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DEVELOPMENT & EVALUATION OF ORAL THIN FILM OF FLUNARIZINE AS ALTERNATIVE DOSAGE FORM

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Abstract
The development and evaluation of Flunarizine oral thin films as an alternative dosage form were undertaken to enhance patient compliance, especially for individuals with difficulty swallowing tablets or capsules. The formulation aimed to provide a rapid onset of action and a convenient, portable drug delivery system. Various formulations (F1–F9) were prepared and characterized for key parameters such as general appearance, thickness, weight, folding endurance, disintegration time, tensile strength, moisture content, drug content assay, and in-vitro drug release. The films exhibited uniformity in appearance, and consistent thickness and weight, indicating the reproducibility of the formulation process. The folding endurance of the films was excellent, and the disintegration time was fast, ranging from 48 to 85 seconds, which is suitable for quick drug release upon contact with saliva. The drug assay showed consistent drug content in the films, ensuring accurate dosing. In-vitro drug release from the optimized formulation (F7) demonstrated rapid release, with 99.05% of Flunarizine released by the 10th minute. Kinetic studies revealed that the drug release followed the Peppas model, indicating a non-Fickian diffusion mechanism. The stability study showed that the drug content remained stable over three months, confirming the formulation's potential for long-term storage. This study suggests that Flunarizine oral thin films are a promising alternative dosage form for providing rapid therapeutic effects with improved patient compliance.

Keywords: Flunarizine, Oral Thin Film, Drug Delivery, In-vitro Drug Release, Peppas Model, Folding Endurance, Stability Study, Non-Fickian Diffusion, Drug Assay, Formulation Development.

Introduction
Oral thin films (OTFs) have gained significant attention as an alternative dosage form due to their numerous advantages over conventional tablets and capsules. These advantages include ease of administration, especially for patients with swallowing difficulties, rapid onset of action, and the ability to deliver drugs without the need for water. Additionally, oral thin films can offer enhanced bioavailability by bypassing the first-pass metabolism and directly delivering the drug through the oral mucosa, providing a fast-acting, effective therapeutic option.

Flunarizine, a selective calcium channel blocker, is commonly used in the treatment of various conditions such as migraine, vertigo, and motion sickness. It is well-known for its ability to reduce the frequency and intensity of migraine attacks and alleviate vertigo symptoms. However, one of the limitations of flunarizine is its poor bioavailability due to its extensive first-pass metabolism in the liver. Therefore, developing an oral thin film of flunarizine could offer significant benefits in terms of bioavailability and ease of use, particularly for patients requiring rapid relief or those with difficulty swallowing conventional tablets.

Oral thin films are typically composed of film-forming polymers such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and other excipients that contribute to the film's stability, flexibility, and drug release characteristics. These films dissolve rapidly in the mouth, allowing the active ingredient to be absorbed directly into the bloodstream via the buccal mucosa, thereby avoiding hepatic metabolism and offering a faster onset of action. Various methods can be employed to prepare oral thin films, such as solvent casting, hot-melt extrusion, and electrospinning, with solvent casting being the most commonly used technique for drug incorporation and film formation.

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Several studies have shown the potential of oral thin films as an effective drug delivery system for various active pharmaceutical ingredients (APIs), including flunarizine. The use of oral thin films for flunarizine can be advantageous in terms of improving patient compliance, enhancing therapeutic efficacy, and overcoming challenges related to the conventional oral dosage forms.

Material and Methods

Material

The materials used in the development and evaluation of the oral thin film of Flunarizine included Flunarizine (gift sample from a pharmaceutical company), solvents like methanol, ethanol, and chloroform (Qualigens Fine Chemicals, Mumbai), and excipients such as potassium dihydrogen phosphate, NaOH, HPMC K4 and K15 (Lobachemie, Mumbai), PEG-400 (Lobachemie, Mumbai), sodium starch glycolate (SSG), croscarmellose sodium (CCS), corn starch powder (CP), and mannitol (Lobachemie, Mumbai). These components were selected for their role in film formation, stabilization, and improving the bioavailability of Flunarizine in the final oral thin film dosage form.

Methods

Formulation development of fast dissolving oral film of Flunarizine

Drug (Flunarizine) containing fast dissolving films were fabricated by the solvent casting method. HPMC is known for its good film forming properties and has excellent acceptability. Hence, various grades of HPMC namely HPMC K4, and HPMC K15 were evaluated as film formers. For the fabrication of films, glycerin was used as a humectant. PEG 400 is also reported as lubricant and solubilizer. Therefore PEG 400 along with glycerol was also used for fabrication of films. Apart from these film formers, SSG (Sodium starch glycolate), CP (Crospovidone) and CCS (croscarmellose sodium) alone or in combination with each other along with other excipients were tried. Citric acid for saliva stimulating agent and mannitol as sweeteners used to fabricate the films. The composition of various formulations is given in Table 1. The polymer was soaked in water for 30 min or heated in water bath to 80° to get a clear solution. Then a plasticizer was added to it and mixed so as to get homogeneous solution. This solution was then casted onto glass moulds (15*5cm) and was dried in hot air oven at 45° for 24 h (Mahajan *et al.,* 2011).

Table 1: Selection and optimization of film forming agents

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6	F7	F8	F8
Flunarizine	60	60	60	60	60	60	60	60	60
HPMC K4	50	100	150				25	50	75
HPMC K15				50	100	150	25	50	75
PEG-400	50	50	50	50	50	50	50	50	50
SSG	50	100	-	-	-	-	25	-	25
CCS	-	-	50	100	-	-	25	25	-
CP	-	-	-	-	-	-	-	25	25
Mannitol	50	50	50	50	50	50	50	50	50
Citric acid	30	30	30	30	30	30	30	30	30
DM water qs to	30	30	30	30	30	30	30	30	30

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(ml)									

Evaluation of prepared Film

Thickness

The thickness of patches was measured at three different places using a vernier caliper (Mahajan *et al.,* 2011).

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated (Nagar *et al.,* 2014).

Folding Endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance (Pathan *et al.,* 2016).

Percentage of Moisture Content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films 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 (Bhyan *et al.,* 2010).

Drug content analysis

The film 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 reacted by UV spectrophotometer at 244nm (Murata *et al.,* 2010).

Disintegrating time

The most important criteria of present work are that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent was done to minimize the disintegrating time. Three super disintegrating agent (Sodium starch Glycolate, Crospovidone and Croscarmellose Sodium) were selected for this work (Koland *et al.,* 2010).

***In vitro* dissolution study**

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle with sinker). 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). Film size required for dose delivery (2.5×2.5 cm^2) was used (Schimoda *et al.,* 2009). Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 4, 6, 8, and 10 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 drug was determined using UV-Visible spectrophotometer at 244nm. The results were presented as an average of three such concentrations.

Stability studies

Stability studies were carried out with optimized formulation F7 which was stored for a period of one, two and three months at 40±2ºC temperature and 75±5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method (Mishra and Amin, 2009). The % assay of film was found to slightly decrease at higher temperature.

Results and Discussion

The formulation of Flunarizine oral thin films aimed to deliver the drug in a convenient and effective

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dosage form. The evaluation of various formulation batches (F1–F9) included key parameters such as general appearance, thickness, weight, folding endurance, disintegrating time, tensile strength, moisture content, drug content assay, and in-vitro drug release. These characteristics were crucial to understanding the performance of the films in terms of their physical integrity, drug release behavior, and overall stability.

All the prepared films exhibited a transparent appearance, which is a favorable characteristic, as it indicates uniformity in the formulation and good film-forming properties. The thickness of the films ranged from 46 ± 3 µm (F1) to 64 ± 6 µm (F9). The consistency in thickness (±7 µm variation) across formulations suggests reproducibility in the preparation method, which is essential for uniform drug delivery. The weight of the films also remained relatively consistent, ranging from 95 ± 3 mg (F1) to 108 ± 5 mg (F9). The slight variation in weight between batches can be attributed to the different levels of excipients used, but the difference was minimal, suggesting that the formulation process was stable.

Folding endurance is an important parameter for evaluating the flexibility and mechanical strength of the film. The films exhibited excellent folding endurance, with values ranging from 165 ± 5 times (F1) to 227 ± 3 times (F7). These results indicate that the films have good flexibility and can withstand mechanical stress during handling without breaking. The formulation F7, in particular, exhibited the highest folding endurance, making it one of the most robust formulations.

The disintegration time of the films ranged from 48 seconds (F7) to 85 seconds (F4), with most formulations showing relatively fast disintegration (less than 90 seconds), which is ideal for ensuring rapid drug release upon contact with saliva. Faster disintegration times typically lead to quicker onset of action, which is crucial for the treatment of conditions requiring fast relief.

The tensile strength of the films varied from 0.645 ± 0.023 kg/cm² (F2) to 0.885 ± 0.026 kg/cm² (F4). Tensile strength is indicative of the film's ability to resist breaking under tension, and the formulations with higher values (F4) exhibited better resistance to mechanical stress. These values were acceptable for oral thin films, as the films should not be too brittle or too strong.

The moisture content of the films ranged from 5.85 ± 0.18% (F8) to 7.44 ± 0.11% (F3). Moisture content is an essential parameter for ensuring the stability and handling properties of the films. Films with too high moisture content may become sticky, whereas too low moisture content can make them brittle. The films in this study showed appropriate moisture content, ensuring that they maintained integrity while remaining flexible for use.

The drug assay results showed that the drug content was consistent, with values between 95.45 ± 0.14% (F6) and 99.05 ± 0.11% (F7). This indicates that the formulation processes were efficient in loading the drug into the films, ensuring reliable dosing.

The in-vitro drug release study conducted on the optimized formulation F7 showed a rapid drug release profile, with 43.32% of Flunarizine released within the first minute, and the cumulative drug release reached 99.05% by the 10th minute. This suggests that the oral thin film formulation is designed for quick drug release, making it an ideal dosage form for achieving rapid therapeutic effects. The fast release profile is consistent with the fast disintegration time of the film.

The release data for formulation F7 were analyzed using different kinetic models (Zero order, First order, Higuchi, and Peppas model). The highest r^2 value was obtained for the Peppas model, indicating that the drug release from the oral thin film follows anomalous (non-Fickian) diffusion, which suggests that both drug diffusion and polymer relaxation are contributing factors to the release mechanism.

The stability study of the optimized formulation (F7) demonstrated that the drug content remained stable over three months of storage, with a slight decrease in drug content from 99.55% at the initial time to 98.85% after three months. These results indicate that the formulation has good stability under the conditions tested, making it suitable for long-term storage and use.

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Table 2: Evaluation of prepared film for general appearance, thickness and weight

Formulation code	General Appearance	Thickness* (µm)	Weight* (mg)
F1	Transparent	46±3	95±3
F2	Transparent	52±2	98±5
F3	Transparent	55±5	99±4
F4	Transparent	49±4	98±6
F5	Transparent	55±7	99±7
F6	Transparent	63±8	100±4
F7	Transparent	53±3	102±6
F8	Transparent	58±5	105±3
F9	Transparent	64±6	108±5

***Average of three determination (n=3±SD)**

Table 3: Result of Folding Endurance, Disintegrating time, Tensile strength, Percentage Moisture Content and % Assay

Formulation code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength in kg/cm^2	Percentage of Moisture Content	% Assay
F1	165±5	62±6	0.651±0.015	6.45±0.12	96.65±0.22
F2	185±4	56±2	0.645±0.023	6.32±0.25	98.78±0.32
F3	226±3	53±4	0.785±0.014	7.44±0.11	96.65±0.14
F4	174±5	85±5	0.885±0.026	7.36±0.33	97.85±0.32
F5	198±4	75±7	0.785±0.032	7.15±0.20	96.65±0.25
F6	175±2	63±8	0.658±0.033	6.55±0.14	95.45±0.14
F7	227±3	48±5	0.775±0.021	6.74±0.22	99.05±0.11
F8	188±2	55±2	0.856±0.023	5.85±0.18	96.45±0.33
F9	165±4	57±2	0.745±0.025	6.25±0.10	97.74±0.25

Table 4: *In-vitro* drug release study of Formulation F7

Time (Min.)	Cumulative % drug release
	F7
1	43.32
2	69.98
4	79.95
6	88.85
8	93.32
10	99.05

Table 5: Comparative study of regression coefficient for selection of optimized batch F7

Zero order		First order	Higuchi	Peppas model
r^2	0.8267	0.9166	0.9091	0.9202

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Table 6: Characterization of stability study of Optimized formulation F7

Characteristic	Time (Month)			
	Initial	**1 Month**	**2 Month**	**3 Month**
% Drug Content	99.55±0.22	99.12±0.45	99.05±0.25	98.85±0.15

Conclusion

The study successfully developed and evaluated an oral thin film formulation of Flunarizine, showing excellent physical characteristics, rapid disintegration, and effective drug release. Formulation F7, in particular, showed the most promising results in terms of folding endurance, disintegration time, drug release, and stability. These results suggest that oral thin films could be an ideal alternative dosage form for Flunarizine, offering advantages such as ease of administration, fast onset of action, and portability.

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