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Original Research Article

FORMULATION AND EVALUATION OF ALOIN LOADED MICROSPONGES GEL FOR WOUND HEALING ACTIVITY

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ABSTRACT

The study aimed to develop and evaluate an aloin-loaded microsponges gel for enhanced wound healing activity. Aloin, a potent bioactive compound, was successfully encapsulated in microsponges using the quasi-emulsion solvent diffusion method. The microsponges were characterized for particle size, zeta potential, and entrapment efficiency, with formulation F2 showing optimal properties: a particle size of 498.5 nm, zeta potential of -2.3 mV, and entrapment efficiency of 91.09%. The microsponges were incorporated into a gel base and evaluated for physical appearance, pH, viscosity, and spreadability. The *in vitro* release study indicated a sustained release pattern following Higuchi kinetics, with 97.05% drug release over 9 hours. The developed aloin-loaded microsponges gel exhibited excellent wound healing potential, making it a promising candidate for future clinical applications.

Keywords: Aloin, microsponges, wound healing, sustained release, in vitro release, Higuchi drug delivery system.

INTRODUCTION

Aloin, a bioactive compound found in Aloe vera, has gained attention in the field of wound healing due to its anti-inflammatory, antimicrobial, and wound-healing properties. It belongs to the anthraquinone class of compounds and has been shown to promote wound contraction and accelerate the healing process (Dat *et al.,* 2020).

Aloin has demonstrated several mechanisms that contribute to its wound healing effects, including the stimulation of fibroblast proliferation, collagen synthesis, and inhibition of inflammatory cytokines. These properties make aloin a promising candidate for incorporation into wound healing formulations (Yimam *et al.,* 2017; Maenthaisong *et al.,* 2007).

Microsponges are highly porous, cross-linked, polymeric microspheres that can entrap a wide range of active pharmaceutical ingredients. They are beneficial for controlled release, protection of the active ingredient, and improving skin adherence and comfort (Gohel *et al.,* 2017).

Gels are semisolid systems consisting of a liquid phase (water or hydroalcoholic) gelled by a polymeric network. They provide an excellent platform for topical drug delivery due to ease of application, good bioadhesion, and hydration of the wound bed (Rathore *et al.,* 2018).

The objective of this study is to formulate and evaluate aloin-loaded microsponges gel for wound healing activity. The microsponges will be used to enhance the stability and controlled release of aloin, while the gel base

will provide a suitable vehicle for topical application. The formulation will be evaluated for its physicochemical properties, drug release profile, and wound healing efficacy.

MATERIALS AND METHODS

Material

The formulation of aloin-loaded microsponges gel for wound healing involved the use of several key chemicals. Aloin, obtained from FDC in Mumbai, India, was the active ingredient chosen for its wound healing properties. Methanol from Rankem and ethanol from Merck India Ltd., Mumbai, India, were used for extraction and formulation purposes, respectively. Acetonitrile, also from Merck India Ltd., Mumbai, India, served as a solvent for the HPLC analysis to quantify aloin content. For the microsponges, ethyl cellulose and PVA (Polyvinyl alcohol) from Sigma Aldrich were utilized as polymeric excipients. The gel was formulated using Carbopol 934 from Sulab as the gelling agent, with pH adjustment done using Triethanolamine sourced from Loba Chemie. Propylene glycol and methyl paraben, both from Merck, were employed as a solubilizer and preservative, respectively, in the gel formulation.

Pre-formulation studies

Organoleptic Properties

Organoleptic properties of Aloin were observed by visual observation. Aloin's organoleptic properties, such as color, odor, and condition, were investigated.

Solubility study

Qualitative solubility of aloin in various solvents was measured using USP NF, 2007. Approximately 1 mg of Aloin was weighed and transferred into a 10 ml test tube and dissolved in the respective solvents (1 ml each of methanol, ethanol, acetonitrile, and water) (Jain and Verma, 2020).

Melting Point

Melting point was analyzed by open Capillary method using Thiele's tube. Few quantity of the Aloin was placed in a thin walled capillary tube 10-15 mm long, about 1mm inside diameter, and closed at one end. Liquid paraffin oil was filled in the thieles tube and placed in the contact of flame. The capillary was suspended into the thiele's tube and heat the sample slowly; thermometer was attached to check the temperature. The temperature at which the sample starts to melt was taken as the melting point of the sample (Kahar and Bagre, 2024).

Determination of Lambda max and calibration curve

A stock standard solution containing 1 mg/mL of Aloin was prepared in methanol. Working standard solution equivalent to 100 µg/mL of Aloin was prepared by appropriate dilution of stock solution with the same solvent. The solution was scanned in the range of 200 – 400 nm UV spectrum using shimadzu 1700 double beam spectrophotometer (Kumbhar and Salunkhe, 2013).

Standard calibration curve

100 mg of Aloin was accurately weighted into 100 ml volumetric flask, dissolved in Methanol and volume was made up with same solvent. Pipette 1ml of this solution into another 10 ml volumetric flask and the volume was made with Methanol and marked as Stock. The resultant solution is scanned in

the range of (200-400 nm) by UV Spectrophotometer to get absorption maximum (λ max).

Preparation of calibration curve

The prepared stock solution was further diluted with solvent to get working standard solution of 40, 50, 60, 70, 80, 90 and 100 µg/ml of Aloin to construct Beer's law plot for the pure drug, the absorbance was measured, against solvent as blank. The standard graph was plotted using the drug concentration (X-axis) and absorbance (Y-axis) in the range of 40-100 µg/ml (Behera *et al.,* 2012).

Fourier transmission Infra-Red Spectroscopy

FT-IR spectrum of Drug was recorded over the range of 4000 to 400 cm−1 by KBr pellet method using a FT-IR spectrophotometer. The KBr disc was prepared using 1 mg of each Drug in 100 mg of spectroscopic grade KBr which has been dried using IR lamp. Both KBr and drug was mixed and subjected to hydraulic pressure to form disc. This disc was placed in FT-IR chamber. Infrared spectrum was recorded in the 4000 - 400 cm-1 region (Kahar and Bagre, 2024).

Formulation of Micro sponges

The micro sponges containing aloin were fabricated by quasi-emulsion solvent diffusion method using an inner phase comprising Eudragit RS-100 and dibutyl phthalate (1%w/v) dissolved in 10 ml of ethanol: dichloromethane (1:1). Dibutyl phthalate was added to improve the plasticity of the polymer. Further aloin was put in and dissolved through ultrasonication at 35°C. This mixture was then poured into an aqueous solution of PVA (outer phase) with stirring rate 500 rpm for 60 min. Next on, micro sponges were formed due to the removal of dichloromethane and ethanol from the system by evaporation. Prepared micro sponges were then filtered washed with distilled water and subjected to drying at 40°C for 12 h in hot air oven. Various formulation batches are prepared as per Table (Bhatia and Saini, 2018; Moin *et al.,* 2016).

Evaluation parameter of Micro sponges

Particle size

The particle size analysis of Aloin loaded Micro sponges was performed by using ''Malvern Zetasizer (Malvern Instruments). The sample under investigation was diluted with distilled water (1: 100) and filled in disposable polystyrene cuvette. Measurement of particle size was done based on the dynamic light scattering (DLS) theory (Ahmed *et al.,* 2021).

Zeta potential

The zeta potential was measured for the determination of the movement velocity of the particles in an electric field and the particle charge. In the present work, the Micro sponges was diluted 10 times with distilled water and analyzed by Zetasizer Malvern instruments. All samples were sonicated for 5-10 minutes before zeta potential measurements (Kumar *et al.,* 2018; Penjuri *et al.,* 2014).

Entrapment efficiency

To calculate the entrapment efficiency accurately weighed the quantity of Micro sponges (100 mg) with 5 ml of methanol in a volumetric flask was shaken for 1 min using vortex mixer. The volume was made up to 10

ml. Then the solution was filtered and diluted and the concentration of entrapped Aloin was determined spectrophotometrically (Solunke *et al.,* 2019).

%EE = Initial amount of drug added - Drug amount in supernatant / Initial amount of drug added * 100

Scanning Electron Microscopic (SEM)

The electron beam from a scanning electron microscope was used to attain the morphological features of the Aloin loaded Micro sponges were coated with a thin layer (2–20 nm) of metal(s) such as gold, palladium, or platinum using a sputter coater under vacuum. The pretreatment specimen was then attacked with an electron beam, which resulted in the creation of secondary electrons known as augers. From this interaction between the electron beam and the specimen's atoms, only the electrons dispersed at 90° were picked and further processed based on Rutherford and Kramer's Law to obtain images of surface topography (Anwer *et al.,* 2019).

Formulation of Micro sponges loaded Gel

Initially, carbopol-934 was immersed in 50 mL of warm water (A) for 2 hours and homogeneously distributed using a magnetic stirrer at 600 rpm. In a separate container, carboxymethyl cellulose and methyl paraben were mixed with 50 ml of warm water (B) and agitated continuously to form a hard gel. Both mixes A and B were stirred continuously. Then tri-ethanol amine (Drop wise) was added to neutralize the pH and Micro sponges of optimized formulation were incorporated into the dispersion to obtained Gel. At this stage, permeation enhancer (Propylene glycol) was added. The final dispersion was agitated until smooth gel was formed without lumps (Abbas *et al.,* 2019; Silpa *et al.,* 2021).

Characterization of microsponges loaded gel

Physical appearance

The prepared Gel formulation was evaluated for appearance, Color, Odor, and homogeneity by visual observation (Kumar and Eswaraiah, 2020).

pH

pH of the formulation was determined by using Digital pH meter (EI). The meter was allowed to stabilize as needed before being calibrated. Rinse the probe with de-ionized or distilled water and blot it dry with lint-free tissue paper. Immerse the sensor tip of the probe in the sample and record the pH reading. Rinse the probe, blot it dry, and repeat step 2 with a fresh sample. The two readings should agree to within the accuracy limits of the meter. The samples were examined in triplicate. If tiny differences in pH were noticed, it was corrected to skin pH by adding tri-ethanolamine solution drop by drop (McGlynn, 2003).

Viscosity

The viscosity of the gel formulations was determined using Brookfield viscometer with spindle no. 61 at 100 rpm at the temperature of 25^0C (Monica and Gautami, 2014).

Spreadability

An ideal topical gel should have a high spreading coefficient when applied or rubbed over the skin's surface. This was assessed by placing approximately 1g of formulation on a glass slide. Another glass slide of the same length was placed above that, and a mass of

50 mg was put on the glass slide so that the gel gets sandwiched between the two glass slides and spreads at a certain distance. The time taken for the gel to travel the distance from the place of its position was noted down. Spreadability was determined by the following formula.

S= M*L/T

Where, S-Spreadability, g.cm/s M-Weight put on the upper glass L-Length of glass slide T-Time for spreading gel in sec (Sandeep, 2020).

In-vitro drug release study

The *in-vitro* drug release study of Aloin loaded Micro sponges formulation was studied by dialysis bag diffusion method. Aloin loaded Micro sponges were dispersed into dialysis bag and the dialysis bag was then kept in a beaker containing 100 ml of pH 7.4 phosphate buffer. The beaker was placed over a magnetic stirrer and the temperature of the assembly was maintained at 37 ± 2 °C throughout the experiment. During the experiment rpm was maintained at 100 rpm. Samples (2 ml) were withdrawn at a definite time intervals and replaced with equal amounts of fresh pH 7.4 phosphate buffers. After suitable dilutions the samples were analyzed using UV–Visible spectrophotometer. To analyze the *in vitro* drug release data various kinetic models were used to describe the release kinetics.

To analyze the *in vitro* release data various kinetic models were use to describe the release kinetics. The zero order rate Eq. (2) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (3) describes the release from system where release rate is concentration dependent. Higuchi described drug release from insoluble matrix as a square root of time dependent process based on Fickian diffusion.

RESULTS AND DISCUSSION

The organoleptic properties of aloin were evaluated to ensure consistency and quality. Aloin was observed to be a yellow-brown, odorless solid powder. These characteristics are crucial as they help in the initial identification and quality control of the raw material. Consistency in color, odor, and physical state indicates the purity and integrity of the aloin sample, which is essential for its therapeutic effectiveness.

The solubility study of aloin was conducted to understand its behavior in various solvents, which is critical for formulating an effective drug delivery system. Aloin was found to be soluble in water and chloroform, and freely soluble in ethanol, methanol, and DMSO. This high solubility in multiple solvents suggests that aloin can be easily incorporated into various pharmaceutical formulations, enhancing its versatility in drug delivery applications.

The melting point of aloin was determined to be 147°C, which is slightly lower but within the reference range of 148°C-150°C. This minor variation can be attributed to experimental conditions and the purity of the sample. The melting point is a key parameter in the characterization of a compound, as it provides insight into its thermal stability and purity. The pH of aloin was measured to be 5.2, which is slightly acidic. The pH of a compound can influence its stability, solubility, and overall compatibility with other formulation components. An acidic pH can also impact the biological activity of

aloin, particularly in wound healing applications, where pH can influence the healing process.

The calibration curve of aloin shows a linear relationship between the concentration and absorbance at 301.0 nm. The absorbance values increase proportionally with the concentration of aloin, indicating good linearity. The mean absorbance is 0.130 with a standard deviation of 0.0375, resulting in a %RSD of 28.84. The high %RSD indicates variability, which could be due to experimental conditions or instrumental precision. This calibration curve is essential for quantifying aloin in various formulations, ensuring accurate dosing and consistency in therapeutic applications.

The particle size of the prepared microsponges formulations varies between 498.5 nm to 750.2 nm. The formulation code MS2 has the smallest particle size at 498.5 nm, while MS5 has the largest at 750.2 nm. Smaller particle sizes are generally preferred for topical applications as they can provide better penetration and a more uniform distribution of the active ingredient. The variations in particle size among different formulations can impact the drug release profile, stability, and overall effectiveness of the wound healing gel.

The zeta potential of the microsponges formulations ranges from -0.9 mV to -4.1 mV. Zeta potential is a measure of the surface charge of particles and is indicative of the stability of colloidal dispersions. A higher magnitude of zeta potential, whether positive or negative, typically implies greater stability due to electrostatic repulsion preventing aggregation. The relatively low zeta potential values suggest that the formulations might be prone to aggregation over time. MS3, with a zeta potential of -4.1 mV, is likely to have better stability compared to MS1, which has the lowest value of -0.9 mV.

The physical appearance of the microsponges loaded gel is characterized by a brownish color, odorless nature, transparent appearance, and homogeneity. These properties are indicative of a well-formulated gel that is aesthetically acceptable for topical application. The pH of the microsponges loaded gel is 6.4, which is within the acceptable range for topical formulations, ensuring it is skin-friendly and unlikely to cause irritation. The viscosity of 6854 cps indicates a thick, yet spreadable consistency, which is ideal for a topical gel, providing adequate adhesion to the skin.

The release kinetics study of the optimized formulation (F2) indicates a sustained drug release profile, with an initial rapid release of 15.12% within the first hour. This is followed by a gradual increase in drug release, reaching 36.45% by the second hour, 57.14% by the fourth hour, and 77.20% by the sixth hour. The release reaches 97.05% by the ninth hour, indicating near-complete drug release.

The release data fit best with the Higuchi model (R2=0.969R2=0.969), suggesting a diffusion-controlled mechanism. This sustained release profile is beneficial for wound healing, ensuring continuous drug availability and reducing the need for frequent reapplication, thereby potentially improving therapeutic outcomes and patient compliance.

Table 1: Composition of formulation

S. No.	Ingredients	MS 1	MS 2	MS 3	MS 4	MS 5
1.	Drug (Aloin) mg	100	100	100	100	100
2.	Eudragit RS 100 (mg)	100	200	300	400	500
3.	Poly vinyl alcohol (PVA) (%)	0.5	0.4	0.3	0.2	0.1
4.	Dibutyl phthalate (%)	1	1	1	1	1
5.	Ethanol:Dichloromethane (ml) (1:1)	10	10	10	10	10
6.	Distilled water (ml)	100	100	100	100	100
7.	Stirring time (min.)	60	60	60	60	60

Table 2: Composition of gel formulation

S. No.	Excipients	Quantity (gm)
1.	Carbopol 934	1.00 gm
2.	Carboxymethyl cellulose	1.00 gm
3.	Propylene glycol	0.5 ml
4.	Methyl paraben	0.2 ml
5.	Micro sponges	1.0 gm
6.	Tri-ethanolamine	q.s
7.	Water	100 ml

Table 3: Organoleptic properties of Aloin

Drug	Organoleptic properties	Observation
Aloin	Color	Yellow-brown
	Odor	Odorless
	Appearance	Powder
	State	Solid powder

Table 4: Solubility study of Aloin

Drug	Solvents	Observation/Inference
Aloin	Water	Soluble
	Ethanol	Freely soluble
	Methanol	Freely soluble
	Chloroform	Soluble
	DMSO	Freely soluble

Table 5: Melting point of Aloin

Drug	Observed	Reference
Aloin	147°C	148°C-150°C

Table 6: pH of Aloin

S. No.	Drugs	Observed
1.	Aloin	5.2

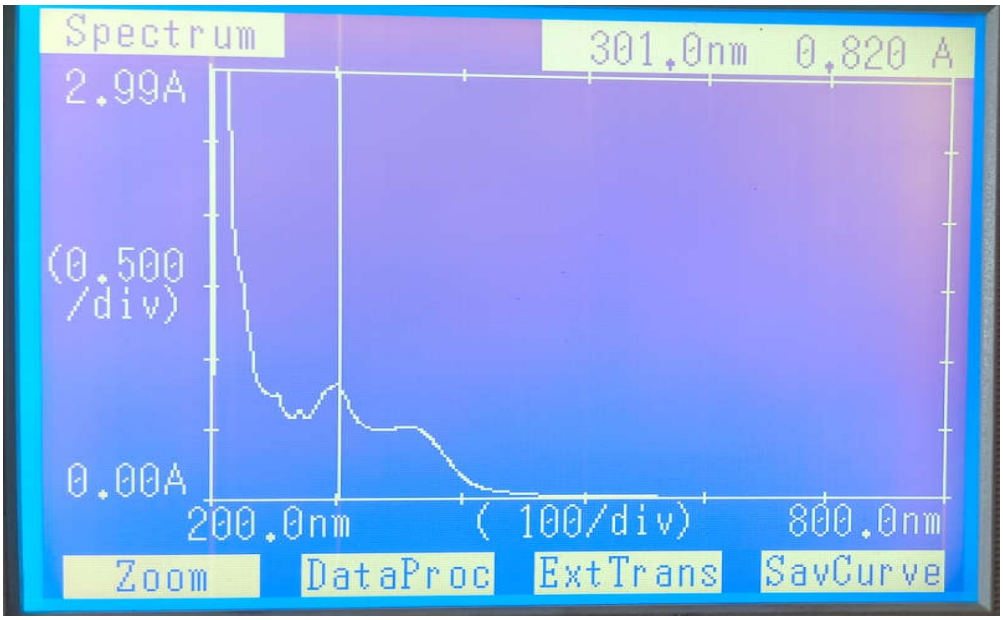


Figure 1: Lambda max of Aloin

Table 7: Calibration curve of Aloin

Concentration (µg/ml)	Absorbance (301.0 nm)
40	0.087
50	0.098
60	0.108
70	0.123
80	0.140
90	0.163
100	0.192
Mean	0.130
SD	0.0375
%RSD	28.84

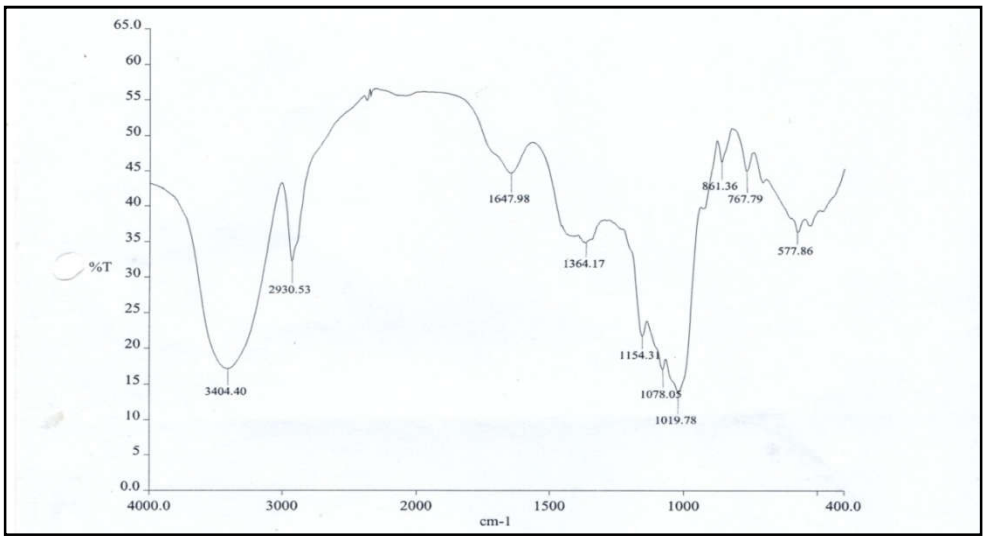
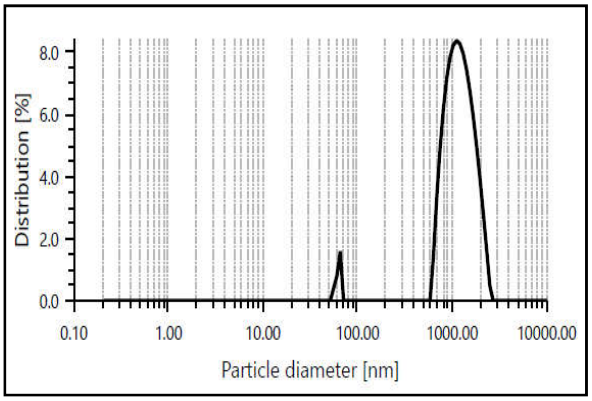
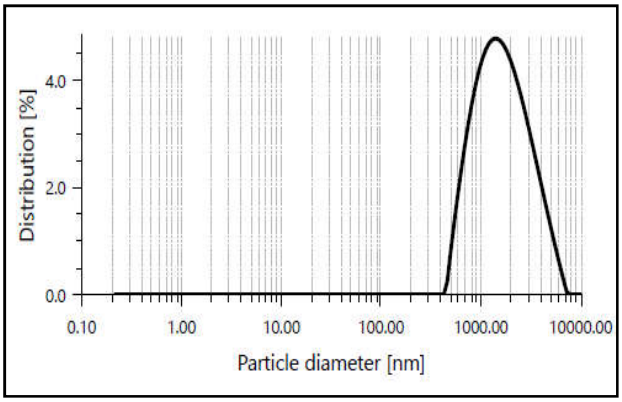


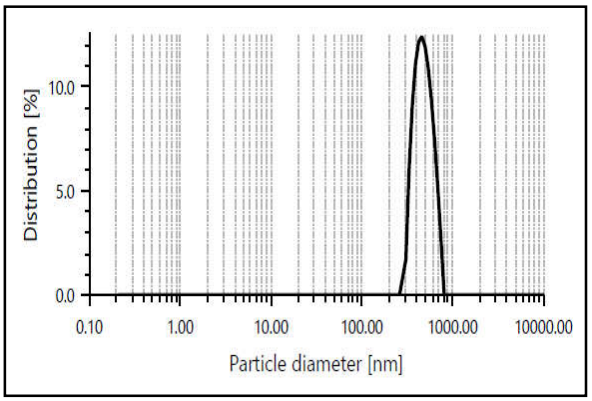
Figure 2: FT-IR Spectra of Aloin



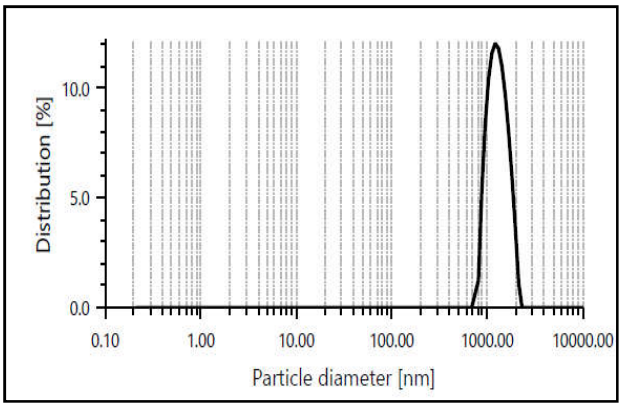
Particle size (F1)



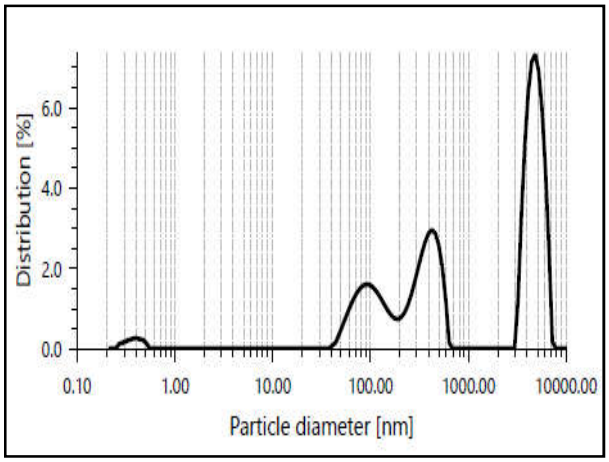
Particle size (F2)



Particle size (F3)



Particle size (F4)



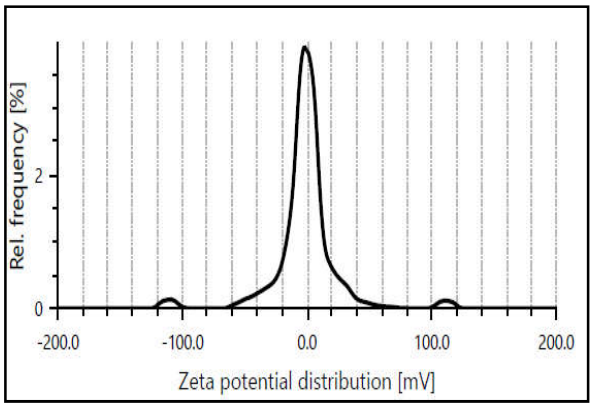
Particle size (F5)

Figure 3: Figure of Particle Size of microsponges formulation F1 To F5

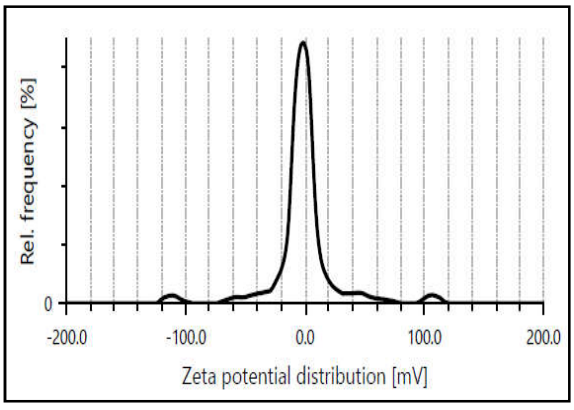
Table 8: Results of particle size of prepared microsponges formulation

S. No	Formulation code	Particle size (nm)
1.	MS1	687.1nm
2.	MS2	498.5 nm
3.	MS3	575.9 nm
4.	MS4	644.2 nm
5.	MS5	750.2 nm

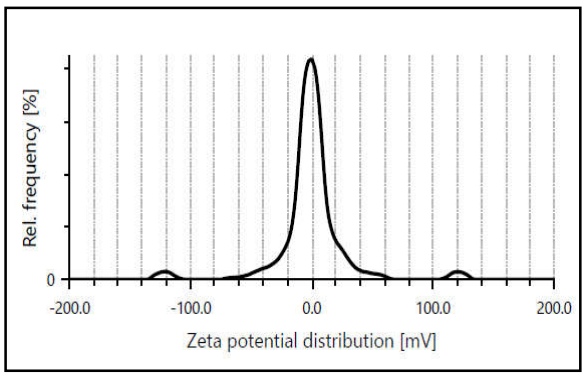
7.8.2 Zeta potential



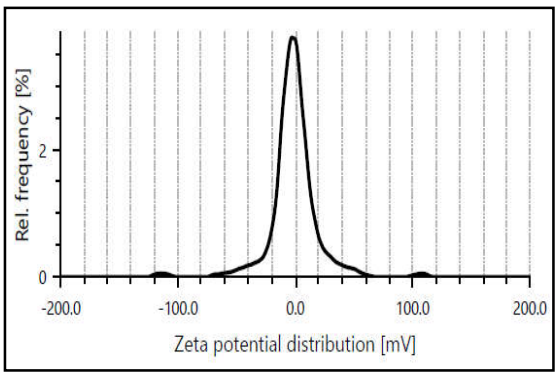
Zeta potential (F1)



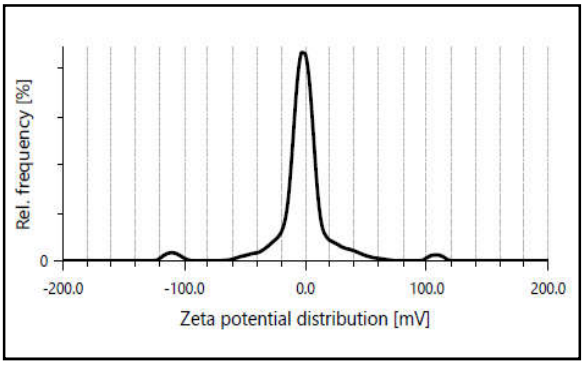
Zeta potential (F2)



Zeta potential (F3)



Zeta potential (F4)



Zeta potential (F5)

Figure 4: Zeta potential of particle Size of microsponges formulation F1 To F5

Table 9: Results of Zeta potential of prepared microsponges formulation

S. No	Formulation Code	Zeta potential
1.	MS1	-0.9 mV
2.	**MS2**	**-2.3 mV**
3.	MS3	-4.1 mV
4.	MS4	-2.9 mV
5.	MS5	-3.7 mV

Table 10: Results of Entrapment efficacy of microsponges formulation F1 To F5

S. No.	Formulations (F1-F5)	Entrapment efficacy (%)
1.	MS1	89.39
2.	**MS2**	**91.09**
3.	MS3	86.32
4.	MS4	78.81
5.	MS5	70.20

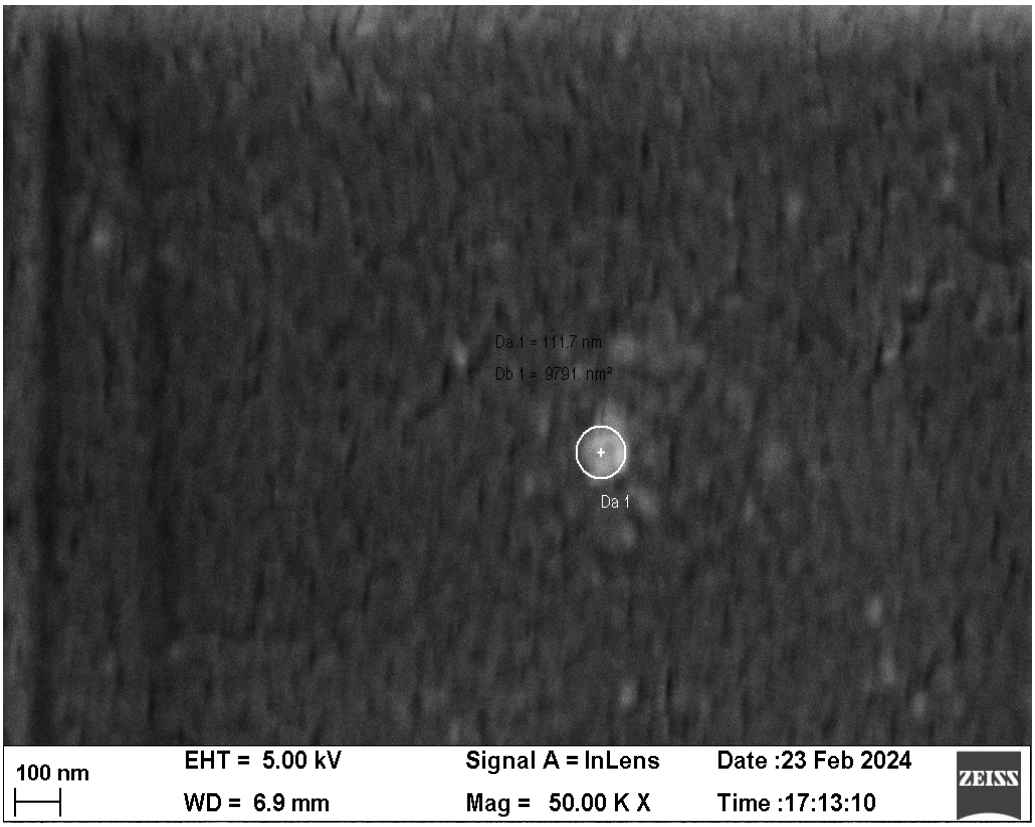


Figure 5: Scanning electron microscope of optimized microsponges formulation F1

Table 11: Results of Physical appearance of microsponges loaded gel

S. No	Parameter	Result
1.	Color	Brownish
2.	Odor	Odorless
3.	Appearance	Transparent
4.	Homogeneity	Homogeneous

Table 12: Results of pH, Viscosity and Spreadability

S. No.	Formulation	pH	Viscosity (cps)	Spreadability (g.cm/s)
1.	Gel	6.4	6854±0.34	12.97

Table 13: Release kinetics study of optimized (F2) formulation

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cum. % drug remaining	log time	log Cum. % drug released
0	0	100	0.000	2.000	0.000	0.000
1	15.12	84.88	1.000	1.929	0.000	1.180
2	36.45	63.55	1.414	1.803	0.301	1.562
3	43.77	56.23	1.732	1.750	0.477	1.641
4	57.14	42.86	2.000	1.632	0.602	1.757
5	66.32	33.68	2.236	1.527	0.699	1.822
6	77.2	22.8	2.449	1.358	0.778	1.888
7	82.75	17.25	2.646	1.237	0.845	1.918
9	97.05	2.95	3.000	0.470	0.954	1.987

Table 14: Correlation value (R^2 value)

Formulation	Model	Kinetic parameter values
Gel	Zero Order	$R^2 = 0.966$
	First Order	$R^2 = 0.824$
	Higuchi	$R^2 = 0.969$
	Korsmeyerpeppas	$R^2 = 0.688$

CONCLUSION

The study successfully developed and evaluated aloin-loaded microsponges gel for wound healing. The optimized formulation (F2) demonstrated excellent physical characteristics, including desirable particle size, zeta potential, and entrapment efficiency. The sustained release profile, fitting well with the Higuchi model, indicates a diffusion-controlled mechanism, ensuring prolonged drug release. This formulation has potential to improve therapeutic efficacy and patient compliance in wound healing applications.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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