Formulation and Evaluation of Mucoadhesive buccal Film of Azilsartan Medoxomil By solvent casting method

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Abstract: The drug azalisartan medoxomil is used to treat hypertension.The high first-pass metabolism in the liver results in limited bioavailability. To increase patient compliance, therapeutic efficacy, and bioavailability, the current effort aims to develop mucoadhesive buccal films of Azilsartan medoxomil. Using the solvent casting process, seven formulations of a mucoadhesive drug delivery system containing azilsartan medoxomil have been developed as buccal films for this study.Mucoadhesive polymers included hydroxyl propyl methylcellulose E-15, hydroxyl propyl methylcellulose E-5, polyethylene glycol 400, polyethylene glycol 200, and methanol. The weight, thickness, surface pH, swelling index, drug content uniformity mucoadhesive time, folding endurance in vitro drug release studies, scanning electron microscopy, and stability study of the prepared films were assessed. In permeation experiments, films showed regulated release over more than 10 hours. The formulation F6, which contained 20 mg of azilsartan medoxomil in 2% w/v hydroxyl propyl methylcellulose and w/v polyethylene glycol, was found to exhibit good swelling, a mucoadhesive time, and promising controlled drug release. As a result, it was determined that this formulation could be chosen for the advancement of buccal films with successful therapeutic applications.

Keywords: Buccalfilm, first-pass metabolism,solvent casting method, Azilsartan Medoxomil.

INTRODUCTION

There are several ways to administer a drug into the body, including sublingual, parenteral, transdermal, and oral (Gorle *et al*.,2015). Among the several drug administration methods, the

buccal route is a good substitute (Balaji *et al*., 2014).The administration of drugs through the mucosal membranes lining the cheeks is known as buccal delivery and is a suitable route for the systemic delivery of drugs with relative permeability with a rich blood supply.

It is ideally suited for administering retentive dose forms due to its great accessibility, expanse of smooth muscle, and generally immobile mucosa. The internal jugular vein, brachiocephalic vein, and deep lingual or face vein all bypass medications in order to absorb them into the systemic circulation (Mahajan *et al*., 2011). Of each of the drug delivery options, oral administration is perhaps the most favoured by both patients and physicians since it circumvents hepatic first-pass metabolism and results in high bioavailability. Certain drugs have inherent problems that can be resolved by changing their composition. Alternative drug delivery pathways are required for the systemic drug delivery system (Gorle *et al*.,2015).

The term "film" refers to a dosage form that uses a water-dispersing polymer to facilitate systemic drug administration by enabling the dosage form to rapidly hydrate, adhere, and dissolve when put on the tongue or in the oral cavity. The primary characteristic of the buccal film is its wide surface area, which facilitates rapid wetting and increases drug absorption compared to tablets. Due to their implicit adhesion to the buccal mucosa and ability to be designed to demonstrate both local and systemic activity, buccal films are the most recently created dosage form for buccal administration (Tajelsir and Khanum, 2016). Buccal films have a high bioavailability because they avoid the drug's first-pass hepatic metabolism and possess direct access through the internal jugular vein to the systemic circulation. These dose forms also offer better patient compliance, are pharmacoeconomic, and may be administered by the patient. Therefore, it is suggested that we use buccal films to reduce the hepatic first-pass metabolism of poor bioavailability antihypertensive medications (Madhavi *et al*., 2013).

Mucoadhesive buccal films are thin, flexible sheets that stick to the buccal mucosa (the inside lining of the cheek) when applied. They are usually made of polymers with adhesive qualities. Through the buccal mucosa, these films are utilised as a drug delivery mechanism to provide drugs either locally or systemically (Sravanthi et al., 20). These films' mucoadhesive qualities aid in their retention, enabling extended contact with the mucosal surface and regulated drug release (Verma *et al*., 2014, Dahiya *et al*., 2009, Dargad *et al*., 2016, Jones *et al*., 2011).

MATERIALS AND METHODS

Materials

The investigation was done on several film-forming polymers, either separately or in combination. We purchased the medication azilsartan medoxomil from USV Pvt. Ltd. in Mumbai, India. and polymer from Sigma-Aldrich Chemical Pvt. Ltd., Powai, Mumbai, such as HPMC E15 and HPMC E5. Chemical chemicals from Glenmark Pharmaceutical Ltd. in Satpur, Nashik, such as PEG-400 and PEG-200. and menthol was brought to Mumbai, India's Rankem Chemical. All compounds were utilised exactly as received, requiring no additional purification or modification. They were all of the pharmaceutical or analytical quality.

Methods

The following procedures are included in the solvent-casting process of creating azilsartan medoxomil buccal films:

• Material Selection: Pick polymers that are appropriate for medication administration and the creation of buccal films. Polyvinyl alcohol (PVA), polyethylene glycol (PEG), and hydroxypropyl methylcellulose (HPMC) are examples of common polymers. Azilsartan medoxomil should also be used as the active pharmaceutical ingredient (API).

• Selecting a Solvent: Choose a solvent or solvent combination that can effectively dissolve the polymer(s) and the API. Water, ethanol, methanol, and isopropyl alcohol are frequently used solvents.

• Preparing the Polymer-Drug Solution: To create a homogenous solution, dissolve the selected polymer(s) and azilsartan medoxomil API in the specified solvent(s). To get the appropriate drug loading in the finished film, the API concentration needs to be closely regulated.
• Additives: Add any excipients or additives to the solution, such as surfactants to increase medication solubility and release or plasticizers (glycerin, propylene glycol) to improve film flexibility and permeability.
• Casting Procedure: Using an appropriate tool, such as a casting knife or spreader, pour or distribute the polymer-drug solution onto a spotless, smooth casting surface, like a glass plate. By varying the solution volume and casting speed, you may control the film's thickness. • Solvent Evaporation: To prevent quick drying and guarantee homogeneous film formation, allow the solvent to progressively evaporate from the film-forming solution under regulated circumstances, such as room temperature or increased temperature. Several hours or even nights may be needed for this process, depending on the solvent and film thickness.

• Film Drying and Solidification: The polymer-drug solution will solidify and create a flexible, transparent buccal film when the solvent has entirely evaporated.
• Film Cutting and Packaging: Using a cutting instrument or punch, cut the solidified film into discrete dose units of the required size and form. Make sure the buccal films are properly protected from light and moisture by placing them in an appropriate bag or container.
• Characterization and Quality Control: Conduct a range of tests and studies to assess the mechanical, chemical, and physical characteristics of the buccal films, such as their thickness, stability during storage, mucoadhesive strength, and uniform drug content.
•Clinical Evaluation:Carry out in vitro and in vivo investigations, such as pharmacokinetic research and bioavailability tests in animal models or human subjects, to evaluate the effectiveness, safety, and performance of the azilsartan medoxomil buccal films for buccal drug administration. For the preparation of azilsartan medoxomil buccal films with regulated drug release characteristics for the management of hypertension and other cardiovascular disorders, the solvent casting process offers an all-around flexible and scalable technique.
Solvent Casting Method:
The oral rapid dissolving films are made by dissolving the plasticizer, saliva-stimulating agent, and strip-forming chemicals in distilled water. The mixture is then continuously agitated for four hours using a magnetic stirrer and left for an hour to eliminate any trapped air bubbles. In the meantime, the remaining water-soluble excipients—sugar, disintegrant, saliva-stimulating agent, taste, and medication—are dissolved for 45 minutes while being continuously stirred in a different container.

After that, leave the mixture still for an hour to allow the foams to subside. The final mixture is dried to create a film before being cast onto an appropriate platform. The film is gently removed when it has, ideally, been air-dried or baked dry (Dahiya *et al*., 2009).

Formulation

Formulation of buccal film (Solvent Casting Method)

Azilsartan Medoxomil buccal patches were made using a solvent-casting method. The drug is dissolved using a magnetic stirrer in 10 millilitres of methanol. Distilled water is used to dissolve the polymer and other excipients. Using a magnetic stirrer, the drug solution is introduced to the polymer solution and combined.

A Petri plate was filled with the entire solution. Over the Petri plate, an inverted funnel was used to prevent abrupt evaporation. The drug polymeric solution on the plate was permitted to dry for 12 hours at room temperature. The film is put in the desiccator when it has dried. Solvent casting is the procedure used to make the Mucoadhesive buccal film of azilsartan medoxomil. Azilsartan medoxomil buccal film is made in seven distinct batches by adjusting the polymer ratio while maintaining a consistent medication concentration. 30 millilitres of distilled water dissolves other excipients and polymers, whereas 10 millilitres of methanol solubilizes azilsartan medoxomil. After adding the drug solution to the polymer solution, mix continuously until the solution turns clear. A Petri plate was filled with the entire solution. Over the Petri plate, an inverted funnel was used to prevent abrupt evaporation. The drug polymeric solution on the plate was permitted to dry for 12 hours at room temperature. The film is carefully removed and put in the desiccator when it has dried.

Figure 1: Buccal Film

Table 1: Composition of Mucoadhesive Buccal Film

Sr.no	Ingredient	Formulation Batch						
		F1	F2	F3	F4	F5	F6	F7
1	AzilsartanMedoxomil	80mg	80mg	80mg	80mg	80mg	80mg	80mg

2	HPMC E15	-	-	150	170	180	200	250
3	HMPC E5	100	150	-	-	-	-	-
4	PEG400	1ml	1ml	1ml	1ml	1ml	1ml	1ml
5	Water	30ml	30ml	30ml	30ml	30ml	30ml	30ml
6	Ethanol	10ml	10ml	10ml	10ml	10ml	10ml	10ml

Polymer HPMC-E5-

Encapsulation of drug with polymer is not proper hence showing vary results in drug release. Polymer HPMC-E 15 are used in different concentrations and various batches are prepared.

Evaluation of buccal film

The size distribution and particle size

The Nano Creek 90 Plus molecule size analyzer (Brookhaven Instruments, USA) was used to ensure the size of the molecules. It is a powerful light-dissipating device that estimates the force of light dispersed by the particles in the example as a function of time, at a constant temperature of 25°C and a dissipating point of 90°. The molecular size analyzer Nano Stream 90 Plus provides a range of options. The most important is the guarantee of a normal width (Eff. Dia.) and a polydispersity percentage that are suitable for certain uses(Shekunov *et al*., 2007).

Zeta Potential

Azilsartan medoxomil buccal film's zeta capacity was ascertained using the Nano Stream 90 Plus Zeta Seizer (Brookhaven Instruments USA). Before the investigation, the cases were frequently made weaker with dissolvable. A zeta potential of around 30 mV is expected for a properly stable buccal film, and this potential is largely balanced by electrostatic repellency. To counteract steric and electrostatic adjustment in the buccal film framework, a zeta potential of around ±20 mV is adequate(Yilmaz and Borchert, 2005; Nakarani et al., 2010).

Physical characteristics and texture of the surface

Surface and the actual look of patches organised using various HPMC groupings.

Weight consistency

Three distinct randomly chosen patches from each formulation were used to evaluate weight. Patches were put directly onto a computerised balance.

Density

Three distinct patches from each formulation were randomly chosen to assess patch thickness. Using a screw gauge, the patch thickness was tested at five distinct, randomly chosen locations.

pH of the surface

For this reason, a connected glass terminal was used. The patches were permitted to swell by being in connection with 1 millilitre of refined water (pH 6.80.1) for two hours at room temperature. The pH was measured at the point at which the patches made terminal contact with the fix's surface and let it acclimatise for one minute. The oral pit's surface pH was not fully stabilised to assess the possibility of any secondary effects. Since an acidic or soluble pH will irritate the buccal mucosa, efforts were taken to maintain the patches' surface pH close to neutral (Rajalakshmi *et al*., 2012).

SEM, or scanning electron microscopy

Azilsartan medoxomil pure powder was verified by direct powder affidavit on double-sided carbon tape as a thin movie, and photos were taken at different amplification levels using the bead dissipation technique, which confirmed SEM for the fluid of the selected detailing of the prepared nanosuspension (Kesisoglou and Mitra, 2012). With the use of a Vega/TESCAN filtering electron magnifying device that operated with an optional finder at different speeds, voltages, and levels of amplification, a bead of fluid was preserved on a double-sided carbon tape and dried at room temperature (Dolenc *et al*., 2010).

Folding endurance

One patch was folded repeatedly at the same location until it broke, or up to 200 times without breaking, to test a patch's folding durability.

Mucoadhesive time

After applying the patches onto freshly-shaved sheep buccal mucosa, three individuals were evaluated for the ex vivo mucoadhesion time. Using a cyanoacrylate stick, the newly acquired sheep buccal mucosa was adhered to the inside of the container, more than 2.5 cm from the base. Each fix was applied with mild pressure using the fingertip for 30 seconds, and one side was moistened with one drop of isotonic phosphate cushion pH 6.8. The measuring utensil was maintained at 37±1 °C and filled with 500 mL of isotonic phosphate cradle pH 6.8. After two minutes, the buccal pit environment was recreated with a 50 rpm blending rate, and the fixed grip was monitored for up to twelve hours. Muco-attachment time was defined as The duration of time required for the fix to come away from the sheep buccal mucosa.

Drug content

The fix was dissolved in 100 millilitres of an isotonic phosphate buffer (pH 6.8) and homogenised under intermittent shaking for eight hours to ascertain the homogeneity of the drug content. Subsequently, 20 millilitres of isotonic phosphate cushion pH 6.8 was used to weaken a 5-millilitre arrangement. The resulting mixture was then sieved using 0.45 µm Whatman channel paper. The drug composition is subject to change upon a valid weakening at the spectrophotometer. The analyses were presented in three different ways.

In-vitro dissolution study

Using the dispersed approach with the USP Apparatus II Paddle, in vitro dissolving research was conducted. The oars were configured to pivot at 50 revolutions per minute. The 900 ml phosphate support with a pH of 6.8 was used as a dissolving media, and the temperature was maintained at 37±20C. Tests that were precisely weighed and had an equivalent of 10 mg of Azilsartan were dispersed throughout the 900 ml dissolving media. Tests were then taken out of the dissolving media at different intervals of 0, 5, 15, 30, 45, 60, 90, 120, and 150 minutes, every 5 millilitres.

To maintain the sink state, the same volume of fresh medium was supplied to the dissolving vessel. The amount of drug fragmentation was determined using a UV spectrophotometer operating at 243 nm. The analysis of the comparatively large number of tests was completed in three stages.

Fourier transforms infrared spectroscopy

The goal of the FTIR analysis was to focus on all potential chemical interactions between the medication and the excipient. FTIR spectrometer-430 (Shimadzu 8400S, Japan) was used to direct the FTIR spectra of the dried improved Buccal film, the real mix, and pure Azilsartan.

Stability study

By placing the plan in a sealed, closed petri plate and exposing it to different temperatures for an extended period of time at room temperature (25±2°C) and lower temperatures (50±3°C), the stability study of advanced detailing was finished. Tests were conducted after two months to observe any changes in thickness, pH, and in vitro drug release.

RESULT AND DISCUSSION

Physical Appearance and Surface Texture

Surface texture and physical characteristics of patches made with varying HPMC concentrations.

Table 2: Buccal film's physical characteristics and surface texture

Formulationcode	Appearance	Surfacetexture
F1	White	Smooth
F2	White	Smooth
F3	Yellowishwhite	Smooth
F4	White	Smooth
F5	White	Smooth
F6	White	Smooth
F7	White	Smooth

Weight Uniformity

The uniformity of weight of the drug-loaded film was evaluated, and the findings are displayed in table: 9. It was discovered that all of the produced batches had very similar weights. The entire film's standard deviation fell between 126 and 142. The variation in the weight of the film was not reflected in the changes in the concentrations of plasticizers and polymers.

Table 3: Weight uniformity of buccal film

Formulationcode	Weight offilms (mg)
F1	129 ± 2
F2	136 ± 2
F3	133 ± 3
F4	142 ± 2
F5	131 ± 3
F6	136 ± 2
F7	140 ± 1

Thickness Uniformity

With the use of an electronic vernier calculator, the drug-loaded film thicknesses were determined. The table displays the mean values.

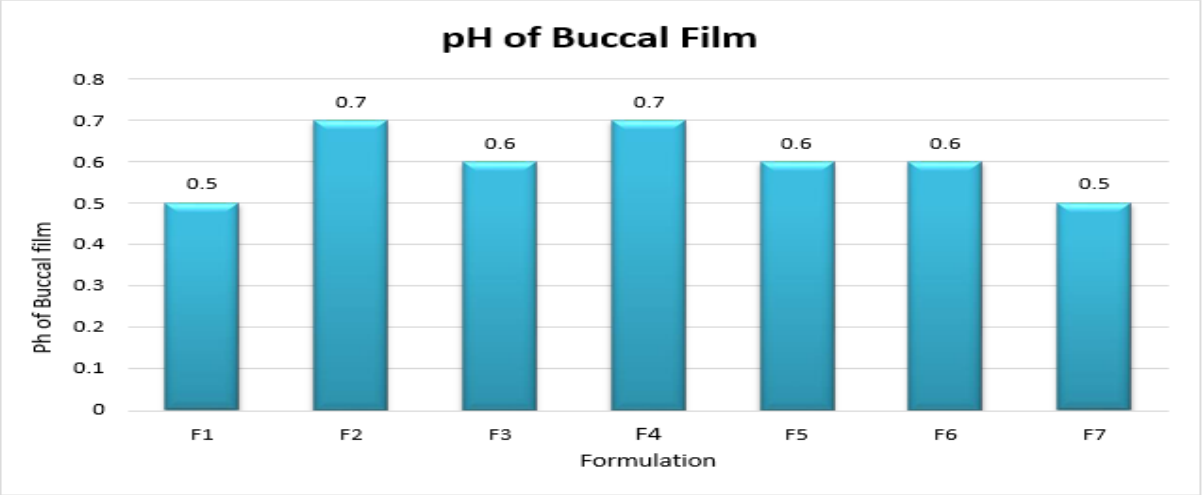

Figure 2: pH of buccal film

An electronic pHmeter was used to test the drug-loaded film's surface pH. Buccal film's surface pH

Table 4: Surface pH of the given formulation

Formulationcode	The pHof Buccal Films
F1	**6.4** ± 2
F2	**6.4** ± 3
F3	**6.3** ± 2
F4	**6.7** ± 3
F5	**6.8** ± 1
F6	**6.7** ± 1
F7	**6.7** ± 1

Folding Endurance

The 2x2cm films' folding endurance was assessed by hand folding one film at a time until it broke up to 300 times, which was deemed sufficient to demonstrate acceptable patch qualities. The number of times the patch could be folded in the same manner without breaking was used to calculate the value of folding endurance. Each formulation batch's two separate films were used for this test.

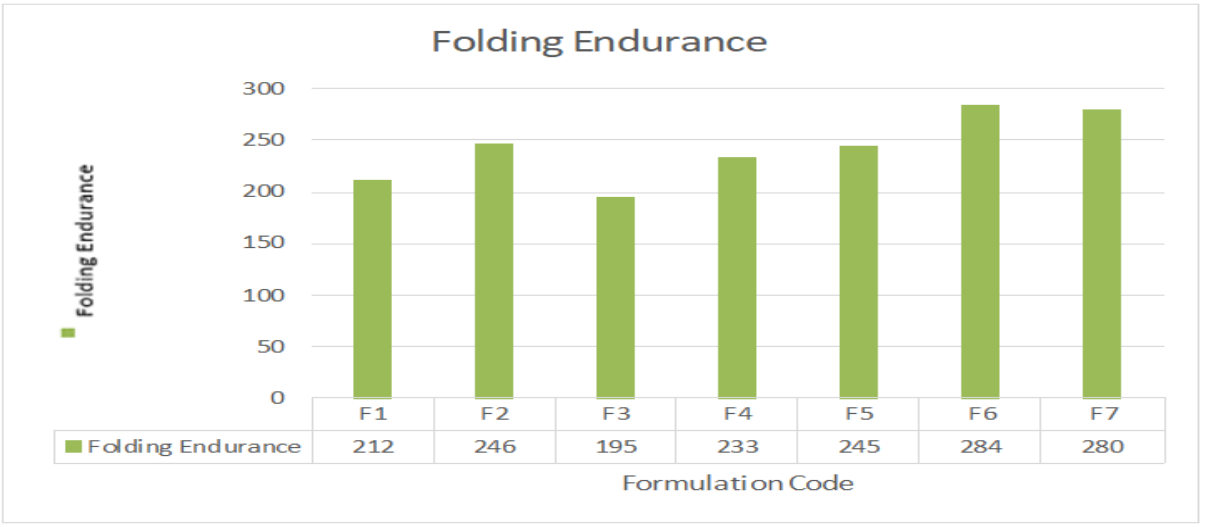

Figure 3: Folding Endurance of a given formulation.

Mucoadhesive Time

Following the placement of the patches onto freshly cut sheep buccal mucosa, the mucoadhesion time was measured (n = 3). Using cyanoacrylate adhesive, the fresh sheep buccal mucosa was adhered to the inside surface of the beaker, more than 2.5 cm from the bottom. After wetting one side of each patch with a single drop of isotonic phosphate buffer (pH 6.8), the patches were lightly pressed with a fingertip for 30 seconds on the sheep's buccal mucosa. The beaker was maintained at 37 ± 1 °C and contained 500 mL of isotonic phosphate buffer with a pH of 6.8. Following two minutes, the environment of the buccal cavity was replicated by applying a 50 rpm stirring rate, and patch adhesion was tracked for a maximum of twelve hours.

The mucoadhesion time was defined as the amount of time needed for the patch to separate from the sheep buccal mucosa.

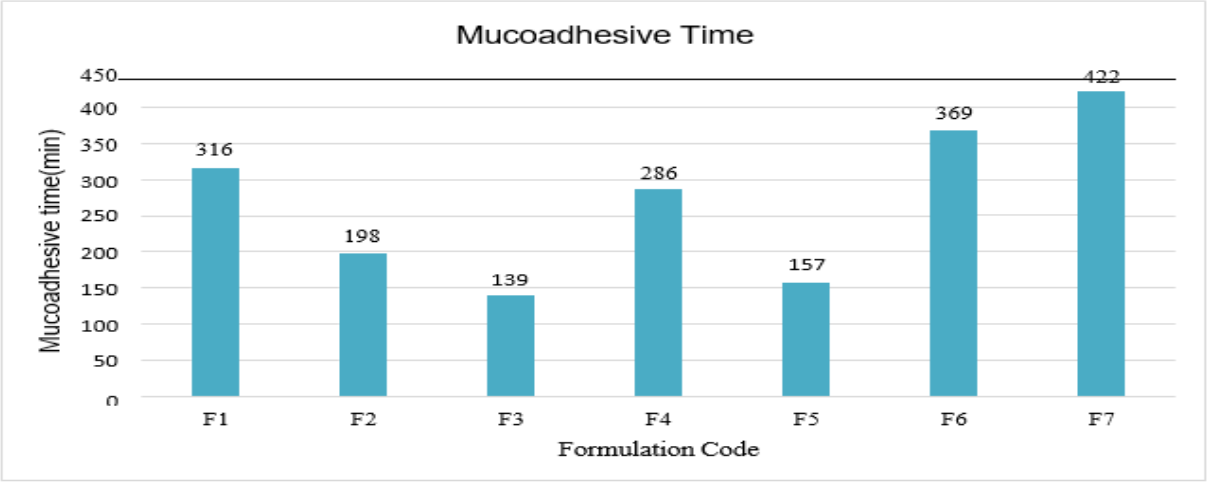

Figure 4: Mucoadhesive time of given formulation

Drug Content Uniformity

When it comes to unit dose forms, the content uniformity test is frequently used. To confirm that the drug was evenly distributed across the picture, the drug content was examined. At 239 nm, the drug content was measured using an appropriate blank. More than 80% of the drug loading was

present in all formulations, suggesting that not all of the drug is lost. The findings were presented and given as AM ± SD. The outcomes showed that the medication was distributed evenly.

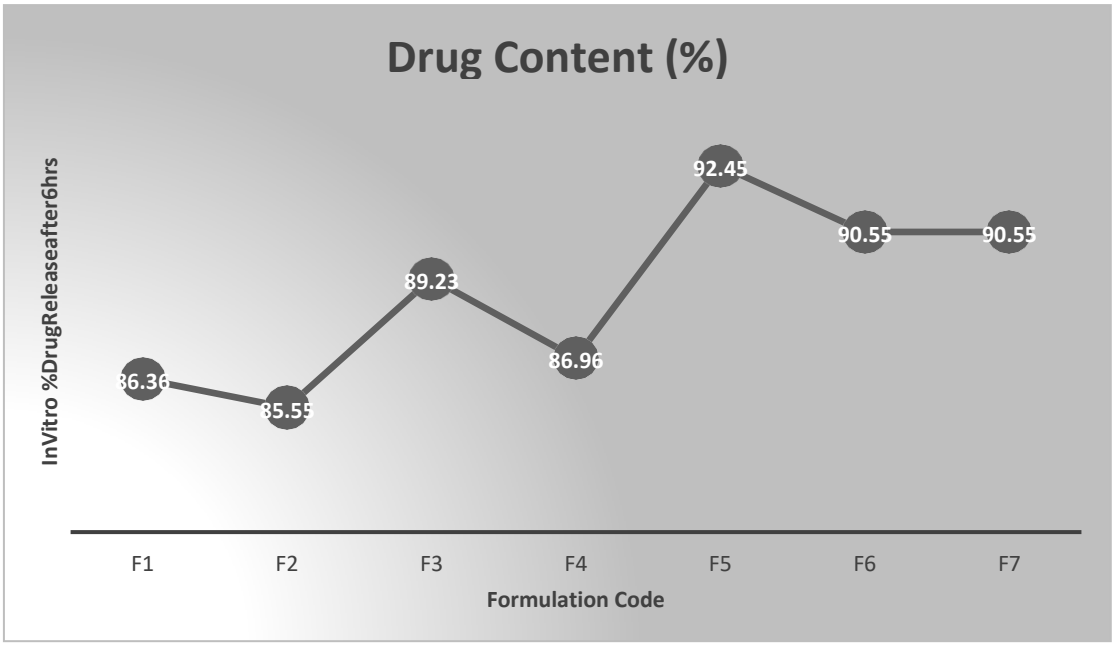

Figure 5: Drug content uniformity of given batches

InVitro Drug Release Study

One film from each batch was fixed within the basket throughout the dissolving investigation, which was conducted utilising a basket-type setup. There are 500 millilitres of distilled water in the dissolving media. A constant temperature of 37°C ± 1°C was sustainedduring the study, and a rotation speed of 50 rpm was utilised for the release investigation. For six hours, the release research was conducted. Five millilitres of sample were taken out of each station every thirty minutes and put back in after that. Every sample that was removed was filtered, appropriately diluted, and then subjected to spectrophotometric analysis at 243 nm. Three duplicates of the tests were run, and average results were given.

Table 5: In-vitro Drug release of Buccal film

Time(h)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
0.5	12.41	13.87	10.28	11.96	10.25	11.23	12.63
1	14.17	14.96	13.74	16.23	14.21	15.96	15.71
2	15.96	16.89	17.36	17.89	18.36	19.25	19.33
3	18.67	17.29	18.34	22.25	25.96	25.11	26.89
4	19.73	19.87	18.99	28.36	29.85	30.85	31.00
5	21.69	20.89	29.23	30.41	31.56	36.74	37.23
6	22.46	22.12	35.23	42.36	36.47	37.23	44.77

Table 6: In-vitro Drug Release After 6 hours

Formulation code	Invitro % drug release after 6 hours
F1	80.56
F2	79.89
F3	80.75
F4	74.23
F5	88.23
F6	92.45
F7	91.78

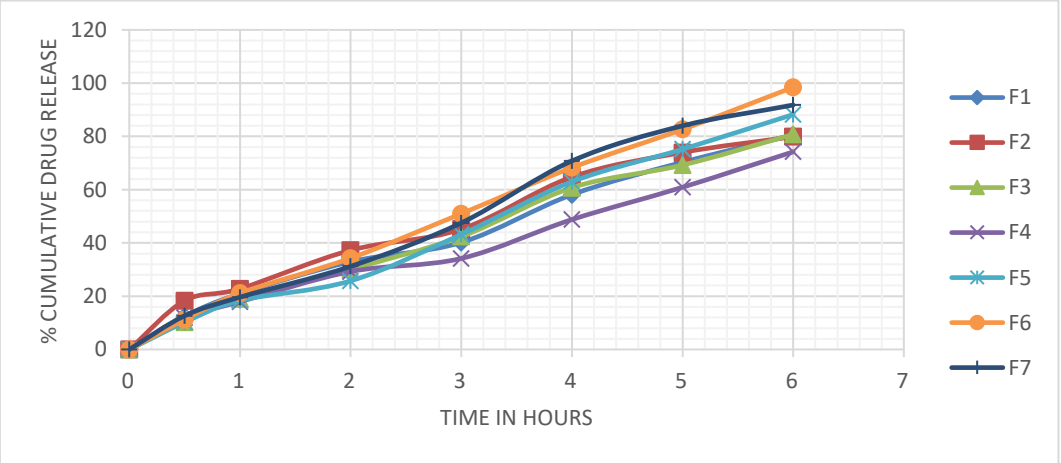

Figure 6: Graphical depiction of an in vitro drug release investigation using several F1, F2, F3, F4, F5, F6, and F7 formulations.

FTIR Spectrum of Optimized Batch

The optimised formulation's IR spectra show that the drug is completely loaded in the formulation since they vary from the F6 Batch's API's (Azilsartan medoxomil) FTIR spectrum.

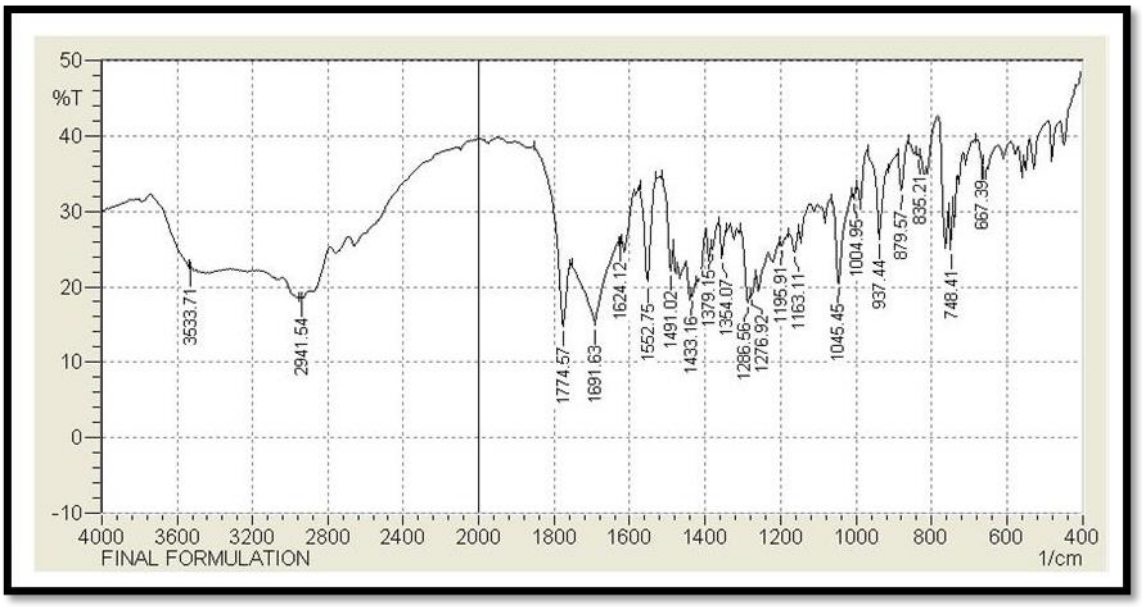

Figure 7: FTIR Spectra of optimized batch (F6)

Scanning Electron Microscope:

The figure presents the SEM of pure azilsartan medoxomil at 100x and 500x magnification. Azilsartan particles were in size from 50 to 350 um and had an irregular form. The unfavourable surface of the particles was seen when the picture was closer at 500x and with more amplification. While the SEM images at different magnifications for the equation of the Buccal film are addressed, they show uniform submicron estimated particles and the results also reveal a nearly round moulded Buccal film with a size inside the nano size. This micrograph was consistent with the ones the Buccal film had decided upon (Mou *et al*., 2011).

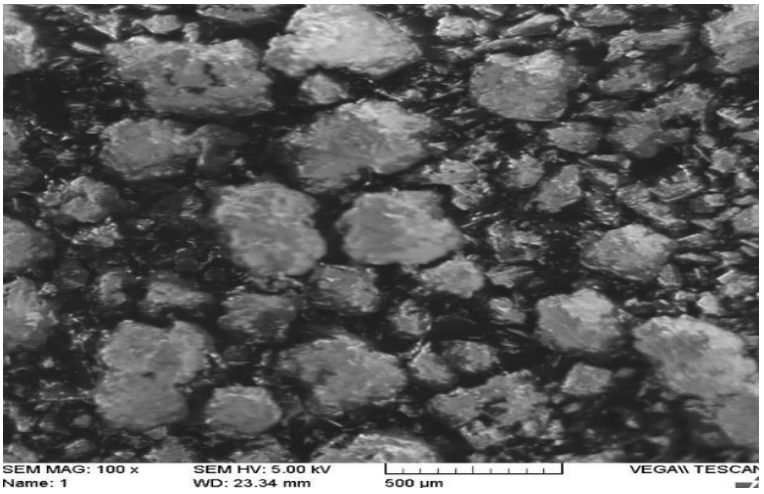

Figure 8: SEM of optimized formulation (F6)

Particle size analysis and polydispersity index measurement:

Using eight distinct formulations, the impact of various factors on the polydispersity index and particle size was investigated. Every developed formulation was nanoscale in size. The formulations' mean particle size (effective diameter) ranged narrowly, from 80.85 ± 0.0 nm to 180 ± 0.0 nm. Important characteristics of buccal film include globule size and PDI, which reveal details about the formulation's quality. The average particle size and PDL of the nano-formulation

were 15.5 nm and 0.495, correspondingly, as indicated in Figure. All formulations have low PDI values, indicating that the creation of a monodispersed system was effective.

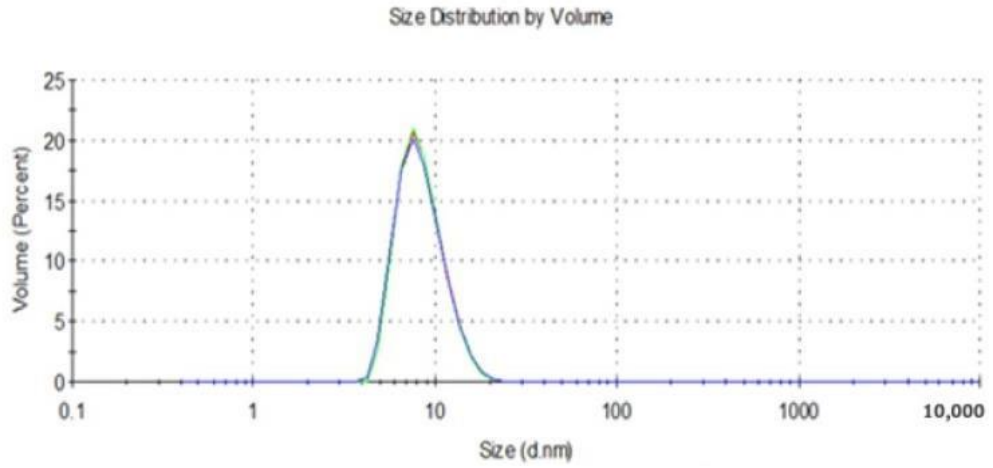

Figure 9: Particle size of the optimized formulation

Stability Study:

At intervals of 60 days, the optimised formulation F6 was assessed for every characteristic, including appearance, weight, thickness, percentage, and medication content. The table provided displays the data from stability studies of the optimised formulation F6, which did not reveal any appreciable changes in these parameters during stability experiments. This attests to the stability of the film formulation throughout storage.

Table 7: Stability study data of optimized formulation

Duration	Appearance	Weightoffilm	Thickness	Drugcontent
0days	Transparent	354 mg	1.81mm	90.35%
30days	Transparent	330 mg	1.68mm	86.96%
60days	Transparent	315mg	1.60mm	84.23%

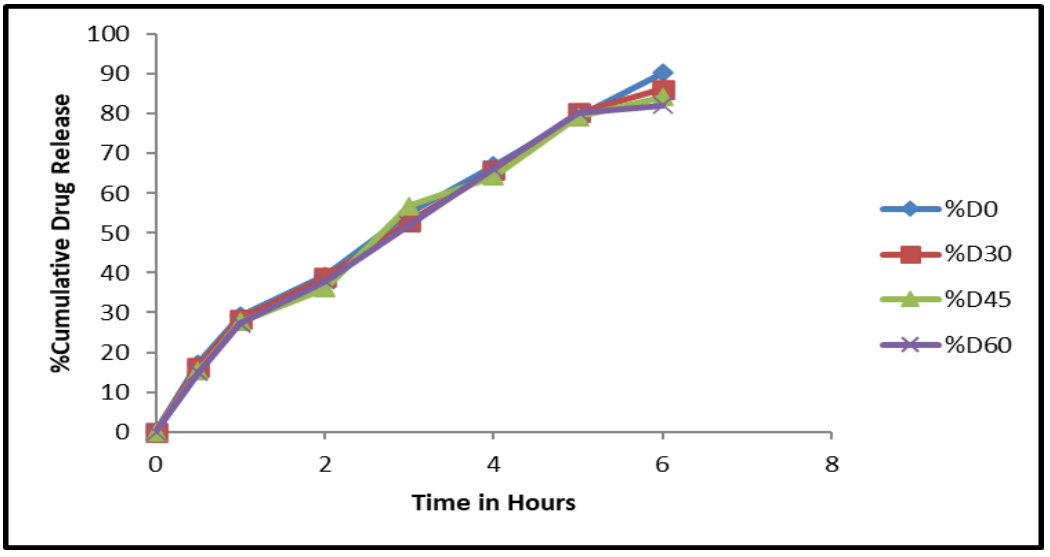

Figure 10: % cumulative Drug Release of optimized batch after Stability study

CONCLUSION

Due to substantial first-pass metabolism, buccal distribution is a desirable alternative for the administration of medications with limited bioavailability. The different experiments might lead one to the following conclusion. There was no interaction between the medication and the excipients, according to FTIR measurements. The solvent casting technique may be used to make the mucoadhesive buccal film with a backing layer that functions as a patch to provide unidirectional drug release of azilsartan medoxomil. HPMC E15 and HPMC E5 are examples of mucoadhesive polymers that can be used in this process. The created films had a homogeneous weight, thickness, medication content, and folding durability. They also looked smooth, flexible, and attractive. Every formulation's physicochemical characteristics were demonstrated to be within acceptable bounds. Every formulation's surface pH fell between 5.8 to 7.4, which is a reasonable range for salivary pH. Better drug release, mucoadhesive qualities, drug content, tensile strength, and accelerated stability conditions were discovered to be present in formulation F6, which was determined to be stable at the ICH-specified levels. Therefore, the F6 batch is regarded as the optimal formulation. Drug permeability was demonstrated satisfactorily in ex vivo experiments for the optimised batch. Good buccal membranes allowed azilsartan medoxomil to pass through, as demonstrated by the ex-vivo permeability trials. Therefore, the current study shows that the buccal route should be used to administer azilsartan medoxomil.

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