FORMULATION, DEVELOPMENT, AND CHARACTERIZATION OF IMMEDIATE RELEASE TABLET OF CLOZAPINE

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Abstract

The tablets are the most common formulation among the other formulations. This is the primary goal of developing a new clozapine formulation, but we are adding a new specific character to these tablets, which is their immediate release property, which provides instant calm to refractive schizophrenic patients. It is possible to provide new dose formulations that have a rapid effect. Two methods are used to formulate the tablets; one is the sublimation method, and the other is the direct compression method, together with the super disintegrants and sublimating agent. The result of the formulation was mainly focused on the dissolution of the tablet, which resulted in 96.23% of the drug released within 20 minutes and 74.85% of the drug released immediately within 2 minutes as a blast. FT-IR studies show that clozapine and excipients are compatible with each other; no interactions are seen. And the formulation A05 is best among the other seven on the basis of the pre and post formulation data, which is prepared with the maximum concentration of disintegrants and the direct compression method. The stability studies of the optimized formulation show the good stability of the formulation, which is the result of 30, 60, and 90 days, respectively.

Keywords: Clozapine, Dissolution, Immediate release tablet, Disintegration time, Stability study

1. Introduction

Due to the patient's desire to take the drug and the fact that it is simple to take without causing pain or adverse effects, oral administration is the favoured approach for systemic effects[1]. Solid oral delivery techniques are also less expensive since they do not need sterile conditions for manufacture[2]. For excipients and equipment, changes in solid dosage form technology due to exceptional improvements in drug development, such as genomics, will have significant consequences[3]. Patients often prefer not to use injections unless they are made easy by advanced auto injectors. Biopharmaceutical research has so far only developed chemical entities with low molecular weights as an alternative manner of delivering these drugs[4].

Immediate release tablets that may release medications at a faster pace are particularly promising to administration of weakly soluble pharmaceuticals with high molecular weight components[5]. Therapeutic agents may still be administered by the oral route because of the cheap cost of treatment, the convenience of administration, and the high degree of patient compliance[6]. It is common for patients to need an immediate release of medication in certain therapeutic circumstances[7]. Approximately 50% of the population is considered to be impacted by this issue, which leads to a high rate of unsuccessful treatment[8].

For the development of clozapine-containing orally disintegrating tablets, direct compression technology will be used to create a cost-effective formulation, and these formulas will be tested for uniformity of mass, friability, and in vitro disintegration time, as well as porosity Fourier transform infrared spectroscopy (FTIR)[9]. In this study, oral disintegrating tablet formulations were created using a novel technology and well-known excipients, as opposed to previous formulations[10]. Other commercially available IRT formulations include ingredients such as magnesium stearate, citric acid, and sodium bicarbonate. Mannitol and microcrystalline cellulose were also used as filler components[11]. When in contact with saliva, the effervescent disintegration pair, which includes the compounds, releases gas. DuraSolv technology is used to create IRTs with low concentrations of active ingredients[12]. As a result, large amounts of pharmacologically active chemicals are not possible to use[13]. When the powdered drug is pressed, the patient may get a bitter taste in their mouth[14].

Immediate release tablets

In tablet and hard-shell capsule formulations, disintegrating agents are chemicals that improve moisture penetration and disperse the dosage form in dissolving fluids[15]. Super disintegrants, which work better than regular disintegrants, could be used to cut down on the amount of disintegrants needed[16].

Mechanism of disintegrates:

- The capacity to easily swell
- High swell ability due to capillary action
- A chemical reaction

Corn starch, soluble starch, and other dry and powdered disintegrants are the most often used. The capillary action of starch in tablet disintegration is owing to its water affinity, which causes the starch to inflate when it is wet[17]. The tablet's porosity is increased because of the

starch's spherical form, which encourages capillary action. The disintegrating properties of gums and cellulose have been well-documented[18]. When water is added, these compounds expand a lot, which makes the tablets break up into smaller pieces. Resistant schizophrenia is treated using this drug, which is one of the most commonly used atypical antipsychotics[19]. Quality criteria for active ingredients are increasing in pharmacotherapy in order to ensure safety and efficacy. Once or twice a day, take 12.5 mg of clozapine by mouth once or twice a day[20]. Oral bioavailability is low, at around 27%, making it nearly insoluble in water. Clozapine's first-pass metabolism is substantial. Individual patient features may dictate dosage modifications[21]. Clozapine usage has been linked to a number of adverse effects, including excessive constipation, nighttime drooling, muscular stiffness, drowsiness, tremors, orthostasis, hyperglycemia, and an increase in body weight[22]. When clozapine is compared to the conventional antipsychotics, the chances of extrapyramidal symptoms such as tardive dyskinesia are substantially lower[23]. Clozapine's active ingredient, clozosine, has eleven more black box warnings about side effects like acute and chronic leukopenia, acute and chronic myocarditis, generalized and focal seizures, and local and systemic bone marrow suppression[24].

Preparations with controlled release are recommended because they provide the best therapeutic benefit with the least chance of side effects. Controlling medication release and making appropriate adjustments to the manufacturing process both have the potential to reduce adverse effects[25]. To avoid taking an atypical antipsychotic, some schizophrenic patients slip a conventional pill beneath their tongue. Clozapine controlled release dosage forms were developed and evaluated to address this issue[26]. The solubility and dissolution rate of clozapine were improved by making matrix pellets. Clozapine's orogastric absorption may be enhanced by this drug[27].

2. Materials and Methods

Clozapine was acquired from Cadila Healthcare Ltd., India. We only utilize pharmacopeial or analytical grade reagents and chemicals for anything else. Throughout the experiment, double-distilled water is used. A01 to A04 were prepared by the sublimation method. In a sublimation technique, Clozapine, Camphor, Mannitol, and powdered stevia leaf were combined and passed through # 45 sieves. Compression was used after the addition of talc and magnesium stearate. The pills were cooked with the help of a hot air oven at 60° till they reached a consistent weight, ensuring that all the volatile components had been removed.

A05 to A08 were prepared by the direct compression method. A # 60 sieve is used to filter out impurities from each component. A glass mortar was used to triturate clozapine, MCC, mannitol, and powdered stevia leaf. As a lubricant, magnesium stearate and talc are added to the powder combination together with Cross carmellose sodium and Cross povidone. A single-station tablet punching machine is used to crush the powder mix using flat-faced surface punches[28].

Formulation

Table 1: Formula for development of tablet formulation

Additives (mg)	**Formulations**							
	A01	**A02**	**A03**	**A04**	**A05**	**A06**	**A07**	**A08**
Clozapine	50	50	50	50	50	50	50	50
Cross carmellose sodium	10	20	30	40	40	30	20	10
Cross povidone	-	-	-	-	50	50	50	50
Camphor	50	50	50	50	-	-	-	-
Mannitol	50	50	50	50	50	50	50	50
Stevia leaf (Powder)	5	5	5	5	5	5	5	5
Micro crystalline cellulose	190	180	170	160	160	170	180	190
Talc	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2
TOTAL	360	360	360	360	360	360	360	360

3. Result and Discussion

It was found that the angle of repose was less than 30, the bulk density was 0.512 g/cm3 to 0.608 g/cm3, the tapped density was 0.613 to 0.680 g/cm3, and the percent compressibility varied from 11.84 to 22.47%. Table 5.2 had all of these values. The hardness of prepared tablets was found to vary from 3.500 kg/cm3 to 5.000 kg/cm3 based on the mean thickness values. Friability was reduced by 0.43 to 0.68 percent. The disintegration times varied from 28 to 58 seconds. Before and after the expedited stability studies, the improved formulation A05 comparative metrics were compared.

Compatibility studies

(a) Pre compression parameters

Table 2. Pre-Compression Parameters

Formulation	**Angle of Repose**	**Bulk Density**	**Tapped Density**	**C I**	**Hausner`s Ratio**
A01	24° 61'	0.530	0.624	17.73	1.17
A02	25° 14'	0.532	0.613	15.30	1.15
A03	24° 70'	0.580	0.661	14.10	1.14
A04	25° 21'	0.586	0.660	12.63	1.13
A05	24° 13'	0.608	0.680	11.84	1.12
A06	26° 27'	0.516	0.618	19.77	1.19
A07	26° 95'	0.512	0.620	21.09	1.21
A08	27° 14'	0.534	0.654	22.47	1.22

(b) Post compression parameters

Formulation	**Average** wt (gm)	**Hardness** (kg/cm^2)	**Friability** (%)	**Thickness** (mm)	**Assay (%)**
A01	295	3.5	0.55	4.52	95.87
A02	301	4.0	0.50	4.56	96.71
A03	297	4.5	0.57	4.58	97.12
A04	307	4.5	0.62	4.51	96.22
A05	304	5.0	0.48	4.65	97.83
A06	302	4.5	0.54	4.54	96.09
A07	301	4.5	0.58	4.62	94.68
A08	309	4.0	0.64	4.49	93.12

Table 3. Post Compression Parameters

(c) In vitro disintegration time

Table 4. In vitro disintegration time clozapine formulations

Formulation	**A01**	**A02**	**A03**	**A04**	**A05**	**A06**	**A07**	**A08**
Disintegration time (sec)	45	42	35	28	30	36	51	58

In vitro dissolution study of tablets

As a result, the dissolving tests of the newly designed IRTs were conducted using the paddle technique. Clozapine tablets must dissolve at least 86% of their listed quantity in 45 minutes for IRTs to meet USP requirements. The dissolution profiles are regarded as comparable when the similarity factor is 50 to 100. When the indicated quantity is dissolved within 20 minutes, however, the dissolving profiles are recognised as being equivalent without the need for any mathematical calculations. The dissolving characteristics of the formulations were not specifically differentiated in this investigation since more than 95% of the formulations were dissolved within 20 minutes. The sublimation method was used to make the first 4 formulations (A01 to A04), and the direct compression method was used to make the next 4

formulations (A05 to A08) Dissolving investigations were conducted on each of them for 20 minutes.

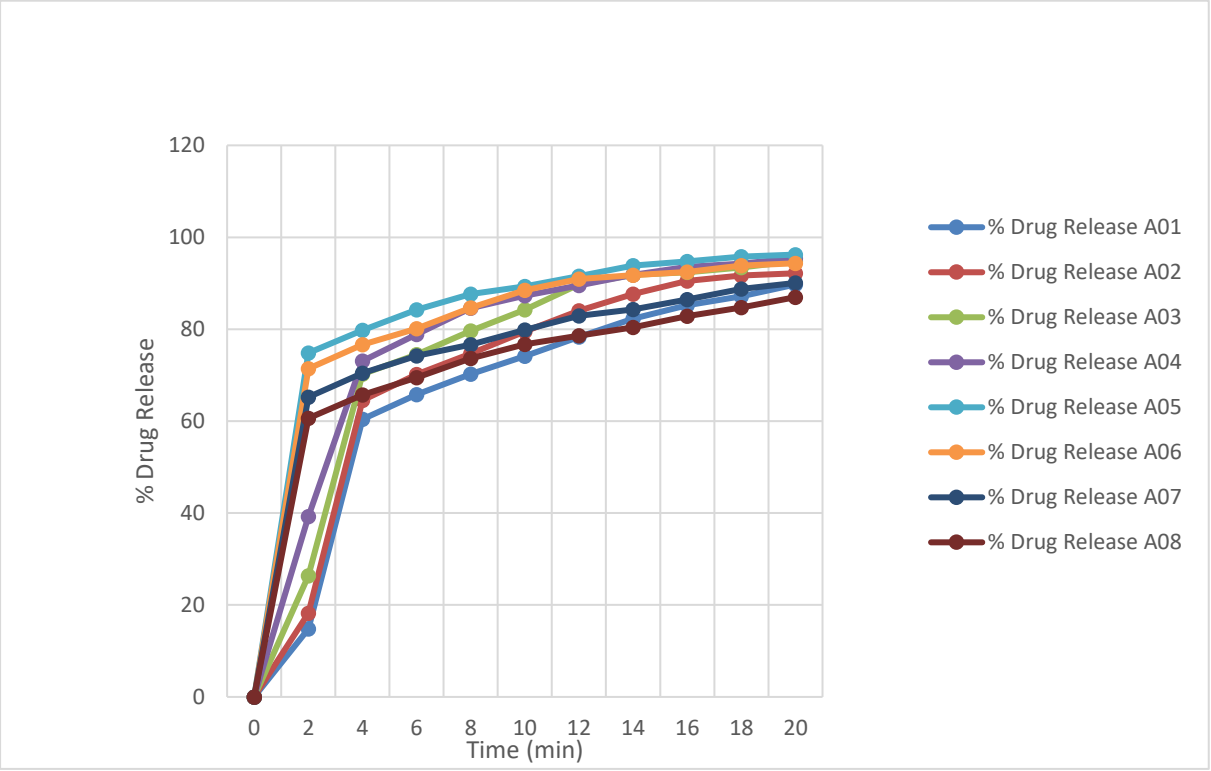

Fig. 1. Dissolution graph of A01, A02, A03, A04, A05, A06, A07, A08 (Liner form)

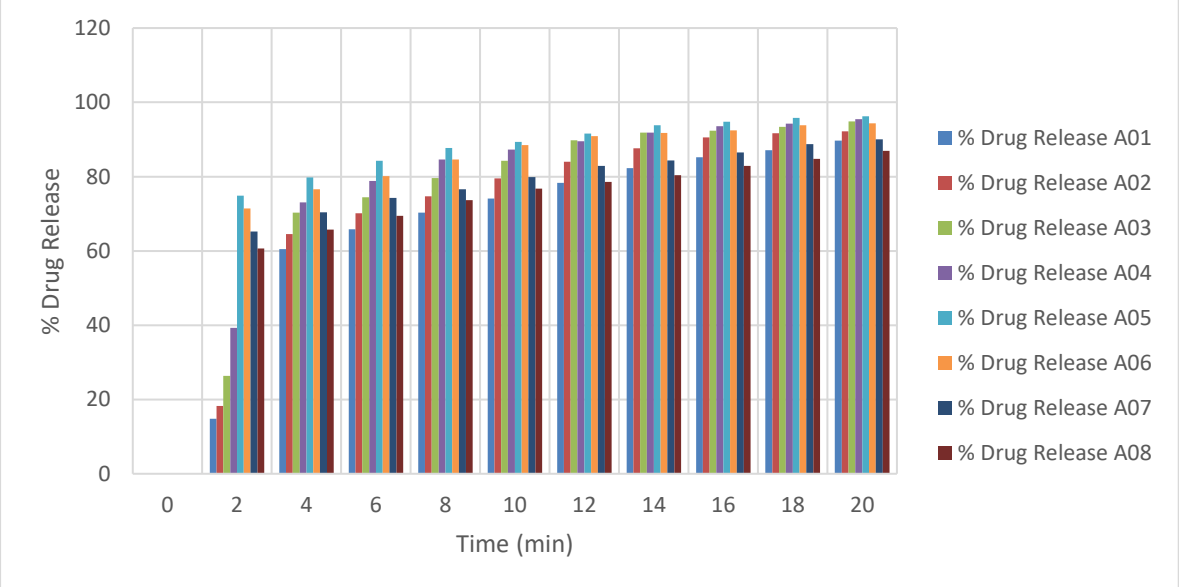

Fig. 2. Dissolution graph of A01, A02, A03, A04, A05, A06, A07, A08 (Column form)

(a) In vitro Drug Release of A01, A02

In the following table, the percentage of drug release for the first two formulations. They don't show how long it takes to get the medication out of A01 and A02.

Table 5. In vitro Release Data of A01, A02

Time (min)	A01	A02
0	0	0
2	14.81	18.24
4	60.44	64.53
6	65.81	70.16
8	70.27	74.71
10	74.12	79.52
12	78.33	84.01
14	82.32	87.62
16	85.24	90.53
18	87.15	91.72
20	89.72	92.16

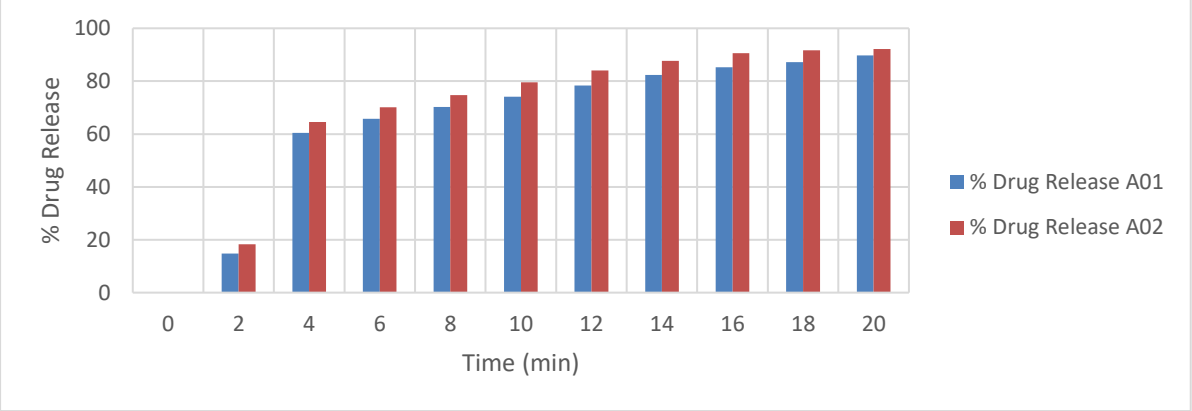

Fig. 3. Dissolution graph of A01, A02

(b) In vitro Drug Release of A03, A04

The table below shows percentage drug release for various concentrations of formulations A03 and A04. These formulations were successful in controlling and shortening the duration of their active ingredient release. The concentration of disintegrant is directly proportional to the medication release rate.

Table 6. In vitro Release Data of A03, A04

Time (min)	A03	A04
0	0	0
2	26.34	39.25
4	70.27	73.08
6	74.46	78.84
8	79.63	84.57
10	84.25	87.31
12	89.76	89.56
14	91.85	91.86
16	92.36	93.56
18	93.42	94.27
20	94.84	95.47

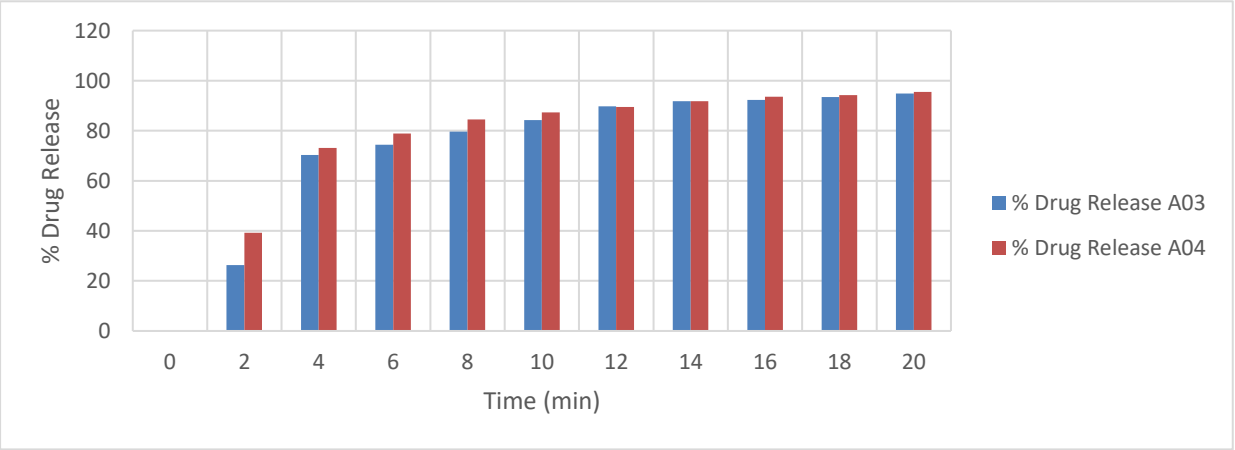

Fig. 4. Dissolution graph of A03, A04

(c) In vitro Drug Release of A05, A06

The existence of a chemical that is extremely water soluble might explain the increase in medication release rate. It's clear that the disintegrants help the instant disintegration of the tablet and facilitate the release of the drug in a short time.

Table 7. In vitro Release Data of A05, A06

Time (min)	A05	A06
0	0	0
2	74.85	71.43
4	79.78	76.62
6	84.27	80.16
8	87.68	84.63
10	89.31	88.51
12	91.58	90.93
14	93.86	91.75
16	94.76	92.42
18	95.82	93.82
20	96.23	94.34

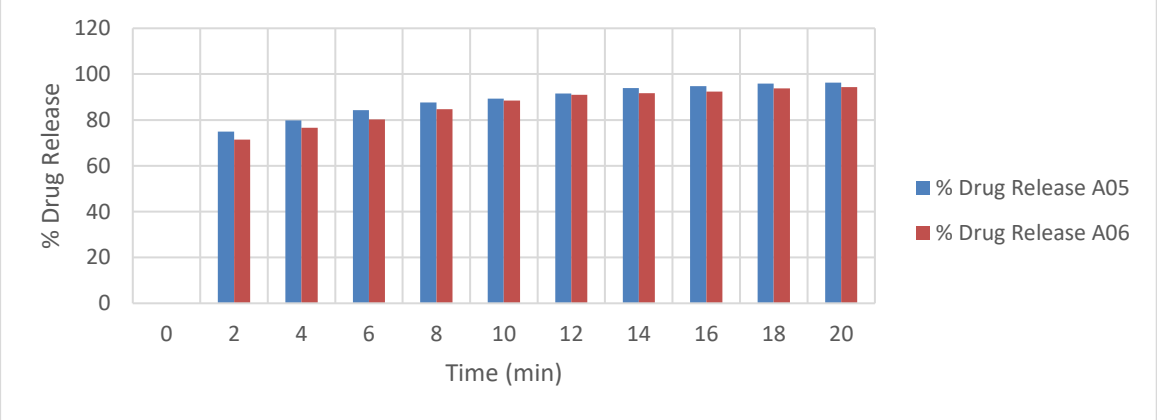

Fig. 5. Dissolution graph of A05, A06

(d) In vitro Drug Release of A07, A08

Percentage Drug release was determined to be 84.75 percent after 18 minutes and 86.97 percent after 20 minutes for formulation A08 which shows increasing concentration of the bulking agent and lowering of disintegrants and drug content.

Table 8. In vitro Release Data of A07, A08

Time (min)	A07	A08
0	0	0
2	65.25	60.62
4	70.43	65.73
6	74.24	69.47
8	76.63	73.65
10	79.85	76.74
12	82.92	78.58
14	84.32	80.41
16	86.49	82.87
18	88.76	84.75
20	90.07	86.97

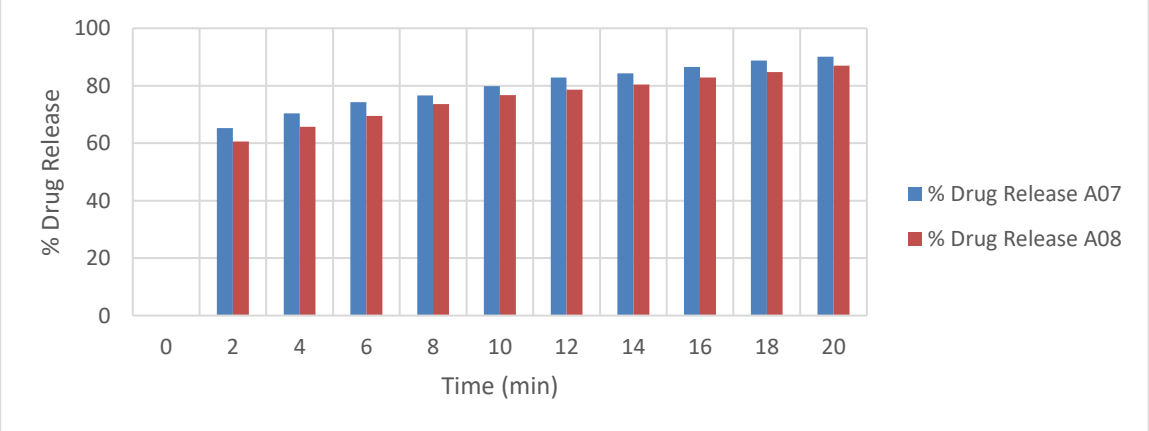

Fig. 6. Dissolution graph of A07, A08

Dissolution Profile of Optimized Formulation

A05 was found to be the optimal formulation based on dissolving data and post compression characteristics.

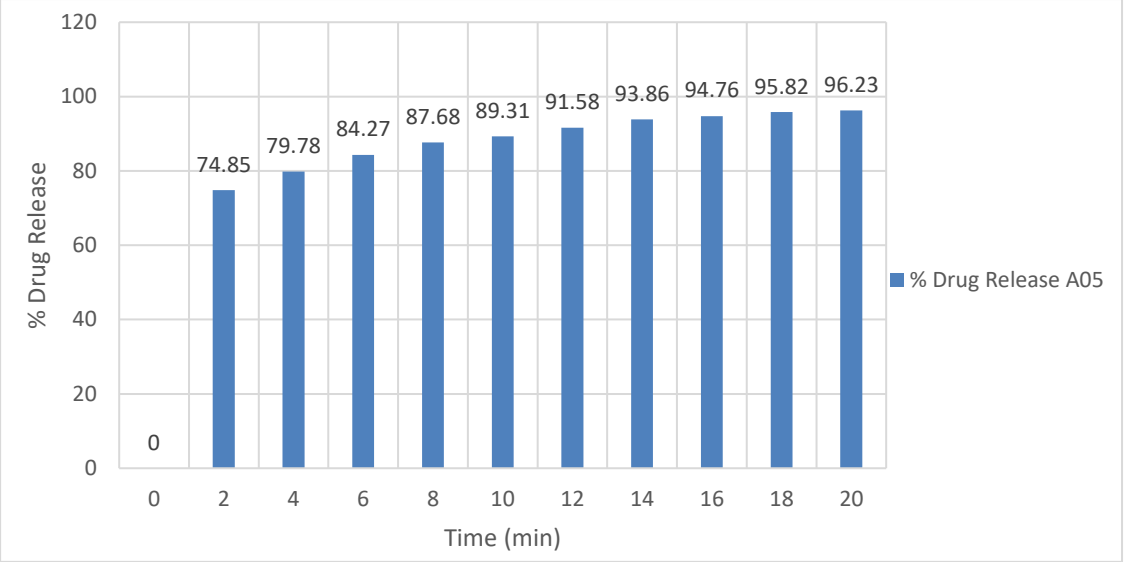

Fig. 7. Dissolution graph of optimized formulation (A05, Columnar form)

Evolution of Drug-Excipient Interactions

(a) FT-IR spectroscopy

Clozapine and the clozapine containing formulation (A05) had their IR spectra obtained. The FTIR spectrum of the constructed blend revealed an active molecular group in both pure clozapine and clozapine loaded formulation (A05).

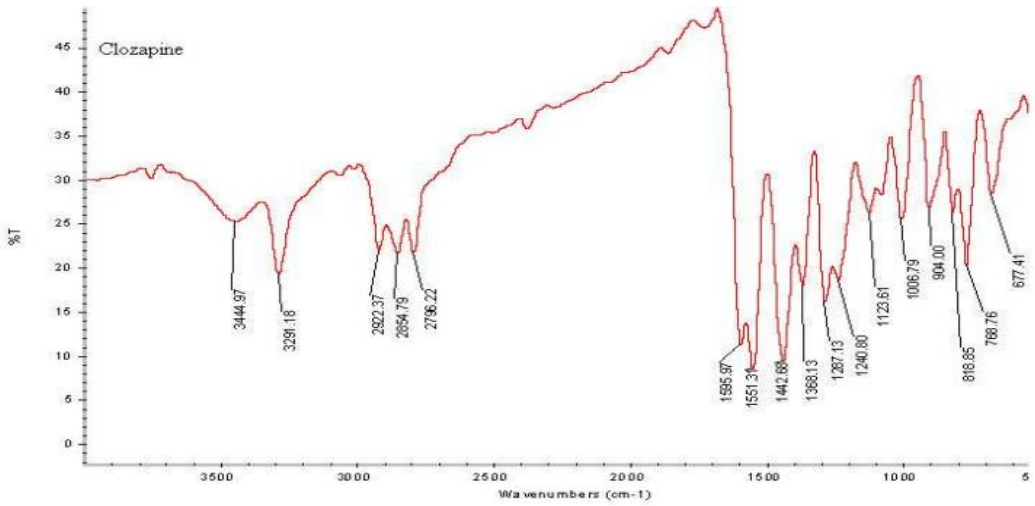

Fig. 8. FTIR spectrum of Clozapine

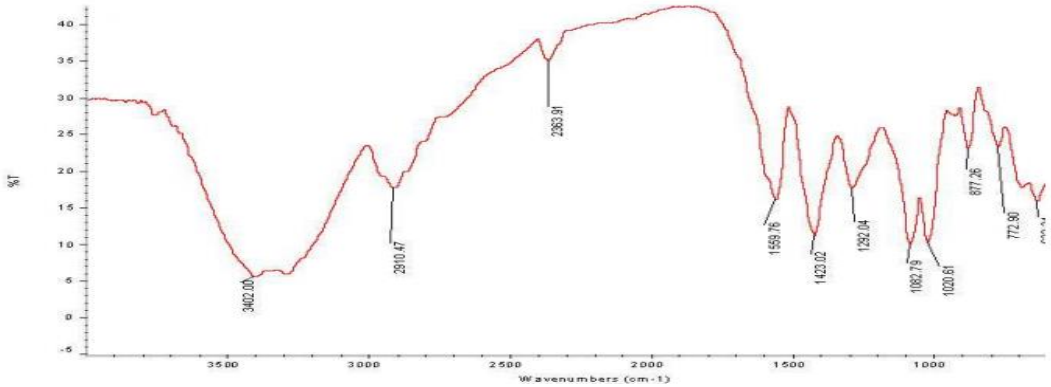

Fig.9. FTIR spectrum of formulation (A05)

(b) Stability Study

The tablets were loaded in a humidity-controlled stability chamber at 40°C2°C/75 percent RH5 percent RH. We took samples at 30, 60, and 90 days and looked at how they looked, what drugs they contained, and how well they dissipated.

Table 9. Stability study (A05)

S.N.	Parameters	Initial	One Month	Two Month	Three Month
1	Physical examination	Greyish	Greyish	Greyish	Greyish
2	Percentage drug content	97.83%	97.69%	97.54%	97.32%
3	Dissolution Rate	96.23%	96.18%	96.03%	95.86%

4. Conclusion

The reason behind the research was to develop and test immediate-release tablets loaded with clozapine for refractive schizophrenia patients. The technique used required no toxic solvents and was quick and cost-effective. These tablets are formulated with the help of super disintegrating agents and sublimating agents like camphor that increase the porosity of the formulation. Even individuals with diabetes who are taking antipsychotics may enjoy the taste of these mouth-dissolving pills because of the sweetener (Stevia). Micromeritic properties, hausner ratio, and friability of the formulations all fell within acceptable ranges, indicating the formulations have good flow potential. FTIR analyses showed that the drug was in a stable state, with no evidence of chemical interaction between the drug and excipients. An analysis of the formulation drug content showed that the drug was evenly distributed in the formulation. It was discovered that the drug release rate varies between formulations due to the disintegrant compositions used. Based on the obtained dissolution data, when administered once daily, A05 is the optimal formulation. analysis of the curve shapes and dissolution data. We got our formulation to pass the desired requirements and formulate according to the referencing standards. Even so, it can be said that of the different ways to make clozapine that were looked at, A05 was the most likely to lead to tablets with the same effects as the others.

Conflict of interest:

The authors declare no conflict of interests.

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