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Research Article

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Abstract

The present work aims to improve patient compliance with fast dissolving lorazepam tablets by the direct compression procedure. The method used crospovidone and croscarmellose sodium (2-8% weight by weight (w/w) as super-disintegrants in solitary as well as disintegrating mixtures (i.e., crospovidone-croscarmellose sodium, crospovidone-sodium starch glycolate), and to enhance the mouth feel, directly compressible mannitol was used. In the prepared tablet formulations, lorazepam estimates were performed Ultraviolet(UV)/ Visible spectroscopic method at 231 nm.The preparation formulations were further assessed for friability, hardness, wetting time, water absorption, drug content uniformity and *in vitro* dispersion time. Based on the *in-vitro* dispersion time of around 12-42 s, *in vitro* drug release patterns (6.8 phosphate buffer), stability studies (3 months; at 40 ºC/75% relative humidity) and drug excipient interactions (Infrared(IR) spectroscopy) were tested for promising formulations. The formulation (containing disintegrant blends of 2% w/w crospovidone and 4% w/w croscarmellose sodium) emerged as the overall best formulation among all the promising formulations. Stability studies on the promising formulation indicated that the drug content and the time of dispersion *in vitro* were not significantly changed.

Key words: Croscarmellose sodium, Crospovidone, Directly compressible mannitol, Disintegrant blends, Fast dissolving tablets, Lorazepam

Introduction

The various advantages such as easy administration, the avoidance of pain, versatility and most importantly, patient compliance continue to make the oral route the most preferred route among all routes of administration of medicine. The different dosage forms include tablets and capsules. Tablets are the most commonly used dosage forms because they are self-administering, compact and easy to manufacture.

Most people have difficulty in swallowing tablets and hard gelatin capsules and thus do not obey a prescription that leads to a high incidence of non-compliance and inadequate treatment[1]. Nearly 35-50% of the general population suffer from swallowing difficulties, which lead to high incidences of non-compliance and ineffective therapy, in particular considering the elderly and children. Swallowing problems are also very common in young adults as their muscle and nervous systems have not been fully formed.Additional groups that might have difficulty in swallowing conventional oral doses are people who have extremity tremors, mentally sick, developmentally disabled, non-cooperative and those who have reduced liquid intakes or nausea patients and those who travel or have no ready access to water. Many may also have swallowing problems, including those with motion sickness, severe allergic outbreaks of coughing and water shortages.

To overcome this problem, the scientist has developed an innovative drug delivery system i.e. "Fast disintegrating tablets" that disintegrates and dissolves rapidly in saliva without the need for water.

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This tablet disintegrates instantaneously or disperses in saliva[5]. These tablets usually dissolve within 15 seconds to 2 mins. In some cases, as the saliva passes from the mouth, pharynx and oesophagus into the stomach, drugs are absorbed to produce the faster onset of drug action. The bioavailability of the drug in these cases is substantially higher than that observed with conventional tablet dosage forms [1,6].

In both industry and academia, the advantages of rapidly disintegrating tablets become increasingly recognized. Recently, the words "orodispersible tablet", which means the mouth tablet, where it dissolves quickly before swallowing, used in the European Pharmacopeia, are becoming increasingly important[7].

Materials

Lorazepam was a gift sample from Centaur Chemicals Pvt Ltd, Chikboli, Maharashtra India. Crospovidone, Sodium Starch Glycolate and Croscarmellose Sodium were obtained as gift samples from Wockhardt Research Centre, Maharashtra.

Methods

Formulation of Lorazepam Fast Dissolving Tablets

The fast-dissolving Lorazepam tablets were prepared using the direct compression process in accordance with the formula shown in Table 1 [6]. Independtly, all the ingredients were passed through mesh #60. The ingredients were then compressed on a rotary tablet (Clit) 10-station in tablets 150 mg with flat, round 8 mm punches and weighed and mixed in geometrical order. A batch of 60 tablets was developed for all formulations.

Evaluation of Fast Dissolving Tablets

The fast-dissolving tablets were evaluated for the various pre-compression parameters like tapped density, bulk density, Carr's compressibility index and angle of repose (shown in Table 2) as well as the parameters after compression, for example, uniformity of drug contents, weight variation, friability, hardness, thickness and *in vitro* dispersion time, were also tested for prepared batches. [7] (shown in Table 3).

Weight Variation

The tablet weight has to be routinely assessed during the production process. The weight variation test

Table No 1: Formulations of Lorazepam Fast dissolving tablets prepared by Direct Compression Method

Ingredients (mg/ tablet)	Formulation code												
	FCP_0	FCP_1	FCP_2	FCP_3	$FCCS_1$	$FCCS_2$	$FCCS_3$	$FCPCS_1$	$FCPCS_2$	$FCPCS_3$	$FCPSG_1$	$FCPSG_2$	$FCPSG_3$
Lorazepam	1	1	1	1	1	1	1	1	1	1	1	1	1
Crospovidone (CP)	–	3	6	12	–	–	–	1.5	2.25	3.0	1.5	2.25	3.0
Croscarmellose Sodium (CCS)	–	–	–	–	3	6	12	3.0	4.5	6.0	–	–	–
Sodium Starch Glycolate (SSG)	–	–	–	–	–	–	–	–	–	–	3.0	4.5	6.0
Microcrystalline Cellulose MCC (PH -102)	30	30	30	30	30	30	30	30	30	30	30	30	30
Aspartame	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3
Sodium Stearylfumarate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Flavor (pineapple)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol SD 200	110	107	104	98	107	104	98	105.5	103.25	101	105.5	103.25	101
Total	150	150	150	150	150	150	150	150	150	150	150	150	150

FCP- Formulation containing crospovidone as disintegrant

FCCS- Formulation containing Croscarmellose as disintegrant

FCPCS- Formulation containing blend of crospovidone and croscarmellose sodium as disintegrant

FCPSG- Formulation containing blend of crospovidone and sodium starch glycolate as disintegrant

Table No 2: Pre-compression parameters of formulations prepared by Direct Compression Method

Parameters	Formulation code												
	FCP_0	**FCP_1**	**FCP_2**	**FCP_3**	**$FCCS_1$**	**FCCS2**	**FCCS3**	**$FCPCS_1$**	**$FCPCS_2$**	**$FCPCS_3$**	**$FCPSG_1$**	**$FCPSG_2$**	**$FCPSG_3$**
Bulk density(gm/cc)	0.510	0.500	0.494	0.558	0.548	0.513	0.560	0.530	0.510	0.517	0.600	0.570	0.530
Tapped density(gm/cc)	0.572	0.565	0.568	0.642	0.638	0.596	0.640	0.589	0.590	0.610	0.690	0.650	0.600
Carr's index (%)	10.83	11.50	13.02	13.08	14.01	13.92	12.46	10.01	13.70	14.03	13.33	11.65	11.83
Hausner's ratio	1.12	1.13	1.14	1.15	1.16	1.16	1.14	1.11	1.15	1.17	1.15	1.14	1.13
The angle of repose(°)	23.74	23.17	25.17	27.94	28.94	28.41	26.56	24.70	26.56	25.20	27.02	28.30	27.02

Table No 3: Post compression parameters of formulations prepared by Direct Compression Method

Parameters	Formulation Code												
	FCP_0	**FCP_1**	**FCP_2**	**FCP_3**	**$FCCS_1$**	**$FCCS_2$**	**$FCCS_3$**	**$FCPCS_1$**	**$FCPCS_2$**	**$FCPCS_3$**	**$FCPSG_1$**	**$FCPSG_2$**	**$FCPSG_3$**
Hardness * (Kg/cm^2)± SD	2.9± 0.10	2.8 ± 0.09	2.9 ± 0.05	2.7 ± 0.07	2.8 ± 0.09	2.76 ± 0.25	2.6 ± 0.17	3.0 ± 0.11	2.9± 0.11	2.8± 0.09	2.07 ± 0.10	2.8 ± 0.06	2.76 ± 0.25
Thickness (mm)	2.48	2.6	2.5	2.62	2.58	2.45	2.35	2.62	2.40	2.52	2.60	2.54	2.50
Friability (%)	0.54	0.64	0.73	0.66	0.57	0.58	0.65	0.60	0.79	0.73	0.69	0.70	0.60
In vitro dispersion time* (sec) ± SD	214 ±2.0	39.74 ± 2.47	26.67 ± 2.30	14.70 ± 2.14	42.59 ± 1.64	30.43 ± 2.58	16.37 ± 2.47	36.44 ± 1..56	23.32 ± 1.46	12.43 ± 1.52	40.64 ± 1.32	32.71 ± 2.32	15.23 ± 1.52
Wetting time* (sec) ± SD	215 ± 2.48	41.59 ± 1.64	27.0 ± 1.12	14.90 ± 0.83	43.20 ± 3.05	32.06 ± 2.08	17.66 ± 2.08	37.40 ± 1..50	24.35 ± 1..46	13.32 ± 1.52	42.12 ± 1.29	34.23 ± 1.32	16.32 ± 2.24
Water absorption ratio* (%)± SD	59.28 ± 3.66	75.75 ± 2.79	92.42 ± 2.80	98.16 ± 1.65	72.63 ± 2.98	80.63 ±1.017	96.63± 1.015	78.40 ± 2.10	94.59 ± 1.59	98.76 ± 3.20	72.38 ± 1.36	85.24± 1.70	94.16 ± 2.43
Drug content* (%)± SD	105.39 ±0.829	103.34 ±2.63	102.82 ±1.15	102.11 ±1.93	105.50 ±0.86	104.04 ±2.63	103.43 ±1.29	101.13 ±1.16	103.36 ± 1.39	102.24 ±1.83	104.59 ±2.47	102.31 ±1.22	103.59 ±1.60
Weight variation	147 to 155 mg (within the IP limits of ±7.5%)												

as per United State Pharmacopoeia (USP) is done by randomly taking 20 tablets, determining their individual weights and then matching the individual weights with an average weight in order to assess the weight variation[8].

Thickness

The tablet's thickness is important for the uniformity of the tablet size. Digital Vernier Caliper was used to measure tablet thickness by testing the thickness for each formulation of three random tablets from the formulation batch.

Hardness

The durability of tablets in terms of storage, transport, and handling prior to use depends on their shipping or breakage resistance. The Monsanto hardness tester was used to check the hardness of each tablet and it was expressed in terms of kg/cm^2. For testing the hardness of tablet, three tablets were chosen randomly and the average hardness determined was 2.5 kg/cm^2.

Friability

Friability usually means the loss of weight of the tablets in the containers because fines have been removed from the surface of the tablet. In fact, friability represents poor tablet cohesion. The weight was recorded, tablets were positioned and rotated at 25 revolutions per minute (rpm) for 100 revolutions in Roche friabilitor. The tablets were collected, dusted, weighed and the percentage friability was determined with the formula[9].

Table No 4: Comparative in vitro **dissolution data of control formulation (without super-disintegrant) promising tablet formulations of Lorazepam and Commercial Conventional Formulation in pH 6.8 Phosphate Buffer**

Time (min)	Cumulative Percent Drug Released					
	FCP_0	FCP_3	$FCCS_3$	$FCPCS_3$	$FCPSG_3$	CCF
2	4.24±2.36	52.14±2.20	46.24±2.60	56.23±3.10	53.24±3.46	6.18±2.40
4	8.10±3.40	68.38±3.81	54.93±3.26	70.24±2.64	66.76±3.14	13.10±3.42
6	13.57±2.10	85.38±3.12	72.36±2.60	86.48±3.42	82.13±2.76	16.42±3.10
8	18.64±3.42	93.47±2.36	86.14±3.14	99.18±3.78	92.64±3.74	22.46±2.40
10	23.36±1.56	99.85±2.44	93.28±2.70	-	99.79±2.76	30.12±3.12
15	27.42±2.24	-	100.24±1.64	-	-	35.16±2.43
20	30.64±2.50	-	-	-	-	42.64±3.54
25	34.73±3.12	-	-	-	-	49.64±3.24
30	38.13±2.60	-	-	-	-	62.24±2.60

Table No 5: Comparative In-Vitro **Dissolution Parameters of Promising Tablet Formulations of Lorazepam Pure Drug (Control) and Commercial Conventional Formulation in pH 6.8 Phosphate Buffer**

Formulation code	D_5 (%)	D_{10} (%)	$DE_{10\ min}$ (%)	$t_{50\%}$ (min)	$t_{70\%}$ (min)	$t_{90\%}$ (min)
FCP_0	10.1%	20.3%	10.93%	>30	>30	>30
FCP_3	76.5%	98%	69.58%	1.9min	4.2min	7.2min
$FCCS_3$	64%	93%	61.01%	2.9min	3.7min	7min
$FCPCS_3$	76%	100%	70.14%	1.8min	3.9min	6.7min
$FCPSG_3$	74.5%	100%	68.25%	1.9min	4.4min	7.5min
CCF	14.5%	30%	14.32%	>30	>30	>30

Table No 6: Stability Data of $FCPCS_3$ Formulation at 40ºC/75% RH

Sl No	Time in days	Physical changes	Percent drug content±SD*	*In vitro* Dispersion time*
1.	1st day (initial)	--	102.24±0.86	12.43±1.52
2.	30th day (1 month)	No changes	101.94±0.73	12.74±1.20
3.	60th day (2 months)	No changes	101.78±0.026	12.93±1.17
4.	90th day (3 months)	No changes	101.10±0.042	13.04±0.96

$$\% \text{ Friability} = \frac{\text{The initial tablet weight– Final tablet weight}}{\text{The initial tablet weight}} \times 100$$

Drug Content Uniformity

A total sum of 10 tablets equivalent to 1 mg of Lorazepam were powdered and dissolved in 40 ml of ethanol in a 50 ml volumetric flask. By vigorously shaking for 15 minutes, the drug was extracted in methanol, made the final volume with ethanol and finally the solution was filtered. The absorbance was estimated at 231 nm after sufficient methanol dilution and the drug concentration was calculated using the normal calibration method. On average, three determinations of the mean percent drug content were computed[10].

In vitro Dispersion Time

The pH 6.8 phosphate buffer solution of 10 ml was taken in a beaker and the tablet was added at 37±0.5°C and the time needed to disperse a tablet completely was calculated (shown in Table 3).

Wetting Time and Water Absorption Ratio

In a small petri dish containing 6 ml of water was a piece of tissue paper folded twice. A tablet has been inserted on the paper and the required time was measured for full wetting. After that, the wetted tablets were weighed [11] (Shown in Table 3).

Water absorption ratio "R" was determined using the following equation:

$R = 100 X (W_a - W_b / W_b)$

Where, W_a =tabletweight before absorption of water

W_b =tabletweight after absorption of water

In vitro drug release study

Lorazepam's fast dissolving tablets have been examined *in vitro* using the Type-II USP dissolution apparatus (Electrolab USP TDT-06 T). The dissolution medium used was 900 ml of pH 6.8 phosphate buffer. The stirrer was calibrated for 50 rpm rotation.The temperature of the dissolution medium was maintained at 37±0.5°C throughout the process. A total of 5 ml of the sample was withdrawn at known time intervals using a pre-filtered syringe and the drug release was analyzed by measuring the absorbance at 233 nm. The removed volume was replaced by the new fresh dissolution medium in every period[12].

Table No 7: Statistical Analysis of Drug Content Data for Stability of $FCPCS_3$ Formulation

Sl No	Trial	First Day (A)	90th day (B)	A – B
1.	1	104.36	103.10	1.26
2.	2	101.24	100.92	0.32
3.	3	101.14	100.84	0.92
4.	Mean percent drug content	102.24	101.62	0.62
5.	Standard Deviation (SD)	1.830	1.282	0.54

t=0.652
(p<0.05)

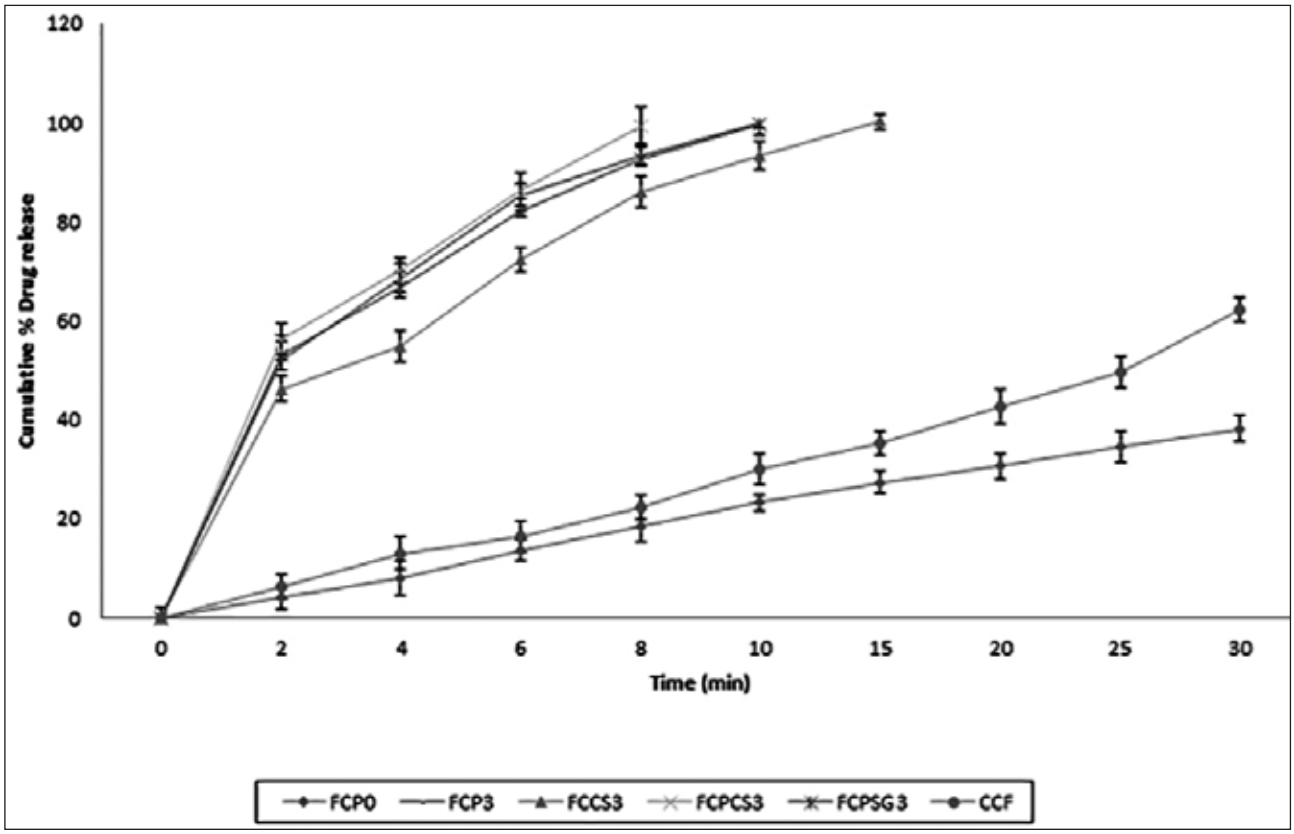

Figure 1: Comparative Cumulative Per cent Drug Release versus Time Plots (Zero Order) of Lorazepam Formulations, Pure Drug (Control) and Commercial Conventional Formulation in pH 6.8 Phosphate Buffer

Accelerated Stability Studies

Promising formulation stabilization studies ($FCPCS_3$) are carried out by storing 15 tablets at a higher temperature of $40\pm2^0C/75\%$ Relative humidity (RH) (Stationary Chamber, Oswald) in a screw-capped amber bottle for three months. At a period of one month, physical changes, percentage of drug content and *in vitro* dispersion time were visually examined for all tablets (given in Table 6 and 7).

Results and Discussion

The current work on the formulation of fast dissolving tablets consisting of lorazepam has been carried out by the use of Crospovidone and Croscarmellose as a super disintegrant in a separate mixture and to improve the mouth feel mannitol was used as diluent. Altogether twelve formulations and the control formulation FCP_0 have been produced (without super disintegrant). All blends had the Carr's index less than 15%, the angle of repose less than 30°, the bulk density less than 0.570, the tapped density less than 0.640 and Hausner'sratio less than 1.15, which indicated that all blends were within the limits of the Indian Pharmacopoeia. The results are shown in Table 2.

Due to uniform die fills the collected tablets were of standardized weight with appropriate differences according to specifications of the Indian Pharmacopoeia. The drug content was in the range of 101.13%--105.39%, hardness in the range of 2.6-3.00 kg/cm2, water absorption ratio of 59.28% to 98.76% and wetting time of 13.32 to 215 seconds (given in Table 3) were found to be product quality, stability, absorption rate, and weight period. The friability of the prepared tablets was less than 1%, suggesting that the tablets are mechanically resistant.

Among the formulations that were designed, the $FCPCS_3$ formula containing 1% w/w and 3% w/w disintegrant combination of crospovidone was promising. The $FCPCS_3$ was observed to be 12.43 sec, 13.32 sec and 98.76 per cent respectively (seen from Table 3 for the water absorption ratios, *in vitro* dispersion and wetting time). Since disintegrants balance each other, the disintegration cycle is accelerated in combination.

In vitro dissolution studies were carried out in pH 6.8 phosphate buffer for the commercial conventional formulations (CCF), promising formulations (FCP_3, $FCCS_3$, $FCPCS_3$,$FCPSG_3$) and control formulation (FCP_0) studies. Table 4 shows the dissolution value for a percentage of drug released in 5 and 10 mins (D5 and D10), 10 minutes dissolution rate (DE_{10}), $t_{50\%}$, $t_{70\%}$, and $t_{90\%}$ and Figure 1 shows the dissolution profile. This results in drug release 16 times($t_{50\%}$ 1.8 min) then to CCF ($t_{50\%}$>30 min) of Lorazepam tablet formulation as shown in the $FCPCS_3$ general formulation.

The drug was found to be compatible with all the excipients as indicated by Infra-Red (IR) spectroscopic studies. All Lorazepam pure drug peaks were shown in the $FCPCS_3$ and FCP_0 IR spectrum. It suggests that there was no drug interference with the formulation portion. The $FCPCS_3$ formulation stability studies presented in Tables 6 and Tables 7 show that in the *in vitro* dispersion time and the drug content there were no significant changes after 3 months as the p value was less than 0.05.

Conclusion

The study concludes that Lorazepam fast dissolving tablets be developed using the disintegrating blends of Crospovidone show better time to release and disintegrate drugs than when used alone. Because disintegrating blends complement one another, the disintegration process is accelerated in combination. A mixture of wicking and swelling types of excipients can also prove beneficial, as a wicking type of Superdisintegrant can more easily bring the medium (generally water) necessary for swelling into a tablet.

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- Conflict of interest: None

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