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# DESIGN AND EVALUATION OF CLOZAPINE ORODISPERSIBLE TABLETS

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**Abstract:**

*In the present investigation, Orodispersible tablets of Clozapine were prepared by direct compression method using Ac-di-sol and Crospovidone as superdisintegrants with various concentrations (2%, 4%, 6% and 8%). The drug and excipient blend was evaluated for bulk density, tapped density, carr's index, angle of repose and hausner's ratio. The prepared tablets were evaluated for hardness, thickness, friability, drug content uniformity, wetting time, water absorption ratio, in vitro dispersion time and dissolution studies. Among all the formulations, formulation containing crospovidone ($F_8$) with the concentration of 8% produced less in vitro dispersion time ( 15 sec), disintegration time (19 sec), wetting time ( 17 sec) and higher drug release rate (94 %) in 30 minutes. Short-term stability studies on the promising formulations indicated that there are no significant changes in drug content and in vitro dispersion time. IR-spectroscopic studies indicated that there are no drug-excipient interactions.*

***Keywords:*** *Clozapine, Ac-di-sol, Crospovidone, Orodispersible tablets.*

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## INTRODUCTION:

Orodispersible tablets are solid single-unit dosage forms that are placed in the mouth, and allowed to disperse or dissolve in the saliva without the need of water and provide a quick onset of action. Other appellations for Orodispersible tablets include, quick dissolves, fast melts, fast dissolving, fast disintegrating, rapid-dissolve, or orally dissolving tablets[1-3]. The fast-dissolving solid dosage form turns into a soft mass or liquid form to facilitate swallowing, consequently, the risk of choking is reduced considerably. Orodispersible tablets offer both the advantages of solid dosage forms and liquid dosage forms along with distinctive properties which include accurate dosing, ease of administration, quick onset of action, enhanced bioavailability, and increased patient complianc[4-6].

Fast dissolving drug delivery can be prepared various techniques like direct compression, wet granulation, compression moulding, volatization and freeze – drying. They involve different mechanisms like use of high amounts of hydrophilic disintegrating agents which allow the dosage forms to disintegrate quickly in the patient's mouth on contact with saliva[7].

A fast disintegrating or dissolving system or tablet can be defined as a solid dosage form that can disintegrate or dissolve within 30 seconds, in the oral cavity resulting in a solution or suspension without administration of water. The fast-disintegrating tablets are synonymous with fast dissolving tablets, melt in mouth tablets, rapidmelts, Porous tablets, Orodispersible, quick dissolving or rapidly disintegrating tablets[8-9].

Clozapine is a class of a typical antipsychotics mainly used for the treatment of schizophrenia, manic and bipolar disorders. The half life of the drug is around 6 to 26 hours and is practically insoluble in water as well as in isopropyl alcohol. Due to higher half life of the drug, it is most suitable for once a day formulation in the form of Orodispersible tablets rather than immediate release tablets. Immediate release tablets are unable to administer to psychic patients. So, orodispersible are most suitable for psychic patients as well as for geriatrics, pediatrics and the persons having less access of water[10].

## MATERIALS AND METHODS:

Clozapine was procured from Aurabindo, Hyderabad, all other ingredients obtained from SD Fine Chemicals Pvt Ltd, Hyderabad.

### Characterization of Drug and Excipients

FTIR studies were conducted for drug substance alone and drug substance with excipients mixture. Weighed approximately one mg of Clozapine drug substance and uniformly mixed with 99 mg of potassium bromide which was previously dried at 60°C for two hours in hot air oven. The mixture was compressed under high pressure to form a transparent pellet, and then it was transferred to IR spectrophotometer and scanned for percentage transmittance. The same procedure was repeated for Clozapine with excipient mixture and scanned respectively.

### Preparation of Standard graph of Clozapine by UV method

Weighed and transferred accurately about 100 mg of Clozapine into 100ml volumetric flask and added 40ml of methanol and sonicated for 10 minutes until it dissolves. Then solution was made upto the mark with pH 7.4 phosphate buffer. From this solution, prepared standard dilutions with concentrations ranging from 1µg/ml to 14µg/ml and the absorbance was measured at 260nm by using UV against 7.4 phosphate buffer as blank and plotted a graph of Concentration on X-axis versus absorbance on Y-axis.

### Development of Clozapine orodispersible tablets

All the materials Clozapine, poloxamer, microcrystalline cellulose (MCC), Mannitol, Menthol, Sodium saccharin, crospovidone and Ac-di-sol (crosscarmellose sodium) passed through the sieve # 60 separately to attain uniformity and proper mixing of all the ingredients and collected separately in polyethylene bag. Talc, Magnesium stearate were passed through sieve # 40 mixed and blended with above powder blend in polyethylene bag. The entire powder blend was directly compressible into tablets with 10 mm round shaped, flat punches using eight station rotary tablet compression machine.

The trial $F_0$ was formulated without adding Superdisintegrants, microcrystalline cellulose, mannitol as diluents, Sodium saccharin as sweetener, talc as glidant, Magnesium stearate as lubricant.

The trial $F_1$ - $F_4$ was formulated with Ac-di-sol as Superdisintegrants with various concentrations (2%, 4%, 6% & 8%), microcrystalline cellulose, mannitol as diluents, Sodium saccharin as sweetener, talc as glidant, Magnesium stearate as lubricant.

The trial $F_5$ - $F_8$ was formulated with crospovidone as Superdisintegrants with various concentrations (2%, 4%, 6% & 8%), microcrystalline cellulose, mannitol as diluents, Sodium saccharin as sweetener, talc as glidant, Magnesium stearate as lubricant (Table 1).

**Table 1: Composition of different batches of Clozapine Orodispersible Tablets**

| Ingredients (mg/tab) | $F_0$ | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ |
|---|---|---|---|---|---|---|---|---|---|
| Clozapine | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Poloxamer | 25 | 25 | 50 | 75 | 100 | 25 | 50 | 75 | 100 |
| Ac-di-sol | - | 05 | 10 | 15 | 20 | -- | - | - | - |
| Crospovidone | - | - | - | - | - | 05 | 10 | 15 | 20 |
| MCC | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Mannitol | 137.5 | 132.5 | 102.5 | 72.5 | 42.5 | 132.5 | 102.5 | 72.5 | 42.5 |
| Menthol | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium stearate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Talc | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Sodium saccharin | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| **Total tablet weight** | **250** | **250** | **250** | **250** | **250** | **250** | **250** | **250** | **250** |

**Micromeritic properties of powder blend**
The prepared powder blend was evaluated for the bulk density, tapped density, angle of repose, carr's index and Hausner's ratio.

**Post compression studies**
The prepared tablets were evaluated for Thickness, Hardness, Friability, Weight Variation test, Wetting Time, In vitro dispersion time, Water absorption ratio, In-vitro disintegration time, Assay, In-Vitro drug release studies, Stability studies, kinetic studies.

**Dissolution studies**
*In vitro* dissolution of Clozapine orodispersible tablets was studied in USP type-II dissolution apparatus employing a paddle stirrer at 50 rpm. 900 ml of pH 7.4 phosphate buffer was used as dissolution medium. The temperature of dissolution medium was maintained at $37 \pm 0.5^{o}$ C throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbances at 260 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent drug released was calculated and plotted against time.

**Stability studies**
According to ICH guidelines the optimized formulation was kept for stability at accelerated conditions (40°C/75% RH) for studying quality of the drug product during its shelf-life. Tablets were withdrawn from stability chamber at 1st, 2nd, 3rd& 6th month and analyzed for assay, friability, disintegration, dissolution, dispersion time and related substances content.

**Kinetic study**
The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation/ Peppas model – Log cumulative percent drug released versus log time.

## RESULTS AND DISCUSSION:
Orodispersible tablets of Clozapine were prepared by direct compression method using Ac-di-sol and Crospovidone as superdisintegrants with various concentrations (2%, 4%, 6% and 8%). Mannitol was used as diluent to enhance mouth feel. A total of eight formulations and control formulation ($F_0$ , without superdisintegrants) were formulated.

Compatibility studies of drug alone and drug with physical mixture of excipients were performed using FT-IR spectrophoto meter. The peaks obtained in the spectra of each sample of drug and excipient correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components.

The powder blend was evaluated for micromeritic properties and the bulk density, tapped density, angle of repose, carr's index and Hausner's ratio values were found in the range of 0.51 to 0.55g/cc, 0.58 to 0.62 g/cc, 17.69° to 31..05° , 8.47% to 12.46% and 1.09 to 1.13 respectively. All the formulations show good results and lies within the acceptable range which indicate good flow properties (Table 2).

**Table 02: Micromeritic Properties of Clozapine Powder blend**

| Formulation code | Bulk Density (g/cc) | Tapped density (g/cc) | Angle of repose (degree) | Carr's index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| $F_0$ | 0.54 | 0.61 | 31.05 | 11.47 | 1.12 |
| $F_1$ | 0.54 | 0.60 | 27.05 | 10 | 1.11 |
| $F_2$ | 0.53 | 0.59 | 23.05 | 10.16 | 1.11 |
| $F_3$ | 0.51 | 0.58 | 22.06 | 12.06 | 1.13 |
| $F_4$ | 0.53 | 0.60 | 28.06 | 11.66 | 1.13 |
| $F_5$ | 0.55 | 0.62 | 30.4 | 11.29 | 1.12 |
| $F_6$ | 0.54 | 0.61 | 28.06 | 11.47 | 1.12 |
| $F_7$ | 0.54 | 0.59 | 17.69 | 8.47 | 1.09 |
| $F_8$ | 0.55 | 0.62 | 32.4 | 11.29 | 1.12 |

The powder blend was compressed into tablets and evaluated for post compression parameters. Weight Variation was found in the range of 249.6±2.458 to 250.9±2.846, Thickness was found in the range of 2.99±0.288 to 3.09±0.314 mm, Hardness was found in the range of 3.08±0.229 to 3.19±0.265 kg/cm$^2$, Friability was found in the range of 0.39±0.026 to 0.53±0.02%, Drug Content uniformity was found in the range of 98.13±0.460 to 99.54±0.860 (Table 3).

**Table 03: Post Compression Parameters of Clozapine Orodispersible Tablets**

| Formulation code | Weight Variation (%) | Thickness (mm) | Hardness (kg/cm$^2$) | Friability (%) | Drug Content (%) |
|---|---|---|---|---|---|
| $F_0$ | 249.8±1.619 | 3.08±0.209 | 3.13±0.205 | 0.53±0.02 | 98.57±0.157 |
| $F_1$ | 250.5±2.549 | 3.01±0.200 | 3.14±0.313 | 0.50±0.03 | 98.92±0.824 |
| $F_2$ | 249.3±2.213 | 3.04±0.177 | 3.18±0.252 | 0.40±0.015 | 98.94±0.703 |
| $F_3$ | 250.3±1.494 | 3.05±0.190 | 3.09±0.223 | 0.39±0.026 | 98.13±0.460 |
| $F_4$ | 250.4±1.897 | 3.02±0.214 | 3.08±0.229 | 0.43±0.02 | 99.54±0.860 |
| $F_5$ | 250.4±2.336 | 3.09±0.314 | 3.18±0.044 | 0.51±0.025 | 98.64±0.332 |
| $F_6$ | 249.6±2.458 | 3.08±0.265 | 3.18±0.265 | 0.46±0.041 | 98.21±0.340 |
| $F_7$ | 250.1±2.131 | 2.99±0.288 | 3.19±0.265 | 0.48±0.025 | 99.03±0.468 |
| $F_8$ | 250.9±2.846 | 3.06±0.189 | 3.16±0.245 | 0.48±0.025 | 98.29±0.605 |

Among all the formulations designed, formulation containing crospovidone (8%) shows less wetting time (17 sec), in vitro dispersion time (15 sec), disintegration time (19 sec) (Table 4) and better drug release characteristics (94%) (Table No.05 & Fig. 01) and the experimental data shows that the results obtained from the crospovidone were better than Ac-di-sol.

**Table 04: Post Compression Parameters of Clozapine Orodispersible Tablets:**

| Formulation Code | Wetting time (sec) | Water absorption ratio (%) | Disintegration time (sec) | In vitro dispersion time (sec) |
|---|---|---|---|---|
| $F_0$ | 463.21±2.41 | 16.02±1.29 | 239±1.62 | 169.42±1.01 |
| $F_1$ | 71.34±1.42 | 71.83±0.69 | 73±0.34 | 75.15±0.34 |
| $F_2$ | 52.68±1.07 | 79.26±0.88 | 54±0.11 | 49.39±0.11 |
| $F_3$ | 33.35±2.64 | 83.56±1.77 | 36±0.29 | 37.23±0.29 |
| $F_4$ | 27.67±1.52 | 87.77±0.65 | 29±0.12 | 24.03±0.12 |
| $F_5$ | 68.66±0.47 | 68.96±0.35 | 71±0.10 | 63.12±0.10 |
| $F_6$ | 46.64±1.13 | 76.75±0.52 | 49±1.26 | 39.19±1.26 |
| $F_7$ | 24.55±2.18 | 81.56±0.15 | 27±1.27 | 21.03±1.27 |
| $F_8$ | 17.45±3.05 | 93.08±1.23 | 19±0.45 | 15.03±0.45 |

**Table 05: In-vitro Drug release studies of Clozapine Orodispersible Tablets**

| Time (Min) | % Cumulative amount of drug release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $F_0$ | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 05 | 10.27±1.4 | 21.34±1.00 | 27.75±1.54 | 34.05±0.54 | 38.55±1.24 | 26.08±1.73 | 31.37±1.56 | 39.42±1.02 | 42.82±1.65 |
| 10 | 13.21±0.5 | 29.70±1.34 | 36.20±1.43 | 43.92±1.37 | 54.83±2.04 | 33.54±2.74 | 45.37±2.34 | 58.01±1.39 | 70.78±2.64 |
| 15 | 20.07±1.2 | 38.39±2.01 | 49.16±2.17 | 59.23±2.05 | 62.80±1.51 | 44.26±2.46 | 56.91±2.68 | 67.32±1.75 | 76.83±2.73 |
| 20 | 24.19±1.4 | 46.50±2.67 | 58.92±2.53 | 65.73±0.84 | 71.77±1.58 | 55.98±2.39 | 62.47±2.47 | 75.89±1.91 | 82.05±2.78 |
| 25 | 28.61±1.9 | 58.22±1.45 | 63.70±1.73 | 77.80±1.54 | 78.52±1.05 | 64.32±1.87 | 77.65±1.47 | 81.92±2.36 | 89.17±2.18 |
| 30 | 30.84±0.6 | 71.56±1.67 | 74.30±1.78 | 81.66±1.54 | 89.53±1.54 | 73.08±2.78 | 81.24±2.43 | 90.37±1.52 | 94.25±1.65 |

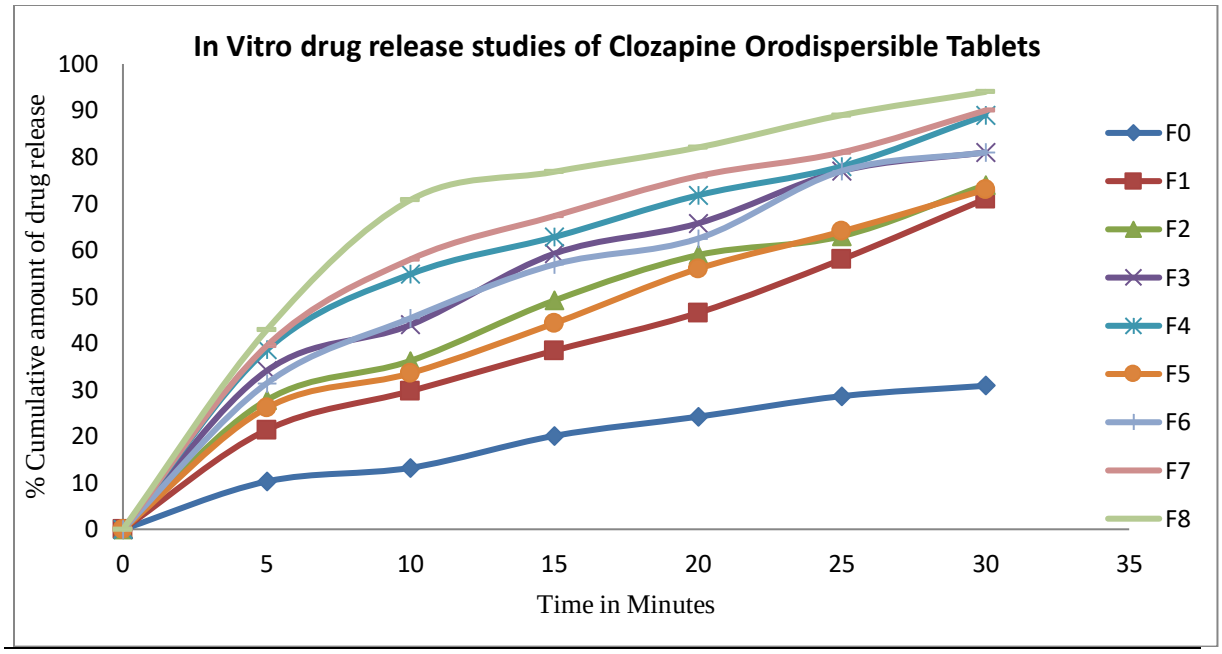


**Fig 01: In Vitro drug release studies of Clozapine Orodispersible Tablets**

Short-term stability studies conducted on formulation ($F_8$) at $40^0$C/ 75% RH for 3 months have shown no significant changes in physical appearance, drug content and *in vitro* dispersion time and dissolution.

The in vitro drug release data of the fast-dissolving tablets were evaluated kinetically by zero order, first order, Higuchi, peppas, Hixon crowell model. Statistical analysis of the data by the method of least squares gives correlation coefficient values in the range of 0.91 to -0.99 for most of the formulations (table 06).

**Table 06: Kinetic studies of Clozapine Orodispersible Tablets:**

| Formulation code | Zero order ($R^2$ value) | First order ($R^2$ value) | Higuchi ($R^2$ value) | Peppas ($R^2$ value) | Hixon Crowell ($R^2$ value) |
|---|---|---|---|---|---|
| $F_0$ | 0.9818 | 0.9864 | 0.9894 | 0.9918 | 0.9736 |
| $F_1$ | 0.9999 | 0.9979 | 0.9924 | 0.9940 | 0.9624 |
| $F_2$ | 0.9854 | 0.9723 | 0.9617 | 0.9641 | 0.9367 |
| $F_3$ | 0.9745 | 0.9531 | 0.9453 | 0.9457 | 0.9519 |
| $F_4$ | 0.9643 | 0.9842 | 0.9870 | 0.9907 | 0.9256 |
| $F_5$ | 0.9894 | 0.9802 | 0.9683 | 0.9686 | 0.9574 |
| $F_6$ | 0.9969 | 0.9999 | 0.9996 | 0.9998 | 0.9246 |
| $F_7$ | 0.9592 | 0.9848 | 0.9838 | 0.9872 | 0.9210 |
| $F_8$ | 0.8775 | 0.9247 | 0.9227 | 0.9411 | 0.9446 |

## CONCLUSION:

In the present study, it can be concluded that the Clozapine Orodispersible tablets prepared with Crospovidone (8%) showed better water absorption ratio, wetting time, in vitro dispersion time and drug release characteristics over Ac-di-sol.

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