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Original Research Article

FORMULATION AND EVALUATION OF MELOXICAM LOADED AQUASOMES FOR ENHANCED TOPICAL DRUG DELIVERY

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ABSTRACT

Traditionally topical drug delivery systems are used to relieve various skin conditions like pain, swelling & inflammation. The most difficult aspect of TDDS is overcoming the stratum corneum barrier effect, delivering the drug to the skin tissue, and passing through the cellular and vascular tissue to reach the target area. The issue is that just a little amount of medication can be administered through skin tissue. This issue can be addressed by aquasome. Aquasomes (AQ) are self-assembling nanostructures with a spherical hydroxyapatite core and a carbohydrate layer on top that are used to distribute bioactive compounds. Thus this study aims at formulation & evaluation of aquasome of Meloxicam for reducing pain & inflammation. The preparation & evaluation of aquasome was done according to standard protocol. Six different formulations were created & tested for various parameters. From the results, it was observed that the vesicle sizes vary among the different formulations. F3 has the smallest vesicle size 115.32 nm, while F6 has the largest vesicle size 155.65 nm. The formulations have negative surface charges, ranging from -29.98 to -39.98 mv. The F3 formulation shows the highest entrapment efficiency 73.32% & F1 has the lowest entrapment efficiency 62.25%. The In vitro drug release study of optimized formulation F3 revealed that about 98.85% drug is released in 12 hrs. The R^2 value for Higuchi kinetics in formulation F3 was 0.998 suggests an excellent fit to this model. Stability study data revealed that the optimized formulation F 3 can remain stable after 3 month of storage at 4°C.

Keywords: Topical drug delivery, Meloxicam, Aquasome, Skin diseases, Pain, Inflammation, Nanotechnology

INTRODUCTION

The term "drug delivery system" refers to a group of physicochemical technologies that can manage the distribution and release of pharmacologically active compounds into cells, tissues, and organs, allowing these active chemicals to exert optimal effects. In other words, DDS addresses drug administration routes and medication formulations that efficiently distribute the drug to maximise therapeutic efficacy while minimising negative effects. There are numerous administration modes available depending on the route of administration, including oral administration, transdermal administration, lung inhalation, mucosal administration, and intravenous injection. Among these, the transdermal drug delivery system (TDDS) is an appealing technique (Vega *et al*., 2020; Vargason *et al*., 2021).

Topical treatments are applied to the skin in order to achieve surface, local, or systemic effects. In rare situations, the base can be utilised on its own for therapeutic purposes, such as emollient, calming, or protecting activity. However, many topical treatments contain therapeutically active chemicals that are disseminated or dissolved in the base. The combination of active components and base allows for a diverse range of topical formulations suitable for a variety of medication delivery and therapy terms. The most difficult aspect of TDDS is overcoming the stratum corneum barrier effect, delivering the drug to the skin tissue, and passing through the cellular and vascular tissue to reach the target area. The issue is that just a little amount of medication can be administered through skin tissue. To address this issue, several unique TDDS strategies have been extensively explored and have emerged as appealing administration solutions (Tadwee *et al*., 2007; Tan *et al*., 2012)..

Chemical enhancers, bio-polymers (e.g. sodium hyaluronate), liposomes, particulate carriers (microspheres and lipid nanoparticles), topical sprays and foams, occlusion (via dressings and patches), topical peels, temperature (heat), iontophoresis, and ultrasound are currently used to optimise the topical delivery of dermatological agents (small and large molecules). These delivery approaches (when used alone or in combination) are a significant improvement over traditional systems (creams, lotions, ointments, and pastes) and have the potential to improve efficacy and tolerability, improve patient compliance (including dermatology life quality), and address other unmet needs in the topical dermatological market (Hafee *et al*., 2013).

In the last few decades, nanotechnology has arisen as a subject of biomedical study. The current context is an attempt to offer concise information regarding nano-biotechnological applications. Aquasomes are a relatively new delivery mechanism for bioactive compounds such as peptides, proteins, hormones, antigens, and genes to specified areas.

Aquasomes are spherical in form and have particle sizes ranging from 60 to 300 nm. Aquasomes are nanoparticulate carrier systems, however rather than being simple nanoparticles, they are three-layered self-assembled structures made up of a solid core coated with an oligomeric film to which biochemically active molecules are adsorbed with or without modification. Non-covalent and ionic bonds self-assemble these structures. The structural stability is provided by the solid core, while the carbohydrate coating guards against dehydration and stabilises the biochemically active components. Based on the self-assembly idea, aquasomes are one of the most important basic and novel drug carriers. Even when conformationally sensitive drug candidates are given via aquasomes, their biological activity is improved. This is most likely owing to the ceramic's unique carbohydrate coating. These formulations also elicited a greater immunological response, implying that they may be employed as an immune adjuvant for proteinaceous antigens. As a result, this approach offers pharmaceutical researchers a new ray of hope for the dispersion of bioactive molecules. Thus this study aims at formulation & evaluation of aquasome of Meloxicam for reducing pain &

inflammation (Sutariya and Patel 2012; Kulkarni *et al*., 2022; Banerjee and Sen, 2018).

MATERIALS AND METHODS

Chemicals

Tween 80, Glutaraldehyde, Gelatin, Water, Ethanol, Methanol was obtained from Fine Chemicals Pvt Ltd. All chemicals & reagents used were of standard laboratory grade.

Formulation of Meloxicam loaded Aquasomes

Preparation of drug solution

Dissolve the drug meloxicam in a suitable solvent, such as water or a water-alcohol mixture, to obtain a drug solution. Ensure that the drug is fully dissolved to achieve a homogenous solution.

Preparation of stabilizer solution

Dissolve the stabilizer gelatin in water to form a stabilizer solution. Heat the solution gently, if required, to ensure complete dissolution of the stabilizer.

Preparation of surfactant solution

Dissolve the surfactant (Tween 80, 1 to 3%) in water to create a surfactant solution. Mix the solution thoroughly to ensure proper dissolution.

Preparation of cross-linking agent solution

Prepare the cross-linking agent solution separately. Glutaraldehyde as the cross-linking agent, prepare a 1% glutaraldehyde solution by diluting it in water.

Formation of Aquasomes

Slowly add the drug solution to the stabilizer solution while continuously stirring. This step forms the drug-stabilizer complex. Gradually add the surfactant solution to the drug-stabilizer complex while maintaining continuous stirring. The surfactant will stabilize the complex and prevent agglomeration (Oviedo *et al.,* 2007).

Cross-Linking of Aquasomes

After the formation of the Aquasome suspension, add the cross-linking agent solution drop wise to the suspension while stirring gently. The cross-linking agent will promote the cross-linking of stabilizer molecules, forming a rigid shell around the drug-stabilizer-surfactant complex, resulting in the formation of Aquasomes.

Characterization and evaluation of Meloxicam 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 264nm using a UV spectrophotometer (Labindia 3000+) (Patel *et al.,* 2018).

***In vitro* drug diffusion study**

The dialysis diffusion approach was used to perform in vitro drug release of prepared tranfersomes 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 tranfersomal 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 tranfersomal 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 264nm, 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. The regression coefficient value for Zero order, first order, Higuchi & Korsmeyer Peppas was then analysed.

Stability Studies

Stability study was carried out for drug loaded Aquasomes at two different temperatures i.e. refrigeration temperature (4.0 ±0. 2°C) and at room temperature (25-28±2°C) for 3 weeks. The formulation subjected for stability study was stored in borosilicate container to avoid any interaction between the formulation and glass of container. The formulations were analyzed for any physical changes and drug content.

Table 1: Different formulation of Aquasomes

Ingredient (%)	F1	F2	F3	F4	F5	F6
Drug	20	20	20	20	20	20
Tween 80	1	2	3	1	2	3
Glutaraldehyde	1	1	1	1	1	1
Gelatin	0.5	1	1.5	0.5	1	1.5
Water	qs	qs	qs	qs	qs	qs

Table 2: Characterization of Optimized formulation of Aquasomes

Characterization .	Average vesicle size (nm)	% Entrapment efficiency	Zeta Potential (mV)
F-13	150.2	78.85	-36.5

Table 3: Results of Vesicle size and Surface Charge

S. No.	F. Code	Vesicle size (nm)	Surface Charge (mv)
1	F1	145.65	-29.98
2	F2	136.85	-31.14
3	F3	115.32	-39.98
4	F4	136.65	-31.14
5	F5	147.85	-36.65
6	F6	155.65	-32.21

Table 4: Results of Entrapment efficiency

S. No.	Formulation Code	Entrapment efficiency (%)
1	F1	62.25
2	F2	68.85
3	F3	73.32
4	F4	66.45
5	F5	65.25
6	F6	68.74

Table 5: ***In vitro*** **drug release study of prepared Aquasomes optimized formulation 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	14.45	85.55	1.932	1.160
2	1	1	0	25.65	74.35	1.871	1.409
3	2	1.414	0.301	36.69	63.31	1.801	1.565
4	4	2	0.602	55.58	44.42	1.648	1.745
5	6	2.449	0.778	69.98	30.02	1.477	1.845
6	8	2.828	0.903	82.23	17.77	1.250	1.915
7	12	3.464	1.079	98.85	1.15	0.061	1.995

Table 6: Release Kinetics of aquasomes optimized formulation F3

Formulation	Zero order	First order	Higuchi	Korsmeyer
F-3	0.954	0.892	0.998	0.994

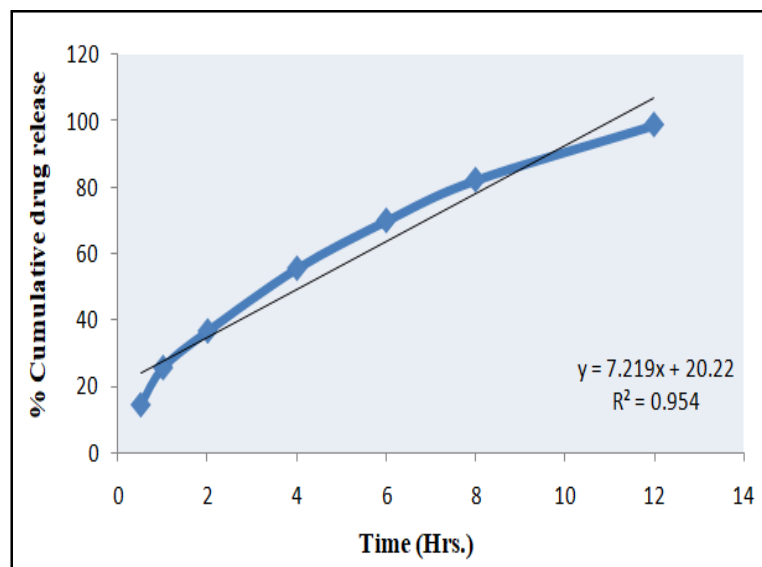

Figure 1: Zero order release of aquasomes optimized formulation F3

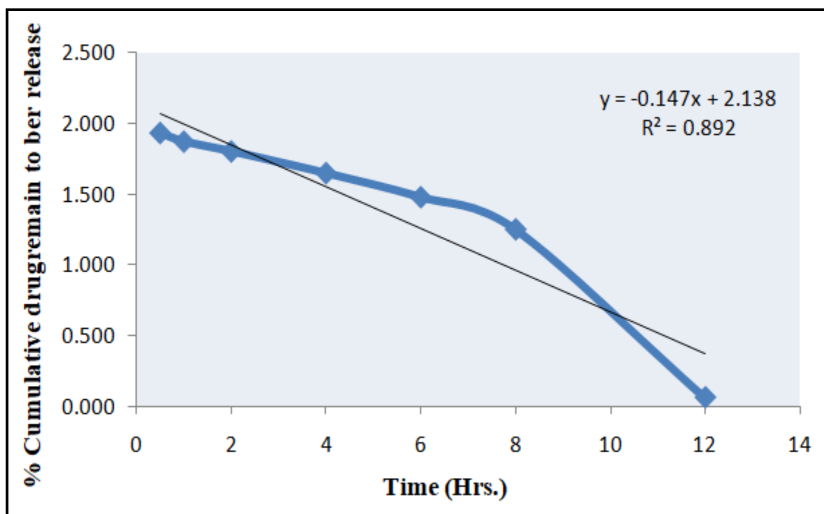

Figure 2: First order release of aquasomes optimized formulation F3

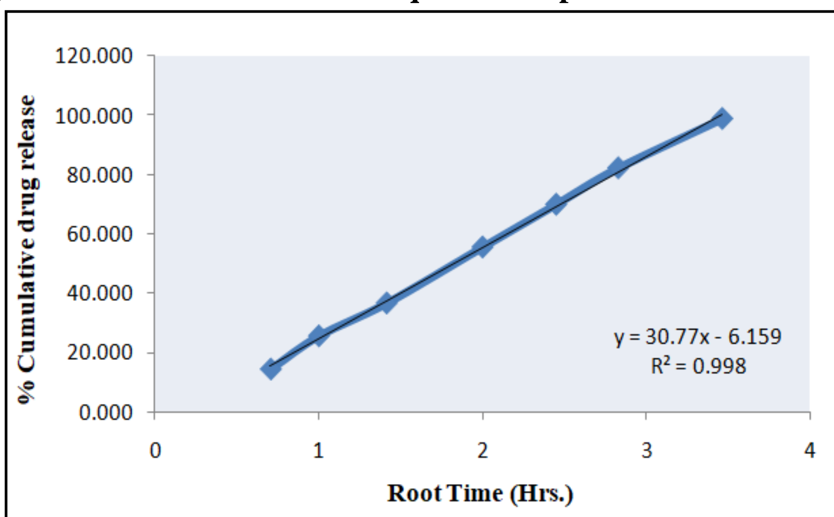

Figure 3: Higuchi order release of aquasomes optimized formulation F3

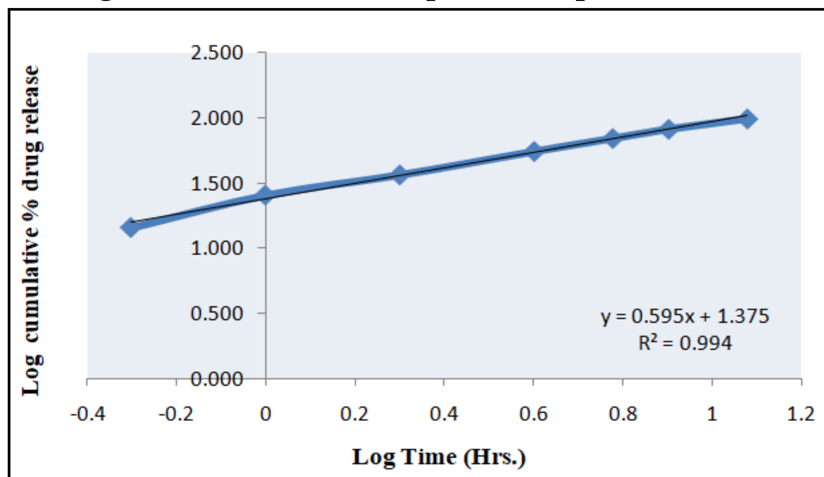

Figure 4: *Korsmeyer* release kinetics of aquasomes optimized formulation F3

RESULTS AND DISCUSSION

The vesicle size is an essential parameter in Aquasomes formulation, as it affects the drug encapsulation efficiency and release characteristics. From the results, it can be observed that the vesicle sizes vary among the different formulations. F3 has the smallest vesicle size (115.32 nm), while F6 has the largest vesicle size (155.65 nm).

The surface charge of vesicles is crucial in determining their stability and interaction with biological systems. It is often measured in terms of zeta potential, which is an indicator of the surface charge. From the results, it can be seen that the formulations have negative surface charges, ranging from -29.98 to -39.98 mv. The negative charge is likely due to the presence of negatively charged components in the formulation, such as phospholipids. The negative charge can enhance the stability of the Aquasomes through electrostatic repulsion and reduce aggregation. the entrapment efficiency varies among different Aquasomes formulations.

F3 shows the highest entrapment efficiency (73.32%), indicating that this formulation has a higher capacity to encapsulate and retain the drug. On the other hand, F1 has the lowest entrapment efficiency (62.25%). The formulation with the highest entrapment efficiency (F3) might be considered as the most optimal formulation among the tested Aquasomes. A high entrapment efficiency indicates that more of the drug is effectively encapsulated and protected within the vesicles, which could lead to improved drug stability and controlled release behavior.

The In vitro drug release study of prepared Aquasomes optimized formulation F3 revealed that about 98.85% drug is released in 12 hrs. The release pattern indicates that the formulation is designed to gradually release the drug over an extended period. A significant initial burst release is observed within the first 0.5 to 2 hours, during which a considerable percentage of the drug is released. This initial release can be attributed to the drug present on the surface of the vesicles or loosely associated with the lipid bilayer.

The drug release profile of formulation F3 can be compared with results from previous formulations to assess the improvements achieved through optimization. The R-squared value for first order kinetics in formulation F3 (0.892) suggests that the drug release is relatively well-described by this model, but it might not be a perfect fit.

The Higuchi release kinetics model indicates that drug release is diffusion-controlled and proportional to the square root of time. The R^2 value for Higuchi kinetics in formulation F3 (0.998) suggests an excellent fit to this model, indicating that the drug release follows Higuchi's square root of time relationship.

Stability study data was revealed that the optimized formulation (F-3) stable after 3 month of storage at 4ºC while at 25-28±2°C, the formulation was found unstable. Stability of formulation was observed on the basis of % Entrapment efficiency, average vesicles size and physical appearance.

CONCLUSION

It can be concluded from that the meloxicam loaded aquasome have several ideal parameters to be used for various skin problems like pain & inflammation. In order to release at further market level, more deep

investigations related to its efficacy, safety, toxicity & stability is needed to be carried out in in vivo model. Also in clinical trials at various levels will help in generating trust on the formulation. Aquasomes can be a ray of hope for overcoming the myriad limitations and obstacles associated with conventional pharmaceutical drug administration.

DECLARATION OF INTEREST

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

REFERENCES

- Vega-Vasquez, P., Mosier, N.S. & Irudayaraj, J. (2020) Nanoscale drug delivery systems: From medicine to agriculture. *Frontiers in Bioengineering and Biotechnology*, 8, 79
- Vargason, A.M., Anselmo, A.C. & Mitragotri, S. (2021) The evolution of commercial drug delivery technologies. *Nature Biomedical Engineering*, 5, 951–967
- Tadwee, I.K., Gore, S. & Giradkar, P. (2012) Advances in topical drug delivery system: A review. Int. J. of Pharm. Res. & All. *Sci.*, 1, 14–23.
- Tan, X., Feldman, S.R., Chang, J. & Balkrishnan, R. (2012) Topical drug delivery systems in dermatology: A review of patient adherence issues. *Expert Opinion on Drug Delivery*, 9, 1263–1271
- Bhowmik, D. (2012) Recent advances in novel topical drug delivery system. *Journal of Pharmaceutical Innovation*, 1.
- Hafeez, A., Jain, U., Singh, J., Maurya, A. & Rana, L. (2013) Recent advances in transdermal drug delivery system (TDDS): An overview. *Journal of Scientific and Innovative Research*, 2, 733–744.
- Sutariya, V. & Aquasomes, P.P. (2012) A novel carrier for drug delivery. *International Journal of Pharmaceutical Sciences and Research*, 3, 688.
- Kulkarni, S., Prabhakar, B. & Shende, P. (2022) Aquasomes: Advanced vesicular-based nanocarrier systems. *Current Pharmaceutical Design*, 28, 2404–2414
- Banerjee, S. & Sen, K.K. (2018) Aquasomes: A novel nanoparticulate drug carrier. *Journal of Drug Delivery Science and Technology*, 43, 446–452
- Rojas-Oviedo, I., Salazar-López, R.A., Reyes-Gasga, J. & Quirino-Barreda, C.T. (2007) Elaboration and structural analysis of aquasomes loaded with indomethecin. *European Journal of Pharmaceutical Sciences*, 32, 223–230
- Goyal, A.K., Khatri, K., Mishra, N., Mehta, A., Vaidya, B., Tiwari, S. & Vyas, S.P. (2008) Aquasomes a nanoparticulate approach for the delivery of antigen. *Drug Development and Industrial Pharmacy*, 34, 1297–1305
- Khopade, A.J., Khopade, S. & Jain, N.K. (2002) Development of haemoglobin aquasomes from spherical hydroxyapatite cores precipitated in the presence of poly (amidoamine) dendrimer. *Drug*

Development and Industrial Pharmacy, 241, 145–154.

- Patel, S. et al. (2018). Banerjee S, Sen KK. Aquasomes: A novel nanoparticulate drug carrier Aquasomes: A novel approach in drug carrier system. *Journal of Drug Delivery Science and Technology*, 43, 446–452.
- Jain, S.S., Jagtap, P.S., Dand, N.M., Jadhav, K.R. & Kadam, V.J. (2012) Aquasomes: A novel drug carrier. *Journal of Applied Pharmacy*, 2, 184–192.
- Rojas-Oviedo, I., Salazar-Lopez, R.A., Reyes-Gasga, J. & Quirino-Barreda, C.T. (2007) Elaboration and structural analysis of aquasomes loaded with indomethacin. *European Journal of Pharmaceutical Sciences*, 32, 223–230