FORMULATION AND EVALUATION OF ORO DISPERSIBLE TABLETS OF CLONAZEPAM BY DIRECT COMPRESSION METHOD

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Summary

The objective of the present investigation was to prepare oro dispersible tablets of clonazepam by direct compression method using three super disintegrants, viz., croscarmellose sodium, crospovidone and sodium starch glycolate at different concentrations with microcrystalline cellulose along with directly compressible mannitol to enhance mouth feel. Oro dispersible tablet is the fast growing and highly accepted drug delivery system, convenience of self administration, compactness and easy manufacturing. Clonazepam is an anticonvulsant, musclerelaxant and anxiolytic properties. It is completely absorb after oral administration. The bland was examined for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The prepared batches of tablets were evaluated for thickness, hardness, friability, and weight variation, content uniformity, wetting time, Water absorption ratio, *in-vitro* dispersion time, dissolution studies and FTIR studies. Twelve formulations F1 to F12 were prepared with three super disintegrants with different concentration. The optimum formulation was choosen and their optimum results were found to be in close agreement with experimental finding.

Keywords: Oro dispersible tablets, Super disintegrants, Clonazepam, Direct compression.

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Introduction

Most of the oral pharmaceutical dosage form like conventional tablets and capsules are formulated but it was difficult to swallow for elderly and children. This problem is also applicable to active working or travelling people who do not have ready access to water[1]. Recent advances in novel drug delivery system aims to provide rational drug therapy by enhanced safety and efficacy of drug molecule by formulating convenient dosage form to administration[2]. One such approach is oro dispersible tablets (ODTs). An oro dispersible tablet is a solid dosage form that disintegrates and dissolves in mouth without water within 60 seconds or less[3]. The various technologies used to prepare ODTs include freeze drying and sublimation[4]. The commonly used super disintegrants are croscarmellose sodium, crospovidone and sodium starch glycolate[5]. In many orally disintegrating tablet technologies based on direct compression, the addition of super disintegrants principally affects the rate of disintegration and hence dissolution and also effervescent agent also further hastens the process of disintegration.

Clonazepam is a benzodiazepine derivative with marked antiepileptic properties. It may be used in the treatment of all types of epilepsy and seizures. It is also indicated in mycoclonus and associated abnormal movements, and for the treatment of panic disorders. It was selected as drug candidate, since it is not available in such dosage form. Aim of the present study was to develop oro dispersible tablets of clonazepam by simple and cost effective direct compression method using three super disintegrants, croscarmellose sodium, crospovidone and sodium starch glycolate at different concentrations. The blend and prepared tablets were evaluated and compared with three super disintegrants, effect on the *in vitro* dispersion time, *in vitro* drug release and FTIR studies were observed. From the twelve formulations, the optimum formulations were selected.

Material and Method

Clonazepam was obtained from as a gift sample from Dr.Reddys, Hyderabad, sodium starch glycolate, croscarmellose sodium was obtained as gift sample from AET Laboratories Hyderabad. crospovidone were gift sample from LOBA chemie pvt. Ltd., Mumbai. All other chemicals used were of Analytical Reagent grade.

Preparation of clonazepam tablets

Clonazepam tablets were prepared by direct compression method. All the ingredients were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order. Tablets were punched by using 8 mm round flat punch by rotary tablet compression machine. Twelve batches F1 to F12 were prepared with various proportions of super disintegrants (croscarmellose sodium, crospovidone and sodium starch glycolate) and excipients were shown in Table 1.

Table 1 Formulation of clonazepam tablets

Ingredients (mg)*	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Clonazepam	2	2	2	2	2	2	2	2	2	2	2	2
Croscarmellose sodium	6	9	12	15	_	_	_	_	_	_	_	_
Crospovidone	−	_	_	_	6	9	12	15	_	_	_	_
Sodium starch glycolate	_	_	_	_	_	_	_	_	6	9	12	15
Microcrystalline cellulose 102	38	38	38	38	38	38	38	38	38	38	38	38
Mannitol (pearlitol SD200)	94	91	88	85	94	91	88	85	94	91	88	85
Aspartame	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	150	150	150	150	150	150	150	150	150	150	150	150

*All the quantities expressed are in mg/tablet.

Characterization of oro dispersible tablets

Evaluation of blends

Angle of repose

Angle of repose was determined using funnel method.[6] The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and the angle of repose (Θ) was calculated using the formula.

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

Bulk density

Apparent bulk density (p_b) was determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula.[6]

$$p_b = M / V_b$$

Tapped density

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

$$p_t = M / V_t$$

Compressibility index

The simplest way for measuring of free flow of powder was compressibility, a indication of the ease with which a material can be induced to flow was given by compressibility index (I).[6]

$$I = (V_0 - V_t / V_0) 100$$

Where, vo is the bulk volume and vt is tapped volume.

Hausner's ratio

Hausner's ratio was an indirect index of ease of powder flow. It was calculated by the following method

$$\text{Hausner ratio} = p_t / p_d$$

Where, p_t is tapped density and p_d is bulk density lower hausner's ratio (< 1.25) indicates better flow properties than higher ones (> 1.25).[8]

Evaluation of tablets

Weight variation

Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and were compared with average weight for determination of weight variation.

Friability

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and

dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were deducted using a soft muslin cloth and reweighed. The friability (f) was given by the formula.

$$F = (1-W_0 / W)\ 100$$

Where, W_0 is weight of the tablets before and W is weight of the tablets after test.

Hardness

Hardness was measured using Monsanto tablet hardness tester.[6]

Thickness

Thickness was measured using digital Vernier calipers.

Wetting time and water absorption ratio

The method reported by Yunixia et al [9] was following to measure the tablet wetting time. A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a petridish containing 6 mL of simulated saliva pH 10, a tablet was put on the paper ,the time required for complete wetting was measured. The wetted tablet was taken and weighed. Water absorption ratio (R) was determined using following equation

$$R = 100 \times (W_a - W_b) / W_b$$

Where W_b is weight of tablet before water absorption and W_a is weight of tablet after water absorption.

***In vitro* dispersion time**

Tablets were placed in 10 mL beaker containing 6 mL of pH 6.8 phosphate buffer at 37 ± 0.5^0C and time required for complete dispersion was determined.[1]

***In vitro* dissolution study**

In vitro dissolution of clonazepam oro dispersible tablets studied in USP XXIII type-2 dissolution apparatus (Electrolab, Model- TDT- 08L) employing a paddle stirrer at 50 rpm using 900 mL of pH 6.8 phosphate buffer at 37 ± 0.5^0C as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium (5 mL) were withdrawn at specific intervals of time and analyzed for drug content by measuring the absorbance at 307.5 nm. The volume withdrawn at each time interval was replaced with fresh quantity of the dissolution medium.

IR spectral analysis

Infrared spectra of drug and its inclusion complexes were recorded by KBr method using Fourier Transform Infrared Spectrophotometer. A base line correction was made using dried potassium bromide and then spectra of dried mixtures of drug and inclusion complexes with potassium bromide were recorded.

Short term stability studies

Short-term stability studies on the promising formulations were carried out by storing the tablets at 40^0C and 75% RH over a 6 month period according to ICH guidelines. At intervals of 1, 3 and 6 month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

Results and Discussion

Twelve formulations of Clonazepam were prepared by direct compression method with varying concentration of three super disintegrants, sodium starch glycolate, crospovidone, croscarmellose sodium with microcrystalline cellulose. Directly compressible mannitol was used as diluents to enhance mouth feel. A total of 12 formulations were designed. The powder blend was evaluated the physical properties such as angle of repose, bulk density, tapped density, compressibility index and hausner‘s ratio for the prepared tablet blend Table 2. The angle of repose between 30 and 33, this indicates passable flowability, the percentage compressibility index and hausner’s ratio were within the limits (< 15%).

The prepared tablets were evaluated for hardness, friability, thickness, weight variation, content uniformity were shown in Table 3. For all the batches were found to be within the acceptable limits. The drug content was found to be in the range of 94 to 102% (acceptable limits) and the hardness of the tablets was found to be 2.9 to 3.5 kg / cm^2 were shown in Table 3. Friability below 1% was an indication of good mechanical resistance of tablets. The wetting time was determined for all the formulations prepared. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in the precence of little amount of water were found within the limits.

In vitro dispersion test was done for all the formulation. Tablet disintegration was affected by the wicking and swelling of the disintegrants from the 12 formulations F5 shown less disintegration time, 24 seconds when compared with others super disintegrants. Crospovidone was used as a super disintegrants in F5 formulation. Water absorption ratio for F5 was 84% it shows good water absorption capacity. *In vitro* drug release studies of clonazepam prepared tablets F1 to F12 using different super disintegrating agents by different concentrations. The maximum drug release for the formulation F1, F2, F3and F4 using different concentration of croscarmellose sodium, at the end of the 15 minutes are 96%, 96%, 97%, 96% were shown in Table 4 and Figure 1 respectively for the formulations F5, F6, F7 and F8 using crospovidone at

different concentrations. The drug release was found to be 97%, 96%, 95% and 96% at the end of 15 minutes were shown in Table 5 and Figure 2. It concluded that F5 formulation gives maximum drug release within 10 minutes respectively for the formulation F9, F10, F11 and F12 using sodium starch glycolate at different concentrations. The drug release was found to 84%, 87%, 84% and 81% at end of 15 minutes were shown in Table 6 and Figure 3 from these three different super disintegrating agent 3% crospovidone formulation F5 show good drug release.

Table 2 Tablet blend evaluation test

Formulations	Angle of repose	Bulk density	Tapped density	Percent compressibility index	Hausner Ratio
F1	$31^0\,62^{"}$	0.49	0.65	16.0	1.22
F2	$32^0\,28^{"}$	0.30	0.36	15.6	1.20
F3	$32^0\,62"$	0.25	0.31	18.3	1.24
F4	$30^0\,20"$	0.21	0.25	15.0	1.19
F5	$31^0\,74"$	0.22	0.25	12.0	1.13
F6	$30^0\,90"$	0.37	0.43	13.9	1.16
F7	$32^0\,12"$	0.37	0.42	11.9	1.13
F8	$32^0\,54"$	0.33	0.37	10.8	1.12
F9	$31^0\,62"$	0.25	0.30	16.6	1.20
F10	$30^0\,94"$	0.25	0.30	15.6	1.21
F11	$31^0\,22"$	0.37	0.45	16.7	1.21
F12	$31^0\,30"$	0.21	0.25	16.0	1.19

The graph were plotted cubic root of 100 cubic root of drug remained vs. time, the drug release for the optimized formulation F5 according to Hixon and Crowell equation. From the results drug release of F5 formulation shows Hixons and Crowell mechanisms. It indicates a change in the surface area and diameter of the tablet with the progressive dissolution

of tablet as the function time. IR spectroscopic studies indicated that the drug was compatible with all the excipients. Short term stability studies of the above formulations indicated that there were no significant changes in drug content and *in vitro* dispersion time at the end of 6 month period ($p < 0.05$).

Table 3 Prepared tablets evaluation test

Formulations	Hardness Kg/cm^2	Friability (%)	Thickness (mm)	Content uniformity (%)	Wetting time (s)	*In vitro* dispersion time (s)	Water absorption ratio (%)
F1	3.3±0.15	0.69	2.48	96	92±0.81	74±1.24	66.3± 0.54
F2	3.5±0.17	0.79	2.44	97	63±0.21	69 ±1.34	71.3± 0.56
F3	3.0±0.11	0.69	2.51	95	42±0.24	54 ±1.32	77.4± 0.45
F4	3.3±0.15	0.64	2.49	97	55±0.25	73 ±1.26	74.6± 0.64
F5	3.5±0.11	0.54	2.55	99	38±0.85	24 ±1.26	84.1 ±0.88
F6	3.0±0.17	0.64	2.48	98	24±0.92	46 ±1.34	78.3± 0.78
F7	3.3±0.15	0.73	2.49	95	63±1.12	53 ±1.45	77.3± 0.24
F8	3.4±0.15	0.59	2.58	94	35±0.13	63 ±1.24	72.0± 0.45
F9	3.0±0.18	0.78	2.55	98	68±1.24	68± 0.98	62.6± 0.65
F10	2.9±0.20	0.54	2.51	101	71±0.25	90 ±1.12	59.6± 0.48
F11	3.3±0.15	0.74	2.50	102	69±0.87	114 ±1.54	53.8± 0.95
F12	3.5±0.05	0.59	2.57	98	53±1.00	120 ±1.25	49.0± 0.35

*Average of three determinations

Table 4 *In vitro* drug release studies of croscarmellose sodium

Time (min)	F1	F2	F3	F4
0	0	0	0	0
2	51.84	52.30	56.35	52.74
5	59.72	75.52	68.25	60.34
7	76.60	87.83	79.30	75.93
10	87.83	92.42	85.90	89.10
15	95.90	96.15	97.48	96.38
30	95.26	92.76	96.35	95.80
45	93.80	91.14	95.74	95.16

Table 5 *In vitro* drug release studies of crospovidone

Time (min)	F5	F6	F7	F8
0	0	0	0	0
2	63.44	60.54	60.24	58.44
5	77.68	72.34	73.14	72.53
7	89.40	87.60	84.83	85.86
10	97.36	96.90	94.64	93.36
15	96.82	96.16	95.34	95.64
30	95.42	94.24	95.15	94.82
45	93.80	93.85	93.64	92.32

Table 6 *In vitro* drug release studies of sodium starch glycolate

Time (min)	F9	F10	F11	F12
0	0	0	0	0
2	50.62	50.72	49.64	48.70
5	53.54	54.83	53.34	53.84
7	63.63	62.74	66.74	62.92
10	74.90	71.88	69.74	73.92
15	83.70	86.88	83.92	81.44
30	95.84	96.10	92.44	88.80
45	93.72	94.20	94.52	92.56

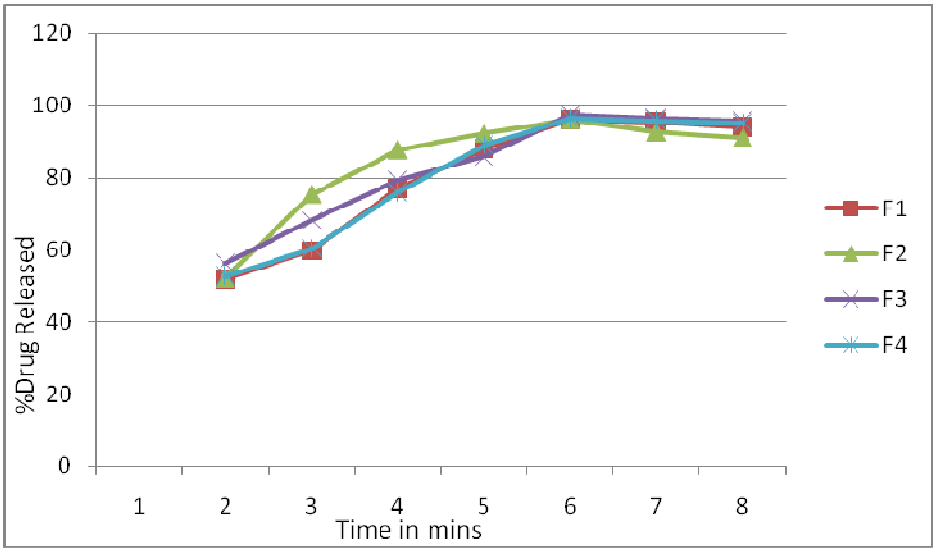

Figure 1 Plot of *In vitro* drug released studies of croscarmellose sodium

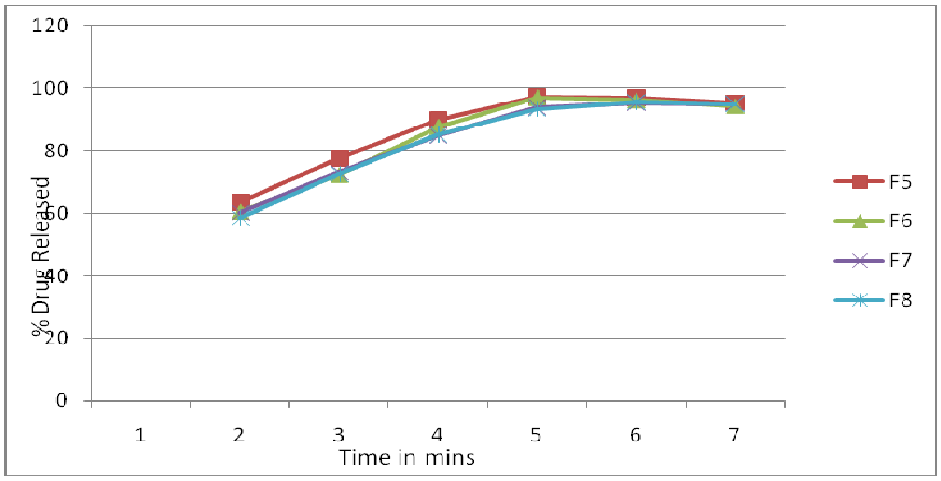

Figure 2 Plot of *in vitro* drug released of crospovidone

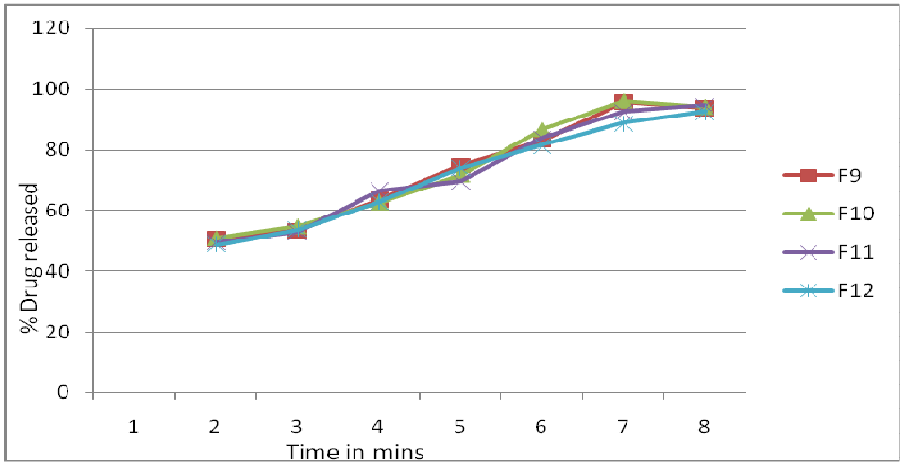

Figure 3 *In vitro* drug release studies of sodium starch glycolate

Conclusion

The oro dispersible tablets of clonazepam were prepared by direct compression method using three super disintegrants, viz., croscarmellose sodium, crospovidone and sodium starch glycolate at different concentrations with microcrystalline cellulose along with directly compressible mannitol to enhance mouth feel. A total of 12 formulations were designed. Amoung these formulations tablets containing 3% crospovidone F5 formulation were optimized due to its fast *in vitro* dispersion when compare to other formulations and 97% drug release with in 15 min.

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