SJIF Impact Factor 2021: 8.013| ISI I.F.Value:1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 6 | Issue: 11 | November 2021 - Peer Reviewed Journal

FORMULATION AND EVALUATION OF CLOZAPINE SUSTAINED RELEASE TABLETS

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ABSTRACT
The sustained release drug delivery is the drug delivery system that achieves the release of drug in the proper amount at regular time interval over an extended period of time and is time independent. The aim of present work was to formulate and evaluate sustained release tablets of Clozapine using natural gums in order to reduce the various side effects associated with Clozapine as well as to overcome the manufacturing difficulties. For formulating sustained release drug delivery system, natural hydrophilic polymers are used. Natural binders provides the tablet formulations with good hardness and friability. These binders prolongs the dissolution rate of some slightly soluble drugs and can be chosen as good candidate for sustained release. Tablets were prepared by direct compression method using different drug-polymer concentration. FT-IR study revealed that there was no chemical interaction between the drug and polymers used. Pre- compression and post-compression parameters complied with Pharmacopoeial limit for the tablets. Four different gums (Cassia roxburghii, Tamarindus indica , Azadirachta indica and Manihot esculenta) were used in 3 different concentrations (35%, 50%, 75%) and was compared with the standard rate retardant polymer HPMC. The in vitro release study was performed and the results indicated that the formulation F12 (Neem gum 75%) was found to be the optimized formulation which can extend the release up to a period of 24 hours. The kinetic release data showed that the optimized formulation followed zero order kinetics. From the stability studies it was clear that the formulation was stable after 3 months at accelerated condition of 400C±20C/75% RH±5% in a stability chamber.
KEYWORDS: *Clozapine, Natural Polymers,Extended release system.*

INTRODUCTION

In recent years, considerable attention has been focused on the development of novel drug delivery system (NDDS). The reason for this paradigm shift is that low development cost and time required for introducing a NDDS, as compared to new chemical entity. In the form of NDDS, an existing drug molecule can get a new life, thereby increasing its market value, competitiveness and product patent life. Among the various NDDS available in the market, oral controlled release system hold a major position because of ease of administration and better patient compliance1. An ideal drug delivery system should be able to deliver an adequate amount of drug, preferably for an extended period of time, for its optimum therapeutic activity. Most drugs are inherently not long lasting in the body and require multiple daily dosing to achieve desired blood concentration to produce therapeutic activity. To overcome such problems, controlled release and sustained release delivery systems are receiving considerable attention from pharmaceutical industries world-wide2. Controlled drug delivery systems not only prolong the duration of action, but also result in predictable and reproducible drug release kinetics3. Clozapine [8-chloro-11-(4-methylpiperazin-1-yl)-5H dibenzo[b,e][1,4]diazepine] is a potential antipsychotic agent used in chemotherapy4.

It is one of the most commonly used atypical antipsychotics, and is also used for treatment of resistant schizophrenia. To achieve a high level of safety and effectiveness in pharmacotherapy, quality requirements of active substances are growing5,6. The starting dose of clozapine is 12.5 mg orally once or twice a day. It is practically insoluble in water, having only < 27% oral bioavailability7. Clozapine undergoes extensive first pass metabolism. Dosage adjustments may be needed based upon individual patient characteristics. The use of clozapine is associated with side effects: extreme constipation, night- time drooling, muscle stiffness, sedation, tremors, orthostasis, hyperglycemia, and weight gain. The risks of extrapyramidal symptoms such as tardive

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dyskinesia are much less with clozapine when compared to the typical antipsychotics. Clozapine also carries eleven black box warnings for agranulocytosis, CNS depression, leukopenia, neutropenia, seizure disorder, bone marrow suppression, dementia, hypotension, myocarditis, orthostatic hypotension and seizures. To achieve maximum therapeutic effect with a low risk of adverse effects, controlled released preparations are preferred 8,9. The side effects could be lowered by controlling the drug release and by employing suitable modifications in the manufacturing process 10. Delivering the drug from the pellet could be manipulated by suitable coating techniques11. Some schizophrenic patients hide a conventional tablet under their tongue to avoid its daily dose of an atypical antipsychotic12. To overcome this problem an attempt was made to formulate and evaluate controlled release dosage forms of clozapine. Matrix pellets were made to improve the solubility of clozapine and to enhance dissolution rate of clozapine. It may enhance the pregastric absorption of clozapine.

FORMULATION AND DEVELOPMENT

Sustained release tablets of Clozapine were prepared by direct compression using different natural polymers like *Cassia roxburghii, Tamarindus indica, Azadirachta indica, Manihot esculenta* and comparing with a standard rate retardant polymer HPMC at three different concentrations of polymers (30%, 50% and 75%).

Table 1: Preparation of sustained release tablets using different natural

Drug	Polymers	Polymer percentage (%)
Clozapine	HPMC	35,50,75
	Cassia roxburghii	35,50,75
	Tamarindus indica	35,50,75
	Azadirachta indica	35,50,75
	Manihot esculenta	35,50,75

POLYMERS

The ingredients in the table above were accurately weighed and passed through sieve #60, then magnesium stearate and talc was passed through sieve #80. Then the materials were blended except magnesium stearate and talc for 20 minutes in ascending order. Later the powder mixture was blended with magnesium stearate and talc for 5 minutes.

Table 2: Formula for development of tablet

FORMULA	DRUG	HPMC	CR	TI	AI	ME	MCC	TALC	Mg.St.
F1	25	35%					120	2	2
F2	25	50%					90	2	2
F3	25	75%					40	2	2
F4	25		35%				120	2	2
F5	25		50%				90	2	2
F6	25		75%				40	2	2
F7	25			35%			120	2	2
F8	25			50%			90	2	2
F9	25			75%			40	2	2
F10	25				35%		120	2	2
F11	2				50%		90	2	2
F12	5 6				75%		40	2	2
F13	25					35%	120	2	2
F14	25					50%	90	2	2
F15	25					75%	40	2	2

Various polymers have been evaluated based on post compression parameters and *in vitro* dissolution data of prepared tablets. The suitable polymer and its concentration has optimised from its

- Process efficiency
- Friability
- Assay of drug loaded

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RESULTS AND DISCUSSION

Determination of λ max

The wavelength showing maximum absorbance (λ max) for Clozapine was determined by scanning the standard stock solution of the drug using UV visible spectrophotometer. The λ max was found to be 237nm for Clozapine which is in accordance with the data available in literature.

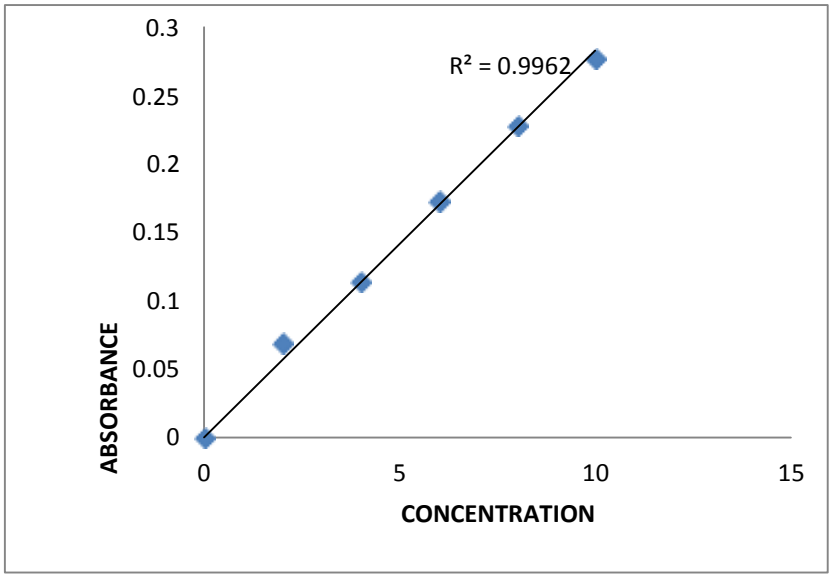

Fig.1: Caliberation Curve of Clozapine

COMPATIBILITY STUDIES

IR spectra matching approach was used for detection of any possible chemical interaction between the drug and the polymer. The samples were prepared by pressed pellet technique. The IR spectra was determined using JASCO FT/IR-4100. The scanning range was between 500- 4000cm^{-1}. The spectrum obtained was shown in figure.

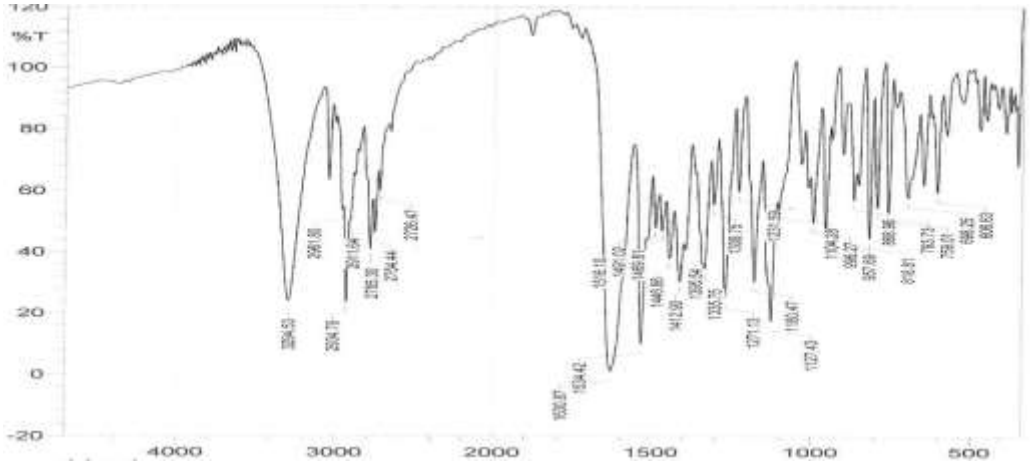

Fig. 2:IR Spectra of Clozapine

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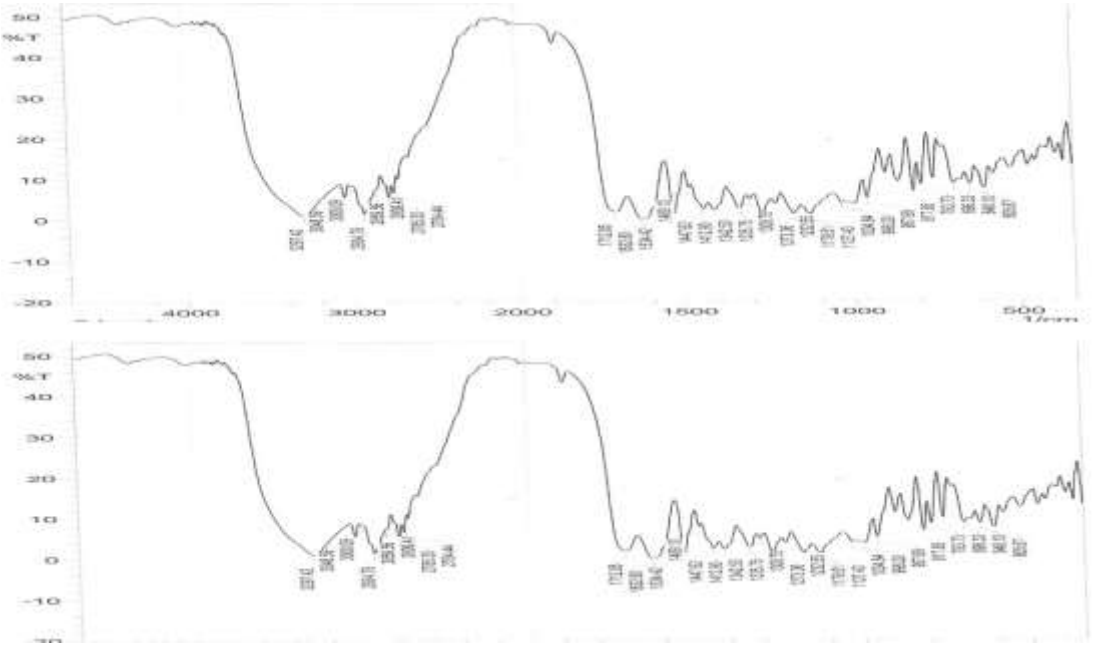

Fig.3:IR spectra of Clozapine + Azadirachta Indica before stability study and after stability study

PREFORMULATION PARAMETERS

Table 3: Results of Preformulation Studies

FORMULATION CODE	ANGLE OF REPOSE	BULK DEDNSITY	TAPPED DENSITY	C I	HAUSNERS RATIOS
F1	28°16'	0.625	0.899	30.47	1.43
F2	30° 23'	0.681	0.883	22.87	1.29
F3	32° 11'	0.423	0.521	18.80	1.23
F4	33° 13'	0.431	0.552	21.92	1.28
F5	33° 61'	0.617	0.819	24.66	1.32
F6	34° 07'	0.625	0.830	24.69	1.33
F7	38° 12'	0.602	0.809	25.58	1.34
F8	38° 73'	0.421	0.529	20.41	1.25
F9	39° 05'	0.683	0.889	23.17	1.30
F10	26° 18'	0.512	0.623	17.81	1.21
F11	27° 07'	0.458	0.537	14.71	1.17
F12	39° 16'	0.465	0.571	18.56	1.22
F13	33° 33'	0.620	0.891	30.41	1.43
F14	34° 17'	0.615	0.811	24.16	1.31
F15	34° 23'	0.601	0.807	25.52	1.34

Evaluation of Post Compression Parameters

The tablets were evaluated for thickness, hardness, friability, average weight and assay. The thickness of the formulated tablets was found to be in the range of 0.31mm to 0.41mm. Hardness and friability was found to be 3.5-6kg/cm^2 and 0.046- 0.523% which indicates the tablet has adequate mechanical strength. Weight variation of the tablets was found to be within the specified limits. . The drug content of all the formulations ranged from 89.78-96.81% indicating the presence of an acceptable amount of drug in the formulations.

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POST COMPRESSION PARAMETERS

Table 4: Results of Evaluation of Tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Average wt(mg)	Assay (%)
F1	0.31	4.0	0.523	199	95.12
F2	0.35	5.5	0.420	209	94.87
F3	0.41	6.0	0.413	203	95.02
F4	0.36	3.5	0.141	194	93.12
F5	0.39	5.0	0.159	198	92.09
F6	0.37	5.5	0.261	212	92.68
F7	0.40	4.5	0.102	200	90.12
F8	0.35	5.0	0.124	207	89.78
F9	0.39	6.0	0.198	203	90.03
F10	0.38	4.5	0.046	209	95.71
F11	0.35	5.5	0.047	201	96.29
F12	0.34	6.0	0.062	207	96.81
F13	0.41	3.5	0.212	208	94.71
F14	0.40	4.5	0.314	207	94.13
F15	0.36	5.0	0.282	209	95.11

In vitro Dissolution Study of Tablets

Clozapine controlled release tablets were formulated using 5 different polymers such as HPMC, *Cassia roxburghii*, Tamarind seed powder, Neem gum, Tapioca starch in the percentage of 35%, 50%, and 75%. A total of 15 formulations were made using these polymers by direct compression method and 24 hours dissolution studies were carried out.

Effect of HPMC on Drug Release

Cumulative percentage drug release for the different concentration of HPMC (35%, 50%,75%) is given the table below. Formulation F1, F2, F3 containing the different concentrations of HPMC are taken. The F1 and F2 do not show the drug release up to the desired period of time. . In case of formulation F3 containing HPMC(75%) also showed prolonged release but could not prolong the release for desired time.

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Table 5: *In vitro* Release Data of F1, F2 and F3

TIME	F1	F2	F3
0	0	0	0
1	6.6	4.12	4.30
2	31.12	30.75	8.71
3	52.01	35.20	17.51
4	58.07	40.12	26.51
5	70.98	57.10	31.10
6	81.12	68.01	35.81
7	85.88	70.33	49.40
8	87.27	77.60	52.09
9	91.95	86.32	60.15
24	95.60	95.96	96.50

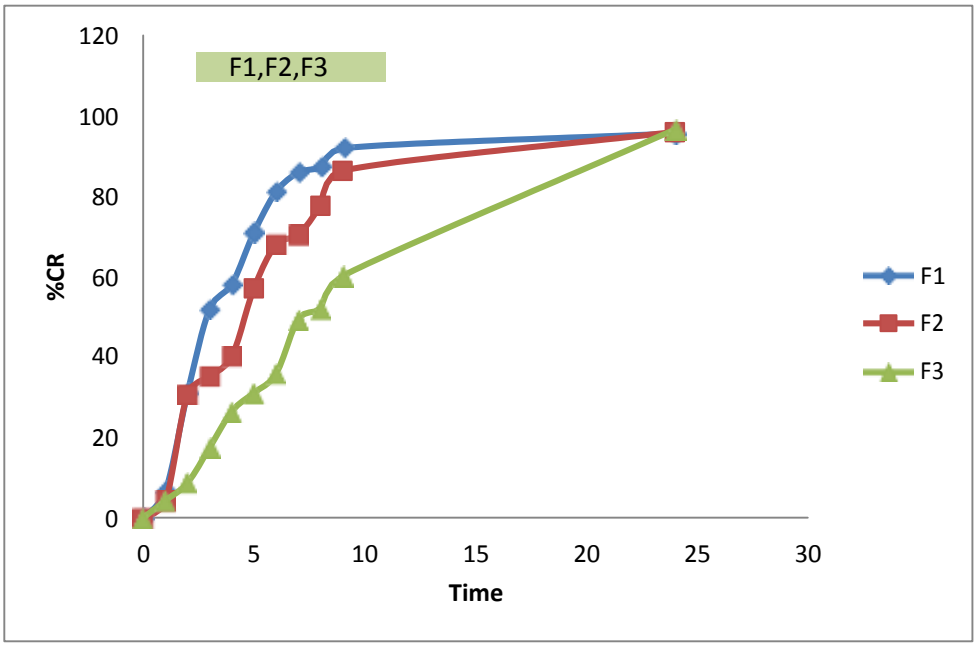

Fig.4: Dissolution graph of HPMC (F1,F2,F3)

Effect of *Cassia roxburghii* on Drug Release

Cumulative percentage drug release for the different concentration of *Cassia roxburghii* (35%, 50% and 75%) is given the table below. These formulations were able to extend and control their release pattern to desired period of time. The drug release rate was found to be decreased when concentration of polymers was increased. This may be due to increased swelling of the polymer when concentration is increased which leads to increased viscosity of the medium and thus increases the mean diffusional path length of the drug molecule to get released into the diffusion medium.

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Table 6: *In vitro* Release Data of F4, F5 andF6

TIME	F4	F5	F6
0	0	0	0
1	8.76	7.16	7.06
2	13.22	11.04	11.08
3	19.94	15.55	16.34
4	26.72	22.42	20.38
5	35.76	24.71	23.76
6	41.71	35.87	34.84
7	56.32	42.80	50.10
8	59.63	58.60	58.18
9	65.60	63.59	62.50
24	95.14	95.31	94.30

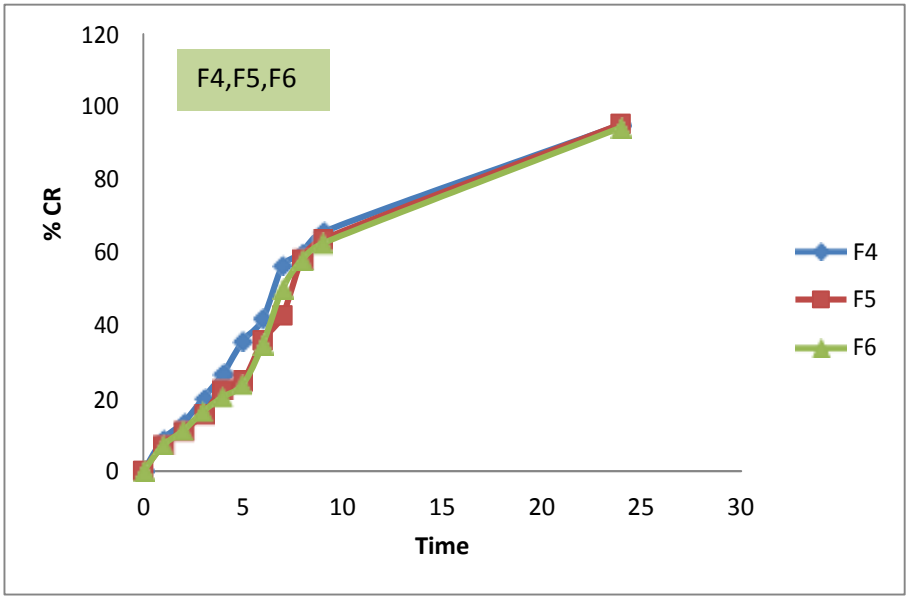

Fig.5: Dissolution graph of Cassia roxburghii (F4,F5,F6) Effect of *Tamarindus*

***Indica* on Drug Release**

Cumulative percentage drug release for the different concentration of Tamarindus indica(35%,50%,75%) is given the table below. The decrease in drug release rate as the concentration of the polymer increases may be attributed to the presence of a highly water soluble compound. It is seen that there is a faster rate of polymer swelling and a large increase in gel thickness to prevent immediate tablet disintegration, and thus controlling the diffusion of the drug.

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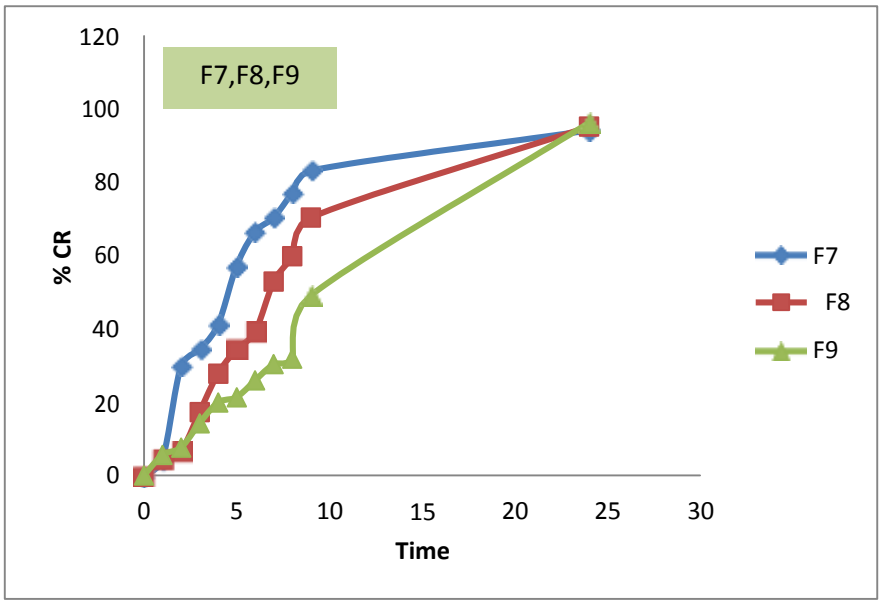

Fig.6: Dissolution graph of *Tamarindus indica* (F7,F8, F9)

Effect of *Azadirachta Indica* on Drug Release

Cumulative percentage drug release for the different concentration of *Azadirachta indica* (35%,50%,75%) is given the table below. For formulation F12 containing 75% polymer the cumulative release was found to be 36.02% in 9 hr and 97.80% at 24 hours. The increase in polymer content delays the drug release as the polymer is hydrophilic and swellable polymer which produces increased swelling with increase polymer which might have increased diffusional path length for the drug to get diffuse across the membrane.

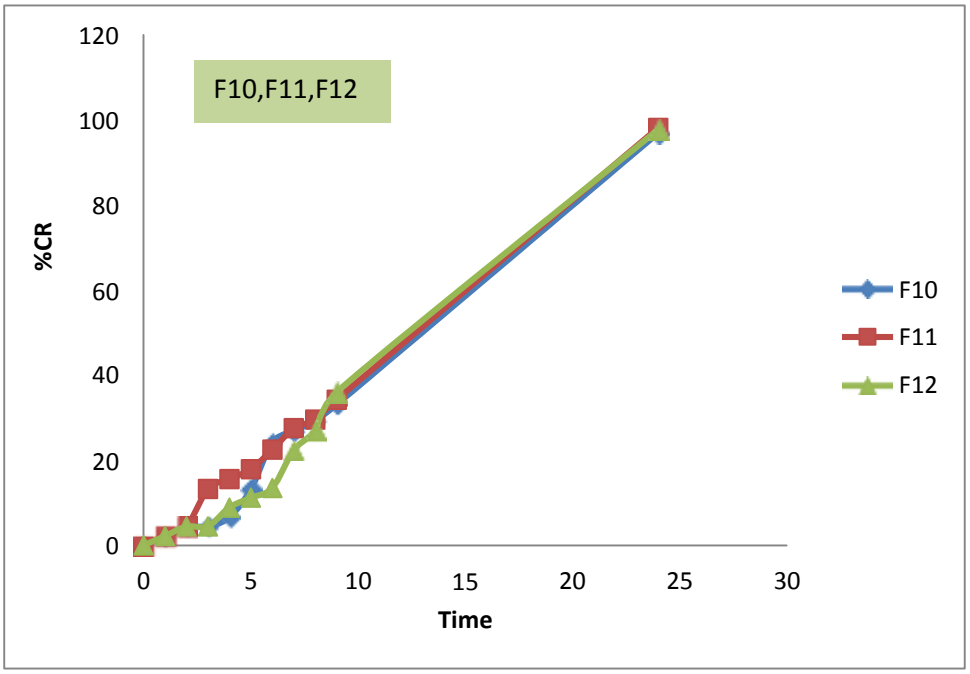

Fig.7: Dissolution graph of Azadirachta indica (F10,F11,F12)

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Effect of *Manihot Esculenta* on Drug Release

Cumulative percentage drug release for the different concentration of Manihot Esculenta (35%,50%,75%) is given the table below. *In vitro* dissolution data showed that these are not the best candidate for once daily dosage form as the release of the drug is not up to the desired extent. After 24 hours, the release of the drug was found to be 94-95% only. As a result, these formulations cannot be considered as optimized formulation.

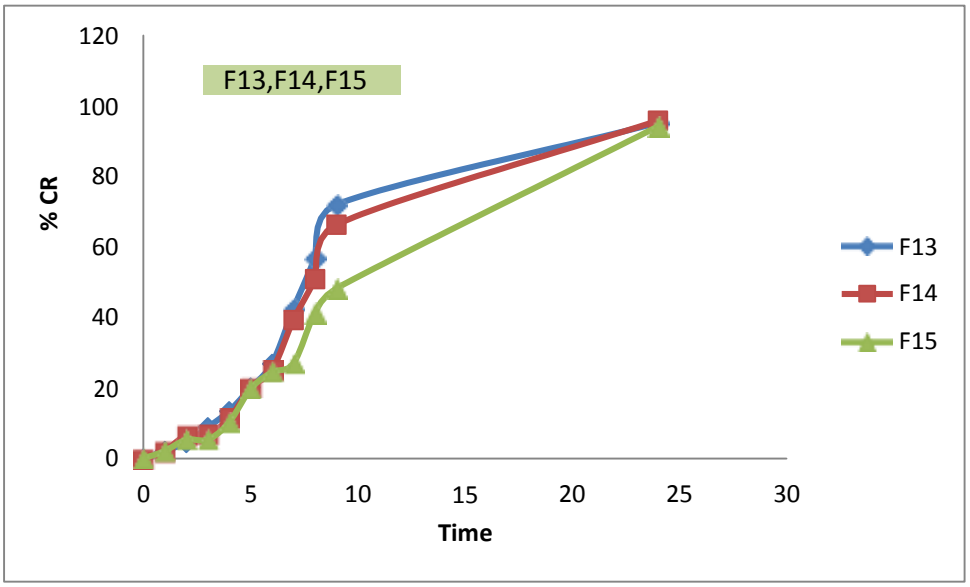

Fig.8: Dissolution graph of *Manihot esculenta* (F13,F14,F15)

From the *in vitro* dissolution data of the 15 formulations, almost all the formulations have the release up to the extended period of time. From these formulations F12 was chosen as the optimised formulation because of their extent their release up to 24 hours. All other post compression parameters like bulk density, tapped density, angle of repose, compressibility index and hausner's ratio are up to the specified limits.

DISSOLUTION PROFILE OF OPTIMIZED FORMULATION

From the dissolution data and from the post compression parameters it is concluded that *Azadirachta indica* 75% was fond to be the optimised formulation.

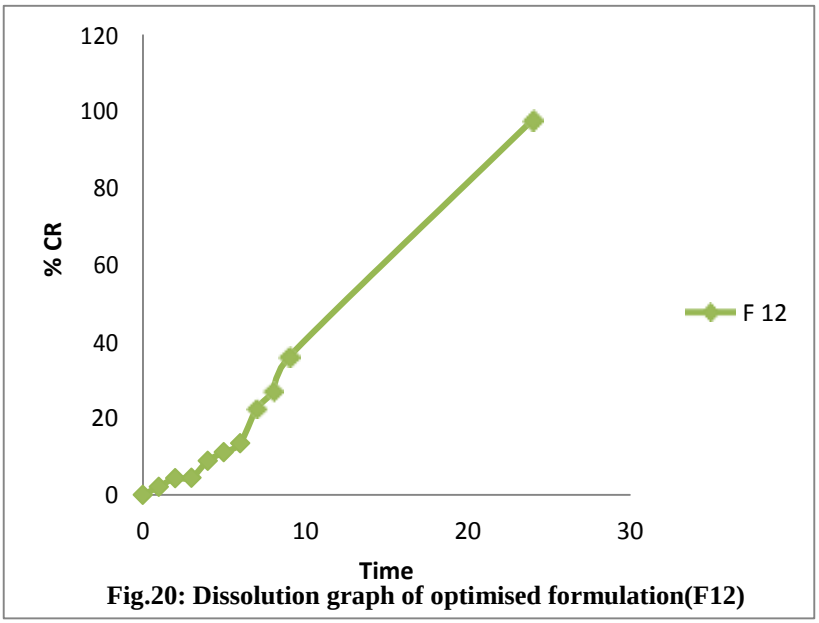

Fig.20: Dissolution graph of optimised formulation(F12)

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DRUG RELEASE KINETICS ANALYSIS

The *in-vitro* drug release data of the optimized formulation was subjected to kinetic analysis by plotting various kinetic equations like zero order, first order and Higuchi plot. The kinetic analysis data of the formulation was shown in the table. The kinetic model that best fits with the release data of formulation was evaluated by the correlation coefficient (R^2) values. According to the values obtained higher linearity was observed with linear plot(zero order) with R^2 value of 0.955. Thus the formulation may follow zero order drug release.

Table 7: Result of kinetic analysis

FORMULATION	Zero order (R^2)	First order (R^2)	Higuchi kinetics (R^2)
F 12	0.955	0.913	0.769

Mechanism of Drug Release

Mechanism of drug release data can be assissed by plotting the drug release data in linear, exponential and power equations. From the regression coefficiant value, it may follow zero order kinetics.

Stability Study

Here the tablets were loaded at accelerated condition at $40^0C \pm 2^0C$/75% RH±5% in a stability chamber. Samples were withdrawn at 30^{th} and 60^{th}day and evaluated for the physical appearance, drug content and dissolution characteristics. The stability analysis data were given in table above. The result showed that storage at 40 ºC had no effect on the hardness, disintegration time and dissolution time.

Table 8 : Stability study of formulation F12(Clozapine+Neem gum 75%)

SL. NO.	PARAMETERS	INITIAL	30^{th} DAY	60^{th} DAY	90^{th} DAY
1	Physical appearance	Grey	Grey	Grey	Grey
2	Drug contenet(%)	96.81%	96.75%	96.34%	96.05%
3	Dissolution (%CR in 24thhr)	97.80%	97.38%	97.06%	96.92%

SEM Image of *Azadirachta Indica*

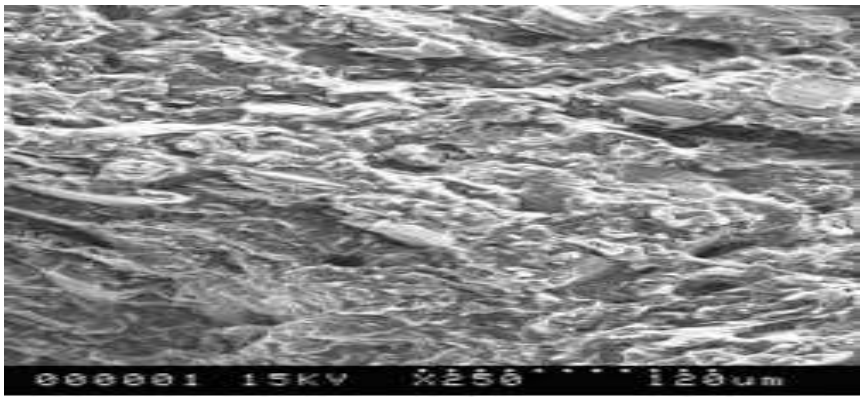

Fig9: SEM image of *Azadirachta indica*

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SUMMARY

The Clozapine has various side effects which may be related to high blood plasma concentration levels excluding its use as a single immediate release dose. Presently Clozapine is available as Clozaril that utilizes OROS technology which has several disadvantages. Hence present study was aimed to formulate sustained release tablet of Clozapine by direct compression method.

Compatibility studies

IR spectra matching approach was used for detection of any possible chemical interaction between the drug and the polymer. The samples were prepared by pressed pellet technique. The IR spectra were determined using JASCO FT/IR-4100. Scanning range was between 500- 4000cm^{-1}. FT-IR study revealed the absence of any chemical interaction between drug and polymer used.

Pre-compression analysis

Preformulation studies of the sustained release and immediate release layer powder blend were done. The results of the evaluation suggests that all the granules exhibit good flow properties, so all the formulations were directly compressed to tablets.

Post formulation studies of Tablets

Tablets were evaluated for their physical parameters like hardness, thickness, friability, weight variation, and drug content uniformity complies with IP standards.

***In-vitro* dissolution studies**

The *in-vitro* drug release studies were performed using USP type 2 paddle type dissolution apparatus using simulated gastric fluid (0.825M hydrochloric acid and 0.2% sodium chloride) for 24 hours. The formulation F12 (*Azadirachta indica* 75%) showed the maximum release of drug (97.8 %) at 24^{th} hour. From the release data it is clear that the best sustaining ability was revealed by the formulation F12.

Drug Release Kinetics Analysis

The *in-vitro* drug release data of the optimized formulation was subjected to kinetic analysis by plotting various kinetic equations like zero order, first order and Higuchi plot. According to the values obtained higher linearity was observed with Higuchi plot, indicates drug is released by diffusion. The kinetic model that best fits with the release data of formulation was evaluated by the correlation coefficient (R^2) values. According to the values obtained higher linearity was observed with linear plot (zero order) with R^2 value of 0.955. Thus the formulation may follow zero order drug release.

Stability studies

The tablets were loaded at accelerated condition at $40^0C \pm 2^0C$/75% RH±5% in a stability chamber. Samples were withdrawn at 30^{th} , 60^{th} and 90^{th} day and evaluated for the physical appearance, drug content and dissolution characteristics. The result obtained from the study reveals that storage at 40 ºC had no effect on the hardness, disintegration time and dissolution time. The stability studies indicate that the sustained release tablet was suitable for drug delivery of Clozapine without having any physical stability issues.

CONCLUSION

The formulation F12, 75% of ***Azadirachta indica*** could give rise to tablets exhibiting sustained drug release. Recent developments in the area of natural gums as excipients in the sustained release of drugs are to be explored and our research work provided the ground work for further studies in zero order release mechanisms.

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