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Development and Evaluation of Naproxen Sodium loaded Eudragit L-100 Nanocarrier by Emulsification Diffusion Method

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

The purpose of this work is to use the practical Emulsification Diffusion Method (EDM) to reduce the particle size to the nanometer range. The application of carefully engineered materials at this length scale to create new therapeutic and diagnostic modalities is the field of nanomedicine, which unites nanotechnology and medicine. Eudragit L 100, a polymeric carrier that is frequently used, was prepared into nanometer-sized particles using the emulsification–diffusion method (EDM). It is necessary to choose the right drug or API (Active Pharmaceutical Ingredient). So, naproxen Sodium was chosen as a model drug. The procedure involves adding too much water after emulsifying a drug and polymer solution in an aqueous phase that has been saturated with stabilizer. Investigations into how process variables affect the average size of nanoparticles have

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been carried out. It was made obvious that the kind and concentrations of stabilizer, the speed at which the magnetic stirrer homogenizes, and the polymer concentration all affected the size of the nanoparticles. Using sodium dodecyl sulfate (SDS) as a surfactant, Naproxen Sodium with Eudragit L 100 nanoparticles smaller than 100 nm was obtained using a Scanning Electron Microscopic (SEM) test. It was discovered that the addition of medications and luminosity did not significantly alter the nanocarrier's morphology. Because of their large surface area and integration of medication, nanocarriers are more effective. The effectiveness of the Emulsification Diffusion Method for enhancing nanoscale particle size reduction is investigated in the study that is being presented. The Eudragit L 100 nanoparticles were found to vary in size from 1 to 100 nm, confirming the particle size data and demonstrating that the Emulsification Diffusion Method (EDM) is an appropriate technique for the development of the nanocarrier.

Keywords: Nanocarrier; diffusion; emulsifying; nanometer; surface area.

1. INTRODUCTION

The science of the very tiny is known as nanotechnology. It offers chances for materials development, including medical applications, where traditional methods might run out of steam. Pharmaceutical nanoparticles are defined as solid, potentially biodegradable drug carriers that are submicron-sized (less than 100 nm in diameter. Nanoparticles are one of the main instruments in nanomedicine and offer enormous benefits in terms of drug delivery and targeting [1]. Particles derived from natural, semi-synthetic, or synthetic polymers are known as polymeric Nanocarriers. Many monomer units polymerize to form polymeric nano systems, which can self-assemble and organise into ananometric (10–100 nm) sizes under specific circumstances [2,3]. Drugs can be bound, entrapped, or encapsulated in polymeric nanocarrier as a drug conjugate, nanosphere, or nanocapsule, depending on the manufacturing technique [4]. The nanostructured carriers need to be made in such a way as to achieve maximum efficacy at the target sites with a precise, suitable dose and dosage form [5]. The dimensions of a nanocarrier can be defined as follows: i) total physical dimension(s) determined by atomic structure; (ii) effective size of the particle in a given matrix based on its diffusion/sedimentation behavior (iii) an effective size of the nanoparticle, determined by its mass/electron distribution [6]. Nanospheres are colloidal particles that trap drugs within their matrix through physical dispersion or adsorption on the particle surface. On the other hand, nanocapsules are systems made up of a polymeric shell enclosing a core cavity that contains an encapsulated drug [7,8]. The ligands allow for cellular selectivity and intracellular delivery of polymeric micelles [9]. The density and binding abilities of targeting ligands, which can improve receptor internalisation and drug biodistribution, determine how effective polymeric carriers modified with these ligands are [10]. Furthermore, a significant influence on the catalytic performance can be exerted by the high surface energy and high number of atoms of nanoparticles [11]. Particularly, they can be tailored for targeted drug delivery, enhance bioavailability, and offer a controlled release of medication from a single adaptation—through system adaptation, the drug can be prevented from being degraded by endogenous enzymes—nanoparticles made of natural and synthetic polymers, both biodegradable and non-biodegradable, have drawn increased attention [12]. The use of nanoparticles in drug delivery has many established benefits. It makes poorly water-soluble drugs more soluble, reduces immunogenicity to prolong the half-life of drug systemic circulation, releases drugs steadily or in a manner that adjusts to the surroundings to reduce the frequency of administration, delivers drugs in a targeted way to reduce systemic side effects, and delivers two or more drugs at once for combination therapy to produce a synergistic effect and suppress drug resistance [13,14]. In recent times, biodegradable polymeric micelles have garnered significant interest as nanocarriers for drug delivery, demonstrating exceptional therapeutic potential. The encapsulated drugs may be released in a few different ways, such as drug diffusion through the polymer matrix, polymer swelling followed by drug diffusion [15]. Polymer-based nanoparticles were successfully synthesized by using the Emulsification Diffusion technique. The objective of the work presented here was to determine the optimal formulation parameters for the synthesis of drug-loaded nanoparticles with a size that might be suitable *In vivo* [16]. The process of preparing biodegradable nanoparticles by dissolving a polymer in a mixture of solvents—

one of which is water immiscible and the other of which is miscible—is known as spontaneous emulsion diffusion. A comparable emulsification-diffusion method for creating nanoparticles has been patented by polymers. Because the continuous aqueous phase is rich in solvent due to saturation, its rapid displacement will prompt a free flux of solvent globules to the continuous phase, the material will aggregate in the form of nanoparticles. The emulsion is diluted by adding excess water. Through interfacial phase changes of the polymer during diffusion, nanoparticles will be produced. Overall, this mechanism provides a satisfactory explanation for the type of particles obtained by the emulsification-diffusion method. The concentration and type of stabilizer, drug, and biodegradable polymer, the amount and kind of diffusion medium, the stirring rate, the ratio of oily to aqueous phases, the viscosity of the external phase, and other factors are the critical variables that impact the method and, in turn, the particle size [17]. Silica is added to pharmaceutical formulations to improve their flowability when taken orally. Solid dispersions become more wettable, which accelerates the rate of dissolution. Naproxen ($C_{14}H_{14}O_3$) is a non-steroidal anti-inflammatory medication belonging to the Class II family [18]. Naproxen demonstrates antipyretic, analgesic, and anti-inflammatory properties [19]. The dose regimen is different from the prescription, which typically calls for taking 500 mg two to three times a day up to a maximum of 1500 mg daily. Naproxen is a superior comparator in many clinical trials due to its excellent analgesic properties and long half-life, which guarantee steady blood levels and efficacy. In order to optimize therapeutic activity and reduce the likelihood of side effects, NSAIDs must be distributed locally in injured tissues [20]. Naproxen exhibits high protein binding (> 99.5%); nevertheless, the free fraction experiences a notable increase with elevated plasma concentrations. Naproxen's volume of distribution is relatively small, approximately 10% of body weight [21]. The benefits of microemulsion for drug delivery via transdermal application have been attributed to three predominant mechanisms [22]. Recent research endeavors have resulted in the creation of novel approaches for the synthesis of nanoparticles through distinct pathways. These include miniemulsion polymerization, which involves the direct reaction of small, uniform, and stable precursor droplets to the ultimate polymer dispersion; emulsion polymerization; the spontaneous formation of nanoparticles [23]. The degree to which the drug has been incorporated into the system and the way the drug and polymer interact are crucial elements that influence the release profile [24]. Different NSAIDs can be nanoencapsulated to reduce upper gastrointestinal damage because the drug will not come into contact with the mucosa. Additionally, the drug may become less toxic, dissolve more readily in water, have a faster onset of action, or be more permeable through biological membranes. Stable dissolution, pore size and volume, uniform size of the nanoparticles, and their shape are, in general, the controlled parameters of greatest interest [25]. Emulsification is the primary unit operation used in this method. To ensure a large superficial area for the diffusion step and to yield nanoparticles, a stable dispersion must be properly prepared. Besides, The Emulsification-diffusion method comes up with numerous advantages: (i) It can be used with standard laboratory equipment; (ii) It can use pharmaceutically acceptable solvents; (iii) Solvent recycling is possible; (iv) It can be easily scaled up to a large scale; and (v) It is highly reproducible and efficient. One major assumption with this process, though, is that low solid concentration dispersions are produced due to the significant dilution needed to cause the solvent to diffuse [26]. Compared to typical medication therapies, nanocarriers have a number of advantages because it is simpler to control the size, charge, surface characteristics, and targeting moieties of these particles to control uptake, biodistribution, targeting, and elimination [27].

2. MATERIALS AND METHODS

Materials and chemicals: Eudragit L 100 [Poly (methacrylic acid-co-methyl methacrylate) 1:1] with a molecular weight of 125000 g/mol was purchased from Sukria Medicine Enterprise, west Bengal, India, and has been used as a polymer. Naproxen sodium [$C_{14}H_{13}NaO_3$] with a molecular weight of 230.26 g/mol was purchased from Sukria Medicine Enterprise, West Bengal, India, and has been used as a model drug. Acetone extra pure [$(CH_3)_2CO$] with a molecular weight of 58.08 g/mol was purchased from Merch KGaA (64271 Darmstadt, Germany) and used as a solvent. Poly Vinyl Alcohol (PVA) [$(C_2H_4O)_x$] with a molecular weight of 1,15,000 g/mol was purchased from Merch KGaA (64271 Darmstadt, Germany) and used as a stabilizer. Sodium dodecyl sulphate [$NaC_{12}H_{25}SO_4$] with a molecular weight of

288.38 g/mol was purchased from Merch KGaA (64271 Darmstadt, Germany) and has been used as surfactant. D.D.I.: Distilled de-ionized water.

The general procedure for the preparation of nanocarrier: An appropriate technique known as the Emulsification Diffusion Method (EDM) was used to manufacture polymeric nanoparticles. There was enough polymer dissolved in 20 ml of acetone. The organic phase was combined with a 30 ml aqueous phase that contained stabilizer.

- The combination was emulsified using a magnetic stirrer run at a high speed for 15 minutes after the organic and continuous phases were mutually saturated.
- To allow the acetone to permeate into the water, 70 ml of water was then added. The mixture was then stirred vigorously for 30 minutes using a magnetic stirrer.
- Placed on a lab rotator for 20 minutes, stirring somewhat with magnets to cause nano-precipitation.
- The nanoparticles were subjected to a hot air oven at 40 °C for four hours after the acetone was eliminated by dialysis using Whatman® Filter Papers.

The drug was added during the first stage of nanoparticle synthesis, and then the same procedure was used to create nanoparticles loaded with Naproxen Sodium. Eudragit L 100 nanoparticle preparation instructions and a basic recipe are provided in (Table 2) below:

The working procedure for the preparation of Eudragit L 100 nanocarrier loaded with Naproxen Sodium: Using the Emulsification Diffusion Method (EDM), 1 g of Eudragit L 100 and 500 g of Naproxen sodium were dissolved in 10 ml of acetone to create Eudragit L 100 nanocarriers loaded with Naproxen sodium. The organic phase was combined with a 30 ml aqueous phase that contained stabilisers in the form of 20 mg each of polyvinyl alcohol (PVA) and sodium dodecyl sulphate (SDS).

1. After the organic and continuous phases were mutually saturated, the mixture was emulsified for 15 minutes at a maximum speed of rpm using a magnetic stirrer.
2. Following that, 70 ml of water was added to allow acetone to diffuse into the water, and the magnetic stirrer continued at a maximum speed of rpm for 30 minutes.
3. While being moderately stirred by magnets, placed on the lab rotator for 20 minutes, resulting in the Eudragit L 100 particle nanoprecipitation.
4. Acetone was removed by dialysis using Whatman® filter paper, therefore, nanoparticles were placed in a hot air oven for 4 hours at a temperature of 40 °C.

Table 1. The equipment have been used in this research is given below

Name of equipment	Model	Manufacturer Name	Origin
Electric Balance	M -310	Denver Instrument, Inc.	Switzerland
Hot Air Oven	JSGI-050T	Jsr Micro korea Co. Ltd.	Korea
Magnetic Stirrer	S46410	Thermolyne Cimarec®	Iowa, U.S.A
Lab. Rotator	DSR-2100	Digisystem Laboratory Instruments, Inc.	Taiwan
Whatman® Filter Papers	Cat No 1001 125	Whatman International Ltd.	Maidstone, England
Scanning Electron Microscope (SEM)	JSM-7610F	JEOL Ltd.	Mitaka, Tokyo.

Table 2. The basic recipe for the preparation of Nanocarrier

	Ingredients	Amount
Organic Phase	Polymer	Variables
	Acetone (Solvent)	Variables
Aqueous Phase	D.D.I water	Variables
	Poly Vinyl Alcohol (PVP) (Stabilizer)	20 mg
	Stirrer Speed	Variables
Emulsification	Drying Temperature and Time	Variables

Table 3. The working recipe for the Eudragit L 100 Nanocarrier loaded with Naproxen Sodium

	Ingredients	Amount
	Eudragit L 100 (Polymer)	1gm
Organic Phase	Naproxen Sodium (model Drug)	500mg
	Acetone (Solvent)	10 ml
	D.D.I water	100 ml
Aqueous Phase	Poly Vinyl Alcohol (PVP) (Stabilizer)	20 mg
	Sodium Dodecyl Sulfate (SDS)	20 mg
	Stirrer Speed	Maximum rpm
Emulsification	Drying Temperature and Time	40 C for 4 hours

To formulate nanoparticles loaded with Naproxen sodium, the drug was added in the initial step of nanoparticle formation, followed by the same sequence as above. The working recipe for the preparation of Eudragit L 100 nanocarrier loaded with naproxen sodium is given (Table 3) above.

3. RESULTS AND DISCUSSION

Nanocarrier loaded with naproxen was successfully prepared by Emulsification Diffusion Method (EDM). This technique presents numerous benefits. It is a straight forward technique, rapid and easy to perform. There is a polymer that performs to act as nanocarrier. The result and discussion for the Eudragit L 100 nanocarrier are given below with comprehensive details.

Result of Eudragit L 100 Nanocarrier loaded with Naproxen Sodium: The emulsification diffusion method (EDM) was used to generate the formulation below, and the standardized parameter indicated that the prospective outcome had the appropriate and required features.

	Ingredients	Amount
Organic Phase	Eudragit L 100 (Polymer)	1gm
	Naproxen Sodium (model Drug)	500mg
	Acetone (Solvent)	10 ml
Aqueous Phase	D.D.I water	100 ml
	Poly Vinyl Alcohol (PVP) (Stabilizer)	20 mg
	Sodium Dodecyl Sulfate (SDS)	20 mg
Emulsification	Stirrer Speed	Maximum rpm
	Drying Temperature and Time	40 C for 4 hours

Particle size analysis with scanning electron microscope (SEM): The nanoparticle's particle size was measured using a scanning electron microscope (SEM) [JSM-7610F, JEOL Ltd. Mitaka, Tokyo] following a 28-day preparation period. To verify that the particles were produced in the nano meter range, a measurement of the particle size was necessary. The nanometer range and particle size data for the naproxen sodium-loaded Eudragit L 100 nanoparticle carriers are displayed in (Figs. 1 & 2). The formulations' average particle sizes ranged up to 100 nm, which is regarded as a nanoparticle carrier. It was discovered that the addition of medications did not alter the nanoparticle carrier's size range in any discernible way.

Morphology Analysis of eudragit L 100 nanocarrier loaded with naproxen sodium: After 28 days of preparation, scanning electron microscopy (SEM) was used to evaluate the nanoparticle's shape and surface morphology. Figs. 3, 4 and 5, respectively, display a few sample photos. Morphologies with spherical, smooth, and discrete shapes were seen. For the other formulas, the outcomes were essentially the same. It was discovered that the shape of the nanoparticle carrier did not change noticeably when medications were added. The drying procedure used to prepare the sample resulted in the discovery of several agglomerates. According to SEM investigations, the average particle size of the nanoparticle carrier also varied, up to 100 nm. The radius of hydration will only slightly diminish as a result of the electron microscopic measurements being performed in a completely dry environment. Size measurements with sub-nanometer precision can be readily obtained using scanning electron microscopy (SEM) techniques.

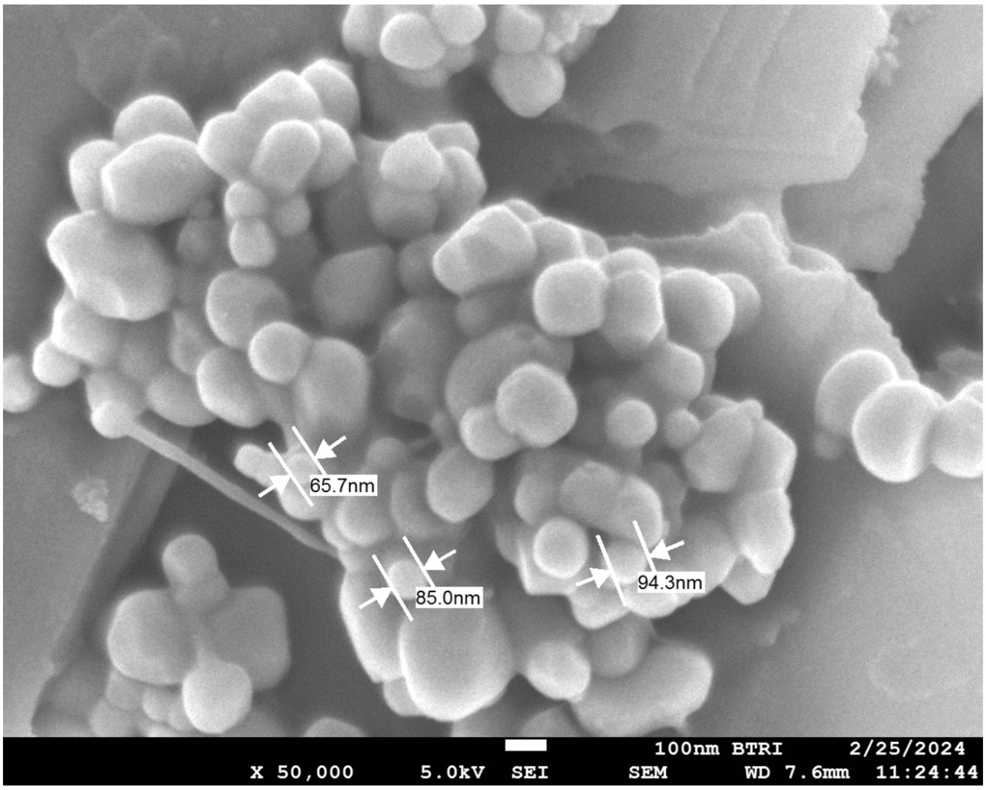

Fig. 1. Partcle size of the Eudragit L 100 nanocarrier loaded with Naproxen sodium

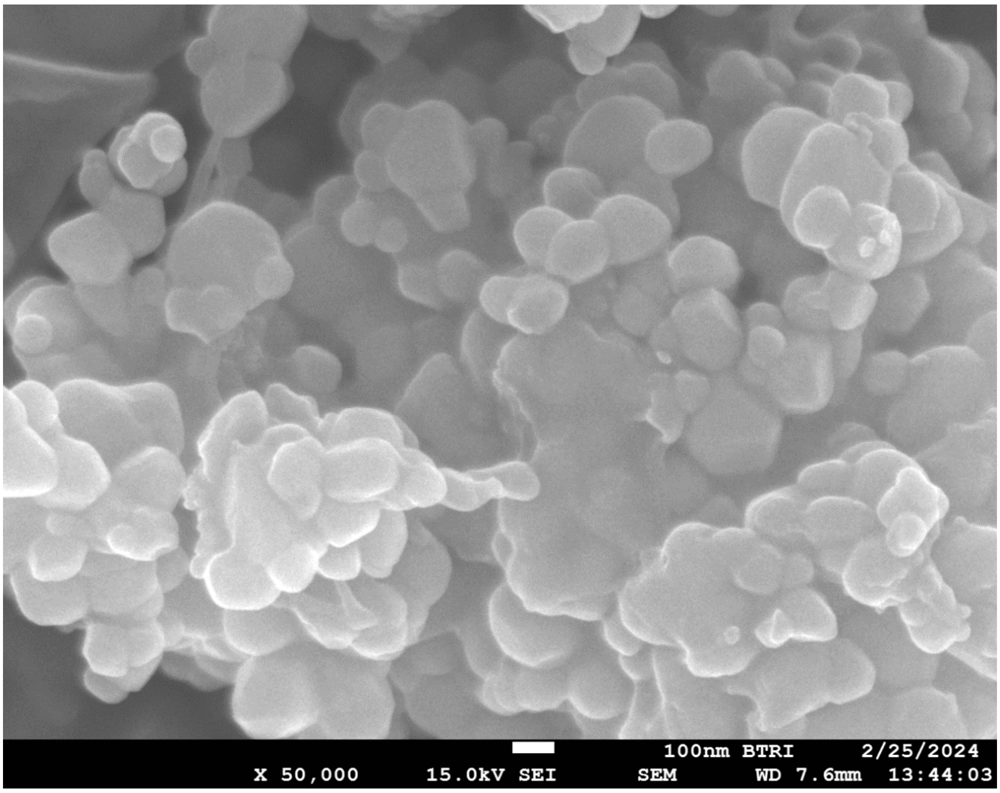

Fig. 2. Nanometer range of the Eudragit L 100 nanocarrier loaded with Naproxen sodium up to 100nm

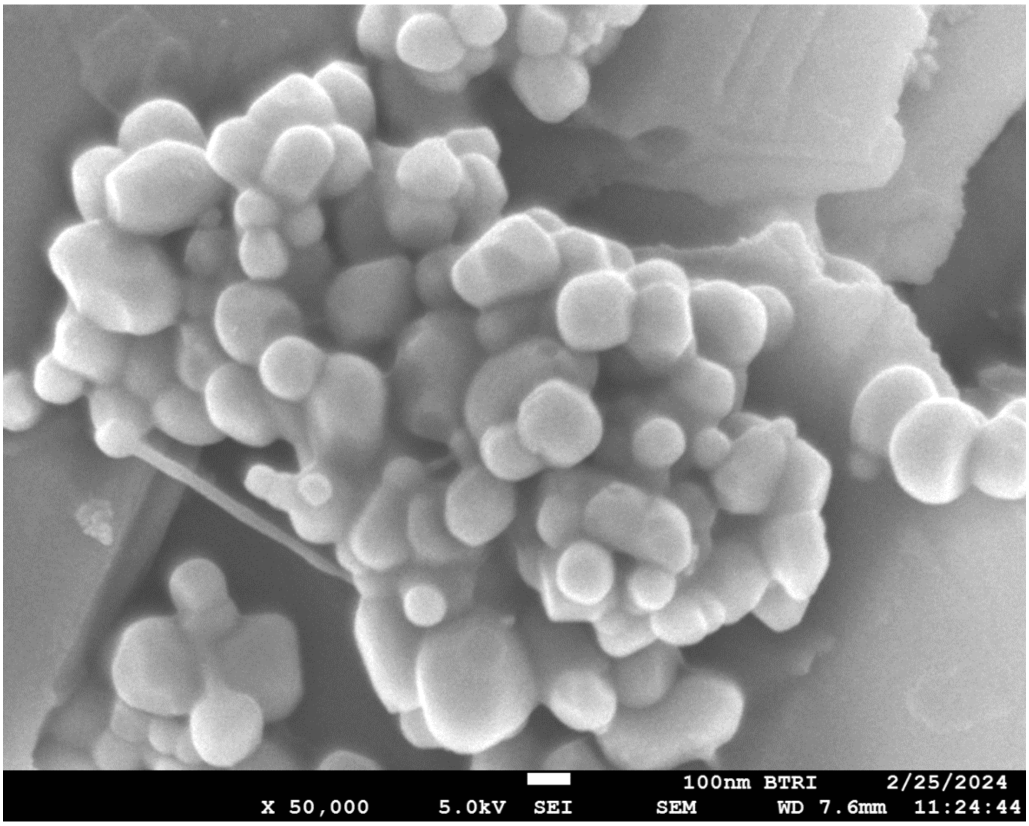

Fig. 3. The morphology of the Eudragit L 100 nanocarrier loaded with Naproxen Sodium

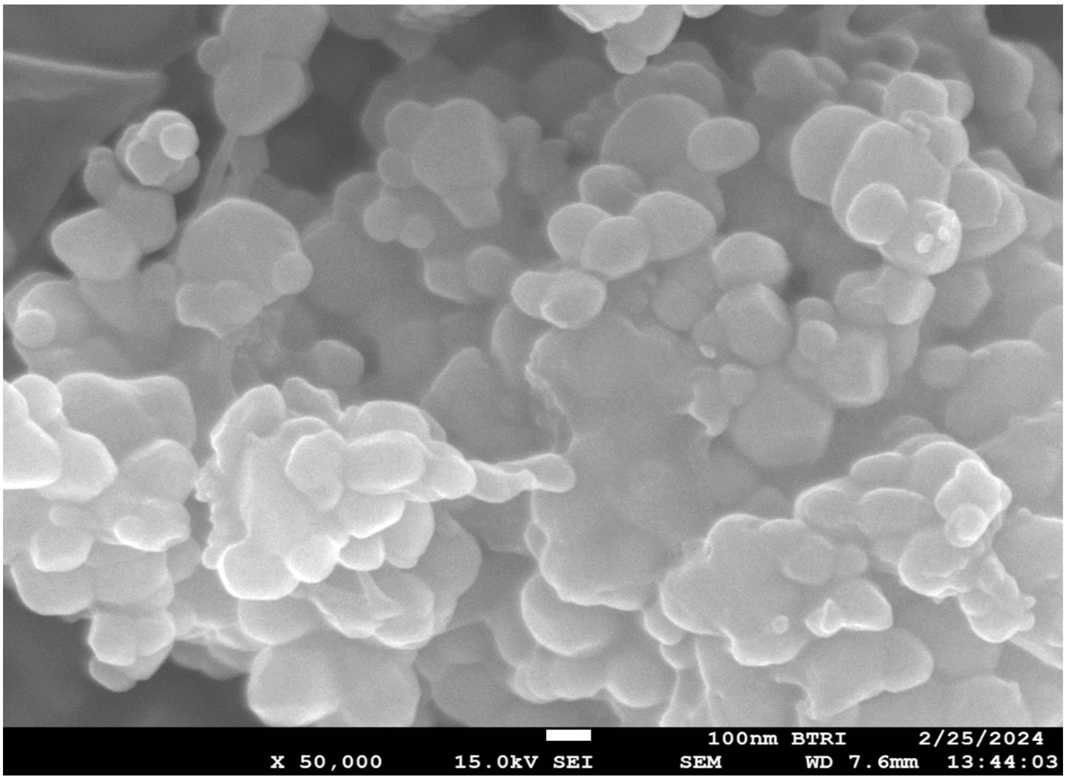

Fig. 4. The morphology of the Eudragit L 100 nanocarrier loaded with naproxen Sodium

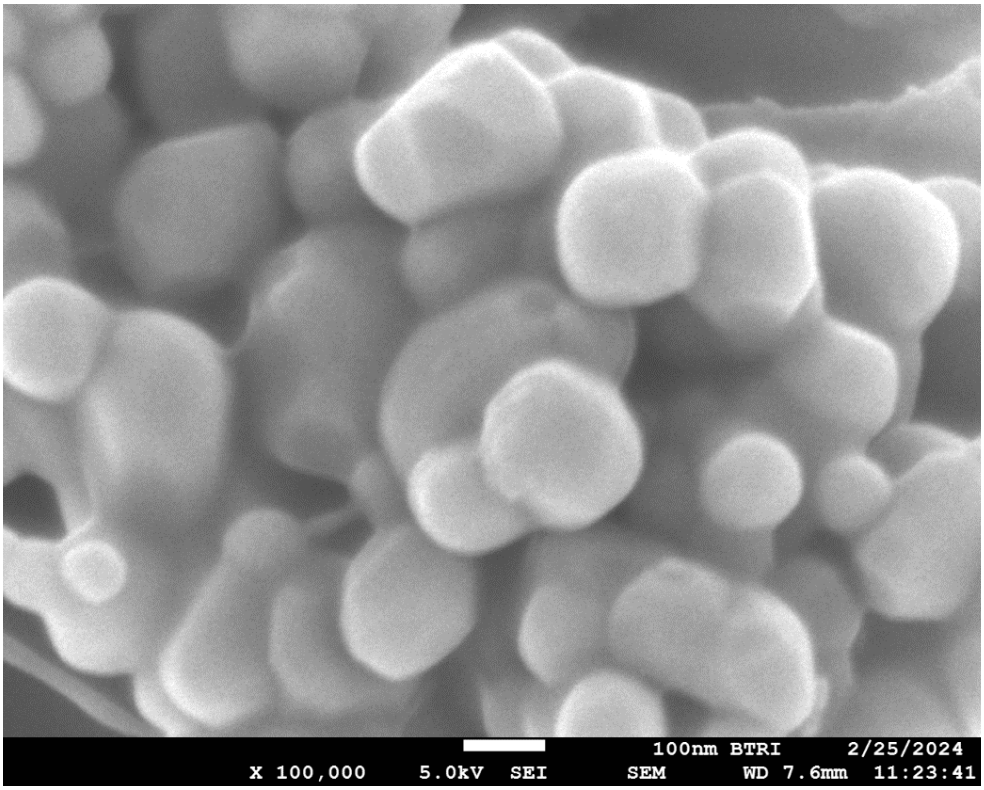

Fig. 5. The morphology of the Eudragit L 100 nanocarrier loaded with naproxen Sodium

Discussion of eudragit L 100 nanocarrier loaded with naproxen sodium: This study investigates whether the Emulsification Diffusion Method is a good fit for enhancing nanoscale particle size reduction. This formulation, which uses Eudragit L 100 polymer as a carrier, indicates that this approach is the most appropriate for creating nanocarriers. The size, shape, and morphology of the Eudragit L 100 Nanocarrier loaded with naproxen sodium were clearly shown by scanning electron microscopy (SEM) analysis. It is believed that the spherical shape and smooth surface character seen in scanning electron microscopy (SEM) are characteristics that arise from having an ideal particle. Verifying the particle size information, Particle sizes for Eudragit L 100 nanoparticles were found to range from 1 to 100 nm. Larger particles seemed brighter, while comparatively small particles appeared darker. Overall, the structure, shape, and morphology of the particles appear uniform, which suggests that the medication application did not compromise any specific integrity and instead assisted in the final creation of uniformly shaped spherical particles. Furthermore, using the Emulsification Diffusion Method (EDM), Eudragit L 100 polymer loaded with naproxen sodium has successfully emerged in the nanoscale size range. As a result, the naproxen-loaded Eudragit L100 Polymer is a fruitful investigation into creating a novel nanocarrier via the appropriate Emulsification Diffusion Method (EDM).

4. CONCLUSION

The current study has demonstrated that the emulsification–diffusion method (EDM) may create drugs containing nanoparticles. It illustrates the possible method to regulate the dimensions and form of the Naproxen Sodium-loaded Eudragit L 100 nanocarrier. The process of creating nanoparticles was supposed to be connected to the globule size reduction brought on by the solvent's quick diffusion. The primary phase of the procedure is crucial to the method's success. During the stage, stability and droplet size generation are crucial factors. The construction of the Eudragit L 100 nanocarrier loaded with naproxen sodium may depend critically on preparatory variables such as the kind and concentrations of stabiliser, the speed of magnetic stirrer polymer concentrations, etc. This study investigates if the Emulsification Diffusion Method is a suitable approach to enhance the reduction of particle size at the nanoscale. The emulsification diffusion approach is thus the appropriate technique for the generation of novel nano carriers, as this work has demonstrated.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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