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FORMULATION AND EVALUATION OF ALOIN LOADED MICROSPHERES TO TREAT DIABETES

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Abstract:

This study focuses on the formulation and evaluation of aloin-loaded microspheres for the treatment of diabetes. Microspheres were prepared using the Solvent Evaporation method with a mixture of ethanol and dichloromethane as solvents. The formulations (F1 to F5) varied in their composition of aloin, HPMC (Hydroxypropyl methylcellulose), and EC (Ethyl cellulose). The physical characteristics including particle size, polydispersity index (PI), zeta potential, entrapment efficacy, and stability of the microspheres were extensively evaluated. The results showed that the particle size of the microspheres ranged from 150.4 nm to 178.1 nm, with formulations F1 and F3 demonstrating the smallest sizes and narrower size distributions. Zeta potential measurements indicated that formulations F2, F4, and F5 had positive potentials, suggesting a tendency towards aggregation, while F1 and F3 had lower potentials, indicating better stability. Entrapment efficacy varied from 84.16% to 93.07%, with formulations F1 and F2 exhibiting the highest encapsulation efficiencies. Stability studies conducted under different conditions (25°C ± 2°C and 60 ± 5% RH, and 40°C ± 2°C and 70 ± 5% RH) demonstrated that formulation F1 maintained consistent particle size and high entrapment efficacy over a 90-day period, indicating good physical and chemical stability suitable for potential clinical applications.

Keywords: *Aloin, microspheres, solvent evaporation method, diabetes treatment, particle size, polydispersity index, zeta potential, entrapment efficacy, stability study.*

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INTRODUCTION:

Diabetes mellitus, characterized by chronic hyperglycemia, remains a significant global health challenge affecting millions worldwide. The management of diabetes often requires lifelong treatment strategies aimed at controlling blood glucose levels to prevent complications such as cardiovascular disease, nephropathy, and retinopathy (Diabetes Care. 2023). Current therapies include oral hypoglycemic agents, insulin therapy, and lifestyle modifications, yet these approaches are often associated with challenges such as patient compliance, side effects, and variable efficacy (Cho *et al.*, 2018) .

Natural products have garnered attention as potential sources for novel anti-diabetic agents due to their diverse chemical compositions and therapeutic properties. Aloe vera (Aloe barbadensis Miller), a succulent plant native to North Africa, has been traditionally used for its medicinal properties, including its potential as an anti-diabetic agent (Yagi *et al*., 1999). One of the bioactive components of aloe vera, aloin, has shown promise in preclinical studies for its hypoglycemic effects, primarily attributed to its ability to enhance glucose uptake and inhibit gluconeogenesis (Rajasekaran et al., 2004).

The encapsulation of bioactive compounds like aloin into microspheres offers a promising approach to enhance stability, bioavailability, and sustained release characteristics, thereby potentially improving therapeutic outcomes and reducing dosing frequency (Jain et al., 2013). Microsphere-based drug delivery systems have been extensively investigated for their ability to protect encapsulated drugs, provide controlled release profiles, and target specific tissues or cells, thereby minimizing systemic side effects (Illum; 1998).

This research aims to formulate and evaluate aloin-loaded microspheres as a novel therapeutic approach for diabetes management. The study will explore the encapsulation efficiency and in vitro release kinetics.

MATERIAL AND METHODS:

Material:

Several reagents and chemicals were used in this study: methanol (Rankem), sodium hydroxide (Merck), HPMC and EC (Sigma-Aldrich), KBr (Sigma-Aldrich), ethanol (Merck), DCM (Merck), methanol (Merck), DMSO (Merck), and n-octanol (Merck). These were essential for extracting aloin, preparing polymer solutions, spectroscopic analysis, and forming aloin-loaded microspheres.

Methods:

Formulation of microspheres by Solvent Evaporation method:

Microspheres containing Aloin as a core material were prepared by Solvent Evaporation method. Aloin, HPMC and EC were dissolved in a mixture of ethanol and dichloromethane (1:1) at room temperature (As in table 4). This was poured into 250 mL water containing 0.01% Tween-80 maintained at a temperature of 30–40 °C and subsequently stirred at 300 rpm agitation speed for 45 minutes to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed with water and dried in oven at 37°C (Fartyal *et al.*, 2011).

Table 1: Composition of microsphere formulation

Formulations (Code)	Polymer HPMC (mg)	Polymer Ethyl cellulose (mg)	Aloin (mg)	Temperature °C	Solvent ratio(1:1) ethanol/DCM
F1	300	50	100	30-40°C	5ml:5ml
F2	250	100	100	30-40°C	5ml:5ml
F3	200	150	100	30-40°C	5ml:5ml
F4	150	200	100	30-40°C	5ml:5ml
F5	100	250	100	30-40°C	5ml:5ml

Evaluation parameter of extract loaded microsphere:

Particle size:

The particle size is one of the most important parameter for the characterization of microspheres. The size of microspheres was measured using Malvern Zeta sizer (Malvern Instruments). The dispersions were diluted with Millipore filtered water to an appropriate scattering intensity at 25°C and sample was placed in disposable sizing cuvette (Singh and Vingkar 2008).

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 microspheres was diluted 10 times with distilled water and analyzed by Zetasizer Malvern instruments. All samples were sonicated for

5-15 minutes before zeta potential measurements (Deshmukh et *al.*, 2023).

Quantitative analysis (Entrapment Efficiency):

%Entrapment efficiency was determined by indirect estimation. Drug -loaded microspheres were centrifuged at 15,000 rpm for 30 min using REMI Ultra Centrifuge. The non-entrapped drug (free drug) was determined in the supernatant solution using UV spectrophotometer. The peak area was determined and amount of free drug is determined by extrapolating the calibration curve. And drug entrapment calculated by using below equation (Bodmeier *et al.*, 1989).

Entrapment efficiency % = Total drug conc. - Supernatant drug conc. / total drug conc.*100

Scanning Electron Microscopic (SEM):

The electron beam from a scanning electron microscope was used to attain the morphological features of the extract loaded microspheres 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 pretreated specimen was then bombarded with an electron beam and the interaction resulted in the formation of secondary electrons called auger electrons. From this interaction between the electron beam and the specimen's atoms, only the electrons scattered at 90° were selected and further processed based on Rutherford and Kramer's Law for acquiring the images of surface topography (Ahmed *et al.*, 2020).

Stability studies:

The Extract loaded Microsphere formulation was packed and were placed in the stability test chamber and subjected to stability studies at accelerated testing ($25^0C \pm 2^0C$ and 60 ± 5% RH) and ($40^0C \pm 2^0C$ and 70 ±5% RH) for 3 months. The formulation was checked for evaluation parameter particle size and Zeta potential studies at the interval of 30, 45, 60, 90 days (3 month) months. The formulation was tested for stability under accelerated storage condition for 3 months in accordance to International Conference on Harmonization (ICH) guidelines. Formulation was analyzed for the change in evaluation parameter particle size and zeta potential studies.

RESULTS AND DISCUSSION:

The particle size of the microsphere formulations (F1 to F5) ranges from 150.4 nm to 178.1 nm, with F1 having the smallest size at 150.4 nm and F2 the largest at 178.1 nm. The polydispersity index (PI), which measures the distribution of particle sizes within a sample, varies from 0.010 (F3) to 0.395 (F2). A lower PI value indicates a narrower size distribution, suggesting formulation F3 has a more uniform particle size distribution compared to F2, which shows greater variability.

Zeta potential values reflect the surface charge of the microspheres, influencing their stability and interaction with surrounding environments. Microspheres F2, F4, and F5 exhibit positive zeta potentials (10.6 mV, 9.9 mV, and 8.4 mV, respectively), indicating a tendency towards aggregation due to electrostatic repulsion. In contrast, F1 and F3 show lower zeta potential values (1.3 mV and 1.2 mV, respectively), suggesting less potential for aggregation and greater stability in suspension.

The entrapment efficacy of the microsphere formulations ranges from 84.16% (F4) to 93.07% (F1). Higher entrapment efficacy values indicate more efficient encapsulation of the active ingredient within the microspheres. Formulation F1 demonstrates the highest entrapment efficacy at 93.07%, followed closely by F2 at 92.58%, while F4 shows the lowest efficacy at 84.16%.

The stability study of microsphere formulation F1 over different time intervals and environmental conditions (25°C ± 2°C and 60 ± 5% RH, and 40°C ± 2°C and 70 ± 5% RH) reveals crucial insights into its physical and chemical stability. The microspheres maintained a solid powder appearance throughout the study period, with slight variations observed in particle size and entrapment efficacy. Notably, the particle size remained relatively stable over 90 days, ranging from 150.4 nm to 158.1 nm, indicating good physical stability. Similarly, the entrapment efficacy remained high, ranging from 93.07% to 94.17%, suggesting minimal degradation or loss of the encapsulated material under the specified storage conditions.

The data from particle size, zeta potential, entrapment efficacy, and stability studies provide a comprehensive overview of the characteristics and performance of microsphere formulations F1 to F5. Formulations with smaller particle sizes and narrower size distributions, such as F1 and F3, exhibit potentially better uniformity and stability in suspension. Higher entrapment efficacy values in F1 and F2 indicate efficient encapsulation of the active ingredient, essential for maximizing therapeutic efficacy and minimizing dosage variability.

The zeta potential values highlight the electrostatic stability of the microspheres, with formulations showing positive potentials potentially requiring careful handling to prevent aggregation. Stability studies indicate that formulation F1 maintains its

physical and chemical integrity over the study period, underscoring its suitability for long-term storage and potential clinical applications.

Table 2: Result of Particle size of all formulations

S. No.	Formulations	Particle size (nm)	PI Value
1.	**F1**	**150.4 nm**	**0.226**
2.	F2	178.1 nm	0.395
3.	F3	154.3 nm	0.010
4.	F4	152.5nm	0.318
5.	F5	157.4nm	0.212

Table 3: Result of Zeta potential of all formulations

S. No	Formulation	Zeta potential
1	**Microsphere (F1)**	**1.3 mV**
2	Microsphere (F2)	10.6 mV
3	Microsphere (F3)	1.2 mV
4	Microsphere (F4)	9.9 mV
5	Microsphere (F5)	8.4mV

Table 4: Results of entrapment efficacy

S. No.	Formulations	Entrapment efficacy (%)
1.	**Microsphere (F1)**	**93.07**
2.	Microsphere (F2)	92.58
3.	Microsphere (F3)	88.53
4.	Microsphere (F4)	84.16
5.	Microsphere (F5)	87.13

Table 5: Stability Study of Microsphere (F1) formulation

S. No	Time (Days)	25^0C±2 ^{0}C and 60 ± 5% RH			40^0C±2 ^{0}C and 70 ±5% RH		
		Appearance	Particle size nm	Entrapment efficacy (%)	Appearance	Particle size nm	Zeta potential mV
1.	0	Solid Powder	150.4 nm	93.07 %	Solid Powder	150.4 nm	93.07 %
2.	30	Solid Powder	151.2 nm	93.10 %	Solid Powder	151.8 nm	93.17 %
3.	45	Solid Powder	153.6 nm	93.21 %	Solid Powder	152.9 nm	93.77 %
3.	60	Solid Powder	154.9 nm	93.78 %	Solid Powder	154.9 nm	93.98 %
4.	90	Solid Powder	156.8 nm	94.03 %	Solid Powder	158.1 nm	94.17 %

CONCLUSION:

In conclusion, formulation F1 emerges as a promising candidate among the microsphere formulations evaluated, demonstrating favorable particle size, high entrapment efficacy, and robust stability under varied conditions. Future research could focus on optimizing formulation parameters to enhance stability and efficacy further, paving the way for potential pharmaceutical applications in drug delivery systems.

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