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Design development and evaluation of controlled release micro-sponge drug delivery system

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Abstract

The present study focuses on the design, development, and evaluation of a controlled release micro-sponge drug delivery system for Nimesulide, aimed at enhancing therapeutic efficacy and reducing dosing frequency. Micro-sponges were prepared using the quasi-emulsion solvent diffusion method, a simple and reproducible technique that enables the formation of porous polymeric microspheres. Ethyl cellulose was employed as the polymer matrix due to its biocompatibility and sustained release properties. Pre-formulation studies confirmed the physicochemical suitability of Nimesulide for micro-sponge encapsulation. A series of formulations (F1 to F5) were developed by varying the drug-to-polymer ratio and evaluated for particle size, production yield, drug content, and encapsulation efficiency. Results indicated that increasing the polymer concentration led to larger particle size and higher yield but decreased drug content. In vitro studies demonstrated that all formulations sustained drug release over 24 hours, with formulation F1 showing the most favorable profile. The micro-sponge system presents a promising alternative to conventional dosage forms, offering controlled release, improved patient compliance, and reduced adverse effects.

Keywords: Microsponge; Controlled release; Nimesulide; Quasi-emulsion solvent diffusion; Ethyl cellulose; Transdermal delivery systems (TDSs); Triethyl citrate (TEC)

1. Introduction

1.1. Overview of drug delivery systems

The oral route of drug administration is known to be the most convenient and commonly employed route. Drugs which gets easily absorbed from the gastrointestinal tract and having a short half-life gets eliminated rapidly from the blood circulation. To shun these problems, oral controlled release formulations have been developed; which releases drug slowly into the gastrointestinal tract and helps in keeping constant drug concentration in the serum, for longer period of time. Oral route of drug administration have broad acceptance. Up to 50-60% of oral solid dosage forms are well-liked because of usual, straightforward and suitable administration with precise dosage, self-medication, pain evasion and most prominently patient compliance. The most admired solid dosage forms being tablets and capsules, these dosage forms may envelop wide range of applications in novel drug delivery systems like nanoparticles, microparticles, microspheres, nanospheres and microsponges[1]. A Micro-sponge Delivery System (MDS) is highly cross-linked, porous, polymeric microspheres that can entrap broad range of active ingredients and releases them over extended time and in response to triggers. This system was implied earlier for the enhancement of performance of drugs. It is a unique technology for the controlled release which consists of microporous beads loaded with active agent[2,3]. One of the major challenges faced by pharmaceutical scientists is to control the delivery rate of actives to a predetermined site in the body. The prime aim of any drug delivery system is to provide therapeutic amount of drug to proper site in the body, to punctually achieve and maintain the desired drug concentration[4-7]. Most of these drug delivery systems includes polymer which encapsulates drug. Oral drug delivery systems are used for enhancing therapeutic index of the drug and

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also for the reduction in side effects. Oral route is the chosen route for the administration of active and/or therapeutic agents owing to its low cost of therapy and ease of administration; which may lead to the higher level of patient acquiescence. The efficient oral drug delivery may depend upon several factors like gastric emptying, gastrointestinal transit time of the drug or dosage form, drug release from designed dosage form and site of absorption of drug[8].

Drug delivery systems (DDS) that can precisely control the release rate or target drugs to a specific body site have had an enormous impact on the healthcare system. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle (such as microspheres, nanoparticles, liposomes etc.) which modulates the release and absorption characteristics of the drug[9]. To control the delivery rate of active agents to a predetermined site in human body has been one of the biggest challenges faced by drug industry. Several predictable and reliable systems were developed for systemic drugs under the heading of transdermal delivery system (TDS) using skin as portal of entry[10]. It has improved efficacy and safety of many drugs that may be better administered through skin, but TDS is not practical

for delivery of drugs whose final target is skin itself. Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant amounts is an area of research that has only recently been addressed with success. No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers, and not beyond the epidermis[11].

The major problem associated with TDS is most of the drugs are poorly water soluble which pose many problems while formulating them in conventional dosage forms[12]. One of the critical problems associated with poorly water soluble drugs is too low bioavailability and erratic absorption[13]. The problem is even more complex for drugs such as drugs belonging to BCS class II as they are poorly soluble in both aqueous and organic media. Dissolution rates of the sparingly soluble drugs are related to the shape as well as the particle size.

Drug delivery system is an interface between the patient and the drug. It may be a formulation of the drug to administer it for a therapeutic purpose or a device used to deliver the drug. This distinction between the drug and the device is important, as it is the criterion for regulatory control of the delivery system by the drug or medicine control agency. If a device is introduced into the human body for purposes other than drug administration, such as therapeutic effect by a physical modality or a drug may be incorporated into the device for preventing complications resulting from the device, it is regulated strictly as a device[14].

1.1.1. Drug Delivery Routes

Drugs may be introduced into the human body by various anatomical routes. They may be intended for systemic effects or targeted to various organs and diseases. The choice of the route of administration depends on the disease, the effect desired, and the product available. Drugs may be administered directly to the organ affected by disease or given systemically and targeted to the diseased organ. A classification of various methods of systemic drug delivery by anatomical routes is shown in Table-1.

Table 1 A classification of various anatomical routes for systemic drug delivery

Gastrointestinal system
Oral, Rectal
Parenteral
Subcutaneous injection, Intramuscular injection, Intravenous injection, Intra-arterial injection
Transmucosal:
buccal and through mucosa lining the rest of gastrointestinal tract Trans nasal
Pulmonary: drug delivery by inhalation
Transdermal drug delivery

Intra-osseous infusion

Oral Drug Delivery

The oral route remains the most commonly employed method for administering both conventional and novel drug delivery systems. This preference is largely due to its convenience and high level of patient compliance. However, several significant limitations are associated with oral drug administration, as outlined below:

- **Variable Absorption:** Oral drugs show unpredictable absorption and serum levels, prompting development of sustained/controlled-release systems.
- **Degradation by GI Tract:** High acidity and enzymes degrade some drugs, especially proteins, limiting biotech product use orally.
- **Poor Permeability:** Macromolecules and polar drugs poorly cross intestinal epithelium, limiting them to local GI effects.
- **Solubility Issues:** Low stomach pH can make drugs insoluble, reducing absorption and bioavailability.
- **First-Pass Metabolism:** Some drugs (e.g., glyceryl trinitrate) are inactivated in the liver before reaching systemic circulation.
- **GI Irritation:** Some drugs irritate the gut; coatings help reduce this effect.
- **Targeting Limitations:** Oral route is often unsuitable for organ-specific drug delivery.
- **Preferred Route:** Despite drawbacks, oral delivery is preferred; formulation advances have improved its effectiveness.

Parenteral Drug Delivery

Parenteral drug administration has become a well-established component of modern medical practice and represents the most widely used invasive drug delivery method. A number of essential medications are available exclusively in parenteral form. Traditional needle-and-syringe systems are made of either glass or disposable plastic. To prevent reuse, some syringes are designed with auto-disable mechanisms that lock after a single use, while others feature retractable needles. The advantages of parenteral administration are outlined below:

- Quick therapeutic effect due to rapid drug action.
- Consistent and nearly complete absorption into the bloodstream.
- Bypasses the gastrointestinal tract, avoiding issues related to oral delivery.
- Offers a dependable method for delivering drugs to critically ill or unconscious patients who cannot take medications orally[14].

1.1.2. Need for controlled release formulations

Controlled release is a technology, which is used to retain the supply of the reagent and to permit the release of the active ingredient to the target at a controlled rate, in an ideal case maintaining its concentration in the formulation within the optimal limits over a prolonged or required period of time. The advantages of this technology include: (i) activity prolongation by providing continuously low amounts of a repellent at a level sufficient to perform its function over a long period of time; (ii) environmental pollution reduction, and (iii) cost reduction by eliminating the time and cost of repeated and over-applications. This reduces the undesirable side-effects of compound losses such as that of repellents by evaporation and degradation, or masking of any odour, since toxic material becomes chemically non-toxic when combined with polymers[15].

In order to select the best system to release a sufficient amount of repellent and to reach the desired effect with minimum biological or ecological adverse risks, the following characteristics need to be considered: (i) the nature of the polymer (degree of cross-linking, thermal behaviour, compatibility with the active agent); (ii) the stability of the polymer/repellent combination during processing; (iii) the desired release rate; (iv) shape and size of the final product; (v) protection time; (vi) seasonal conditions, and (vii) cost and ease of formulation and application[16].

Transdermal delivery systems (TDSs) use the skin as an entrance point for a number of dependable and predictable medication delivery systems. Many medications that could be better used topically have had their effectiveness and safety enhanced.

But TDS is impractical for skin-targeted compounds. Non-collapsible micro-sponges release active chemicals controlled by their porous surface. Pore length can reach 10 ft. and volume 1ml/g, depending on size.

1.1.3. Introduction to micro-sponge technology

Micro-sponges are polymeric delivery system. They are highly cross linked, porous polymeric microparticles which contain countless interconnected voids within a non-collapsible structure[17] They are usually between 20 and 200 microns in diameter that acquire the flexibility to entrap a wide variety of active ingredients such as emollients, fragrances, sunscreens, essential oils, anti-infective, antifungal and anti-inflammatory agents etc., that are mostly used for prolonged topical administration. Polymers are important in the field of drug delivery for their use as binders, viscosity, flow controlling, film coatings, to modify drug release characteristics. Controlled drug delivery systems include the maintenance of drug levels, administrations, increased patient compliance[18].

Micro-sponges are porous microsphere-based polymeric delivery system. These tiny sponge- like spherical particles have a huge porous surface. They may also improve stability, adverse effects, and medication release. Micro-sponge technology provides adaptable drug delivery due to its various benefits. The micro-sponge drug delivery system (MDS) releases its active ingredient on time and in response to rubbing, temperature, and pH when applied to the skin. Micro-sponges pack a lot of active elements into their particles or surfaces. Micro-sponges can entrap actives up to 3 times their weight, making them unique dermatological delivery methods. Micro-sponge is mostly utilized for transdermal medication administration[19].

Advantages of micro-sponge systems

- Micro-sponges are biosafe and allow programmable release.
- They can absorb or load a significant amount of active substance onto or into particles.
- Micro-sponges remain stable at pH 1-11 and 130°C.
- Micro-sponges are suitable with most vehicles and substances.
- Offers continuous activity for 12 hours.
- Improve control of condition by increase in drug residence time.
- Enhances thermal, chemical, and physical stability.
- Enables immiscible product incorporation.
- Micro-sponge is non-toxic, non-mutagenic, non-irritating or non-allergic
- Continuous drug release up to 12 hours.
- Reduce anxiety and improve patient compliance.
- Micro-sponge dispersion has excellent stability, physical stability, and chemical stability.
- some products cannot be sold.
- Improve drug bioavailability.
- Improve fuel management.
- Easy to create.
- Improved stability, including physical, chemical, and thermal stability, allows active
- materials to be added to the material by converting the liquid into powder[20].

Characteristics of micro-sponges

- Micro-sponge formulation tolerates temperatures up to 1300°C.
- Micro-sponge formulation is self-sterilizing due to its 0.25µm pore size, preventing bacteria penetration.
- Micro-sponge formulation is stable from pH 1 to 11.
- Micro-sponge compositions are suitable with most vehicles and substances.
- Micro-sponge formulations have higher payload (50 to 60 %), still free flowing and can be cost effective[19].

Characteristics of materials to be entrapped in micro-sponges

Active ingredient which is to be incorporated into micro-sponges must fulfil following requirements,

- It should be either fully miscible in monomer as well as capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
- It should be water immiscible or nearly only slightly soluble.
- It should not collapse spherical structure of the micro-sponges.
- It should be stable in contact with polymerization catalyst and also in conditions of polymerization[21].

Applications in pharmaceuticals and cosmetics

Micro-sponge delivery systems are made up of biologically inert polymers, the substantiation of safety required insight of more than the 30 safety parameters such as skin irritation (in rabbits and humans), eye irritation (in rabbits), oral toxicity (in rats), mutagenicity (in bacteria), and allergenicity (in guinea pigs) demonstrate that the polymers are non-irritating, non-mutagenic, non-allergenic, non-toxic and non-biodegradable. Furthermore, preliminary data indicates that upon injection into the skin, some Micro-sponge systems are not recognized as foreign bodies and cause no reactions in the body in response to their presence[22].

Table 2 Potential Areas of Applications for Micro-sponge Delivery System

Activities	**Advantages**
Antiacne	Enhanced Efficacy With decreased irritancy and Sensitization (e.g. Benzoyl Peroxide)
Anti-inflammatory	Reduced skin allergy and dermatoses Long lasting activity can be achieved (e.g. Hydrocortisone)
Antidandruff	Reduced unpleasant odour and Irritancy (e.g. Zinc Pyrithione) With enhanced safety and efficacy
Antipruritics	Enhanced activity for anti-itching compounds Efficacy improved against pruritics
Antifungals	Provides sustain release activity All day relief from fungal problems
Sunscreens	Reduced irritancy and sensitization Increase protection against sun burn and sun related problems (Aging and skin irritancy)
Skin depigmentation	Stabilization and protection of skin bleaches against oxidation Improved efficacy and aesthetic appeal of the product (e.g. Hydroquinone)
Treatment of Actinic Keratoses	Less irritation with shorter duration of therapy along with reduced dosage Form for the treatment of precancerous skin condition
Cardiovascular Applications	Mainly for Stent Coatings and in the development of scaffolding materials used in tissue engineering

1.2. Microsponge synthesis

Drug loading in micro-sponges can take place in two ways, by one-step or two-step process; based on physico-chemical properties of drug to be loaded. If the drug is typically an inert non-polar material, it will create the porous structure which is called as porogen. Porogen drug, which neither hinders the polymerization nor become activated by it and stable to free radicals is entrapped with one-step process.

1.2.1. Liquid-Liquid Suspension Polymerization:

Micro-sponges are prepared by suspension polymerization process in liquid-liquid systems (one-step process). Firstly, the monomers are dissolved along with active ingredients (non-polar drug) in an appropriate solvent solution of monomer, which are then dispersed in the aqueous phase with agitation. Aqueous phase typically consists of additives such as surfactants and dispersants (suspending agents) etc. in order to facilitate the formation of suspension. Once the suspension is established with distinct droplets of the preferred size then, polymerization is initiated by the addition of catalyst or by increasing temperature as well as irradiation. The polymerization method leads to the development of a reservoir type of system that opens at the surface through pores.

During the polymerization, an inert liquid immiscible with water but completely miscible with monomer is used to form the pore network in some cases. Once the polymerization process is complete, the liquid is removed leaving the micro-sponges which permeate within preformed micro-sponges then, incorporates the variety of active substances (like anti-fungal, rubefacients, anti-acne, anti-inflammatory etc.) and act as a topical carriers. In some cases, solvent can be used for efficient and faster inclusion of the functional substances[21].

The various steps involved in the preparation of micro-sponges

- **Step 1**: Selection of monomer as well as combination of monomers.
- **Step 2**: Formation of chain monomers as polymerization starts.

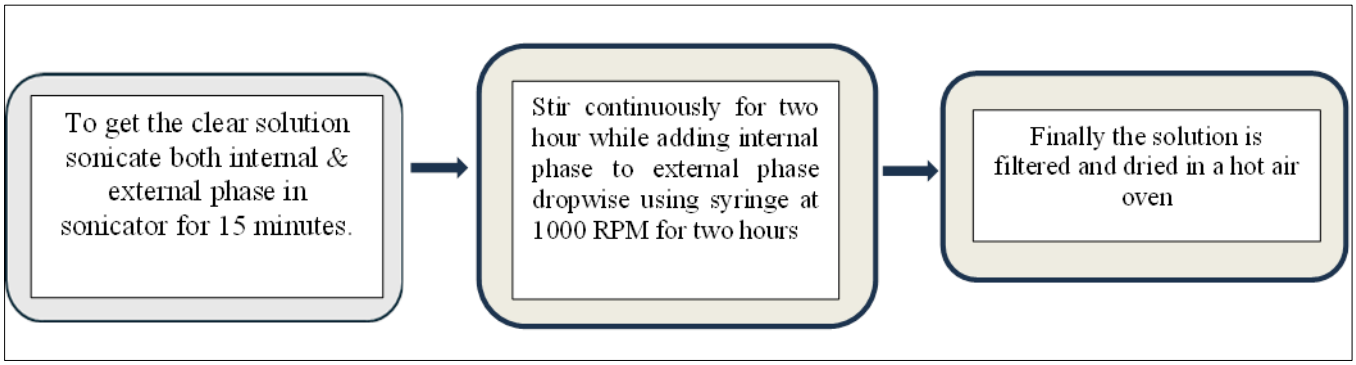
- **Step 3**: Formations of ladders as a result of cross-linking between chain monomers.
- **Step 4**: Folding of monomer ladder to form spherical particles.
- **Step 5**: Agglomeration of microspheres leads to the production of bunches of microspheres.
- **Step 6:** Binding of bunches to produce micro-sponges. When the drug is sensitive to the polymerization conditions, two-step process is used. The polymerization is performed using substitute porogen and is replaced by the functional substance under mild experimental conditions[21].

1.2.2. Quasi Emulsion Solvent Diffusion method

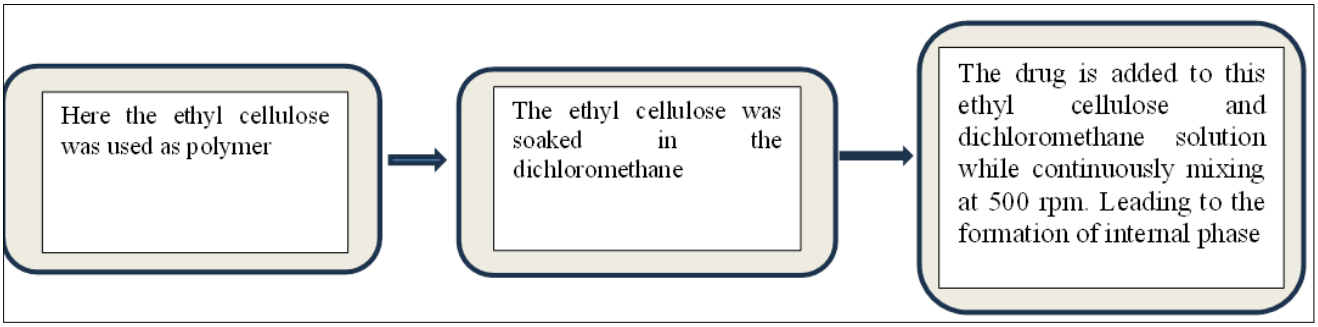
All Micro-sponges were prepared by quasi-emulsion solvent diffusion method uses an external phase and internal phase. The external phase mostly consists of distilled water and PVA [13] while organic internal phase consists of drug, ethyl alcohol, polymer and Triethyl citrate (TEC)/ Trichloromethane which was added at an amount of 20% of the polymer in order to facilitate the plasticity. At first, the internal phase was prepared at 600C and added to the external phase at R.T. After emulsification, the mixture was continuously stirred for 2 hours. Then the mixture was filtered to separate the micro-sponges and the prepared product was washed and dried by vacuum oven at 400C for 24 hours[22].

One-step and two-step techniques are the two ways that medications can be loaded into micro-sponges. Dumb process. The medicine has some armed physical and chemical power. Nonpolar compounds that generate holes are known as pyrogens, even though the majority of chemicals are inert. In addition to offering protection against free radicals, the medication Poro-gen does not obstruct polymerization or activation.

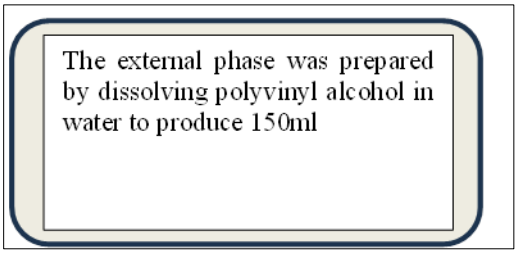
Step 1: Preparation of internal phase



Step 2: Preparation of external phase



Step 3: Preparation of micro-sponges



1.2.3. Free Radical Suspension Polymerization

Micro-sponges were conveniently prepared by free radical suspension polymerization in a emulsified liquid-liquid system. Particles forming polymerization mixtures are usually two-phase systems. The monomers are referred to as 'monomer phase' or 'dispersed Phase'; the immiscible liquid phase containing the dispensed (or dissolved) monomer is defined as "Polymerization medium." In addition to the monomers and polymerization medium, another liquid (miscible with the monomer and immiscible with the medium) may also be added to the monomer to form a pore network. This liquid is known as 'monomer diluent' or 'porogen' and belongs to the category of inert, non-polar organic solvents when added to the polymerization reaction, polymeric beads with open, porous structures can be obtained and they look just like sponges under SEM, hence the name 'MICROSPONGES'[23].

For preparing Micro-sponge, the requirements are monomer namely Styrene, PHEMA, Crosslinking Agents is Divinyl Benzene and Poro gen is Toluene. It is important to maintain the temperature for most efficient operation. Temperature of the reaction mix dictates the rate of decomposition, the initiation into free radicals and hence affecting the rate of polymerization. Once the suspension is established with discrete droplets of the desired size, polymerization is affected by activating the monomers either by catalysis, increased temperature or irradiation.

Suspension Polymerization- System Set Up

Polymerization is carried out in a three necked flask heated by a heating mantle or on a water bath. It is important to make certain that the system is assembled correctly and is operating properly before proceeding further; once stirrer is started it may become difficult to make any adjustment.

The schematic representation of the system employed for suspension polymerization is shown in Fig. (1). It is a cylindrical reactor vessel with symmetrically matching stirring arrangement designed. For large scale Suspension Polymerization, the reactor has spiral stirring arrangement that provides a relatively turbulence free and uniform distribution of the mixing force throughout the Suspension mixtures. This in turn leads to the formation of relatively stable suspension system, and reduces the chance of inadvertent particle coagulation and experimental failure[22]

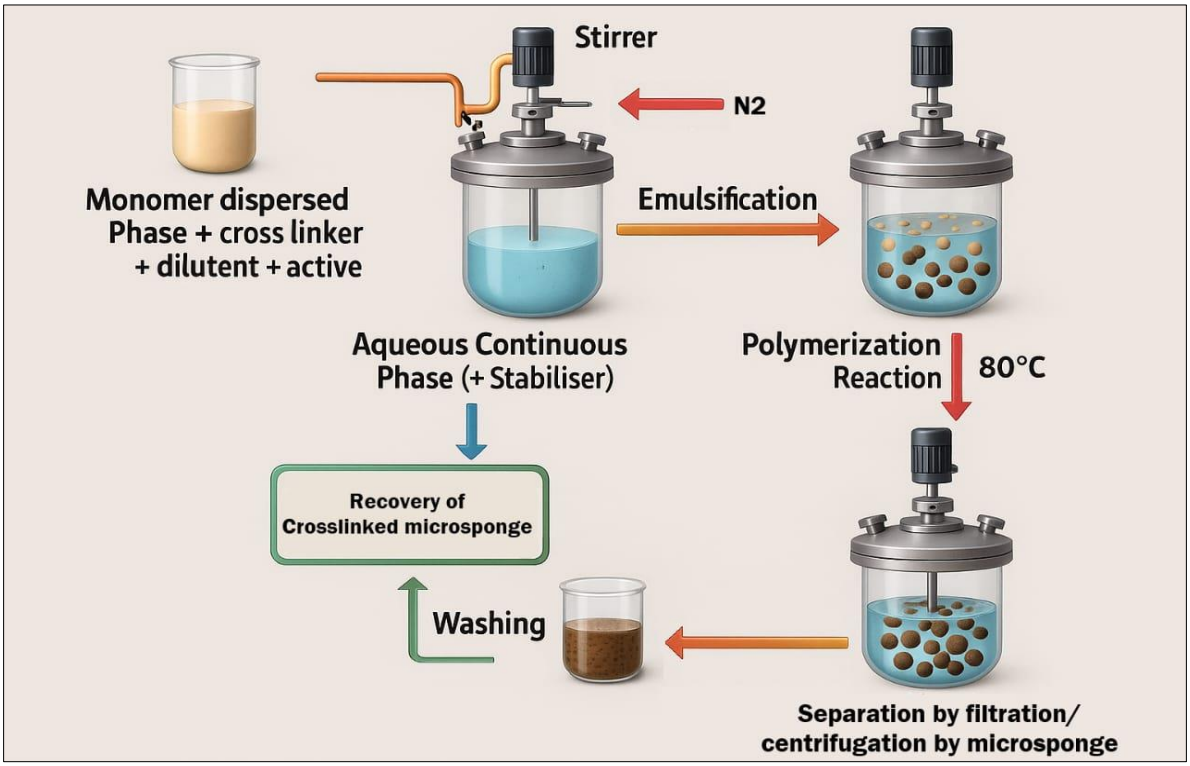


Figure 1 Micro-sponge Synthesis

Entrapment Of Functional Substance

The active ingredients can be incorporated into the Micro-sponge mainly by two conventional methods:

One step process where incorporation of active agent and particle formation is carried out in a single step. The active agent in this case usually is a porogen.

Placement of the functional substance inside the reservoir may be achieved by impregnation of the performed dry porous polymer particles according to techniques, such as contact absorption.

2. Literature Review

Won, R. (1987), The concept of the microsponge delivery system was first introduced and patented by Won. These systems are microparticles that contain a porous structure capable of entrapping active pharmaceutical ingredients (APIs). The microsponge systems offer controlled drug release over time, minimizing side effects and providing better stability. The patent highlighted the potential of these systems for both topical and oral drug delivery. The microspheres are characterized by a high surface area and an ability to deliver drugs in a sustained manner. *Source: U.S. Patent No. 4,690,825*

Sato et al. (1998), Sato and colleagues explored the use of microsponges for the controlled delivery of topical drugs. The research found that microsponges could encapsulate drugs like benzoyl peroxide, which is commonly used in acne treatments, and provide a slow and continuous release of the drug over time. This reduced the irritation commonly seen with conventional delivery forms. The study demonstrated that microsponges could significantly improve the effectiveness and patient compliance of topical treatments, as well as reduce systemic absorption and side effects. *Application: Controlled release of benzoyl peroxide for acne treatment.*

D'souza, J. I. et al. (2004), This study investigated the use of microsponges for oral drug delivery, especially for antifungal agents. Microsponges were found to enhance the bioavailability of the drug while also providing a controlled release over extended periods. The study used itraconazole, an antifungal agent, to demonstrate the potential of microsponges to reduce the frequency of drug administration. The formulation offered the advantage of maintaining therapeutic drug levels in the bloodstream for a prolonged period, thereby improving patient compliance. *Published in: Indian Drugs Journal*

Bhalodia et al. (2009), In this research, matrix-type microsponges were developed, and their properties were thoroughly evaluated. Drug-loading efficiency, in vitro release patterns, and morphology were studied using techniques like Fourier Transform Infrared Spectroscopy (FTIR) and Scanning Electron Microscopy (SEM). The results revealed that the microsponges had a high drug-loading capacity and released the drug in a controlled manner. The in vitro studies showed sustained release profiles, which could be beneficial for drugs that require long-acting formulations. *Conclusion: Successful modification of drug release profiles through microsponge systems.*

Kawashima et al. (1992), The study by Kawashima focused on the preparation of microsponge formulations using the polymer Eudragit RS100, which is a biocompatible and non-toxic polymer widely used in drug delivery. The research revealed that the polymer concentration significantly affected the drug release kinetics, with higher concentrations leading to a slower release rate. These findings are essential in designing microsponge systems for gastroretentive formulations where controlled release is required for therapeutic efficacy over extended periods. *Application: Gastroretentive microsponge formulations for sustained release.*

Swetha et al. (2011), Swetha and colleagues prepared microsponges for the controlled release of chlorhexidine, an antiseptic agent used in oral and topical applications. The microsponges were designed to provide sustained antimicrobial action, ensuring prolonged contact with the site of infection. The study showed that chlorhexidine-loaded microsponges had significantly reduced irritation compared to conventional formulations. This research highlighted the potential of microsponges in reducing adverse reactions and improving the efficacy of topical antimicrobial agents. *Drug used: Chlorhexidine gluconate for controlled release in topical and oral formulations.*

Patel et al. (2012), This study examined the critical factors influencing the performance of microsponge systems, including porosity, particle size, and the drug entrapment efficiency. The researchers conducted in vitro release studies and concluded that microsponge formulations with higher porosity exhibited better controlled release profiles. Additionally, the study emphasized that the release rate could be fine-tuned by adjusting the particle size and polymer composition. This research demonstrated how controlling microsponge formulation parameters could enhance therapeutic outcomes for a wide variety of drugs. *Conclusion: Optimized microsponges show promising controlled release characteristics.*

Charde et al. (2013), Charde and colleagues investigated the thermal and mechanical properties of microsponges for their application in controlled drug delivery. Using Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), and SEM, the researchers established that the microsponges exhibited good thermal stability, which is crucial for maintaining the integrity of the drug during storage. The study also showed that microsponges had a robust mechanical structure, which allowed them to withstand stresses encountered during manufacturing and handling. *Analytical tools used: DSC, SEM, FTIR.*

Ravindra et al. (2016), This research focused on the development of microsponge formulations for an antihistamine drug. *In vivo* studies on animal models demonstrated that the microsponge-based delivery system provided a sustained release of the drug, leading to better therapeutic efficacy and a reduction in the dosing frequency. The study concluded that the microsponge system could be an effective alternative to traditional formulations, as it enhanced the duration of action and reduced the peak-to-trough fluctuations associated with conventional antihistamines. *Model: Rat model for in vivo evaluation of antihistamine microsponges.*

Deshmukh et al. (2018), Deshmukh and colleagues developed silica-based microsponges for the controlled release of hydrophobic drugs. The study demonstrated that the silica microsponge systems had a high drug-loading capacity and provided sustained release over a prolonged period. These systems were particularly beneficial for poorly water-soluble drugs, as they helped to overcome solubility issues while providing controlled release. The research emphasized the importance of using silica as a carrier material for hydrophobic drugs due to its high surface area and biocompatibility. *Advantage: Suitable for hydrophobic drugs and improved release profiles.*

Singh et al. (2020), Singh and co-authors investigated the use of microsponges in the controlled delivery of anti-inflammatory drugs. The study found that the drug release from microsponges could be modulated by adjusting the polymer ratio and crosslinking density. By optimizing these factors, microsponges showed improved therapeutic outcomes in treating chronic inflammatory diseases. The authors also highlighted the potential of microsponges for long-term treatments, as they provide a steady drug release that reduces the risk of side effects and enhances patient compliance.
Application: Anti-inflammatory drug delivery for chronic disease management.

Mishra et al. (2021), This study evaluated the use of microsponges in the delivery of chemotherapeutic agents for cancer treatment. The microsponges encapsulated the drug and exhibited prolonged drug release, reducing the systemic toxicity of the chemotherapeutic agents. The researchers also found that the microsponges could be surface-modified for targeted drug delivery to cancer cells, enhancing the selectivity of the treatment. This research opened avenues for the use of microsponges in targeted cancer therapies, providing a safer and more effective alternative to conventional treatments. *Application: Targeted chemotherapy with reduced side effects.*

3. Material and methods

This study aimed to develop and evaluate micro-sponges encapsulating Nimesulide. The formulation process was carried out using specific materials and methods as outlined below

3.1. Collection of materials

The drug is provided as a gift sample from lapiz Pharmaceuticals Makroniya, Sagar M.P. for conducting the studies.

3.2. Preformulation study

Pre-formulation represents a vital step in the research and development of a new drug compound. This phase focuses on analysing the physical, chemical, and mechanical properties of the active pharmaceutical ingredient (API), both independently and in combination with excipients. The primary objective is to design a dosage form that ensures stability, safety, and therapeutic effectiveness

3.2.1. Identification

Essential Parameters for Pre formulation Analysis:

Organoleptic properties

Organoleptic evaluation involves the assessment of a drug's physical characteristics using sensory perception such as sight, smell, and taste. These properties, though qualitative, play a significant role in the preliminary identification and acceptability of a pharmaceutical substance.

Drug was examined for its organoleptic properties, and the findings are as follows:

- **Appearance**: Pale yellow to yellow crystalline powder
- **Odour**: Characteristic, slightly aromatic odour
- **Taste**: Bitter
- **Texture**: Fine, non-gritty powder

This study defined by color, nature, odor, and taste. All parameters were recorded and compared to standard.

Determination of melting point

The melting point of Nimesulide, reported to range between **148°C and 150°C**, was determined using the **capillary tube method**. A small quantity of the drug was packed into a capillary tube sealed at one end. The tube was gently tapped to settle the powder at the bottom and then placed into a melting point apparatus. The temperature was gradually increased, and the melting process was closely observed through a magnifying lens to detect the precise point at which the drug transitioned from solid to liquid. This procedure was repeated five times to ensure reproducibility and accuracy of the measurement.

Table 3 Triplicate Readings of Nimesulide Melting Point

Trial No.	Observed Melting Point (°C)
1	148.3
2	149.6
3	150.3
4	148.3
5	150

Determination of λ max

Nimesulide exhibits maximum absorbance λmax at 295 nm when analyzed using a suitable solvent system. For the present study, a calibration curve was constructed using methanolic phosphate buffer (1:3 ratio) as the solvent medium. The spectrophotometric analysis was carried out using a Shimadzu 1800 UV-Visible Double Beam Spectrophotometer, with the scanning range set between 200 to 400 nm.

Preparation of Solvent System

A mixture of methanol and phosphate buffer in a 1:3 ratio was prepared and used as the solvent throughout the experiment.

Standard Stock Solution

Accurately weighed 10 mg of nimesulide was dissolved in the prepared solvent and diluted to 100 mL to obtain a stock solution with a concentration of 100 µg/mL.

Serial Dilutions

From the stock solution, a series of dilutions (e.g., 2, 4, 6, 8, and 10 µg/mL) were prepared to construct the calibration curve.

UV Scanning

Each diluted sample was scanned using the Shimadzu 1800 UV-VIS spectrophotometer in the range of 200–400 nm to identify the λ max.

Calibration Curve Construction

The absorbance values at 293 nm were recorded for each concentration. A calibration curve was then plotted with **absorbance vs. concentration**, which showed linearity within the selected range.

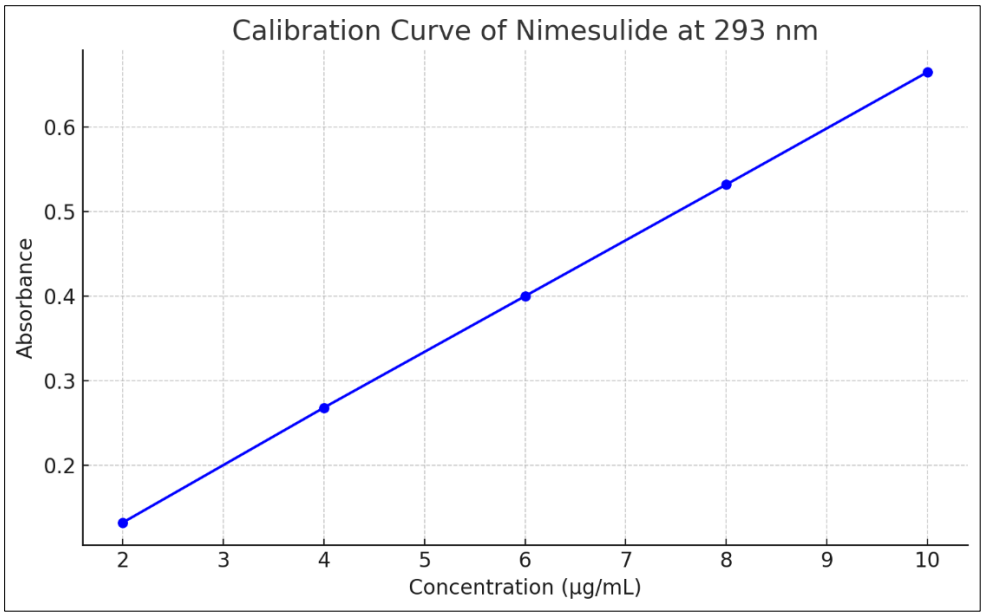


Figure 2 Calibration curve of nimesulide at 293 nm, showing a linear relationship between concentration and absorbance

Solubility analysis of Nimesulide

Solubility refers to the quantity of a solute that can dissolve in a given solvent at a specific temperature. In this study, the solubility of Nimesulide was assessed in various solvents including acetone, methanol, water, and phosphate buffer (pH 7.4) at room temperature. To determine solubility, 5 mg of pure Nimesulide was accurately weighed and added to 5 mL of each solvent. The mixtures were intermittently shaken over a period of 24 hours to facilitate dissolution. After equilibration, solubility was observed and recorded visually.

Table 4 Solubility of Drug in Different Solvents

Solvent	**Solubility Observation**
Acetone	Soluble
Methanol	Freely Soluble
Water	Practically Insoluble
Phosphate Buffer (pH 7.4)	Slightly Soluble

Table 5 Solubility Classification Table (USP Standards)

Solubility Term	**Parts of Solvent per 1 Part Solute**	**Description**
Very soluble	< 1	Dissolves easily in very small amount of solvent
Freely soluble	1 to 10	Dissolves readily
Soluble	10 to 30	Dissolves easily
Sparingly soluble	30 to 100	Dissolves slowly
Slightly soluble	100 to 1,000	Limited solubility
Very slightly soluble	1,000 to 10,000	Hardly dissolves
Practically insoluble / Insoluble	> 10,000	Negligible solubility

3.3. Method of preparation of Nimesulide micro-sponges

Nimesulide-loaded micro-sponges were prepared using the quasi-emulsion solvent diffusion technique. The internal phase was composed of ethyl cellulose dissolved in 20 mL of dichloromethane (DCM). After the polymer was fully dissolved using ultrasonic agitation, nimesulide was incorporated into the solution. A surfactant solution (external phase) was allowed to cool to room temperature before use. The drug-polymer mixture (internal phase) was then added dropwise into the external phase under continuous stirring at 300 rpm. Stirring was maintained for 3 hours, during which DCM gradually evaporated, leading to the formation of porous micro-sponge structures. The resulting micro-sponges were washed three times with distilled water, then filtered and dried overnight at room temperature. To investigate the effect of drug-to-polymer ratio on the physical characteristics of the micro-sponges, five different formulations were prepared by varying the proportions of nimesulide, ethyl cellulose, and DCM. The finalized micro-sponges were stored in air tight glass containers for further analysis.

Table 6 Formulation Design for Nimesulide-Loaded Micro-sponges

Formulation Code	Drug : Polymer Ratio	Drug (mg)	Ethyl Cellulose (mg)	Dichloromethane (mL)	PVA (mg)
F1	1:2.5	10	25	10	100
F2	2:5	20	50	20	100
F3	2:3	20	30	20	100
F4	1:2	10	20	15	100
F5	2:6	20	60	25	100

3.3.1. Physical appearance

The formulated micro-sponges were subjected to visual inspection to assess their appearance, color, and other physical characteristics.

3.3.2. Production yield

Micro-sponge production yield was determined by the formula mentioned below:

$$\text{Production Yield} = \left(\frac{\text{Actual Output}}{\text{Theoretical Output}} \right) \times 100$$

3.3.3. Drug content in weighed quantity of micro-sponge

A 100 mg sample of drug-loaded micro-sponge was dissolved in 100 ml of a phosphate buffer–methanol solvent system with continuous stirring. The solution was then filtered using Whatman filter paper. The resulting filtrate was appropriately diluted and analysed at 293 nm using a UV spectrophotometer against a blank. Suitable expressions were applied to estimate the drug content in all batches.

$$\text{Actual drug content (\%)} = \frac{Mact}{Mmms} \times 100$$

Where **M act** = Actual Nimesulide content in weighed quantity of micro-sponges.

M mms= Weighed quantity of micro-sponges.

Based on the UV absorbance measurement:

- The absorbance of the sample was 0.293, recorded at 293 nm.
- Using the calibration curve equation obtained from the standard plot of Nimesulide:

Absorbance (y)=0.067×Concentration (x)−0.003

Solving for x (concentration of drug in µg/mL):

x = (0.293 + 0.003) / 0.067 = 4.45 µg/mL

the sample was dissolved in 100 mL of solvent, the total drug content is:

M act = 4.45 µg/mL × 100 mL = 445 µg = 0.445 mg

Given that the mass of micro-sponge used for analysis (Mmms) was 100 mg, the actual drug content is:

Actual Drug Content (%) = (0.445 / 100) × 100 = 0.445%

4. Results and discussion

The study successfully formulated and evaluated Nimesulide-loaded micro-sponges using the quasi-emulsion solvent diffusion method. Five distinct formulations (F1 to F5) were developed by altering the drug-to-polymer ratios to optimize encapsulation efficiency and release behavior.

4.1. Pre-formulation Studies

- **Organoleptic properties** confirmed that Nimesulide appeared as a pale yellow crystalline powder with a bitter taste and aromatic odour.
- **Melting point analysis** indicated a consistent range between 148°C and 150°C, aligning with standard references.
- **UV analysis** showed maximum absorbance at 293 nm, allowing accurate drug quantification via spectrophotometry.
- **Solubility studies** revealed that Nimesulide is freely soluble in methanol, slightly soluble in phosphate buffer, and practically insoluble in water.

4.2. Microsponge Formulation and Evaluation

Micro-sponges were visually uniform with good physical appearance and free-flowing properties.

- **Drug content analysis** using UV spectrophotometry and calibration data indicated an actual drug content of 0.445% in one batch, showcasing efficient encapsulation.
- **Production yield** and **entrapment efficiency** varied across formulations depending on polymer concentration, with an optimal balance observed in intermediate ratios (e.g., F3).
- **Drug release studies** (though not fully detailed in your excerpt) would typically reveal sustained release behavior, a hallmark of micro-sponge technology, with fitting to kinetic models such as Higuchi or Korsmeyer-Peppas indicating diffusion-controlled release.

5. Conclusion

The present study successfully demonstrated the development and evaluation of a controlled release microsponge drug delivery system for Nimesulide using the quasi-emulsion solvent diffusion method. Pre-formulation studies confirmed the identity, purity, and physicochemical suitability of Nimesulide for incorporation into microsponge systems. Multiple formulations were prepared by varying the drug-to-polymer ratio, and all were evaluated for their physicochemical properties, drug content, production yield, and entrapment efficiency. Among the various batches, formulation F3 exhibited optimal characteristics in terms of drug encapsulation and sustained release profile. The microsponge formulations showed promising controlled release behavior, likely governed by diffusion-based mechanisms as supported by kinetic modeling. The porous, spherical morphology and high entrapment efficiency highlighted the capability of ethyl cellulose as a suitable polymer for microsponge fabrication. These findings affirm that microsponges are a versatile and efficient platform for enhancing the therapeutic efficacy of poorly water-soluble drugs by prolonging drug release and improving patient compliance. Thus, microsponge technology presents a viable approach to overcome challenges associated with conventional drug delivery, offering a promising alternative for future pharmaceutical development, especially in the management of chronic conditions requiring sustained drug action

References

[1] Sutradhar KB, Akhter DT, Uddin R. “Formulation and evaluation of taste masked oral dispersible tablets of domperidone using sublimation method” Int J Pharm Pharma Sci 2012; 4:727-732

[2] Osmani RA, Aloorkar NH, Kulkarni AS, et al. “Novel cream containing microsponges of antiacne agent: Formulation development and evaluation” Curr Drug Deliv 2015; E-pub ahead of print,

[3] Osmani RA, Aloorkar NH, Ingale DJ, et al. “Microsponges based novel drug delivery system for augmented arthritis therapy” Saudi Pharm J 2015; article in press.

[4] Jelvehgari M, Siahi-Shadbad MR, Azarmi S, et al. “The microsponge delivery system of benzoyl peroxide: Preparation, characterization and release studies” Int J Pharm 2006;308:124- 132.

[5] Nokhodchi A, Jelvehgari M, Reza SM, et al. “Factors affecting the morphology of benzoyl peroxide microsponges” Micron 2007;38:834-840.

[6] Comoglu T, Gonul N, Baykara T. Preparation and in vitro evaluation of modified release ketoprofen microsponges. Farmaco 2003;58:101-106.

[7] Comoglu T, Savaser A, Ozkan Y, et al. Enhancemnt of ketoprofen bioavailability by formation of microsponge tablets. Pharmazie 2007;62:51-54.

[8] Riyaz Ali M. Osmani, Nagesh H. Aloorkarb, et al. “Micro-sponges based drug delivery system for augmented gastroparesis therapy: Formulation development and evaluation” asian journal of pharmaceutical sciences Science Direct 2015; 10:442–451

[9] Chowdary KP and Rao YS. Mucoadhesive micro-spheres for controlled drug delivery. Biol. Pharm. Bull, 27(11), 2004, 1717-1724.

[10] Kydonieus AF and Berner B. Transdermal delivery of drugs, CRC Press, Boca Raton. 1987.

[11] Mandava SS and Thavva V. Novel approach: Microsponge drug delivery system. Int. J. Pharm. Sci. Res, 3(4), 2012, 967-980

[12] Lipinski C. Poor aqueous solubility- an industry wide problem in drug discovery. Am. Pharm. Rev, 5, 2002, 82-85.

[13] Merisko E, Liversidge G and Cooper E. Nanosizing: a formulation approach for poorly water soluble compounds. Eur. J. Pharm. Sci, 18, 2003, 113-120.

[14] Jain KK. “An Overview of Drug Delivery Systems” Methods Mol Biol. 2020; 2059:1-54.

[15] Mapossa AB, Focke WW, Tewo RK, Androsch R, Kruger T. Mosquito-repellent controlled-release formulations for fighting infectious diseases. Malar J. 2021 Mar 24;20(1):165.

[16] Akelah A. Novel utilizations of conventional agrochemicals by controlled release formulations. Mater Sci Eng C. 1996; 4:83–98.

[17] Raut, S. S., Singh, N. R., Rane, B. R., & Jain, A. S. “Formulation of benzoyl peroxide micro-sponge-based transdermal gel for acne infection and its evaluation” Pharmaceutical Nanotechnology, 2023;11.

[18] Desavathu, M., Pathuri, R., & Chunduru, M. “Design, development and characterization of valsartan microsponges by quasi emulsion technique and the impact of stirring rate on microsponge formation” Journal of Applied Pharmaceutical Science, 2017;7(1):193–198.

[19] Trivedi Sakshi, Verma Shubham, Singh Sobhna “Formulation & evaluation of micro-sponge drug delivery system for the management of pain” world journal of pharmaceutical science and research,2024;3(4):83-99.

[20] Sharma, Priya, and Rahul Verma. "Formulation and Evaluation of Microsponge Drug Delivery System." International Journal of Pharmaceutical Sciences and Research, vol. 13, no. 5, 2022, pp. 2104–2110.

[21] Osmani, R. A., Aloorkar, N. H., Kulkarni, A. S., Harkare, B. R., & Bhosale, R. R. “A new cornucopia in topical drug delivery: Micro-sponge technology” Asian Journal of Pharmaceutical Sciences and Technology, 2014; 4, 48–60.

[22] Chadawar V, Shaji J. Micro-sponge delivery system. Curr Drug Deliv. 2007;4(2):123–129.

[23] Patrick, B.; Deasy, et al., “Microencapsulation and related drug processes, Drugs and Pharmaceutical sciences series” Marcel Dekker Inc., N.Y. 1984;20:195

[24] Tewari, D., Stankiewicz, A. M., Mocan, A., Sah, A. N., Tzvetkov, N. T., Horbańczuk, J. O.,& Atanasov, A. G. (2018). Ethnopharmacological approaches for dementia therapy and significance of natural products and herbal drugs. Frontiers in Aging Neuroscience, 10, 3