RESEARCH PAPER

# Development and Optimization of Kaempferol and Dexamethasone Loaded Lipospheres for Controlled Drug Delivery

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**ABSTRACT**

Lipid-based drug delivery systems have gained significant attention due to their ability to enhance the stability, bioavailability, and controlled release of poorly soluble therapeutic agents. Lipospheres, consisting of a solid lipid core stabilized by a phospholipid layer, offer several advantages over conventional delivery systems, including improved drug protection, reduced toxicity, and ease of formulation. Kaempferol, a naturally occurring flavonoid, and dexamethasone, a potent glucocorticoid, possess significant pharmacological activities. So, the present study aimed to develop and optimize liposphere-based drug delivery systems for kaempferol and dexamethasone in order to enhance their stability, bioavailability, and controlled release characteristics.

**Materials and Methods:** The hot emulsion method was used to create lipospheres. Tween-80 served as the surfactant, stearic acid as the lipid core, and soybean phosphatidylcholine as the phospholipid covering. Both dexamethasone and kaempferol were added separately and together. The produced lipospheres were assessed for surface shape using scanning electron microscopy, entrapment efficiency using spectrophotometric analysis, zeta potential using a zetasizer, and particle size using dynamic light scattering. The dialysis method was used for in vitro drug release in phosphate buffer (pH 7.4), and zero-order, first-order, Higuchi, and Korsmeyer–Peppas models were used to analyze the release kinetics.

**Results:** The successful production of nanosized carriers was demonstrated by the optimized liposphere formulations, which showed particle sizes in the range of 176.67–204.8 nm. The entrapment efficiency showed good drug incorporation inside the lipid matrix, ranging from 85.75% to 87.54%. Zeta potential readings ranged from –19.7 mV to –37.3 mV, with greater negative values signifying better formulation stability. Spherical morphology with homogeneous distribution and little aggregation was confirmed by scanning electron microscopy. Studies on drug release in vitro revealed a continuous release profile. Drug release mostly followed first-order and Higuchi models, according to kinetic analysis, suggesting diffusion-controlled release with matrix degradation as a contributing factor.

**Conclusion:** The developed liposphere formulations demonstrated desirable physicochemical characteristics, high entrapment efficiency, and controlled drug release behavior. The findings indicate that lipospheres are a promising delivery system for improving the therapeutic performance of kaempferol and dexamethasone, particularly in overcoming limitations related to solubility and bioavailability.

**Keywords:** Kaempferol, Dexamethasone, Lipospheres, Phospholipid, Particle sizes.

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## 1. Introduction

Lipospheres are solid water-insoluble microparticles with solid hydrophobic core and a layer of phospholipids embedded on the surface of the core shielding a biologically active agent in the core. **(Satheesh et al., 2013).** The average particle diameter

of liposphere is between 0.3–250 μm based on an earlier researcher. **(Momoh et al., 2011).** Lipospheres have several advantages over other lipid delivery systems such as emulsions, vesicles, and liposomes, in terms of stability, low cost of reagents, ease of manufacture, high dispersibility in aqueous medium, and a release rate for the entrapped substance that is controlled by the phospholipid coating and the carrier. In a liposphere, there is no equilibrium of substances in and out of the vehicle as in an emulsion system. Lipospheres also have a lower risk of reaction of substance to be delivered with vehicle than in emulsion systems because the vehicle is a solid inert material. Moreover, the release rate of a substance from the lipospheres can be manipulated by altering either or both inner solid vehicle or the outer phospholipids **(Wang et al., 2010).**

Kaempferol (KFP) is a flavonoid present in a wide variety of edible plants like onions, green tea, grapes, potatoes, tomatoes, apples, cucumbers, broccoli, blackberries and green beans **(Alam et al., 2020)**. KFP exerts its chemo preventive effect via a variety of mechanisms of action such as cell cycle arrest, anti-proliferation, anti-angiogenesis, and induction of apoptosis **(Ashrafizadeh et al., 2020).** Despite its broad range of pharmacological properties, KFP's usage in biomedical applications is restricted due to its poor water solubility, poor permeability, instability of chemicals in water alkaline medium, extensive metabolic processing before entering the systemic circulation and poor bioavailability at oral administration **(Dara et al., 2020).**

Dexamethasone is a glucocorticoid with a relevant clinical use mainly due to its anti-inflammatory and immunosuppressive effects. However, the great number of side effects, such as: hypertension, hydroelectrolytic disorders, hyperglycemia, peptic ulcers and glucosuria restricts the use of dexamethasone in prolonged therapy **(Ali et al., 2013).**

## 2. Materials and methods

### 2.1 Preparation of Lipospheres by Hot Emulsion Congealing Technique:

Liposphere formulations were prepared by the hot emulsion congealing technique. An aqueous solution of Tween-80 (T-80) was prepared and maintained at 75°C. A specific amount of drug was dissolved in melted stearic acid, soyabean phosphatidylcholine, cetyl alcohol at 80°C which was then added to hot aqueous surfactant solution along with continuous stirring at 2000, 2500, and 3000 RPM for 30min by employing a high speed stirrer. Afterwards, the obtained preemulsion was then directly conveyed to an ice-box to initiate generation of Lipospheres. The yielded lipospheres were allowed to recrystallize at room temperature, and the obtained formulation was then separated by centrifugation at 10000rpm for 30 minutes at 3-4°C. The separated Lipospheres were then subjected to lyophilization process for 24h to produce completely dried Lipospheres **(Rasul et al., 2021)**. Kaempferol and Dexamethsone liposphere formulations were optimized by using $3^2$ full factorial design using Design Expert software (Version 8.0.4.1 Stat-Ease Inc., Minneapolis, USA). Parameters such as lipid concentration (Stearic acid) and phospholipid concentration (soybean phosphatidylcholine) were independent variables and Particle size and entrapment efficiency were response parameters or dependent variables. **(Bhosale et al., 2016).**

### 2.2 Evaluation of Lipospheres

#### 2.2.1 Determination of Entrapment Efficiency

The entrapped drug concentration was determined by lysis of the lipospheres using absolute alcohol followed by sonication. The concentration of Kaempferol and Dexamethsone in absolute alcohol was determined spectrophotometrically (Shimadzu UV-1700) at 262 nm after appropriate dilution **(Nasr et al., 2008).**

The entrapment efficiency was calculated using the following equation:

$$\textbf{Entrapment efficiency (\%)} = \frac{Entrapped\ drug}{Total\ drug} \times 100$$

#### 2.2.2 Particle size

The particle size of the prepared lipospheres formulation was measured using Dynamic Light Scattering (DLS) with a particle size analyzer. **(Sangolkar et al., 2012).**

#### 2.2.3 Zeta Potential

The zeta potential of the lipospheres formulation was measured using a Malvern Zetasizer to evaluate the surface charge and predict colloidal stability **(Clogston and Patri, 2010).**

#### 2.2.4 SEM

Surface morphology lipospheres was characterized by scanning electron microscopy. The prepared sample was subjected to SEM analysis by using Analytical Scanning Electron Microscope (Carl Zeiss Sigma 300).

#### 2.2.5 *In vitro* release study by dialysis method

Drug release was determined by dialysis method; two ml of lipospheres formulation was poured into dialysis bags and put into a 25 ml phosphate buffer (pH 7.4) and stirred (100 rpm, room temperature). At predetermined

time intervals, 2 ml of phosphate buffer was taken and then substituted with fresh phosphate buffer. Finally, the amounts released in the phosphate buffer were measured by a spectrophotometer at 366, 238 and 262 nm for LSD, LSK and LSKD. Aliquots withdrawn were assayed at each time interval for the drug released at λ max of 366, 238 and 262 nm for LSD, LSK and LSKD using a UV-visible spectrophotometer by keeping phosphate buffer pH 7.4 blank and the amount of released drug was estimated by the standard curve **(Chime et al., 2013)**.

- **In vitro drug release kinetics**

The drug release kinetics of lipospheres were determined by plotting the following kinetic models, using the data collected from *in vitro* release studies (zero order, first order, and Higuchi equations). The mechanism of drug release was determined by using the Korsmeyer-Peppas equation **(Paarakh et al., 2018)**.

$$C = K_0 t \quad (1)$$

Where $K_0$ is the zero-order rate constant expressed in units of concentration/time and *t* is the time.

$$\text{Log } C_t = \text{Log } C_o + K_1 t / 2.303 \quad (2)$$

$$\text{Log } C_o - \text{Log } C_t = K_t / 2.303 \quad (3)$$

Where $C_t$ is the amount of drug released in time t, $C_O$ is the initial concentration of the drug, $k_1$ is the first order constant, and *t* is the time. Here the graphical representation of the log cumulative of % drug remaining versus time will be linear with a negative slope.

$$Q = K_H t^{1/2} \quad (4)$$

Q is the amount of drug released in time t per unit area, $K_H$ is the Higuchi dissolution constant and *t* is the time in hours.

$$Mt / M\infty = Ktn \quad (5)$$

The logarithm form of equation (Eq 6) could be written as:

$$\text{Log } (Mt / M\infty) = \text{Log } k = n \text{ Log } t \quad (6)$$

Where Mt/M∞ is the fraction of drug released at time t, n is the diffusion exponent indicative of the mechanism of transport of the drug, and K is the kinetic constant (having units of t) incorporating structural and geometric characteristics of the delivery system.

## 3. Results

### 3.1 Optimization process by Design of experiment approach

**Table 1 Response 1: Particle Size**

| Source | Sequential p-value | Lack of Fit p-value | Adjusted $R^2$ | Predicted $R^2$ | |
|---|---|---|---|---|---|
| Linear | < **0.0001** | | **0.9774** | **0.9648** | **Suggested** |
| 2FI | 0.6955 | | 0.9729 | 0.9339 | |
| Quadratic | 0.7451 | | 0.9622 | | |
| Cubic | | | | | Aliased |

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 173.97 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

**P-values** less than 0.0500 indicate model terms are significant. In this case C is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Particle size (R1) = +501.73 Intercept +0.3375AX1 -11.15BX2 -299.04CX3

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

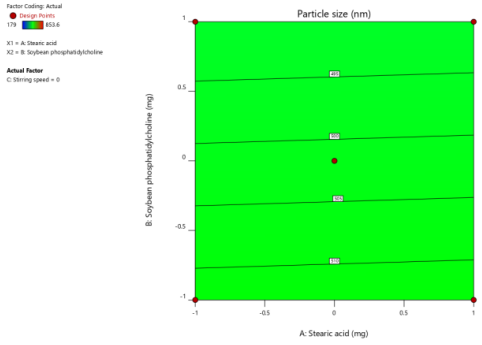



**Figure 1 Two-dimensional (2D) contour plots for the effect of Stearic acid and Soybean phosphatidylcholine concentration on particle size**

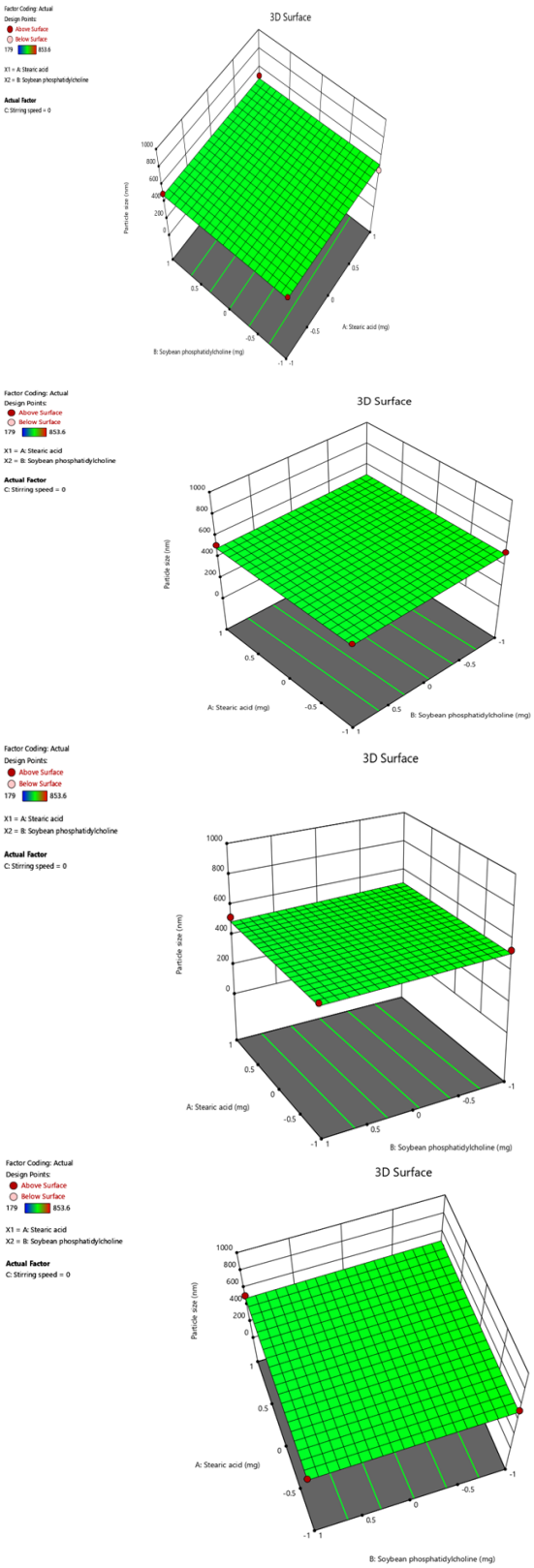



**Figure 2 Three-dimensional (3D) Response surface plot showing combined effect of Stearic acid and Soybean phosphatidylcholine on particle size of lipospheres formulation**

**Table 2 Response 2: Entrapment efficiency**

| Source | Sequential p-value | Adjusted $R^2$ | Predicted $R^2$ | |
|---|---|---|---|---|
| Linear | **< 0.0001** | **0.9705** | **0.9531** | **Suggested** |
| 2FI | 0.1963 | 0.9786 | 0.9484 | |
| Quadratic | 0.2887 | 0.9859 | | |
| Cubic | | | | Aliased |

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**
The **Model F-value** of 132.56 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.
**P-values** less than 0.0500 indicate model terms are significant. In this case C is a significant model term.
Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.
Entrapment efficiency (R2) = +68.07 Intercept -0.2013 AX1-1.02 BX2 +14.65CX3
The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients

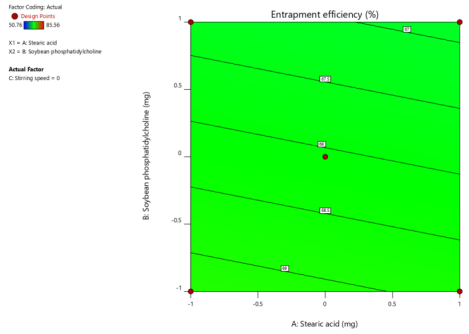
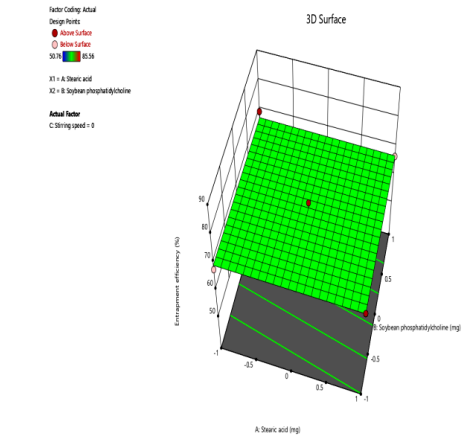
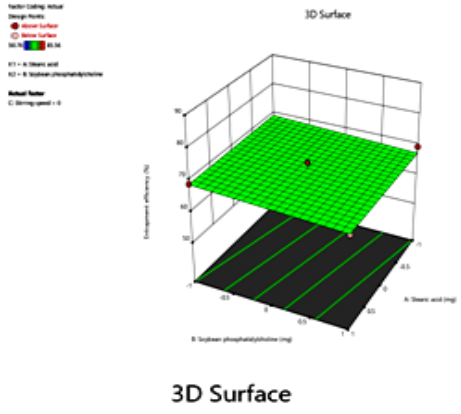
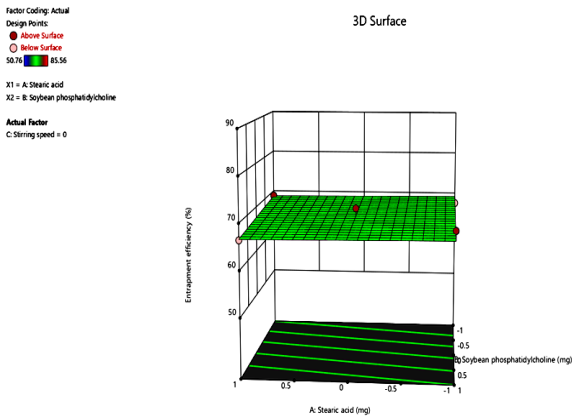



**Figure 3 Two-dimensional (2D) contour plots for the effect of Stearic acid and Soybean phosphatidylcholine concentration on entrapment efficiency**



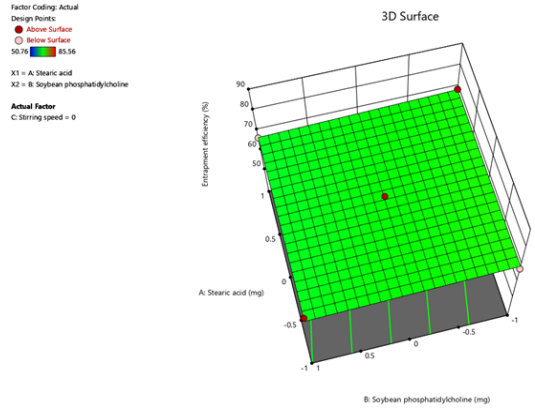




**Figure 4 Three-dimensional (3D) Response surface plot showing combined effect of Stearic acid and Soybean phosphatidylcholine on entrapment efficiency of drug loaded formulation**

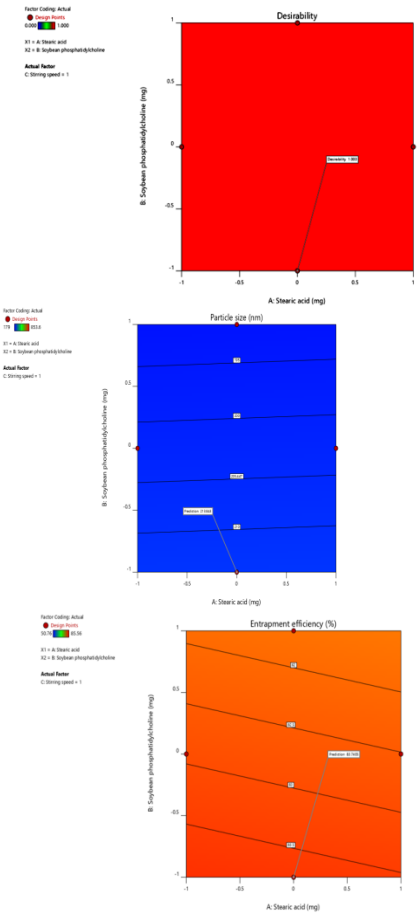



**Figure 5 Response surface plot showing prediction data for optimization**

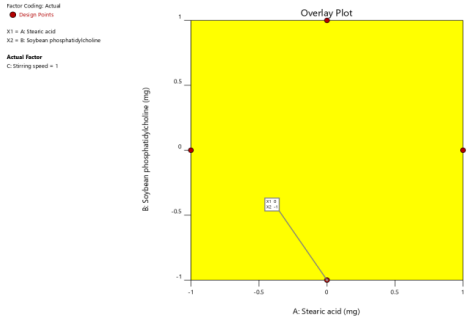



**Figure 6 Overlay plots of optimization formulation**

## 3.2 Evaluation of Liposphere formulation

### 3.2.1 Particle size analysis

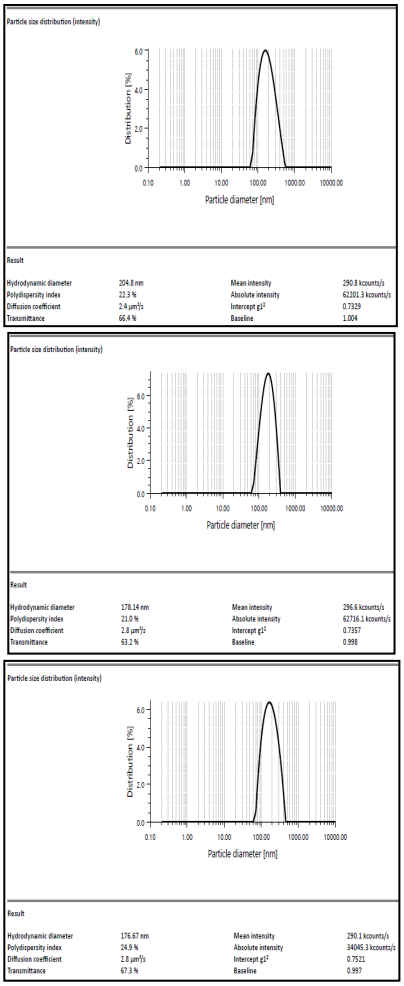



**Figure 7 Particle size of optimized Dexamethsone, Kaempferol, and Kaempferol liposphere**

**Figure 8 Particle size of optimized Dexamethsone, Kaempferol, and Kaempferol liposphere**

| S. No | Formulation | Particle size (nm) |
|---|---|---|
| 1. | LSD | 204.8 |
| 2. | LSK | 178.14 |
| 3. | LSKD | 176.67 |

The particle size of liposphere formulations is a critical parameter influencing drug release, stability, and bioavailability. In the present study, the particle size of the formulations ranged from 176.67 nm to 204.8 nm, indicating successful preparation of nanoparticles within the desired nanometric range.

Among the formulations, LSD exhibited the highest particle size (204.8 nm), whereas LSK and LSKD showed comparatively smaller particle sizes of 178.14 nm and 176.67 nm, respectively.

### 3.2.2 Entrapment efficiency

**Table 3 Entrapment efficiency of Liposphere formulations**

| S. No | Formulation | Entrapment efficiency (%) |
|---|---|---|
| 1. | LSD | 87.54 |
| 2. | LSK | 86.24 |
| 3. | LSKD | 85.75 |

LSD showed the highest entrapment efficiency (87.54%), followed by LSK (86.24%) and LSKD (85.75%).

.11.3 Zeta potential

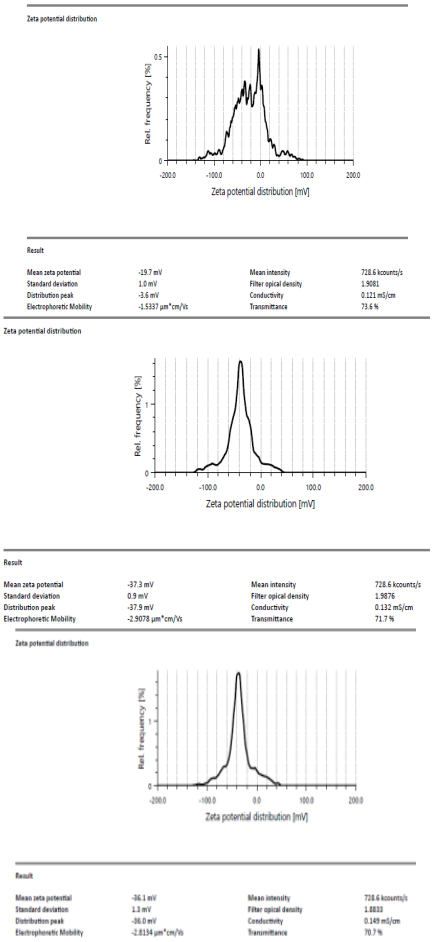



**Figure 9 Zeta potential of optimized Dexamethasone, Kaempferol, Dexamethsone + Kaempferol liposphere**

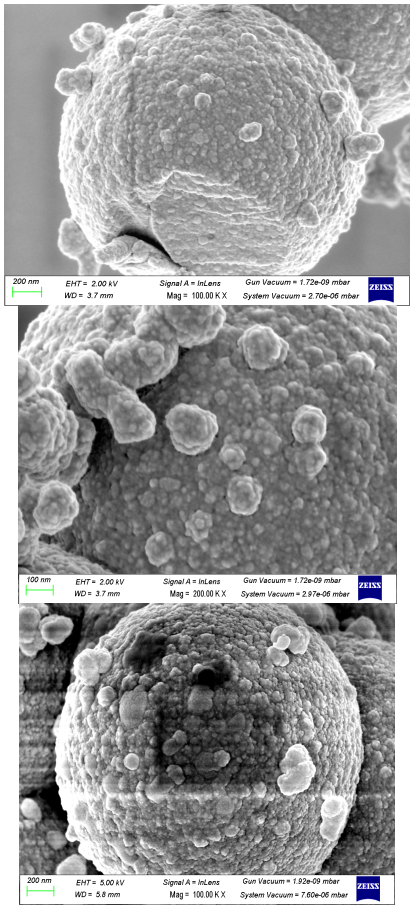
**Table 4 Zeta potential of Liposphere formulations**

| S. No | Formulation | Zeta potential (mV) |
|---|---|---|
| 1. | LSD | -19.7 |
| 2. | LSK | -37.3 |
| 3. | LSKD | -36.1 |

The zeta potential values of liposphere formulations ranged from –19.7 mV to –37.3 mV. Among the

formulations, LSD showed a zeta potential of –19.7 mV, On the other hand, LSK (–37.3 mV) and LSKD (–36.1 mV) exhibited higher negative zeta potential values, suggesting better electrostatic repulsion between particles and, therefore, improved stability of the formulations.

### 3.2.3 SEM



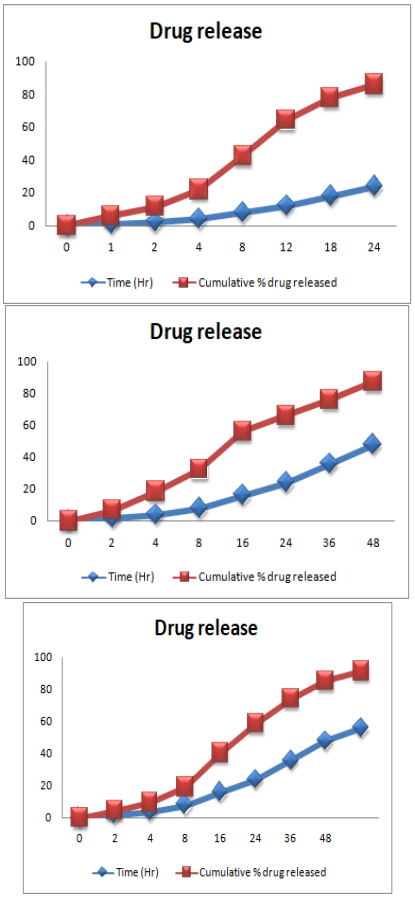
**A)**

**B)** **C)**

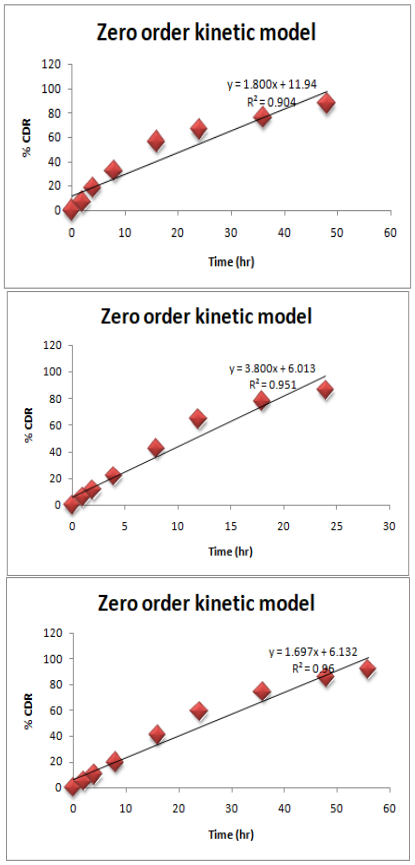
**Figure 10: SEM Image of Dexamethsone, Kaempferol, Dexamethsone + Kaempferol liposphere**

SEM analysis confirmed that all formulations exhibited spherical morphology with particle sizes in the nanometric range (~160–220 nm) and minimal aggregation. The combination formulation showed slightly smaller and more uniform particles, which may contribute to enhanced stability and improved drug delivery performance.

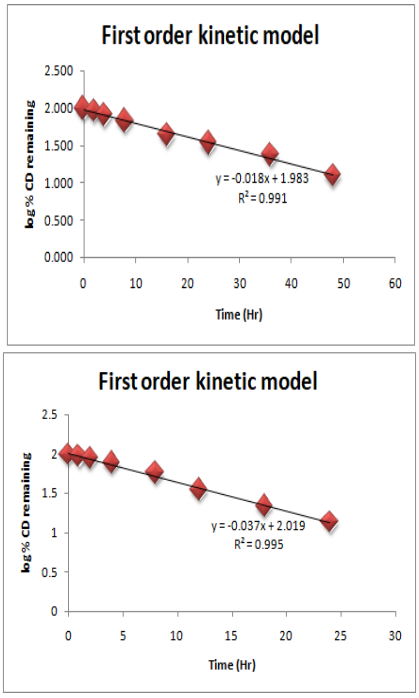
### 3.2.3 *In-vitro* drug release (kinetic model) study

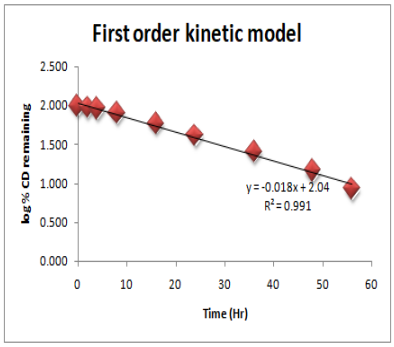



**Graph 1: In-vitro drug release for Dexamethasone, Kaempferol, Dexamethsone + Kaempferol liposphere**

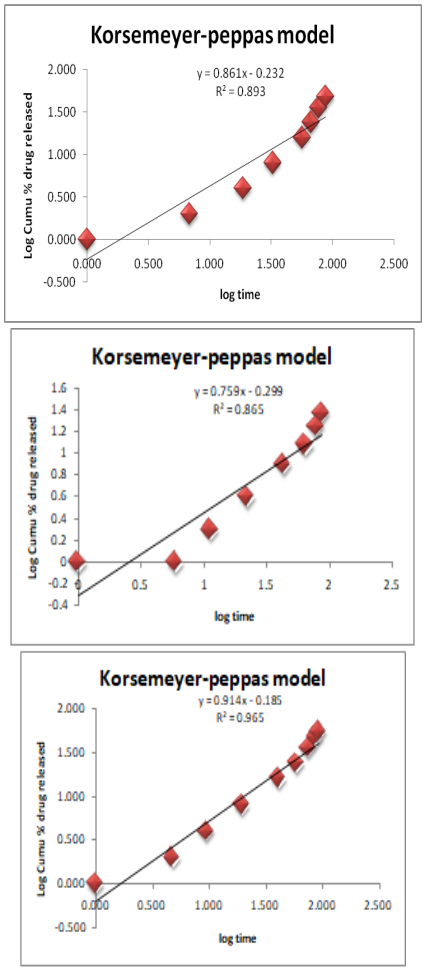



**Graph 2: Zero order plot for Dexamethasone, Kaempferol, Dexamethsone + Kaempferol liposphere liposphere**

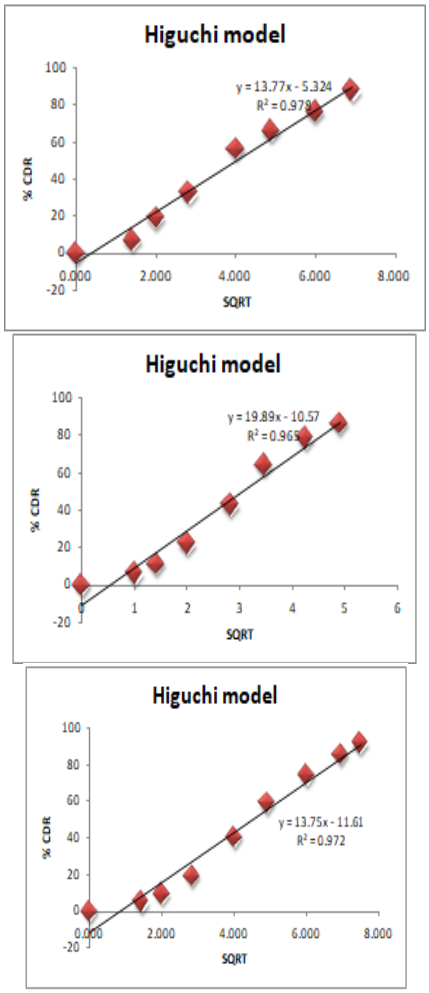



**Graph 3 First order plot for Dexamethasone, Kaempferol, Dexamethsone + Kaempferol liposphere**




**Graph 4 Korsemeyer-peppas plot for Dexamethasone, Kaempferol, Dexamethsone + Kaempferol liposphere liposphere**




**Graph 5 Higuchi plot for Dexamethasone, Kaempferol, Dexamethsone + Kaempferol liposphere**

**Table 5 Correlation Value ($R^2$ value)**

| Formulation | Kinetic Model | Regression value |
|---|---|---|
| Dexamethasone liposphere | Zero order | 0.904 |
| | First order | 0.991 |
| | Korsemeyer-peppas | 0.893 |
| | Higuchi | 0.978 |
| Kaempferol liposphere | Zero order | 0.951 |
| | First order | 0.995 |
| | Korsemeyer-peppas | 0.865 |
| | Higuchi | 0.965 |
| Dexamethasone and Kaempferol liposphere | Zero order | 0.960 |
| | First order | 0.991 |
| | Korsemeyer-peppas | 0.965 |
| | Higuchi | 0.972 |

## 4. Discussion

The current work effectively created and refined liposphere-based delivery systems for dexamethasone and kaempferol using the hot emulsion congealing method. Particle size and entrapment efficiency were two important quality variables that were shown to be highly impacted by lipid and phospholipid concentrations using the factorial design approach. Statistically significant models confirmed the robustness of the optimization procedure.

Particle sizes in the nanometric range (176.67–204.8 nm) were seen in the adjusted formulations, suggesting uniform dispersion and suitable for improved drug administration. The successful integration of both medications into the lipid matrix was validated by high entrapment efficiencies (85.75–87.54%). Zeta potential readings showed good colloidal stability because of adequate electrostatic repulsion, particularly for Kaempferol-loaded and combination formulations (−36.1 to −37.3 mV). The spherical shape, nanoscale size distribution, and low aggregation of the lipospheres were further confirmed by SEM examination. *In-vitro* drug release studies revealed a controlled and sustained release profile, with release kinetics predominantly following first-order and Higuchi models, suggesting diffusion-controlled drug release mechanisms. The Korsmeyer–Peppas model further supported the involvement of anomalous transport behavior.

These results show that lipospheres are an effective and promising lipid-based drug delivery technology for combination therapy, with potential uses in enhancing patient compliance and therapeutic efficacy.

## 5. Conclusion

The study showed that it is possible to successfully create lipospheres of dexamethasone and kaempferol with nanoscale particle size, high entrapment efficiency, and sufficient stability. The developed systems offer controlled and prolonged drug release primarily controlled by diffusion mechanisms, and the results revealed that formulation variables have a considerable impact on particle size and entrapment efficiency.

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