CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.14006171

https://www.iajps.com/volumes/volume11-october-2024/54-issue-10-october-24/

Available online at: http://www.iajps.com *Review Article*

FORMULATION OF COLON TARGETING NANOSPONGES FOR EFFECTIVE TREATMENT OF AMOEBIASIS

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Abstract
This study explores the formulation of diloxanide furoate-loaded nanosponges aimed at enhancing the drug's bioavailability for the effective treatment of amoebiasis. Various formulations were developed using poly-methyl-methacrylate and Eudragit S-100, optimizing parameters such as yield, entrapment efficiency, and in vitro drug release. The results indicated that formulation F3 achieved the highest percentage yield (84.45%) and entrapment efficiency (82.23%). In vitro release studies demonstrated a significant improvement in drug release profiles, with 98.74% of diloxanide furoate released over 12 hours, indicating a sustained release mechanism. The study suggests that these nanosponges may offer a promising strategy for targeted drug delivery to the colon, potentially improving therapeutic outcomes in amoebiasis treatment.

Keywords: *Diloxanide furoate, nanosponges, amoebiasis, targeted drug delivery, bioavailability, Eudragit S-100, sustained release.*

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Please cite this article in press Anjali Verma et al., ***Formulation Of Colon Targeting Nanosponges For Effective Treatment Of Amoebiasis.,****Indo Am. J. P. Sci, 2024; 11 (10).*

INTRODUCTION:

Amoebiasis, primarily caused by the protozoan parasite *Entamoeba histolytica*, is a significant health concern, particularly in developing regions. It affects approximately 50 million people globally, leading to symptoms that can range from mild diarrhea to severe dysentery and can even result in life-threatening complications (Kabat et al., 2017). The conventional treatment for amoebiasis is diloxanide furoate, an effective amoebicide that works by inhibiting the parasite's growth and reproduction. However, its clinical efficacy is often limited due to its low solubility, poor bioavailability, and rapid metabolism, which lead to suboptimal drug concentrations at the target site (Thompson, 2014).

To enhance the therapeutic outcomes of diloxanide furoate, innovative drug delivery systems are being explored. Among these, nanosponges have emerged as a promising technology. Nanosponges are hypercrosslinked polymeric structures that can encapsulate a wide range of drugs, providing controlled release and improved solubility (Tiwari et al., 2017). These nanocarriers can significantly enhance the bioavailability of poorly soluble drugs by increasing their solubility and enabling targeted delivery to specific sites in the gastrointestinal tract, such as the colon (Kumar et al., 2019).

The colon-targeting feature is particularly relevant for amoebiasis treatment, as the primary action of diloxanide furoate needs to occur in the lower gastrointestinal tract. By employing biodegradable polymers for nanosponges, it is possible to achieve a controlled release of the drug, maximizing therapeutic effectiveness while minimizing systemic side effects (Bhatt et al., 2020).

This study aims to formulate and characterize diloxanide furoate-loaded colon-targeting nanosponges to enhance drug delivery specifically to the colon, thereby improving the overall treatment of amoebiasis.

MATERIAL AND METHODS:

Material

The formulation of colon-targeting nanosponges for diloxanide furoate utilized a variety of chemicals sourced from reputable suppliers. The active pharmaceutical ingredient, diloxanide furoate, was obtained as a gift sample from Bioplus Life Science in Bangalore. Poly-methyl-methacrylate (PMMA) and Eudragit S-100, both crucial for creating the nanosponges, were sourced from Research Lab Fine Chem Industries and Evonik Industries, respectively. Dibutyl phthalate, which serves as a plasticizer, was procured from Loba Chemie Pvt Ltd. Solvents including ethanol, dichloromethane, methanol, and chloroform, were acquired from Qualigens Fine Chemicals. Additionally, disodium hydrogen phosphate, dipotassium hydrogen orthophosphate, and sodium chloride were sourced from S. D. Fine Chem Ltd., and were used to maintain the necessary pH and ionic strength during the preparation process. These materials collectively facilitated the successful development of the targeted delivery system.

Methods

Formulation Development of Nanosponges

Diloxanide furoate nanosponges were prepared by different proportions of Eudragit S-100, polyvinyl alcohol and Pluronic F68 by emulsion solvent diffusion technique (Shameem *et al.*, 2020). The disperse phase consisting of 100 mg Diloxanide furoate and specified quantity of Eudragit S-100 (Table 6.4) dissolved in 30 mL of dichloromethane was slowly added to a definite amount of PVA in 100 mL of aqueous continuous phase. The mixture was stirred at 1000 rpm on a magnetic stirrer for two hours. The formed Diloxanide furoate nanosponges were collected by vacuum filtration and dried in an oven at 40ºC for 24 hrs.

Table 1: Composition of Diloxanide furoate nanosponges

Ingredients	F1	F2	F3	F4	F5	F6
Diloxanide furoate (mg)	250	250	250	250	250	250
Polyvinyl alcohol (mg)	200	300	400	500	600	800
Eudragit S-100 (mg)	100	150	200	250	300	350
Pluronic F68 (mg)	100	100	100	100	100	100
Dichloromethane	15	15	15	15	15	15
Distilled water (ml)	100	100	100	100	100	100

Characterization of Nanosponges

Percentage yield

The Diloxanide furoate nanosponges obtained after drying was weighed. Percentage yield value was calculated as follows:

% yield = Weight of nanosponges×100/Total solids weight

Entrapment efficiency

UV spectrophotometric method was used to estimate entrapment efficiency of Diloxanide furoate nanosponges (Waghmare *et al.*, 2017). A calibration curve was plotted for Diloxanide furoate in pH 7.2 phosphate buffer in the range of 5-25 µg/mL (Beer's Lambert's range) at 256nm. A good linear relationship was observed between the concentration of Diloxanide furoate and its absorbance (r^2=0.999, m=0.020, n=3). 10 mg of Diloxanide furoate nanosponges of each batch were selected, powdered in a mortar and placed in 10 mL of pH 7.2 phosphate buffer. Diloxanide furoate was extracted by centrifuging at 1000 rpm for 30 min, filtered and analyzed concentration from calibration curve data after necessary dilution. Percentage entrapment was calculated as follows:

% Entrapment efficiency= Actual drug

Particle size, polydispersity index

Average particles size, polydispersity index (PDI) of prepared nanosponges was determined using zetasizer (DTS were 4.10, Horriba instrument, India). The nanosponges formulation was diluted with deionized water (1:9 v/v) and analysed for average size and PDI (Richhariya *et al.*, 2015).

Shape and surface morphology

The shape and surface morphology of the nanospongess were investigated using scanning electron microscopy (IISER, Bhopal). The nanospongess were fixed on supports with carbon-glue, and coated with gold using a gold sputter module in a high-vacuum evaporator. Samples were then observed with the Scanning Electron Microscope at 10 kV.

***In vitro* drug release from nanosponges**

Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition. It is a dynamic property that changes with time and explains the process by which a homogenous mixture of a solid or a liquid can be obtained in a solvent. The test determines the time required for formulation to release percentage of drug under specified conditions (Patil *et al.*, 2017).

Dissolution Parameters

Medium	900ml, pH 7.2 Phosphate Buffer
Apparatus	Paddle (USP-II)
RPM	55
Temperature	37^0C±0.5
Time Points	0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hrs.

Procedure: For the oral dosage forms the *in vitro* dissolution study must be conducted in the dissolution medium which simulate the in-vivo conditions (actual physiological conditions). The *in vitro* drug release studies for the prepared formulation were conducted for a period of 12 hrs using an Labindia DS 8000 model dissolution tester USP Type-2 apparatus (rotating paddle) set at 100 rpm and a temperature of 37± 0.5°C formulation was placed in the 900ml of the medium. At specified intervals 5ml samples were withdrawn from the dissolution medium and replaced with fresh medium to keep the volume constant. The absorbance of the sample solution was analyzed at 256nm for the presence of model drug, using a UV-visible spectrophotometer.

Mathematical treatment of *in-vitro* release data:

The quantitative analysis of the values obtained in dissolution/release tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used.

RESULTS AND DISCUSSION:

The development of diloxanide furoate-loaded nanosponges aimed to enhance the drug's therapeutic efficacy against amoebiasis by enabling targeted delivery to the colon. The percentage yield of various formulations (Table 2) ranged from 68.98% to 84.45%, with formulation F3 showing the highest yield, indicating optimal processing conditions. This is crucial, as a higher yield often correlates with better scalability and cost-effectiveness in industrial applications.

Entrapment efficiency is a significant parameter in drug delivery systems, reflecting the ability of the nanosponges to encapsulate the drug effectively. As shown in Table 3, formulation F3 again exhibited the highest entrapment efficiency at 82.23%, which suggests that the formulation's composition and preparation method effectively retained diloxanide furoate within the nanosponges.

Particle size and zeta potential measurements are vital for understanding the stability and distribution of the nanosponges. The mean particle size (Figure 1) provides insights into the formulation's ability to permeate biological membranes, while zeta potential (Figure 2) indicates the stability of the nanoparticles in suspension. An optimal zeta potential ensures reduced aggregation, leading to enhanced bioavailability.

In vitro drug release studies (Table 4) demonstrated that nanosponges significantly improved the release profile of diloxanide furoate compared to the plain drug. The initial burst release observed for nanosponges at 0.5 hours (24.45%) suggests rapid drug availability, which is beneficial for quick therapeutic action. The sustained release up to 12 hours (98.74%) indicates a potential for prolonged action, which can lead to improved patient compliance and effectiveness in treating amoebiasis.

The regression analysis (Table 5) indicates that the drug release kinetics of formulation F3 followed the Korsmeyer-Peppas model with an R^2 value of 0.993, suggesting a diffusion-controlled release mechanism. This controlled release is advantageous for targeted therapy, particularly in the colon, minimizing systemic side effects and maximizing localized drug action.

Table 2: Percentage yield for different formulation

Formulation	Percentage Yield*
F1	70.32±0.25
F2	68.98±0.36
F3	84.45±0.14
F4	73.35±0.22
F5	69.98±0.24
F6	74.45±0.32

Table 3: Entrapment Efficiency for Different Formulation

Formulation	Entrapment Efficiency of prepared nanosponges
F1	69.98±0.35
F2	67.74±0.22
F3	82.23±0.14
F4	72.25±0.20
F5	68.85±0.35
F6	72.25±0.12

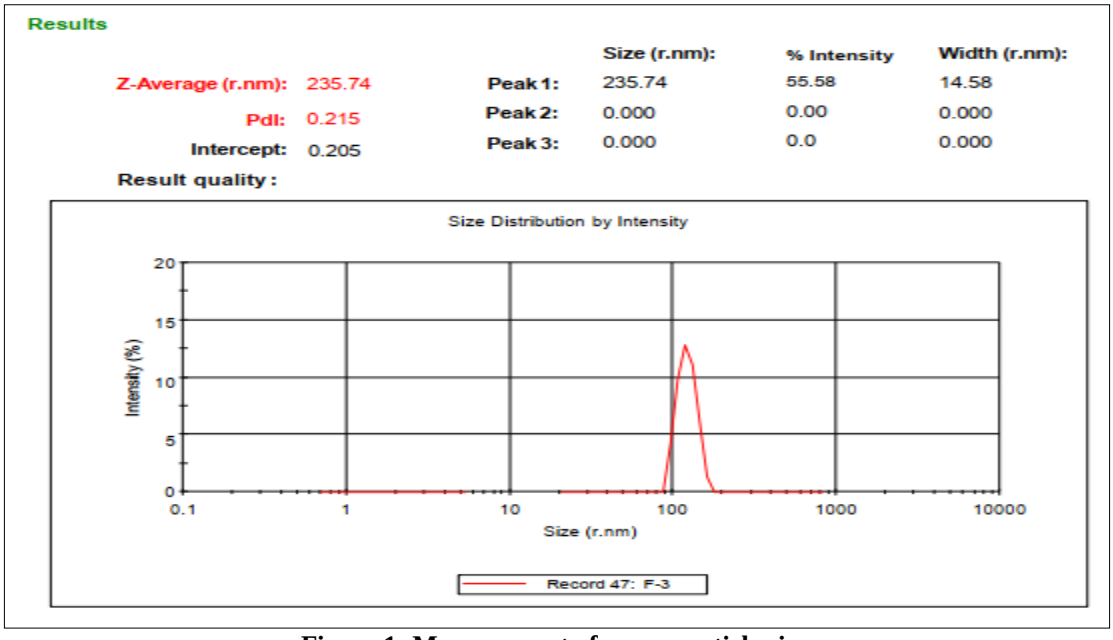

Figure 1: Measurement of mean particle size

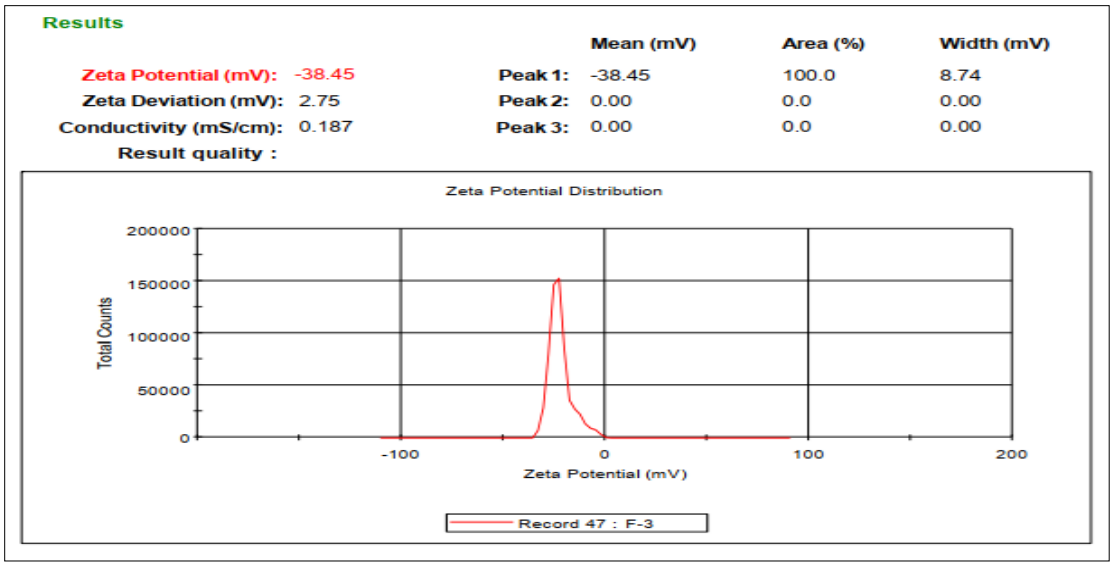

Figure 2: Graph of zeta potential

Table 4: *In vitro* drug release study of Diloxanide furoate loaded nanosponges

S. No.	Time (hrs.)	Plain Drug	Nanosponges
1.	0.5	8.95	24.45
2.	1	16.65	32.25
3.	1.5	32.25	39.98
4.	2	49.98	46.65
5.	3	-	55.58
6.	4	-	68.87
7.	6	-	75.45
8.	8	-	86.66
9.	12	-	98.74

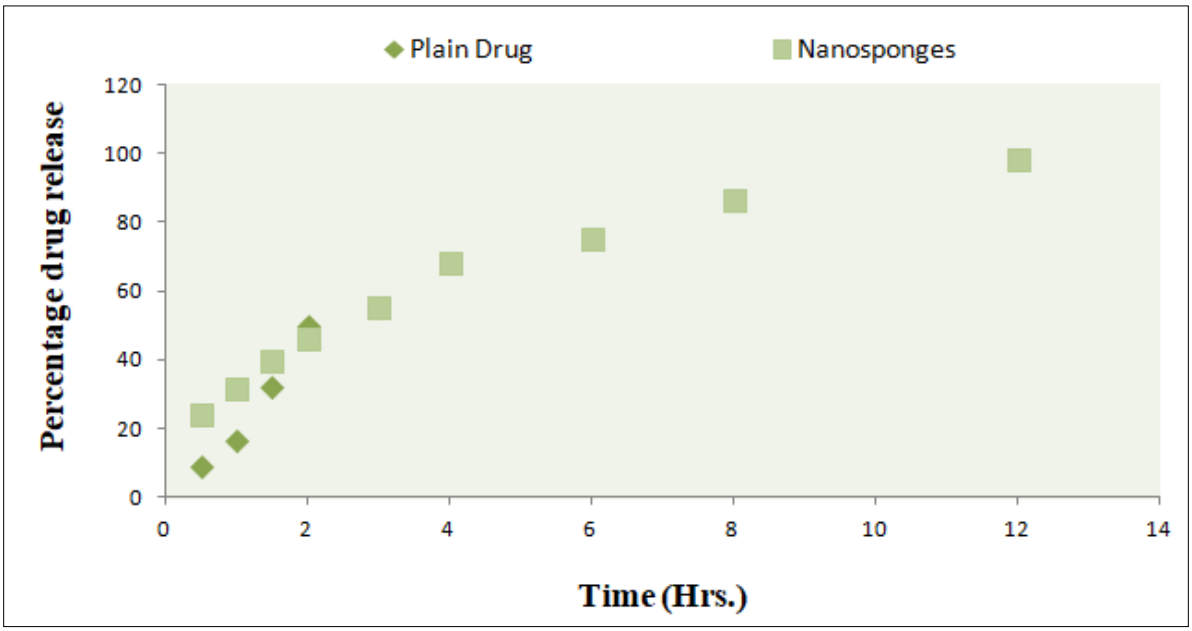

Figure 7.9: Graph of *In vitro* drug release study

Table 5: Regression analysis data of Diloxanide furoate loaded nanosponges

Batch	Zero Order	First Order	Higuchi	Korsmeyer Peppas
	R^2	R^2	R^2	R^2
F3	0.9138	0.9345	0.9857	0.993

CONCLUSION:

The formulation of diloxanide furoate-loaded nanosponges represents a significant advancement in the targeted treatment of amoebiasis. The optimized formulation, particularly F3, demonstrated superior percentage yield and entrapment efficiency, highlighting the effectiveness of using poly-methyl-methacrylate and Eudragit S-100 in creating a viable drug delivery system. In vitro drug release studies confirmed a sustained release profile, with nearly complete drug release achieved within 12 hours, suggesting enhanced bioavailability and therapeutic effectiveness. These findings indicate that nanosponges can effectively deliver diloxanide furoate to the colon, potentially improving treatment outcomes for patients suffering from amoebiasis. Future studies may focus on in vivo evaluations and further optimization to ensure clinical applicability.

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