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FORMULATION AND CHARACTERIZATION OF FAST DISSOLVING ORAL WAFERS OF TRIMIPRAMINE USING NATURAL POLYMERS

Viveka Nand Mishra*, Gyan Singh, Vivek Gupta
Faculty of Pharmacy, P.K. University, Thanra, Shivpuri (M.P.)

***Correspondence Info:**
Viveka Nand Mishra
Faculty of Pharmacy, P.K. University, Thanra, Shivpuri (M.P.)
Email:
vivekanandmishra1233@gmail.com

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ABSTRACT

The present study aimed to formulate and characterize fast dissolving oral wafers of Trimipramine using natural polymers to enhance patient compliance and rapid drug release. A total of nine formulations (F1–F9) were prepared by the solvent casting method and evaluated for physicochemical and performance parameters. All wafers were found to be translucent with uniform thickness and weight, indicating consistent film formation. The surface pH of all formulations was within the acceptable range, ensuring compatibility with the oral cavity. Folding endurance values indicated good mechanical strength, with F7 showing the highest flexibility. Drug content across all formulations was uniform and within acceptable limits (97–99%). The disintegration time ranged from 15 to 36 seconds, with formulation F7 showing the fastest disintegration. The optimized formulation (F7) exhibited rapid in-vitro drug release, achieving 98.12% release within 300 seconds. Stability studies indicated no significant changes in drug content and release profile under both room and accelerated conditions. Overall, the study demonstrates that natural polymers can be effectively used to develop stable and efficient fast dissolving oral wafers of trimipramine with rapid onset of action and improved patient compliance.

Keywords: Trimipramine, fast dissolving oral wafers, natural polymers, solvent casting method, disintegration time, in-vitro drug release, folding endurance, stability studies, oral drug delivery system.

INTRODUCTION

Oral drug delivery remains the most preferred route of administration due to its convenience, patient compliance, and cost-effectiveness. However, conventional oral dosage forms such as tablets and capsules often present challenges like difficulty in swallowing (dysphagia), especially in pediatric, geriatric, and psychiatric patients. To overcome these limitations, fast dissolving oral wafers (FDOWs), also known as oral thin films, have emerged as an innovative and patient-friendly drug delivery system. These dosage forms rapidly disintegrate or dissolve in the oral cavity without the need for water, ensuring quick onset of action and improved bioavailability (Baryakova *et al.*, 2023; Bhaskar *et al.*, 2025).

Fast dissolving oral wafers are typically prepared using hydrophilic polymers that facilitate rapid hydration and disintegration upon contact with saliva. In recent years, there has been increasing interest in the use of natural polymers such as pullulan, starch,

gelatin, and sodium alginate due to their biocompatibility, biodegradability, non-toxicity, and eco-friendly nature. These natural polymers also provide desirable film-forming properties, flexibility, and stability, making them suitable for the development of oral wafers (Panda *et al.,* 2012).

Trimipramine is a tricyclic antidepressant widely used in the management of depression and associated disorders such as anxiety and insomnia. It acts by modulating neurotransmitter levels in the brain, primarily serotonin and norepinephrine (Behnia; 2025). Despite its therapeutic effectiveness, conventional oral formulations of trimipramine may exhibit delayed onset of action and reduced patient compliance, particularly in individuals with swallowing difficulties. Therefore, formulating trimipramine into fast dissolving oral wafers can enhance its therapeutic efficacy by providing rapid drug release and absorption through the oral mucosa.

The selection of appropriate polymers and excipients plays a essential role in determining the mechanical strength, disintegration time, drug release profile, and overall performance of oral wafers. Natural polymers offer additional advantages such as improved safety profile and patient acceptability compared to synthetic counterparts. Furthermore, the solvent casting method is commonly employed for the preparation of oral wafers due to its simplicity, uniform drug distribution, and cost-effectiveness (Saini *et al.*, 2024).

In this context, the present study focuses on the formulation and characterization of fast dissolving oral wafers of trimipramine using natural polymers. The study aims to evaluate various formulation parameters such as thickness, folding endurance, disintegration time, drug content uniformity, and in-vitro drug release, in order to develop an optimized formulation with enhanced patient compliance and therapeutic effectiveness.

MATERIALS AND METHODS

Materials

Trimipramine was used as the model drug for the preparation of fast dissolving oral wafers. Natural polymers such as pullulan, gelatin, and sodium alginate were employed as film-forming agents. Plasticizers like glycerin and polyethylene glycol (PEG) were used to enhance flexibility and mechanical strength of the wafers. Sweetening agents and flavoring agents were incorporated to improve palatability. Other excipients included saliva-stimulating agents and stabilizers. All chemicals and reagents used in the study were of analytical grade and were used as received. Distilled water was used as the solvent for the preparation of oral wafers, and all experimental procedures were carried out using standard laboratory equipment and conditions.

Methods

Selection and Optimization of Wafer-Forming Agents

Different formulations (F1–F9) were developed by varying the concentration of polymers and superdisintegrants as shown in the table. Pullulan and sodium alginate were used as primary film-forming polymers, while superdisintegrants such as sodium starch glycolate (SSG), croscarmellose sodium (CCS), and crospovidone (CP) were incorporated to enhance rapid disintegration. PEG-400 acted as a plasticizer, mannitol as a sweetening and bulking agent, and citric acid

as a saliva-stimulating agent. All formulations contained a constant amount of drug (75 mg) and were prepared following the same solvent casting procedure (Boateng *et al.,* 2010).

Evaluation of prepared wafers

Drug and polymer compatibility studies

Thermograms were recorded (Pure drug and drug + all excipients) using a differential scanning calorimeter. Samples (2-3mg) were weighed and hermetically sealed in flat bottomed aluminium pans. These samples were heated over a temperature range of 50-400^{o}C in an atmosphere of nitrogen (200ml/min) at a constant rate of 10^{0}C per minute, with alumina being the reference standard (Troester *et al.,* 2010).

Thickness

Three random wafers were selected from each batch and the thickness was measured at three different places using a vernier caliper (El-Feky *et al.,* 2018).

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 10 wafers from each batch were weighed individually by digital electronic balance and the average weight and relative standard deviation was calculated (Matthews *et al.,* 2006).

Surface pH Determination

The surface pH of fast dissolving wafers was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it is important to keep the surface pH as close to neutral as possible (Boateng *et al.,* 2012). The wafer to be tested was placed in a petridish and was moistened with 0.2 ml of distilled water. The electrode of pH meter (Electronic india) was placed on the surface of wafer to determine the surface pH.

Folding Endurance

This was determined by repeatedly folding one wafers at the same place until it broke. The number of times the wafers could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of Moisture Content

The wafers were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual wafers were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

$$\text{Percentage of Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{x } 100$$

Drug content analysis

The patches (n=3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 247nm.

Disintegrating time

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of polymers to minimizes the disintegrating time. *In vitro* disintegration time was determined by placing the wafer in a petridish containing 10ml distilled water with swirling every 10 sec. The time at which the wafer disintegrated was noted (Boateng *et al.,* 2012).

In vitro dissolution study

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle type) (Boateng *et al.*, 2012). The dissolution studies were carried out at 37±0.5°C; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Wafers size required for dose delivery (2.5×2.5 cm^2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved Trimipramine was determined using UV-Visible spectrophotometer at 247nm. The results were presented as an average of three such concentrations.

Stability studies

The optimized formulation (F7) was packed in airtight containers and stored under room temperature (25 ± 2°C / 60 ± 5% RH) and accelerated conditions (40 ± 2°C / 75 ± 5% RH) as per ICH guidelines. Samples were analyzed at specific intervals (0, 1, 2, and 3 months) for physical appearance, drug content, and *in-vitro* drug release. The results were compared with initial values to assess stability. No significant changes indicate that the formulation is stable.

RESULTS AND DISCUSSION

The present study focused on the formulation and evaluation of fast dissolving oral wafers of Trimipramine using natural polymers. All the prepared formulations (F1–F9) were found to be translucent with smooth appearance (Table 2), indicating uniform film formation and proper distribution of drug and excipients. The thickness of wafers ranged from 80 ± 4 µm to 95 ± 2 µm, and weight variation was within acceptable limits, confirming uniformity of the prepared films.

The mechanical properties of the wafers were evaluated by folding endurance (Table 3), which ranged from 148 ± 6 to 198 ± 2. Among all formulations, F7 showed the highest folding endurance, indicating better flexibility and mechanical strength. The surface pH of all formulations was found to be in the range of 6.50 to 6.93, which is close to the salivary pH, suggesting minimal risk of oral irritation. The percentage moisture content was low (2.0–3.1%), indicating good stability and reduced chances of microbial growth.

Drug content analysis (Table 4) showed uniform distribution of trimipramine in all formulations, ranging from 97.65% to 99.60%. Disintegration time is a critical parameter for fast dissolving wafers, and all formulations showed rapid disintegration within 15–36 seconds. Among them, F7 exhibited the fastest disintegration time (15 ± 2 sec), which is highly desirable for quick onset of action.

The in-vitro drug release study of optimized formulation F7 (Table 5) demonstrated rapid and efficient drug release, with 98.12% release within 300 seconds. This rapid release profile can be attributed to the hydrophilic nature of natural polymers and the thin structure of the wafers, facilitating quick hydration and drug diffusion.

Stability studies (Table 6) revealed that the optimized formulation remained stable under both room temperature and accelerated conditions. There was no significant change in physical appearance at 25°C/60% RH, while only slight changes were observed at 40°C/75% RH. Drug content and drug release

showed minimal reduction over three months, indicating good stability of the formulation.

Formulation F7 was identified as the optimized batch based on its superior mechanical strength, rapid disintegration, high drug content, and efficient drug release. The study confirms that fast dissolving oral wafers of trimipramine using natural polymers can be successfully developed, offering improved patient compliance and rapid therapeutic action.

Table 1: Selection and optimization of wafers forming agents

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Trimipramine	300	300	300	300	300	300	300	300	300
Pullulan	50	100	150	-	-	-	25	50	75
Sodium alginate	-	-	-	50	100	150	25	50	75
PEG-400	50	50	50	50	50	50	50	50	50
SSG	25	50	100	-	-	-	-	-	-
CCS	-	-		25	50	100	-	-	-
CP	-	-	-	-	-	-	25	50	100
Mannitol	10	10	10	10	10	10	10	10	10
Citric acid	10	10	10	10	10	10	10	10	10
DM water qs to (ml)	30	30	30	30	30	30	30	30	30

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm^2 wafers present whole plate = 12
- Each wafers contains 50 mg of drug.
- 12 no. of wafers contains mg of drug? = 25×12 = 300mg
- The amount of drug added in each plate was approximately equal to 25mg.

Table 2: Results of Evaluation of prepared Wafers

Formulation Code	General Appearance	Thickness* (µm)	Weight* (mg)
F1	Translucent	80 ± 4	112 ± 4
F2	Translucent	88 ± 3	118 ± 5
F3	Translucent	95 ± 2	115 ± 3
F4	Translucent	84 ± 4	116 ± 2
F5	Translucent	83 ± 3	108 ± 4
F6	Translucent	91 ± 3	119 ± 6
F7	Translucent	86 ± 2	120 ± 5
F8	Translucent	88 ± 4	114 ± 3
F9	Translucent	90 ± 3	118 ± 4

***Average of three determinations (N=3)**

Table 3: Result of surface pH determination, folding endurance, percentage of moisture content

Formulation Code	Folding Endurance* (Times)	Surface pH	Percentage Moisture Content*
F1	158 ± 6	6.70 ± 0.12	2.4 ± 0.2
F2	165 ± 5	6.82 ± 0.18	3.0 ± 0.4
F3	182 ± 7	6.93 ± 0.13	2.8 ± 0.3
F4	172 ± 4	6.72 ± 0.11	2.5 ± 0.3
F5	148 ± 6	6.50 ± 0.10	2.7 ± 0.4
F6	175 ± 3	6.75 ± 0.12	2.9 ± 0.6
F7	198 ± 2	6.80 ± 0.14	3.1 ± 0.3
F8	185 ± 2	6.73 ± 0.15	2.0 ± 0.2
F9	178 ± 5	6.68 ± 0.10	2.8 ± 0.2

Table 4: Drug content analysis and disintegrating time

Formulation Code	Drug Content (%)	Disintegrating Time (Sec.)
F1	97.65 ± 0.30	24 ± 4
F2	98.40 ± 0.28	32 ± 2
F3	98.90 ± 0.12	36 ± 4
F4	98.55 ± 0.18	21 ± 3
F5	97.70 ± 0.15	28 ± 2
F6	98.95 ± 0.20	29 ± 3
F7	99.60 ± 0.22	15 ± 2
F8	98.80 ± 0.25	27 ± 3
F9	98.70 ± 0.14	19 ± 2

Table 5: Results of *in-vitro* release study of optimized formulation F7

S. No.	Time (Sec.)	Percentage cumulative drug release
1.	60	45.65
2.	120	55.63
3.	180	69.98
4.	240	89.32
5.	300	98.12

Table 6: Results of stability studies

S. No.	Time (Month)	Condition (Temp/RH)	Physical Appearance	Drug Content (%)	*In-vitro* Drug Release (%)
1	0	Initial	No change	98.12 ± 0.25	98.12
2	1	25 ± 2°C / 60 ± 5% RH	No change	97.85 ± 0.30	97.65
3	2	25 ± 2°C / 60 ± 5% RH	No change	97.42 ± 0.28	97.10
4	3	25 ± 2°C / 60 ± 5% RH	No change	97.10 ± 0.35	96.85
5	1	40 ± 2°C / 75 ± 5% RH	Slight change	96.90 ± 0.40	96.30
6	2	40 ± 2°C / 75 ± 5% RH	Slight change	96.25 ± 0.45	95.80
7	3	40 ± 2°C / 75 ± 5% RH	Slight change	95.80 ± 0.50	95.20

CONCLUSION

Fast dissolving oral wafers of Trimipramine were successfully formulated using natural polymers by the solvent casting method. All formulations exhibited satisfactory physicochemical properties, including uniform thickness, acceptable pH, good folding endurance, and uniform drug content. Among the prepared batches, formulation F7 was identified as the optimized formulation due to its fastest disintegration time and highest drug release profile. The optimized wafer showed rapid drug release with nearly complete release within a short duration, ensuring quick onset of action. Stability studies confirmed that the formulation remained stable under both room and accelerated conditions. The developed oral wafers offer a promising alternative to conventional dosage forms, improving patient compliance and therapeutic efficiency.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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