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To Design And Development Of Liquid Crystals Containing Sulfamethoxazole Capsule For Oral Delivery

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Abstract

The objective of the present work was to formulate, develop, and evaluate liquid crystals formulation containing Sulfamethoxazole for oral delivery to deliver in sustain release manner. It sustain release of drug leading to minimize the peak and valley effect in plasma and provide patient convenience. The primary objective of liquid crystals drug delivery system is to ensure safety and to improve the efficacy of the drug as well as patient compliance, by lessen the frequency of dosing. In present study total numbers of nine formulations are prepared while applying the central composite factorial design. The formulation was prepared by magnetic stirrer method using oleic acid as a base. The formulations were then optimized on the basis of minimum particle size and maximum entrapment efficiency. The poloxamer 407 is used as a stabilizer and 2% is used to formulate the optimized batch because this ratio is providing the smaller globule size. It helps to reduce the particle size by the reduction in interfacial tension between aqueous and lipid phase. (Ola, 2016) Optimized batch (F2) dried with the help of a spray dryer..

Keywords Liquid crystals, Sulfamethoxazole, Infrared Spectroscopy, Differential scanning calorimeter.

Introduction

The study of liquid crystals began in 1888 when an Austrian botanist named Friedrich Reinitzer observed that a material known as cholesteryl benzoate had two distinct melting points. In his experiments, Reinitzer increased the temperature of a solid sample and watched the crystal change into a hazy liquid. As he increased the temperature further, the material changed again into a clear, transparent liquid. Because of this early work, Reinitzer is often credited with discovering a new phase of matter – the liquid crystal phase. A liquid crystal is a thermodynamic stable phase characterized by anisotropy of properties without the existence of a three-dimensional crystal lattice, generally lying in the temperature range between the solid and isotropic liquid phase, hence the term mesophase. Liquid crystal materials are unique in their properties and uses. As research into this field continues and as new applications are developed, liquid crystals will play an important role in modern technology. This tutorial provides an introduction to the science and applications of these materials. What are Liquid Crystals? Liquid crystal materials generally have several common characteristics. Among these is a rod like molecular structure, rigidness of the long axis, and strong dipole and/or easily polarizable

substituents. A dipole is present when we have two equal electric or magnetic charges of opposite sign, separated by a small distance. In the electric case, the dipole moment is given by the product of one charge and the distance of separation. Applies to charge and current distributions as well. In the electric case, a displacement of charge distribution produces a dipole moment, as in a molecule. The distinguishing characteristic of the liquid crystalline state is the tendency of the molecules (mesogens) to point along a common axis, called the director (the molecular direction of preferred orientation in liquid crystalline mesophases). This is in contrast to molecules in the liquid phase, which have no intrinsic order. In the solid state, molecules are highly ordered and have little translational freedom. The characteristic orientational order of the liquid crystal state is between the traditional solid and liquid phases and this is the origin of the term mesogenic state, used synonymously with liquid crystal state. Note the average alignment of the molecules for each phase in the following diagram. (Zhao, 2005; Dierking, et. al., 2017)

Characterizing Liquid Crystals:

The following parameters describe the liquid crystalline structure: • Orientational order: Measure of the tendency of the molecules to align along the director on a long-range basis. • Positional order: The extent to which the position of an average molecule or group of molecules shows translational symmetry.

Classification of Liquid Crystals:

The liquid crystals are categorized into two main categories i.e. thermo tropic and lyotropic. These categories are further illustrious into various phases reliant on the variations in their orientational or positional order under the effect of external factors such as per temperature. They are shows in Figure 1.

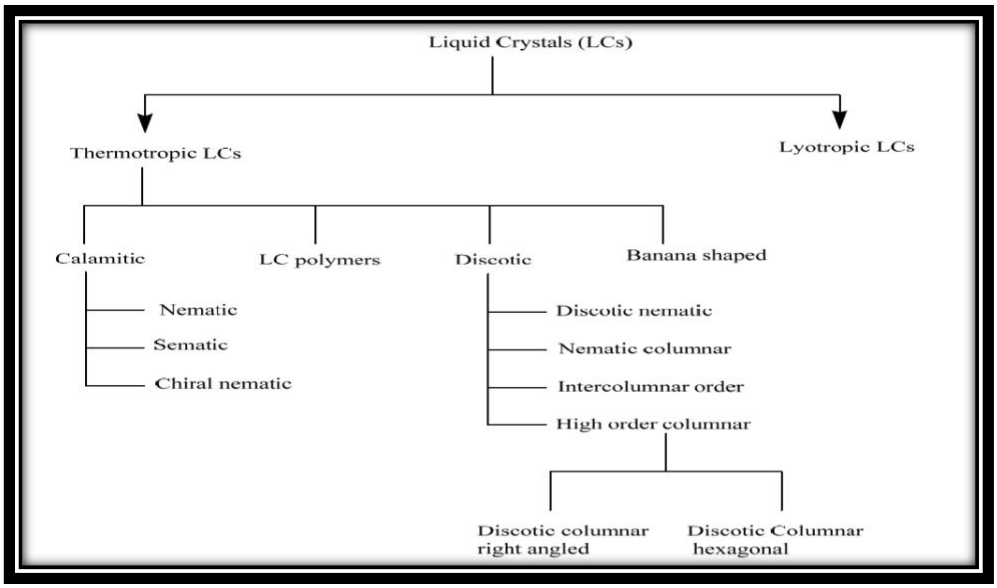

Fig No 1. Classification of Liquid Crystals

Advantage of liquid crystals:

1. Greater drug contents surface area and cubic crystalline structures because of the high center.
2. The comparatively simple process of preparation.
3. Biodegradability of lipids.
4. The capability of encapsulating amphiphilic, hydrophilic, hydrophobic substances possible.
5. Controlled release & targeted release of bioactive agents

6. Although maximum liquid crystalline systems convert into micelles at advanced levels of dilution.

Method of preparation of LCs:

(a) Probe Sonication
(b) Spray drying
(c) Bottom-up approach
(d) Heat treatment
(e) Top-down approach
(f) Magnetic Stirrer

Applications of Liquid Crystals:

1. Oral drug delivery
2. In topical and mucosal depositions
3. Controlled-Release Drug Delivery
4. Intravenous drug delivery systems
5. Topical drug delivery systems

EXPERIMENTAL WORK

Materials and Methods

Confirmation of Drug:

Confirmation of drug was carried out by using following method such as melting point determination, UV spectroscopy, infrared spectroscopy, and differential scanning calorimetry (DSC) and compared with standard.

1. Melting Point Determination:

Melting point determination is prime requirement for the confirmation of drug.

2. UV Spectrophotometer:

Accurately weighed 10 mg of Sulfamethoxazole was dissolved in 100 mL of ethanol to obtain working standard solution of 100µg/ml.

3. Infrared Spectroscopy:

IR spectrum of drug was measured in the solid state as potassium bromide (KBr) mixture.

4 DSC Study:

The thermal behavior of pure drug was determined by using, Differential Scanning Calorimetry.

Standard calibration curve of Sulfamethoxazole in 1.2, 6.8 and 7.4 pH buffer:

a) Standard calibration curve in Ethanol:

Accurately weighed 10 mg of Sulfamethoxazole was dissolved in 100 mL of ethanol to obtain working standard solution of 100 µg/ml.

b) Standard calibration curve in pH 1.2 buffer:

Accurately weighed 10 mg of Sulfamethoxazole was dissolved in 100 mL of pH 1.2 buffer solution to obtain working standard solution of 100 µg/ml.

c) Standard calibration curve in pH 6.8 Phosphate Buffer:

Accurately weighed 10 mg of Sulfamethoxazole was dissolved in 100 mL of pH 6.8 buffer to obtained working standard of 100 µg/ml.

d) Standard calibration curve in pH 7.4 Phosphate Buffer:

Accurately weighed 10 mg of Sulfamethoxazole was dissolved in 100 mL of pH 7.4 buffer to obtained working standard of 100 µg/ml.

Solubility Study of drug:

a) Solubility study of Sulfamethoxazole in various lipids:

The solubility of Sulfamethoxazole in oleic acid, GMS, GMO and labrafac.

b) Solubility study of Sulfamethoxazole in ethanol, water and various buffers:

The solubility of Sulfamethoxazole in ethanol, water and various media with varying pH was studied.

Drug Polymer Interaction Study:

The drug-excipients interaction study was carried out by using FTIR & DSC.

1. FTIR spectroscopy study:

IR spectroscopy was used to determine the molecular interaction between polymer and drug.

2. DSC study:

Plain drug, physical mixtures of drug and polymers were filled in the prewashed, dried ampoules and sealed.

Formulation and Development:

A) Magnetic stirring method:

In the magnetic stirring method, a pre-emulsion was obtained under stirring by adding liquid lipid to a mixture of surfactants and water.

B) Composition of process optimization:

In the process used drug, lipid, surfactant and aqueous phase.

C) Process of preliminary trials for set the different ratio:

For the preparation of oleic acid-based liquid crystals containing Sulfamethoxazole,

Development and Optimization Sulfamethoxazole loaded LCs:

Following Table 8 is the central composite design with the content of concentration of lipid (X1), and Surfactant (X2) as independent variables or MPS and EE as responses.

Characterization of Liquid crystals formulation:

Particle Size Measurements: The particle size was determined by photon correlation spectroscopy using a Zetasizer Nano® (Malvern Instruments, Malvern, UK) at 25°C. Samples were diluted with deionized water prior to the measurement, and dispersant viscosity was set to 0.8872 cP at 25°C.

Zeta potential of the P-LCs: Zeta potential measurements were run at 25°C with an electric field strength of 23 V/m, using zetasizer (Nano ZS 90, Malvern Instruments, UK).

Encapsulation Efficiency: Here ethanol used for determination of entrapment efficiency (EE) because the solubility of both drug and lipid in the same solvent as ethanol, so used the mobile phase for EE.

Spray Drying of P-LCs:

The P-LCs aqueous dispersion with 3 % lactose was spray dried in at 120°C till the dried powder is obtained. Then the samples were kept in desicator seal pack in a suitable container.

Characterization of spray-dried liquid crystals:

The characterization of dried powder LCs process is same as done before in LCs characterization.

1.Particle Size and PDI Measurements

2.Zeta potential

3.Encapsulation Efficiency

4.Scanning Electron Microscopy

5.X-Ray Diffraction

Preformulation study of spray dried LCs:

Preformulation parameter like Bulk density, Tap density, Angle of repose, Hausner's ratio was obtained from LCs powder.

1. Bulk density:

A suitable amount of powder blend from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 100 mL measuring cylinder.

2. Angle of repose:

The angle of repose was measured according to the fixed funnel and free-standing core method of Banker and Anderson.

3. Hausner's ratio:

It is the ratio of tapped to bulk density and was calculated by using the eqn.

Hard gelatin capsule as a finished product:

Sulfamethoxazole after preparation of P-LCs enhanced solubility as well as the minimized the dose frequency al., 2015)

Evaluation of filled capsules:

The capsules evaluated for weight variation, drug content uniformity.

1. Weight variation test:

Filling the 20 capsules in equal amount with powder formulation, each capsule is contained 92.89 mg powder formulation weighed individually and the average weight was determined.

2. Drug content uniformity:

For the drug content uniformity test 10mg of liquid crystals, the powders was weighted and dry LCs to a fine powder, and a quantity of powder equivalent to 100 mg of the formulation was dissolved in 100 mL ethanol and the liquid was filtered using whatman filter paper and diluted up to 50mg/ml.

3. In vitro dissolution study:

The drug release study was carried out using a dissolution study apparatus (USP Apparatus I, basket type). The dissolution medium was having pH 1.2.

Stability studies of P-LCs:

The LCs powder sample of final optimized formulation was utilized for carrying out accelerated stability.

RESULT AND DISCUSSION

Confirmation of Drug:

Confirmation of the drug was carried out by the following methods:

UV Spectroscopy:

Sulfamethoxazole solution was scanned at 400 nm to 200 nm, the maxima were observed at 256nm.

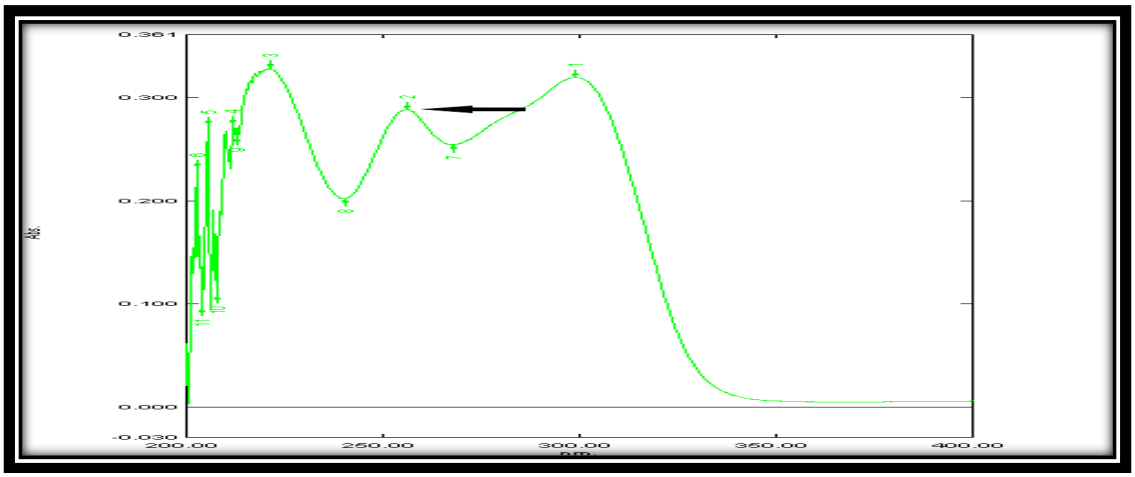

Fig-2 UV Spectra of Sulfamethoxazole Pure drug

Infrared Spectrum:

IR spectrum of the drug was measured in the solid state as potassium bromide dispersion.

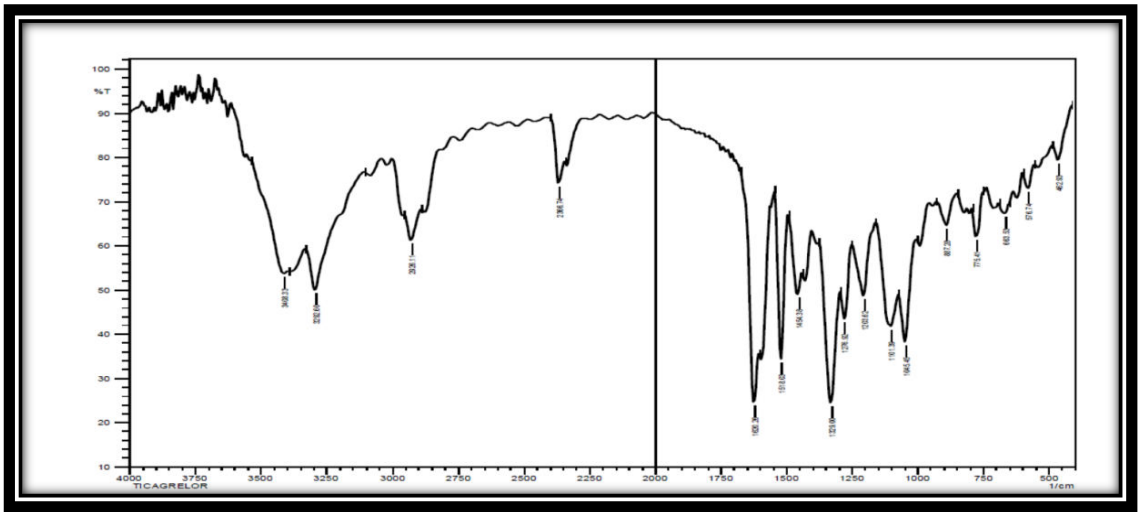

Fig-3 IR Spectra of Pure Sulfamethoxazole

DSC:

Sulfamethoxazole was confirmed by differential scanning calorimetry at a scan rate of 10°C/min and corresponding to its melting point with end set temperature 200°C.

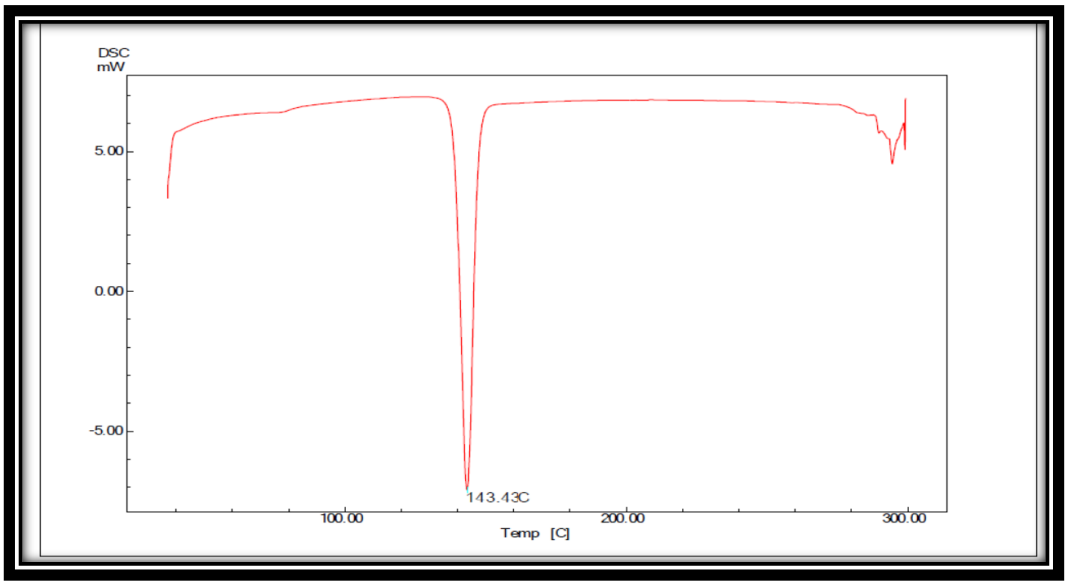

Fig-4 DSC Thermogram of a) Pure Sulfamethoxazole b) Reference

Table-1 DSC of Pure Drug

Sr no.	Parameter	Values Obtained (°C)
1	Onset Point	138.80
2	Peak Point	141.03
3	End Point	143.44

Melting point determination:

The melting point of Sulfamethoxazole was measured by capillary method and found to be in the range of 139° -142°C.

Standard calibration curve of Sulfamethoxazole:

Standard calibration curve of Sulfamethoxazole in 1.2 pH buffer:

Graph of absorbance Vs concentration was plotted and found to be linear over the range of 0.5 to 3µg/ml, indicating its compliance with Beer's Lambert's law.

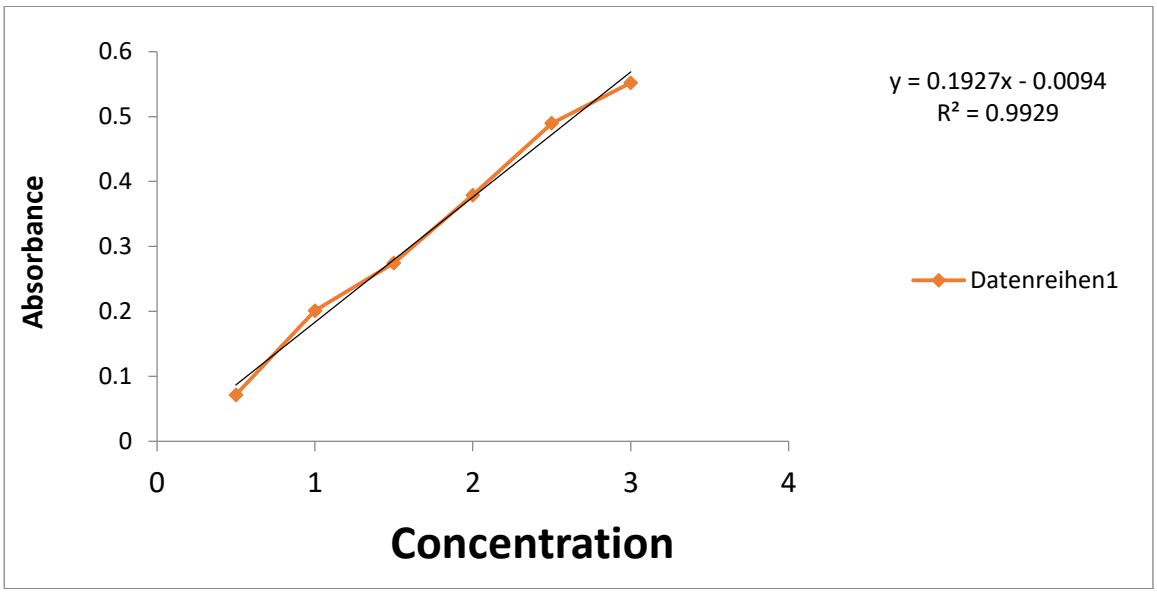

Fig- 5 Standard calibration curve of Sulfamethoxazole in 1.2 pH buffer

Standard calibration curve of Sulfamethoxazole in 6.8 pH phosphate buffer:

Graph of absorbance Vs concentration was plotted and found to be linear over the range of 0.5 to 3µg/ml indicating its compliance with Beer's and Lambert's law.

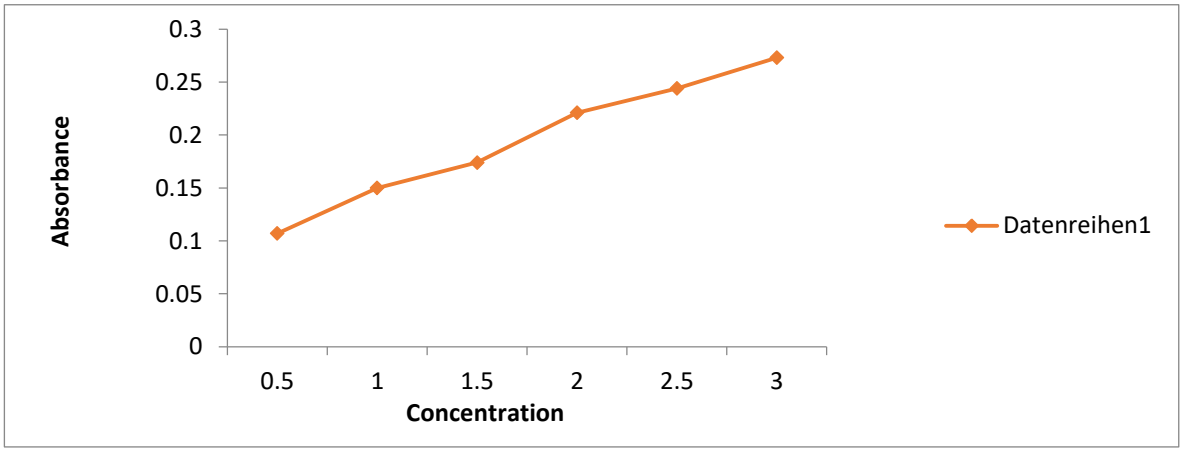

Fig-6 Standard calibration curve of Sulfamethoxazole in 6.8 pH buffer

Standard calibration curve of Sulfamethoxazole in Ethanol:

Graph of absorbance Vs concentration was plotted and found to be linear over the range of 0.5 to 3µg/ml indicating its compliance with Beer's and Lambert's law.

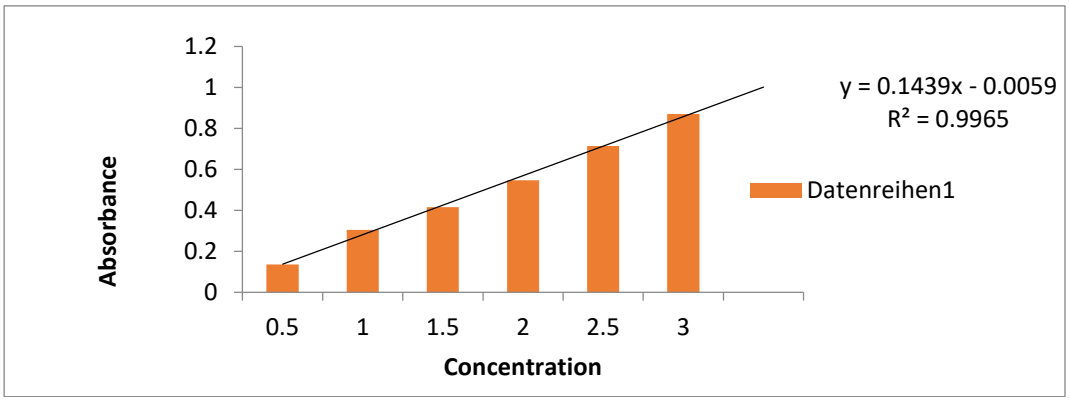

Fig-7 Standard calibration curve of Sulfamethoxazole in Ethanol

Standard calibration curve of Sulfamethoxazole in pH 7.4 buffer solution:

Graph of absorbance Vs. concentration was plotted and found to be linear over the range of 0.5 to 3µg/ml indicating its compliance with Beer's and Lambert's law.

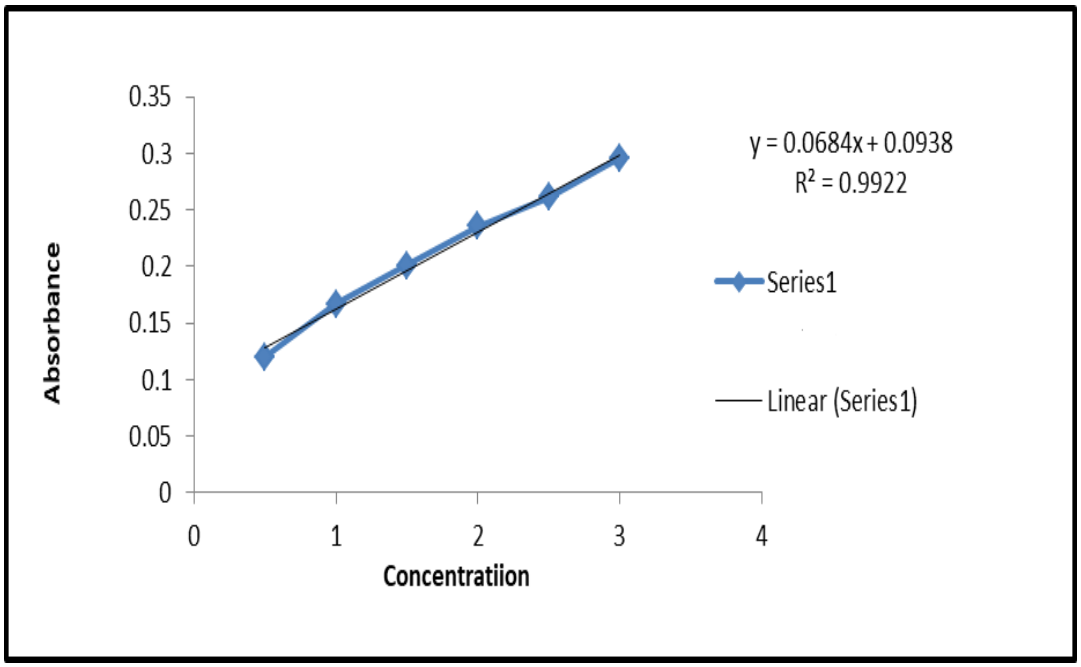

Fig-8 Standard calibration curve of Sulfamethoxazole in pH 7.4 buffer solution

Solubility study of the drug:

Solubility study of Sulfamethoxazole in various lipids:

Based on the solubility of lipids for the maximum solubility of the drug as tabulated in Table15

Solubility study of Sulfamethoxazole in ethanol, water and various buffers:

According to the study drug is freely soluble in ethanol, slightly soluble in phosphate buffer pH 1.2 in which 1.8 µg/ml drug is soluble, pH 6.8 in which 18.2µg/ml, pH 7.4 in which 16.3µg/ml and the insoluble in water.

Drug-excipients interaction study:

DSC:

The DSC thermogram for pure Sulfamethoxazole observed endothermic peak at 141.03 °C.

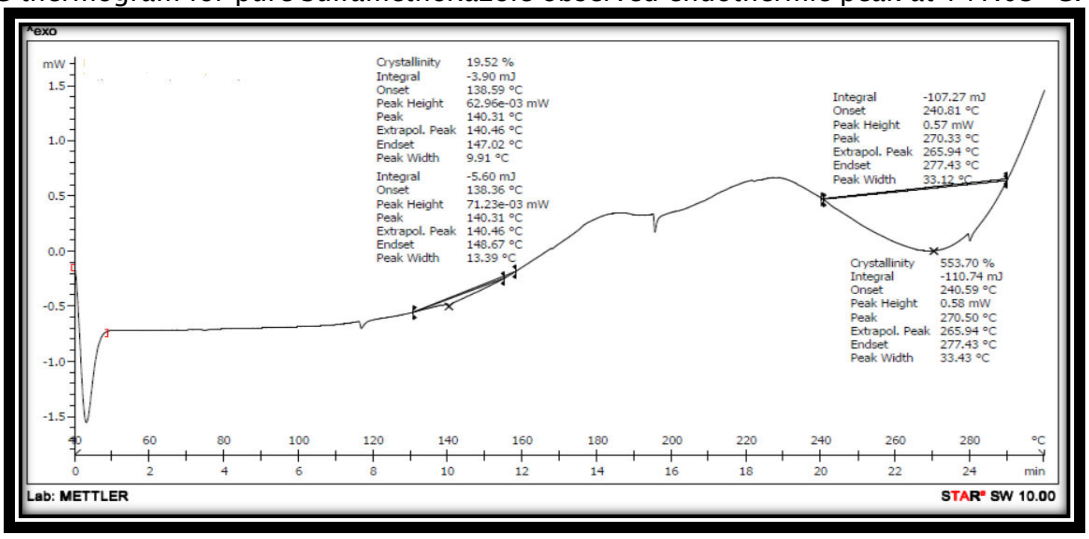

Fig-9 DSC Thermogram of Physical Mixture and Drug

Fourier transformed infrared spectroscopy:

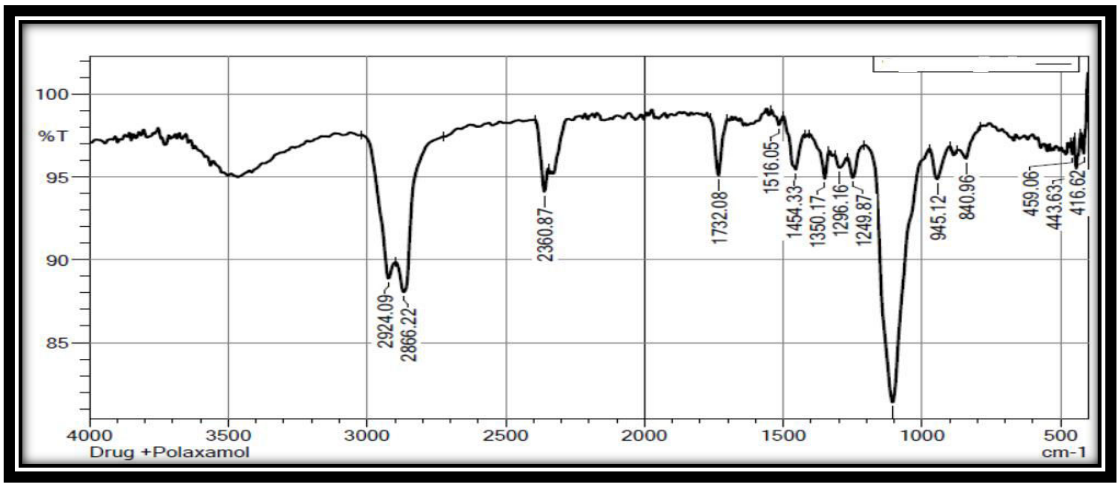

Fig-10 Drug and Poloxamer407

Characterization of LCs formulation:

1) Particle size and PDI of LCs formulations:

The particle size of pure drug obtained 3560 nm, with PDI 1.0 and at peak 118.7, shown in Figure 29, the optimized batch of LCs particle size obtained 241nm, PDI 0.285 at peak 220.5

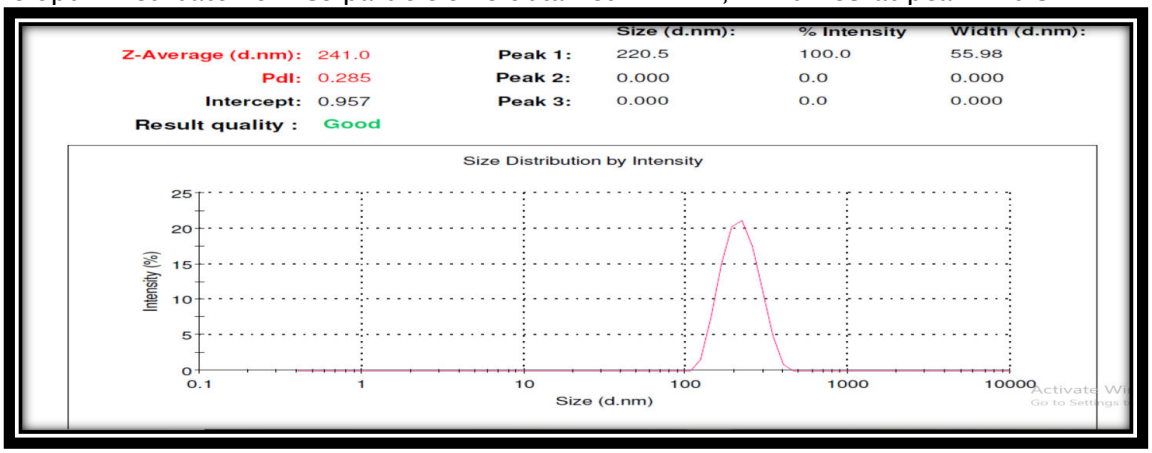

Fig-11 Particle size of the optimized batch of liquid crystals

2) Zeta Potential:

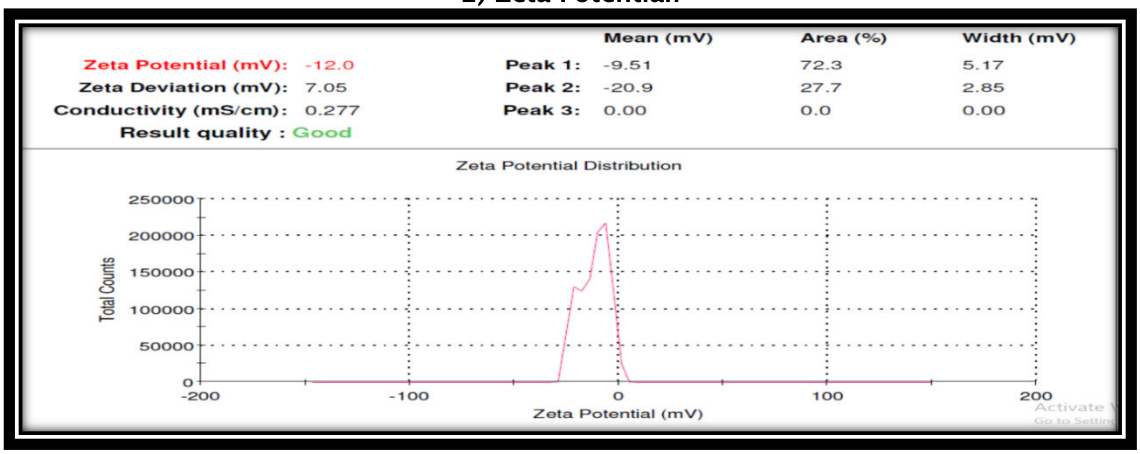

Fig-12 zeta potential of an optimized batch of liquid crystals

3) Entraptment efficiency (EE %):

%EE is an important parameter for characterization of lipid loaded formulation.

Table-2 Characterization of liquid crystals

Sr. No	Particle size (nm)	PDI	Zeta Potential	EE%
1	241	0.28	-12Mv	95

Spray drying P – LCs:

The lipid dispersion was successfully spray dried using the spray dryer. Drying was carried out for an optimized batch.

Characterization of spray dried LCs:

LCs dried powder Zeta size 301.5, PDI 0.5 at peak 185.7, shows Figure 32, 33. Hence, the pure drug particle size and PDI is more than the prepared LCs formulation.

1)Particle size and PDI:

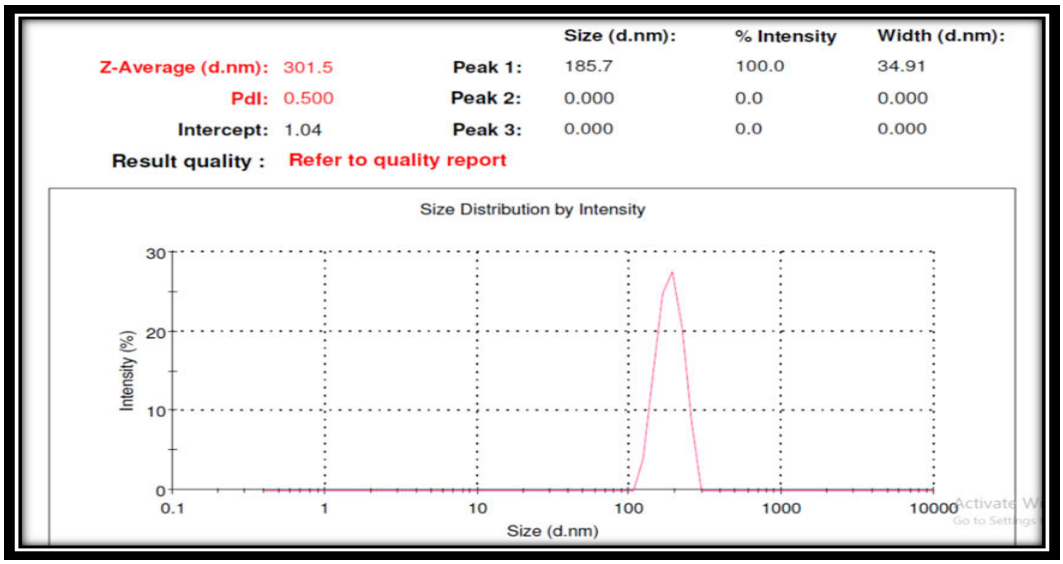

Fig-13 Particle size & PDI of liquid crystals dry powder

2) Zeta Potential:

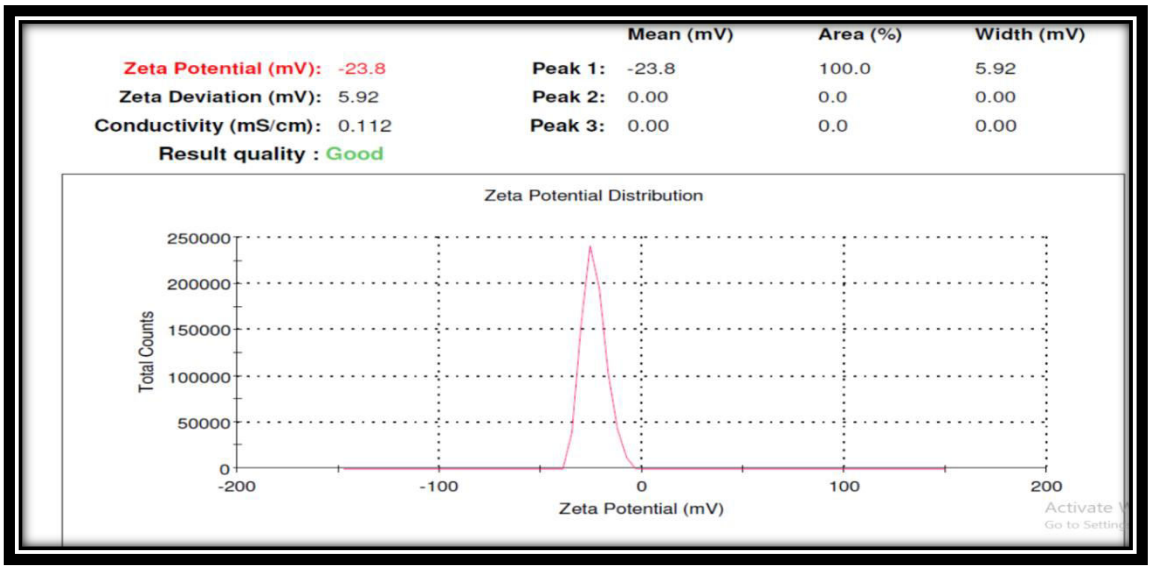

Fig-14 Zeta potential of liquid crystals dry powder

3) X-ray diffraction pattern (XRD):

The liquid crystals phase can be fragmented into stable submicron sized particles, which retain the internal structure of the original liquid crystals.

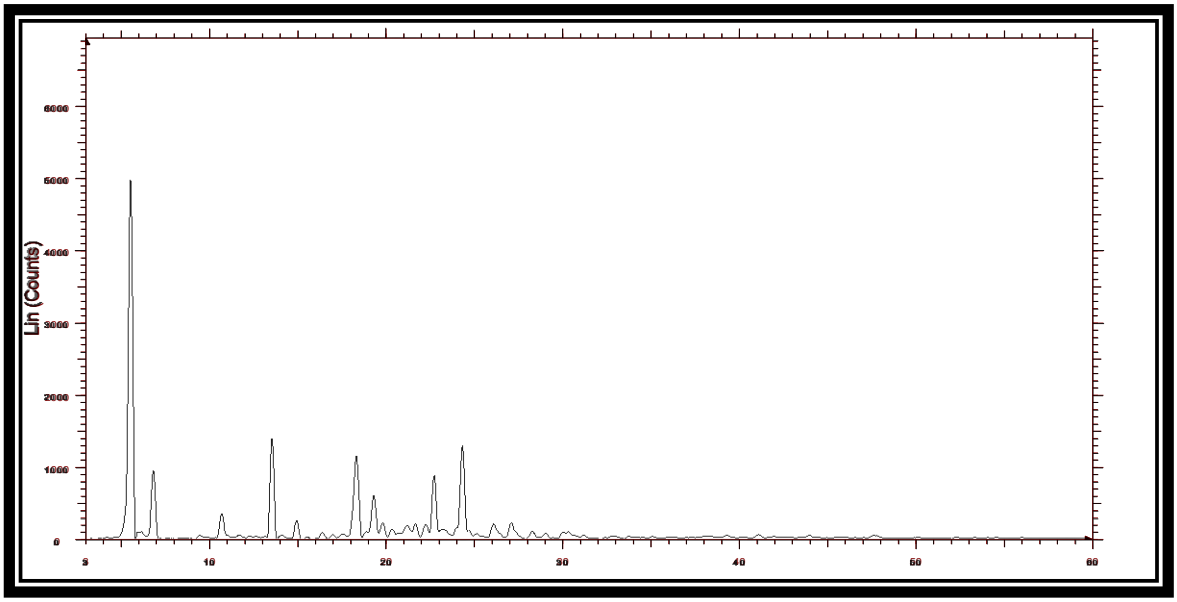

Fig-15 X-ray diffraction of Sulfamethoxazole

Table-3 X-ray diffraction of Sulfamethoxazole

Caption	Angle 2-Theta°	d-value angstrom	Intensity count	Intensity %
16.173	**5.460**	**16.17**	**4995**	**100**
13.074	6.755	13.07	941	18.8
6.558	13.489	6.560	1393	27.9
4.850	18.276	4.851	1150	23
4.604	19.262	4.604	607	12.2
3.913	22.701	3.915	878	17.6
3.659	24.300	3.660	1296	25.9
3.290	27.075	3.291	219	4.4
2.194	41.101	2.194	58.5	1.2

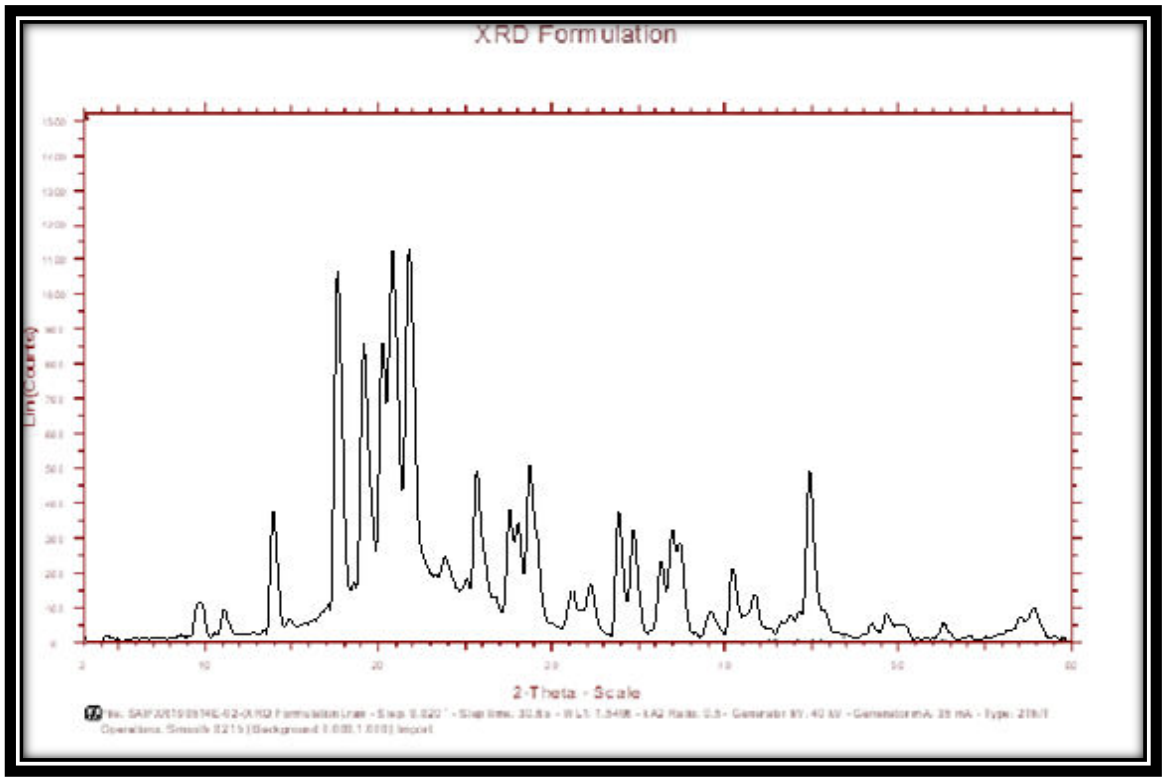

Fig-16 X-ray diffraction of Sulfamethoxazole loaded liquid crystals

Table- 4 X-ray diffraction of Sulfamethoxazole loaded liquid crystals

Caption	Angle 2-Theta°	dvalue angstrom	Intensity count	Intensity %
5.05481	17.531	5.05986	1176	94.4
4.42163	20.066	4.41948	951	76.3
4.29998	20.639	4.3028	1243	99.8
4.11539	**21.576**	**4.11509**	**1246**	**100**
3.13897	28.011	3.14062	557	44.7
2.615337	34.258	2.61663	353	28.4
2.04651	44.219	2.04715	539	43.3

4) SEM:

Electron microscopy and transmission electron microscopy are used for morphological characterization at the nanometer to micrometer scale.

Evaluation filled capsules:

The prepared capsules of Sulfamethoxazole were evaluated for quality control tests like weight Variation, thickness, diameter, drug disintegration time.

Table-5 Result of capsule evaluation

Sr.No.	Parameter	Result	Limit
1	Weight variation	8.6±59	IP/BP±7.5% USP±10%

The result of study is gives the average weight of capsule 129.8 mg.

In-vitro dissolution data:

Table-6 a) In vitro dissolution data for oleic acid based LCs containing Sulfamethoxazole in 1.2 pH phosphate buffer 1-12 hours.

Time (h)	%CDR (Marketed immediate formulation)	%CDR (S-LCs)
0	0	0
0.5	15±1.17	19.408±0.46
1	30±0.70	24.686±0.57
1.5	79.04±0.61	28.632±0.43
2	90.08±1.19	36.020±0.65
3	90.08±0.49	57.598±0.32
4	-	69.253±0.17
5	-	72.324±0.58
6	-	74.689±0.60
7	-	81.243±0.52
8	-	84.720±4.51
9	-	86.782±0.33
10	-	90.916±1.03
11	-	94.093±1.25
12	-	96.080±0.41

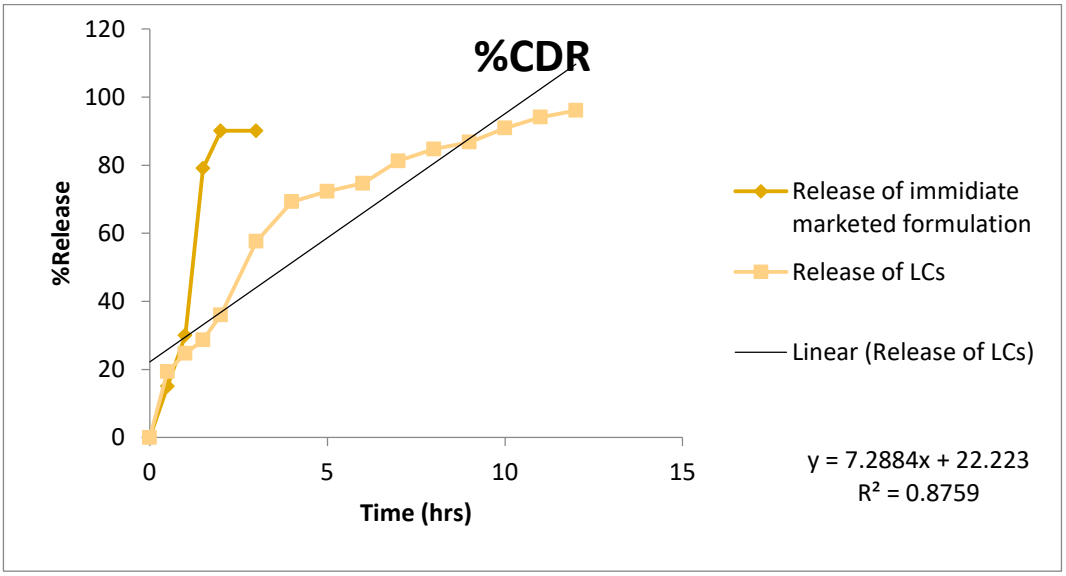

Fig-17 Plot of % CDR vs. Time (min)

Drug release kinetics:

To study the release kinetics, the in vitro dissolution data of optimized formulation applied to various kinetic models viz.

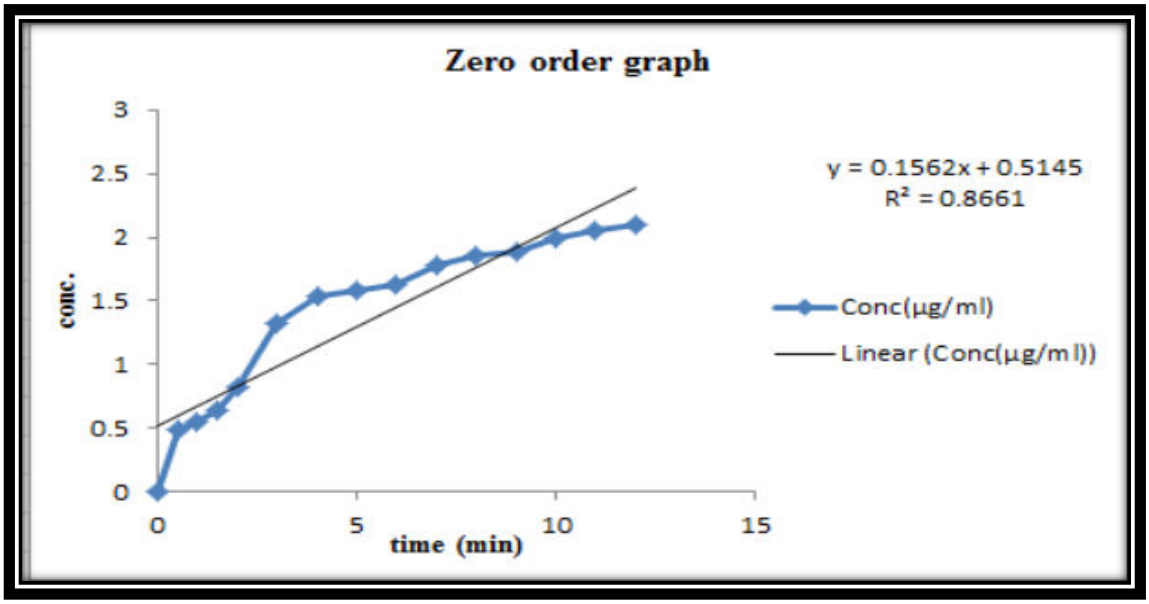

Fig-18 Plot of Conc vs. Time (min)

Stability of Optimized P-LCs:

For formulation to see the market, it should be stable during the self-life (storage and transports.

Table-7 Stability study of lyophilized LCs loaded in terms of PS, PDI and zeta potential studied.

Stability Parameter	Test period			
	0 month	1 month	2 months	3 months
Particle size(nm)	301 ± 3	301 ± 10	301±11	301. 2 ± 12
PDI	0.5 ± 0.04	0.580 ± 0.08	0.580 ±0.09	0.581 ± 0.09
Zeta potential(mV)	-23 ± 2.6	-23.1 ± 1.4	- 23.3 ± 1.6	-23.4 ± 1.2

Conclusions

The objective of the present work was to formulation, development, and evaluation, of liquid crystals formulation containing Sulfamethoxazole for oral delivery, in a sustain release. The compatibility of the drug, excipients was determined by DSC and IR spectroscopy. A result shows that the drugs are compatible with excipients. The structure and particle size of formulation characterized by the SEM and crystalline nature of the drug characterized by X-ray diffraction. Oleic acid-based LCs provided significant in the sustained drug delivery which helps to reduce the frequency of dose and improve bioavailability. In-vitro dissolution study confirmed the sustain release profile.

LCs are performed under the stability study and the shows the stable nature in their particle size and PDI. The drug having a high dose of frequency and having poor dissolution rate from its oral solid dosage forms. Liquid crystal formulations have lesser drug particles size which help to speed up dissolution by enlarging the effective surface area. According to the Ostward-Freundlich, and Noyes-Whitney equation, the dissolution rate of a drug can be increased by reducing the particle size to increase the interfacial surface area. The main objective of the research is to improve the

dissolution and solubility of this poorly water-soluble drug, to increase its oral bioavailability. Also by delivering in sustain manner the patient compliance increased.

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