

Formulation, Evaluation and Process Validation of Topical Piroxicam Microsponge Gel

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Abstract: Transdermal drug delivery system (TDDS) were developed for systemic delivery of drugs using the skin as portal of entry. But TDDS is not practicable for delivery of materials 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 pronounced amounts is an area of research. The goal of present work is to overcome the gastro-intestinal side effects of Piroxicam and to provide a better drug release in the form of microsponge (MS) entrapped topical drug delivery system. Microsponge of Piroxicam was formulated by quasi-emulsion solvent diffusion technique by using polymer/drug carrier like Eudragit RS 100 and optimized batch of MS was selected to incorporate into gel with a view to prevent the gastric side effect, to avoid first pass metabolism and to achieve best release pattern of the Piroxicam from Piroxicam MS gel. This research article discusses the characterization of drug and polymers, analysis of microsponge via DSC, SEM and FTIR, formulation and evaluation of topical Piroxicam microsponge gel.

Keywords: Microsponge, Transdermal drug delivery systems, controlled release, Piroxicam, NSAIDs

1. Introduction

1.1. Micro Sponge Drug Delivery System:^[1]

The micro sponge technology was invented by Won in 1987, and the original patents were given to Advanced Polymer Systems. Micro sponges are porous microspheres having myriad of interconnected voids of particle size ranging between 5-300 μm . These micro sponges have ability to entrap wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective, anti-fungal and anti-inflammatory agents etc. and are used as a topical carrier system. Further these porous microspheres with active ingredients can be incorporated into formulations such as creams, gel, lotions and powders and share a broad package of benefits. Micro sponges consist of non-collapsible structures with porous surface through which active ingredients are released in controlled manner. Depending upon the size.^[2]

Micro sponges have the ability to Adsorb or Load a high degree of active materials into the particle or onto its surface. Its large capacity for entrapment of actives up to 3 times its weight differentiates micro sponges from other types of dermatological delivery systems. Recently, micro sponge delivery system has been recommended for the controlled release of drugs onto the epidermis with commitment that the drug remains substantially localized and does not enter the systemic circulation in major amounts which gives rise to a new creation of highly efficacious and well tolerated novel products.

Micro sponges have capacity to absorb skin secretions consequently, decreasing oiliness and shine from the skin. Micro sponge particles are significantly small, inert, indestructible spheres that do not travel through the skin. To a certain extent, they pile up in the tiny nooks and crannies of skin and slowly release the entrapped drug, as the skin needs it. The micro sponge system can also avoid unwanted

pile up of ingredients within the epidermis and the dermis. Likely, they can reduce markedly the irritation of effective drugs without reducing their efficacy. Similar like a true sponge, each microsphere consists of an innumerable of interconnecting voids within a non-collapsible structure with a large porous surface. When it is applied to the skin, the drug release can be controlled through diffusion.

This controlled release of active ingredient onto skin over time is a tremendously important tool for assuring the benefits of enhanced product efficacy, tolerability, mildness and reducing the irritation usually associated with powerful therapeutic agents like retinoid or benzoyl peroxide etc. and extended wear to a wide range of skin therapies. This system has been employed for the improvement of performance of topically applied drug. MDS technology is now being presently used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products very popularly.^[2]

Benefits of Micro sponge Technology

Micro sponge technology offers:

- Enhanced product performance.
- Extended release.
- Lessen irritation and hence improved patient compliance.
- Improved product elegance.
- Improved oil control as it can absorb oil up to 6 times its weight without drying.
- Improved formulation flexibility.
- Improved thermal, physical, and chemical stability.
- Flexibility to develop novel product forms.
- In contrast to other technologies like microencapsulation and liposome's, MDS has wide range of chemical stability, higher payload and are easy to formulate.
- Micro sponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic^[2].

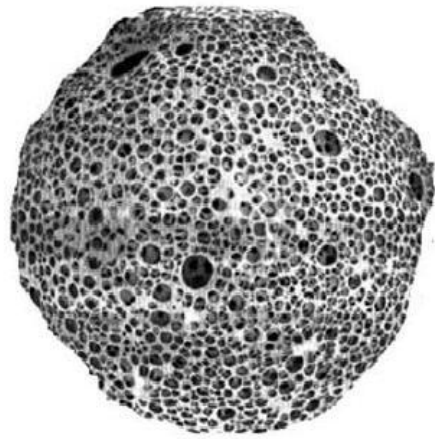


Figure 1: Image of micro sponge

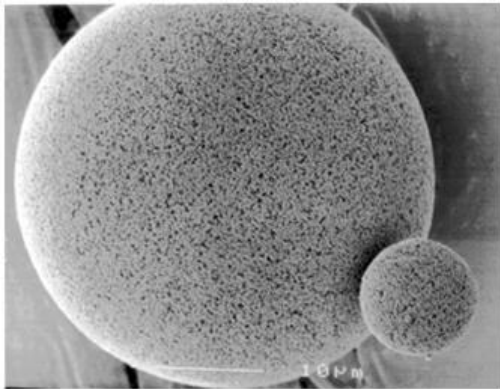


Figure 2: Image showing porosity of micro sponge

Method of preparation of micro sponge

1. Liquid-Liquid suspension polymerization

In this method of polymerization the monomer is dissolved along with the active Ingredients in suitable solvent and then added in aqueous phase containing additives i.e. surfactant, suspending agents etc. The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation. Polymerization of styrene or methyl methacrylate is carried out in round bottom flask. A solution of nonpolar drug is made in the monomer, to which aqueous phase, usually containing surfactant and dispersant to promote suspension is added. Polymerization is effected, once suspension with the discrete droplets of the desired size is established, by activating the monomers either by catalysis or increased temperature. (Reaction vessel shown in fig.) 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.^[3]

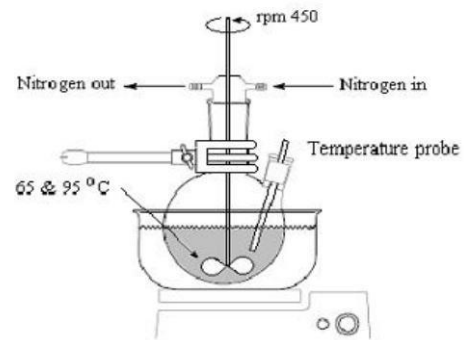


Figure 3: Reaction vessel for preparation of micro sponge by liquid – liquid suspension polymerization.

The various steps in the preparation of micro sponges are summarized as follows.

- Selection of monomer or combination of the monomer.
- Formation of chain monomer as polymerization begins.
- Formation of monomer ladder as result of cross linkage between chain monomer.
- Folding of monomer ladder to form spherical particles.
- Agglomeration of microspheres lead to formation of bunches of microspheres. Binding of bunches lead to formation of micro sponge.^[3]

2. Quasi-emulsion solvent diffusion.

Micro sponges were prepared by quasi emulsion solvent diffusion method. In this method the internal phase consists of Eudragit RS100 dissolved in an organic solvent dichloromethane (DCM) then Glycerol was added as plasticizer and followed by the addition of piroxicam under ultra-sonication at 35 C for 15 min. The internal phase was then poured into the external phase (0.05% polyvinyl alcohol in distilled water) after one hour of stirring by mechanical stirrer (from Copley scientific, UK) at a rate of 500 rotations per minute (r. p. m); the micro sponges were formed due to the removal of organic solvent from the system. The micro sponges were filtered and dried at 40°C for overnight. The fabricated micro sponge was evaluated for production yield, loading efficiency, particle size and, FTIR, differential scanning calorimetry, and scanning electron microscopy.^[4]

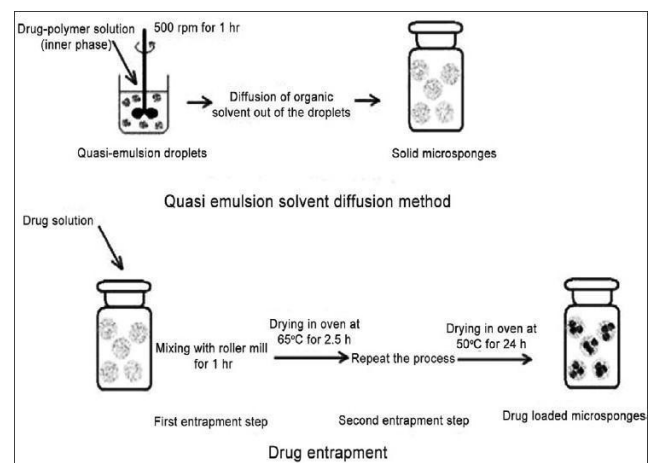


Figure 4: Quasi-emulsion solvent diffusion method

Applications of Microsponge Systems:

Microsponges are porous, polymeric microspheres that are used mostly for topical and recently for oral administration. It offers the formulator a range of alternatives to develop drug and cosmetic products. Micro-sponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release.

1. Microcapsules cannot usually control the release rate of the active pharmaceutical ingredients (API). Once the wall is ruptured the API contained within the microcapsules will be released
2. Pay load is up to 50 – 60%.
3. Free flowing and cost effective.
4. Microsponges are microscopic spheres capable of absorbing skin secretions, therefore, reducing oiliness and shine from the skin.

Products under development or in the market place utilize the Topical Microsponge systems in three primary ways:

1. As reservoirs releasing active ingredients over an extended period of time.
2. As receptacles for absorbing undesirable substances, such as excess skin oils,
3. As closed containers holding ingredients away from the skin for superficial action. Releasing of active ingredients from conventional topical formulations over an extended period of time is quite difficult.

Objectives of the research:

- Delivery of piroxicam through topical formulation with the intention overcoming its GI side effect.
- To prepare and evaluate piroxicam micro sponge using Eudragit RS 100 as a polymer.
- To validate the process for various process parameters.
- To study in vitro drug release and permeability study of micro sponge incorporated into gel formulation.

Validation of Process Parameters: ^[5]

- Validation

The documented evidence of proving high degree of assurance that any procedure, process, equipment, material, activity or system actually leads to expected result.

- Process Validation

“Process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

Process validation is both us FDA or U.S requirement. Similar requirements are included in the world health organization (WHO), the pharmaceutical inspection co-operation scheme and the European Union (EU) requirements along with those of Australia, Canada, Japan and other international authorities.

Reason for Process Validation

The possible reason of performing process validation may include:

- New product or existing products as per SUPAC changes.
- Change in site of manufacturing.
- Change in batch size
- Change in equipment.
- Change in process existing products.
- Change in composition or components.
- Change in the critical control parameters.
- Change in vendor of API or critical excipients.
- Change in specification or input material.
- Abnormal trends in quality parameters, of product through review during annual product review.

Benefits of process validation

- Consistent through output
- Reduction in rejections and re work
- Reduction in utility cost
- Avoidance of capital expenditures.
- Reduced testing in process and finished goods.
- Easier maintenance of equipment.
- Improve employee awareness of processes.
- More rapid automation.

2. Literature Survey**1. Vikas Jain and Ranjit Singh:****Development and characterization of eudragit RS 100 loaded micro sponges and its colonic delivery using natural polysaccharides**

Work on, paracetamol loaded eudragit based micro sponges were prepared using quasi emulsion solvent diffusion method. The compatibility of the drug with various formulation components was established. Process parameters were analyzed in order to optimize the formulation. Shape and surface morphology of the micro sponges were examined using scanning electron microscopy. The formulations were subjected to in vitro release studies and the results were evaluated kinetically and statically. The in vitro release data showed a bi-phasic pattern with an initial burst effect. In the first hour drug release from micro sponges was found to be between 17-30%. The cumulative percent release at the end of 8th hour was noted to be between 54-83%. The release kinetics showed that the data followed Higuchi model and the main mechanism of drug release was diffusion. The colon specific tablets were prepared by compressing the micro sponges followed by coating with pectin: hydroxyl propylmethyl cellulose (HPMC) mixture. ^[4].

2. Nevine s Abdelmalak1, Shahira f el-menshawe;**A new topical fluconazole micro sponge loaded hydrogel: preparation and characterization**

The aim of the present study was to formulate topical micro sponge-based delivery system containing FLZ for controlled release of the drug and consequently avoiding its oral side effects. Ethyl cellulose (EC) and Eudragit RS 100 based micro sponges were prepared using quasi-emulsion solvent diffusion method. The effect of formulation variables such as drug to polymer ratio, polymer type, polyvinyl alcohol (PVA) concentration and type of internal phase on the physical characteristics of the micro sponges was examined using 24 factorial designs. Results revealed that FLZ loading and micro sponge particle size were increased with increasing the polymer fraction. Moreover, EC significantly increased the drug entrapment efficiency (EE %) and the mean particle size. A selected FLZ micro sponge (F3, containing FLZ and EC in 1:1 ratio and prepared using 0.75% PVA and methylene chloride) was incorporated in carbopol gel formulation and evaluated for its in vitro release characteristics. The developed micro sponges were spherical and porous^[42].

3. Riyaz Ali Osmani et al;

A new cornucopia in topical drug delivery: micro sponge technology.

The work shows the expanding arena of emerging drugs, increased sensitivity to clinical outcomes and healthcare costs are driving the need for alternative drug delivery methods and devices. More and more developments in delivery systems are being integrated to optimize the efficacy and cost effectiveness of the therapy. New classes of pharmaceuticals, biopharmaceuticals are fueling the rapid evolution of drug delivery technology. Micro sponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. Micro sponge consists of micro porous beads loaded with active agent. When applied to the skin, the micro sponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH etc.) that are used mostly for topical and recently for oral administration. Micro sponge technology has many favorable characteristics which make it a versatile drug delivery vehicle. Micro sponge Systems can suspend or entrap a wide variety of substances, and then be incorporated into a formulated product such as a gel, cream, liquid or powder. The outer surface is typically porous, allowing the sustained flow of substances out of the sphere. Micro sponge delivery system (MDS) can provide increased efficacy for topically active agents with enhanced safety, extended product stability, enhanced formulation flexibility, reduced side effects and improved aesthetic properties in an efficient and novel manner. In addition these are non-irritating, non-mutagenic, non-allergenic, and nontoxic.^[3]

4. Yerram Chandramouli et al;

Preparation and evaluation of micro sponge loaded controlled release topical gel of acyclovir sodium

The present work shows that, Micro sponge containing acyclovir sodium as active constituent with four different

formulations by changing the proportions of drug (acyclovir sodium), polymer (ethyl cellulose), emulsifier (Poly vinyl alcohol) were obtained successfully using emulsion solvent diffusion method. These formulations were studied for particle size and physical characterization. Scanning electron microscopy (SEM) images showed the micro sponges porous and spherical in shape. The physical characterization showed that micro sponge formulation coded by M2 showed a better loading efficiency and production yield. This micro sponge formulation was prepared as gel in carbopol and studied for pH, viscosity, spread ability, drug content, and in-vitro release. The micro sponge formulation gel, F1 showed viscosity 206.72 cps, spreadability of 11.75g cm/s and drug content of 92.37%. The micro sponge acyclovir sodium gel formulations showed an appropriate drug release profile. From the various release kinetic models the F1 formulation was found to be optimized. F1 released 50.85% of drug at 8 hours. Diffusion exponent (n) value of F1 formulation was found to be 0.912 suggesting that the Ficks law of diffusion was not followed. The F1 formulation followed Zero order kinetics in its in vitro drug release.^[5]

5. Anilkumar J. Shinde, et al ;

Development and Evaluation of Fenoprofen Micro sponges and its Colonic Delivery using Natural Polysaccharides.

The aim of the present study was to prepare microsponges containing fenoprofen by quasi emulsion- solvent diffusion method. In rheumatoid arthritis there is a need of a release the drug after some lag time, colonic specific delivery of drug serve this purpose. The colon specific formulations were prepared by compression coating using chitosan: HPMC mixture followed by tableting of micro sponges. Micro sponges were spherical, uniform in shape, between 40.32 to 197.32 μ min diameter and showed porosity values 15.85%. The production yield, actual drug content and encapsulation efficiency was found in the range of 24.54 \pm 1.54 to 67.08 \pm 2.57%, 29.52 \pm 0.43% to 64.48 \pm 0.71%, and 39.34 \pm 0.56% to 73.66 \pm 0.82% respectively. The results of compatibility tests FTIR, PXRD and showed that no chemical interaction or changes take place during preparation of the formulations. Cumulative percent drug release for the microsponges over 8h ranged from 54-70%. In vitro release studies exhibited that compression coated colon specific tablet formulations started releasing the drug at 8 h corresponding to the arrival time at proximal colon. The study presents a new approach based on microsponges for colon specific and sustained drug delivery.^[6]

6. R. Ravi, S.K. Senthil Kumar, S. Parthian;

Formulation and evaluation of the micro sponges gel for an anti acne agent for the treatment of acne.

The present work shows that Acne is a common inflammatory skin disease that mainly affects the face, neck, chest and upper back. Treatment depends on severity. Erythromycin has bacteriostatic activity which inhibits the growth of bacteria. They mainly act by binding to the 50s subunits of bacteria, 70s r-RNA complex, and protein synthesis. Erythromycin is also used topically to treat acne.

They are used to treat moderate to severe inflammatory acnes or acne that isn't getting better with other treatments. Erythromycin works to treat acne by reducing the amount of acne causing bacteria called "propionibacteria" acnes on the skin; it also lessens inflammation and redness. Erythromycin is easily inactivated by the gastric environment and produce gastric disturbances such as diarrhoea, nausea, abdominal pain and vomiting. Erythromycin micro sponges were prepared using quasi emulsion solvent diffusion method. Erythromycin micro sponges were then incorporated into a Carbopol-940 gel prepared by hydro gel technique for release studies. The best formulation was found to be stable at room temperature for 3 months. Thus it was concluded that erythromycin can be formulated as micro sponge gel that can release the drug upto 8hrs with reduced side effects. [7]

7. Markand Mehta et al;

Formulation and in-vitro evaluation of controlled release micro sponge gel for topical delivery of clotrimazole

In the present study, Clotrimazole, BCS class II drug was used which having very less aqueous solubility, a shorter half-life (2.5-3 hr) and certain side effects like earythma, oedema and skin irritation. So, encapsulation of Clotrimazole into micro sponge would modified the release rate and also reduce side effects. In this study Clotrimazole micro sponge was prepared by emulsion solvent diffusion technique by using Ethyl cellulose, HPMC K4M, Carbopol 934, Eudragit RS100, Eudragit S100, Eudragit RL100 and evaluated for % Practical yield, % Loading efficiency and In vitro drug release study. Drug- excipients compatibility was performed by FTIR study. Optimized batch of micro sponge was further formulated as gel formulation for topical delivery. Prepared gel formulations were evaluated for physical parameters like viscosity, pH, clarity and In vitro drug permeation study. The drug release data of optimized batch were fitted into different kinetic models which show that the drug release from gel formulations follows zero order release. Optimized gel formulation was compared with the marketed formulation and pure drug for anti fungal activity, which shows that the prepared formulation is having comparative anti fungal activity with marketed formulation. [8]

8. Ramani Gade et al;

Design and development of hydroxyzine hydrochloride controlled release tablet Based on micro sponge technology

The purpose of the present study aims to design novel drug delivery system containing hydroxyzine hydrochloride micro sponges and to prepare controlled release micro sponge tablets. Hydroxyzine hydrochloride is an anti-histaminic drug used in the treatment of urticaria and pruritus. It has a half-life of about 3-4hrs. The Micro sponge Delivery System is a unique technology for the controlled release of active agents, and it consists of porous polymeric microspheres, typically 10–50 µm in diameter. Micro sponges of the drug were prepared by using polymer Methocel 10000cps and in combination with Eudragit -S 100, Eudragit-L 100,

Eudragit-RL 100 and Eudragit-RS 100. These are prepared by oil in oil emulsion solvent diffusion method using acetone as dispersing solvent and liquid paraffin as the continuous medium. Magnesium stearate was added to the dispersed phase to prevent flocculation of polymeric micro sponges. Compatibility of the drug with adjuncts was studied by FT-IR. Production yield, loading efficiency, particle size analysis, surface morphology and invitro release studies were carried out. The micro sponge formulation (F8) was found to be stable at 40°C and 75% relative humidity with respect to particle size, loading efficiency and invitro drug release. [11]

9. Hamid Hussain et al ;

Formulation and evaluation of gel-loaded micro sponges of diclofenac sodium for topical delivery

In this study ethyl cellulose facilitated micro sponges were prepared by the double emulsificationTechnique (Quasi emulsion technique) and subsequently dispersed in a carbopol gel base for controlled Delivery of diclofenac sodium to the skin. The micro sponges' formulations were prepared by quasiemulsion solvent diffusion method employing ethyl cellulose as a polymer. The compatibility of the drug with formulation components was established by Fourier Transform Infra-Red (FTIR) spectroscopy. The surface morphology, particle size, production yield, and drug entrapment efficiency of micro sponges were examined. Shape and surface morphology of the micro sponges were examined using scanning electron microscopy. Particle size of prepared micro sponges was observed in the range of 28.7 ± 1.02 - 23.9 ± 1.19 µm. Scanning electron microscopy revealed the porous, spherical nature of the micro sponges. SEM photographs revealed the spherical nature of the micro sponges in all variations; however, at higher ratios, drug crystals were observed on the micro sponge surface. [10]

10. Pande, et al

Fabrication and Characterization of Sertaconazole Nitrate Micro sponge as a Topical Drug Delivery System

Present study was taken up to develop a topical formulation that releases the drug in controlled manner, reduce the side effects associated with topical drug delivery and improve product efficacy with aid of micro sponges. Micro sponges loaded with sertaconazole nitrate were prepared by using quasi emulsion solvent diffusion with five different proportions of the polymer (Eudragit RS 100). The developed micro sponges were analyzed for particle size, production yield, entrapment efficiency and drug content. Scanning electron microscopic images of micro sponges revealed that they are spherical in shape and contain pores. Pore structure analysis was done by using mercury intrusion porosimetry technique, which confirmed the porous nature of micro sponges. Micro sponges were then incorporated in to a 1% corbopol gel and evaluated for pH, drug content, texture profile analysis and in vitro drug release. The batch F IV was found to be optimal as it shown 69.38% controlled drug release in 8 h that followed Higuchi model. [9]

11. Shireesh Acharagonda et al ;**Formulation and evaluation of famotidine floating micro sponges**

The present study shows that floating drug delivery system have particular interest for drug that locally active and have narrow absorption window in stomach our an upper small intestine, unstable in stomach colonic environment, and exhibit low solubility at high ph values, the micro sponges delivery systems consisting of patented polymeric system consisting of porous microspheres, they consist of myriads of inter connecting voids within non collapsible structure with large porous surface through wick active ingredients are release in a controlled manner .famotidine floating micro sponge are prepared to improve site specific absorption of drug to improve peptic ulcer treatment .modified quasi emulsion solvent diffusion method was used to prepare micro sponges .different concentration of Eudragit RS 100 and poly vinyl alcohol was used and evaluated for entrapment efficiency and % cumulative drug release it was found that % entrapment efficiency was 88% and cumulative drug release was 86.9 % for F6 formulation .this study present a new approach based on floating ability of micro sponges based on the treatment of ulcer.^[12]

12. Mohan Kumar V et al;**Formulation and Evaluation of Micro sponges for Topical Drug Delivery of Mupirocin**

The aim of the study was to produce mupirocin entrapped micro sponges to control the release of the drug to the skin. Mupirocin micro sponges were prepared using an emulsion solvent diffusion method. In order to optimize the micro sponge formulation, factors affecting the physical properties of micro sponges were determined. FT-IR and SEM was used to study the shape an morphology of micro sponges. Mupirocin micro sponges were then incorporated into a vanishing cream base for release studies. It was shown that the drug: polymer ratio, stirring rate, volume of external and internal phase influenced the particle size and drug release behaviour of micro sponges. The results showed that an increase in the ratio of the drug: polymer resulted in a reduction in the release rate of Mupirocin from micro sponges. Kinetic analysis showed that the main mechanism of drug release was by Higuchi matrix- controlled diffusion.^[13]

13. Katkade Mayur et al;**Ethyl cellulose based micro sponge delivery system for anti-fungal vaginal Gels of tioconazole.**

The present study shows that Valvovaginal Candidiasis is a fungal infection of the vagina and causes are itching, burning, soreness, dysparunia and phenotypical signs such as vaginal and vulvar erythema and edema caused by various species of the genus Candida. Tioconazole is an antifungal medication of the Imidazole class used to treat infections caused by a fungus or yeast. Negative aspects associated with oral systemic antifungal therapy for Vulvovaginal Candidiasis include its limited success rate, toxicity,

contraindications, drug interactions, high cost of medication and increased microbial resistance. Orally administered tioconazole is extensively metabolized, major metabolites are glucuronide conjugates. Topical therapy does not lead to systemic side effects or drug interactions. The aim of the study was to produce Ethyl Cellulose micro sponge loaded with Tioconazole gel which was able to control the release of Tioconazole to the vaginal tissue. Drug content, Encapsulation efficiency and Percentage yield as such 73.97±0.01, 92.15±0.02 and 81.57±2.87 were determined in the prepared micro sponges. The Scanning electron microscopy (SEM) of micro sponges showed that they were spherical in shape and contained pores. Tioconazole micro sponges were then incorporated into gel for release studies. It was found that the 12 hrs in-vitro drug release study of micro sponge was best studied by KorsmeyerPeppas model.^[17]

14. Yerram Chandramouli et al;**Micro sponges: a novel drug delivery system for controlled delivery of topical drugs.**

The study shows that Even though possess several advantages topical formulations have some drawbacks such as the need to contain high concentrations of active agents for effective therapy due to the low efficiency of delivery system, resulting into irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential in-compatibility of drugs with the vehicles. These drawbacks are overcome by micro sponge drug delivery system. Micro sponge delivery system consists of a polymeric bead having network of pores held with an active ingredient which maximizes the retention time of an active ingredient either on skin surface or within the epidermis thereby providing controlled release of drugs. Micro sponge possess the versatility to load a wide range of actives providing the benefits of enhanced product efficacy, mildness, tolerability, and extended over to a wide range of skin therapies.^[18]

15. Manisha K. Tile and A.Y. Pawar**Micro sponges: A Novel Strategy for Drug Delivery.**

Micro sponge technology has been introduced in topical drug products to facilitate the controlled Release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. Micro sponge consists of macro porous beads, typically 10-25 Micron in diameter, loaded with active agent. When applied to the skin, the micro sponge releases its Active ingredients on a time mode and also in response to other stimuli. Micro sponge drug delivery Technology holds a great promise for reaching the goal of controlled and site-specific drug delivery And hence, has attracted wide attention of researchers. This article presents a broad review of Micro sponges' delivery system discussing the principles and preparation methods. Appropriate Analytical techniques for characterization of Micro sponges like Particle size and its distribution, Surface morphology, porosity, density are covered. These micro sponges are used in the sunscreens,

Creams, ointments, over-the-counter skin care preparations, which are meant for topical application. Micro sponge drug delivery can provide increased efficacy for topically active agents with enhanced Safety, extended product stability and improved aesthetic properties in an efficient and novel Manner.^[19]

16. Rekha.u, b. p. manjula et al;

Formulation and evaluation of micro sponges for topical drug delivery of mometasonefuroate.

Mometasonefuroate is a medium potency, synthetic, non-fluorinated topical Corticosteroid, indicated for the relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses including psoriasis. The percutaneous absorption increases risk associated with systemic absorption of topically applied formulation. Controlled release of the drug to the skin could reduce the side effects while reducing percutaneous absorption. Therefore, the aim of present study was to produce mometasonefuroate entrapped micro porous micro particles (micro sponges) to control the release of the drug to the skin. Mometasonefuroate micro sponge was prepared using an emulsion solvent diffusion method. In order to optimize the micro sponge formulation, factors affecting the physical properties of micro sponges were determined. Compatibility of the drug with excipients was studied by FT-IR. Production yield, loading efficiency and surface morphology of micro sponges were performed. It was shown that the drug: polymer ratio, stirring rate, volume of external and internal phase influenced the particle size and drug release behaviour of micro sponges. The results showed that, generally an increase in the ratio of the drug: polymer resulted in a reduction in the release rate of mometasonefuroate from micro sponges.^[14]

17. Rajendra Jangde

Micro sponges for colon targeted drug delivery system: An overview.

The drug delivery technology landscape has become highly competitive and rapidly evolving. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy. Peptides, proteins and DNA-based therapeutics cannot be effectively delivered by conventional means. 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. 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 is successively done by the micro sponge delivery system. When applied to the skin, the micro sponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc). Micro sponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. In addition, numerous studies have confirmed that micro sponge systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic. MDS technology

is being used currently in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products.^[15]

18. Garish Joshi et al;

Micro sponges: A Novel Drug Delivery System.

Micro sponge is recent novel technique for control release and target specific drug delivery system. Micro sponges are polymeric delivery system composed of porous microspheres. They are tiny sponge-like spherical particle with a large porous surface. Micro sponge system offers entrapment of ingredient and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. Micro sponge systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as gel, cream, liquid or powder and have recently been used for oral administration.^[16]

19. Tushar Shetgaonkar, R. Narayana Charyulu.

Microsponge Drug Delivery of Terbinafine Hydrochloride for Topical Application.

Micro sponges are porous, polymeric microspheres that are used for prolonged topical administration. The purpose of present study was to prepare terbinafine hydrochloride micro sponges to avoid the side effects and further incorporate the same into gel. Terbinafine hydrochloride micro sponges were prepared by emulsion solvent diffusion technique using Eudragit RS 100 and Ethyl cellulose polymers in different drug: polymer ratios. The formulations were then evaluated for particle size, percentage yield, Percentage loading efficiency and in vitro drug release study. The SEM image showed micro sponges with porous and spherical nature. The optimized formulation of each polymer was incorporated into gel bases of carbopol 940P and HPMC K100M. The prepared gels were further characterized for appearance, pH, viscosity, spreadability, drug content, in vitro diffusion and in vitro antifungal activity. The gels were homogenous and consistent with sufficient viscosity and spreadability. The drug was uniformly distributed and was released upto 80 % at the end of 10th h. HPMC K100M gels released the drug at a faster rate than carbopol 940P gels.^[20]

20. Neelam Jain et al ;

Recent advances on micro sponge delivery system.

Conventional topical formulations are intended to work on the surface of the skin. Normally, upon application such formulations release their active ingredients and producing a highly concentrated layer of active ingredient that is quickly absorbed. Therefore, need exists for a system to increase the amount of time that an active ingredient is present either on skin surface as well as within the epidermis, at the same time, minimizing its transdermal penetration in the body. Recently, micro sponge delivery system (MDS) has been successively addressed for the controlled release of drugs onto the epidermis with assurance that the drug remains chiefly localized and does not enter the systemic circulation

in major amounts. MDS is a unique technology for the controlled release of topical agents, also use for oral as well as biopharmaceuticals (peptides, proteins and DNA-based therapeutics) drug delivery. It consists of micro porous beads having a range of 10-25 microns in diameter that possess a versatility to entrap wide range of active agents.^[21]

21. M. S. Charde et al;

Micro sponge A Novel New Drug Delivery System: A Review

Shows that Microsponge is recent novel technique for control release and target specific drug delivery system. Therefore many scientist or researcher attracted towards the micro sponge drug delivery system. Also Micro sponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy. Microsponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. In addition, numerous studies have confirmed that microsponge systems are non-irritating, nonmutagenic, non-allergenic, and non-toxic. MDS technology is being used currently in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. One of the best feature of micro sponge is it is self-sterilizing.^[23]

22. Nirav Patel et al;

Formulation and evaluation of microsponge gel for topical delivery of fluconazole for fungal therapy.

The aim of the present research was to develop Fluconazole loaded micro sponge-based topical delivery system for controlled release and enhanced drug deposition in the skin. Micro sponges containing fluconazole were prepared by an emulsion solvent diffusion method. The effect of formulation variables (drug: polymer ratio, internal phase volume and amount of emulsifier) and process variables (stirring time and stirring speed) on the physical characteristics of micro sponges like Production yield, Mean particle size, Entrapment efficiency were investigated. The effect of internal phase volume and amount of emulsifier on the physical characteristics of micro sponges were examined on optimized drug/polymer ratio, stirring speed and stirring time by 32 factorial designs.^[24]

23. Atmaram P Pawar et al;

Formulation and evaluation of optimized oxybenzenemicrosponge gel for topical delivery.

The present study shows that oxybenzene is a wide spectrum sunscreen agent used in the form of cream and lotions. Has been reported to cause skin irritation, dermatitis, and systemic absorption. The aim of present study was to prepare oxybenzene loaded microsponge gel for enhance sun

protecting factor for reduced toxicity. Microsponge for was successfully prepared by quasi emulsion solvent diffusion method. The effect of dichloromethane and ethylcellulose was optimized by 3² factorial designs. The optimized micro sponge gel was dispersed in to hydro gel and was evaluated. The microsponge was spherical with pore size in the range of 0.10-0.22. The optimized formulation possesses the particle size and entrapment efficiency 76µm and 96.9% respectively. The microsponge formulation was controlled release and was non-irritant to rat skin. In creep recovery test it was show highest recovery indicating elasticity.^[25]

24. Pentewar RS et al

An Approach for Topical, Oral Controlled and Cosmetic Formulations.

The study shows that, Microsponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin. The size of the microsponges can be varied usually from 5-300µm in diameter, depending upon the degree of smoothness or after-feel required for the end formula. Although the microsponge size may vary, a typical 25µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10ft in length providing a total pore volume of about 1ml/g. This approach opens up entirely new opportunities for MDS by colon specific targeting of drugs. Microsponges are extremely small, inert, indestructible spheres that do not pass through the skin. Rather, they collect in the tiny nooks and crannies of the skin and slowly release the entrapped drug, as the skin needs it. They are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release. They can be incorporated into conventional dosage forms such as creams, lotions, gels, ointments, tablets and powder and share a broad package of benefits and thus provide formulation flexibility.^[26]

3. Materials and Methods

Materials:

Following are the drug, polymer excipients and chemicals were used for formulation and evaluation studies.

Table 1: List of materials

Sr. no	Drug / excipients	Category
1	Piroxicam	Drug
2	Eudragit RS 100	polymer
3	Polyvinyl alcohol	Emulsifier
4	Dichloromethane	Solvent
5	Carbopol 934	Gelling agent
6	Methyleparaben	Preservative
7	Triethanolamine	pH adjustant
8	Glycerol	Moisturizer

All chemicals used were for analytical grades.

Equipments

Equipment which are required are listed in table

Table 2: list of equipment's

Sr. No,	Instrument	Make
1	UV visible spectrophotometer	Shimadzu UV -1800 Japan
2	IR spectrophotometer	JASCO FTIR -4100, Japan
3	Differential scanning calorimetry	Shimadzu DSC 60
4	Scanning electron microscope	JEOL, JSM.6510
5	Diffusion cell	Electrolab, TDT Mumbai
6	Hot air oven	Eli electrolab
7	Magnetic stirrer	REMI
8	Mechanical stirrer	Remi Motors
9	Ultra Sonicator	Toschon XT -56
10	Digital weighing balance	Shimadzu AX 200
11	Digital pH meter	Henna instruments, Italy
12	Mechanical shaker	REMI instruments LTD, Mumbai

Experimental Work: [6]**Identification and Characterization of Piroxicam:****Description:**

Piroxicam was characterized for colour, odour, and taste.

Melting point:

Melting point of Piroxicam was determined by capillary method

Solubility:

The solubility studies of Piroxicam were carried out in, ethanol, dichloromethane, Distilled water and phosphate buffer 5.5 by adding 1mg/ml of solvent.

Ultraviolet spectrum:

The maximum wavelength of Piroxicam was identified by UV spectrophotometry. A solution of Piroxicam containing concentration 1000ug/ml was prepared in Phosphate buffer pH 5.5 and UV spectrum was taken using shimadzu (UV – 1800) double beam spectrophotometer and scanned between 200 to 400 nm. The maxima obtained the graph was considered as maximum wavelength of Piroxicam and shown in figure 7.

Infrared spectrum:

IR spectrum of Piroxicam was obtained using KBr pellet technique. The drug sample was mixed with IR grade potassium bromide and scanned in the range of 4000 – 400cm⁻¹. Infrared spectrum of Piroxicam was shown in figure 8.

Differential scanning calorimetry (DSC):

The Piroxicam thermal behaviour was examined by DSC. Accurately weighed 10 mg of Piroxicam was run at the

scanning rate of 20⁰C /min over a temperature range of 100 to 300 ⁰C. DSC thermogram of Piroxicam was shown in figure 9.

Calibration of Piroxicam by UV spectrophotometer:

Standard solution of drug (1000ug/ml) was prepared by dissolving 10 mg of drug in 10 ml of Phosphate buffer pH 5.5.

Preparation of calibration curve:

For preparing calibration curve a standard solution was filtrated like 2, 4, 6, 8, 10 ug/ml was prepared .for this aliquots of 2ml, 4ml, 6ml, 8ml, from solution of 10ug/ml was transferred into the 10 ml standard volumetric flask, and volume was adjusted with Phosphate buffer pH 5.5, were scanned at 372nm against blank solution. Calibration curve is shown in figure 10.

Identification Characterization of Eudragit RS100:**Description:**

Eudragit RS100 was characterized for colour, odour, and taste.

Melting point:

The melting point of Eudragit RS 100 was determined by capillary method.

Solubility:

Solubility of Eudragit RS 100 was determined in solvents like Acetone, Alcohol, Dichloromethane, petroleum ether, and Distilled water.

Infrared spectrum:

The IR spectrum of Eudragit RS 100 was obtained using Kbr pellet technique. The Eudragit RS 100 sample was mixed with IR grade potassium bromide and scanned in the range of 4000–400⁻¹.infrared spectrum of Eudragit RS 100 was shows in figure 11 and values are given in table 9.

Identification Characterization of PVA:**Description:**

Polyvinyl alcohol was characterized for colour, odour, and taste.

Melting point:

The melting point of polyvinyl alcohol was determined by capillary method.

Solubility:

Solubility of polyvinyl alcohol was determined in organic solvents like Alcohol, Acetone, DCM, and Distilled water.

Infrared spectrum:

The IR spectrum of polyvinyl alcohol was obtained using KBr pellet technique. The polyvinyl alcohol sample was mixed with IR grade potassium bromide and scanned in the range of 4000 – 400⁻¹ infrared spectrum polyvinyl alcohol was shown in figure 12 and tabular values are given in table 10.

Preparation and Method Optimization:**Method of preparation of micro sponges:**

The micro sponge was prepared by quasi emulsion solvent diffusion method. It is two step process methods. In first step, inner phase was prepared by dissolving the Eudragit RS100 in dichloromethane then the drug was added in to the solution of Eudragit RS100 and dissolved under ultrasonication at 35°C for 15 min. the outer phase was prepared by dissolving the PVA in to the distilled water and the process was carried out at room temperature. The inner phase was then poured in to the outer phase drop wise and mixture was continuously stirred using mechanical stirrer at 1000 rpm for 2hr after the formation of micro sponges the mixture was filtered to separate the drug loaded micro sponge. The product was washed and dried in oven at 40°C [7].

Formulation composition of Piroxicam micro sponge:**Table 3:** Formulation composition of Piroxicam

Sr. No.	Batch code No	Drug : polymer Ratio (mg)	DCM (ml)	Glycerol (ml)	Water (ml)	PVA conc. (%)
1	B - 1	1:1	10	0.5	100	0.5
2	B - 2	1:2	10	0.5	100	0.5
3	B - 3	1:3	10	0.5	100	0.5
4	B - 4	1:4	10	0.5	100	0.5
5	B - 5	1:5	10	0.5	100	0.5
6	B - 6	1:6	10	0.5	100	0.5

Evaluation of Piroxicam Microsponge: [6]**Drug polymer interaction (FTIR) studies:**

FTIR studies was performed on Fourier transform infra red spectroscopy (JASCO FTIR -4100, Japan) the pellets was prepared by compressing the powder at 20 psi for 10 min on Kbr press and the spectra were scanned in the range of 4000 – 400 cm⁻¹. FTIR study was done on the Piroxicam, physical mixture, and Piroxicam loaded microsponge.

Particle size analysis:

The average particle size of Piroxicam microsponge was determined by optical microscopy which stage micrometer was used. A minute quantity of Piroxicam microsponge was spread on the clean glass slide an average size of 50 microsponge was determined for each batch.

$$D_{av} = \sum d / \sum n$$

Where: D_{av} is the average diameter of particles (um) n is the no. of particle of particles per group, and d is the middle value (um). [4]

Calibration of eye piece micrometer:

One division of stage micro meter = 10um

$$C = (SM \times 100) / EM \dots \text{Equation no (1)}$$

Where, C = correction factor

SM = reading of stage micro meter which coincides with reading of ocular meter

The average particle size was determined using the equation

$$D (\text{mean}) = \sum nd / \sum n \dots \text{Equation no (2)}$$

Where, n = no of microsponge observed,

D = mean size range

Production yield:

The production yield of microsponge was determined by calculating accurately the initial weight of raw material and the last weight of microsponge obtained after drying. [4]

$$\text{Production yield} = \frac{\text{final obtained mass of micro sponges}}{100}$$

Initial mass of polymer and drug

Theoretical drug content:

Drug content was determined by calculating assuming that the entire Piroxicam present in the polymer solution used gets entrapped in Piroxicam microsponges, and no loss occurs at any stage of preparation of Piroxicam microsponge.

Practical drug content:

Drug content was done by following procedure. Weighed amount of Piroxicam microsponges equivalent to 10 mg of Piroxicam was dissolved in 10 ml of dichloromethane solution. The solution was shaking continuously for complete dissolution of Piroxicam in dichloromethane this solution was filtered and further diluted to make a conc. of 10 ug / ml solution. The absorbance of solution was measured at 350 nm using blank and calculated for the percent of drug present on the sample.

Scanning electron microscope (SEM)

Scanning electron microscopy has been used to determined particle size distribution. Surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing the drug delivery system. Owing in the large simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOI JSM – 6510 scanning electron microscope. Dry Piroxicam were placed on an

electron microscope brass stub and coated with platinum coating. Picture of Piroxicam micro sponge were taken by random scanning of the stub.

Differential scanning calorimetry (DSC):

Thermogram of Piroxicam micro sponge formulation was obtained using differential scanning calorimeter (shimadzu DSC16) outfitted with an intercooler. Indium standard was implied for calibrating DSC enthalpy and temperature scale. Microsponge samples were kept in aluminium pan hermetically and heated at constant rate of 100C/min over temperature range of 80 to 300° C.

Preparation and evaluation of microsponge gel formulation:

Preparation of microsponge gel:

For preparing Piroxicam micro sponge gel, 0.5g of carbopol 934 was uniformly dispersed in a beaker containing sufficient quantity of water and soaked for overnight. Then it was mixed with 5g of glycerine containing methyl paraben as a preservative to form paste. And later 95 ml of water was added to form paste under constant stirring, by the drop wise addition of triethanolamine to adjust the pH between 6.5-7.5 and evaluated for visual inspection, pH measurement, viscosity, spreadability, extrudability, and in vitro drug release study.

Evaluation of Microsponge Gel:

Visual inspection:

The organoleptic properties like colour, texture, consistency, homogeneity and physical appearance of gels containing microsponges were checked by visual observation.

PH measurement:

Diverse gel formulations pH was recorded using digital pH meter. 5 g gel was dispersed in 45 ml distilled water at 27°C and solution pH was measured.

Spreadability studies:

One of the requisite qualities for an ideal gel is to encompass excellent spreadability. Spreadability is used to express extent of area of skin or affected part to which formulation readily spreads; which significantly affects therapeutic efficacy of formulation. Expression of spreadability is given in terms of time (in seconds) taken by two slides to slip off from gel placed in between under application of specific load. Better spreadability is indicated by minimum time required for slides separation. Mathematical expression used for spreadability calculation was:

$$S = ML / T \quad \dots \text{Eqn (4)}$$

Where, M = weight (in g) attached to upper slide, L = length (in cm) of glass slides, T = time (in sec) taken to separate the slides.

Wooden block-glass slides apparatus was used and by applying weight about 20 g, time for complete separation of upper slide (movable) from lower slide (fixed) was estimated.



Figure 5: Spreadability Test

Tube extrudability:

An ideal gel should possess good tube extrudability; so that when slight pressure is applied on tube, formulation should extrude out uniformly with an ease. Technique based upon percent quantity of gel extruded from tube on finger pressure application was adopted for examining extrudability. More the quantity extruded better the extrudability. Formulations were filled in clean, lacquered, collapsible aluminium tubes with 5 mm nasal tip opening and pressure was applied on tubes by means of first finger and thumb. Afterward tube extrudability was estimated in percentage by measuring amount of gel extruded through tip and compared with marketed formulation considering its extrudability as 100%.

Viscosity measurement:

The viscosity of all gel formulation was measured with a Brookfield viscometer (Capcalc V2.2) using 1x model and spindle number 64, with angular velocity of 5 rpm at 25°C. An average of five readings was used for viscosity calculation.

In vitro drug release:

The in-vitro release of gel formulations were studied using Franz diffusion cells. The cellophane membrane (0.45 µm) previously soaked overnight in dissolution medium was mounted onto Franz diffusion cell with 20 ml receptor compartment and effective diffusion area 2.84 cm². PBS (pH 5.5) was used as receptor medium, and system was thermostated to 37±1°C under constant stirring. All batches of drug microsponge gels (B1-B6) and Marketed formulation (B7) was assessed for the diffusion study. Aliquots of 3 ml volume were withdrawn at specific time intervals by maintaining sink condition. Withdrawn aliquots were then diluted using receptor medium and analyzed by UV spectrophotometer (Shimadzu UV -1800 Japan) at 372 nm against PBS pH 5.5. To reveal drug release mechanism and to contrast release profiles disparities amongst

formulations, data obtained from timely drug release was used.



Figure 6: In vitro drug releases

4. Result and Discussion

Identification and Characterization of Piroxicam:

Description:

Piroxicam is white to off-white amorphous powder, odourless and possesses determined taste.

Melting point:

The melting point of Piroxicam was found to be in the range of 198 – 200°C which confirms the purity of Piroxicam.

Solubility:

Table 4: Solubility of Piroxicam in various solvents

Sr. No.	Solvents	Solubility
1	Distilled water	(23mg/L)
3	Ethanol	5mg/ml
4	Dichloromethane	19.8mg/ml
5	Phosphate buffer PH 5.5	0.054mg/ml

The literature survey shows Piroxicam solubility in water is very low, and it is BCS class 2 drugs.

Ultraviolet spectrum:

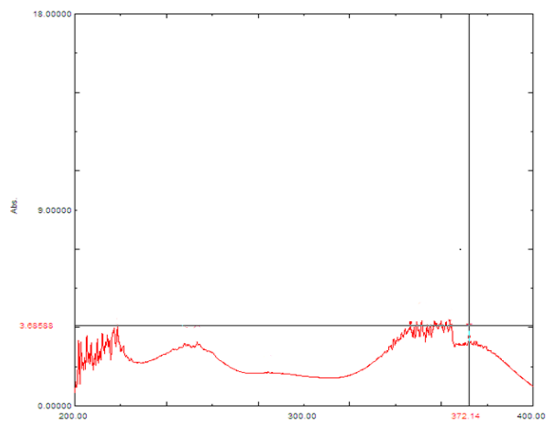


Figure 7: UV spectrum of Piroxicam

The λ max of Piroxicam in dichloromethane solution was found to be 350nm.

Infrared spectrum:

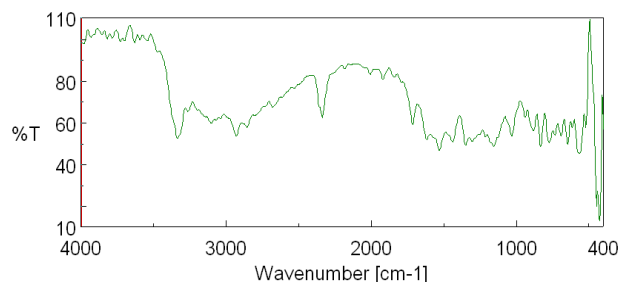


Figure 8: Infrared spectrum of Piroxicam

The drug shows characteristic peaks as shown in table 7.

Table 7: Tabular values of IR spectrum of Piroxicam

Sr. No.	Functional Group	Frequency (cm ⁻¹)
1	-NH of amide group	3332.39
2	CH stretching of aromatic ring	2927.41
3	Keto (C=O) of amidegroup	1616.06
4	OH group of benzothiazine	3540.67
5	C=N of pyridine	1531.2
6	Sulphur oxide group benzothiazine ring	1153.22

The FTIR spectra shown in figure 8, the main characteristic peak of PIR was the secondary amine N-H stretching which appeared at 3332.39cm⁻¹, it has been reported that Piroxicam has two inter convertible crystalline forms, namely the needle and cubic forms. The PIR spectra also show other characteristics peak like C=N Stretching vibration of pyridyl nitrogen assigned at 1616.06cm⁻¹, C=C stretching of Aromatic ring at 1438.64cm⁻¹, C-N stretching at 1346.07cm⁻¹, C-O stretching at 1211.08cm⁻¹, S=(O)₂ Stretching at 1153.22cm⁻¹, SO₂-N Stretching at 1029.8cm⁻¹, Aromatic CH bending at 879.38cm⁻¹, and C-S Stretching at 690.39cm⁻¹.

Differential Scanning Calorimetry (DSC):

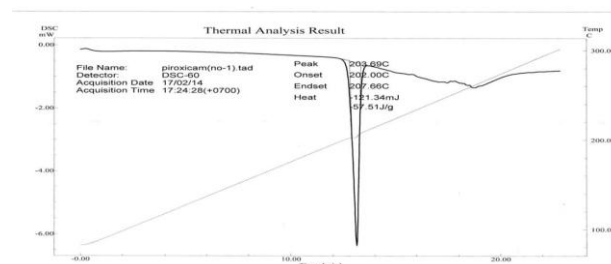


Figure 9: Differential Scanning thermogram of Piroxicam

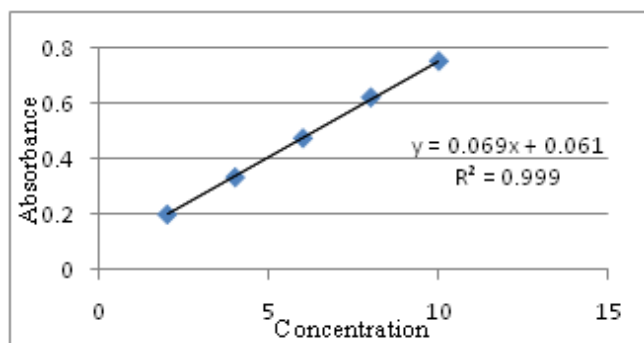
Differential scanning calorimetry of Piroxicam showed sharp endothermic peak at 203.69°C which corresponding to the melting point of drug in the crystalline form which is reported in the other studies.

Preparation of calibration curve by UV:

Calibration curve of Piroxicam was prepared by UV spectrophotometer in Phosphate buffer pH5.5 at λ max of 372nm for minimum of five different concentrations.

Table 8: Calibration curve of Piroxicam in Phosphate buffer 5.5pH

Sr. no.	Concentration (ug/ml)	Absorbance
1	2	0.202
2	4	0.335
3	6	0.475
4	8	0.621
5	10	0.751

**Figure 10:** Calibration Curve of Piroxicam in Phosphate buffer 5.5pH**Identification and Characterization of Eudragit RS 100****Description:**

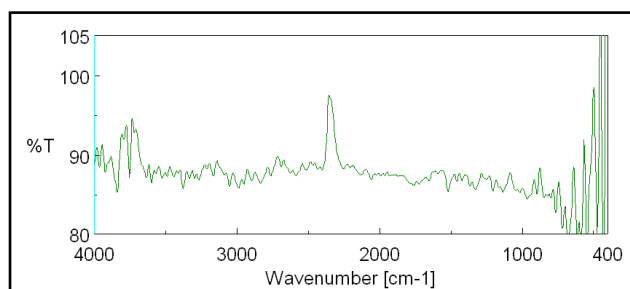
Eudragit RS 100 is a solid substance in the form of colourless, clear to cloudy granule with a faint amine like odour.

Melting point:

The melting point of Eudragit RS 100 was found to be 160°C.

Solubility:

Solubility of Eudragit RS 100 was determined in different solvents, it is found to be soluble in acetone, alcohol, dichloromethane, and practically insoluble in petroleum ether and distilled water.

Infrared spectrum of Eudragit RS 100:**Figure 11:** Infrared spectrum of Eudragit RS100**Table 9:** Tabular values of IR spectrum of Eudragit RS 100

Sr. no.	Wave number (cm ⁻¹)	Characteristics
1	2985.27	Aliphatic C-H stretching
2	1133.94	C – N (amines)
3	1133.94 - 964.233	C-O bending
4	964.23	CH2 bending
5	1519.63	Presence of C-O stretching

Identification and Characterization of Polyvinyl Alcohol:**Description:**

Polyvinyl alcohol was found to be white odourless powder.

Melting point:

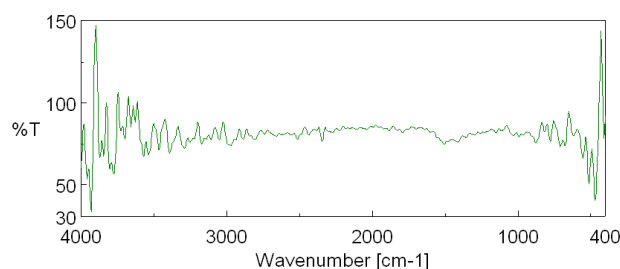
The melting point of poly vinyl alcohol was found to be 228°C.

Solubility:

Solubility of poly vinyl alcohol was determined in different solvents, it was found to be soluble in water and in soluble in organic solvent.

Infrared spectrum:

The IR spectrum of polyvinyl alcohol was obtained using KBr pellet technique. The polyvinyl alcohol sample was mixed with IR grade potassium bromide and scanned in the range of 4000 – 400⁻¹.infrared spectrum polyvinyl alcohol was shown in figure 8.6 and tabular values are given in table 8.5.

**Figure 12:** Infrared spectrum of poly vinyl alcohol**Table 10:** Tabular values of PVA

Sr. no.	Wavenumber (cm ⁻¹)	Characteristics
1	3050.83 - 2345.02	Aliphatic C-H stretching
2	3586.81 – 3390.24	Hydroxyl group
3	1149.37 – 991.23	C-O bending
4	991.23 – 779.10	CH2 bending

Preparation and Method Optimization:

6 batches of micro sponges were prepared by different drug: polymer ratios by quasi – emulsion solvent diffusion method as shown in table 8.6 and evaluated for;

- Production yield
- Entrapment efficiency
- Particle size
- Drug content

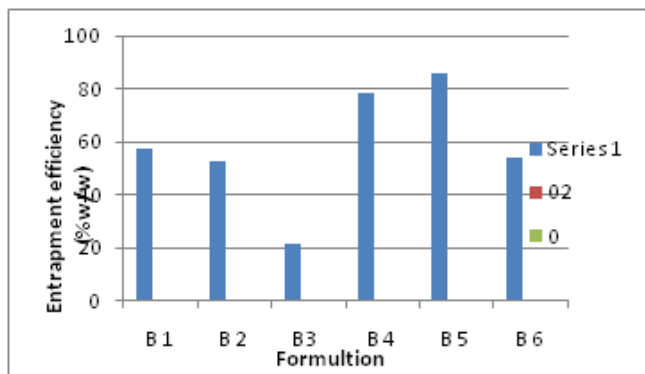


Figure 16: % Entrapment efficiency of piroxicam microspunge

The mean amount of drug entrapped in prepared microsponges was found to be lesser than theoretical value for every drug polymer ratio employed, the fact is that drug entrapment efficiency did not attain 100%. the reason is that some drugs is gets dissolved in aqueous phase or solvents used. The percentage entrapment efficiency was found to be in the range of 21.06 – 85.48. The results obtained are given in table 11. And their histogram is shown in figure 16. A maximum of 85.48% Entrapment efficiency was obtained in the Piroxicam B5 batch which is prepared by using Eudragit RS 100.

Scanning Electron Microscope (SEM):

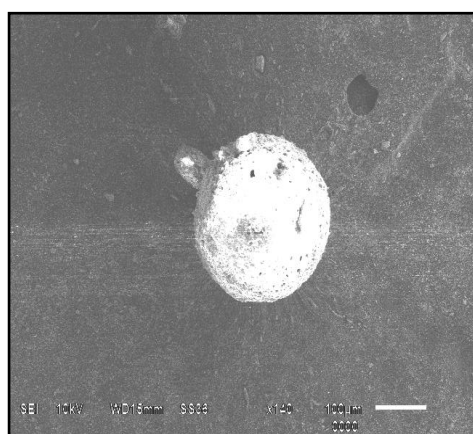
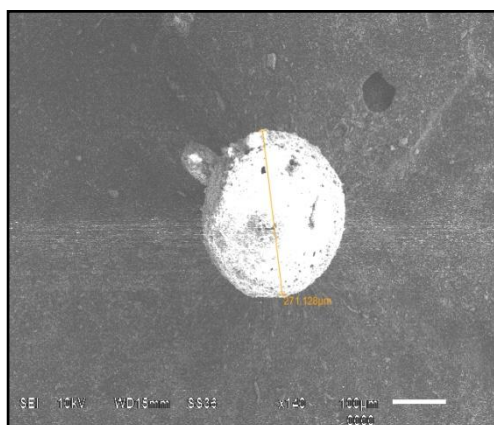


Figure 17: SEM image showing diameter and porous nature of single micro sponge particle

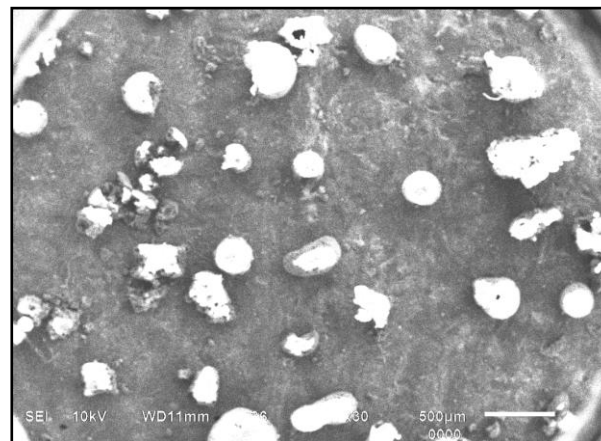


Figure 18: Scanning Electron microscopy of Piroxicam microspunge (B 5)

The surface of the Piroxicam microspunge (B5) was studied by scanning electron microscopy; it was show in figure 17. the prepared microspunge have a spherical shape with sponge like structure, and the surface topography shows that B5 microspunge batch contained tiny pores .and studying the outer surface revealed the formation of drug crystals on the surface of microspunge particles because the optimum microspunge formulation are prepared with the higher drug/polymer ratios (1:5) the reason is more drugs will reach the surface of microspunge being dissolved in the solvent during diffusion.

Differential Scanning Calorimetry:

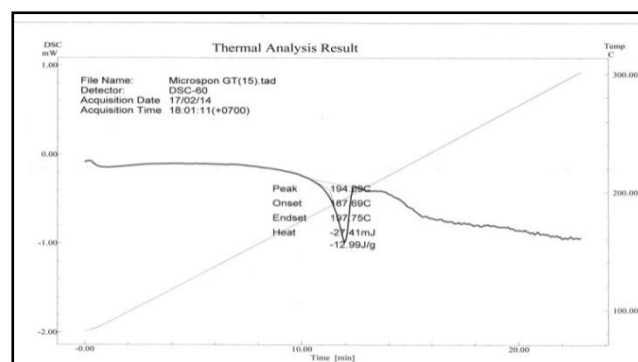


Figure 19: DSC Thermo gram of Piroxicam B5 batch

The DSC thermo gram of Piroxicam B5 optimized batch shows sharp endothermic peak at 194.09°C with lower intensity as compared to the pure PIR peak which indicating that some amount of drug is absorbed on the surface of micro sponge and some of the amount is loaded in to the micro sponge formulation, thus showing that there was no chemical interaction between drug and the polymer and other excipients used in the formulation in the solid state which shows their compatibility in formulation.

Evaluation of Piroxicam Microspunge Gel:

Visual Inspection:

All the prepared micro sponge gels are yellowish white in colour, viscous in nature with smooth texture, with good homogeneity, with no any lumps and syneresis.

PH Measurement:

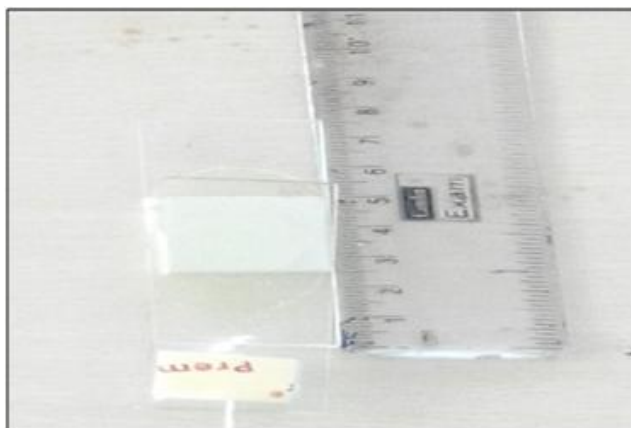
The pH values of all gel formulation were found in the range of 6 to 6.8 which are suitable to pass through the skin on application.

Table 14: PH Measurements of all Piroxicam gel batches

Sr. no.	Batch	pH
1	B1	6
2	B2	6.2
3	B3	6
4	B4	6.4
5	B5	6.5
6	B6	6.7

Spreadibility Study:

By the Spreadibility study it was depicted that formulated gel get spread easily on applying small amount of shear, spreadibility of unentrapped gel was found to be 4.5g cm/s; while that of the micro sponge gel formulations it was found from 4.5 gcm/s; to 7.5gcm/s. indicating that drug loaded micro sponge is having good spreadibility as compared to marketed gel.

**Figure 20:** Image showing Spreadibility study**Table 15:** Spreadibility Studies of all batches

Sr. no	Batch	Spreadibility (gcm/s)
1	B1	5.62 gcm/s
2	B2	7.5 gcm/s
3	B3	4.5 gcm/s
4	B4	5.62 gcm/s
5	B5	7.5 gcm/s
6	B6	4.5 gcm/s

Tube Extrudability:

The extrudability of all Piroxicam micro sponge gel was found to be from 92.02 % to 98.5% calculated by considering the extrudability of un-entrapped gel (marketed) as 100%. The prepared micro sponge exhibited better extrudability.

Table 16: Tube extrudability of all batches

Sr. no	Batch	Extrudability (%)
1	B1	92.02 %
2	B2	94.20 %
3	B3	94.92 %
4	B4	97.10 %
5	B5	98.5 %
6	B6	97.82 %

Viscosity measurement:

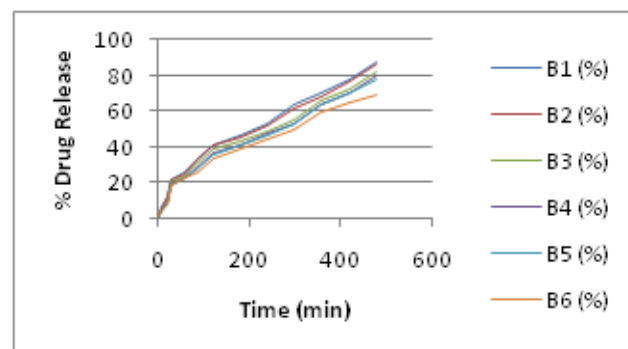
The viscosity of all micro sponge gel was found to be from 55690 to 91900 cps by using the spindle no 64 at 5 rpm at 25°C.

Table 21: Viscosity of all batches

Sr. no	Batch	Viscosity (cps)
1	B1	86661
2	B2	69760
3	B3	86900
4	B4	81650
5	B5	91900
6	B6	55960

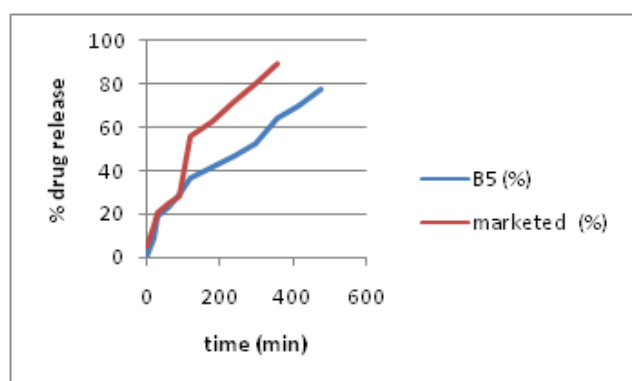
In Vitro Drug Release:**Table 22:** In Vitro Drug Release

Time (min)	B1 (%)	B2 (%)	B3 (%)	B4 (%)	B5 (%)	B6 (%)
0	0.21	0.007	0.010	0.28	0.35	0.354
10	7.014	5.248	4.49	4.37	4.53	4.53
20	12.06	11.58	9.73	9.06	8.69	8.09
30	22.14	21.65	20.58	20.15	18.37	18.08
60	25.92	24.97	23.97	22.97	22.50	22.39
90	34.03	33.53	31.24	29.23	28.55	26.21
120	41.62	41.00	38.45	36.53	35.97	33.70
180	46.35	45.79	42.89	41.46	41.18	38.58
240	53.52	52.55	48.94	47.41	46.55	44.22
300	63.58	61.79	55.45	53.05	52.44	49.69
360	70.26	68.68	65.67	64.14	63.48	59.08
420	78.45	77.38	72.04	70.29	69.41	64.67
480	87.89	86.79	82.08	79.92	77.23	68.80

**Figure 21:** In vitro drug release data of Piroxicam micro sponge gel (All batches)

In-vitro drug release of marketed formulation:**Table 23:** Drug release of marketed formulation(pirox gel)

Time (min)	Marketed Formulation (%)
0	04.50
10	9.35
20	14.70
30	20.04
60	24.36
90	28.17
120	55.61
180	62.45
240	71.22
300	80.07
360	89.23

**Figure 22:** Comparison of optimized batch B5 and marketed formulation

The drug release of all microsp sponge batches was observed to decrease within the range of 87.89 to 68.80% with respect to rise in drug polymer ratio from 1:1 to 1:6. The reason is that as the drug polymer ratio has increased; in each micro sponge, to load the drug the amount of polymer available was more, and it led to thickening of polymer matrix wall, thus extended diffusion path and ultimately lesser drug release in higher drug polymer ratio. The highest drug release 87.89 was found in B1 formulation, while the lowest drug release 68.80 was found to be in B6 formulation. Initial burst release was observed in formulation B1 and B2 can be allocated to existence of non-encapsulated drug near the surface or the exterior of micro sponges. Comparative graphical representation of all batches B1 to B6 is shown in figure 21.

The conventional marketed Pirox gel formulation shows 89.23% release in 6 hrs which is shown in figure 21. While the B5 optimized micro sponge gel formulation releases 77.23% in 8 hrs. Thus it is concluded that the micro sponge which is prepared showing sustained release as compared to marketed Pirox gel formulation.

5. Conclusion

Formulation studies like solubility, melting point, and UV analysis of piroxicam were complied with BP standards. The drug content and loading efficiency increased with drug: polymer ratio. From the result it can be inferred that there was a proper distribution of piroxicam in micro sponges. Process validation concluded that effect of internal phase

volume, concentration of PVA, stirring speed, stirring time affect much on the particle size, production yield and loading efficiency. As the drug to polymer ratio increased % production yield and % entrapment efficiency is increased. For drug release study of MS formulation batches from B1 to B6, it can be concluded that B5 and B6 formulation shows drug release in controlled manner.

The release profile of piroxicam microsp sponge gel was compared with marketed pirox gel, it can be concluded that microsp sponge gel could sustained the drug release over a period of 8 hrs.

From the study it is evident that promising microsp sponge drug delivery system of piroxicam may be developed by quasi-emulsion solvent diffusion technique by using Eudragit RS100 as a polymer and successfully incorporated in to topical gel formulation to avoid oral side effects and for better patient compliance with reduced application frequency with higher incorporation capacity.

6. Future Scope

- Future study on the same can be carried out for in vivo evaluation of the formulation using different animal model.
- Other polymers and methods can be tried for the same drug to prepare micro sponges.
- The sample can be analyzed by TEM (transmission electron microscopy) for particle size estimation.
- Photo stability study of the formulation can be done because piroxicam is more prone to photo degradation.

References

- [1] Vyas SP, Khar RK, Targeted and controlled drug delivery- Novel carrier system: New Delhi: CBS publication, 2002, pages no 453-95.
- [2] Riyaz Ali Osmani, Nagesh H. Aloorkar, Ajit S. Kulkarni, Bhargav R. Harkare, Rohit R. Bhosale, A new cornucopia in topical drug delivery: micro sponge technology, Asian journal of pharmaceutical science and technology vol 4, 2014, pg no.48-60.
- [3] TusharShetgaonkar, R. NarayanaCharyulu, Micro sponge Drug Delivery of Terbinafine Hydrochloride for Topical Application, Int. J. Pharm. Sci. Rev. Res., 33(1), July – August 2015; Article No. 11, Pages: 48-54.
- [4] M. S. Charde, P. B. Ghanawat, A. S. Welankiwar, J. Kumar and R. D. Chakole; Micro sponge a Novel New Drug Delivery System: A Review, International Journal of Advances in Pharmaceutics, 2013, vol 3, page no. 64 – 70.
- [5] Lachman L, Lieberman H.A, KanigJ.L., theory and practice of industrial pharmacy .4th Indian edition .1991, verghese publication house.pg no.534-56.
- [6] Riyaz Ali M. Osmani, Nagesh H. Aloorkar, Dipti J. Ingale, Parthasarathi K. Kulkarni, Umme Hani, Rohit R. Bhosale, DandasiJayachandraDev: Microsp sponge based novel drug delivery system for augmented arthritis therapy, Saudi pharmaceutical journal, 2015, page no. 562-572.

- [7] Nawal a. rajab¹, Mohammed s. jawad¹, formulation and in vitro evaluation of piroxicam micro sponge as a tablet, International Journal of Pharmacy and Pharmaceutical Sciences, vol 8, issue 2, 2016 page no. 104 – 114.
- [8] AshniVerma, Sukhdev Singh, RupinderKaur, Upendra K Jain; Topical Gels as Drug Delivery Systems. Int. J. Pharm. Sci. Rev. Res.23 (2), Nov; – Dec 2013, page no 60, 374-382.
- [9] NayankS.h, Nikhat P.D, and yoel P.G “the Indian pharmacist”, vol 3. no.27, sept 2004, pg no 7-14.
- [10] Vikasjain and ranjitsingh ; development and characterization of eudragits 100 loaded micro sponges and its colonic delivery using natural polysaccharides, ActaPoloniae Pharmaceutical ñ Drug Research, Vol. 67 No. 4 pp. 407ñ415, 2010.
- [11] Anilkumar J. Shinde¹, Manoj B. Paithane¹, and Sujata S. Sawant¹; Development and Evaluation of Fenoprofen Micro sponges and its Colonic Delivery using Natural Polysaccharides, American journal of pharmaceutical science and technology, 19 July 2014, vol no.1 page no, 27-48.
- [12] R. Ravi, S.K. Senthil Kumar, S. Parthian; Formulation and evaluation of the micro sponges gel for an anti acne agent for the treatment of acne, Indian Journal of Pharmaceutical Science & Research, Vol 3, Issue 1, 2013, page no.32-38.
- [13] Markand Mehta, Amish Panchal, Viral H Shah, UmeshUpadhyay; formulation and in-vitro evaluation of controlled release micro sponge gel for topical delivery of clotrimazole, international journal of advanced pharmaceuticals, vol 2, issue 2, 2012, page no .93-101.
- [14] V. V. Pande, N. A. Kadnor, Rupali N. Kadam and S. A. Upadhye; Fabrication and Characterization of Sertaconazole Nitrate Micro sponge as a Topical Drug Delivery System, 26 June 2014, Indian J Pharm Sci 2015, page no .678-680.
- [15] Hamid Hussain, ArchanaDhyani, DivyaJuyal, AbhishekBahuguna; Formulation and evaluation of gel-loaded micro sponges of diclofenac sodium for topical delivery, The Pharma Innovation Journal 2014; 3(10): page no 58-63.
- [16] Ramani Gade¹, Anitha Makineni¹, Aparna.A, Krishna, Keerthi.B, T.E.G.K.Murthy, ChanduBabuRao, SreekanthNama; design and development of hydroxyzine hydrochloride controlled release tablets based on micro sponge technology, Caribbean Journal of Science and Technology, 2013, Vol.1, page no.172-184.
- [17] ShireeshaCharagonda, RamyaDeepthiPuligilla, MadhuBabuAnanthula, VasudhaBakshi ;Formulation and evaluation of famotidine floating micro sponges, international research journal of pharmacy, 2016, page no.62-67.
- [18] Mohan kumar V, Veena NM, Manjula BP.; Formulation and Evaluation of Micro sponges For Topical Drug Delivery of Mupirocin, International Journal of PharmTech Research, July-Sept 2013, Vol.5, No.3, page no.1434-1440.
- [19] Rekha. U, b. p. Manjula et al; Formulation and evaluation of micro sponges for topical drug delivery of mometasonefuroate, International Journal of Pharmacy and Pharmaceutical Sciences, 23 July 2011, vol 3, page no. 133- 137.
- [20] RajendraJangde, Micro sponges for colon targeted drug delivery system: An overview, Asian J. Pharm. Tech. year. 2011; Vol. 1: Issue 4, Page no. 87-93.
- [21] Garish Joshi, RajandeepKaur, HarpreetKaur; Micro sponges: A Novel Drug Delivery System, International Research Journal of Pharmaceutical and Biosciences, 24 Jan 2016.
- [22] Katkade Mayur¹, Kalkotwar Ramesh², Jain Nitin ¹, Patil Prashant¹, Gadakh Rajendra², Naikwade Jeevan¹, ethyl cellulose based micro sponge delivery system for anti-fungal vaginal gels of tioconazole, international research journal of pharmacy, Oct 2011, page no.64 – 69.
- [23] YerramChandramouli, ShaikFiroz, B. RubiaYasmeen, AmaravathiVikram, B. Mahitha, U. Aruna, microsponges: a novel drug delivery system for controlled delivery of topical drugs, International Journal of Pharmaceutical Research & Analysis, Vol 2, Issue 2, 2012, page no. 79-86.
- [24] Manisha K. Tile and A.Y. Pawar, Micro sponges: A Novel Strategy for Drug Delivery, international journal of pure & applied bioscience, 2015, vol 3, page no. 224 – 234.
- [25] Neelam Jain, Pramod Kumar Sharma, ArunabhaBanik, Recent advances on micro sponge delivery system, Volume 8, Issue 2, May – June 2011; Article-003.page no. 13 – 23.
- [26] Nirav Patel et al; Formulation and evaluation of micro sponge gel for topical delivery of fluconazole for fungal therapy, Journal of Pharmaceutical Investigation, 24 January 2016, page no, 1 – 18.
- [27] Atmaram p pawar et al; Formulation and evaluation of optimized oxybenzene micro sponge gel for topical delivery, journal of drug delivery, January 2015, page no.1-9.
- [28] Pentewar RS, SumaiyaKazi, RohitBharti and GajananPulgamwar; MDS Technology: An Approach for Topical, Oral Controlled and Cosmetic Formulations, Research Journal of Pharmaceutical, Biological and Chemical Sciences, may, June 2014, page no.1170 – 1190.
- [29] Specification and test method for Eudragit; pharma polymers, Degussa.
- [30] Raymond C R Sheskey P J and Marian E Q, Editors;”handbook of pharmaceutical excipients “sixth edition 2009 pharmaceutical press and the American Pharmacist Association, page no 553, 592.
- [31] Robert A. Nash, Alfred H. Wachter, “pharmaceutical process validation” 3rd edition, 2003, vol.129, chapter 2.
- [32] Mithal B.M., and saha R.N., “A handbook of cosmetics”, 1st edition vallabhprakashan Delhi, 2003, pg no.11-17, 21-22, 37-38, 61-89, 90-93, 177, 214-215.
- [33] Gupta p., Garg S., Recent advances in semisolid dosage form for dermatological application. Pharmaceutical technology. March 2002.pg no.144-162.
- [34] Yerram Chandramouli¹, Shaik Firoz¹, R. Rajalakshmi¹, Amaravathi Vikram¹, B. Rubia Yasmeen¹, R. Naveen Chakravarthi²; preparation and evaluation of micro sponge loaded controlled release topical gel of acyclovir sodium, international journal of Biopharmaceutics, and 2012; 3(2), pg no.96-102.

- [35] Shahira F et al; "A new topical fluconazole micro sponge loaded hydro gel"; International Journal of pharmacy and pharmaceutical sciences, 2012, vol 1.
- [36] Saraf A, Dasani A, Pathan H. Micro sponge drug delivery system as an innovation in Cosmetic world A Review. Asian Journal of Pharmaceutical Education and Research, 2012;1(2) : 2278 – 7496.
- [37] Mishra MK, Shikhri M, Sharma R and Goojar MP. Optimization, formulation development and characterization of Eudragit RS 100 loaded microsponges and subsequent colonic delivery. Int J Drug Dis Herbal Res, 1(1), 2011, 8-1.
- [38] Swetha A., GopalRao M.; "formulation and in vitro evaluation of etodolac entrapped in micro sponge based drug delivery system"; international J.of pharmacy 2011, 1(2), page no.73-80.
- [39] Jain N.K., "controlled and novel drug delivery", 1st edition, CBS publishers and distributors, Delhi, 1997 pg no.100-106.
- [40] Nevine s Abdelmalak1, Shahira f el-menshaweh; a new topical fluconazole micro sponge loaded hydro gel: preparation and characterization, International Journal of Pharmacy and Pharmaceutical Sciences, 2012, vol 4, page no. 460-468.
- [41] MahajanAniruddha G, jagtapLeenaS, ChaudhariAtul L, Mali Prabha R, Formulation and evaluation of micro sponge drug delivery system using indomethacin, international research journal of pharmacy, 2(10), 2011, page no.64-69.
- [42] Karthika.R, Elango.K, Ramesh Kumar.K, Rahul.K, formulation and evaluation of lornoxicam micro sponge tablets for the treatment of arthritis, international journal of pharmaceutical innovations, Volume 3, Issue 2, March - April 2013, page no.29-40.
- [43] NamrataJadhav, Vruti Patel, SiddeshMungekar, GauravBhamare, ManishaKarpe, VilasraoKadams; Microsponge Delivery System: An updated review, current status and future prospects, Journal of Scientific and Innovative Research 2013; 2 (6), page no.1097-1110.

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