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RESEARCH ARTICLE

# Orodispersible Films for Enhanced Bioavailability of Carvedilol

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**Abstract:** Orodispersible films (ODF) represent an innovative approach in drug delivery systems, offering solutions to enhance patient compliance and address challenges associated with traditional dosage forms. Particularly beneficial for patients with swallowing difficulties, ODFs can be easily ingested without the need for water, chewing, or swallowing. Carvedilol, characterized by low bioavailability due to hepatic first-pass metabolism, prompted the focus of this research on developing carvedilol ODFs to enhance its bioavailability. Employing the solvent casting method, carvedilol ODFs were formulated employing the film-forming polymer hydroxypropyl methylcellulose (HPMC). Comprehensive evaluations were conducted, including assessments of physical attributes, weight variation, film thickness, folding endurance, surface pH, swelling properties, water permeation, tensile strength, disintegration, drug content, and in vitro dissolution studies. Optimization of the formulation was achieved through a systematic trial and error approach. The preparation involved dissolving HPMC (50/5 cps) in methanol, with the addition of polyethylene glycol (PEG) and propylene glycol (PG) to attain a homogeneous mixture. After incorporating the drug and excipients, entrapped air was removed, and the solution was cast onto microscopic glass slides and dried at room temperature. The resulting film was divided into halves, each containing 10mg of the drug. Six formulations (F1 to F6) were developed using the solvent casting technique, with formulation F4 emerging as the optimal choice based on assessments of drug content and dissolution studies. This study shows the potential of carvedilol ODFs as a promising strategy to enhance its bioavailability and therapeutic efficacy.

**Keywords:** Carvedilol; Orodispersible films; Bioavailability; First-pass metabolism; HPMC

## 1. Introduction

Orodispersible films (ODFs) represent a recent advancement in dosage forms designed to facilitate the release of medication in the oral cavity, eliminating the necessity for water or chewing. This innovative delivery system holds significant promise in enhancing drug bioavailability and simplifying administration, particularly for patients with mental illness or those in a coma state, where traditional oral medications may present challenges [1,2]. One of the key advantages of ODFs lies in their ability to bypass first-pass metabolism, allowing the drug to enter the systemic circulation directly, thereby facilitating rapid onset of action [3,4]. This direct absorption route can lead to improved therapeutic outcomes and enhanced patient compliance. Moreover, ODFs offer versatility in dosing, allowing for precise control over the release kinetics of the active ingredient by adjusting the type, concentration, and ratios of polymers and other components in the formulation [5-7].

Carvedilol, a β-blocker indicated for the treatment of hypertension, heart failure, and angina, presents a compelling case for formulation as an orodispersible film. Oral administration of carvedilol is associated with low bioavailability due to the significant first-pass hepatic effect. Consequently, the development of an ODF formulation offers a strategic approach to mitigate this limitation and optimize therapeutic efficacy [8]. Several manufacturing methods are available for the production of fast-dissolving films, each offering unique advantages and considerations. These include the solvent casting method, rolling method, solid dispersion method, and hot melt extrusion [9]. Among these techniques, the solvent casting method is widely utilized for its simplicity, scalability, and ability to accommodate a broad range of drug and polymer combinations. By dissolving the polymer and active ingredient in a suitable solvent, followed by casting and drying, uniform films with tailored drug release profiles can be achieved.

The rolling method involves the preparation of a homogeneous blend of drug and polymer, which is then compressed between two rollers to form thin films. While this technique offers advantages in terms of efficiency and reproducibility, it may be less suitable for heat-sensitive drugs due to the mechanical force involved in the process. In contrast, the solid dispersion method

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involves dispersing the drug within a hydrophilic carrier matrix to enhance solubility and dissolution rate. This approach is particularly beneficial for poorly water-soluble drugs, as it facilitates rapid dissolution and absorption in the oral cavity. Finally, hot melt extrusion involves the extrusion of a molten blend of drug and polymer through a die to form films of uniform thickness. This method offers advantages in terms of scalability and process efficiency, although careful consideration must be given to the selection of excipients and processing parameters to ensure product quality and stability. [10,11] Overall, the development of orodispersible films represents a promising strategy to improve drug delivery and patient outcomes, with carvedilol serving as a compelling candidate for formulation in this innovative dosage form. Through careful selection of manufacturing methods and formulation parameters, tailored ODFs can be engineered to meet the specific needs of patients and optimize therapeutic efficacy.

## 2. Materials and methods

### 2.1. Materials

Carvedilol, provided as a gift sample by Aurobindo Limited, served as the active pharmaceutical ingredient (API) for this study. The following polymers and excipients were employed in the formulation: Hydroxypropyl methylcellulose (HPMC) of both 5cps and 50cps grades, Polyethylene glycol (PEG), Propylene glycol, methanol, sodium starch glycolate, citric acid, saccharin, vanillin, and amaranth. The solvent casting method was adopted to fabricate the sublingual films containing carvedilol, aimed at achieving rapid dissolution characteristics. To facilitate the casting process, flat, rectangular glass slides purchased from local store were utilized as substrates [12].

### 2.2. Methodology

*2.2.1. Preparation of carvedilol ODFs by solvent casting method*

A polymeric solution was meticulously prepared in methanol by dissolving Hydroxypropyl Methylcellulose (HPMC) of both 50/5 cps grades, followed by the addition of Polyethylene Glycol (PEG) and Propylene Glycol (PG) to achieve a homogeneous blend. Subsequently, the drug along with excipients were incorporated into the solution, and the mixture was allowed to stand for 1-2 hours to facilitate the removal of entrapped air. The resulting solution was then carefully cast onto microscopic glass slides and left to dry at ambient temperature. [13] Upon drying, the film was peeled and halved, ensuring an equal distribution of the drug, with each half containing 10mg. All formulations (denoted as F1 to F6) were prepared utilizing the solvent casting technique in accordance with the specified formulation outlined in Table 1.

**Table 1.** Formulation of orodispersible films

| INGREDIENTS | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Carvedilol (mg) | 20 | 20 | 20 | 20 | 20 | 20 |
| HPMC 5 cps (mg) | 2000 | 3000 | 3500 | - | - | - |
| HPMC 50 cps (mg) | - | - | - | 500 | 750 | 1000 |
| PG (ml) | 2 | 2 | 2 | 2 | 2 | 2 |
| PEG (mg) | 100 | 100 | 100 | 100 | 100 | 100 |
| SSG (mg) | 10 | 10 | 10 | 10 | 10 | 10 |
| Citric acid, Saccharin & Vanillin (mg) | 5 | 5 | 5 | 5 | 5 | 5 |
| Amaranth | q.s | q.s | q.s | q.s | q.s | q.s |
| Methanol (ml) | q.s | q.s | q.s | q.s | q.s | q.s |

*2.2.2. Determination of absorption maxima*

To establish the absorption maximum (λ max) for carvedilol, a UV spectrum was obtained for the working standard solution of carvedilol by scanning the solution within the wavelength range of 200–400 nm against a reagent blank. The analysis revealed a

prominent absorption peak at 241 nm, indicating the λ max for carvedilol. Subsequently, this wavelength was consistently employed for all subsequent analyses and experiments involving carvedilol. [14]

### 2.3. Evaluation of orro-dispersible films of carvedilol

#### *2.3.1. Physical appearance*

The formulated films were inspected visually to check the factors like colour, clarity, flexibility, smoothness.

#### *2.3.2. Weight Variation*

The test was performed by weighing the 5 films of every formulation individually and average weights and standard deviations were calculated.

#### *2.3.3. Thickness*

Using a screw gauge, the thickness of each film was measured three times, and the average thickness and standard deviation were computed.

#### *2.3.4. Folding Endurance*

Determination of folding endurance is done by folding the strip of film of (2×2 $cm^2$) at the same place repeatedly until it is broken. Based on number of times the film could be folded without any breaking the value of folding endurance is known.

#### *2.3.5. Film Surface pH*

Each formulation's surface pH was ascertained by letting the film swell in a closed petri dish filled with 5 ml of distilled water at room temperature for 30 minutes. A digital pH meter was then used to measure the pH of the solution.

#### *2.3.6. Swelling Property*

Swelling properties of films were conducted by placing weighed film in a pre-weighed mesh made of stainless steel wire which is dipped in 15ml of buffer solution. Increase in the weight of film was determined at a particular time interval until a constant weight was observed.

The degree of swelling property was determined by using a formula,

Degree of swelling= (final wt-initial wt)/(initial wt)

#### *2.3.7. Water Permeation Test*

The amount of moisture that is transferred across a unit area of film in a unit of time is known as the water vapour transmission rate. Two grams of anhydrous calcium chloride were placed within glass cells, and the rim of each cell was covered with a predetermined section of film. The assembly was precisely weighed and kept at 27ºC in a humidity chamber with an 85% relative humidity for a whole day. [15]

#### *2.3.8. Tensile Strength*

Tensile strength is defined as "The ratio of maximum stress applied to the film at which the Oro-dispersible film specimen breaks" by using modified physical balance. Tensile strength of the films can be determined by this method. On one side of the balance semipermeable membrane (egg membrane) is used as a model membrane and the buffer is used as moistening fluid. Mucoadhesive dosage form and the semipermeable membrane are adhered together by placing a 10g preload on the correct pan for 5 minutes (preload time). There is no change in the preload or preload time. Following the preload period, water was added to the left pan and the preload was withdrawn from the right pan. When the mucoadhesive dosage form was detached from the membrane, addition of water was halted. The weight of water needed to detach dosage form from membrane is noted as tensile/bio-adhesive strength in gm. [16]

Force of adhesion (N)= (mucoadhesive strength ×9.81)/1000

Bond strength($N/M^{2)}$ = (force of adhesion (N))/(Surface of film)

*2.3.9. Disintegration Test*

The moment a film begins to shatter or dissolve is known as the disintegration time. A single film of every formulation was put in a petri dish with a pH 6.8 phosphate buffer (5 ml). Disintegration time in vitro was measured visually by whirling every ten seconds. [17]

*2.3.10. Drug Content Uniformity*

Films of each formulation were dissolved in 10 milliliters of methanol to determine this criterion. From the above solution, 0.1 ml was extracted and diluted with 6.8 pH phosphate buffer to get 10 ml. The absorbance was determined with a UV Spectrophotometer at 241 nm. [18]

*2.3.11. In vitro Dissolution Studies*

The dissolution study was performed by using a 6.8 phosphate buffer as a dissolution medium. The drug release from carvedilol films was determined by using a unilateral drug release system. The solution was stirred continuously with magnetic bead at 50 rpm speed and 37°C temperature. 5ml dissolution media was withdrawn at regular time intervals of 2, 5, 10, 20 & 30 minutes and fresh medium of same volume is added. Withdrawn samples were filtered and analysed by using UV Spectrophotometer. [19]

*2.3.12. Compatibility Studies*

The drug (carvedilol), combination of drug-polymer and combinations of drug-excipients were intended for fourier transform infrared (FT-IR) spectroscopy for their characteristic peaks. [20]

## 3. Results and discussion

### 3.1. Physical appearance

The visually examined films were opaque and flexible in nature. It was observed that the film was dried at the upper surface and sticky at the lower surface.

### 3.2. Weight variation test

Each formulation's specific weight was recorded, and an average weight for the entire film was computed with 5% tolerances. The weight of the entire film sample was found to be consistent.

### 3.3. Thickness

The thickness of the prepared films ranged from 0.56 ± 0.04 to 1.84 ± 0.02 mm. It was found that the amount of polymer had an impact on the film's thickness. Each and every film was detected with uniform thickness, as this is directly related to accuracy of dose distribution of the film. [21]

### 3.4. Folding endurance

All of the films exhibited good flexibility and folding endurance of more than 150 indicating that they were able to withstand mechanical strain.

### 3.5. Surface pH

The surface pH of the film was noticed around the neutral pH which ranges from 6.62 to 6.82.Thus we can conclude that there will be no irritation to the oral mucosa

### 3.6. Swelling property

It was observed that films were having better swelling property with the swelling index ranging from 0.02±0.04 to 0.99±0.04 and thereby increases the rate of absorption [22]

### 3.7. Water permeation test

The water vapor transmission rate of the films ranges from 0.015±0.002 to 0.045±0.004. It was shown that the property of the film penetrates the moisture content through its interconnecting voids.

### 3.8. Tensile strength

The tensile strength of the films ranges from 0.004±0.00 to 0.031±0.00 kg/cm². It was noticed that the tensile strength of the films increased with increase in the quantity of polymer used in formulation. The results of physicochemical parameters were given in Table 2 and the Figure 1 shows prepared orodispersible films and some evaluation tests performed.

**Table 2.** Results of physicochemical parameter tests

| Formulation Code | Wt. Variation (gm) | Thickness (mm) | Folding Endurance (No of Folds) | Tensile Strength (Kg/cm²) | Surface pH | Swelling Index | Water Vapour Transmission Rate (gm/cm²) |
|---|---|---|---|---|---|---|---|
| **F1** | 2.9±0.25 | 1.90±0.07 | 144.33±4.72 | 0.009±0.00 | 6.62 | 0.55±0.31 | 0.015±0.002 |
| **F2** | 4.03±0.81 | 1.84±0.02 | 148.66±2.88 | 0.014±0.00 | 6.63 | 0.66±0.03 | 0.016±0.003 |
| **F3** | 4.70±0.30 | 1.70±0.07 | 164.33±4.03 | 0.031±0.00 | 6.69 | 1.02±0.04 | 0.019±0.001 |
| **F4** | 1.76±0.56 | 0.64±0.03 | 182.66±4.16 | 0.004±0.00 | 6.70 | 0.73±0.03 | 0.025±0.002 |
| **F5** | 2.01±0.30 | 0.56±0.04 | 183.33±5.03 | 0.008±0.00 | 6.79 | 0.77±0.01 | 0.036±0.003 |
| **F6** | 2.08±0.18 | 1.26±0.02 | 187.66±5.50 | 0.010±0.00 | 6.82 | 0.b 95±0.04 | 0.045±0.004 |

* Mean ± SD n=3 observations

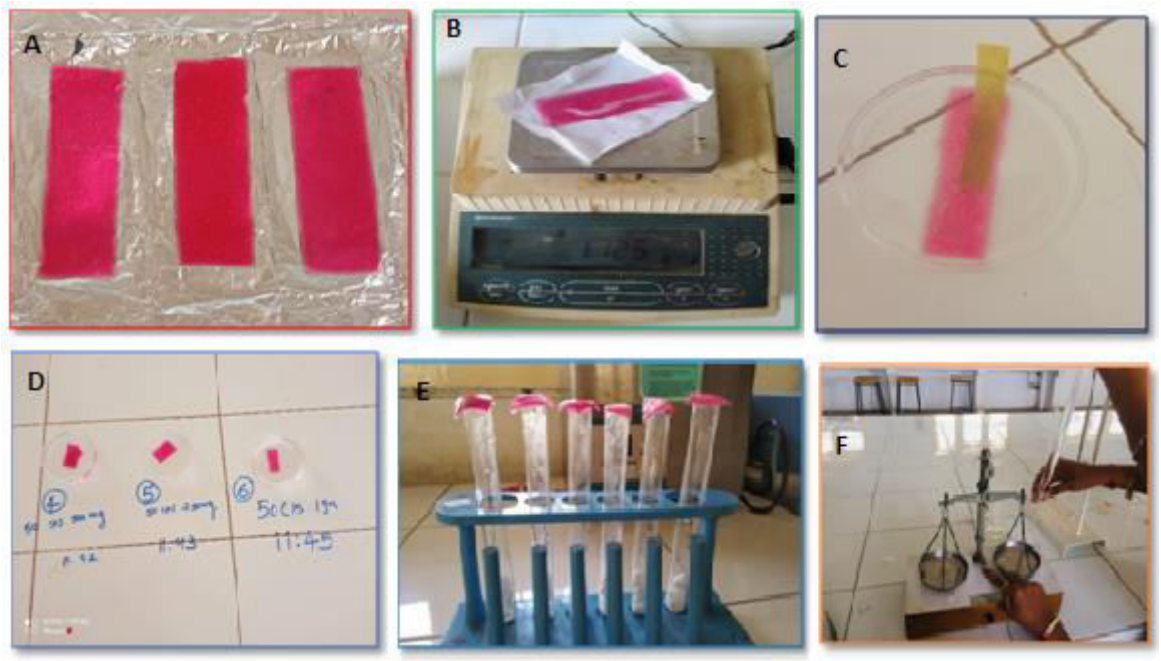


**Figure 1.** Evaluation tests of carvedilol orodispersible films A. Physical Appearance, B. Weight variation test, C. Surface pH, D. Disintegration test, E. Water Permeation test, F. Tensile strength

### 3.9. Disintegration test

It was noticed that the thickness of the films affects the in vitro disintegration time which was varied from 3 ± 1 to 18 ± 2 mins. The results of disintegration test are shown in Table 3.

**Table 3.** Results of Disintegration and Drug Content

| Formulation code | Disintegration time in minutes | Drug content (%) |
|---|---|---|
| **F1** | 3.00 ± 1.000 | 94.85 ± 0.65 |
| **F2** | 6.33 ± 1.528 | 92.86 ± 1.47 |
| **F3** | 7.00 ± 1.000 | 91.12 ± 0.45 |
| **F4** | 8.66 ± 1.526 | 97.67 ± 0.45 |
| **F5** | 9.00 ± 1.000 | 96.56 ± 0.78 |
| **F6** | 18.00 ± 2.000 | 92.10 ± 0.45 |

### 3.10. *In vitro* dissolution

The dissolution results in Table 4 of formulations from F1 to F6 revealed the rapid release of carvedilol that indicates the efficacy of the formulations. HPMC was the most suitable as the film forming material and it provided fast dissolution of the films that were not sticky

**Table 4: Comparative Percentage Drug Release Profiles of Oro-Dispersible Films**

| TIME (mins) | % Cumulative drug release | | | | | |
|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
| 1 | 11.2% | 8.6% | 13.8% | 28.3% | 13.6% | 11.2% |
| 5 | 27.8% | 13.5% | 26.3% | 57.9% | 38.2% | 28.6% |
| 10 | 37.4% | 31.8% | 48.9% | 86.4% | 73.5% | 57.9% |
| 15 | 54.3% | 62.1% | 72.5% | 92.8% | 82.7% | 76.2% |
| 20 | 65.6% | 76.3% | 85.1% | 98.5% | 89.9% | 84.3% |
| 25 | 79.8% | 87.5% | 92.3% | 98.6% | 91.3% | 94.8% |

### 3.11. Compatibility studies:

Fourier transform infrared (FT-IR) spectra of drug and drug-polymer and drug-excipients were determined. From the results it was concluded that there was no interference in the functional groups as the principle peaks of the drug, which were found unaltered in the spectra of drug-polymer mixture and drug-excipient mixture as shown in Figure 2.

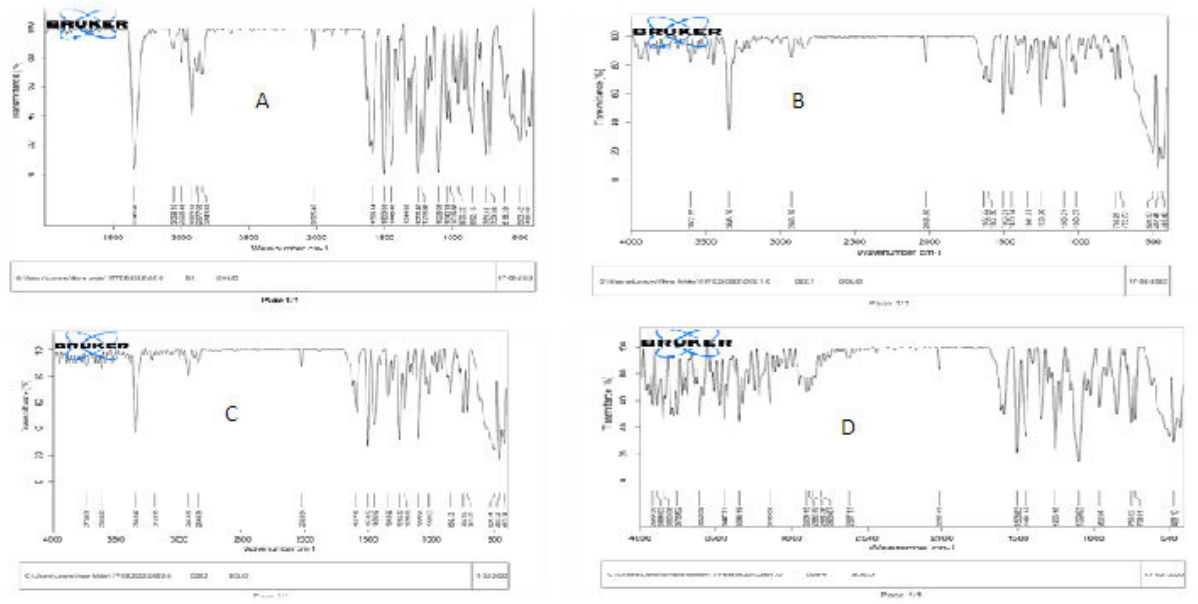


**Figure 2.** FT-IR Spectrum of A. Carvedilol, B. Carvedilol + HPMC, C. Carvedilol + SSG, D. Carvedilol + PEG

## 4. Conclusion

Formulation and evaluation of carvedilol orodispersible films was successfully achieved by solvent casting method with HPMC as film forming polymer. The films obtained were evaluated for various parameters for physicochemical characteristics and for drug release. FTIR studies revealed good compatibility between drug, polymers and excipients. The prepared films were elegant, non irritable, readily soluble and possessed sufficient tensile strength and folding endurance. Among the six formulations, F4 was selected as best considering the results of drug content and dissolution studies.

## Compliance with ethical standards

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*Conflict of interest*

None

*Statement of ethical approval*

Not applicable for this study

*Statement of informed consent*

Not applicable for this study

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## Author's short biography

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Dr. N. Divya holds a Master's degree in Pharmacy (M.Pharm.) and a Doctorate (Ph.D.) in the same field. With a decade of experience, Dr. Divya serves as an Associate Professor at Aditya College of Pharmacy. Her expertise lies in pharmaceutical analysis, and she has contributed significantly to research and academia in her field. Dr. Divya's work encompasses various aspects of pharmacy, including analytical method development and validation, drug delivery systems, formulation development, and pharmacology. She is committed to advancing pharmaceutical education and research to benefit both students and the broader community.

**Dr. Uday Kumar Thummala**

Dr. Thummala Udaya Kumar is a seasoned Professor specializing in Pharmaceutics. He holds a Master's degree in Pharmacy (M.Pharm) and a Doctorate (Ph.D.) in the same field. With a cumulative experience of 16.5 years in the pharmaceutical sector, Dr. Uday Kumar has spent 2.5 years in industry and 14 years in academia, honing his expertise in teaching and research. Throughout his career, Dr. Uday Kumar's commitment to pharmaceutical education and research has been unwavering, making him a respected figure in the academic and scientific community.