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FORMULATION AND *IN VITRO* EVALUATION OF TEMAZEPAM ORAL DISPERSIBLE TABLETS

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ABSTRACT

This study presents development of temazepam tablets, which could provide rapid disintegration and immediate release of drug in oral cavity. Tablets were prepared by using direct compression method with different super disintegrants like Sodium starch glycolate, Croscarmellose sodium, and Crospovidone. The prepared tablets were evaluated for hardness, thickness, weight variation, percentage friability, wetting time, disintegration time and *in vitro* studies. The *in vitro* drug release study was carried out for 15 min. Among all formulations, the formulation of F_1 (98.15%) oral dispersible tablets has been showed better release of dosage forms.

KEYWORDS

Temazepam, Superdisintegrants, Oral dispersible tablets, Direct compression technique and *In vitro* studies.

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INTRODUCTION

The conventional dosage forms (tablet and capsule) have wide acceptance upto 50-60 % of the total dosage forms. Tablet is still most popular dosage form existing forms because of ease of self administration, compact in nature, easy to manufacture and it can be delivered in accurate dose. One drawback of solid dosage form is difficulty in swallowing (dysphasia) and chewing in some patients particularly in geriatric and paediatric patients. The problem of choking is common phenomenon in geriatric patients due to fear of choking, hand tremors, dysphasia[1]. Orally disintegrating tablets are also called as

orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rap melts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing[2].

Temazepam is a benzodiazepines derivative. Benzodiazepines are active orally and differ mainly in respect of their duration of action. Short-acting agents (e.g. temazepam, half-lives 8-12 h) are metabolised to inactive compounds and are used mainly as sleeping pills[3].

MATERIALS AND METHODS

Materials

Temazepam was obtained from Centaur Pharmaceuticals Pvt. Ltd, Mumbai, India. Sodium starch glycolate, Croscarmellose sodium, Crospovidone, Mannitol, Micro crystalline cellulose, Talc and Magnesium Stearate were purchased from Qualigens fine chemicals, Mumbai, India. All other chemicals and ingredients were used for study are of Analytical grade.

Methods

Preparation of Oral Dispersible Temazepam Tablets[4,5]

Weigh accurate required amount of Temazepam and all ingredients. Then mix all the ingredients in a proportion. Then punch the tablets by using tablet punching machine by direct compression technique (Table No.1).

EVALUATION PARAMETERS[4-7]

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

The Fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, super disintegrants and formulations were recorded by using BOMEN MB SERIES FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR range from 500 to 3500 cm^{-1}, with a resolution of 4 cm^{-1}.

Pre-compression studies of Oral dispersible tablet powder

Bulk density

3gm of powder were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated bulk density according to the formula

Formula

Bulk density = Mass / Volume

The packing properties of the drugs and their formulations widely depend upon bulk density. It has been stated that bulk density values less than 1.2gm/cm^3 indicate good flow and values greater than 1.5 gm/cm^3 indicate poor flow.

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of powder and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the powder in the cylinder and this minimum volume, the tapped density may be computed.

Formula

Tapped density = Weight of Powder/ Tapped volume of Powder

Angle of Repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal.

Formula

$$\theta = Tan^{-1} (h/r)$$

Where,

θ = Angle of repose,

h = Height of the powder cone,

r = Radius of the powder cone.

Angle of repose is less than or equal to 40° indicates free flowing properties of the powders. However

angle of repose is greater than 40° indicates poor flow of material.

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density.

The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where,

TD = Tapped density

BD = Bulk density.

Carr's Index is less than or equal to <10 indicates free flowing properties of the powders. However Carr's Index is greater than <10 indicate poor flow of material.

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder.

Formula

Hausner's Ratio = Tapped density/Bulk density

Hausner's Ratio is less than or equal to 1.069 indicates free flowing properties of the powders. However Hausner's Ratio is greater than 1.35 indicates poor flow of material.

Post compression studies of Temazepam Oral dispersible tablets

Hardness or Crushing strength Test[8]

Hardness of the tablet was determined using the Monsanto hardness tester (The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg ; however, hypodermic and chewable tablets have a hardness of 3 kg and some sustained release tablets have a hardness of 10 -20 kg.

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be used as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Venire caliper and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight

F - Final weight

Weight variation test

Weights of 20 individual tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula,

$$\text{Percentage deviation} = [X-X^*/ X] \times 100$$

X - Actual weight of the tablet

X^*- Average weight of the tablet

Estimation of Drug Content

An accurately weighed amount of powdered Temazepam (100 mg) was extracted with water and the solution was filtered through 0.45µ membrane filter paper. The absorbance was measured at 230 nm after suitable dilution.

Calculation

The amount of Temazepam present in tablet can be calculated using the formula

$$A_t/As \times S_w/100 \times 100$$

Where,

A_t = Absorbance of sample preparation

A_s = Absorbance of Standard preparation

S_w = weight at Temazepam working standard (mg)

Disintegration time study

Tablet was put into 100 ml distilled water at 37 ± 2^0C. Time required for complete dispersion of a tablet was measured with the help of digital tablet disintegration test apparatus.

Wetting time study

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds.

***In vitro* drug release studies**

The dissolution was carried out using rotating paddle method; freshly prepared 0.1N Hcl (pH 1.2) (900 ml) was placed in dissolution flask and allowed to obtain temperature at 37±0.5°C. The tablets were placed in beaker and rotated with 50rpm for 15 minutes. 1 ml of sample was withdrawn at different time intervals (0, 1, 3, 6, 9, 12 and 15 min). After each withdrawal, medium was replaced by equal amount of fresh 0.1N Hcl (pH 1.2). The sample were diluted to 10 ml with dissolution medium and used for measurement of absorbance at 230 nm. Before this, add 1 ml of 1% $FeCl_3$ solution to it. The dissolution data obtained were plotted as percentage drug release versus time.

RESULTS AND DISSCUSION

Pre formulation studies

Compatability studies (Fourier Transform Infrared Spectroscopic studies)

The fourier transform infra-red analysis was conducted for the surface structure characterization. FTIR spectrum of the formulated tablets, pure drug and different super disintegrants was recorded. The tablets were taken in a KBr pellet by using BOMEN MB SERIES FTIR instrument. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the different super disintegrants and pure drug. Then all the functional groups are found in the IR spectrum of pure drug and different super disintegrants.

Precompression studies of powders

Bulk density

From the results it can be seen that the bulk density values are less than 1.2gm/cm^3. This indicates good flow characteristics of the powders. Values showed Table No.2.

Tapped density

From the results it can be seen that the tapped density values are within the limits. This indicates good flow characteristics of the powders. Values showed Table No.2.

Angle of Repose

It can be observed that the angle of repose for various batches of the powders is found to be less than 40^0, it indicates good flow properties of the powders. Values showed Table No.2.

Compressibility Index or Carr's Index

It can be observed that the Carr's Index for various batches of the powders is found to be less than >10; it indicates good flow properties of the powders. Values showed Table No.2.

Hausner's Ratio

It can be observed that the Hausner's Ratio for various batches of the powders is found to be less than 1.35; it indicates good flow properties of the powders. Values showed Table No.2.

Postcompression studies

Hardness Test

The hardness of the tablet various batches were determined. The various batches of the tablets of hardness values are found within limits and it indicates good strength of the oral dispersible tablets. Values showed Table No.3.

Thickness Test

The thicknesses of tablets were almost uniform in the all formulations and were found to be in the range of 0.32mm. Values showed Table No.3.

Friability Test

The oral dispersible tablets friability values are found to be less than 1 % in all cases and considered to be satisfactory. Values showed Table No.3.

Weight variation test

All this oral dispersible tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weight of the all tablets was found to be uniform with low standard deviation values. Values showed Table No.3.

Estimation of Drug Content

Drug content of all the batches are within the acceptable range which shows the proper mixing of drug and excipients. Values showed Table No.3.

Disintegration time study The disintegration time (D.T) of all formulations is shown in the Table No.4.

Wetting time study

The wetting time study of all formulations is shown in the Table No.4.

***In vitro* drug release studies**

Among all the batches F_1 formulation showed the better dispersible and dissolution of drug Table No.5 and Figure No.1 (a and b).

Table No.1: Formulation of different batches of Temazepam Oral Dispersible Tablets

S.No	Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	Temazepam	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
2	Sodium starch glycolate	30 mg	-	-	15 mg	-	15 mg	10 mg
3	Cross carmellose sodium	-	30 mg	-	15 mg	15 mg	-	10 mg
4	Crospovidone	-	-	30 mg	-	15 mg	15 mg	10 mg
5	Mannitol	160 mg	160 mg	160 mg	160 mg	160 mg	160 mg	160 mg
6	Micro crystalline cellulose	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg
7	Talc	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg
8	Magnesium stearate	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg

Table No.2: Precompression studies of powders

S.No	Formulations	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Angle of Repose (θ)	Carr's Index (%)	Hausner's Ratio
1	F_1	0.588	0.638	25.52	7.83	1.085
2	F_2	0.576	0.631	25.16	8.71	1.105
3	F_3	0.566	0.625	24.34	9.44	1.104
4	F_4	0.584	0.634	26.05	7.88	1.085
5	F_5	0.582	0.632	27.23	7.91	1.086
6	F_6	0.579	0.631	28.24	8.24	1.089
7	F_7	0.576	0.630	30.15	8.57	1.093

Table No.3: Postcompression studies of Temazepam Oral Dispersible Tablets

S.No	Formulations	Hardness Test (kg/cm)	Thickness Test (cm)	Friability Test (%)	% of Weight variation test	Estimation of Drug Content
1	F_1	2.23	0.32	0.8	99.8	99.9
2	F_2	2.18	0.32	0.8	99.6	99.8
3	F_3	2.16	0.32	0.8	99.5	99.8
4	F_4	2.20	0.32	0.6	99.4	99.6
5	F_5	2.18	0.32	0.6	99.4	99.7
6	F_6	2.16	0.32	0.6	99.6	99.6
7	F_7	2.15	0.32	0.6	99.5	99.5

Table No.4: Postcompression studies of Temazepam Oral Dispersible Tablets

S.No	Formulations	Disintegration time (sec)	Wetting time (sec)
1	F_1	15	12
2	F_2	18	15
3	F_3	18	15
4	F_4	16	12
5	F_5	16	12
6	F_6	17	14
7	F_7	17	14

Table No.5: Comparative dissolution study of Temazepam Oral Dispersible Tablets

S.No	Time (mints)	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	0	00.00	00.00	00.00	00.00	00.00	00.00	00.00
2	5	08.42	06.12	04.85	07.35	05.92	04.42	04.26
3	10	23.58	18.52	16.52	21.80	16.82	14.65	12.86

4	15	42.62	35.62	31.96	40.03	32.79	29.24	27.15
5	20	63.64	54.15	50.84	60.32	51.92	48.52	47.05
6	25	80.48	72.69	68.47	78.28	69.35	65.71	63.84
7	30	98.15	93.12	89.26	96.38	91.56	87.48	85.16

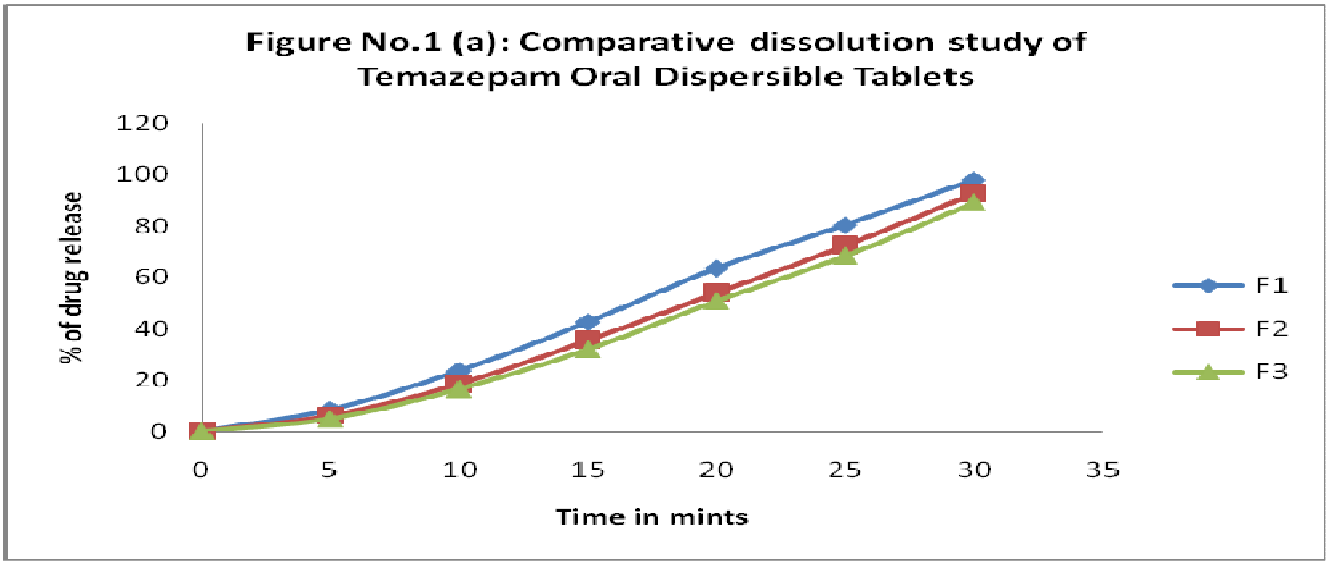

Figure No.1 (a): Comparative dissolution study of Temazepam Oral Dispersible Tablets

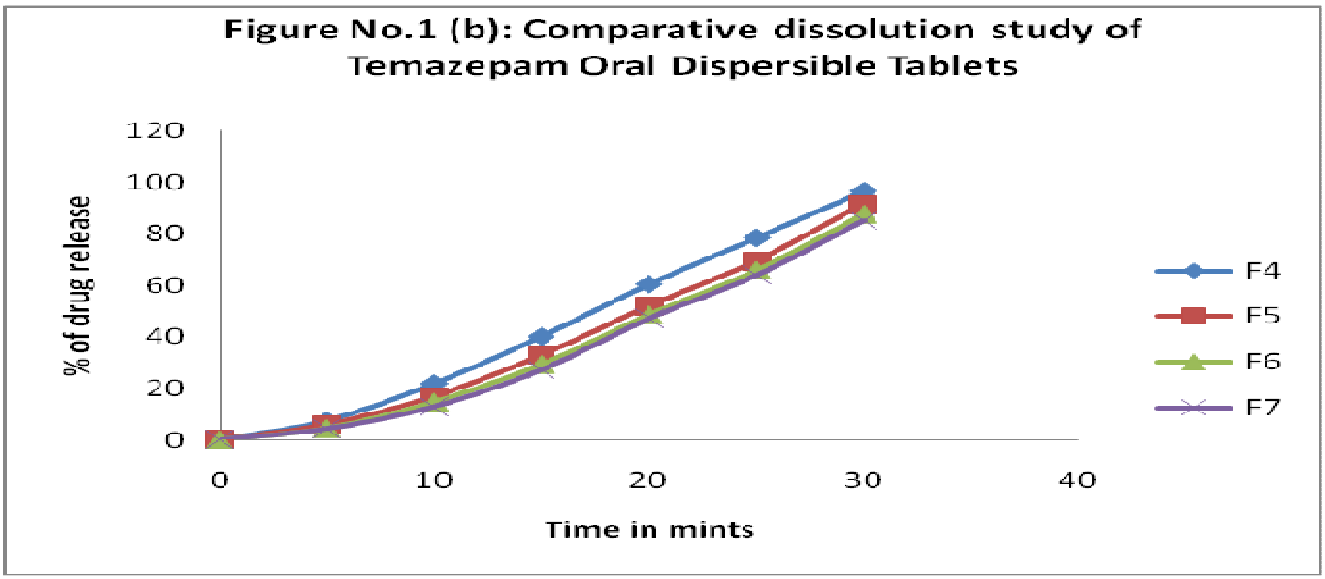

Figure No.1 (b): Comparative dissolution study of Temazepam Oral Dispersible Tablets

CONCLUSION

The study was concluded that, all the batches showed good to satisfactory free flowing properties which made it suitable for direct compression. A F_1 formulation showed a wetting time of 12 sec and disintegrating time of 15 sec, which was the minimum among all the formulations. *In vitro* dissolution studies showed that the formulation F_1 gave the maximum percentage drug release (98.15%) with in 30min. The formulation of Sodium starch glycolate (F_1) was found to be the best superdisintegrant in the preparation of ODT of temazepam. Thus, the objective of preparing temazepam and formulating into oral dispersible tablets was successfully achieved. The formulated oral dispersible tablets of temazepam may be useful for hypnotic, which can improve the patient compliance and hence can minimize the premature therapeutic dropouts leading to better therapeutic efficacy.

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