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Research Article

Formulation Development and Evaluation of Nanofibers Containing Antifungal Drug using Electrospining Technique for the Treatment of Oral Candidacies

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ABSTRACT

Oral Candidiasis is common disease caused due to overgrowth of Candida albicans. To treat this type of infection different dosage forms are marketed. The purpose behind this research is to provide knowledge about nanofibers as a novel drug delivery for the treatment of oral candidiasis. For the formulation of nanofibers electrospinning technique was used. To determine the effectiveness of nanofiber drug delivery evaluation was done.

Keywords: oral, candidiasis, clotrimazole.

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INTRODUCTION

These days Drug formulations that combine nano-sized drug particles into carriers are frequently developed using nanof0rmulations. Normally, a drug must travel through the entire body before it can reach a diseased location, but nanof0rmulations enable target-specific drug delivery since the drug is more effective, has fewer potential adverse effects, and has a higher bioavailability.[1,2]

Oral candidiasis is a disorder where the common oral bacterium Candida albicans overgrows and accumulates on the mucosal layers of the mouth (OC). For many years, the mucosa has received topically administered medications. However, there has recently been interest in exploiting the mouth cavity as a portal for delivering drugs to the systemic circulation. The demand for creating more patient-friendly and acceptable dose forms has grown recently. Despite the availability of other drug delivery methods, the buccal route is still advised for the administration of active ingredients due to dose accuracy, affordable production, and the possibility of self-medication, all of which contribute to high patient compliance [3, 4]. To treat OC, a variety of oral dosage forms are available on the market, including films, creams, gels, tablets, patches, and more. Films will dislocate, which prevents them from providing a full drug release at the site of action. In contrast, nanofiber patches include backing membranes, which prevent dislocation and provide a full drug release at the site of action in a specified amount of time. Due to the baked membrane, drug release is controlled and drug loss is prevented. Poor patient compliance and increased first pass metabolism are needed for tablets, but there is no drug loss in nanofiber patches, therefore they cannot be ingested and do

not exhibit first pass metabolism It demonstrates complete bioavailability, is simple to administer and remove in the event of toxicity, irritation, or discomfort, resulting in good patient compliance [5,6,7].Therefore, the nanofiber patch is the most effective and acceptable dose form among all those used to treat oral candidiasis.

Oral Candidiasis: Opportunistic infections can be brought on by Candida species in patients with both local and systemic risk factors; these infections are quite common in people with the human immunodeficiency virus (HIV) and immunocompromised patients. Oral candidiasis is a condition in which the common oral microorganism Candida albicans overgrows and accumulates on the mucosal layers of the mouth (OC). Candida albicans is a tiny, oval-shaped yeast form with a 2-4 m-diameter unicellular budding. [8, 9]

Mechanism of absorption through buccal mucosa:

There are two ways that a medication can enter the oral mucosa through the squamous stratified epithelium: i. (intracellular, passing through the cell). ii. Intercellular, or paracellular (moving between cells). Drugs are absorbed through the buccal mucosa via passive diffusion of nonionized species across the epithelium's intercellular gaps, which is primarily controlled by a concentration gradient. The main transport mechanism is the movement of non-ionic species passively through the membrane lipidique of the buccal cavity. Like many other mucosal membranes, the buccal mucosa has been described as a lipidic barrier to the passage of medications; The ease of absorption increases with the lipophilicity of the drug's molecule. Drug buccal absorption kinetics may be sufficiently first order rate procedure described.[10, 11,12]

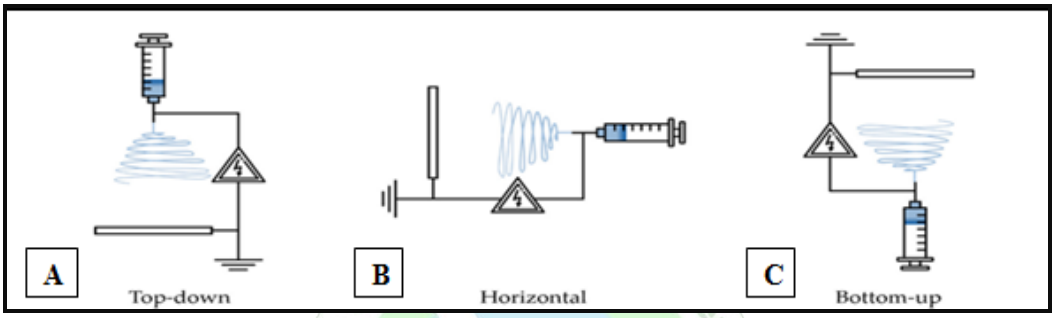

Figure 1: Schematic view of conventional vertical and horizontal electrospinning setup

MATERIALS AND METHOD

MATERIALS

Clotrimazole(API) was ordered from Glenmark Pvt. Ltd. Goa, polymers namely chitosan and polycaprolactone were purchased from Benglore Fine Chem. And BLD Pharma. Respectively. The solvents as acetone (pearl chemical supplier), Acetic acid (Ruchak chemicals), Chloroform (Loba chem. Pvt. Ltd) were ordered. Analytical development method studies were performed by UV-visible spectrophotometer at maximum wavelength of 263nm.

EXPERIMENTAL WORK:

Preformulation Study

Preformulation study refers to the research conducted before formulation. Before creating a dosage form, it is important to avoid further excipient incompatibility in order to evaluate the drug's stability and purity. For the preformulation investigation, the test parameters listed below were employed.

- **Drug Authentication** (USP)
- **Organoleptic characteristics**

The sample was tested for odor, color, and appearance.

- **Solubility:**[13]
- **Melting point (M.P.):**[14]

Thiele's tube was used to determine the clotrimazole (CTZ) melting point using the open capillary tube method. The assembly was heated continuously using a one-sided closed capillary loaded with medication, a graded thermometer, and a thiele's tube containing paraffin oil. The temperature at which a solid medication turned liquid was reported.

Spectroscopic analysis by UV Spectrophotometric method[15,16,17]

Calibration curve of CTZ in Acetone.

The stock solution of CTZ was made by accurately weighing 10 mg of CTZ and dissolving it in 10 ml of acetone to obtain a conc. of 1000 gram per milliliter. From the stock solution, 1 mg of solution was taken and added to a 100 milliliter volumetric flask to obtain concentration of 100 gram per milliliter. From the above solution, various aliquot part of I, II, III, and IV milliliter were taken and added to a 10 milliliter volumetric flask The spectrophotometer was used to scan the solutions in the UV 200-400 nm range.

Fourier Transform Infrared Spectroscopy (FTIR) [18]

Utilizing the KBr powder press process, the FT-IR spectra of CTZ was recorded to check its purity on an FTIR spectrophotometer (FTIR 8400S, Shimadzu). Potassium bromide that has been dried was used for the baseline correction. In the range of 4000-400 cm^{-1}, the instrument was wielded under dry air purge with a resolution of cm^{-1}. The scans were inspect for the appearance of the main drug sample peaks. The principal peaks of the reported IR spectra were contrasted with the detected peaks.

XRD of CTZ: [19]

XRD analysis I is a tech. used in material research to determine a substance's crystal structure. XRD is used to

measure the X-ray intensity and dispersion angles within the material.

Preparation of viscous solution of CTZ:

Two different polymers are used in preparation of CTZ Nanofibers, i.e. Chitosan which is hydrophilic cationic polymer and Polycaproactone which is hydrophobic polymer. Four different conc. ratios 1:1:1, 1:1.5:1, 1:1:1.5, 1:1:2 % w/w of drug and polymers are taken for preparation of viscous solution by sonication.

Table 1: Composition of CTZ nanofiber solutions

Sr.no.	Composition	Ratio (Drug : Polymer)
1	CTZ+ Chitosan+ Polycaprolactone	1:1:1
2	CTZ+ Chitosan+ Polycaprolactone	1:1.5:1
3	CTZ+ Chitosan+ Polycaprolactone	1:1:1.5
4	CTZ+ Chitosan+ Polycaprolactone	1:1:2

Characterization of CTZ Nanofiber:

XRD of CTZ: [20]

XRD analysis I is tech. used in material research to determine a substance's crystal structure. XRD is used to measure the X-ray intensity and dispersion angles within the material.

Drug-Excipients compatibility study of selected CTZ nanofiber patch

The drug and excipients compatibility study of selected nanofiber patch of batch P2 performed by FT-IR.

Formulation and evaluation of Nanofiber patch of CTZ:[21,22]

Electrospun nanofibers with various polymer concentrations were used to create the nanofiber patch for the CTZ, and the influence of the electrospinning voltage was also investigated. Patches were made utilising the electrospining technique. Accurate weights were taken for all the materials. I used a 10 ml beaker that contained the required amount of acetone (1-2 ml) to dissolve the CTZ and polycaprolactone. I used a second 10 ml beaker with diluted (1:1) acetic acid, added a calculated amount of chitosan, and stirred to dissolve. Drop by drop, sonicate the CTZ and polycaprolactone solution for 15-20 minutes at 36°C with the aforementioned solution. The solution should be taken out, poured into a clear glass bottle, and left in desiccators overnight.

Table 2: Compositions of nanofiber patch of CTZ

Sr. No.	Ingredients	Pi(mg)	Pii(mg)	Piii(mg)	Piv(mg)
I	CTZ	10	10	10	10
II	Chitosan	10	15	10	10
III	Polycaprolactone	10	10	15	20
IV	Acetone	Q.s	Q.s.	Q.s.	Q.s.
V	Dil. Acetic Acid	Q.s.	Q.s.	Q.s.	Q.s.

Evaluation of nanofiber patch

Weight uniformity:[23]

By contrasting the average weights of 10 distinct patches that were randomly chosen from each batch, we examined the weight fluctuation.

Thickness:[24,25]

Micrometer screw gauze should be used to measure the patch sample's thickness at five different points (the centreand the fourcorners), and the mean thickness of patch should then be determined. The study excludes samples with airbubbles, nicks, or tears as well as those with mean thickness changes of patch of more than 5%

Swelling Index:[26,27]

Weight gain brought on by swelling: A 1x1 cm2 drug-loaded patch was weighed on a cover slip that had been previously weighed. It was housed in a petridish and given 50 milliliter of pH 6.6 phosphate buffer. The cover slip was taken off after 5 minutes and weighed for up to thirty minutes. Due to the patch swelling and buffer solution absorption the weight differential results in weight gain.

Scanning electron microscope (SEM): [28,29]

SEM was used to investigate these patches' cross sections (SEM). After applying a gold sputter coating, the dried patches were examined under a scanning electron microscope (JEOL, JSM 840, Japan).

Folding Endurance:[30,31,32]

The prepared patches' folding endurance was manually tested by repeatedly folding them in the same spot until they broke. The value of folding endurance was determined by how many times the patches could be folded in the similar position with out breaking or cracking.

Determination of Drug Content:[33,34,35]

Patch parts of each formulation were taken in separate 100 milliliter volumetric flasks, 100 milliliter of PH 6.8 phosphate

buffer was placed, and the mixture was agitated continuously for 24 hrs to determine the drug content uniformity. The solutions were filtered, appropriately diluted, and subjected to Ultra Violate spectrophotometer analysis at 263 nm. The final reading was determined by averaging the drug amounts of three patches.

In-vitro Drug Release:[36,37,38]

The test used a Franz diffusion cell apparatus for the in vitro drug release test using a commercially available dialysis membrane (obtained from Sigma Chemicals). There was 1.8 cm2 of effective diffusion area. Phosphate buffer saline (PBS), with a pH of 6.8, was added to the receptor compartment (40 ml). The patches were placed on the dialysis membrane that was positioned between the donor and receptor compartments of the diffusion cell when in occlusion. Using a magnetic stirrer at a stirring speed of 50 rpm, the drug release was carried out at 37°C±0.5 °C. At regular time intervals, five milliliters of the sample from the receptor medium were taken out and immediately replaced with an equivalent volume of phosphate buffer saline, pH 6.8. Using a UV-visible spectrophotometer at 263 nm and a control sample, the amount of CTZ released into the receptor media was measured.

Antifungal test [39,40]

Antifungal test was performed for optimised batch Piii by using agar diffusion test method using candid albicans strain which compared with marketed cream for oral candidiasis.

RESULT AND DISCUSSION:

Authentication of Drug

The purity of a medicine can be determined with the use of its physicochemical qualities. As a result, the CTZ was verified by the following tests.

Organoleptic Characteristics

The obtained sample of CTZ was studied for organoleptic properties such appearance, color and odor. Results of organoleptic properties of CTZ were found to be complies with US pharmacopoeia as shown in **Table 3**

Table 3: Organoleptic properties of CTZ with the reported standards

Identification	Observation	Inference
Appearance	Crystalline powder	Complies with USP
Color	White	Complies with USP
Odor	Odorless	Complies with USP

Sr.no.	Concentration(µg/ml)	Absorbance at 263nm
A	0	0
B	10	0.050
C	20	0.096
D	30	0.142
E	40	0.186

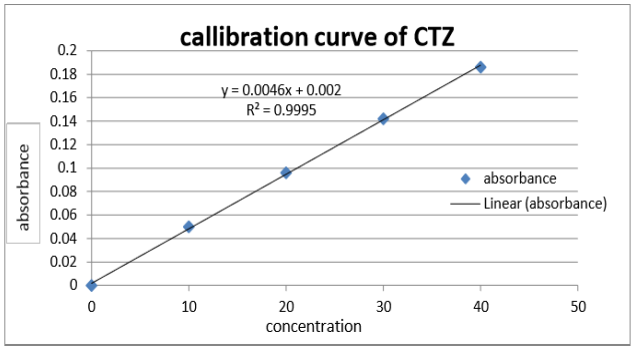

Figure 2: Callibration curve of CTZ

Solubility study of CTZ

A study on the solubility of CTZ in various solvent systems, including distilled water, acetone, chloroform, and methanol, was conducted as shown in **Table 4**. It was determined that the presented sample is a pure medication after comparing the measured values to USP.

Table 4: Solubility of CTZ

Sr.no.	Medium	Solubility mg/ml	Observation	Inference
a	Acetone	5.03	Highly soluble	Complies with USP
b	Chloroform	3.008	Soluble	Complies with USP
c	Methanol	1.003	Poor soluble	Complies with USP
d	Water	0.0032	Very poor soluble	Complies with USP

Melting point (M.P.)

Table 5: Melting point of CTZ

Method	**Reported M.P. as per USP**	**Observed M.P.**
Open capillary tube method	147-149ºc	146ºc

Fourier Transform Infrared Spectroscopy (FTIR)

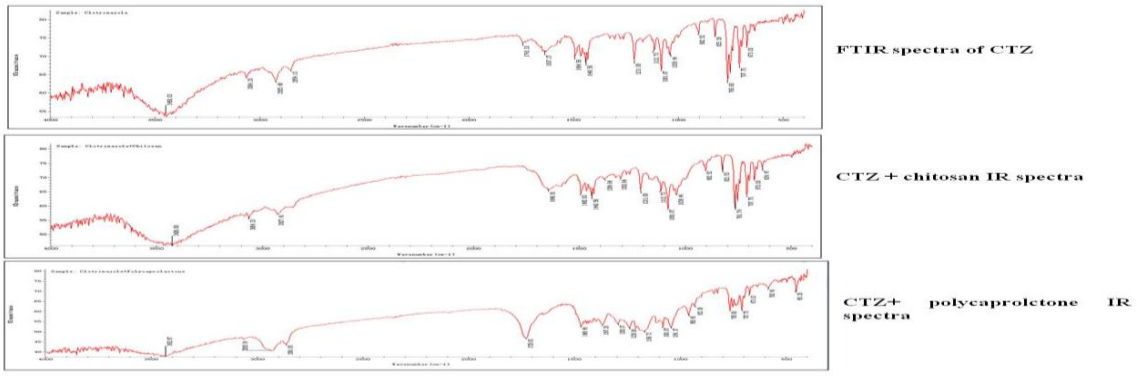

Figure 2: Fourier Transform Infrared Spectroscopy (FTIR)

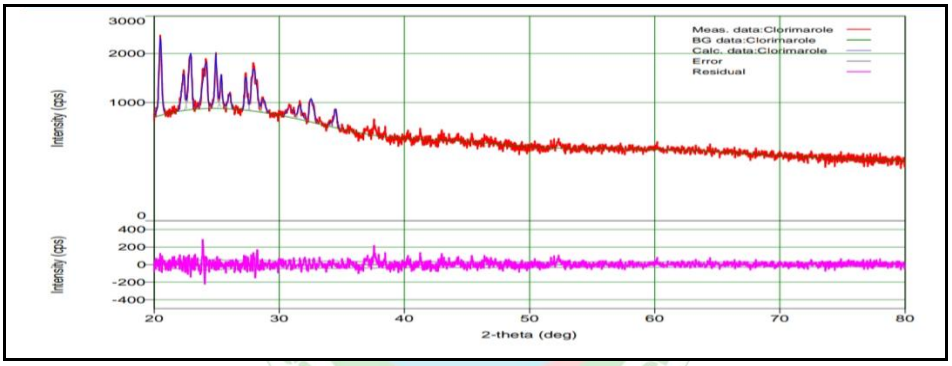

Figure 3: XRD

Table 6: Peak list

Sr. No.	2- Theta(deg)	D (deg)	Height (cps)	FWHM (deg)	Int (cps deg)	Int w (deg)	Size (ang)
1	20484(7)	4.3322	1109(53)	0.216(6)	288(7)	0.259(18)	402(12)
2	22.359(10)	3.9731	452(34)	0.280(15)	142(6)	0.31(4)	302(16)
3	22.912(10)	3.8783	764(44)	0.278(10)	238(8)	0.31(3)	304(10)
4	24.159(15)	3.681	595(39)	0.395(13)	250(11)	0.42(5)	215(7)
5	24.944(6)	3.5668	801(45)	0.139(11)	175(6)	0.218(19)	612(49)
6	25.368(6)	3.5081	461(34)	0.121(12)	88(5)	0.19(3)	705(71)
7	26.034(9)	3.4199	176(21)	0.263(16)	49(3)	0.28(5)	324(20)
8	27.286(8)	3.2658	430(33)	0.225(14)	103(5)	0.24(3)	380(23)
9	27.906(15)	3.1946	539(37)	0.458(14)	263(10)	0.49(5)	186(6)
10	28.680(14)	3.1102	150(19)	0.31(4)	50(5)	0.33(8)	274(33)
11	30.75(2)	2.9056	101(16)	0.67(7)	80(7)	0.80(19)	128(14)
12	31.580(11)	2.8308	144(19)	0.32(3)	54(4)	0.37(8)	272(27)
13	32.488(6)	2.7537	256(25)	0.36(2)	109(5)	0.42(6)	240(13)
14	34.07(2)	2.694	37(10)	0.07(7)	4(2)	0.11(9)	1191(1186)
15	34.447(10)	2.6015	217(23)	0.19(3)	61(4)	0.28(5)	447(58)

From the above data and intensity of peaks, it was clear that the sharp peaks were formed which indicates that the nature of CTZ was crystalline

Characterization of CTZ nanofiber

SEM of CTZ nanofiber

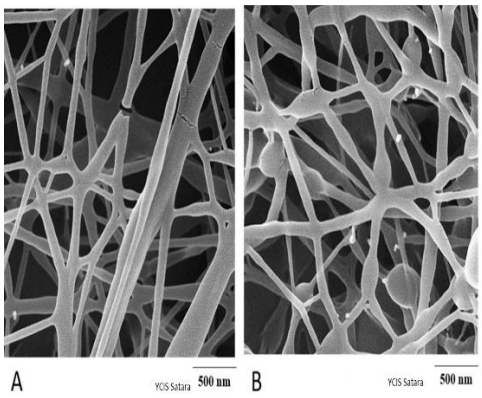

Figure 9: SEM of CTZ nanofiber

All four batches of nanofiber have undergone SEM analysis; batch Pii shows a diameter of less than 5 m among the four batches; as a result, from the photos above, Pii batch exhibits a uniform diameter that ranges between 2-3 nm.

In-vitro diffusion study of nanofiber

Table 6: Data of In-vitro drug release profile of nanofiber patch

Time (Hrs)	Amount of drug release of Pi	Amount of drug release of Pii	Amount of drug release of Piii	Amount of drug release of Piv
1	2.677	2.929	2.738	2.370
2	4.372	3.999	4.336	3.987
3	5.416	4.894	5.224	4.302
4	6.1	5.996	6.068	5.092
5	7.135	6.648	6.668	6.079
6	7.930	7.172	7.799	6.875
7	8.184	7.964	7.842	7.130
8	8.404	9.648	8.581	7.992

From the above data within 8hrs Pi batch shows 84.04% release, the Pii batch gives 96.48% release of the drug, the Piii batch shows 85.81% release and the Piv batch shows 79.92% release it means that all the 4 batches shows controlled release but Pii batch shows controlled and complete release within 8hrs. Therefore batch Pii was selected as optimized batch.

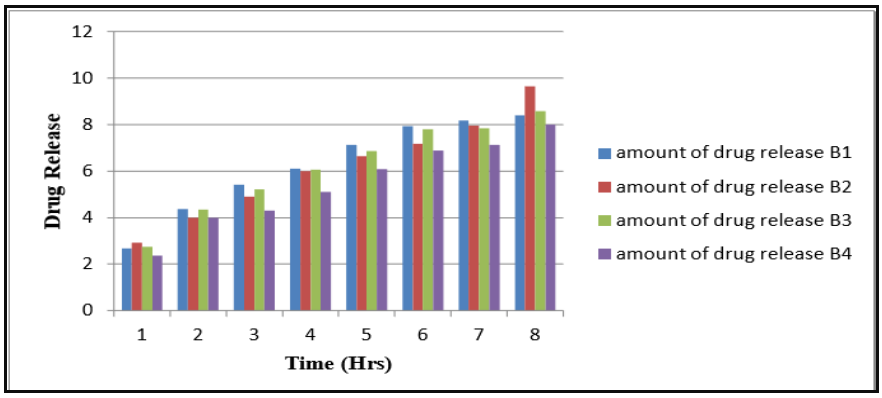

Figure 10: Graphical presentation of In-vitro drug release was given

Antifungal test:

Table 7: Zone of inhibition

Sr. No.	Zone of inhibition of Marketed preparation	Zone of Inhibition of Batch pii
1	10mm S.D. 5.673	17mm S.D. 6.568

Physical evaluation of nanofiber patch:

Table 8: Data of physical evaluation of nanofiber patches

Batch	Wt variation	Thickness of patch	Folding endurance(F.E.)	Drug Content	Moisture Content	Swelling index(S.I.)
Pi	2.06±0.05	0.052±0.02	86	96.40±0.10	0.96	69.64±1.6
Pii	2.10±0.04	0.54±0.03	94	98.50±0.10	0.99	92.40±1.3
Piii	2.09±0.03	0.53±0.03	83	93.20±0.11	0.97	80.55±1.7
Piv	2.12±0.08	0.56±0.05	89	9.30±0.10	0.94	78.61±1.5

SUMMARY AND CONCLUSION

SUMMARY:

Oral candidiasis is treated with the antifungal medication CTZ. Because the therapeutic conc. of clotrimazole are only maintined for a brief length of time after the delivery of standard doses, another dose must be given. In order to do this, an effort was prepared to sustain the therapeutic conc. for longertime. By creating a controlled release drug delivery device, this was accomplished. These mucoadhesive controlled release buccal patches are designed to release the medication over a longer time period, namely eight hours, and to use the medication as effectively as possible while avoiding frequent dosage. Chitosan is a polymer that is used to create buccal patches that adhere to mucous membranes and have extra antifungal properties. Chitosan also improves the drug's absorption. Additionally possessing a sticky quality, polycaprolactone improves chitosan's capacity for spinning. Transform of Fourier There were no interactions between the drugs, polymers, or excipients, according to infrared spectroscopy. The electrospinning process was used to create the buccal mucoadhesive patches. The manufactured controlled release mucoadhesive buccal patches underwent thickness of patch, folding endurance(F.E.), wt. variation, swelling index(S.W.), uniformity of drug content, surface pH, scanning electron microscopy (SEM), and in vitro release test evaluations. When comparison made to all other formulations, Formulation Pii had the best regulated drugrelease and best results for all other metrics. As a result, formulation Pii is regarded as the optimal formulation. Polymer ratios were found to have a considerable impact on medication release. Thus, it may be concluded that stable dosage forms for Clotrimazole can be created for controlled release via buccal patches.

CONCLUSION:

In the current work, an effort was made to create a novel mucoadhesive drug delivery system in the form of buccal patches for the controlled release of CTZ in order to sustain continuous therapeutic levels of the drugsample for an extended period of time. In terms of drug release, content homogeneity, %water uptake, surface PH, thickness, buccal formulations of CTZ in the form of mucoadhesive patch have been created to a satisfactory level. Despite the fact that all buccal patches had positive results, the best outcomes were obtained with the optimised formulation Pii, which contained the drug, chitosan, and polycaprolactone in the ratios of 1:1.5:1. According to the study mentioned above, there is a chance to create a mucoadhesive dds for CTZ that will be more effective and most acceptable than current CTZ drug delivery methods. It will also likely have a satisfactory controlled release profile, which could lead to a rise in therapeutic efficacy.

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