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Enhancement of Solubility and Formulation of Fast Dissolving Oral Films of an Antiemetic Drug

Snehil Tiwari*[1], Deepali Lariya[1], B. K. Dubey[2], Deepak Kumar Basedia[2]

TIT - College of Pharmacy, Bhopal (M.P.)

Technocrats Institute of Technology – Pharmacy, Bhopal (M.P.)

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Corresponding author: Snehil Tiwari
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Abstract

This study investigates the development of a fast-dissolving oral film formulation (F3) for efficient delivery of Astemizole, an antiemetic drug. The formulation incorporates solubility enhancers, PEG 400 and PVP K-90, to improve the solubility and bioavailability of the drug. The solubility enhancement study revealed significant improvements, especially at higher concentrations, ensuring rapid dissolution and enhancing therapeutic efficacy. The drug content analysis of formulation F3 demonstrated 98.50% of the label claim, indicating high uniformity and reliable dosing. Further characterization of formulation F3 showed superior folding endurance (235 folds), the fastest disintegration time (63 minutes), and a high assay value (99.12%), reflecting excellent mechanical properties and rapid drug release. The in-vitro release study revealed nearly complete drug dissolution (98.85%) within 15 minutes, making the formulation ideal for drugs requiring a rapid onset of action. Stability studies over three months confirmed the formulation's minimal degradation and stable drug content (98.32%). In conclusion, formulation F3 is a promising candidate for fast-dissolving oral films, with excellent drug release, stability, and consistency. Further clinical trials and stability assessments are recommended to validate its efficacy and optimize its clinical application.

Keywords:

Fast-dissolving oral film, Astemizole, Solubility enhancement, PEG 400, PVP K-90, Bioavailability, Drug content analysis, Folding endurance, Disintegration time, In-vitro release, Stability studies, Patient compliance, Pharmaceutical formulations.

Introduction

The solubility of a drug plays a essential role in its bioavailability, as poorly soluble drugs often face challenges in achieving therapeutic concentrations within the body. Astemizole, an antiemetic drug, is one such compound that suffers from limited aqueous solubility, which can affect its absorption and, consequently, its therapeutic efficacy (Hedges et al., 2016). Fast-dissolving oral films (FDOFs) are an innovative drug delivery system that can enhance the solubility and bioavailability of poorly soluble drugs while providing a convenient and patient-friendly dosage form (Almeida et al., 2020). These films rapidly dissolve upon contact with moisture, bypassing the need for water intake and thus providing rapid drug release for fast therapeutic action, which is particularly beneficial in managing conditions like nausea and vomiting.

To address the solubility issues of Astemizole and improve its pharmacokinetic profile, various

solubility-enhancing techniques have been explored, including the use of solubilizing excipients like polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP). PEG 400 has been shown to enhance the solubility of hydrophobic drugs by acting as a solubilizing agent that improves the drug's dissolution rate (Singh et al., 2017). Similarly, PVP K-90, a widely used water-soluble polymer, is known to enhance the solubility and dissolution rate of poorly soluble drugs through its ability to form solid dispersions, which increase the surface area for dissolution (Mansoor et al., 2019).

The fast-dissolving oral film formulation is particularly suitable for patients who have difficulty swallowing tablets or capsules, including pediatric and geriatric populations, as well as those on the go. These films are easy to administer, rapidly dissolve in the oral cavity, and do not require water for ingestion, which increases patient compliance, especially in cases of antiemetic drugs that need quick onset of action (Jain et al., 2018).

In this study, the aim was to enhance the solubility of Astemizole using PEG 400 and PVP K-90 and formulate a fast-dissolving oral film (F3) with improved dissolution properties. This formulation was evaluated for its physicochemical properties, drug release profiles, and stability, aiming to provide an efficient, patient-friendly dosage form that improves the bioavailability of Astemizole.

Material and Methods

Optimization of Drug: Polymer Ratio

In order to optimize the drug is to polymer ratio, we have prepared the matrices by both i.e. physical mixture method and solid dispersion method (Serajuddin, 1999).

Physical Mixture Method: All the ingredients were weighed accurately and passed through sieve no. 85 in order to obtain powder of fine particle size with narrow size distribution. The physical mixtures of drug with carrier PEG 4000 and PVP K-90 was prepared in different concentration by slightly grinding the drug and carrier in mortar for 2 min. The drug: PEG 4000 and drug: PVP K-90 ratio which was taken as 1:1, 1:2, and 1:3 respectively. Then the resultant powder was passed through sieve no 85 and was stored in desiccator for 2-6 hrs to carry out further analysis. The prepared physical mixture was subjected to spectrophotometric method.

Preparation of Solid Dispersion Of Astemizole

For the preparation of Astemizole-PEG 4000 and Astemizole-PVP K-90 solid dispersion by conventional method, PEG 4000 and PVP K-90 was weighed and melted at 58°C (±1°C) and a measured amount of Astemizole was added and stirred. After solidification at room temperature, sample was pulverized with use of a pestle and mortar and sieved through a 400-mm mesh. 10mg of Astemizole - PVP K-90 powder (containing 10mg of Astemizole and 30mg of PVP K-90) and was used for further investigations (Chiou and Riegelman, 1971).

Evaluation of Dispersion Dispersion

Percentage Drug Content:

For the determination of Astemizole content, dispersion equivalent to 10 mg of Astemizole, were weighed and extracted with 10 ml of methanol by mechanical mixing for 5min followed by centrifugation at 10,000 rpm for 5 min on a centrifuge. The supernant was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed for Astemizole at 256nm using a validated UV spectrophotometric method.

Formulation of Oral Film Of Astemizole

Casting process of Fast Disintegrating Oral Film

Various methods are available for casting of oral films. This is fast disintegrating oral film hence on the laboratory scale solvent casting technique was adopted for formulation of films.

Solvent Casting Technique

Astemizole containing fast dissolving films were

fabricated by the solvent casting method (Mahesh *et al.,* 2010). The optimized amount of HPMC was dissolved in 5ml of water and stirrered continuously for 1 hour, optimized amount of plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, the optimized amount of drug was dissolved in 2ml of water and kept in sonicator for proper dispersion. Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm^2 12 films area and was dried at controlled room temperature (25°-30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use.

Table 1: Selection and Optimization of Film Forming Agents

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6
API Equivalent to 10 mg	480	480	480	480	480	480
HPMC	400	600	800	400	600	800
Glycerin	-	-	-	-	-	-
PEG-400	100	100	100	100	100	100
SSG	50	100	150	-	-	-
CCS	-	-	-	50	100	150
Aspartame	10	10	10	10	10	10
Citric acid	20	20	20	20	20	20
DM water qs to (ml)	30	30	30	30	30	30

HPMC=Hydroxypropyl methylcellulose, PEG 400= Polyethylene glycol 400, SSG= Sodium starch glycolate, CCS =Croscarmellose sodium.

Evaluation of Prepared Film

Thickness

The thickness of films was measured at three different places using a vernier caliper.

Weight Uniformity

For each formulation, three randomly selected films were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated (Lakshmi *et al.,* 2005).

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 (Patel *et al.,* 2010).

Percentage 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.

Drug Content Analysis

The films (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 256nm.

Disintegrating Time

The objective of present work is that films should be dissolved within few seconds. Three super disintegrating agent were selected for minimizing the disintegration time.

In Vitro Dissolution Study

The *in vitro* dissolution test was performed using the USP 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. 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 Astemizole was determined using UV-Visible spectrophotometer at 256nm. The results were presented as an average of three such concentrations.

Stability Studies

Stability studies were carried out for optimized formulation F3 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. The % assay of film was found to slightly decrease at higher temperature.

Results and Discussion

The study evaluated the formulation and performance of a fast-dissolving oral film (F3) for the antiemetic drug, Astemizole. The findings highlight the effectiveness of formulation F3 in enhancing drug solubility, providing optimal physical properties, and demonstrating good stability over time. The results from different evaluation parameters provide a clear insight into the formulation's potential for improving the drug's bioavailability and therapeutic outcomes. Table 2 presents the percentage solubility enhancement of Astemizole when combined with polyethylene glycol (PEG 400) and polyvinylpyrrolidone (PVP K-90) in different ratios. The data indicates a significant improvement in the solubility of Astemizole, particularly with PVP K-90. For example, the highest enhancement was observed in the 1:3 ratio of Astemizole to PVP K-90 (363.16%), which suggests that PVP K-90 at higher concentrations significantly improved the solubility of the drug. This enhancement is crucial for improving the bioavailability of the drug, ensuring faster dissolution, and ultimately aiding in quicker onset of action, which is critical for antiemetic drugs.

Table 3 shows the drug content analysis of the physical mixture. The formulation achieved 99.50% of the label claim, indicating high uniformity and accuracy in the drug content, which is essential for the consistency and reliability of the formulation. This result reflects the precision of the formulation process, ensuring that each unit delivers the intended dose of Astemizole.

The physical characteristics of the fast-dissolving oral films were assessed, as shown in Table 4. The formulations exhibited translucency, and the thickness of the films varied from 124 µm (F1) to 147 µm (F3), with formulation F3 having the highest thickness. The weight of the films ranged from 145 mg (F1) to 173 mg (F3). These parameters are important as they directly affect the film's integrity, drug release, and ease of handling. The slight variation in film weight and thickness across the formulations is acceptable, as it falls within a reasonable range for uniformity in dose delivery.

The mechanical properties, such as folding endurance, tensile strength, and disintegration time, were evaluated in Table 5. Formulation F3 demonstrated the best folding endurance (235 folds), which is an indicator of its flexibility and durability. This characteristic is essential to prevent the film from breaking during handling or administration. Formulation F3 also showed the fastest disintegration time (63 minutes), which is desirable for achieving rapid drug release. The tensile strength of F3 (0.72 kg/cm^2) indicates its optimal mechanical properties, making it suitable for the intended application as a fast-dissolving film. The assay value of 99.12%

in F3 confirms that the drug content is within the acceptable limits, ensuring that the formulation will deliver the intended therapeutic dose. The in-vitro release study of the optimized formulation F3 (Table 6) demonstrated excellent drug release kinetics, with nearly complete drug release (98.85%) within 15 minutes. This rapid release is ideal for an antiemetic drug like Astemizole, which requires quick onset of action. The cumulative drug release profile (Figure 1) shows that F3 achieved over 45% drug release within the first minute, and 98.85% by the 15th minute, making it highly suitable for fast-dissolving applications where rapid dissolution is necessary for therapeutic efficacy.

The stability of the optimized formulation F3 was monitored over three months (Table 7). The % assay values showed minimal changes, with a slight decrease from 99.05% to 98.32%, indicating that the formulation is stable over time. The stability data (Figure 2) further supports the viability of F3 as a long-lasting dosage form. The consistency in drug content suggests that formulation F3 is likely to maintain its therapeutic efficacy over extended storage periods, a important factor in the development of pharmaceutical products.

Table 2: Percentage cumulative drug release of physical mixture

S. No.	% solubility Enhancement						
	Drug: PEG 400			Drug: PVP K-90			
Absorbance	1:1	1:2	1:3	1:1	1:2	1:3	Pure Drug
	0.165	0.185	0.228	0.118	0.195	0.345	0.095
% Solubility Enhancement	173.684211	194.736842	240	124.210526	205.263158	363.157895	-----

Table 3: Results of drug content

Formulation	Label claim	Amount found*	Label claim (%)
Physical mixture	10mg	9.95	99.50±0.15

Table 4: Results of Evaluation of prepared film

Formulation code	General Appearance	Thickness (µm)	Weight (mg)
F1	Translucent	124±4	145±6
F2	Translucent	132±3	165±8
F3	Translucent	147±6	173±5
F4	Translucent	129±5	155±4
F5	Translucent	135±4	162±3
F6	Translucent	138±3	169±2

Table 5: Result of folding endurance, disintegration time, tensile strength moisture content and assay

Formulation code	Folding endurance	Disintegration time (min.)	Tensile strength (kg/cm^2)	Moisture Content (%)	Assay (%)
F1	198±5	92±5	0.65±0.05	1.32±0.05	96.34±0.15
F2	210±4	85±4	0.69±0.02	1.85±0.06	98.78±0.32
F3	235±3	63±2	0.72±0.04	1.25±0.08	99.12±0.15
F4	185±6	99±3	0.86±0.03	1.65±0.05	97.65±0.32
F5	176±5	85±6	0.76±0.02	1.74±0.03	96.36±0.15
F6	163±2	76±3	0.69±0.03	1.69±0.04	97.32±0.25

Table 6: Results of *In-vitro* release study of optimized formulation of fast dissolving oral film F3(n=3)

S. No.	Time (Min.)	Cumulative % Drug release
1.	1	45.65
2.	2	69.98
3.	5	73.32
4.	10	88.85
5.	15	98.85

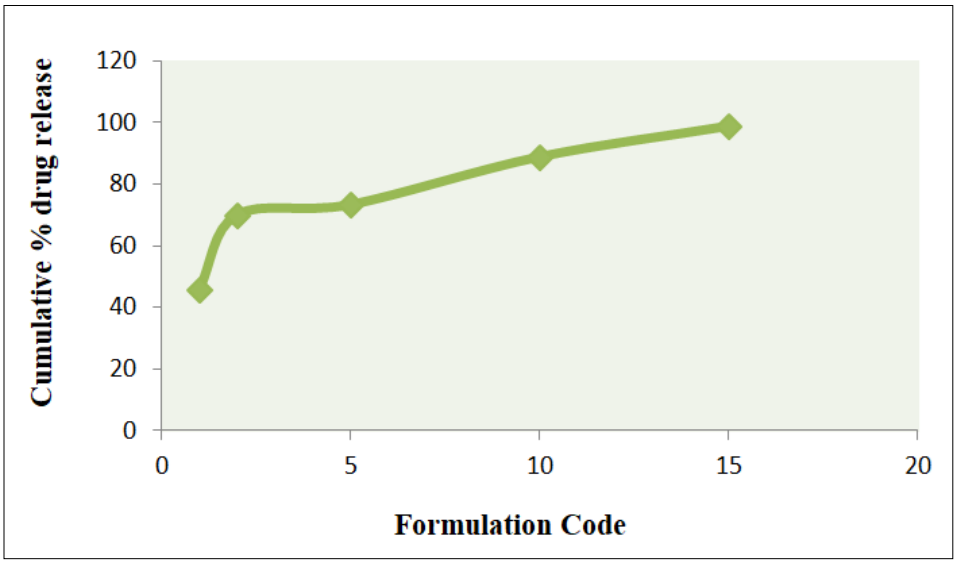

Figure 1: *In-vitro* release study of optimized formulation F3

Table 7: Characterization of stability study of Optimized Film (F3)

Characteristic	Time (Month)			
	Initial	1 Month	2 Month	3 Month
% Assay*	99.05±0.12	98.95±0.23	98.45±0.45	98.32±0.32

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

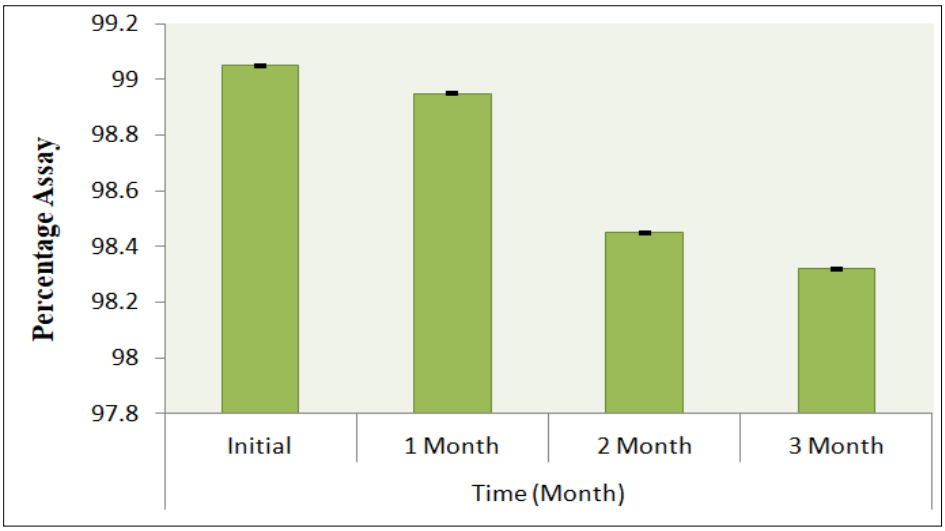

Figure 2: Graph of stability study of Optimized Film (F3)

Conclusion

The results of this study confirm that formulation F3 is a promising candidate for a fast-dissolving oral film for Astemizole. The film demonstrated enhanced solubility, ideal physical and mechanical properties, rapid drug release, and good stability, making it an effective delivery system for Astemizole. Further clinical trials and additional long-term stability studies are recommended to fully assess its therapeutic potential and optimize its application in clinical practice.

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