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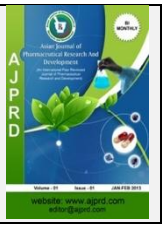

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Research Article

Formulation and Characterization of Curcumin-Loaded Aquasomes for Topical Fungal Treatment

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A B S T R A C T

The topical treatment of fungal infections remains a significant challenge due to the limited bioavailability of many therapeutic agents when applied on the skin. Curcumin, a naturally occurring polyphenolic compound derived from *Curcuma longa*, has demonstrated notable antifungal, anti-inflammatory, and antioxidant properties, making it an ideal candidate for the treatment of skin infections. However, its hydrophobic nature and poor solubility in water limit its therapeutic efficacy. To address these limitations, this study aimed to develop and evaluate curcumin-loaded aquasomes as a novel drug delivery system for topical fungal treatment. Aquasomes are a type of nanoparticulate carrier composed of a stabilizer, such as gelatin, and a surfactant, such as Tween 80, which are cross-linked with glutaraldehyde to form a stable, nanostructured system that encapsulates the drug. The curcumin-loaded aquasomes were prepared using the solvent evaporation method, followed by characterization of vesicle size, surface charge, entrapment efficiency, in vitro drug release, and release kinetics. The results showed that the optimized formulation (F3) had a vesicle size of 125.65 nm, a surface charge of 36.85 mV, and an entrapment efficiency of 82.23%. The in vitro release studies revealed a sustained release of curcumin over 12 hours, with 98.12% of the drug being released. The release data followed Korsmeyer-Peppas kinetics, indicating a diffusion-controlled release mechanism. The TEM analysis confirmed the formation of spherical nanoparticles with a uniform size distribution. The developed curcumin-loaded aquasomes exhibited promising characteristics, including enhanced solubility, controlled release, and high stability, making them a potential candidate for topical fungal treatment. These findings suggest that aquasome-based formulations can significantly improve the therapeutic efficacy of curcumin, offering a novel approach for the treatment of fungal skin infections.

Keywords: Curcumin, Aquasomes, Drug Delivery System, Topical Fungal Treatment, Nanoparticles.

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INTRODUCTION

Fungal infections represent a significant public health concern, affecting millions of people worldwide, especially in immunocompromised individuals. Conventional antifungal therapies, while effective, often face limitations such as poor bioavailability, systemic side effects, and patient non-compliance. To address these challenges, targeted drug delivery systems that enhance the therapeutic efficiency of antifungal agents are being actively developed. One promising approach is the use of nanocarriers for drug delivery, particularly for topical applications. Among these, aquasomes have garnered attention as versatile drug delivery vehicles for various dermatological conditions, including fungal infections.

Aquasomes are a class of nanocarriers composed of a core structure made of colloidal particles and a coating that ensures the sustained release of the active ingredient at the target site. These nanocarriers offer advantages over conventional delivery systems, including increased stability, controlled drug release, and the ability to incorporate both lipophilic and hydrophilic drugs. Curcumin, a bioactive polyphenolic compound derived from *Curcuma longa* (turmeric), has shown potent antifungal, anti-inflammatory, and antioxidant properties, making it a candidate for treatment of fungal infections, especially when delivered via nanocarrier systems like aquasomes.

Curcumin has been shown to possess antimicrobial activity against various pathogenic fungi, including *Candida*

albicans, *Aspergillus niger*, and *Trichophyton rubrum*. However, its clinical application has been hindered by its poor water solubility, low bioavailability, and rapid metabolism. These challenges can be overcome by using nanocarriers such as aquasomes that can encapsulate curcumin and improve its solubility, stability, and controlled release at the site of infection.

Aquasomes are unique in their ability to provide a protective environment for the drug, enhancing its penetration through the skin, particularly for topical antifungal treatment. The surface modification of aquasomes with polymers or ligands can further improve their mucoadhesive properties, facilitating prolonged contact with the skin and allowing for localized drug delivery. This property is particularly valuable in the case of fungal infections, where sustained drug exposure at the site of infection can increase therapeutic efficacy and minimize the need for systemic administration, reducing the risk of side effects.

In the current study, we aim to formulate and characterize curcumin-loaded aquasomes for topical fungal treatment. We hypothesize that curcumin encapsulated within aquasomes will demonstrate enhanced antifungal efficacy, improved skin penetration, and controlled release compared to conventional curcumin formulations. The study will include the preparation of aquasomes, followed by detailed characterization of their physicochemical properties, drug encapsulation efficiency, in-vitro drug release, and antifungal activity against common dermatophytes.

MATERIAL AND METHODS

MATERIAL

For the preparation of curcumin-loaded aquasomes, high-quality chemicals were sourced from reputable suppliers. Curcumin was obtained from PhytodrugPvt. Ltd. (Bhopal), while Tween 80, a surfactant, was sourced from Ash Chemie India (Thane). Gelatin and glutaraldehyde, essential for nanoparticle formation and stabilization, were supplied by S. D. Fine Chem. Ltd. (Mumbai). Sodium chloride was used to adjust osmolarity, and solvents like methanol, ethanol, and chloroform from Qualigens Fine Chemicals (Mumbai) were used for purification. Hydrochloric acid and sodium hydroxide (Qualigens Fine Chemicals) were used for pH adjustments to optimize formulation stability.

Methods Formulation of Curcumin loaded Aquasomes

The formulation of curcumin-loaded aquasomes begins by preparing a drug solution, where curcumin is dissolved in a water or water-alcohol mixture to create a homogeneous solution. Next, a stabilizer solution is prepared by dissolving gelatin in water, with gentle heating if necessary. A surfactant solution is then made by dissolving Tween 80 (1-3%) in water, followed by the preparation of a cross-linking agent solution using 1% glutaraldehyde in water. To form aquasomes, the drug solution is added to the stabilizer solution under continuous stirring, followed by the incorporation of the surfactant. Finally, the glutaraldehyde solution is added dropwise to cross-link the complex, resulting in the formation of the stable aquasomes (Oviedo et al., 2007).

Table 1: Different Formulation of Aquasomes

Ingredient (%)	F1	F2	F3	F4	F5	F6
Curcumin	0.5	0.5	0.5	0.5	0.5	0.5
Tween 80	0.5	1.0	1.5	2	2.5	3.0
Glutaraldehyde	1	1	1	1	1	1
Gelatin	0.5	1	1.5	0.5	1	1.5
Water (ml)	10	10	10	10	10	10

Characterization and evaluation of Curcumin loaded Aquasomes

Characterize the Aquasomes using various techniques, Surface charge and vesicle size, entrapment efficiency, transmission electron microscopy (TEM), and *in-vitro* diffusion study (Vyas *et al.*, 2008).

Surface charge and vesicle size

The vesicles size and size distribution and surface charge were determined by Dynamic Light Scattering method (DLS) (Malvern Zetamaster, ZEM 5002, Malvern, UK). Zeta potential measurement of the Aquasomes was based on the zeta potential that was calculated according to Helmholtz–Smoluchowsky from their electrophoretic mobility. For measurement of zeta potential, a Zetasizer was used with field strength of 20 V/cm on a large bore measures cell. Samples were diluted with 0.9 % NaCl adjusted to a conductivity of 50 lS/cm (Khopade*et al.*, 2002).

Entrapment efficiency

One milliliter of MIC Aquasomes suspension was centrifuged at 15.000 rpm for 1 h to allow the separation the entrapped drug from the un-entrapped drug. After removal of the supernatant, the sediment was lysed using methanol and then analyzed spectrophotometrically at 428nm using a UV spectrophotometer (Labindia 3000+). The EE% of MIC in the prepared Aquasomes was calculated applying the following equation (Patel *et al.*, 2018):

$$\%\ Entrapment\ Efficiency\ = \frac{Terotical\ drug\ content - Practical\ drug\ content}{\text{Therotical drug content}} \times 100$$

Transmission electron microscopy

Transmission Electron Microscopy (TEM) is a powerful microscopy technique used to observe the ultrastructure of materials at a very high resolution. It allows researchers to visualize the internal structures of samples, such as cells, nanoparticles, and materials, at the nanometer scale. Here is a general outline of the TEM procedure:

Prepare a thin sample of the prepared aquasomes. Mount the prepared sample on a TEM grid, which is a small metal or carbon-coated grid. The sample should be placed in a way that the region of interest is exposed on the grid. Stain the sample with heavy metal stains (e.g., uranyl acetate or lead citrate) to increase contrast and improve image visibility, especially for biological samples. Turn on the TEM instrument and allow it to reach the required vacuum level for optimal imaging (Jain *et al.,* 2012).

Align the electron beam, adjust focus, and calibrate the imaging settings for the specific sample being analyzed. Load the TEM grid with the sample into the TEM column. Use the electron beam to illuminate the sample, which interacts with the sample and forms a transmission image. The transmitted electrons are collected by an electron detector, forming the TEM image on a fluorescent screen or a digital camera.

In vitro drug diffusion study

The dialysis diffusion approach was used to perform *in vitro* drug release of prepared aquasomes utilizing the dissolution test apparatus. The dissolving media was phosphate buffer pH 7.4 (Oviedo *et al.,* 2007). The dialysis technique was carried out utilizing a cellulose acetate dialysis membrane with a molecular weight cutoff of 12,000–14,000 moles. This membrane ensures drug penetration while retaining aquasomes vesicles. Before usage, the membrane was soaked in fake tears for 12 hours. A glass cylinder with a length of 8 cm and a diameter of 1 cm was filled with four ml of aquasomes dispersion, and a dialysis membrane was threaded to the mouth of the cylinder. Each glass cylinder was attached to the shaft of the dissolution apparatus (USP Dissolution tester, Labindia DS 8000) and descended down into a 100 ml beaker containing

50 ml of as dissolution medium without touching the bottom surface of the beaker. The beaker was then placed into vessels of dissolution apparatus that contained about 100 ml of water to keep temperature at 34 ± 0.5°C. The glass cylinders were adjusted to rotate at a constant speed of 20 rpm. One ml of dissolution medium was withdrawn at predetermined time intervals (0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 and 6 h).

To maintain a consistent volume, the samples were changed with new dissolving media. The concentrations of drugs in samples were measured spectrophotometrically at 428nm, the wavelength of the drug.

The release tests were done in triplicates, with the mean and standard deviation reported. At the end of each sampling period, samples are removed and replaced with equal quantities of fresh receptor fluid.

Mathematical treatment of *in-vitro* release data: When mathematical formulae that represent dissolve findings as a function of some of the dosage form parameters are utilized, quantitative analysis of the values obtained in dissolution/release tests becomes easier.

RESULTS AND DISCUSSION

The formulation and characterization of curcumin-loaded aquasomes have been assessed in terms of vesicle size, surface charge, entrapment efficiency, and drug release characteristics. The results of these evaluations provide valuable insights into the physical properties, stability, and release behavior of the curcumin-loaded aquasomes, which are essential for their application in topical fungal treatment.

The vesicle size of the prepared formulations (F1 to F6) ranged from 125.65 nm (F3) to 192.32 nm (F1), with the optimized formulation, F3, showing the smallest size (125.65 nm). This size is ideal for enhancing the skin penetration of curcumin for topical applications, as smaller nanoparticles generally have better diffusion and absorption properties. The surface charge of the aquasomes, measured in terms of zeta potential, ranged from -25.45 mV (F2) to -36.85 mV (F3). A negative zeta potential suggests good colloidal stability, as the particles are less likely to aggregate, which is crucial for maintaining the uniformity and effectiveness of the formulation over time. The optimized formulation (F3) exhibited the highest negative charge, indicating its enhanced stability and potential for sustained release.

The entrapment efficiency of curcumin in the aquasomes ranged from 68.87% (F6) to 82.23% (F3), with formulation F3 showing the highest entrapment efficiency of 82.23%. High entrapment efficiency is critical for maximizing the amount of curcumin loaded into the aquasomes, ensuring an effective dose while minimizing the amount of drug loss during the preparation process. This high entrapment efficiency also suggests that the aquasome system is highly effective at encapsulating the hydrophobic curcumin, which is essential for its stability and controlled release in topical applications.

The in vitro drug release study of formulation F3 revealed a sustained release profile over a period of 12 hours. Initially, the drug release was slow, with only 22.32% of curcumin released after 0.5 hours. However, the release increased progressively, reaching 98.12% at 12 hours. This controlled release behavior is ideal for topical applications, where sustained drug availability at the site of action is desired. The gradual release over time ensures that curcumin is continuously delivered to the target site, potentially enhancing its therapeutic effects in treating fungal infections.

The release kinetics of formulation F3 were evaluated using various models, and the data suggested that the release followed Korsmeyer-Peppas kinetics, with a correlation coefficient (r^2) of 0.991. This model indicates that the release of curcumin from the aquasomes is governed by diffusion-controlled processes, typical for systems designed to provide sustained release. The high r^2 values for all models (Zero order, First order, Higuchi, and Korsmeyer) indicate that the release mechanism is well-fitted to these models, reinforcing the controlled and predictable release profile of the optimized formulation.

The TEM image of the optimized formulation (F3) demonstrated a well-defined, spherical nanoparticle structure,

which is consistent with the desired properties of aquasomes. The image confirmed that the nanoparticles were uniform in size and shape, further validating the successful preparation of curcumin-loaded aquasomes.

Table 2: Results of vesicle size and surface charge of curcumin loaded aquasomes

S. No.	F. Code	Vesicle size (nm)	Surface Charge
1	F1	192.32	-26.36
2	F2	183.32	-25.45
3	F3	125.65	-36.85
4	F4	163.32	-34.47
5	F5	171.12	-30.25
6	F6	185.65	-26.69

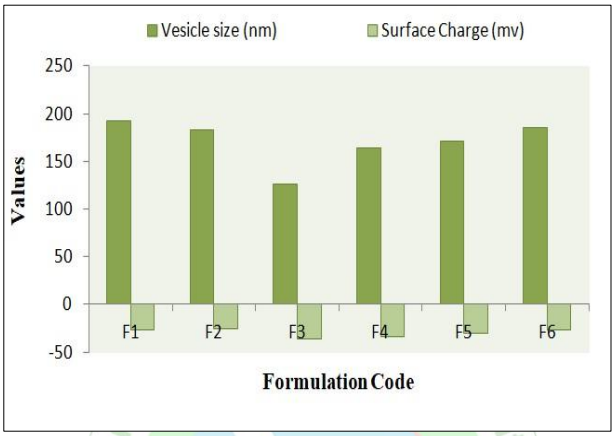

Figure 1: Graph of Vesicle size and Surface Charge for formulation F1 to F6

Table 3: Results of Entrapment efficiency curcumin loaded aquasomes

S. No.	F. Code	Entrapment efficiency (%)
1	F1	73.32±0.25
2	F2	76.65±0.32
3	F3	82.23±0.14
4	F4	69.98±0.33
5	F5	73.32±0.41
6	F6	68.87±0.22

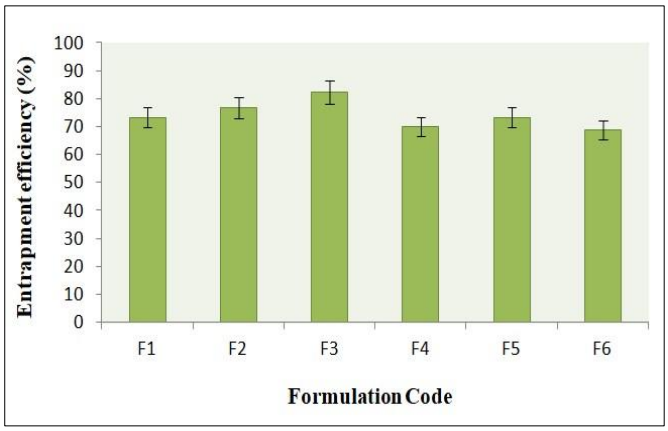

Figure 2: Graph of Results of Entrapment efficiency for formulation F1 to F6

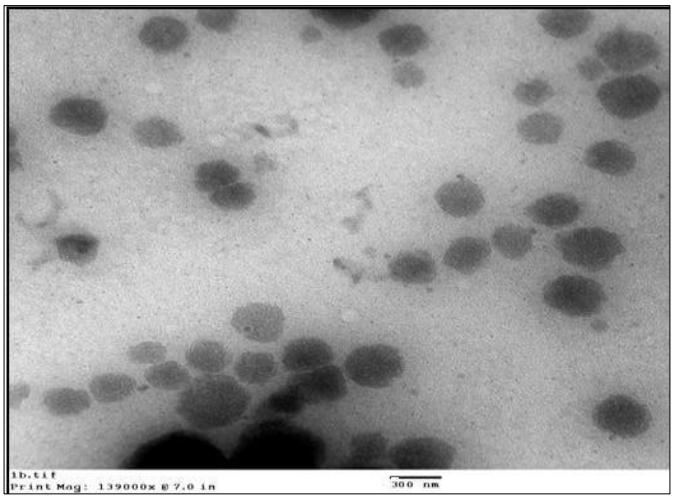

Figure 3: TEM image of optimized formulation F3

Table 4: In vitro drug release study of prepared Aquasomes F3

S. No.	Time (hr)	Root T	Log T	% Cumulative Drug Release	% Cumulative Drug Release Remain	Log % Cumulative Drug Remain to be Release	Log % Cumulative Drug Release
1	0.5	0.707	-0.301	22.32	77.68	1.890	1.349
2	1	1	0	31.14	68.86	1.838	1.493
3	2	1.414	0.301	43.32	56.68	1.753	1.637
4	4	2	0.602	55.65	44.35	1.647	1.745
5	6	2.449	0.778	79.98	20.02	1.301	1.903
6	8	2.828	0.903	86.65	13.35	1.125	1.938
7	12	3.464	1.079	98.12	1.88	0.274	1.992

Table 5: Release Kinetics of aquasomes optimized formulation F3

Formulation	Zero order	First order	Higuchi	*Korsmeyer*
F3	0.9282	0.9563	0.9818	*0.991*

CONCLUSION

The results of the vesicle size, surface charge, entrapment efficiency, in vitro drug release, and release kinetics studies suggest that curcumin-loaded aquasomes have promising potential as a novel delivery system for topical fungal treatments. The optimized formulation (F3) exhibited desirable characteristics such as small vesicle size, high entrapment efficiency, good stability, and sustained drug release, making it a suitable candidate for further development in the treatment of fungal infections. Future work may focus on further optimizing the formulation for enhanced drug loading, stability, and in vivo performance.

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