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DEVELOPMENT OF NATURAL POLYMER BASED FAST DISSOLVING ORAL FILMS OF CINNARIZINE

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ABSTRACT

The present study was aimed at the formulation and evaluation of fast dissolving films of Cinnarizine using natural film-forming agents such as gelatin and pectin by the solvent casting method. Fast dissolving films were prepared to improve patient compliance, enhance drug release, and achieve rapid onset of action. A total of six formulations (F1–F6) were developed using varying concentrations of gelatin and pectin as film-forming polymers, along with glycerin as plasticizer, croscarmellose sodium as superdisintegrant, aspartame as sweetening agent, and Tween 80 as solubilizing agent. The prepared films were evaluated for various physicochemical and mechanical parameters including thickness, weight variation, folding endurance, surface pH, drug content uniformity, disintegration time and *In Vitro* drug release. All formulations showed satisfactory film-forming characteristics with acceptable mechanical strength and uniform drug distribution. Rapid disintegration was observed in all formulations within a short period of time. *In Vitro* drug release studies demonstrated that the type and concentration of film-forming polymer significantly influenced the release behavior of Cinnarizine. Among all formulations, formulation F4 containing pectin exhibited the highest drug release of 99.12 ± 2.26% within 10 minutes along with rapid disintegration characteristics. Pectin-based films showed comparatively faster drug release than gelatin-based films due to the hydrophilic and rapid swelling nature of pectin. Stability studies of the optimized formulation F4 revealed no significant changes in physicochemical properties and drug release profile, indicating good stability of the formulation. The study concluded that fast dissolving films of Cinnarizine prepared using natural polymers could serve as a promising oral drug delivery system for rapid drug release, improved patient compliance, and enhanced therapeutic efficacy.

INTRODUCTION

Oral drug delivery remains the most preferred and widely accepted route of administration due to its convenience, ease of administration, cost effectiveness, and improved patient compliance. However, conventional oral dosage forms such as tablets and capsules may present difficulties in swallowing, particularly in pediatric, geriatric, and dysphagic patients. In addition, delayed onset of action and reduced bioavailability due to first-pass metabolism are major limitations associated with conventional dosage forms. To overcome these drawbacks, fast dissolving drug delivery systems have gained considerable attention in recent years. [1]
Fast dissolving films (FDFs), also known as oral thin films or orodispersible films, are thin polymeric strips designed to disintegrate or dissolve rapidly when placed on the tongue without the need for water. [2,3]These films offer several advantages such as rapid onset of action, improved patient compliance, ease of administration, accurate dosing, portability, and enhanced bioavailability. Due to their rapid disintegration and dissolution characteristics, fast dissolving films are considered an effective alternative to conventional oral dosage forms. [4] Cinnarizine is an antihistaminic and calcium channel blocking agent widely used in the treatment of motion sickness, vertigo, nausea, and vestibular disorders. It belongs to Biopharmaceutical Classification System (BCS) Class II drug, characterized by low aqueous solubility and high permeability, which may result in delayed dissolution and variable oral bioavailability. Development of a fast dissolving film formulation of Cinnarizine may enhance its dissolution rate, improve drug release, and provide rapid therapeutic action.Natural polymers have gained increasing importance in pharmaceutical formulations because of their biocompatibility, biodegradability, non-toxicity, and cost effectiveness. Gelatin and pectin are natural film-forming agents commonly employed in the preparation of oral films due to their excellent film-forming ability and safety profile. Gelatin provides good mechanical strength and flexibility, whereas pectin offers rapid hydration and disintegration properties. The selection and concentration of film-forming polymers play a crucial role in determining the physicochemical and drug release characteristics of fast dissolving films.In the present study, an attempt was made to formulate and evaluate fast dissolving films of Cinnarizine using gelatin and pectin as natural film-forming agents by the solvent casting method. The prepared films were evaluated for various physicochemical, mechanical, and drug release parameters to determine the influence of polymer type on the performance of the films and to identify an optimized formulation suitable for rapid oral drug delivery. [5]

MATERIALS AND METHODS

Cinnarizine was received as a gift sample from Mankind Pharma Ltd, India. All other materials used was of analytical grade and procured from commercial sources.

Preparation of Fast Dissolving Film

Fast dissolving films of Cinnarizine were prepared by the solvent casting method using natural film-forming polymers such as gelatin and pectin. The compositions of formulations F1–F6 are shown in the formulation table 1. A hydroalcoholic solvent system consisting of Isopropyl alcohol and water (1:1) was used for film preparation. Initially, the required quantity of gelatin (for formulations F1–F3) or pectin (for formulations F4–F6) was accurately weighed and dispersed in a sufficient quantity of distilled water with continuous stirring using a magnetic stirrer. The polymeric solution was allowed to hydrate properly to obtain a clear and uniform viscous solution. Separately, Cinnarizine was dissolved in a small quantity of Isopropyl alcohol containing Tween 80 to enhance the solubility and uniform dispersion of the drug. Glycerin was added as a plasticizer to improve

flexibility and reduce brittleness of the films. Croscarmellose sodium was incorporated as a superdisintegrant to facilitate rapid disintegration of the films in the oral cavity. Citric acid was added as a saliva stimulating agent, while aspartame and flavoring agent to improve palatability and taste masking. The drug solution was then added slowly to the polymeric solution under continuous stirring to obtain a homogeneous casting solution. The final volume was adjusted using the Isopropyl alcohol: water mixture (1:1). The prepared solution was stirred continuously to remove entrapped air bubbles and ensure uniform distribution of all ingredients. The resultant bubble-free solution was poured carefully into clean and leveled glass petri dishes and dried at room temperature or in a hot air oven maintained at 40°C for 24 hours. After complete drying, the films were carefully peeled off from the petri dishes and cut into strips of 2X3 cm containing the required dose of Cinnarizine. The prepared films were wrapped in aluminum foil and stored in a desiccator until further evaluation.[6,7,8]

Table 1: Composition of Fast Dissolving Film of Cinnarizine

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Cinnarizine	25	25	25	25	25	25
Gelatin	300	400	500	-	-	-
Pectin	-	-	-	300	400	500
Glycerin	10	10	10	10	10	10
Croscarmellose Sodium	2	2	2	2	**2**	2
Citric acid	20	20	20	20	20	20
Aspartame	30	30	30	30	30	30
Tween 80	10	10	10	10	10	10
Flavor	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Isopropyl Alcohol : Water (1:1)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation of Fast Dissolving Film

Weight Uniformity of films

Three films of the size 2×3 cm2 were weighed individually using digital balance and the average weights were calculated.

Thickness of Film

The thickness of the film should be measured at five locations (center and four corners), using verniercallipers and the mean thickness is calculated. Samples with air bubbles, nicks or tears and having mean thickness variation of greater than 5% are excluded from analysis. [9]

Folding Endurance of Films

Folding endurance is another procedure to estimate the mechanical properties of a film. Folding endurance value is number of times the film is folded without breaking. Higher folding endurance value depicts the more mechanical strength of a film. Folding endurance of the films was determined by repeatedly folding a film at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance. [10]

Surface pH of films

Surface pH was determined to reduce the irritation of oral mucosa due to alkaline or acidic pH. It was kept in the range of salivary pH. Surface pH was determined by the films were allowed in contact with 1 ml of distilled water. The surface pH was noted by bringing a combined glass electrode near the surface of films and allowing equilibrate for 1 min. Reading was recorded in pH meter. [11]

Drug Content Uniformity Study

The films were tested for drug content uniformity by U.V-Spectrophotometric method. Films of 2×3 cm2 were each film was placed in 10 ml volumetric flask and diluted with phosphate buffer pH 6.8 up to 10 ml. The absorbance of the solution was measured at 254 nm using U.V visible spectrophotometer after suitable dilution. The percentage drug content was determined.[12]

***In-vitro* Disintegration Time**

In-vitro disintegration time is a critical parameter measured during pharmaceutical product testing, particularly for solid oral dosage forms. It refers to the time taken for a film to disintegrate when subjected to specific conditions in a laboratory setting. Once disintegration occurs, the surface area of the dosage form increases, facilitating the dissolution of the active pharmaceutical ingredient (API) and its subsequent absorption in the body.Disintegration time of fast dissolving film was determined by petri dish method. This technique was carried out on a petri plate. The oral thin film was placed in the centre of a petri dish filled with 10 mL of distilled water. The time taken for the thin layer to disintegrate is measured, and the procedure is done triplicate. [13,14]

***In Vitro* Dissolution Study**

In-vitro dissolution of Cinnarizinefast dissolving films was studied using USP Type 2 dissolution test apparatus, 900 ml phosphate buffer solution pH 6.8 was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution medium was maintained at 37±0.5°C throughout the experiment. Samples of dissolution medium (5ml) were withdrawn at regular time interval. Solution was filtered with Whatman filter Paper. Sample were withdraw after 1,2,4,6,8 and 10 minute time intervals. The sample ware analyzed for drug release by measuring the absorbance at 254 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent released of cinnarizinewas calculated and plotted against time. [15,16]

Stability Study

The accelerated stability studies were carried out according to ICH guidelines on optimized fast dissolving oral film formulation. The formulation was packed in strip of aluminum foil and was stored in stability chamber maintained at 40°C and 75% RH for the period of 3 months. The film were evaluated before and after 3 months for change in appearance, folding endurance, disintegration time, drug content and *In Vitro* drug release. [17]

RESULTS AND DISCUSSION

Table 1. Evaluation Parameters of Cinnarizine Fast Dissolving Films

Formulation	Thickness (mm)	Weight Variation (mg)	Folding Endurance	Surface pH	Drug Content (%)	Disintegration Time (sec)
F1	0.18 ± 0.01	78.42 ± 1.12	165 ± 4.24	6.72 ± 0.05	96.42 ± 1.18	34 ± 1.52
F2	0.22 ± 0.02	84.65 ± 1.34	184 ± 5.11	6.68 ± 0.04	97.86 ± 1.06	39 ± 1.73
F3	0.27 ± 0.01	92.84 ± 1.48	201 ± 4.58	6.75 ± 0.06	98.54 ± 0.94	45 ± 1.31
F4	0.20 ± 0.01	80.26 ± 1.26	158 ± 3.84	6.64 ± 0.07	95.88 ± 1.24	31 ± 1.42
F5	0.24 ± 0.02	87.46 ± 1.52	176 ± 4.62	6.70 ± 0.05	97.24 ± 1.12	36 ± 1.63
F6	0.29 ± 0.01	95.38 ± 1.64	193 ± 5.06	6.73 ± 0.04	98.12 ± 0.88	42 ± 1.84

The fast dissolving films of Cinnarizine were successfully prepared by the solvent casting method using natural film-forming polymers gelatin and pectin. All formulations showed smooth appearance, satisfactory flexibility, and good film-forming characteristics without any visible cracks or air bubbles. The thickness of the prepared films was found to be in the range of 0.18 ± 0.01 mm to 0.29 ± 0.01 mm, indicating uniform casting of the polymeric solution. An increase in polymer concentration resulted in a corresponding increase in film thickness and weight variation. Folding endurance values ranged from 158 ± 3.84 to 201 ± 4.58, demonstrating good mechanical strength and flexibility of the films. Higher polymer concentrations exhibited improved folding endurance due to enhanced polymeric matrix formation. The surface pH of all formulations was found to be near neutral (6.64 ± 0.07 to 6.75 ± 0.06), suggesting that the films would not produce irritation to the oral mucosa. Drug content uniformity studies indicated uniform distribution of Cinnarizine throughout the films, with drug content ranging from 95.88 ± 1.24% to 98.54 ± 0.94%. Disintegration time is a critical parameter for fast dissolving films. The formulations showed rapid disintegration within 31 ± 1.42 to 45 ± 1.31 seconds. Among all formulations, formulation F4 exhibited the fastest disintegration time, which may be attributed to the hydrophilic nature of pectin and the presence of croscarmellose sodium as superdisintegrant.

***In Vitro* Drug Release Study**

The *In Vitro* drug release study of Cinnarizine fast dissolving films (F1–F6) was carried out and the cumulative percentage drug release was determined over a period of 10 minutes. The obtained results demonstrated rapid drug release from all prepared formulations, confirming the suitability of the solvent casting method for the preparation of fast dissolving oral films.

The percentage drug release of all formulations increased progressively with time. At the end of 10 minutes, the cumulative drug release was found to be 96.82 ± 2.18%, 92.14 ± 2.06%, 88.36 ± 1.94%, 99.12 ± 2.26%, 95.48 ± 2.12%, and 90.62 ± 1.96% for formulations F1, F2, F3, F4, F5, and F6 respectively (figure 1). Among all formulations, F4 exhibited the highest drug release of 99.12 ± 2.26%, whereas F3 showed comparatively slower release with 88.36 ± 1.94% drug release at the end of the study. The results indicated that the concentration and type of film-forming polymer had a significant influence on drug release behavior. Formulations F1–F3 containing gelatin as the film-forming agent exhibited comparatively slower drug release with increasing gelatin concentration. This may be attributed to the formation of a dense and strong polymeric matrix by gelatin, which reduced the penetration of dissolution medium and subsequently retarded drug diffusion. As the concentration of gelatin increased from F1 to F3, the viscosity and thickness of the films also increased, leading to slower film hydration and delayed drug release. In contrast, formulations F4–F6 prepared using pectin exhibited faster drug release profiles compared to gelatin-based films. Pectin is a highly hydrophilic natural polymer that undergoes rapid swelling upon contact with dissolution media, thereby promoting quick disintegration and faster drug diffusion. Formulation F4 containing the lowest concentration of pectin showed the highest drug release due to rapid hydration. However, increasing the concentration of pectin in formulations F5 and F6 slightly reduced the drug release rate because of increased matrix density and film thickness. Furthermore, the presence of croscarmellose sodium as a superdisintegrant enhanced water uptake and facilitated rapid disintegration of the films, thereby contributing to faster release of Cinnarizine. The study demonstrated that both the type and concentration of film-forming

agent markedly affected the drug release characteristics of the fast dissolving films. Among all formulations, F4 was considered the optimized formulation due to its rapid disintegration and maximum drug release within a short period of time, making it a promising candidate for fast onset of action and improved patient compliance.

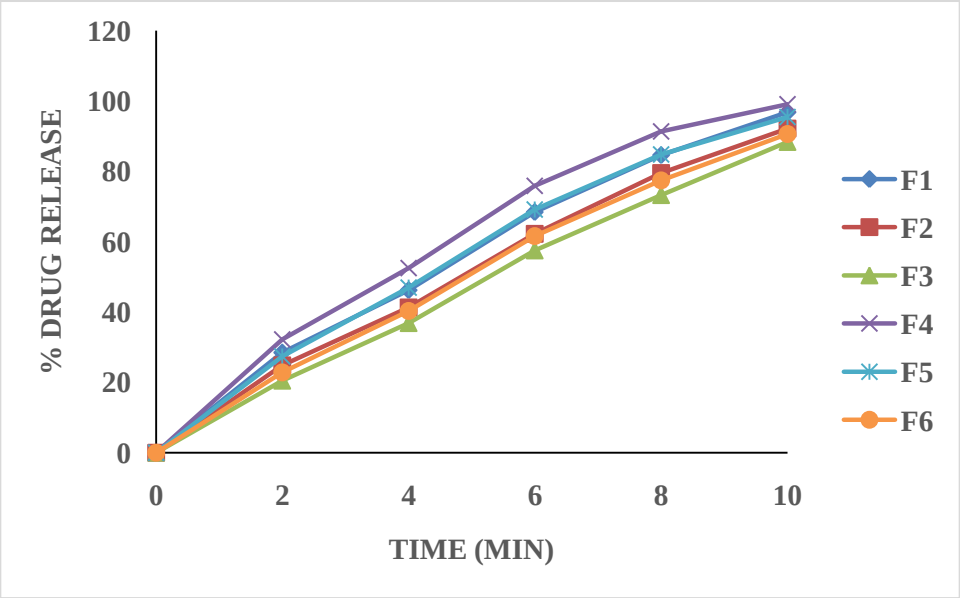

Fig.1- *In Vitro* Dissolution Profile of Cinnarizine Fast Dissolving Oral Film

Stability Study

The stability study of the optimized fast dissolving film formulation F4 was carried out under accelerated storage conditions for the specified study period. The formulation showed no significant changes in physical appearance, folding endurance, drug content, disintegration time, and *In Vitro* drug release profile after storage. The results indicated that formulation F4 retained its mechanical integrity and drug release characteristics throughout the study period. Therefore, it can be concluded that the optimized formulation F4 was stable under the applied storage conditions and suitable for further pharmaceutical application.

CONCLUSION

The present study successfully demonstrated the formulation and evaluation of Cinnarizine fast dissolving films using natural film-forming agents such as gelatin and pectin by the solvent casting method. The prepared films exhibited satisfactory physicochemical properties including uniform thickness, acceptable folding endurance, suitable surface pH, uniform drug content, rapid disintegration, and efficient drug release characteristics. The study revealed that the type and concentration of film-forming polymer significantly influenced the mechanical properties and drug release behavior of the films. Among all the formulations, formulation F4 containing pectin showed the best overall performance with rapid disintegration and maximum drug release within a short period of time. The enhanced drug release from pectin-based films was attributed to the hydrophilic and fast swelling nature of the polymer.The optimized formulation F4 also showed good stability under accelerated storage conditions without significant changes in evaluation parameters. Therefore, the developed fast dissolving film of Cinnarizine can be considered a promising alternative oral drug delivery system for achieving rapid onset of action, improved patient compliance, and enhanced therapeutic efficacy.

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