Original Research Article

Formulation and evaluation of taste-masked orally disintegrating tablets of nicergoline based on β-cyclodextrin inclusion complexation

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A b s t r a c t

Complexation of nicergoline with β-cyclodextrin (β-CD) into an inclusion complex has been used successfully to improve the drug's solubility, dissolution rate and hence per oral absorption. In addition, masking of the bitter taste was also achieved. The preparation of inclusion complexes was performed using two different techniques, namely; physical mixing and kneading. The apparent stability constant (K_c) of the complex was calculated from the phase solubility analysis. Compatibility of nicergoline and β-CD complex with disintegrants and superdisintegrants were evaluated using powder x-ray diffractometry (PXRD), differential scanning calorimetry (DSC), and fourier transform infrared spectroscopy (FTIR). The morphology of complex particles was studied using scanning electron microscopy. Pharmaceutical characterization confirmed that all additives were compatible with the drug and no signs of physical or chemical interaction were detected. Orodispersible tablets (ODTs) of nicergoline complexed with β-CD and containing 7-9 % camphor had rapid disintegration time (7-12 seconds) and fast drug release profiles (90-100 % in 10 minutes). Therefore, nicergoline ODTs are considered a valuable choice dosage form with improved per oral absorption and taste acceptability.

Keywords: β -cyclodextrin; Inclusion Complex; Nicergoline; Orodispersible; Sublimation

Introduction

Orodispersible tablets have become extremely popular per oral dosage forms in recent years [1]. Food and Drug Administration (FDA) defines orally disintegrating tablets as solid dosage forms containing a active pharmaceutical ingredient and disintegrate rapidly within few seconds when placed on the tongue [2]. ODTs offer the convenience of ease of swallowing in a liquefied form, provide good stability and accurate dosing [3]. They also possess simple manufacturing methodologies, small packaging size and favourable handling by patients [4]. Rapid disintegrating tablets result in quick dissolution and rapid absorption which provide rapid onset of action and increased bioavailability of drugs that are absorbed from mouth, pharynx and oesophagus [5]. The bitter after-taste of many drugs makes it difficult to be formulated as ODTs. The taste-masked tablet should give appropriate mouth feel using flavours and sweeteners included into ODTs formulations [6]. Numerous techniques have been used for producing highly-porous structure in the tablet matrix to facilitate and shorten disintegration time. These may include sublimation methods, inclusion of one or more disintegrant and/or superdisintegrants and also using fast dissolving sugar excipients such as mannitol and lactose. Conventional tablets contain highly water soluble ingredients; however, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tableting process, which are then sublimated from the formed tablet. Undesirable taste is one of several important formulation problems that are encountered with certain drugs taken by per oral route and the problem of bitter taste is always a challenge to the formulator pharmacist [7]. Nicergoline is a semi-synthetic ergoline derivative indicated for treatment of Alzheimer's disease and other types of dementia [8]. It has a molecular weight of 484.4 gm and melting point from 136°C to 138 °C, soluble in ethanol, chloroform and slightly soluble in ether [9]. The chemical name of nicergoline is: [(8β)-10-methoxy-1,6-dimethylergoline-8-methanol-5-bromo-3-pyridine carboxylate.] [10]. Nicergoline is extensively metabolised mainly by hydrolysis and N-demethylation and excreted in the urine as free and conjugated (glucuronide) metabolites [9]. Nicergoline has poor water solubility (0.002 mg/ml), therefore its absorption is expected to be dependent on dissolution rate [11]. This study aims at resolving problems of nicergoline regarding its poor water solubility, decreased bioavailability and its remarkable bitter after taste using drug complexed with β-cyclodextrin (β-CD). β-cyclodextrin provides essential and first choice properties for poorly soluble drugs by virtue of its hydrophilic surface and hydrophobic core [7] and [12]. It has a molecular weight of 1134.98 gm and extensively used for improvement of dissolution of many drugs such as gliclazide [13], corticosteroids [14], warfarin [15], Ibuprofen [16] and colchicine [17]. In this study, β -CD was used together with superdisintegrants

and a subliming agent to formulate and evaluate improved orodispersible tablet formulations of nicergoline with high bioavailability and patient acceptability.

Material and Methods

Materials

Nicergoline was a gift from Delta Pharma, Cairo Egypt. Granular mannitol, Pharmaburst and Sodium stearyl fumarate (SSF) were purchased from (SPI Pharma, USA). Ac-di-sol (sodium crosscarmellose) was purchased from E. Merk-Germany. Explotab (sodium starch glycolate) was obtained from FMC, CoLtd., Pennsylvania U.S.A. Saccharin sodium and crosspovidone (crosslinked sodium carboxymethyl cellulose) were kindly supplied by Chemical Industries Development Company (CID), Giza, Egypt. Camphor was obtained as a free sample from El-Nasr pharmaceutical chemical company, Cairo, Egypt.

Preparation and evaluation of nicergoline physical mixtures

Accurately weighed amounts of nicergoline (200 mg) and each of the used excipients namely granular mannitol, Ac-Di-Sol, Explotab (SSG), Crosspovidone, sodium stearyl fumarate (SSF), saccharin sodium, and camphor in ratios of 1:1 were mixed in a mortar. Samples from the freshly prepared mixtures were stored in glass vials and kept in hot air oven at 60 C for four weeks. Samples of the drug-excipient mixtures were removed at appropriate time intervals for examination of physical changes in appearance and/or colour, caking or signs of liquefaction. Other physico-pharmaceutical characterizations were performed using DSC, FTIR, SEM and Phase solubility analyses.

Preparation of nicergoline- β-cyclodextrin inclusion complex

The inclusion complex of nicergoline and β-cyclodextrin were prepared at stoichiometric molar ratio of 1:1 using two approaches; a) physical mixing after appropriate sieving of accurately weighed amounts of nicergoline (100 mg) and β-cyclodextrin (234.31 mg) using a mortar and pestle. b) Kneading method, in which the inclusion complex of nicergoline and β-cyclodextrin was prepared by kneading *B*-CD into a paste using a small amount of water. A solution of the drug in a small volume of methanol (3 ml) was added and the mixture was ground in the mortar till evaporation of the organic solvent. The theoretical drug content in the complex should be 29.91 % (w/w) based on 1:1 molar ratio. However, the actual content of entrapped nicergoline was determined practically by dissolving 100 mg of complex in 100 ml phosphate buffer (pH 6.8) followed by measuring the UV-absorbance at 280 nm. The drug content in the binary system of β-cyclodextrin/drug was calculated and found to be 20.38 %. This means that more than 68 % of theoretical drug content was entrapped into the complex.

Phase Solubility analysis of Nicergoline - Betacyclodextrin

The phase solubility technique permits the evaluation of the affinity between β-CD and nicergoline in water. Phase solubility studies were performed according to the method reported by Higuchi and Connors [18]. Nicergoline samples in amounts that exceeded its maximum solubility were taken into 10 mls volumetric flasks then 10 mls of distilled water containing various concentrations of β-CD (2, 4, 6, 8 and 10 mmol.) were added. The flasks were sealed and continuously shaken using a magnetic stirrer for 48 hours at 25 ºC. Aliquots from the suspension were withdrawn using, filtered immediately through a whattman filter paper and approximately diluted with distilled water. Samples were then analyzed using UV spectrophotometer (Jasco-V-530, Japan) at 280 nm. Blank solution was prepared from β-CD in water and measured in the same way.
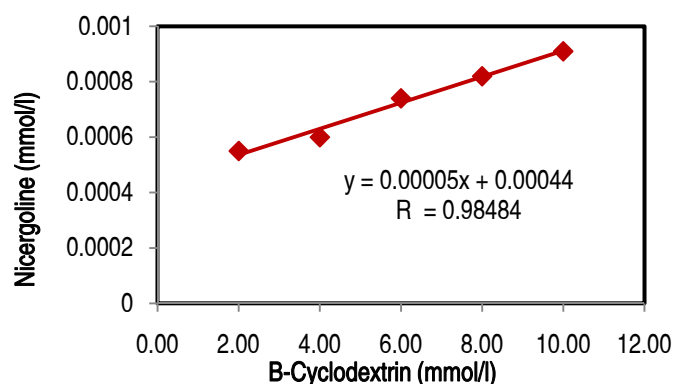

Figure.1: Phase solubility diagram of nicergoline-β-cyclodextrin inclusion complex

The apparent stability constant (K_c) according to the hypothesis of (1:1) stochiometric ratio of complex was calculated after plotting of phase solubility diagram (see Fig.1) and applying equation-1

$$K_{C\ 1:1} = slope / S^o(1\text{-slope}) \text{.......................Eq. 1}$$

Where S^o is the equilibrium solubility of nicergoline in water determined experimentally. The aqueous solubility of nicergoline increased linearly as a function of β-cyclodextrin concentration (see Fig.1). The slope of the regression line was less than 1 suggesting formation of a 1:1 complex [18]. The calculated apparent stability constant (K_c) obtained from the slope of the linear phase solubility diagram and experimentl S^o value was found to be 125 mol^{-1} [20-22].

Scanning Electron Microscopy

The surface morphology of the binary mixtures was examined and compared to both of β-cyclodextrin and nicergoline particles. Few spikes of powders were precisely fixed to aluminium stubs using double sided adhesive carbon discs and then were made electrically conductive by coating with gold sputter under vacuum (SPI-Module Sputter Coater, SPI Supplies Inc., USA). Samples

were then examined using scanning electron microscope (JEOL-JSM-6510LA, JEOL Ltd., Japan). Scanning electron micrographs are shown in Fig.2.
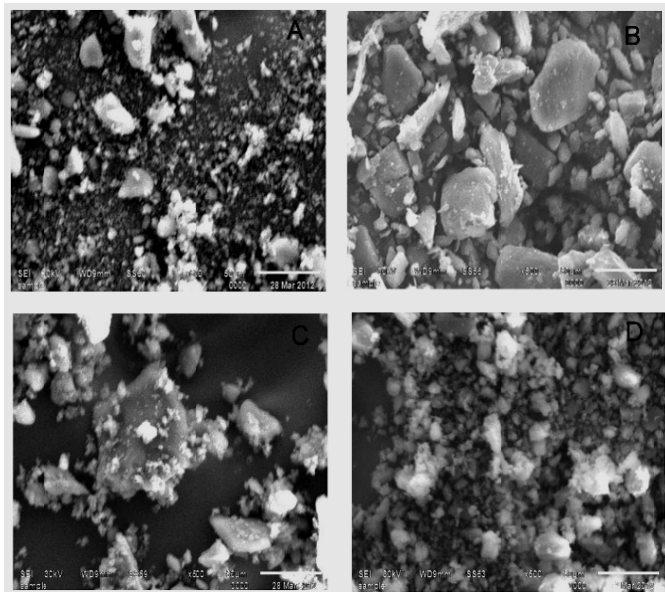

Figure.2: Scanning electron micrographs of nicergoline (A); Beta-cyclodextrin (B); physcial mixture (C) and kneaded mixture (D)

Differential Scanning Calorimetry (DSC)

This technique was used to evaluate the physico-chemical changes in nicergoline – excipient mixtures. Samples of 5 mg of the individual excipients, drug and mixtures both fresh and stored (at 60 ºC) were filled into tightly sealed aluminium flat bottomed pans and heated in DSC-60 instrument (Schimadzu, Japan) in an atmosphere of nitrogen to eliminate the oxidative and pyrrolytic effects. The range of heating temperatures was set between 20 – 250 ºC which exceeds the melting points of all used materials and the heating rate was kept at 5 ºC / minute.

Fourier Transform Infrared Spectroscopy (FTIRS)

Samples of nicergoline, excipients and their mixtures weighing about 2 to 3 mg were mixed with about 400 mg of dry potassium bromide. The powder was compressed into discs under pressure of 10.000 to 15.000 pounds per square inch using a hydrostatic press. The infrared spectra were determined at a scanning range of 400-4000 cm^{-1} using a Fourier Transform Infra red instrument (Thermo Scientific Nicolet 6700, USA).

Powder X-ray Diffractometry

The powder X-RD patterns of drug, β-cyclodextrin and complexes were recorded using X-ray diffractometer (X-Pert Graphics, Philips Analytical, Netherlands) using Cu as anode material and operated at a voltage of 25 Kv with a current of 40 mA. The samples were analyzed in the 2Theta angle range of 4 to 50 degree with scanning speed 1.2 degree/minute [23].

Preparation of nicergoline orodispersible tablets

The calculated amounts of the drug complex (24.53 mg) equivalent to 5 mg nicergoline and various excipients were mixed using a mortar and pestle. Then the calculated amount of sodium stearyl fumarate was added. The powder mixtures were compressed into tablets using flat bottom 8 mm punche and die set using a single punch tablet press (Model TDP, Shanghai Tianhe China). Camphor was subjected to sublimation from compressed tablets by placing tablets in petri dishes and exposing to a temperature of 40 ºC for 48 hours in a hot air oven [24].

Table 1: Composition of Orodispersible tablet formulations

Formula	Drug-complex (mg)	SSG	Cross-povidone	Ac-Di-Sol	Camphor (mg)	Saccharin sod.	Pharmaburst (mg)	SSF	Mannitol (mg)	Tablet Wt. (mg)
F1	24.53	-	-	-	3.60	1.20	24	1.20	65.46	120
F2	24.53	-	-	-	7.20	1.20	24	1.20	61.86	120
F3	24.53	-	-	-	10.80	1.20	24	1.20	58.26	120
F4	24.53	4.80	-	-	3.60	1.20	24	1.20	60.66	120
F5	24.53	4.80	-	-	7.20	1.20	24	1.20	57.06	120
F6	24.53	4.80	-	-	10.80	1.20	24	1.20	53.46	120
F7	24.53	-	4.80	-	3.60	1.20	24	1.20	60.66	120
F8	24.53	-	4.80	-	7.20	1.20	24	1.20	57.06	120
F9	24.53	-	4.80	-	10.80	1.20	24	1.20	53.46	120
F10	24.53	-	-	4.80	3.60	1.20	24	1.20	60.66	120
F11	24.53	-	-	4.80	7.20	1.20	24	1.20	57.06	120
F12	24.53	-	-	4.80	10.80	1.20	24	1.20	53.46	120

In-vitro dissolution rate studies

The dissolution behaviour of nicergoline/β-CD tablet formulations was performed using USP XXIV Basket apparatus (Hanson Research, SR 8 plus model, U.S.A). Samples of six tablets corresponding to each formulation were placed individually into stainless steel baskets and immersed into the dissolution medium (900 ml phosphate buffer pH 6.8) operated at a temperature of 37º ± 0.5ºC. The rate of agitation was kept at 50 r.p.m. Five milliliter samples were withdrawn at specific time intervals, filtered and the absorbance was measured spectrophotometrically at 280 using U.V spectrophotometer (UV-VIS spectrophotometer; Jasco, V-530, Japan).

Evaluation of taste masking character of drug/ β-CD complex

Taste masking ability of prepared formulations was evaluated using taste panel of six healthy human volunteers. The test was carried out according to University approved protocol indicating the ethics of dealing with volunteers. They were asked to sign a voluntary consent indicating their agreement and awareness about sharing in this experiment [25]. In this test, volunteers were given a little sample of pure drug (2 mg) or equivalent sample from β-CD complex formulations to taste and evaluate the bitterness and give their response after ten seconds. The response was evaluated on a scale from 0-4, where 0 = good, 1= tasteless, 2= slightly bitter, 3= bitter and 4 = very bitter. Each volunteer was asked to detect the taste of both drug and the complex to act as his or her own control. The results of this test indicated a score of 2 for the complex between nicergoline and β -CD on the scale which means a slightly bitter taste. Further improvement can be done by the use of a sweetener [26].

Pharmaceutical characterization of Nicergoline Orodispersible tablets

The prepared tablets were evaluated for various official and nonofficial specifications including weight variation, hardness and friability. Twenty tablets were weighed accurately and their average weight was calculated. Tablet thickness and diameter of 10 tablets were evaluated using Vernier caliper (Shanghai, China). The average value of diameter and thickness was then calculated (see Table 2). Tablet hardness was determined for ten tablets from each formulation using a tablet hardness tester (Dr-Schleuniger, Pharmaton, USA). The percentage friability was evaluated using a tablet friabilator (Pharma Test, Germany). The apparatus was rotated at 25 r.p.m for a period of 4 minutes and then the solid contents re-weighed. The percentage loss in weights was calculated and taken as a measure of friability (see Table 2). Drug content was evaluated for the prepared tablets after grinding of ten tablets and dissolving in 500 ml phosphate buffer (pH 6.8) followed by spectrophotometric analysis at 280 nm. The disintegration time was determined using disintegration test apparatus (Erweka, USA). A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The test medium was composed of 500 ml pH 6.8 phosphate buffer [27]. The time (in seconds) taken for complete disintegration of tablets with no large masses remained in the apparatus was measured.

Table 2: Pharmaceutical characteristics of prepared Orodispersible tablets:

Formula No.	Mean Weight mg ± S.D.	Mean Diameter (mm) ± S.D.	Mean Thickness (mm) ± S.D.	Hardness (kg) ± S.D	% Friability ± S.D	Disintegration time (sec) ± S.D
F1	119.33 ± 2.08	8.10 ± 0.02	2.06 ± 0.01	2.90 ± 0. 60	0.28 ± 0.02	9.74 ± 0.43
F2	121.33 ± 1.15	8.08 ± 0.01	2.05 ± 0.01	2.80 ± 1.46	0.58 ± .001	9.27 ± 0.07
F3	118.33 ± 2.08	8.08 ± 0.01	2.05 ± 0.02	2.20 ± 0.54	0.30 ± 0.04	7.48 ± 0.24
F4	121.53 ± 1.56	8.11 ± 0.01	2.05 ± 0.02	3.10 ± 1.36	0.28 ± 0.03	12.98 ± 0.28
F5	118.57 ± 2.40	8.14 ± 0.01	2.10 ± 0.01	3.60 ± 0.77	0.29 ± 0.02	11.09 ± 0.35
F6	119.57 ± 2.69	8.08 ± 0.01	2.08 ± 0.01	3.60 ± 0.95	0.29 ± 0.02	10.81 ± 0.66
F7	119.57 ± 2.30	8.13 ± 0.01	2.06 ± 0.01	3.30 ± 1.45	0.56 ± 0.05	9.76 ± 1.37
F8	116.83 ± 0.99	8.08 ± 0.01	2.12 ± 0.01	3.20 ± 0.76	0.86 ± 0.04	9.64 ± 0.22
F9	115.43 ± 1.33	8.09 ± 0.00	2.10 ± 0.01	3.30 ± 1.27	0.29 ± 0.03	9.63 ± 0.89
F10	120.37 ± 0.85	8.16 ± 0.01	2.14 ± 0.01	3.80 ± 1.45	0.42 ± 0.05	10.94 ± 2.27
F11	119.00 ± 1.73	8.07 ± 0.01	2.06 ± 0.01	3.60 ± 0.76	0.43 ± 0.04	9.54 ± 0.47
F12	121.63 ± 1.21	8.13 ± 0.01	2.10 ± 0.02	3.10 ± 1.27	0.43 ± 0.02	9.54 ± 0.47

Effect of storage at high temperature on tablet disintegration and drug release

This test aimed at studying the effect of ageing at high temperature on the disintegration and release of nicergoline from the selected formulation after 6 and 12 weeks. The release data of nicergoline from fresh and stored formulation (F3) at 40 ± 0.5 °C for 6 and 12 weeks are given in Fig. 11. The results showed insignificant difference ($p < 0.05$) in the disintegration or release pattern of nicergoline from the stored formulation compared to freshly prepared analogues.

Results and Discussion

Physical characterization

Drug-excipients physical mixtures fresh and those stored at 60°C for 4 weeks showed no change in physical appearance. All the prepared nicergoline ODTs showed acceptable weight variation range from 115.43 to 121.63 mg with standard deviation less than 2%. The prepared tablets showed uniformity of thickness and diameter (2.053 to 2.143 mm) and (8.076 to 8.17 mm) respectively. It was also observed that all the prepared tablets showed a percentage of fines which did not exceed the permissible limit of friability (1.4%). All nicergoline tablets showed hardness values ranging from 2- 4 kilograms. After tablet compression and subjecting to sublimation, the constant weight indicated complete removal of subliming agent [28]. Increasing camphor concentration from 3-9 % led to decreased disintegration time (<7.5 seconds) and formulations ($F_1 – F_3$) had the most rapid disintegration due to the porous structure formed [29]. However, formulations $F_4 – F_{12}$ containing superdisintegrants as well as camphor showed higher disintegration time values. This can be attributed to swellability and viscous matrices formed by the superdisintegrants leading to delay of the disintegration time (see Table 1 &2). Therefore sublimation can be considered as an effective method of preparing high porosity tablets that can undergo rapid disintegration in saliva [24].

Scanning Electron Microscopy

The SEM of nicergoline, nicergoline–β-cyclodextrin systems are shown in Fig.2. Nicergoline appeared as irregular shaped particles, whilst β-cyclodextrin showed a parallelogram shape. In nicergoline – β-cyclodextrin physical mixture small particle (nicergoline) adhered on the surface of β-cyclodextrin. However, the kneaded product appeared as relatively bulky agglomerated particles and the original morphology of raw materials disappeared and it was not possible to differentiate between its 2 components. This prominent change in particles' shape was indicative of the presence of new solid phase.

Differential Scanning Calorimetry

The DSC thermogram of nicergoline showed one main prominent characteristic endothermic melting peak at 137 °C (see Fig. 3). The DSC thermograms of the drug with other excipients are shown in Fig. 3-4. The therrmogram of β-cyclodextrin showed that it has one endothermic peak at 88.93°C, while its physical mixture with nicergoline in molar ratio (1:1) showed three endothermic peaks at 80.52, 98.49 and 133.86°C representing the sum of the individual curves of nicergoline and β-cyclodertrin with slight reduction in peak height of drug. This reduction can be attributed to dilution (reduced purity of both due to co-mixing) indicating no interaction. However, the inclusion complex prepared by kneading method showed three endothermic peaks at 72.24, 95.91 and 120.39 °C with disappearance of the characteristic peak of the drug which suggested the insertion of the drug molecule inside the β-CD cavity forming a true inclusion complex [30]. As there was no appearance, shift or disappearance of peaks and absence of variations in the corresponding enthalpy of the characteristic peaks, incompatibility of the ingredients can be excluded [31]. However, some broadening of peaks leading to changes in the area, onset and little changes in peak temperature may occur due to just mixing of components (dilution) without indicating any significant interaction [32]. Based on the previous DSC results, all the used additives were found to be compatible with the drug. The compatibility of nicergoline with the used excipients was further confirmed using IR spectroscopy.
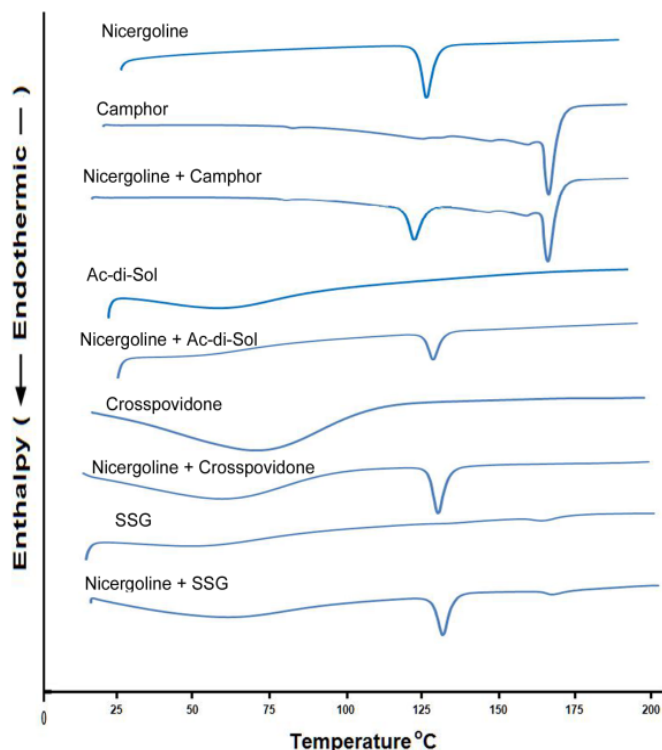

Figure.3: DSC thermograms for nicergoline, disintegrants and their physical mixtures
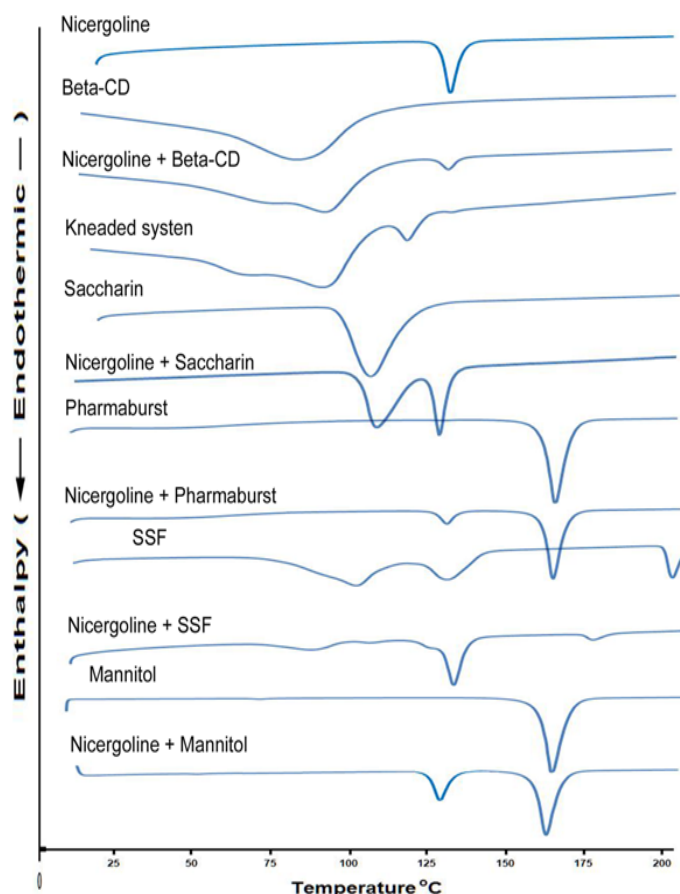
Figure.4: DSC thermograms for nicergoline, superdisintegrants and their physical mixtures

Fourier Transform Infrared (IR) Spectroscopy

IR spectrum of nicergoline (Fig. 5) exhibited the characteristic bands corresponding to the functional groups of the drug at 3423.99 cm^{-1} characteristic for (- N – H stretch) from (3500 – 3300), at 1720.19 cm^{-1} from (1760 – 1665 cm^{-1}) characteristic for (C = 0 stretch), at 1081.87 cm^{-1} characteristic for (C – O) and at 1463.71 and 1427.07 cm^{-1} for (C = C) stretching of aromatic rings. The β-cyclodextrin IR spectrum exhibited a broad strong band at 3396.99 cm^{-1} (3500 – 3200) cm^{-1} of (O – H stretch) and at 1030 cm^{-1} of (C – O). IR spectra of nicergoline with β-cyclodextrin in both physical mixture and kneaded complex (Fig.6) showed the same characteristic bands of the drug in the same regions and the same ranges. IR spectra of nicergoline with all the excipients (see Fig. 5-6) under test in mixtures showed the same characteristic bands of the drug in the same regions and ranges, indicating no sign of chemical interaction between the drug and excipients.
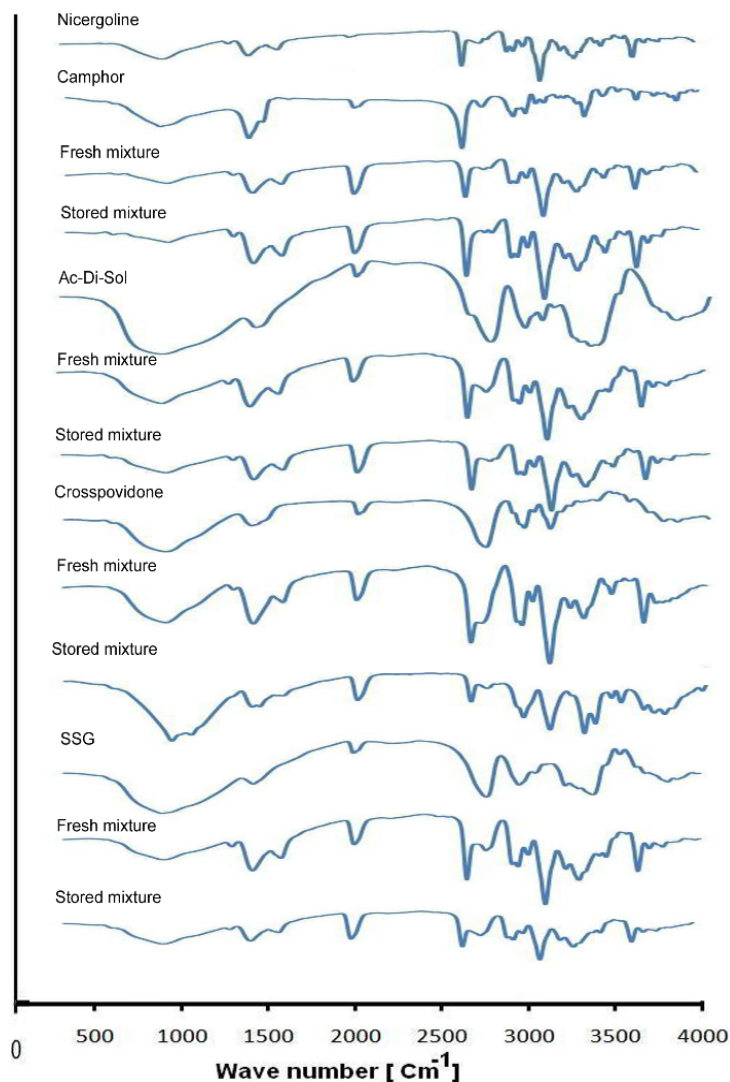

Figure.5: IR spectra of Nicergoline; disintegrants, fresh physical and stored mixtures at 60 C

Powder X-ray Diffractometry

The presence of several different peaks in nicergoline diffraction pattern (Fig. 7) indicated that the drug is in crystalline form. The diffraction patterns of physical mixture showed simply the sum of each component, indicating the presence of nicergoline in crystalline state. In contrast, diminution of the diffraction peaks in the kneaded complex suggested that it is less crystalline than the physical mixture indicating that nicergoline and β-cyclodxtrin formed an inclusion complex.
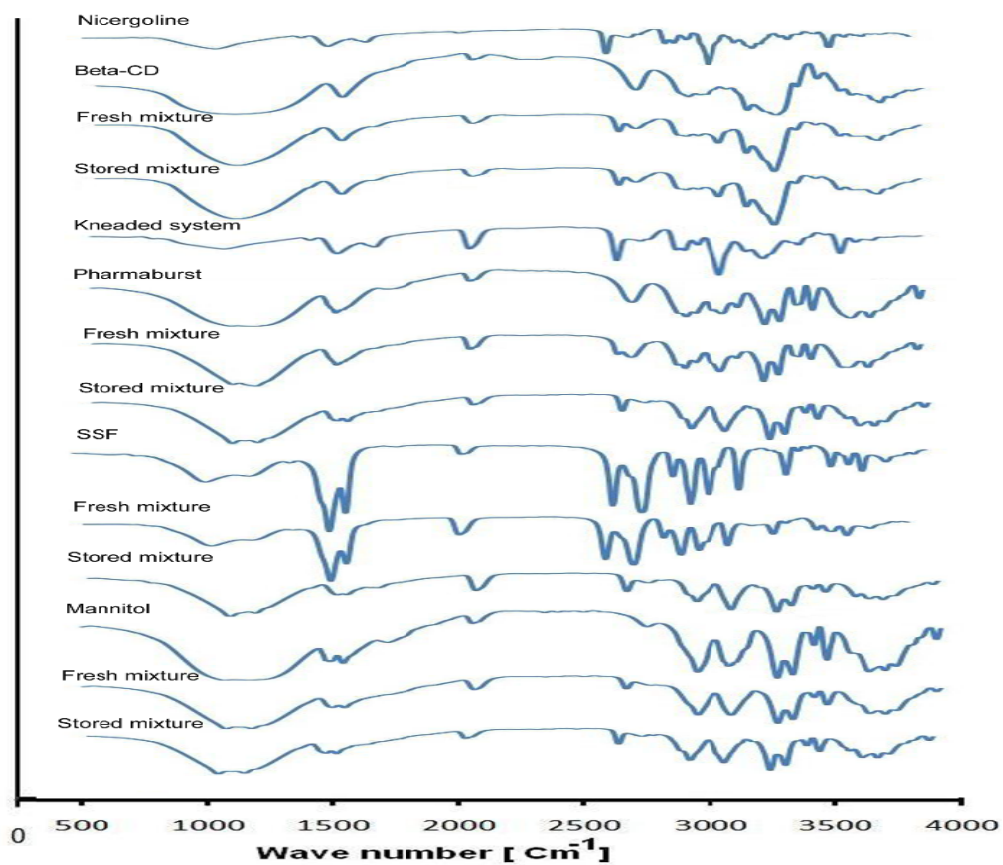
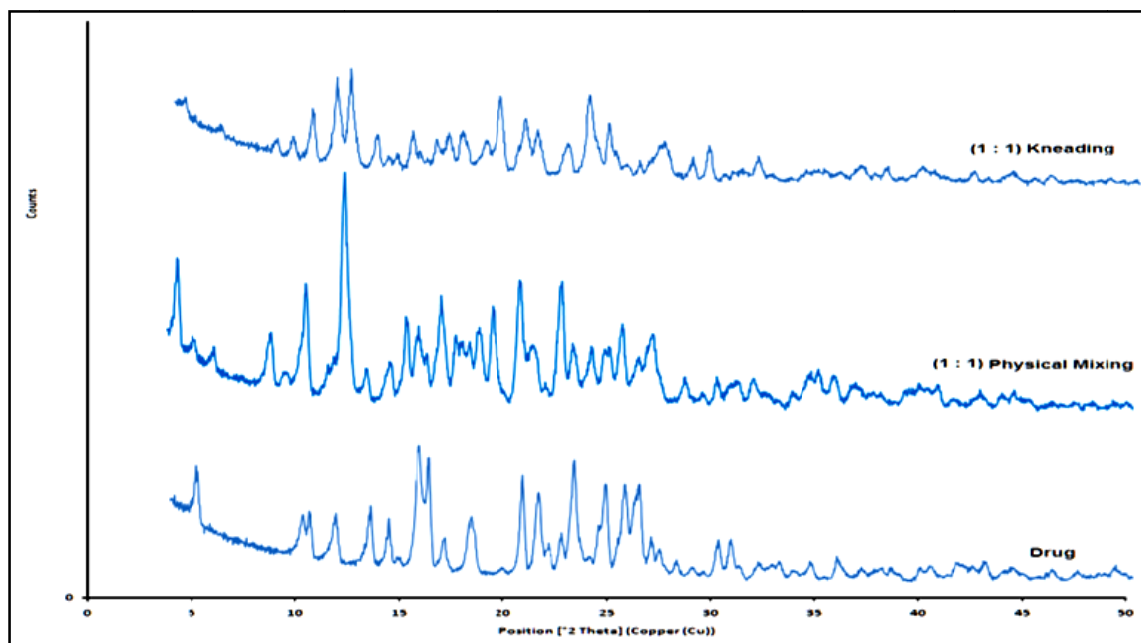**Figure. 6**: IR spectra of nicergoline, superdisintegrants, fresh physical and stored mixtures at 60°C

Figure.7: X-ray powder diffractometry for nicergoline, nicergoline/Beta-Cyclodextrin physical mixture and kneaded mixture

In-vitro dissolution rate studies

The dissolution profiles of pure nicergoline, nicergoline/β-cyclodextrin physical mixture and kneaded complex (see Fig. 8) showed that the inclusion complex released up to 91.92% of the drug in 30 minutes and 97% of the drug in 60 minutes respectively. Nicergoline released 52.70 % in 30 minutes and 72.23 % of initial amount in 60 minutes. The enhancement in dissolution profile has been attributed to the formation of inclusion complex in the solid state and the reduction in the crystalline form of the product (confirmed by powder X-RD study).
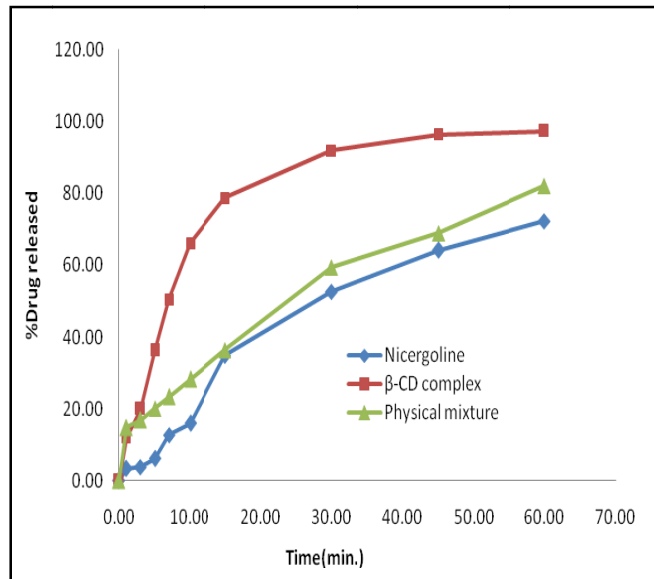

Figure.8: percentage nicergoline dissolved versus time as compared to β-CD complex and physical mixture

The dissolution profile of nicergoline from the different ODTs formulations (F$_1$ – F$_{12}$) are shown in Fig. 9 and 10. All formulations showed acceptable dissolution rate, where more than 85% of the labeled dose is dissolved in 30 minutes. Formulations F3, F6, F9 and F12 showed the highest dissolution rates (> 95% in 10 minutes) and shortest disintegration time (< 9 seconds) in most formulations. Such enhanced drug dissolution rate can be mainly attributed to the inclusion complex of nicergoline with β-CD and also to the presence of camphor. The increased concentration of camphor from 3-9 % resulted in decreased disintegration time and increased dissolution rate. This is due to faster uptake of water through the porous structure created after sublimation thus facilitating the drug complex dissolution.
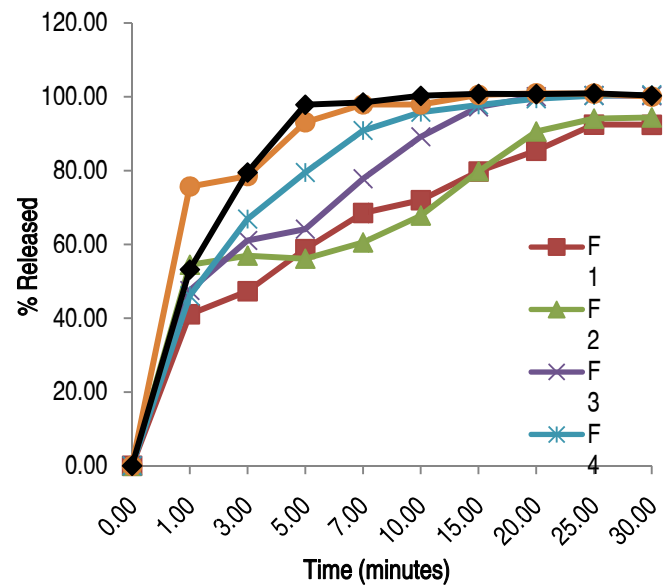

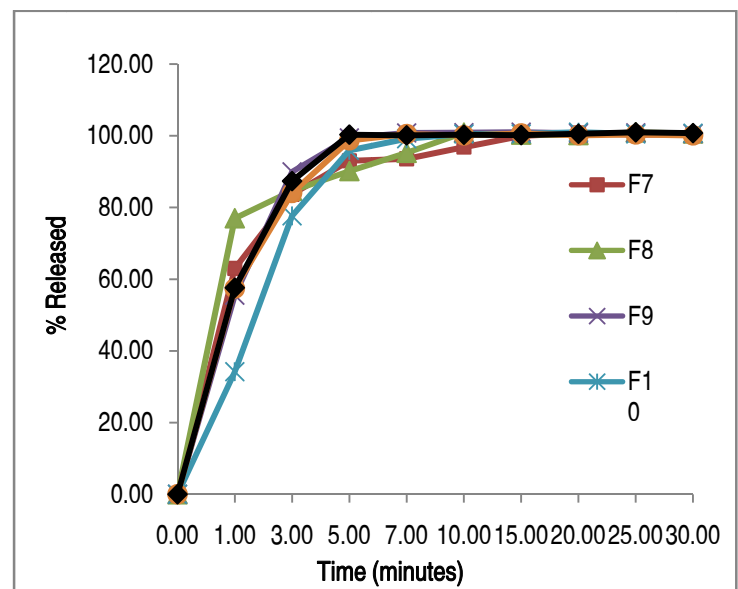**Figure.9**: Percentage nicergoline released versus time for formulations F1-F6

Figure.10: Percentage nicergoline released versus time for formulations F7-F12
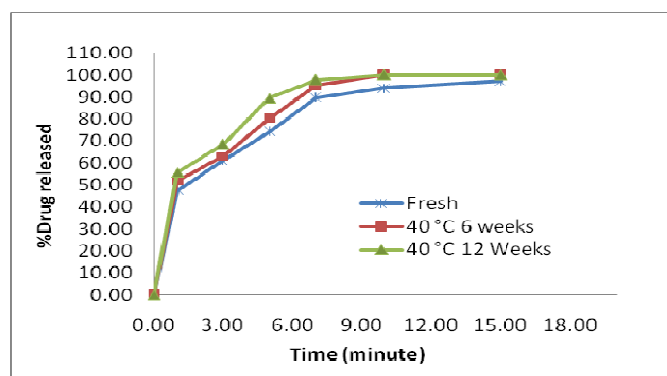
Figure.11: Percentage nicergoline released from fresh and stored formulation F3 at 40ºC

Kinetic analysis of release data

The mechanism of release of nicergoline from different tablet formulations was determined using linear regression according to; Zero order [$C_t = C_o - Kt$], First order [$\log C_t = \log C_o - (Kt/2.303)$] and simplified Higuchi diffusion model [$Q = [D_t (2A - C_s) C_s]^{1/2}$] [33]. The results showed that release from all formulations followed Higuchi diffusion kinetics. The regression r^2 values are shown in Table 3.

Table 3: Percentage dissolved (in first 10 minutes) and regression r^2 calculated from zero, first and Higuchi diffusion models

Formulation	% dissolved (10 minutes) ± SD	Regression (r^2)		
		Zero order	First order	Higuchi diffusion
F1	72.00 ± 0.10	0.884	0.812	0.967
F2	67.80 ± 0.04	0.950	0.940	0.936
F3	89.16 ± 0.05	0.863	0.796	0.956
F4	95.82 ± 0.03	0.728	0.629	0.860
F5	97.93 ± 0.02	0.669	0.638	0.756
F6	100.00 ± 0.01	0.643	0.549	0.792
F7	96.81 ± 0,01	0.657	0.585	0.802
F8	100.00 ± 0.01	0.807	0.773	0.919
F9	100.00 ± 0.01	0.683	0.572	0.833
F10	100.00 ± 0.01	0.602	0.460	0.765
F11	100.00 ± 0.01	0.659	0.571	0.818
F12	100.00 ± 0.01	0.654	0.563	0.812

Conclusion

From the previous findings; it could be concluded that using nicergoline/β-CD complex combined with a subliming agent in preparing ODTs resulted in effectively fast disintegration time (7-12 seconds). The complex also improved drug release properties from 95-100 % after 20 minutes in absence of superdisintegrants. Whilst the release was further improved (97-100 %) after only 5-7 minutes in presence of superdisintegrants. Cross carmellose sodium (Ac-Di-Sol) formulations (F10-F12) were the fastest in release pattern. The prepared ODTs disintegrate within few seconds; have high apparent stability constant and rapid dissolution rates which are expected to increase the oral bioavailability and taste of nicergoline.

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