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FORMULATION & EVALUATION 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 formulate and optimize orodispersible tablets of diazepam. Orodispersible tablets of diazepam were prepared using different types of superdisintegrant [sodium starch glycolate and Crospovidone (CP)] and subliming agent camphor and ammonium bicarbonate. The study presents development of diazepam tablets, which could provide rapid disintegration and immediate release of drug in oral cavity. Tablets were prepared by conventional wet granulation.

Crospovidone, sodium starch glycolate were used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation. The formulations were evaluated for flow properties, wetting time, hardness, friability, content uniformity, disintegration time (DT), release profiles. It was observed that all the formulations were acceptable with reasonable limits of standard required for dispersible tablets. The results revealed that the tablets containing CP as a superdisintegrant have good dissolution profile with shortest DT. The optimized formula F4 was prepared using 10% CP as a superdisintegrant and 20% ammonium bicarbonate as a subliming agent shows the shortest DT and good dissolution profile.

Key Words: Oro-dispersible tablets, Diazepam, Superdisintegrating agents, Tablets, Sublimation agents

INTRODUCTION

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional

dosage forms such as tablet when water is not available, in the case of the motion sickness and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also ideal for active people.

Patients belonging to 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 Orodispersible tablets (ODTs), quick-disintegrating tablets, mouth-dissolving tablets, fast-disintegrating tablets, fast dissolving tablets, rapid-dissolving tablets, porous tablets, and rapid melts. The disintegration time for ODTs generally ranges from several seconds to about a minute *[6]*. 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 disintegrates *[10–13]*. The basic approach to

the development of ODTs is the use of superdisintegrants such as Crospovidone 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 volatile 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 sec and have a pleasant mouth feel *[17]*. Diazepam is an important member of the group of 1, 4-benzodiazepine derivatives. 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 by studying the effects of formulation processing variables on the properties of tablets.

MATERIALS AND METHODS

Materials

Diazepam pure drug powder was obtained from the Taj pharmaceutical Ltd, Andheri, Mumbai, India as a gift sample. Crospovidone, sodium starch glycolate, camphor, Ammonium bicarbonate, mannitol USP grade, lactose, PVP, talc, sodium bicarbonate, citrate, magnesium stearate were purchased from central drug house, New Delhi.

Methods

Formulation of orodispersible tablets of diazepam

The orodispersible tablets of diazepam were prepared by wet granulation method, by using superdisintegrant (Crospovidone, Sodium starch glycolate), sublimating agent (camphor and ammonium bicarbonate), mannitol as a diluent, alcoholic solution of polyvinylpyrrolidone (PVP) in isopropanol (5%, w/v) as binder and talc with magnesium stearate as a flow promoter (See Table 1). The drug and other ingredients were mixed together, and a specified volume of PVP was added and mixed to form a coherent. 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 talc and magnesium

stearate and compressed into tablets using a 7.6 mm multi punch tablet machine *[19]*.

Table-1: **Composition of ODTs of Diazepam**

S. No.	Ingredients mg/tablet	Formulations					
		F1	F2	F3	F4	F5	F6
1	Diazepam	10	10	10	10	10	10
2	Crospovidone	25(10%)	-	25(10%)	25(10%)		
3	Sodium starch glycolate	-	25(10%)	-	-	25(10%)	25(10%)
4	Camphor	-	-	25(10%)	-	25(10%)	
5	Ammonium bicarbonate	-	-	-	25(10%)		25(10%)
6	Sodium bicarbonate	10	10	10	10	10	10
7	Citrate	10	10	10	10	10	10
8	Polyvinyl pyrrolidone	5	5	5	5	5	5
9	Talc	10	10	10	10	10	10
10	Magnesium stearate	10	10	10	10	10	10
11	Mannitol q.s.	250	250	250	250	250	250

q.s.= Quantity sufficient

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 using formula *[20]*:

$$\tan\theta = \frac{h}{r}$$

Compressibility (Carr's) Index:-

An accurate weight of formula granules was poured into a volumetric cylinder to occupy a volume (Vo) and then subjected to a standard tapping procedure onto a solid surface until a constant volume was achieved (Vf). The Carr's index was calculated using formula *[20];*

$$\text{Compressibility index} = 100 \times \frac{Vo - Vf}{Vo}$$

Evaluation of Orodispersible Diazepam Tablets

1. **Weight Variation**

20 tablets were selected randomly from each batch and the mean weight was determined. None of the tablets deviated from the average weight by more than ±7.5%.

2. **Uniformity of Content**

The content of diazepam was determined according to the method described by IP for diazepam tablets. In brief, 1 ml of water was added to one diazepam tablet, stood for 15 min, then 80 ml of methanol. The obtained solution was stirred for 15 min and the volume was adjusted to 100 ml with methanol was added. The filtered solution was diluted appropriately and the drug content was measured spectrophotometrically at 230 nm (using UV–visible spectrophotometer) *[21]*.

3. 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 calulated.

4. Friability

Twenty tablets were weighed and placed in a Roche friabilator (Electrolab) 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 Formula *[22]*:

$$\%friability = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

5. Wetting Time

Apiece 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 calulated *[21]*

6. Disintegration time

Disintegration test was performed on six tablets using disintegration test apparatus using distilled water (900ml) as a disintegrating media at 37°C± 2°C.

7. Dispersion Time

Tablet was added to 10 ml of water and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and Dispersion time was performed.

8 Dissolution Studies

In vitro dissolution studies was performed using type II (paddle) dissolution apparatus (Electrolab) 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 *[23]*.

Table-2: Micrometrics Properties of ODTs of Diazepam

Formulations	Angle of repose	Carr's index	Flow rate
F1	27.5±0.95	20.5±1.50	Good
F2	26.5±0.5	15.5±1.18	Good
F3	28.4±1.18	17.5±0.95	Good
F4	22.7±0.63	17.1±1.25	Good
F5	25.2±0.18	12.5±0.12	Good
F6	23.3±0.43	19.1±1.11	Good

±SD, N=3

Table-3: Evaluation of the Prepared Orodispersible Tablets of Diazepam

Parameters	Formulations					
	F1	F2	F3	F4	F5	F6
Wetting time(sec)	204±6.22	>5 min	183 ±4.15	121±1.13	181±3.76	153±2.43
Hardness (kg/cm2)	4.1±0.11	3.8±0.15	4.2±0.13	3.6±0.56	4.2±0.06	3.8±0.13
Friability (%)	0.25 ±2.7	0.22±2.7	0.31±2.7	0.23±2.7	0.21±2.7	0.29±2.7
Drug content (%)	98.8±1.37	99.6±1.14	100.6±2.5	99.3±1.05	99.7±0.45	101.1±1.05
Disintegration time (sec)	38±1.01	42±1.17	29±0.21	22±0.55	39±1.08	32±1.02
Dispersion Time	Passes	Passes	Passes	Passes	Passes	Passes

±SD, N=3

RESULT AND DISCUSSION

Evaluation of Orodispersible Diazepam Tablets

For each formulation blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blends of all the formulations had compressibility index between 12.5±0.12 and 20.5±1.50 and angle of repose between 22.7±0.63 and 28.4±1.18 result shown in Table No.2 which indicating good flowability of the powder blend. Diazepam dispersible tablets were prepared in six formulations with of two superdisintegrants: Crospovidone and Sodium starch glycolate and two sublime agent camphor and ammonium bicarbonate, mannitol was used as diluents. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using wet granulation technique. Tablets were obtained of uniform weight due to uniform die fill. The data obtained of post-compression parameters such as hardness, friability, weight variation, amount of drug content, wetting time, dispersion time and disintegration time are shown in Table No.3.The hardness was found to be in the range of 4.2±0.13 to 3.6±0.56 kg/cm^2 for all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations the friability values are less than 1% and meet the IP limits indicating good mechanical resistance of tablets.

Weight variation of all the formulations was found to lie within the Pharmacopoeial limits. The weight of all the tablets was found to be uniform with low standard deviation values indicating efficient mixing of drug, disintegrants and excipients. The percentage drug contents of all the tablets were found between 98.8±1.37 percent to 101.1±1.05 % of diazepam, which was within the Pharmacopoeial acceptable limits. All the batches pass the Uniformity of dispersion as per IP and the Dispersion time of all the batches tablet was within the range of

35.66- 78.33 sec. Fast wetting of tablets of all formulations as reflected from wetting time ranging between >5 min to121±1.13 see Table no. 3

The Dispersion time of all the batches tablets and results of wetting time and disintegration time of all the tablets were found to be within the prescribe limits and satisfy the criteria of Dispersible tablets.

Effect of Superdisintegrant

F1and F2 formulations were prepared by using two type of superdisintegrant Crospovidone and Sodium starch glycolate. The results shown in Table no. 3 indicate that Crospovidone is the best than sodium starch glycolate. Although these two formulas (F1, F2) had acceptable flowability and compressibility as shown in Table no 2 as well as had acceptable hardness and friability. The tablets contain Crospovidone have the shortest wetting time, rapid disintegration time than other one see Table no. 3 which may be attributed to the strong wicking action of this superdisintegrant.

Effect of Subliming Agent

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, ammonium bicarbonate can be used in tableting process, which sublimates from the formed tablet. The effect of subliming agent type was studied by preparing formulations F3- F6 containing camphor and Ammonium Bicarbonate respectively, as subliming agents.

Formulations F3, F4 were used to study the effect of camphor and ammonium bicarbonate as subliming agent with Crospovidone and respectively formulations F5, F6 with sodium starch glycolate. Wetting time of the ODT is an important 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. Table 3 indicates that the wetting time is lower for tablet containing ammonium bicarbonate (F4, F6) than other formulations *[24]*.

***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 a batch-to-batch consistency can be assured, and dissolution data of the tablets are frequently predictive of the bioavailability of the product. All the formulations exhibit rapid and complete dissolution profile. Formulation F-4 exhibits the better dissolution profile than that of all

diazepam ODT formulations. On comparing the dissolution profile (fig 1) of other ODT formulations with that of F-4 formulation, it can be concluded that diazepam ODT formulation (F-4) have much faster drug release rate than that of other formulations of diazepam within 15 minute time point.

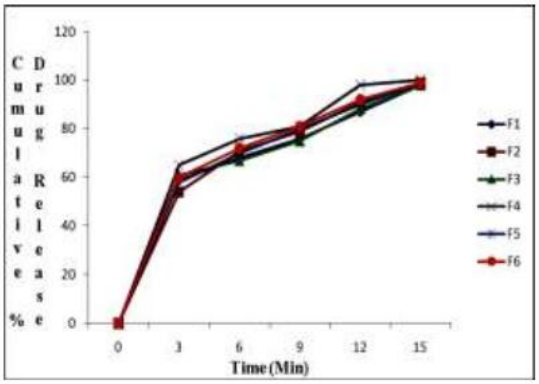

Fig 1: Cumulative % drug release versus time profile of F-1 to F-6.

Conclusion

Oral disintegrating tablets (ODTs) of diazepam are successfully prepared by using wet granulation compression method. Undoubtedly the availability of various technologies and the manifold advantages of ODTs will surely enhance the patient compliance, low dosing, and rapid onset of action, fast disintegration, low side effect, good stability and its popularity in the near future. From the present study it can be concluded that oral dispersible tablets of diazepam can be successfully prepared employing two different disintegrants viz. sodium starch glycolate and Crospovidone with two subliming agent camphor and ammonium bicarbonate by wet granulation method. The prepared tablets disintegrate within few seconds so enhance the patient compliance and the absorption leading to its increased bioavailability. From the characterization of oral dispersible tablets of diazepam it can be concluded that formulation containing Crospovidone with ammonium bicarbonate is most acceptable, it has fast *in vitro* disintegration, high dissolution rate.

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