

## Novel Approach in Designing of Mouth Dissolving Tablets for Bitter Drugs: Taking Clozapine as Model Drug

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### ABSTRACT

*The main merits of mouth dissolving tablets are faster onset of action, elegance, ease of administration, manufacturing, storage and transport. A novel attempt has been made to designing mouth dissolving tablets of Clozapine by the inclusion of clove oil as flavoring agent which also has local anesthetic action on taste buds of tongue. Additionally Stevia leaf powder was included as sweetener which has 400 times sweeter than Sucrose. The mouth dissolving tablets were prepared by direct compression technique. The formulated mouth dissolving tablets were evaluated for Pre compression and post compression parameters which were found to be satisfactory. The formulated mouth dissolving tablets possessed good drug release property, good mouth feel and improved bioavailability with better patient compliance.*

**Key words:** Mouth dissolving tablet, Clozapine, clove oil, stevia leaf powder, direct compression method.

### INTRODUCTION

Patients, particularly pediatric and geriatric patients, have difficulty in swallowing solid dosage forms. These patients are unwilling to take these solid preparations due to a fear of choking. In order to assist these patients, several mouth dissolving drug delivery systems has been developed. Mouth dissolving tablets can be prepared by direct compression, wet granulation, moulding, spray drying, freeze drying or sublimation methods [1]. Mouth dissolving tablets dissolve rapidly in the saliva without the need for water and release the drug [2]. Some drugs are absorbed from the oral cavity as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [3].

Clozapine is an antipsychotic drug used to alleviate the symptoms and signs of schizophrenia, hallucinations, delusions and unusual behavior. The usual dosage of clozapine is 300–600 mg per day [4]. However, some patients may require daily dosages of up to 900 mg. To minimize side effects, the initial dose of clozapine is 12.5 mg twice a day, and the dose is increased by 25–50 mg each day, until the dose reaches 300–450 mg per day. The main criteria for mouth dissolving tablets is to disintegrate/dissolve rapidly in oral cavity with saliva in 60 sec, without need of water and should have pleasant mouth feel. It has been reported that Clozapine possess bitter taste hence the primary objective is to mask the bitter taste and further developing the drug into mouth dissolving tablets.

In this formulation Clove oil was added as flavoring agent which has additional local anesthetic property to block the sensory taste buds for bitter taste. The inclusion of Stevia leaf powder in the formulation which has 400 times sweeter than Sucrose [5] makes the formulation still elegance and diabetic friendly.

## MATERIALS AND METHODS

### Materials

Clozapine was a gift sample from Aurobindo Pharma Ltd. Hyderabad, India. Stevia leaf powder was obtained from the medicinal garden of Sri Krishnadevaraya University, Anantapur, India and authenticated by the Botany department of Sri Krishnadevaraya University, Anantapur, India. Mannitol, Clove oil, talc, micro crystalline cellulose, Cross carmellose sodium, Cross Povidone, magnesium stearate and talc were purchased from S.D. Fine Chemicals, Mumbai, India. All other chemicals, solvents and reagents were used of either pharmacopoeial or analytical grade. Double distilled water was used throughout the experiment.

### Methods

#### Preparation of Mouth Dispersible Tablets: [6]

All the ingredients were passed through a # 60 sieve. Clozapine, Mannitol, Micro Crystalline Cellulose and stevia leaf powder were triturated in a glass mortar. Cross carmellose sodium and Cross Povidone were incorporated in the powder mixture and finally magnesium stearate and talc were added as lubricant. The powder mix was weighed individually and compressed with 10mm flat face surface punches using single station tablet punching machine. The composition of formulated mouth dissolving tablets was shown in table 1.

#### Evaluation of the prepared tablet: [7-10]

##### Pre-compression parameters

##### *Compatibilities study*

The compatibility of drug and polymers under experimental condition was conducted using FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

##### *Flow properties*

The powdered blend was evaluated for flow properties viz., Angle of repose, loose bulk density (LBD), tapped bulk density (TBD), Carr's compressibility index and hausner's ratio.

##### Post compression parameters:

##### *Thickness*

The thickness of the tablets was determined using a thickness screw gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used and average values were calculated.

**Hardness test**

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer's hardness tester. It is expressed in kg/cm<sup>2</sup>. Three tablets were randomly picked and analyzed for hardness. The mean and standard deviation values were also calculated.

**Friability test**

The friability of tablets was determined using Roche Friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The % friability was then calculated by eq.1.

$$F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100 \dots\dots\dots (1)$$

Where

F = friability (%), W<sub>initial</sub> = initial weight, W<sub>final</sub> = Final weight

**Weight variation test**

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado) and the test was performed according to the official method.

**Drug content uniformity**

Tablet containing 50mg of drug is dissolved in 100ml of 0.1N HCl taken in volumetric flask. The drug is allowed to dissolve in the solvent. The solution was filtered, 1ml of filtrate was taken in 50ml of volumetric flask and diluted up to mark with 0.1N HCl and analyzed spectrophotometrically at 225 nm. The concentration of Clozapine in mg/ml was obtained by using standard calibration curve of the drug. Claimed drug content was 50mg per tablet. Drug content studies were carried out in triplicate for each formulation batch.

**Wetting time**

The tablet was placed in a petridish of 6.5 cm in diameter, containing 10 ml of water at room temperature, and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out six times and the mean value calculated.

**Water absorption ratio**

A piece of tissue paper folded twice was placed in a small petridish containing 6ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using eq.2

$$R = 10 \times \frac{(W_a - W_b)}{W_b} \dots\dots\dots (2)$$

Where,

W<sub>b</sub> = weight of the tablet before water absorption

W<sub>a</sub> = weight of the tablet after water absorption

Three tablets from each formulation were analysed performed and standard deviation was also determined.

**In vitro dispersion time**

Tablet was placed in 10 ml phosphate buffer solution, pH 6.8±0.5°C. Time required for complete dispersion of a tablet was measured.

***In-vitro disintegration time***

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at  $37\pm 2^{\circ}\text{C}$  as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at  $37\pm 2^{\circ}\text{C}$ . The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

***Mouth feel***

To know mouth feel of the tablets, selected human volunteers were given placebo tablets and the taste sensation felt was evaluated.

***In-vitro dissolution studies***

*In vitro* release studies were carried out using tablet dissolution test apparatus USP XXIII. The following procedure was employed throughout the study to determine the *in-vitro* dissolution rate for all the formulations.

***Accelerated Stability studies:***

The promising formulation (F5) was tested stability for a period of 3 months at accelerated conditions of a temperature  $40^{\circ}\text{C}$  and a relative humidity of 75% RH, for their drug content.

## RESULTS AND DISCUSSION

The FTIR spectrum of formulated blend showed characteristic peaks of drug which indicated that the compatibility of the drug with the excipients used. The spectrum was shown in Fig. 1 and 2. The results obtained for angle of repose of the powdered blends was less than  $30^{\circ}$ , the loose bulk density was ranged from  $0.56\pm 0.55$  to  $0.59\pm 0.45$   $\text{g}/\text{cm}^3$ , the tapped bulk density was ranged from  $0.64\pm 0.15$  to  $0.70\pm 0.16$   $\text{g}/\text{cm}^3$ , the percent compressibility was ranged from 12.10 to 21.51 %. All these values were represented in table 2. The mean thickness values were found in the range from  $2.98\pm 0.15$  to  $3.28\pm 0.02$  mm, the hardness of formulated tablets was found to be  $5.16\pm 0.07$  to  $8.50\pm 0.07$   $\text{kg}/\text{cm}^3$ . The loss in friability was ranged from  $0.38\pm 0.11$  to  $0.87\pm 0.07$  %. The Wetting Time was ranged from  $94 \pm 1.49$  to  $99 \pm 0.51$  sec, the disintegration Time was ranged from  $29\pm 8.45$  to  $38\pm 4.844$  sec. These values were represented in Table 3. The *in-vitro* dissolution profile of formulated tablets was shown in Fig.3. The comparative parameters of optimized formulation (F5) before and after the accelerated stability studies were shown in Table 4.

All the formulations showed angle of repose within  $30^{\circ}$  which indicates good flow. All formulations show good compressibility. The formulated tablets were elegant and almost uniform thickness. All the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness. The weight loss after friability test was found well within the approved range ( $<1\%$ ) in all the formulation, indicates the tablets possess good mechanical strength. All the tablets passed weight variation test as per the pharmacopoeial limits. All formulations showed quick wetting, this may be due to ability of swelling and also capacity of absorption of water. All superdisintegrants have high water absorption capacity and cause swelling. All formulations showed disintegration time less than 95 seconds, indicates the swelling of disintegration substance suggested mechanism of disintegration. The volunteers felt good taste in all the formulations. As the formulation was not bitter due to the presence of stevia

leaf powder, which is 400 times sweeter than sucrose and the Eugenol in clove oil which acts as both flavoring and local anesthetic agent to block the sensation of taste buds. In oral disintegration all the formulations showed rapid disintegration in oral cavity. By observing the above results use of cross cormilose sodium and cross Povidone, in direct compression method results in hydrophilicity and swelling which in turn causes rapid disintegration. Thus these disintegrants are suitable in preparing the rapidly disintegrating tablets. This rapid dissolution might be due to fast breakdown of particles of superdisintegrants. In all formulations the drug release was nearer to 100% within 12 min. The optimized formulation F5 were selected for accelerated stability studies and the tablets possessed the same parameters even after the stressed conditions, indicates good stability properties of formulation.

## CONCLUSION

This is easiest and economical approach of formulating bitter taste drugs. As Clove oil has both flavoring property and local anesthetic action. On the other hand the inclusion of Stevia leaf powder in the formulation as sweetener which has 400 times sweeter than Sucrose and makes the mouth dissolving tablets still sweeter even for antipsychotic patients with diabetes.

## Acknowledgement

Authors are thankful to Prof. Sreenivasulu, principal College of Pharmacy, Sri Krishnadevaraya University, Anantapur, India for providing all the facilities for this research work.

**Table 1: Composition of Mouth Dissolving Tablets of Clozapine**

Ingredients (mg)	Formulations				
	F1	F2	F3	F4	F5
Clozapine	50	50	50	50	50
Cross carmellose sodium	10	20	30	40	50
Cross povidone	10	20	30	40	50
Mannitol	50	50	50	50	50
Stevia leaf Powder	5	5	5	5	5
Micro crystalline cellulose	264	244	224	204	184
Magnesium stearate	3	3	3	3	3
Talc	3	3	3	3	3
Clove oil (Flavoring & local anesthetic agent)	5	5	5	5	5
<b>Total weight of the tablet 400mg</b>					

**Table 2: The physicochemical properties of granules**

Formulation	Angle of Repose ( $\theta$ )	Bulk Density ( $\text{g/cm}^3$ )		Carr's Index (%)
		Loose Bulk Density	Tapped Bulk Density	
<b>F1</b>	29.11 $\pm$ 0.21	0.56 $\pm$ 0.55	0.69 $\pm$ 0.05	15.19
<b>F2</b>	29.77 $\pm$ 0.41	0.57 $\pm$ 0.49	0.70 $\pm$ 0.16	21.51
<b>F3</b>	29.69 $\pm$ 0.32	0.59 $\pm$ 0.45	0.69 $\pm$ 0.45	13.53
<b>F4</b>	27.98 $\pm$ 0.24	0.58 $\pm$ 0.44	0.64 $\pm$ 0.15	13.31
<b>F5</b>	30.01 $\pm$ 0.98	0.58 $\pm$ 0.55	0.65 $\pm$ 0.12	12.10

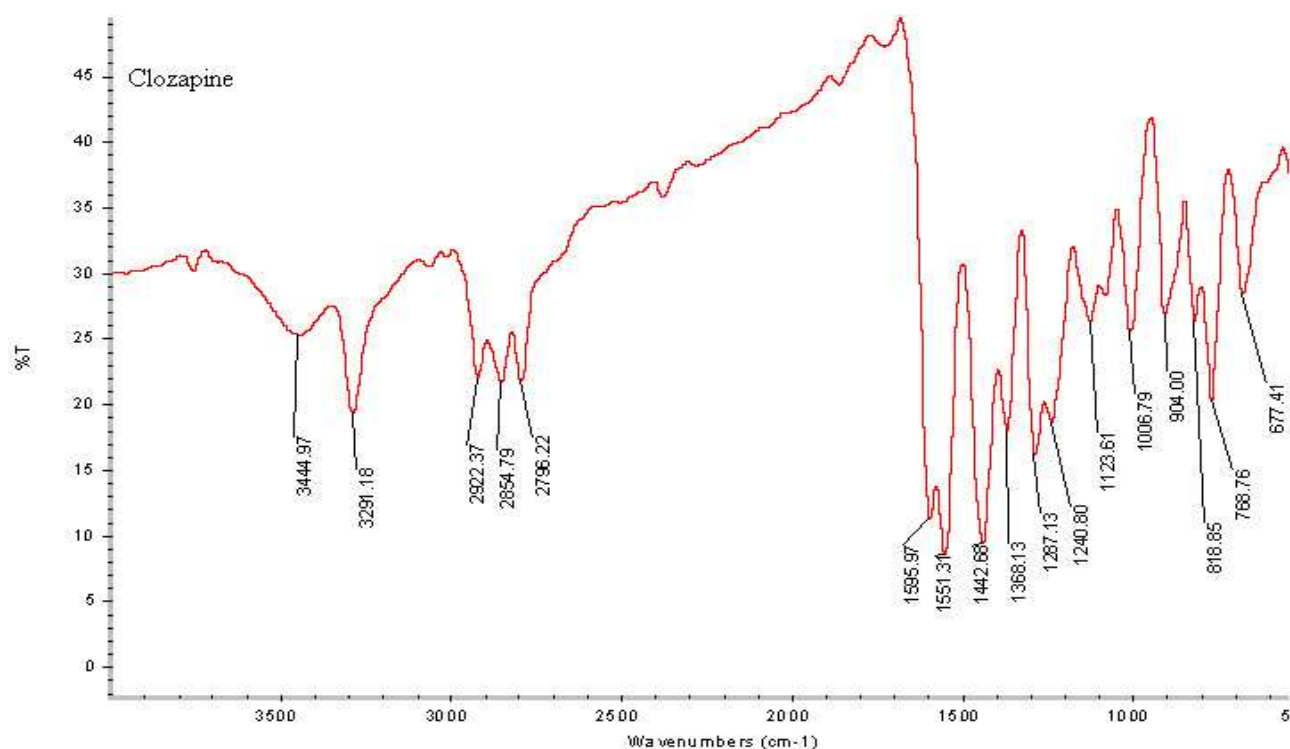
**Table 3: Evaluation parameters of Tablets**

Formulation	Thickness (mm)	Hardness (kg/cm <sup>3</sup> )	Friability (%)	Wetting Time (sec)	Disintegration Time (sec)
<b>F1</b>	2.98±0.24	8.50±0.07	0.38±0.11	99±0.51	38±4.84
<b>F2</b>	3.17±0.15	5.16±0.07	0.84±0.09	96±1.68	36±2.11
<b>F3</b>	2.98±0.15	5.38±0.13	0.45±0.07	94 ±1.49	32±6.48
<b>F4</b>	3.05±0.01	6.48±0.04	0.87±0.07	98±1.48	29±8.45
<b>F5</b>	3.28±0.02	7.50±0.07	0.69±0.09	98±1.46	31±4.15

Number of trials (n) = 3

**Table 4: Optimized Formulation (F5) for accelerated Stability Studies (at 40<sup>0</sup>C and at 75% RH)**

Formulation	Tested after time (days)	Hardness (kg/cm <sup>2</sup> )	Disintegration time (sec)	Wetting time (sec)	Friability (%)
<b>F5</b>	0	7.50±0.09	31±4.15	98±1.48	0.69±0.09
	10	7.48±0.46	30±2.64	98±2.34	0.70±0.02
	20	7.44±0.15	31±3.16	99±1.55	0.69±0.03
	30	7.46±0.33	30±6.56	98±2.55	0.71±0.01

**Fig.1. FTIR spectrum of Clozapine**



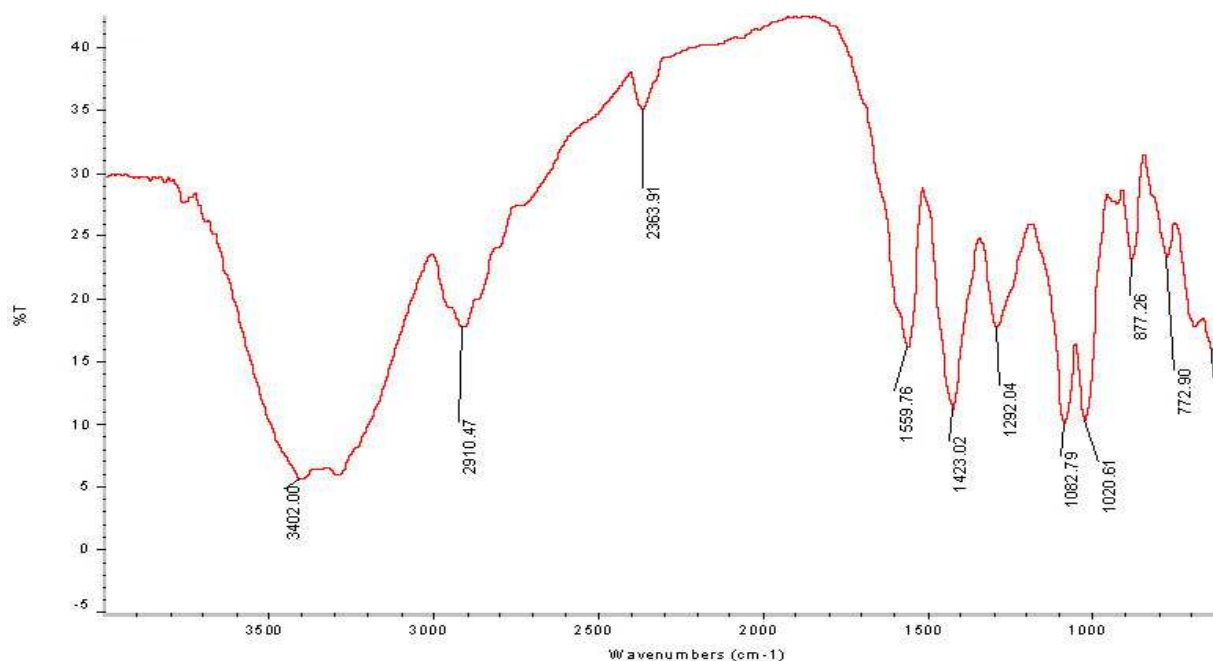
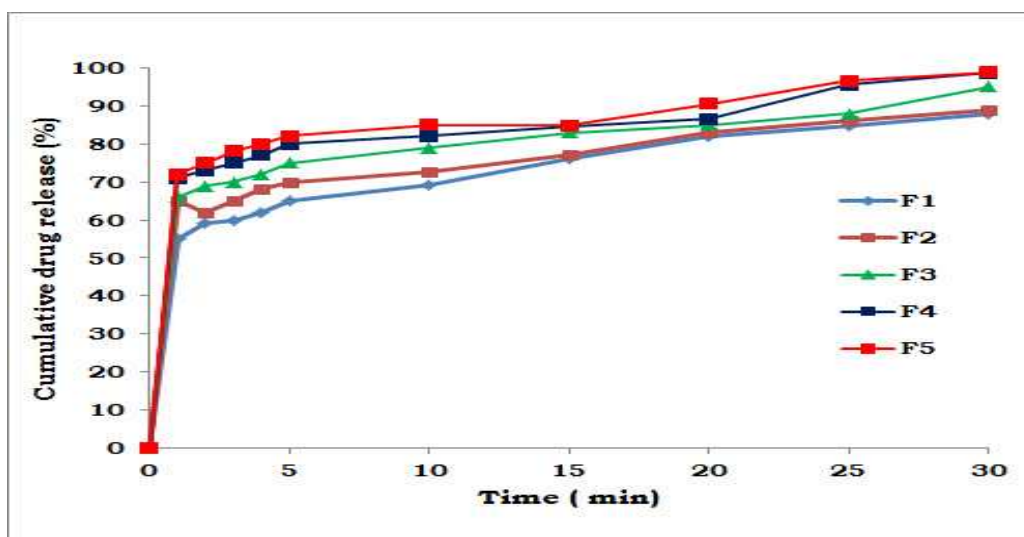


Fig.2. FTIR spectrum of formulation (F5)

Fig.3. *In-vitro* drug release profile of formulated tablets

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