Research Article

Formulation and Optimization of Orodispersible Tablets of Diazepam

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Abstract. Diazepam is one of the most prescribed benzodiazepines. The purpose of the present research was to optimize the formulation of orodispersible tablets of diazepam. Orodispersible tablets of diazepam were prepared using different types of superdisintegrants (Ac-Di-Sol, sodium starch glycolate, and crospovidone (CP)) and different types of subliming agents (camphor and ammonium bicarbonate (AB)) at different concentrations and two methods of tablets preparations (wet granulation and direct compression methods). The formulations were evaluated for flow properties, wetting time, hardness, friability, content uniformity, *in vivo* disintegration time (DT), release profiles, and buccal absorption tests. All formulations showed satisfactory mechanical strength except formula F5 which contains camphor and formula F9 which is prepared by direct compression method. The results revealed that the tablets containing CP as a superdisintegrant have good dissolution profile with shortest DT. The optimized formula F7 is prepared using 10% CP as a superdisintegrant and 20% AB as a subliming agent by wet granulation method which shows the shortest DT and good dissolution profile with acceptable stability. This study helps in revealing the effect of formulation processing variables on tablet properties. It can be concluded that the orodispersible tablets of diazepam with better biopharmaceutical properties than conventional tablets could be obtained using formula F7.

KEY WORDS: ammonium bicarbonate; crospovidone; diazepam; orodispersible tablet; sublimation.

INTRODUCTION

Many patients of different age groups complain of some solid conventional dosage forms such as tablets and capsules due to difficulty in swallowing (1). In order to solve this problem and improve patient acceptance and compliance, the development of solid dosage forms that disintegrate rapidly or dissolve even when taken orally without water is being undertaken.

Oral fast-disintegrating dosage forms (tablet or a capsule) are a relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form (2) into a solution or suspension in the mouth without the need for water (3). The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50 s after administration (4). The solution containing the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect.

Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing (5). Orally disintegrating tablets are also called as orodisprsible tablets, quick-disintegrating tablets, mouth-dissolving tablets, fast-disintegrating tablets, fast-dissolving tablets, rapid-dissolving tablets, porous tablets, and rapimelts. However, of all the above terms, the United States

Pharmacopoeia (USP) approved these dosage forms as orodispersible tablets (ODTs). Recently, the European Pharmacopoeia has used the term orodispersible tablets for tablets that disperse readily and within 3 min in the mouth before swallowing.

The United States Food and Drug Administration defines ODT as "a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute (6).

In addition to children and the elderly who either experience difficulty and cannot swallow or have not learnt how to swallow the conventional solid dosage forms, the target groups for ODTs include institutionalized psychiatric patients as well as hospitalized or bedridden patients suffering from a variety of disorders such as stroke, thyroid disorders, Parkinson's disease, and other neurological disorders such as multiple sclerosis and cerebral palsy (7).

Other advantages of ODTs that have been investigated are their potential to increase the bioavailability of poorly water-soluble drug through enhancing the dissolution profile of the drug (8). Moreover, pharmaceutical companies also have commercial reasons for formulating ODTs. As a drug reaches the end of its patent, the development and formulation of the drug into new dosage forms allow pharmaceutical companies to extend the patent life and "market exclusivity" (9).

The ODTs could be prepared using various techniques such as tablet molding, spray drying, sublimation, lyophilization, solid dispersion, or addition of disintegrants (10–13).

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The basic approach to the development of ODTs is the use of superdisintegrants such as croscarmellose sodium and sodium starch glycolate. Another approach used in developing ODTs is maximizing the pore structure of the tablet matrix. Freeze drying and vacuum drying techniques have been tried by researchers to maximize the pore structure of the tablet matrix (14–16). However, freeze drying is cumbersome and yields a fragile and hygroscopic product. Vacuum drying along with the sublimation of volatilizable ingredient has been employed to increase tablet porosity. While in designing dispersible tablets, it is possible to achieve effective taste masking as well as a pleasant feel in the mouth. The main criterion for ODTs is the ability to disintegrate or dissolve rapidly in saliva of the oral cavity in 15 to 60 s and have a pleasant mouth feel (17).

Diazepam is an important member of the group of 1,4-benzodiazepine derivatives (Fig. 1); it is a colorless to light yellow crystalline compound insoluble in water. Diazepam exerts anxiolytic, sedative, muscle-relaxant, anticonvulsant, and amnestic effects (18). After oral administration, more than 90% of diazepam is absorbed, and the average time to achieve peak plasma concentrations is 1–1.5 h with a range of 0.25 to 2.5 h. The aim of this study was to prepare diazepam ODTs through studying the effects of formulation processing variables on the properties of tablets.
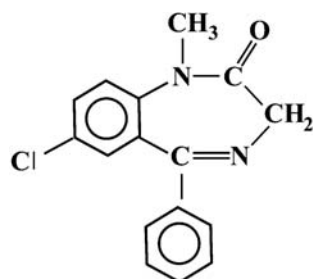
MATERIALS AND METHODS

Materials

Diazepam (DZ) pure powder and sodium starch glycolate-USP 26-NF2**1** (SSG) were supplied by Samara Drug Industries (SDI), Iraq. Crospovidone, Ac-Di-Sol, and mannitol USP grade were supplied by Dar Al Dawa Pharmaceutical Manufacturing Co., Jordan. Cab-O-Sil was purchased from (Sigma-Aldrich, Germany). Ammonium bicarbonate (AB), talc, and Mg stearate were purchased from (BDH, England). Diazepam tablets (10 mg) are from Roche®. All other ingredients used were of pharmaceutical grade.

Methods

Formulation of Orodispersible Tablets of Diazepam

The orodispersible tablets of DZ were prepared using superdisintegrant (SSG, Ac-Di-Sol, and crospovidone), subliming agent (AB, camphor), mannitol as a diluent, sodium saccharin as sweetening agent, alcoholic solution of polyvinylpyrrolidone (PVP) in ethanol (10%, *w/v*) as binder and

Chemical formula	$C_{16}H_{13}ClN_2O$
Molecular weight	284.7
Melting point	131 - 134°C
pKa	3.4
Solubility	0.05 mg/ml

Fig. 1. Diazepam chemical structure

cab-o-sil, talc with magnesium stearate, as a flow promoter (Table I). The drug and other ingredients were mixed together, and a specified volume of alcoholic solution of PVP (10%, *w/v*) was added and mixed to form a coherent mass (except for F9, the binder was added as dry powder). The wet mass was granulated using sieve no. 10 and dried in a tray dryer at 65°C for 10 min then screened through sieve no. 18. The dried granules were then blended in a tumbling cylindrical blender with cab-o-sil, talc, and magnesium stearate and compressed into tablets using a 7.6-mm punch single-tablet machine (Manesty Type F, Liverpool, England). Tablets from formulations F4 to F9 containing subliming agent were further dried at 80°C until they reached constant weight (19).

Evaluation of the Prepared Granules

Angle of Repose. The angle of repose was measured by passing the prepared granules through a sintered glass funnel of internal diameter 27 mm on the horizontal surface. The height (*h*) of the heap formed was measured with a cathetometer, and the radius (*r*) of the cone base was also determined. The angle of repose (Φ) was calculated from Eq. 1 (20):

$$\text{Tan } \Phi = h/r. \qquad (1)$$

Compressibility (Carr's) Index. An accurate weight of formula granules was poured into a volumetric cylinder to occupy a volume (V_0) and then subjected to a standard tapping procedure onto a solid surface until a constant volume was achieved (V_f). The Carr's index was calculated using Eq. 2. (20):

$$\text{Compressiblity index} = 100 \times \frac{V_0 - V_f}{V_0}. \qquad (2)$$

Evaluation of the Prepared Orodispersible Diazepam Tablets

Weight Variation. Randomly, 20 tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±7.5%.

Uniformity of Content. The content of diazepam was determined according to the method described by BP for diazepam tablets. In brief, 1 ml of water was added to one diazepam tablet, stood for 15 min, then 80 ml of a 0.5% (*w/v*) solution of sulfuric acid in methanol. The obtained solution was stirred for 15 min and the volume was adjusted to 100 ml with 0.5% (*w/v*) solution of sulfuric acid in methanol. The filtrated solution was diluted appropriately and the drug content was measured spectrophotometrically at 284 nm (Carry UV–visible spectrophotometer) (20).

Wetting Time. A piece of tissue paper (12×10.75 cm) folded twice was placed in a Petri dish (internal diameter=9 cm) containing 10 ml of buffer solution simulating saliva, pH 6.8, and amaranth. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was recorded (21).

Table I. Composition of Different Batches of ODTs of Diazepam

Formulation ingredients (mg)	Formula no.								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diazepam	10	10	10	10	10	10	10	10	10
Sodium starch glycolate	18 (10%)								
Ac-Di-Sol		18 (10%)							
Crospovidone			18 (10%)	18 (10%)	18 (10%)	18 (10%)	18 (10%)		18 (10%)
Ammonium bicarbonate				18 (10%)		27 (15%)	36 (20%)	36 (20%)	18 (10%)
Camphor					18 (10%)				
Sodium saccharin	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Cab-o-sil	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Talc	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
Magnesium stearate	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Mannitol Q.S to	180	180	180	180	180	180	180	180	180

Hardness. The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading ± SD was recorded.

Friability. Twenty tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted, and reweighed. The percentage friability of the tablets was calculated using Eq. 3 (22):

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100.$$

(3)

In Vivo Disintegration Time. Six healthy human volunteers were selected and their written consent was obtained. Each volunteer randomly took one tablet and kept on the tongue. The time taken for complete disintegration of the tablet on the tongue was noted. It is expressed in seconds. Before the test, mouth was washed with distilled water. Three trials were performed with 10-day interval between trials (23).

Dissolution Studies. In vitro dissolution studies were performed using type II (paddle) dissolution apparatus (Copley, UK) at 100 rpm, and 900 ml of phosphate buffer (pH 6.8) was used as a dissolution medium. Temperature of dissolution medium was maintained at 37±0.5°C. Five milliliters aliquot of the dissolution medium was withdrawn at specific time intervals. Absorption of filtered solution was measured by UV–visible spectrophotometer at λ=230 nm, and the percent of drug released was determined using standard curve. Dissolution rate was studied for the prepared formulations and conventional tablet. The time required for 80% of drug to be released ($t_{80\%}$) and percent drug dissolved in 2 min ($D_{2\ min}$ %) were considered for comparing the dissolution results. The i$_{80\%}$ and $D_{2\ min}$ were determined by fitting the dissolution data to a four parametric logistic model using the Marquardt–Levenberg algorithm (Sigmaplot 11 SPSS) (24).

In Vivo Buccal Absorption Test. In vivo test was performed to study the buccal absorption of prepared diazepam formulas (F4, F6, and F7). Each formula was administered to five healthy volunteers (21–35 years old), keeping the tablet in the oral cavity (on the tongue) for 1 min. The subjects then rinsed their mouths with distilled water. The rinsed water was then subjected to a quantitative assay using HPLC (Knauer, Germany) to determine the amount of diazepam remaining in the oral cavity. A washout period of 10 days before second trial was considered (25).

The chromatographic system consisted of an LC-10AD pump, injector, and an SPD-10A UV detector. Separation was performed on column (Lichrosorb® 5 μm C18, 300× 3.9 mm; Merck, Darmstadt, Germany). The mobile phase was acetonitrile/water/methanol (2:2:1). The UV detector was set at 254 nm. The flow rate was 1.4 ml/min (26). Stock solution of DZ (0.049 mg/ml) was prepared in H_2O. Calibration standard solutions were prepared from the stock solution by sequential dilution with H_2O to yield final concentrations of 0.01225, 0.0245, and 0.03675 mg/ml. A sharp peak was obtained at 3.733-min retention time as shown in Fig. 2, and the peak area was linear as a function of DZ concentrations (straight line equation: $Y = 159333X$) with a correlation coefficient of 0.9997.

Stability Studies. Stability study was carried out on optimized formula. The tablets were stored at 40±2°C/75± 5% RH using saturated sodium chloride solution desiccator for 1 month, then the samples were evaluated for various physical tests and drug release study (27). Moreover, the study of drug–excipient interaction is one of the most important stability studies, and Fourier transform infrared
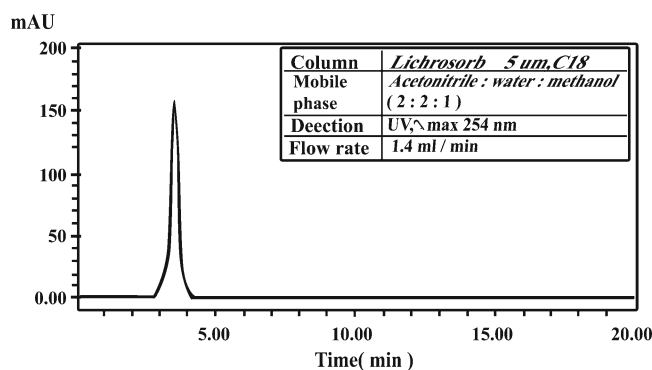
Fig. 2. HPLC chromatogram of diazepam

spectroscopy (FTIR) spectroscopy was used here for this purpose. FTIR spectra of pure DZ and physical mixture as well as the spectrum of the selected formula of ODT of DZ were obtained using a Shimadzu 8300 FTIR spectrophotometer according to the potassium bromide disk method. Analyses were performed at room temperature. The disks were scanned over a wavenumber range of 4000–500 cm^{-1}.

Statistical Analysis. The mean ± standard deviation of the experiment results were analyzed using one-way analysis of variance by using Sigma Plot 11 software.

RESULTS AND DISCUSSION

Evaluation of the Prepared Orodispersible Diazepam Tablets

The weight variation (percent weight within the pharmacopial limits of ±7.5% of the average weight) and content uniformity tests (99.42±3.59%) of the prepared diazepam orodispersible tablets complied with USP specifications.

Effect of Superdisintegrant Type

The assessment of disintegration time for the ODT is difficult using the tests for conventional tablets due to its rapid disintegration rate even in a small volume of water in addition to the strong agitation used during this test, and consequently, the disintegration time obtained from the conventional disintegration tests appears not to be reflective of the disintegration time in the human mouth (28). Thus, *in vivo* disintegration time was used in this study.

The superdisintegrants alleviate most of the problems associated with long tablet disintegration time; also, the use of the superdisintegrants in ODT is possible as the tablet shows optimum physical properties. Formulas F1–F3 were prepared to study the effect of type of superdisintegrant, Ac-Di-Sol, SSG, and crospovidone, on the *in vivo* disintegration time of the prepared diazepam ODT. The results shown in Table II indicate that crospovidone is the strongest among other superdisintegrants, which results in the fastest *in vivo* disintegration time followed by Ac-Di-Sol then SSG. This result is in agreement with the result obtained by Setty *et al.* (29) in the development of fast dispersible aceclofenac tablets.

Although all the three formulas (F1–F3) had acceptable flowability and compressibility as shown in Table III as well

as had acceptable hardness and friability, the tablets that contain crospovidone have the shortest wetting time (Table II), which may be attributed to the strong wicking action of this superdisintegrant. So it was selected as the best superdisintegrant and used (10%) in formulas F4–F7 and F9 to investigate other formulation variables.

Effect of Subliming Agent Type

The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of ODT. Even though the conventional tablets contain highly water-soluble ingredients, 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 sublimates from the formed tablet. The effect of subliming agent type was studied by preparing F4 and F5 containing AB and camphor, respectively, as subliming agents.

Although the addition of camphor in the formulation improved the tablet properties with respect to *in vivo* DT and showed excellent flow properties, poor hardness and friability observed, also, they did not exhibit complete removal of camphor independently on the sublimation time, and this is felt by the stinging effect in the mouth of volunteers. Thus, AB was preferred over camphor as subliming agent in this study.

Effect of Method of Tablet Preparation

The method of tablet preparation plays an important role in the physical properties of the prepared tablets; thus, F4 and F9 were used to investigate this effect on the preparation of ODT of DZ. The final blends in direct compression method F9 have very poor flowability, while granules prepared by wet granulation method F4 have good flowability. In addition, F9 tablets have no acceptable hardness, friability, and wetting time as shown in Tables II and III. The results suggest that the wet granulation method is preferable to the direct compression for preparation of ODT of DZ.

Effect of Subliming Agent Concentration

Formulas F3, F4, F6, and F7 were used to study the effect of concentration of AB as subliming agent on the properties of ODT of DZ. Wetting time of dosage form is related to the contact angle. Wetting time of the ODT is an important

Table II. Evaluation of the Prepared Orodispersible Tablets of Diazepam (Mean ± SD)

Properties	Formula no.								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Wetting time (s)	>5 min	>5 min	204.6±10	173.6±8	183 ±6.5	132±9.92	121±10.5	>5 min	>5 min
In vivo DT (s)	227±11.6	112.3±6.5	62±3	41.6±3.5	34±1.73	35±1.73	30.8±2.4	55.6±4.04	35±2
Hardness (kg/cm^2)	3.5±0.1	3.4±0.15	3.46±0.11	3.8±0.56	1.43±0.7	3.3±0.49	3.5±0.6	3.7±0.7	2.3±0.49
Friability (%)	0.35	0.5	0.34	0.43	1.51	0.61	0.73	0.87	1.2
Drug content (%)	98.8±2.7	99.6±3.4	100.6±4.5	98.3±3.05	99.4±3.8	96.6±3.2	101.6±4.7	100.3±4.1	100.1±2.9
Buccal absorption of diazepam (%)				11.25±1.7		12.1±1.93	14.1±1.65		

Table III. Micromeritics Properties of ODTs of Diazepam (Mean ± SD, n=3)

Formula no.	Angle of repose	Carr's index	Flow character
F1	37.5±0.95	20.5±1.50	Fair
F2	32.9±1.18	21.8±0.76	Good and passable
F3	34.0±0.57	18.8±1.25	Good and fair
F4	33.9±1.51	18.6±1.52	Good and fair
F5	25.5±0.69	10.1±0.76	Excellent
F6	31.9±0.57	18.0±1.00	Good and fair
F7	32.7±0.63	17.1±1.25	Good and fair
F8	29.1±1.25	13.5±1.00	Excellent and good
F9	50.1±2.70	39.0±1.80	Very poor

parameter which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet.

The results in Table II indicate that the wetting time decreases with the increase in AB concentration, which may be attributed to the increase in water uptake rate by the porous structure formed after sublimation. Moreover, a good correlation (R^2=0.9194) between the concentration of the subliming agent and friability is observed. Because when a higher percentage of subliming agent is used, more porous and consequently more mechanically weak tablets are produced (30).

Effect of Combining Superdisintegrant and Subliming Agent

Combination of superdisintegrants and subliming agent in formula F7 improved disintegration (30.8±2.4) in comparison to formula F8 (55.6±4.04) which is kept as control (without superdisintegrant) to assess the importance of superdisintegrant for ODTs as shown in Table II.

Optimization of Diazepam ODT Formula

The second stage of the research includes further studies to optimize the formula as selected ODTs of DZ.

In Vitro Dissolution Studies

For all oral solid dosage forms, dissolution study serves as a control test. The same is true for ODTs. This is because batch-to-batch consistency can be assured, and dissolution data of the tablets are frequently predictive of the bioavailability of the product. The results of dissolution studies of formulas F4, F6, F7 and conventional diazepam Roche tablet in Table IV and Fig. 3 indicate that the dissolution rate is increased in the following order: F7>F6>F4>Roche tablet.

Table IV. *In Vitro* Dissolution Parameters of Diazepam in Phosphate Buffer, pH 6.8

Formula no.	$t_{80\%}$ (min)	$D_{2\ min}$ (%)
F4	1.560	83.90
F6	0.859	90.18
F7	0.937	92.90
Valium 10 mg (Roche)	6.170	52.60
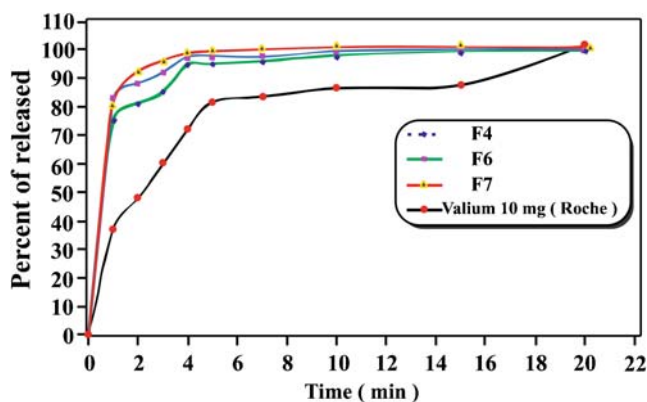
Fig. 3. Diazepam release profile from different formulas and a commercial conventional tablet in phosphate buffer, pH 6.8, at 37±0.5°C

In Vivo Buccal Absorption Test

Because of disintegration of ODTs in saliva while still in the oral cavity, there can be pre-gastric absorption from some. Buccal, pharyngeal, and gastric regions are all areas of absorption of the many formulations. Any pre-gastric absorption can be a great advantage to produce rapid onset and high
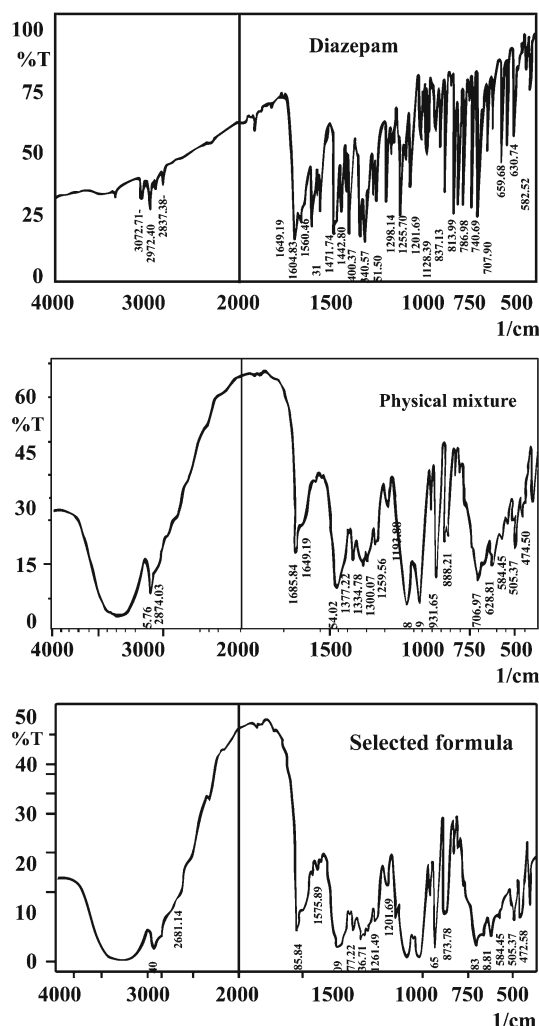
Fig. 4. FTIR spectra of diazepam, physical mixture, and selected formula of orodispersible tablet of diazepam

bioavailability. The results of buccal absorption tests of formulas F4, F6, and F7 in Table II indicate that the buccal absorption percent given is ranked in the following order: F7>F6>F4. It is clearly observed that this result is related to the disintegration time.

Stability Studies

In terms of overall parameters, formula F7 was considered as the selected formula; thus, it was subjected to stability studies. Comparison of FTIR spectra of pure DZ and physical mixture with the spectrum of the selected formula of ODT of DZ in Fig. 4 show all the characteristic peaks of DZ in the physical mixture and selected formula of ODT of DZ, thereby indicating that there is no interaction drug with the components of the formulation. Moreover, the short-term stability studies of the selected formula (F7) show no significant changes ($p<0.05$) in tablet hardness, friability, drug content, *in vivo* disintegration time, and dissolution rate at the end of the stability study period.

CONCLUSION

Overall, the results suggest that suitably formulated orodispersible tablets of diazepam containing 10% CP as a superdisintegrant and 20% AB as a subliming agent by wet granulation method can be achieved. The wet granulation method shows superior flow properties over direct compression method. The optimum selected formula (F7) has satisfactory physical resistance, fast *in vivo* disintegration time, high dissolution rate, and appreciable buccal absorption and good stability.

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