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R E S E A R C H A R T I C L E

Development and *In-Vitro* Evaluation of Liposphere of Pravastatin Sodium

Nancy Dixit*, Avinash Gupta, Rajesh Asija, Manish Sharma

Department of Pharmaceutics, Maharishi Arvind Institute of Pharmacy, Mansarover, Jaipur, Rajasthan, India-302020.

A B S T R A C T

The purpose of the present investigation was the formulation and characterization of lipospheres of pravastatin sodium for continuously release to improve bioavailability and to improve drug entrapment. There were various formulations of pravastatin sodium were prepared by melt dispersion technique using Poloxamer 118, Tween 80, Gelatin as surfeactent and they were evaluated for particle size, surface morphology, drug entrapment efficiency, flow properties, buoyancy percentage and *In-vitro* drug release and stability studies. The shape and surface morphology of prepared lipospheres were characterized by optical and scanning electron microscopy, respectively. The particle was found to be discrete and spherical and average particle size of formulations was found to be 45.6 µm. As the concentration of polymers increases, it affects the various evaluation parameters like particle size, in-vitro drug release. The lipospheres of optimized formulation exhibited the prolonged release of 97.1% in a constant way up to 4 hours. From this study it is concluded that the optimized formulation of pravastatin sodium lipospheres can be selected targeted drug delivery system for improved bioavailability and better drug entrapment.

Keywords: Lipospheres, Pravastatin Sodium, Poloxamer 11, Tween 80

A R T I C L E I N F O

***Corresponding Author**
Nancy Dixit
Department of Pharmaceutics, Maharishi Arvind Institute of Pharmacy, Mansarover, Jaipur, Rajasthan, India-302020.
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C O N T E N T S

1. Introduction

Lipids usually enhance drug absorption in the gastrointestinal tract (GIT), and when formulated as nanoparticles, these molecules improve mucosal adhesion due to small particle size and increasing their GIT residence time[1,2]. In addition, lipid nanoparticles may also protect the loaded drugs from chemical and enzymatic degradation and gradually release drug molecules from the lipid matrix into blood, resulting in improved therapeutic profiles compared to free drug[3,4].

Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of water insoluble drug[5,6]. Solid dispersion, drug micronization, lyophilisation, microencapsulation, inclusion of the drug solution or liquid drug into soft gelatin capsules are some of the methods that have been used to enhance dissolution characteristics of water insoluble drugs. Among them, lipospheres are amongst the promising particulate drug delivery systems for improving dissolution rate of water insoluble drugs that were initially reported as a particulate dispersion of solid spherical particles between 0.2-100µm in diameter consisting of solid hydrophobic fat core such as triglycerides or fatty acids derivatives, stabilized by monolayer of phospholipids[7,8,9].

Lipospheres represent a new type of fat based encapsulation system developed for parenteral and topical delivery of bioactive compounds and have been utilized in the delivery of anti-inflammatory compounds, local anaesthetics; antibiotics, anticancer agents, insect repellent, vaccines, proteins and peptides. The lipospheres are distinct from microspheres of uniformly dispersed material in homogenous polymer since they consist of two layers, the inner solid particle that contains the entrapped drug with phospholipids outer layer[10,11].

2. Materials and Methods

The anti-diabetic drug pravastatin sodium was obtained from Heliox Pharma. GMS, Compritol 888, Steric acid were obtained from Gattefosse, France and Poloxmer 118 were obtained from Signet chemical Pvt. Ltd., Mumbai. All other chemicals/reagents used were of analytical grade and were used as received. A UV/Vis spectrophotometer (UV-1800/Schimadzu), FTIR (Bruker Alpha, Berlin) was used for drug analysis.

Preparation of microspheres

Liposphere was prepared by melt dispersion method. At first Lipid phase lipids (Compritol 888, streaic acid, GMS), Gelucire was taken in a beaker and was melted at 70°C then the drug was dispersing into it while stirring. Then aqueous phase containing surfactants or stabilizers (Poloxamer 118, Tween 80, Gelatin) was taken in another beaker and was heated at 70°C. Aqueous phase was added into lipid phase at same temperature with stirring to form emulsion. Then continues stirring was done up to 15 min with maintained temperature using mechanical stirrer 5000 rpm to obtain uniform emulsion Milky formulation cooled down at chilled water (4°C temperature)[12-28]. Composition of different formulations is given in Table 1.

3. Results and Discussion

Characterization of Floating Microspheres[19-28]:

1. Microscopical evaluation:

The shapes of the particles were smooth and spherical in Figure 1. There was a slight change in the shape as the concentration of the drug increased an indication that the drug entrapment affected the shape as well as the size of the particles. The average particle size of formulations was found to be 45.6 µm.

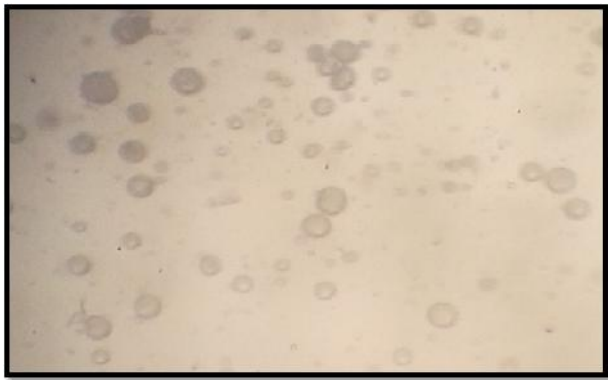

Figure 1: Microscopic images of formulation

2. Percentage yield

Percentage yield of all formulation was given in a Table 2. Ability of lipospheres to entrap drug at high level is important property. It is expressed as percentage entrapment efficiency. Entrapment efficiency of Pravastatin sodium lipospheres formulations F4 to F15 was evaluated. From results, entrapment efficiency was varied in the range of 19.73± 0.33% for F13 Formulation to 59.64± 0.25% for F8. Formulation F8 was the optimized formulation among all Pravastatin sodium loaded lipospheres formulations. F8 showed good entrapment of drug and compatibility with lipid. Formulation technique was also responsible for entrapment of drug. Melt dispersion technique was used for preparation of lipospheres.

4. Zeta potential Analysis

Zeta potential of the liposphere was determined by Malvern Nano Zetasizer instrument. Zeta potential of the elastic liposphere formulation is as follows. The zeta potential study depicts good stability of the liposphere formulations which lies within desired mV range. Zeta potential which from -26.2 provides the best stability for lipospheres.

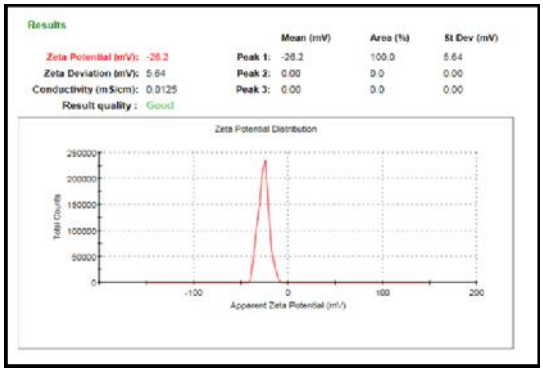

Figure 2: Zeta potential of liposphere (F8)

5. *In-vitro* dissolution studies: *In-vitro* drug release study of Pravastatin sodium lipospheres. Results of Pravastatin sodium loaded liposphere in vitro release from optimized F8 formulation and drug dispersion are illustrated in Figure 3. It was apparent that the incorporation of Pravastatin sodium lead to significant sustained and controlled profiles compared to its pure drug suspension released. It was found that there was an initial rapid removal of the drug possibly by the drug associated loosely on the surface of the lipid matrix. This initial release was rapid, achieved at 2 hr and is

termed as burst release. At 4th and 7th hr. time intervals the drug release rate was achieved at nearly 48- 76%. The total drug release of Pravastatin sodium was observed 76.57±1.15 at the end of 8 hr.

6. Drug release kinetics:

In-vitro drug release kinetic study data of formulation F8 was given below:

Zero order: Zero order graph %drug release vs. Time

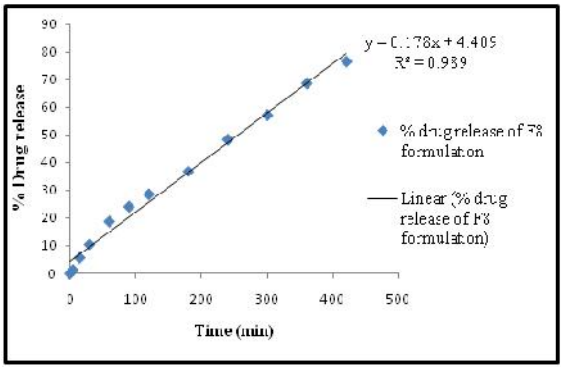

Figure 4: Zero order kinetics of F8 formulation

First order: First order graph Log % drug remaining vs. time

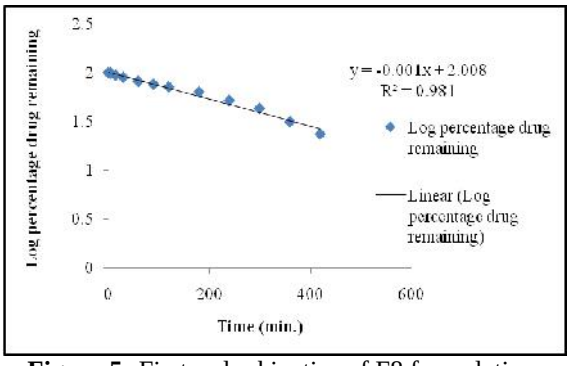

Figure 5: First order kinetics of F8 formulation

Higuchi kinetics: Higuchi release kinetics log %drug release vs. Square root of time

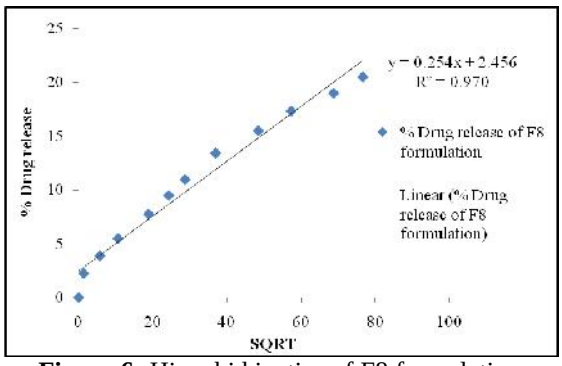

Figure 6: Higuchi kinetics of F8 formulation

Korsmeyer peppas: Korsmeyer peppas release kinetics Log % drug release vs. Log time

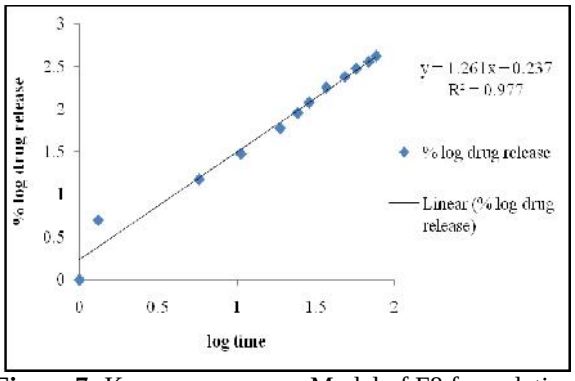

Figure 7: Korsmeyer peppas Model of F8 formulation

The data obtained for in vitro release were fitted into equation for the zero order, first order and higuchi release models. The interpretation of data was based on the value of the resulting regression coefficients. The calculated regression coefficients for zero order, first order and higuchi models were shown in table no.18. It was found that the in vitro drug release of F8 formulation was best explained by zero order as the plot showed the highest linearity.

Table 1: Composition of different liposphere formulations

Formulation code	Drug (mg)	Stearic acid (mg)	Compritol 888 (mg)	GMS (mg)	Paraffin wax (mg)	Cetyl alcohol (mg)	Tween 80 (mg)	Poloxomers 118 (mg)	Gelucire 43/01 (mg)	Gelucire 44/13 (mg)	Gelucire 50/13 (mg)	Gelucire 48/16 (mg)	Gelatin (mg)	Water (ml)
F1	**40**	**300**	**-**	**-**	**250**	**-**	**0.1 %**	**-**	**-**	**-**	**-**	**-**	**2**	**25**
F2	**40**	**200**	**-**		**250**	**-**	**0.1 %**	**-**	**-**	**-**	**-**	**-**	**2**	**25**
F3	**40**	**400**	**-**	**-**	**250**	**-**	**0.1 %**	**-**	**-**	**-**	**-**	**-**	**2**	**25**
F4	**40**	**-**	**400**	**-**	**250**	**-**	**0.1 %**	**-**	**-**	**-**	**-**	**-**	**2**	**25**
F5	**40**	**-**	**400**	**-**	**-**	**250**	**0.1 %**	**-**	**-**	**-**		**-**	**2**	**25**
F6	**40**	**-**	**-**	**300**	**-**	**250**	**0.1 %**	**-**	**-**	**-**	**-**	**-**	**2**	**25**

F7	**40**	**-**	**-**	**300**	**-**	**-**	**-**	**0.1 %**	**-**	**-**	**--**	**-**	**2**	**100**
F8	**40**	**-**	**-**	**600**	**-**	**-**	**-**	**0.1 %**	**200**	**-**	**-**	**-**	**2**	**100**
F9	**40**	**-**	**-**	**300**	**-**	**-**	**-**	**0.1 %**	**-**	**-**	**-**	**-**	**2**	**100**
F10	**40**	**-**	**-**	**900**	**-**	**-**	**-**	**0.1 %**	**200**	**-**	**-**	**-**	**2**	**100**
F11	**40**	**-**	**-**	**600**	**-**	**-**	**-**	**0.1 %**	**400**	**-**	**-**	**-**	**2**	**100**
F12	**40**	**-**	**-**	**300**	**-**	**-**	**-**	**0.1 %**	**300**	**-**	**-**	**-**	**2**	**100**
F13	**40**	**-**	**-**	**300**	**-**	**-**	**-**	**0.1 %**	**-**	**-**	**200**	**-**	**2**	**100**
F14	**40**	**-**	**-**	**300**	**-**	**-**	**-**	**0.1 %**	**-**	**400**	**-**	**-**	**2**	**100**
F15	**40**	**-**	**-**	**300**	**-**	**-**	**-**	**0.1 %**	**-**	**-**	**-**	**400**	**2**	**100**

Table 2: Percentage yield of different liposphere formulations

Sr. No.	Formulation Code	Percentage Yield (Mean ± SD)
1	F4	64.38±0.0041
2	F5	68.49±0.0068
3	F8	82.10±0.041
4	F9	78.19±0.027
5	F10	89.26±0.074
6	F11	60.51±0.053
7	F12	74.49±0.014
8	F13	71.37±0.073
9	F14	84.26±0.017
10	F15	82.64±0.035

Table 3: Entrapment efficiency of different drug loaded liposphere formulations

Sr. no.	Formulation code	% Drug Entrapment Efficiency (mean±SD)
1.	F4	54.11 ±0.34
2.	F5	54.76 ±0.21
3.	F8	59.64± 0.25
4.	F9	31.14 ± 0.12
5.	F10	31.66 ± 0.36
6.	F11	41.66± 0.16
7.	F12	25.43± 0.28
8.	F13	19.73± 0.33
9.	F14	21.49± 0.27
10.	F15	35.52± 0.18

Table 4: *In-vitro* drug release data of optimized formulation (F8) and drug dispersion

Time (min.)	Drug dispersion	Liposphere Formulation
0	0±0	0±0
5	17.10±0.05	1.31±1.42
15	57.63±0.036	5.75±1.35
30	89.34±1.523	10.59±1.41
60	99.34±1.741	18.84±1.45
90	100.39±1.91	24.25±1.68
120	99.21±2.854	28.67±1.55
180	99.34±2.44	36.90±1.45
240	97.10±3.021	48.42±1.86

300	-	57.23±1.75
360	-	68.73±1.52
420	-	76.57±1.15

Table 5: Kinetic equation parameter of F8 formulation

Formulation Name	Zero order		First order		Higuchi		Korsymer-peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F8	0.989	7.404	0.981	-0.066	0.970	28.39	0.977	1.211

4. Conclusion

Lipospheres prepared by melt dispersion technique. For the optimization of Pravastatin sodium loading; 15 different formulations were prepared with different amounts of lipid and stabilizer. Microscopically evaluation of lipospheres formulation showed spherical size with average size 45.6 µm. Entrapment efficiency of Pravastatin sodium lipospheres formulations F1 to F15 was evaluated. From results, entrapment efficiency entrapment efficiency was found to be 59.64± 0.25% for F8 Pravastatin sodium loaded lipospheres formulations. Optimized formulations were incorporated in to capsules and *in vitro* drug release was studied in aqueous media using USP 1 dissolution apparatus. To know precisely, the rate and mechanism of drug release, the *in vitro* data was fitted to zero order, first order, Higuchi and Korsmeyer-Peppas model. The results showed that the drug release from all formulations followed zero order which describes that the Pravastatin sodium follows a diffusion mechanism for release from lipospheres.

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