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Research Paper

Polymeric Micelles of Coriandrum Sativum Seed Oil – Preparation and In-Vitro Evaluation

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Abstract: Polymeric micelles are well known for their advantages like enhancement of bioavailability of poorly soluble drugs and herbal drug constituents. The present research work was aimed to prepare polymeric micelles of Coriandrum sativum seed oil (CSSO) and to evaluate them for in-vitro properties and antibacterial activity. Extraction of CSSO from Coriandrum sativum seed powder was performed by hydro distillation technique. Phytochemical evaluation of CSSO reveals the presence of tannins, alkaloids & saponins followed by the measurement of chemical indices and GC-MS analysis of CSSO. The polymeric micelles containing CSSO were prepared by solvent diffusion method using PEG 6000 as a polymer & Pluronic F127 as a stabilizer. The Box-Behnken design was employed considering drug & polymer concentration along with stirring time as independent variables and particle size, % entrapment efficiency and % cumulative drug release as the dependent variables. The optimized formulation had shown low CMC value, which indicates that it was stable. The particle size & zeta potential values were 220.5±0.21nm and -0.5±0.2 mV & % entrapment efficiency of 55.34%, % cumulative drug release of polymeric micelles after 24 hrs was found to be 70.86%. Drug-Excipient compatibility studies were carried out to find out the interactions between drug and other excipients. Phase contrast microscopy was employed to find out the morphology. FT-IR analysis had revealed that polymer & CSSO were compatible with each other & Morphology of the optimized formulation was spherical & well distributed. The in-vitro antibacterial studies using agar diffusion process had shown that the optimized polymeric micelles were found to be more effective against gram positive bacteria than gram negative bacteria.

Keywords: *Coriandrum sativum* seed oil, Polymeric micelles, PEG 6000, Solvent diffusion technique.

1. Introduction

Polymeric micelles hold a great ability for the compounds that are hydrophobic in nature and also for the compounds with poor bioavailability [1, 2]. Polymeric micelles possess beneficial characteristics like tunable physicochemical properties, smaller particle size, controlled drug release, high kinetic stability, high drug loading capacity and maintains the integrity [3, 4]. Formation of polymeric micelles occurs when the concentration of the polymer increases beyond the certain concentration i.e. critical micelle concentration (CMC) [5.6] Coriander (*Coriandrum sativum*) is an aromatic, annual herb, which is native to the Mediterranean & middle east region, & well cultivated in India, Russia, Central Europe, Asia & Morocco & belongs to Apiaceae family [7].

Materials & Methods

Coriander seeds were purchased from local market at Nellore, Andhra Pradesh, Polyethylene glycol 6000&Pluronic F127 were procured from S.d fine chemical Pvt, Ltd, Mumbai, & Acetone from Merck Ltd, Mumbai.

Physicochemical analysis of *Coriandrum sativum* seed powder (CSSP): Physicochemical analysis of CSSP i.e. loss on drying, ash values, extractive values, swelling index & fluorescence analysis were investigated [8, 9].

Extraction of Coriandrum sativum seed oil (CSSO): Extraction of chemical constituents from coriander seed powder is done by hydrodistillation technique. 30 grams of coriander seed powder was taken into the round bottom flask and 225 ml of distilled water was added. The distillation process should be performed for 2hr at 60◦c and the oil-water mixture was extracted with dichloromethane in a separating funnel inorder to separate organic phase & aqueous phase and dried over sodium sulphate. The organic phase was collected and concentrated by keeping in water bath for 2hrs at 80°c.The final extract was filtered and used for further analysis [10].

Phytochemical evaluation of Coriandrum sativum seed oil (CSSO): The phytochemical tests i.e. test for alkaloids, carbohydrates, terpenoids, tannins & saponins were performed for the CSSO [8,11].

Physicochemical Characterization of CSSO: Solubility, boiling point & p^H of CSSO were determined.

***Measurement of chemical indices of essential oil*:** Acid number, ester number, saponification index & iodine value were determined [7,12].

***Construction of standard plot for the coriander seed oil*:** 4ml of CSSO was placed in the cuvette and absorbance was measured from 200-400 nm, λ_{max} of CSSO was noted.

***Determination of chemical constituents by GC-MS (Gas-Chromatography-Mass spectroscopy)*:** The Clarus 680 GC was used in the analysis as described by Nejad Ebrahimi *et al.,* employing a fused silica column, and the components were separated using Helium as carrier gas at a constant flow of 1 ml/min. The injector temperature was at 260°C, 1µL of extract sample injected into the instrument the oven temperature was as follows: 60 °C (2 min); followed by 300 °C at the rate of 10 °C min−1; and 300 °C, where it was held for 6 min. The spectrums of the components were compared with the database of spectrum of known components stored in the GC-MS NIST (2008) library. [13]

***Design of Experimentation (Box-Behnken design) BBD*:**

By employing the BBD, polymeric micelles containing CSSO were prepared using solvent diffusion method with PEG6000 and poloxamer407 as polymers. A13 run Box-Behnken design with the three factors and three levels with three triplicate at the center point was employed. The three independent variables were drug concentration(X1), polymer concentration (X2) and stirring time (X3) and these vary at three different level i.e. low, medium and high (-1, 0, +1) and the dependent variables were particle size (Y1), entrapment efficiency (Y2) and cumulative drug release (Y3).

***Method for the preparation of polymeric micelles containing Coriander seed oil*:**

Solvent diffusion method: [14]

The polymeric micelles containing coriander seed oil was prepared by employing solvent diffusion technique. The accurate quantity of coriander seed oil & PEG6000 were dissolved in acetone(10ml). The above solution is to be added slowly drop wise into the 20 ml of distilled water under constant stirring. The resulting solution is to be stored in amber colored bottles until for further use.

Characterization of polymeric micelles: [15]

Particle size &Zeta potential: The average size & polydispersity index of the polymeric micelles along were determined by zeta sizer (Nanoparticle SZ 100, Horiba scientifics) using dynamic light scattering method at an angle of 173^0 and the cell temperature was 25◦c. All the trails were performed in triplicate and the data is represented as mean ± standard deviation (SD).

%Encapsulation Efficiency:

After lyophilization,1 mg of polymeric micelles were taken accurately in an amber colored glass vial&1ml of ethanol was added, and subjected to sonication for 2-3 min, and kept in darkling at room temperature for 1hr.Then, the absorbance was checked at 320nm using UV-spectrophotometer. The %encapsulation efficiency was calculated using the following equation,

$$\%EE = \frac{\text{weight of coriander seed oil in the micelles}}{\text{weight of initial amount of coriander seed oil}} \times 100$$

***In vitro* drug release:**

The *in vitro* drug release profiles of the prepared polymeric micelles containing coriander seed oil were assessed by dialysis bag method. 2ml of the prepared micelles were placed in the dialysis bag and closed on both the sides with clips and is immersed in a glass container with the 100 ml of release medium i.e. phosphate buffer saline (with 0.5% Tween 80), p^H 7.4.

The container was placed on the magnetic stirrer at 37◦c and about 2ml of release medium was withdrawn at different time intervals (1,2,4, 6, 8, 12& 24 hrs) and replaced with the fresh medium. The amount of coriander seed oil released into the medium was determined using UV spectrophotometer at 300 nm.

The % cumulative drug release of CSSO at certain time intervals was calculated by using the following equation,

Critical micelle concentration (CMC):

$$\%\text{cumulative drug release} = \frac{\text{Amount of coriander seed oil in the medium (µg)}}{\text{Amount of coriander seed oil loaded in the micelles (µg)}} \times 100$$

CMC of the polymeric mixture was determined by UV at 366nm using hydrophobic probe as iodine.0.5g of iodine (I_2) and 1.0 g of potassium iodide (KI) was dissolved in 50ml of distilled water in order to prepare standard solution (KI/I_2). Different concentrations of the polymeric mixture were prepared in the range of (0.1 to 1.0 %). 25 micro liters (µl) of KI/I_2 standard solution is to be added to the various concentrations of the polymeric mixture. The mixtures were kept in darkling for 12h at room temperature & the absorbance was measured at 366nm. The graph is plotted for the absorbance & logarithm of polymer concentration. The CMC value of the polymeric mixture corresponds to the concentration of the polymer, when there is an increase in the absorbance.

Particle shape & Morphology: The polymeric micelles containing CSSO were visualized through phase contrast microscopy. The sample was dispersed on the glass slide and observed at high magnification with an Olympus optical microscope (model CH3ORF200, Olympus Tokyo, Japan).

Drug Excipient Compatibility studies:

Fourier Transform Infrared (FT-IR) Analysis: [13]

The FT-IR spectra of pure extract, extract + polymer mixture & optimized formulation of polymeric micelles were recorded using Bruker T type FT-IR spectrometer. The drug is dispersed in potassium bromide i.e. 1:100 ratio. The sample was scanned in the range of wavelengths 400 to 4000cm^{-1}.

Evaluation of Antibacterial Activity:

To perform antibacterial studies four microorganisms were selected: *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Proteus vulgaris.* The culture media was prepared using nutrient broth and agar powder and the components were mixed until homogenous and the mixture was heated with simple agitation. After this, the mixture was kept at 121◦c for 20 minutes in the autoclave.

Agar diffusion process [17]: This process was done by taking three petri plates filled with the culture media of uniform surface and depth. The three petri plates were filled with coriander seed oil, polymeric micelles containing coriander seed oil and the marketed formulation i.e. Ciprofloxacin 500mg tablet considered as standard. The plates were incubated 24 hrs at 37◦c for the antibacterial test. Diameter of the zone of inhibition was measured in cm is considered as important step in the determination of antibacterial activity.

Statistical analysis: The optimization of polymeric micelles containing CSSO by DoE Software (Design Expert @ v-13). Inserting the values of dependent variables in the design expert software gives the optimized formulation through ANOVA, surface response plots and also with contour & overlay plots.

2. Results & Discussion

Physicochemial analysis of *Coriandrum sativum* seed powder like loss on drying, total ash, acid insoluble ash & water-soluble ash, soluble extractive values, swelling index & fluorescence analysis are described in table 1& 2.

Table 1: Describes the physicochemical properties of Coriandrum sativum seed powder

S.No	Evaluation Parameters	Values
1.	Loss on drying	4%±0.3%w/w
2.	Total ash	5.0±0.6%w/w
3.	Acid insoluble ash	0.3±0.1%w/w
4.	Water soluble ash	2.66±0.4%w/w
5.	Water soluble extractive	25±0.5%w/w
6.	Alcohol soluble extractive	10±0.2%w/w
7.	Swelling index	1 ml

Table 2: Flourescence analysis of Coriandrum sativum seed powder

S.No	Reagent	Day light	UV light
1.	Sample+Dil HCl	Yellow	Green
2.	Sample + Dil HNO_3	Yellow	Light green
3.	Sample + Conc.HNO_3	Orange	Yellow
4.	Sample + Dil CH_3COOH	Yellow	Orange
5.	Sample + Dil H_2SO_4	Yellow	Green
6.	Sample +Conc H_2SO_4	Beet root red	Black
7.	Sample + Glacial CH_3COOH	Yellow	Light brown
8.	Sample + $HClO_4$	Brown	Black
9.	Sample + Hg_2Cl_2	Yellow	Green
10.	Sample + NH_4OH	Light green	Yellow
11.	Sample + 10% NaOH	Orange	Light brown
12.	Sample + 40% NaOH	Orange	Light brown

Fluorescence analysis is an essential parameter for the standardization of crude drug. Fluorescence test on CSSP helps in qualitative analysis, which can be used as a reference data for the identification of adulterants.

Physicochemical characterization of Coriandrum sativum seed oil (CSSO): The solubility studies of CSSO in various solvents was performed and it is soluble in distilled water, ethanol & methanol, where as it is slightly soluble with acetone, chloroform & carbon tetrachloride.

Boiling point & p^H of CSSO: Boiling point & p^H of CSSO was found to be 195°c±0.2&6.87±0.05.

Phytochemical Evaluation of CSSO: Phytochemical evaluation of *Coriandrum sativum* seed oil indicates the presence of tannins, alkaloids & saponins and the results are tabulated in Table 3.

Chemical indices of CSSO: The results of chemical indices like acid value, ester value, saponification value & iodine value are tabulated in table 4.

Determination of Chemical constituents from Coriandrum sativum seed oil by GC-MS:

The chemical constituents of *Coriandrum sativum* seed oil was analyzed by gas chromatography-mass spectroscopy (GC-MS).The results of GC-MS analysisof CSSO had shown 15 compounds and listed in table 5,where 2,3-Anhydro-D-Galactosan is responsible for antibacterial activity.

Table 3: Results of phytochemical evaluation

S.No	Test	RESULT
1.	Ferric chloride test (Tannins)	Positive
2.	Molisch's test (Carbohydrates)	Negative
3.	Dragendroff's test (Alkaloids)	Positive
4.	Salkowski's test (Sterols)	Negative
5.	Foam test (Saponins)	Positive

Table 4: Results of chemical indices

S.No	Chemical indices	Value
1.	Acid value	11.781±0.4
2.	Ester value	144.177±1.6
3.	Saponification value	155.958±2.2
4.	Iodine value	33.56±3.7

Table 5: GC-MS analysis of Coriandrum sativum seed oil

S.No	RT	Scan	Height	Area	Area %	Norm%	Name of the compound
1	14.608	2421	7,811,346	1,475,894.9	8.679	46.52	1,3-Dioxolane 2HeptanenitrileAlpha.-methyl-delta.oxo-2-phenyl
2	17.074	2914	60,346,780	3,172,427.0	18.655	100.00	Z-2-Octadecen-1-ol
3	17.519	3003	15,210,604	824,515.2	4.848	25.99	1-Octadecyne
4	25.838	4666	8,957,601	405,356.9	2.384	12.78	Coprostan-16.beta-ol
5	25.988	4696	16,427,744	841,216.4	4.947	26.52	Pregnan-3,11-diol-20-one
6	26.823	4863	10,474,685	583,953.1	3.434	18.41	Cholest-8-en-3-ol,14- methyl(3.beta.,5.alpha)-
7	26.853	4869	9,983,861	1,027,765.4	6.044	32.40	Oleicacid
8	27.088	4916	9,094,523	924,488.3	5.436	29.14	7-Hydroxy-3-(1,1-dimethylprop-2-enyl) coumarin
9	27.358	4970	11,899,070	857,206.2	5.041	27.02	Spiro(androst-5-ene-17,1'-cyclobutan)-2'-one,-3-hydroxy-, (3.beta.,17.beta)-
10	27.488	4996	5,754,617	334,598.6	1.968	10.55	1-Butanol,4-butoxy-
11	27.638	5026	11,064,260	1,359,883.4	7.997	42.87	Dihydroartemisinin,10-O-(T-Butyloxy)-
12	28.114	5121	8,239,310	1,244,230.5	7.317	39.22	2,3-Anhydro-D-Galactosan
13	28.819	5262	10,321,005	914,655.0	5.379	28.83	3,4-Anhydro-D-Galactosan
14	28.889	5276	9,072,620	1,126,772.5	6.626	35.52	Dihydroartemisinin,10-O-(T-Butyloxy)-
15	29.444	5387	21,179,972	1,912,652.0	11.247	60.29	Cyclohexane,1-(1,5-Dimethylhexyl)-4-(4-methylpentyl)-

Preparation & Characterization of polymeric micelles containing *Coriandrum sativum* seed oil: Polymeric micelles were prepared by employing solvent diffusion method by dispersing the acetone solution containing CSSO & PEG6000 along with Pluronic F127 as a stabilizer.Polyethylene glycol is nontoxic , non-immunogenic & non- antigenic water soluble polymer.[17]

Optimization of polymeric micelles: The prepared polymeric micelles containing *Coriandrum sativum* seed oil using DoE software (Design Expert @v.13) using box-behnken design as shown in table 6 & 7 shows the particle size, % entrapment efficiency & *in vitro* drug release of the polymeric containing *Coriandrum sativum* seed oil.

Table 6: Layout of Box-Behnken design

S.No	Independent variables	Levels		
		Low(-1)	Medium(0)	High(+1)
1.	Drug concentration(ml)(X1)	1.0	1.5	2.0
2.	Polymer concentration(mg)(X2)	50	100	150
3.	Stirring time(min)(X3)	20	30	40

Table 7: Results of dependent variables on polymeric micelles containing Coriandrum sativum seed oil

Runs	X1	X2	X3	Particle size (nm) Mean± S.D Y1	Entrapment efficiency (%) Y2	Cumulative drug release (%)Y3
F1	1	100	20	128.53±0.32	24±0.020	51.84±0.63
F2	1	50	30	135.47±1.04	27.7±0.026	56.41±0.37
F3	1	100	40	191.2±1.15	37±0.015	61.53±0.42
F4	1	150	30	246.27±0.50	43±0.022	65.2±0.15
F5	1.5	50	20	242.33±0.67	45.7±0.037	67.58±0.59
F6	1.5	50	40	253.33±0.31	57±0.033	71.04±0.46
F7	1.5	150	20	250.3±3.82	61±0.010	74.35±0.75
F8	1.5	100	30	191.23±0.40	57.33±0.003	76.8±0.38
F9	2	100	40	385.60±0.92	65.4±0.036	78.72±0.63
F10	1.5	150	40	347.11±0.85	62±0.111	80.64±0.23
F11	2	50	30	364.43±0.57	64±0.057	82.05±0.49
F12	2	100	20	275.20±1.57	64.4±0.040	84.48±0.52
F13	2	150	30	397.33±0.99	73.7±0.004	87.17±0.35

Particle shape and morphology of the optimized formulation: The morphology of polymeric micelles was imaged by phase contrast microscopy and the results had shown that well distributed particles and mostly found to be spherical in shape as shown in Figure 1.

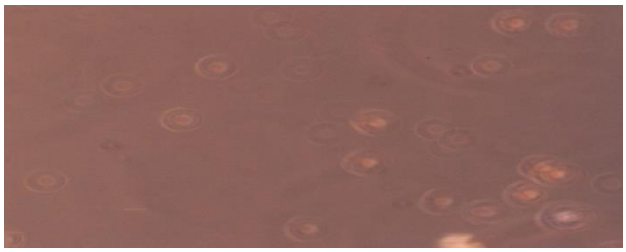

Figure 1: Phase contrast image of optimized formulation

Particle size & Zeta potential (optimized formulation): The particle size and zeta potential of the optimized formulation was found to be 220.5±0.21nm and -0.5±0.2 mV as shown in the Figure 2. It is observed that, increasing X_1, X_2, X_3 concentration i.e. increase in drug concentration & polymer concentration along with increase in stirring time had shown increase in particle size, this indicates that more drug is loaded into the core of the micelles at higher concentrations of drug & polymer [18], increase in stirring time had shown increased particle size due to particle agglomeration [19].

%Entrapment efficiency: The % entrapment efficiency of the optimized formulation was found to be 55.34%. In this study it is observed that increase in drug and polymer concentration along with stirring time had increased the entrapment efficiency of the polymeric micelles.

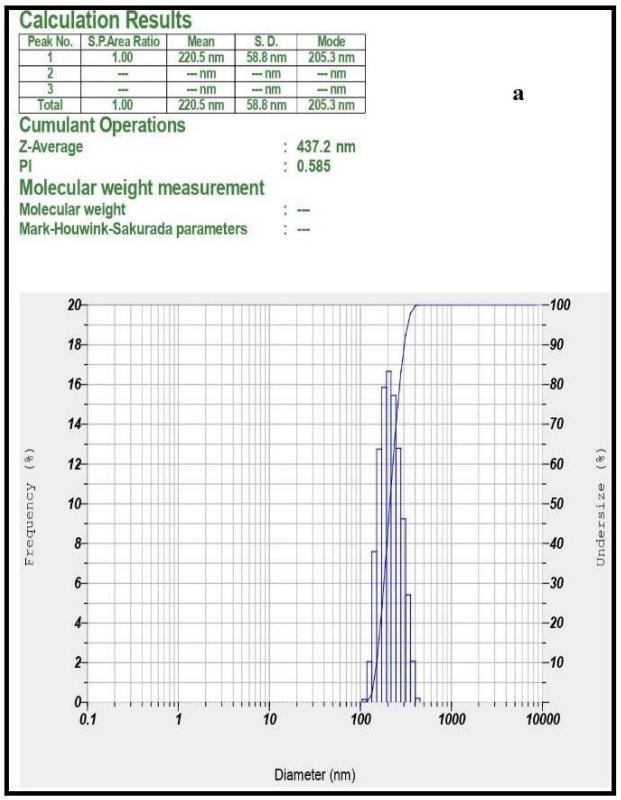

Figure 2 (a) particle size

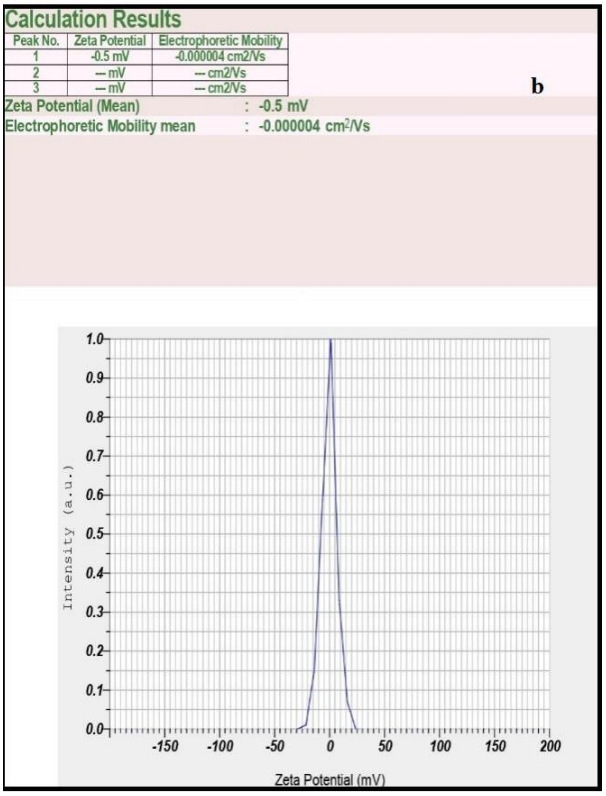

Figure 2 (b) zeta potential of the optimized formulation

***In vitro* drug release:** The *in vitro* drug release of the optimized formulation & pure CSSO are compared and it is found to be 70.86% & 48.26% and it is represented in figure 3. Here, it is observed that increase in drug and polymer concentration & stirring time increases the % cumulative drug release.

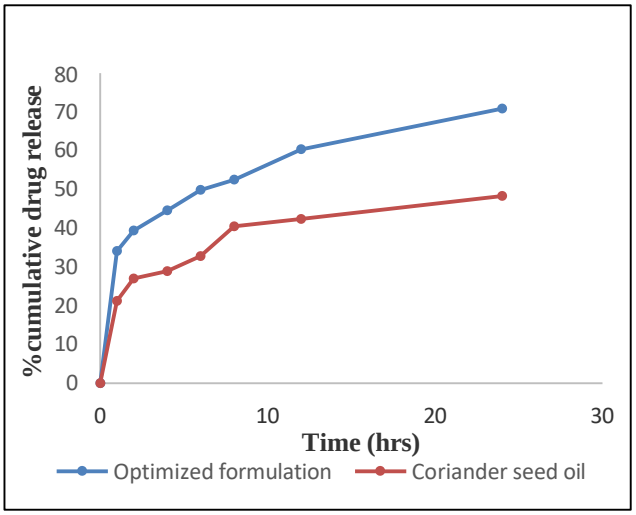

Figure 3: % Cumulative drug release of pure Coriandrum sativum seed oil and optimized formulation

Determination of CMC of the optimized formulation: Low CMC value indicates that the polymeric micelles are highly stable and maintains the integrity after dilution in the body. CMC was determined by plotting the absorbance Vs polymer concentration (µg/ml) as shown in figure 4. The CMC value of the optimized formulation was found to be 0.8µg/ml. Hence, the optimized formulation is stable.

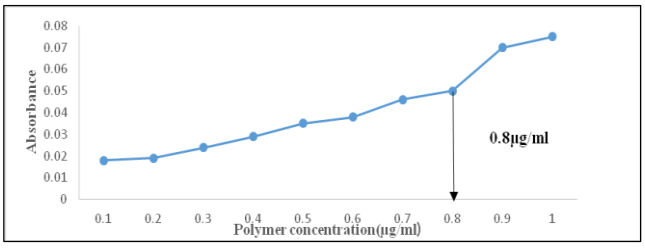

***Figure 4:** CMC of the optimized formulation*

p^H of the optimized formulation: Measurement of p^H is very important for the oral preparations, where it may lead to GIT irritation. P^H of the optimized formulation was found to be in a neutral range of 7.7±0.1.

Drug release kinetics: The *in vitro* drug release data of optimized formulation is fitted in different mathematical models as shown figure 5. The model with highest R^2 value is considered as best one. According to the data the model meeting criterion is first order with R^2 value 0.974. The polymeric micelles had shown sustained release characters. The drug release data is fitted with Higuchi (R^2 value -0.99) & the released mechanism of polymeric micelles containing *Coriandrum sativum* seed oil might be drug diffusion and dissolution as shown in Figure 5.

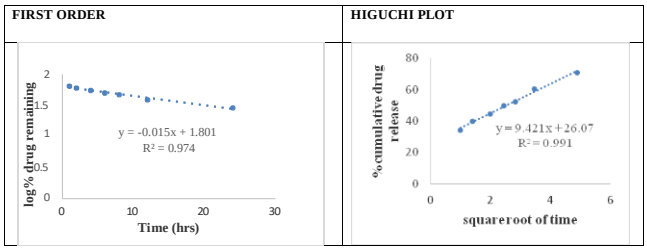

Figure-5 Drug release kinetics of polymeric micelles containing Coriandrum sativum seed oil.

Drug-excipient compatibility studies (FT-IR) analysis of the optimized formulation

FTIR spectra of *Coriandrum sativum* seed oil along with *Coriandrum sativum* seed oil + polymer mixture was compared, it can be noticed that, the absence of additional peaks, which indicates that, the polymer and *Coriandrum sativum* seed oil are compatible to each other.

***In-vitro* antibacterial activity:** The *in-vitro* antibacterial activity of polymeric micelles containing *Coriandrum sativum* seed oil was compared with the marketed ciprofloxacin tablet 500mg tablet i.e. standard and *Coriandrum sativum* seed oil. The activity in terms of zone of inhibition is given in the Table 8

Table 8: Results of In vitro antibacterial activity

Formulation	Zone of inhibition (cm) Mean ± S.D			
	Staphy-lococcus aureus	Proteus	E.coli	Bacillus subtilis
Test formulation	2.3±0.1	1.5±0.2	1.2±0.1	2.0±0.3
Marketed formulation	1.2±0.2	1.4±0.3	1.0±0.3	1.8±0.1
Coriandrum sativum seed oil	1.0±0.05	1.2±0.01	1.0±0.03	0.4±0.01

The polymeric micelles exhibits a high zone of inhibition when compared with that of CSSO and positive control antibiotic i.e. ciprofloxacin. Presence of CSSO increased the antibacterial activity of polymeric micelles against both gram positive and gram negative bacteria. In this study two strains of gram positive bacteria i.e. *Staphylococcus aureus* & *Bacillus subtilis* and two strains of gram negative bacteria i.e. *Proteus vulgaris* & *Escherichia coli* were taken. Polymeric micelles containing CSSO i.e. test formulation was more effective against gram positive bacteria with high zone of inhibition.

3. Conclusion

Polymeric micelles containing *Coriandrum sativum* seed oil were formulated by solvent diffusion technique & Box-Behnken response surface methodology was selected in order to investigate the effect of independent variables on responses. The optimized formulation of polymeric micelles has low CMC, smaller particle size and negative zeta potential, high % entrapment efficiency and spherical in shape. Low CMC suggests stability of micelles upon

dilution. Polymeric micelles containing *Coriandrum sativum* seed oil had shown high drug release, *in-vitro* drug release kinetics follows first order, so the formulation shows sustained release characters and the drug release mechanism is drug diffusion and dissolution of polymer material. The FT-IR analysis demonstrated no drug-excipient interactions. Formulated polymeric micelles were stable during the period of study and there were no alterations. The prepared polymeric micelles had shown antibacterial activity against gram positive and gram-negative bacteria with high zone of inhibition. The results obtained in proposed research polymeric micelles containing *Coriandrum sativum* seed oil enhances the solubility and ultimately enhanced the bioavailability.

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