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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL TABLETS OF NITRAZEPAM

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ABSTRACT
The present study aimed to develop and evaluate fast dissolving oral tablets of Nitrazepam to improve its solubility, disintegration, and patient compliance. Preformulation studies confirmed that Nitrazepam is a white, bitter, crystalline powder with slight solubility in water and 0.1 N HCl, but good solubility in ethanol, methanol, chloroform, phosphate buffer (pH 6.8), and 0.1 N NaOH. The melting point, FTIR spectrum, and loss on drying were consistent with standard specifications, confirming the purity and stability of the drug. Pre-compression studies revealed that the powder blends exhibited fair to acceptable flow properties, with formulations F1, F5, and F6 showing better compressibility. Post-compression evaluation demonstrated that all formulations met pharmacopeial standards for hardness, friability, weight variation, thickness, and drug content. Disintegration studies revealed that formulation F3, containing 20 mg Crospovidone, showed the shortest disintegration time (53±8 seconds), while other formulations showed slower disintegration, particularly those containing Croscarmellose sodium. In-vitro dissolution studies indicated that formulation F3 released 96.65% of drug within 15 minutes, exhibiting rapid and complete release. Kinetic modeling showed that drug release followed Zero Order (r^2 = 0.9951) and Higuchi kinetics (r^2 = 0.9888), suggesting a concentration-independent, diffusion-controlled release mechanism. These findings establish formulation F3 as the optimized fast dissolving Nitrazepam tablet, offering rapid onset of action, consistent release, and improved therapeutic effectiveness, thereby enhancing patient compliance.

KEYWORDS: Nitrazepam, Fast dissolving tablets, Preformulation studies, Superdisintegrants, Crospovidone, In-vitro dissolution, Release kinetics, Zero-order kinetics.

INTRODUCTION
Fast dissolving drug delivery systems (FDDTs) were introduced in the late 1970s as an alternative to conventional dosage forms for patients experiencing difficulty in swallowing, particularly pediatric and geriatric populations. These tablets are designed to dissolve or disintegrate rapidly in saliva, typically within 60 seconds, eliminating the need for water. FDDTs offer advantages such as improved patient compliance, faster onset of action, and partial bypassing of first-pass metabolism, thereby enhancing drug bioavailability.

Superdisintegrants such as sodium starch glycolate, crospovidone, and croscarmellose sodium play a crucial role in promoting rapid disintegration. Despite their advantages, challenges such as achieving mechanical strength, taste masking, and environmental sensitivity remain. Nitrazepam, a benzodiazepine with sedative and hypnotic properties, suffers from limited aqueous solubility and variable bioavailability. Formulating Nitrazepam as an FDDT may provide enhanced therapeutic efficacy and better patient compliance.

MATERIALS AND METHODS
Materials
Nitrazepam was obtained from Bioplus Life Sciences Pvt. Ltd., Bangalore. Superdisintegrants including sodium starch glycolate, crospovidone, and croscarmellose sodium were procured from Loba Chemie Pvt. Ltd., Mumbai. Other excipients such as microcrystalline cellulose, talc, and magnesium stearate were used as received.

Preformulation Studies
Physicochemical properties of Nitrazepam including solubility, melting point, and FTIR spectra were studied. The λmax was determined using UV-Visible spectrophotometry in phosphate buffer pH 6.8.

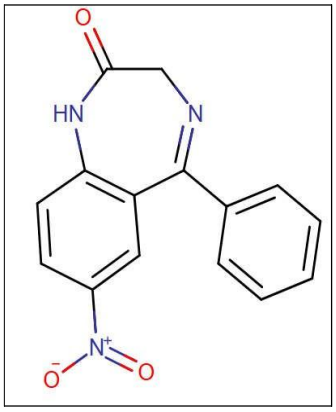

Figure 1: Chemical structure of drug: Nitrazepam.

Formulation Development

Nine formulations (F1–F9) were prepared by direct compression using different concentrations of superdisintegrants. All powders were passed through sieve no. 60, mixed, and lubricated with talc and magnesium stearate before compression into tablets (150 mg each).

Table 1: Composition of Nitrazepam mouth dissolving tablets.

Ingredients (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nitrazepam	10	10	10	10	10	10	10	10	10
Sodium Starch glycolate	10	15	20	-	-	-	10	15	20
Crospovidone	10	15	20	10	15	20	-	-	-
Croscarmellose sodium	-	-	-	10	15	20	10	15	20
Microcrystalline cellulose	109	99	89	109	99	89	109	99	89
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	150	150	150	150	150	150	150	150	150

Evaluation Parameters

- **Pre-compression:** Angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio.
- **Post-compression:** Hardness, friability, thickness, weight variation, drug content, disintegration time, and in-vitro dissolution (USP Type II apparatus, 75 rpm, 900 ml phosphate buffer pH 6.8 at 37±0.5 °C).
- **Kinetic modeling:** Zero Order, First Order, Higuchi, and Korsmeyer-Peppas models were applied to the drug release data.

RESULTS

Preformulation Studies

Nitrazepam was confirmed as a white, crystalline, slightly bitter drug with solubility consistent with pharmacopeial data. FTIR spectra confirmed no drug-excipient interaction.

Pre-compression Studies

Powder blends demonstrated fair to good flow properties, with Carr's index values within acceptable ranges.

Post-compression Studies

All formulations complied with pharmacopeial standards for hardness (2.9–3.5 kg/cm²), friability (<1%), and content uniformity (95–102%).

Disintegration Studies

Formulation F3 (20 mg Crospovidone) showed the fastest disintegration (53±8 seconds). Formulations with croscarmellose sodium showed longer disintegration times.

In-vitro Dissolution

Formulation F3 achieved 96.65% drug release within 15 minutes, significantly outperforming other formulations.

Kinetics

Drug release from F3 followed Zero Order ($r^2 = 0.9951$) and Higuchi ($r^2 = 0.9888$) models, indicating concentration-independent, diffusion-controlled release.

Results of Physical evaluation

Table 2: List of Sensory characters.

1.	Color	White
2.	Taste	Bitter
3.	Appearance	Crystalline powder

The Nitrazepam was identified as a white, bitter-tasting crystalline powder based on its sensory characteristics.

Table 3: Solubility of Nitrazepam.

S. No.	Solvent used	Solubility of Nitrazepam
1.	Water	Slightly soluble
2.	0.1 N HCl	Slightly soluble
3.	Ethanol	Soluble
4.	Methanol	Soluble
5.	Chloroform	Soluble
6.	Phosphate buffer pH 6.8	Soluble
7.	0.1 N NaOH	Soluble

Nitrazepam was found to be slightly soluble in water and 0.1 N HCl, while it showed good solubility in ethanol, methanol, chloroform, phosphate buffer (pH 6.8), and 0.1 N NaOH.

Table 4: Melting point of Nitrazepam.

S. No.	Standard melting point	Sample melting point
1.	227°C	226-228°C

Result: The melting point of Nitrazepam was found to be 226-228°C.

Results of Identification test using FTIR Spectroscopy

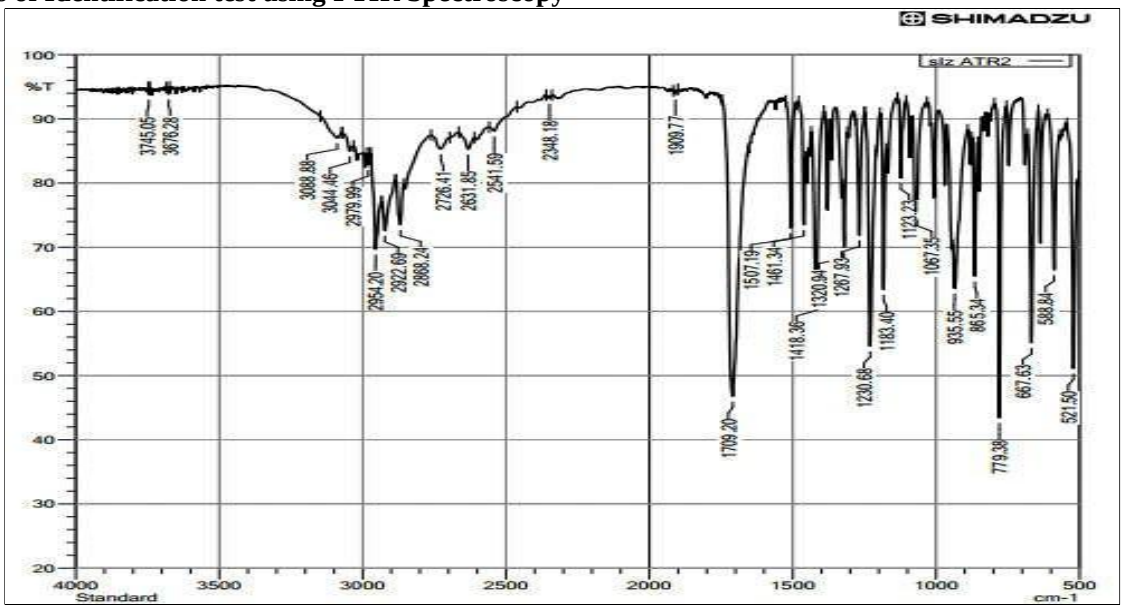

Figure 2: FT-IR Spectrum of pure drug (Nitrazepam).

Table 5: Interpretation of FT-IR spectra.

S. No.	Peak Position (cm^{-1})	Functional Groups
1	3088.88	N–H stretching
2	1709.20	C=O stretching
3	1507.19	Aromatic ring vibrations
4	1320.94	C–N stretching

Table 6: Results of pre-compression parameters of Nitrazepam.

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.385	0.486	20.782	1.262
F2	0.345	0.475	27.368	1.377
F3	0.365	0.482	24.274	1.321
F4	0.347	0.476	27.101	1.372
F5	0.365	0.477	23.480	1.307
F6	0.374	0.485	22.887	1.297

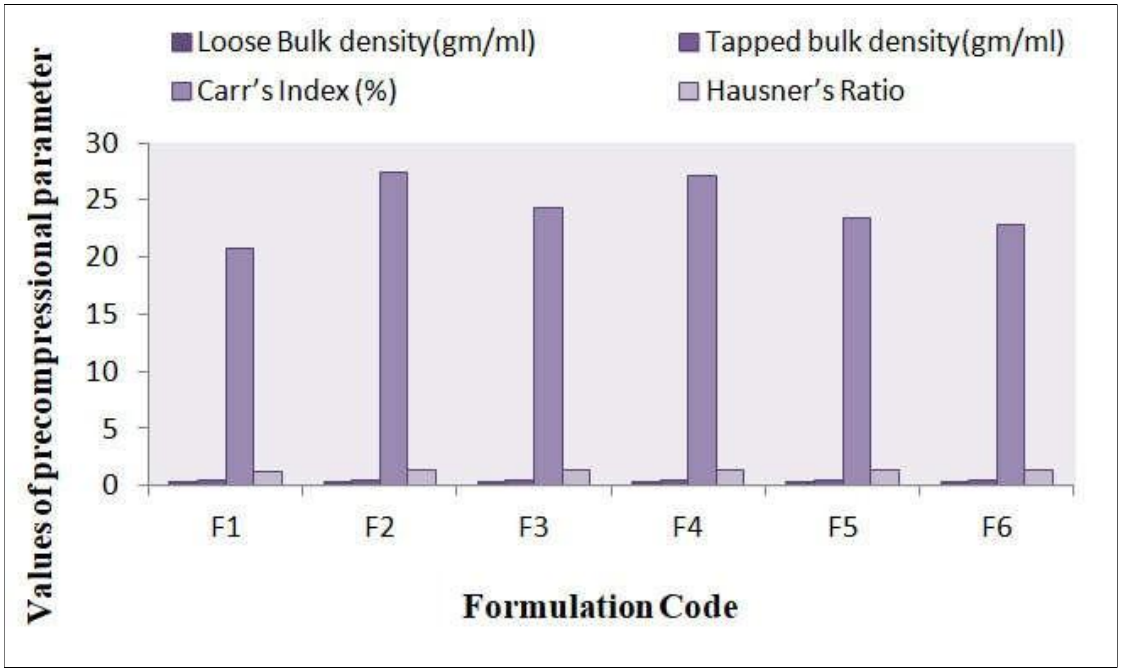

Figure 3: Results of pre-compression parameters.

The pre-compression parameters of Nitrazepam formulations (F1–F6) provide important insights into the flowability and compressibility of the powder blends, which are critical for efficient tablet manufacturing. The loose bulk density of the formulations ranged from 0.345 g/ml (F2) to 0.385 g/ml (F1). This indicates that F1 had the most densely packed powder initially, while F2 had a more loosely packed structure. The tapped bulk density values ranged from 0.475 to 0.486 g/ml, reflecting how well the powders can be packed upon mechanical tapping.

Carr's Index, which measures compressibility, ranged from 20.782% (F1) to 27.368% (F2). According to standard guidelines, Carr's Index below 15% indicates excellent flow, 15– 20% good, 20–25% fair, and above 25% poor flow. Therefore, most formulations fall into the fair to poor flowability range, with F2 and F4 showing poorer flow properties due to higher compressibility indices. Hausner's Ratio, another indicator of flow, ideally should be close to 1.00, with values ≤1.25 indicating good flow. Here, the ratio varied from 1.262 (F1) to 1.377 (F2). Again, F1, F5, and F6 showed better flow properties, while F2 and F4 had higher ratios, suggesting more resistance to flow and potential issues in tablet uniformity and weight variation during compression. F1, F5, and F6 demonstrated acceptable pre- compression characteristics, including relatively good compressibility and flow, making them more suitable for direct compression.

Table 7: Results of post-compression parameters of all formulations.

F. Code	Hardness test (kg/cm2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
F1	3.3±0.2	0.658±0.025	149±5	1.25±0.05	97.78±0.15
F2	3.4±0.3	0.774±0.036	150±4	1.29±0.03	98.85±0.25
F3	3.5±0.5	0.698±0.085	155±8	1.25±0.06	99.45±0.36
F4	3.3±0.4	0.758±0.038	148±5	1.26±0.07	97.74±0.41
F5	3.4±0.3	0.695±0.045	155±6	1.28±0.06	96.56±0.38
F6	3.6±0.6	0.774±0.036	168±3	1.29±0.07	95.45±0.45

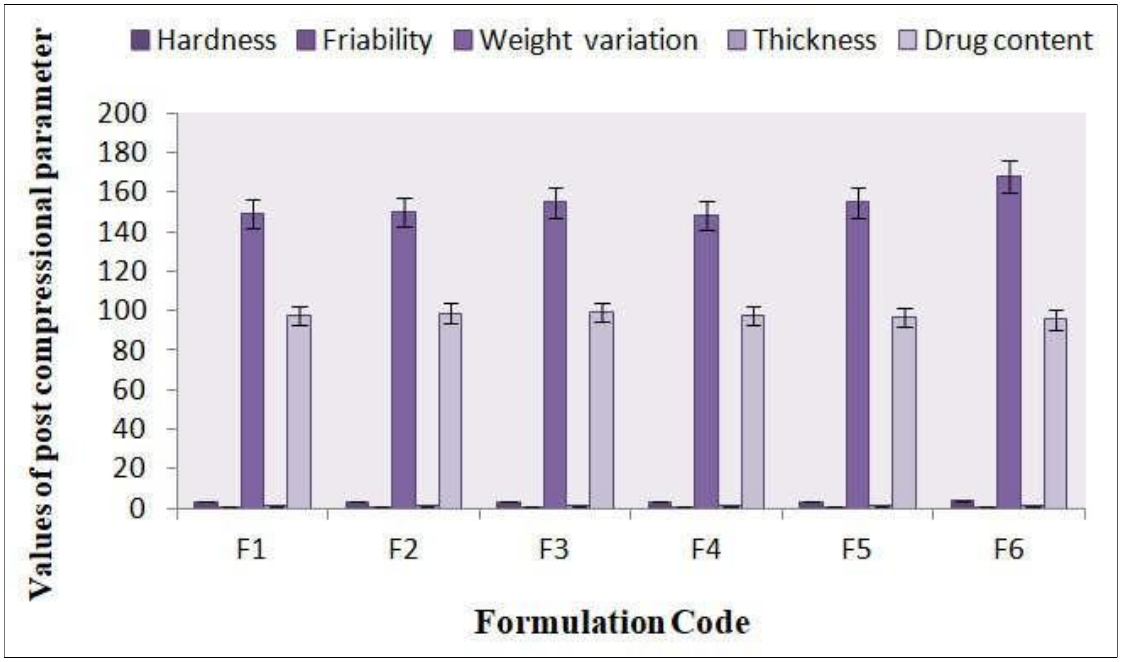

Figure 4: Results of post-compression parameters of all formulations.

Tablet hardness ranged from 3.3 to 3.6 kg/cm², which indicates that all formulations had acceptable mechanical strength suitable for handling and transportation. F6 exhibited the highest hardness (3.6±0.6 kg/cm²), suggesting better compression and binding properties, while F1 and F4 had the lowest hardness (3.3±0.2 and 3.3±0.4 kg/cm²). This suggests slightly weaker bonding, but still within acceptable limits for fast dissolving tablets.

DISCUSSION

This study highlights the effectiveness of crospovidone as a superdisintegrant in FDDTs of Nitrazepam. Formulation F3 demonstrated superior performance in terms of disintegration and dissolution, aligning with literature on the role of crospovidone in enhancing rapid drug release. The diffusion-controlled release mechanism supports the suitability of F3 for immediate therapeutic effect. Compared with previous FDT studies of other drugs, the optimized formulation showed competitive or superior performance.

CONCLUSION

Formulation F3, containing 20 mg Crospovidone, was identified as the optimized fast dissolving Nitrazepam tablet. It exhibited rapid disintegration, high dissolution efficiency, and consistent release kinetics. This formulation offers potential benefits of improved bioavailability, rapid onset of action, and enhanced patient compliance. Further in-vivo studies and stability evaluations are recommended to confirm clinical applicability.

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