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FORMULATION AND EVALUATION OF LORAZEPAM FAST DISSOLVING TABLETS

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ABSTRACT

Lorazepam is treatment of anxiety disorders, sedative, as hypnotics, convulsant first line treatment for early stage of status epilepsy, pre-operation medication, tension, terminal agitation, alcohol withdrawal, serotonin syndrome and symptomatic treatment of nausea and vomiting associated with chemotherapy. In the present study, fast dissolving tablets of lorazepam were prepared by direct compression method. Fast disintegrating tablet (FDT) of Lorazepam was formulated using different concentration (3, 6, 9 and 12% w/w) of synthetic superdisintegrants like Crosspovidone, Croscarmellose sodium, Sodium Starch Glycolate, Low-Substituted Hydroxypropylcellulose were compared. Disintegration time and drug release were taken as the basis to optimize the rapidly disintegrating tablet. Prepared tablets were evaluated for thickness, hardness, friability, uniformity of weight, disintegration time, wetting time and dissolution study. The formulated tablets had good appearance and better drug release properties as compared to the marketed conventional tablets. Croscarmellose Sodium in the concentration of 12% gives shorter disintegration in 33sec. and shows 95.99% drug release within 10 min. is selected as the optimized formulation (B-8). Croscarmellose sodium showed better disintegrating property than the most widely used synthetic superdisintegrants like Crosspovidone, Sodium Starch Glycolate, Low-Substituted Hydroxypropylcellulose, But Low-Substituted Hydroxypropylcellulose in the concentration of 12% gives larger disintegration in 96 sec. and shows 54.21 % drug release within 10 min. -Substituted Hydroxypropylcellulose showed poor disintegrating property than above three synthetic superdisintegrants. Optimized formulation was subjected to stability studies as per ICH guidelines at 25°C and 65% RH, 40°C and 75% RH showed insignificant change in hardness, disintegration time and *in vitro* drug release at the end of three months.

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Key Words

Fast dissolving tablets,
Lorazepam, Crosspovidone,
Croscarmellose Sodium, Sodium
Starch Glycolate, Low-
Substituted
Hydroxypropylcellulose.

INTRODUCTION

A fast dissolving system can be defined as a solid dosage form for oral administration, which when placed in mouth, rapidly dispersed or dissolved and can be swallowed in the form of liquid. Fast dissolving tablets are solid tablets and designed to dissolve/disintegrate in the patient's mouth within few seconds or minutes, without the need to drink or chew¹. The fear of taking solid tablets and the risk of choking for certain patient populations still exists despite their short disintegration/dissolution times. However some patients, particularly pediatrics and geriatric patients have difficulty swallowing or chewing solid dosage forms (conventional dosage forms) to fear of choking and unwillingness². Fast dissolving and fast dispersing drug delivery system may offer a solution to these problems. Excipients are the additives used to convert active pharmaceutical ingredients into pharmaceutical dosage form suitable for administration to patients³. New and improved excipients continue to be developed to meet the needs of conventional drug delivery systems and to meet the needs of advanced tablet manufacturing.

Status epilepticus (SE) is a life-threatening condition in which the brain is in a state of persistent seizure. Definitions vary, but traditionally it is defined as one continuous unremitting seizure lasting longer than 30 minutes. Anxiety is a natural human reaction that involves mind and body. It serves an important basic survival function: Anxiety is an alarm system that is activated whenever a person perceives danger or threat. When the body and mind react to danger or threat, a person feels physical sensations of anxiety — things like a faster heartbeat and breathing, tense muscles, sweaty palms, a queasy stomach, and trembling hands or legs. These sensations are part of the body's fight-flight response. There are many types of anxiety disorders that include panic disorder, obsessive compulsive disorder, post traumatic stress disorder, social anxiety disorder, specific phobias, and generalized anxiety disorder⁴

Lorazepam is treatment of anxiety disorders, sedative, as hypnotics, convulsant first line treatment for early stage of status epilepsy, pre-operation medication, tension, terminal agitation, alcohol

withdrawal, serotonin syndrome and symptomatic treatment of nausea and vomiting associated with chemotherapy. Lorazepam has slightly metallic test, has half life of 7-16 hours and has poor water solubility. Lorazepam has Oral Bioavailability 85%, BCS Class-II, and its reaches within 2 hr after oral administration. The conditions mentioned above require immediate release of drug from the dosage form, which make lorazepam suitable candidate for fast dissolving tablets⁵.

In this research work, fast dissolving tablet for lorazepam was made by direct compression technique, using synthetic superdisintegrants. In this work, comparison of synthetic different superdisintegrants, like Crosspovidone, Crosscarmellose Sodium, Sodium Starch Glycolate, Low-Substituted Hydroxypropylcellulose. The prepared fast dissolving tablets were evaluated for hardness, thickness, diameter, disintegration time, friability, wetting time, percent drug content, weight variation, water absorption ratio, dissolution profile.

MATERIALS

Lorazepam was obtained from Aril Pharma, Ahmedabad, India as gift samples. Crosspovidone, crosscarmellose sodium, Sodium Starch Glycolate, Low-Substituted Hydroxypropylcellulose & Direct compression Mannitol (Pearlitol SD 200) were obtained from Zydus Cadila Heath Care, Ahmedabad, India as gift samples. Microcrystalline cellulose, Aspartame, Magnesium Stearate, Purified Talc were obtained from Suvidhinath Laboratories, Baroda, India. All the other solvents, reagents and chemicals used were of either pharmacopoeial or analytical grade. Different instruments viz Monsanto hardness tester, Roche friabilator and disintegration apparatus Dissolution apparatus, were supplied by Electrolab Pvt Limited, Mumbai, India and 1601 PC Shimadzu UV Spectrophotometer from Tokyo, Japan. Fourier Transform Infrared Spectroscopy (FTIR) apparatus was supplied Model : FTIR-8400S,CE by Shimadzu Corporation, Japan and Tablet Compression Machine apparatus was supplied Model : Rimek minipress-1, Karnavati Engineering Ltd, Ahmedabad, India.

METHODS

Preparation of Mixed Blend of Drug and Excipients All the materials were passed through sieve no. 60. Required quantity of each ingredient was taken for each specified formulation (Mentioned in Table no. 1 & 2) and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate). The powdered blend was evaluated for flow properties as follows.

Angle of repose⁶

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ) was calculated using the formula.

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

Bulk density⁶

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V) and weight of the powder (M) was determined. The bulk density was calculated by using the below mentioned formula,

$$\text{Bulk density} = \frac{\text{Mass of granules}}{\text{Volume of granules}}$$

Bulk density = -----

Tapped density⁶

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the following formula,

$$\text{Tapped density} = \frac{\text{Weight of the blend}}{\text{Volume occupied in the cylinder (Vt)}}$$

Tapped density = -----

Compressibility index⁷

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows,

$$I = \frac{V_o - V_t}{V_{bx}}$$

I = -----

Here, Vo is bulk volume and Vt is tapped volume. The value below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flowability.

Hausner's Ratio⁷

Hausner's ratio is an indirect index of ease of powder flow.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Hausner ratio = -----

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Compression of tablets by using direct compression Technique⁽⁸⁻⁹⁾

Finally magnesium stearate was added to prepared blend. The mixed blend of drug and excipients was compressed using a single punch tablet punching machine at 30 PCI to produce convex faced tablets, weighing 150 mg each with a diameter of 6.5 mm. A minimum of 30 tablets were prepared for each batch.

Characterization of Drug and Excipients**Drug-excipient compatibility studies**

This study has been done to check whether there is any compatibility related problems are associated with drug and the excipients used for the formulation of Fast dissolving tablets. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, and easy to administer and safe. If the excipients are new and not been used in formulations containing the active substance, the compatibility studies are of paramount importance. FTIR, can be used to investigate and predict any physicochemical interactions between components in a formulation and can therefore be applied to the selection of suitable chemically compatible excipients.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Shimadzu Corporation, (Tokyo, Japan) Model-1601 PC. Samples were prepared in KBr disks by means of a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000 cm^{-1} .

Standard Calibration Curve of Lorazepam

Solutions ranging from 2 to 12 µg/ml were prepared in phosphate buffer (pH 6.8). Absorbance was measured for each solution at λ_{max} of 230 nm, using 1601 PC Shimadzu UV Spectrophotometer. Correlation coefficient was found to be 0.9980 in phosphate buffer.

Formulation of Fast Dissolving Tablets

Fast dissolve tablets of Lorazepam were prepared by the conventional direct compression technique using

Superdisintegrants concentrations of 3, 6, 9 and 12 % w/w. All ingredients were passed through mesh no.60. Required quantity of each was taken for particular formulation and the blend was mixed by tumbling in a polythene bag. The composition of each formulation is given.

Ingredients	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8
Lorazepam (mg)	2	2	2	2	2	2	2	2
Crossprovidone	4.5	9	13.5	18	-	-	-	-
Crosscarmellose Sodium	-	-	-	-	4.5	9	13.5	18
Microcrystalline Cellulose	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Purified Talc	3	3	3	3	3	3	3	3
Aspartame	3	3	3	3	3	3	3	3
Direct compression Mannitol (Pearlitol SD200)	83.5	79	74.5	70	83.5	79	74.5	70
Quantity (mg)	150	150	150	150	150	150	150	150

Ingredients	B-9	B-10	B-11	B-12	B-13	B-14	B-15	B-16
Lorazepam (mg)	2	2	2	2	2	2	2	2
Sodium Starch Glycolate	4.5	9	13.5	18	-	-	-	-
Low-Substituted Hydroxypropylcellulose	-	-	-	-	4.5	9	13.5	18
Microcrystalline Cellulose	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Purified Talc	3	3	3	3	3	3	3	3
Aspartame	3	3	3	3	3	3	3	3
Direct compression Mannitol (Pearlitol SD200)	83.5	79	74.5	70	83.5	79	74.5	70
Quantity (mg)	150	150	150	150	150	150	150	150

EVALUATION OF LORAZEPAM FAST DISSOLVING TABLETS

Evaluation was done on tablets of all formulations batches considering following parameters and results were reported in Table no.3

1. Weight variation test¹⁰

Twenty tablets were selected randomly and average weight was determined. Then individual tablets were

weighed and was compared with average weight. The comparison variation within the I.P limits, it passes the weight variation test.

2. Tablet hardness⁶

Tablet crushing strength (Fc) or hardness, the force required to break a tablet in a diametric compression, was measured using Monsanto tablet hardness tester.

3. Thickness¹¹

The thickness of individual tablets was measured using Vernier caliper, which permits accurate measurements and provides information of the variation between tablets.

4. Wetting time¹²

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. Ten millimeters of water containing Eosin, a water soluble dye, is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

5. Water absorption ratio¹⁰

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio indicated with R, which is calculated by using the below mentioned equation.

$$R = 10 \times \frac{W_a - W_b}{W_b}$$

6. Drug content uniformity¹⁰

Twenty tablets were weighed and taken in mortar and crushed to make powder. A quantity of powder weighing equivalent to 2 mg of Lorazepam was taken in 100 ml volumetric flask and Phosphate buffer pH 6.8 was added. Then the solution was filtered using membrane filter 0.45 µm and then the solutions absorbance was measured at 230 nm. Then the amount of drug present was calculated using standard graph.

7. Tablet friability^(8,9)

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W₀) or a sample of 6 tablets were dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \text{ friability} = \frac{W_0 - W}{W_0} \times 100$$

8. In-Vitro Disintegration time¹³

The test was carried out on 2 tablets using tablet disintegration tester ED – 20, Electrolab, distilled water at 37°C ± 2°C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

9. Dissolution studies^(14- 16)

In Vitro dissolution studies for all the prepared tablets available tablets was carried out using USP paddle method at 50 rpm in 900 ml of Phosphate buffer solution (pH - 6.8) as dissolution media, maintained at 37 ± 0.5°C. 5 ml of sample was withdrawn from the dissolution medium at the specified regular intervals, filtered through Whattmann filter paper and assayed spectrophotometrically at 230 nm. An equal volume of pre warmed (37°C) fresh medium was replaced into the dissolution medium after each sampling, to maintain the constant volume throughout the test. Then the cumulative percentage of drug release was calculated and represent graphically.

Table – 3 Different evaluated parameters

Batch No	% Friability	Hardness (kg/cm ²)	Diameter (cm)	Thickness (cm)	Disintegration Time (sec.)	Wetting Time (sec.)
B-1	0.219	3.5±0.2	0.64	0.40	64	66
B-2	0.220	3.2±0.3	0.65	0.41	46	26
B-3	0.216	4.0±0.3	0.63	0.43	40	18
B-4	0.327	3.2±0.5	0.67	0.42	35	14
B-5	0.217	3.7±0.2	0.64	0.44	58	45
B-6	0.223	3.9±0.3	0.64	0.42	43	22
B-7	0.442	3.0±0.7	0.67	0.40	39	15
B-8	0.218	3.4±0.2	0.64	0.42	33	10
B-9	0.224	3.9±0.1	0.63	0.42	92	70
B-10	0.339	4.1±0.3	0.66	0.38	52	47
B-11	0.218	3.4±0.2	0.64	0.40	47	39
B-12	0.223	3.5±0.7	0.64	0.37	41	28
B-13	0.221	3.5±0.9	0.63	0.40	132	92
B-14	0.330	3.2±0.1	0.67	0.40	118	80
B-15	0.109	3.8±0.2	0.63	0.39	109	60
B-16	0.218	3.5±0.4	0.65	0.40	96	44

Batch No	Water abs. ratio	Percent Drug Content	Weight Variation
B-1	71.14	96.88±0.8	150±0.92
B-2	77.48	104.68±0.5	149±0.8
B-3	79.87	102.34±0.9	149±0.66
B-4	85.33	100.00±0.7	151±0.75
B-5	69.12	103.13±0.4	149±0.8
B-6	75.00	102.34±0.7	149±0.53
B-7	80.41	98.44±0.8	149±0.79
B-8	81.33	104.68±0.7	149±0.83
B-9	70.47	98.44±0.3	148±0.79
B-10	77.33	102.34±0.9	148±0.91
B-11	82.00	103.90±0.6	149±0.49
B-12	86.98	100.00±0.9	150±0.42
B-13	70.97	99.22±0.2	150±0.44
B-14	81.08	104.68±0.8	149±0.35
B-15	82.67	96.88±0.4	150±0.32
B-16	87.42	101.56±0.6	150±0.52

Table-4 In Vitro Dissolution Study

Time (min)	CPR of Preparations							
	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8
5 min	12.60	22.95	40.50	45.00	13.95	54.00	55.35	53.10
10 min	20.84	57.86	64.80	67.10	20.40	74.40	77.56	95.99
20 min	28.27	80.99	79.00	88.09	76.88	74.32	95.52	107.40
30 min	25.88	91.78	90.23	92.65	79.08	80.98	106.47	109.48
45 min	42.36	94.13	97.00	98.61	84.89	89.95	111.22	116.51
60 min	56.77	107.74	109.36	110.92	93.46	98.57	113.76	119.11

Time (min)	CPR of Preparations							
	B-9	B-10	B-11	B-12	B-13	B-14	B-15	B-16
5 min	4.05	8.10	28.80	30.15	1.35	2.70	4.50	4.05
10 min	61.69	51.84	66.92	65.58	4.06	4.53	5.45	9.49
20 min	72.28	59.62	82.51	79.81	9.06	11.78	14.51	21.75
30 min	78.47	75.12	87.01	88.33	15.91	23.16	22.77	25.59
45 min	87.88	86.29	92.90	94.24	25.98	27.47	39.67	40.72
60 min	96.03	98.47	100.65	102.00	29.42	41.27	48.66	54.21

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