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Research Article

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Formulation and *In-vitro*-evaluation of Isotretinoin Tablets

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ABSTRACT

Isotretinoin (13-cis-Retinoic acid) is a poor water soluble drug, commonly used in the treatment of severe cases of acne. The aim of this project is to formulate isotretinoin in form of tablet and enhance its solubility and dissolution rate; by the use of formulations containing either surfactant (SLS and Tween20) or HP-β-CD. The critical micelle concentration for each surfactant was determined. Surfactant enriched tablets were prepared by physical mixture and co-precipitation method. Binary system of the drug with HP-β-CD was prepared using different ratios and techniques. The freeze drying technique gave the best drug-HP-β-CD complexation. The in-vitro dissolution study for the prepared mixtures and the prepared tablets was performed. Binary system of molecular ratio 1: 5 of the drug to HP-β-CD gave the highest solubility and dissolution rate for isotretinoin in comparison with other formulae. Therefore, it could be concluded from the study that, incorporation of surfactant and HP-β-CD in the formulation of isotretinoin tablets significantly improved Isotretinoin solubility.

Key words: Isotretinoin, surfactant enriched tablets, HP-β-CD, co-evaporation, Freeze drying.

INTRODUCTION

The solubility of poorly soluble drugs is a very important criterion in drug formulation [1, 2], because such physicochemical property may lead to therapeutic failure in solid dosage form [5]. Isotretinoin, a synthetic retinoid isomer of the naturally occurring all-*trans*-retinoic acid, is a therapeutically active anticancer drug with a lot of therapeutic benefits [3]. It is used in the treatment and prevention of numerous cancer conditions due to its proven ability to rapidly kill dividing cells. Therefore, it has been shown to prevent malignant lesions and primary head and neck tumors in the clinical trials and it reduces the severity of highly invasive urinary bladder carcinomas, decreases proliferation and induces differentiation in neuroblastoma cell lines [3]. A study conducted on mice showed that inhalation of low dose of isotretinoin was effective in prevention of lung cancer [4]. Moreover, isotretinoin is renowned for its ability to provide prolonged remission of acne lesions.

However, one of the major hurdles that face the development of Isotretinoin in a solid dosage form is the presence of a large hydrophobic moiety that renders its molecule poor water solubility. Moreover, the compound exhibit photosensitive instability and is susceptible to oxidation and isotretinoin [3].

Surfactant mainly used for improvement of the dissolution of poorly soluble drugs [8]. Surfactant can self assemble to form micelles once the surfactant monomer concentration reaches the critical micelle concentration [6], micelles are nanosized, spherical colloidal particles with a hydrophobic interior (core) and a hydrophilic exterior (shell) .

Sodium lauryl sulfate (SLS) is a widely used surfactant with a human lethal oral dose of 0.5-5g/Kg body-weight [21].

Cyclodextrins are cyclic non reducing water soluble oligosaccharides [7] with a conical, cylinderical cage- like shape, it, produced by the enzymetic digestion of starch by cyclodextrin-transglycosidase enzyme (CTG). [16]. Their supramolecular structure has a hydrophilic outer surface with a hydrophobic inner cavity that capable of entrapping a large variety of hydrophobic guest molecules [17].

Hydroxypropyl-β-cyclodextrin (HP-β-CD) is a chemically modified derivative of β-cyclodextrin that has been reported to be safer and less irritating than the parent cyclodextrin [3, 6]. The aforementioned derivative also provides higher solubility and stability to inclusion compounds than β-cyclodextrin[3]. Therefore, based on the above mentioned benefits HP-β-CD was selected in this study.

Hirlekar, 2009 reported that the incorporation of water soluble polymer with cyclodextrins gave a synergistic effect on drug solubility [18]. This was due to the formation of ternary complexes and reduction of the complex particle size, leading to improvement of the pharmaceutical and biological properties of drug-CD complexes.

There are limited studies reported in the literature on the development of solid dosage form of isotretinoin such as tablet with a good solubility, dissolution or bioavailability. Thus, the aim of this study was to evaluate the use of surfactant and (HP-β-CD) in the development of a solid tablet formulation of isotretinoin that would enhance the drug solubility, dissolution and subsequently bioavailability.

EXPERIMENTAL SECTION

Materials:

Isotretinoin, MW = 300.44 was purchased from Sigma Chemical Co. USA; Sodium lauryl sulphate (SLS), MW=288.5 was brought from BDH, England while HP-β-CD was purchased from Alfa Aesar, Germany; Disodium hydrogen phosphate and potassium dihydrogen phosphate by E-Merk, pharmaceutical company, Darmstadt, Germany; Polyethylene glycol (PEG6000) and Polyvinylpyrrolidone-K25 (PVP-K25) by Fluka, Buchs, Switzerland; Tween20 was purchased from Sigma, UK; Megnesium stearate by Prolabo, france; Ac-Di-Sol (crosscarmellose sodium) and Avicel PH 101 was brought from FMC corp., Pennsylvania, USA.

Isotretinoin Solubility in surfactant containing solutions:

All experiments for the phase solubility study were performed under dark conditions to avoid destructive effect of light [11].

Isotretinoin solubility was determined in phosphate buffer solution (pH7.4) of SLS and Tween20. Excess amount of isotretinoin was added to 5ml volumes of phosphate buffer (pH7.4) containing series of concentrations of the surfactant in the range of 0.1 – 20 mM or 0.02-20 mM for either sodium lauryl sulphate or Tween20 respectively. Individual samples were prepared in stopper amber glass vials and incubated in thermostatically controlled water bath shaker at 37±0.5ºC for 72 hours. The solutions were then filtered using 0.45 µm Millipore filters and diluted as necessary. The samples were analyzed using UV/VIS spectrophotometer (UV-6705, Jenway, Barloworld scientific Ltd., UK) at a wavelength of 344nm. The equilibrium molar concentration of isotretinoin was plotted against the corresponding concentration of the surfactant on a natural logarithmic scale according to Ruddy et al. [9]. The molar solubilization capacity (X) defined as the number of moles of drug solubilised by one mole of micellar surfactant (drug to surfactant micellar molar ratio) was calculated [10]

$$X= (Stot-Sw)/(Csurf-CMC) \text{ ..... } (1)$$

Where Stot is the total molar concentration of the drug in the surfactant containing solution, Sw is the molar solubility of the drug in the buffer, Csurf is the molar concentration of surfactant in the buffer and CMC is the critical micelle concentration.

Phase solubility studies

The effect of HP-β-CD on the solubility of isotretinoin was investigated according to the phase solubility technique established by Higuchi and Connors [19]. Excess amounts of isotretinoin (50mg) were added to 25ml buffer solution

pH7.4 containing increasing concentrations of HP-β-CD (ranging from 2 to 20 mM) in a series of 50 ml dark bottle. The obtained suspensions were shaken at 37±0.5 ºC for 72 hours. Aliquots were withdrawn and filtered using 0.45µm diameter Millipore filter. The filtered solutions were analyzed spectrophotometrically for isotretinoin content by measuring the absorbance at λmax 344nm against blank solutions containing the same concentrations of HP-β-CD. Each experiment was carried out in triplicate. Phase solubility diagram was obtained by plotting the molar concentration of solubilized isotretinoin versus the molar concentrations of HP-β-CD used. The apparent stability constant (Ks) was estimated from the straight line of the phase solubility diagram according to the following equation of Higuchi and Connors [19]:

Ks = slope / So (1- slope)

Where So represents the drug solubility in absence of HP-β-CD, where the molar aqueous solubility of isotretinoin in absence of HP-β-CD was found to be 0.790±0.022.

The complexation efficiency (CE) was also calculated according to the following equation[20]:

$$CE = S_o K_{1:1} = \frac{drug - CD}{CD} = \frac{slope}{1 - slope}$$

Where [drug-CD] is the concentration of the drug-CD complex and [CD] is the concentration of the free cyclodextrin.

Physicochemical Characterization

Differential Scanning Calorimetry

The differential scanning Calorimetry (DSC) measurements were performed using a Shimadzu DSC-60 (Kyoto, Japan). Samples (4 mg) were sealed in aluminium pans and analyzed in an atmosphere of nitrogen at a constant heating rate of 10ºC/min. from 20ºC to 300ºC.

Fourier-transform infrared spectroscopy (FTIR):

The FTIR spectra of the samples were measured using FTIR spectrophotometer (M/s Shimadzu, Japan) using the KBr disc technique. The spectra were saved using a Lotus 123 computer program. The FTIR measurements were performed in the scanning range of 4000-400 cm-1 for 10 number of scan.

X-ray diffractometry

The X-ray diffraction patterns were recorded at room temperature with Scintage XGEN-4000 diffractometrer (XD-610 Shimaduz, Japan). The scanning rate employed was 2 ºC per minute over a diffraction angle (2θ) range from 3º-50º.

Formulation and preparation of Isotretinoin surfactant-enriched tablets:

A solid dispersion of the drug with SLS was prepared by dissolving the appropriate amounts of each in 50ml of 95% ethanol solution followed by solvent evaporation under reduced pressure at 60ºC. Two formulations for the surfactant-enriched tablets of isotretinoin were prepared. The first tablet formulation (F1T) was prepared as simple physical mixture of all the constituents whereas the other (F2T) was a mixture of the drug – surfactant solid dispersion with the rest of the ingredients (Table2).

The amount of SLS used calculated from the molar solubilization capacity of the surfactant for the drug, was 58.2mg. This amount of surfactant was sufficient to dissolve 20mg of isotretinoin in 30ml buffer solution pH7.4. The tablets were directly compressed to get round shape tablets using single punch tablet press, (Bruker, model 22, UK) with round punches and die 14 mm in diameter.

Preparation of isotretinoin- cyclodextrin binary solid systems:

Solid binary complexes of isotretinoin with HP-β-CD was prepared in 1:1, 1:3 and 1:5 molar ratios by kneading, co-evaporation[14] and freeze drying techniques [3]. Physical mixture of isotretinoin and HP-β-CD with the same ratios as the complexes were also prepared and used as controls.

In the kneading method an accurately weighed amount of isotretinoin and HP-β-CD in molar ratio 1:1, 1:3 and 1:5 drug to HP-β-CD, were triturated with small volume of ethanol- water (50:50, v/v) solution [3]. The slurry obtained

was kneaded for 30 minutes and then dried at room temperature in presence of calcium chloride as a dehydrating agent.

For the co-evaporation method aqueous solutions of HP-β-CD (0.93%, 2.79% and 4.65% w/v %) were prepared by dissolving the necessary amount of cyclodextrin in distilled water.

Isotretinoin (20mg) was added to the solution and stirred for 48 hours [1] at 25°C. The resulting suspensions were dried under vacuum at 100°C in a rotary evaporator (Rotavap, model laborota 4000, Heidolph, Germany).
The freeze dried complexes of isotretinoin –HP-β-CD in the ratios of 1:3 and 1:5 were prepared by adding the required amount of the drug in an aqueous solution of the cyclodextrin. The slurry formed was shaken at 25°C for 48 hours, and then filtered to remove excess drug. The resulting solution was frozen at -80°C for 24hours and then subjected to lyophilization in a freeze-dryer for 24 hours [1] (Freeze dryer, Novalyphe-NL 500; Savant Instruments Corp. Holbrook, NY, USA) to obtain the powder.
Lyophilized ternary systems of drug-SLS-HP-β-CD were prepared from an aqueous solution of the drug with HP-β-CD in the molar ratios of 1:1 and 1:3. The solution was prepared first by placing the formed suspension of drug and HP-β-CD on a shaker for 48 hours before adding the SLS. Stirring of the resulting solution was maintained for another 2 hours, before it was allowed to freeze dry in the same way used for preparing the drug-HP-β-CD lyophilized complex.

Preparation of tablets containing isotretinoin-HP-β-CD Freeze drying binary system:
Two tablet formulations, F13T and F14T were prepared from the 1:3 and 1:5 molar ratio freeze dried isotretinoin-HP-β-CD complexes, respectively. Suitable amounts of adjuvant were added to each formulation to maintain the tablet weight at 500mg (Table1).

Two other formulations (F15T and F16T) were also prepared from the 1:1:3 and 1:3:3 molar ratios of drug- SLS-HP-β-CD ternary systems respectively. Then suitable adjuvant was added to each formula to increase the tablet weight to 500mg (Table 1).

The powder blends of the binary and ternary systems were directly compressed into tablets with the same tablet press specifications used for the Isotretinoin surfactant-enriched tablets.

Table (1): Nomenclature of the complexes of the (drug-HP-β-CD) that prepared by different methods

Formula name	Method prepared with	Amount of SLS in the formulae in mg	Amount of the drug in the formula in mg	Molar ratio of the (drug: HP-B-CD)
F1	Physical mixture	58.2	20	-
F2	Co evaporation	58.2	20	-
F3	Physical mixture	-	20	1:1
F4	Physical mixture	-	20	1:3
F5	Physical mixture	-	20	1:5
F6	Kneading	-	20	1:1
F7	Kneading	-	20	1:3
F8	Kneading	-	20	1:5
F9	Co evaporation	-	20	1:1
F10	Co evaporation	-	20	1:3
F11	Co evaporation	-	20	1:5
F12	Freeze-drying	-	20	1:1
F13	Freeze-drying	-	20	1:3
F14	Freeze-drying	-	20	1:5
F15	Freeze-drying	58.2	20	1: 1
F16	Freeze-drying	58.2	20	1:3
F13T	Tablet	-	20	1:3
F14T	Tablet	-	20	1:5

Table (2): Composition of formulated isotretinoin tablets in percent

Formula Constituent	F1T*	F2T*	F13T**	F14T**
Isotretinoin	6.67%	6.67%	4%	4%
HP-β-CD	-	-	56%	93.33%

SLS	19.4%	19.4%	-	-
Lactose monohydrate	33.53%	33.53%	15.946%	-
PVP25	10%	10%	6%	1.25%
PEG6000	10%	10%	6%	-
AC-DI-SOL	8.33%	8.33%	5%	1.25
Editate disodium	0.017%	0.017%	0.01%	0.01%
Avicel PH 101	10%	10%	6%	-
Sodium citrate	1.67%	1.67%	1%	0.12%
Talck	0.1%	0.1%	0.06%	0.04%
Mg-stearate	0.27%	0.27%	-	-

** Tablets weight was 300mg*
***Tablets weight was 500mg*

In-vitro evaluation for the powder mixture and prepared tablets:
The prepared tablets (F13Tand F14T) were evaluated for content uniformity, friability, hardness, disintegration, and dissolution test.

In-vitro dissolution studies:
Dissolution of Isotretinoin from the prepared powder mixture of binary, ternary systems and the prepared tablets was performed according to USP XXVIII Basket method using a Hanson dissolution Tester, (Model Vision Classic, Hnson Research, CA, USA [12].

A dissolution media of 900ml phosphate buffer (pH7.4) equilibrated at 37ºC ±0.5 ºC was used. The samples were placed into the apparatus baskets, which were rotated at a speed of 100 rpm. The weight of the powder mixtures placed into the basket was equivalent to 20mg of isotretinoin. The amount of drug in the tablets used was also 20mg. At appropriate time intervals of 5, 10, 15, 20, 30, 45, 60, 90, 120, 150 and 180 minutes, samples (5ml each) were withdrawn from the dissolution medium and filtered using 0.45 µm Millipore filters. The withdrawn sample was replaced with an equivalent amount of fresh dissolution medium to maintain the volume in the vessel constant. The filtered samples were analyzed spectrophotometrically for isotretinoin content by measuring the absorbance at λmax 344nm against phosphate buffer (pH7.4) as a blank.

RESULTS AND DISCUSSION

Solubility of Isotretinoin in the surfactants
The initial aim of this study was to minimize the quantities of surfactants used in tablet formulation by determining the minimal surfactant to drug ratio that would be required for drug solubilization in micellar surfactant solutions. Figure1 showed the solubility diagram of isotretinoin in dilute surfactant solutions.

Consistent with micellar solubilization mechanism, the equilibrium solubility of drug remained relatively constant below the threshold surfactant concentration of the CMC. Above the CMC the drug solubility increased markedly with increasing the surfactant levels. The CMC values of SLS and Tween20 were found to be about 1mM and 0.2mM, respectively. The literature reported that the CMC values of SLS and Tween20 in pure water at 25°C are 8.2 mM and 0.08mM; respectively [22]. The change in CMC value depends on several factors such as the temperature, pressure, electrolytes and others [23]. In this study the presence of isotretinoin in the media leads to change the CMC values of SLS and Twee20.

The surfactant molar solubilization capacity (X) for isotretinoin computed based on the slope of the solubility data of the CMC [10], was 0.33 and 0.416 for SLS and Tween20 respectively. According to these X values the amount of surfactant required to be in the tablets to solubilize isotretinoin via micellization was calculated to be 58.2mg and 196.8mg for SLS and Tween20, respectively. Based on these values, the use of Tween20 was excluded from further study due to the large amount needed in the tablet formulation (66%) and the negative effect that had compressibility. On the other hand, the amount of SLS required in the formulation was 19% w/w which was reasonable to compress and below the oral lethal dose of dose 0.5-5g/Kg body weight [21], hence the latter was chosen for further studies.

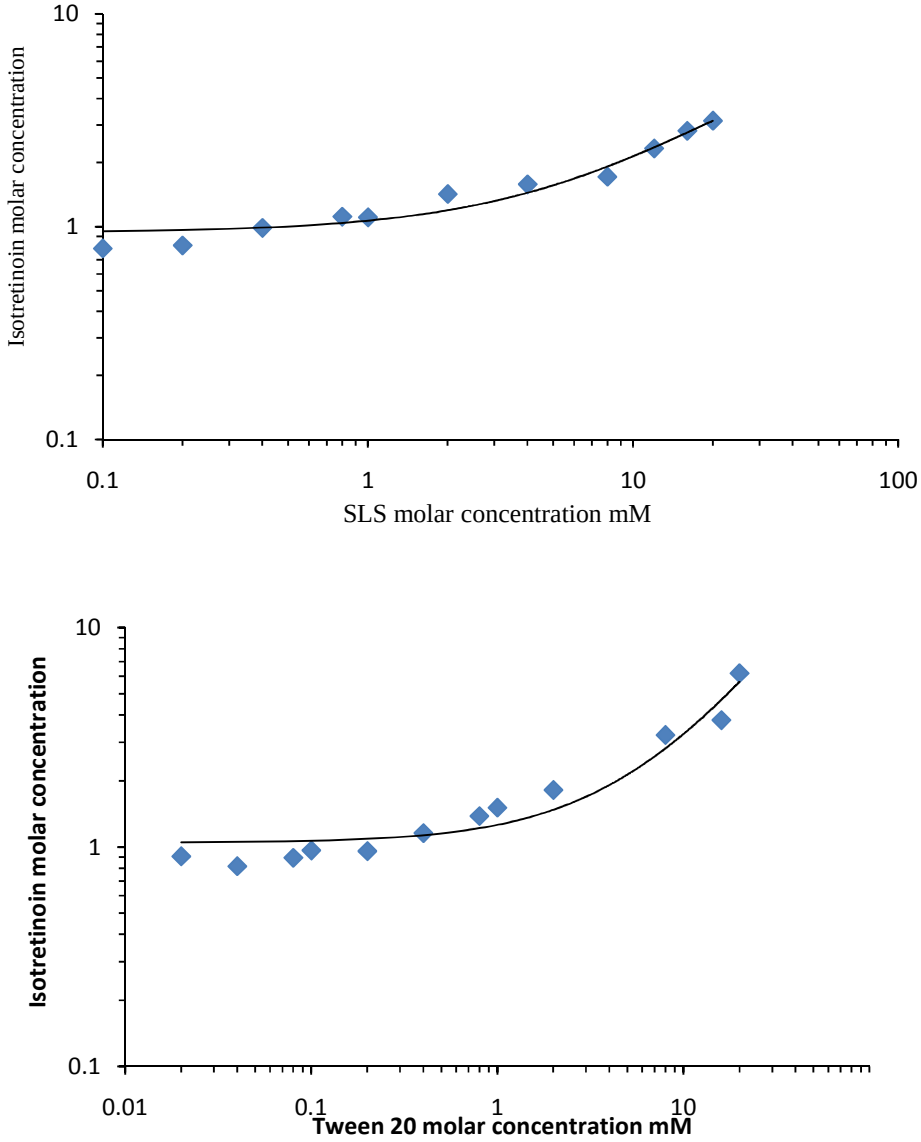


Figure (1): Equilibrium solubility of Isotretinoin (µmol/l) as a function of SLS and Tween20 concentrations (mmole/l) in at 37 ± 0.5 ºC

Solubility of isotretinoin in HP-β-CD solutions

The linear increase in isotretinoin concentration with that of HP-β-CD was in accordance with the AL type phase diagram (Figure 2). This increase in drug concentration with cyclodextrin was due to the formation of inclusion complexation, which in case of the A_L type diagram is assumed to be of 1:1 stoichiometric ratio [19].

The stability constant (KS) of the complex calculated from equation 2 was 336.46M-1.

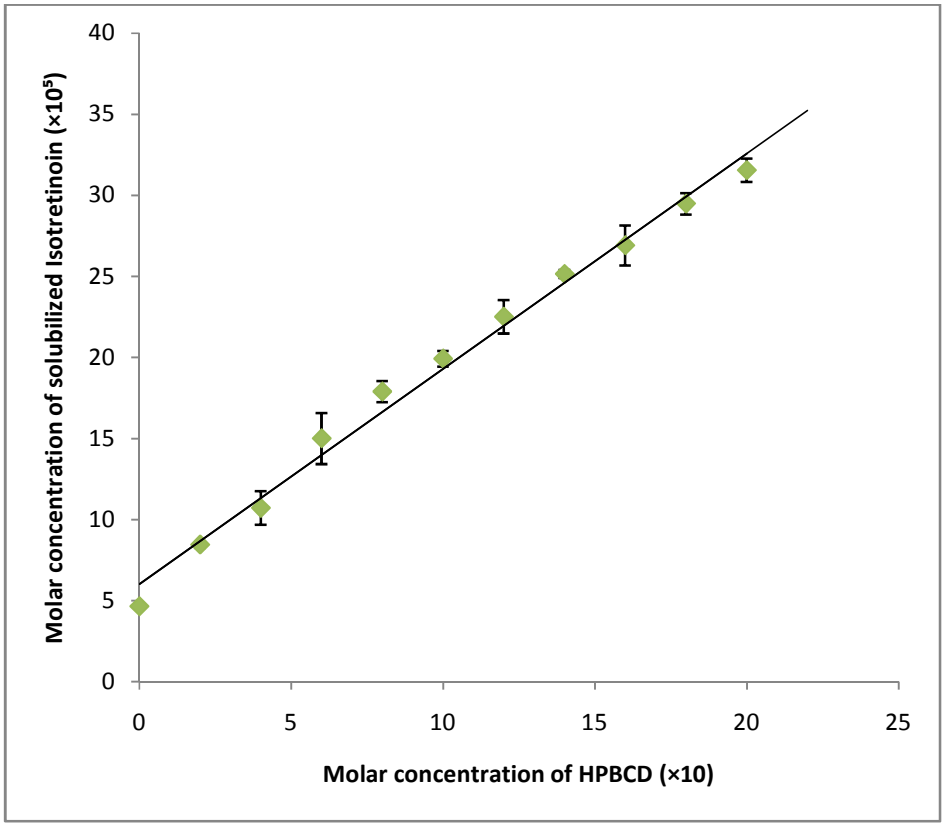


Figure (2): Phase solubility profile of Isotretinoin with HP-β-CD in pH7.4 at 37±0.5°C

Differential scanning calorimetery

The DSC thermogram of pure Isotretinoin, SLS, pure HP-β-CD and their mixtures are shown in (Figures 3 and 4). The thermogram of isotretinoin showed a sharp peak around 177ºC corresponding to its melting with an associated enthalpy of -29.72Jg-1. The melting point of isotretinoin reported in the literature was 174 to 177 ºC [24]. Literature reported that changes in quantity of material used for the test affect peak shape and enthalpy [26]. Other peaks occurring beyond 250ºC reflect the degradation of the drug. DSC thermogram of SLS showed small endothermic peaks around 100°C representing its dehydration and an endothermic peak at 184.5ºC due to its melting. A number of small peaks were also observed beyond the melting peak of SLS due to its degradation. The physical mixture and co-evaporation systems of isotretinoin with SLS showed change in the drug peak where it was shifted to a lower melting temperature of 158.24 ºC and 157.04 ºC in case of the physical mixture and co-evaporation system respectively. This minor changes in the melting endotherm of drug could be attributed to mixing effect which lowers the purity of each component in the mixture but not necessarily indicate potential incompatibility [15].

The DSC thermogram of HP-β-CD showed a characteristic endotherm around 100 corresponding to its dehydration. The drug- HP-β-CD physical mixture showed a clear decrease in the drug peak due to dilution effect. The kneading and co-evaporate systems showed slight shift in the drug peak to a higher melting temperature 179.04℃ and 178.75℃ for kneading and co-evaporate system respectively. In the drug-HP-β-CD freeze dried system a complete disappearance of the drug melting peak of the drug was observed, which is an indications of complete inclusion of the drug molecules within the HP-β-CD cavity.

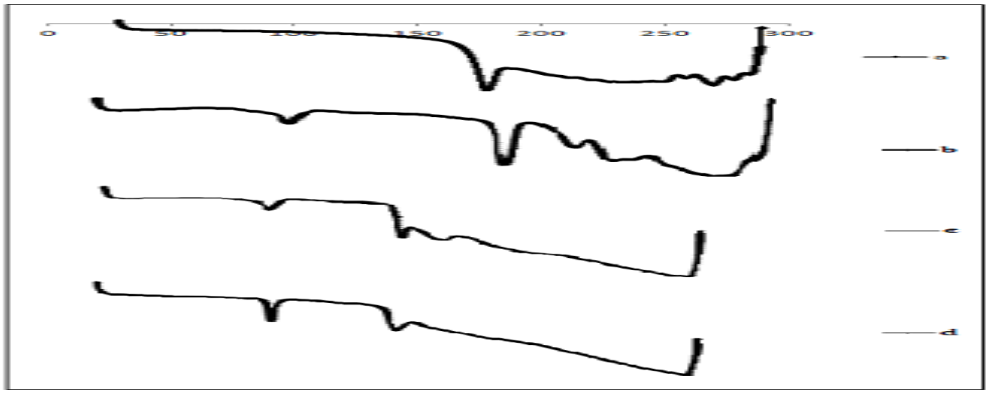


Figure (3): DSC thermogram of Pure Isotretinoin (a), SLS (b) their physical mixture(c) and co-evaporates blend (d).

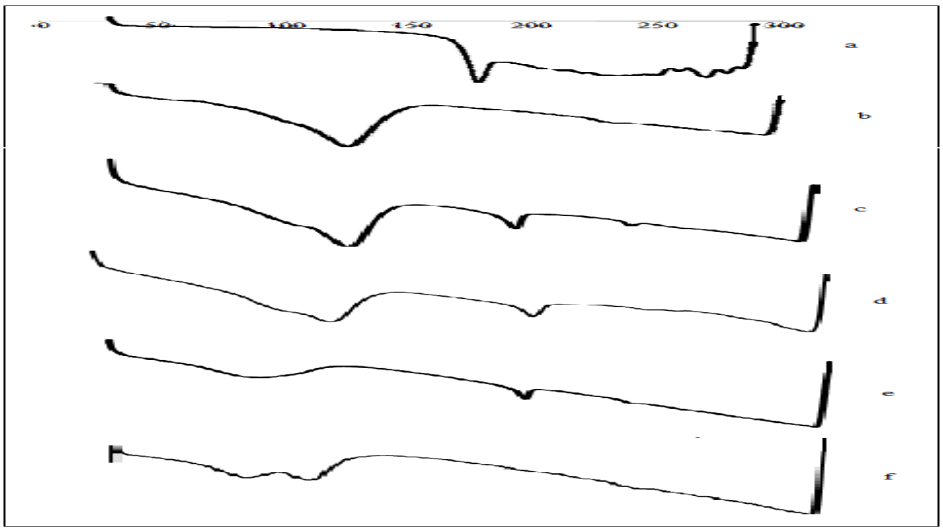


Figure (4): DSC thermogram of isotretinoin (a), HP-β-CD (b) their physical mixtures(c) , kneading blend (d), co-evaporate blend (e) and freeze drying blend (f).

Fourier transfer infra-red (FTIR)

The FTIR spectrum of Isotretinoin showed characteristic absorption bands at 2927 cm−1 corresponding to -CH2- and at 1674 cm−1 corresponding to C = O stretching vibration and at 1250 cm−1 corresponding to OH group, (Figure 5).

SLS have an absorption band at 1222 cm-1 which is present in both the physical mixture and in the co-evaporate system. Also there is no changes in the peak of the drug at 1250 cm−1 in the physical mixture of the drug with SLS also there is no appearance of new bands in the FTIR spectra of each mixture, so that strongly indicate unchanged on the drug structure lack of chemical interaction between isotretinoin and SLS and that confirm the DSC findings.

The FTIR spectra of isotretinoin, HP-β-CD and their mixtures showed in figure 6. The spectra of HP-β-CD showed characteristic peak at 3383.1 cm-1 due to – OH groups and at 1680 cm-1 corresponding to C = O stretching vibration, the FTIR spectra of isotretinoin and its blends with HP-β-CD showed the presence of characteristic bands corresponding to drug, also there was no appearance of new bands in the FTIR spectra of mixtures. Hence, there was strong evidence of unchanged active structure and absence of chemical interaction between the drug and HP-β-CD.
The freeze dried mixture of isotretinoin and HP-β-CD showed clear decrease in the intensity of the drug characteristic peaks in comparison with other mixtures of the drug and HP-β-CD, the indicate the inclusion of isotretinoin into HP-β-CD cavity [27].

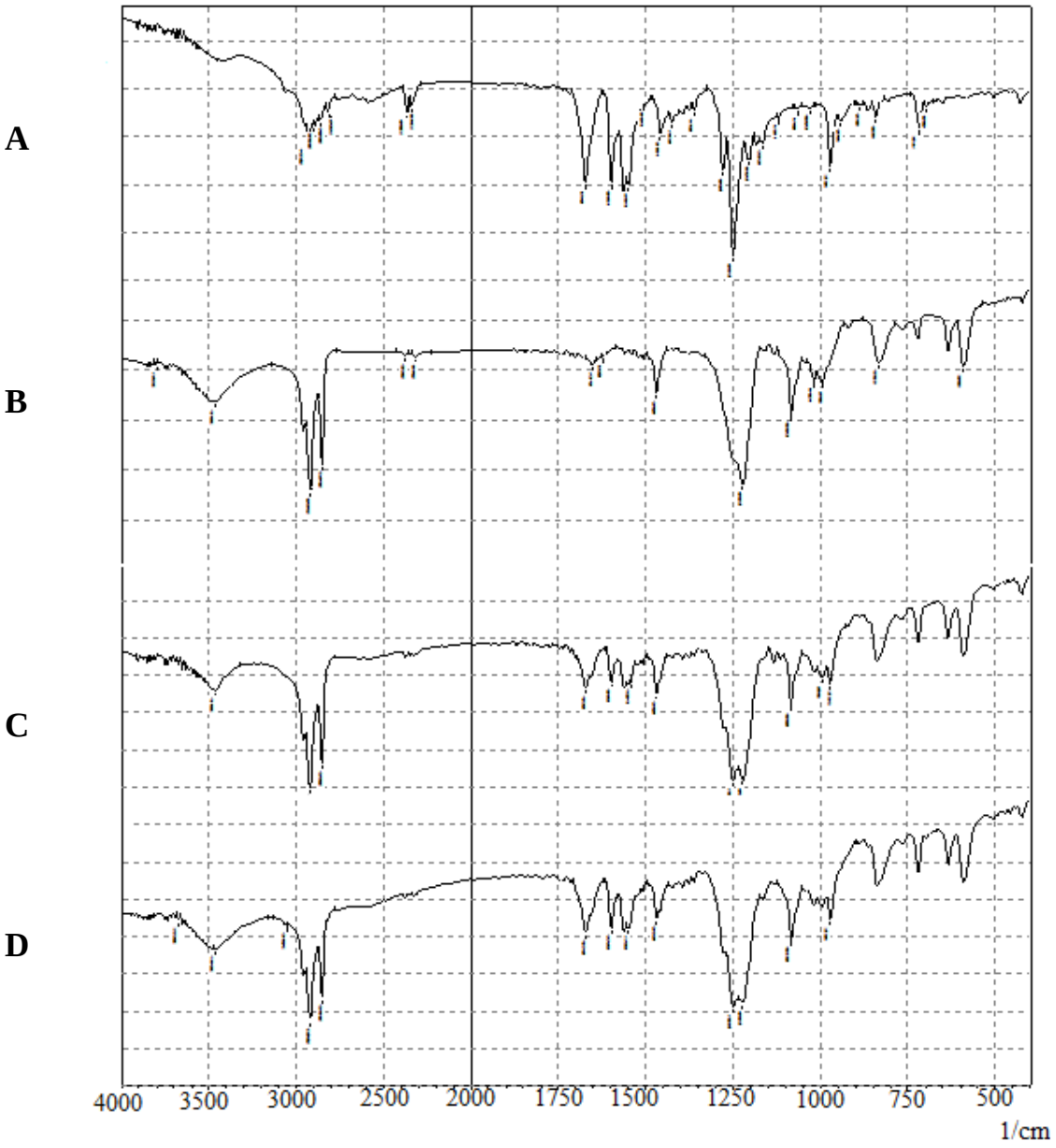


Figure (5): FTIR spectra of pure Isotretinoin (A), SLS (B), their physical mixtures(C) and Co-evaporate blend (D).

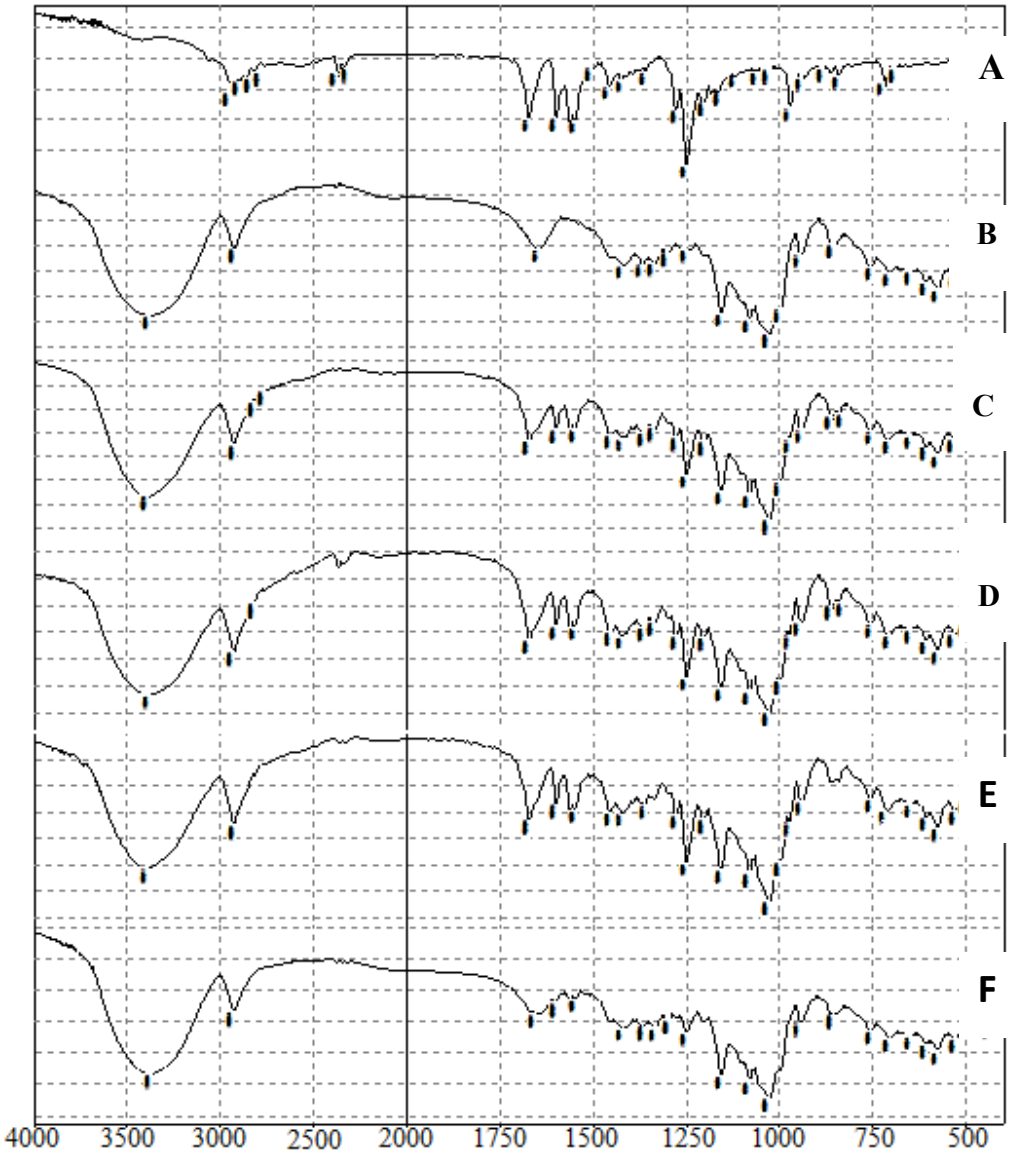


Figure (6): FTIR spectra of pure Isotretinoin (A) HP-β-CD (B), their physical mixture (C), Kneading blend (D) C0-evaporated blend (E) and freeze drying blend(F).

Powder X-ray diffraction

The XRD pattern of Isotretinoin showed numerous distinctive peaks at, 5.567° 2θ, 5.403° 2θ and 3.600° 2θ indicating its crystalline nature (Figure 7). XRD patterns of SLS showed characteristic peaks at 14.203° 2θ, 4.35° 2θ and 4.086° 2θ and the XRD patterns of their mixture showed disappearance of some drug peaks and reduction in the intensity of the remaining detectable isotretinoin characteristic peaks indicating conversion of Isotretinoin to more soluble state furthermore, the presence of some characteristic peaks of the drug indicating that, the drug is partially crystalline in the mixture and that confirm the dissolution result.

Drug peak at 5.567° 2θ was used for calculating the relative degree of crystallinity (RDC) according to the following relation:

RDC= I Sam/I drug

Where I Sam is the height of the mixture peak and I drug is the height of the drug peak. (25)

XRD analysis shows that the degree of Isotretinoin crystalinity in mixture with SLS was 0.240.

The XRD pattern of isotretinoin – HP-β-CD mixtures showed either disappearance or strong decrease in the intensity of the drug peak (Figure 8). significantly appear in freeze drying mixture than co-evaporate than kneading than physical mixture. Disappearance of the drug peak significantly appear in freeze drying mixture than co-evaporate than kneading than physical mixture.

The RCD of isotretinoin – HP-β-CD mixtures was calculated, it was 0.351, 0.180, 0.135 and 0.105 for physical mixture, kneading mixture, co-evaporate system and freeze drying mixture respectively. Indicated that the freeze drying mixture gave the lowest degree of crystallinity in compare with other mixtures.

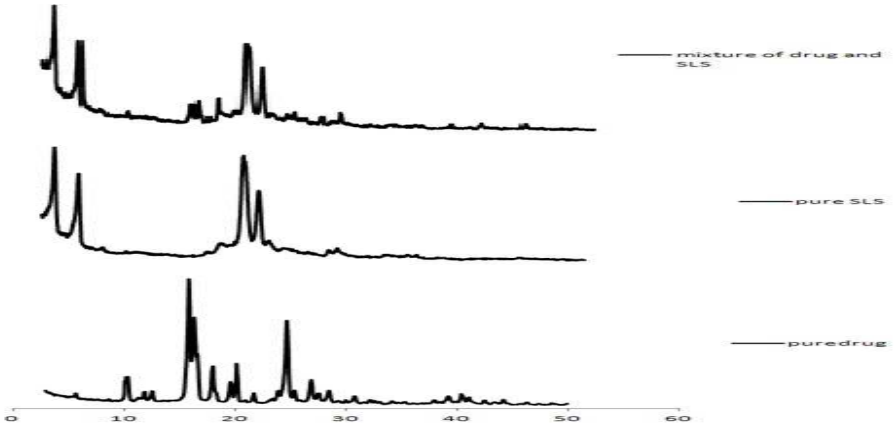


Figure (7) X-ray diffraction pattern of isotretinoin SLS system.

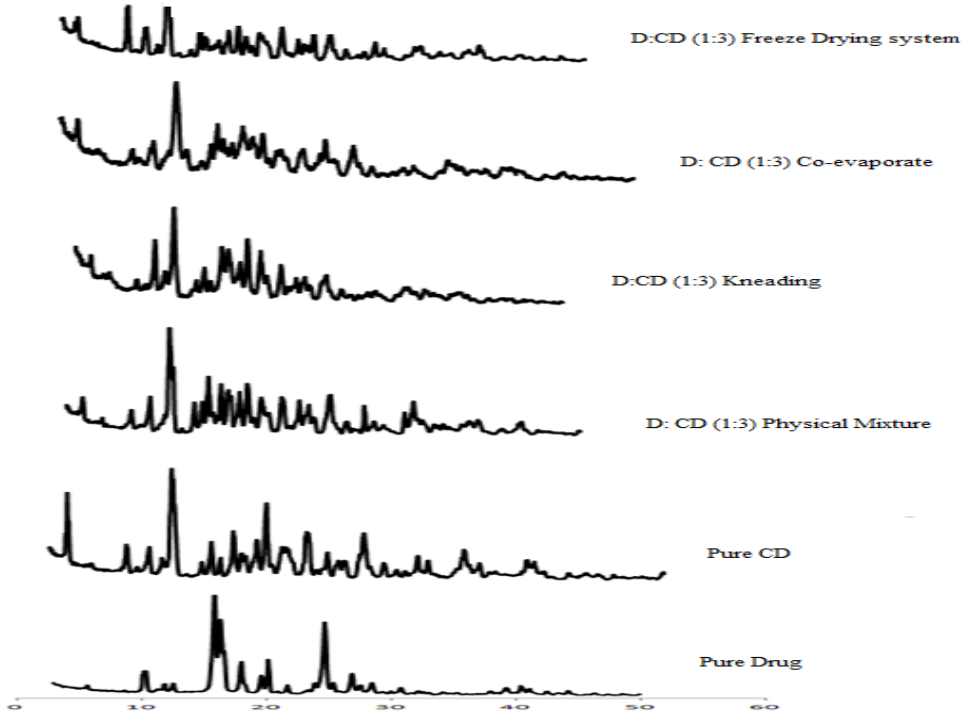


Figure (8) X-ray diffraction pattern of isotretinoin HP-β-CD system.

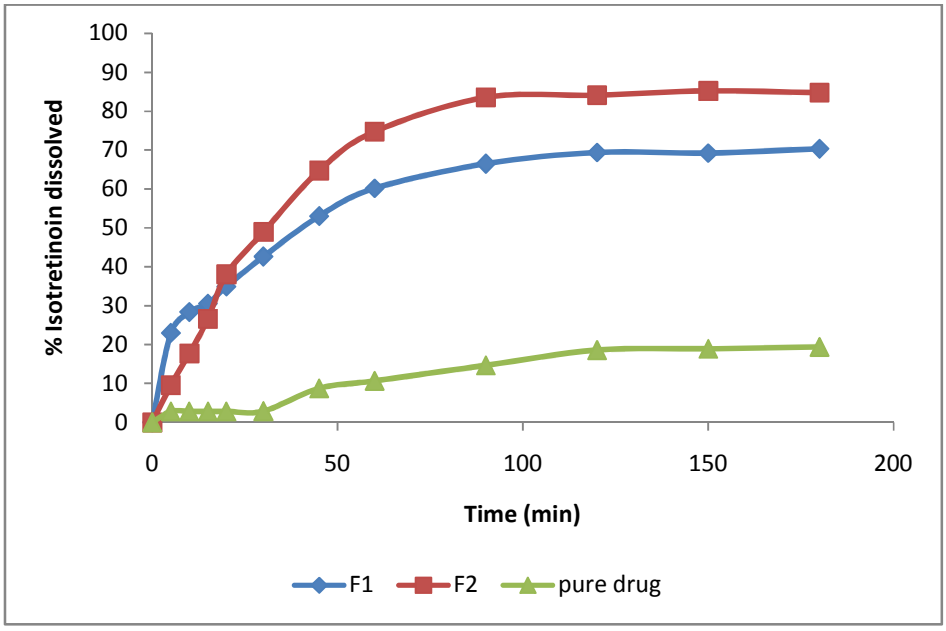
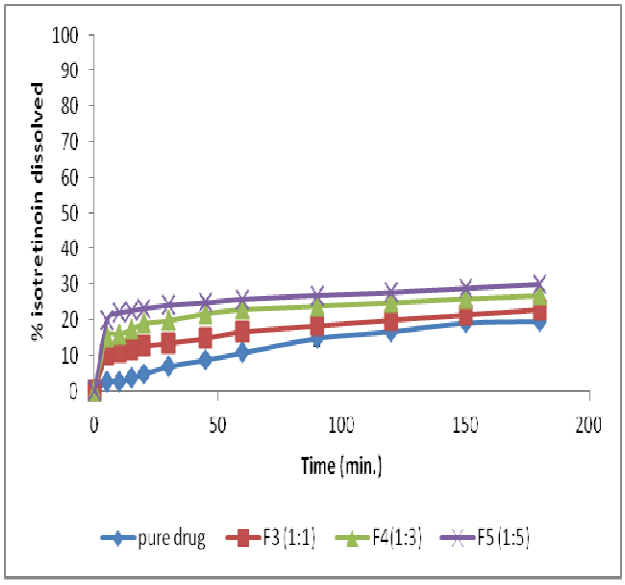
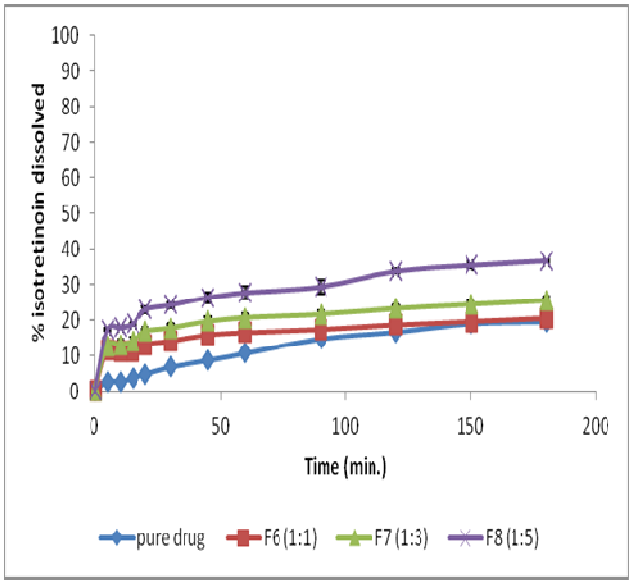


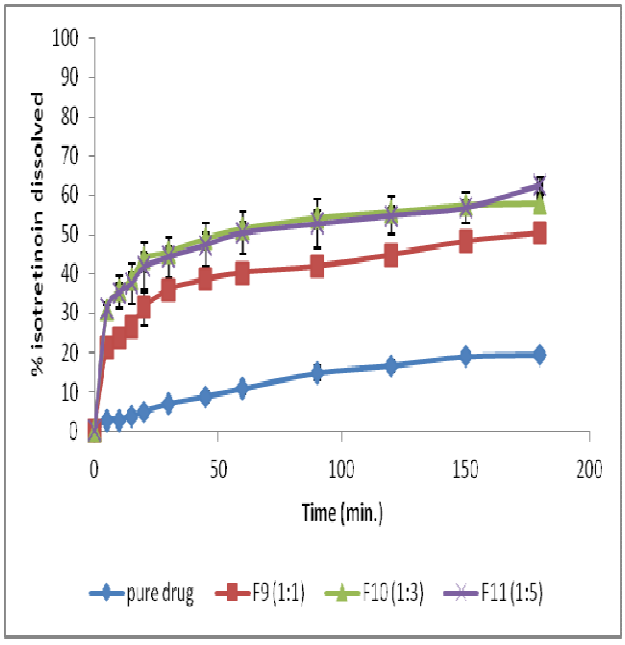
Figure (9): Dissolution profile of pure Isotretinoin and two formulation of surfactant enriched tablets (F1 (physical mixture) & F2 (co-evaporate) at phosphate buffer pH 7.4



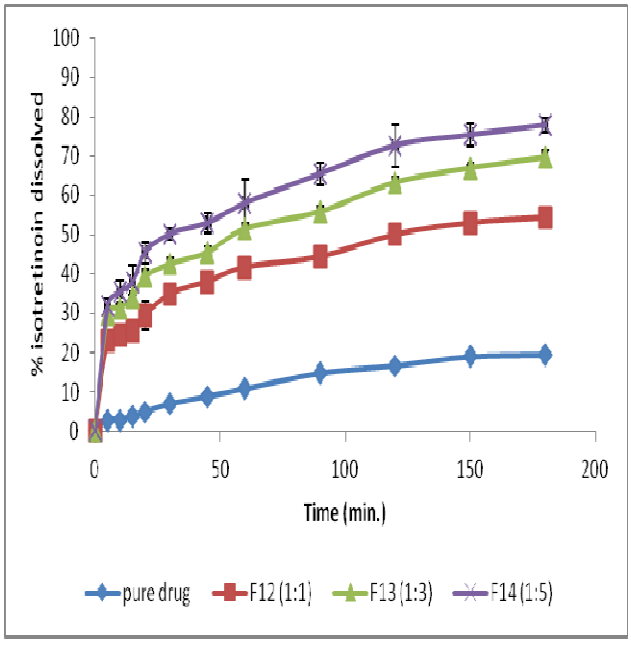
Physical mixture



Kneading



Co-evaporate



Freeze dry

Figure (10): Dissolution profile of isotretinoin from the binary system in phosphate buffer pH 7. 4

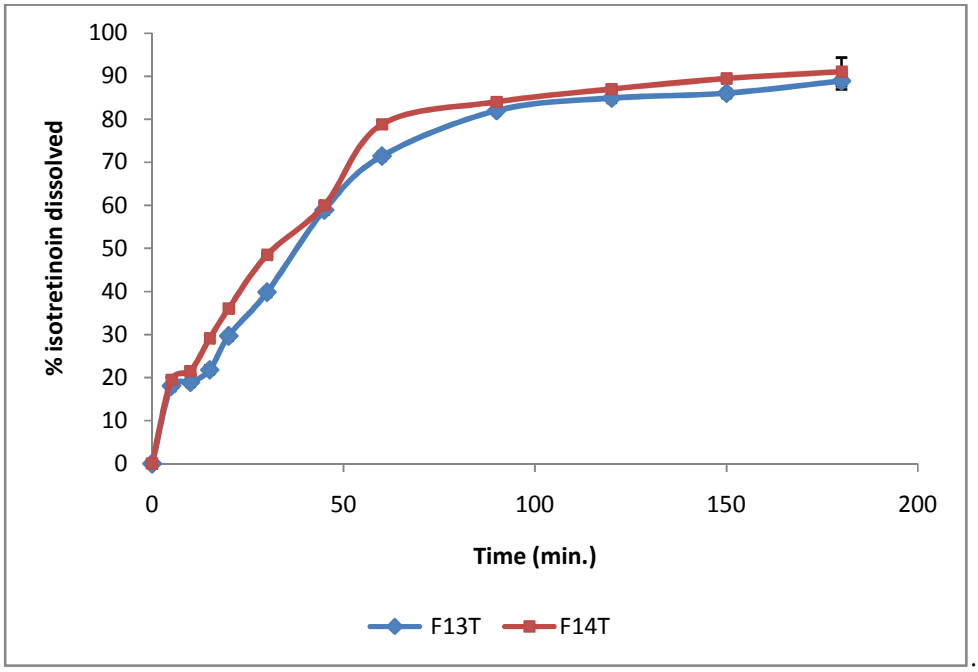


Figure (11): Dissolution profile of F13T and F14T in phosphate buffer pH 7.4

In-vitro dissolution test

The dissolution profile of two formulated surfactant enriched tablets showed in Figure 9, where F2, which the co-evaporate formula showed an overall faster dissolution and higher extent of drug dissolved (84.78% ± 0.75) compare to F1 formula (70.36% ± 1.69). The incomplete dissolution of the drug confirmed the DSC, FTIR and the XRD results which showed the existence of some the drug in the crystalline form, hence providing an incomplete dissolution for the drug.

Sink condition achieved in dissolution medium of surfactant enriched tablet, where the concentration of SLS in 900ml dissolution medium was 0.25^{x} 10-3 M this concentration suppose to dissolve 243g/L or 0.81M of isotretinoin. That indicates the availability of sink condition; sink condition is kept by replacing the amount withdrawn by fresh dissolution medium.

The dissolution profile of the binary system formulae of the drug with HP-β-CD was performed (Figure 10) and was found that the rate and extend of drug release increase as HP-β-CD ratio increase. The drug dissolution from physical mixture binary system formulae of the drug and HP-β-CD could be of a lowest extent, but generally the dissolution of the drug was increased if compared with raw drug, this enhancement in drug dissolution could be related to inclusion complexation that might have happened between the drug and cyclodextrin during dissolution test resulting in more drug dissolution also it may relate to the surfactant- like properties of HPBCD, which reduce the interfacial tension between the water insoluble drug particles and the dissolution medium, thus improving the wettability and dissolution of the drug. [13]

The kneaded formulae shows slight increase in the dissolution of isotretinoin but it is better than physical mixture.
It is clear that as the technique elongate, the time of exposure between the drug and cyclodextrin, the solubility becomes better.

The co-evaporate show more enhancement in the dissolution of isotretinoin compared to the physical mixtures and the kneaded products (Figure 9). The freeze-dried systems shows marked increase in isotretinoin dissolution compared with the other methods (Figure10). This marked enhancement could be attributed mainly to the formation of complete inclusion complex of the drug with the cyclodextrin. Also could be related to the particle size reduction

to the molecular size when the carrier brought the drug into the dissolution medium, leading to fast dissolution. Thus this enhancement in the dissolution would probably improve the biological performance of the drug.

CONCLUSION

Based on the results, it can be concluded that, both SLS and HP-β-CD showed a beneficial effect on the enhancement of isotretinoin solubility.

Thus, by aid of these polymers, isotretinoin can be formulated in form of tablets of acceptable mechanical strength and enhanced dissolution properties.

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