties release. Another, contributing factor triggers the release of the ingredients is the partition coefficient of the ingredients between the microsponge and the surrounding media. (81)

pH

Coating the conventional microsponge delivery system with an enteric coating provides pH responsiveness. According to pH responsiveness studies, there was no noticeable release at an acidic pH of nearly 3, however, as the pH was elevated to 8, a discharge of up to 80% was obtained. Thus, a diminished pH resulted in a reduced discharge rate, whereas increasing the pH resulted in an enhanced discharge rate. So the rate of drug release should be regulated as per the necessities (82). Thus, adapting the coating on a micro sponge the stimuli (pH) responsive release of the active ingredient will be attained. (83)

Pressure

Pressure or rubbing application resulted in enhancing active ingredients released from their captured sponge into the skin; the quantity released depends upon various characteristics of the sponge which in turn depends on the kind of material and different process variables. For instance, mineral oil in microsponge revealed more softening effect in contrary to microcapsules containing mineral oil that has an irritant effect. (84)

Safety Parameters

Although microsponges are made of biologically inactive polymers, establishing its safety necessitated understanding more than 30 safety factors. Microsponges safety is frequently proved by an allergic response in guinea pigs, rabbit eye irritation investigations, bacterial mutagenicity, rat oral toxicity studies and rabbit skin irritation research (85)

Conclusion

As researchers deliberate innovative and pioneering ways to deliver active ingredient starting from their comprehensive insight for importance of these innovated approaches in offering safety, improved stability and diminished side effects, multi-purpose drug delivery

systems, and boosted ingredients compatibility. Microsponge-based drug delivery technology is expected to be one of valuable drug delivery systems with wide therapeutic applications. The overall characteristics of this technology afford a platform for effective and controlled release dosage forms whose merits and limitations may offer diminished toxicity, reduced skin irritancy and, conceivably, increased efficacy and patient acceptability.

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