WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 14, Issue 20, 1171-1183. Research Article ISSN 2277–7105

DEVELOPMENT OF CONTROLLED RELEASE BUCCAL FILMS OF VERAPAMIL HYDROCHLORIDE: A SOLVENT CASTING APPROACH

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Article Received on 15 Sept. 2025,
Article Revised on 30 Sept. 2025,
Article Published on 15 October 2025,
https://doi.org/10.5281/zenodo.17462838

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How to cite this Article: Parthiban S., Yashaswini N. R.* (2025). Development Of Controlled Release Buccal Films Of Verapamil Hydrochloride: A Solvent Casting Approach. World Journal of Pharmaceutical Research, 14(20), 1171–1183.

ABSTRACT

Objective: The study aimed to develop and evaluate mucoadhesive buccal films of Verapamil Hydrochloride, a calcium channel blocker used for hypertension, angina pectoris, and cardiac arrhythmias. The objective was to enhance bioavailability by bypassing first-pass metabolism and to achieve a controlled release drug delivery system for effective management of cardiovascular conditions. **Methods:** Verapamil Hydrochloride buccal films were prepared using the solvent casting technique with various polymers including Gelzan CM, Sodium Alginate, HPMC E15, and Polyvinyl Alcohol. Preformulation studies including melting point, UV spectroscopy, FTIR, and DSC were conducted to confirm drug identity and compatibility. Films were evaluated for physical parameters such as thickness, weight variation, surface pH, folding endurance, swelling index, moisture uptake/loss, drug content, and *in vitro* drug release. Drug release kinetics was analyzed using mathematical models. Stability studies were performed under ambient and accelerated conditions to assess long-term performance. **Results:** Preformulation studies confirmed the identity and compatibility of Verapamil Hydrochloride with the selected polymers. All formulations exhibited acceptable physical and mechanical properties without irritation potential. Drug content was within pharmacopeial limits, and surface pH values were close to physiological buccal pH. In vitro drug release studies demonstrated sustained and controlled release pattern, following non-Fickian (anomalous) diffusion kinetics.

Stability studies indicated minimal changes in drug content and release profile, confirming good formulation stability over time. **Conclusion:** The formulated Verapamil Hydrochloride buccal films showed satisfactory physicochemical characteristics, good stability indicating their potential as an effective controlled-release system for cardiovascular therapy.

KEYWORDS: Buccal Films, Mucoadhesive, Hypertension, Controlled Release, Solvent Casting.

INTRODUCTION

The oral route is the most frequently used method for drug administration, favored for its benefit like being non-invasive, enhancing patient compliance, and providing convenience in drug delivery. Several factors influence oral drug absorption, such as the drug's solubility, permeability through the mucosal lining, and its stability within the gastrointestinal tract.[1] The main challenges in oral drug delivery include overcoming issues like difficulty swallowing pills, delivering unpleasant-tasting medications, and minimizing the frequency of doses.[2] Buccal drug delivery is an innovative method of administering medication through the mucous membrane lining the inside of the cheek. This route offers several advantages over traditional oral and intravenous administration. One of the primary benefits is improved bioavailability, as buccal delivery bypasses the gastrointestinal tract and hepatic first-pass metabolism, allowing more of the drug to enter systemic circulation directly.[3] This can result in a quicker onset of action, which is particularly beneficial for conditions requiring rapid relief.

Buccal films, in particular, are thin, flexible, and mucoadhesive strips that adhere to the buccal mucosa, releasing the drug in a controlled manner. This delivery system enhances patient convenience and compliance due to its ease of use and non-invasive nature.[4] Patients can administer the medication themselves without the need for water or complicated instructions, and the films can be removed if necessary, providing an additional safety measure.[5]

Verapamil hydrochloride is a widely recognized calcium channel blocker; BCS class I and commonly prescribed for the treatment of various cardiovascular conditions such as hypertension, angina pectoris, and specific arrhythmias. Its mechanism of action involves inhibiting the influx of calcium ions into cardiac and smooth muscle cells, which reduces myocardial contractility, lowers heart rate, and relaxes vascular smooth muscles, ultimately

leading to reduced blood pressure and enhanced cardiac perfusion. Despite the efficacy of traditional oral and intravenous forms of Verapamil hydrochloride, these routes of administration often come with limitations, including gastrointestinal side effects, first-pass metabolism, and the necessity for frequent dosing.[6]

The development of a buccal film formulation of Verapamil hydrochloride aims to capitalize on these benefits, offering an effective and patient-friendly alternative for managing cardiovascular conditions.[7] This innovative delivery system involves incorporating Verapamil hydrochloride into a mucoadhesive film matrix that adheres to the buccal mucosa and releases the drug in a controlled manner.

MATERIALS AND METHODS

Verapamil Hydrochloride was purchased from Balaji drug store Mumbai, Gelzan CM and Polyvinyl alcohol and Propylene glycol collected from SD Fine Chem., Mumbai, Hydroxypropyl methylcellulose E15 and Sodium alginate collected from Loba cheme Pvt Ltd.

Preformulation studies

Determination of melting point of the drug[8]

Melting point of Verapamil Hydrochloride was determined by using capillary tube method using melting point apparatus.

Fourier transforms infrared spectroscopy (FTIR) studies[9]

Drug-excipients compatibility studies were carried out using FTIR. Infrared spectrum of pure drug (Verapamil Hydrochloride) and physical mixture of Verapamil Hydrochloride and HPMC E 15, Gelzan CM, Sodium alginate and Polyvinyl alcohol was recorded by using the Potassium bromide (KBr) disk technique. FTIR measurement over the range of 4000-500cm^{-}1 is performed with FTIR 8400S.

Thermal Analysis by Differential Scanning Calorimetric[10]

Thermal properties of pure drugs were analyzed by using differential scanning calorimeter (model name). 2mg of the sample was weighed and placed on the thematically sealed pan and empty pan was used for blank. Now keep both the pans on respective slots. Then samples were heated by maintaining a temperature range of 20 to 350°C at a ramped temperature of 10 °C / min, using nitrogen at a flow rate of 50 mL/min for maintaining the inert atmosphere.

Determination of absorption maximum (λ max) of the drug[11]

Verapamil Hydrochloride 10 µg/ml concentration was prepared by using phosphate buffer 6.8 and Methanol. The solution was scanned from 200-400 nm by UV Spectrometer and a spectrum was observed for absorption maxima.

METHOD

Solvent casting technique

The buccal film is prepared by solvent casting technique it is one of the simple methods than the other buccal film formulation methods and is the most widely accepted manufacturing process utilized for the production of films. Solvent casting technique has greater clarity and uniformity of thickness than extrusion method. In this method, the required quantity of polymer dissolved in distilled water. On the other hand, active pharmaceutical ingredients (API) and other excipients are dissolved in a suitable solvent system. Afterwards both the solutions are mixed and stirrer to form homogeneous mixture. This resultant solution is called as "casting solution". The casting solution is poured into casting mould and the solvent is evaporated. The method for preparation of Verapamil Hydrochloride of buccal film given below as follows.[5]

Preparation of Buccal Film

The buccal films of Verapamil Hydrochloride were prepared by solvent casting method. Initially, the polymers HPMC E 15, Gelzan CM, Sodium alginate and polyvinyl alcohol were weighed accurately and dissolved in 20 ml distilled water. The beaker containing polymers and water was kept aside for 15 min for swelling of polymers. Then the polymeric solution stirred for 30min on the magnetic stirrer to get the clear and bubbles-free solution. Plasticizer 10% w/w of polymeric concentration was added to the polymeric solution with continuous stirring. In another beaker Verapamil Hydrochloride were dissolved in a sufficient quantity of solvent. The solution was continuously stirred for 1 h. Then the drug-containing solution and polymeric solution with other excipients mixed evenly with the help of a magnetic stirrer to form the homogeneous casting solution. The whole solution poured into the pre-lubricated glass petri-plate and dried. The film was removed carefully after drying and cut into 2×2 cm^2. The film was stored in butter paper covered with aluminum foil and stored at room temperature.[12]

Table 01: Composition of buccal films.

F. Code	Drug (g)	Gelzan CM (mg)	Sodium alginate (mg)	Polyvinyl alcohol (mg)	HPMC E 15 (mg)	Propylene glycol (%)	Solvent (ml)
F 1	2	400	200	150	100	3	20
F 2	2	100	300	300	100	3	20
F 3	2	400	200	300	100	3	20
F 4	2	400	300	150	100	3	20
F 5	2	100	200	300	100	3	20
F 6	2	100	200	150	100	3	20
F 7	2	100	300	150	100	3	20
F 8	2	400	300	300	100	3	20

Evaluation of Verapamil Hydrochloride buccal films

Thickness, Weight variation, Folding endurance, Surface pH, Percentage moisture loss, Percentage moisture uptake, Swelling index.[13-19]

Drug Content[20]

Film of dimension 2×2 cm^2 was added in 100 ml of phosphate buffer pH 6.8, stirred continuously in bench top orbital shaker for 24h. Additionally, this solution was filtered, suitably dilution, and analysed at 278 nm using a UV spectrophotometer. The average and standard deviation of drug content for three films was taken as final reading.

***In vitro* drug release[21]**

For in vitro drug release study USP type I apparatus (Basket type) dissolution test apparatus Containing 400 ml of PBS of pH 6.8 as a dissolution medium at 37 ± 0.5°C temperature and speed at 50 rpm.1ml of sample solution was withdrawn at time intervals of 1h, 2h, 3h, 4h, 5h 6h, 7h and 8h equilibrated with a new or fresh dissolution medium to maintain sink state. Drug release was analyzed spectrophotometrically at a λ max of 278 nm using UV visible spectroscopy.

Kinetic Analysis of Dissolution Data[22]

The drug release kinetic studies were done by various mathematical models. The model that gives high 'r' value is considered as he best fit of the release data. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined.

Stability studies[23]

The buccal films were packaged in tightly sealed aluminium foils to prevent moisture from penetration into the package. The films underwent stability testing at ambient temperature and at an accelerated temperature of 40°C for 3 months. During the study period, the films were evaluated for physical appearance of drug content and *in-vitro* drug release to assess any changes in stability and performance.

RESULTS AND DISCUSSION

Thermal properties of pure drug Verapamil Hydrochloride and physical mixture of drug and excipients were evaluated by the DSC method. The endothermic peak of pure drug was retained in the Thermogram of physical mixture of drug and excipients and confirming that there was no interaction between drug and excipients. Determination of λ max Verapamil Hydrochloride at a concentration of 10 µg/ml solution was scanned by UV spectrophotometer in the range 200-400 nm and the observed absorbance maximum (λ max) was found to be 278 nm Evaluation of prepared buccal films Folding endurance Folding endurance remained constant at 350 for all batches, indicating good mechanical strength and flexibility. This suggests that the concentration of PVA was adequate to provide elasticity across all formulations. Thickness ranged between 0.17 and 0.22 mm, which is acceptable for buccal films (<0.3 mm). Higher PVA levels tended to increase thickness (F2, F8). Weight variation test Weight variation ranged from 0.14 mg (F6) to 0.35 mg (F8). High Gelzan CM (2%) and sodium alginate (1.5%) led to higher Weight variation (F4, F8), while lower polymer levels improved uniformity (F1, F6). Percentage Moisture Uptake Moisture uptake increased with higher Gelzan and alginate concentrations (F3, F8), while low polymer levels (F1, F7) showed minimal uptake. Percentage Moisture loss Moisture loss was highest for F7 (5.8%) at low polymer concentration, indicating films prone to drying, while F3 (3.1%) retained moisture due to high polymer load. Drug Content uniformity Drug content ranged between 85.0% (F4) and 91.37% (F7). Most formulations fell within pharmacopeia acceptance limits (85–115%). Slightly lower values in F3 and F4 suggest uneven distribution at higher polymer concentrations, while F1 and F7 showed the best uniformity with drug content above 90%.The percentage of drug content of the Buccal Films prepared by Solvent Casting Method respectively. The results were within the range and thus indicating uniformity of mixing. Surface pH Surface pH remained within 6.65–6.81 across all batches, close to the buccal cavity pH, indicating all films are non-irritant. Swelling index Swelling index ranged from 22.18% (F8) to 35.27% (F7). Higher swelling was observed in F7, F4, F6, and F3, due

to higher concentrations of Gelzan CM and sodium alginate, while F5 and F8 showed lower swelling because of lower polymer content. In-vitro drug release profile All formulations exhibited controlled drug release over 8 hours, starting gradually with no burst effect. F2, F3, and F8 showed relatively faster release, while F4, F5, and F6 had slower, more sustained profiles. F1 and F7 emerged as optimized batches, offering balanced and complete drug release (~91–92%) by 8 hours. The release kinetics followed the Korsmeyer–Peppas model, indicating non-Fickian diffusion controlled by both polymer swelling and drug diffusion. Stability studies over 90 days showed minimal changes in drug content and release, Confirming the films' good stability and suitability for long-term storage.

Differential scanning Calorimetry

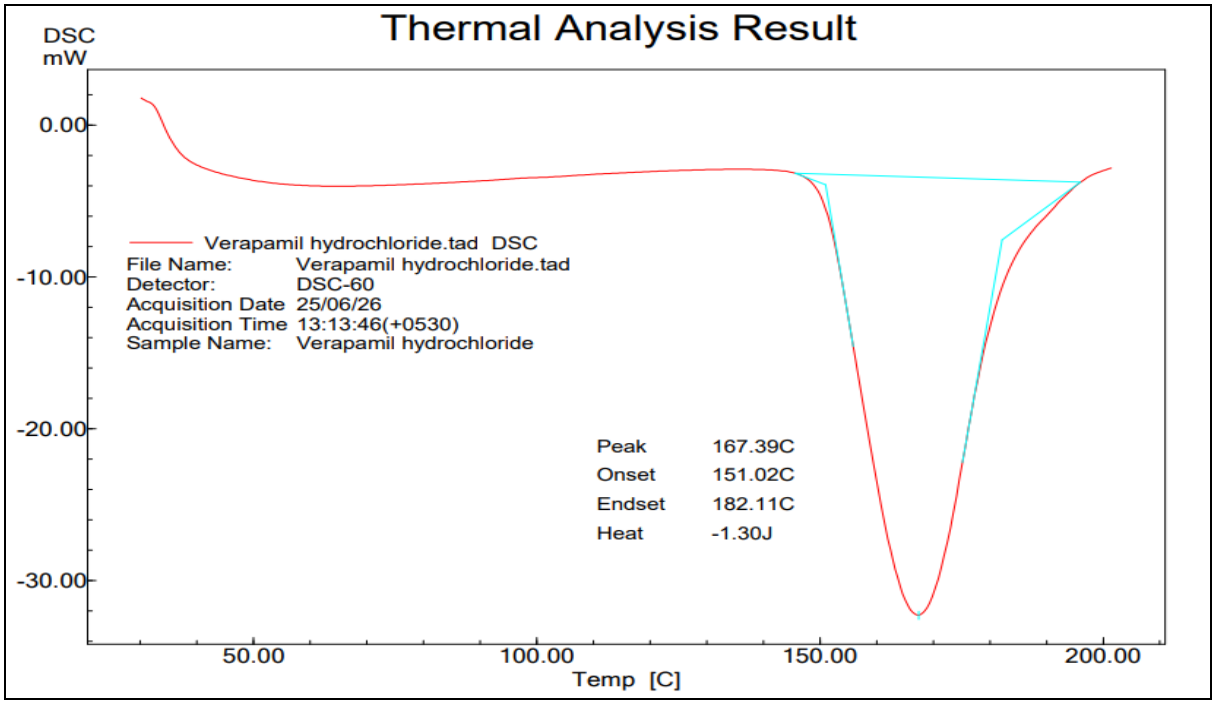

Figure 01: DSC graph of pure Verapamil Hydrochloride.

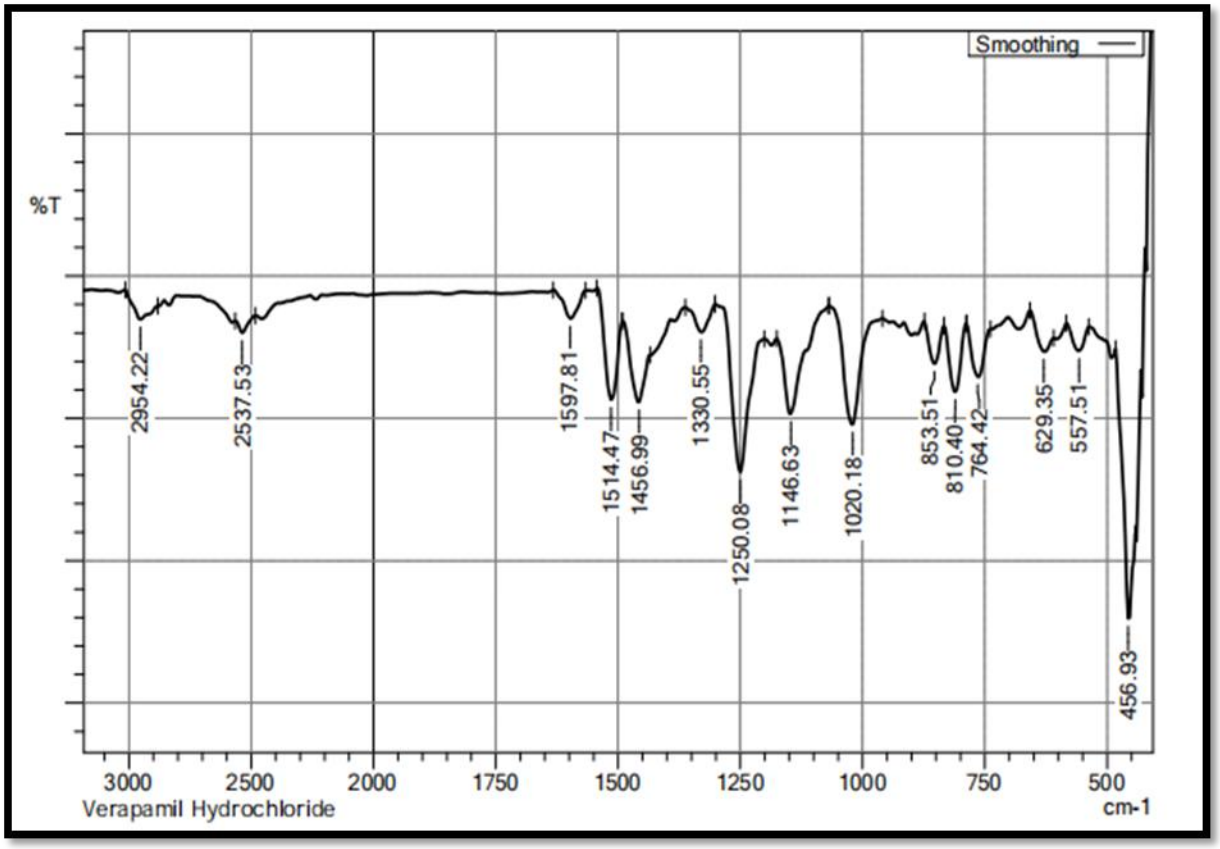

Figure 02: FT-IR Spectra of Verapamil Hydrochloride.

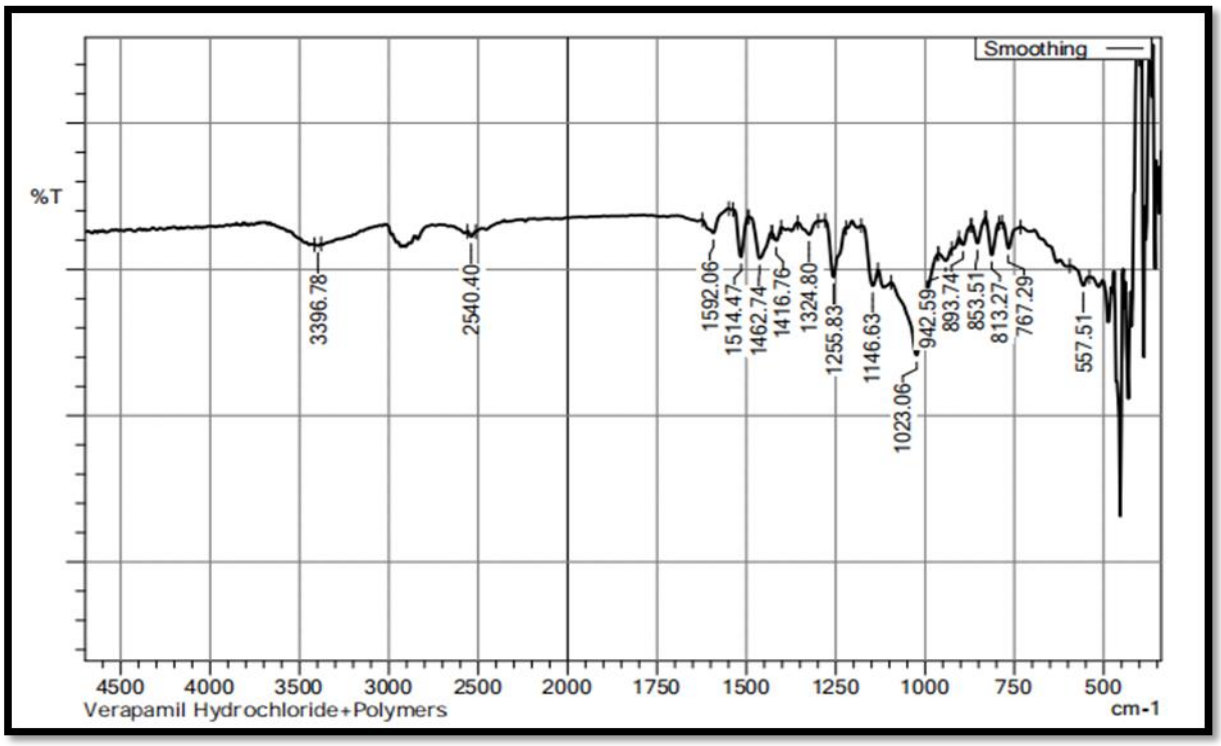

Figure 03: FT-IR Spectra of Verapamil Hydrochloride and physical mixture (Gelzan C M, Sodium alginate, polyvinyl alcohol, HPMC E 15).

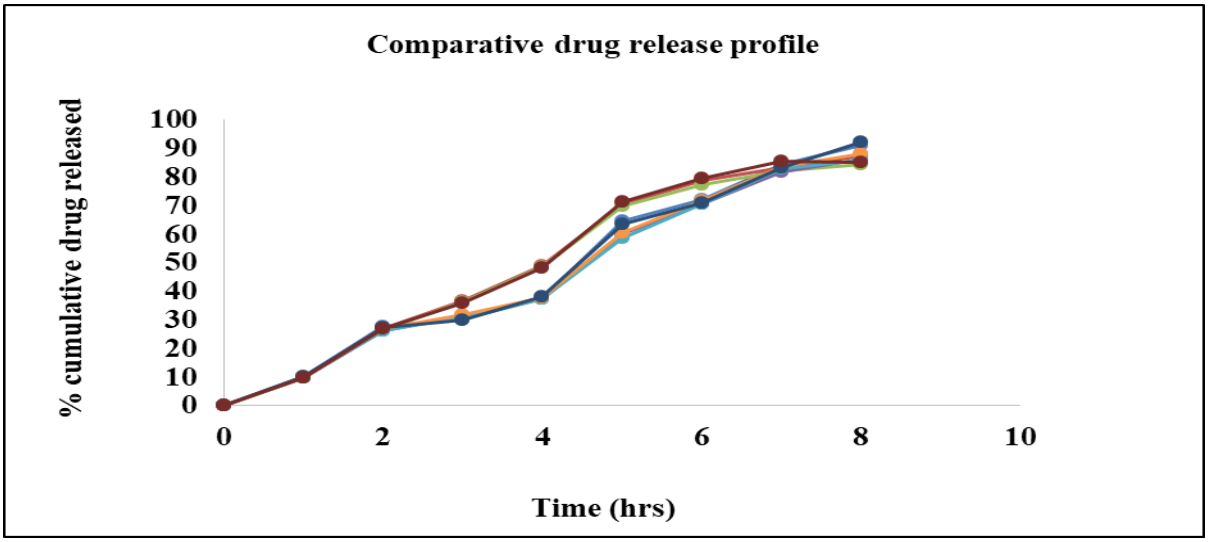

Figure 04:% Cumulative drug release of formulation F1-F8.

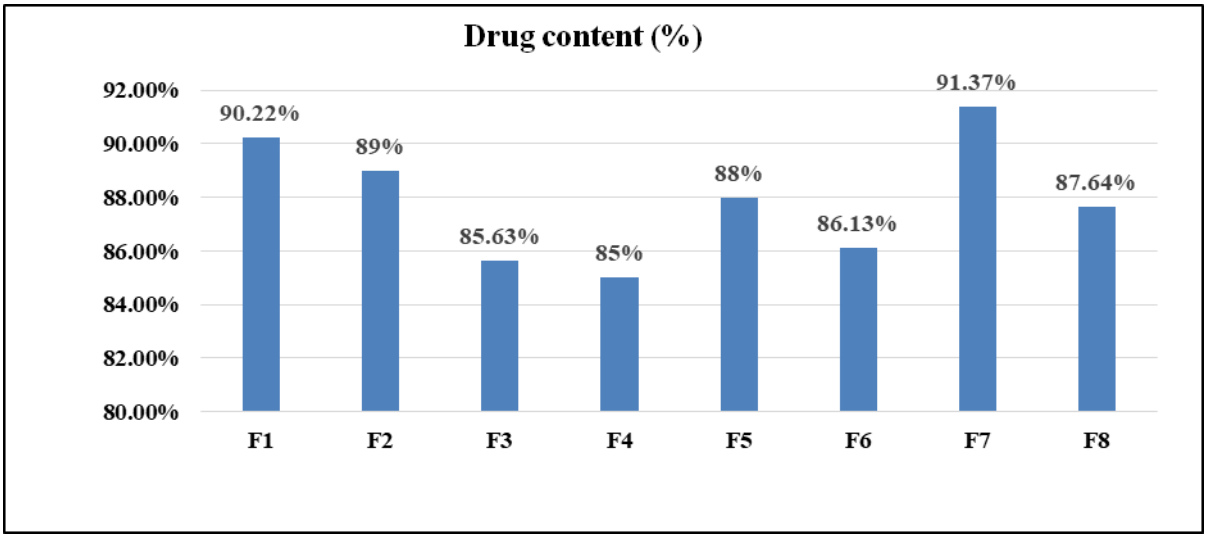

Figure 05: % Drug content.

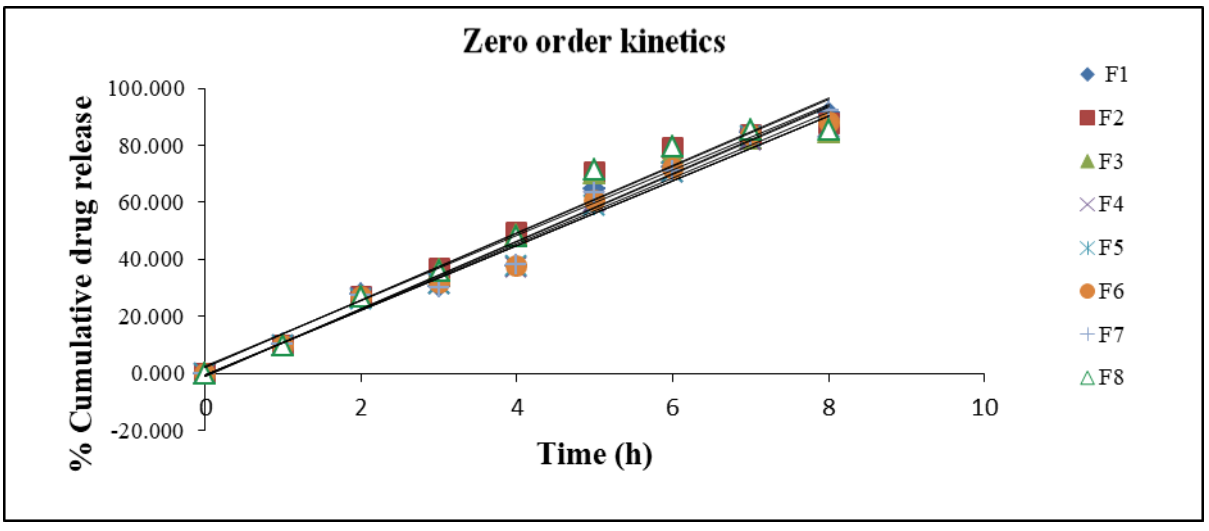

Figure 06: Graphical representation of Zero order kinetics.

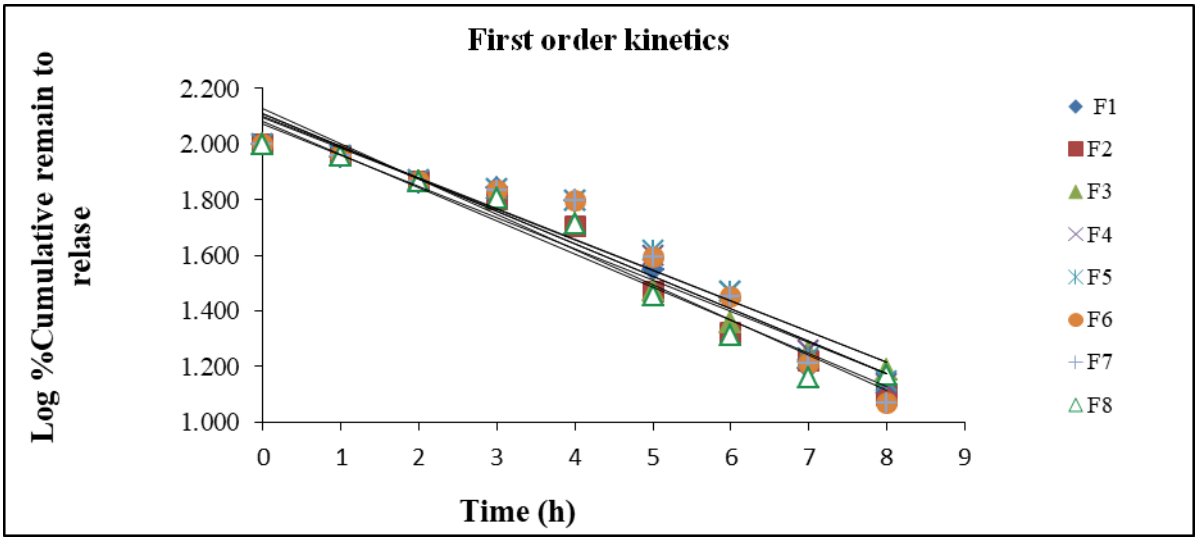

Figure 07: Graphical representation of First order kinetics.

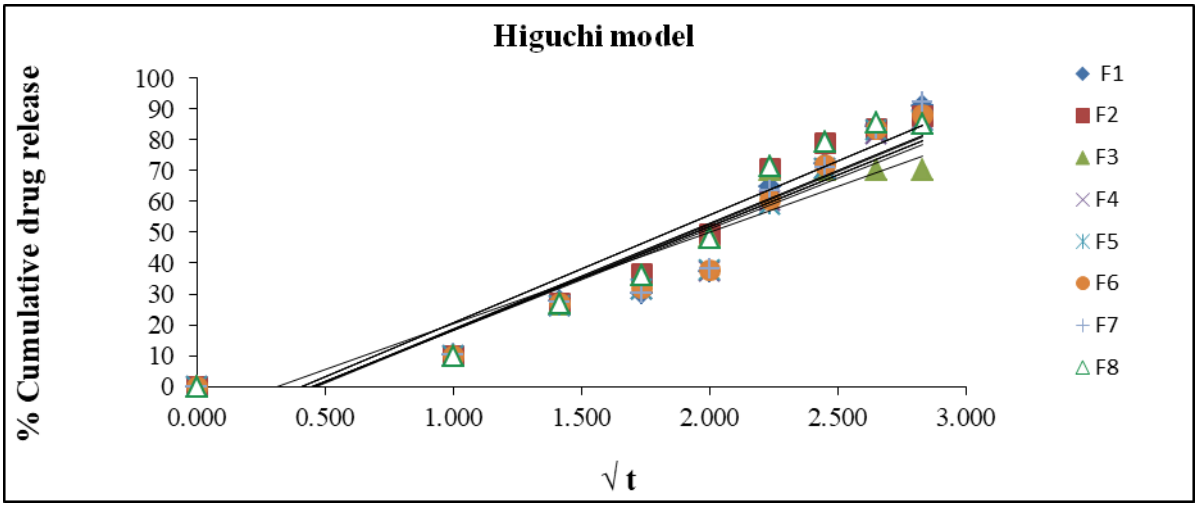

Figure 08: Graphical representation of Higuchi model.

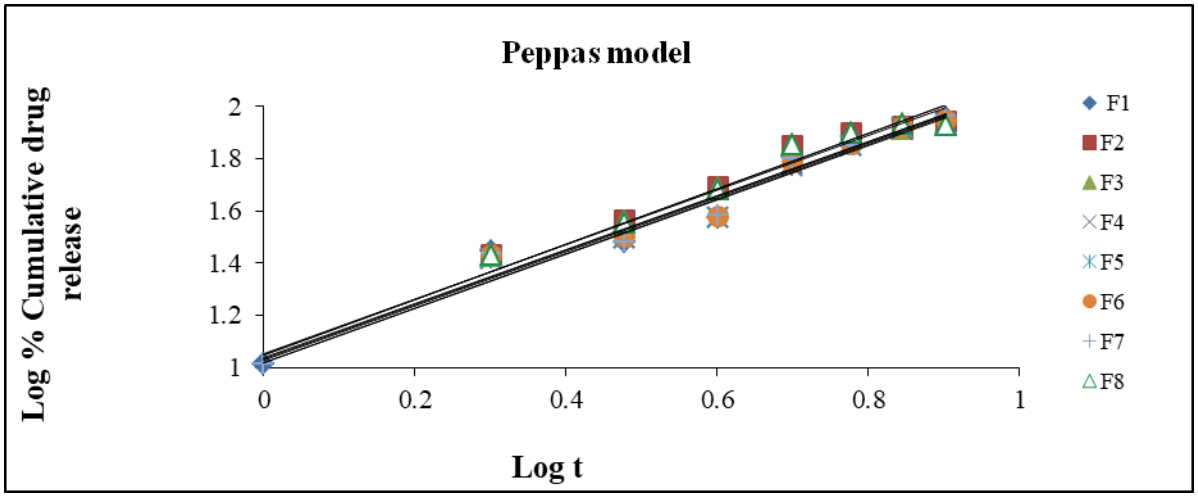

Figure 09: Graphical representation of Peppas model.

Table 02: Results of Intermediate stability study of optimized formulation.

Parameter	Duration in days		
	0	45	90
%DC	91.37	90.86	89.71
%CDR	92.18	91.84	90.89

CONCLUSION

Buccal drug delivery is an appealing alternative route for the administration of drugs that has low bioavailability because of extensive first-pass metabolism. The study successfully confirmed the identity and purity of Verapamil Hydrochloride through melting point analysis, UV spectroscopy, FT-IR, and DSC. Preformulation studies established the drug's compatibility with selected polymers, indicating no chemical interaction and good thermal stability. The developed buccal films demonstrated acceptable physical and mechanical properties, with variations influenced by polymer concentration. Drug release studies showed controlled and sustained release over 8 hours, with certain formulations achieving optimal performance in terms of release kinetics and mucoadhesion. Stability testing confirmed the formulations remained stable under normal conditions, though higher temperatures led to slight degradation, highlighting the importance of appropriate storage conditions.

ACKNOWLEDGEMENT

I express my sincere gratitude towards Dr. Parthiban S, Head of the department, Department of Pharmaceutics, and Bharathi College of Pharmacy who has been abundantly helpful in numerous ways for this research work. The authors also thank Bharathi College of Pharmacy, Mandya, Karnataka, India, for providing the required facilities to carry out this research work.

Funding

No funding was provided for this study.

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