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Design Development and Evaluation of Tenoxicam Microsponge as Gel

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ABSTRACT: In the field of topical drug delivery, the microsponge system was first introduced to reduce the systemic and local side effects of the drug by providing controlled and desired release of active drugs. Microsponges are polymeric delivery systems. Which consisting of porous microspheres that can entrap wide range of active ingredients. The size of the microsponges is usually from 5 – 300 µm in diameter. The microsponge particles are too large which is absorbed into the skin and this adds a measure of safety to microsponge materials. Microsponge has stability over a pH range of 1–11. Tenoxicam, Ethyl cellulose, Xanthan gum were used to create microsponges through an emulsion technique of the W/O type created by combining an acetone/water/xanthan gum. Tenoxicam is a component of the TM8 formulation of the microsponge, which was round and smooth. The prepared tenoxicam-loaded microsponge contained particles with a size distribution of 6.64±0.11µm to 34.59±0.19µm. The percentages of drug entrapment and loading for the entire manufactured tenoxicam-containing microsponge formulation were found to be between 76.21±0.29 percent to 95.52±0.10%. It concluded that the most effective and promising dosage form was microsphere made from the drug (Tenoxicam) and Xanthan gum in the ratio of 2:8. Higuchi's model, which has a high regression coefficient of 0.9708 compared to other kinetic models, best explains the in vitro drug release of tenoxicam from microsponge containing gel formulation TM8G2. This indicates the presence of a diffusion controlled release mechanism from the porous microsponge.

KEYWORDS: Microsponge, Tenoxicam, Polymerization, Dissolved, Administration, Topical.

I. INTRODUCTION

[1] In the field of topical drug delivery, the microsponge system was first introduced to reduce the systemic and local side effects of the drug by providing controlled and desired release of active drugs. The approach is being used to enhance the protection and effectiveness of certain active ingredients that can be administered through the skin, but is not appropriate for the administration of those drugs whose main target is the skin itself. Skin is one of the most willingly accessible organs of human body for topical administration and main route of topical drug delivery system in human body. Topical preparations are applied on the skin for systemic or local effects. In few cases, the base may be used individual for its therapeutic properties such as emollient, soothing or protective action. Large number of topical preparations contains therapeutically active ingredients which is dissolved or dispersed in the base. The combination active ingredients and base are provides the occasion for a wide range of topical preparations, suitable for many types of drug delivery and therapy terms used to classify the bases of topical preparations in which therapeutically active ingredients are incorporated, possibly be based on their physical properties (suspension) or on their intended use (liniments) or on their composition (hydrophilic creams). Drugs applied topically for local action like anti-septic, anti-fungal, anti-inflammatory agents as well as skin emollients for protective effects

[2] Microsponges are patented polymeric delivery systems consisting of porous microspheres that can entrap with wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents.

[3,4] Each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface. The size of the microsponges can be varied, normally from 5 – 300 µm in diameter. Although the microsponge size may vary from 25 µm sphere can have up to 250000 pores and an internal pores structure is equivalent to 10 ft in length, providing a total pore volume of about 1ml/g. The microsponge particles themselves are too large to be absorbed into the skin and this adds a measure

International Journal of Pharmaceutical Research and Applications
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of safety to these microsponge materials. Another safety concern is the potential bacterial contamination of the materials entrapped in the microsponge. Microsponges pore diameter is smaller in size, the bacteria ranging from 0.007 to 0.2 µm cannot penetrate into the tunnel structure of the microsponges.

Advantages of the microsponge drug delivery system

- Microcapsules cannot generally control the release rate of the API. One time the wall is ruptured the API contained within the microcapsules will be released.
- Microsponge stable at a pH range of 1–11.
- Microsponge Stable up to temperature 130°C.
- Pay load is up to 50-60%.
- Free flowing and cost effective.

[5, 6] Methods of preparation of microsponges

- **Liquid–liquid suspension polymerization:** In general, Solution comprising of monomers and the active ingredients or functional, which are immiscible with water. This phase is then suspended in an aqueous phase with agitation, usually containing additives, such as surfactants and dispersants, to promote suspension. As the polymerization process continues, a spherical structure is produced containing thousands of microsponges bunched together like grapes, forming once the polymerization is complete the solid particles that result from the process are recovered from the suspension.

- **Quasi-emulsion solvent diffusion:** To prepare the inner organic phase, Eudragit RS 100 is dissolved in ethyl alcohol. Next, the drug is added to the solution and dissolved under ultra sonication at 35 ^{0}C. The inner phase is poured into the polyvinyl alcohol solution in water (outer phase). Following 60 minutes of stirring, the mixture is filtered , to separate the microsponges. The microsponges are dried in an air-heated oven at 40° C for 12 hours.

[7,8] Hypothetical mechanism of action

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles have an open structure, the active is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. Once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will start a flow of the active from the microsponge particle into the vehicle, and from it to the skin, until the vehicle is either absorbed or dried. Even after that the microsponge particles retained on the surface of the stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. This proposed mechanism of action highlights the importance of formulating vehicles for use with microsponge entrapments If the active is too soluble in the desired vehicle during compounding of the finished products, the products will not provide the desired benefits of gradual release. Instead, they will behave as if the active was added to the vehicle in a free form. Therefore, while formulating microsponge entrapments, it is important to design a vehicle that has minimal solubilizing power for the actives. This principle is contrary to the conventional formulation principles usually applied to topical products. For these conventional systems it is normally recommended to maximize the solubility of the active in the vehicle. When using microsponge entrapments, some solubility of the active in the vehicle is acceptable, because the vehicle can provide the initial loading dose of the active until release from the microsponge is activated by the shift in equilibrium from the polymer into the carrier. Another way to avoid undesirable premature leaching of the active from the microsponge polymer is to formulate the product with some free and some entrapped active, so the vehicle is pre-saturated. In this case there will not be any leaching of the active from the polymer during compounding. The rate of active release will ultimately depend not only on the partition coefficient of the active ingredient between the polymer and the vehicle (or the skin), but also on some of the parameters that characterize the beads.

[9, 10] Microsponge based delivery systems for drug triggering: Microsponges are often used for topical delivery as antacids, anti-ulcer, anti-fungal, anti-inflammatory in the therapy of actinic keratoses and may be included in a variety of products such as gel, creams and lotion. The microsponge technique is also used in the engineering of cardiac tissue as well as bone. Microsponge technique is used to minimize skin irritation, inflammation and sensitization in the sunscreen.

International Journal of Pharmaceutical Research and Applications
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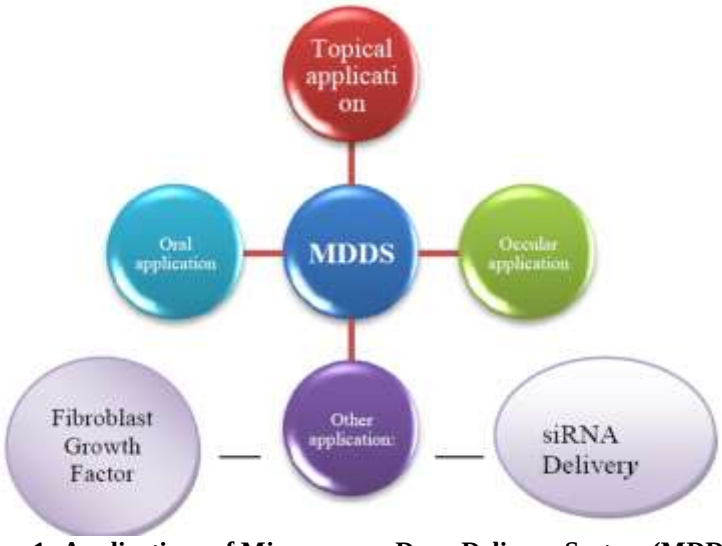

Figure 1: Applications of Microsponge Drug Delivery System (MDDS)

1. **Topical drug delivery using microsponge technology:** Microspongic delivery of Benzyl peroxide was developed using an emulsion solvent diffusion method, by adding an organic internal phase containing benzyl peroxide, dichloromethane and ethyl cellulose into a stirred aqueous phase containing polyvinyl alcohol and by suspension polymerization of styrene and divinyl benzene. The prepared microsponges were dispersed in a gel base and the microsponge gels were evaluated for anti-bacterial and skin irritancy. The entrapped system released the drug at a slower rate than the system containing free BPO. The topical delivery system with reduced irritancy was successfully developed. A new formulation of Hydroquinone (HQ) 4%, with retinol 0.15%, entrapped in microsponge reservoirs was developed to release HQ gradually, to prolong exposure to treatment and to minimize skin irritation. The safety and efficacy of this product were evaluated in 12 week, open label study. In this open-label study, HQ 4% and retinol 0.15% was safe as well as effective. The microsponge system for topical delivery of fluconazole gel was observed to have the potential to extend the release. An MDS system for retinoic acid was developed and tested for drug release and anti-acne efficacy. Statistically significant, greater reductions in inflammatory and non-inflammatory lesions were obtained with tretinoin entrapped in the microsponge. Topical analgesic, anti-inflammatory, and counter-irritant drugs in a microsponge are used for the management of the musculoskeletal system.

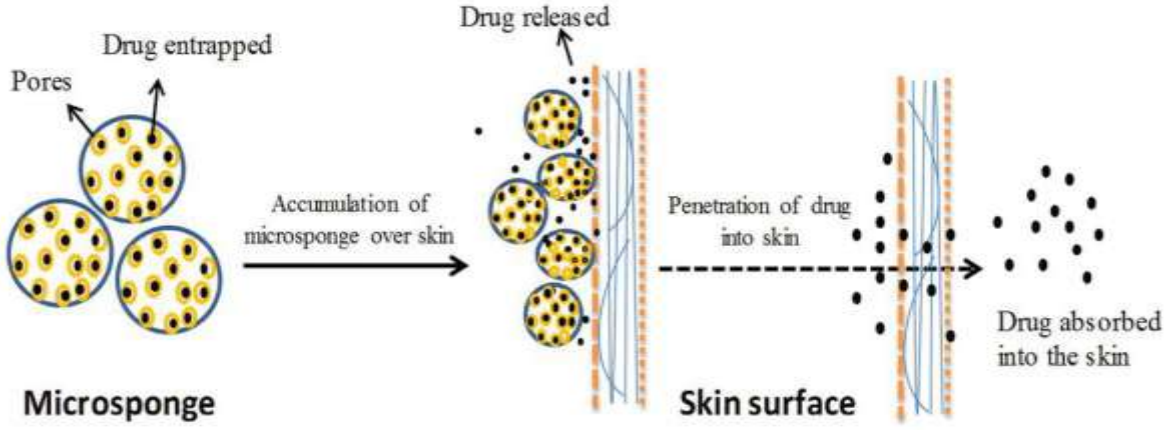

Figure 2: Drug release from topical application

International Journal of Pharmaceutical Research and Applications
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2. **Oral drug delivery using microsponge technology:** In oral applications, the microsponge system has been shown to increase the rate of solubilization of poorly water-soluble drugs by entrapping such drugs in the Microsponge system's pores. As these pores are very small, the drug is in effect reduced to microscopic particles and the significant increase in the surface area thus greatly increases the rate of solubilization. Controlled oral delivery of microsponges is achieved with an acrylic polymer, eudragit RS, by changing their intraparticle density. Sustained release formulation of chlorpheniramine male ate, using powder-coated microsponges, is prepared by the dry impact blending method for oral drug delivery. Controlled oral delivery of Ketoprofen prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 and afterwards tablets of microsponges were prepared by the direct compression method. Results indicated that compressibility was much improved in the physical mixture of the drug and polymer due to the plastic deformation of the sponge-like microsponge structure, producing mechanically strong tablets. In vitro studies exhibited that compression-coated colon-specific tablet formulations started to release the drug at the eighth hour, corresponding to the proximal colon arrival time, due to addition of the enzyme, following a modified release pattern, while the drug release from the colon-specific formulations prepared by pore plugging the microsponges showed an increase at the eighth hour, which was the point of time when the enzyme addition was made.

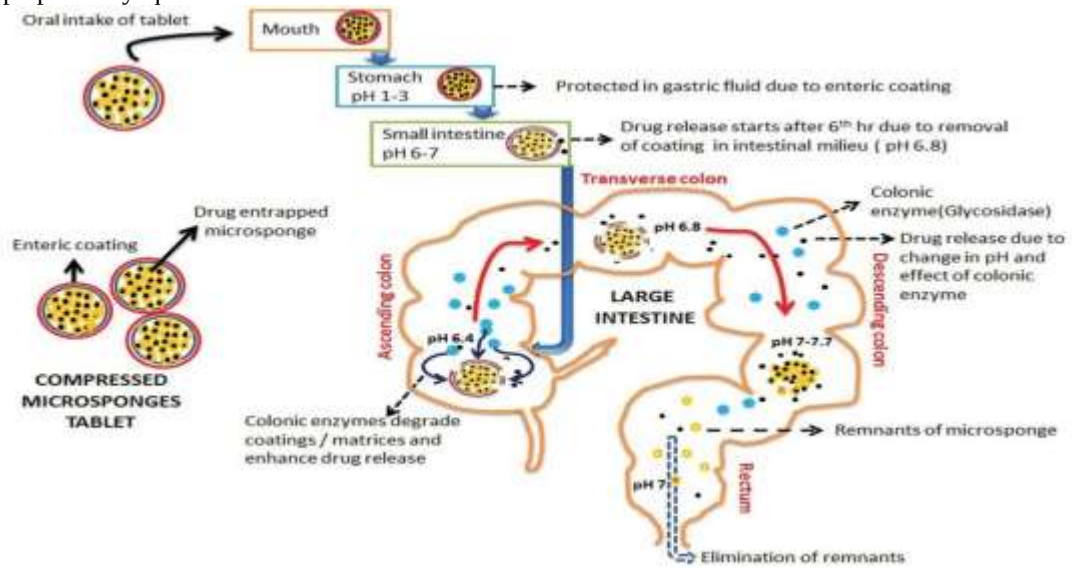

Figure 3: Drug release from oral microsponge application

3. **Microsponge based delivery systems for bone and tissue engineering:** Bone substitute compounds were obtained by mixing pre-polymerized powders of polymethyl methacrylate and liquid methyl methacrylate monomer with two aqueous dispersions of tricalcium phosphate grains and calcium efficient hydroxyapatite powders. The final composites appear to be porous and acted as microsponges. The necessary fibroblast growth factor incorporated in a collagen sponge sheet was sustained released in the mouse sub-cutis according to the biodegradation of the sponge matrix and exhibit local antigenic activity in a dose dependent manner. Intra muscular injection of collagen microsponges incorporating bFGF, induced a significant increase in the blood flow, which could never have been attained by the bolus injection of bFGF. These results recommend the significance and therapeutic utility of the type I collagen as a reservoir of bFGF. A biodegradable graft material contain the collagen microsponge was developed for cardiovascular tissue grafting, as it would permit the regeneration of the antilogous vessel tissue. A thin biodegradable hybrid mesh of synthetic poly (L-lactic-co-glycolic acid) (PLGA) and naturally derived collagen was used for a three-dimensional culture of

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human skin fibroblasts. The hybrid mesh was constructed by forming web like collagen microsponges in the openings of a PLGA-knitted mesh. A tissue-engineered patch made of our biodegradable polymer and collagen microsponge provided good in situ regeneration at both the arterial and venous wall, suggesting that this patch could be used as a novel surgical material for the repair of the cardiovascular system.

4. **Potential applications of microsponge systems:** Microsponges are used broadly to develop drug and cosmetic products for topical administration and recently for oral administration. These are designed to deliver the drug efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release.

[10] Recent advancements in microsponge drug delivery system

In Microsponge technologies, pharmaceutical companies are taking a stride forward in marketed preparations and patented technologies. Nowadays they are engaged in nanosponges, nano ferro sponges, and porous micro beads by changing the process. Such preparations are better and more durable than the microsponges.

II. MATERIALS AND METHODS:

Tenoxicam was procured from Sienna biotech, Ethyl cellulose was obtained from ASHA Cellulose (Pvt. Ltd), Xanthan gum (Swastika Gum Industries), HCl (Finar), n-octanol (Finar), Methanol (Finar), Potassium Dihydrogen orthophosphate(Thomas Baker), Disodium hydrogen orthophosphate (Thomas Baker). All the chemicals used were of fine grade.

III. PREFORMULATION STUDY:

A. **Organoleptic properties (API):** Tenoxicam was identified by examining its external characteristics which including color, odor, and appearance. In order to compare it to the previous batches while formulating, it was noted and preserved as a reference.

B. **Melting Point:** The USP method was used to find out the melting point of tenoxicam. A small amount of medication was added to a capillary tube that was sealed. The melting point device was used with the tube. The apparatus's temperature was gradually raised, and it was observed at what temperature the drug began to melt and at what temperature it finished melting..

C. **Determination of Absorption Maxima (λ_{max}) of Drug by UV- Spectrophotometer**

Scanning of absorption maxima λmax of tenoxicam: Tenoxicam solution was prepared by dissolving an accurately measured amount of 10 mg of tenoxicam in a 100 ml volumetric flask containing 50 ml of 0.1MNaoH, mixing well, and volume was made up to 100 ml with 0.1NaoH. This procedure produced a straightforward, accurate, and reproducible method for the estimation of tenoxicam. 1ml of accurately measured stock solution was placed into a 10ml volumetric flask and appropriately diluted with 0.1M NaOH. The absorption maxima (max) of this solution were identified by scanning it with a UV-visible spectrophotometer from 400 to 200 nm.

D. **Construction of calibration curve for estimation of tenoxicam:**

- **Preparation of stock solution:** A stock solution of tenoxicam was prepared by dissolving an accurately determined quantity of 10 mg of the drug in a 100 ml volumetric flask containing 50 ml of 0.1 M NaOH mixed well volume was made up to 100 ml with 0.1NNaoH to give a solution of strength 0.1 mg/ml.

- **Preparation of working samples:** Pipetting various aliquots of the stock solution at concentrations of 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, and 2.5 µg/ml and diluting it with 10ml of 0.1MNaoH in a 10ml volumetric flask resulted in a concentration range between 2.5 µg/ml and 25 µg/ml. The baseline was adjusted, and it was then scanned between 200 and 400 nm using a UV spectrophotometer. Drug absorption at various concentrations was measured, and a graph was drawn.

E. **Solubility studies:** An excessive amount of the medication was placed in test tubes that had been meticulously cleaned and contained 5.0 ml of various solvents (Distilled water, 0.1MNaoH, 0.1NHCl, methanol, acetone, dichloromethane), which were then shaken on a water bath shaker for 24 hours at room temperature. Each sample was centrifuged at 5000 rpm after 24 hours and the supernatant

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

was removed. The filtrate was then appropriately diluted and spectrophotometrically measured after the supernatant had been filtered.

F. Partition coefficient of drug: A substance is distributed into two phases when it is placed in an environment with an organic and an aqueous phase. The partition coefficient is a ratio that expresses the relative amounts that are dispersed. Tenoxicam partition coefficient was determined using the formula below:

$$\text{Partition coefficient} = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}}$$

A small variation of the "Shake Flask Method" was used to measure the partition coefficient of tenoxicam between n-octanol and water. An excess of API was added to a 10ml n-Octanol and water combination (1:1). For attaining equilibrium, the system was made in triplicate and gently shaken in the separating funnel for 24 hours. The two phases were then separated, and the partition coefficient was computed using the equation after determining the concentration of API in each phase using UV spectroscopy. Drugs classed as lipophilic have P values significantly higher than 1, whereas hydrophilic drugs have P values significantly lower than 1.

G. FT-IR Analysis: To identify that specific chemical, several substances were subjected to Fourier transform infrared spectroscopy. Using KBr pellets, FT-IR spectroscopy of the final, improved formulation of the pure medication was performed. Different peaks in the FT-IR spectrum were interpreted to identify various groups in the pure drug's structure and its ideal formulation. The investigation and forecasting of any physicochemical interactions between various components can also be done using FT-IR spectroscopy.

Preparation of microsponge

The xanthan gum-facilitated W/O/W emulsion solvent evaporation process was used to create the microsponges. To achieve a concentration of 0.2%w/v, xanthan gum was slowly dissolved in 8 ml of doubly distilled water, followed by the addition of 2 ml of acetone. Using a rotor-stator homogenizer for 5 minutes at 2000 rpm, this internal aqueous phase was emulsified into a 3 ml 1%w/v solution of ethyl cellulose in dichloromethane containing 0.5%w/v Span 80 and 1%w/v tenoxicam medication. A W/O/W type emulsion was created by transferring the created water-in-oil (W/O) emulsion into 100 ml of water that contained 0.6% m/v Tween 80 while being continuously mechanically stirred at 1300 pm. For an additional 1.5 hours, the stirring was done using a three-blade propeller to allow the organic solvent to evaporate. The resulting microsponge was filtered apart and then allowed to air dry.

Table1: Composition of different microsponge concentration

Sr.No.	Formulation code	Tenoxicam (%w/v)	Ethyl cellulose (%w/v)	Xanthan gum (%w/v)	Stirring speed (rpm)
1	TM1	1	1	0.2	1300
2	TM2	1	1.5	0.2	1300
3	TM3	1	2	0.2	1300
4	TM4	1	2.5	0.2	1300
5	TM5	1	1.5	0.1	1300
6	TM6	1	1.5	0.15	1300
7	TM7	1	1.5	0.25	1300
8	TM8	1	1.5	0.15	1500
9	TM9	1	1.5	0.15	2000

Characterization of microsponges

A. Physical appearance of the formulation: Visual observation was used to determine the physical characteristics of all created mixtures.

B. **Percentage yield:** Microsponge that had been prepared were gathered and weighed. The total weight of the drug and excipients was divided by the measured weight. The formula below was used to compute the percent yield.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

$$\text{Percentage yield} = \frac{\text{Total powder weig ht}}{\text{Total weig ht of all excipients drug}}$$

C. Particle Size: The optical microscope was used to measure the microsponges particle size. On a slide, the sample was mounted before being set down on the mechanical stage. By measuring more than 100 particles with a calibrated ocular micrometer, the mean particle size was determined.

D. Entrapment efficiency and drug loading: Weigh a microsponge that has been loaded with tenoxicam in an amount equal to 100 mg, dispersed in 10 ml of dichloromethane and 0.1 M NaOH. After the proper dilution, the sample was centrifuged at 10,000 rpm for 15 minutes, filtered, and spectrophotometrically measured at 367 nm. The ratio of the theoretical to the practical drug content was used to calculate drug entrapment. By dividing the amount of drug that was practically entrapped into the overall amount of drug, the entrapment efficiency of the microsponge was calculated.

$$\text{E ncapsulation Efficiency(EE)} = \frac{\text{Final Amount}}{\text{Initial Amount}} \times 100$$

$$\text{Percentage drug loading} = \frac{\text{Amount of the drug encapsulated}}{\text{Amount of the microsponge taken}} \times 100$$

E. Micrometric property of the tenoxicam-loaded Microsponge

- **Determination of bulk density and tapped density:** A 25 ml measuring cylinder was filled with a microsponge that was equal to 100 mg of tenoxicam (W) from each formula. After the initial volume was measured, the cylinder was allowed to drop by itself from a height of 2.5 cm to a hard surface at intervals of 2 seconds. The tapping persisted until a subsequent shift in volume was noticed. The following formulas were used to get the bulk density and the tapped density.

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}}$$

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped volume of the powder}}$$

- **Carr's index:** It aids in determining the amount of force needed to reduce friction between the hopper's particles and surface. The following equation yields it in percent form:

$$\text{Carrs index} = \frac{\text{Tapped desntiy} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

- **Hausner's ratio:** The Hausner's ratio is a fictitious measure of the ease of powder flow. The ratio of tapped density to bulk density was used to calculate Hausner's ratio. The following equation is used to calculate the Hausner's ratio's value.

$$\text{Hausners ratio} = \frac{\text{Tapped desntiy}}{\text{Bulk density}}$$

F. SEM (Scanning electron microscopy): A scanning electron microscope was used to look at the drug loaded microsponges (JEOL-JSM-6360, Japan). Uncoated sample images were captured using an SEM camera at a 20 kV acceleration voltage and a 79.99 Pa chamber pressure. On NEM TAPE adhesive paper, the dry samples were mounted before being photographed.

G. Tenoxicam loaded microsponge gel: The formulation was added after neutralizing the pH of the carpool by adjusting the concentration of carpool 980 as 1%w/w, 1.5%w/w, and 2%w/w. To prepare the gel, the necessary amount of carbopol was dipped in enough water for 24 hours. The following factors were assessed to improve the microsponge-based gel. Similarly, the control gel was prepared by mixing the amount of the tenoxicam instead of the microsponge.

Table 2: Composition of different tenoxicam loaded microsponge gel formulations

S.No.	Formulation code	Tenoxicam loaded microsponge (%w/w)	The concentration of carbopol 980 (%w/w)
1	TM8G1	Equivalent to the 1% of tenoxicam	1
2	TM8G2	Equivalent to the 1% of	1.5

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

		tenoxicam	
3	TM8G3	Equivalent to the 1% of tenoxicam	2

H. Evaluation of tenoxicam loaded microsponge gel

- **Visual appearance:** After being put in the container, all generated gels were visually inspected to determine their homogeneity. For appearance and the presence of any aggregates, they underwent testing.

- **Measurement of pH:** A digital pH meter was used to measure the pH of different formulations. After being dissolved in 100 ml of distilled water, 1 gm of gel was let to stand for two hours. Each formulation's pH was tested in triplicate, and the average values were computed. To treat skin infections, the pH of the topical gel formulation should be between 3 to 9.

- **Drug content:** Each gel formulation's weighted 2gm was added to a 250 ml volumetric flask with 20 ml of alcohol and swirled for 30 minutes. The volume was filtered and made up to 100 ml. Once more, 1 ml of the aforementioned solution was diluted to a final concentration of 10 ml with alcohol after being previously diluted to 1 ml. At 367 nm, the solution's absorbance was determined spectrophotometrically.

- **Viscosity study:** The viscosity of gel was determined using a Brookfield viscometer (S-62, model LVDV-E) at 25°C with a spindle speed of the viscometer rotated at 20 rpm, 50rpm, and 100rpm.

I. In- vitro drug release of microsponge gel: The Franz diffusion apparatus was used to gauge the release of tenoxicam from its microsponge gel and compare the result with the drug release from the control gel. Before usage, the membrane was immersed in the medium for 24 hours. It was then installed between the donor and receiver compartments of the Franz diffusion cell, where the gel was evenly disseminated over the majority of the surface. The donor chamber of the Franz diffusion apparatus received a precisely determined amount of microsponge gel 1gm equivalent to 1%w/w tenoxicam and 1gm of the control gel of the 1%w/w tenoxicam separately. The device's reception chamber houses the 30ml of phosphate buffer, pH 7.4. The experiment was run at a constant speed of 50 rpm and a temperature of 37°C. Aliquots of the solution were taken out at specified intervals, filtered using a sterile Millipore filter, and the amount of medication was measured spectrophotometrically at 367 nm. The outcomes were the averages of the three runs.

J. Drug release kinetics: When mathematical formulas are employed to express the dissolution results as a function of certain of the dosage forms features, quantitative analysis of the values obtained in the dissolution/release test is made simpler.

- **Zero-order kinetics:** Dissolution of drug from a dosage form that does not disaggregate and release the drug slowly that is where drug release rate is independent of its concentration can be represented as follows:

$$A0 - At = kt \text{---------- (I)}$$

$$1 - (At/A0) = \frac{kt}{A0}$$

$$\text{Or} \quad 1 - \frac{At}{A0} = k_0 t \text{---------- (II)}$$

The fraction of medication dissolved in time to and the zero-order release constant is represented by 1-(At /A0) and k_0, respectively, for drug dissolution from a dosage form that does not disaggregate and releases the drug slowly. A linear graph will show the percentage of medication dissolved with time.

Different types of modified release dosage forms, such as some transdermal systems, matrix tablets with low soluble drug-coated forms, and others, can all have their drug dissolving rates determined using this relationship. It is the optimal way of drug release to create a sustained pharmacological response because the dosage forms that follow this profile release the same quantity of medication per unit period.

- **First order kinetics:** Gibaldi and Feldman 1967 (Gibaldi and Feldman, 1970) and Wagner 1969 were the first to use first-order kinetics for drug dissolution experiments (Wagner, 1967). As shown by the decimal logarithm:

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

where A_t is the amount of drug released in time t, A_0 is the starting concentration of the drug in the solution, and K_1 is the first order release constant. In this situation, the drug release rate is concentration-dependent. Here, the decimal logarithm of drug release versus time will be represented graphically using a linear graph.

$$\text{Log At} = \text{LogA0} + \text{K1}\frac{t}{2.303} \text{ ---------- (III)}$$

Example: The drug is released from the dosage form in a manner that is proportionate to the amount of drug released per unit time diminish, such as those that include a water-soluble medication in a porous matrix.

- **Hixon – Crowell model:** Hixon Crowell recognized in 1931 that the particle's regular area is proportional to the cubic root of its volume, and he sought an equation with the following formula: Where A_0 is the initial amount of drug in the dosage form, At is the amount of drug left in the dosage form at a time 't', and s_{ki} is a constant incorporating the surface volume relation.

$$A_0^{1/3} - At^{1/3} = k_s t \text{ ---------- (IV)}$$

Example: Tablets that dissolve in planes parallel to the drug surface if the tablet dimensions decrease proportionately in a way that maintains the initial geometric form over time. If the equilibrium conditions are not met and the geometrical shape of the dosage form degrades proportionally with time, the cubic root of the unreleased fraction of the medication will be shown graphically here as a linear function of time. This model is applied under the presumption that drug particle dissolving rate, not diffusion, controls the release rate.

- **Higuchi model:** To explore the release of pharmaceuticals contained in semisolid and solid matrices that are water soluble and low soluble, Higuchi created models in 1961 and 1963.The relationship discovered when studying the dissolution from a planer system with a homogeneous matrix was as follows:

$$A = [D\,(2C\text{-}C_s)\,C_s\,t]^{1/2} \text{ ---------- (V)}$$

Where A is the amount of drug released in time 't' per unit area, C is the initial drug concentration, C_s is the drug solubility in the matrix media, and D is the diffusivity of drug molecules in the matrix substance. Using this relation, one may illustrate the dissolution of medicine in suspension from the bases of an ointment. The following relationship was discovered while studying the dissolution of a spherical heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release happens through holes in the matrix:

$$A = D\varepsilon/\tau\,(2C\text{-}\varepsilon C_s)\,C_s\,t \text{ ---------- (VI)}$$

Where A, D, C, C_s and t has the same meaning as in equation (V), ε is the matrix porosity, and τ is the tortuosity factor of the capillary system.
In a general way, Higuchi model can be simplified (generally known as the simplified Higuchi model) as,

$$A = K_H\,t^{1/2} \text{ ---------- (VII)}$$

Where K_H is the Higuchi dissolution constant. Higuchi describes drug release as a diffusion process based on Fick's law, square root time dependent.

- **Korsmeyer peppas model:** When diffusion is the primary drug release mechanism, Korsmeyer devised a straightforward semi-empiric model that exponentially relates drug release to time (t).

$$\frac{At}{A\infty} = at^n \text{ ---------- (VIII)}$$

Where "a," which incorporates the dosage form's structural and geometrical characteristics, "n," which indicates the drug release mechanism, and "t," whose function is A_t/A_∞ (fractional release of drug).
This n number was utilized in 1985 by Peppas (Peppas, 1985) to define various release mechanisms, leading to slab values for Fickian Diffusion of n = 0.5, between n = 0.5 and 1.0, or n = 1.0, and mass transfer based on a non-fiction model of n = 1.0. For anomalous transport, 0.5 <n <1.0.
In 1985 Peppas(Peppas, 1985) used this n value to characterize different release mechanisms concluding for values for a slab, of n = 0.5 for Fickian Diffusion, between 0.5 and 1.0 or n = 1.0, for mass transfer following a non-fiction model. 0.5 < n < 1.0, for anomalous transport. To determine the exponent 'n' the position of the release curve where $At/A\infty < 0.6$ should only be used. This model is generally used to analyze the release of polymeric dosage form, where the release mechanism is not well known or when more than one type of release phenomenon could be involved.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

IV. RESULT AND DISCUSSION

Preformulation study

A. Organoleptic properties (API): Tenoxicam is a solid, color yellow, odorless crystalline powder.

B. Melting point: Tenoxicam's melting point was dete

C. rmined to be 205±1.52°C -212.34±1.52°C, which is close to the literature-recommended range of 205°C to 213°C.

D. Determination Absorption Maxima by UV Spectroscopy

Tenoxicam solution at a certain concentration of 10µg/ml in 0.1M NaOH underwent UV scanning, and the absorption maxima were discovered to be at 367nm, which is similar to the value of 368nm reported in the literature.

E. Preparation of tenoxicam in 0.1M NaOH

Table 3: Calibration curve of tenoxicam in 0.1MNaoH at 367nm

Con. (µg/ml)	Absorbance at 367 nm
2.5	0.09±0.003
5	0.19±0.004
7.5	0.28±0.004
10	0.37±0.003
12.5	0.46±0.002
15	0.55±0.004
17.5	0.64±0.004
20	0.73±0.005
22.5	0.82±0.005
25	0.92±0.004

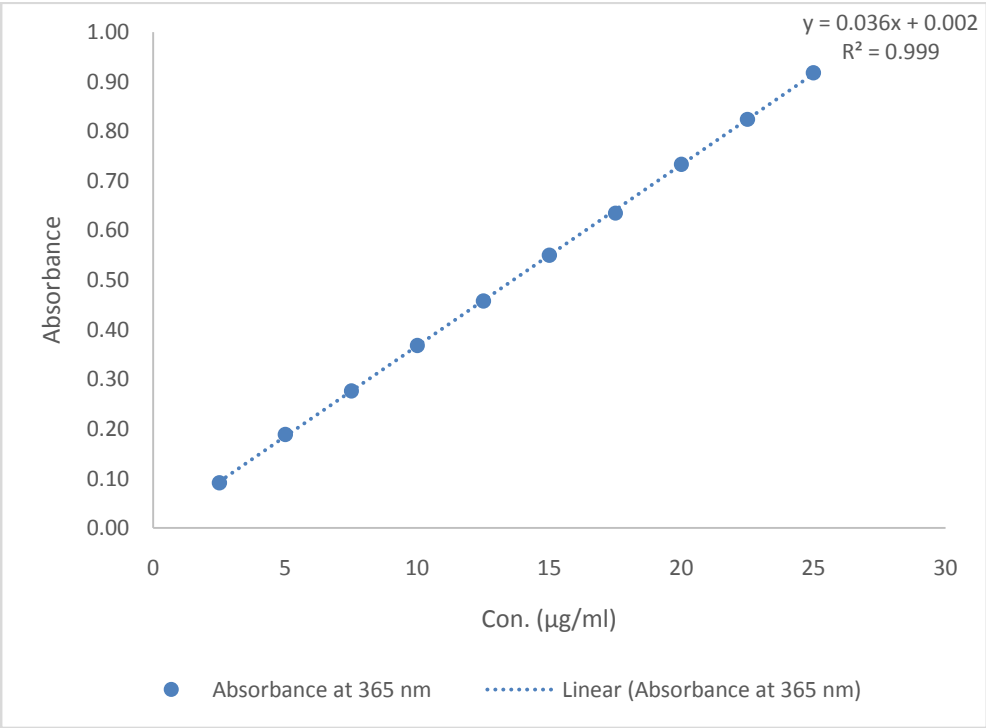


Figure 4: Calibration curve of tenoxicam in0.1NNaoH

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

The 2.5 to 5 µg/ml solution of tenoxicam in 0.1NNaoH was used to create the calibration curve for tenoxicam. At 367nm, the absorbance was measured. The regression equation Y = 0.0365x + 0.0022 and R^2 value of 0.999, which indicates high linearity, is shown by the calibration curve of tenoxicam in 0.1NNaoH as given in Table 3.

F. Solubility studies of drug: The solubility of tenoxicam in different solvents was as follows:

Table 4: Solubility studies of tenoxicam in 0.1NNaoH

Name of solvent	Solubility (mg/ml)
Water	0.66±0.02
0.1MNaoH	14.90±0.76
0.1NHcl	1.21±0.13
Methanol	3.45±0.23
Acetone	2.96±0.24
Dichloromethane	9.32±0.11

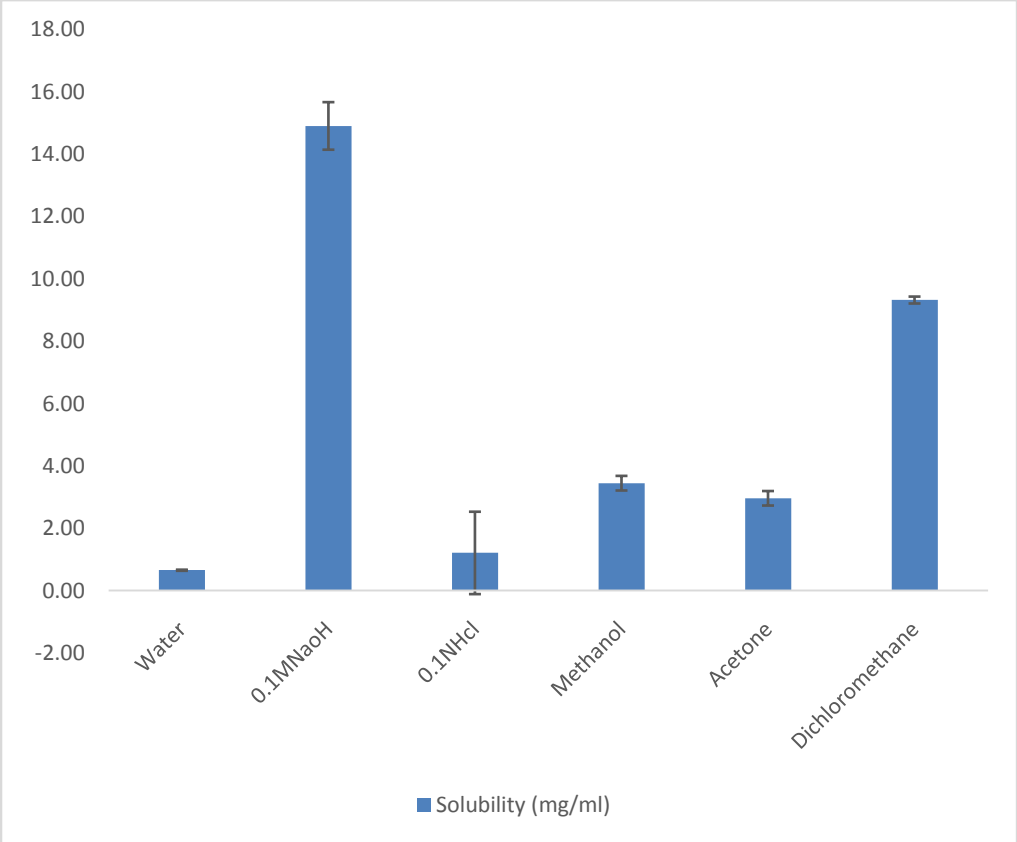


Figure 5: Solubility studies of tenoxicam in different solvents

The solubility of tenoxicam was found to be maximum for 0.1MNaoH because it is a weak acid with Pk of 5.3 and 1.1 followed by the chloroform. It was insoluble in water and less soluble in alcohols.

G. Partition coefficient of drug: Using n-octanol and water, the partition coefficient of the tenoxicam was calculated. Drugs having partition coefficients less than one are indicative of hydrophilic drugs, while those with log P greater than one are lipophilic. This demonstrated the drug's lipophilicity and purity.

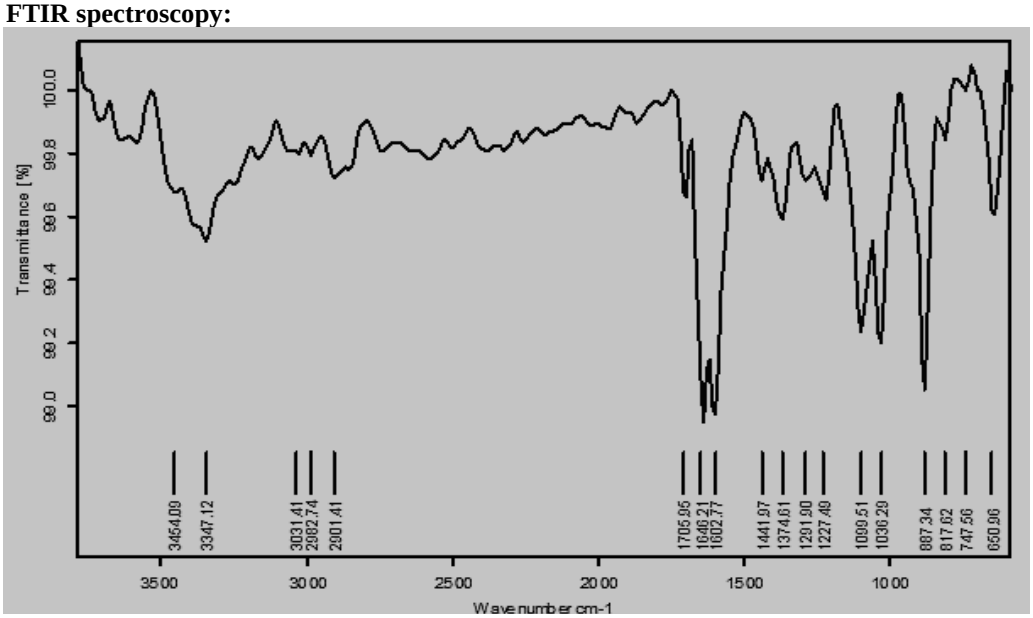
International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

Table 5: Partition coefficient determination of tenoxicam

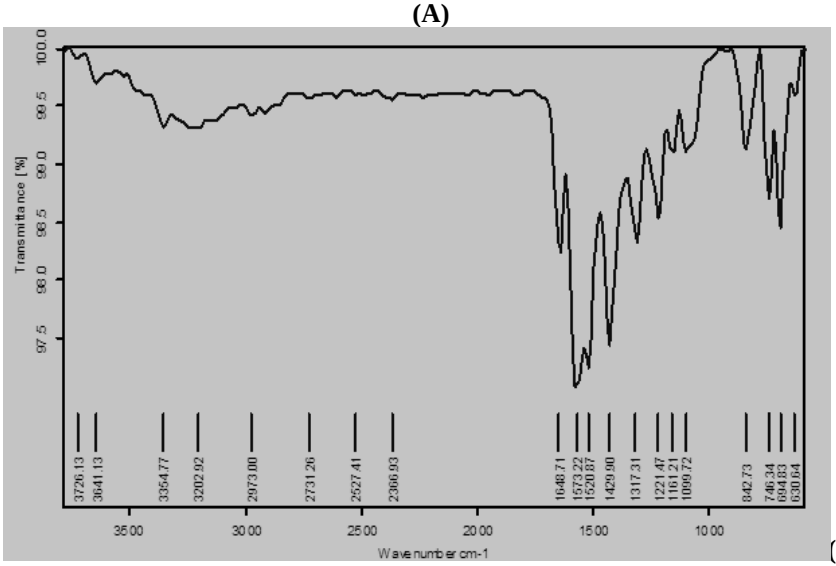
Partition coefficient of drug	Solvent system	Log p Values
Tenoxicam	n-octanol: water	2.36± 0.009

The partition coefficient of tenoxicam in n-Octanol: water was found to be 2.36± 0.009close to reference value of 2.4 this indicates that the drug is lipophilic (Table 7).

H. FTIR spectroscopy:



(A)



(B)

Figure 6: FTIR Spectrum A) Tenoxicam B) Optimized microsponge formulation

The FTIR spectrum of pure tenoxicam figure 13 showed the characteristic peak of the drug at 3454.09 cm^{-1} of O-H stretching vibration and other peaks at 1646.21 cm^{-1} due to amide carbonyl stretching, 1374.671 cm^{-1} due to CH_3 deformation, C=C stretching of the aromatic group at 1602.77 cm^{-1} and 1471.10cm^{-1} due to C-H deformation. Some major peaks of tenoxicam were found in the final formulation with a reduced intensity which indicates that and the drug was incorporated into

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

the polymer matrix, there was no interaction between drug and excipients and the formulation remains stable through its expiry period.

Preparation of microsponge: To create microsponges, an emulsion of the W/O type was created by combining an acetone/water/xanthan gum (2:8) dispersion with an ethyl cellulose solution in dichloromethane. Acetone and dichloromethane rapidly combined at the droplet interface during initial emulsification. When this emulsion was transferred into an external aqueous phase, a W/O/W emulsion was created, and the organic solvents slowly diffused from the droplet surface. Diffusion allows the organic solvents to be completely removed from the finely distributed polymer droplets.

In vitro-characterization of microsponges

A. Surface appearance of microsponge

Table 6: Visual appearance of different formulation

Sr.No.	Formulation Code	Visual appearance
1	TM1	Irregular shape particles were formed
2	TM2	Spherical particle formed
3	TM3	Spherical particle formed
4	TM4	Spherical particle formed
5	TM5	An irregular shape particle was formed
6	TM6	Spherical particle formed
7	TM7	An irregular shape particle was formed
8	TM8	Spherical particle formed
9	TM9	Spherical particle formed

Table 6 demonstrated that every generated formulation was spherical, except formulations TM1 and TM7. Low concentrations of the matrix-forming polymer were not sufficient to produce spherical particles; however, higher concentrations resulted in the production of spherical particles. As a result, TM1 and TM7 were not selected for additional evaluation.

B. Percentage yield

Table 7: Percentage yield of the drug-loaded microsponges

Sr.No.	Formulation Code	Percentage yield
1	TM2	90.94±0.44
2	TM3	95.83±0.51
3	TM4	96.06±0.41
4	TM5	95.83±0.55
5	TM6	97.79±0.16
6	TM8	98.72±0.17
7	TM9	98.84±0.66

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

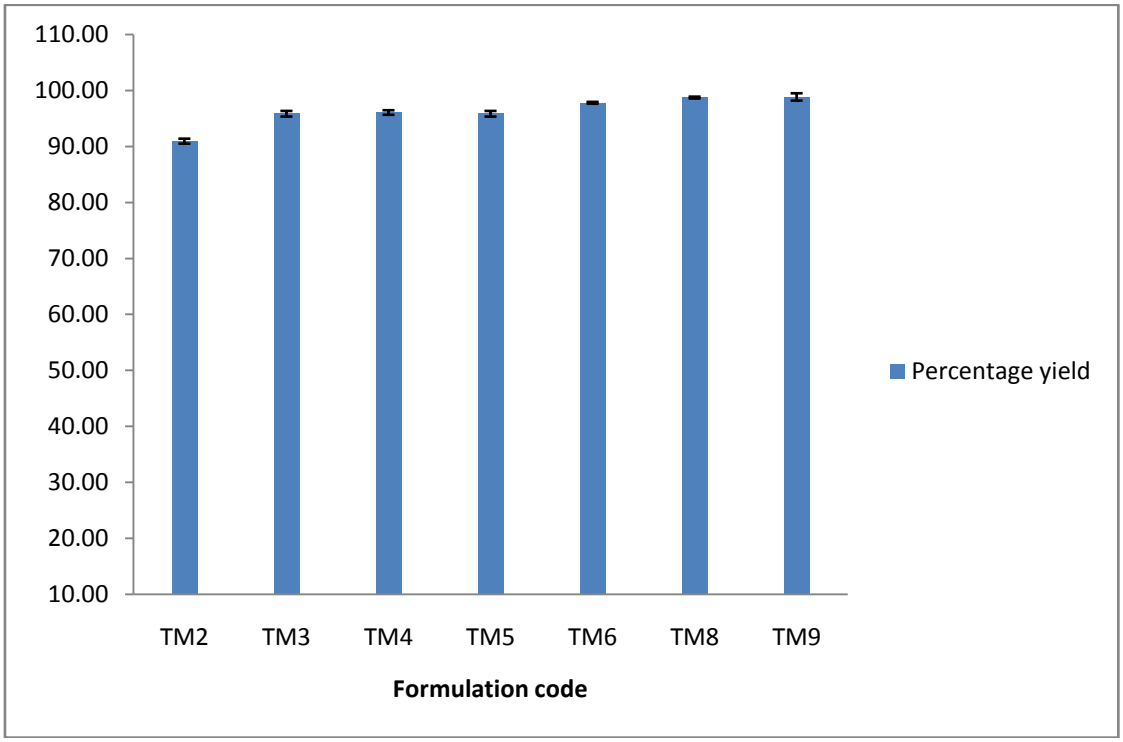


Figure 7: Percentage yield of the drug-loaded microsponges

The yield of the formulation of all-prepared microsponges was 90.94±0.44 to 98.84±0.66%. With an increase in ethyl cellulose and xanthan gum concentration, the yield percentage also rises. A high concentration of ethyl cellulose slows the diffusion of the organic phase into the aqueous phase, delaying the precipitation of the polymer and giving more time for the production of droplets, boosting yields. On the other hand, a less viscous organic phase (low ethyl cellulose content) results in quick mixing and quicker solvent removal, which shortens the time needed for drug and polymer solidification before droplet formation and lowers yield. Changes in starring have no impact on the microsponges % yield.

C. Percentage entrapment efficiency

Table 8:Percentage of drug entrapment of different microsponge formulations

Sr.No.	Formulation Code	Percentage drug entrapment
1	TM2	62.71±0.29
2	TM3	88.81±0.10
3	TM4	82.44.±0.77
4	TM5	68.47±0.39
5	TM6	93.88±0.29
6	TM8	95.52±0.10
7	TM9	93.88±1.45

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

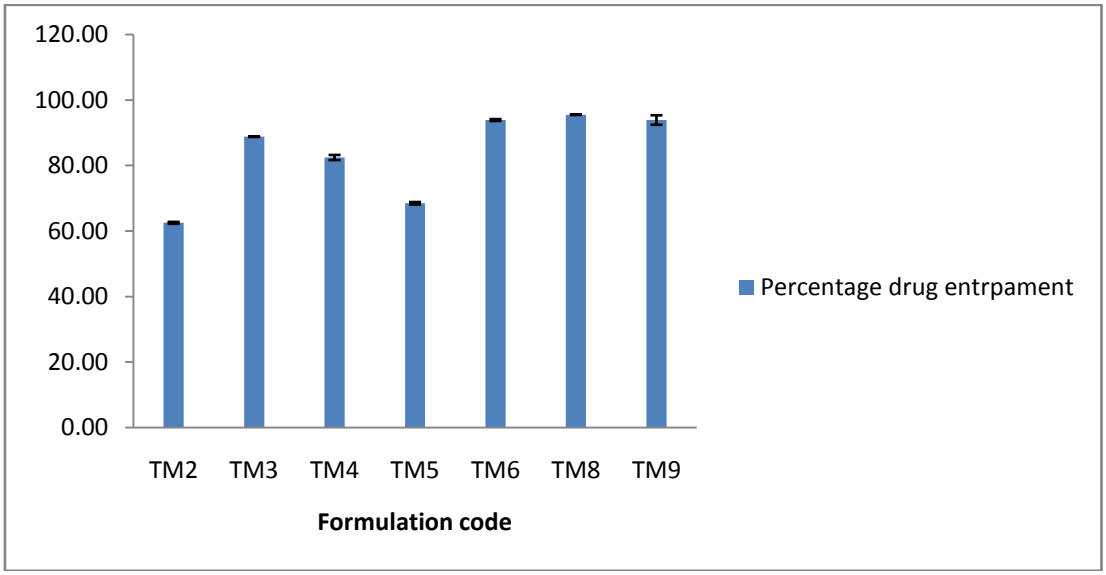


Figure 8:Percentage of drug entrapment of different microsponge formulations

Table 9:Percentage of drug loading of different microsponge formulations

Reno.	Formulation Code	Percentage drug loading
1	TM2	19.53±0.09
2	TM3	21.14±0.02
3	TM4	15.85.±0.15
4	TM5	16.70±0.09
5	TM6	21.83±0.07
6	TM8	22.21±0.02
7	TM9	21.83±0.34

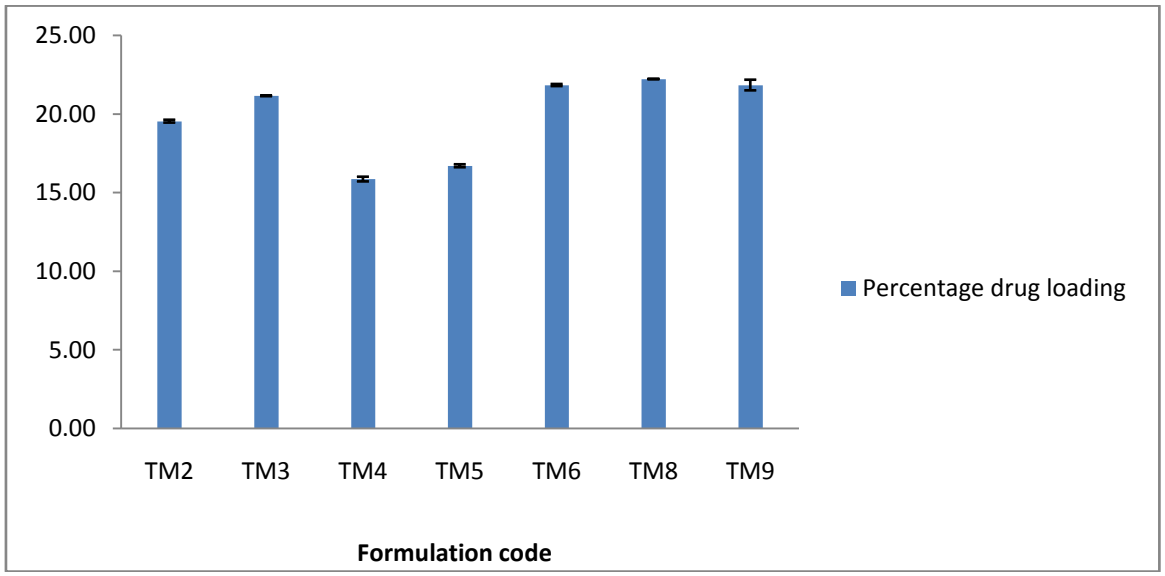


Figure 9: Percentage of drug loading of different microsponge formulations

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

The percentages of drug entrapment and loading for the entire manufactured tenoxicam-containing microsponges formulation were found to be, respectively, between 76.21±0.29% to 95.52±0.10%, and 15.85±0.15 to 22.21±0.02% respectively. Tenoxicam encapsulation was found to increase in microsponge with higher ethyl cellulose and xanthan gum concentrations. Tenoxicam percentage drug loading in microsponges is depicted in Figure 16. In addition to being adsorbed on polymer surfaces, drugs are also expected to enter the matrix of microsponges. The maximal drug loading and entrapment values of tenoxicam for formulation code TM8 were determined to be 95.52±0.10% and 22.21±0.02%, respectively. The porosity of microsponges can be associated with high values of entrapment efficiency. According to studies in the literature, the pores in microsponges are uniformly dispersed over the entire sphere and are related to one another. This network of closely spaced pores encourages medication loading.

D. Particle size: The sizes of several tenoxicam-containing microsponge formulations.

Table 10: Size of different microsponge formulations

Sr.No.	Formulation Code	Particle size(µm)
1	TM2	21.11±0.09
2	TM3	26.98±0.602
3	TM4	31.14±0.05
4	TM5	28.86±0.16
5	TM6	34.59±0.19
6	TM8	16.64±0.11
7	TM9	15.83±0.10

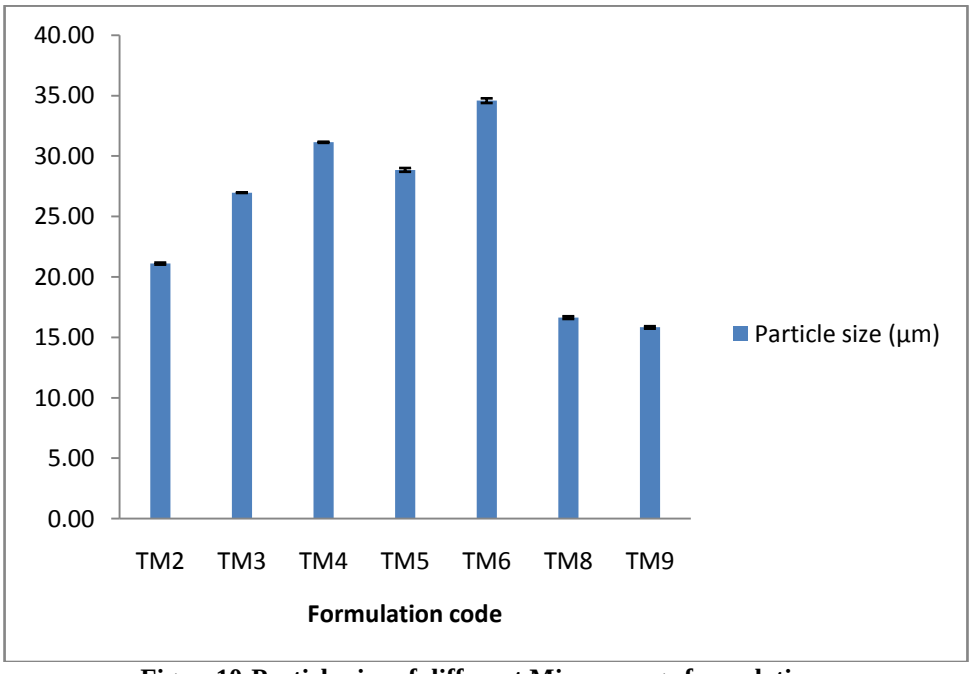


Figure10:Particle size of different Microsponge formulations

The prepared tenoxicam-loaded microsponge contained particles with a size distribution of 6.64±0.11µm to 34.59±0.19µm. The average particle size of the TM8 formulation is lower (16.64±0.11µm) than that of other formulations. The rise in particle size is due to a viscous organic phase produced by ethyl cellulose at greater concentrations, which led to larger emulsion droplets and, in turn, larger microsponges. The particle size of the microsponge also depends on the mixing speed, although only to a certain extent. A decrease in mean particle size

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

was seen as the stirring rate was increased. Any rise in mean particle size at slower stirring rates can be attributed to globules' increased propensity to clump and consolidate.

Higher stirring rates, on the other hand, impose a vigorous, uniform, enhanced mechanical shear, which causes a quick dispersion of the produced droplets and may reduce their likelihood of consolidating into larger droplets. This implies that the size of the droplets generated during the encapsulation procedure may thus be directly related to the size of the resulting microsponges.

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E. Bulk density, tapped density, Cars index, and Hausner ratio of microsponge: The bulk density, tapped density, Cars index, and Hausner ratio for every microsponge formulation that was created

Table 11: Bulk density, tapped density, Cars index, and Hausner ratio of microsponge

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Cars index	Hausner ration
TM2	0.28±0.02	0.31±0.07	5.48±4.09	1.13±0.11
TM3	0.25±0.08	0.28±0.03	12.82±1.63	1.15±0.02
TM4	0.27±0.01	0.32±0.02	13.16±4.60	1.16±0.06
TM5	0.40±0.03	0.54±0.01	25.52±8.04	1.35±0.14
TM6	0.39±0.04	0.43±0.05	6.25±5.33	1.09±0.15
TM8	0.31±0.03	0.33±0.02	2.73±1.30	1.07±0.04
TM9	0.36±0.01	0.38±0.01	3.24±0.47	1.03±0.03

For every formulation, precompression investigations were conducted. Powder qualities including bulk density, tapped density, Hausner's ratio, and carr's index were determined and are displayed in table 13. Bulk density for the formulations was shown in pre-formulation studies to range between 0.27 and 0.4 g/cm^3, indicating packing characteristics in dies. It was discovered that the microsponges compressibility index could reach up to 25%, which indicated good compressibility. While the Hausner ratio and angle of repose values ranged from 1.03 to 1.16, indicating good flow characteristics, formulation code TM5 revealed a value of 1.35, indicating poor flow.

Based on the above evaluation parameter, the TM8 formulation was selected for further evaluation.

F. Scanning electron Microscopic examination: The shape of the formulation TM8 particle.

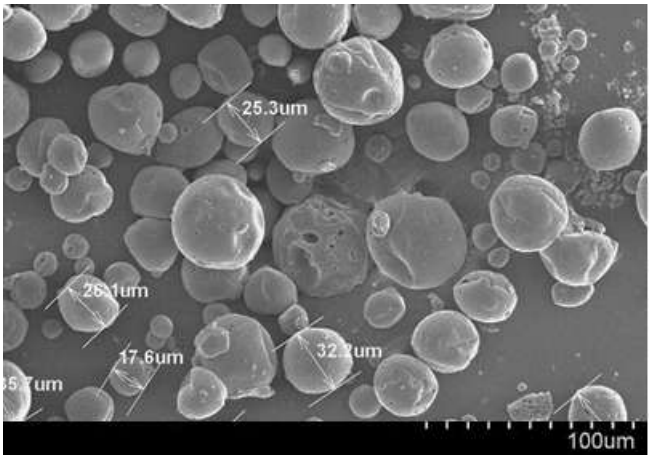

Figure 11: Microscopic images of optimized TM8formulation

Tenoxicam is a component of the TM8 formulation of the microsponge, which was round and smooth. The absence of drug crystals on the surface suggests that the drug molecules are

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

dispersed throughout the polymeric matrix. Visually, the integrity of the microsponges was preserved; nevertheless, the pores were more noticeable in terms of size and number, which may be related to drug molecules detaching from the surface of the microsponges together with slight surface erosion.

Evaluation of Microsponge-loaded gel

A. Visual appearance

The following describes the physical appearance of each prepared formulation:

Table 12: Physical appearance of all prepared formulation

S. No.	Formulation Code	Physical appearance
1	TM8G1	Homogenous, Uniform gel
2	TM8G2	Homogenous, Uniform gel
3	TM8G3	Homogenous, Uniform gel

All of the prepared gel had a homogenous, uniform look, and no clumps or aggregation was observed.

B. pH Estimation: pH of all formulations is as follows:

Table 13: pH of formulations

S. No.	Formulation Code	pH
1	TM8G1	6.41±0.46
2	TM8G2	6.55±0.36
3	TM8G3	6.53±0.35

The pH of all formulations was discovered to be between 6.41 and 6.55, which is close to the pH of the skin.

C. Percentage drug content of the gel: The percentage drug content of all formulations as follows:

Table 14:Percentage of drug content of different Microsponge-loaded gel

Sr. no	Formulation code	Percentage drug content
1	TM8G1	95.45±0.13
2	TM8G2	99.15±0.72
3	TM8G3	94.26±0.48

It was discovered that both formulations had drug content that ranged from 94.260.48 to 99.150.72.

D. Viscosity: Viscosity of the developed gel composition.

Table 15: Viscosity of the microsponge gel at different rpm

Formulation Code	Viscosity at rpm (cp)		
	20	50	100
TM8G1	899	2264	2964
TM8G2	1298	3257	3987
TM8G3	2599	4857	5104

The prepared three formulations' viscosities were found to range from 899 to 5104 cp at various rpm, as shown in table 17. The viscosity rises proportionately with the concentration of the gelling ingredient. At various shear speeds, the gel's viscosity was measured. It was found that viscosity reduced as the shear rate increased. As the shear rate rises, the internal gel microstructure degrades, reducing the apparent viscosity (the gel "shear-thins").

The evaluation of TM8PG2 was selected based on the evaluation parameters mentioned above.

E. In-vitro Drug release study: In vitro drug release of formulation TM8G2 and a 1%w/v tenoxicam control gel was published.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

Table 16: Percentage of drug release of Formulation TM8G2and control gel

Time (hr)	% Drug release formulation TM8G2	% Drug release of 1%w/v Control gel
0	0±0	0±0
0.5	16.50±0.73	8.33±0.00
1	21.90±0.26	12.31±0.17
2	54.18±0.34	20.82±0.23
4	64.61±0.33	28.38±0.06
6	78.47±1.26	34.38±0.17
8	89.97±2.64	41.53±0.07
10	97.10±0.47	48.85±0.29
12	97.92±1.71	49.38±0.23

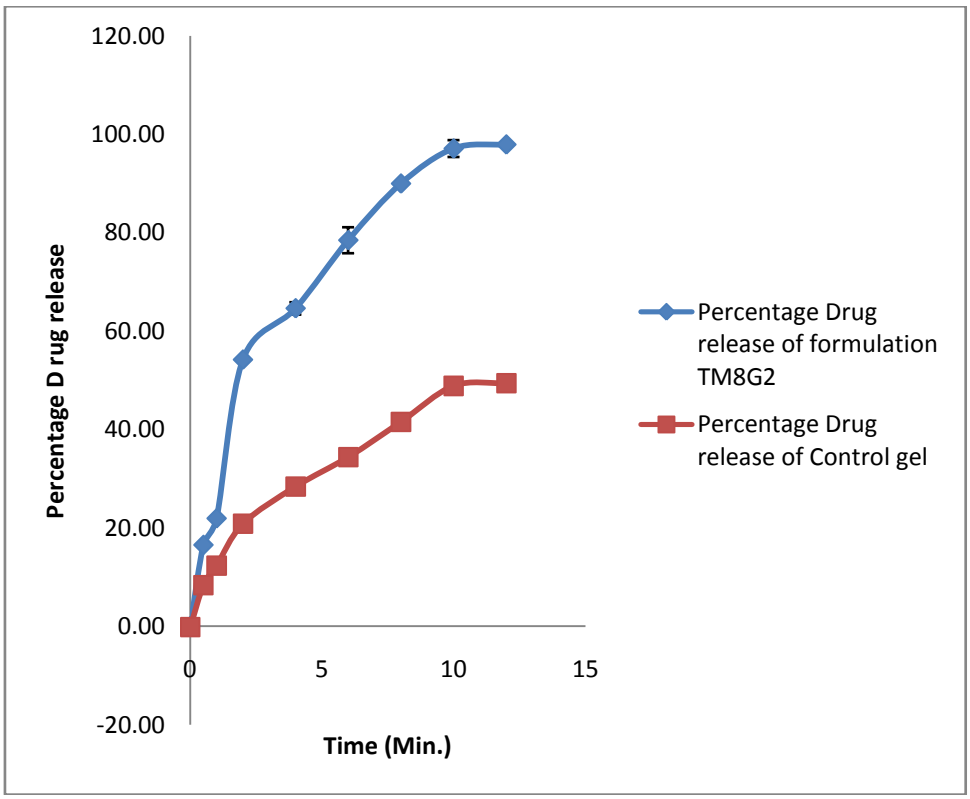

Figure 12:Comparison of in-vitro % drug release of control gel and % drug release ofTM8G2 formulation.

An artificial cellophane membrane with phosphate buffer was used to examine the effects of composition and vehicle on the release patterns of the various formulations (pH 7.4). Because it was a topical formulation, the release medium's pH was changed to match the skin's (i.e., pH 7.4).

Tenoxicam was released from the in-vitro drug formulation in a regulated and prolonged manner as opposed to an immediate release of the pure medication in an aqueous solution. Compared to the rate of drug release over the second hour, the rate of drug release during the first hour was higher (Figure 19). This might be because the formulations contain non-encapsulated tenoxicam. The release of free tenoxicam was continuous for up to 12 hours, and this slower is probably related to the release of the entrapped drug from the microsponge for a longer duration.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

In-vitro drug release kinetic

The data from the formulation TM8G2 in-vitro drug release kinetic research are shown below.

- **Zero order**

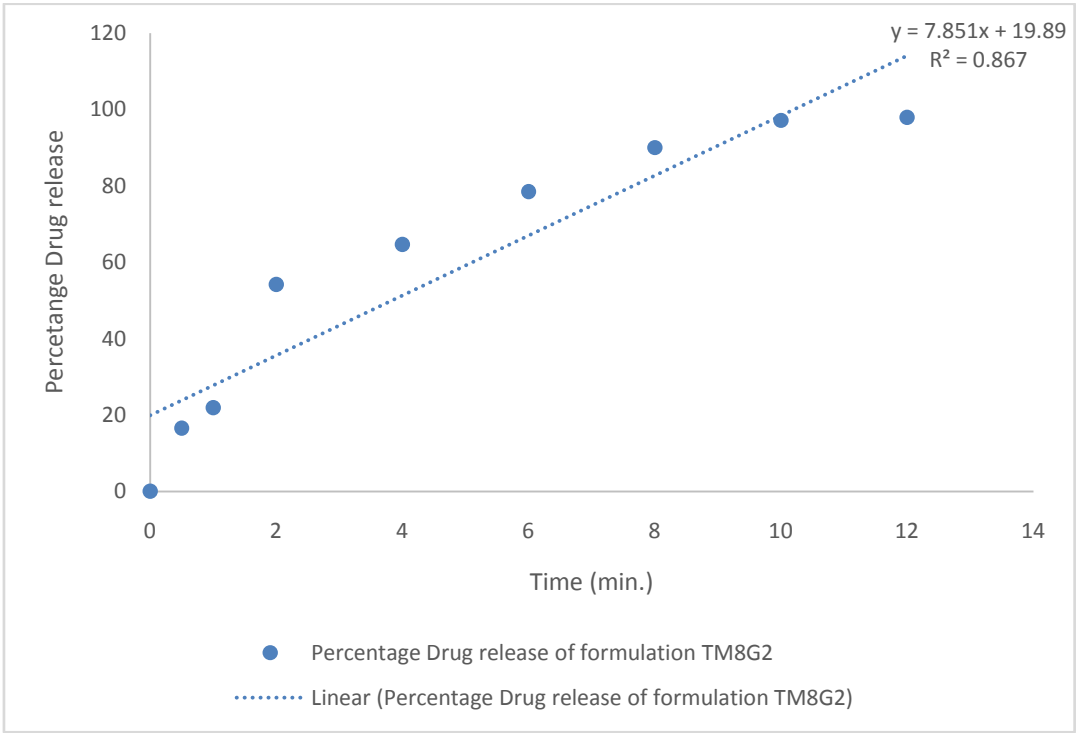

Figure 13: Zero order graph of formulation TM8G2

- **First Order**

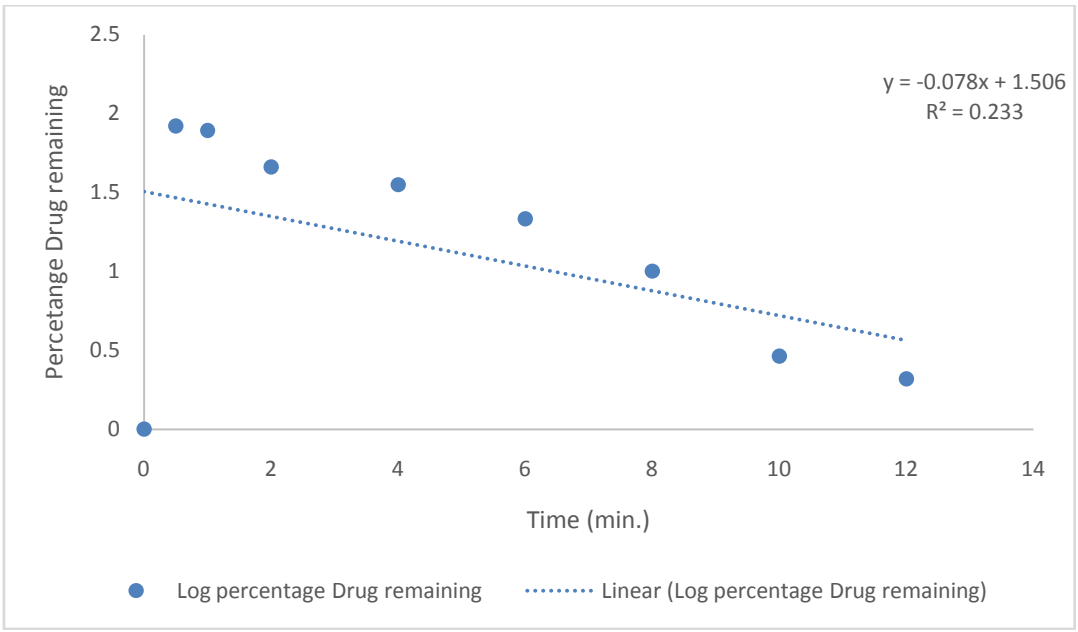

Figure 14: First order graph of formulation TM8G2

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

- **Higuchi Order**

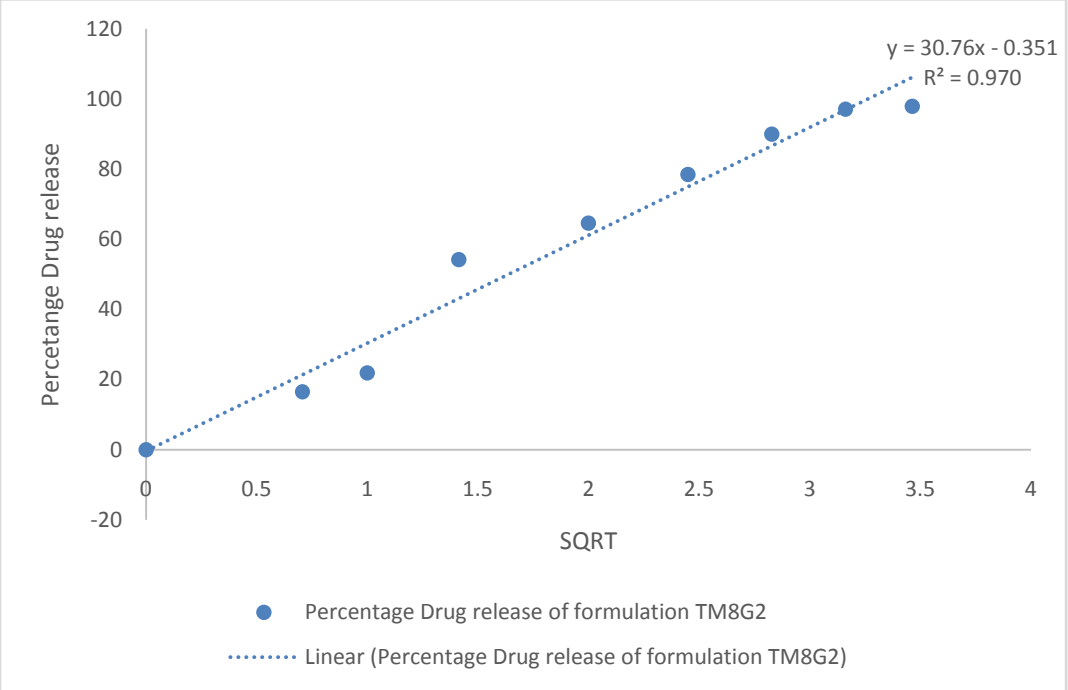

Figure 15:Higuchi order graph of formulation TM8G2

- **Korsmeyer Peppas**

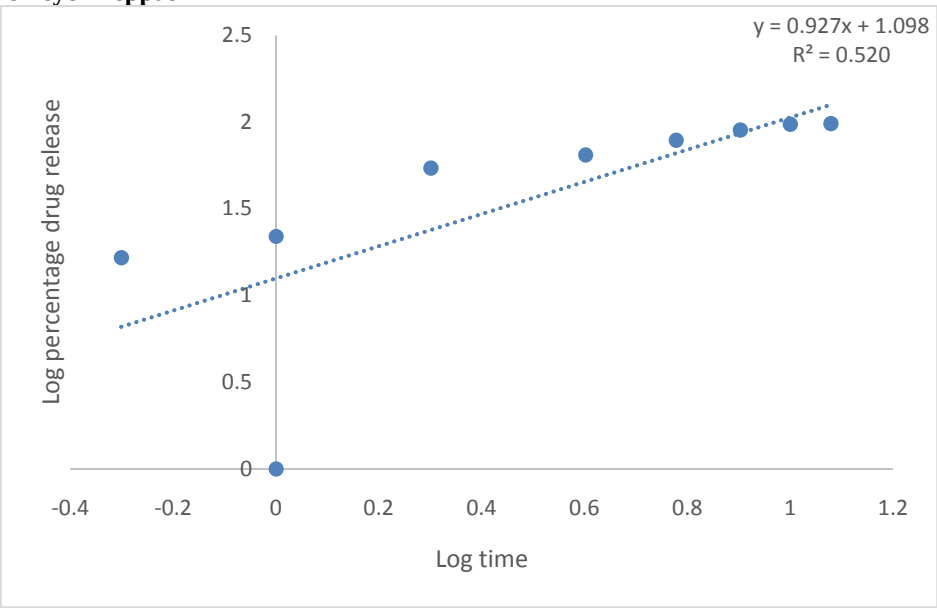

Figure 16:Korsmeyer Peppas model graph of formulation TM8G2

The in vitro drug release profile of formulation TM8G2's estimated regression coefficients for zero order, first order, and Higuchi were established. Higuchi's model, which has a high regression coefficient of 0.9708 compared to other kinetic models, best explains the in-vitro drug release of tenoxicam from Microsponge-containing gel formulation. This indicates the presence of a diffusion-controlled release mechanism from the porous microsponge.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1988-2011 www.ijprajournal.com ISSN: 2249-7781

V. CONCLUSION

In this study, an effort was made to create Tenoxicam microsphere gel with goal of treating control release of drug. Tenoxicam, Ethyl cellulose, Xanthan gum were used to create microsponges through an emulsion technique of the W/O type created by combining an acetone/water/xanthan gum. Tenoxicam is a component of the TM8 formulation of the microsponge, which was round and smooth. The prepared tenoxicam-loaded microsponge contained particles with a size distribution of 6.64±0.11µm to 34.59±0.19µm. The percentages of drug entrapment and loading for the entire manufactured tenoxicam-containing microsponges formulation were found to be between 76.21±0.29% to 95.52±0.10%.It concluded that the most effective d osage form was microsphere
made from the drug (Tenoxicam) and Xanthan gum in the ratio of 2:8. Higuchi's model, which has a high regression coefficient of 0.9708 compared to other kinetic models, best explains the in vitro drug release of tenoxicam from microsponge containing gel formulation TM8G2. This indicates the presence of a diffusion controlled release mechanism from the porous microsponge.

AUTHOR'S CONTRIBUTIONS: All the authors have contributed equally.

CONFLICTS OF INTEREST: The authors declare that they have no conflicts of interest.

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