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The formation of starch microparticle loaded with naproxen sodium

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Abstract
The purpose of this study is to reduce the particle size in micrometer range through a suitable method called Emulsification diffusion Method (EDM). Microparticles offer advantages over bulk particles and macroscale materials due to their higher surface to volume ratio. As biomaterials, microparticles play a crucial role in pharmacological and biomedical research because of their controlled interaction with the biological system. To create micrometer-sized starch particles-which are frequently employed as polymeric carriers-the emulsification-diffusion method (EDM) was employed. Any appropriate medication or API (Active Pharmaceutical Ingredient) ought to be selected. Naproxen Sodium was thus selected as the model medication. Saturating an aqueous phase with stabilizer, emulsifying a drug and polymer solution, and then adding too much water are the steps involved in the preparation process. Research has been done on how process variables affect the average size of microparticles. It was made apparent 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 microparticles. Naproxen Sodium with starch particles smaller than 10 µm was obtained using a Scanning Electron Microscopic (SEM) test. It was discovered that the morphology of the microparticle showed no distinctive changes upon incorporation of drugs or luminosity. Furthermore, because of their large surface area, the medication is integrated into the microcarrier, which increases their effectiveness. The effectiveness of the Emulsification Diffusion Method for enhancing microscale particle size reduction is investigated in the study that is being presented. In support of the particle size data, starch microparticles were found to exhibit a range of 1-10 µm, indicating that the Emulsification Diffusion Method (EDM) is a viable technique for the creation of microcarriers.

Keywords: Emulsifying, microscale, diffusion, polymer, surface area

Introduction
The successful use of drug microcarriers as the drug delivery systems in the treatment of a variety of disorders has been documented in numerous research. Controlling the rate and site of drug release, ensuring stability, uniform particle size, and scaling up are the primary problems in their development. Unquestionably, the benefits of these microcarrier systems and the plethora of opportunities.

They present are demonstrated by the drug technology's recent lightning-fast development [1, 2]. Structures with sizes ranging from 1 to 1000 micrometer are called microparticles. Typically, they consist of an active ingredient mixed into a polymer matrix. There are primarily two types of microparticles, depending on how the medication molecules are incorporated: tiny spheres microcapsules (Drug core covered with polymer) and homogenous combination of active ingredient and polymer [3]. Effective distribution of powerful medications, lowering of drug concentration in location other than the target tissue, and the delivery of insoluble or sporadically water soluble active substances are all made possible by microparticles [4]. Due to their increased surface to volume ratio, microparticles have some benefits over particles in bulk and macroscale materials. Because of their regulated interaction with the biological system, microparticles, as biomaterials, are also essential in pharmacological and biomedical research [5]. Naturally occurring polymers possess crucial qualities as components for drug delivery systems, including biocompatibility and biodegradability. The capacity to degrade naturally is crucial to preventing long-term or acute toxicity [6]. Two other categories for microparticles are microspheres and microcapsules. Micrometric reservoir systems are called microcapsules.

Unlike microspheres, these have the medication centered inside the polymeric shell of it is possible to regulate finite thickness and release by diffusion, dissolution, or both. The majority of the time, high-quality microcapsules with thick walls release their medications at a zero order rate. Microspheres are micrometric matrix structures that are solid and almost spherical. They consist of biodegradable and biocompatible polymers, such as polylactic acid (PLA) and polylactic-co-glycolic acid (PLGA). Waxy (or) additional barrier components such gums, proteins, lipids, and starches [7]. From the standpoint of mass transport, microcapsules' spherical shape is thought to be favourable because it provides the ideal surface-to-volume ratio for the diffusion of proteins and nutrients. Cellular survival in comparison to alternative immobilisation scaffolds, which enhances the permeability of nutrients and oxygen. The capsules' small size (Between 100 and 500 μm) permits them to be inserted into the bloodstream in close proximity, which may be advantageous for the long-term functionality of the encapsulated cells in some applications that will be covered later on because of the improved oxygen transport into the capsules. Furthermore, compared to macrocapsules, microcapsules are usually more robust and challenging to mechanically break [8, 9]. The purpose of this research is that micro structured 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. The technique known as spontaneous emulsion diffusion involves dissolving a polymer in a mixture of solvents, one of which is water immiscible and the other of which is miscible, in order to create biodegradable microparticles. When added to an aqueous phase, this solution forms a microemulsion because it dissolves fast in the miscible solvent. Microparticles are created as the immiscible solvent evaporates. The microemulsion is first created by the interfacial turbulence that arises during the solvent displacement of the miscible solvent. This serves as a crucial reminder that there isn't actually a diffusion step. Consequently, this procedure can be thought of as a combination of the solvent evaporation and displacement procedures. Since the modified spontaneous emulsification solvent method exclusively employs miscible solvents, it is obvious that it is a solvent displacement method. In certain scientific articles and patents, the words "solvent quenching," "self-emulsifying solvent diffusion," "emulsification-solvent diffusion," "emulsion solvent diffusion and emulsified solvent diffusion," and "water-in-oil emulsification-diffusion" are equivalent. Overall, this mechanism explains satisfactorily the kind of particles obtained by the emulsification-diffusion method, and they are associated with the properties and transformation of the supersaturated region. The key variables that affect the procedure and, consequently, the particle size are the concentration and kind of stabilizer, drug, and biodegradable polymer; the amount and kind of diffusion medium; the rate of stirring; the ratio of oily to aqueous phases; the viscosity of the external phase; and other factors [10]. Silica is added to pharmaceutical formulations to improve their flowability when taken orally. Naproxen (C14H14O3) is a member of the Class II family of non-steroidal anti-inflammatory drugs. Its disintegration limits its bioavailability. Treatments for mild to severe pain, heat, stiffness, and inflammation are common uses. Nonetheless, it may cause gastrointestinal issues in certain persons [11]. Naproxen provides antipyretic, analgesic, and anti-inflammatory properties [12]. vcFor non-prescription dosing, local regulatory agencies allow a maximum daily over-the-counter dose of 440–660 mg; this should happen every 8–12 hours. The prescribed dosing regimen, which usually entails taking 500 mg two to three times a day up to a maximum of 1500 mg daily, is not the same as this one. Because of its exceptional analgesic qualities and extended half-life, which provide consistent blood levels and effectiveness, naproxen has proven to be a superior comparator in numerous clinical trials. NSAIDs must be administered topically to wounded tissues to maximise therapeutic efficacy and minimise the possibility of adverse effects [13]. There are three main theories that explain why microemulsions are beneficial for transdermal medication delivery. First, the increased solubility potential of lipophilic and hydrophilic medications in microemulsion systems may increase their skin-directed thermodynamic activity. Second, the permeation enhancer chemicals in the microemulsion may break down the integrity of the stratum corneum and encourage drug absorption through the skin. Third, a drug's affinity for a microemulsion's internal phase can be easily adjusted to favour partitioning into the stratum corneum, changing its portion in the microemulsion and perhaps increasing the drug's rate of permeation out of it [14]. Additionally, the emulsification-diffusion process has a lot of benefits. It can be easily scaled up to a big scale, is extremely reproducible and efficient, compatible with conventional laboratory equipment, and can use solvents permitted by pharmaceutical companies. It can also be recycled. On the other hand, a fundamental tenet of this procedure is that dispersions with low solid concentrations are produced due to the high dilution needed for the solvent to disperse [15]. This research has been conducted to evaluate the suitability of emulsification diffusion method (EDM) in order to successfully produce starch microparticles loaded with naproxen sodium.

Methods and Materials

Starch [(C6H10O5) n] with molecular weight of 10 ^5 g/mol was purchased from Polafix (made in korea) and has been used as polymer. Naproxen Sodium [C14H13NaO3] with molecular weight of 230.26 g/mol was purchased from Sukria medicine enterprise, west Bengal, India, has been used as model drug. Acetone extra pure [(CH3)2CO] with molecular weight of 58.08 g/mol was purchased from Merch KGaA (64271 Darmstadt, Germany) has been used as solvent. Poly Vinyl Alcohol (PVA)[(C2H4O)x] with molecular weight of 1,15,000 g/mol was purchased from Merch KGaA (64271 Darmstadt, Germany) has been used as stabilizer and D.D.I--- Distilled De-Ionized (water).

List of Equipment

Table 1: The equipment have been used in this project 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®	Lowa, 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.

General Procedure for the Preparation Microparticle

Microparticles were prepared through a suitable method called Emulsification Diffusion Method (EDM).In 20 ml of Acetone, sufficient amount of polymer were dissolved. A 30 ml aqueous phase containing stabilizer was mixed with the organic phase.

- An emulsification of the mixture occurred following the mutual saturation of the organic and continuous phases using a magnetic stirrer at a high speed for 15 minutes.
- Following that, 70 ml of water was added to allow acetone to diffuse into the water and continue with magnetic stirrer at a high speed for 30 minutes.
- While being moderately stirred by magnets, place to the lab rotator for 20 minutes and resulting in the precipitation.
- Acetone was removed by dialysis, there after nanoparticles were placed to hot air oven for 4 hours at a temperature of 40C.

To formulate microparticles loaded with API (active pharmaceutical ingredients), the drug was added in the initial step of microparticle formation, followed by the same sequence as above. The basic recipe for the preparation of microparticle is given in (Table-2) below:

Table 2: The basic recipe for the preparation of polymeric microparticles:

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

The working procedure for the Formation of starch microparticle loaded with Naproxen Sodium

In order to prepare Starch microparticles loaded with naproxen sodium through the Emulsification Diffusion Method (EDM), 1g of starch and 500 mg of Naproxen Sodium were dissolved in 20 ml of Acetone. A 30 ml aqueous phase containing stabilizer as 20 mg of Polyvinyl Alcohol (PVA) was mixed with the organic phase.

1. An emulsification of the mixture occurred following the mutual saturation of the organic and continuous phases using a magnetic stirrer at a maximum speed of rpm for 15 minutes.
2. Following that, 70 ml of water was added to allow acetone to diffuse into the water and continue with magnetic stirrer at a maximum speed of rpm for 30 minutes.
3. While being moderately stirred by magnets, placed to the lab rotator for 20 minutes and resulting in the starch microparticle precipitation.

Acetone was removed by dialysis using Whatman® filter paper, there after microparticles were placed to a hot air oven for 4 hours at a temperature of 40 C. To formulate microparticles loaded with API (Active pharmaceutical ingredients), the drug was added in the initial step of microparticle formation, followed by the same sequence as above. The working recipe of the preparation of starch microparticle loaded with naproxen sodium is given below.

Table 3: The working recipe for the formation of Starch microparticle loaded with Naproxen sodium

	Ingredients	Amount
Organic Phase	Starch (polymer)	1 g
	Naproxen (model drug)	500 mg
	Acetone (Solvent)	20 ml
Aqueous Phase	D.D.I water	100 ml
	Poly Vinyl Alcohol (PVP) (Stabilizer)	20 mg
Emulsification	Stirrer Speed	Maximum rpm
	Drying Temperature and Time	40 for 4 hours

Results and Discussion

Starch Microparticle loaded with naproxen sodium was successfully prepared by the Emulsification Diffusion Method (EDM). This technique presents numerous advantages. It is a straight forward technique, rapid and easy to perform. There is a polymer perform to act as microcarrier. The result and discussion for the respective polymer is given below with detail information.

Result of Starch microparticle loaded with Naproxen Sodium: The following formulation has been prepared through Emulsification Diffusion Method (EDM) and revealed the prospective result and having the desired characteristics according to the standardized parameter.

Table 4: The working recipe for the formation of Starch microparticle loaded with Naproxen sodium

	Ingredients	Amount
Organic Phase	Starch (polymer)	1 g
	Naproxen (model drug)	500 mg
	Acetone (Solvent)	20 ml
Aqueous Phase	D.D.I water	
	Poly Vinyl Alcohol (PVP) (Stabilizer)	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 particle size of starch particle, assessed after 28 days of preparation and performed by the Scanning Electron Microscope (SEM) [JSM-7610F, JEOL Ltd. Mitaka, Tokyo].Particle size measurement was required to confirm the production of the particles in micrometer-range. Particle size data and micrometer range for the particle of starch loaded with naproxen sodium is shown in (Figure 1&2). The mean particle size for formulations varied in range and appeared as microparticle in micro meter range between 1µm to 10 µm which is completely considered to be as considered to be as micro particle in the accordance with the range of standard micrometer (1-100 µm). Incorporation of drugs were found to show no characteristic amendment in the size range of these particle.

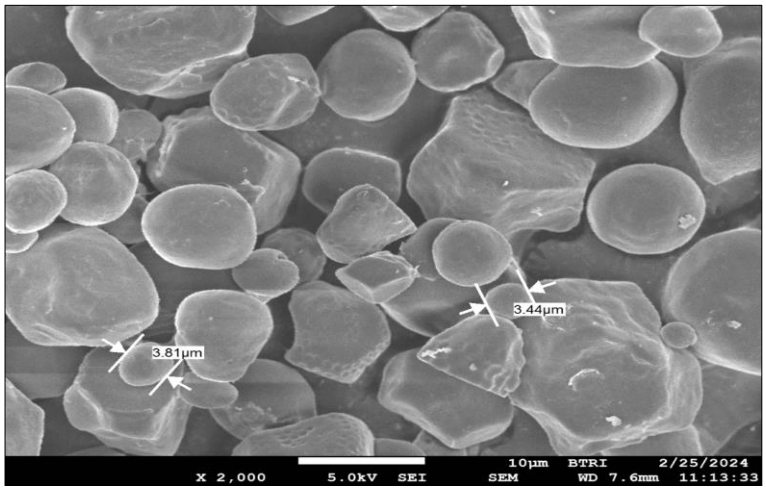

Fig 1: Illustration of the partcle size of the starch microparticle loaded with Naproxen sodium

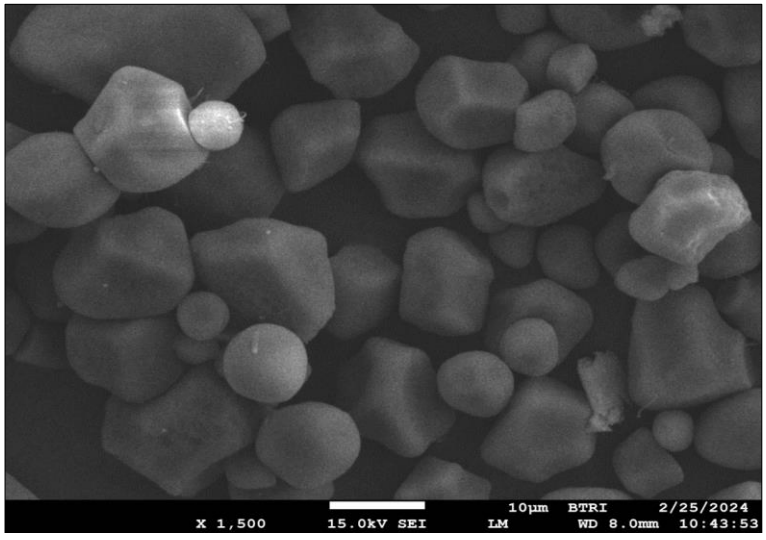

Fig 2: Illustration of Micrometer range of starch microparticle loaded with Naproxen sodium revealing the range of 1-10 µm

Morphology Analysis of Starch microparticle loaded with Naproxen:

Shape and surface morphology of microparticle, assessed after 28 days of preparation by scanning electron microscopy (SEM). Some representative images have been shown in (Fig. 3, 4, 5) respectively. Discrete, smooth and spherical shaped morphologies were noted. Results were more or less similar for the other formulations. Incorporation of drugs were found to show no characteristic amendment in the morphology of the microparticle. Some agglomerates were found due to the drying process during sample preparation. The average particle size of microparticle calculated from SEM (Scanning electron microcope) studies as well and the range between 1µm to 10

µm. The electron microscopic measurements were carried out at complete dry condition which would lead to the little shrinkage of the radius of hydration. Scanning Electron microscopic (SEM) techniques can easily provide accurate size measurements with micrometer resolution.

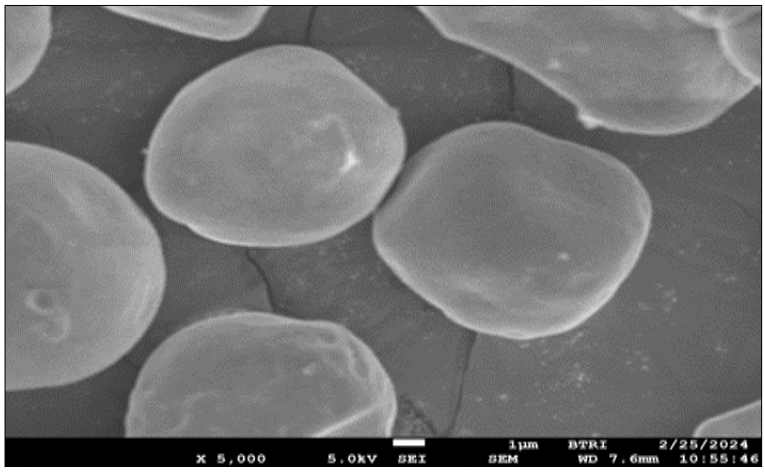

Fig 3: The morphology analysis of starch microparticle loaded with naproxen sodium.

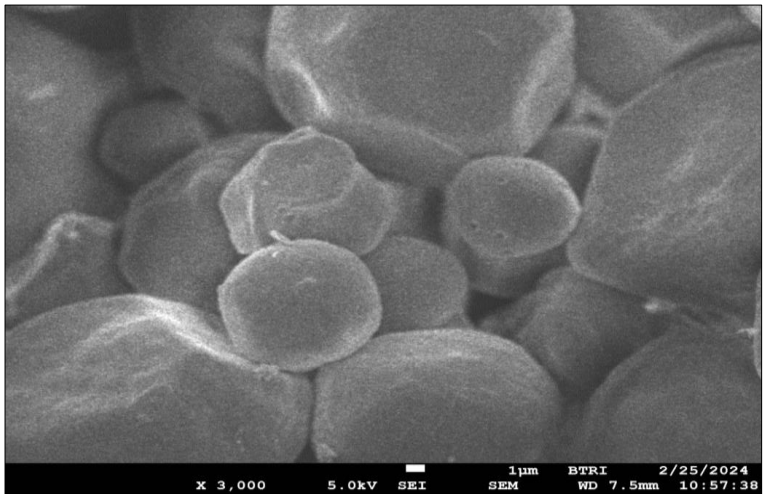

Fig 4: The morphology analysis of starch microparticle loaded with naproxen sodium

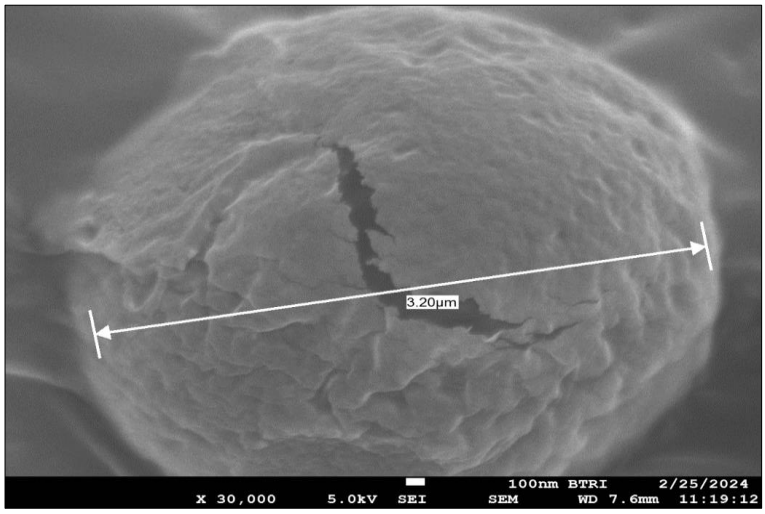

Fig 5: The morphology analysis of starch microparticle loaded with naproxen sodium

Discussion for the Starch microparticle loaded with Naproxen Sodium: The presented study explores the formation of the microparticle and the suitability of the Emulsification diffusion method (EDM) for improving the particle size reduction in micrometer scale. According to the formulation containing starch polymer, this method has been proved to be the suitable to develop a microparticle. Scanning Electron Microscope (SEM) analysis clearly demonstrated the size, shape and morphology of Starch microparticle loaded with naproxen sodium. The spherical

shape and the smooth surface character displayed in Scanning Electron Microscope (SEM), is considered to be a property resulting in as an outcome of having an impeccable particle. Confirming the particle size data, particles with relatively small sizes appeared dark, while particles with larger sizes appeared brighter, particle diameters were observed to vary between 1-10 µm which defines the appropriate size according to the standardized parameter (1-100µm). Overall, the particles seem to have uniform character in both structure, shape and morphology, which further indicated that the applied drug do not harm the particular integrity but eventually help the formation of spherical particles with uniformity. In addition, Starch polymer loaded with naproxen sodium has successfully appeared in micrometer scale range through Emulsification Diffusion Method (EDM). Consequently, Starch microparticle loaded with naproxen sodium is a successful study of developing a new microparticle through a suitable method called Emulsification Diffusion Method (EDM).

Conclusion

The present work has shown that drug containing microparticle formation by the emulsification–diffusion method (EDM). It demonstrates the potential process to control the size and shape of starch microparticles loaded with Naproxen Sodium. The microparticle formation process was to be related to the reduction of globule size due to the rapid diffusion of solvent. The significant step for success of this method is the main stage of the process. The stability and the size of droplets formation during the stage are important factor. Preparative variables such as the type and concentrations of stabilizer, speed of magnetic stirrer polymer concentrations, could be the crucial factors for the formation of starch microparticles loaded with naproxen. As the presented study explores the suitability of the Emulsification diffusion method for improving the particle size reduction in micrometer scale. So this study has proved that emulsification diffusion method is the suitable method for the formation and development of microparticle.

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