



Formulation and Evaluation of Eudragit RL100 Polymeric Drug Loaded Microsponge for Ophthalmic Use

Rajashri B. Ambikar^{1*} and Ashok V. Bhosale²

¹PDEA's S. G. R. S. College of Pharmacy, Saswad, Purandar, Pune, Maharashtra, India.

²PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration between both authors. Author RBA designed the study, carried out experimental work, drafted the manuscript. Author AVB helped in designing of study, interpreted the experimental data and contributed in revising of the manuscript. Both the authors read and approved the final manuscript.

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ABSTRACT

Aims: The aim of this work is the formulation of Eudragit RL100 polymeric microsponges. The Microsponge Delivery System is a patented technique in which there is a polymeric system consisting of porous particles.

Methodology: The ratio of Diclofenac sodium and eudragit RL100 varied from 1:1 to 13: 1 to formulate microsponge. Dichloromethane was used as internal phase and polyvinylalcohol was used as an external phase. The formed microsponges were characterized for particle size, entrapment efficiency, drug content, in vitro drug release and SEM.

Results: With increase in drug: polymer ratio there is increase in production yield from 20.04% to 72.14%, and entrapment efficiency from 20.11% to 70.77%. Drug content of formed microsponge varied between 50.18% to 91.09% whereas particle size ranged from 1.41 μm to 17.66 μm . Microsponge formulations F3, F4 and F5 showed desired particle size hence studied for further evaluation. Formulation F3, F4 and F5 showed controlled release of 89.54%, 98.5% and 98.76%

*Corresponding author: E-mail: rajashriwin@gmail.com;

respectively up to 6 hr. F3 showed more controlled release at the end of 6 hr. The drug release from microsponges was best fitted to Higuchi's diffusion kinetics for all microsphere formulations with non-Fickian diffusion mechanism. The formed microsphere particles have spherical porous structure.

Conclusion: Study showed significance of Microsphere Delivery System for ophthalmic administration.

Keywords: Microsphere; diclofenac sodium; eudragit RL100; ophthalmic drug delivery; kinetic release.

1. INTRODUCTION

The Microsphere Delivery System (MDS) is a patented technique in which there is a polymeric system consisting of porous particles. They have tiny sponge like rounded particles, having a countless interconnecting voids. Microspheres exhibit a non collapsible structure with a spongy surface, those pores act as channel for controlled drug release [1]. Particle size of microsphere particles fall in between 5-300 μm . Microspheres are used as a drug carrier system as they have the good ability to entrap a wide range of drugs. The drug loaded microspheres could be formulated as different formulation such as tablets, capsules, creams, gel, lotions etc [2].

Ocular drug delivery is a challenge for pharmaceutical researchers due to the complex nature and structure of the eye. Most drugs are formulated as simple eye drops and ointments for ophthalmic use. More than 90% of ocular preparations are formulated as Eye drops. Eye drop formulations are cost effective to formulate, have good patient compliance and easy to formulate [3]. A major fraction of the drug administered topically is drained out with tears or removed by other mechanisms. Due to precorneal drainage, drug needs several applications in a day to achieve therapeutic effect. Ocular defense mechanism reduces the drug residence time over the cornea and minimizes its absorption. With conventional ophthalmic dosage form only 5% of the drug enters the eye intact. Particulate carriers are gaining considerable attention, as they provide more the patient compliance by avoiding eye irritation, foreign body sensation, and thus minimize patient discomfort [4]. The various researches have been carried out to increase the bioavailability and the duration of the therapeutic action of ocularly administered drugs. One of the approaches is to disperse the drug in polymer matrix to achieve sustained drug delivery [5].

Diclofenac, 2(2, 6-dichloroanilino) phenyl acetic acid, has a poor aqueous solubility. For

ophthalmic use diclofenac is commercially available as 0.1% w/v aqueous solution [3]. Diclofenac is applied topically in the eye for the management of pain in corneal epithelial defects following surgery or accidental trauma, treatment of postoperative ocular inflammations, chronic non-infectious inflammations, and prevention of intra-operative miosis during cataract surgery and for symptomatic relief of seasonal allergic conjunctivitis [6,7].

Eudragit RL 100 cationic polymer is a copolymer of poly(ethylacrylate, methyl-methacrylate, and chloro trimethyl-ammonioethyl methacrylate) this polymer consist of 8.8% to 12% of quaternary ammonium groups. At physiologic conditions eudragit RL 100 is insoluble. It is capable of mucoadhesion at ocular site for prolong period of time [8,9].

This study aims at formulation of Diclofenac sodium containing microspheres for ophthalmic use. Eudragit RL 100 was used as polymer. Characterizations of microsphere formulations were performed.

2. MATERIALS AND METHODS

2.1 Materials

Diclofenac Sodium was gifted by Nulife Pharmaceuticals, Pune, India. Eudragit RL 100 was gifted from Evonik India Pvt. Ltd., Mumbai. Dichloromethane, Triethylcitrate and Polyvinylalcohol 30,000–70,000 were procured from Research lab fine chem. Industries, Mumbai. All other chemicals used for analysis were analytical grade.

2.2 Preparation of Diclofenac sodium Loaded Microspheres

Diclofenac Sodium loaded microspheres prepared by quasi-emulsion solvent diffusion technique. Eudragit RL 100 polymer dissolved in 15 mL Dichloromethane and then weighed

quantity of Diclofenac Sodium was added, to prepare internal phase. Triethylcitrate (plasticizer) was added and mixture ultrasonicated (Spectrolab) for 15 min to form homogenous dispersion. Drug: Polymer ratio was varied as 1:1 to 13:1. 1% w/v Polyvinylalcohol solution prepared and internal phase emulsified into Polyvinylalcohol (PVA) solution. Mixture stirred for 4 hr using magnetic stirrer at 1000 rpm at room temperature. Microsponge filtered using whatman filter paper (Grade 42) and dried for about 48 hrs at room temperature [10].

2.3 Characterization of Diclofenac Sodium Loaded Microsponge

2.3.1 Determination of percentage yield

The percentage yield of Diclofenac Sodium loaded microsponges was determined by [11],

Production yield=

$$\frac{\text{Practical mass of Diclofenac Sodium loaded microsponges}}{\text{Theoretical mass of Drug and polymer added to microsponge}} \times 100$$

2.3.2 Drug content

Microsponge formulation containing 10 mg of drug was grinded in a glass mortar. Formed powder was added to 60 ml of phosphate buffer (pH 7.4) and volume was made up to 100ml. the solution was shaken for 4 hr, and filtered. Appropriate dilutions were made with 7.4 phosphate buffer and Analyzed spectrophotometrically (UV1Jasco, Japan) at 275.5 nm against phosphate buffer (pH 7.4) as blank. The Diclofenac sodium content of the microsponges were calculated.

2.3.3 Entrapment efficiency (%):

Entrapment Efficiency (%) of Diclofenac sodium contained microsponge was calculated with equation [11],

Entrapment Efficiency (%)=

$$\frac{\text{Actual drug content in obtained microsponges}}{\text{Weight of DIC added in microsponges}} \times 100$$

2.3.4 Particle size

Particle size of microsponge was determined using digital microscope (Motic CV5-2). Digital microscope was first calibrated using micrometer slide (AmScope MR400 Microscope calibration

slide). Microsponges were dispersed in water and drop was taken on a glass slide and observed under Digital microscope [12].

2.4 In Vitro Drug Release from Diclofenac Sodium Loaded Microsponges

In vitro drug release of DIC loaded microsponges was performed by Franz diffusion method. The receptor compartment filled with 50ml freshly prepared STF and stirred by a magnetic bar at 100 rpm. A dialysis membrane (12 000–14 000 Dalton MW, Hi-media, India) soaked overnight in the STF and placed between donor and receptor chambers. Microsponges dispersed in distilled water and placed in donor compartment; and covered with cover slip. Samples 1 ml were taken out at specific time intervals from the receptor and replaced with diffusion media. Study was performed in triplicate. Samples were analyzed at 275.5nm using UV spectrophotometer [13-14].

2.5 In Vitro Drug Release Kinetic Study form Diclofenac Sodium Loaded Microsponges

Kinetic study of in vitro release data was performed to interpret the DIC release mechanism. In vitro release data was analyzed using different models and regression coefficient values (r^2) were determined. The regression coefficient values (r^2) were calculated for Zero-order, First order, Hixson-crowell and Higuchi model The diffusion exponent (n) of Korsmeyer–Peppas model was used to study the diffusion mechanism [15].

2.6 Scanning Electron Microscopy (SEM)

A Field Emission Scanning Electron Microscope (FEI Nova NanoSEM 450) was used to study morphology of microsponge. Scanning Electron Microscope operated at 3.00 kV with magnification of 10 kx to observe microsponge coated with gold–palladium alloy for 45s under an argon atmosphere.

3. RESULTS AND DISCUSSION

Diclofenac sodium containing microsponges were prepared by the quasi emulsion solvent diffusion method using Eudragit RL 100 polymer. Quasi emulsion solvent diffusion method is effortless, reproducible and fast process [16]. In this method solvent toxicity reduced as organic solvent completely removed by evaporation. In PVA solution organic phase containing drug and

polymer, was emulsified to form small sized droplets. As organic solvent evaporates emulsion droplets got converted into microspunge particles. A small sized microspunge obtained by increasing surfactant concentration to 1% w/v polyvinylalcohol and stirring rate was increased to 1000 rpm [17]. Polyvinylalcohol acts as surfactant to emulsify the internal phase. As polyvinylalcohol concentration increases in external phase, internal phase breaks into smaller droplet to form small sized microspunge particles. Stirring rate also helps to achieve small sized microspunge particles [18].

With increase in drug: polymer ratio there is increased in production yield from 20.04% to 72.14%, whereas Entrapment Efficiency decreased from 20.11% to 70.77% [19] Table 1. Drug content varied between 50.18% to 91.09%.

Particle size is vital parameter for ocular drug delivery system. Particle size ranged from 1.41 μm to 17.66 μm . Particle size decreased as increase in drug: polymer ratio [20]. Particle size of less than 10 μm is suitable for ocular administration. Therefore formulations having particle size larger than 10 μm were not suitable for ophthalmic use [21]. Microsponges have particle size range 5-300 μm , so microspunge particles of range 5-10 μm were considered for further studies [22,23].

In vitro drug release is graphically interpreted in Fig. 1. The % cumulative drug release of microspunge formulations F3, F4 and F5 found to be 89.54%, 98.5% and 98.76% respectively up to 6 hr. Microspunge formulation F3 showed more controlled release.

Table 1. Characterization data of diclofenac sodium loaded microsponges prepared using polymer Eudragit RL 100

Formulation code	Drug: Polymer ratio	Particle Size (μm)	Production Yield (%)	Drug content (%)	Entrapment efficiency (%)
F1	1: 1	17.66 \pm 2.10	20.04 \pm 4.86	50.18 \pm 3.82	20.11 \pm 3.76
F2	3:1	14.32 \pm 3.01	36.25 \pm 3.13	79.31 \pm 2.67	38.33 \pm 4.11
F3	5:1	9.68 \pm 1.03	71.67 \pm 4.92	72.09 \pm 3.29	62.00 \pm 4.35
F4	7:1	7.11 \pm 1.39	69.38 \pm 2.58	82.88 \pm 3.40	65.71 \pm 4.41
F5	9:1	5.86 \pm 1.84	73.00 \pm 5.13	84.25 \pm 2.68	68.33 \pm 2.31
F6	11:1	2.31 \pm 1.04	73.75 \pm 1.81	89.27 \pm 3.71	71.82 \pm 2.69
F7	13:1	1.41 \pm 0.89	72.14 \pm 2.37	91.09 \pm 3.45	70.77 \pm 1.53

*n=3, mean \pm S.D

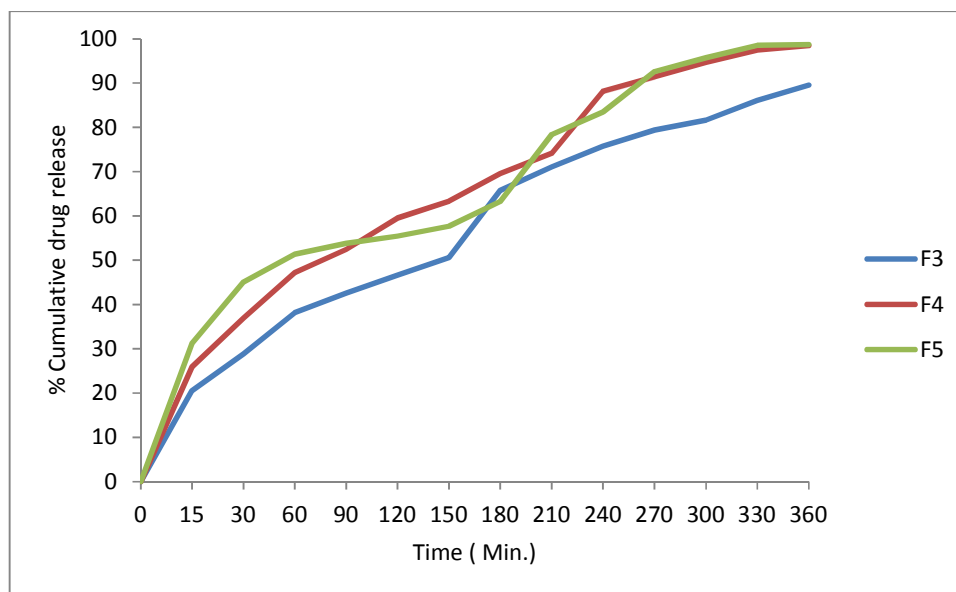


Fig. 1. In vitro release profiles of microspunge formulations (n=3, mean \pm S.D.)

Table 2. Release kinetics study of diclofenac sodium loaded microsp sponge formulations

Formulation code	Zero order model (r^2)	First order model (r^2)	Higuchi model (r^2)	Hixson–Crowell model (r^2)	Korsmeyer–Peppas model (n)
F3	0.9335	0.9819	0.9874	0.9844	0.7
F4	0.9108	0.9201	0.9877	0.9735	0.7
F5	0.8888	0.8722	0.9536	0.9391	0.68

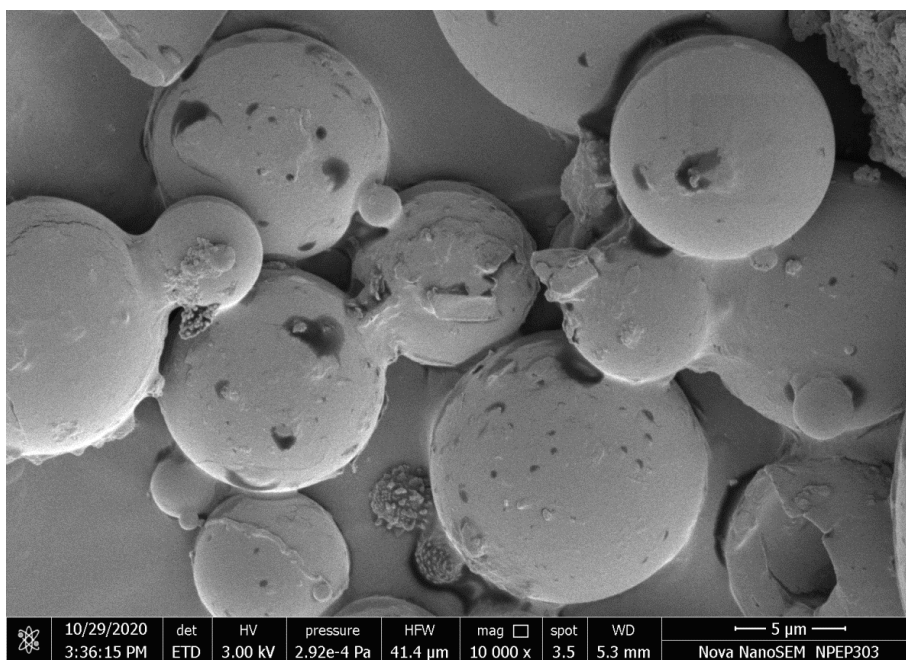


Fig. 2. Scanning electron microscope images of microsp sponge formulation (F3)

The drug release from microsponges was best fitted to Higuchi's diffusion kinetics for all microsp sponge formulations Table 2. The result of diffusion exponent value was found to be 0.7 indicating non-Fickian diffusion [24].

Microsp sponge formulation F3 was selected to further study of SEM. The captured SEM image of F3 microsp sponge formulation is shown in Fig. 2. Formed microsp sponge particle have pores and spherical structure. Drug particles were present on the microsponges as drug got deposited on particles during evaporation [25].

4. CONCLUSION

Diclofenac sodium containing microsponges were successfully prepared by the quasi emulsion solvent diffusion method using Eudragit RL 100 polymer for ocular administration. Diclofenac sodium containing microsponges exhibit satisfactory production yield, entrapment

efficiency, drug content and particle size. SEM images showed spherical porous microsp sponge particles. Diclofenac sodium release was extended up to 6 hrs. Microsponges offer good potential for ophthalmic drug delivery.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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