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Formulation and In-vitro Evaluation of Cabergoline Nanoparticles

Mala Jayaprakash[1], Dr. Chakka Gopinath[2]

[1,2]Jntua-Oil Technological and Pharmaceutical Research Institute

ABSTRACT

The study focused on the development and validation of a Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC) method for the quantification of cabergoline, followed by the formulation and characterization of cabergoline-loaded solid lipid nanoparticles (SLNs) for ocular delivery. The RP-HPLC method utilized a Hypersil ODS column with a mobile phase of acetonitrile: acetate buffer (60:40, pH 6.2) at a flow rate of 1.0 mL/min, achieving a retention time of 5.7 min and demonstrating linearity (R^2 = 0.9961) over 100–1000 ng/mL. Method validation confirmed precision, robustness, and stability.Cabergoline suspensions and aqueous dispersions were formulated using Carboxy Methyl Cellulose (CMC) as a suspending agent, exhibiting particle sizes of 0.97 µm and 2.9 µm, respectively. In-vitro drug release studies revealed 37.32% release from suspensions and 16.39% from dispersions over 8 hours. Ex-vivo corneal permeation studies demonstrated superior permeation from suspensions (2494.73 ng) compared to dispersions (67.63 ng).SLNs were prepared via hot homogenization and ultrasonication, with particle sizes ranging from 161–228 nm and zeta potentials of -25 to -33 mV. Drug release from SLNs followed sustained kinetics (Higuchi model, R^2 = 0.72–0.98), with 18.60% release over 8 hours. Stability studies confirmed the robustness of SLNs over three months. The findings suggest cabergoline SLNs as a promising system for enhanced ocular delivery and intraocular pressure (IOP) reduction.

Key words: Cabergoline, RP-HPLC, Solid lipid nanoparticles, Ocular delivery, Intraocular pressure, Sustained release

INTRODUCTION

Cabergoline, a dopamine agonist, has potential applications in managing intraocular pressure (IOP). However, its poor aqueous solubility and corneal permeability limit its efficacy. Nanoparticulate systems, particularly solid lipid nanoparticles (SLNs), offer a viable solution by enhancing drug solubility, stability, and corneal penetration.

This study aimed to:

1. Develop and validate an RP-HPLC method for cabergoline quantification.
2. Formulate cabergoline suspensions and aqueous dispersions for preliminary evaluation.
3. Optimize cabergoline-loaded SLNs for ocular delivery, assessing particle size, zeta potential, drug release, and corneal permeation.
4. Evaluate stability and release kinetics of SLNs.

The hypothesis was that SLNs would improve cabergoline's ocular bioavailability through sustained release and enhanced corneal permeation.

MATERIALS AND METHOD

Materials
Cabergoline, Carboxy Methyl Cellulose (CMC), tripalmitin, Span 80, Tween 80, PVP K-30, acetonitrile (HPLC grade), acetate buffer.

METHODS

RP-HPLC Method Development

Column: Hypersil ODS (250 × 4.6 mm, 5 µm).

Mobile phase: Acetonitrile: acetate buffer (60:40, pH 6.2).

Flow rate: 1.0 mL/min.

Detection: UV at 280 nm.

Validation: Linearity (100–1000 ng/mL), precision (intra-day, inter-day), robustness (wavelength, flow rate variations).

Formulation of Cabergoline Suspensions
Prepared using CMC as a suspending agent via homogenization.
Characterized for particle size, zeta potential, PDI, and pH.

Preparation of SLNs

Method: Hot homogenization coupled with ultrasonication.

Drug:lipid ratios: 1:1, 1:2, 1:3, 1:4 (w/w).

Characterization: Particle size (PCS), zeta potential, TEM, AFM, DSC, FTIR.

In-vitro and Ex-vivo Studies

Drug release: Dialysis membrane method (8 h).

Corneal permeation: Goat cornea model (2 h).

Stability Studies
Stored at 8°C and 25°C for 3 months; evaluated monthly for particle size, zeta potential, and drug content.

RESULTS AND DISCUSSIONS

RP-HPLC METHOD DEVELOPMENT FORCABERGOLINE
Method Validation

Table 1 Evaluation of the system suitability parameters for the determination of cabergoline

Parameters	Cabergoline
Retention time (min)	5.7
Tailing factor	0.74
Area	12516

Table 2 Evaluation of the system, method, inter-day and intra-day precision and analyst variation for the determination of cabergoline

Parameters	Cabergoline
	RSD (%) of peak area
System precision	0.03
Method precision	2.1
Analyst-1 variation	1.74
Analyst-2 variation	2.29
Inter-day variation	2.43
Intra-day variation	2.57

Table 3 Evaluation of robustness and solution stability for the determination of Cabergoline

Parameters	Test conditions	% RSD of peak area
Altered wavelength (nm)	275	1.74
Altered wavelength (nm)	280	0.05
Altered wavelength (nm)	285	2.02
Solution stability	Refrigerated temperature (8°C)	2.40
Solution stability	Room temperature (25°C)	2.37

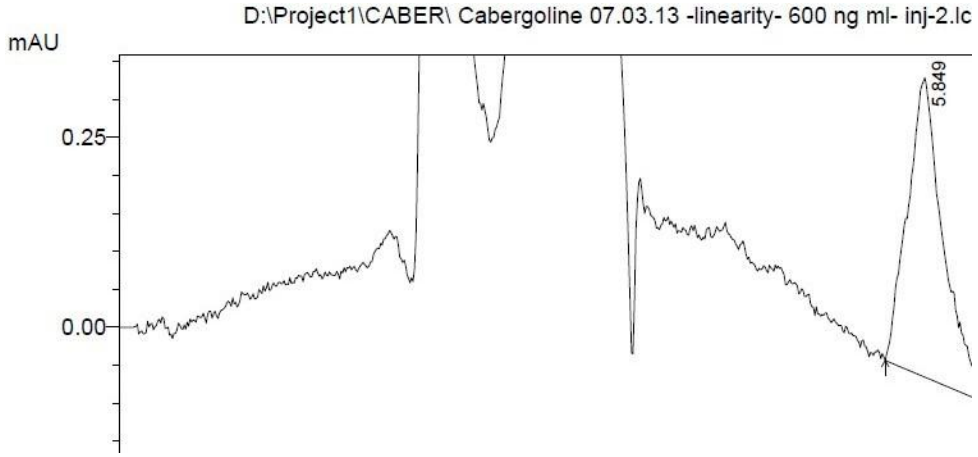


Figure 1 A typical HPLC chromatogram of Cabergoline

SCREENING OF IOP REDUCTION EFFICACY OF CABERGOLINE

Table 4 Average particle size, zeta potential, PDI and pH of cabergoline suspension and cabergoline aqueous dispersion

Formulations	Average particle size* (µm)	Zeta potential* (mV)	PDI	pH
Cabergoline suspension	0.97 ± 0.3	-38 ± 2.3	0.931	7.0
Cabergoline aqueous dispersion	2.9 ± 0.2	-17 ± 1.7	0.724	7.0

*Results are depicted as mean ± SD (n = 3).

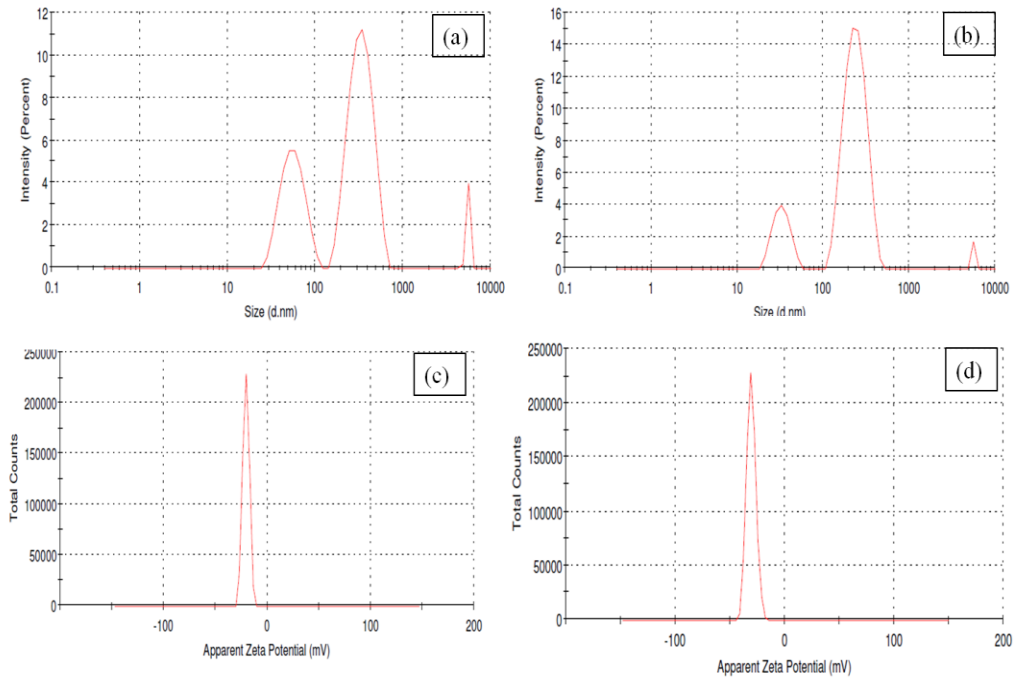


Figure 2 Average particle size and zeta potential

(a) Particle size of cabergoline suspension (b) Particle size of cabergoline aqueous dispersion (c) Zeta potential of cabergoline suspension and (d) Zeta potential of cabergoline aqueous dispersion

***In-vitro* Drug Release of formulated cabergoline suspension**

Table 5 *In-vitro* release data of cabergoline from cabergoline suspension and cabergoline aqueous dispersions

Time (min)	Amount of Cabergoline released (%)	
	Cabergoline suspensions*	Cabergoline aqueous dispersions*
0	00.00±0.00	00.00±0.00
15	05.95±0.63	02.56±0.23
30	07.14±0.65	02.67±0.24
45	08.56±0.68	03.44±0.30
60	09.81±0.70	03.90±0.35
90	12.40±0.83	05.54±0.58
120	13.17±1.13	08.06±0.81
180	16.50±1.24	09.85±0.88
240	17.33±1.46	11.70±1.05
300	21.61±1.96	12.17±1.09
360	26.61±1.52	13.60±1.13
420	29.05±1.96	15.39±1.47
480	37.32±1.38	16.39± 1.56

*Results are depicted as mean ± SD (n = 3).

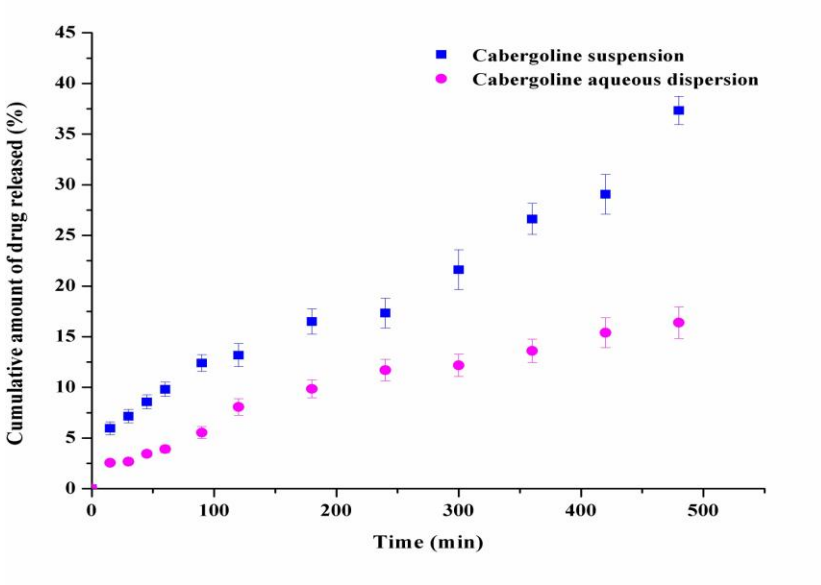


Figure 3 *In-vitro* release profile of cabergoline from cabergoline suspension and cabergoline aqueous dispersion

***Ex-vivo* Corneal Permeation by Using Goat Cornea**

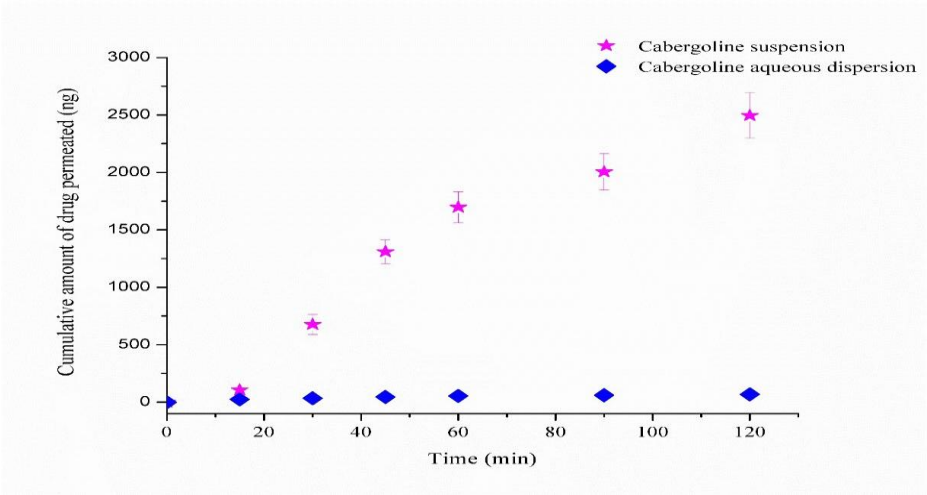


Figure 4 *Ex-vivo* corneal permeation of cabergoline from cabergoline suspension and cabergoline aqueous dispersion across goat cornea

Table 6 *Ex-vivo* drug permeation of cabergoline suspension and cabergoline aqueous dispersions

Time (min)	Amount of Cabergoline permeated (ng)	
	Cabergoline suspensions*	Cabergoline aqueous dispersions*
0	00.00±0.00	00.00±0.00
15	106.01±8.48	24.31±0.72
30	676.20±86.09	34.23±1.02
45	1309.13±104.73	44.79±1.34
60	1697.19±135.77	54.18±1.62
90	2004.73±160.37	59.52±1.78
120	2494.73±199.57	67.63±2.02

*Results are depicted as mean ± SD (n = 3).

STERILIZATION OF CABERGOLINE

Drug - Excipients Compatibility Study by using FTIR

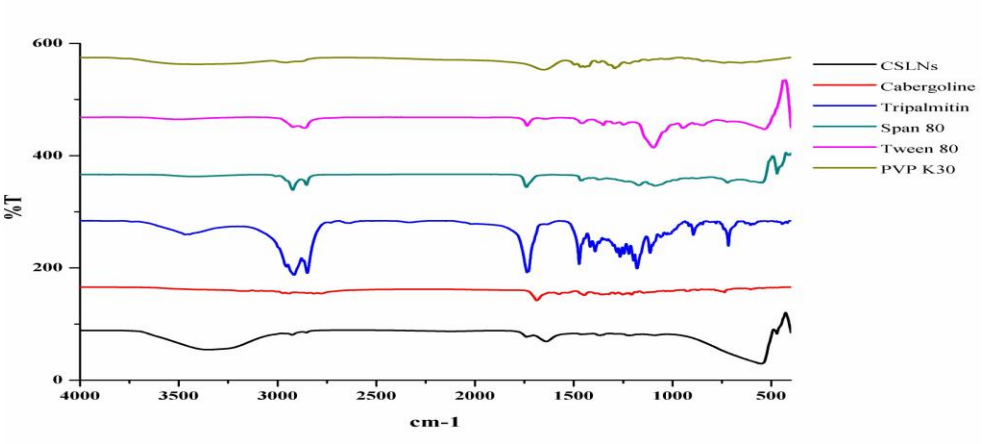


Figure 5 FTIR graph of Cabergoline SLNs, pure drug Cabergoline and other excipients compatibility

Differential Scanning Calorimetry Analysis

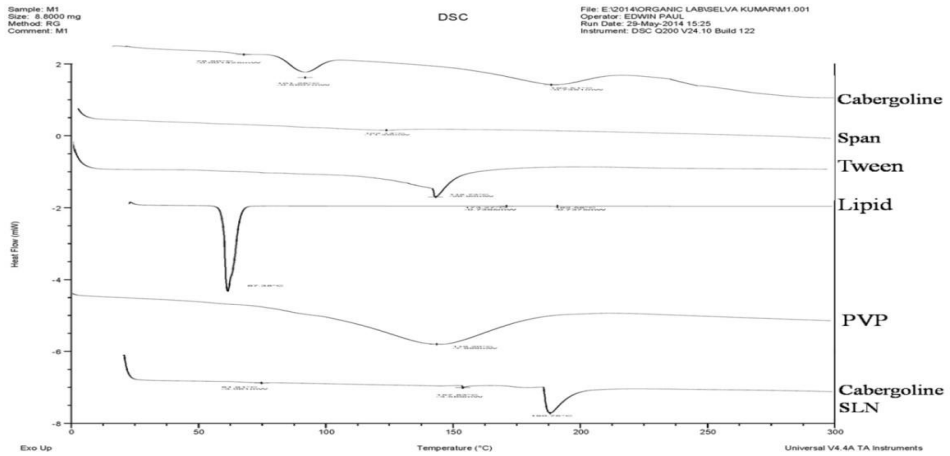


Figure 6 Differential Scanning Calorimetry of Cabergoline Solid lipid nanoparticles and excipients

Particle Size and Zeta Potential Measurements

Table 7 Average particle size and zeta potential & PDI of various concentrations of Cabergoline SLNs

Formulation Code	Average particle size (nm)	Zeta potential (mV)	PDI
CSLNs-F1	161.1 ± 16.1	-27 ± 2.7	0.461
CSLNs-F2	182.7 ±18.2	-33 ± 3.3	0.268
CSLNs-F3	224.4 ± 22.4	-26 ± 2.6	0.290
CSLNs-F4	228.4 ± 22.8	-25 ± 2.5	0.358

Results are depicted as mean ± SD (n = 3).

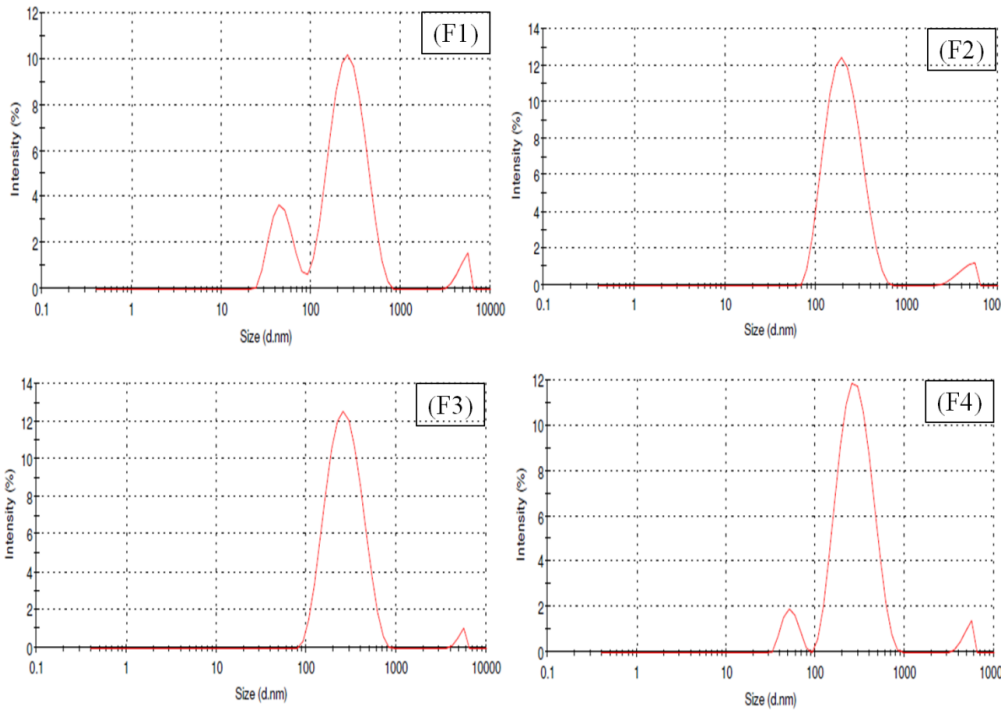


Figure 7 Average particle size of Cabergoline Solid Lipid Nanoparticles. CSLNs-F1, CSLNs-F2, CSLNs-F3 and CSLNs-F4

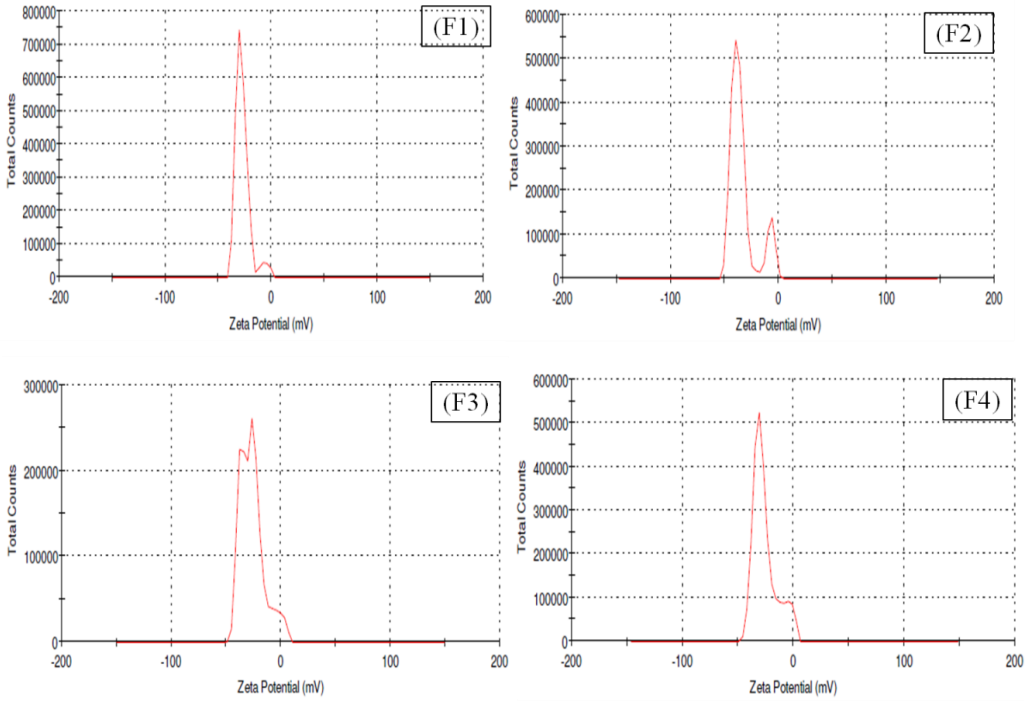


Figure 8 Zeta potential of Cabergoline Solid Lipid Nanoparticles. CSLNs-F1, CSLNs-F2, CSLNs-F3 and CSLNs-F4 Osmolality, pH and Drug Content

Table 8 Osmolality, pH and Drug content of Cabergoline SLNs

Formulation Code	Osmolality Osmol/kg	pH	Drug content (%)
CSLNs-F1	337±10	7.0±0.10	98±1
CSLNs-F2	337±15	7.1±0.15	99±.5
CSLNs-F3	338±10	7.2±0.20	99±.5
CSLNs-F4	339±20	7.3±0.10	98±1

Results are depicted as mean ± SD (n = 3).

Morphological Analysis

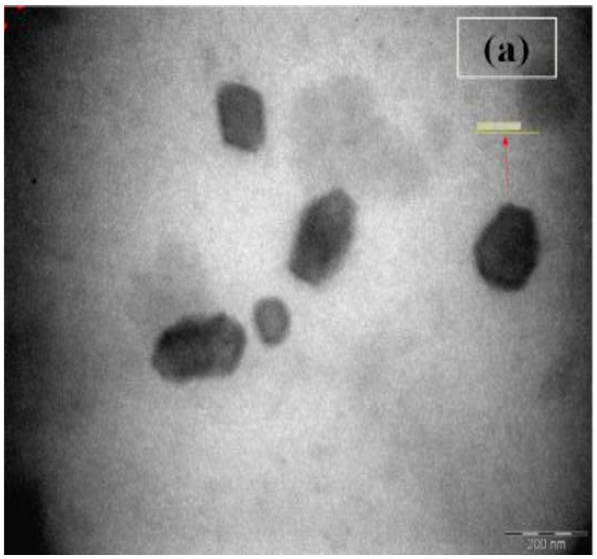


Figure 9 TEM photograph. (a) Cabergoline solid lipid nanoparticles

Atomic Force Microscopy

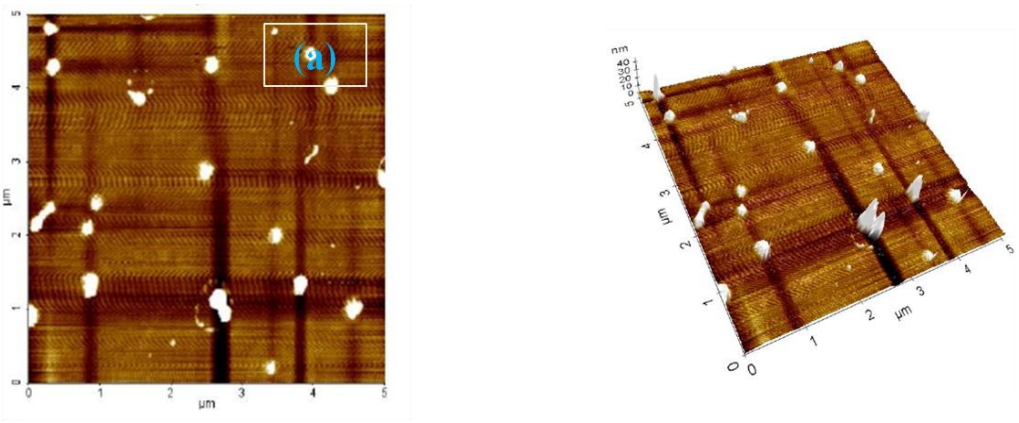


Figure 10 AFM images Cabergoline solid lipid nanoparticles

***In-vitro* Drug Release**

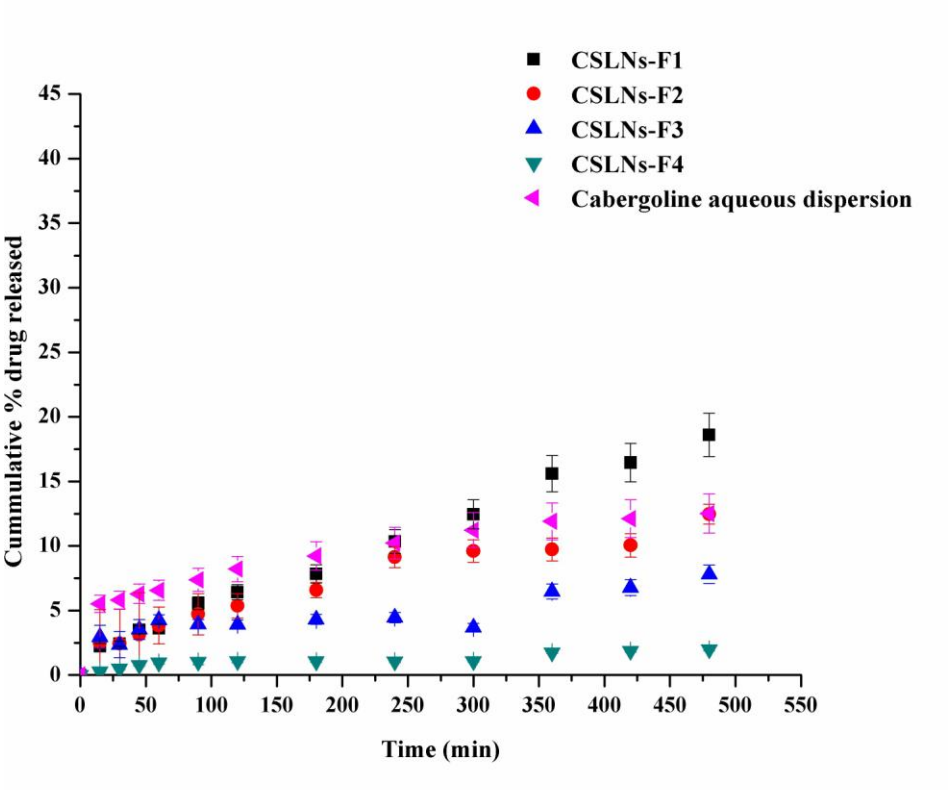
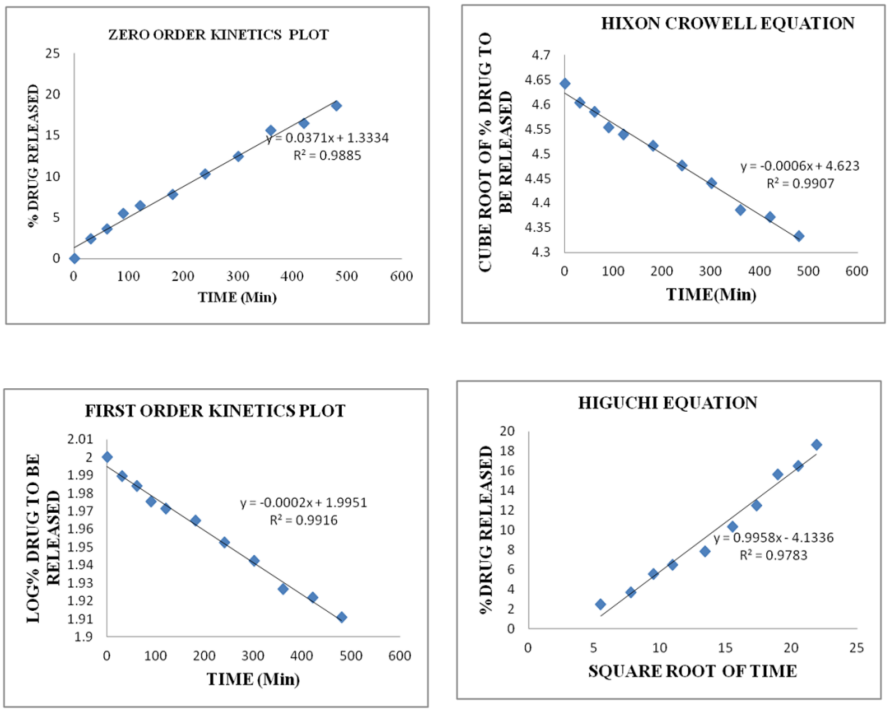


Figure 1 1 *In-vitro* drug release of Cabergoline solid lipid nanoparticles and Cabergoline aqueous dispersion

Release Kinetics



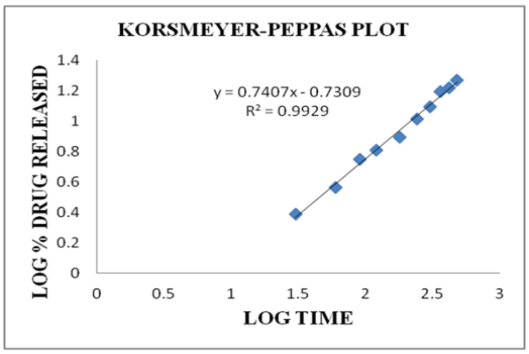


Figure 12 Drug release kinetics model plots for Cabergoline SLNs (CSLNs-F1)

Table 9 Release kinetics model fitting parameters for the release of Cabergoline from the Cabergoline SLNs

Formulation code	Model					
	Zero order	First order	Higuchi	Korsmeyer-peppas		Hixson crowell
	R^2	R^2	R^2	R^2	"n"	R^2
CSLNs-F1	0.988	0.991	0.978	0.992	0.740	0.990
CSLNs-F2	0.903	0.901	0.905	0.909	0.414	0.920
CSLNs-F3	0.767	0.772	0.734	0.712	0.445	0.771
CSLNs-F4	0.892	0.793	0.874	0.784	0.285	0.894
Cabergoline aqueous dispersion	0.777	0.796	0.722	0.989	0.297	0.994

Stability Studies

Table 10 Stability Studies

Formulations	Months	Average particle size (nm)	Zeta potential (mV)	PDI	pH	Drug content (%)
Cabergoline	1	221	-33	0.342	7.2	97±1.2
Solid	2	223	-33	0.342	7.2	97±1.4
Nanoparticle	3	225	-33	0.342	7.2	97±1.6

CONCLUSION

The study successfully developed a validated RP-HPLC method for cabergoline analysis and demonstrated that cabergoline-loaded SLNs significantly enhance corneal permeation and sustain drug release compared to suspensions and aqueous dispersions.

The optimized SLNs (161 nm, -27 mV) exhibited excellent stability and release kinetics, making them a promising candidate for ocular delivery to reduce IOP. Future studies should focus on in-vivo efficacy and safety evaluations.

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