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Formulation and Evaluation of Lorazepam Fast Dissolving Tablets using Synthetic and Natural Disintegrants

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Abstract

The main objective of present work was to formulate and optimize the fast dissolving tablets of lorazepam using synthetic and natural disintegrants. Crossprovidone, Crosscarmellose Sodium, Sodium Starch Glycolate and Low-Substituted Hydroxypropylcellulose were used as synthetic super disintegrants from synthetic form. Fenugreek Mucilage and Plantago Ovata Mucilage were used as super disintegrants from natural source. Tablets were prepared by direct compression method and the formulation of tablets was optimized to get minimum disintegration time and maximum drug release. From in vitro dissolution and drug release studies, Crosscarmellose Sodium was found to be the best superdisintegrant at all concentrations as it showed maximum drug release; while Low substituted Hydroxypropylcellulose was found to be the poor superdisintegrant with least drug release. Plantago Ovata Mucilage and Fenugreek Mucilage were found to be better super disintegrant than L-Hydroxypropylcellulose, but poor than Crosscarmellose Sodium, Crossprovidone and Sodium Starch Glycolate.

Keywords: lorazepam, natural super disintegrants, synthetic super disintegrants, disintegration time, drug release study.

Introduction

Fast dissolving tablets offer advantages of easy dosing and convenience of dosing, they are also designed to dissolve or/and disintegrate quickly in mouth within minimum time.[1]

Advantages of Fast Dissolving Drug Delivery System[1-3]: i. Good mouth feel property, ii. Administration to those patients who cannot swallow, as elders, bed ridden patients, patients facing renal failure, iii. Increased bioavailability, iv. Convenient for administration and patient compliance

Superdisintegrants are used at low levels with a maximum concentration of 10% w/w to total weight of the pharmaceutical dosage unit. Different disintegrants have different mechanism of action. [2]

Crossprovidone has synonyms such as Kollidon, Polyplasdone, polyvinylpolypyrrolidone and PVPP. It is a water-insoluble disintegrant which is mainly used at 2-5% concentration in oral pharmaceutical formulations.[4,5]

Crosscarmellose sodium is also known as Ac-Di-Sol, Primellose, Solutab and Vivasol. Crosscarmellose sodium can be used at concentrations up to 5% as a disintegrant in tablets.[6-7]

Low substituted hydroxypropyl cellulose is also known as Hyprolose, low-substituted, L-HPC. Its concentration in a formulation ranges within 5–25%.[8]

Sodium starch glycolate is also known as Vivastar and Tablo. It can be used in a range of 2-8%[9-10].

Fenugreek seed mucilage is also known as Billy-goat Clover, Camel Grass and Common Fenugrec and is widely used as a natural disintegrant in conventional formulations[11].

Plantago ovate husk is also known Psyllium husk, Psyllium seed, Plantago, Isabgol, Fleam and Spogel seed and is widely used as a natural disintegrant in conventional formulations[11].

Anxiety is an emotion characterized by an unpleasant state, accompanied with nervous behavior, muscular tension, worry, uneasiness and many a times over reactions of the person going through it. Diazepam, lorazepam, clonazepam and alprazolam are the first line treatment in treating anxiety.

Lorazepam falls in the class of short –acting benzodiazepine. It is white in color, odorless and is crystalline in nature, is practically not soluble (insoluble) in water and show polymorphism. It is used in the treatment of anxiety disorders, as sedative, as hypnotic and anticonvulsant. Lorazepam is used as first line treatment for early stage of status epilepsy, tension, alcohol withdrawal, serotonin syndrome as well as symptomatic treatment of nausea and vomiting that is associated with chemotherapy.

At present many formulations are available for treating anxiety, such as tablets and capsules, but this approach of making fast

dissolving tablet offers more advantage as increased bioavailability and rapid pharmacological action.

Material and Methods

Materials: Lorazepam BP was procured from R.L.Fine Chemical, Bangalore. All synthetic super disintegrants were procured from Zydus Cadila Heath Care Ltd.,Ahmedabad. Fenugreek Seed Powder was obtained from Akhand Ayurved Sevashram, Ahmedabad. Plantago Ovata Seed Powder was procured from Unjha Formulations Ltd, Sidhpur, Gujarat. Other required chemicals were obtained from Baroda Chemical Industry Ltd. Dabhoi and Suvidhinath Laboratories,Baroda.

Methods: Preparation of calibration curve of Lorazepam BP[12]: Calibration curve of lorazepam was successfully constructed in the range of 4-12 µg/ml at wavelength maxima of 230nm, in phosphate buffer Ph 6.8

Isolation of Mucilage from Fenugreek Seeds[13]: 20 gm Fenugreek seeds were taken in a mechanical blender for 5 min, then they were soaked in 600 ml distilled water for a duration of 24hr in 1000 ml beaker. It was later on exposed to microwave irradiation at 600W intensity for 7 minutes time duration. The beaker was then kept aside to release mucilage for 2 hr into water. Finally it was filtered through a muslin bag and hot distilled water (100 ml) was added and squeezed to remove all possible mucilage. Equal volume of ethanol then added to the above filtrate for the precipitation of mucilage and kept at low temperature (inside a refrigerator) for one day. It was dried completely in an incubator at 30^0C, finally filtered by using #60 mesh.

Isolation of Mucilage from Plantago Ovata Husk[14]: 8 gm Plantago ovata husk was soaked in 500 ml distilled water for 48 hr in 1000 ml beaker. It was exposed to microwave irradiation at 800W intensity for duration of 10 min. The beaker was removed from oven. The material was filtered by squeezing muslin cloth. Equal volume of acetone was then added to the above filtrate for precipitation of the entire possible mucilage. It was dried in an oven at a temperature of 60^0C, finally filtered by using #60 mesh.

Physico-chemical characterization of isolated Fenugreek Seed extract powder and Plantago Ovata extract powder[13]: Isolated powder of fenugreek seeds and plantago ovata seeds was characterized for their physicochemical properties using various tests such as Fehling Test, Osazone Test, etc.

FTIR analysis: FTIR spectra were recorded for Lorazepam and its physical mixture with different disintegrants.

An FTIR spectrum was also recorded for the final optimised formulation.

Preparation of fast dissolving tablets: All ingredients i.e. drug, disintegrants, dilutents, lubricants, glidants and sweetners were weighted accurately and passed through mesh no.60. and mixed thoroughly This blend was evaluated for pre compression parameters. Tablets were formulated by direct compression method as per the formula mentioned in table no.1 and after that evaluation for all post compression parameters was carried out.

Precompression parameters[15]: Angle of Repose, Bulk density and Tapped density, Compressibility Index, Hausner ratio and Total Porosity was determined as follows:

Angle of repose: Angle of repose of powder blend was carried out by using funnel method and calculated by the following equation:

$\tan Ø = h/r$
$Ø = \tan\text{-}1(h/r)$
Where, h= height of the powder cone r= radius of the powder cone.

Bulk density and Tapped density: 2 gm of blend of powder from each formula was filled in to a measuring cylinder after that initial volume was noted and the cylinder was tapped for 100 times at an interval of 2-3 seconds. Later on reading was noted and bulk density and tapped density was calculated.

Compressibility Index: It was calculated by using the following equation:

Carr's index (%) = Tapped density- Bulk density × 100
Tapped density
Hausner ratio = I t was determined using the following equation:
Hausner ratio= Tapped density
Bulk density

Post compression parameters: Tablets[16-19]: Evaluation of the tablets was carried out for - Weight variation test, Drug content, Hardness, Thicknesses and Diameter, Disintegration time, Friability and in Vitro dissolution studies.

Weight variation test: Tablets were weighed by using a Sartorius electronic balance and test was performed following the pharmacopeial method.

Drug content: Five tablets were weighed individually, and the drug was extracted in 6.8 pH Phosphate Buffer the drug content was determined as per the official method.

Hardness: Hardness tester was used to determine hardness of the tablets and average was taken into consideration.

Thicknesses and Diameter: Vernier calipers was used to determine thickness and diameter.
Disintegration time: USP Disintegration apparatus was used to know the disintegration time.

Friability: Roche friabrator was used for calculating friability.

In Vitro dissolution studies: Dissolution apparatus type- II was used to determine release rate of Lorazepam Fast dissolving tablets. 900 ml of 6.8 pH Phosphate buffer was used and temperature was kept at 37^0C at 50 rpm. Absorbance of the solutions was measured at 230 nm by UV/Vis spectrophotometer. %CPR i.e Cumulative percentage durg release was calculated

Table-1
Formula for preparing fast dissolving tablet

Batch no.	L	CP	CCS	SSG	HPC	FMP	POP	MCC	MS	Talc	A	M	Total
1	2	1.33	-	-	-	-	-	64.17	1.5	3	3	75.0	150
2	2	4.5	-	-	-	-	-	61.0	1.5	3	3	75.0	150
3	2	6.0	-	-	-	-	-	59.5	1.5	3	3	75.0	150
4	2	7.5	-	-	-	-	-	58.0	1.5	3	3	75.0	150
5	2	-	1.33	-	-	-	-	64.17	1.5	3	3	75.0	150
6	2	-	4.5	-	-	-	-	61.0	1.5	3	3	75.0	150
7	2	-	6.0	-	-	-	-	59.5	1.5	3	3	75.0	150
8	2	-	7.5	-	-	-	-	58.0	1.5	3	3	75.0	150
9	2	-	-	1.33	-	-	-	64.17	1.5	3	3	75.0	150
10	2	-	-	6.0	-	-	-	59.5	1.5	3	3	75.0	150
11	2	-	-	9.0	-	-	-	56.5	1.5	3	3	75.0	150
12	2	-	-	12.0	-	-	-	53.5	1.5	3	3	75.0	150
13	2	-	-	-	15.0	-	-	50.5	1.5	3	3	75.0	150
14	2	-	-	-	22.5	-	-	43.0	1.5	3	3	75.0	150
15	2	-	-	-	30.0	-	-	35.5	1.5	3	3	75.0	150
16	2	-	-	-	37.5	-	-	28.0	1.5	3	3	75.0	150
17	2	-	-	-	-	3.75	-	61.75	1.5	3	3	75.0	150
18	2	-	-	-	-	5.25	-	60.25	1.5	3	3	75.0	150
19	2	-	-	-	-	6.75	-	58.75	1.5	3	3	75.0	150
20	2	-	-	-	-	9.75	-	55.75	1.5	3	3	75.0	150
21	2	-	-	-	-	-	9.0	56.5	1.5	3	3	75.0	150
22	2	-	-	-	-	-	12.0	53.5	1.5	3	3	75.0	150
23	2	-	-	-	-	-	15.0	50.5	1.5	3	3	75.0	150
24	2	-	-	-	-	-	18.0	47.5	1.5	3	3	75.0	150

Where, L- Lorazepam. CP- Crossprovidone. FMP- Fenugreek Mucilage Powder. CCS- Crosscarmellose Sodium. HPC- Low-Substituted Hydroxypropylcellulose. POP- Plantago Ovata Mucilage Powder. MCC- Microcrystalline Cellulose. MS- Magnesium stearate. Talc- Purified talc. A- Asparatme. M- Direct Compression Mannitol (Pearlitol SD200)

Results and Discussion

FTIR analysis: FTIR spectra of lorazepam and optimized formulation containing crosscarmellose sodium indicated no incompatability between lorazepam and excipients of the optimized formulation.

Phsicochemical characterization of natural super disintegrants: Isolated powder ofextract of fenugreek seeds and plantago ovata seeds was characterized for their physicochemical properties using various tests such as Fehling Test and Osazone Test which resulted into positive tests, which indicated presence of Carbohydrate, Fructose, Lactose, Maltose, Arabinose.

Pre compression parameters: Results of pre compression parameters of all the batches are recorded in table 2, which indicate that the powder is free flowing and compressible and hence can be taken for direct compression.

Post compression parameters: Results of post compression tests suggested that weight variation test and friability were in the specified limits. Hardness, thickness and diameter of all formulated tablets were found to be within a range of 2.2-4.6 kg/cm^2, 0.40-0.44 cm and 0.217-0.337 cm respectively.

Table-2
Results of pre compression parameters

Parameters	Results
Bulk density	0.224-0.254
Angle of repose	29.51-30.25
Tapped density	0.294-0.312
Compressibility index	17.01%-17.38%
Hausner ratio	1.2049%-1.218%

Disintegration time: Disintegration time along with the wetting time and water absorption ratio of all batches is as shown in table-3.

The result obtained by carrying out in vitro dissolution studies of first 8 batches of tablets, containing Crossprovidone and Crosscarmellose Sodium as disintegrant is as shown in figure-1 and figure-2 (indicating disintegration time and wetting time):

Table-3
Disintegration time and some other related parameters

Batch no.	Disintegration Time (Second)	Wetting Time (Second)	Water Abs. Ratio R=100(Wb-Wa) Wa
1	64	66	71.14
2	46	26	77.48
3	43	18	79.87
4	35	14	85.33
5	58	45	69.12
6	43	22	75.00
7	39	15	80.41
8	33	10	81.33
9	92	40	70.47
10	52	47	77.33
11	47	39	82.00
12	41	28	86.98
13	132	92	70.97
14	118	80	81.08
15	109	60	82.67
16	96	44	87.42
17	135	85	70.27
18	110	71	78.66
19	97	52	82.11
20	91	38	86.18
21	98	72	69.59
22	58	52	77.85
23	45	39	79.33
24	42	29	85.52

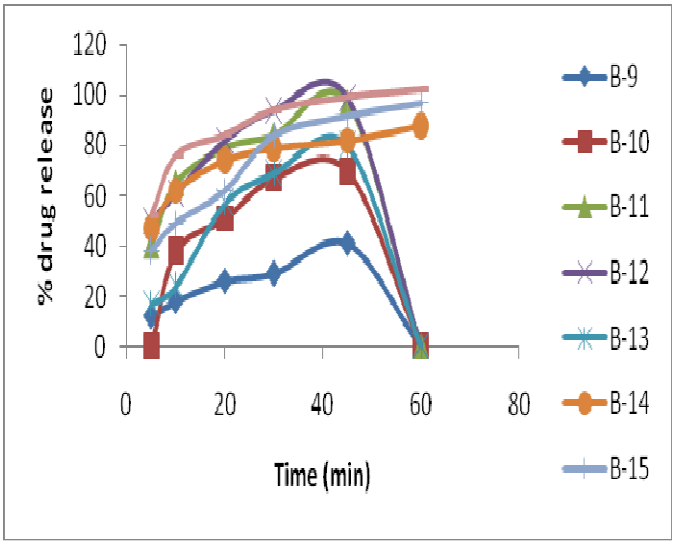

Figure-1
In vitro dissolution studies of batch 1-8

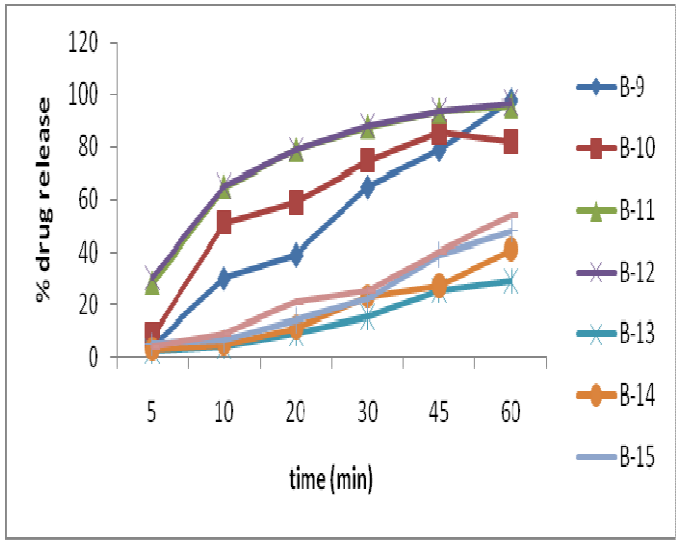

Figure-3
In vitro dissolution studies of batch 9-16

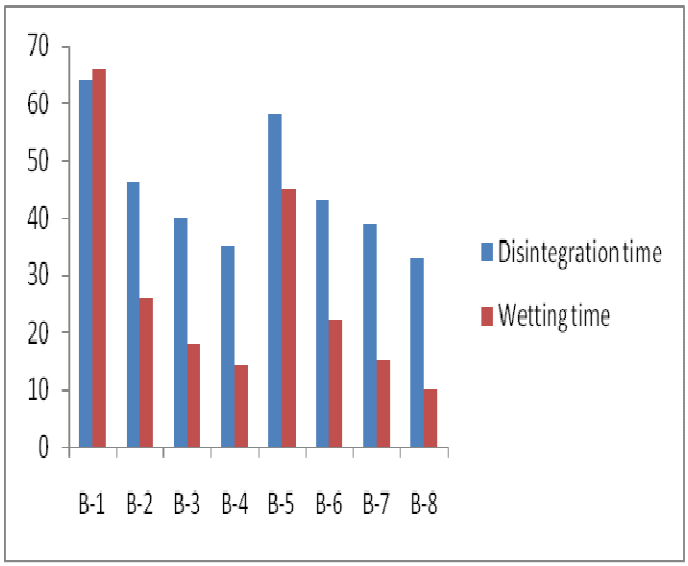

Figure-2
Disintegration time and wetting time of batch 1-8

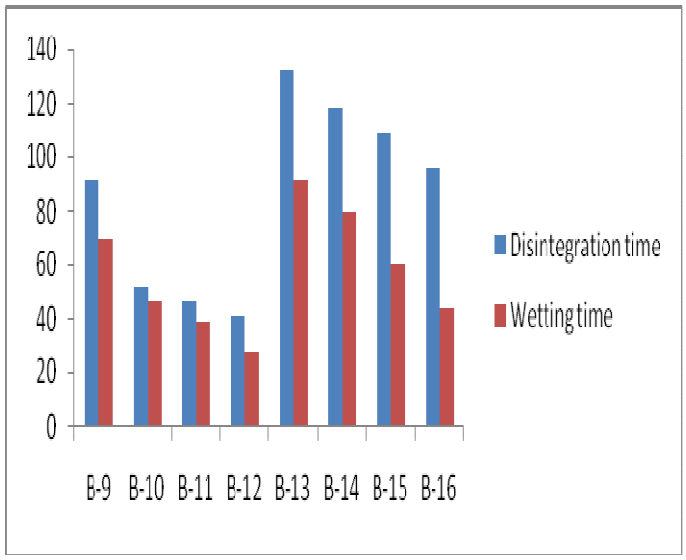

Figure-4
Disintegration time and wetting time of batch 9-16

From the above obtained results, it was found that in first 4 batches, where crosspovidone was used as super disintegrant batch-4 showed good result, while in next 4 batches, batch no. -8 showed good results. Comparing Crossprovidone and Crosscarmellose Sodium superdisintegrant it was found that, crosspovidone was poor disintegrant than crosscarmellose sodium.

Result of batch 9 to 16, containing Sodium Starch Glycolate and HPC- Low-Substituted Hydroxypropylcellulose as disintegrant is as indicated in figure-3 and figure-4.

Batch 9-16, where Sodium Starch Glycolate and Low-Substituted Hydroxypropylcellulose were used as superdisintegrants, it was found that Low-Substituted Hydroxypropylcellulose was poor superdisintegrant as compared to Sodium Starch Glycolate.

Results obtain from batch 17 to 24 containing Mucilage Powder and Plantago Ovata Mucilage Powder as natural super disintegrants are as represented in figure-5 and figure-6.

Batches 17 to 24, where natural super disintegrants, Fenugreek Mucilage powder and Plantago Ovata Mucilage powder were used as super disintegrants, it was found that Fenugreek

Mucilage powder was poor natural superdisintegrant as compared to Plantago Ovata Mucilage powder.

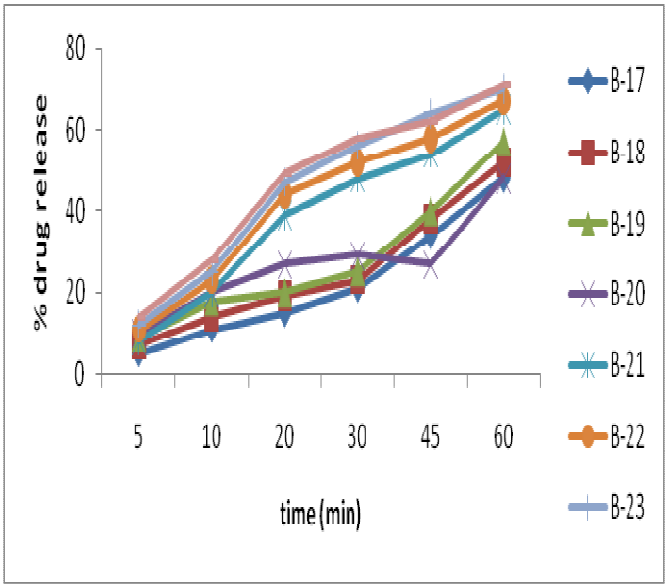

Figure-5
In vitro dissolution studies of batch 17-24

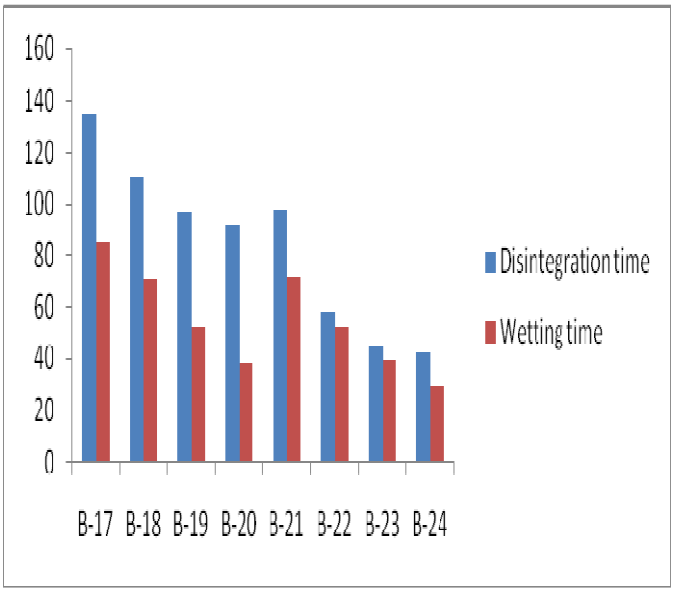

Figure-6
Disintegration time and wetting time of batch 17-24

Comparison between synthetic superdisintegrants and natural superdisintegrants: Crosscarmellose Sodium was found to be the best superdisintegrant from all other Superdisintegrants, L-Hydroxypropylcellulose was found as poor superdisintegrant as compared to all other Superdisintegrants because Crosscarmellose Sodium showed maximum drug release and L-Hydroxypropylcellulose showed minimum drug release. Thus effectiveness of disintegrants can be ordered as follows: Crosscarmellose Sodium > Crossprovidone > Sodium Starch Glycolate > Plantago Ovata Mucilage > Fenugreek Mucilage > L-Hydroxypropylcellulose.

Thus from above obtained results, formulation containing Crosscarmellose Sodium with the concentration of 5% in batch-8 was found to comply with all the necessary parameters. It was concluded to be an optimized tablet with disintegration time of 33 second and % CPR of 95.99% in 10 minutes. Hence it was concluded that batch-8 containing Crosscarmellose sodium as the superdisintegrant was ideal.

Conclusion

From dissolution and drug release studies, Crosscarmellose Sodium was found to be the best superdisintegrant at all concentrations as it showed maximum drug release; while Low substituted Hydroxypropylcellulose was found to be the poor superdisintegrant with least drug release. Plantago Ovata Mucilage and Fenugreek Mucilage were found to be better super disintegrant than L-Hydroxypropylcellulose, but poor than Crosscarmellose Sodium, Crossprovidone and Sodium Starch Glycolate.

Effectiveness of disintegrants can be ordered as follows: Crosscarmellose Sodium > Crossprovidone > Sodium Starch Glycolate > Plantago Ovata Mucilage > Fenugreek Mucilage > L-Hydroxypropylcellulose.

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