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Design of Zolmitriptan Liquisolid Orodispersible Tablets and Their *In Vitro* Evaluation

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ABSTRACT

The aim of the present work was to formulate Zolmitriptan as orodispersible tablets by liquisolid systems technique and to evaluate the possibility of enhancing the rate of drug dissolution and in vivo absorption by such formulation to enhance bioavailability, also the aim to improve patient compliance suffering from migraine attack. The drug was dissolved in non- volatile vehicle propylene glycol (PG) and its solution was converted into dry- looking powder using liquisolid systems technology. The drug solution was absorbed onto microcrystalline cellulose (carrier material) and any excess liquid was adsorbed by colloidal silicon dioxide (coating material). The appropriate amounts of the liquisolid system components were calculated by measuring the flow properties of the systems containing three different superdisintegrants namely; croscarmellose sodium, sodium starch glycolate and crospovidone, each one with three different concentrations (2.5, 5, 7.5 %). The flow properties were measured using the angle of repose and the compressibility index. FT-IR showed that, there was no interaction between drug and the excipients. Liquisolid powder formula with suitable flowability and compressibilty was compressed into tablets. The main physical properties of the prepared tablets were found to comply with the pharmacopoeial requirements. The in vitro dissolution rate of Zolmitriptan was found to be enhanced from the prepared liquisolid orodispersible tablets compared to that from direct compressed orodispersible tablets. On storage, no significant differences between freshly prepared and stored tablets was found.

Keywords: Orodispersible tablet; Zolmitriptan; Liquisolid technique; Loading factor

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INTRODUCTION

Many newly developed drugs are poorly water soluble compounds, which lead to problems in the development of dosage forms with sufficient bioavailability [1]. Solubility is the most important parameter to achieve the desired concentration of the drug in the systemic circulation for therapeutic response to be obtained [2]. The majority of the hydrophobic drugs are sparingly soluble, slightly soluble, very slightly soluble and practically insoluble drugs. For each drug substances mentioned above, the dissolution is the rate limiting step; so, the challenges for absorption of poorly water soluble drugs are to improve the dissolution rate. This lead to enhancement of the absorption and bioavailability of these drugs [3].

The term liquisolid systems (LS) refers to the powdered forms of liquid drugs formulated by changing liquid lipophilic drugs, drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile vehicle systems into dry, non-adherent, freely flowing and readily compressible powder mixtures by simple mixing with selected powder excipients known as the carrier and coating materials. Generally, microcrystalline cellulose (Avicel®) is utilized as the carrier material and amorphous silicon dioxide (colloidal silica) as a coating material [4].

Many patient groups like elderly, children and mentally retarded patients who are uncooperative, nauseated or on decreased liquid-intake/diets have difficulties in swallowing the solid dosage forms. Those who are traveling or have

little water access are evenly affected [5]. To accomplish these medical needs, pharmaceutical technologists have developed a patient-friendly novel oral dosage form known as "Orally Disintegrating Tablets (ODT)" which disintegrate fastly in saliva, usually within seconds, without needing for water. Drug dissolution, absorption, onset of therapeutic effect and drug bioavailability may be significantly better than those obtained from conventional dosage forms [6].

Zolmitriptan(4*S*)-4-[[3-[2-(dimethylamino)ethyl]-1Hindol-5-yl]methyl]oxazolidinone, is a white to almost white powder, slightly soluble in water. It has a pKa value of 9.6. The bioavailability of Zolmitriptan is about 40% from oral and nasal dosage forms and problem arises from its low water solubility and dissolution rate. Zolmitriptan used for patients with migraine attacks, with or without an aura, and cluster headaches. It acts selectively on serotonin (5-HT1B/1D) receptors. It is presently available as a conventional tablet, an oral disintegrating tablet and a nasal spray (2.5 mg and 5 mg per dose) [7,8]. Patients with migraine generally suffer from nausea and vomiting. Furthermore, in migraine attack there is delayed gastric emptying with a resulting delayed absorption during attacks; therefore, oral treatment could be inconvenient or could fail. Therefore, Zolmitriptan given as ODT might provide rapid-acting, non-invasive delivery system for anti-migraine drugs to enhance patient compliance [9].

EXPERMENTAL SECTION

Materials

Zolmitriptan Microcrystalline Celullose (Avicel PH-102), Silicon Dioxide (Aerosil 200), Croscarmellose sodium, Crospovidone, Sodium Starch Glycolate are obtained by Hangzhou Hyper Chemicals Limited, China. Propylene glycol (PG) was purchased from Fluka Chemi AG, Switzerland. Na saccharin, Vanillin, Disodium Hydrogen Orthophosphate and Potassium Dihydrogen Orthophosphate were purchased from BDH chemical LTD, UK.

Methods

Solubility studies:

Solubility studies of Zolmitriptan were carried out in PG, PEG 400 and Tween 80 to select the best non-volatile solvent for dissolving of Zolmitriptan in liquid vehicle. Also simulated gastric fluid (SGF), pH 1.2 and simulated intestinal fluid (SIF), pH 6.8 were utilized to study solubility behavior of Zolmitriptan. Saturated solutions were prepared by adding much of Zolmitriptan to the vehicles and shaking with the shaker for 48 hr with constant vibration. Then the solutions were filtered through a 0.45 mm millipore filter, diluted and analyzed by UV-spectrophotometer. The sample was analyzed in triplicate to calculate the solubility of Zolmitriptan [10].

Use of a mathematical model to design liquisolid systems: The formulation design of the liquisolid systems was done according to the mathematical model proposed by Spireas. In this study, propylene glycol (PG) was used as a liquid vehicle, Avicel PH-102 was used as carrier material and Aerosil 200 as coating material. According to this model, the carrier and coating powder can hold only definite amount of the liquid while maintaining sufficient flowability and compactibility.

Firstly, the liquid loading factor (Lf) is defined as the ratio of the weight of liquid medication (W) to the weight of the carrier material (Q) in the formulation. This ratio can be correlated with the flow and the compression properties of the liquisolid system. The liquid loading factor (Lf) can be calculated using the following equation:

$Lf = W / Q$ - - - - -(1)

Secondly, the excipient ratio (R value) of the powder is defined as,

$R = Q / q$ - - - - -(2)

Where R: Ratio of the weight of carrier (Q) and coating (q) materials present in the formulation.

It can also be calculated from the following equation:

$L f = \Phi Cr + \Phi Co\ (1/ R)$ - - - - -(3)

Where Φ Cr, Φ Co are the flowable liquid retention potentials (Φ – values) of Carrier (Avicel PH-102) and Aerosil 200, respectively.

The flowable liquid retention potentials (Φ – values) of powder ingredient were used to calculate the required excipients quantities [11.12].

Formulation of the liquisolid oral dispersible tablet of Zolmitriptan (ODTs)

Eleven liquisolid ODTs batches of Zolmitriptan (denoted as F1 to F11) were prepared by direct compression technique as shown in table (1). The effect of different types and concentrations of the superdisintegrants on the physical properties of Zolmitriptan liquisolid orodispersible tablets (ODTs) was studied by utilizing formulas F1-F9 that contain croscarmellose (CSS), sodium starch glycolate (SSG) and crospovidone (CP), at three levels

concentrations (2.5 %, 5% and 7.5%) of total tablet weight. The load factor was kept constant in the above formulas which equal to 0.25, this loading factor was decreased to 50% from its original value in formula F10 to become 0.175, while in formula F11, the loading factor 0.25 was decreased to 100% to become 0.125. This change in the loading factor was done to study this effect on the physical properties and dissolution behavior of the prepared ODTs of Zolmitriptan. Liquisolid systems were prepared at a ratio of 35: 1 (trial and error methods were used, i**.** e. changing the carrier***:*** coating material ratio (R) from 10, 15, 20, 25, 30 and 35:1 until get good result (flow properties) is obtained. R 35:1 was used in all formulations since it gave the optimal flow property**.** Firstly, a mathematically calculated quantity of pure drug based on the equations shown in the above pages was weighted in 20 ml glass beaker and then the calculated weight of non-volatile solvent (PG) was added, heated to 60 ̊C in sonicater for 15 minutes until homogenous drug solution of the liquid medication was achieved. After that, the obtained liquid medication (drug and solvent) was incorporated into the calculated quantity (Q) of the carrier material (Avicel PH-102) and (q) coat material (Aerosil 200) and the resulting blend was mixed thoroughly in mortar and pestle. Vanillin was used as flavoring agent and sodium saccharin as sweetener. The blend was mixed with superdisintegrant and other additives. Finally the final blend was lubricated with 1% magnesium stearate to be compressed into cylindrical tablet using single punch tablet machine of 6 and 8mm die size [13].

Preparation of directly compressible ODTs (DCT)

A conventional ODTs formulation of Zolmitriptan was prepared by utilizing drug, carrier, coating material, superdisintegrant and lubricant (without addition of any non-volatile liquid solvent). This formulation was denoted as directly compressed tablets (DCT-ODT) and each tablet contains 2.5 mg Zolmitriptan, 221.2mg of Avicel PH 102, 6.31mg of Aerosil200, 12.5mg of crospovidone and 2.5mg of magnesium stearate, sodium saccharin and vanillin, respectively. Zolmitriptan conventional ODTs were produced by mixing the drug with Avicel PH-102 and Aerosil 200 (ratio of Avicel PH-102 to Aerosil 200 was set at 35:1) for a period of 10 min. The blend was mixed with crospovidone (as disintegrating agent) and other additives for 10 min then magnesium stearate was added and mixed for 2 minutes. After that, the final mixture was directly compressed using a single punch-tableting machine 8mm die size [14].

Table 1: Composition of different zolmitriptan liquisolid ODTs formulas

Formula No./ Material (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	DCT
Zolmitriptan	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
PG	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	
CSS	3.5	7	10.5									
	2.50%	5%	7.50%									
SSG				3.5	7	10.5						
				2.50%	5%	7.50%						
CP							3.5	7	10.5	9.3	12.5	12.5
							2.50%	5%	7.50%	5%	5%	5%
Avicel PH-102	104.5	101	97.5	104.5	101	97.5	104.5	101	97.5	142.1	199.5	221.2
Aerosil 200	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	4	5.5	6.31
Na saccharin -1%	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.86	2.5	2.5
Vanillin -1%	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.86	2.5	2.5
Mg stearate -1%	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.86	2.5	2.5
Total weight	140	140	140	140	140	140	140	140	140	186	250	250

Pre-compression evaluation of zolmitriptan liquisolid ODTS:

Determination of the angle of repose: One of the methods for measuring flow properties of powder is the angle of repose. The angle of repose for liquisolid system powder was determined using fixed funnel method. It can easily be determined by permitting a powder to flow through a funnel and pass freely onto a surface. The angle of repose was calculated based on the height and diameter of the resultant cone using this equation:

$\tan(\theta) = h/r$ - - - - - (4)

Where, h: height of the powder cone, r: radius of the powder cone [15].

Determination of compressibility carr's index: The powder mixture was poured in a measuring glass cylinder, the untapped volume (V_0) was determined, then the tapped volume (V_f) was measured after successive 100 tap cycles until the volume became constant [16].

The Carr's index was determined by the equation :
Carr's Index=$(V_0-V_f)/V_0.100$- - - - - (5)

Post-compression evaluation of zolmitriptan liquisolid ODTs:
Hardness test: A hardness tester apparatus (Monsanto) was used to determine the tablet hardness. Three tablets were randomly selected from each batch of ODTs tablets for determination of hardness. The mean of three determinations ± SD was recorded. The hardness was expressed as a force in kg/cm2 required to crush the tablets [17].

Friability test: Friability test was performed to evaluate the effect of friction and shocks, which may often cause tablets to chip, cap or break. Roche friabilator apparatus was used for this purpose. It is expressed as a percentage (%). Ten tablets were initially weighed (W initial) and put in the friabilator. The friabilator was operated at up to 100 revolutions. The tablets were weighed again (W final). The percentage friability was then calculated using the following equation:
% Friability = {(W initial- W final) / W initial} x 100 % - - - - (6)
Friability of tablets less than 1% are considered acceptable [18].

Content uniformity test: Ten tablets from each batch were grounded in mortar to a fine powder then powder mass equivalent to 2.5 mg of Zolmitriptan was transfered into 100 ml volumetric flask, then the volume was completed to 100 ml with phosphate buffer (pH 6.8). The solution was sonicated and shaken intermittently for 1 hr sonication and filtered. After desired dilution, the solution was analyzed for drug content at λ max 222 nm with UV-Visible spectrophotometer using phosphate buffer (pH 6.8) as blank [19].

Wetting time test: The wetting time of tablets were measured using a simple procedure. A piece of sponge (0.5 cm thickness) was placed in a small petridish (internal diameter =12 cm) containing 10 ml of artificial saliva containing methylen blue (a water soluble dye). The dye solution is utilized to recognize the complete wetting of the tablet surface. The method was performed by maintaining artificial saliva at 37 ºC. A tablet was placed on the sponge surface carefully and the time required for the complete wetting of the tablet was recorded as a wetting time as shown in figure (1). The mean of three determinations was used ± SD. The artificial saliva used was composed of NaCl (8g/L), KH_2PO_4 (0.19g/L) and Na_2HPO_4 (2.38g/L) [20].

Figure 1: Wetting time test performed on the prepared ODTs of Zolmitriptan

***In-Vitro* disintegration time test:**
One of the most important characteristics of the ODT is the disintegration time in the oral cavity; yet, the disintegration time of ODTs is measured using the conventional tests (for tablets) that were described in the Pharmacopoeias. However, it is hard to determine the disintegration time for the ODT with these tests due to its rapid disintegration rate even in a small amount of water. Further, the conventional tests use a volume of 800-900 ml of the test solution compared to the volume of saliva in humans, which is less than 6 ml. Thus, the disintegration time obtained from the conventional disintegration tests show not to be reflective of the disintegration time in the human mouth. To overcome this problem, A new modified apparatus represented as a suitable method to determine the disintegration time of ODTs was developed. A modified apparatus figure (2) consisting of a glass beaker of 10 ml capacity contained 6 ml of salivary phosphate buffer pH 6.8 as a disintegration medium was placed on the magnetic stirrer. A very small magnetic bead was put at the bottom of a beaker and temperature was maintained at 37 ± 2 ^{0}C. Disintegration time was determined at 50 rpm. The disintegration test was performed on six tablets [21,22].

Figure 2: Modified disintegration test apparatus used to determine the disintegration time of the prepared ODTs of Zolmitriptan

***In-Vitro* dissolution studies of zolmitriptan liquisolid ODTs**:

The release profile of selected formula of Zolmitriptan liquisolid orodispersible tablets was performed in 500 ml phosphate buffer pH 6.8 maintained at 37 ± 0.5 ^{0}C using the USP Dissolution Tester Apparatus II, at a rotation speed of 50 rpm. Also dissolution study was performed for DCT-ODT. Aliquots from the dissolution medium (5ml) were withdrawn at 1, 2, 3,4, 5, 6, 7, 8, 9, 10, 12.5, 15, 20, 25 and 30 min time intervals. The samples were replaced with fresh dissolution medium of same quantity in order to maintain the volume in the vessels constant. Samples were filtered using 0.45 millipore filter and drug content was determined spectrophotometrically at λ max 222 nm. The percentage of drug dissolved in 2 minutes (D_{2min}) and the time required for 80% of drug to be released ($T_{80\%}$) were considered for comparing the dissolution results for the prepared Zolmitriptan liquisolid ODTs formula and DCT-ODT. Each preparation was tested in triplicate and the mean value was calculated [23].

Fourier transform infrared spectroscopy (FTIR): This study was achieved to identify any sign of complexation and interaction between Zolmitriptan and other excipients used in the preparation of Zolmitriptan liquisolid ODTs. The samples are grinded and mixed with potassium bromide. The spectrum was obtained between the wave number of 4000-400 cm^{-1}.

Accelerated stability study (effect of humidity): The stability study was done for the best formula. The tablets were stored at 40 ^{0}C /75 ± 5 % RH using stability chamber for duration of four months. After an interval of four months, samples were withdrawn and tested for various physical tests (wetting time, hardness, friability, disintegration time and uniformity of dosage unit tests) and drug release study [24].

Statistical analysis: The results of the experiments were presented as a mean of triplicate samples ± standard deviation, and analyzed by one-way analysis of variance (ANOVA) at the level of ($P < 0.05$).

RESULTS AND DISCUSSION

The solubility of Zolmitriptan in various solvents is given in table (2). The table shows that the solubility of Zolmitriptan was increased with decreasing pH; this is because that Zolmitriptan is a basic drug with a pK of 9.6 (i.e Zolmitriptan become ionized by decreasing pH). The table shows that the solubility of Zolmitriptan was markedly ($P < 0.05$) increased in the presence of PG, because PG (an alcoholic compound) might exhibit hydrogen bonding due to the presence of hydroxyl groups, furthermore, PG has a low viscosity (48 mPa s) and molecular weight (76.1g/mol), compared to tween 80 that has high viscosity (425 mPa s) and molecular weight (1310 g/mol) [25,26].

Table 2: Solubility of Zolmitriptan in various solvents

Solvents	Solubility (%w/w) Mean ± S.D*
Distiled water	0.122 ± 0.0546
(0.1 N HCl)	1.873 ± 0.1162
(phosphate buffer pH 6.8)	0.235 ± 0.0972
Propylene glycol PG	7.721 ± 0.6553
PEG 400	0.737 ± 0.0475
Tween 80	0.132 ± 0.0126

*S.D. standard deviation from mean. n=3

Application of new mathematical model for design of liquisolid systems

The values of the flowable liquid retention potentials for Avicel PH-102 and Aerosil 200 in PG were (0.16) and (3.33), respectively [11,12]. The loading factor (Lf) was calculated from the following equation:

Lf =0.16 +3.31 (1/R) for PG - - - - -(7)

The optimal R-value was 35:1, the corresponding optimal liquid load factor of a given excipients ratio was calculated and it was equal to 0.25, A reasonable flow was achieved when the liquid load factors (Lf) equal to or lower than 0.25, this is in agreement with what was stated in literature that it is hard to prepare formulation with good flowability and compactability when loading factor is above 0.25, because fewer amounts of carrier and coating materials are used during preparation of these formulations, and excess liquid is not completely adsorbed, leading to the formation of agglomerates [27].

Based on the value of W (liquid medication), the amount of carrier material can be calculated according to equation (1), and then the amount of coating material can be calculated by applying equation (2).

Precompression studies of the prepared liquisolid orodispersible powder system

The data obtained for pre-compression parameters for formulas F1-F11 and DCT such as carr's index and angle of repose are shown in table (3) and were within acceptable limits according to USP [28].

Table 3: Angle of repose and carr's index of powder formulas according to USP

Formula no.	Angle of repose*	Carr's index*	Flow-compression character
1	33.4±0.22	19.6±0.47	Good to fair
2	34.6±1.78	18.4±0.79	Good to fair
3	34.7±1.94	19.4±0.85	Good to fair
4	33.6±0.70	18.8±1.62	Good to fair
5	33.1±2.06	16.7±1.42	Good to fair
6	32.3±0.55	16.6±2.12	Good to fair
7	30.0±0.69	15.7±2.39	Excellent to Good
8	30.1±0.65	14.3±0.56	Excellent to Good
9	29.7±0.47	12.6±0.91	Excellent to Good
10	27.5±0.87	14.3±0.94	Excellent to Good
11	25.1±1.80	15.1±0.91	Excellent to Good
DCT	32.4±0.57	19.2±0.219	Good to Fair

*S.D. standard deviation from mean. n=3.

Post-compression evaluation of Zolmitriptan liquisolid ODTs: **hardness, friability, and content uniformity**

Post-compression parameters like hardness, friability and content uniformity were mentioned in table (4). The tablets measured hardness was found to be in the range of 3.03 to 4.75 kg/cm2. The percentage of friability was less than 1% for all formulations ensuring optimum mechanical stability of the formulated tablets. The percentage of the drug content for the all formulas was found in the range of 97.4-100.6% which complies with the USP limits [28].

Table 4: Hardness, friability, content uniformity percentage, wetting time and disintegration time of Zolmitriptan liquisolid orodespersible tablets

Formula code	Hardness (Kg/cm2) mean ± S.D, n=3	% Friability (w/w) Mean, n=10	% Content uniformity mean ± S.D, n=10	Wetting time mean(sec.) ± S.D, n=3	Disintegration time mean(sec.) ± S.D, n=6
F1	4.20 ± 0.20	0.72	99.4 ± 2.07	288 ± 7.45	185 ± 9.87
F2	4.13 ± 0.05	0.86	98.6 ±3.20	253± 5.54	201± 7.52
F3	3.90± 0.26	0.46	99.6 ±4.15	217±8.61	221± 7.78
F4	3.70 ± 0.17	0.4	100.2±2.16	246 ±7.57	126 ± 5.62
F5	3.36 ± 0.11	0.89	97.8±2.68	207± 5.72	101± 3.09
F6	3.03± 0.15	0.73	100.6±2.70	167 ± 9.45	118± 5.33
F7	4.00 ± 0.00	0.21	97.4±3.50	76 ± 3.31	79± 2.40
F8	4.23 ± 0.20	0.75	100.8±0.83	68 ±3.12	48± 1.63
F9	4.75 ± 0.25	0.28	99.8±3.91	53 ±5.34	61± 3.73
F10	4.10 ± 0.42	0.7	98.8±2.38	54 ± 2.74	33± 2.43
F11	4.11 ± 0.39	0.35	100.2±1.30	40 ± 1.41	24± 1.53
DCT	4.29 ± 0.29	0.66	100.2±2.23	71 ±2.37	44± 3.17

Wetting time (WT) and In-Vitro disintegration time (DT)

The wetting and disintegration behaviour of the prepared Zolmitriptan liquisolid orodispersible tablets in salivary phosphate buffer pH 6.8 was shown in table (4). It was observed that the WT and DT for F1-F9 formulas were influenced by the type and concentration of superdisintegrant (Figure 3). Table (4) shows that the best super

disintegrant type was CP compared to the other superdisintegrants CSS and SSG, this is due to the fact that CP rapidly wicks water into the tablet to create the volume expansion and hydrostatic pressure required to provide rapid disintegration. The results are in agreement with those reported in literature [29]. Concerning the concentration of the superdisintegrant, a rational concentration should be utilised in the formulation of ODTs, because increasing concentration over an optimum one lead to an increase in the DT of the tablet. From data in table (4), as the concentration of the superdisintegrant increase, the DT was increased. This increase in DT was more marked in formulas F3, F6 and less in F9. The reason behind this increase may be due to the formation of viscous gel layer on the surface of the tablet which prevents the penetration of water to the core of the tablet especially for superdisintegrant CSS and SSG [30], as shown in figure (4). More gel was formed with CCS than SSG that makes DT of tablets with CCS more than SSG (DT of tablets prepared with CCS 7.5% (F3) and SSG 7.5% (F6) were 221 and 118 seconds, respectively). In contrast, CP has less tendency to gelling [29]. In F9 which contains 7.5% CP there is a slight increase in DT, because quick expansion of the largest capillaries isolates other areas of fine pores structure in which air cannot escape. These areas make no role to the overall uptake of liquid [31]. Moreover, it can be concluded that as the concentration of the superdisintegrant increase, the WT decrease steadly. The formulas F10 and F11 were prepared with different loading factors 0.175 and 0.125, respectively; and their WT and DT were compared to formula F8 with loading factor 0.25. From the results shown in table (4), a significant ($p<0.05$) decrease in the WT and DT was seen as the loading factor decrease as in figure (5), this is due to that as the loading factor decrease, the amount of Avicel PH-102 will increase, according to the equation Lf=W/Q, where Q is the weight of Avicel PH-102. Microcrystalline cellulose (Avicel PH-102) has a very high intraparticle porosity. This high porosity support swelling and disintegration of ODTs, due to the penetration of water into the hydrophilic tablet matrix by capillary action which generate pressure for fast and complete disintegration of the tablets. So microcrystalline cellulose acts as auxiliary tablet disintegrant because of its high water absorption capacity [32].

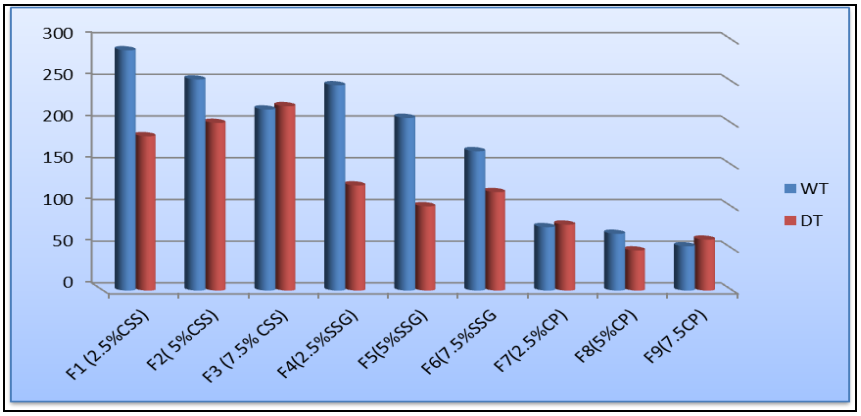

Figure 3: Effect of superdisintegrant type and concentrations on the WT and DT of Zolmitriptan liquisolid orodispersible tablet

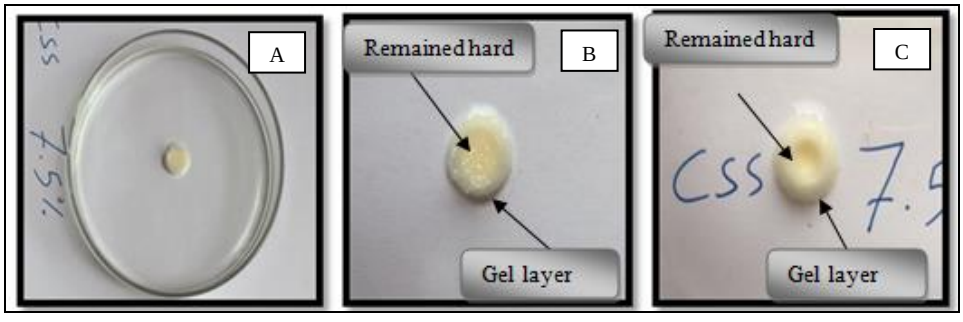

Figure 4: The process of disintegration time test for F3 with 7.5% croscarmellose sodium as superdisintegrant: (A) beginning (B) at 30th second and (C) at 60th second

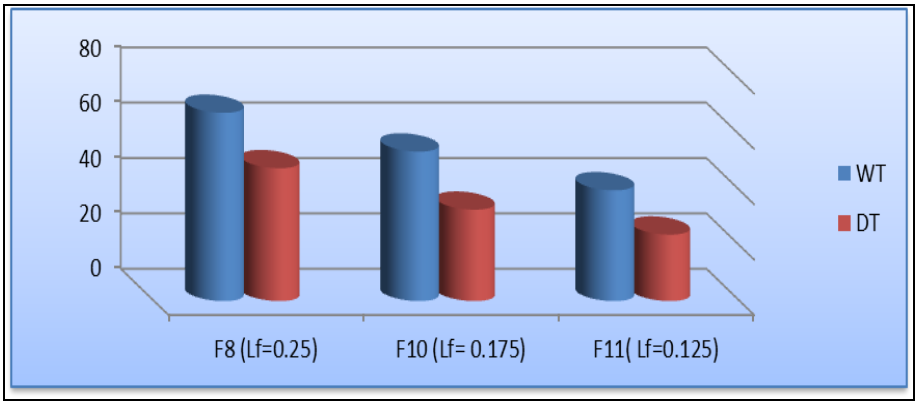

Figure 5: Effect of the decreasing loading factor on the WT and DT of Zolmitriptan liquisolid orodispersible tablets

The disintegration time and wetting time of DCT orodispersible tablet of Zolmitriptan were compared to F11. The results showed that F11 had significantly ($p<0.05$) lower WT and DT compared to DCT formula [table (5), figure (6)]. This is due to that solubilization of the drug in nonvolatile liquid by liquisolid technique results in enhancing the wettability of the formulation (F11) compared to the DCT orodispersible tablet of Zolmitriptan [33]. From result shown in table (4), it can be concluded that formula F11 complies with USP specification of the disintegration time which is less than 30 seconds [28].

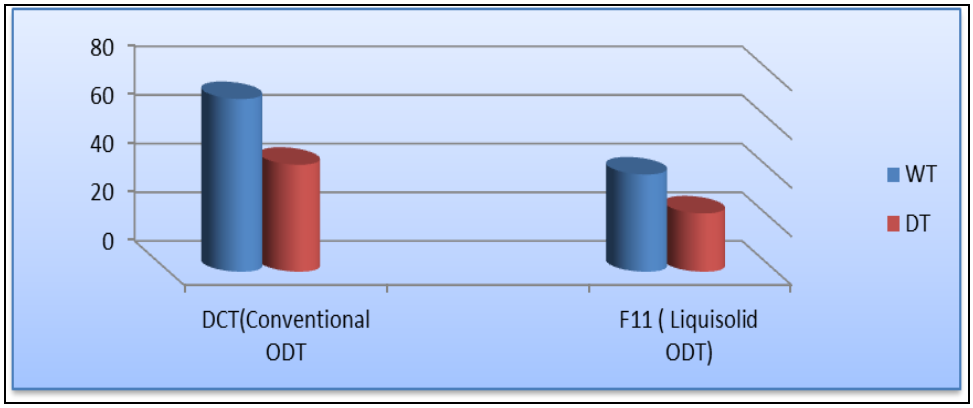

Figure 6: Difference in WT and DT between F11 and DCT ODT of Zolmitriptan

In-Vitro dissolution Studies

The liquisolid ODTs of Zolmitriptan F11 was the best formula among all the formulas of the liquisolid ODTs tablets; in terms of rapid disintegration and acceptable tablet properties**.** The dissolution of the Zolmitriptan from formula F11 was compared to the DCT-ODTs of Zolmitriptan as in figure (7). From the data in table (5), it was found that F11 showed significant ($p<0.05$) faster dissolution compared to DCT-ODTs of Zolmitriptan, this attributed to the fact that Zolmitriptan is already in solution form in PG, at the same time, it is hold by the powder particles (Avicel PH-102 and Aerosil 200). When the drug within the liquisolid system is completely dissolved in the liquid vehicle, it is located in the powder substrate still in a solubilized state. The accelerated release in Zolmitriptan liquisolid ODTs (F11) is due to its markedly increased wettability and surface area available to the dissolution medium [34].

Table 5: In Vitro dissolution parameters of the liquisolid ODTs of Zolmitriptan and DCT-ODT in phosphate buffer pH 6.8 at 37°C

Formula Code	D_2 min (%)*	$T_{80\%}$ (min)*
F11	87.59	1.84
DCT	29.41	7.52

* Results are expressed as mean, (n=3)

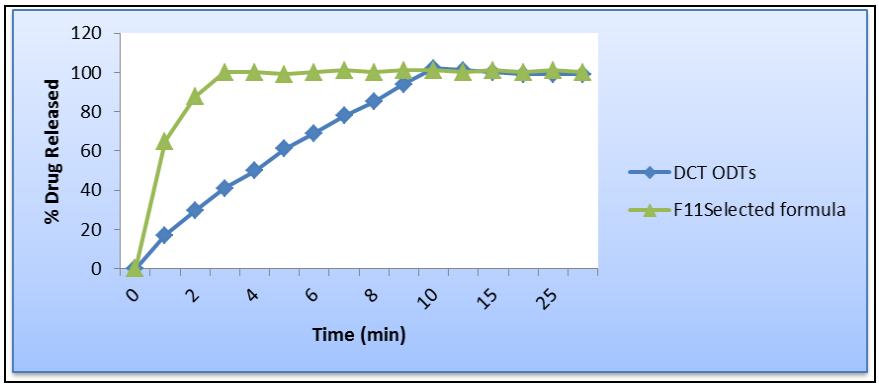

Figure 7: A comparison in the dissolution profile of the prepared Zolmitriptan liquisolid ODTs (F11) and DCT-ODT in phosphate buffer pH 6.8 at 37°C. (Results are expressed as mean, n=3)

Compatibility studies

FTIR of Zolmitriptan showed three main characteristic absorption bands of strong absorbance at 1738 cm^{-1} due to C = O stretching vibrations of amino ester functional group OCONHR , N-H stretching band of secondary and tertiary amine appears at 3350 cm^{-1} as a single sharp band and C-O (stretching) of ester group[22] at 1252 cm^{-1} as in figure (8). It was noted that the peaks of major functional groups of Zolmitriptan, which are present in spectrum of pure drug, were present in Zolmitriptan liquisolid formula figure (9) (C = O stretching vibrations and C-O stretching of ester group except N-H stretching of pure drug at 3350 cm^{-1} was overshadow with OH stretching of Avicel PH-102 this due to the amount of the drug is too low compared to Avicel PH-102 (the ratio of the drug : Avicel PH-102 was 1:80 in the selected formula F18, also might be attributed to the formation of hydrogen bonding between the drug and liquid vehicle; this indicated lack the possibility of interaction between Zolmitriptan and polymers used in the preparation of the liquisolid orodispersible tablets.

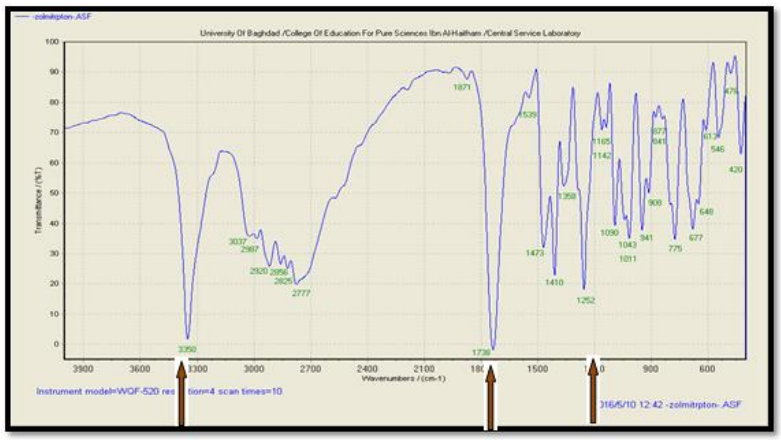

Figure 8: FTIR spectrum of Pure Zolmitriptan

Accelerated stability Study (Effect of humidity)

Stability studies of the selected formula (F11) showed no significant difference ($p>0.05$) in tablet hardness, % friability, drug content, disintegration time, wetting time and release profile after storage at 40±2°C /75 ±5% RH for duration of four months.

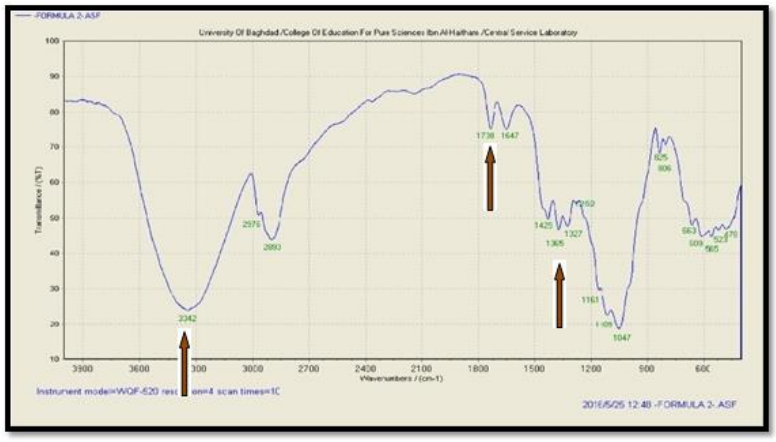

Figure 9: FTIR Spectrum of the liquisolid formula F11

CONCLUSION

The orodispersible tablets of Zolmitriptan were prepared by liquisolid technique method using different superdisintegrant such as crospovidone, sodium starch glycolate, and croscarmellose sodium. Among all superdisintegrant, formulation containing crospovidone as superdisintegrant is fulfilling all the parameters satisfactorily compared to other superdisintegrant. The relative efficiency of these superdisintegrant to improve the disintegration time in order of crospovidon > sodium starch glycolate > croscarmellose sodiume. In vitro release studies revealed that almost 95.2% drug was released from the formulation were within 2 min. The physicochemical properties and stability of the prepared liquisolid tablets were satisfactory. This study indicates the possibility of using the selected best formula (F11) in the preparation of Zolmitriptan orodispersible tablet for oral administration because of desired properties of the prepared tablets concerning sufficient hardness, low friability, fast disintegration and dissolution.

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