IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
December 2019 Vol.:17, Issue:1

Formulation and Evaluation of Solid Liquid Microparticles in Provastatin Sodium Drug

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Ravindra Dhakad[1]*, Gurdeep Singh[1], M.K. Gupta[1], Naveen Sharma[2]

[1]Oriental College of Pharmacy and Research, Oriental University, Indore (M.P.)

[2]Amity Institute of Pharmacy, Amity University, Gwalior (M.P.)

Submission: 23 November 2019
Accepted: 29 November 2019
Published: 30 December 2019

Keywords: Solid-Liquid Microparticles (SLMs), Pravastatin Sodium, Poloxamer 11, Tween 80, Glycerol Mono Stearate

ABSTRACT

Pravastatin Sodium has a cholesterol-lowering agent. It has a shorter half-life and undergoes first-pass metabolism. The frequent dose is required in the case of the conventional dosage form. The purpose of the study is to formulate and evaluate the solid-liquid microparticles in the pravastatin sodium drug. There were nine formulations prepared by the homogenization method using Glycerol Mono Stearate (GMS), Tween 80, Poloxamer 188, Span 20 and PVPk40. The shape and surface morphology of prepared solid-liquid microparticles were characterized by optical and scanning electron microscopy respectively. They were evaluated for drug entrapment efficiency. From results, entrapment efficiency was varied in the range of 46.325±0.001 to 96.988±0.001. Formulation F6 was the optimized formulation among all Pravastatin Sodium formulations. Optimized formulations were tested for *in-vitro* drug release. Solid lipid microparticle showed the release of drug in a sustained manner 92.47±0.001 up to 12 hr. 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 Higuchi kinetics which describes that the SLMs follow a diffusion mechanism for release from SLMs. Pravastatin Sodium microcapsules were released and absorbed slowly over a prolonged period.

INTRODUCTION

Solid lipid particles were introduced in the early 1990s as an alternative drug carrier system to emulsions, liposomes, and polymeric microparticles. Although lipid nanoparticles have been the object of a substantial number of reviews, fewer are available on lipid microparticles (LMs), despite their distinct advantages, including biocompatibility, ease of production and characterization, extended-release properties and high loading. [1]

Pravastatin Sodium is a class of lipid regulating the drug, the statins which reduce cholesterol biosynthesis. This agent is a competitive inhibitor of HMG CoA reductase. It is an odor-free, white to faded white, fine or crystalline powder. It is a moderately polar, hydrophilic compound. It is, to some extent, rapidly absorbed from the gastrointestinal tract and undertakes extensive first-pass metabolism in the liver. The absolute bioavailability of Pravastatin Sodium is 17%. About 50% of the circulating drug is bound to plasma proteins. Plasma elimination half-life is 1.5 to 2 h. About 70% of the oral dose is excreted in the feces and about 20% is excreted in the urine. [2] Also, 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 the oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of the water-insoluble drugs.[5,6] Solid dispersion, drug micronization, lyophilization, microencapsulation, the 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 the 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 the solid hydrophobic fat core such as triglycerides or fatty acids derivatives, stabilized by a monolayer of phospholipids. [7,8,9]

MATERIALS AND METHODS:

MATERIALS:

Pravastatin sodium (PS) was a kind gift from Dr. Reddy Ltd., Ahemdabad, India. Glycerol Mono Stearate was purchased from Degussa India Pvt. Ltd., Germany; Poloxamer 188 was purchased from S. D. Fine Chemicals Ltd., Mumbai, India. tween80, span20, PVPk40 and other reagents were of analytical grade.

Drug Polymer Compatibility Studies:

Drug polymer interaction studies were carried out by using FTIR, UV, and X-ray diffraction studies. FTIR spectroscopy is a powerful tool for identifying types of chemical bonds and functional groups and checks the integrity of drug in the formulation. In the present study, a pinch of the pure drug was placed in the spectrophotometer and the spectrum was recorded. The characteristic peaks of the pure drug and drug peaks from the formulations were identified. It was performed by FTIR over frequency range 4000–400 cm^{-1} using Bruker Tensor 27 Germany. Absorption maxima (λ max) of the drug were determined by a UV spectrophotometer (Shimadzu Pharma. Spec 1800).

Preparation of SLMs:

Solid lipid microparticles dispersion was prepared by a hot homogenization technique on a weight basis. In the hot homogenization technique, a lipid matrix content of GMS (based on the total weight of SLM dispersion) was melted at 10°C above its melting point. 10mg w/w calculated as a percentage of lipid matrixes was added to the melted lipid. The dispersion was kept at the same temperature until it appeared optically clear. Poloxamer 188 (2.5% w/w used as a stabilizer) was dissolved in distilled water and heated to the same temperature as the lipid mixture. Hot poloxamer solution was added to the melted lipid–drug mixture and emulsified by a Remi high shear homogenizer basic at 8000 rpm for 15 min. The formulation was then removed from the water bath and mixed until cool**.** [10,11]

RESULTS AND DISCUSSION:

Characterization of SLMs:

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.

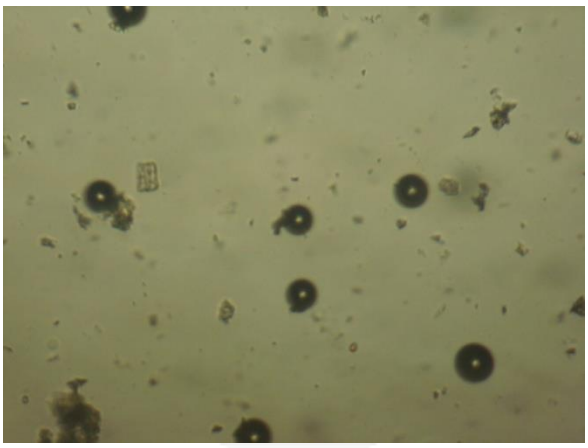

Figure No. 1: Optical microscope image of F6 formulation

Percentage Entrapment Efficiency, Yield and Drug Loading:

The nanoparticles were separated from the aqueous medium. In this method, 1 ml of final formulation was dissolved in 1ml of (1:1) ethanol and acetone then centrifuged at 15,000 rpm for 30 min at 4˚C, the resulting supernatant was analyzed using UV spectrophotometer scanning at 239 nm. The calibration curve of Pravastatin Sodium as shown in Figure 2 indicated the regression equation $Y = 0.055x + 0.015$ and R^2 value 0.998, which shows good linearity.

The amount of drug entrapped in the nanoparticles was determined as the difference between the total amount of drug used to prepare the nanoparticles and the amount of drug present in the aqueous medium. It was found that increasing the concentration of lipid percentage drug entrapment will increase an, but this increase and drug entrapment will follow a certain concentration of lipid after that no percentage entrapment will increase on the increasing

concentration of lipid. The maximum percentage of drug entrapment was found of formulation F6 that was 96.988±0.001.

Table No. 1: Percentage drug entrapment of different Pravastatin Sodium solid lipid nanoparticle formulations

S. No.	Formulation Code	Percentage drug entrapment
1	F1	46.325±0.001
2	F2	60.22±0.002
3	F3	72.386±0
4	F4	54.62±0.031
5	F5	23.181±0.006
6	F6	96.988±0.001
8	F7	58.958±0.001
9	F8	55.075±0.0005
9	F9	93.655±0.001

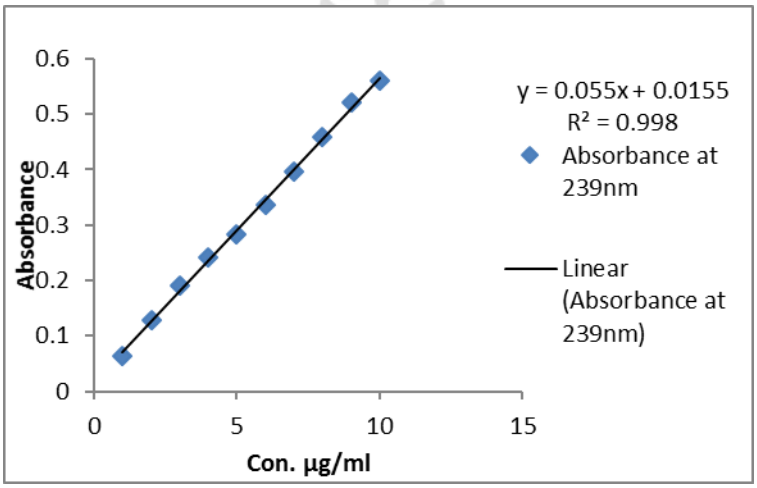

Figure No. 2: Calibration curve of Pravastatin Sodium in Water

FT-IR of Pure Drug

Drug polymer interaction studies were carried out to eliminate the possibility of interaction between drug and polymer used with the analytical method of drug estimation. The FT-IR spectrum of pure Pravastatin Sodium is shown in Figure 3. The infrared spectra of pure Pravastatin Sodium presented characteristic peaks at 3039.32 cm^{-1} (C-H stretching aromatic),

2912.29 cm^{-1} (C-H stretching alkane), 1669.64 cm^{-1} (C=O stretching), and 1297.54 cm^{-1} (C-N stretching).

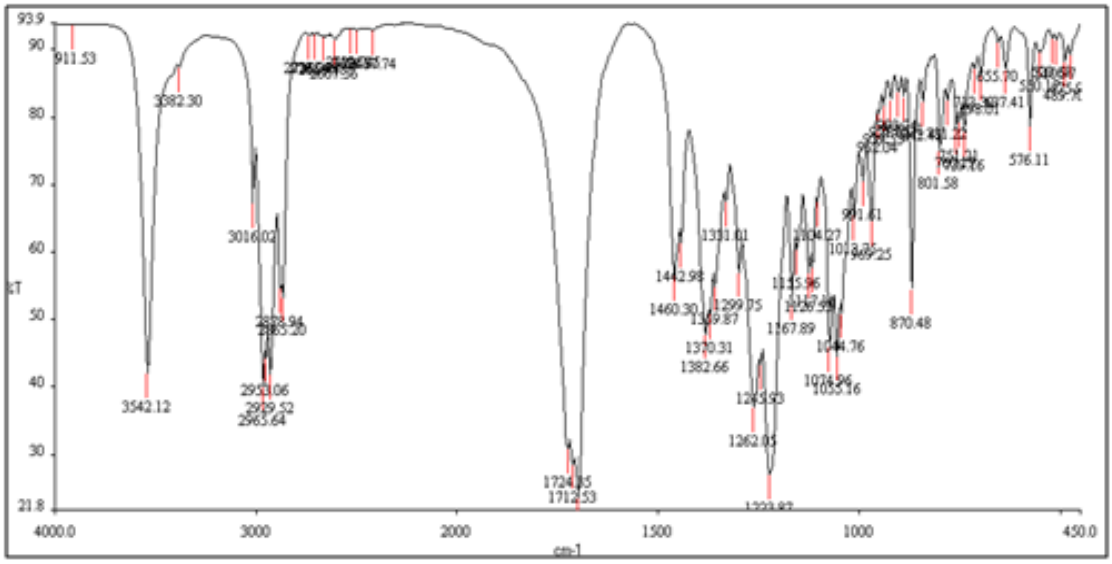

Figure No. 3: FT-IR spectra of pure Pravastatin Sodium

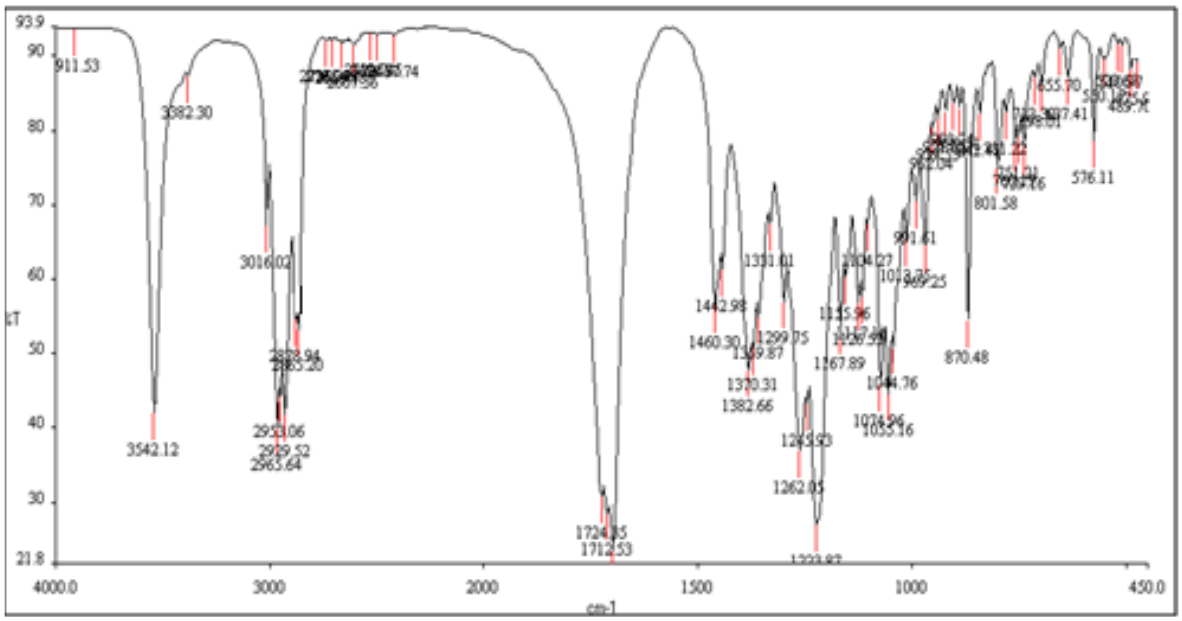

Figure No. 4: FT-IR spectra of Physical mixture (Pravastatin Sodium, GMS & Tween-80)

***In-vitro* Drug Release Studies:**

The *in-vitro* release rate of microparticles was evaluated by the dialysis bag method in distilled water up to 48 hr incubation period. The microparticulate lyophilized powder

equivalent to 10 mg of Pravastatin sodium-based SLMs was dispersed in 1 ml of media and placed in a dialysis membrane-70 (HIMEDIA, LA393 Mumbai, India) and sealed at both ends. The dialysis bag which acts as a donor compartment was immersed in the Receptor compartment containing 100 ml of simulated intestinal fluid 6.8 pH without enzyme which was stirred at medium speed and maintained at 37±2ºC. The receptor compartment was cover to prevent the evaporation of the diffusion medium. Samples were withdrawn at regular time intervals and the same volume was replaced by fresh diffusion medium. The samples were analyzed (simultaneous analysis) using a UV-visible spectrophotometer (Shimadzu UV 1800) at 239nm.

Drug release kinetics

The release kinetics was studied by various kinetic models like zero order plot, first-order plot, Higuchi plot, and Korsmeyer-Peppas.

To study the release kinetics of optimized formulation, data obtained from in vitro drug release studies were plotted in various kinetic models: zero-order as the amount of drug releases Vs time, first-order as log percentage of drug remaining Vs time, Higuchi model as a percentage of drug released Vs square root of time. The best fit model was confirmed by the value of the correlation coefficient near to 1.

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

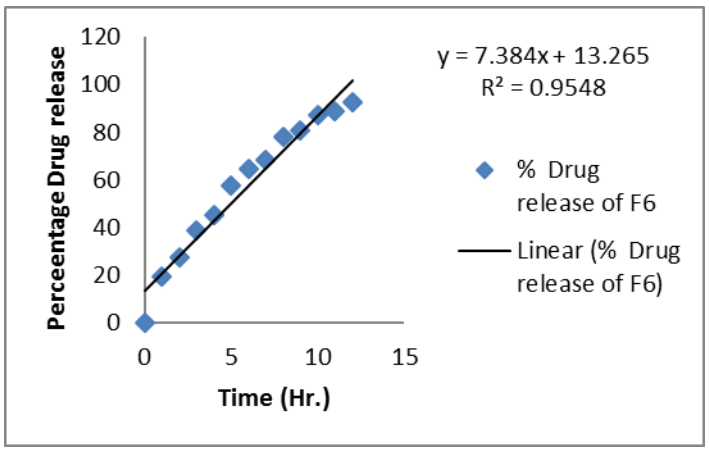

Figure No. 5: Zero-order graph for F6 solid lipid microparticles

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

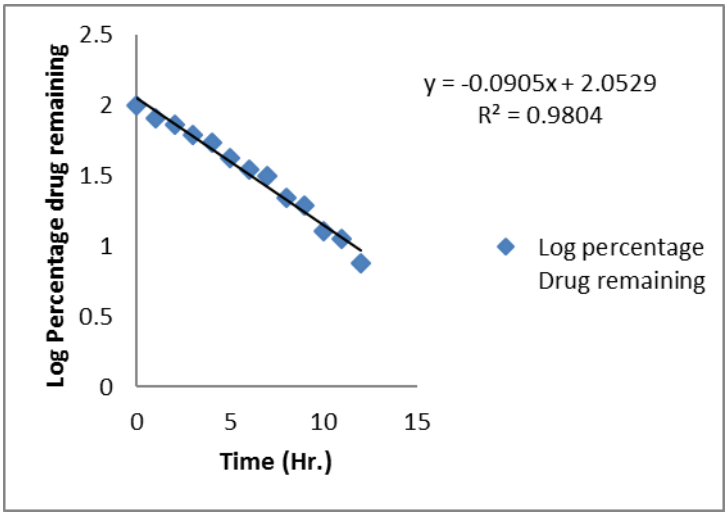

Figure No. 6: First order graph for F6 solid lipid microparticles

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

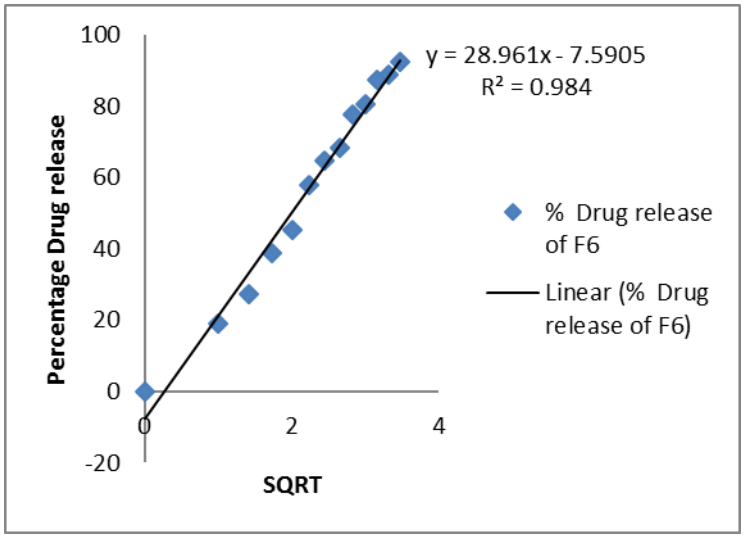

Figure No. 7: Higuchi model graph for F6 solid lipid microparticles

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

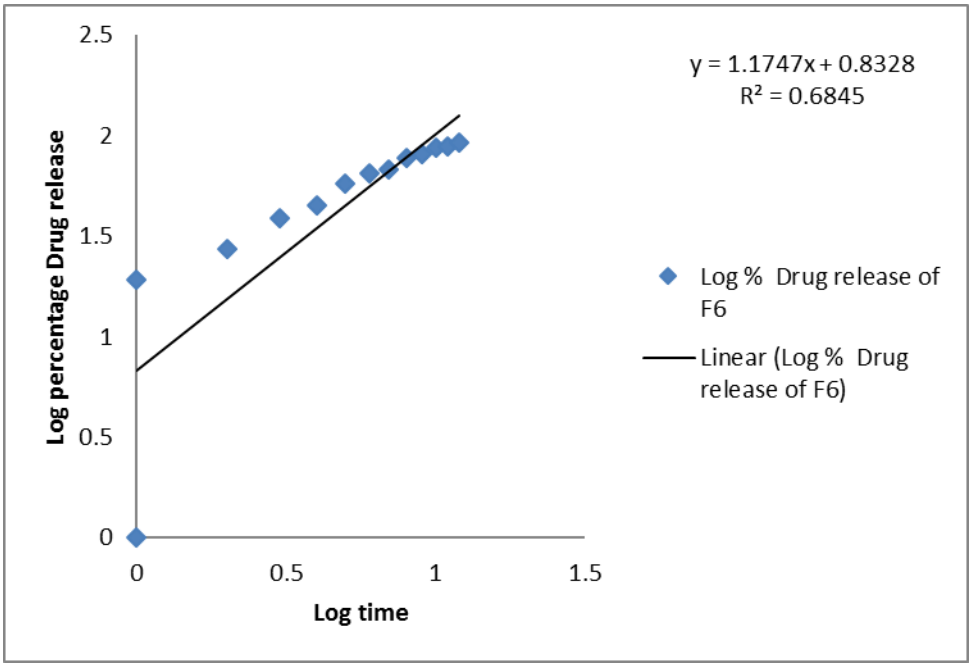

Figure No. 8: Korsmeyer –Peppas model graph for F6 solid lipid microparticles

The zero-order rates describe the system where the drug release independent of its concentration shows the cumulative amount of drug release Vs time for zero-order kinetics. The first-order rate describes the release from systems where the release of drugs from a matrix as a square root of a time-dependent process based on Fickian diffusion.

The calculated regression coefficients for zero-order, first-order, and Higuchi models and Korsmeyer were shown in Table No. 2, it was found that the *in-vitro* drug release of F6 solid lipid microparticles was best explained by Higuchi model as the plot showed the highest linearity. The value of R^2 found to be highest for the Higuchi model.

Table No. 2: Composition of Different Formulation Pravastatin Sodium solid lipid Microparticle

Formulation code	Pravastatin Sodium (mg)	GMS (mg)	Tween-80 (mg)	Poloxamer-188 (mg)	Span-20 (mg)	PVP k 40 (mg)
F1	10	100	-	-	-	-
F2	10	200	-	-	-	-
F3	10	300	-	-	-	-
F4	10	400	-	-	-	-
F5	10	500	-	-	-	-
F6	10	300	10	-	-	-
F7	10	300	-	10	-	-
F8	10	300	-	-	10	-
F9	10	300	-	-	-	10

Measurement of the particle size distribution

The particle size distribution of optimized formulation F6 was determined using zeta sizer.

The Polydispersity index (PI) was determined as a measure of homogeneity.

Table No. 3: Particle size distribution of F6 formulation

Formulation code	Size (d.nm)	PDI
F6	349.8nm	0.398

Percentage drug release study of solid lipid Microparticles

Percentage drug study of solid lipid nanoparticles was given in a table no.3.

Table No. 4: Percentage drug release study of solid lipid microparticles in simulated intestinal Fluid

Time(Hr.)	Percentage drug release of pure drug in simulated intestinal Fluid	Percentage drug release of F6 in simulated intestinal Fluid
0	0±0	0±0
1	8.56±0.003	19.06±0.001
2	12.67±0.002	27.46±0.002
3	19.55±0.004	38.9±0.005
4	25.69±0.001	45.13±0.001
5	32.42±0.001	57.80±0.001
6	38.00±0.001	64.76±0.004
7	39.87±0.006	68.26±0.002
8	41.23±0.0073	77.8±0.002
9	44.25±0.002	80.67±0.007
10	45.12±0.001	87.35±0.003
11	45.39±0.002	88.74±0.003
12	47.62±0.001	92.47±0.001

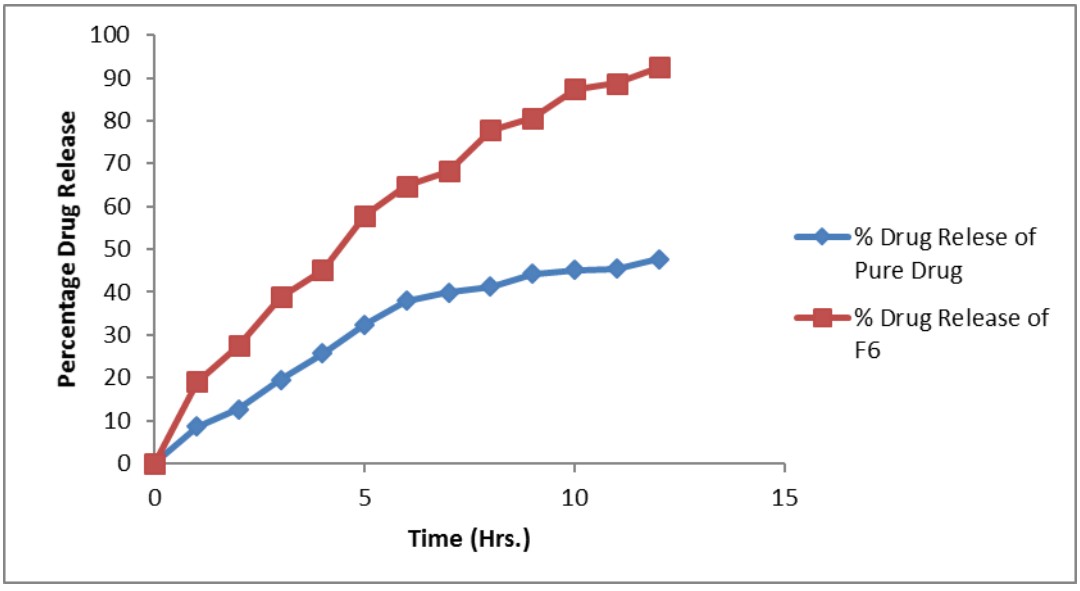

Figure No. 9: *In-vitro* Drug release of Pure Drug & F6 Formulation

Table No. 5: Kinetic equation parameter of formulation F6

Formulation name	Zero-order		First-order		Higuchi		Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F6 Solid lipid nanoparticle gel	**0.954**	**7.384**	**0.980**	**-0.090**	**0.984**	**28.96**	**0.684**	**1.174**

The zero-order rates describe the system where the drug release independent of its concentration shows the cumulative amount of drug release Vs time for zero-order kinetics. The first-order rate describes the release from systems where the release of drugs from a matrix as a square root of a time-dependent process based on Fickian diffusion.

The calculated regression coefficients for zero-order, first-order, and Higuchi models and Korsmeyer were shown in table no.5, it was found that the *in-vitro* drug release of F6 solid lipid microparticles was best explained by Higuchi model as the plot showed the highest linearity. The value of R^2 found to be highest for the Higuchi model.

SUMMARY AND CONCLUSION

Pravastatin Sodium is in a group of drugs called HMG CoA reductase inhibitors, or "statins." It reduces levels of "bad" cholesterol (low-density lipoprotein, or LDL) and triglycerides in the blood while increasing levels of "good" cholesterol (high-density lipoprotein, or HDL). By incorporation of Pravastatin Sodium in SLMs, the drug can be targeted directly to the site of action, thus enhancing its therapeutic efficacy.

Before the development of dosage forms, preformulation studies were carried out to characterize the chemical and physical properties of the drug substance. UV spectrum (λ_{max}-239nm), FTIR spectrum and melting point determination (169-175˚C) confirmed the identity and purity of the drug; Pravastatin Sodium. The lipid solubility of Pravastatin Sodium was determined in various lipids including Stearic acid, compritol, precious and GMS. It was observed from the lipid solubility studies that Pravastatin Sodium shows higher efficacy towards GMS i.e. 3.49±0.001. The results of preformulation studies suggested that the Pravastatin Sodium was pure and good in quality for the formulation development.

The calibration curve of Pravastatin Sodium in water was found to be linearly regressed with R^2 value of 0.998.

SLMs prepared by the homogenization method. For the optimization of Pravastatin Sodium loaded solid lipid microparticle; nine different formulations were prepared with different amounts of lipid and different types of stabilizers. The entrapment efficiency of Pravastatin Sodium SLMs formulations F1 to F9 was evaluated. From results, entrapment efficiency was varied in the range of 46.325±0.001 to 96.988±0.001. Formulation F6 was the optimized formulation among all Pravastatin Sodium formulations. The optimized batch of Pravastatin Sodium SLMs F6 formulation shows particle size distribution 349.8 nm measured by particle size analyzer.

Optimized formulations were tested for *in-vitro* drug release. Solid lipid microparticle showed the release of drug in a sustained manner 92.47±0.001 up to 12 hr. 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 Higuchi kinetics which describes that the SLMs follow a diffusion mechanism for release from SLMs.

REFERENCES

1. Scalia S, Young PM, Traini D. Solid lipid microparticles as an approach to drug delivery. Expert Opin Drug Deliv. 2015; 12(4): 583-99.
2. P. Kathleen, Ed., Martindale: The Complete Drug Reference, The Pharmaceutical Press, London, UK, 32nd edition, 1999.
3. MC Wake. Effects of biodegradable polymer particles on rat marrow-derived Stromal osteoblasts in vitro. Biomaterials. 1998; 19: 1255- 1268.
4. R Cortesi. Preparation of liposomes by reverse-phase evaporation using alternative organic solvents. J. Microencapsul. 1999; 16: 251-256.
5. SP Vyas, R Singh, D Dimitrijevic. Development and characterization of nifedipine lipospheres. Pharmazie. 1997; 52: 403-404.
6. V Jenning, AF Thünemann, SH Gola. Characterization of a novel solid lipid nanoparticle carrier system based on binary mixtures of liquid and solid lipids. Int. J. Pharm, 2000; 199: 167-177.
7. N Mohammed, K Bhise. Formulation and development of fenofibrate loaded liposphere. Int. J. Pharm. 2013; 3(1): 1-10.
8. P Leeladhar. lipospheres: recent advances in various drug delivery systems. Int. J. Pharm. 2013; 5(1): 2446-2464.
9. V Jannin, V Berard, A N'Diaye. Comparative study of the lubricant performance of Compritol 888 ATO either used by blending or by hot melt coating. Int J Pharm. 2003; 262: 39-45.
10. Swathi G, Prasanthi NL, Manikiran SS, Ramarao N. Solid Lipid Nanoparticles: Colloidal Carrier Systems for Drug Delivery. Int. J Pharm. Sci. Res. 2010; 1(12): 1-16.
11. Saraf S, Mishra D, Asthana A, Jain R, Singh S, Jain NK. Lipid Microparticles for mucosal immunization against Hepatitis B. Vaccine. 2006; 24: 45-56
12. Jahnke S. The Theory of High-pressure homogenization. In: Muller RH, Benita S and Bohm B, editors. Emulsions and Nanosuspensions for the formulation of poorly soluble drugs. Stuttgart: Medpharm Scientific Publishers. 1998; 177-200.
13. Yadav VR, Suresh S, Devi K, Yadav S. Novel Formulation of solid lipid microparticles of curcumin for an anti-angiogenic and anti-inflammatory activity for optimization therapy of inflammatory bowel disease. J Pharm Pharmacol. 2009; 61:311-321.