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Fabrication And In Vitro Evaluation of Buccal Mucoadhesive Tablet of Antihypertensive Drug

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ABSTRACT

The buccal route offers excellent opportunities and potential advantages for systemic drug delivery as compared to per-oral administration. The present study involves designing, developing, and optimizing the buccal tablet formulation of Carvedilol (CA) by using the QbD approach. The Carvedilol buccal tablets were prepared using the dry granulation method. Based on the DoE, the composition of the optimized formulation of CA BT consists of 20 mg of CA, 10 mg Carbopol 934p, 17.75 mg HPMC K100, 15 mg Chitosan, 30 mg PVP K-30, 1 mg Magnesium stearate, 15.25 mg Mannitol, 1 mg Aspartame, and 50 mg Ethyl cellulose. The optimized formulation of CA BT 18 was found to have a mucoadhesive strength of 22.28±0.35 g, a swelling index of 79.35 ± 0.35%, and drug release was sustained up to 10th h, compared to the marketed product, the release was up to 8h. The drug release kinetics were best explained by the Korsmeyer Peppas plot, which demonstrates drug release by stress-induced swelling and slow erosion from the polymer. An attempt was made to design a buccal tablet of Carvedilol individually for sustained drug release in the treatment of hypertension. The formulation can be given in case of a patient who cannot take medication orally, in trauma, and unconscious patients. The development of a new pharmaceutical product is very time-consuming, extremely costly, and high-risk, with very little chance of a successful outcome. Hence, in the study already marketed drug product Carvedilol was chosen as a buccal drug delivery system by a novel approach using QbD tools to target the quality product accurately.

Keyword: *Fabrication, In Vitro Evaluation, Buccal Mucoadhesive, Tablet, and Antihypertensive Drug*.

1. INTRODUCTION

Carvedilol is a potent antihypertensive drug of class angiotensin II receptor antagonist class. Carvedilol selectively blocks the binding of angiotensin II to AT1 in many tissues, including vascular smooth muscle and the adrenal glands. This inhibits the AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in an overall decrease in blood pressure. Carvedilol is greater than 10,000 times more selective for AT1 than AT2. But this drug exhibits poor water solubility and extensive first-pass metabolism. To overcome these problems, a lot of research has been performed by many people throughout the world, but a complete solution is still awaited. Carvedilol cilexetil is a pro-drug of carvedilol, which on action of the esterase enzyme present in the intestinal wall hydrolyses to the active carvedilol moiety in the gastrointestinal tract (1, 2).

Unfortunately, pro-drug form of carvedilol has not completely overcome poor oral bioavailability, but rather raised Bioavailability approximately 40% from 15% in humans. The reasons for carvedilol's low bioavailability and low absorption are low water solubility and efflux by drug resistance pumps in the gastrointestinal tract. Traditional oral dosage forms are prone to first-pass metabolism and or degradation due to enzymes, but mucoadhesive films can bypass first-pass metabolism

and related degradation with more patient compliance without risk of choking in pediatric and geriatric populations. Oral

drug delivery is the most frequent route of drug administration. However, some important restrictions strengthen the necessity for developing new drug delivery systems. Mucoadhesive drug delivery systems through buccal, sublingual, rectal, and nasal mucosa can be a faster and systemic mode of non-invasive drug administration to bypass first-pass metabolism (3, 4).

Faster delivery and enhanced Bioavailability of drugs are observed through mucoadhesive administration. Buccal drug delivery is the most promising drug delivery in mucoadhesive systems. A range of dosage forms can be incorporated in buccal drug delivery. But buccal films are more popular due to simplicity in preparation, drug loading, and characterization. First-pass metabolism-prone drugs can be administered by this non-invasive drug delivery system of buccal film. Mucoadhesive oral films are promising dosage forms because of the fast onset of action, ease of transportation, and handling. Direct systemic delivery of the drug reduces dosing frequency and thus reduces unnecessary toxicity of high doses. Antihypertensive drugs require rapid absorption for rapid onset of action, and hence, buccal film type dosage form is beneficial for drugs that have poor oral bioavailability. Despite the known benefits, the number of marketed films is still quite small. Moreover, it is reasonable to expect an increase in the number of products on the market due to their great potential to satisfy unmet medical needs. Similarly, very little research is being carried out in the design and development of systems that could increase the absorption and bioavailability of poorly water-soluble and extensively first-pass metabolism-prone drug-carvedilol. This research would provide a unique and simple muco-adhesive buccal film system, which is an alternative to the other conventional types of drug delivery systems of antihypertensive drug-carvedilol (5, 6)

2. MATERIAL AND METHODOLOGY

Materials

The standard, pharmaceutical, and analytical grade reagents and chemicals were purchased from Sigma-Aldrich Chemical. Pvt. Ltd., Bangalore, India. Carvedilol pharmaceutical grade was purchased from Cadila Pharmaceuticals Ltd, Ahmadabad, India.

Preformulation studies of Carvedilol

For the Preformulation studies of CA BT, the physicochemical characterization of the drug substance, selection of excipients, compatibility studies, estimation of drug content in the CA by UV-Visible Spectroscopy, and HPLC were carried out. CA was characterized and identified by its physical appearance, melting point, ultraviolet (UV) spectroscopy, solubility profile, and infrared (IR) spectroscopy (7).

Drug-excipient compatibility studies by FTIR and DSC

The compatibility studies were conducted between CA and selected excipients by FTIR and DSC analysis.

Compatibility studies of the excipients by using FTIR spectroscopy

The drug-excipient compatibility studies are carried out to ensure the interaction between the drug and polymer when they are physically mixed together. CA was subjected to an IR spectroscopic study. Spectra were taken after preparing the pellet with 2-3 mg of sample using potassium bromide in the ratio of 1:100 and were scanned from 4000-400cm^{-1}. The FTIR spectra were scanned for pure CA, polymer, and CA-physical mixture individually to detect any appearance or disappearance of characteristic peaks (8, 9).

Compatibility studies of the excipients by using DSC analysis

DSC studies were used to perform thermal analysis as per Swamy et al., 2012. The thermal behaviors of CA, Carbopol 934p, HPMC K100, and Chitosan with their physical mixture were studied using DSC analysis to confirm the compatibility between them. It is based on the principle of measurement of heat flow in and out of the sample & reference for the period of controlled temperature cycle. DSC was performed with a 2mg sample in T T-zero pan-Aluminum, encapsulated with T T-zero lid-Aluminum by T-zero press. An inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 mL/min. Samples were heated at a temperature range of 0 to 300°C with ramping at 10°C/min under nitrogen gas at a flow rate of 40 mL/min, and thermograms were obtained. The thermal behaviors of the pure drug substance were compared with the physical mixture (10, 11).

Formulation of CA buccal tablets

The composition of the CA BT was shown in Table 4.8; each tablet contains 20 mg of Carvedilol. Before direct compression, all the ingredients were screened through a sieve with a 4.8 mm. The backing layer (EC) was compressed using an 8.0 mm flat-faced punch on a tablet compression machine. CA was mixed manually with different ratios of polymers such as Carbopol 934p, HPMC K-100, and Chitosan. To this PVP K-30 (binder), Mannitol and Aspartame (sweetening agent) were added and mixed for 10 min. The above blend was mixed with magnesium stearate (lubricant) for 3 min. The tablets were compressed using a sixteen-station CEMACH rotary tablet-punching machine by the direct compression method using 8.0 mm flat-faced punches. The results of the composition of DoE trials for the prepared CA BT were mentioned in Table 1 (12).

Evaluation of CA buccal tablets

The tablets were compressed using a sixteen-station CEMACH rotary tablet-punching machine by the direct compression method using 8.0 mm flat-faced punches. The compression force was adjusted to get the desired hardness of 3 –5 kg/cm^2, depending on the weight of the tablet and ingredients in the formulation. The following parameters were investigated for the prepared CA-BT (13-15).

- ✓ Weight variation test
- ✓ Tablet thickness and diameter
- ✓ Tablet hardness test
- ✓ Disintegration test
- ✓ Friability
- ✓ Drug content
- ✓ Surface pH Study
- ✓ Measurement of bioadhesive strength
- ✓ Swelling index study

Table 1: Composition of the CA BT by the trial and error method

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17
Carvedilol	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Carbopol 934p	7.5	7.5	10	5	7.5	5	7.5	7.5	5	10	10	5	5	10	7.5	7.5	7.5
HPMC K100M	20	15	17.5	17.5	15	20	20	17.5	17.5	17.5	20	17.5	15	15	17.5	17.5	17.5
Chitosan	0	15	0	0	10	7.5	15	7.5	7.5	15	7.5	15	7.5	7.5	7.5	7.5	7.5
PVP K-30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mannitol	30.5	20.5	30.5	35.5	25.5	25.5	15.5	25.2	28	15.5	20.5	20.5	30.5	25.5	25.5	25.5	25.5
Aspartame	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Ethyl cellulose	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Total weight	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160

3. RESULT AND DISCUSSION

Preformulation studies of Carvedilol

Physical appearance

The physical appearance of Carvedilol was found to be white crystalline powder, which meets the description criteria mentioned in the CoA of Cadila Pharmaceuticals Ltd, Ahmadabad, and also as per USP-41 Monograph, 2018 specification.

Melting point

The melting point of Carvedilol by capillary method was found in the range of 142-144°C and the average of three reading was found to be 143.3°C as shown in Table 2; it meets the melting point criteria as observed in the CoA of Cadila pharmaceuticals ltd, Ahmedabad and also as per USP-41 Monograph, 2018 specification.

Table 2: Results of the melting point of Carvedilol

✓ S. No	✓ Melting point of Carvedilol (°C)
✓ 1	✓ 142
✓ 2	✓ 144
✓ 3	✓ 144
✓ Average	✓ 143.3

Solubility studies

The results of the solubility studies performed in the selected solvents /media, such as distilled water, methanol, ethanol, and PB (pH 6.8), are provided in Table 3. Based on the solubility data, it can be inferred that the solubility in distilled water (22 µg/mL) < ethanol (41 µg/mL) < PH (pH 6.8) (58 µg/mL).

Table 3: Results of solubility studies of Carvedilol

✓ Solvents /media	✓ Solubility (µg/mL)	✓ Absorbance
✓ Distilled water	✓ 22	✓ 0.125
✓ Methanol	✓ 86	✓ 0.486
✓ Ethanol	✓ 41	✓ 0.354
✓ Phosphate buffer pH 6.8	✓ 58	✓ 0.234

Ultraviolet (UV) absorption maxima (λmax)

The spectral scanning was carried out by using methanol as a solvent by using a UV-VIS spectrophotometer. The UV-visible spectrum of Carvedilol was shown in Table 4 and Fig. 1. The spectra showed a sharp peak at 212 nm. The wavelength provided sensitivity and high repeatability in absorbance values, as mentioned by the earlier authors; λ max of 212 nm was selected for all further studies.

Table 4 Results of determination of λ max in methanol

✓ S.no	✓ Solvent	✓ λ max
✓ 1	✓ Methanol	✓ 212 nm

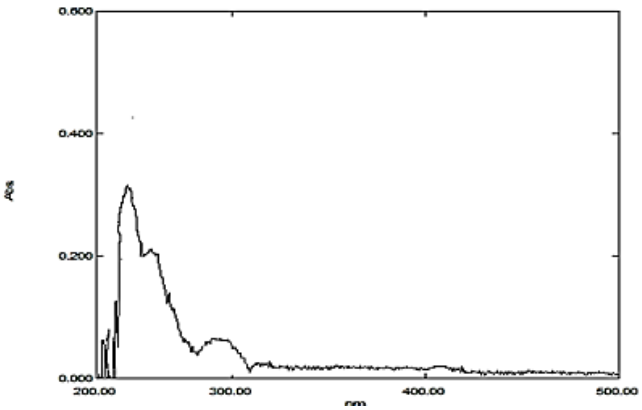

Figure 1: Results of UV Spectrum scanning for Carvedilol

Fourier Transform Infra-Red (FT-IR) spectroscopy

Carvedilol was characterized by FT-IR; the Carvedilol working standard was compared with a reference standard of Carvedilol with their spectral data from the scanned sample at 4000-400 cm^{-1}. It was observed that the presence of N-H stretching amide, C=O carboxylic acid stretching, C=O amide stretching, C=O ester stretching, and COOH stretching were characteristic peaks of Carvedilol, which were similar to those of the working sample. Carvedilol indicates that both the working standard and reference standard of Carvedilol were similar. The results are shown in Figs 2 and 3, and the interpretation of the FT-IR Spectrum of the pure drug is mentioned in Table 5.

Table 5: Results of FTIR values of pure drug (Carvedilol)

✓ **Characteristic peak**	✓ **Standard range (cm^{-1})**	✓ **Carvedilol peaks (cm^{-1})**
✓ N-H stretching amide	✓ 3500-3310	✓ 3210.02
✓ C=O carboxylic acid stretching	✓ 1760-1720	✓ 1751.28
✓ C=O amide stretching	✓ 1690-1630	✓ 1647.07
✓ C=O Stretching ester	✓ 1750-1735	✓ 1726.81
✓ COOH	✓ 3300-2500	✓ 3024.19

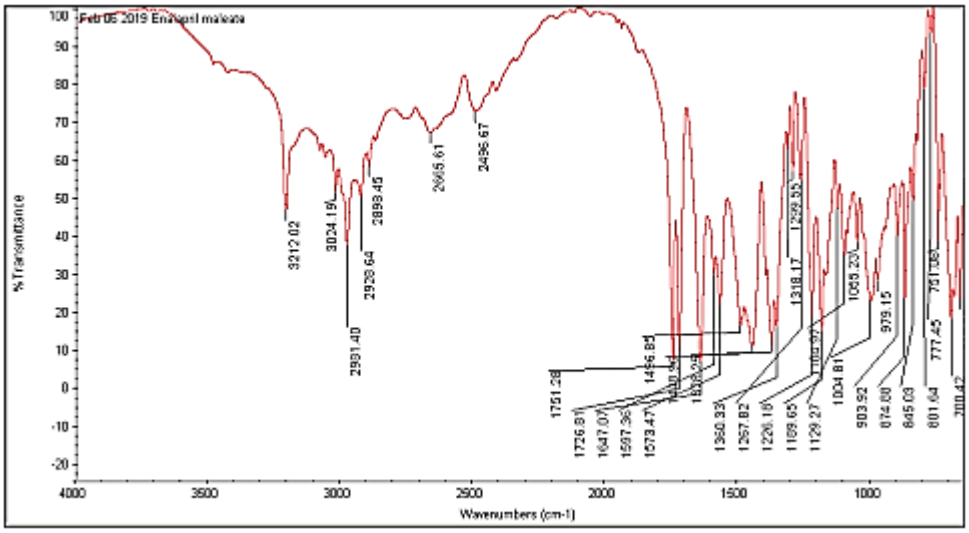

Figure 2: Results of FTIR of the working standard

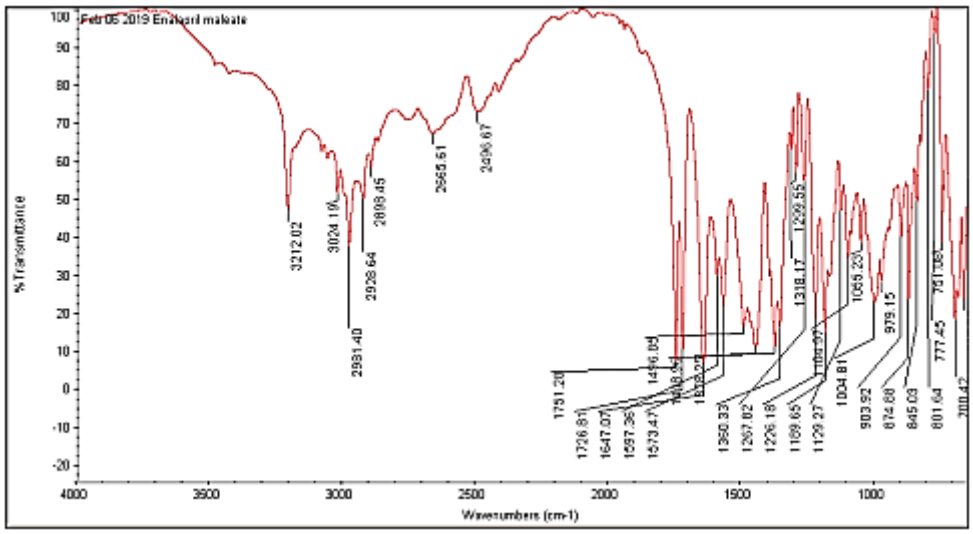

Figure 3: Results of FTIR of reference standard

Selection of Excipients in the Pre-Formulation Studies of CA

The selection of the polymers for the preparation of Carvedilol was based on the literature and following the criteria of the earlier authors, Punitha and Girish. 2010. HPMC K100 was selected due to its impact on the flow properties of the blend, good mechanical strength, and slow erosion of release from the buccal tablet. The polymer Carbopol 934P has the highest viscosity, a readily swellable nature, sustained release behavior, excellent hardness, and low friability in the tablet. The polymer Chitosan has influenced the retention time of the formulated buccal tablet. PVP K30 was selected as a binding agent due to its pH-stable, biocompatible, bonding nature, catering to both hydrophilic & lipophilic drugs, and is safe certified by the FDA. Magnesium stearate is a lubricant, chemically stable, improves the flow ability of the lubricated blends by reducing the adhesion forces between powder/equipment as well as particle/particle in terms of wall friction, interparticle friction, and is FDA approved. Mannitol was a free-flowing granular form, odorless, inert, and non-hygroscopic, commonly used as a diluent in the manufacture of buccal tablet formulations. Aspartame was a sweetening agent with a low calorie, poorly absorbed by the intestine, and commonly used in buccal tablets. The backing membrane plays a major role in the attachment of the bioadhesive tablet to the mucus membrane. Ethyl cellulose was selected in the study as a backing membrane, which was inert, impermeable to the drug, and prevented the drug loss by a unidirectional approach.

Drug-excipient compatibility studies by FTIR and DSC

Compatibility studies by FTIR

The compatibility between Carvedilol and excipient was evaluated using the FTIR peak matching method. The IR spectra of the physical mixture of Carvedilol, HPMC K100, Carbopol 934p, Chitosan, and PVPK-40 were superimposable with that of Carvedilol, which confirmed the absence of any chemical interaction between the drugs with excipients. Further, it can be found that it involves only weak physical bonding interaction of and studied excipients, which was confirmed by the shifting of the FTIR spectrum of the pure drug was recorded, and interpretation was done. The original characteristics IR absorption peaks of pure drug (Carvedilol) at 3210.02cm^{-1} (N-H stretching amide), 1751.28cm^{-1} (C=O carboxylic acid stretching), 1647.07cm-1 (C=O amide stretching), 1726.81cm^{-1} (C=O Stretching ester), 3024.19cm^{-1} (COOH), these peaks are observed in physical mixture spectra, with less intensity. The compatibility studies coincided with the previous author's work of **Vineela Sangu (2017**. The result was shown in Table 6 and Figs. 4 to 5.

Table 6: Results of the FTIR peaks of the pure drug and the physical mixture

✓ Characteristic peaks	✓ Frequency cm-1	
✓	✓ Carvedilol	✓ Carvedilol + Physical mixture
✓ N-H stretching amide	✓ 3210.02	✓ 3212.01
✓ C=O carboxylic acid stretching	✓ 1751.28	✓ 1750.95
✓ C=O amide stretching	✓ 1647.07	✓ 1647.37

✓ C=O Stretching ester	✓ 1726.81	✓ 1726.64
✓ COOH	✓ 3024.19	✓ 2981.25

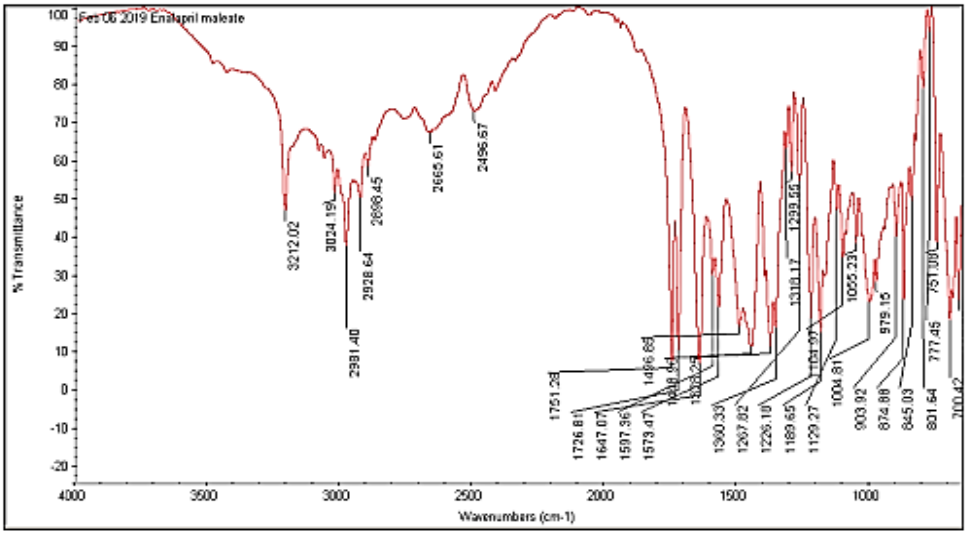

Figure 4: Result of FTIR spectra of pure drug Carvedilol

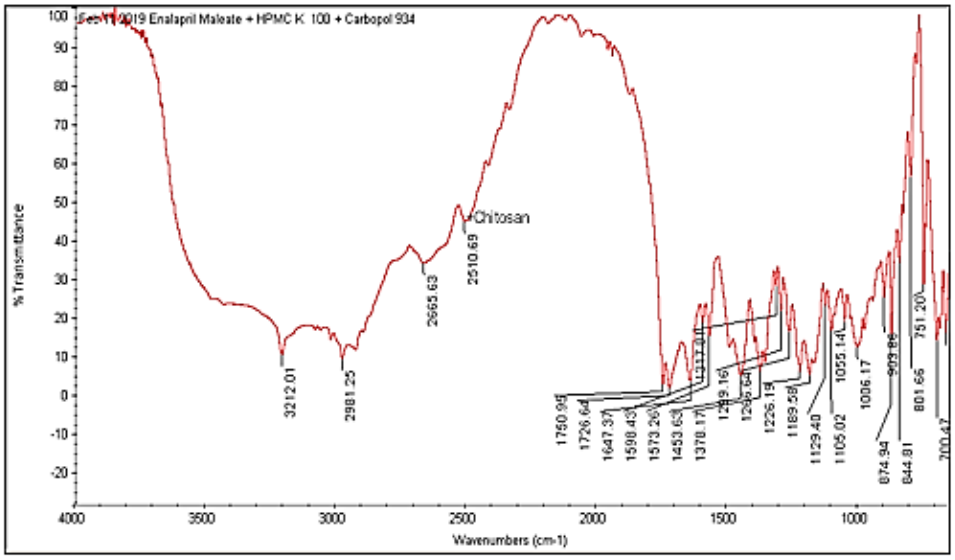

Figure 5: Result of FTIR spectra of pure drug Carvedilol + physical mixture

Compatibility studies by DSC

DSC thermogram of Carvedilol shows a sharp endothermic peak at 143.19ºC; and the physical mixture HPMC K100, Carbopol 934p, Chitosan, and PVP K40 shows an endothermic peak at 143.20°C. The thermogram suggests that there was no interaction between Carvedilol and the excipient selected. The results coincided with the earlier author's work of Rezende et al., 2008. The results of compatibility studies of pure drug Carvedilol (A) and the physical mixture (B) are shown in Figs. 6 and 7.

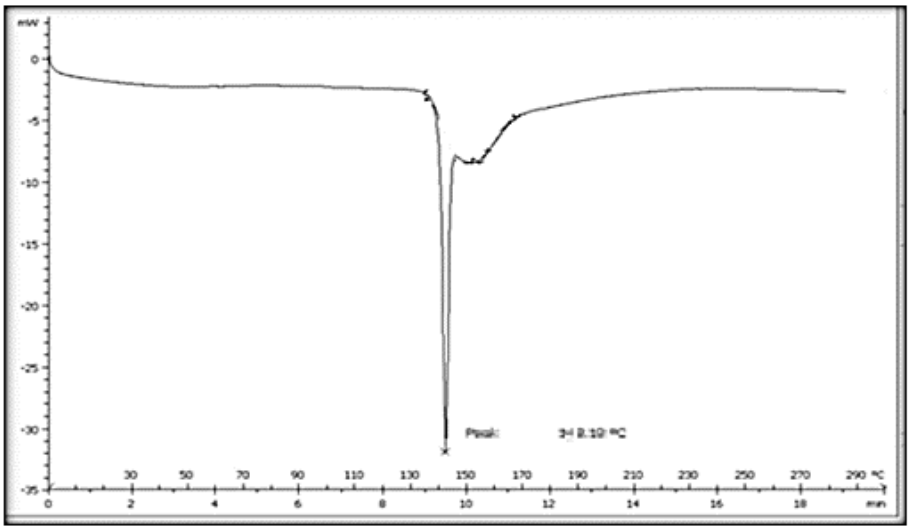

Figure 6: Results of the Pure drug Carvedilol

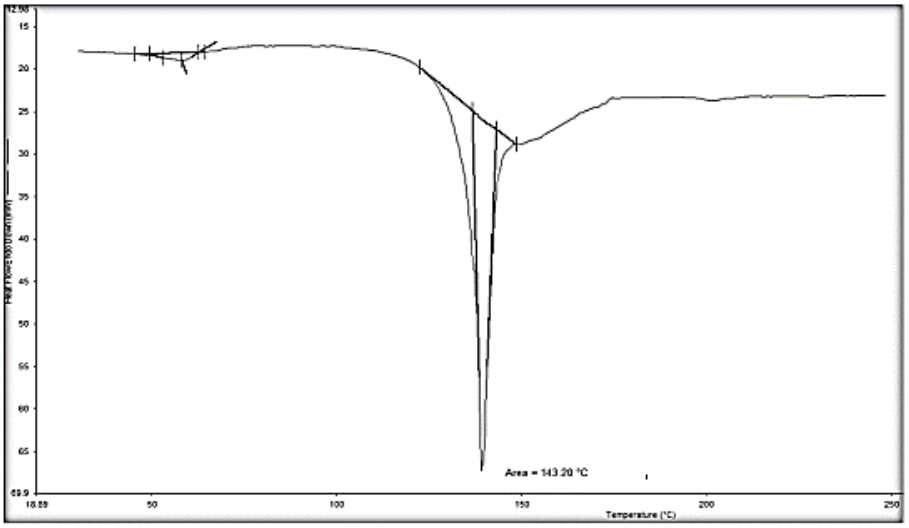

Figure 7: Results of the Pure drug Carvedilol + Physical mixture

Evaluation of Carvedilol blend for buccal tablet.

Carvedilol mix buccal tablet flow characteristics were measured by angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's compressibility index. Carvedilol buccal tablet components were dry mixed and sieved through a #40 mesh. Table 7 shows the flow characteristics of the mix. The observed angle of repose for Carvedilol BT 18 mix was 36.5±0.20. Research indicates that powder flow is best at <25 angle of repose, followed by 25-30 Good, 30-40 Passable, and >40 Very Poor. Dry mixing Carvedilol for buccal tablet yielded acceptable blend properties. The Carvedilol BT 18 blend has a loose bulk density of 0.46 ± 0.08gm/cm3 and a tapped density of 0.60 ± 0.08gm/cm3. Hausner's ratio was 1.30, and Carr's compressibility index was 23.33 for Carvedilol buccal tablet mix. Table 5.18 shows that the prepared mix flowed well. The Carvedilol blend's micromeritics are acceptable based on the compressibility index (%) and Hausner's flowability scale.

Table 7: Results of evaluation of flow properties of Carvedilol BT 18 blend

✓ Formulation Code	✓ Angle of repose (θ)	✓ Bulk density (g/cm3)	✓ Tapped density (g/cm	✓ Hausner's ratio	✓ Carr's compressibility index

			^{3})		
✓ EM BT 18	✓ 36.5 ± 0.2	✓ 0.46± 0.08	✓ 0.60± 0.08	✓ 1.30	✓ 23.33

Moisture absorption test

Moist absorption indicates bioadhesive polymers' ability to preserve formulation integrity following wetness. The Carvedilol BT 18 absorbs 20.13 to 23.05 % v/w of moisture, with no notable change in the 8th due to maintaining integrity. As the tablets absorb moisture well, they may be utilised directly. The formulation's mucoadhesive polymers, HPMC K100, Carbopol 934p, and Chitosan, become adhesive on hydration, swell, and spread, initiating deep contact with the mucosal layer and slowly releasing the drug. Table 8 and Fig. 8 show moisture absorption test results.

Table 8: Results of the evaluation of the moisture absorption test for Carvedilol BT 18

✓ **Tablet No.**	✓ 1	✓ 2	✓ 3	✓ 4	✓ 5	✓ 6	✓ 7	✓ 8
✓ **Moisture absorbed in** ✓ **Carvedilol BT 18**	✓ 22.89 ✓ ±0.56	✓ 20.13 ✓ ±1.08	✓ 20.47 ✓ ±0.55	✓ 22.28 ✓ ±1.10	✓ 22.95 ✓ ±0.98	✓ 23.05 ✓ ±1.22	✓ 22.66 ✓ ±0.24	✓ 20.79 ✓ ±0.98

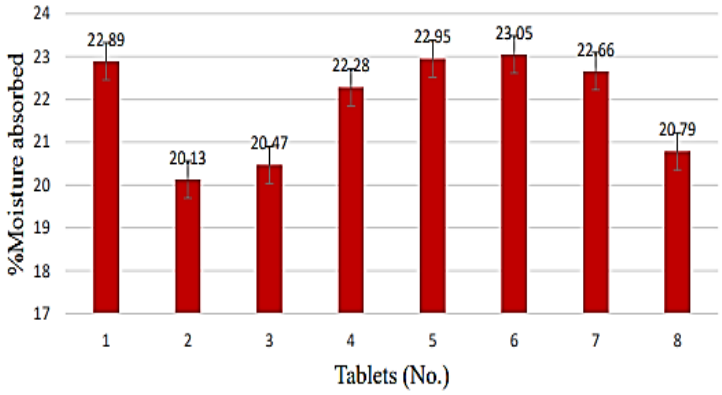

Figure 8 Results of the evaluation of the moisture absorption test Carvedilol BT 18

Residence time

The ex vivo residence time was assessed via a modified USP disintegration equipment. The duration required for the total erosion or detachment of the tablet from the glass surface was documented and regarded as the ex vivo residence period. In the disintegration test device, Carvedilol BT 18 has a residence duration of 8.15 ± 0.10 hours. The ex vivo residence time is a crucial physical property of buccal mucoadhesive tablets. Carvedilol BT 18, compounded with HPMC K100, Carbopol 934P, and Chitosan, demonstrated an extended residence duration. With the augmentation of mucoadhesive polymer concentration, the retention duration escalated. This assessment indicates the adhesive properties of polymers used in formulations.

Ex vivo permeation study of Carvedilol BT 18

Drug absorption kinetics via biological membranes are usually studied in ex vivo permeation studies. Drug molecules and physiological barriers govern drug transport via any membrane. Pig buccal mucosa was used for drug permeation tests because it is most similar to human buccal mucosa in structure and content. Franz diffusion cell studies showed sluggish and consistent drug penetration of Carvedilol BT 18. Polymers like HPMC K100 delay drug release, Carbopol 934p sustains it, and Chitosan affects buccal tablet retention. The backing membrane in the ex vivo investigation renders release unidirectional. Table 10 shows that drug penetration from buccal tablets to porcine buccal mucosa was slow and consistent, releasing 99.12±0.19% of the medication in 8 hours with a flux of 0.055 ± 0.012mg h–1 cm–2 and a permeability coefficient of 0.02753 ± 0.001. Increased polymer content increases gel viscosity, which may lengthen diffusion. QbD emphasizes product, process understanding, and process control, which can lower the drug's effective diffusion coefficient and reduce the dissolution medium's penetration into the tablet matrix and drug release rate during formulation and optimization. Based on strong science and quality risk management, HPMC K100, Carbopol 934p, and Chitosan dominate buccal tablet Carvedilol release. Results are in Table 9 and Fig. 9.

Table 9 Results of Ex vivo permeation study of Carvedilol BT 18

✓ Time	✓ Drug permeated (%)
✓ 1	✓ 15.58±0.10
✓ 2	✓ 30.93±0.24
✓ 3	✓ 46.81±0.25
✓ 4	✓ 68.73±0.47
✓ 5	✓ 76.02±0.11
✓ 6	✓ 82.45±0.22
✓ 7	✓ 88.76±0.26
✓ 8	✓ 99.12±0.19

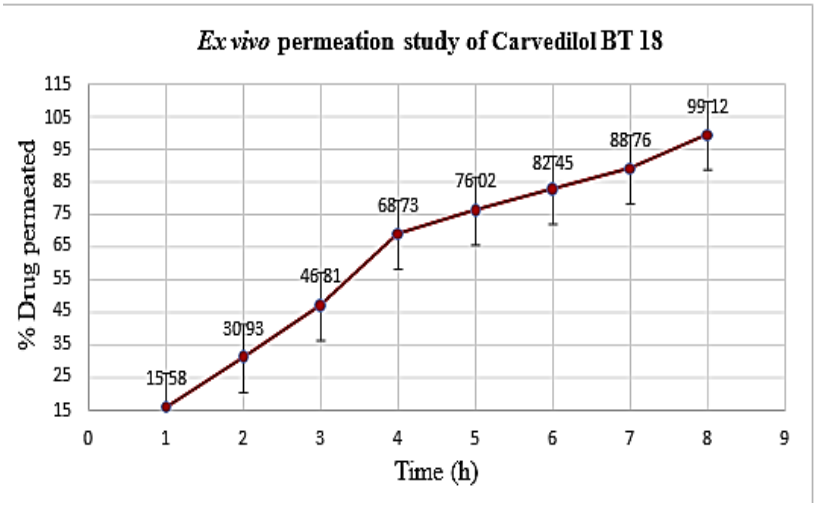

Figure 9 Results of the Ex vivo permeation study of Carvedilol-BT 18

Table 10 Results: Flux and Permeability Coefficient of Carvedilol BT 18

✓ Formulation	✓ Flux (mg/cm2/hr)	✓ Permeability coefficient
✓ EM BT 18	✓ 0.055 ± 0.012	✓ 0.02753 ± 0.001

Pharmacokinetics and in vivo drug release study for Carvedilol BT 18

In the in vivo evaluation, rabbits were separated into A and B. Carvedilol BT 18 was buccally administered in Group A and intragastrically in Group B. In vivo drug absorption was compared between groups A and B using HPLC plasma analysis. Table 11 and Fig. 10 show rabbits absorbed API for 12 h and generated medicine for 20 h. Carvedilol BT 18 (tmax 6h, Cmax 99.32ng/mL, AUC899.6 mg xh/L, AUMC 162713.46 h 2µg/mL, mean residence 18.02 h) and API (tmax 6h, Cmax 98.1ng/mL, AUC 677.54 mg xh/L, AUMC 7942 h2µg/mL, mean residence 11.22 h) have pharmacokinetic data. Compared to API, Carvedilol BT 18 increased AUC by 14% and AUMC by 35%. API has worse pharmacokinetics than carvedilol BT 18. API has 1.327 F bioavailability and 1.32 F adjusted. Table 12 displays rabbit pharmacokinetic data for Carvedilol BT 18's >0.12 acceptance threshold, which enhanced bioavailability.

Table 11: Result of in vivo drug release study of Carvedilol BT 18

✓ Time (h)	✓ Group A (Carvedilol BT 18)	✓ Group B (Carvedilol -API)
✓ 0.5	✓ 9.0±1.04	✓ 15±1.20
✓ 1	✓ 13.90±1.50	✓ 32.4±0.23
✓ 2	✓ 25.54±3.42	✓ 56.98±1.34
✓ 4	✓ 51.05±1.58	✓ 76.21±0.14
✓ 6	✓ 99.32±0.71	✓ 98.05±0.19
✓ 8	✓ 83.92±5.08	✓ 69.37±0.86
✓ 10	✓ 64.24±3.00	✓ 28.33±0.91
✓ 12	✓ 38.33±6.81	✓ 6.7±1.54
✓ 16	✓ 27.79±1.52	✓ 0
✓ 20	✓ 6.37±1.02	✓ 0
✓ 24	✓ 0	✓ 0

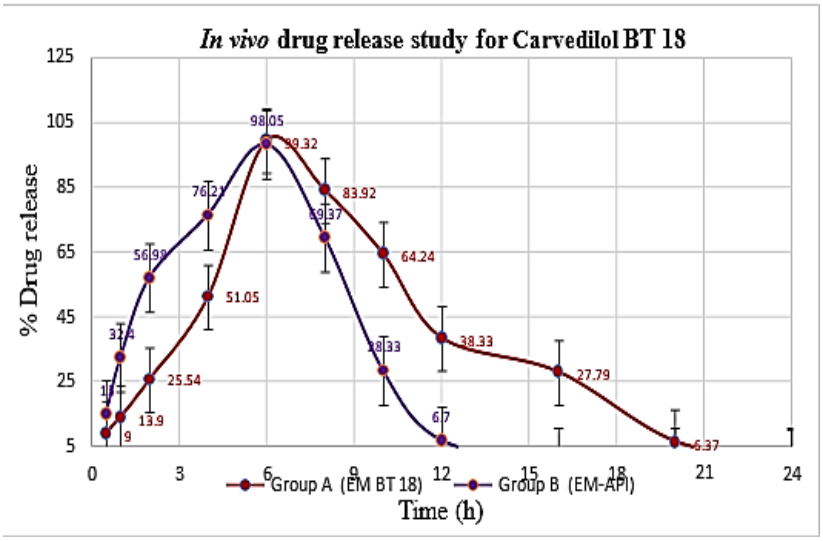

Figure 10: Result of in vivo drug release study, Carvedilol BT 18

Table 12: Result of Pharmacokinetic study for Carvedilol BT 18 and pure drug

✓ Pharmacokinetic parameters	✓ Carvedilol BT 18	✓ Carvedilol API
✓ tmax (h)	✓ 6	✓ 6
✓ Cmax (ng/mL)	✓ 99.32	✓ 98.1
✓ AUC (mgxh/L)	✓ 899.6	✓ 677.54
✓ AUMC(h2µg/mL)	✓ 16213.46	✓ 7942
✓ Mean residence time (h)	✓ 18.02	✓ 11.22

In vitro release kinetics of the optimized Carvedilol BT 18

The release profiles of the optimized formulation of Carvedilol BT 18 were used to assess the release data and regression coefficient values of several release kinetics equations. The optimized Carvedilol BT 18 was best described by the Korsmeyer Peppas plot, which exhibited greatest linearity (R2 = 0.99903 and Y 1.023x + 1.093) and zero order (R2 = 0.9858). Table 13 shows that the Korsmeyer-Peppas equation had strong linearity, and the release component n was 1.0200, following non-Fickian super case II diffusion. This Korsmeyer-Peppas model release kinetics indicates that stress-induced swelling and delayed degradation of the polymer release medication from prepared tablets. Figure 11 shows the optimized formulation kinetic model graphs.

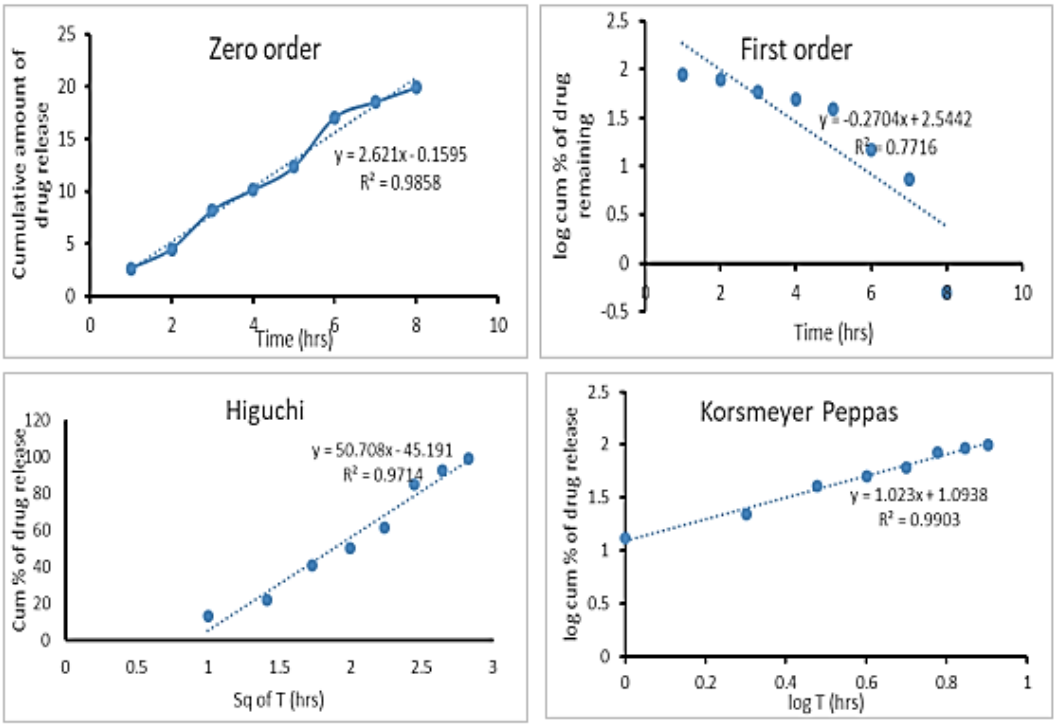

Figure 11: Result of Release Kinetics for Carvedilol BT 18

Table 13: Result of Release Kinetics for Carvedilol BT 18

✓ ✓ Formulation code	✓ Mathematical models (Release Kinetics)				
	✓ Zero order	✓ First order	✓ Higuchi	✓ Korsemeyer-Peppas	
	✓ R^2	✓ R^2	✓ R^2	✓ R^2	✓ "n"

✓ **Carvedilol BT 18**	✓ 0.9858	✓ 0.7716	✓ 0.9714	✓ 0.9903	✓ 1.0200

Stability studies for Carvedilol BT 18

Stability study results for Carvedilol-BT 18 stored at 25°C ± 2°C, 60% ± 5% RH for 6 months. Results from Carvedilol -BT 18 descriptions at 0, 1, 2, 3, and 6 months are given in Table 14. Stability experiments showed no significant changes in appearance, hardness, friability, thickness, or weight. The drug content ranged from 18.1±0.02 to 18.6±0.52 mg of the label claim. The study found no significant changes in Carvedilol BT 18 storage at 25°C ± 2°C and 60% ± 5% RH for 6 months.

Table 14 Results of the stability studies for Carvedilol BT 18 on Storage at (25°C ± 2°C and 60% ± 5% RH)

✓ **Description**	✓ **Storage conditions (25°C ± 2°C/60% RH ± 5%)**				
	✓ **Initial**	✓ **After 1 month**	✓ **After 2 months**	✓ **After 3 months**	✓ **After 6 months**
✓ **Physical appearance**	✓ Off white color tablet	✓ Off white color tablet	✓ Off white color tablet	✓ Off white color tablet	✓ Off white color tablet
✓ **Hardness** ✓ **(Kg/cm)^2**	✓ 4.65±0.68	✓ 4.64±0.61	✓ 4.54±0.68	✓ 4.57±0.61	✓ 4.54±0.62
✓ **Friability (%)**	✓ 0.54±0.12	✓ 0.51±0.12	✓ 0.52±0.12	✓ 0.54±0.12	✓ 0.54±0.12
✓ **Thickness (mm)**	✓ 2.24±0.02	✓ 2.24±0.02	✓ 2.24±0.02	✓ 2.23±0.02	✓ 2.24±0.02
✓ **Weight variation (mg)**	✓ 163.42±7.5	✓ 1623.22±7.5	✓ 163.24±7.5	✓ 163.51±7.5	✓ 163.39±7.5
✓ **Drug content (mg) label claim**	✓ 18.6±0.52	✓ 18.1±0.02	✓ 18.4±0.11	✓ 18.2±0.46	✓ 18.1±0.02

4. SUMMARY AND CONCLUSION

In the present study, a buccal mucoadhesive tablet of Carvedilol was successfully prepared. An attempt was made to design a buccal tablet of Carvedilol for sustained drug release in the treatment of hypertension. The formulation can be given in case of a patient who cannot be able take medication orally in trauma and unconscious patients (16). The development of a new pharmaceutical product is very time-consuming, extremely costly, and high-risk, with very little chance of a successful outcome. Hence, in the study already marketed drug product Carvedilol was chosen as a buccal drug delivery system by a novel approach using QbD tools to target the quality product accurately. In a stability study, optimized formulation Carvedilol was found to be stable at 25±2ºC / 60% ±5%RH and 5°C ± 3°C for 6 months. There was no significant change observed in physical appearance and drug content during this six-month stability study period under the studied stability conditions (17, 18).

Abbrivations:

°C Degree Celsius

µg Microgram

µL	Microliter
µm	Micrometer
CA	Carvedilol
BA	Buccal Tablet
ANOVA	Analysis of variance
API	Active Pharmaceutical Ingredients
AUC	Area under the Curve
AUMC	Area Under the first Moment Curve F Bioavailability
BBD	Box-Behnken Design
BCS	Biopharmaceutical classification system
MDDS	Mucosal Drug Delivery System
CMAs	Critical Material Attributes
CPPs	Critical Process Parameters
CV	Coefficient of variation
D.T	Disintegration Test
DDS	Drug Delivery System
DoE	Design of Experiments
DSC	Dynamic Scanning Calorimetry
FD	Factorial Design
FTIR	Fourier Transform Infrared Spectroscopy
$T_{1/2}$	Half life
FDA	Food and Drug Administration
G/mol	gram-molecule
PKa	acid dissociation constant
Log P	Partition coefficient
CVD	Cardiovascular disease
ACE	Angiotensin Converting Enzyme
g	Gram
GMO	Gyceryl Monooleate
HPMC	Hydroxy Propyl Methyl Cellulose
HEC	Hydroxy Ethyl Cellulose
HPC	Hydroxypropyl cellulose
PAA	polyacrylic acid
PVA	polyvinyl alcohol
PVP	Polyvinylpyrrolidone
Na CMC	Sodium Carboxy Methyl Cellulose
h	Hour
HPLC	High-Performance Liquid Chromatography
ICH	International Conference on Harmonization
IP	Indian Pharmacopoeia
IR	Infrared Spectroscopy

Mg	Milligram
Min	Minute
ML	Milliliter mm Millimeter
NDDS	Novel Drug Delivery System
QbD	Quality by Design
QTPP	Quality Target Product Profile
R^2	correlation coefficient
Rpm	Rotation per minute
RSM	Response Surface Methodology

REFERENCES

[1] Abruzzo, A., Cerchiara, T., Bigucci, F., Gallucci, M. C., & Luppi, B. (2015). Mucoadhesive buccal tablets based on chitosan/gelatin microparticles for delivery of propranolol hydrochloride. Journal of pharmaceutical sciences, 104(12), 4365-4372.

[2] Choi, H. G., & Kim, C. K. (2015). Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. Journal of controlled release, 68(3), 397-404.

[3] Bahri-Najafi, R., Rezaei, Z., Peykanpour, M., Shabab, L., Solooki, R., & Akbari, P. (2018). Formulation of nicotine mucoadhesive tablet for smoking cessation and evaluation of its pharmaceuticals properties. Advanced Biomedical Research, 2(1), 88.

[4] Çelik, B., Özdemir, S., Barla Demirkoz, A., & Üner, M. (2017). Optimization of Piribedil mucoadhesive tablets for efficient therapy of Parkinson's disease: physical characterization and ex vivo drug permeation through buccal mucosa. Drug Development and Industrial Pharmacy, 43(11), 1836-1845.

[5] Kadam, P. B., Dias, R. J., Mali, K. K., Havaldar, V. D., & Mahajan, N. S. (2018). Formulation and evaluation of buccoadhesive tablets of atenolol. J Pharm Res, 1(2), 193-199.

[6] Gaikwad, S. S., Thombre, S. K., Kale, Y. K., Gondkar, S. B., & Darekar, A. B. (2015). Design and in vitro characterization of buccoadhesive tablets of timolol maleate. Drug Development and Industrial Pharmacy, 40(5), 680-690.

[7] Daswadkar, S. C., Roy, M. A., Walode, S. G., & Kumar, M. C. (2016). Quality by design approach for the development and validation of saxagliptin by RP-HPLC with application to formulated forms. International Journal of Pharmaceutical Sciences and Research, 7(4), 1670.

[8] Grewal, P., Mundlia, J., & Ahuja, M. (2019). Thiol modified Moringa gum–A potential bioadhesive polymer. Carbohydrate polymers, 209, 400-408.

[9] Hassan, N., Khar, R. K., Ali, M., & Ali, J. (2019). Development and evaluation of buccal bioadhesive tablet of an anti-emetic agent ondansetron. Aaps PharmaSciTech, 10, 1085-1092.

[10] Kalaichelvi, R., & Jayachandran, E. (2021). Validated spectroscopic method for estimation of saxagliptin in pure and from tablet formulation. Int J Pharm Sci, 3(3), 179-180.

[11] Shirsand, S. B., Suresh, S., Keshavshetti, G. G., Swamy, P. V., & Reddy, P. V. P. (2017). Formulation and optimization of mucoadhesive bilayer buccal tablets of atenolol using simplex design method. International journal of pharmaceutical investigation, 2(1), 34.

[12] Iswariya, V. T., Babu, V. L., & Avanapu, S. R. (2015). Formulation and evaluation of oro dispersive tablets of saxagliptin. Int. J. Pharm. Sci Rev. Res. January—Febr, 30(2), 42.

[13] El-Nahas, A. E., Allam, A. N., & El-Kamel, A. H. (2017). Mucoadhesive buccal tablets containing silymarin Eudragit-loaded nanoparticles: formulation, characterization and ex vivo permeation. Journal of microencapsulation, 34(5), 463-474.

[14] Onishi, H., Yumoto, K., & Sakata, O. (2015). Preparation and evaluation of Ritodrine buccal tablets for rational therapeutic use. International Journal of Pharmaceutics, 468(1-2), 207-213.

[15] Moghimipour, E., Aghel, N., & Adelpour, A. (2022). Formulation and characterization of oral mucoadhesive chlorhexidine tablets using Cordia myxa mucilage. Jundishapur journal of natural pharmaceutical products, 7(4), 129.

[16] Acholu, P. K., Yajaman, S., & Jayaveera, K. N. (2015). Formulation and In-vitro evaluation of novel buccal

mucoadhesive tablets of Felodipine. The International Research Journal of Pharmacy, 5(11), 14-19.

[17] Munasur, A. P., Pillay, V., Chetty, D. J., & Govender, T. (2016). Statistical optimisation of the mucoadhesivity and characterization of multipolymeric propranolol matrices for buccal therapy. International journal of pharmaceutics, 323(1-2), 43-51.

[18] Kumar, B. P., Kavitha, P., & Devi, K. J. (2024). Formulation design and evaluation of mucoadhesive buccal tablets of nitroglycerin. Int J Pharm Sci, 6(7), 251-9.

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