World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: https://wjpsonline.com/
Research Article

FORMULATION AND EVALUATION OF CLOZAPINE ORALLY DISINTEGRATING TABLETS

[1]CH. Praveen Kumar, [2]I. Nagaraju, [3]Dr. G. Vijaya Kumar

[1]Student, Department of Pharmaceutics, KGR Institute of Technology & Management, Rampally, Secunderabad, Telangana – 501301.

[2]Professor, Department of Pharmaceutics, KGR Institute of Technology & Management, Rampally, Secunderabad, Telangana – 501301.

[3]Principal, Department of Pharmaceutics, KGR Institute of Technology & Management, Rampally, Secunderabad, Telangana – 501301.

Received: 25-07-2025 / Revised Accepted: 28-07-2025 / Published: 01-08-2025

ABSTRACT:
An Orally disintegrating tablet disperses readily in saliva and the drug is available in solution or suspension form for the immediate absorption and resulting in rapid onset of action. In the present research work Clozapine Oral disintegrating tablet were prepared by wet granulation method using varying concentrations of Lycoat, Croscarmellose sodium and Ludiflash as super disintegrants. The formulations prepared were evaluated for precompression & post compression parameters. Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Clozapine) and optimized formulation (Clozapine+ excipients) which indicates there are no physical changes. Post compression parameters was found to be within the limits. Among the formulation prepared the tablet containing concentration of Ludiflash shows 99.26±1.28% of the drug release within 60 min & follows first order kinetics. The overall result indicated that the formulation F12 containing Ludiflash is better and fulfilling of the needs of the Orally disintegrating tablet.

Key words: Orally disintegrating tablets, Clozapine, Ludiflash, FTIR.

INTRODUCTION

Oral drug delivery system is the most convenient and widely accepted route of administration for various therapeutic agents. Among many oral drug delivery systems, oral disintegrating drug delivery systems have gained importance over past 3 decades. Other than other conventional dosage forms like capsules oral disintegrating tablets are defined as one of the sophisticated novel drug delivery systems that have medicinal substances which dissolve or disintegrate rapidly in the mouth without water or chewing[1]. Oral disintegrating tablets are suitable for patients who have dysphasia [2], paediatric, geriatric and psychiatrics. It is also suitable for patients with nausea, vomiting and motion sickness.[3]

Oral administration is the most widely used and convenient route with high stability and a small packaging size [4, 5]. The orally disintegrating tablet (ODT), as a delivery system, rapidly disintegrates in the mouth upon contact with saliva; therefore, it does not need additional water. It is available for absorption through pregastric mucosa. Mouth dissolving/disintegrating tablets (MDTs), quick disintegrating tablets, fast/rapid dissolving or disintegrating tablets (FDTs), quick/rapid melt tablets, orodispersible tablets, and porous tablets are the other recorded names for this type of dosage form [6, 7]. The need for rapid disintegration, rapid onset of action, and patient compliance, especially for pediatric, geriatric, psychiatric, paralyzed, and bedridden patients, leads to the emergence of OTDs in the 1980s [8] and the first articles on the formulation of ODTs using cellulose derivatives published by Watanabe et al. in 1995 [9].

Although ODTs own several merits, they are still a niche product in the market as they have additional requirements. Taste perception is an important issue to consider; formulation of bitter drugs as ODTs is challenging, and taste masking materials should be employed [10], since they are compressed with a low force and

Address for Correspondence: CH. Praveen Kumar, Student, Department of Pharmaceutics, KGR Institute of Technology & Management, Rampally, Secunderabad, Telangana – 501301, Email ID: cheerlapraveenkumar3@gmail.com.

How to Cite this Article: CH. Praveen Kumar, FORMULATION AND EVALUATION OF CLOZAPINE ORALLY DISINTEGRATING TABLETS, World J Pharm Sci 2025; 13(03): 76-87; https://doi.org/10.54037/WJPS.2022.100905

possess a porous matrix [11]. Therefore, handling friable and brittle ODTs is challenging. Hygroscopic characteristics and thermal and humidity sensitivity of ODTs can influence their physical integrity and lead to stability problems. Hence, using special materials is essential for their packaging.

Moreover, decreased amount of saliva in patients on anticholinergic medicines may affect bioavailability [12]. There is a restriction on drug load in ODT minitablets (ODMTs) [13]. Therefore, the preparation of high-dose substances like antibiotics is complex [14]. Environmental pollution and toxicity risks are two other drawbacks related to OTDs' preparation methods. In the coating technique, organic solvents dissolve polymers, and organic solvents are connected with toxicity risk, and solvent removal during the drying process is time-consuming [15]. In this review article, the features of active ingredients and excipients used in the formulation of ODTs were explained. In addition, the manufacturing method of multiple ODT formulations with their pros and cons alongside solutions for associated problems with ODTs were discussed in detail. The depicted quality control steps with required considerations were also discussed.[16]

Clozapine is a tricyclic dibenzodiazepine, classified as an atypical antipsychotic agent. Clozapine displays affinity to various neuroreceptors with a particularly low affinity to the dopamine receptors, thus breaking the mold of first-generation antipsychotics and deeming it "atypical". This low affinity to dopamine receptors results in fewer extrapyramidal side effects, especially tardive dyskinesia. However, its promiscuity toward the muscarinic and adrenergic receptors can result in other side effects, notably gastrointestinal hypomotility and orthostatic hypotension. Despite its effectiveness in treating both positive and negative symptoms of schizophrenia, clozapine was briefly removed from the market in various jurisdictions in 1970 due to severe agranulocytosis. However, continued evidence of its effectiveness led to clozapine's eventual reintroduction, although with a reluctance to prescribe it.[17]

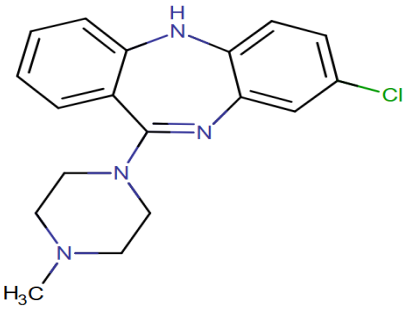

Figure.No: 1 Structure of Clozapine

MATERIALS USED: Clozapine API was procured from Aurore Life Sciences and Ludiflash, Lycoat, Croscarmellose sodium, Aspartame were procured from S.D Fine Chemicals, MCC, Talc and Magnesium stearate were procured from S.D. Fine Chem. Ltd.

METHODOLOGY:

Solubility

Solubility of Clozapine was determined in pH 1.2, pH 7.4, pH 4.5 and 6.8 phosphate buffers. Solubility studies were performed by taking excess amount of Clozapine in beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no.41. The filtered solutions are analyzed by spectrophotometrically.

Determination of λmax: -

10 mg of Clarithromycin was dissolved in 10 ml of 6.8pH Phosphate Buffer by slight shaking (1000 µg/ml). 1 ml of this solution was taken and made up to 10 ml with 6.8pH Phosphate Buffer, which gives 100 µg/ml concentration (stock solution). From this Stock solution (100µg/ml) pipette out 1ml to 10ml volumetric flask and makeup with 6.8 pH buffer upto 10ml was prepared in 6.8 pH Phosphate Buffer. This solution was appropriately diluted with 6.8 pH Phosphate Buffer to obtain a concentration of 10µg/ml. The resultant solution was scanned in range of 200-400nm on Single beam spectrophotometer(YIS-294).

Calibration Curve for Clozapine In 6.8 phosphate buffer

Procedure:

Preparation of Standard Stock Solution: -

10 mg of Clozapine was accurately weighed into 10 ml volumetric flask and dissolved in small quantity of 6.8 phosphate buffer. The volume was made up to 10 ml with the 6.8 pH Buffer to get a concentration of (1000 µg/ml) SS-I. From this, 1 ml was withdrawn and diluted to 10 ml with distilled water to get a concentration of (100 µg/ml) SS-II.

Calibration Curve in 6.8 pH Phosphate Buffer: -
From the standard stock solution (SS-II), 0.2, 0.4, 0.6, 0.8,1 and 1.2 ml were withdrawn and volume was made up to 10 ml with 6.8 phosphate buffer to give a concentration of 2, 4, 6,8 10 and 12µg/ml. Absorbance of these solutions was measured against a blank of 6.8 phosphate buffer at 237 nm for Clozapine and the absorbance values are summarized in Table Calibration curve was plotted, drug concentrations versus absorbance was given in the Figure.

Schematic representation of compatibility studies

Infra Red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

Method:- The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Formulation Of Oral Disintegrating Tablets Of Clozapine:

Oral disintegrating tablets of Clozapine were prepared by wet granulation technique according to the formulae given in the table. All the ingredients were weighed as per weighing record. Clozapine, MCC, and povidone were sifted together through mesh#30.

Preparation of binder solution:

Weighed quantity of purified water was dispensed in a stainless steel container and kept aside.

Dry mixing:

Clozapine, MCC, and povidone were transferred into rapid mixer granulator and mixed for 10 minutes with impeller at slow speed(100rpm) and chopper off.

Granulation:

The binder solution was added to the above mixture and mixed for 2minutes with impeller at slow speed (70rpm) and chopper at high speed (100rpm). Purified water was added to the dry mix blend for 2minutes with impeller at slow speed(70rpm) and chopper at high speed(100rpm). The wet mass was kneaded for 1minute with impeller at slow speed (100rpm) and chopper at high speed(200rpm). The kneaded mass was milled using cone mill through 8mm screen at 15HZ speed.

Drying:

The wet mass was dried using hot air oven by maintaining 600c for 1 hour 45 minutes .

Sifting & milling:

The dried granules were sifted through mesh#24. particles retain on the sieve were further milled using multi mill through 1.5 mm screen at 100rpm with knives in forward direction.

Milled granules were sifted through mesh #24.

Sifting of extra granular materials:

Super disintegrants were sifted through #40. Magnesium stearate was sifted through mesh #60. Finally the granules were transferred into 5litre double cone blender and blended for 5minutes at 20rpm.Then the granules were compressed using tablet punching machine. The formulated tablets were evaluated for post compression parameters.

Drug-Excipient Compatibility Studies By I.R.: -

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation.

Table.No.1 Formulation Table for Clozapine Oral Disintegrating Tablet

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Clozapine	100	100	100	100	100	100	100	100	100	100	100	**100**
MCC	129	126	123	120	129	126	123	120	129	126	123	**120**
Povidone K30	10	10	10	10	10	10	10	10	10	10	10	**10**
Lycoat	3	6	9	12	-	-	-	-	-	-	-	**-**
Croscarmellose sodium	-	-	-	-	3	6	9	12	-	-	-	**-**
Ludiflash	-	-	-	-	-	-	-	-	3	6	9	**12**
Aspartame	4	2	2	2	2	2	2	2	2	2	2	**2**
Talc	2	3	3	3	3	3	3	3	3	3	3	**3**
Magnesium stearate	2	3	3	3	3	3	3	3	3	3	3	**3**
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	**Q.S**
Total	250	250	250	250	250	250	250	250	250	250	250	**250**

EVALUATION PARAMETERS

Precompression Parameters

Method Preparation of Mixed Blend of Drug and Excipients

All the materials were passed through sieve no. 80. Required quantity of each ingredient was taken for each specified formulation (Mentioned in Table)

and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate and talc). The powdered blend was evaluated for flow properties as follows.

Angle of repose: Angle of repose is determined by using funnel method. The accurately weighed blend is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug-excipient blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation. Angle of Repose less than 30 ° shows the free flowing of the material.

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

Bulk density: Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight.

The bulk density was calculated by using the below mentioned formula

$$D_b = \frac{M}{Vo}$$

Where, M is the mass of powder, V0 is the bulk volume of the powder

Tapped density It is determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping is continued until no further change in volume is noted.

The tapped density was calculated using the following formula,

$$D_T = \frac{M}{Vt}$$

Where, M is the mass of powder, V_T is the tapped volume of the powder

Compressibility index: The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index(I) which is calculated as follows,

Carr's Index (I) = (Tapped Density-Bulk Density)/(Tapped Density) x100

The value between 13-19% indicates a powder with usually good flow characteristics, whereas above 21% indicate poor flowability.

Hausner's Ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Hausner's Ratio} = \frac{\text{BulkDensity}}{\text{Tapped Density}}$$

Where D_t is tapped density and D_b is bulk density

Lower Hausner"sratio (<1.25) indicates better flow properties and higher Hausner"s ratio (>1.25) indicates poor flow properties.

EVALUATION OF TABLETS

Post compression parameters

Weight variation test: The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation.

Tablet Hardness: The hardness of tablet is an indication of its strength. It is the force required to break a tablet by compression in the radial direction. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc. Excessive hardness significantly reduces the disintegration time.

Tablet Friability: Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the 20 tablets from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. All the tablets are dedusted and weighed again. The percentage of friability can be calculated using the formula.

% Friability = [(W1-W2)100]/W1

Where, W1= Weight of tablet before test, W2 = Weight of tablet after test

The pharmacopoeial limit of friability test for a tablet is not more than 1%. This test is not applicable for lyophilized and flash dose tablets, but is done for tablets prepared by direct compression and moulding. It is a difficult to achieve friability within this limit for MDT and to keep hardness to the lowest to achieve a minimum possible disintegration time.

In-Vitro Disintegration time: Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing pH 6.8 buffer solution at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The

time taken for the complete disintegration of the tablets was noted.

Thickness and Diameter: Tablet thickness and diameter can be measured using a simple procedure. Five tablets are taken and their thickness is measured using Vernier calipers. The thickness and diameter is measured by placing tablet between two arms of the Vernier calipers.

Drug Content Uniformity: The tablets were tested for their drug content uniformity. At random 20 tablets were weighed, powdered & dissolved in 100ml of 6.8 phosphate buffers. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatmann No.41 filter paper. Then the dilute the solution to obtain 10µg solution. The absorbance of the diluted solutions was measured at 237 nm.

Dissolution studies: In-vitro dissolution study is performed by using USP Type II Apparatus (Paddle type) at 100 rpm. 6.8 phosphate buffers 900 ml is used as dissolution medium which is maintained at 37±0.5°C. Aliquots of dissolution medium (10 ml) are withdrawn at specific time intervals and filter. An equal amount of fresh dissolution medium is replaced immediately following withdrawal of test sample. The percentage of drug released at various intervals is calculated using beer-lamberts law.

Data Analysis (Curve fitting analysis): To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted as:

Cumulative percentage drug released Vs time (Zero order plot)

Log cumulative percentage drug remaining Vs Time (First order plots)

Zero order model:

The pharmaceutical dosage forms following these profiles release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$Qt = Q0 + K0t$$

Where,

Qt is the amount of drug dissolved in time t,

Q0 is the initial amount of drug in the solution and K0 is the zero order release constant.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time

First order model:

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969). This model has been also used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualise this mechanism in a theoretical basis .

$$\log Qt = \log Q0 + (K1/2.303)$$

Where,

Qt is the amount of drug released in time t,

Q0 is the initial amount of drug in the solution and K1 is the first order release constant.

The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of-K/2.303.

RESULTS & DISCUSSION

Solubility studies:

Solubility of Clozapine was carried out at 250C using 0.1N HCL, 6.8 phosphate buffer, 7.4pH buffer and purified water.

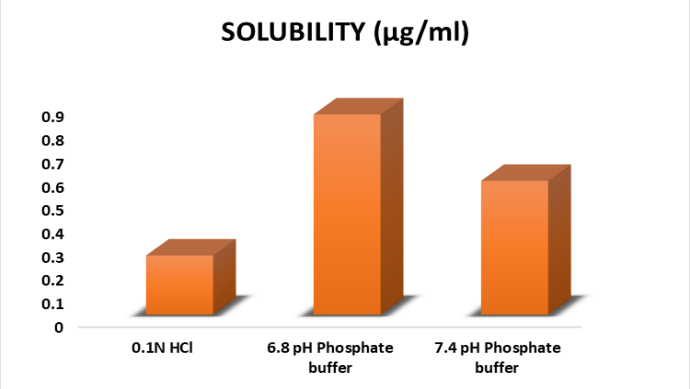

Figure.No.2 Solubility studies

Discussion: From the above conducted solubility studies in various buffers we can say 6.8 pH phosphate Buffer has more solubility when compared to other buffer solutions.

Determination of λmax:-

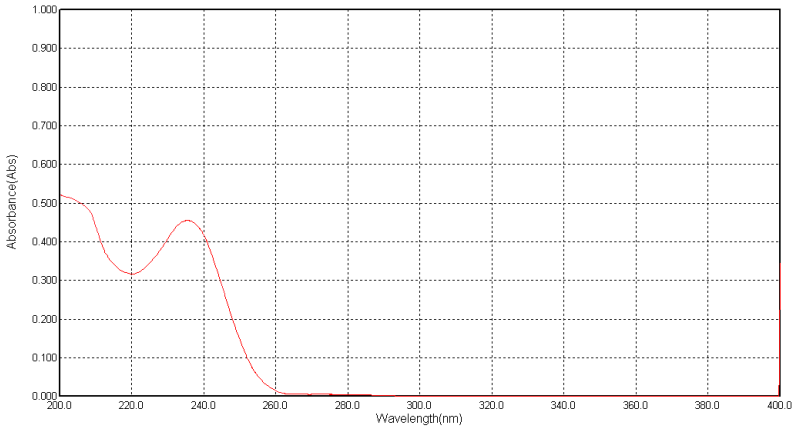

Figure.No.3 UV Spectrum curve of Clozapine

Discussion: The Absorption maxima of clozapine drug in the 100% concentration by using 6.8pH Phosphate buffer was found to be at 237nm.

Calibration curve of Clozapine in 6.8 pH phosphate Buffer

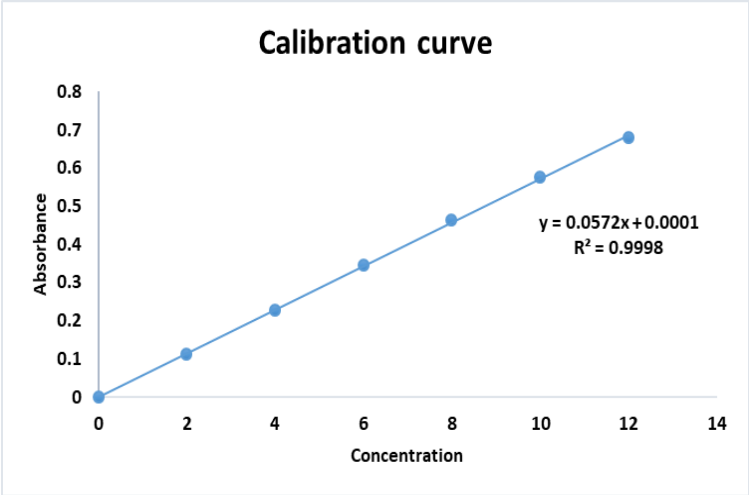

Figure.No.4 Standard graph of Clozapine

Discussion:

The linearity was found to be in the range of 2-12 µg/ml using 6.8pH Phosphate Buffer. Regression analysis was selected because it minimizes the deviation and correct the variance heterogeneity. The regression line was defined by its slope (m) and its intercept (C) for normal regression analysis was found as 0.0572 and 0.0001, with regression coefficient of 0.9998 respectively. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

FTIR STUDIES:

Drug excipient compatibility:

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

PURE DRUG:

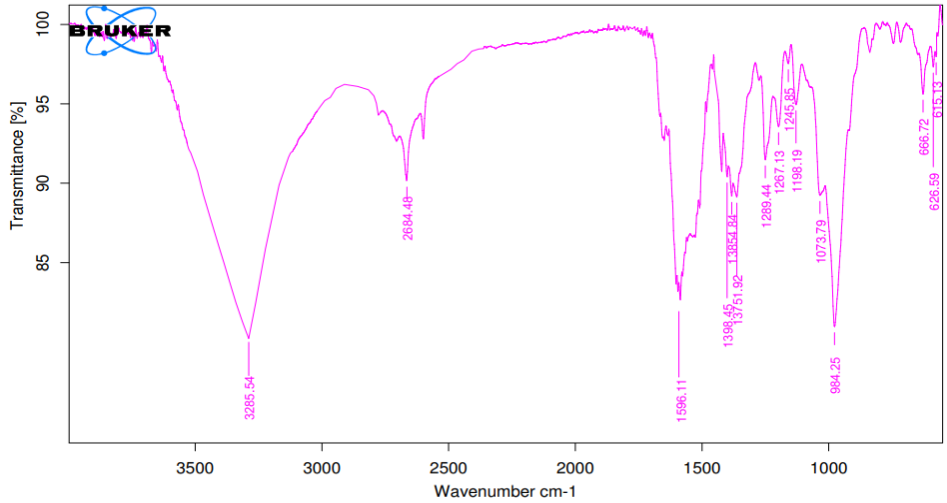

Figure.No.5 IR spectrum of Clozapine

Optimized formulation:

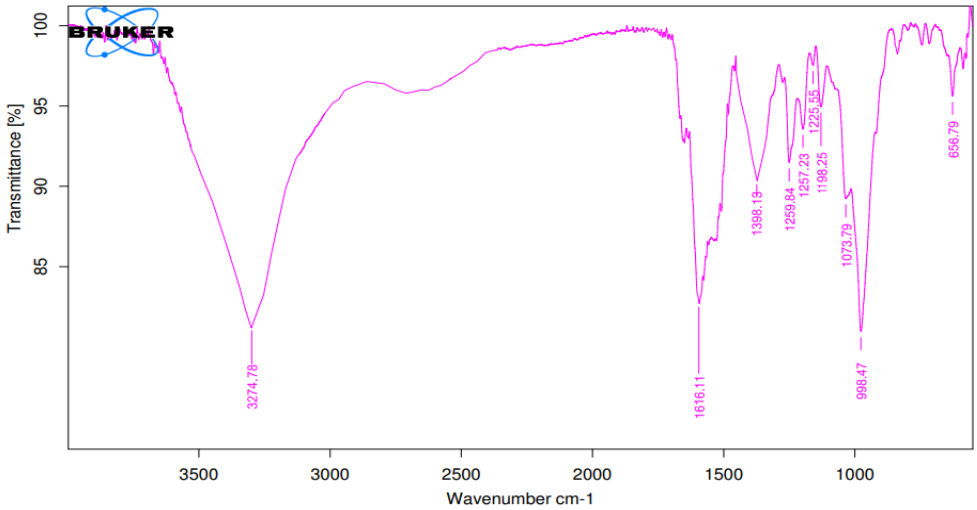

Figure.No.6 IR spectrum of Optimized formulation

Discussion: Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Clozapine) and optimized formulation (Clozapine+ excipients) which indicates there are no physical changes.

Table.No.2 FTIR Interpretation Table for Pure and Optimized Drug:

Functional groups	Stretching/deformation	Pure drug(cm-1)	Drug+polymers(cm-1)
C=C (alkene)	Bending	984.25	998.47
N-C	Stretching	1198.19	1198.25
C=C	Stretching	1596.11	1616.11
N-H	Stretching	3285.54	3274.78

Characterization of blend:

Table.No.3 Pre-Compression parameters:

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean± SD)	Tapped density (mean± SD)	Angle of repose (mean± SD)	Carr's index (mean± SD)	Hausner's ratio (mean± SD)
F1	0.518±0.08	0.624±0.09	22.58±0.42	11.84±1.16	1.12±0.09
F2	0.611±0.02	0.689±0.01	23.87±0.28	14.26±1.25	1.21±0.14
F3	0.585±0.07	0.654±0.05	25.65±0.47	15.26±2.15	1.20±0.22
F4	0.529±0.01	0.612±0.04	27.66±0.26	10.64±1.18	1.21±0.14
F5	0.571±0.05	0.667±0.08	25.85±0.78	13.68±1.19	1.18±0.12
F6	0.536±0.01	0.634±0.05	26.58±0.22	15.84±1.26	1.19±0.15
F7	0.541±0.08	0.646±0.04	27.29±0.48	13.54±1.47	1.18±0.12
F8	0.529±0.02	0.634±0.07	25.97±0.35	11.25±1.36	1.14±0.19
F9	0.581±0.01	0.674±0.05	27.55±0.74	11.74±2.25	1.18±0.15
F10	0.536±0.09	0.645±0.01	26.66±0.28	12.65±1.15	1.12±0.16
F11	0.571±0.07	0.685±0.07	24.85±0.36	13.85±1.26	1.15±0.17
F12	0.569±0.01	0.688±0.03	27.66±0.48	15.85±0.98	1.24±0.42

Discussion: The angle of repose of different formulations was ≤ 27.66±0.48 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.518±0.08 g/cm3 to 0.611±0.02 g/cm3.Tapped density was found between 0.612±0.04 g/cm3 to 0.688±0.03 g/cm3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 10.64±1.18-15.85±0.98 and Hausner's ratio from 1.12±0.09-1.24±0.42 which reveals that the blends have good flow character.

Characterization of tablets

Post Compression parameters All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table.

Table.No.4 Characterization Clozapine oral disintegrating tablets

Formulation	Average Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegrating time(sec)
F1	201.4±0.14	3.8±0.14	4.2±0.01	0.65±0.02	25.41±0.12
F2	202.2±0.16	3.3±0.18	4.5±0.03	0.72±0.06	19.25±0.19
F3	198.3±0.19	3.6±0.12	3.9±0.02	0.71±0.08	22.31±0.21
F4	199.4±0.12	3.5±0.16	3.8±0.01	0.69±0.02	15.48±0.16
F5	200.5±0.09	3.6±0.11	4.3±0.01	0.62±0.08	19.14±0.17
F6	201.3±0.14	3.4±0.12	4.3±0.06	0.67±0.06	15.25±0.24
F7	204.5±0.12	3.6±0.19	4.5±0.05	0.69±0.04	21.16±0.15
F8	203.4±0.11	3.5±0.12	4.0±0.07	0.71±0.08	20.24±0.02
F9	201.6±0.10	3.6±0.10	4.3±0.08	0.85±0.02	18.17±0.06
F10	198.9±0.09	3.7±0.15	4.5±0.22	0.62±0.46	20.16±0.02
F11	197.2±0.12	3.5±0.12	3.9±0.28	0.59±0.31	19.29±0.12
F12	200.1±0.14	3.3±0.09	4.4±0.46	0.51±0.58	8.12±0.04

Discussion: Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 4.0±0.07– 4.4±0.46kg/cm2. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 – F12 and considered to be satisfactory ensuring that all the formulations are mechanically stable. Disintegration time as per IP, for all the formulations was found to be within 08.12 seconds, which was well within IP limit. Formulations with Ludiflash as super disintegrants shows quicker disintegration among all the formulations. Ludiflash with 12mg concentration as a super disintegrant shows very less disintegration time.

Drug content uniformity of formulations: The prepared formulations were analyzed for drug content and the data is reported in below Table. The drug content was found to be within the limits which show that the drug was uniformly distributed in all the formulations.

Table.No.5 Drug content uniformity of formulations F1-F12

Formulation	%of Drug content
F1	94.25±1.74
F2	92.68±1.61
F3	94.15±1.85
F4	90.42±1.25
F5	94.29±1.69
F6	90.45±1.20
F7	89.26±1.75
F8	92.16±1.09
F9	93.26±1.25
F10	94.18±1.64
F11	96.44±1.78
F12	98.71±1.29

Discussion: % drug content values of formulation F1 –F12 was found to be in the range of 90.45±1.20-98.71±1.29%.

Dissolution studies:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release. As the concentration of super disintegrant increased, the drug release time decreased.

Table.No.6 % Cumulative drug release of formulations F1-F6

Time (Min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	35.25±1.45	37.28±1.54	39.18±1.32	45.42±1.51	36.28±1.20	37.17±1.67
10	42.75±1.64	44.15±1.95	48.17±1.02	59.26±1.45	43.15±1.62	45.42±1.54
20	48.86±1.84	49.48±1.67	56.31±1.65	64.18±1.36	55.47±1.27	58.16±1.20
30	55.38±1.57	55.26±1.57	78.46±1.25	88.25±1.20	66.15±1.54	67.25±1.65
45	73.21±1.78	77.18±1.29	87.82±1.20	93.41±1.74	78.87±1.56	79.41±1.84
60	85.44±1.62	89.48±1.58	93.12±1.36	95.58±1.62	83.48±1.28	85.84±1.26

Table.No.7% Cumulative drug release of formulations F7-F12

Time (Min)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
5	51.25±1.28	55.17±1.57	39.38±1.21	41.86±1.42	45.21±1.74	48.94±1.54
10	65.47±1.67	66.26±1.02	43.85±1.45	46.24±1.67	51.81±1.56	53.13±1.47
20	73.15±1.25	74.74±1.36	53.23±1.61	54.72±1.55	59.98±1.25	61.47±1.59
30	82.26±1.75	86.19±1.45	65.53±1.28	68.32±1.67	65.85±1.57	75.21±1.47
45	89.78±1.61	94.28±1.67	78.74±1.64	80.48±1.45	78.25±1.68	86.43±1.64
60	96.29±1.74	97.47±1.25	86.85±1.94	89.42±1.84	92.46±1.21	99.26±1.28

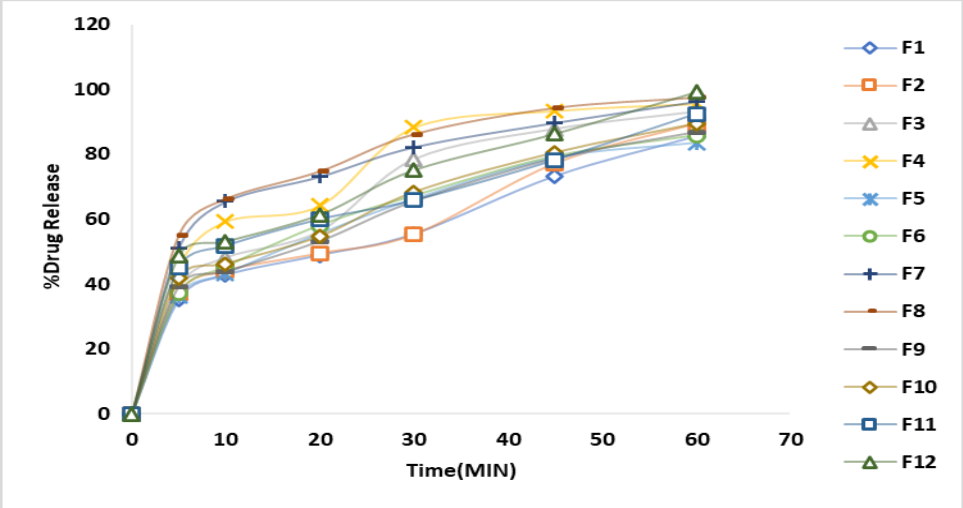

Figure.No.7 %DR of F1-F12

Discussion:

From the invitro drug release studies it was observed that the formulations containing Lycoat (F1-F4) as super disintegrant in the concentrations of (3,6, 9, 12mg). F1, F2, F3 shows 85.44±1.62%, 89.48±1.58%, 93.12±1.36% drug release at the end of 30minutes. Whereas F4 shows 95.58±1.62% drug release at the end of 60 minutes. Whereas the formulations containing Croscarmellose sodium (F5-F8) as super disintegrant in the concentrations of (3,6, 9, 12mg) shows 83.48±1.28%, 85.84±1.26%, 96.29±1.74%, 97.47±1.25%, drug release at the end of 60minutes. While the formulations containing natural super disintegrants such as Ludiflash (F9-F12) as super disintegrant in the concentrations of (3, 6, 9, 12mg) shows 86.85±1.94%, 89.42±1.84%, 92.46±1.21%, & 99.26±1.28% drug release at the end of 60 minutes. By comparing the dissolutions profiles of formulations F1-F12 containing super disintegrants in the concentrations of 3, 6, 9, 12mg, the drug release was not found to be satisfactory Ludiflash shows satisfactory drug release at the end of 30mins. Among all the formulations F12 containing 12mg Ludiflash shows 99.26±1.28% drug release at the end of 60min. So F12 formulation was considered as the optimized formulation. Further kinetics were measured for F12 formulation.

DRUG RELEASE KINETICS STUDIES:

ZERO ORDER:

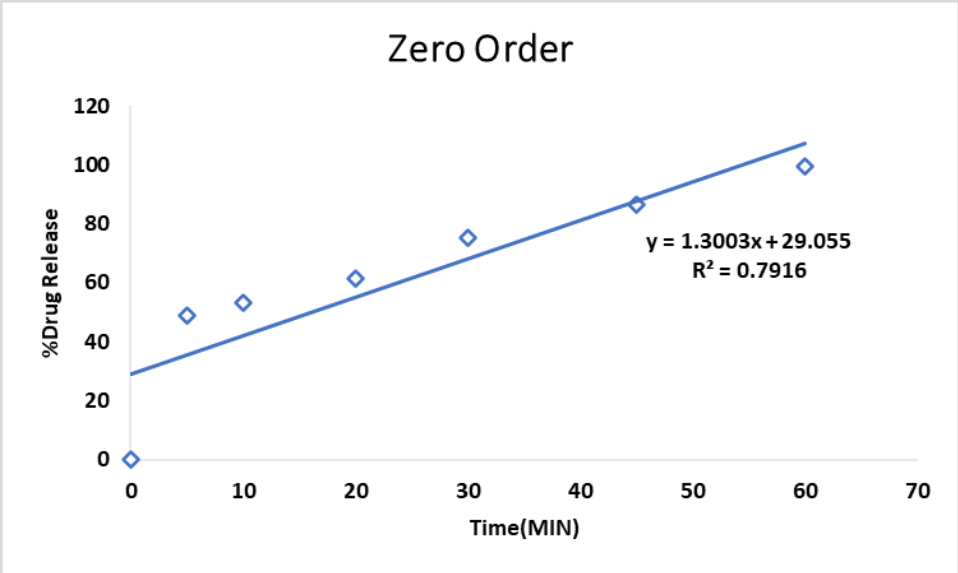

Figure.No.8 Zero order plot of Clozapine F12 Formulation

FIRST ORDER:

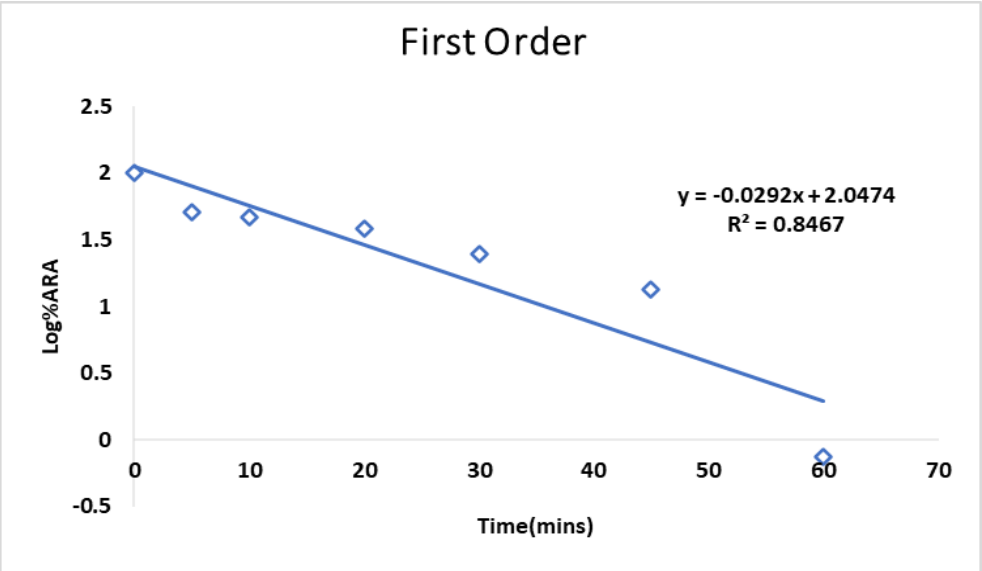

Figure.No.9 First order plot of Clozapine F12 Formulation (Time Vs Log% ARA)

Table.No.8 Order of kinetic values of Formulation F12

Order of kinetics	Zero order	First order
Regression values	0.791	0.846

Discussion: The drug release from the oral disintegrating tablets was explained by the using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized formulation F12 follows First order drug release.

SUMMARY AND CONCLUSION:

SUMMARY

The present study is an attempt to select the best possible diluent - disintegrant combination to formulate Oral disintegrating tablets of Clozapine, which disintegrates in matter of seconds in the oral cavity, thereby reducing the time of onset of pharmacological action. Lycoat, Croscarmellose sodium and Ludiflash, were used as disintegrants. In all the formulations, and Magnesium stearate and talc were used as lubricant and glidant respectively. The results of the drug – excipient compatibility studies revealed that there was no chemical interaction between the pure drug and excipients. Wet granulation technique was employed to formulate the tablets, because of its cost effectiveness and due to reduced number of manufacturing steps. The precompression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. All the formulations showed acceptable flow properties.The post compression parameters like the hardness, thickness, friability and weight variation, disintegration time, disintegration time in oral cavity and Invitro release were carried out and the values were found to be within IP limits. The percentage drug content of all the tablets was found to be between 85.18-96.71% of Clozapine, which was within the acceptable limits. Among all the formulations F12 shows 99.26±1.28% drug release at the end of 60min. F12 contains Ludiflash (12mg), it shows better % drug release when compared to other formulations. So, F12 was considered as the optimized formulation. The drug release kinetics shows that the optimized formulation F12 follows First order drug release.

CONCLUSION

From the compatibility studies, it is concluded that, Lycoat, Croscarmellose sodium and Ludiflash, were compatible with drug Clozapine and thus suitable for the formulation of Clozapine Oral disintegrating tablets were prepared by wet granulation technique. The pre evaluation and post evaluation parameters like like bulk density, tapped density, Carr's index and angle of repose and the hardness, thickness, friability and weight variation, disintegration time, disintegration time studies were performed for all the formulations, F1 to F12 by using 6.8 pH phosphate Buffer solution at 370C. Tablet containing Ludiflash (12mg), showed 99.26±1.28% drug release. In-Vitro release study is performed for 60min. Optimized formula containing Ludiflash (F12) showed

better release compare to other formulations and it followed First order drug release. From this study, it was concluded that Ludiflash can be used in formulation of Clozapine oral disintegrating tablet.

ACKNOWLEDGEMENT
The authors are thankful to the Department of Pharmaceutics, KGR Institute of Technology & Management, Rampally, Secunderabad, Telangana – 501301 and Spectrum Pharma Research Solutions, Hyderabad, Telangana, India.

REFERENCES:

1. Sastry SV et al, Recent technological advances in oral drug delivery: A review. Pharmaceutical Science and Technology Today. 2000; 3:138-45.
2. Seager H. Drug-delivery products and the Zydis fast-dissolving dosage form. Journal of Pharmacy and Pharmacology. 1998; 50(4):375-82.
3. Lindgren S; Prevalence of swallowing complaints and clinical findings. Medical clinics of North America., 1993; 77: 3-5.
4. Velmurugan S., Vinushitha S. Oral disintegrating tablets: an overview. International Journal of Chemical and Pharmaceutical Sciences . 2010;1(2):1–12.
5. Vanbillemont B., De Beer T. Application of polyvinyl acetate in an innovative formulation strategy for lyophilized orally disintegrating tablets. International Journal of Pharmaceutics . 2020;588, article 119717 doi: 10.1016/j.ijpharm.2020.119717.
6. Cantor S. L., Khan M. A., Gupta A. Development and optimization of taste-masked orally disintegrating tablets (ODTs) of clindamycin hydrochloride. Drug Development and Industrial Pharmacy . 2015;41(7):1156–1164. doi: 10.3109/03639045.2014.935392.
7. Gupta S., Saquib Hasnain M., Agarwal S. Formulation and evaluation of oral disintegrating tablets of itopride hydrochloride using ion exchange resins as drug carrier. Asian Journal of Pharmaceutical Sciences . 2012;7(3).
8. Doenicke A., Melchart D., Bayliss E. Effective improvement of symptoms in patients with acute migraine by GR43175 administered in dispersible tablets. Cephalalgia . 1989;9:89–92. doi: 10.1111/J.1468-2982.1989.TB00079.X.
9. Watanabe Y., Koizumi K., Zama Y., Kiriyama M., Matsumoto Y., Matsumoto M. New compressed tablet rapidly disintegrating in saliva in the mouth using crystalline cellulose and a disintegrant. Biological and Pharmaceutical Bulletin. 1995;18(9):1308–1310. doi: 10.1248/bpb.18.1308.
10. Comoglu T., Dilek Ozyilmaz E. Orally disintegrating tablets and orally disintegrating mini tablets–novel dosage forms for pediatric use. Pharmaceutical Development and Technology . 2019;24(7):902–914. doi: 10.1080/10837450.2019.1615090.
11. Mostafa M., Gardouh A. R., Abogresha N. M., Gad S. Factorial design, formulation, in vitro and in vivo evaluation of rapid orally disintegrating tablets prepared by sublimation technique using captopril as a model drug. Journal of Drug Delivery Science and Technology . 2020;57, article 101635 doi: 10.1016/j.jddst.2020.101635.
12. Ascher-Svanum H., Furiak N. M., MS, Lawson A. H., MA, et al. Cost-effectiveness of several atypical antipsychotics in orally disintegrating tablets compared with standard oral tablets in the treatment of schizophrenia in the United States. Journal of Medical Economics . 2012;15(3):531–547. doi: 10.3111/13696998.2012.662923.
13. Lin Z., Xuan J. Cost-effectiveness of aripiprazole orally disintegrating tablets in the treatment of schizophrenia in China. Expert Review of Pharmacoeconomics & Outcomes Research . 2020;20(5):549–557. doi: 10.1080/14737167.2020.1807331.
14. Sotoyama M., Uchida S., Kamiya C., et al. Ease of taking and palatability of fixed-dose orally disintegrating mitiglinide/voglibose tablets. Chemical and Pharmaceutical Bulletin . 2019;67(6):540–545. doi: 10.1248/cpb.c18-00902.
15. Ghosh T., Ghosh A., Prasad D. A review on new generation orodispersible tablets and its future prospective. International Journal of Pharmacy and Pharmaceutical Sciences .2011;3(1):1–7.
16. Souza J. C., Tajiri H. A., Morsch C. S., et al. Tribocorrosion behavior of Ti6Al4V coated with a bio-absorbable polymer for biomedical applications. Journal of Bio-and Tribo-Corrosion . 2015;1(4):1–6. doi: 10.1007/s40735-015-0029-5.
17. https://go.drugbank.com/drugs/DB00363.