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DESIGN, DEVELOPMENT AND EVALUATION OF POSACONAZOLE BUCCAL PATCHES FOR ENHANCED RELEASE USING NATURAL POLYMERS

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ABSTRACT

It has been demonstrated that buccal patches are an effective method of delivering drugs locally as well as systemically. This study examines the use of natural polymers in the formulation of oral patches containing posaconazole. As natural polymers, Xanthan Gum and Guar Gum were used to prepare the patches. In order to characterize the formulations, the physical appearance, thickness, weight variation, flatness, moisture uptake, swelling study, and the in vitro drug release profiles were assessed. Posaconazole is compatible with the polymers used in this study according to FTIR spectroscopy. Furthermore, the patches demonstrated good mucoadhesive properties, suggesting that the patches would remain at the application site for a longer period of time and that drug absorption would be enhanced through the buccal mucosa. In general, natural polymers have been effective in improving the bioavailability and therapeutic efficacy of posaconazole buccal patches. A major contribution of this research is the development of innovative drug delivery systems utilizing natural polymers in order to enhance therapeutic outcomes in antifungal therapy.

KEY WORDS: Oral, Posaconazole, Natural, Buccal Patches.

INTRODUCTION

There are numerous ways of drug administration for delivering the medicine. Among them in recent years, various researches are done in the field for delivering the medicine locally to the tissues in the mouth cavity, notably for treating bacterial and fungal infections, and periodontal therapies. Bioadhesive drug delivery plays a significant function in delivering medicine locally in the oral cavity since it keeps the drug at the site of action. Adhesive material may be natural or manufactured. Surface of adhesion might be either epithelial tissue or mucous coat of the tissue. If adhesion is to a mucous coat, then it is called as mucoadhesion. Over the decades mucoadhesion has become popular for its potential to optimise localised drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. buccal cavity) (e.g. buccal cavity) [1]. Mucoadhesive polymers have significant utility in buccal medication administration method. Recently, several mucoadhesive forms have been produced as patches, films, discs, strips, ointments, tablets, gels etc. However, buccal patch gives better flexibility and comfort than the other kinds. Apart from that buccal patches can address challenges like short residence duration like that of gels which is readily wiped away by saliva [2].

Buccal route of drug administration gives great bioavailability since it has direct access to the systemic circulation through the jugular vein skipping the first pass hepatic processing. Apart from that, it has great accessibility, low enzymatic activity, suited for medications or excipients that slightly and reversibly harm or irritate the mucosa.

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Other advantages include the fact that drugs are administered without discomfort and that withdrawal is simple.]. Added flexibility in formulation design, including the ability to incorporate a permeability enhancer, enzyme inhibitor or pH modulator. Multidirectional or unidirectional release systems for local or systemic activity are also available [3].

BUCCAL MUCOSA

Buccal mucosal drug delivery is classified into three categories

(i) Sublingual delivery,

(ii) buccal delivery,(iii)Local delivery,

1. Sublingual administration: This medicine is delivered to the systemic circulation through the sublingual mucosa, which is the membrane that covers the ventral surfaceof the tongue and the floor of the mouth, in this case.
2. Buccal delivery: This medicine is delivered to the systemic circulation through the buccal mucosa, which is the lining of the cheek.
3. Local delivery: This kind of distribution is most commonly used to treat illnesses such as ulcers in the oral cavity, fungal infections, and periodontal disease, among other things. They differ from one another in terms of anatomy, permeability to a drugadministered to them, and their ability to retain a drug for a certain period of time after application of the drug.

The mucosa has a plentiful supply of blood, and it is also relatively porous [4, 5].

Functions of Oral Cavity

- It helps in chewing, mastication and mixing of food stuff.
- Helps to lubricate the food material and bolus.
- To identify the ingested material by taste buds on the tongue.
- To initiate the carbohydrate and fat metabolism.
- As a portal for intake of food material and water.
- To aid in speech and breathing process [6].

Physiological aspects and functions of oral cavity

- As a portal for intake of food material and water.
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- To initiate the carbohydrate and fat metabolism.
- To aid in speech and breathing process [7].

Composition of Buccal Patches [8]

- Active ingredient.
- Polymers
- Diluents
- Sweetening agents
- Flavouring agents
- Backing layer
- Penetration enhancer
- Plasticizers

Methods of Preparation

Two methods are used to prepare adhesive patches [9].

Solvent casting.

In this method, all patch excipients, including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner toform a laminate that is die-cut to form patches of the desired size and geometry.

Direct milling

In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described. While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

Advantages of Buccal Patches [10]

The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein and bracio cephalic vein into the systemic circulation. Through buccal administration, the drug gains direct enters into the systemic circulation, thereby bypassing the first pass effect. Contact with the digestive fluids of the gastrointestinal tract is avoided which might be unsuitable for the stability of many drugs like insulin or other proteins, peptides and steroids. In addition, the rate of drug absorption is not influenced by food or gastric emptying rate. The surface area of buccal membrane is large, due to this drug can be placed at different places. Additionally; there are two areas of buccal membranes per mouth, which would allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes. Buccal patch has good access to the membranes that line the oral cavity, which makes application painless and with comfort. Patients can easily withdraw the drug and can control repeated administrations in case of emergencies. Better

patient compliance is exhibited through novel buccal dosage forms.

MATERIALS AND METHODS

MATERIALS

List of Materials:

Posaconazole, Guar Gum, Xanthan, Dichloromethane, Methanol, PEG-400, Tween-80.

List of Equipment:

Digital weighing balance, Digital pH meter, cyber pH- 14L, Franz diffusion cell, Glassware, UV-Spectrophotometer.

METHODS

Determination of UV Absorption maxima

Posaconazole solution was prepared with 6.8 pH phosphate buffer and diluted suitably. The UV spectrum of the solution was taken on Lab India 3200 UV/Vis double beam Spectrophotometer. The solution exhibited UV maxima at 274 nm. The procedure was repeated with pH 6.8 phosphate buffer.

Preparation of Standard Calibration Curve of Posaconazole

100 mg of Posaconazole was accurately weighed and dissolved in little amount of Methanol and the final volume is make up to 100 ml with pH 6.8 phosphate buffer to prepare stock solution. The 10 ml of stock solution was further diluted with pH 6.8 phosphate buffer in 100ml to get 100µg/ml (working standard). Then 5, 10, 15, 20and 25 µg/ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with pH 6.8 phosphate buffer. Then the absorbance was measured in a UV spectrophotometer at 274 nm against pH 6.8 phosphate buffer as blank.

Selection of drug and other ingredients

Posaconazole was selected as model drug based on its physico-chemical and biological properties and also based on its suitability for Buccal drug delivery system.Guar Gum and Xanthan Gum were selected as matrix forming polymers. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer [11].

Drug excipients interaction studies

FT-IR spectrum interpretation:

IR spectral analysis was carried out using FT-IR by the KBr disc method. The sample and KBr were triturated and compressed to get the discs. The samples of pure drug, dummy formulation and optimized formulation were analyzed between wave numbers 4000.0 and 400.0 cm^{-1}.

Formulation of Buccal patches

Development of Buccal patches: Buccal drug delivery patches were prepared by solvent casting method.

Solvent casting method: Polymers Guar Gum and Xanthan Gum were weighed accurately and dissolved in dichloromethane and methanol as solvent using magnetic stirrer. Posaconazole, Propylene glycol, Tween80 is added to the above dispersion with continuous stirring. The uniform dispersion was poured in the petri plate. The rate of evaporation of solvent was controlled by inverting cut funnel over the patches.

Evaluation of Buccal patch by physical methods [12]

Physical appearance: All the Buccal patches were visually inspected for color, clarity, flexibility & smoothness.

Thickness: This thickness of the patches was assessed at 3 different points using screw gauze. For each formulation, three randomly selected patches were used.

Weight variation: The three disks of 2x2 cm2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

Flatness: Longitudinal strips were cut out from each patch, one at the center and two from either side. The length of each strip was measured and the variation in the length because of uniformity in flatness was measured by determining present constriction, considering constriction equivalent to 100% flatness.

Moisture uptake: The percent moisture absorption test was carried out to check the physical stability and integrity of the patch at high humid conditions. In the present study the moisture absorption capacities of the patch were determined in the following manner. The patches were placed in the desiccators containing 200 ml saturated solution of potassium chloride, to get the humidity inside the desiccators with 84 % RH. After 3 days the films were taken and weighed the percentage moisture absorption of the patch was found.

$$\text{Percentage moisture absorbed} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture content: The patches were weighed individually and kept in a desiccators containing fused calcium chloride at 40 ºC for 24 h. The patches were reweighed until a constant weight was obtained. Moisture content was calculated in percentage based on the difference between the initial and the constant final weights of the patches.

Swelling study: Completely dried patches with a specified area (3.83 cm2) were weighed and put in desiccators for 24 h. They were removed and exposed to relative humidity conditions of 75 %(containing saturated

solution of sodium chloride) in desiccators. Weight was taken on a single pan balance periodically until a constant weight was obtained. The swelling capacity of the patch (in weight %) was calculated in terms of percentage increase in weight of patch over the initial weight of the specimen. The experiments were carried out in triplicate and the average values were used for the calculation. The percentage degree of swelling (DS) was calculated as

DS (%) = Ws-Wd/Wd× 100

Where, Ws and Wd indicate the weight of the swollen and dry patch respectively. 36 Drug content determination: The patch of area 3.83 cm2 was cut and dissolved in phosphate buffer solution with pH 7.4. Then solvent methanol and dichloromethane, to make polymer soluble, were added to the mixture and the remaining volume was made up with buffer pH 7.4 to 100 ml in 100 ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 274 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

Surface pH: For the determination of surface pH of the patch, each formulation is allowed to swell for 2 hrs in a petri dish containing 5 ml of phosphate buffer pH 6.8. The surface pH was measured by pH paper placed on the surface of patches and allowed to equilibrate for 1 min.

Evaluation of Buccal patch for permeation studies [13] Permeation studies were carried out on Franz diffusion cells. The Franz diffusion cell contains two compartments, the donor and receptor compartment. The receptor compartment is 5mm and holds a volume of 15 ml. The receptor compartment is attached to a collecting tube which allows easy collection of hourly sample while the process of diffusion. The donor and the receptor compartment are held together with help of a clap and the diffusion cell was placed on the magnetic stirrer while diffusion studies carried. The total area of the receptor compartment that is exposed to the buccal patch for diffusion is 3.83 cm2. Invitro permeation studies using dialysis membrane [14].

In vitro permeation of Posaconazole from Buccal patches through dialysis membrane (Hi-Media) with molecular weight cut off of 12000 was studied. The membrane was mounted over a Franz diffusion cell along with the patch buccal patch. The receiver compartment of the diffusion cell was filled with 15. ml of phosphate buffer solution pH 7.4 and the setup was placed over a magnetic stirrer with temperature maintained at 370C. Samples of 3 ml were withdrawn and replenished immediately from the receiver compartment at 1, 2, 3, 4, 6 and 12h. They were stored in refrigerated condition till the analysis was performed. The content of Posaconazole in the samples was analyzed by UV-Visible spectrophotometer. The concentrations of drug were determined at 274 nm.

Kinetic modeling of drug release [15 - 17]

Mechanism of drug release: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release model: To study the zero–order release kinetics the release rate data are fitted to the following equation.

Q= K0 t

Where, Q= amount of drug released at time t K0=zero order release rate constant

The plot of % drug release versus time is linear.

First order release model: The release rate data are fitted to the following equation ln (100-Q) = ln100- k1 t

Where, Q= percent drug release at time t K1= first order release rate constant

The plot of log % drug release versus time is linear.

Higuchi's Release Model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation

Q= KH t1/2

Where, Q= percent drug release at time t

KH= Higuchi's (diffusion) rate constant

In Higuchi's model, a plot of % drug release versus square root of time is linear. Korsmeyer-peppas release model: The release rate data were fitted to the following equation

F= (Mt/M) = Kmtn Where, Mt= drug release at time t

M= total amount of drug in dosage form F= fraction of drug release at time t

Km=constant dependent on geometry of dosage form n=diffusion exponent indicating the mechanism of drug release.

If n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or non-fickian diffusion (Swellable & Cylindrical Matrix).In this model, a plot of log (Mt/M) versus log (time) is linear..

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Table 1: Composition of Posaconazole Buccal Patch

INGREDIENTS	F1	F2	F3	F4	F5	F6
DRUG	300	300	300	300	300	300
Xanthan Gum	200	300	400	100	100	100
Guar Gum	100	100	100	200	300	400
DICHLOROMETHANE	10ml	10ml	10ml	10ml	10ml	10ml
METHANOL	13.2ml	13.2ml	13.2ml	13.2ml	13.2ml	13.2ml
PEG 400	1ml	1ml	1ml	1ml	1ml	1ml
TWEEN 80	1ml	1ml	1ml	1ml	1ml	1ml

Table 2: Calibration curve of Posaconazole in (pH 6.8)

S. No.	Concentration (µg/ml)	Absorbance* (at 274 nm)
1	0	0
2	5	0.129
3	10	0.244
4	15	0.359
5	20	0.490
6	25	0.601

Table 3: Evaluation of Buccal patches for their physical characters

Formulationcode	Thickness(mm)	Drug content (%)	Moisture uptake (%)	Moisture content (%)	SurfacepH
F1	0.35±0.05	45.2±1.5	7.98	3.77	6.59±0.29
F2	0.35±0.03	65.5±3.9	25.05	9.2	6.34±0.48
F3	0.34±0.08	57.5±5.2	13.09	5.16	5.89±0.51
F4	0.35±0.07	60.6±5.1	15.63	5.66	6.34±0.84
F5	0.34±0.05	67.5±4.8	11.73	4.87	6.18±0.27
F6	0.35±0.06	92.5±8.3	19.65	12.67	5.98±0.82

Values were represented as Mean±SEM

Table 4: In-vitro permeation studies of the formulations

Time (hrs)	F1	F2	F3	F4	F5	F6
1	10.31	11.19	22.28	8.14	16.28	13.46
2	12.11	18.51	29.88	12.61	18.39	15.24
4	23.19	23.76	43.24	15.77	27.21	23.54
6	34.09	33.28	55.56	22.48	36.59	27.62
8	45.69	39.22	67.38	33.41	43.47	34.49
10	57.58	52.74	83.29	41.23	54.38	45.58
12	68.11	66.61	95.67	56.81	66.08	58.20

Table 5: kinetics of In-vitro permeation studies using dialysis membrane of F3

CUMULATIVE (%) RELEASE Q	TIME(T)	ROOT(T)	LOG (%) RELEASE	LOG(T)	LOG (%) REMAIN
20.2	1	1.000	1.305	0.000	1.902
27.8	2	1.414	1.444	0.301	1.859
42.8	4	2.000	1.631	0.602	1.757
53.5	6	2.449	1.728	0.778	1.667
66.3	8	2.828	1.822	0.903	1.528
82	10	3.162	1.914	1.000	1.255
94.7	12	3.464	1.976	1.079	0.724

Figure 1: Anatomy of oral cavity

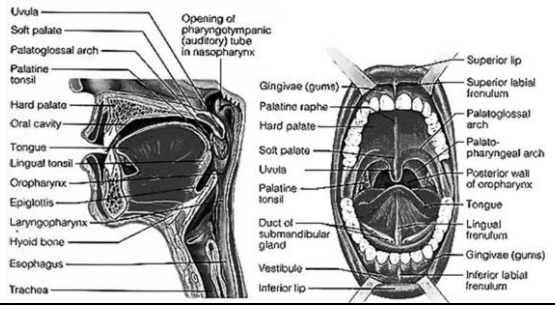


Figure 2: Structure of oral mucosa

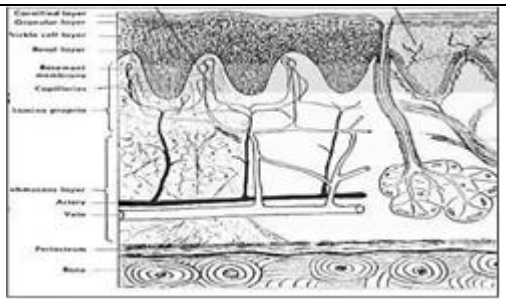


Figure 3: Standard graph of Posaconazole in pH 6.8 Phosphate buffer

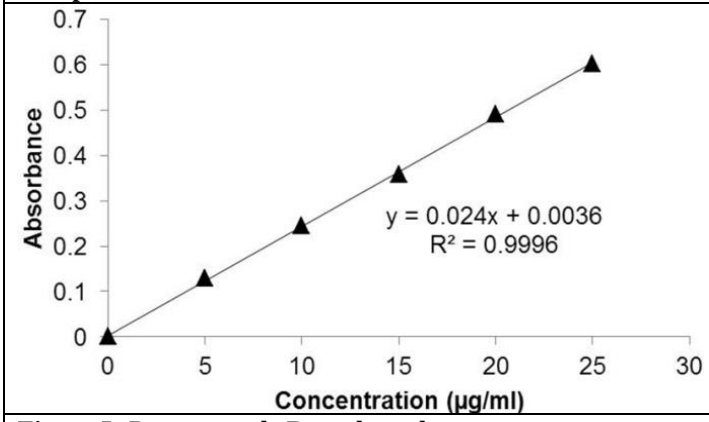


Figure 4: FTIR analysis of drug and formulation

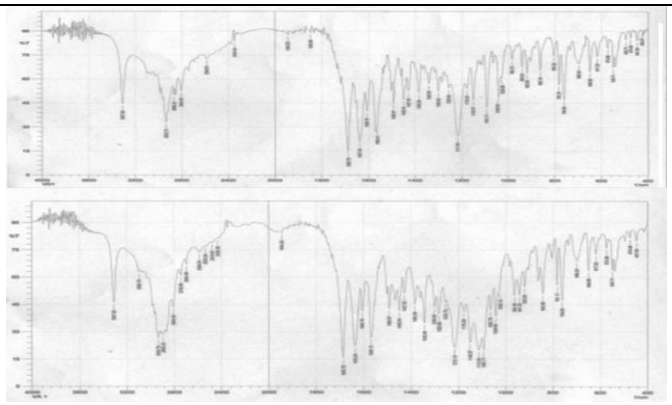


Figure 5: Posaconazole Buccal patches

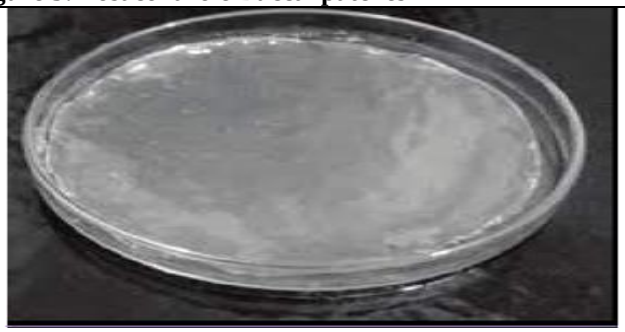


Figure 6: Cumulative drug release from patches

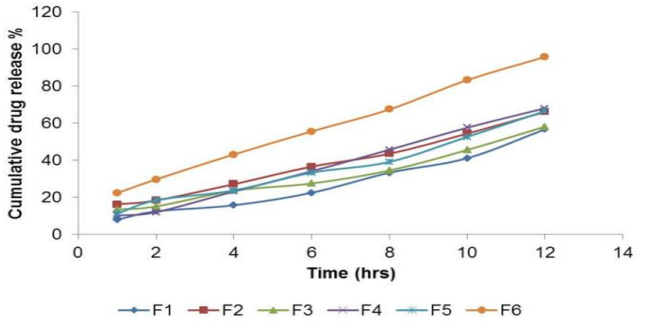
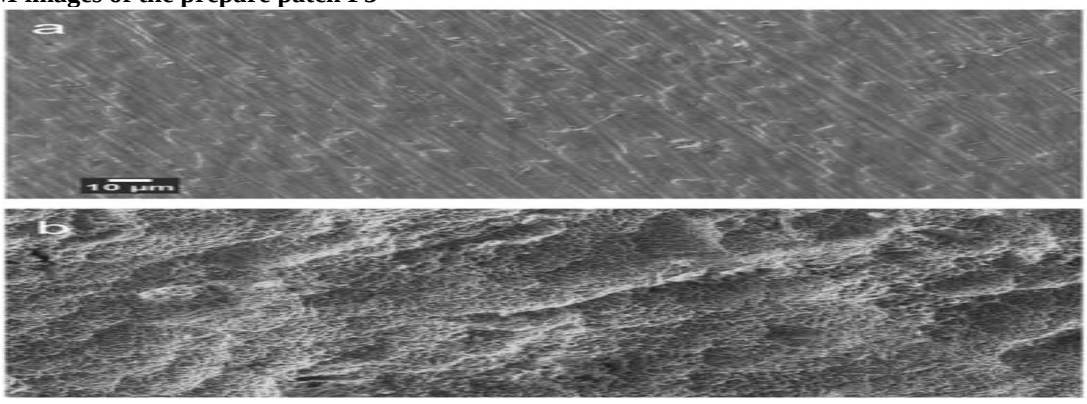


Figure 7: SEM images of the prepare patch F3



RESULTS AND DISCUSSION

Standard Calibration curve of Posaconazole

It was found that the estimation of Posaconazole by UV spectrophotometric method at λmax 274 nm in 6.8 pH phosphate buffers had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml.

FTIR analysis

FTIR spectrum of the drug was characterized with various peaks corresponding to various bonds like 1636.39 cm-1 for C=O stretching 2988.18 cm-1 for C—H stretching, 1211.77 cm-1 for --CH3, 3301.82cm-1 for N—H stretching. The peaks that correspond to C=O of the drug had been shifted to 1682.97 cm-1and –CH3 had been shifted to 1216.76 cm-1 indicating that there are strong bonds between drug and polymer but there was no other distinctive new peaks seen indicating that there is no chemical interaction between them.

Evaluation of Posaconazole Buccal patches

The evaluation of buccal patches for their physical characteristics is a crucial aspect in determining their efficacy and stability. Six formulations (F1-F6) were assessed based on various parameters, including thickness, drug content, moisture uptake, moisture content, and surface pH.

The thickness of the patches was fairly consistent across all formulations, with values around 0.35 mm. F1, F2, F4, and F6 had a thickness of 0.35 mm, while F3 and F5 were slightly thinner at 0.34 mm. The standard deviations indicate minor variations, suggesting uniformity in the preparation process.

Drug content varied significantly among the formulations. F1 exhibited the lowest drug content at 45.2%, while F6 had the highest at 92.5%. This variation in drug content could influence the therapeutic effectiveness of the patches. The standard deviations also highlight variability, especially in F2 (65.5% ± 3.9) and F6 (92.5% ± 8.3), indicating potential inconsistencies in drug distribution within these patches.

Moisture uptake is a critical parameter as it affects the patch's ability to adhere to the buccal mucosa and its stability. F2 showed the highest moisture uptake at 25.05%, followed by F6 at 19.65%. In contrast, F1 had the lowest moisture uptake at 7.98%. High moisture uptake in F2 might indicate a higher propensity for swelling and potentially better mucoadhesion, but it could also lead to faster degradation or altered drug release profiles.

Moisture content, which impacts the storage and shelf-life of the patches, also varied. F6 had the highest moisture content at 12.67%, while F1 had the lowest at 3.77%. Higher moisture content in F6 suggests it may be more prone to microbial growth and degradation over time, necessitating careful consideration of storage conditions.

The surface pH of the patches is vital for ensuring compatibility with the buccal mucosa to avoid irritation. The surface pH ranged from 5.89 in F3 to 6.59 in F1. All formulations exhibited surface pH values close to neutral, indicating that they are unlikely to cause significant irritation to the mucosal tissues. However, minor variations exist, with F3 having a slightly more acidic pH and F1 having a slightly more alkaline pH.

The in-vitro permeation studies of the six buccal patch formulations (F1-F6) provide valuable insights into the drug release profiles over a 12-hour period. The permeation data, recorded at intervals of 1, 2, 4, 6, 8, 10, and 12 hours, demonstrate significant differences in drug release rates among the formulations. At the 1-hour mark, F3 showed the highest permeation with 22.28%, while F4 exhibited the lowest at 8.14%. This early stage data suggests that F3 has a rapid initial release, which could be advantageous for achieving a quick onset of action. On the other hand, the slower release in F4 might be beneficial for sustained drug delivery.

By the 2-hour point, F3 continued to lead with 29.88% permeation, followed by F2 with 18.51%. F4 remained the lowest at 12.61%, but all formulations showed an increase in drug permeation, indicating a continuous release pattern. At 4 hours, the trend remained consistent, with F3 reaching 43.24%, significantly higher than the others. F1 and F4 showed more modest increases, with permeation values of 23.19% and 15.77%, respectively. This further underscores F3's potential for rapid drug delivery. By the 6-hour mark, F3's permeation had reached 55.56%, maintaining its lead. F1, F2, and F5 showed moderate increases, with values around 33.28% to 36.59%. F4 lagged behind at 22.48%, indicating a more controlled release profile.

At 8 hours, F3's permeation was 67.38%, while the other formulations showed more balanced increases, with F2 and F5 reaching 39.22% and 43.47%, respectively. F4, at 33.41%, still demonstrated a slower release compared to others. By the 10-hour point, F3 had achieved 83.29% permeation, highlighting its potential for almost complete drug release within a 12-hour period. F2 and F5 showed notable increases to 52.74% and 54.38%, respectively, while F4 remained lower at 41.23%.

At the final 12-hour mark, F3 reached an impressive 95.67% permeation, indicating near-total drug release. F1, F2, and F5 had permeation values of 68.11%, 66.61%, and 66.08%, respectively, suggesting a substantial release. F4 and F6 had values of 56.81% and 58.20%, respectively, showing they released a significant but comparatively lower amount of drug over the same period. In summary, F3 demonstrated the highest and most rapid drug permeation across all time points, making it suitable

for applications requiring quick and extensive drug release. F1, F2, and F5 showed moderate permeation, suggesting balanced release profiles. F4 exhibited the slowest permeation, indicating a controlled and sustained release, which could be advantageous for prolonged therapeutic effects. F6 had an intermediate permeation rate, suitable for moderate release requirements.

SEM Analysis.

The surface morphology using SEM was analyzed which showed a smooth surface and the film was even without any ruggedness. There are no visible tears on the surface of the patch. Invitro Release kinetics study of formulation F3

CONCLUSION

This investigation scopes for a future research in establishing the biological profiles of drug in blood serum, bioavailability and bioequivalence of drug invivo. This research hopes for the improvement of release of other drugs using the buccal patches technique. It was concluded that the method adopted for the improvement of release of Posaconazole was appropriate and yielded a positive result all through the research..

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