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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF CLONAZEPAM PREPARED BY SUBLIMATION METHOD

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Abstract:
The objective of the present study was to formulate and evaluate mouth dissolving tablets (MDTs) of Clonazepam using the sublimation method to enhance patient compliance, provide rapid onset of action, and improve bioavailability. Tablets were prepared by direct compression incorporating sublimating agents to create porosity and facilitate faster disintegration. The prepared formulations were evaluated for pre-compression parameters such as angle of repose, bulk density, tapped density, and compressibility index, as well as post-compression parameters including hardness, friability, weight variation, wetting time, drug content uniformity, disintegration time, and in vitro dissolution. All pre-compression and post-compression parameters were found to be within pharmacopeial limits, confirming the suitability of the formulations. Among the different batches, formulation F9 was identified as the optimized formulation, showing rapid disintegration and an in vitro drug release of 99.84% within 60 minutes, indicating its effectiveness in delivering Clonazepam quickly.
The study concludes that the sublimation method is a simple and effective technique for developing mouth dissolving tablets of Clonazepam, providing a patient-friendly dosage form especially useful for paediatric, geriatric, and dysphagic patients.
***Keywords**: Clonazepam, Mouth Dissolving Tablets*

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INTRODUCTION:

Mouth Dissolving Tablet

The oral route is still the best way to administer therapeutic agents despite amazing advancements in drug delivery because it allows for accurate dosage, affordable therapy, self-medication, non-invasive administration, and high patient compliance.[1] However, some elderly patients may find it inconvenient or impractical to take traditional tablets and capsules with a glass of water due to changes in a number of physiological and neurological conditions associated with aging, such as hand tremors, difficulty swallowing (dysphagia), deterioration in eyesight, hearing, memory, and risk of choking, in addition to taste and smell changes. When using solid dosage forms, other patient groups such as children, the mentally challenged, bedridden patients, and uncooperative patients also present significant administration challenges. Younger patients may have trouble swallowing because of their developing nervous and muscular systems. Moreover, patients who are traveling with little or no access to water may find that conventional oral tablets or capsules are not as helpful. In response to recent technological advancements, effective dosage alternatives have been developed to meet the needs of patients such as oral disintegrating tablets (ODTs), a term that has gained popularity. In the past ten years, mouth dissolving tablet (MDT) technology has attracted a lot of attention. It enables the dissolution or disintegration of tablets in the mouth without the need for additional water consumption. Quick disintegrating, fast dispersing, rapid dissolve, rapid melt, mouth disintegrating, and oral disintegrating tablets are some other names for this technology. The MDT formulation is described as "a solid dosage form containing medicinal substances which dissolve rapidly when placed upon the tongue, usually within a matter of seconds" by the Food and Drug Administration (FDA). The capacity of the tablets to transform or dissolve into smaller granules from a hard, solid structure to a gel-like structure in the mouth, making it easier for sick people to swallow. The time it takes for those tablets to break down varies from a few seconds to more than a minute. MDT administration is different from that of conventional tablets, and several unique features should be included in MDTs to accommodate the mouth disintegration time. Given that the patient's saliva serves as the disintegration fluid, they should dissolve or break down entirely or almost entirely in water in the mouth. The broken-down tablet should transform into a silky paste or liquid suspension with a pleasant mouthfeel that is easy to swallow. The terms "mouth dissolution" and "mouth disintegration" generally refer to the ability of a tablet to dissolve or disintegrate in less than minute.[1,2]



Figure 1.1; Mouth Dissolving Tablet

Ideal properties of mouth dissolving tablets: An ideal MDT should:

1. No aftertaste of bitterness
2. Less than a 20 mg dose
3. Modest to medium molecular weight
4. Excellent stability in saliva and water
5. Partial non-ionization at the pH of the oral cavities
6. Capacity to permeate and divide into the upper GIT epithelium (log p>1, or better yet>2)

7. Capacity to penetrate the oral mucosa
8. Brief half-life and repeated dosage
9. Extremely bitter or unsatisfactory taste due to the inability to mask flavours
10. Needed steady or regulated release.[3,4]

Advantages of mouth dissolving tablets

1. Simple administration for patients who refuse to swallow (paediatric, geriatric, and psychiatric patients), should not swallow (renal failure patients), or cannot swallow (older adults, stroke victims, and bedridden patients)
2. Water is not required for swallowing the tablet.
3. Precise dosing in contrast to liquids.
4. Drugs dissolve and absorb quickly, providing a quick start to action.
5. Some medications are absorbed through the mouth, pharynx, and oesophagus and enter
The stomach through saliva, their bioavailability is increased.
6. Reduced first pass metabolism during transportation provides better bioavailability, which lowers dosage and adverse effects.

Disadvantages of mouth dissolving tablets

1. To maintain the drug's sublingual absorption during medication therapy, patients must refrain from chewing, eating, and possibly speaking.
2. Another possible issue with mouth-dissolved tablets is swallowing some of the tablet before it dissolves sublingually.
3. Patients who experience oral foreign objects typically remove the tablet before the formulation's active ingredients are fully released.
4. Tooth discoloration and decay can occasionally be caused by MDTs.
5. MDTs are hygroscopic by nature, they must be stored in a dry environment and require specialized packaging to ensure product safety and proper stabilization.[5,6]



Figure 1.2 Mouth dissolving tablets

7.METHODOLOGY:

7.1. DETERMINATION OF λ_{max} :

- Accurately weighed 100 mg of drug was transferred to 100 ml volumetric flask and dissolved in pH 6.8 phosphate buffer, this was considered as stock solution (I) which contained 1000µg/ml.
- To 10 ml of stock solution (I) 90 ml of pH 6.8 phosphate buffer was added and this was considered as stock solution (II) which contained 100µg/ml.
- To 10 ml of stock solution (II) 90ml of pH 6.8 phosphate buffer was added which was known as 10 µg/ml.

7.1.1 CONSTRUCTION OF CALIBRATION CURVE OF CLONAZEPAM USING pH 6.8 PHOSPHATE BUFFER.

- Accurately weighed 100 mg of drug was transferred to 100 ml volumetric flask and dissolved in pH 6.8 phosphate buffer, this was considered as stock solution (I) which contained 1000µg/ml.
- To 10 ml of stock solution (I) 90 ml of pH 6.8 phosphate buffer was added and this was considered as stock solution (II) which contained 100µg/ml.
- From stock solution (II) 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1ml were taken and made the volume up to 10ml with pH 6.8 phosphate buffer to get respective concentrations of (2,4,6, 8 and 10) µg/ ml.

- Prepared samples were analyzed by using ultra violet double beam spectrophotometer at λmax 252nm.
- The calibration curve was plotted by taking concentration on x-axis and absorbance on y-axis.

7.2. PREPARATION OF CLONAZEPAM TABLETS

7.2.1 Preparation of Clonazepam tablets by direct compression method

- Drug, Super disintegrant (Sodium starch glycolate) and different concentrations of sublimating agents (Camphor and Menthol) were weighed and permitted for blending for 5 min.
- The obtained blend was lubricated with magnesium stearate and glidant (talc) was added and blending was continued for further 5 minutes.
- The resultant mixture was directly compressed into tablets by using 6mm round flat faced punch of rotary tableting machine. Compression force was kept constant for all formulations.

Table 7.1 Composition of Clonazepam tablet

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F8	F8	F9
Clonazepam	8	8	8	8	8	8	8	8	8
Sodium starch glycolate	4	4	4	4	4	4	4	4	4
Camphor	2	4	6	8	-	-	-	-	8
Menthol	-	-	-	-	2	4	6	8	4
talc	2	2	2	2	2	2	2	2	2
Mg stearate	2	2	2	2	2	2	2	2	2
MCC pH 102	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Total weight of tablet	100	100	100	100	100	100	100	100	100

8. RESULTS AND DISCUSSION:

- In the present investigation, nine set of formulations (F1-F9) of Clonazepam, Fast Dissolving Tablets were prepared and evaluated.
- These powder blends were evaluated for flow properties prior to compression and tablets prepared by this powder blend through direct compression method were evaluated for hardness, friability, thickness, weight variation, wetting time, water absorption ratio *In vitro* dispersion time, *In vitro* disintegration time and *In vitro* dissolution studies after compression
- The most important parameter that needs to be optimized in the development of Fast dissolving tablets is the disintegration time of tablets. In the present study, tablets of all nine formulations disintegrated in less than 40 sec fulfilling the official requirements (USFDA).

8.1 DETERMINATION OF λ_{max} AND PREPARATION OF CALIBRATION CURVE OF CLONAZEPAM.

The regression coefficient was found to be 0.999 which indicates a linearity with an equation of
Y = 0.039x + 0.0018. Hence Beer - Lambert's law was obeyed.

Table.8.1 Calibration curve data of Clonazepam in pH 6.8 buffer at λ max of 282 nm

Concentration (µg/ml)	Absorbance
0	0
2	0
4	0.151
6	0.311
8	0.459
10	0.625

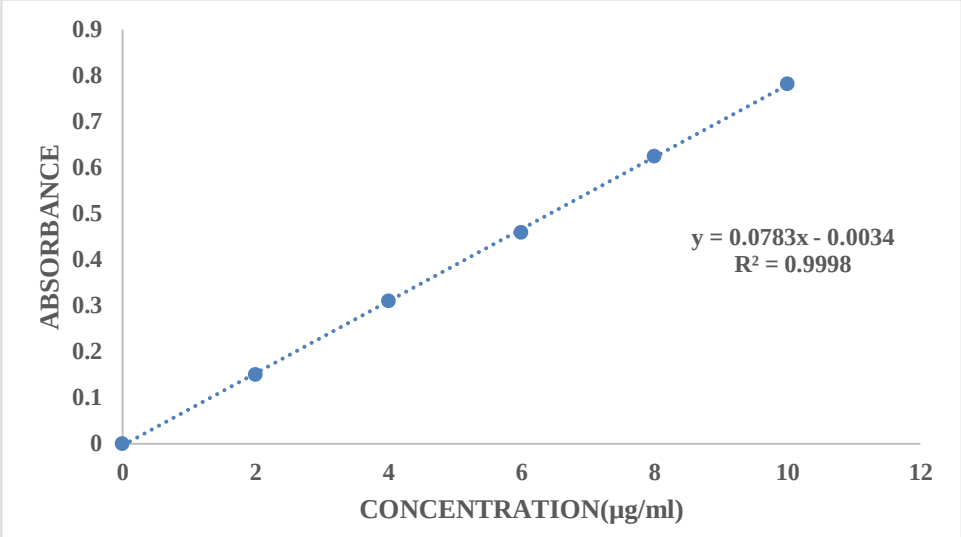


Fig: 8.1 Calibration curve of Clonazepam

8.2 EVALUATION OF PRE - COMPRESSION PARAMETERS OF POWDER BLEND

Table.8.2 Evaluation of pre-compression parameters of powder blend

Formulation	Bulk Density* (g/ml)	Tapped density* (g/ml)	Carr's index* (%)	Angle of Repose* (θ)	Hausner's ratio*
F 1	0.51±0.04	0.59 ±0.05	13.55±0.04	27 ±0.05	1.15±0.08
F2	0.48 ±0.05	0.56 ±0.06	14.28±0.06	25 ±0.02	1.16±0.08
F3	0.55 ±0.05	0.63 ±0.06	12.69±0.04	29±0.02	1.14±0.09
F4	0.46±0.08	0.55±0.03	16.36± 0.05	25 ±0.06	1.19±0.07
F5	0.46±0.06	0.53 ±0.02	13.20±0.05	26 ±0.08	1.15±0.07
F6	0.52±0.07	0.60±0.07	15.38 ±0.04	26±0.07	1.15±0.08
F7	0.49 ±0.06	0.56 ±0.07	12.50±0.06	28 ±0.06	1.14±0.06
F8	0.53±0.06	0.63±0.02	15.87±0.03	28±0.06	1.18±0.06
F9	0.48±0.06	0.55±0.02	12.72±0.06	27±0.06	1.14±0.05

* Results are the mean of 3 observations ± SD

- For each formulation blend of drug and excipients were prepared and evaluated for various precompression parameters described earlier in methodology chapter
- The bulk density of all formulations was found in the range of (**0.46**±0.06 **- 0.55**±0.05**)** and tapped density was in range of (**0.53**±0.02 **- 0.63**±0.07**)**.
- The carr's index and Hausner's ratio was calculated from tapped density and bulk density.
- The powder blend of all six formulations with Hausner's ratio **< 1.25** and carr's index **< 18** indicates good flow ability of all powder blends
- The flow properties for all the powder blends were good as evidentially proved by the angle of repose values obtained, which range between **(25^o – 30^o)**.

8.3 EVALUATIONS OF POST COMPRESSION PARAMETERS OF CLONAZEPAM FDTs

Table 8.3 Evaluation of post compression parameters of Clonazepam Fast dissolving tablets (I)

Formulation	Weight variation	Thickness (mm)	Hardness Kg/cm^2	% Friability	Drug content
F1	96.4 ±1.35	2.60± 0.05	1.5 ±0.05	0.62±0.08	98.85 ±0.54
F2	98.2 ±1.12	2.65 ±0.04	1.9 ±0.03	0.58±0.06	99.86 ±0.38
F3	99.8 ±1.05	2.73 ±0.06	1.6±0.05	0.65 ±0.06	99.54 ±0.67
F4	97.3 ±1.24	2.79 ±0.06	1.7±0.06	0.62 ±0.05	99.12±0.56
F5	99.6 ±1.31	2.71 ±0.08	1.5±0.08	0.66 ±0.04	98.23±0.36
F6	97.2 ±1.02	2.64 ±0.07	1.9±0.09	0.58 ±0.04	98.64±0.68
F7	98.7±1.46	2.69±0.06	1.8±0.07	0.66±0.05	99.76±0.53
F8	99.8±1.18	2.80±0.05	1.7±0.05	0.60±0.03	97.58±0.67
F9	100.6±1.51	3.66±0.08	1.6±0.07	0.56±0.07	98.36±0.48

* Results are the mean of 20 observations ± SD, **Results are the mean of 10 observations ± SD
***Results are the mean of 3 observations ± SD

Weight variation and thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 8.3. The average tablet weight of all the formulations was found to be between **(96.4** ± 1.35 **to 100.6**±1.51**).** The maximum allowed percentage weight variation for tablets weighing 80-250 mg by I.P is 7.5% (B. Jayakar *et al.*, 2010), and no formulations are exceeding this limit. Thus, all the formulations were found to comply with the standards given in I.P.

Hardness and friability: All the ODT formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table 8.3. The average hardness for all the formulations was found to be between **(1.5**±0.05 **to 1.9** ±0.09**) Kg/cm^2** which was found to be acceptable (Avinash *et al.*, 2010).

Friability was determined to evaluate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the ODT formulations were evaluated for their percentage friability using Roche friabilator and the results are shown in table 8.3. The average percentage friability for all the formulations was between **0.56±0.07 and 0.66±0.05,** which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 8.3. The assay values for all the formulations were found to be in the range of **(97.58** ±0.67 **to 99.86**±0.38**).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the *FDT* formulations comply with the standards given in IP.

Table. 8.4 Evaluation of post compression parameters of Clonazepam Fast dissolving tablet(I)

Formulation	Disintegration time*(seconds)	Wetting time* (seconds)	*Invitro* dispersion time*(sec)	%Water absorption ratio*
F1	29	26	32	96
F2	27	24	29	98
F3	20	21	26	95
F4	25	23	29	95
F5	32	29	35	95
F6	30	27	36	96
F7	26	24	28	95
F8	22	19	24	96
F9	**18**	**16**	**19**	**98**

*Results are the mean of 3 observations±SD

***In vitro* disintegration time:** *In vitro* disintegration studies showed from 18 to 35 secs. These results indicate that the F9formulation which enclosed camphor and Menthol as porous forming agent was shown less disintegration time than remaining formulations.

Wetting time: Wetting time to the time required to wet completely when kept motionless on the tissue paper in a Petri dish.

- All the FDT formulations were evaluated for their wetting time as per the procedure described in the methodology section, and the results are shown in table 8.4.
- The average wetting time for all the formulations was in the range of **(16 to 29)** seconds.
- It was also observed that formula F9 which had the least wetting time also had the minimum disintegration time showing a strong correlation between disintegration time and wetting time.

***In vitro* dispersion time:** Clonazepam FDTs F9 formulation containing camphor and menthol as Porous forming agent dispersed time was 19secs. It was known that less dispersion time than other formulation

The *In vitro* dispersion time for all formulation was found to be in a range of **19 to 36** seconds

Water Absorption ratio: All the formulations were evaluated for water absorption ratio according to the procedure described in methodology section and the results are shown in table 8.4.

- The maximum water absorption ratio was shown by formulation F2, F9showed **98%.**
- Water absorption ratio is proportional to dissolution rate profile as higher the water absorption ratio faster the dissolution

Table 8.5 *In vitro* dissolution study of Clonazepam *FDT* tablets containing Camphor

Time (min)	F1	F2	F3	F4
0	0	0	0	0
5	27.43	28.14	21.18	17.43
10	35.24	39.66	31.27	26.24
15	45.51	52.36	48.61	45.51
20	56.47	64.93	56.34	69.47
30	65.21	76.43	68.19	74.22
45	76.85	87.61	77.86	88.85
60	87.34	98.65	89.97	96.34

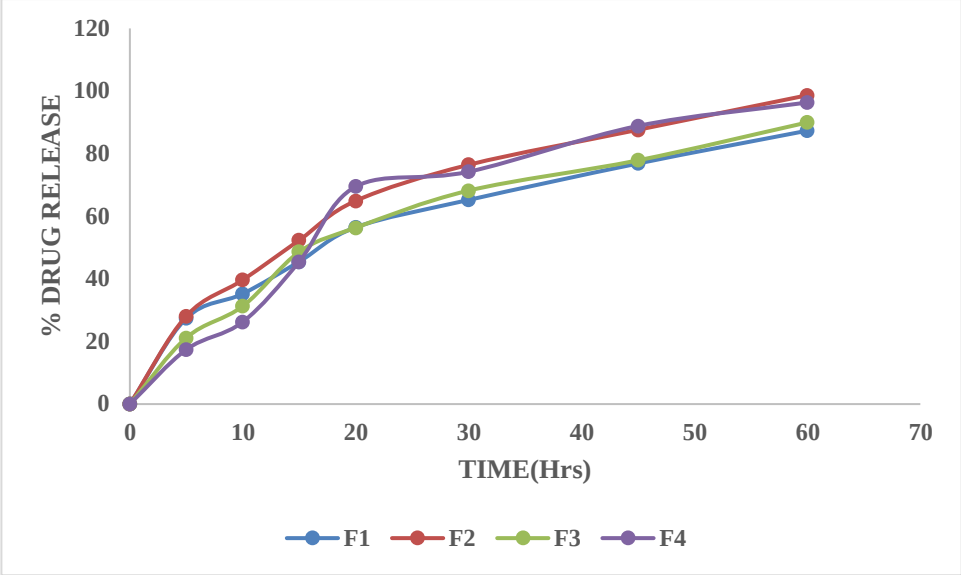


Figure 8.2: *In vitro* drug release of Clonazepam FDT tablets containing Camphor

- The maximum % drug release for the formulations F3 prepared by Camphor as porous forming agent at 30 min were found to be **98.65.**

Table 8.6 *In vitro* dissolution study of Clonazepam *FDT* tablets containing Menthol

Time (min)	F5	F6	F7	F8
0	0	0	0	0
5	25.64	29.88	22.73	14.33
10	36.93	48.27	35.81	25.41
15	53.22	62.61	44.93	39.63
20	59.19	85.34	53.86	56.85
30	74.45	97.15	66.71	66.62
45	93.41		75.94	76.53
60	96.82		83.84	92.85

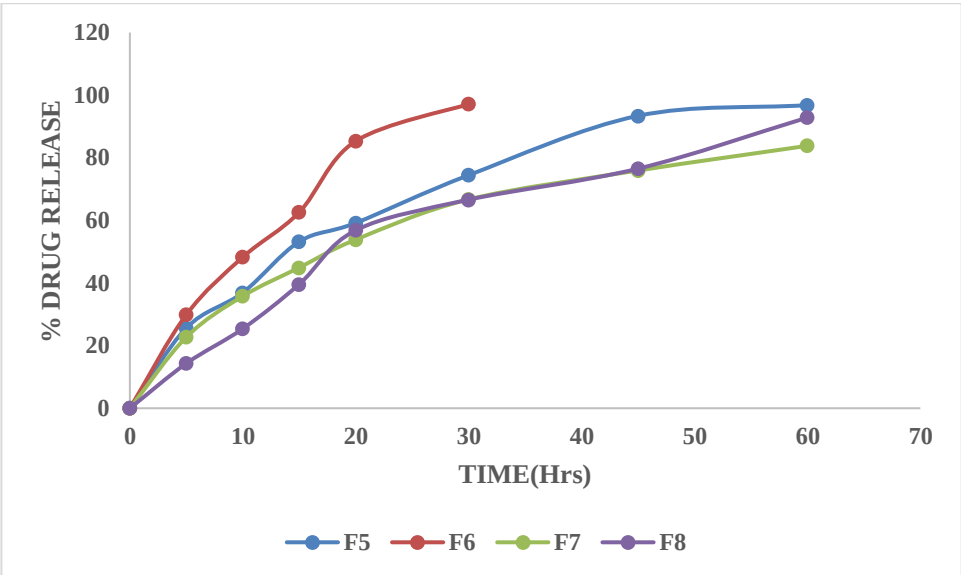


Figure 8.3: *In vitro* drug release of Clonazepam *FDT* tablets containing Menthol

- The maximum % drug release for the formulations F6 prepared by Menthol as porous forming agent at 30 min were found to be **97.15%.**
-

Table8.7 *In vitro* drug release of F9 formulation containing two porous forming agents' camphor and menthol

Time (min)	%DRUG RELEASE (F9)
0	0
5	32.87
10	52.92
15	66.24
20	81.91
30	98.84
45	99.84

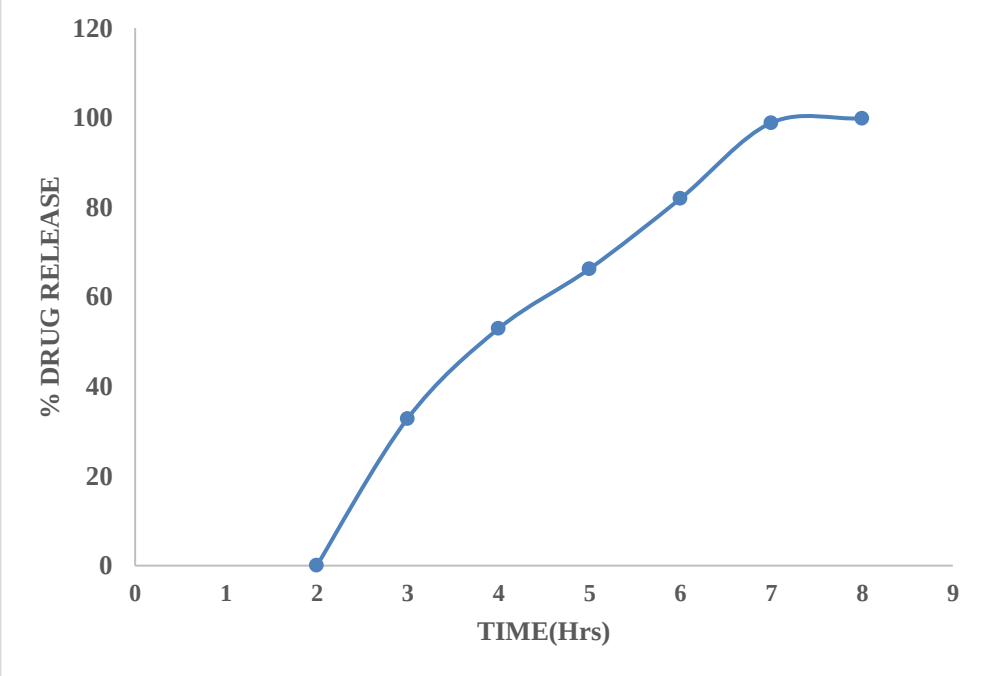
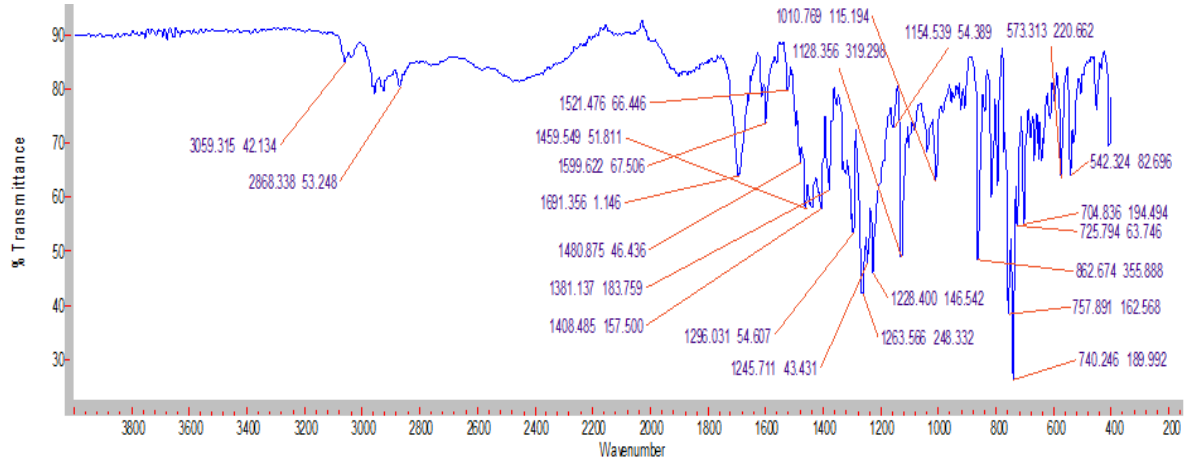


Figure 8.4 *In vitro* drug release F9 formulation containing camphor and menthol

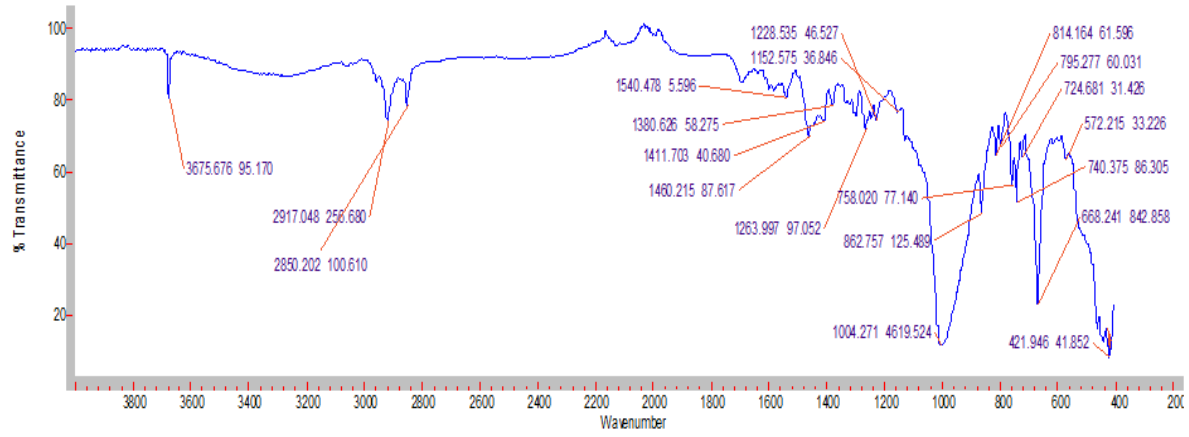
- The maximum % drug release for the formulations F9 prepared by two porous forming agents' camphor and menthol were found to be **99.84** at 30 min.

From the drug release data from F1 to F9 formulations, In the F1 and F4 formulations, F3 formulation shows drug release was found to be 98.9% drug release in 30 minutes. These four formulations F1-F4 containing camphor as porous forming agent. In that 7.5 mg of the camphor is sufficient drug release in 30 minutes. In the F5 and F8 formulations, F6 formulation shows drug release was found to be 96.51% drug release in 30 minutes. These four formulations F5-F8 containing Menthol as porous forming agent. In that 5mg of the Menthol is sufficient drug release in 30 minutes. Remaining formulation F9 containing both camphor and Menthol as porous forming agents which shows better drug release and within 5 minutes the amount of drug release more compared to other formulations. And not only good drug release, less disintegration time, less dispersion time, and very less time to take to wetting of the tablets. From those formulations F9 formulation which contains camphor and Menthol as porous forming agents in combination was shown drug release at 30 min. It was found to be **99.84.** Among those formulations F9 formulation was considered as optimized formulation.

- **FTIR RESULTS:**



FT-IR: PURE DRUG



FT- IR: OPTIMISED DRUG

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence, they were compatible.

CONCLUSION:

The present study was undertaken to formulate and evaluate mouth dissolving tablets of Clonazepam using the sublimation method in order to improve patient compliance and enhance drug release for rapid therapeutic action. Various formulations were prepared with different sublimating agents and evaluated for pre-compression and post-compression parameters, all of which were found within acceptable limits. The sublimation technique successfully imparted porosity to the tablets, resulting in reduced disintegration time and faster wetting. Among the formulations, the optimized batch exhibited superior characteristics with excellent mechanical strength, rapid disintegration, and maximum drug release in a short time compared to conventional dosage forms.

Thus, it can be concluded that the sublimation method is a simple, effective, and promising approach for the development of mouth dissolving tablets of Clonazepam, offering a patient-friendly dosage form especially beneficial for paediatric, geriatric, and dysphagic patients.

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