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Formulation and in-vitro evaluation of fast dissolving tablets containing a poorly soluble antipsychotic drug

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Abstract

The aim of the present study was to formulate olanzapine fast dissolving tablets (FDT). Olanzapine is a poorly water soluble drug that undergoes first pass metabolism in liver resulted in low oral bioavailability. The water solubility is enhanced by formation of co-amorphous dispersion by solvent evaporation under vacuum method using a polycarboxylic acid (ascorbic acid) as a coformer in two different molar ratios (1:1 and 1:2). The prepared systems were evaluated using differential scanning calorimeter (DSC), Fourier Transform Infra-Red analysis (FTIR), X-ray powder diffraction (XRPD), Scanning electron microscopy (SEM) and saturated solubility. The co-amorphous dispersion system in a molar ratio 1:2 is higher in solubility than 1:1, so it was selected for incorporation into FDT formulation. Compatability study between olanzapine and different tablet excipients including DSC and FTIR showed that the drug is compatible with the selected tablet excipients. Direct compression method was used in FDT formulations using different types and concentrations of superdisintegrants. FDTs were evaluated for weight variation, hardness, friability, wetting time, drug content uniformity, invitro disintegration time and invitro dissolution study. All the prepared FDTs were complied with the compendia standards. F3 and F8 showed lower disintegration time and higher percent of drug dissolved, so they were selected for stability study. After storage for 3 months at 30ºC at 65% relative humidity, both formulations were physically stable regarding color and integrity and had only minor increases in disintegration time, drug content and friability after three months' storage. The results indicate that olanzapine FDT tablets may serve as a successful strategy for enhancing the bioavailability of olanzapine.

Keywords: olanzapine; ascorbic acid; co-amorphous dispersion; evaporation under vacuum.

Introduction

Oral route is the most important and preferable route of administration for solid dosage forms among all routes of administration [1]. But it still need some advancements to be made because of its drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms [2,3]. Fast release tablets have emerged as alternative oral dosage forms. These are novel types of tablets that disintegrate/dissolve/ disperse in saliva within few seconds without the need of water or chewing [4]. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets [4], [5,8]
Olanzapine or 2-methyl-4-(4-methyl-1-piperazinyl) - 10H-thieno [2, 3-b] [1, 5] benzodiazepine {8- Firdous S, #8} is an atypical antipsychotic that belongs to the thienobenzodiazepine class. Olanzapine is widely used in the treatment of schizophrenia and acute mixed or manic episode. It has been proved to be very efficient with no or minimal side effects. However, olanzapine exhibits poor water solubility and belongs to Biopharmaceutical Classification System (BCS) class II of drugs (low solubility and high permeability), highly bound to plasma protein (about 93%), undergoes extensive pre-systemic metabolism in the liver, resulting in relatively very low oral bioavailability [9,11]. Hence many trials were conducted to improve dissolution rate of olanzapine [12,13]
Co-amorphous dispersions are a recent and highly effective approaches used to improve water solubility and bioavailability of poorly soluble crystalline drugs [14]. It is commonly known as multi-component dispersions composed of an active ingredient with one or more neutral molecules known as co-formers [15]. Amorphous solids are non-crystalline materials in which the arrangement of the component atoms does not have a long-range order. They provide higher dissolution rates, also considered suitable and easy alternatives to co-crystals which often need complicated methods for its preparation and quantification, in addition to the physical instability and possible formation of polymorphs and hydrate [16]. Co-amorphous dispersions can be prepared from solutions of the crystalline drugs especially when rapid co-precipitation is pursued using carboxylic acids as plasticizing agents [17,19], neutral

molecules capable of forming strong H-bonding such as saccharin [20] or nicotinamide [21]or small molecular mass amino acids [22]. Plasticized co-amorphous dispersions prepared from crystalline drugs with polycarboxylic acids are rare [23]. Therefore, the aim of the present work is to enhance solubility of olanzapine before integration into tablet formulations via formation of stable olanzapine co-amorphous dispersions with polycarboxylic acids using solvent evaporation under vacuum method followed by incorporation into different tablet formulations. This lead to maximization of the oramucosal absorption of olanzapine which in turn improve its therapeutic efficacy [24]

Materials and Methods

Materials

Olanzapine was obtained as a free sample from the Egyptian Pharmaceutical Industries Company (EPICO, Egypt); Microcrystalline cellulose (Avicel® PH102) provided by (FMC Corp., Pennsylvania, USA); Emcosoy (RS PHARMA GmbH & Co. KG, Rosenberg, Germany); Pharmaburst® 500 (SPI Pharma, USA); Granular mannitol, Sodium stearyl fumarate (SPI Pharma, USA); Sodium starch glycolate (Explotab®) provided by (FMC Corp., Philadelphia, USA); Disodium hydrogen phosphate, Potassium dihydrogen orthophosphate (Sigma-Aldrich, Germany); Cross linked polyvinyl pyrrolidine (Crospovidone®), Na Saccharine (Fluka, Germany); anhydrous ascorbic acid was purchased from El Nasr, Chemical and Pharmaceutical Company (Egypt); Ethanol (95 %) and acetone were purchased from El-Gomhoria Company (Egypt).

Enhancement the solubility of olanzapine through formation of olanzapine/ascorbic acid co-amorphous dispersions

The calculated equivalent amounts of anhydrous ascorbic acid (coformer) according to the selected molar ratios (Table I), were dissolved in ethanol,95% (10 mls), The weighted amount of olanzapine (200 mg) was dissolved in acetone (10 ml)and then mixed with the ethanolic solution of ascorbic acid in a rotary evaporation flask.

The flask contents were sonicated for 10 min in a water bath sonicator (Ultrasonic Cleaner Model 57 H, Ney Instruments Co. Ltd, USA) until all contents were completely dissolved. The resulting solution was evaporated under vacuum (0.25 MPa) using a rotary evaporator (Barloworld Scientific Ltd., UK). The water bath temperature was kept at 50 C. After complete dryness, the collected mass was pulverized and passed through sieve number 60 (250 µm apertures), then kept in a desiccator until further examination.

Solid state characterization of olanzapine/ascorbic acid co-amorphous dispersions

Differential scanning calorimetry (DSC)

DSC analysis of pure olanzapine, ascorbic acid, drug- ascorbic acid physical mixture (PM) and the prepared co-amorphous dispersion (CD) formulations (5 mg each) were carried out using DSC (DSC-50, Shimadzu, Kyoto, Japan). The instrument was calibrated using purified Indium (99.99%). Samples (5mg) were sealed in a flat bottomed aluminum pan. The pan was placed in the DSC instrument and scanned between 30 and 300/C at a rate of 10ºC/min.

Fourier Transform Infra-Red analysis (FTIR)

Each sample (5mg) of olanzapine, coformer, drug-coformer PM and prepared dispersions were individually mixed with 100 mg dry potassium bromide. The powder mixtures were compressed into discs under a pressure of 10,000 to 15,000 pounds per square inch. The infrared spectrum was determined at a scanning range of 400-4000 cm^{-1} using a Fourier Transform Infra-red instrument (Shimadzu IR-345, Japan).

X-ray powder diffraction (XRPD)

Samples of olanzapine, coformer, drug-coformer PM as well as the solid dispersion formulations were subject to X-ray diffraction analysis. A Shimadzu XRD-6000 X-ray powder diffractometer coupled with a standard Cu sealed X-ray tube with voltage, current (40 kV and 30 mA) was used to characterize the amorphous or crystalline state of formulations. Data collection was performed at 2- theta of 5 - 80 in steps of 0.05 and scanning speed of 0.5 per step.

Scanning electron microscopy (SEM)

The morphology of the prepared dispersions was examined using scanning electron microscopy (JEOL-JSM-6510LA, JEOL, Japan). Few specks from each formulation were placed on the carbon stubs and then coated using a gold sputter followed by microscopical scanning.

Saturated solubility

Saturated solubility measurements of the prepared CDs in comparison to the drug were carried out by adding known excess amount of each formula to water (10 mL) and was kept in a shaking water bath (37ºC) for 24 h. The samples were left for 12 h to equilibrate then were filtrated using membrane filter (0.45µm). The filtrate was analyzed spectrophotometrically (Shimadzu, model-UV-1601 PC (s), Kyeto, Japan) at λ max 253nm.

Compatibility Studies of olanzapine with different excipients used in tablets formulations

The physical mixtures of the drug with the different excipients used in tablet preparation in the ratio of 1:1 were subjected to the following:

Visual examination

Samples of physical mixtures of the drug with the different excipients were subjected to visual examination either fresh or after storage for two weeks at 60 ºC. Samples were withdrawn daily during the subsequent period. The withdrawn samples were tested visually for any changes in appearance such as; discoloration, caking and liquefaction of clumps.

Differential Scanning Calorimetry (DSC)

DSC of the used excipients; namely sodium starch glycolate (SSG), emcosoy, microcrystalline cellulose (MCC), granular mannitol, crospovidone (CP), Na Saccharine, pharmaburst® 500, sodium stearyl fumarate (SSF) and their physical mixtures were studied.

Fourier Transform Infra-Red analysis (FTIR)

Infrared spectra of all materials used in preparing fast dissolving tablets were studied.

Formulation of olanzapine fast dissolving tablets (FDT) by direct compression method

A total number of eighteen formulations were prepared by direct compression. All ingredients were passed through 60- mesh sieve. The calculated amount of drug CD (1:2 molar ratio), superdisintegrant (emcosoy, SSG, or crospovidone), pharmaburst, Na Saccharine and MCC or granular mannitol were well mixed using morter and pestle then the calculated amount of sodium stearyl fumarate was added and mixed thoroughly. Tablets were compressed into 120 mg tablets using single punch machine of 8 mm flat punch and die set (Model TDP, SHANGHAI TIANHE, China).

Quality control tests of olanzapine FDTTablet weight and weight variation

Weight variation test was done by weighing twenty tablets individually then calculating the average weight and comparing the individual tablet weight to the average one.

Uniformity of tablet diameter and thickness

The diameter and thickness of ten tablets were measured using Vernier caliber (Shanghai, China) at two different positions. The average value was then calculated.

Tablet Hardness

Ten tablets from each formula were tested for their hardness using hardness tester (Dr-Schleuniger, pharmaton, USA) then the mean hardness in kg of each formula was determined.

Friability

The percentage friability was evaluated using a tablet friabilator (Pharma Test, Germany). Pre-weighted sample of tablets was placed in the drum, which was then rotated at 25 r.p.m for a period of four minutes. Tablets were dusted and reweighed and the percentage loss in weight was calculated.

Wetting time

Five circular filter papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten milliliters of water-soluble dye (eosin) solution 5% (w/v) is added to petridish. A tablet is carefully placed on the surface of the filter paper. The time required for water to reach upper surface of the tablet is noted as the wetting time.

Drug Content

Ten tablets were used in this test, where each one was crushed and transferred into 100 ml volumetric flask. The flasks were brought to volume by phosphate buffer pH 6.8. The flasks were placed onto a sonicator till complete dissolution; 1ml of the solution was filtered through a millipore filter of 0.45 µm pore size (Millpore, Milford, USA) then introduced into 25 ml volumetric flask which was completed to volume by phosphate buffer. The absorbance of the solution was measured spectrophotometrically against buffer as a blank at 253 nm.

In-vitro disintegration time

The disintegration time of fast dissolving tablets was performed using the compendial disintegration test apparatus (Hanson Research, Chatsworth, USA). In this experiment, 900 ml of phosphate buffer pH=6.8 kept at 37 ± 1 C was used as the disintegration medium and the basket was raised and lowered at a constant frequency of 30±2 cycles/min. The test results were presented as the average of six determinations. The time of total disintegration was considered to be achieved when no tablet fragments remain on the screen.

In-vitro dissolution studies

The *in-vitro* dissolution of all prepared formulations was investigated using USP type II dissolution apparatus (Hanson Research, Chatsworth, USA) at 50 rpm with temperature of 37±0.5ºC and 900 ml of phosphate buffer pH 6.8. At specified time intervals (1, 3, 5, 7, 10, 15, 20, 25 and 30 min); aliquots of 5 ml of dissolution medium was withdrawn and replaced with an equal volume of medium to maintain a constant total volume. Samples were then filtered through 0.45 µm Millipore filter and assayed for drug content spectrophotometrically at 253 nm. Cumulative percent of drug dissolved in the preparations was calculated using calibration equation. Dissolution efficiency % (DE%) and initial dissolution rate (IDR) were measured for each formula.

Effect of ageing

Formulations F3 and F8 was stored for 3 months at 30ºC at 65% relative humidity. The effect of ageing was studied by measuring both the in vitro drug release and disintegration time.

Result and Discussion

Solid state characterization of the prepared olanzapine/ascorbic acid co-amorphous dispersions

Differential scanning calorimetry (DSC)

DSC thermograms of the drug, physical mixture and co-amorphous dispersions systems are shown in figure 1. It is clear from the figure that the thermogram of the drug was that of a highly crystalline drug with a sharp endothermic peak at 194.01ºC (H = 126.83 J/g) corresponding to its melting point. The thermogram of ascorbic acid showed a melting endothermic peak at 191.24ºC. Thermograms of the CDs (containing ascorbic acid at 1 and 2 molar ratios, respectively) showed broad peaks with complete disappearance of characteristic melting endotherms of parent components suggesting formation of co-amorphous phases.

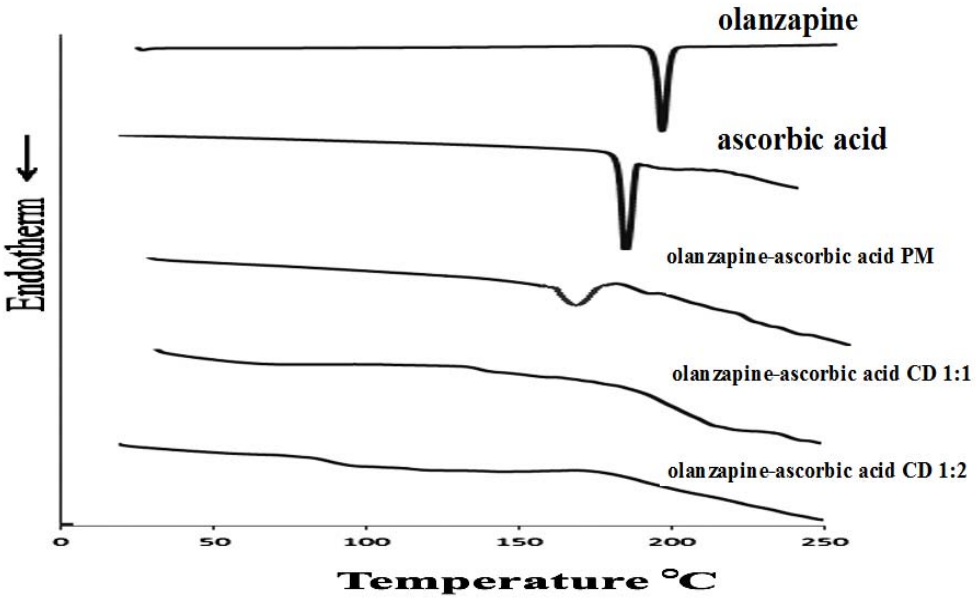

Figure. (1): DSC thermogram of a) pure olanzapine, b) anhydrous ascorbic acid, c) olanzapine-ascorbic acid PM d) olanzapine-ascorbic acid CD 1:1 molar ratio, e) olanzapine-ascorbic acid CD 1:2 molar ratio.

Fourier Transform Infra-Red analysis (FTIR)

The FT-IR spectra of OLZ, physical mixtures (1:1) and CDs are presented in figure 2. Pure OLZ showed characteristic absorptions at 3217 cm^{-1} (NH stretching), 2929 , 2836, and 2791cm^{-1} (C–H stretching), 1586 cm^{-1} (C=C stretching), 1461 cm^{-1} (C=N stretching) and 1283 cm–1 C–N stretching) [25]. The FTIR spectra of ascorbic acid indicated a characteristic peak at 1754 cm^{1} which is attributed to the C=O stretching vibration in carboxyl groups. The characteristic peaks of pure OLZ were found to be present in the spectra of PM. Formulations CD1 and CD2 showed shortening or disappearance of certain peaks of olanzapine (C-H stretching and C=N stretching), Broadened shallow peak of N-H stretching shifting to 3394 cm^{-1} instead of 3217 cm^{-1}. These results suggest that the interaction between olanzapine and ascorbic acid most probably through H bonding.

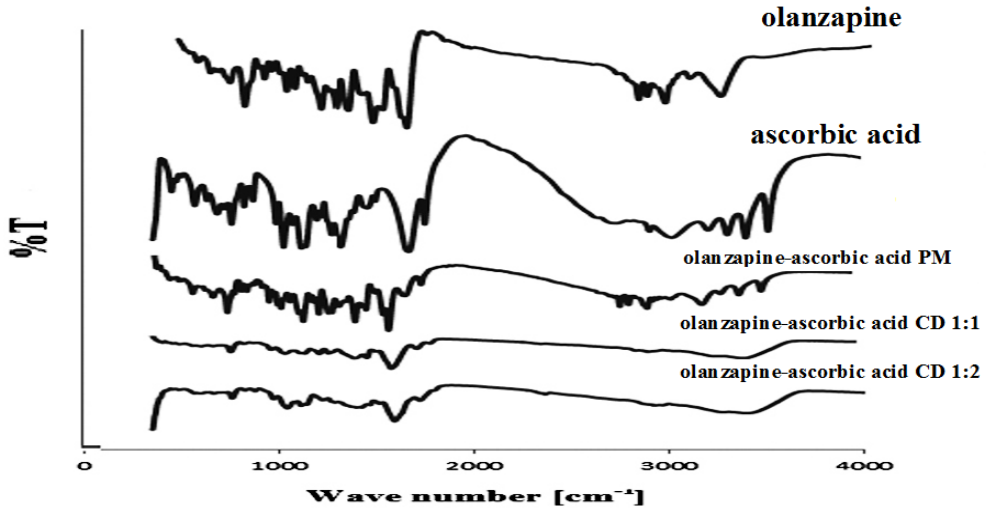

Figure. (2): FTIR spectra of a) pure olanzapine, b) anhydrous ascorbic acid, c) olanzapine-ascorbic acid PM d) olanzapine-ascorbic acid CD 1:1 molar ratio, e) olanzapine-ascorbic acid CD 1:2 molar ratio.

X-ray powder diffraction (XRPD)

As shown in figure 3, the diffraction spectrum of pure olanzapine show that the drug was crystalline in nature as demonstrated by characteristic intense peaks at 2 theta 8.67, 17.09, 19.87, 21.05, 21.54, and 23.95º. These results are in good agreement with what was reported for olanzapine in the literature {25- AJIT, #25}. The XRD pattern for ascorbic acid also showed multiple sharp characteristic peaks at 2 theta 10.63, 15.89, 17.59, 25.33, 27.25, 28.19, 30.18, and 34.85º. The XRD spectra of the drug-ascorbic acid PM showed sharp characteristic peaks at 2 theta 8.65, 10.47, 19.88, 21.03, 25.21, 26.83, and 29.97 that indicate compatibility between drug and ascorbic acid. The diffraction spectrum of the co-amorphous dispersions demonstrated disappearance of the characteristic peaks of both olanzapine and ascorbic acid and appearance of amorphous halo. The results of DSC, IR, and XRPD strongly suggest that amorphous systems were obtained through H-bonding interactions between the drug and ascorbic acid.

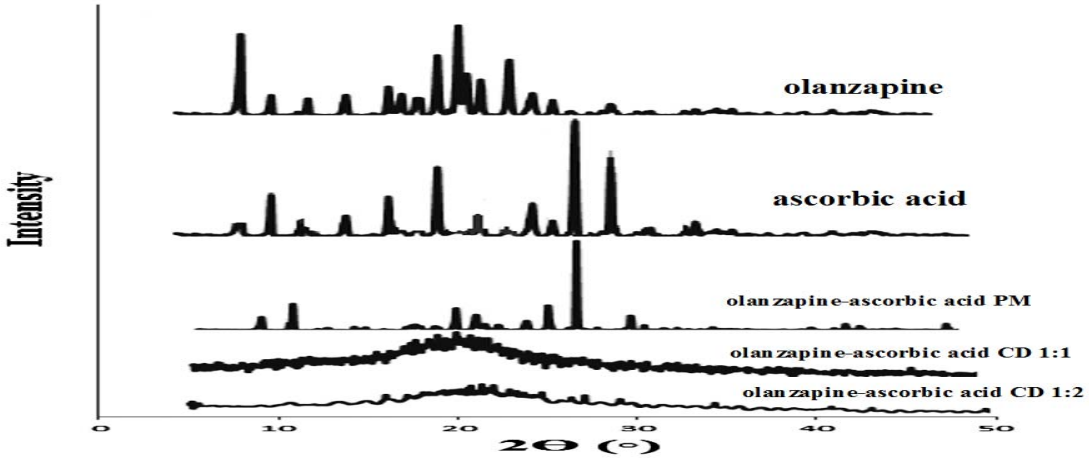

Figure. (3): X-ray diffractograms of a) pure olanzapine, b) anhydrous ascorbic acid, c) olanzapine-ascorbic acid PM d) olanzapine-ascorbic acid CD 1:1 molar ratio, e) olanzapine-ascorbic acid CD 1:2 molar ratio.

Scanning electron microscopy (SEM)

Figure (4, A) is a photomicrograph of olanzapine powder; the figure clearly illustrates the crystalline nature of the drug that was previously proven by the x-ray diffraction test.

Figure (4, B) show the crystals of the drug mixed with the large crystals of ascorbic acid, while the micrographs of the co-amorphous systems (Figure. 4, C, D) show a matrix in which no crystals of olanzapine or ascorbic acid could be seen.

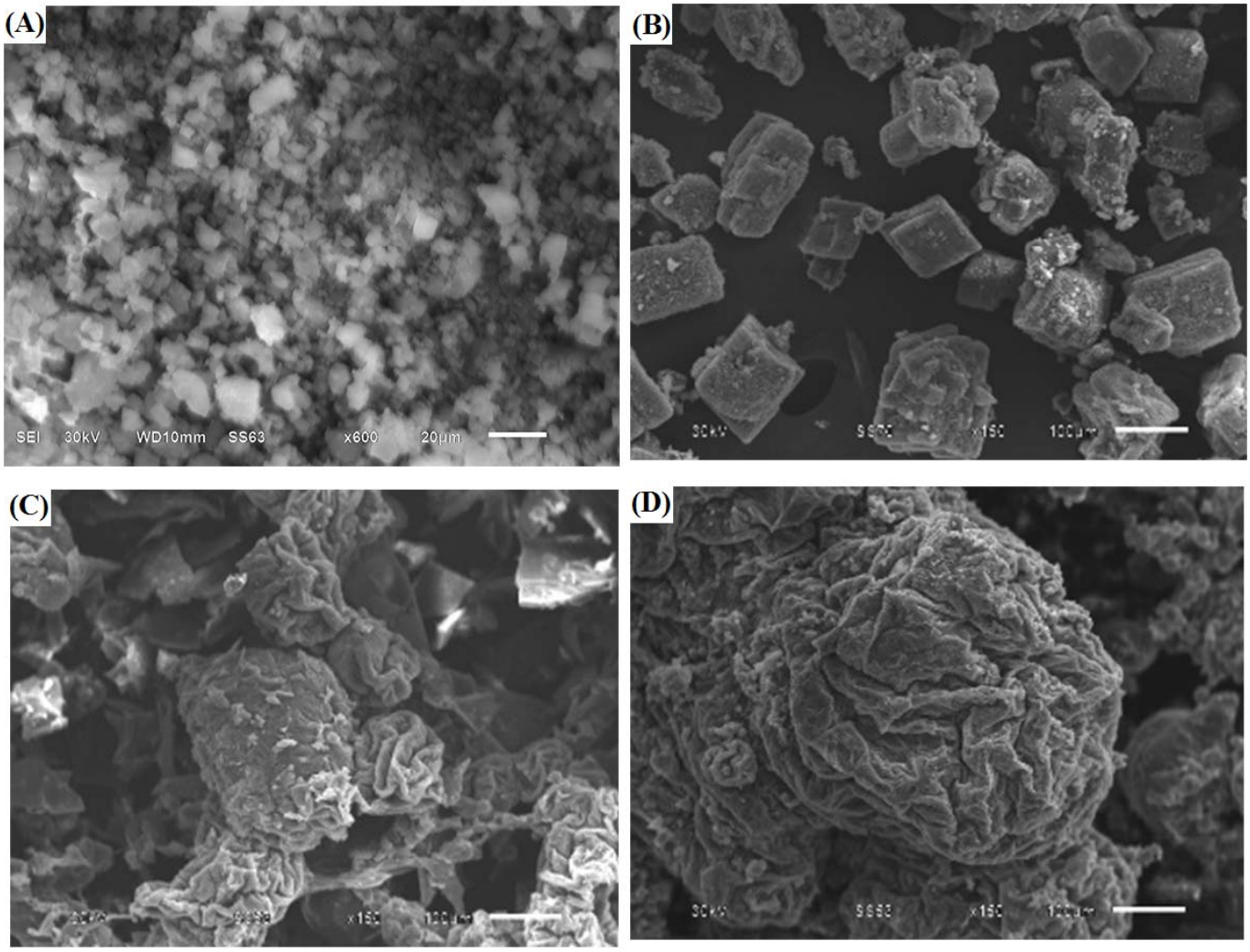

Figure. 4: SEM microphotographs of (A) pure olanzapine (B) olanzapine-ascorbic acid PM d) olanzapine-ascorbic acid CD 1:1 molar ratio, e) olanzapine-ascorbic acid CD 1:2 molar ratio.

Saturated solubility

All the test samples showed an increase in drug solubility over crystalline olanzapine (Table 1). the drug-coformer molar ratio 1:2 enhanced solubility greater than that of 1:1, so it was selected for incorporation into FDT formulations.

Table I. Composition of olanzapine-ascorbic acid co-amorphous dispersions and their saturated solubility

Formulation	olanzapine(mg)	Ascorbic acid (mg)	Stoichiometricratio	Saturated solubility (mg/mL)
M.wt	312.44		-	0.00234±0.0015
		176.12	-	-
CD1	200	112.74	1.00:1.00	6.303±1.83
CD2	200	225.48	1.00:2.00	19.855±1.42

Compatibility Studies of olanzapine with different excipients

Neither the fresh mixtures nor the stored ones showed any change in color or appearance throughout the storage period. The absence of such signs is a good preliminary step of physical stability.

The DSC (Figure. 5, 6) and IR spectra of olanzapine (Figure. 7, 8) in mixtures with all excipients showed the same characteristic bands of the drug in the same regions and the same ranges, indicating that there was no interaction between the drug and any of the excipients used. Also, there is no remarkable change between the fresh and the stored mixtures indicating the stability of the mixtures.

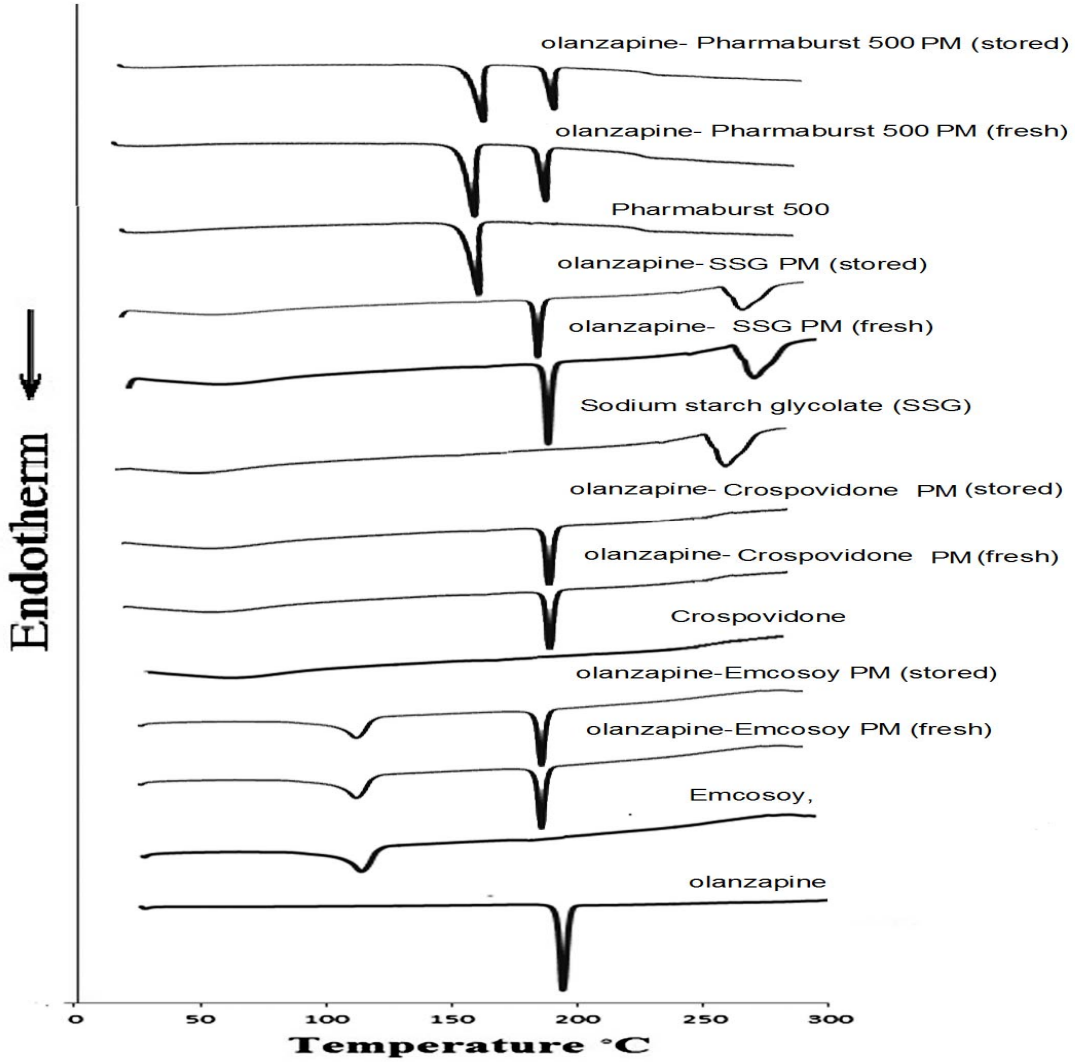

Figure. (5): DSC thermogram of olanzapine and different tablet excipients (fresh and stored)

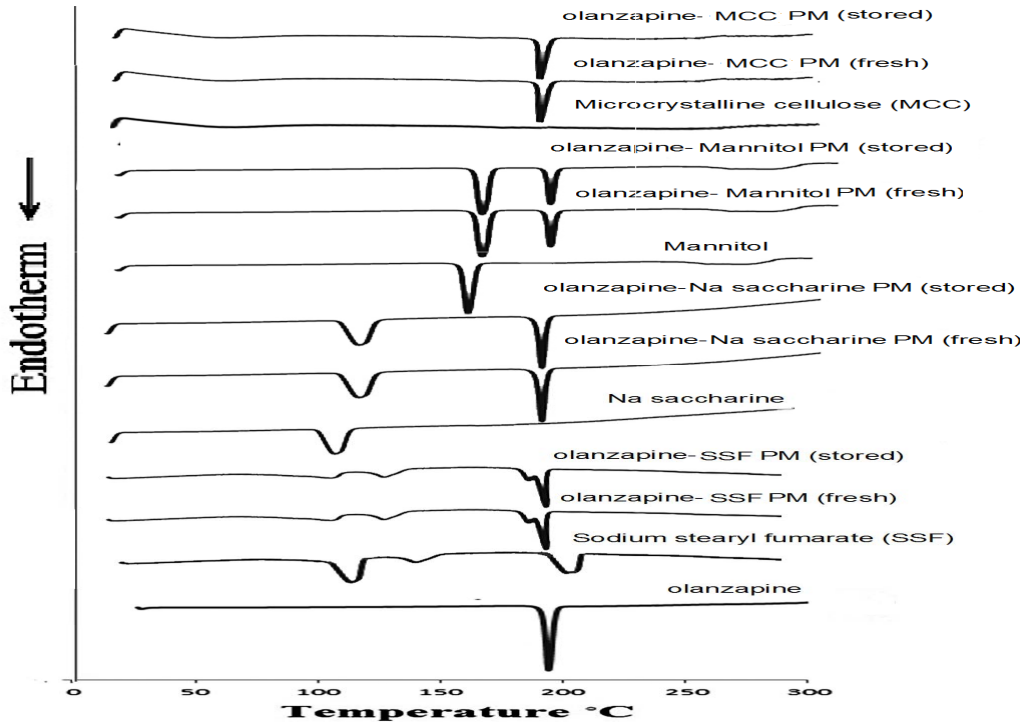

Figure. (6): DSC thermogram of olanzapine and different tablet excipients (fresh and stored)

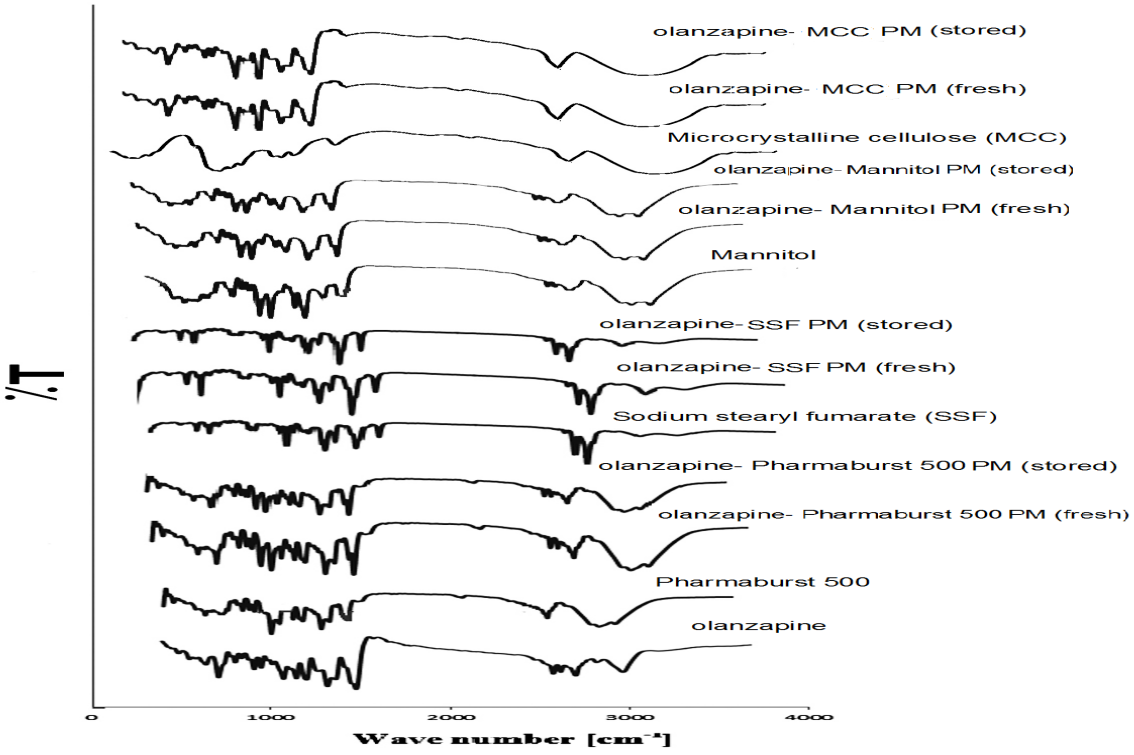

Figure. (7): FTIR of olanzapine and different tablet excipients (fresh and stored)

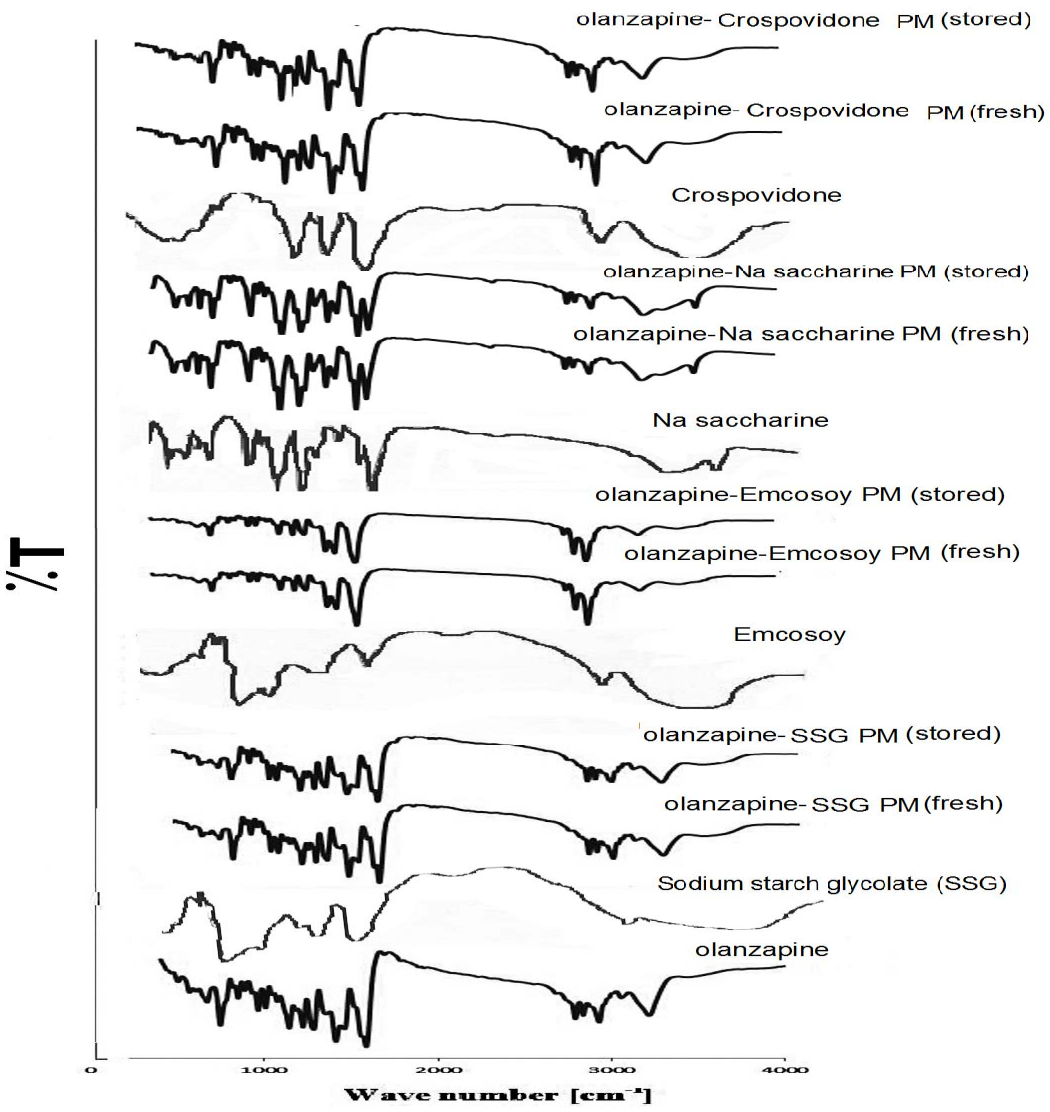

Figure. (8): FTIR of olanzapine and different tablet excipients (fresh and stored).

Quality control tests of olanzapine FDT

As shown in table 3, all the prepared olanzapine FDT formulae complied with the compendia standards for the weight variation and content uniformity tests (all tablet formulae were found to conform to pharmacopoeial limit 85% - 115%) of the label claim. The prepared tablets showed a uniformity of diameter and thickness.

All olanzapine FDT formulae showed hardness values ranged from 2.75 to 4.12 kilograms, with standard deviation less than 2%. A significant strength of FDT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of crushing strength for FDT is usually kept in a lower range to facilitate early disintegration in the mouth {26- Bandari S., #26}. According to compendial standards, the prepared formulae comply with the friability test if the weight loss during the friability test was less than 1%; in addition, the tablets should not break or show any capping or cracking during the test [26]. All FDT formulations showed rapid wetting time ranging from 9 to 31 seconds. These results correlated well with disintegration testing results.

Table (2): Composition of different olanzapine fast dissolving tablets formulae prepared by direct compression method

Formula No	Ingredient per tablet (mg)				
	*Drug coformer	Super Disintegrant			Diluent
		Emcosoy	Sodium starch glycolate	Crospovidone	
F1	10.637 equivalent to 5 mg olanzapine	2.4			Mannitol up to 120 mg
F2		4.8			
F3		7.2			
F4			2.4		
F5			4.8		
F6			7.2		
F7				2.4	
F8				4.8	
F9				7.2	
F10		2.4			MCC up to 120 mg
F11		4.8			
F12		7.2			
F13			2.4		
F14			4.8		
F15			7.2		
F16				2.4	
F17				4.8	
F18				7.2	

* Olanzapine/ascorbic acid co-amourphous dispersion 1:2 molar ratio

** All FDT contain Pharmaburst (20%) 24mg, SSF (1%) 1.2mg, Na saccharine (1%) 1.2mg

Table 3: Pharmaceutical characteristics of the prepared fast dissolving tablet

Formula NO.	Mean Weight mg ± S.D	Mean Thickness cm ± S.D	Mean Diameter cm ± S.D	Hardness Kg ± S.D	% Friability	Wetting time sec ± S.D	% Drug Content ± S.D	Disintegration time sec ± S.D
F1	121.4 ± 0.99	0.22 ± 0.033	0.81 ± 0.041	3.7 ± 0.91	0.58	16.3 ± 0.05	99.0 ± 1.32	11.77 ± 0.63
F2	120.0 ± 1.13	0.22 ± 0.024	0.82 ± 0.015	3.1 ± 1.31	0.69	13.1 ± 0.03	99.5 ± 0.95	10.9 ± 0.33
F3	119.81 ± 1.13	0.23 ± 0.04	0.81 ± 0.025	3.5 ± 0.53	0.75	11 ± 0.09	98.2 ± 0.73	9 ± 0.68
F4	119.83 ± 1.49	0.21 ± 0.017	0.81 ± 0.012	3.2 ± 0.55	0.99	23.2 ± 1.15	99.8 ± 0.81	18.2 ± 1.33
F5	121.2 ± 1.01	0.20 ± 0.023	0.81 ± 0.006	3.8 ± 0.45	0.91	19.3 ± 0.70	102.1 ± 0.85	16.3 ± 0.88
F6	120.2 ± 0.52	0.21 ± 0.017	0.81 ± 0.014	4.1 ± 0.88	0.93	25.1 ± 0.51	100.3 ± 1.16	20.3 ± 1.02
F7	120.2 ± 1.50	0.20 ± 0.026	0.80 ± 0.004	3.7 ± 0.74	0.66	21.7 ± 0.42	99.8 ± 1.69	21.2 ± 1.03
F8	120.6 ± 0.36	0.21 ± 0.029	0.80 ± 0.005	3.2 ± 1.44	0.63	20.8 ± 0.44	100.1 ± 0.78	13.3 ± 0.24
F9	120.2 ± 0.98	0.21 ± 0.013	0.80 ± 0.023	3.9 ± 1.05	0.94	28.3 ± 0.49	99.9 ± 2.25	22.5 ± 0.52
F10	120.1 ± 0.75	0.24 ± 0.023	0.80 ± 0.037	3.4 ± 1.03	0.67	20 ± 0.08	97.8 ± 0.65	13.5 ± 1.30
F11	120.2 ± 0.92	0.23 ± 0.021	0.81 ± 0.021	3.7 ± 0.56	0.32	18.3 ± 0.07	99.1 ± 0.74	13 ± 2.50
F12	119.9 ± 0.64	0.22 ± 0.024	0.82 ± 0.007	3.3 ± 1.03	0.63	17.4 ± 0.11	99.8 ± 1.38	11.1 ± 1.45
F13	122.41 ± 0.63	0.22 ± 0.08	0.81 ± 0.009	3.4 ± 1.06	0.84	24 ± 0.07	100.1 ± 1.39	19 ± 0.92
F14	121.6 ± 0.86	0.23 ± 0.020	0.81 ± 0.010	3.5 ± 1.21	0.85	20 ± 0.49	98.5 ± 0.85	18.6 ± 1.57
F15	120.3 ± 1.26	0.22 ± 0.039	0.80 ± 0.009	4.12 ± 0.91	0.97	26 ± 0.18	98.9 ± 0.45	22 ± 0.68
F16	120.0 ± 1.71	0.21 ± 0.054	0.81 ± 0.011	3.1 ± 0.77	0.72	25.3 ± 0.76	99.1 ± 0.58	22 ± 0.64
F17	120.4 ± 0.99	0.21 ± 0.016	0.81 ± 0.014	3.0 ± 0.78	0.84	24.1 ± 0.59	99.1 ± 1.18	19.6 ± 0.11
F18	120.7 ± 1.03	0.21 ± 0.019	0.81 ± 0.016	2.75 ± 1.05	0.39	31 ± 0.12	101.5 ± 0.94	23 ± 0.35

In-vitro disintegration time

Regarding the *in-vitro* disintegration, all the formulae of olanzapine FDT disintegrated in a period less than one minute.

To study the effect of superdisintegrant type and concentration on disintegration time, it was found that: in tablet formulations containing SSG and crospovidone, as the superdisintegrant concentration increase from 2% to 4%, the disintegration time decreased, this may be due to the fact that with the increase in the superdisintegrant concentration, the particles were exposed to disintegration medium at comparatively faster rate. Also, the agglomeration of drug particles was avoided because of increased medium viscosity.

At the concentration of 6%, crospovidone showed slight increase in disintegration time because of rapid penetration of the largest capillaries isolates other areas of finer pore structure from which air cannot escape making no contribution to the overall uptake of liquid. It disintegrate tablets rapidly but into larger masses of aggregated particles which not small enough to pass through the screen of the disintegration vessel, accordingly a longer disintegration time.

While, at the concentration of 6%, SSG showed a remarkable increase in disintegration time due to, the higher concentration of SSG which may act as a binder instead of swelling which cause gelling thus, causing viscosity change of the penetrating liquid. Thus, the optimum concentration of crospovidone and SSG was 4%.

Emcosoy showed different behavior, increasing its concentration from 2% to 6%, decreasing disintegration time. This is because it acts as a superdisintegrant at a concentration of 3-15% while the previous ones the maximum concentration to be superdisintegrant was 5%.

To study the effect of diluents, formulations prepared using MCC have higher values of disintegration time than those prepared using granular mannitol. This is because MCC is an insoluble diluent while granular mannitol is a soluble diluent, dissolve rapidly thus facilitate the disintegrant to bring about faster disintegration.

In-vitro dissolution studies

The dissolution of olanzapine from FDTs into phosphate buffer showed that olanzapine was rapidly released from all formulations, much more rapidly than olanzapine alone (Figure 9). It was clear that formulations have mannitol as a diluent had higher dissolution parameters than those contain MCC as a diluent. As shown in figure 10, Formulations F3 and F8 showed the highest DE% and IDR, so they were selected for stability study.

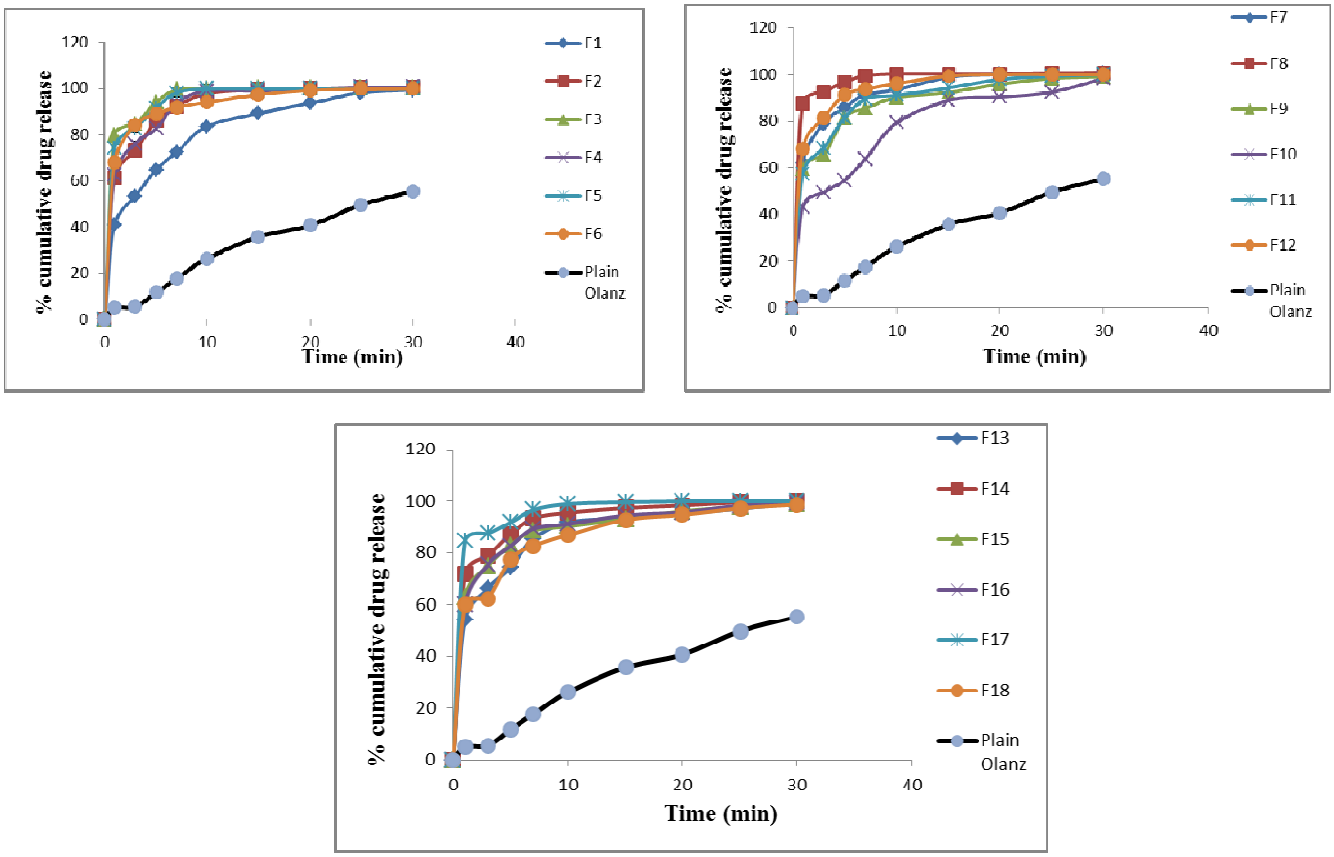

Figure. (9): Dissolution profiles of olanzapine from FDTs tablets, and olanzapine alone in phosphate buffer at 37ºC (n = 3± S.D.)

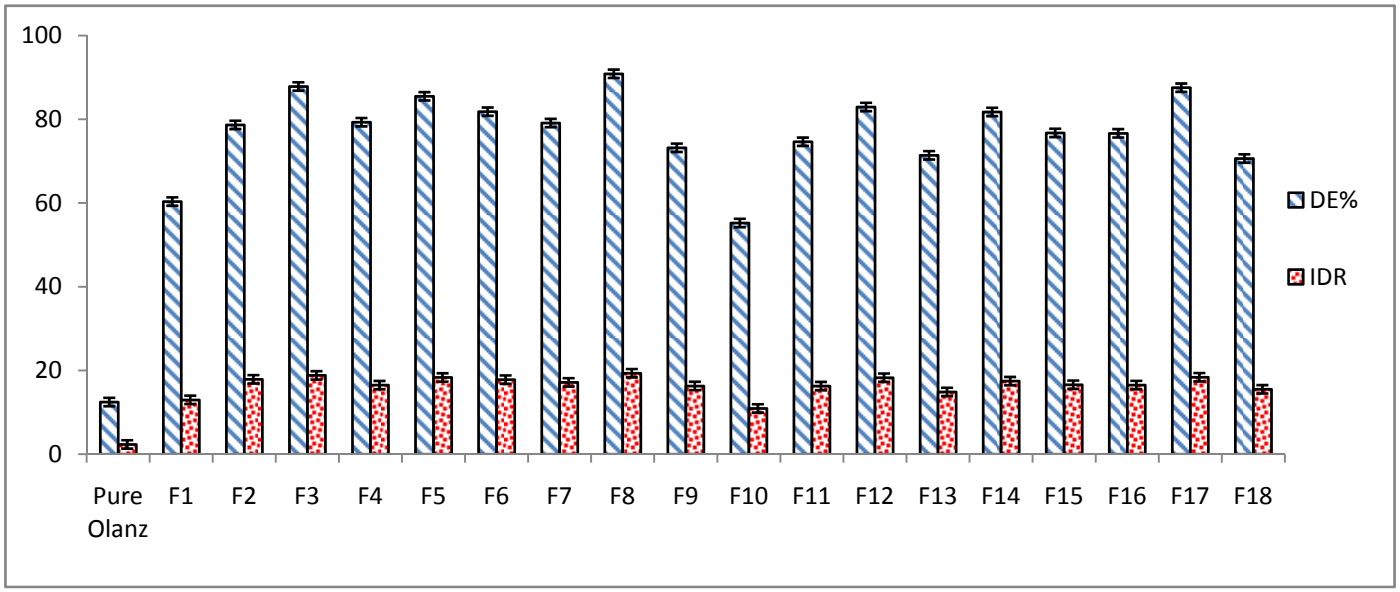

Figure. (10): Histogram of initial dissolution rate (IDR), and dissolution efficiency (DE %) of pure olanzapine (Olanz) and the FDT formulations

Stability of stored FDT tablets

Both formulations (F3 and F8) were physically stable regarding color and integrity and had only minor increases in disintegration time, drug content and friability after three months' storage.

Conclusion

From the dissolution data of all formulations developed, solubility of olanzapine, a poorly water soluble drug was enhanced by the co-amorphous dispersion technique using anhydrous ascorbic acid as a coformer. This effect may be due to formation of new phases between drug and the conformer through H-bonding, thus facilitate conversion of crystalline drug to flexible co-amorphous system characterized by enhanced solubility and percentage dissolution.

Finally, it could be concluded that using olanzapine-ascorbic acid co-amorphous system in a molar ratio 1:2 in FDT formulations in presence of a superdisintegrant resulted in fast disintegration time and rapid dissolution rate which are expected to increase oral bioavailability of olanzapine.

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References

[1]. Kouchak M and Atyabi F. Ion-exchange, an approach to prepare an oral floating drug delivery system for diclofenac. *Iran J. Pharm. Res.* 2004; 2: 93-97.

[2]. Garg G. Siddiqui M. and Sharma P. A short review on a novel approach in oral fast dissolving drug delivery system. Adv. Boil Res. 2011; 5(6): 291-303.

[3]. Deepak s, Dinesh K. Mankaran S. and Gurmeet S. Fast disintegrating tablets: a new era in novel drug delivery system and new market opportunities. Int J drug delivery. 2012; 2(3): 74-86.

[4]. Kaur S, Kumar S. and Gill B. Mouth dissolving tablet: a novel approach to drug delivery. Int J curr Pharm Res. 2011; 3(1): 1-7.

[5]. Gupta A. Recent trends of fast dissolving tablet- an overview of formulation technology. Int J pharm biol. 2010; 85: 28-35.

[6]. Kumar G. and Gauri S. Fast dissolving drug delivery and its technologies. The pharma innovation, 2012; 1: 32-7.

[7]. Wagh M, Kothawade D. and Salunkhe K. Techniques used in orally disintegrating drug delivery system. Int J drug delivery. 2011; 2(2): 27-31.

[8]. Firdous S, Aman T, and Alim UN. Determination of olanzapine by UV spectrophotometry and non-aqueous titration. J Chem Society of Pakistan 2005; 27(2):163-167.

[9]. Patel C, Sahoo U, Seth AK, Shah V, and Upadhyay U. Formulation and evaluation of solid dispersion of

olanzapine. Int J Pharm Sci. 2011; 1598-1605.

[10]. Ayala AP, Siesler HW, Boese R, Hoffmann GG, Polla GI, Vega DR. Solid state characterization of olanzapine polymorphs using vibrational spectroscopy. Int. J. Pharm., 2006; 326: 69-79.

[11]. Dinunzio JC, Willilams RO. CNS disorders – Current treatment options and the prospects for advanced therapies. Drug. Dev. Ind. Pharm., 2008, 34:1141-1167.

[12]. Venkateskumar KS, Verma PRP. Physicochemical characterization and in vitro dissolution behavior of olanzapine-mannitol solid dispersions. Braz J Pharm Sci. 2012; 48(2): 243-256.

[13]. VinayakMundhe SB, Arun K, Vilas AS Z . Formulation and Evaluation of Mouth Dissolving Tablet of Olanzapine by Coprocessing Superdisintegrants; Asian J of Pharm Tech & Innov. 2013; 01 (01): 01-20.

[14]. Vasconcelos T B, Sarmento and P. Costa, Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Disc Today. 2007; 12: 1068-1075.

[15]. Arora KK and Zaworotko MJ. Pharmaceutical co-crystals: A new opportunity in pharmaceutical science for a long-known but little studied class of compounds. Polym Pharm Solids. 2009; 2: 281-313.

[16]. Crowley KJ. and Zografi G. Cryogenic grinding of indomethacin polymorphs and solvates: assessment of amorphous phase formation and amorphous phase physical stability. J Pharm Sci. 2002; 91: 492-507.

[17]. Gagniere E, Mangin D, Veesler S, and Puel F. Co-crystallization in solution and scale up issues, In; Pharm salts co-crystals. (E.d, John Wouters, Luc Quere and David E. Thurston), Royal Society of Chemistry, London 2011, pp. 188-208.

[18]. Elbagerma MA, Edwards HGM, Munshi T, and Scowen IJ. Identification of a new co-crystal of salicylic acid and benzamide of pharmaceutical relevance. Anal Bioanal Chem. 2010; 397: 137-146.

[19]. Lemmerer A, Bernstein V, and Kahlenberg V. Hydrogen Bonding Patterns of the Co-Crystal Containing the Pharmaceutically Active Ingredient Isoniazid and Terephthalic Acid. J Chem Crystal. 2011; 41: 991-997.

[20]. Gao Y, Liao J, Qi X, and Zhang J. Coamorphous repaglinide-saccharin with enhanceddissolution. Int J Pharm. 2013; 450: 290-295.

[21]. Shayanfar A, Ghavimi H, Hamishekar H, and Jouyban A. Coamorphous atorvastatin calcium to improve its physicochemical and pharmacokinetic properties. J Pharm Pharmaceut Sci. 2013; 16: 577-587.

[22]. Lobmann K, Grohganz H, Laitinen R, Strachan C, and Rades T. Amino acids as co amorphous stabilizers for poorly water soluble drugs-Part 1: Preparation, stability and dissolution enhancement. Eu J Pharm Biopharm. 2013; 85: 873-881.

[23]. Ali AM, Ali AA, Maghrabi IA. Clozapine-carboxylic acid plasticized co-amorphous dispersions: Preparation, characterization and solution stability evaluation. Acta Pharm. 2015; 65(2):133-46. doi: 10.1515/acph-2015-0014.

[24]. Amir B, Fazal S, and Khalid R. Controlled release matrix tablets of olanzapine: Influence of polymers on the in-vitro release and bioavailability. AAPS. 2010; 11(3):1397-1404

[25]. AJIT SK, GHADGE DM, KOKATE PB. Formulation and In-vitro evaluation of orally disintegrating tablets of olanzapine-2-hydroxypropyl-β-cyclodextrin inclusion complex Iranian J. Pharm. Res., 2010., 9: 335-347.

[26]. Bandari S, Mittapalli R, Gannu R and Madhusudan Y. Orodispersible tablets: An overview. Asian J Pharm. 2008; 2(1): 2-11.