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Enhancement of dissolution rate of slightly soluble drug Clomiphene Citrate by Solid Dispersion

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Abstract: In the present study, a series of solid dispersions of the drug clomiphene citrate using polyethylene glycol as carrier were prepared following the kneading and solvent evaporation method. This article investigate enhancement of the dissolution rate of clomiphene citrate using solid dispersion with PEG (4000 & 6000). Dissolution studies using the USP XXIV apparatus were performed for solid dispersions of clomiphene citrate. Infrared (IR) spectroscopy was performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. IR spectroscopy showed no change in the crystal structure of clomiphene citrate. Dissolution of clomiphene citrate improved significantly in solid dispersion products (78.20±0.79% in 1 hr) by PEG 6000 as compare to PEG 4000 as well as there was also increase in amount of drug release of drug in 30 min form solid dispersion as compared to free drug release. All solid dispersion showed burst release on increasing the drug : polymer ratio (maximum in SE_{14}-75.24% in 30 min). In solid dispersion, PEG 6000 showed greater improvement in dissolution profile of clomiphene citrate prepared by solvent evaporation method as compare to kneading and physical mixture method. Thus, the solid dispersion technique can be successfully used for improvement of dissolution of clomiphene citrate.
Key words: Clomiphene citrate (CC), Solid Dispersion (SD), Polyethylene glycol (PEG).

Introduction

The rate and extent of dissolution of the drug from any solid dosage form determines the rate and extent of absorption of the drug.[1,2] In case of poorly water soluble drug dissolution rate is rate limiting step in the process of drug absorption, potential bioavailability problem an relevant with extremely hydrophobic drug due to erratic and incomplete absorption from GIT.[3] Potential absorption problem occur if the aqueous solubility is less than 1mg/ml. Several techniques have been developed for the solubility enhancement of poorly soluble drugs such as solid dispersion[4-8], inclusion complex[9.10], ultra rapid freezing process[11], melt sonocrystallization[12], solvent change method[13], melt granulation technique[14], supercritical solvent, supercritical and cryogenic technique, cosolvent approach. Some drug have high bioavailability.

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs, which was introduced in the early 1970s is a multicomponent system, such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, ursodeoxycholic acid, and albendazole. Various hydrophilic carriers, such as polyethylene glycols, polyvinylpyrrolidone, hydroxypropyl methylcellulose, gums, sugar, mannitol and urea have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs[15].

Francis et al. (2007)[16] in their patent describes the no. of the drugs from which solid dispersion can prepared. Because of poorly aqueous solubility of Clomiphene citrate may possess dissolution related absorption problem, hence an attempt was made to improve the dissolution of Clomiphene citrate through the formulation containing SD of Clomiphene citrate.

Materials and Methods

Materials

Clomiphene citrate was obtained as gift sample from PALAM PHARMA PVT.LTD Ahemdabad, India. PEG 4000, PEG 6000 and all other chemicals used as analytical reagent/pharmaceutical grade.

Preparation of solid dispersions

The preparation of drug Clomiphene citrate:PEG (4000 & 6000) solid dispersion were prepared by different techniques, which are described below in detail:(Table -1)

1. Physical mixture (PM)

The drug (Clomiphene citrate) and the selected carriers/ polymers were first sieved through sieve no. 4o they were then mixed with a spatula in a glass pestle mortar for 45 min. for uniform mixing as per batches designed.

2. Kneading Method (KN)

A mixture of polymer and Clomiphene citrate were weighed accurately in specified quantity. The powder was wetted with methanol: water (2:3) and kneaded thoroughly for 30 min. in glass mortar. Further, the product was dried at 40^0C for 48 h., passed through sieve no.85 and stored in a desiccator over fused calcium chloride.

3. Solvent-Evaporation method (SE)

Drug and polymer were dissolved in methanol to get a clear solution. The resulting solution was stirred at ambient temperature for 30 minutes. The resulting preparation were kept in a desiccator for the least 48 h and then grounded in a glass mortar for size reduction and passed through sieve no.85 and stored in a desiccator over fused calcium chloride.

Characterization of Solid Dispersion (SD)[17-18]

Fourier Transform Infra red spectroscopy (FTIR):

IR spectra of Clomiphene citrate and solid dispersions were obtained by KBr pellet method using Zasco FTIR series model 117 spectrometer in order to rule out drug carrier interaction occurring during the formulation process.(Fig: 1-5)

Drug content analysis

An accurately weighed quantity of solid dispersion equivalent to 20 mg of Clomiphene citrate was taken into a 100 ml volumetric flask, dissolved in a small quantity of 0.1N HCl and make up to the mark with 0.1N HCl. Then the solution was suitably diluted and assayed for drug content by measuring the absorbance at 232 nm. (Table: 2-4)

In vitro dissolution

The experiments were conducted according to the following procedure: 900 millilitres of water, maintained at 37±0.5°C was used as a dissolution medium. The stirring speed of the paddle was at 100rpm. After the required amount of each sample had been placed into the dissolution medium, an aliquot portion of the solution was withdrawn at appropriate time intervals and diluted with 0.1N HCl then analyzed by spectrophotometer for the amount of the dissolved drug. Each point on the dissolution profiles represented the average of three determinations (Table: 2-4).

Table 1: Formulation Code of Solid Dispersion for Different Method of Preparation

Name of method	Drug:Polymer ratio	Solid dispersion(SD)	
		PEG 4000	PEG 6000
Physical mixture	1:1	PC_1	PC_2
Kneading method	1:1	SK_1	SK_9
	1:2	SK_2	SK_{10}
	1:3	SK_3	SK_{11}
	1:4	SK_4	SK_{12}
	1:5	SK_5	SK_{13}
	1:6	SK_6	SK_{14}
	1:7	SK_7	SK_{15}
	1:8	SK_8	SK_{16}
Solvent evaporation method	1:1	SE_1	SE_9
	1:2	SE_2	SE_{10}
	1:3	SE_3	SE_{11}
	1:4	SE_4	SE_{12}
	1:5	SE_5	SE_{13}
	1:6	SE_6	SE_{14}
	1:7	SE_7	SE_{15}
	1:8	SE_8	SE_{16}

Table 2: Drug content and invitro release of prepared solid dispersions of Clomiphene citrate & PEG 4000 by kneading and solvent evaporation method

S.No.	Kneading method			Solvent evaporation method		
	Batch code	% Drug Content±S.D	% vitro drug release	Batch code	% Drug content±S.D.	% vitro drug release
1	SK_1	96.80±0.86	37.86±1.94	SE_1	96.55±1.08	41.58±1.85
2	SK_2	97.44±1.08	45.62±0.67	SE_2	97.41±0.86	51.20±1.22
3	SK_3	95.25±0.95	49.03±1.91	SE_3	96.98±0.89	56.17±1.32
4	SK_4	95.25±1.54	56.17±0.86	SE_4	96.98±1.08	62.37±1.84
5	SK_5	96.12±0.44	61.1±1.39	SE_5	97.84±1.13	66.10±1.53
6	SK_6	97.84±0.86	62.37±1.25	SE_6	97.41±1.73	71.68±1.11
7	SK_7	96.80±1.14	65.79±1.12	SE_7	96.55±0.86	74.79±0.58
8	SK_8	95.68±1.41	57.72±1.93	SE_8	95.40±0.66	64.55±1.73

Table 3: Drug content and invitro release of prepared solid dispersions of Clomiphene citrate & PEG 6000 by kneading and solvent evaporation method

S.No.	Kneading method			Solvent evaporation method		
	Batch code	% Drug Content±S.D	% vitro drug release	Batch code	% Drug content±S.D.	% vitro drug release
1	SK_9	96.58±0.26	45.31±1.076	SE_9	96.80±1.07	48.10±1.075
2	SK_{10}	96.98±0.89	53.68±0.74	SE_{10}	94.22±0.99	57.72±0.98
3	SK_{11}	97.41±0.43	58.96±0.84	SE_{11}	96.55±1.14	64.86±2.02
4	SK_{12}	96.55±1.97	64.55±0.48	SE_{12}	95.68±0.25	70.75±0.72
5	SK_{13}	96.58±0.45	72.62±0.57	SE_{13}	96.58±1.55	76.96±1.07
6	SK_{14}	97.84±0.86	78.20±0.79	SE_{14}	97.84±1.00	86.27±0.46
7	SK_{15}	96.12±0.51	74.17±1.63	SE_{15}	96.12±0.86	82.55±0.75
8	SK_{16}	96.58±1.35	72.62±1.74	SE_{16}	96.55±1.31	75.10±0.56

Table 4: Drug content and invitro release of prepared SDs of Clomiphene Citrate by physical mixture

PEG4000 (PC_1)		PEG6000 (PC_2)	
% Drug Content±S.D	% vitro drug release	% Drug Content±S.D	% vitro drug release
96.98±1.08	35.06±1.01	98.27±0.99	38.48±0.62

Figure 1: IR-Spectra of Clomiphene citratre

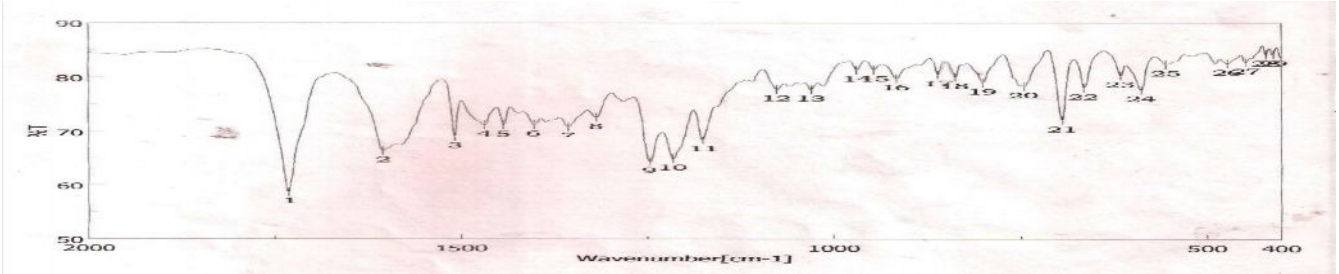


Figure 2: IR-Spectra of PEG 4000

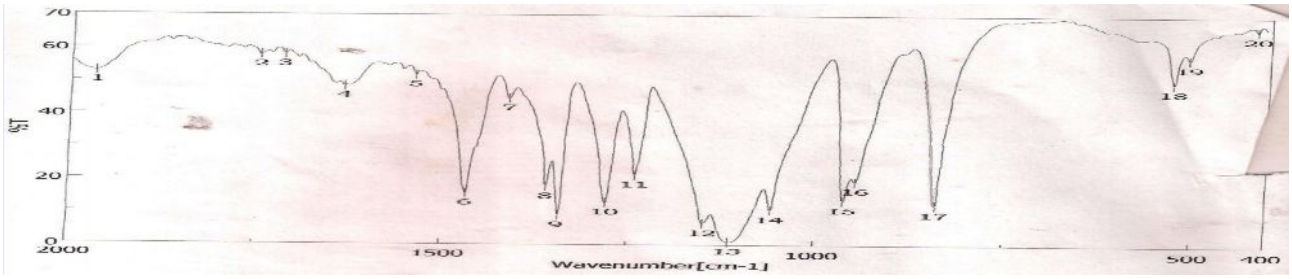


Figure 3: IR-Spectra of PEG 6000

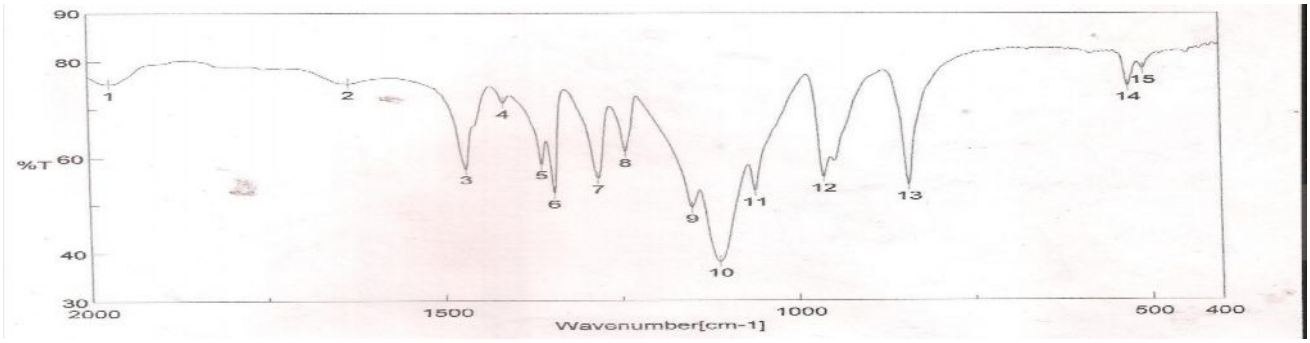


Figure 4: IR-Spectra of Drug : PEG 4000 (1:1) Physical mixture

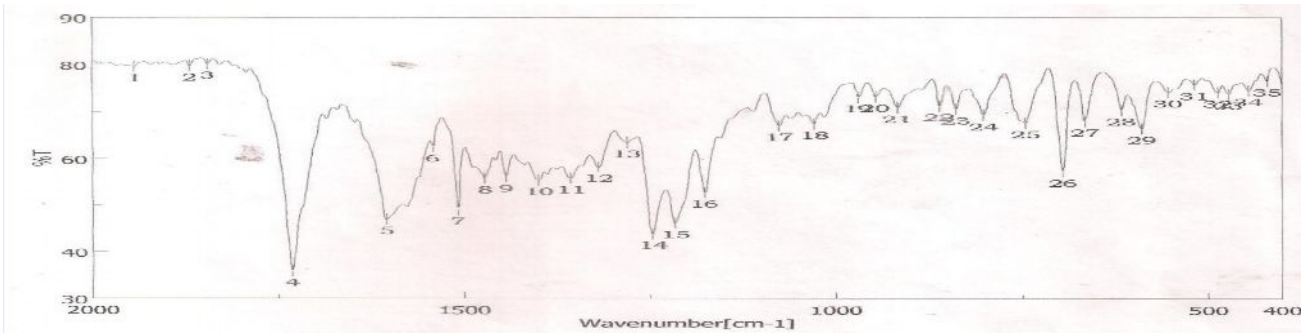
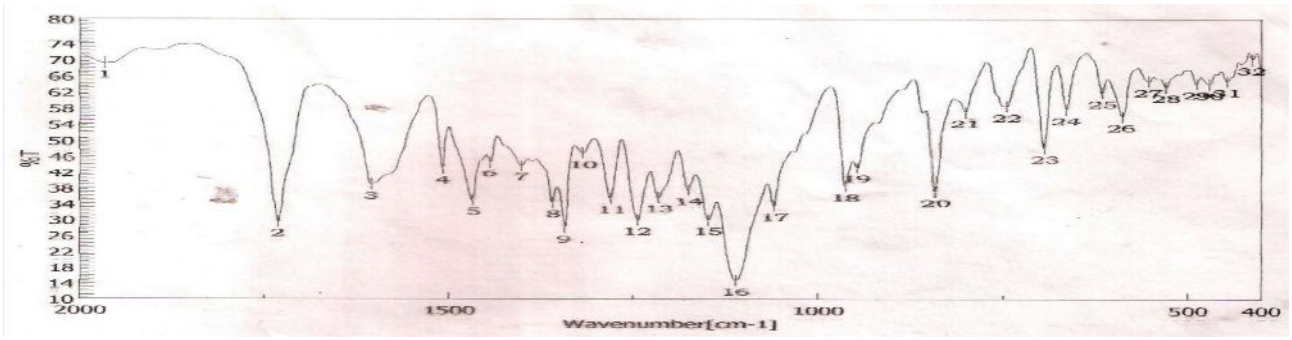


Figure 5: IR-Spectra of Drug:PEG 6000 (1:1) Physical mixture



Result and Discussion

Solid dispersion were found to be fine and free flowing prepared by kneading method and solvent evaporation method as compare to physical mixture method with low standard deviation values in percent drug content ensured uniformity of drug content in each batch, all the dispersions contained 95±5% of the drug**.** IR spectra (figs. 1-5) of Clomiphene citrate, PEG 4000, PEG 600 and its solid dispersions were not found to be identical, thus indicates interaction between Clomiphene citrate and carriers in the prepared SDs.

Disappearance in the intensity of peak sharpness also indicates the formation of complex.

Figure 6,7 shows the in vitro dissolution profiles of Clomiphene citrate from SDs containing various ratios of drug to PEG 4000 (1:1 to 1:8) in which max % drug release was obtained in batch SE_7 (74.79±0.58). Figure 8, 9 shows the in vitro dissolution profiles of clomiphene citrate from SDs containing various ratios of drug to PEG 6000 (1:1 to 1:8) in which max % drug release was obtained in batch SE_{14} (86.27±0.46). In contrast, the dissolution rate of clomiphene citrate from all PEG 6000 and PEG 4000 SDs was significantly higher than that of clomiphene citrate alone. Physical mixture of PEG also improves the dissolution profile of clomiphene citrate due to its hydrophilic nature but not such an extent as by kneading method and solvent evaporation method. As the proportion of PEG increased, clomiphene citrate dissolution rates increased up to an extent after that decreased that may be due to the localization of higher amounts of carrier itself. The improvement of dissolution may be due to reducing particle size of clomiphene citrate and hence improving drug wettability and significantly improved dissolution. In the solid dispersion state because of solvent evaporation of clomiphene citrate with the polymers, it was converted into amorphous form or change in crystal form may changes the different physicochemical properties.

Figure 6: Dissolution profiles of Clomiphene citrate and their SDs of PEG 4000 prepared by solvent evaporation method in 0.1N HCl at 37±0.5°C

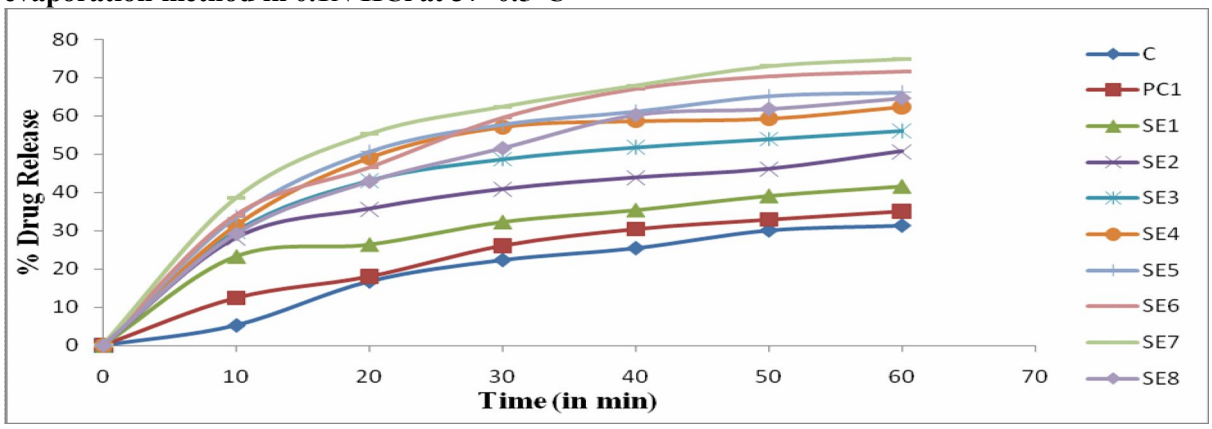


Figure 7: Dissolution profiles of Clomiphene citrate and their SDs of PEG 4000 prepared by kneading method in 0.1N HCl at 37±0.5°C

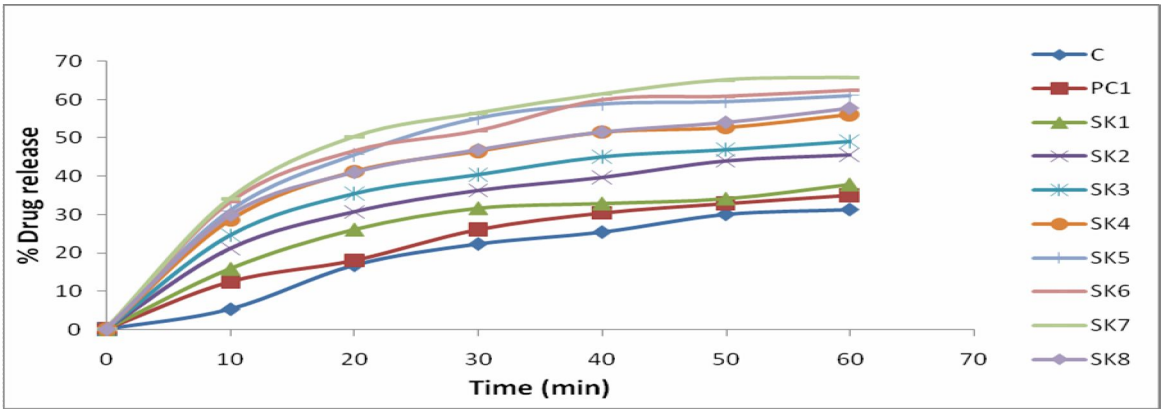


Figure 8: Dissolution profiles of Clomiphene citrate and their SDs of PEG 6000 prepared by solvent evaporation method in 0.1N HCl at 37±0.5°C

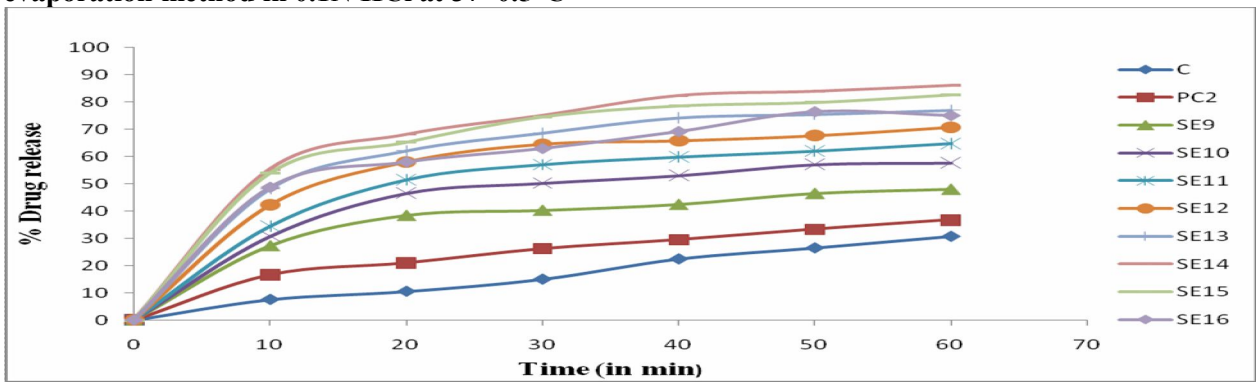
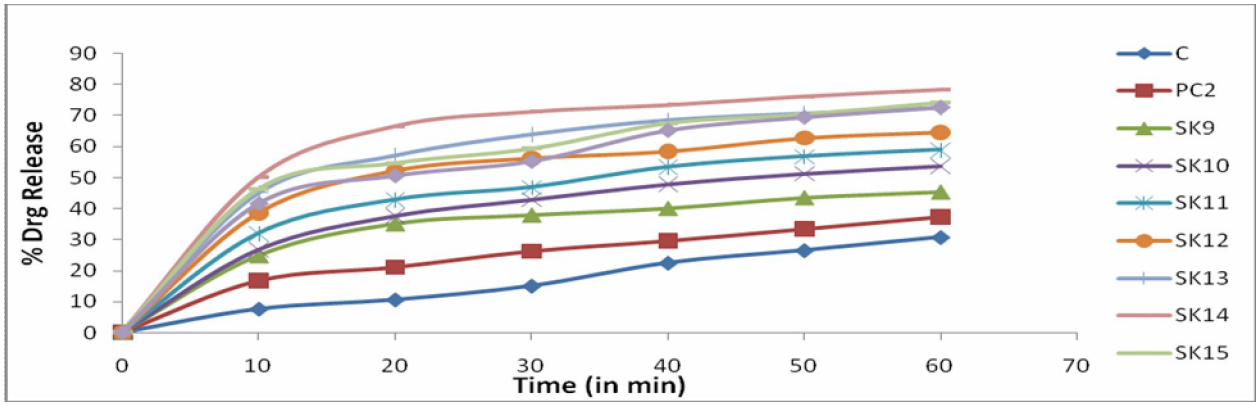


Figure 9: Dissolution profiles of Clomiphene citrate and their SDs of PEG 6000 prepared by kneading method in 0.1N HCl at 37±0.5°C



Conclusion

The solid dispersion with polyethylene glycol have been prepared by different methods in different ratios and found that solvent evaporation (SE_{14}) shows the better enhancement of solubility in comparison to the kneading and physical mixing method. As the both the carriers PEG 4000 and 6000 has been compared, it is observed that PEG 6000 showed greater enhancement in dissolution rate at low drug: polymer ratio (1:6).

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