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FORMULATION AND DEVELOPMENT OF SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEM FOR CIPROFLOXACIN

P. S. Gawade *, H. A. Joshi and R. N. Patil

Department of Pharmaceutics, Shivnagar Vidya Prasarak Mandal's College of Pharmacy, Malegaon (BK), Baramati, Pune - 413115, Maharashtra, India.

Keywords:

Ciprofloxacin, S-SEDDS, Solubility enhancement, Adsorption technique

Correspondence to Author:
Dr. Priyanka Shivlal Gawade

Assistant Professor,
Department of Pharmaceutics,
Shivnagar Vidya Prasarak Mandal's College of Pharmacy, Malegaon (BK),
Baramati, Pune - 413115,
Maharashtra, India.

E-mail: priyanka.gawadesvpm@gmail.com

ABSTRACT: The purpose is to formulate the solid self emulsifying drug delivery system (S-SEDDS) to improve poor aqueous solubility and dissolution of ciprofloxacin. A solubility study was carried out, and then Soyabean oil (as oil phase), Tween 20 (as surfactant), and Span 80 (as co-surfactant) were selected for preparation of emulsion by titration method. Adsorption to solid carrier technique was used for solid SEDDS, areosil (Colloidal silica) used as adsorbent. In that formulation, I was having carbopol 934 and another formulation II HPMC K 4 M. The flow properties of all formulation were within the acceptable range; therefore, they can be easily filled into capsule. IR spectral and DSC thermograph analysis showed that there was chemical interaction between drug and polymer. *In-vitro* release studies were carried out in phosphate buffer pH 7.4. Release profile of pure drug formulation showed 38%, formulation I showed highest 54% cumulative drug release and formulation II showed lowest *i.e.* 14% drug release. Student's t-test was determined for *In-vitro* drug release data for different polymeric formulations and showed a p-value of 0.001891 (<0.01) 99.99% significant.

INTRODUCTION: The oral route is the easy, most convenient route for administration and the major route of drug delivery for the chronic treatment of many diseases [1]. Nowadays, new chemical entities (NCE) have poor water solubility and low oral bioavailability [2]. Poor water-soluble drug formulation is very difficult for pharmaceutical scientists as formulating new drug discovery methods and oral delivery are related with low bioavailability [3-5]. Lipid-based drug delivery systems (LBDDS) have more importance in the present due to their ability to improve the solubility and bioavailability of drugs with low aqueous solubility [6-7].

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The absorption of a drug having lipid-based formulation depends on a few factors, including particle size, degree of emulsification and rate of dispersion and precipitation [8]. Lipid-based formulations may include oil preparations or suspensions, emulsions, and self-emulsifying drug delivery systems (SEDDS) [9]. SEDDS is mixture of having equal physical properties of oils, surfactants, co-surfactants and co-solvents, formulations to improve the oral absorption of hydrophobic dug compounds.

SEDDS is formulated in solid form for oral administration like soft or hard gelatin capsules, liquisolid tablets and form fine stable oil-in-water (o/w) emulsions when contact with aqueous media and gentle agitation of the gastrointestinal fluids [10]. LBDDS have excellent prospects for improving bioavailability of BCS class II and IV drugs [11]. Some marketed lipid based formulations are efavirenz (Sustiva), saquinavir (Fortovase),

ritonovir (Norvir), clofazamine (Lamprene) and cyclosporine A (Sandimmune and Sandimmun Neoral) [6, 10]. In the present study, ciprofloxacin is selected for formulation. It is an anti-infective agent (Antibiotics) having Quinolones subclass and belongs to BCS Class IV, and because of its low solubility and permeability, it becomes difficult to formulate [12-13].

At present in the market, it is available in the form of its hydrochloride salt. The work aims to improve the solubility and increase its dissolution by formulating it in a Solid self-emulsifying drug delivery system. In SMEDDS of Ciprofloxacin using oleic acid (oil), tween-80 and pluronic F_{127} (surfactant) and ethanol (co-surfactant) were selected, which improves drug solubility, absorption rate, and dissolution [14].

MATERIALS AND METHODS:

Materials: Ciprofloxacin was procured from Yarrow Chemicals Mumbai., Tween-20 was procured from Merk Pvt Ltd, Mumbai, Span-80, Methanol, carbopol 934, Aerosil and Talc were procured from Loba Chemi, Mumbai. Hydroxy Propyl Methyl Cellulose K-4M was procured from Colorcon, Asia Pvt Ltd, Goa. Olive oil and Soyabean oil were procured from Cosmo Chem. Empty hard gelatin capsules were procured from Yarrow Chemicals, Mumbai.

Method:

Solubility studies [15]: Solubility studies of ciprofloxacin were performed; by the excess amount (100 mg) of solid ciprofloxacin was added to 5 ml oils (Soyabean oil and Olive oil) and various concentrations of Smix (15%, 20%, 25%, 30% and 35%). These solutions fill in 10 ml vial using rotary shaker and at rotation speed 25 RPM for 48 hours. The contents of each vial were filtered through a 0.45 um whatman filter paper using sintered glass grade 1 and filtrate was diluted with respective solutions. The absorbance were measured UV- Spectrophotometer. The concentration of ciprofloxacin was quantified by calculating concentration of dissolved drug by using calibration curve equation.

Partition Coefficient [16-17]: Partition coefficient of ciprofloxacin was determined by Shake-Flask method using n-octanol as organic phase and water as aqueous phase. Accurately weighed 25 mg and 50 mg of ciprofloxacin transferred to 10 ml of water and 10 ml of n-octanol was added to each separating funnel. Flask was shaken for vigorously for 15 minutes, and stay as it is to stable. The contents from each separating funnel were filtered through a 0.45 um whatman filter paper using sintered glass grade 1 and filtrate was diluted with respective solutions. The absorbance of solutions was measured UV spectrophotometer.

Pseudo Ternary Phase Studies [18-21]: Ternary mixtures with varying composition of Tween-20 as surfactant, Span-80 as co-surfactant and Soyabean oil were prepared. Surfactant and co-surfactant were mixed in different ratios [4:1(A), 3:2(B), 2:3(C), 4:1(D), 1:1(E)].

For each phase diagram, oil and specific surfactant to co-surfactant ratio (1A-5A, 1B-5B, 1C-5C, 1D-5D and 1E-5E) were titrated. Twenty-five combinations of oil and Smix were made to find out the maximum emulsion area in the phase diagrams. Selected oil and Smix ratio was taken for further preparation of S-SEDDS.

TABLE 1: BATCHES OF EMULSION ON BASIS OF SURFACTANT MIXTURES CONCENTRATIONS

S. no.	Oil Phase (Soybean Oil)	Surfactant Mixtures Concentrations (Tween-20: Span-80) in ml				
		A (8:2)	B (6:4)	C (4:6)	D (2:8)	E (5:5)
		Distilled Water Added (ml)				
1.	1	2.5	2.8	5.4	5.7	3.5
2.	2	3.2	2	5	6	3.7
3.	3	4	3.6	5.3	6.3	4
4.	4	4.4	3.9	5.8	6.5	5
5.	5	3	4.2	4.9	6.9	5.4

Preparation of S-SEDDS [22-24]: Ciprofloxacin drug was solubilized in oil phase and then added in that Tween 20 and Span 80 mixtures (Smix) and methanol as co-solvent with titration method. That mixture was mixed properly to get emulsion formed by the cyclo mixer. The emulsion was kept overnight for evaporated solvent at room temperature. For solid preparation of SEDDS,

adsorption to solid carrier technique was applied. Aerosol as an adsorbent was added to that emulsion, and then the emulsion gets fine powder form. Further, that powder was evaluated and prepared capsule formulation of Ciprofloxacin SEDDS.

TABLE 2: COMPOSITIONS OF S-SEDDS FORMULATIONS

Formulation I			Formulation II		
S. no.	**Ingredients**	**Quantity Taken**	**S. no.**	**Ingredients**	**Quantity Taken**
1.	Ciprofloxacin SEDDS Powder	250 mg	1.	Ciprofloxacin SEDDS Powder	250 mg
2.	Carbopol 934	100 mg	2.	HPMC K 4 M	100 mg
3.	Aerosil	3 g	3.	Aerosil	3 g
4.	Talc	20 mg	4.	Talc	g

Formulation Characterization:

Infrared Spectroscopy [26]: FT-IR spectrum of drug, polymers, excipient, and physical mixtures were recorded as potassium bromide (KBr). Over the region 4000-400cm^{-1} for its authentication and to study characteristics peaks of drug and polymer using FT-IR spectrophotometer (JASCO Model FT/IR-4100, JASCO FT/IR 6100, Brucker). The observed peaks were compared with the characteristic peaks from the reported IR spectrum; the sample was authenticated.

Differential Scanning Calorimetry [26-27]: The DSC study was carried out for drugs, polymers, and physical mixtures and formulations. The DSC thermograms were recorded on a Hitachi 7020 instrument. Each sample (2-10mg) was heated in crimped aluminium pans at a scanning rate of 5^{0}C/min from 0 to 300°C. An empty aluminium pan was used as a reference.

Micromeritics Properties [28-30]: The powder properties include bulk density (BD), tap density (TD), angle of repose (AR), Hausner ratio (HR), Carr's index (CI) were determined.

Drug Content Uniformity [31]: 100 mg sample powder of optimized solid formulation of ciprofloxacin was dissolved in 100 ml Phosphate buffer pH 7.4. Then this solution was kept for a night for complete solubility.

After 24 hrs 1 ml solution was withdrawn and diluted up to 10 ml with Phosphate buffer p^H 7.4 and absorbance of obtained sample was determined with UV spectrophotometer at wavelength of 278 nm.

***In-vitro* Drug Release Studies [33-35]:** Drug release studies from S-SEDDS formulations were performed with 900 ml of phosphate buffer pH 7.4 as a medium at 37±0.5°C. Ciprofloxacin-loaded S-SEDDS capsules (equivalent to 250 mg of ciprofloxacin) were placed in a dissolution apparatus (Tab machines DRS-8) at the basket speed of 100 rpm. At predetermined time intervals (15, 30, 45, 60, 120, 180, 240, 300, 320, and 400 min), an aliquot (5ml) of samples were collected, filtered, and analyzed for the consent of ciprofloxacin by spectrophotometrically at λmax of 278 nm.

Statistical Analysis [36]: Statistical analysis was applied for In-vitro drug release data for different polymeric formulations at a significance level <0.01 for student's t-tests.

RESULT AND DISCUSSION:

Solubility Studies [37-39]: Ciprofloxacin was insoluble in water. Among various lipids studied, the maximum solubility of ciprofloxacin was observed in Soyabean oil (0.18 mg/ml).

However, the minimum solubility was found in olive oil (0.17 mg /ml). Similarly, amongst various surfactants and co-surfactants, the maximum solubility of ciprofloxacin was observed in Tween 20 (0.17 mg/ml), and the minimum solubility was found in Span 80 (0.10 mg/ml).

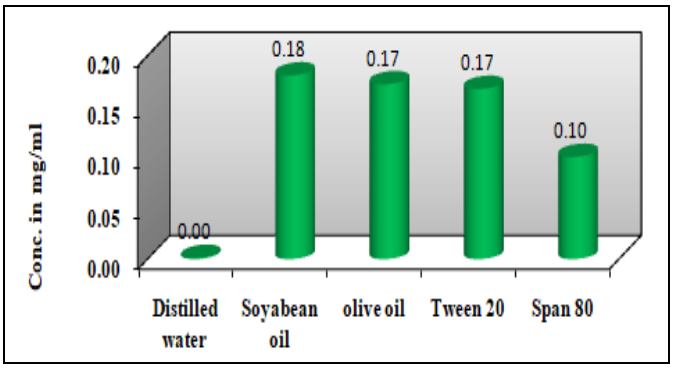


FIG. 1: SOLUBILITY STUDIES OF CIPROFLOXACIN IN VARIOUS MEDIUMS

Partition Coefficient [16-17]:

TABLE 3: PARTITION COEFFICIENT OF CIPROFLOXACIN IN WATER/ N-OCTANOL PHASE

S. no.	Drug added (mg)	n-Octanol (ml)	Water (ml)	Log P
1	25	10	10	0.0513
2	50	10	10	0.3698

Pseudo Ternary Phase Studies [37-39]: Fig. 2A, B, C, D and **E** represent the phase diagram constructed to identify the area of stable emulsion in the presence of ciprofloxacin. Initially, based on the results of maximum solubility, the pseudo-ternary diagram was plotted between Soyabean oil and Tween 20: Span 80. The said system yielded a significant emulsion region. Further, titration of Soyabean oil was conducted with various combinations of Tween 20 and Span 80 (i.e., 4:1, 3:2, 2:3, 1:4, and 1:1). It was subsequently observed that a combination of Soyabean oil, Tween 20 and Span 80 (4:1) yielded the maximum emulsion region for the formulation of SEDDS.

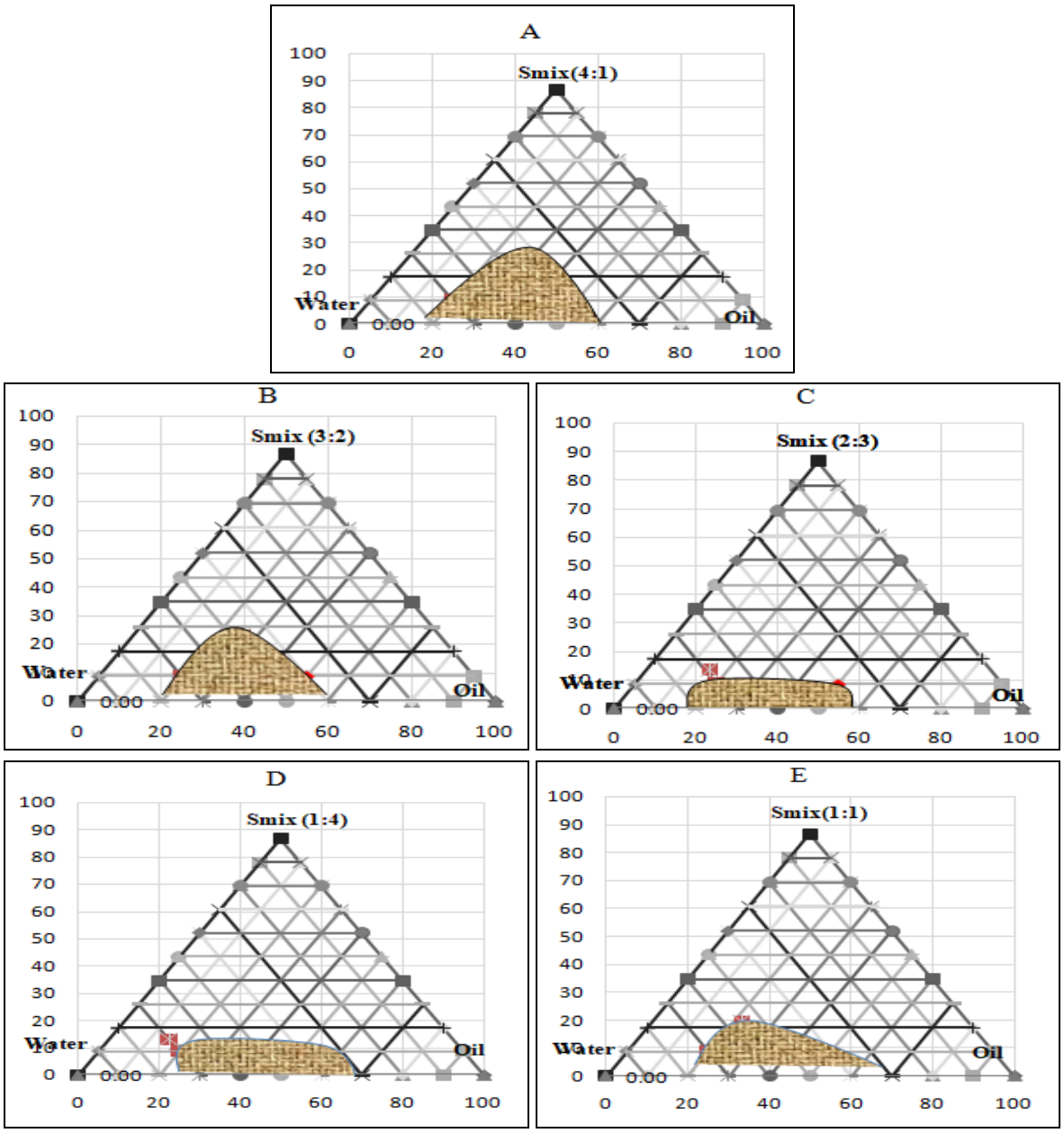
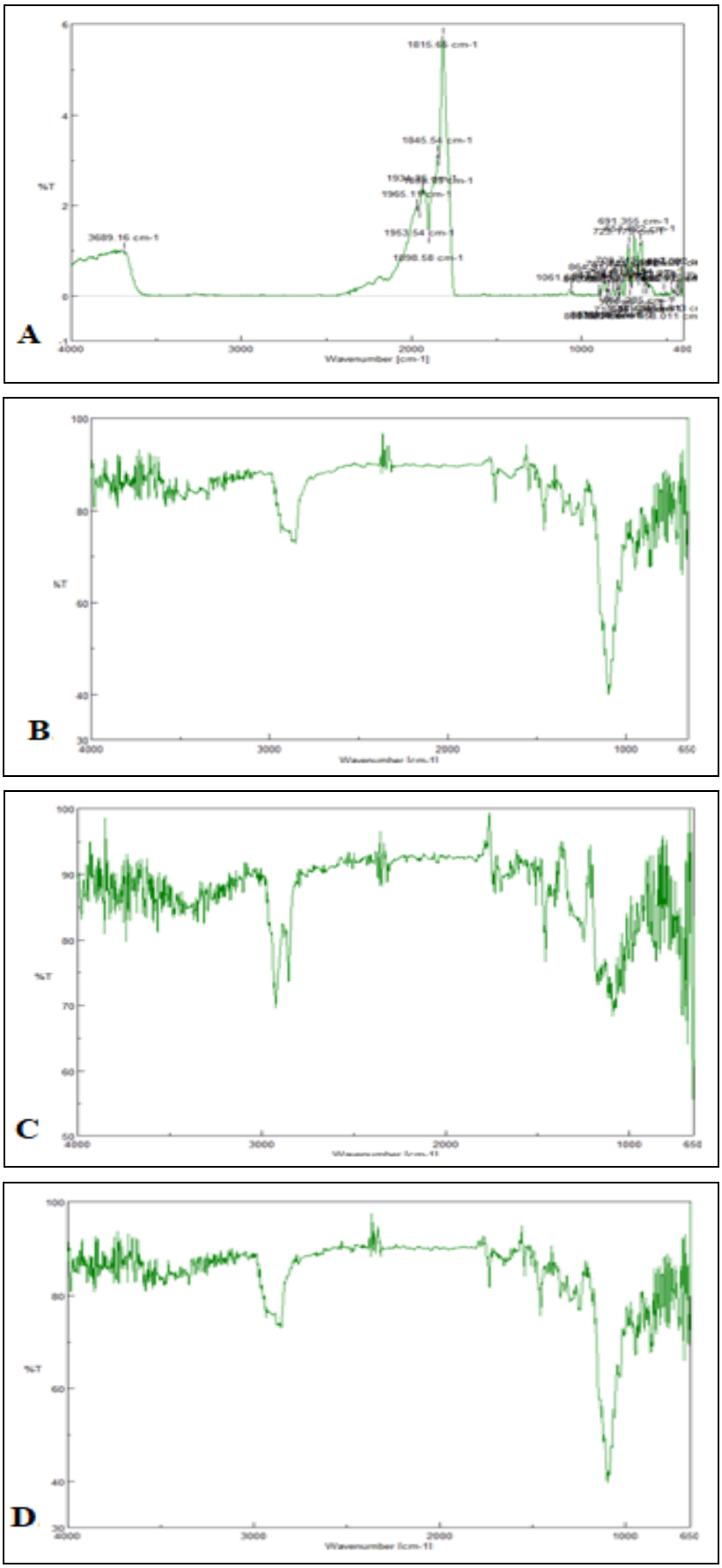
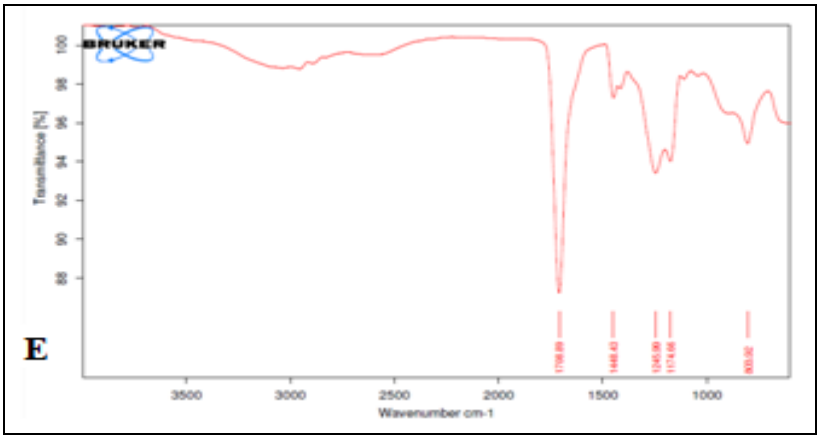


FIG. 2: TERNARY PHASE DIAGRAM OF SYSTEM A (SOYABEAN OIL/SMIX (4:1)/WATER); SYSTEM B (SOYABEAN OIL/SMIX (3:2)/WATER); SYSTEM C (SOYABEAN OIL/SMIX (2:3)/WATER); SYSTEM D (SOYABEAN OIL/SMIX (1:4)/ WATER); SYSTEM E (SOYABEAN OIL/ SMIX (1:1)/ WATER). SHADED AREAS REPRESENT THE REGION OF EFFICIENT SELF-EMULSIFICATION.

Infrared Spectroscopy [40-43]:




BRUKER
Transmittance [%]
100
98
96
94
92
90
88
1709.89
1449.43
1345.90
1174.66
833.92
3500
3000
2500
2000
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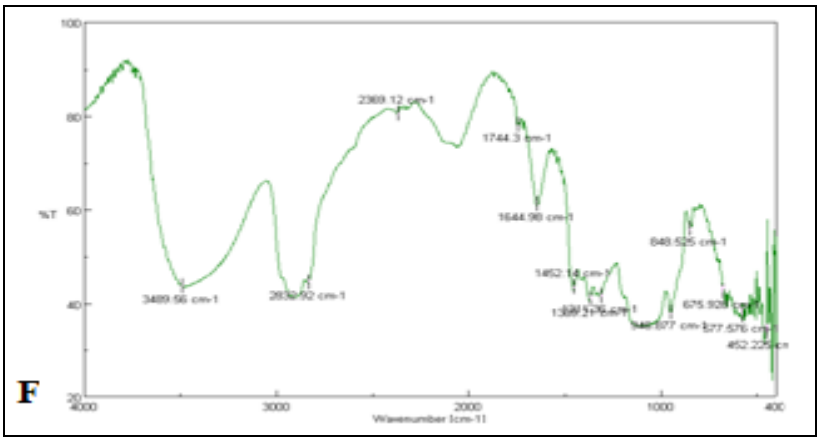
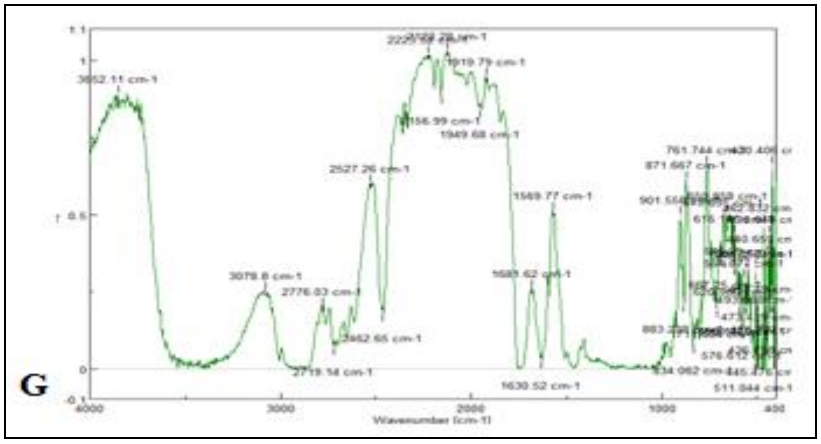
Wavenumber cm-1
E


%T
100
80
60
40
20
3489.56 cm-1
2859.92 cm-1
2369.12 cm-1
1744.3 cm-1
1644.98 cm-1
1452.14 cm-1
848.525 cm-1
675.928 cm-1
577.576 cm-1
462.225 cm-1
4000
3000
2000
1000
400
Wavenumber [cm-1]
F


1.1
1
0.5
0
-0.1
3652.11 cm-1
3078.8 cm-1
2776.03 cm-1
2719.14 cm-1
2527.26 cm-1
2462.65 cm-1
2156.99 cm-1
1949.68 cm-1
1919.79 cm-1
1569.77 cm-1
1630.52 cm-1
871.667 cm-1
761.744 cm-1
511.044 cm-1
4000
3000
2000
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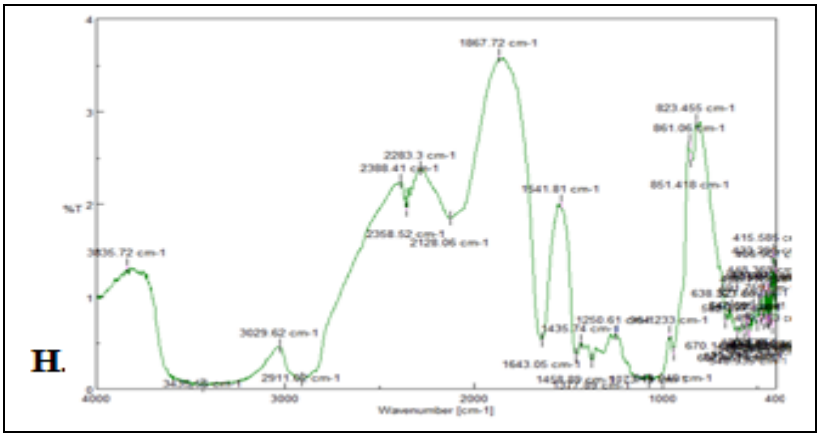
Wavenumber [cm-1]
G


%T
4
3
2
1
0
3635.72 cm-1
3029.62 cm-1
2911.99 cm-1
2388.41 cm-1
2283.3 cm-1
2358.52 cm-1
2128.06 cm-1
1867.72 cm-1
1643.05 cm-1
1541.81 cm-1
1435.74 cm-1
1256.61 cm-1
1233 cm-1
1049 cm-1
861.06 cm-1
851.418 cm-1
823.455 cm-1
670 cm-1
638 cm-1
415.585 cm-1
4000
3000
2000
1000
400
Wavenumber [cm-1]
H.

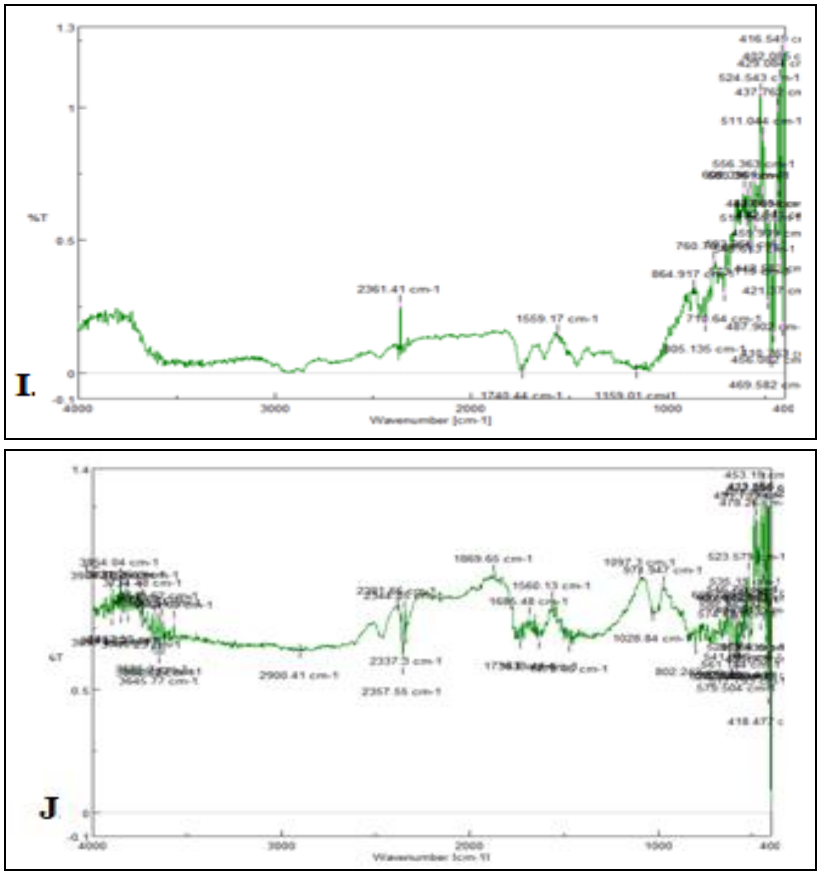


FIG. 3: IR SPECTRA OF CIPROFLOXACIN, SOYABEAN OIL, TWEEN 20, SPAN 80, CARBOLPOL 934, HPMC K 4 M, PHYSICAL MIXTURE CIPROFLOXACIN AND CARBOPOL 934 (1:0.25), PHYSICAL MIXTURE CIPROFLOXACIN AND HPMC K 4 M (1:0.25), FORMULATION I AND FORMULATION II SHOWED A, B, C, D, E, F, G, H, I AND J RESPECTIVELY

Identification of Drug, Polymer and Other Excipients: The FTIR spectrum of ciprofloxacin showed characteristics peak of O-H stretch at 3689.16 cm^{-1}, anhydride C=O stretch at 1815.65 cm^{-1}, C-F stretch at 1061.66 cm^{-1} and N-H wagging at 715 cm^{-1}. The FTIR spectrum of Soyabean oil showed characteristics peak of C=O stretch at 1298.82 cm^{-1}, ester C-O-C stretch at 1097 cm^{-1} and C=C stretch at 1578.45 cm^{-1}. The FTIR spectrum of Tween 20 showed characteristics peak of C=O stretch at 1700.61 cm^{-1}, ester C-O-C stretch at 1097.3 cm^{-1}, O-H stretch at 2760.6 cm^{-1}, C-H stretch at 2960.2 cm^{-1}. The FTIR spectrum of Span 80 showed characteristics peak of C=O stretch at 1698.98 cm^{-1}, ester C-O-C stretch at 1103.08 cm^{-1}, O-H stretch at 32.92.86 cm^{-1}, C-H stretch at 2961.16 cm^{-1} and CH=CH stretch 2929.34 cm^{-1}.The FTIR spectrum of Carbopol 934 showed characteristics peak of C=O stretching at 1708.89 cm^{-1}, C-C stretching at 1448.43 cm^{-1}, O-H bending at 1245.99 cm^{-1} and C-H bending at 1311.36 cm^{-1}. The HPMC K 4 M FTIR spectrum showed characteristics peak of O-H bond in alcohols at 3489.56 cm^{-1}, C-H stretching at 2832 $cm^{-1,}$ and C-O bond in ethers at 1744.3 cm^{-1}.

FTIR of Physical Mixtures: The FTIR spectrum of physical mixture Ciprofloxacin powder and Carbopol 934 (1:0.25) showed a peak of O-H stretching at 3852.11 cm^{-1}, C=O stretching at 1569 cm^{-1} and N-H wagging at 711 cm^{-1}. In this physical mixture absence of C-F stretch and =C-H bending. The FTIR spectrum of the physical mixture of Ciprofloxacin powder and HPMA K 4 M (1:0.25) showed peak of O-H stretching at 3435.56 cm^{-1}, =C-H bending at 607 cm^{-1}, C-F stretching at 1073.19 cm^{-1} and C-H stretching at 3029.62 cm^{-1}. In this physical mixture absence of anhydride C=O stretch and amide N-H wagging.

FTIR of Formulations: The FTIR spectrum of formulation I showed a peak of C=O stretching at 1740.44 cm^{-1}, =C-H bending at 609.39 cm^{-1}, N-H wagging at 711.604 cm^{-1} and C-O stretching 1159.01 cm^{-1}. In this formulation absence of O-H stretch and C-F stretch. The FTIR spectrum of

formulation II showed peak of =C-H bending at 620.966 cm^{-1}, C-H stretching at 2900.41 cm^{-1}, C-F stretching at 1028.54 cm^{-1}, C-O stretching at 1633.41 cm^{-1}, C-O-C stretch at 1097.3 cm^{-1}, C=C stretching at 1470.46 cm^{-1} and C-C stretch at 1633.41 cm^{-1}. In these formulation absences of C=O stretch and N-H wagging.

Differential Scanning Calorimetry [44-47]:

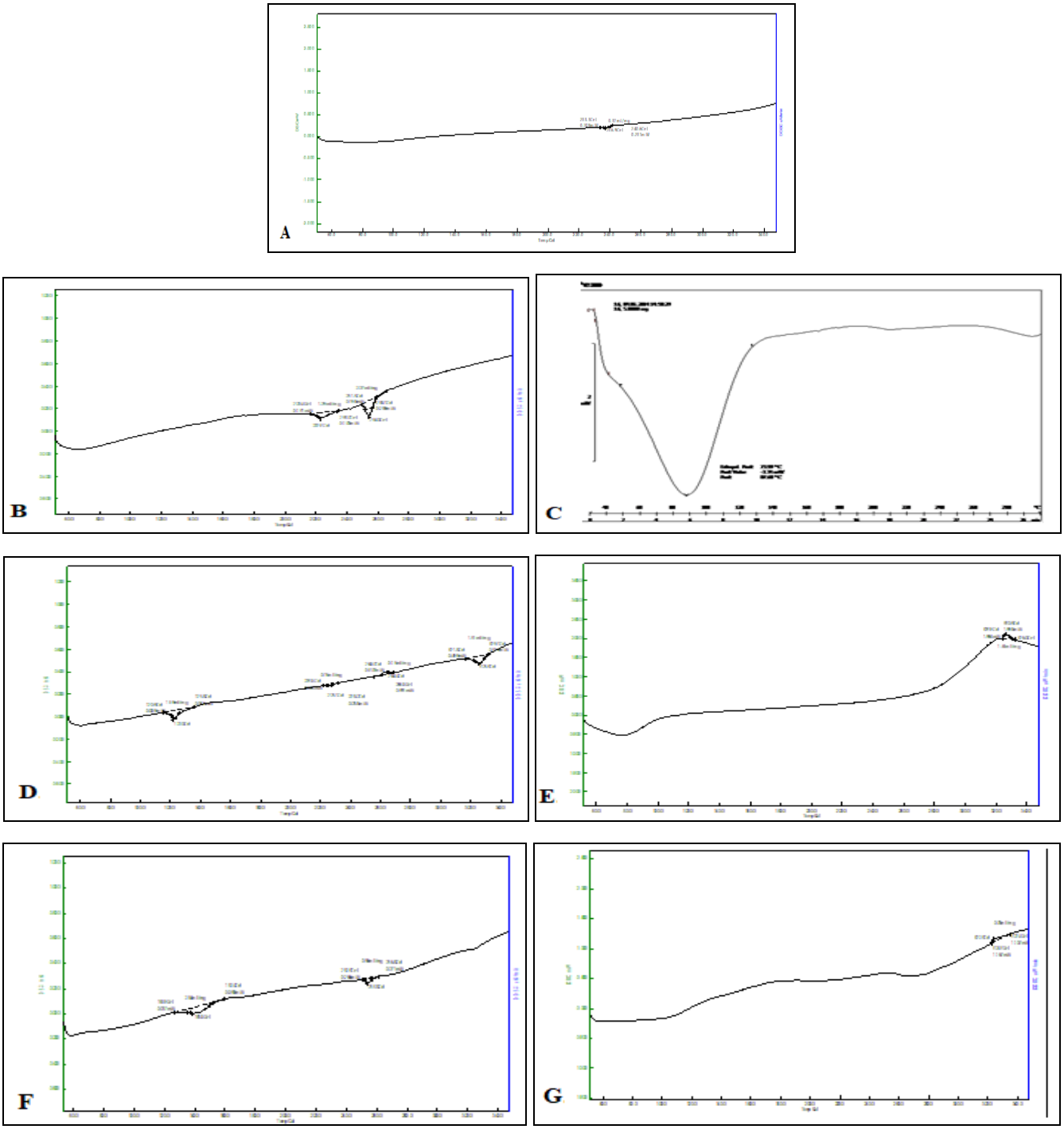


FIG. 4: DSC THERMOGRAM OF CIPROFLOXACIN, CARBOPOL 934, HPMC K 4 M, PHYSICAL MIXTURE OF CIPROFLOXACIN AND CARBOPOL 934 (1:0.25), PHYSICAL MIXTURE OF CIPROFLOXACIN AND HPMC K 4 M (1:0.25), FORMULATION I AND FORMULATION II SHOWED A, B, C, D, E, F AND G RESPECTIVELY

DSC Study of Drug and Polymers: DSC thermogram of ciprofloxacin showed an endothermic peak at 236.9°C indicated the drug's melting point with amorphous nature. DSC

thermogram of Carbopol 934 showed endothermic peaks at 222.3°C and 254°C. In that 254°C was the relevant endothermic peak of its melting point. DSC thermogram of HPMC K 4 M was showed endothermic peak at 87.68°C.

DSC Study of Physical Mixtures: DSC thermogram of physical mixture Ciprofloxacin powder and Carbopol 934 (1:0.25) showed an endothermic peak at 122°C, indicating the formation of a homogeneous mixture between drug and polymer. DSC thermogram of the physical mixture of Ciprofloxacin powder and HPMC K 4 M (1:0.25) was not show any endothermic peak. The drug peak completely emerged, indicating the formation of a homogeneous mixture between drug and polymer and would be in amorphous form.

DSC Study of Formulations: The DSC thermogram of formulation I showed an endothermic peak at 138.8°C indicating the formation of a homogenous mixture between drug and polymer and also indicates amorphous nature in between 160°C to 252°C regions. Another obtained endothermic peak at 253.8°C indicates that some quantity of polymer remains uncomplex in the formulation. For that, we could be increased the ratio of drug and polymer. The DSC thermogram of formulation II did not show any endothermic peak. The drug peak completely emerged, indicating the formation of a homogeneous mixture between drug and polymer in the amorphous nature. The exothermic peak was at 322.3°C because of decomposition.

Micromeritics Properties [28]

TABLE 4: MICROMERITICS PROPERTIES OF POWDER

Batch	Mean bulk density (g/ml) ± SD	Mean tapped density (g/ml) ± SD	Mean angle of repose° ± SD	Mean percent compressibility Index % ± SD	Mean hausners ratio ± SD
F	0.4327±0.0030	0.5278±0.0014	33.51±0.2274	17.50±0.1594	1.2230±0.0103

Bulk Density and Tapped Density: The bulk density and tap density of formulations was found to be 0.4327 g/ml and 0.5278 g/ml respectively.

Angle of Repose: The angle of repose of formulations ranges from 29.42° to 33.86°, indicating acceptable flow properties.

Percent Compressibility Index: The compressibility index of formulations is in the range of 12.121%-18.182%, indicating the good flow properties.

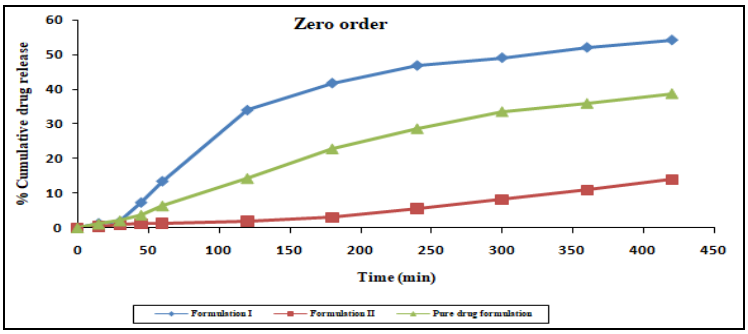
Hausner's Ratio: Hausner's ratio of all formulations <1.25 indicate good flow ability. Capsule preparations comply with the test if not more than one individual content is outside the limits of 85 to 115 percent of the average content and none was outside the limits of 75 to 125 percent of the average content.

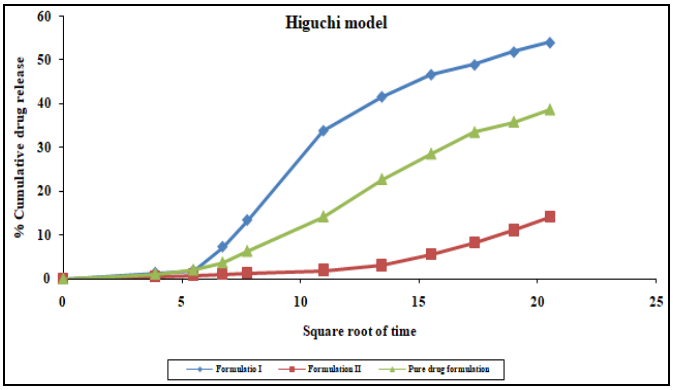
Drug Content Uniformity [48]:

TABLE 4: DRUG CONTENT UNIFORMITY OF FORMULATION

S. no.	Batch code	Absorbance	% Drug content
1.	Formulation I	0.187	96.84
2.	Formulation II	0.175	90.15

In-vitro drug Release Study [49-50]:





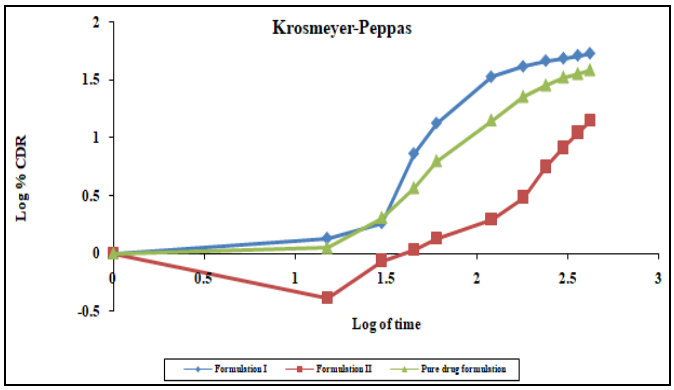


FIG. 5: A, B AND C SHOWED ZERO-ORDER KINETIC MODELING FOR FORMULATION, MATRIX (HIGUCHI) KINETIC MODELING FOR FORMULATION, AND KROSMAYER - PEPPAS KINETIC MODELING FOR FORMULATION, RESPECTIVELY

Dissolution data were fitted in zero order, Higuchi (Matrix) model and Krosmayer-Peppas model. The best-fitted model for formulation I and pure drug formulation was the Higuchi model, and formulation II was fitted in the Zero-order model. The release profile of pure drug formulation showed 38%, formulation I showed the highest 54% cumulative drug release, and formulation II showed the lowest i.e. 14% drug release.

Dissolution data also fitted into Peppas and Krosmayer model it shows n-value 0.7362, 0.8184, and 0.5095, respectively, for pure drug formulation, formulation I and formulation II respectively, which was greater than 0.1 shows non-fickian or anomalous transport diffusion release mechanism.

Statistical Analysis [51]: Student's t-test was determined for In-vitro drug release data for different polymeric formulations showed a p-value 0.001891 (<0.01) it was 99.99% significant.

CONCLUSION: S-SEDDS of ciprofloxacin was prepared from aerosil (colloidal silica) filled in hard gelatin capsules, while liquid SEDDS was composed of soyabean oil, tween 20 and span 80. In vitro release studies were carried out in phosphate buffer pH 7.4. The release profile of pure drug formulation showed 38%, formulation I showed the highest 54% cumulative drug release, and formulation II showed the lowest, i.e., 14% drug release. Formulation II follows the Zero-order model, while formulation I follow Higuchi (matrix) model. Dissolution data also fitted into Peppas and Krosmayer model it shows n-value 0.7362, 0.8184, and 0.5095, respectively, for pure drug, formulation I and formulation II, which was greater than 0.1 showing non-fickian or anomalous transport diffusion release mechanism. So, finally from all results, it was concluded that the Solid self emulsifying drug delivery system is a suitable approach for solubility and dissolution enhancement of poorly water-soluble ciprofloxacin.

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CONFLICTS OF INTEREST: Nil

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