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Formulation and evaluation of indapamide mucoadhesive buccal film

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Abstract
The present study focused on the formulation and evaluation of a mucoadhesive buccal film of Indapamide for the treatment of hypertension, aiming to enhance bioavailability and therapeutic efficacy while reducing first-pass metabolism. Indapamide, a thiazide-like diuretic, undergoes extensive hepatic metabolism when taken orally. To overcome this limitation, mucoadhesive buccal films were developed using the solvent casting method, incorporating sodium carboxymethyl cellulose (Na-CMC) and hydroxypropyl methylcellulose (HPMC E15) as polymers, with propylene glycol serving as both a plasticizer and permeation enhancer. Six formulations (F_1-F_6) were prepared and evaluated for various physicochemical parameters, including thickness, folding endurance, surface pH, swelling ratio, drug content uniformity, *in vitro* disintegration time, and dissolution profile. Among them, formulation F_6 demonstrated optimal characteristics, exhibiting uniform thickness (0.151 mm), average weight (103 mg), folding endurance (243), surface pH (6.72), and swelling ratio (24.5%). It also showed a high drug content (92.17%) and rapid disintegration (9.25 min), achieving a maximum drug release of 91.4% within 60 minutes. FTIR analysis confirmed the absence of chemical interactions between the drug and polymers, indicating compatibility and stability. Kinetic modelling revealed that drug release followed the Higuchi model ($R^2 = 0.9822$), suggesting a diffusion-controlled mechanism. Stability studies over 60 days indicated negligible changes in film properties, confirming the formulation's stability. Overall, the optimized Indapamide mucoadhesive buccal film (F_6) proved to be a stable, effective, and patient-compliant dosage form, offering a promising alternative to conventional oral therapy for hypertension by enhancing bioavailability and therapeutic performance.

Keywords: Indapamide, mucoadhesive buccal film, solvent casting method, bioavailability, drug release kinetics, hypertension

Introduction
The oral route is the most commonly preferred method for drug administration. Among the oral routes, the buccal mucosal route offers several advantages. It allows direct entry of the drug into the systemic circulation via the jugular vein, thereby avoiding first-pass hepatic metabolism and improving bioavailability. Drugs with low bioavailability, short half-lives, or those that undergo extensive first-pass metabolism are ideal candidates for this route. Several dosage forms have been developed for buccal delivery, with buccal films being one of the most effective options [1]. A buccal film is a dosage form that dissolves within the buccal mucosa or mouth, releasing the drug to achieve either local or systemic therapeutic effects. It utilizes water-soluble polymers, also known as hydrocolloid bioadhesive polymers, which allow the film to stick to the mucosal surface, absorb moisture, and gradually dissolve in the oral cavity. These thin film strips are usually intended for oral use, where the user places them on or beneath the tongue. As the strip dissolves, the medication is absorbed into the bloodstream either through the buccal or sublingual route [2, 3].
Mucoadhesive buccal films offer significant therapeutic benefits, particularly for special patient groups such as paediatric and geriatric populations, where dysphagia and swallowing difficulties are common. In children, these difficulties are often linked to conditions such as respiratory, cardiac, gastrointestinal, and neurological disorders, as well as congenital abnormalities, maternal or perinatal complications, iatrogenic effects, and caustic injuries [4, 5]. Swallowing issues in this group are often part of the natural developmental process, necessitating the use of alternative dosage forms or aids [6].

Indapamide, a thiazide-like diuretic, is widely prescribed for the treatment of hypertension and oedema associated with congestive heart failure. Although it's chemically a sulfonamide, its action is similar to thiazide diuretics. It works by helping the kidneys remove excess salt and water from the body, which lowers blood pressure [7]. In the present study, mucoadhesive buccal films of indapamide were formulated using hydroxypropyl methylcellulose (HPMC) and carboxymethyl cellulose (CMC) through the solvent casting technique, aiming to enhance bioavailability and therapeutic efficacy while reducing the adverse effects linked to conventional oral administration [8].

Materials and Methods

Materials

Indapamide was kindly provided as a gift sample by Kausikh Therapeutics Pvt. Ltd., Chennai. Hydroxypropyl methylcellulose (HPMC E15) and sodium carboxymethyl cellulose were procured from S.D. Fine Chemicals Ltd. All other reagents used were of analytical grade, and the water employed in the study was double distilled.

Methods

Formulation of Indapamide Mucoadhesive buccal films

Indapamide-containing films were formulated using the solvent casting technique. Various formulations were prepared employing sodium CMC as a mucoadhesive and release-retarding polymer, while HPMC E15 served as both a film-forming and release-retarding agent. Propylene glycol was incorporated as a plasticizer. The required quantities of polymers were dispersed in water, and the accurately weighed drug was added to the polymeric solution after levigating with propylene glycol, which functioned as both a plasticizer and a permeation enhancer. The resulting drug-polymer mixture was sonicated in a bath sonicator to eliminate air bubbles. The plasticized polymeric solution was then poured into Petri dishes and dried in a vacuum oven at 50°C for 24 hours. The dried films were cut into 2 cm × 2 cm squares, each containing 1.5 mg of drug, and subsequently wrapped in aluminium foil, stored in a desiccator, and used for further evaluation [9]. The various formulations of mucoadhesive films are presented in Table 1.

Table 1: Composition of Mucoadhesive buccal film of Indapamide (F_1-F_6)

Ingredients	Formulation					
	F_1	F_2	F_3	F_4	F_5	F_6
Indapamide (mg)	16.5	16.5	16.5	16.5	16.5	16.5
Na - CMC (mg)	100	*	150	*	200	*
HPMC E15 (mg)	*	100	*	150	*	200
Carbopol 934 (mg)	40	40	40	40	40	40
Polyvinyl alcohol (mg)	600	600	600	600	600	600
Propylene Glycol (ml)	0.2	0.2	0.2	0.2	0.2	0.2
Glycerine (ml)	0.1	0.1	0.1	0.1	0.1	0.1
Sucrose (mg)	q. s	q. s	q. s	q. s	q. s	q. s
Vanillin (mg)	q. s	q. s	q. s	q. s	q. s	q. s

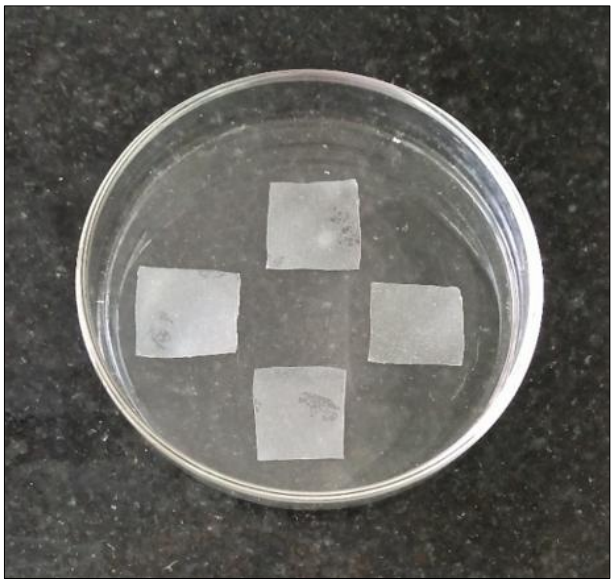

Fig 1: Prepared Mucoadhesive Buccal Films

Evaluation of Buccal Films

Surface Morphology: The surface characteristics of the optimized formulation were analyzed through Scanning Electron Microscopy (SEM).

Weigh Uniformity of Films

Mucoadhesive buccal films were weighed using an analytical balance, and the average weight was determined for each formulation. To meet acceptance criteria, no more than two films should deviate by ±7.5% from the average weight, and none should vary by more than ±15%. Accordingly, five individual films of "Indapamide" buccal formulation were cut from different areas of the cast film, weighed separately, and the mean weight was calculated [10, 11].

Film thickness: Film thickness was determined using a vernier micrometre by taking measurements at five different points the centre and four corners and calculating the mean value. Evaluating thickness uniformity is vital, as it has a direct impact on the precision of the drug dose distributed throughout the film [12].

Folding Endurance

Folding endurance was assessed by continuously folding the film at the same point until it broke. The total number of folds the film could endure before tearing was noted as its folding endurance value [13].

Drug content uniformity

A 2×2 cm^2 film sample was transferred into a 100 ml volumetric flask containing phosphate buffer of pH 6.8 and left to dissolve for 24 hours. From this stock solution, suitable dilutions were prepared with the same buffer to achieve a final concentration of 10 µg/ml. The absorbance of the prepared solution was then determined at 241 nm using a UV spectrophotometer [14, 15].

Surface pH

The pH of the surface film was investigated to determine the probable side effect, since that incompatible alkaline or acidic pH may irritate the mucosa of the mouth. The test film was placed in a test tube, moistened with 1.0 ml of distilled water, and allowed to stand for 30 seconds. The electrode of a pH meter was then gently placed in contact with the film surface, and the pH was recorded after allowing it to equilibrate for 1 minute. The average of three readings was calculated for each formulation, along with the standard deviation. The surface pH of all formulations was found to be within the acceptable range of 6 to 7 [16, 17].

Swelling ratio [18]

The initial weight of the 2×2 cm² film (W1) was recorded, and its swelling behaviour was evaluated by immersing the film in phosphate buffer saline (PBS, pH 6.8) maintained at 37°C. At predetermined time intervals of 5 minutes, the films were removed, and excess surface fluid was carefully blotted with filter paper until the films began to degrade. The swollen films were then weighed (W2), and the swelling ratio was calculated using the following equation.

$$S(\%) = \frac{w1 - w2}{w1} \times 100$$

***In vitro* disintegration test [19, 20]**

Disintegration time refers to the duration required for an oral film to begin breaking apart upon contact with water or saliva. The test was carried out using a disintegration test apparatus. A 2-square-inch film was placed in the basket, which was raised and lowered at a frequency of 30 cycles per minute. The test medium consisted of 900 ml of phosphate buffer (pH 6.0), maintained at a temperature of 37°C.

***In vitro* Drug Release Study**

The dissolution study was performed using a USP Type I (basket) apparatus containing 900 ml of phosphate buffer (pH 6.8) as the dissolution medium, maintained at 37 ± 0.5°C. The medium was stirred at 50 rpm for 30 minutes. Samples were withdrawn at 5-minute intervals up to 60 minutes, with an equal volume of fresh buffer replaced each time to maintain sink conditions. A 10 ml aliquot of each sample was diluted to 25 ml with buffer solution and analyzed using a UV spectrophotometer at a wavelength of 241 nm [21].

***In-vitro* drug release kinetics**

The release order and mechanism of drug release from indapamide films were evaluated using in-vitro diffusion data. The results were analyzed by fitting the data into various kinetic models, including Zero-order, First-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models, using the corresponding equations to determine the release behaviour and mechanism [22].

Results and Discussion

The present study focuses on the formulation of mucoadhesive buccal films of indapamide, a drug used in the management of hypertension. The objective was to identify the optimal combination of polymers and excipients for developing effective mucoadhesive buccal films. The films were prepared using the solvent casting technique, employing different concentrations of HPMC E15 and sodium CMC as polymers. Propylene glycol was incorporated as a plasticizer to improve film flexibility. FTIR studies were conducted for indapamide, HPMC E15, sodium CMC, and their physical mixtures within the spectral range of 4000-400 cm^{-1}. The appearance of characteristic peaks for both the pure drug and the physical mixture confirmed the absence of any chemical interaction between the drug and excipients. All films were prepared under identical conditions to minimize processing variations and were subsequently evaluated for various physicochemical properties.

Evaluation of Buccal Films

Surface Morphology

The surface morphology of the mucoadhesive buccal films was examined using scanning electron microscopy (SEM). The prepared films exhibited a needle-like structure, as illustrated in the figure.

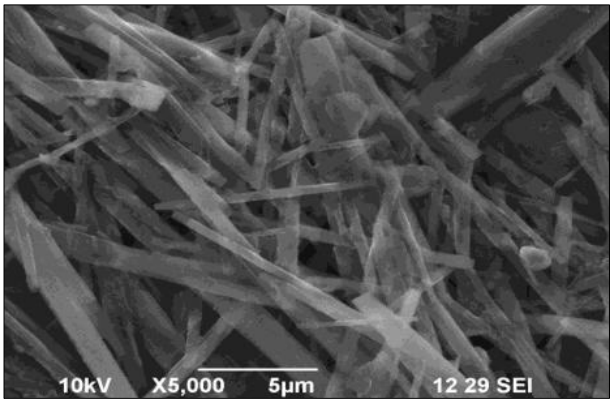

Fig 2: SEM Formulation of F_6 (5000x)

Weight Uniformity of Films

The average weight of formulations F_1 to F_6 ranged from 78 ± 0.53 mg to 105 ± 0.78 mg. The results indicated that an increase in polymer concentration led to a corresponding rise in the film's weight. As shown in the table, all films displayed uniformity in weight with no significant variations among the formulations. Weight variation is a crucial parameter, as any deviation can result in under or over-medication.

Film thickness

The thickness of all formulations (F_1-F_6) was measured using a digital micrometre. Thickness uniformity is essential to ensure consistent drug concentration throughout each film. All measurements were performed in triplicate, and the thickness values for formulations F_1 to F_6 ranged from 0.128 ± 0.02 mm to 0.153 ± 0.01 mm. The results, presented in the table, indicate that the films exhibited good uniformity.

Folding Endurance

The folding endurance of all formulations (F_1-F_6) was determined by repeatedly folding each film at the same point until it broke. The folding endurance values for F_1 to F_6 ranged from 187 to 247. This parameter was assessed to evaluate the films' resistance to rupture and their mechanical strength. An increase in folding endurance corresponded to enhanced mechanical strength. The results,

presented in the table, indicate that the films exhibited good flexibility.

Surface pH

The average of three readings was taken for each formulation, and the standard deviation was calculated. The surface pH of all formulations was within the range of 6 to 7. The surface pH, measured to assess its effect on the buccal mucosa, ranged from 6.24 ± 0.02 to 6.90 ± 0.03. These values indicate that the films had a surface pH close to that of human saliva.

Swelling Ratio

The swelling ratio of each film was evaluated by monitoring it until the film started to degrade. The observed swelling ratio ranged between 12.2% and 27.2%. Among all formulations, F_4 containing the highest concentration of HPMC E15 showed the maximum swelling ratio of 27.2% at 5 minutes.

***In vitro* Disintegration Test**

The disintegration time of all formulations F_1-F_6 was found by using USP disintegration apparatus. The disintegration time was found in the range of 5.15±0.11 to 9.47±0.61. Increment in the polymer concentration and viscosity could enhance the disintegration time. Disintegration time increased with higher amount of HPMC E15 and Na-CMC.

Drug Content Uniformity

The drug content reflects the uniform distribution and accuracy of the drug concentration across different regions of each film. The percentage of drug content was found to range from 73.35 ± 0.58% to 92.17 ± 0.63%. Among all formulations, F_6 exhibited the highest drug content (92.17%) and was therefore considered the most optimized formulation.

Table 2: Evaluation Parameters of Indapamide Mucoadhesive Buccal Films

Batch	Weight uniformity (mg) ±SD	Thickness (mm) ±SD	Folding endurance ±SD	Surface pH±SD	Swelling index	Disintegration Time(min) ±SD	Drug content (%) ± SD
F_1	78±0.53	0.128±0.02	187±8.08	6.87±0.03	12.2%	7.34±0.14	73.35±0.58
F_2	85±0.75	0.137±0.03	195±7	6.58±0.03	15.4%	8.15±0.24	85.16±1.84
F_3	105±0.78	0.153±0.01	247±3	6.90±0.03	22.4%	9.47±0.61	91.18±1.14
F_4	97±0.91	0.141±0.03	224±2	6.24±0.02	27.2%	6.47±0.56	79.34±1.61
F_5	81±0.61	0.133±0.01	191±2.5	6.50±0.02	21.8%	5.15±0.11	86.13±0.81
F_6	103±0.84	0.151±0.02	243±2.5	6.72±0.03	24.5%	9.25±0.09	92.17±0.63

***In vitro* Drug Release Study**

The *in-vitro* drug release study was performed to assess the release profile of indapamide from different mucoadhesive buccal film formulations over a period of one hour. Formulations F_2 and F_4, which contained higher concentrations of HPMC, exhibited a slower drug release rate compared to the other formulations. In contrast, formulations F_1 and F_5 demonstrated a burst release of indapamide. The burst release in mucoadhesive buccal films is influenced by the swelling ratio, with lower swelling ratios leading to a more pronounced burst effect. An increased concentration of HPMC resulted in greater film thickness, thereby reducing the release rate. Among all formulations, F_6 showed the highest drug release (95.37 ± 1.63%). The in-vitro drug release data for all formulations are presented in Table 3 and Figure 3.

Table 3: Comparison of *in-vitro* drug release study of different formulations (F_1- F_6)

Time (Minutes)	Cumulative percentage release of film (%)					
	F_1	F_2	F_3	F_4	F_5	F_6
0	0	0	0	0	0	0
5	26.4	29.2	27.8	26.9	25.1	28.5
10	32.4	33.3	30.6	31.2	27.3	34.3
15	37.3	37.3	35.4	35.9	29.5	39.06
20	40.9	41.5	40.6	37.3	31.4	44.5
25	47.6	44.9	45.7	41.4	35.1	50.6
30	54.2	50.5	51.8	45.6	38.1	56.2
35	58.2	55.7	54.6	49.4	45.9	62.2
40	66.03	61	60.7	52.4	50.6	68.1
45	73.5	67.5	65.9	57.4	55	74.3
50	79.2	74.6	69.3	62.9	61.1	79.8
55	82.7	79.9	73.4	67.7	65.5	85.3
60	87.3	84.7	76.6	72.4	68.6	91.3

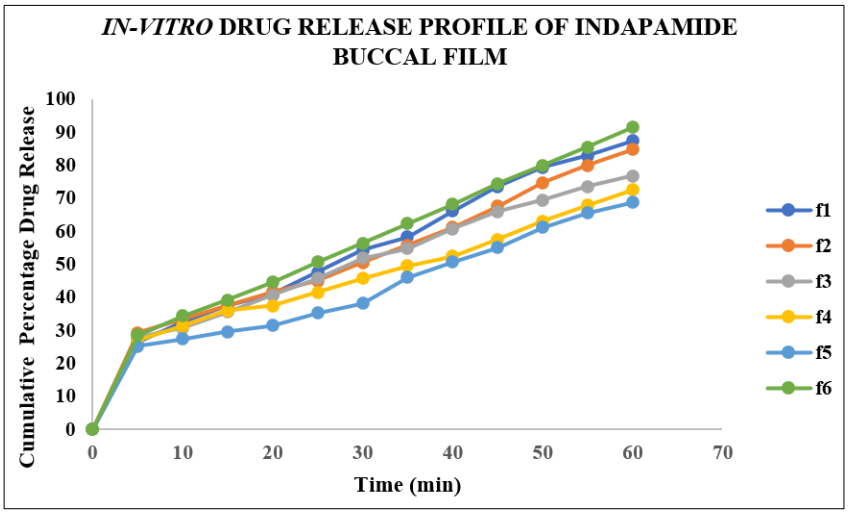

Fig 3: Comparison of *in-vitro* drug release study of different formulations (F_1 - F_6)

Drug Release Kinetics

To analyze the in-vitro drug release data, various kinetic models including zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell were applied to describe the release mechanism. Among these models, the Higuchi model showed the highest coefficient of determination (R^2 = 0.9822), suggesting that the drug release from the film matrix is primarily governed by a diffusion-controlled mechanism. The Korsmeyer-Peppas model showed an R^2 value of 0.9582 with an n value of 0.482, suggesting that the release mechanism follows anomalous (non-Fickian) diffusion, where both diffusion and polymer chain relaxation (erosion) contribute to the overall release process. Furthermore, the Hixson-Crowell model (R^2 = 0.9707) and the Zero-order model (R^2 = 0.9551) also demonstrated good correlation, implying that surface area changes and film erosion may have a minor influence on the release kinetics. The results confirm that the Indapamide buccal film provides a controlled release profile, mainly governed by diffusion through the polymeric matrix, ensuring prolonged therapeutic action and improved bioavailability.

Conclusion

To enhance bioavailability, minimize side effects, and improve patient compliance, mucoadhesive buccal films were developed using suitable polymers. FTIR spectroscopic studies were performed to evaluate drug-polymer compatibility, and the results confirmed the absence of any chemical interaction, indicating that the selected polymers were compatible with indapamide. The mucoadhesive buccal films of indapamide were prepared by the solvent casting method using two polymers Na-CMC and HPMC E15 in varying ratios. The prepared films were evaluated for several quality control parameters, including thickness, weight variation, folding endurance, SEM analysis, surface pH, disintegration time, drug content, in-vitro dissolution, and kinetic studies.

The average weight of formulations F_1 to F_6 ranged from 78 ± 0.53 mg to 105 ± 0.78 mg, indicating uniformity without significant variation. The thickness was found to be between 0.128 ± 0.02 mm and 0.153 ± 0.01 mm, showing good uniformity and compliance with the acceptable limits. Folding endurance values ranged from 187 to 247, confirming adequate mechanical strength and flexibility. SEM analysis of the optimized formulation (F_6) revealed a needle-like surface morphology. The surface pH values were within the acceptable range (6-7), ensuring compatibility with the buccal environment. The swelling ratio of the films ranged from 12.2% to 27.2%, while the disintegration time varied between 5.15 and 9.47 minutes. The drug content uniformity of all formulations was within 73.35-92.17%, complying with pharmacopeial standards. Among the six formulations, F_6 was identified as the optimized formulation due to its superior drug release characteristics, achieving a maximum dissolution of 92.14% within 60 minutes.

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