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FORMULATION, DEVELOPMENT AND EVALUATION OF LIPOSPHERES OF TOLBUTAMIDE

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ABSTRACT

This study aims to formulate, develop and evaluate lipospheres of tolbutamide to enhance its solubility, stability, and therapeutic efficacy. Lipospheres were prepared using various lipids and surfactants through the melt-emulsification technique. The prepared lipospheres were characterized for percentage yield, drug entrapment efficiency, particle size distribution, zeta potential, and flow properties. *In vitro* drug release studies were conducted, and the release kinetics were analyzed using various models. The percentage yield of the formulations ranged from 74.45% to 85.45%, with formulation F2 showing the highest yield (85.45% ± 0.32). The drug entrapment efficiency ranged from 71.12% to 82.25%, with formulation F2 exhibiting the highest efficiency (82.25% ± 0.25). Particle size analysis of the optimized formulation F2 showed a uniform distribution, and the zeta potential indicated good stability. Flow properties of the formulations were satisfactory, with Carr's Index values below 16% and Hausner's Ratio close to 1.1. The in vitro drug release profile of formulation F2 demonstrated a controlled release pattern, with 98.74% of the drug released over 12 hours. Release kinetics analysis suggested that the first-order model best described the drug release, indicating a concentration-dependent release mechanism.The formulation and evaluation of tolbutamide lipospheres were successful, with formulation F2 showing optimal characteristics. The lipospheres provided a sustained release of tolbutamide, potentially enhancing its therapeutic efficacy and patient compliance. This study highlights the potential of lipospheres as an effective drug delivery system for tolbutamide, addressing its solubility and stability challenges.

Key words: Tolbutamide, Lipospheres, Drug entrapment efficiency, Controlled release, Formulation, Characterization

INTRODUCTION

Tolbutamide is a first-generation sulfonylurea widely used in the management of type 2 diabetes mellitus. It acts by stimulating insulin release from the pancreatic beta cells, thereby lowering blood glucose levels. However, tolbutamide's therapeutic efficacy can be limited by its poor aqueous solubility and short half-life, necessitating frequent dosing and leading to fluctuations in blood drug levels. To overcome these limitations, various drug delivery systems have been explored, with lipospheres emerging as a promising option due to their ability to enhance solubility, prolong drug release, and improve bioavailability.

Lipospheres are solid lipid particles composed of a solid lipid core stabilized by surfactants. They are an advantageous drug delivery system due to their biocompatibility, ability to incorporate both hydrophilic and lipophilic drugs, and capability to control drug release. The lipid matrix of lipospheres can protect the encapsulated drug from degradation and improve its stability (Westesen, Siekmann, & Koch, 1997). Furthermore, lipospheres can enhance the oral bioavailability of poorly water-soluble drugs by facilitating their absorption through the lymphatic system (Müller, Mäder, & Gohla, 2000).

The formulation of tolbutamide into lipospheres aims to address the drug's solubility and stability issues. By incorporating tolbutamide into lipospheres, the drug can be solubilized in the lipid matrix, enhancing its solubility and dissolution rate. The controlled release properties of lipospheres can maintain therapeutic drug levels over an extended period, reducing the frequency of administration and minimizing blood glucose fluctuations. Additionally, the protection provided by the lipid matrix can enhance the stability of tolbutamide, reducing its degradation and improving its shelf life (Attama & Nkemnele, 2007).Previous studies have demonstrated the potential of lipospheres in improving the bioavailability and therapeutic efficacy of various drugs. For example, Sharma, Sarma, and Rani (2014) reported the successful formulation of glibenclamide lipospheres, showing enhanced bioavailability and prolonged release. Similarly, Vyas and Khar (2006) formulated lipospheres of nifedipine, achieving improved solubility and controlled release. These studies highlight the feasibility and benefits of using lipospheres for drug delivery. The primary objective of this study is to formulate, develop, and evaluate lipospheres of tolbutamide to enhance its solubility, stability, and therapeutic efficacy.

MATERIALS AND METHODS

Formulation and development of Liposphere

Drug encapsulated Liposphere were developed by melt dispersion technique (Bhosale *et al.,* 2016). The formulation of different batches is depicted in Table 7.1. Briefly, the lipid core was melted on a water bath maintained at 70-72°C. Finely powdered drug was dispersed into the molten lipidic phase. The aqueous phase was prepared by heating a blend of water and surfactant to 70-72°C with a stabilizer. The molten lipidic phase was slowly transferred to the hot aqueous phase (o/w emulsion) and the emulsification was assisted by stirring the content on a sonicator continuously. The milky dispersion was then rapidly cooled to 20°C by immersing the formulation in an ice bath without stopping the agitation to yield a uniform dispersion of lipospheres. The obtained lipospheres were then washed with water and isolated by filtration.

Characterization of Tolbutamide encapsulated lipospheres

Percentage yield of Lipospheres

Yield of Lipospheres percent w/w was calculated according to the following formula:

$$\%\ \text{Yield}\ \frac{\text{Weight of lipospheres}}{\text{Wt. of drug}\ +\ \text{Wt. of excipients}} \text{X}100$$

Drug loading and Entrapment efficiency

The amount of Tolbutamide present in lipospheres was determined by taking the known amount of lipospheres in which 10mg of drug should be present theoretically.

Then the lipospheres were crushed and the powdered microspheres was taken and dissolved in 10 ml of methanol and stirred for 15 minutes with an interval of 5 minutes and allowed to keep for 24 hours (Cherniakov *et al.,* 2012). Then the solution was filtered through whatmann filter paper. Then the absorbance after appropriate dilution was measured spectrophotometrically at 230nm by UV-visible spectrophotometer.

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Experimental drug content}}{\text{Initial drug content in the formulation}} \text{X100}$$

Microscopic Evaluation

An optical microscope (Cippon-Japan) with a camera attachment (Minolta) was used to observe the shape of the prepared microspheres for each drug: lipid ratio (Brown *et al.,* 2013).

Measurement of mean particle size

The mean size of the lipospheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the lipospheres suspended in 5 ml of distilled water was used for the measurement (Nasr *et al.,* 2008).

Determination of zeta potential

The zeta potential of the drug-loaded lipospheres was measured on a zeta sizer (Malvern zetasizer instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water.

Surface morphology (Scanning electron microscopy)

Morphology and surface topography of the lipospheres were examined by scanning electron microscopy. The lipospheres from the optimized batch were mounted on the SEM sample stab using a double-sided sticking tape and coated with gold (~200 nm) under reduced pressure (0.133 Pa) for 5 min using an Ion sputtering device. The gold coated lipospheres were observed under the scanning electron microscope and photomicrographs of suitable magnifications were obtained.

Flow property determination of the Lipospheres

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined (Newman, 1995). Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\textbf{LBD (Loose bulk density)} = \frac{\text{Mass of powder}}{\text{Volume of Packing}}$$

$$\textbf{TBD (Tapped bulk density)} = \frac{\text{Mass of powder}}{\text{Tapped Volume of Packing}}$$

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula (Newman, 1995):-

$$\textbf{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X100}$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation (Wells, 1998):-

$$\textbf{Housner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose Bulk density}}$$

***In-vitro* drug release studies**

The dissolution of Tolbutamide from the prepared lipospheres was monitored using USP XXV paddle II apparatus. The Amount of the lipospheres equivalent to 10mg of Tolbutamide was dispersed into the

dissolution medium. The dissolution media was 900 ml of pH 1.2 buffers maintained at 37 ±0.5ºC and rotating at 50 ±1 rpm. The 5ml aliquots were withdrawn at pre-determined time intervals and the withdrawn samples were replaced with fresh dissolution medium. The samples were then analyzed spectrophotometrically at 230 nm for Tolbutamide content.

RESULTS AND DISCUSSION

The percentage yields of various liposphere formulations (F1 to F6) are shown in Table 2. The yields ranged from 74.45% to 85.45%, with formulation F2 exhibiting the highest yield of 85.45% ± 0.32. High yield percentages indicate the efficiency of the liposphere preparation method and the suitability of the chosen lipid and surfactant combination.

Table 3 presents the drug entrapment efficiency of the prepared tolbutamide lipospheres. The entrapment efficiencies ranged from 71.12% to 82.25%, with formulation F2 showing the highest entrapment efficiency of 82.25% ± 0.25. High entrapment efficiency is crucial for ensuring that a significant amount of the drug is incorporated into the lipospheres, which can enhance the drug's bioavailability and therapeutic effect.

Figures 1 and 2 show the particle size distribution and zeta potential of the optimized formulation F2, respectively. The particle size analysis revealed a uniform size distribution, which is important for consistent drug release and absorption. The zeta potential indicates the stability of the liposphere formulation, with higher absolute values suggesting better stability due to reduced aggregation of the particles.

The flow properties of different liposphere formulations are detailed in Table 4. Parameters such as loose bulk density, tapped bulk density, Carr's Index, and Hausner's Ratio were measured. These properties are critical for ensuring good flowability and handling characteristics of the liposphere powders. Formulations F1 to F6 showed acceptable flow properties, with Carr's Index values below 16% and Hausner's Ratio close to 1.1, indicating good flowability.

The in vitro release profile of the optimized formulation F2 is presented in Table 5. The cumulative percentage drug release showed that formulation F2 released 98.74% of the drug over 12 hours, with a consistent and controlled release pattern. The initial burst release (28.85% in the first 0.5 hours) was followed by a sustained release phase, which is beneficial for maintaining therapeutic drug levels over an extended period.

The regression coefficient values for different kinetic models (zero order, first order, Higuchi, and Peppas) are compared in Table 6. The first-order model ($r^2 = 0.9730$) best described the drug release from the lipospheres, suggesting that the rate of drug release is concentration-dependent. The Higuchi model ($r^2 = 0.8641$) also showed a good fit, indicating that diffusion is a significant mechanism of drug release from the lipospheres. The Peppas model ($r^2 = 0.7972$) further supported the diffusion-controlled release mechanism.

Table 1: Preparation of Liposphere of Tolbutamide

F. Code	Drug (mg)	Lipid core (mg)		Tween 80 as Surfactant (ml)	Gelatin or pectin as Stabilizer (mg)	Water (ml)
		Stearic acid (mg)	Cetyl alcohol (mg)			
F1	250	100	100	1.5ml	2	98
F2	250	150	200	1.5ml	2	98
F3	250	200	300	1.5ml	2	98
F4	250	100	300	1.5ml	2	98
F5	250	150	150	1.5ml	2	98
F6	250	200	100	1.5ml	2	98

Table 2: Percentage yields of lipospheres

S. No.	Formulation Code	% Yield*
1	F1	74.45±0.25
2	F2	85.45±0.32
3	F3	80.23±0.15
4	F4	81.15±0.65
5	F5	79.98±0.24
6	F6	76.65±0.15

Table 3: % Drug entrapment efficiency of prepared Tolbutamide lipospheres formulation

S. No.	Formulation Code	% Drug entrapment efficiency
1.	F1	71.12±0.35
2.	F2	82.25±0.25
3.	F3	76.65±0.14
4.	F4	78.84±0.36
5.	F5	74.45±0.30
6.	F6	75.65±0.22

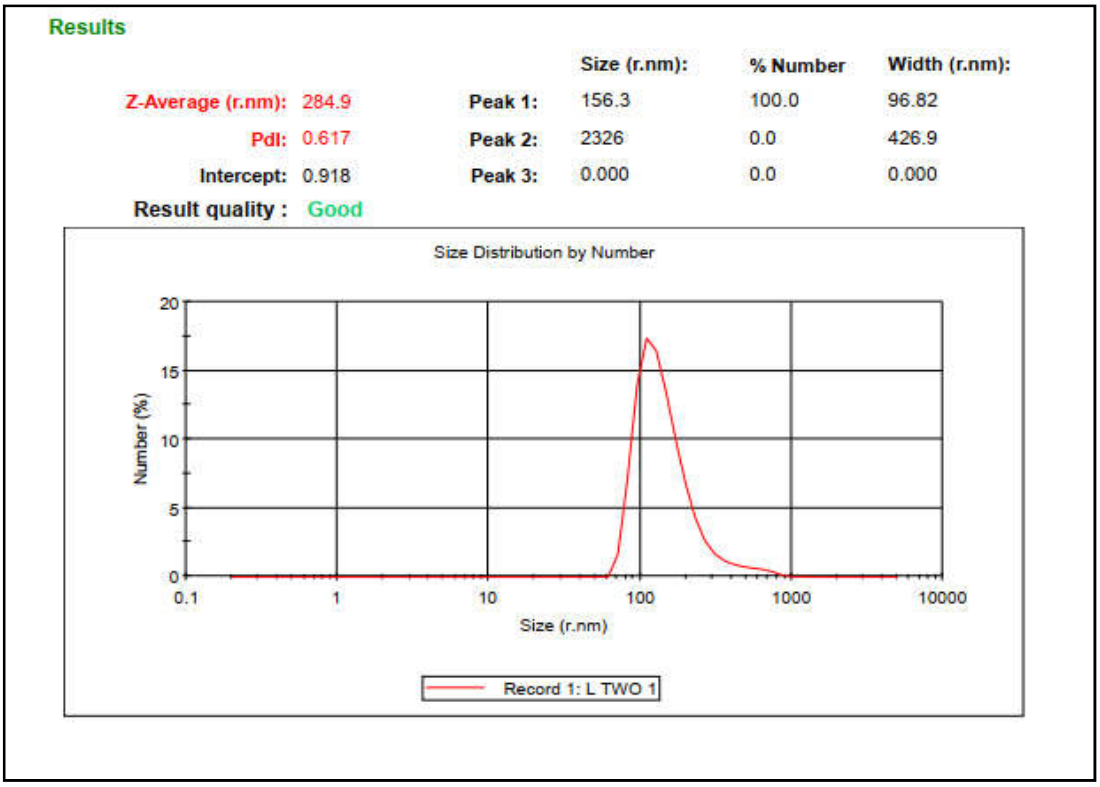

Figure 1: Particle size data of optimized lipospheres formulation F2

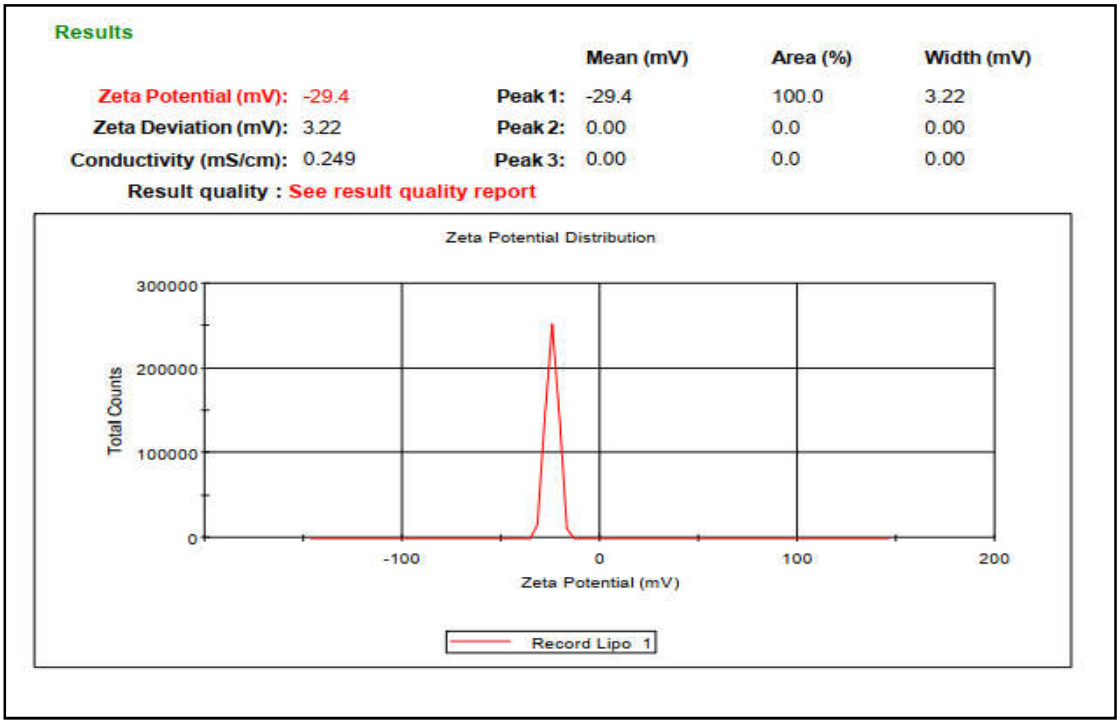

Figure 2: Zeta potential data of lipospheres formulation F2

Table 4: Result of flow properties of different liposphere formulation

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.745	0.845	11.83	1.134
F2	0.785	0.898	12.58	1.144
F3	0.845	0.956	11.61	1.131
F4	0.712	0.845	15.74	1.187
F5	0.779	0.896	13.06	1.150
F6	0.658	0.782	15.86	1.188

Table 5: Release study of optimized formulation F-2

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	28.85	1.4601	71.15	1.852
1	1	0	36.65	1.5641	63.35	1.802
1.5	1.225	0.176	48.98	1.6900	51.02	1.708
2	1.414	0.301	57.74	1.7615	42.26	1.626
3	1.732	0.477	76.65	1.8845	23.35	1.368
4	2	0.602	88.85	1.9487	11.15	1.047
6	2.449	0.778	92.23	1.9649	7.77	0.890
8	2.828	0.903	96.65	1.9852	3.35	0.525
12	3.464	1.079	98.74	1.9945	1.26	0.100

Table 6: Comparative study of regression coefficient for selection of optimized batch

Zero order		First order	Higuchi	Peppas model
r^2	0.7176	0.9730	0.8641	0.7972

CONCLUSION

The formulation and development of tolbutamide lipospheres have shown promising results in terms of percentage yield, drug entrapment efficiency, particle size distribution, zeta potential, and flow properties. The optimized formulation F2 exhibited the highest yield and drug entrapment efficiency, along with a consistent and controlled drug release profile. The in vitro release studies and release kinetics analysis suggest that the lipospheres can provide a sustained release of tolbutamide, potentially improving its therapeutic efficacy and patient compliance. This study demonstrates the potential of lipospheres as an effective delivery system for tolbutamide, addressing its solubility and stability challenges, and enhancing its overall therapeutic profile.

DECLARATION OF INTEREST

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

REFERENCES

- Westesen, K., Siekmann, B. & Koch, M.H. (1997) Investigations on the physical state of lipid nanoparticles by synchrotron radiation X-ray diffraction. *International Journal of Pharmaceutics*, 151, 35–45.
- Muller, R.H., Mäder, K. & Gohla, S. (2000) Solid lipid nanoparticles (SLN) for controlled drug delivery – A review of the state of the art. *European Journal of Pharmaceutics and Biopharmaceutics*, 50, 161–177.
- Attama, A.A. & Nkemnele, M.O. (2007) In vitro evaluation of drug release from self-microemulsifying drug delivery systems using a biodegradable homolipid from Capra hircus. *International Journal of Pharmaceutics*, 334, 48–55.
- Sharma, S., Sarma, G.S. & Rani, M. (2014) Formulation and evaluation of lipospheres for the controlled delivery of glibenclamide. *International Journal of Pharmaceutical Sciences and Research*, 5, 4386–4391.
- Vyas, S.P. & Khar, R.K. (2006). *Targeted and Controlled Drug Delivery: Novel Carrier Systems*. CBS Publishers & Distributors Pvt Ltd.
- Bhosale, U.M., Galgatte, U.C. & Chaudhari, P.D. (2016) Development of pioglitazone hydrochloride lipospheres by melt dispersion technique: Optimization and evaluation. *Journal of Applied Pharmaceutical Science*, 6, 107–117.
- Elgart, A., Cherniakov, I., Aldouby, Y., Domb, A.J. & Hoffman, A. (2012) Lipospheres and pro-nano lipospheres for delivery of poorly water soluble compounds. *Chemistry and Physics of Lipids*, 165, 438–453.
- Brown, S.A., Chime, S.A., Attama, A.A., Agu, C.I. & Onunkwo, G.C. (2013) In vitro and in vivo characterisation of piroxicam-loaded dika wax lipospheres. *Tropical Journal of Pharmaceutical Research*, 12, 33–38.
- Nasr, M., Mansour, S., Mortada, N.D. & El Shamy, A.A. (2008) Lipospheres as carriers for topical delivery of aceclofenac: Preparation, characterization and *in vivo*

evaluation. *AAPS PharmSciTech*, 9, 154–162.

- Newman, A.W. (1995a). *Micromeritics: Brittain HG; Physical Characterization of Pharmaceutical Solids*, Vol. 70. Marcel Dekker, Inc.: New York, USA, pp. 293–294.
- Newman, A.W. (1995b). *Micromeritics: Brittain HG; Physical Characterization of Pharmaceutical Solids*, Vol. 70. Marcel Dekker, Inc.: New York, USA, pp. 271–275.
- Wells, J. (1998). *Pharmaceutical Preformulation: Aulton ME; Pharmaceutics: The Science of Dosage Form Design. 3rd Edi*. Edinburg, USA, p. 247.