Original Article

Formulation and evaluation of mucoadhesive buccal tablet of Anastrozole

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ABSTRACT

The study is related to the formulation and evaluation of mucoadhesive buccal tablets of Anastrozole to enhance its bioavailability by avoiding 1st pass effect. The study succeeded in developing mucoadhesive buccal tablets containing two layers (mucoadhesive and backing layer) in a design that permits the unidirectional release of the drug. Tablets of Anastrozole were prepared by double direct compression method using (carbopol 934) as a primary mucoadhesive polymer, Sod.alginate, Na CMC, and HPMC as secondary polymers, Ethyl Cellulose as a backing layer. The tablets are determined for Weight variation, Hardness, Swelling index, Friability, Surface pH, Content Uniformity, Ex vivo Residence time, Mucoadhesive Strength Study, and in-vitro Release Study and Differential Scanning Calorimetry (DSC) studies revealed no evidence of any interaction between drugs, polymers, and additives. Six formulations were prepared to study different factors (different concentrations of primary polymer, different secondary polymers, different methods of formulation, and the effect of adding a Co-binder). The optimum formula (F1) was chosen due to its reasonable results, the cumulative percentage of release (93%), mucoadhesive strength (81.5gm), ex vivo Residence time exceeds the dissolution time (8.1hr), Surface pH is compatible with oral pH (6.1), good mechanical strength with acceptable values for content uniformity, weight variation, and swelling index. These gathered results make a formula that may avoid the 1st pass effect of Anastrozole and improve its bioavailability and consequently may reduce its dose and dosing frequency leading to decrease its side effects and increase compliance of patient.

Keywords: Buccal drug delivery system, Mucoadhesion, Breast cancer, In-vitro dissolution study, Mucoadhesive strength, Anastrozole

Introduction

The attraction between the biological membrane and a polymer whether it is synthetic or natural, is the key to avoiding many obstacles of the traditional drug delivery systems [1]. The bioadhesion is successful in many mucosal areas ex. mouth, skin, vagina, nose, and eye but the buccal route are the most preferable to solve the limitations of oral drug delivery system like first-pass effect and enzymatic degradation despite its many advantages like easy ingestion and self-medication [2]. The preference of the buccal mucoadhesive route is not only due to its affordable accessibility, improving acceptability by the patient but also due to the nature of the buccal mucosal surface which is relatively static and smooth, and highly vascularized leading to direct the flow of blood into the jugular vein which aids to evade the possible metabolism of drugs by the gastrointestinal route and liver, and as an inevitable result enhancing the bioavailability. However buccal mucoadhesive route still has a little bit of discomfort to the buccal cavity because of the solid nature of the dosage form [3].

Anastrozole is a nonsteroidal inhibitor of estrogen synthesis similar to paclitaxel in chemical structure. As a fourth-generation aromatase inhibitor, anastrozole selectively joins to and inhibits aromatase reversibly, a cytochrome P450 enzyme complex discovered in many tissues including those of the liver, breast, and premenopausal ovary, aromatase catalyzes the aromatization of testosterone and androstenedione into estradiol and estrone, the last step in estrogen biosynthesis [4]. In estrogen-dependent breast cancers, Anastrozole may inhibit the growth of the tumor. Anastrozole's chemical formula 2-[3-(2-cyanopropan-2-yl)-5-(1,2,4-triazole-1- ylmethyl) phenyl]-2-methylpropanenitrile and

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molecular formula C17H19N5. It is freely soluble in ethanol, acetone, methanol, tetrahydrofuran, and very soluble in acetonitrile. It is very poorly soluble in water, (0.5 mg/mL at 25°C) and solubility is dependent on pH in the physiological range. Anastrozole is belonged to class III in BCS (Biopharmaceutical Classification System) [5]. This research aims to study the possibility of preparation of mucoadhesive bilayer buccal tablets of Anastrozole and to choose the most prominent formula after characterization of the tablets for each formula by measuring surface pH, weight variation, friability, hardness, mucoadhesive strength, content uniformity, ex vivo residence time, swelling index, drug compatibility study and in vitro drug release.

Materials and Methods

Anastrozole was gifted from Torrent Pharmaceutical Ltd., Ahmedabad, India. Hydroxy Propyl Methyl Cellulose (HPMC) was purchased from Alladin Industrial Corporation. Carbopol 934 was obtained from Chemdyes Corporation (Ahmedabad, India). Na-CMC and Na alginate were purchased from Loba Chemie Pvt. Ltd (Mumbai, India). Sod.Saccharine was obtained from Finisar Chemical Ltd (Ahmedabad, India). Ethyl Cellulose (EC) was purchased from SD Fine Chem. Ltd (Mumbai, India). Talc, lactose, PVP, Mg Stearate, ethanol, and acetonitrile from the chemicals store of College of Pharmacy/Baghdad University. Using desk top single punch tablet press TDP O-China (Sinopharm) with 6 mm punch, type II dissolution apparatus (Faithful, China), UV spectrophotometer (Varian Copley, Australia), magnetic sterrier (Stuart, UK), tablet Disintegration tester BJ 2 model (Tianjin Gouming, China) and TAXT texture analyzer.

Tablet formulation

Anastrozole bilayer buccal mucoadhesive tablet was consisting of a mucoadhesive layer of the drug reservoir and backing layer of impermeable polymer (EC), made by compression of drug reservoir then covered by EC layer and recompressed to make a tablet release the drug unidirectionally [6]. Six different formulas were prepared to study the effect of different factors on the ANZ buccal mucoadhesive tablet **(Table 1)**.

Table 1. Formulations used for Anastrozole buccal mucoadhesive tablet preparation

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Anastrozole	1	1	1	1	1	1
Carbopol 934	3	3	3	6	6	6
HPMC			24			
Na –CMC		24				
Na-alginate	24			21	21	21
Sod.Saccharine	0.7	0.7	0.7	0.7	0.7	0.7
Lactose	46.3	46.3	46.3	46.3	41.3	46.3
Talc	1	1	1	1	1	1
Mg-stearate	2	2	2	2	2	2
EC	19	19	19	19	19	19
PVP					5	
Ethanol						Qs.
Total	100	100	100	100	100	100

Double direct compression method

First of all, weigh all the ingredients including the drug, mucoadhesive polymer, inert impermeable polymer, and other excipients, then sieve the blends to get uniform particles. The drug and other excipients except the lubricant were blended for 15 min. After mixing and blending, add the lubricant and blend for another 5 min to cover the tablet from outside only. The resulting blend for each formulation was compressed using a TDP-O china Desk tablet press (6 mm punch). After compression, the upper punch was removed to recompress the backing layer [7, 8]. This method was applied for the formulas (F1-F5).

Wet granulation method

Formula (6) was prepared by mixing Anastrozole, primary polymer Carbopol 934, and secondary polymer Na Alginate) and lactose for 15 minutes. The powder was granulated by an adequate quantity of suitable granulating solvent (ethanol) until a wet mass (positive ball test) was formed. The cohesive mass obtained was passed using a 1.25 mm sieve and for 1 hr, the granules were dried at 40°C. The dried granules were screened through a 0.630 mm mesh size sieve14. Then, the granules were mixed for 5 minutes with Mg-stearate and talc [9]. Using the same machine, the tablets were compressed and was utilized for the first five formulas.

Evaluation of the flow properties for pre-compressed bulk powder

Compressibility (carr's) index

Pour a sample of each formula into a 10 ml graduated cylinder to calculate the initial bulk volume, then was subjected to the pressure of tapping, till a constant volume was achieved [10].

$$\text{Compressibility Index} = (V0 - Vt / V0)100 \quad (1)$$

Angle of repose

Fixed funnel and petri dish was used to determine the angle of repose for each sample, where the powder blend was poured into the funnel and allowed to flow gently over the fixed diameter petri dish. Then the angle of repose was calculated using the following equation:

$$\text{Tan } Ø = h/r \quad (2)$$

Where Tan Ø is the tan of the angle of repose, h is the height of the resulting con after pouring, r is the radius of the fixed Petri dish [10].

Evaluation of the prepared buccal mucoadhesive tablets of Anastrozole

Weight variation

Individually, 20 buccal tablets were weighed. The requirement met the USP 30, if no more than 2 tablets deviate from the average weight by more than 7.5 % and no tablet deviates in weight by double that percentage, the batch will be accepted [10].

Hardness test (structural integrity test)

During shipping and storage, one of the most important criteria of the tablet is the resistance and strength to mechanical shocks. Determination of hardness test was made using YD-2 tablet hardness tester (GUOMING). Randomly, six tablets were picked from each formulation and the standard deviation and mean values were calculated [11].

Surface pH

The surface pH of the tablet was measured to study the possibility of tablets side effects in vivo. It must be kept as close to neutral pH because an acidic and basic pH may irritate the buccal cavity. For the tablet to swell, it was kept in contact with 1 ml of distilled water for 2 hours at room temperature. The surface of the tablet was kept in contact with the electrode to calculate the pH and allow it to equilibrate for 1 minute, using a combined glass electrode [12]. The procedure was repeated thrice and the average was calculated.

Tablet friability

A Roche-type friabilator was used to calculate the friability (tablet strength). The number of tablets was weighed accurately according to USP rules and put in the tumbling apparatus that rotates at 25 rpm. The tablets were dedusted and reweighed after 4 min and the percentage of loss was calculated to see if it was less than 1% or not [10, 13].

$$\text{Percentage Friability} = (W1–W2/\ W1) \times 100 \quad (3)$$

Swelling index (water uptake test) measurement

The buccal tablet was placed on a glass slide, weighed precisely and its weight was recorded. Then the tablet together with the cover slide was placed in a Petri dish containing 15 ml of phosphate buffer (simulated to the oral cavity_ conditions pH 6.8 solution. At regular intervals and followed for 6 hrs, the tablet together with the cover slide was taken from the Petri dish, and extra surface water was dried cautiously using the filter paper. The swollen tablet was then reweighed (W2). This experiment was repeated thrice and the average was taken. The swelling index (water uptake) is measured according to the following equation [14, 15].

$$\text{Swelling Index} = ((W2 – W1)/\ W1) \times 100 \quad (4)$$

Content uniformity

This test depends on the assay of the content of the active substance in the individual tablet. Ten tablets of all formulas were chosen randomly and powdered in a glass mortar. Apowder equivalent to 1 mg of drug was placed in a stoppered 10 ml conical flask. The drug was extracted with acetonitrile with forceful shaking and filtered into a 10 ml volumetric flask. Additional suitable dilutions were made by employing phosphate buffer pH 6.8 to make known concentration and absorbance was calculated at 210 nm by UV-Visible spectrophotometer (Varian Copley, Australia) [16].

Mucoadhesive strength study

The TA.XT plus texture analyzer is an established tool for measuring bioadhesion strength. Fresh sheep intestinal mucosal membrane (instead of buccal mucosa), texture analyzer, and magnetic stirrer were used to study the ex. vivo mucoadhesive strength. The mucosal membrane was detached by separating the underlying loose connective tissues. The membrane was rinsed with distilled water and then equilibrated with phosphate buffer pH 6.8 solution for 15 min [16]. A piece of intestinal mucosa was tied to and spread over the tissue holder of the accessory of texture analyzer, then the tissue membrane was covered with a lid somehow so the orifice of the lid should expose a small section of the tissue then fixed using thumbscrews. A magnetic stirrer was placed on the base of the accessory, the whole accessory was placed in a beaker containing phosphate buffer pH 6.8, and the temperature adjusted to 37oC. A piece of double-sided tape was firmly fixed on the probe, the tablet was securely stuck to the probe which was attached to the probe shaft of the instrument, the instrument arm was lowered and align the orifice of the accessory to the probe above, at the tissue membrane surface, the probe applied 50 gm force for five seconds and withdrawn then the force required to separate the tablet from the membrane was measured and multiplied by 0.0098 (because the strength was recorded in gm, not in kg) to get the result in newton unit [17, 18].

$$\text{Mucoadhesive Force (N)} = \text{mucoadhesive strength(gm)} \times 0.0098 \quad (5)$$

Ex-vivo residence time

Using disintegration apparatus, ex vivo residence time was evaluated by a reformed method. This method was applied by taking the disintegration medium composed of 800 ml phosphate buffer of pH 6.8 reserved at 37 °C. The fresh sheep intestinal

mucosal tissue was tied to the surface of a glass slab, vertically attached to the apparatus. The duration of the whole detachment of the tablet from the mucosal surface was recorded and considered as ex-vivo residence time [19].

In-vitro drug release

The release from the buccal mucoadhesive tablets from one side (unidirectional release) was studied using USP type II dissolution test apparatus (Paddle type) (Faithful, China). As we know before the buccal tablet was designed with an impermeable backing layer, furthermore the tablet was covered with an aluminum foil to guarantee the unidirectional release. Then it was placed in the dissolution apparatus containing 500 ml of pH 6.8 phosphate buffers and the paddle was rotated at 50 rpm at a temperature of 37 ± 0.5oC. Samples of 5 ml were collected at different time intervals up to 6 hrs and analyzed by spectrophotometer (Varian Copley, Australia) at 210 nm. Then the cumulative amount of anastrozole release from the prepared tablets at different time intervals was calculated by fitting absorbance values into the calibration curve equation [20].

Drug excipients compatibility study

Differential Scanning Calorimetry (DSC) studies were done to assure the compatibility of the drug with the primary, secondary polymers, and other additives in the selective formula. DSC is a highly sensitive technique to study the thermotropic properties of drugs [21, 22].

Results and Discussion

Evaluation of powder blends of formulas

The results in **(Table 2)** for the angle of repose and Carr's index showed that the powder blends and granules in F6 were flowable and had acceptable compressibility [10].

Table 2. Rheological properties of the prepared powder blends

Formula	Angle of repose	Carr's index	Flow character
F1	25.2	15.3	Good –Good
F2	24.4	9.9	Excellent-Excellent
F3	26	15.7	Good-Good
F4	27	16.1	Good-Fair
F5	30.1	17.1	Passable-Fair
F6	29.7	16.6	Good-Fair

Evaluation tests of the formulated buccal tablets

Numerical values of physicochemical characteristics of the prepared tablets are depicted in **(Table 3)**, weight variation test indicated that all the formulated tablets met the USP requirements [10] and the hardness was in the range of 4.32 to 8.4 indicating that the tablets had enough structural integrity forces to resist the conditions of storage and shipping, it was noticed that the hardness value increased with increase the primary mucoadhesive polymer and in the tablets were prepared by wet granulation method due to using a liquid binder [23]. Friability test results are ranged from o.21to 0.51 without any cracks, indicating that all formulas had excellent mechanical resistance to any stress. Surface pH values are not more than 7 and not less than 5.5 which leads to its suitability to the oral (salivary) pH and assurance of use without any sensitization [24].

Table 3. Mechanical and physical characteristics of buccal tablets of Anastrozole

Formula	Hardness Kg/cm2	Friability%	Weight variation	Surface pH
F1	6.1±0.02	0.21	passed	6.1
F2	5.9±0.08	0.31	passed	5.57
F3	5.8±0.1	0.34	passed	6.9
F4	6.39±0.16	0.51	passed	5.7
F5	6.9±0.03	0.31	passed	6.23
F6	8.4±0.07	0.46	passed	6.07

Swelling index

The proper swelling behavior of buccal adhesive tablet is required for perfect mucoadhesion and sustained release for at least 6 hours [25]. The swelling behavior test was done for all formulas (F1-F6). It was noticed that the highest swelling index for formulas containing 2 secondary polymers (sodium alginate and Na. CMC) with the primary carbopol due to fast hydration and swelling properties of sod. Alginate and Na.CMC with less contact time [14]. F3 showed less swelling and hydration, in which HPMC was used as a secondary polymer, this is due to the hydrophilicity of hydrophilic polymers is varied according to the viscosity, degree, and type of substituted functional groups [26]. Generally, the formulas with higher carbopol concentration showed an increase in the swelling index but a nonsignificant increase($P>0.05$), and this belongs to the ionization of carboxylic acid at higher pH 6.8 which lead to ionic repulsion [27].

Mucoadhesion study

Mucoadhesion study was performed for all formulas and the resulted values are shown in **(Table 4)**. As a result of rapid hydration and swelling properties of formulas containing Sod. alginate and Na CMC (F1, F2, F4, F5, F6) which lead to the opening of the polymer chain, so the ionizable functional groups in a direction that available for mucoadhesion F1, F2 and because of the same reason but in inverse, the formulas were formulated with HPMC as a secondary polymer, less mucoadhesion due to less efficient hydration and swelling as mentioned in swelling index test due to the viscosity of the polymer, degree, and type of functional groups substitution, in general to the nonionic nature of HPMC and there was a significant increase ($P<0.05$) in the mucoadhesion with the increase of carbopol concentration (F4, F5, F6) (24,28).

Table 4. Mucoadhesion study of buccal tablets of Anastrozole

Formula no.	Mucoadhesion strength (gm)	Mucoadhesion force (N)
F1	18.5	0.1813
F2	17.9	0.1754
F3	12.67	0.1241
F4	20.2	0.1979
F5	19.21	0.1882
F6	16.23	0.1590

In vitro residence time

The residence time is different from each formula to another according to the difference in the type and percentage of primary and secondary polymers which in turn affect the complete erosion time from the mucosal membrane due to polymeric chain interpenetration into the mucus membrane, increased with increasing the carbopol concentration [24, 28].

In-vitro release study

In vitro release study was carried out in pH 6.8 by (type II) Dissolution apparatus, it was noted in **(Figure 1)** that formulas with Sod. alginate release the drug in a higher percentage due to water solubility which leads to pores and channels within the tightly cross-linked viscous gel layer [29]. F2 was formulated with Na.CMC showed a lower cumulative percentage of drug release than formulas with Na.alginate, this may be due to a difference in viscosity that affects the penetration of dissolution media within the highly viscous layer of carbopol which allows the drug to release (29). While (F3) was formulated with HPMC as a secondary polymer, showed a lower cumulative percentage of drug release as compared to those with Sod. alginate and Na.CMC as a secondary polymer, due to synergistic increase in viscosity as a result of water uptake from both polymers (carbopol, HPMC) resulting in the formation of the strong gel layer and turn slower diffusion and erosion [30]. Increasing carbopol concentration cause a significant ($p<0.05$) reduction in the release cumulative percentage of drug which is due to the inductive effect of ionized carboxylate residues that affect the ionization potential of neighboring groups and the result of high coiling and the carboxylic acid group (compared with linear polymer). This leads to intermolecular H-bonding, which causes entrapment of a drug inside the cross-linked network of the polymer [30]. The method of preparation effect was studied in F4, F6, greater retardation effect was obtained in F6 which is due to the coating of drug particles by carbopol and Na alginate, drug granulation process which in turn slow down the penetration of water into granules and diminish the direct contact with the dissolution medium [31]. As for the F5, in which the effect of addition PVP as a co-binder was studied, decreasing in the cumulative percentage of release was noticed when compared with F4, this may due to the binding effect of PVP that resulted in increasing the mechanical strength (hardness) of the tablets which lead to reducing the drug release [30, 31].

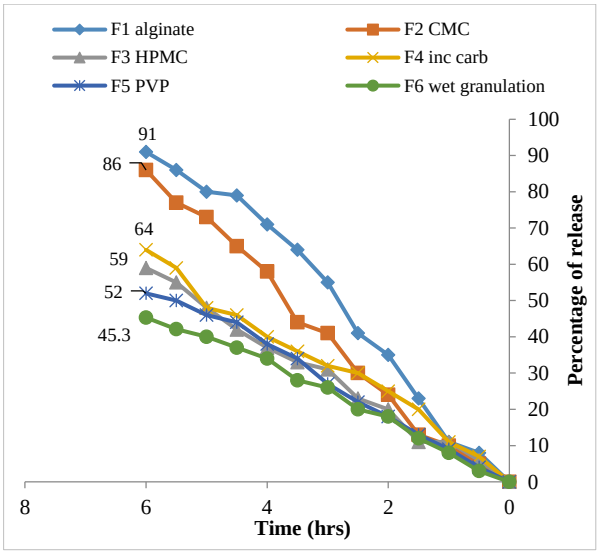

Figure 1. The dissolution profile of buccal tablets of Anastrozole

Content uniformity

The concentration of the drug in ten tablets for each formula was within the range (99.2 -99.7) these values approved the uniform distribution of the drug within the tablets, so the content uniformity does not affect the selection of the optimized formula [10]. F1 is a selective formula due to a good release profile up to (93%) within 6 hr.s and acceptable mucoadhesive strength (18.5 gm) which is required to remain in contact with the buccal cavity during the dissolution time, besides to be considered mucosal friendly because of its pH value (6.1), and surely good mechanical characteristics approved by values of hardness (6.1Kg/cm2)and friability (0.21).

Drug–polymer compatibility study

DSC spectra for the drug alone and its optimum formula in **(Figures 2 and 3)** showed that the drug solubility is enhanced because the peak is converted from sharp to broad one and there is no interaction between the drug and the other ingredients [32].

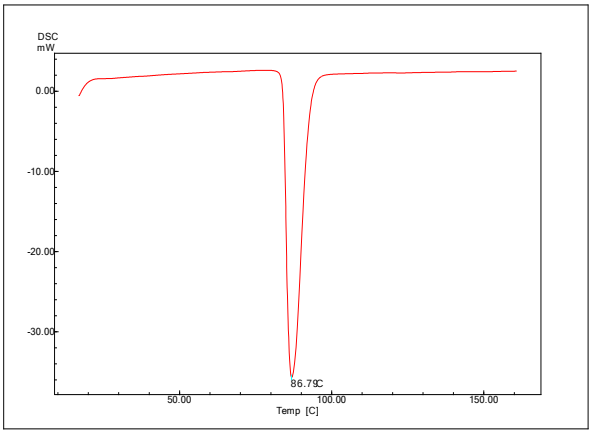

Figure 2. DSC spectrum of the pure Anastrozole

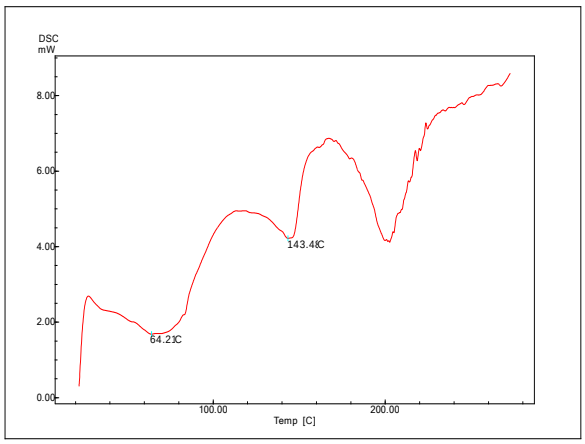

Figure 3. DSC spectrum of the optimum formula

Conclusion

The overall study revealed that Anastrozole can be prepared as buccal mucoadhesive tablets that release the drug through the buccal mucosa for a prolonged duration that may get the benefits of buccal drug delivery system like avoiding 1st pass metabolism leading to bioavailability improvement.

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References

1. Singh R, Sharma D, Garg R. Review on mucoadhesive drug delivery system with special emphasis on buccal route: an important tool in designing of novel controlled drug delivery system for the effective delivery of pharmaceuticals. J Dev Drugs. 2017;6(01):1-2.
2. Wadageri GV, Raju SA, Shirsand SB, Reddy PVP. Design and evaluation of mucoadhesive bilayerd buccal tablet of Atenolol. Int J Novel Drug Deliv Tech. 2012;2(1):256-64.
3. Kraisit P, Limmatvapirat S, Luangtana-Anan M, Sriamornsak P. Buccal administration of mucoadhesive blend films saturated with propranolol loaded nanoparticles. Asian J Pharm Sci. 2018;13(1):34-43.
4. Robert NJ, Denduluri N. Patient case lessons: endocrine management of advanced breast cancer. Clin Breast Cancer. 2017;18(3):192-204.
5. Bhavsar D, Gajjar J, Sawant K. Formulation and development of smart pH responsive mesoporous silica nanoparticles for breast cancer targeted delivery of anastrozole: In vitro and in vivo characterizations. Microporous Mesoporous Mater. 2019;279:107-16.
6. Puri V, Sharma A, Kumar P, Singh I, Huanbutta K. Synthesis and Characterization of Thiolated Gum Ghatti as a Novel Excipient: Development of Compression-Coated Mucoadhesive Tablets of Domperidone. ACS Omega. 2021;6(24):15844-54.
7. Saeb O. Study the sustain release effect of different polymers used in the formulation of aspirin-rosuvastatin tablets. Int J Pharm Pharm Sci. 2015:7(12):166-72.
8. Salih OS, Hamoddi ZM, Taher SS. Development and Characterization of Controlled Release Tablets of Candesartan Cilexetil/β-Cyclodextrin Inclusion Complex. Int J Drug Deliv Technol. 2020:10(2):273-83. doi:10.25258/ijddt.10.2.15
9. Kara DD, Govindarajulu HK, Shivaprasad H, Krishna V, Tippavajhala MJ, Kulyadi GP. Detailed Research on a Comparative Evaluation of Diclofenac Sodium Tablets Manufactured by Using DC Grade Excipients and Wet Granulation Methods. Reason. 2021;4:6.
10. The United State Pharmacopeia (USP) 30, NF28, 2010, USA: The United State Pharmacopia Convention Inc.
11. Kurćubić I, Vajić UJ, Cvijić S, Crevar-Sakač M, Bogavac-Stanojević N, Miloradović Z, et al. Mucoadhesive buccal tablets with propranolol hydrochloride: Formulation development and in vivo performances in experimental essential hypertension. Int J Pharm. 2021;610:121266.
12. Koirala S, Nepal P, Ghimire G, Basnet R, Rawat I, Dahal A, et al. Formulation and evaluation of mucoadhesive buccal tablets of aceclofenac. Heliyon. 2021;7(3):e06439.
13. Jovanović M, Tomić N, Cvijić S, Stojanović D, Ibrić S, Uskoković P. Mucoadhesive gelatin buccal films with propranolol hydrochloride: Evaluation of mechanical, mucoadhesive, and biopharmaceutical properties. Pharmaceutics. 2021;13(2):273.
14. Hanif S, Sarfraz RM, Syed MA, Mahmood A, Hussain Z. Smart mucoadhesive buccal chitosan/HPMC scaffold for sore throat: In vitro, ex vivo and pharmacokinetic profiling in humans. J Drug Deliv Sci Technol. 2022:103271.
15. Gajdošová M, Vetchý D, Muselík J, Gajdziok J, Juřica J, Vetchá M, et al. Bilayer mucoadhesive buccal films with prolonged release of ciclopirox olamine for the treatment of oral candidiasis: In vitro development, ex vivo permeation testing, pharmacokinetic and efficacy study in rabbits. Int J Pharm. 2021;592:120086.
16. Hanif S, Sarfraz RM, Syed MA, Mahmood A, Minhas MU, Irfan M. Development and optimization of tibezonium iodide and lignocaine hydrochloride containing novel mucoadhesive buccal tablets: A pharmacokinetic investigation among healthy humans. Drug Dev Ind Pharm. 2021:1-35.
17. Gajdošová M, Vetchý D, Muselík J, Gajdziok J, Juřica J, Vetchá M, et al. Bilayer mucoadhesive buccal films with prolonged release of ciclopirox olamine for the treatment of oral candidiasis: In vitro development, ex vivo permeation testing, pharmacokinetic and efficacy study in rabbits. Int J Pharm. 2021;592:120086.

18. Göbel A, da Silva JB, Cook M, Breitkreutz J. Development of buccal film formulations and their mucoadhesive performance in biomimetic models. Int J Pharm. 2021;610:121233.
19. da Silva JB, Dos Santos RS, da Silva MB, Braga G, Cook MT, Bruschi ML. Interaction between mucoadhesive cellulose derivatives and Pluronic F127: Investigation on the micelle structure and mucoadhesive performance. Mater Sci Eng C. 2021;119:111643.
20. He M, Zhu L, Yang N, Li H, Yang Q. Recent advances of oral film as platform for drug delivery. Int J Pharm. 2021;604:120759.
21. Alexander KS, Riga AT, Haines PJ. Thermoanalytical Instrumentation and Application. In: Ewing's Analytical Instrumentation Handbook. Third edition: Marcel Dekker; 2009. p.462.
22. Raju KN, Kumar RA, Deepika B, Eswaraiah MC, Rao AS. Formulation and in vitro evaluation of buccal tablets of captopril. Int Res J Pharm App Sci. 2012;2(2):21-43.
23. Weller PJ. Hand Book of Pharmaceutical Excipients, London: Pharmaceutical Press, Sixth edition, 2009, 622-624.
24. John AS, Sathesh BPR, Divakar G, Jangid MK, Purohit KK. Development and evaluation of buccoadhesive drug delivery system for atorvastatin calcium. J Curr Pharm Res. 2010;1:31-8.
25. Darwish KM, Elmeshad AN. Buccal mucoadhesive tablet of flurbiprofen characterization and optimization. Drug Discov Ther. 2009;3(4):181-9.
26. Nair ST, Kamalasanan K, Moidu A, Shyamsundar P, Nair LJ, Venkatesan P. Ethyl cellulose coated sustained release aspirin spherules for treating COVID-19: DOE led rapid optimization using arbitrary interface; applicable for emergency situations. Int J Biol Macromol. 2021;182:1769-84.
27. Perioli L, Ambrogi V, Rubini D, Giovagnoli S, Ricci M, Blasi P, et al. Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease. J Control Release. 2004;95:521-33.
28. Singh S, Govind M, Bothara SB. A Review on in vitro-in vivo mucoadhesive strength assessment. Pharma Tech Medica. 2013;2(1):211-29.
29. Singh I, Kumar P, Kumar S, Rana V. Formulation and development of matrix tablet of tramadole using katira gum as release modifier. Yakugaku Zasshi. 2010;130(9):1225-31.
30. Techie-Menson R, Rono CK, Etale A, Mehlana G, Darkwa J, Makhubela BC. New bio-based sustainable polymers and polymer composites based on methacrylate derivatives of furfural, solketal and lactic acid. Mater Today Commun. 2021;28:102721.
31. Obeidat WM, Gharaibeh SF, Jaradat AA, Abualsuod O. Preparation and evaluation of ternary polymeric blends for controlled release matrices containing weakly basic model drug. Curr Drug Deliv. 2021;18(1):54-64.
32. Hussein AA. Preparation and Evaluation of Darifenacin Hydrobromide Loaded Nanostructured Lipid Carriers for Oral Administration. Iraqi J Pharm Sci. 2018;27(1):60.