IJPSR (2020), Volume 11, Issue 1 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 November 2019; received in revised form, 05 December 2019; accepted, 07 December 2019; published 01 January 2020

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF ERLOTINIB HYDROCHLORIDE BY SOLID DISPERSION TECHNIQUE WITH POLOXAMER 188: PREPARATION AND *IN-VITRO* EVALUATION

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Keywords:

Solubility enhancement, Solid dispersion, Solvent evaporation, Erlotinib hydrochloride

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ABSTRACT: Solid dispersions (SDs) of Erlotinib hydrochloride (ETN) were prepared to enhance the solubility by solvent evaporation (SE) and Melting (MM) method using poloxamer 188 (PL 188) in the ratio of 1:1, 1:3 and 1:5 (w:w). The solubility of the drug was increased in a concentration-dependent manner of polymer and follow linearity order. The solid dispersion was characterized by Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD), and differential scanning calorimetry (DSC). The FTIR spectra revealed the drug was found compatible and did not show any interaction with polymer, PXRD spectra, and DSC thermographs showed a clear transformation of crystalline to an amorphous form of drug particles. *In-vitro* dissolution study was performed in dissolution medium *i.e.* 0.1N HCl (pH 1.2). Cumulative percent drug release from SDs prepared by the SE method was faster than from the pure drug, physical mixture (PM), and SDs prepared by the MM method. The maximum percent drug release (90.07 ± 0.78) was found with PL 188 in the ratio of 1:5 (w/w). Among the used techniques, the SE method demonstrating maximum increased in solubility as well as *in-vitro* drug release profile. Therefore, it is concluded that the use of the SE method is a promising approach to enhance the solubility and dissolution rate of ETN.

INTRODUCTION: Poor water solubility of drugs in a gastrointestinal fluid is a rate-limiting step of bioavailability and it is a challenging task for researchers to improve water solubility [1]. ETN is a weak base and poorly soluble in water.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(1).387-93

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(1).387-93

According to Biopharmaceutical Classification System (BCS), ETN comes under the BCS class II characterized high permeability low solubility drugs [2]. In order to improve the solubility, various approaches have been developed by the researchers *viz.* SDs [3], spray drying [4], size reduction [5], salt formation [6], alteration of pH [7], addition of surfactants [8], inclusion complex formation [9], polypeptide nanocapsule [10], surface modification [11], lipid nanoparticles [12], nanoliposomal formulation [13], self emulsifying [14] electrospraying, lyophilisation using proper hydrophilic carriers in suitable concentrations [15].

In the SDs techniques HPMC E5 LV, PEG 6000 and PL 188 are used most frequently as solubilizing agents [16]. Chemically Erlotinib hydrochloride is N-(3-ethynylphenyl)-6, 7-bis (2-methoxyethoxy) quinazolin-4amine, with a molecular weight of 429.90 g/mol and pKa of 5.42 at 25 °C [17]. It is a selective and potent epidermal growth factor receptors (EGFR) tyrosine kinase inhibitor, inhibits the downstream signaling pathways such as cell proliferation, metastasis, angiogenesis and prevents autophosphorylation of tyrosine kinase. ETN is used for the treatment of different types of tumor *i.e.* non-small cell lung cancer, head, neck, and ovarian cancer. In the few decades, the surface tension reducing agents have been used alone and in combination for SDs formulation [18].

Hydroxypropyl methylcellulose also known as methocel is a low viscosity water-soluble polymer. Polyethylene glycol is a polyether and also known as carbowax [19]. PL 188 is a non-ionic polymer containing hydrophilic and hydrophobic cavities, used to increase the solubility of poorly aqueous soluble drugs [20]. Some physicochemical properties of polymers such as biocompatibility, wettability, prevent drug precipitation, prevention of crystal formation, surface area enhancement, and plays a vital role to improve the water solubility by SDs method [21]. SDs method has been employed to enhance the solubility and dissolution of many BCS class II drugs. Aqueous soluble surface-active agents and synthetic polymers have been introduced, as a solubilizing carrier in the SDs formulation. The purpose of this present work was to improve solubility and owing to this, better bioavailability with reduced side effects [22]. ETN structure shown in **Fig. 1**.

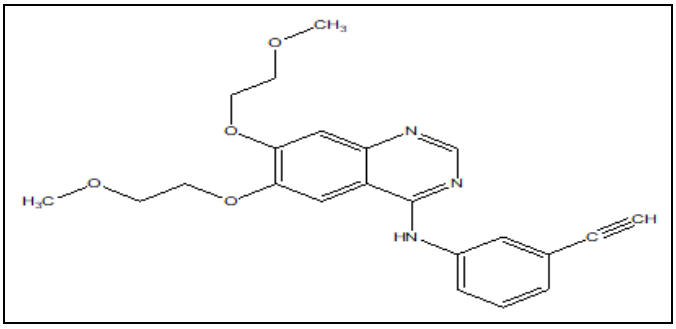

FIG. 1: CHEMICAL STRUCTURE OF ETN

MATERIALS AND METHODS:

Materials: ETN was gifted by Cipla Pharmaceutical Company Mumbai, India, PL 188 from Sigma-Aldrich India. All other reagents were used for an analytical grade.

Methods:

Phase Solubility Studies: The solubility studies of ETN and SDs prepared by SE and MM were determined in distilled water, 0.1N HCl (pH 1.2) and phosphate buffer of pH 7.4 at 25 °C. For every preparation, an excess amount of SDs was added to the 25 ml of distilled water, 0.1 N HCl and phosphate buffer (pH 7.4) in a glass vial (screw-capped) respectively. The vials were placed in an incubator shaker at 25 °C temperature for 24 h. The solutions were then filtered through a millipore membrane filter 0.45 (micrometer), and the filtrates were further diluted and analyzed by UV spectrophotometer at λ_{max} of 246 nm [23].

Preparation of Physical Mixtures: ETN and PL 188 in the ratio of 1:1, 1:3 and 1:5 triturated in a pestle and mortar for 3 min screened by #40 sieve and were stored in desiccators till further use [24].

Preparation of SDs by Melting Method: ETN and PL 188 in different weight ratios 1:1, 1:3 and 1:5 were heated on oil bath until it PL 188 melted completely. The ETN was then dispersed to the melted PL 188. The obtained mixture was immediately cooled on ice cubes, crushed by and mortar pestle then shifted through a #40 sieve [25].

Preparation of SDs by SE Method: Weighed accurately ETN and PL in the ratio of 1:1, 1:3 and 1:5, drug and polymer were dispersed in methanol. Then the solvent was evaporated rapidly by heating up to 45 °C with stirring on a magnetic stirrer, a uniform solid mass was formed. The prepared solid dispersions were crushed and desiccated for 24 h under vacuum, further pulverized, through #40 sieve was screened and stored in desiccators [26].

TABLE 1: FORMULATIONS OF SDs OF ETN

Method	PL 188		
	Mixing ratio		
	1:1	1:3	1:5
PM	EPM1	EPM2	EPM3
MM	EMM1	EMM2	EMM3
SE	ESE1	ESE2	ESE3

Characterization of SDs:

Drug Content: SDs of ETN equivalent to 10 mg were accurately weighed and dissolved in 10 ml of methanol, in a 100 ml volumetric flask, then the

volume was made up with 0.1N HCl, solutions were mechanically shaken for 30 min and filter by 0.45 (micrometer) millipore membrane filter. Then the concentration of 10µg/ml was prepared, and drug content was measured by UV spectrophotometer at λ_{max} of 246 nm [27].

Fourier Transform Infrared Spectroscopy (FTIR): ETN, PL 188, PM and SDs were made into fine powder by mortar and pestle, placed into the sample holder of FTIR and recorded FTIR spectra in the spectral range of 4000-400 cm^{-1} of FTIR (Alpha II Bruker Germany) [27].

Differential Scanning Calorimetry (DSC): DSC thermal analysis of ETN, PM, PL 188 and SDs were obtained using differential scanning calorimeter unit (PerkinElmer, STA 6000, USA) in aluminum stage, sample about 5-10 mg was placed in the reference of a similar stage. Then the samples of pure drug, physical mixture, and SDs heating with the rate of 10 ºC/min from 40 ºC to 300 ºC in a pursing with nitrogen gas at a flow rate of 50 ml/min [27].

Powder X-Ray Diffraction Pattern (PXRD): ETN, PL 188 and SDs were analyzed by PXRD diffractogram (Rigaku, Ultima IV, Japan) using Cu-Kα radiation of (40 kV, 320 mA) at 2º/min of analysing speed and 2º/2 cm per 2°θ of chart speed [28].

***In-vitro* Drug Dissolution Studies:** The *in-vitro* dissolution study of Pure drug, SDs prepared by SE method drug equivalent to 10 mg of ETN was filled into the hard gelatine capsule and performed in 900 ml of 0.1N HCl (pH 1.2) at 37 ºC ± 0.5 ºC by USP type II dissolution test apparatus, (paddle type) at 50 rpm for 120 min. A 5 ml of aliquots were withdrawn from the vessels, maintaining sink environment with replacement of 5 ml fresh medium at time interval of 0, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 min, filtered by millipore membrane filter 0.45 (micrometer), then filtrates were diluted, and analysed by spectrophotometer (UV1800 Shimadzu, Japan) at λ_{max} of 246 nm; the experiment was repeated three times [28].

RESULTS AND DISCUSSION:

Phase Solubility Studies: The profile of phase solubility of ETN was found to be 2.96 ± 0.22, 4.13 ± 0.71, 2.23 ± 0.25 µg/ml in distilled water, 0.1N HCl, and phosphate buffer pH 7.4, respectively. The results strongly suggest for the need to enhance the solubility and dissolution rate of ETN. The ESE3 SDs prepared by SE method demonstrating maximum solubility in 0.1N HCl (29.71 ± 0.29 µg/ml) and was selected for further dissolution studies.

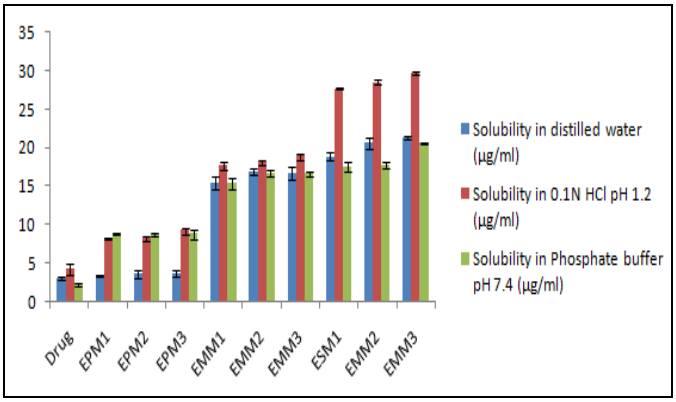

FIG. 2: BAR GRAPH OF SOLUBILITY OF ETN, PM AND SDS IN DISTILLED WATER, 0.1N HCl (pH 1.2) AND PHOSPHATE BUFFER (pH 7.4)

TABLE 2: PHASE SOLUBILITY STUDIES DATA OF PM AND SDs OF ETN IN DISTILLED WATER, 0.1N HCl (pH 1.2) AND PHOSPHATE BUFFER (pH 7.4)

S. no.	Formulations	Solubility in distilled water (µg/ml)	Solubility in 0.1N HCl pH 1.2 (µg/ml)	Solubility in phosphate buffer pH 7.4 (µg/ml)
1	Pure Drug (ETN)	2.96 ± 0.22	4.13 ± 0.71	2.23 ± 0.25
2	EPM1	3.38 ± 0.16	8.13 ± 0.11	8.82 ± 0.13
3	EPM2	3.56 ± 0.62	8.19 ± 0.32	8.71 ± 0.27
4	EPM3	3.66 ± 0.41	9.18 ± 0.45	8.77 ± 0.62
5	EMM1	15.42 ± 0.82	17.69 ± 0.51	15.38 ± 0.74
6	EMM2	16.91 ± 0.44	18.11 ± 0.34	16.72 ± 0.41
7	EMM3	16.63 ± 0.87	18.88 ± 0.42	16.66 ± 0.34
8	ESE1	18.81 ± 0.51	28.72 ± 0.11	17.59 ± 0.66
9	ESE2	20.56 ± 0.71	28.53 ± 0.27	17.78 ± 0.38
10	ESE3	21.26 ± 0.21	29.71 ± 0.29	20.63 ± 0.12

Data are expressed as mean ± S.D. (n=3)

Characterization of Physical Mixtures and Solid Dispersions:

Drug Content:

TABLE 3: DRUG CONTENTS OF SDs OF ETN

S. no.	Formulations	% Drug content
1	EPM1	99.26 ± 0.21
2	EPM2	98.38 ± 0.17
3	EPM3	99.41 ± 0.62
4	EMM1	91.96 ± 0.41
5	EMM2	93.63 ± 0.57
6	EMM3	94.66 ± 0.81
7	ESE1	95.29 ± 0.49
8	ESE2	96.76 ± 0.51
9	ESE3	97.56 ± 0.71

Data are expressed as mean ± S.D. (n=3)

The drug content for PM (98.38 ± 0.17 to 99.41 ± 0.62) and SDs prepared by MM (91.96 ± 0.41 to 94.66 ± 0.81) and by SE method (95.29 ± 0.49 to 97.56 ± 0.71) was obtained respectively, given in **Table 4**.

Fourier Transform Infrared Spectroscopic (FTIR) Studies: FTIR spectra of ETN, PL, and SDs are presented in **Fig. 3** and **Fig. 4**. The spectra of ETN exhibit characteristic peaks at 3269.58 cm^{-1} (=NH- stretching), 2711.46 cm^{-1} (≡C-H stretching), 2995.60 cm^{-1} (H-CH_3 stretching), 1628.84 cm^{-1} (NH bending), 1237.38 cm^{-1} (Ar-O bending), 1024.98 cm^{-1} (aliphatic-O-stretching), 646.34 cm^{-1} (≡C-H bending), 2311.92 cm^{-1} (C≡C stretching) and 1436.82 cm^{-1} (Ar-C-N stretching). In the spectra of PL principal peaks at the 2883.84 cm^{-1} (aliphatic C-H stretching), 1342.25 cm^{-1} (O-H bending), and 1100.87 cm^{-1} (C-O stretching) were observed. No interaction between the drug and polymer was seen, and the peaks of the functional groups of ETN were reserved well in the solid dispersion and intensity of peaks of the polymer was increased while the intensity of ETN peaks decreased in the. These findings revealed that excellent compatibility found between the drug and polymer.

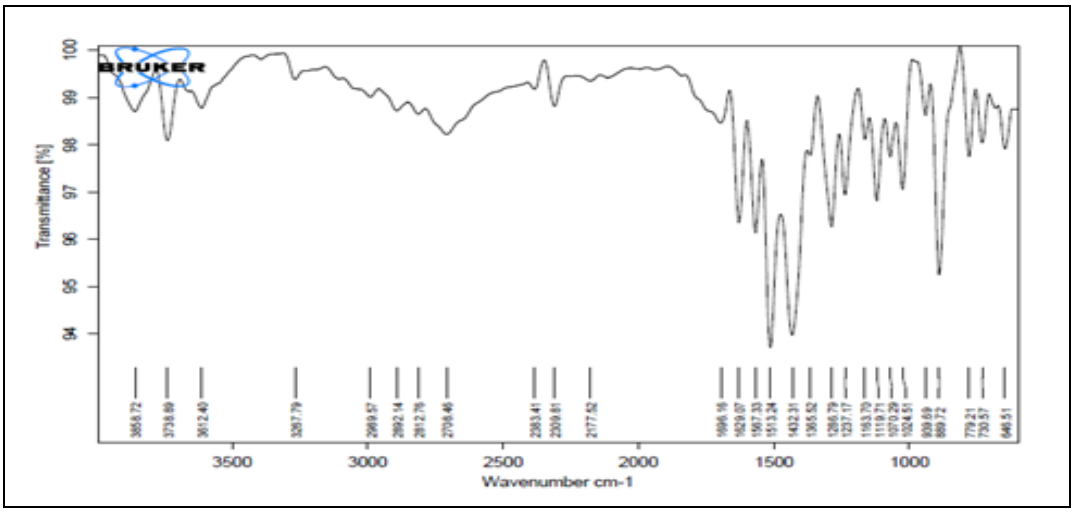

FIG. 3: FTIR SPECTRA OF ETN

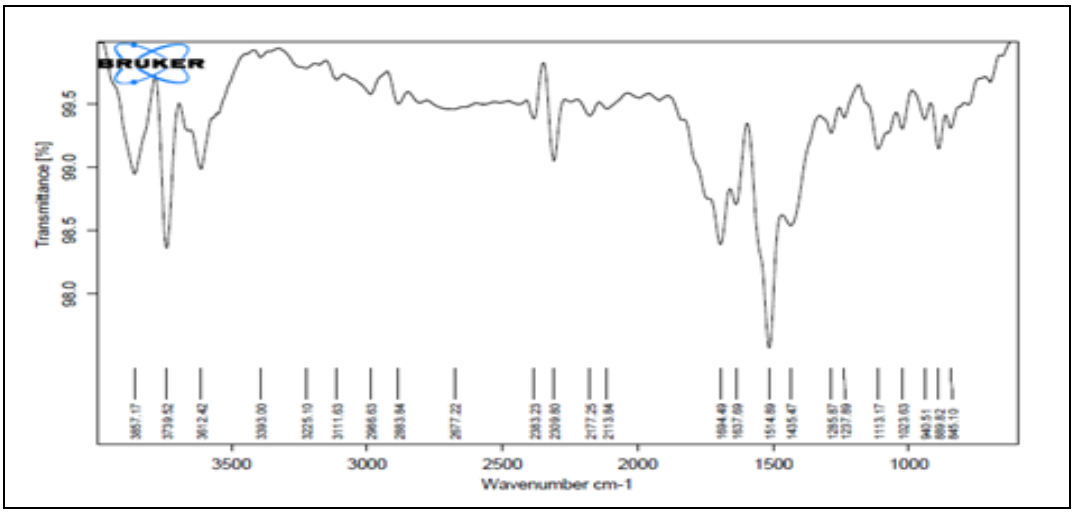

FIG. 4: FTIR SPECTRA OF (A) ETN, (B) PL 188, (C) SDs (SE 1:5)

Differential Scanning Calorimetric (DSC) Studies: DSC curves of ETN, PM, PL 188, and SDs prepared by the solvent evaporation method are presented in **Fig. 5**. The DSC curves of ETN and PL 188 showed the sharp endothermic peaks corresponding to their melting points, at around 232.52 ºC and 55.53 ºC respectively. From the curves of the SDs, it was observed that there is no peak corresponding to the melting point of the drug and the curve was shifted to lower temperature i.e. 190.83 ºC with less sharp endothermic peak, suggesting a reduction in crystallinity of drug (ETN) in the SDs.

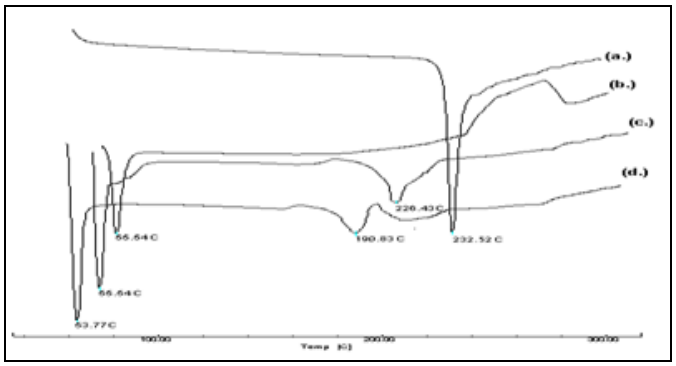

FIG. 5: DSC CURVES OF (A) ETN, (B) PL 188, (C) PM (D) SDs (SE 1:5)

Powder X-Ray Diffraction (PXRD) Studies: PXRD spectra of ETN, PL 188, and SDs prepared by SE method are presented in **Fig. 6**. The PXRD spectrum of the pure drug showed distinct sharp peaks at a diffraction angle (2°θ); it confirms that the drug was present in the crystalline form.

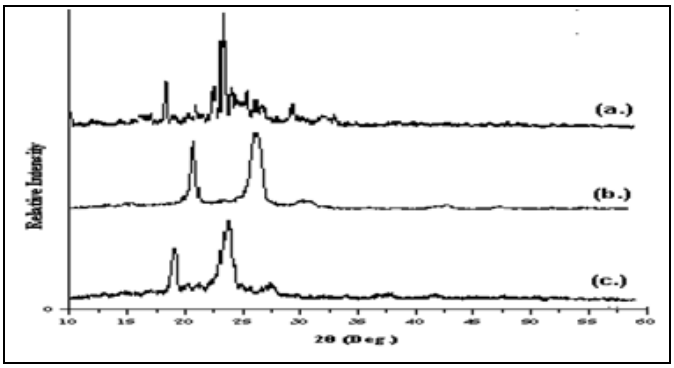

FIG. 6: PXRD PEAKS OF (A) ETN, (B) PL 188, (C) SDs (SM 1:5).

The PXRD of SDs prepared by the SE method indicating the reduction in intensity and number of typical diffraction peaks of ETN. Suggests the reduction in the crystalline nature of the drug. Thus, the drug must have been converted from the crystalline state to the amorphous state in the SDs.

In-vitro Drug Dissolution Studies:

TABLE 4: DISSOLUTION DATA OF ETN, PM, SDs PREPARED BY MM AND SE METHODS (1:5) IN 0.1N HCl (pH 1.2)

Time (min)	Drug	EPM1 (1:1)	EPM2 (1:3)	EPM3 (1:5)	EMM1 (1:1)	EMM2 (1:3)	EMM3 (1:5)	ESE1 (1:1)	ESE2 (1:3)	ESE3 (1:5)
0	0	0	0	0	0	0	0	0	0	0
10	5.37 ±0.41	8.86 ±0.50	9.57 ±0.83	8.28 ±1.35	14.36 ±0.62	14.91 ±1.10	16.28 ±1.07	18.18 ±0.29	17.23 ±0.67	18.56 ±1.14
20	9.75 ±0.53	15.45 ±0.25	12.91 ±1.07	11.23 ±0.42	28.93 ±0.89	29.45 ±0.76	26.77 ±0.83	27.43 ±1.13	28.75 ±0.54	32.67 ±0.50
30	17.20 ±0.82	22.77 ±0.48	25.36 ±1.11	24.17 ±1.02	35.33 ±0.69	34.85 ±0.56	31.67 ±0.71	38.45 ±0.93	39.86 ±1.18	45.46 ±0.43
40	25.61 ±0.62	28.72 ±0.17	30.04 ±0.82	28.72 ±1.60	44.67 ±1.21	43.78 ±0.53	37.92 ±0.80	51.34 ±0.43	51.62 ±1.16	55.91 ±0.95
50	29.84 ±0.78	35.08 ±0.47	36.18 ±0.98	31.97 ±1.21	47.92 ±0.57	52.43 ±0.83	46.87 ±0.63	55.47 ±1.15	58.34 ±0.47	63.11 ±0.26
60	33.53 ±0.48	40.27 ±1.38	42.56 ±1.19	42.89 ±0.39	52.64 ±0.51	58.09 ±0.58	53.57 ±0.67	61.35 ±1.57	66.49 ±0.81	68.55 ±0.57
70	38.59 ±0.73	44.92 ±0.87	46.37 ±1.10	46.22 ±0.56	60.45 ±0.37	63.73 ±1.09	59.21 ±0.78	65.32 ±0.72	71.46 ±0.59	76.53 ±0.73
80	40.18 ±0.55	48.25 ±0.51	50.06 ±0.72	48.68 ±0.71	68.66 ±0.71	69.66 ±0.43	66.88 ±0.95	76.22 ±0.63	78.52 ±0.69	81.45 ±0.72
90	42.88 ±0.80	51.54 ±0.65	52.37 ±1.30	50.78 ±0.49	72.78 ±0.90	72.85 ±0.40	70.23 ±0.43	78.64 ±0.36	82.36 ±1.03	85.93 ±0.58
100	44.14 ±0.44	52.82 ±0.52	54.06 ±0.60	51.73 ±0.26	73.22 ±0.63	78.42 ±0.68	74.56 ±0.59	80.73 ±0.72	85.13 ±0.55	88.27 ±0.40
110	45.45 ±0.87	53.48 ±1.04	56.52 ±0.52	51.81 ±1.10	74.33 ±0.87	80.99 ±0.61	78.72 ±0.31	81.51 ±0.48	86.13 ±0.80	89.75 ±0.60
120	45.45 ±0.62	53.50 ±1.38	56.63 ±0.73	51.84 ±0.83	75.23 ±0.87	81.13 ±0.63	79.66 ±0.71	81.64 ±0.56	86.73 ±0.64	90.07 ±0.78

Data are expressed as mean ± S.D. (n=3)

In-vitro dissolution profiles in 0.1N HCl (pH 1.2) of ETN, PM, and its SDs prepared by SE and MM method with the PL 188 in the different ratios were shown in **Fig. 7**. Pure drug (ETN) release was found to be only 45.45 ± 0.62 in 120 min, the result strongly suggests for the need to enhance the dissolution. The results of the *in-vitro* cumulative percent drug release indicated that the SE method improved the dissolution rate of ETN to a great extent. Drug release from SDs prepared by the SE method was faster than from the pure drug, PM and SDs prepared by MM method.

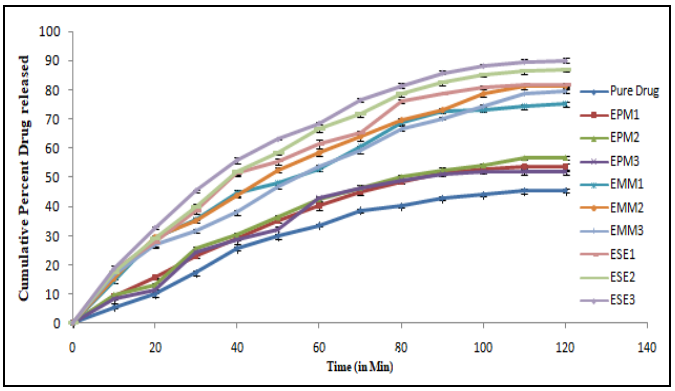

FIG. 7: DISSOLUTION PROFILES OF ETN, PM, SDs PREPARED BY MM AND SE METHODS (1:5) IN 0.1N HCl (pH 1.2)

The drug release from the SDs prepared by SE method (ESE3) was found maximum at 100 min (88.27 ± 0.40), but after 100 min it becomes constant. The maximum Cumulative percent drug release shown by ESE3 formulation was 90.07 ± 0.78 in 120 min, this may be due to the molecular and colloidal dispersion of drug in the hydrophilic carrier matrix of PL 188. The reduction of crystallinity of drugs resulting in improved release (supported by PXRD and DSC); reduction of particle size to expand the effective surface area for dissolution solubilizing effect of PL 188.

CONCLUSION: The objective of present research work was the preparation of SDs, by the SE and MM using different combinations with PL 188 polymer. Among the used techniques, the SE method demonstrating maximum increased in solubility as well as *in-vitro* drug release profile. Therefore, it is concluded that the use of the SE method is a promising approach to enhance the solubility and dissolution rate of ETN, which is a poorly water-soluble drug. Reduction in surface tension and wetting properties was the major cause of enhancing the dissolution rate and solubility of SDs made by PL 188.

ACKNOWLEDGEMENT: Authors are grateful to Cipla Company, Mumbai, India, for providing gift samples of Erlotinib hydrochloride. The authors are thankful to Head, Department of Pharmaceutical Sciences, Chemistry and Physics, University College of Science, Mohanlal Sukhadia University, Udaipur for providing all necessary facilities to carry out this research work.

CONFLICTS OF INTEREST: We declare that we have no conflicts of interest.

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How to cite this article:
Meena MK, Choudhary D, Chouhan M, Shukla P and Sinha SK: Enhancement of solubility and dissolution rate of erlotinib hydrochloride by solid dispersion technique with poloxamer 188: preparation and *in-vitro* evaluation. Int J Pharm Sci & Res 2020; 11(1): 387-93. doi: 10.13040/IJPSR.0975-8232.11(1).387-93.