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Research Article

Formulation and Evaluation of Mucoadhesive Buccal Tablets of Carvedilol

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Abstract

The aim of the study was to formulate and evaluate the carvedilol buccal tablets using HPMC K4M and xanthan gum as polymer. Buccal tablets of carvedilol were prepared by direct compression technique by using polymer in combination at different concentration. Drug excipient compatibility study indicates that there is no interaction between the excipient and the drug. Total seven batches were prepared and subjected to evaluation parameters. Pre-compression parameters for all batches showed excellent flow propertied of powder bled. Prepared buccal tablets were evaluated for various post compression parameters like hardness, thickness, weight variation, drug content, and friability, % swelling index, muco-adhesive strength and in vitro drug release. The harness of all batches was optimum showed good mechanical strength; thickness of tablets was uniform in all formulations the weight variation test of all the formulation was found to be within the limits of pharmacopoeial standard. % swelling index for all the batch formulation was optimum and seen to increase with increase in polymer concentration. Mucoadhesive strength was also showed acceptable results for all batch formulations which satisfy the need of mucoadhesive tablets. The in vitro dissolution profile of all the formulation showed sustained release of drug, for extended periods of time. The optimized formulation of F4 prepared with was consider as the optimized formulation with respect to drug content, % swelling index, Mucoadhesive strength and in vitro drug release pattern for 8 hrs. Formulation F4 showed highest 98.32±1.55 % drug release at the end of 8 hrs. Optimized formulation F4 was found to be stable during the stability studies for 3 month indicating good stability of the formulation.

Keywords: carvedilol, Mucoadhesive strength, Optimized formulation, buccal tablets.

INTRODUCTION

Bioadhesive drug delivery formulations were introduced in1947 when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa. In recent years delivery of therapeutic agents via Mucoadhesive drug delivery system has become highly interesting. Certain drugs have lack of efficacy due to decreased bioavailability, GI intolerance, unpredictable and erratic absorption or pre-systemic elimination of other potential route for administration. The recent development in the drug delivery has intensified the investigation of mucosal drug delivery. Such route includes oral, buccal, ocular, nasal and pulmonary routes etc. Mucoadhesive drug delivery systems are delivery systems, which utilized the property of bioadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to particular region of the body for extended period of time. The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability. Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of drug.[1,2]

Buccal drug delivery systems represent a significant advancement in the field of pharmacology and therapeutics, providing an alternative route for drug administration via the buccal mucosa—the inner lining of the cheek. This method offers several advantages over traditional oral and parenteral routes, making it an attractive option for both patients and healthcare providers. The buccal mucosa is a highly vascularized region, which facilitates rapid and efficient drug absorption directly into the systemic circulation, bypassing the gastrointestinal tract and first-pass hepatic metabolism. This characteristic is particularly beneficial for drugs that are poorly absorbed from the gastrointestinal tract, are unstable in the acidic environment of the stomach, or are extensively metabolized by the liver. Consequently, buccal drug delivery can enhance bioavailability, reduce dosage requirements, and minimize systemic side effects. A variety of dosage forms are used in buccal drug delivery, including tablets, films, patches, and gels. These formulations are designed to adhere to the buccal mucosa and release the drug in a controlled manner

over a specified period. Mucoadhesive polymers are often incorporated to improve the adhesion and retention time of the dosage form, ensuring consistent and prolonged drug release. The buccal route is especially advantageous for patients who have difficulty swallowing (dysphagia), such as the elderly, children, and those with certain medical conditions. It also offers a non-invasive alternative for drugs that are typically administered by injection, enhancing patient compliance and comfort. Furthermore, buccal drug delivery can provide localized treatment for oral conditions, such as mouth ulcers, fungal infections, and periodontal diseases, by delivering high drug concentrations directly to the site of action.[3,5]

Carvedilol works by blocking beta-adrenergic receptors (beta-1 and beta-2) and alpha-1 adrenergic receptors, leading to decreased heart rate and contractility, and vasodilation. This reduces blood pressure and improves heart function. Carvedilol is about 25% to 35% bioavailable following oral administration due to extensive first-pass metabolism. Absorption is slowed when administered with food. The compound is metabolized by liver enzymes, CYP2D6 and CYP2C9 via aromatic ring oxidation and glucuronidation, then further conjugated by glucuronidation and sulfation.[6,7]

MATERIALS AND METHODS

Materials

Carvedilol was obtained as kind sample from Cipla Pharma. Mumbai. HPMC K4M was gifted by Colorcon Asia Pvt Ltd. all other chemicals are analytical grade.

Methods

Drug Excipient Compatibility study

Drug-excipient compatibility studies using Fourier Transform Infrared (FTIR) spectroscopy are vital for detecting potential interactions that may affect the stability, efficacy, and safety of a pharmaceutical formulation. FTIR spectroscopy identifies and characterizes chemical bonds and functional groups in both the drug and excipients by measuring the absorption of infrared radiation at different wavelengths. By comparing the FTIR spectra of the pure drug, individual excipients, and their physical mixtures, can able to detect any shifts in characteristic peaks, indicating possible chemical interactions or incompatibilities. This technique is particularly useful for identifying changes in functional groups that could result from reactions between the drug and excipients. FTIR provides a rapid, non-destructive means of ensuring compatibility, helping to select the most suitable excipients for a stable and effective final product. By ensuring no adverse interactions. A physical mixture of drug and polymer in 1:1 ratio was prepared and mixed with suitable quantity of potassium bromide. The mixture was compressed to form a transparent pellet using a hydraulic press. It was scanned from 400 cm^{-1} to 4000 cm^{-1}in a Shimadzu FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peaks.[8-9]

Formulation of Buccal Tablets of Carvedilol

Buccal tablets of Carvedilol were prepared by direct compression technique using xanthan gum and HPMC K4M (30%) as a polymer. All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula and were passed through #40 to get uniform particle size. The drug and all the ingredients except lubricants were taken on a butter paper with the help of a stainless steel spatula and the ingredients were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend of each formulation was compressed by using 8 mm flat face punch on a rotary tablet punching machine (Karnavathi engineering ltd, Gujarat.). The formulation details of buccal tablets of Carvedilols was shown in table 1[10,12]

Table 1: Composition of Buccal Tablets of Carvedilol

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Carvedilol	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Xanthan Gum	50	40	30	10	20	60	-
HPMC K4M	10	20	30	50	40	-	60
Magnesium Stearate	02	02	02	02	02	02	02
Talc	02	02	02	02	02	02	02
PVP K30	10	10	10	10	10	10	10
Aspartame	1	1	1	1	1	1	1
Microcrystalline Cellulose	118.75	118.75	118.75	118.75	118.75	118.75	118.75
Total Weight	200	250	200	200	200	200	200

Evaluation of powder blend

Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml.[13]

Tapped Density (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for multiple times and the tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml.

Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.[14]

$$\tan(\theta) = h / r$$

$$\theta = \tan^{-1}(h / r)$$

Where, θ is the angle of repose.

h is the height in cms

r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particals slip and roll over each other through the sides of the funnel.

% Compressibility

The Carr's compressibility index, also known as the Carr index or Carr's index, is a parameter used to assess the compressibility and flow properties of powdered or granular materials, particularly pharmaceutical powders. It is calculated based on the bulk density and tapped density of the powder and provides insights into its flowability and compaction characteristics. It indicates powder flow properties.

Hausner Ratio

Hausner's ratio, is a parameter used to assess the flowability of powdered or granular materials, particularly pharmaceutical powders. It is calculated based on the tapped density and bulk density of the powder and provides insights into its flow properties. The Hausner ratio is defined as the ratio of tapped density to bulk density. Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25). [18,19]

Evaluation of Buccal Tablets

Weight Variation Test:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. The average weight per unit is then calculated by dividing the total weight by the number of units in the sample.

Hardness

The hardness test is a crucial quality control measure in pharmaceutical manufacturing, particularly for solid oral dosage forms like tablets. Tablet hardness, often measured in terms of breaking force or resistance to crushing, provides an indication of the mechanical strength and robustness of the tablet. Hardness testing ensures that tablets can withstand handling, packaging, and transportation without breaking or crumbling, thereby maintaining their integrity and appearance throughout their shelf life. Hardness or tablet crushing strength ie the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.

Content Uniformity:

Ten tablets were randomly selected and tested for their drug content. Each tablet was powdered and quantity of powder equivalent to 50 mg of drug was taken and transfer it to 10 ml of methanol. The volume was made up to 100 ml with phosphate buffer pH 6.8. The resulting solution was then diluted appropriately and measured using a UV-Visible spectrophotometer at 241 nm. A concentration of drug was calculated from a standard calibration curve. [15]

Swelling Index:

The swelling index of the buccal tablet was determined in phosphate buffer pH 6.8 The initial weight of the tablet was determined and then tablet was placed in 15 ml phosphate buffer pH 6.8 in a petridish and then was incubated at 37 ± 1° C. The tablet was removed at different time intervals (1, 2, 3, 4, 5, 6, 7 and 8 h) blotted with filter paper and reweighed (W2). The swelling index is calculated by using he formula: [16,17]

$$\text{Swelling index} = 100\,(W2-W1) / W1$$

Where,
W1 = Initial weight of the tablet.
W2 = Final weight of tablet.

Mucoadhesion Strength:

Mucoadhesion strength of the buccal tablet of Carvedilol was determined using modified physical balance using sheep buccal mucosa as model mucosal membrane.

Fresh sheep buccal mucosa was obtained from a local slaughter house and was used within 2 h of slaughtering. The mucosal membrane was washed with distilled water and then with phosphate buffer pH 6.8. A double beam physical balance was taken and to the left arm of balance a thick thread of suitable length was hanged and to the bottom side of thread a glass stopper with uniform surface was tied. The buccal mucosa was tied tightly with mucosal side upward using thread over the base of inverted 50 ml glass beaker which was placed in a 500 ml beaker filled with phosphate buffer pH 6.8 kept at 37° C such that the buffer reaches the surface of mucosal membrane and keeps it moist. The buccal tablet was then stuck to glass stopper from one side membrane using an adhesive. The two sides of the balance were made equal before the study, by keeping a weight on the right hand pan. A weight of 5 g was removed from the right hand pan, which lowered the glass stopper along with the tablet over the mucosal membrane with a weight of 5 g. The balance was kept in this position for 3 min. Then, the weights were increased on the right pan until tablet just separated from mucosal membrane. The excess weight on the right pan i.e. total weight minus 5 g was taken as a measure of the mucoadhesive strength. [18]

In-vitro dissolution study:

The in-vitro dissolution study was carried out in USP dissolution test apparatus type II (paddle) with a dissolution medium of 900 ml of phosphate buffer pH 6.8, at 50 rpm (37±0.5°C). 5 ml aliquot was withdrawn at the specified time interval, filtered through whatmann filter paper, and measured spectrophotometrically after suitable dilution at 241 nm using UV-Visible spectrophotometer. An equal volume of fresh medium, which was pre warmed at 37°C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. The results in the form of percent cumulative drug released were calculated. [19, 20]

Stability study:

The accelerated stability studies were carried out according to ICH guidelines on optimized formulation. The formulation was packed in strip of aluminium foil and was stored in stability chamber maintained at 40°C and 75% RH for the period of 3 months. The Tablet were evaluated before and after 3 months for change in appearance, Hardness, drug content and In vitro release. [21]

RESULT AND DISCUSSION

Compatibility Studies (FT-IR)

Both the polymer and pure drug's infrared spectra are examined. It has been found in this investigation that there is no chemical interaction between the polymer and carvedilol. The major peak in the drug and polymer mixture's infrared spectra was found to remain unchanged, indicating that there was no physical interaction due to bond formation between the two substances.

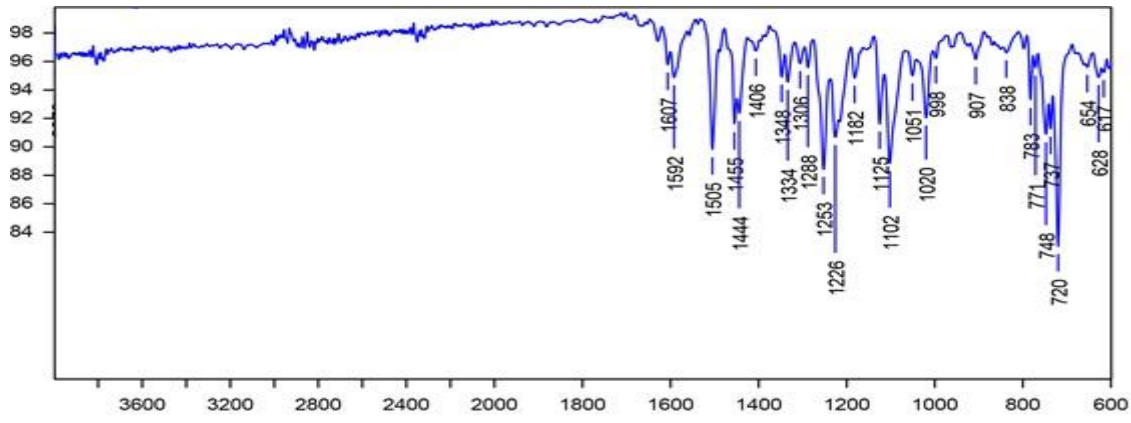

Figure 1: IR spectra of pure drug Carvedilol

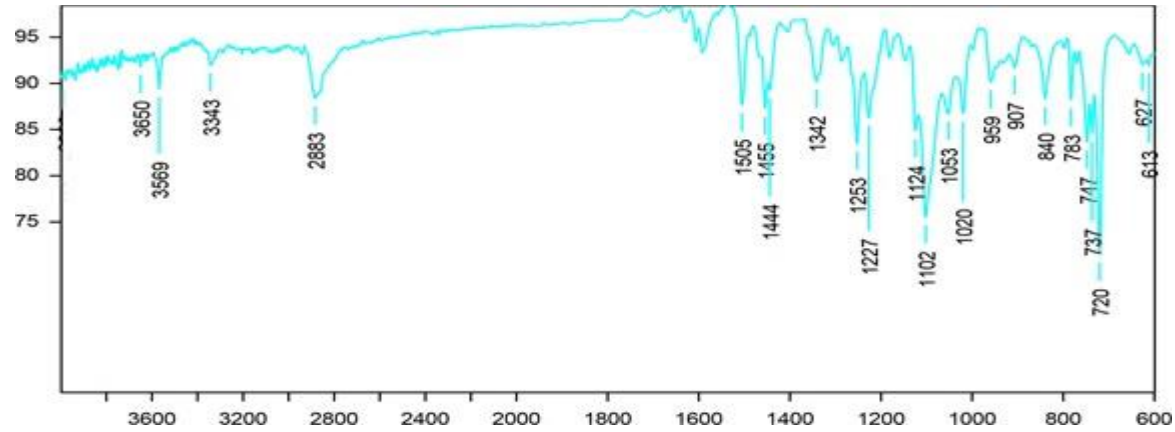

Figure 2: IR Spectra of Carvedilol Buccal Tablets

Evaluation of Powder Blend

Pre-compression parameters play an important role in improving the flow properties of pharmaceuticals especially in tablet formulation. These include Bulk density, Tapped density, Carr's index, Haunser's ratio and Angle of repose. Before formulation of tablets the drug and excipients powder blends were evaluated for all the above precompression parameters and it was found that all the observations were within the prescribe pharmacopoeial limits. Bulk density of all the batch formulations was found to be ranging from 0.622±0.017 to 0.640±0.014 gm/cc, tapped density was found between 0.712±0.036 to 0.738±0.040gm/cc. Angle of repose for all batch formulation was found to be between 22.15±0.70 to 25.65±0.56. Carr's compressibility index was found to be between 11.11 to 18.52 and Hausner's ratio was found to be between 1.13 to 1.15. From the precompression study it was concluded that all tablets batch formulation possesses good flow properties. The results of precompression parameters study was shown in table 2.

Table 2: Pre- Compression parameter of formulation F1 to F7

Formulation Batch	Bulk Density (g/cc)*	Tapped Density (g/cc)*	Compressibility Index (%)	Hauser's Ratio	Angle of Repose (Θ)*
F1	0.630±0.018	0.714±0.017	11.76	1.13	23.58±0.88
F2	0.628±0.027	0720±0.025	12.77	1.14	24.24±0.65
F3	0.632±0.015	0.732±0.020	13.66	1.15	23.08±0.53
F4	0.640±0.014	0.725±0.034	11.72	1.13	22.15±0.70
F5	0.635±0.019	0.738±0.040	13.95	1.16	25.65±0.56
F6	0.622±0.017	0.711±0.036	12.78	1.14	24.26±0.70
F7	0.626±0.035	0.720±0.037	13.06	1.15	25.41±0.52

* Indicates (N=3) ± SD

Evaluation of Carvedilol Buccal Tablets.

Weight variation Test:

The weight of the all batches of buccal tablets was found to be passed showing that, weight variation test for all batches was within the standard pharmacopoeia limits of ±7.5% of the weight. Lower standard deviation value also indicating that tablets weight is uniform and drug is distributed in all tablets formulation uniformly. The results for weight variation test are shown in table 3

Hardness:

The hardness of tablets of each batch ranged between 5.0±0.21 to 5.6±0.18 kg/cm2. This ensures good mechanical strength of tablets for all batches. The results for hardness test are shown in table 3

Thickness:

The thickness of tablets of each batch ranged between 2.14±0.01 to 2.18±0.01 mm. This ensures good handling characteristics and uniform distribution of drug among all tablets. The results for tablets thickness test are shown in table 3

Friability:

The friability of all the formulated tablets was found to be below 1 %. All the formulated tablets showed the % friability within the official limits, which indicating the optimum mechanical strength of all batches of tablets formulation. The results for friability test are shown in table 3

Content Uniformity:

All the formulated mucoadhesive buccal tablets were evaluated for uniformity drug content and it was found to be between 95.39±0.21 to 99.12±0.18 %. The results for content uniformity of all batches formulation are shown in table 3

Table 3: Results of Post Compression Parameters of Carvedilol Buccal Tablets

Formulation Batches	Hardness (Kg/cm^2)*	Thickness (mm)*	Friability (%)*	Weight variation (gm)*	Drug content (%)*
F1	5.2±0.18	2.14±0.01	0.27±0.014	203±0.31	96.76±0.17
F2	5.0±0.24	2.16±0.03	0.40±0.031	208±0.24	95.39±0.21
F3	5.4±0.27	2.15±0.03	0.35±0.013	197±0.50	96.30±0.15
F4	5.0±0.21	2.16±0.04	0.45±0.042	201±0.44	99.12±0.18
F5	5.6±0.18	2.15±0.01	0.42±0.017	205±0.33	98.64±0.12
F6	5.2±0.17	2.18±0.01	0.34±0.028	204±0.17	96.36±0.16
F7	5.0±0.25	2.16±0.03	0.46±0.0.030	202±0.42	95.51±0.19

* Indicates (N=3) ± SD

Swelling Index:

The swelling index of the prepared buccal tablet was evaluated in phosphate buffer pH 6.8 in petri dish. The swelling of tablet involves the absorption of liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecules. The liquid enters the particles through pores and binds to longer molecules, braking the hydration bond and resulting in swelling of particles. Formulation F1, F2, F3, F4 and F5 prepared with combination of HPMC and xanthan gum showed 33.36±0.37, 36.78±0.28, 37.30±0.29, 42.57±0.42 and 40.82±0.38 % of swelling index value respectively. Batch F6 and F7, prepared with xanthan gum and HPMC alone at 30% concentration showed percentage swelling index of 38.47±0.45 and 44.65±0.43 respectively. From the study it was observed that as formulation F7 gives highest swelling index, while batch F1 gives lowest swelling index. The results data of swelling index are shown in figure 3

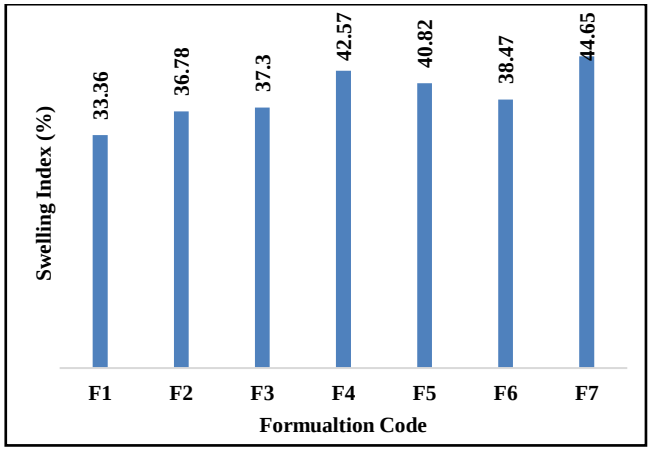

Figure 3: Swelling Index of Batch F1 to F7

Mucoadhesion Strength:

Mucoadhesion strength of the buccal tablet of carvedilol was determined using modified physical balance using sheep buccal mucosa as model mucosal membrane. The Mucoadhesion strength of all batches of tablets formulation was found in the range of 6.28±0.53 to 10.85±1.12. Formulation F1 showed lowest mucoadhesion strength, while batch F4 showed highest mucoadhesion strength. From the study it was observed that as the concentration of HPMC increases, the mucoadhesive strength also increases. The results of mucoadhesion strength of all batches of buccal tablets formulations was shown in figure 4.

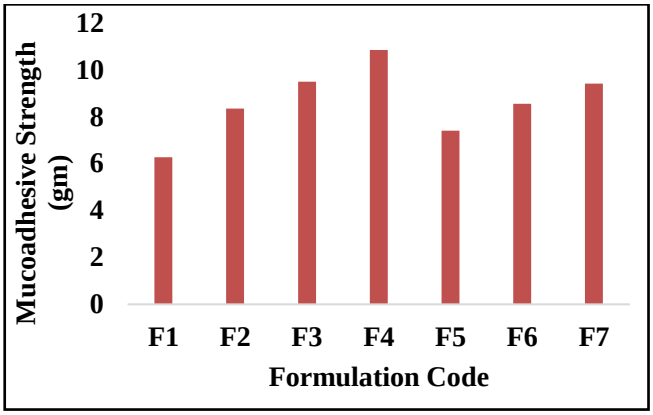

Figure 4: Mucoadhesive Strength of Formulation F1 to F7

***In Vitro* Drug Release Study**

In vitro dissolution study of buccal tablets of carvdilol was determined using USP dissolution test apparatus II (Paddle type) (Esico International, Mumbai) using phosphate buffer pH 6.8 as dissolution medium. Dissolution study showed that, formulation F1 give drug release of 97.45±1.18% in 5 hrs. Formulation F2 showed drug release of 95.04±2.10% in 6 hr. Batch F3 gives drug release of 95.1±1.33% in 7 hrs. Formulation F1, F2 and F3 was not able to hold the drug for long time and hence not able to sustain the drug release up to 8 hrs. Batch F4 and F5 showed the slower drug release of 98.32±1.55% and 96.3±1.65% respectively in 8 hrs. Batch F6 and F7 prepared with xanthan gum and HPMC alone showed drug release of 96.87±1.65 and 76.28±1.22% in 7 and 8 hrs respectively. Among all the formulations batch F4 formulation is optimized, as it showed slower and complete drug release at the end of 8 hrs which suits the buccal drug delivery system criteria. The Dissolution data for carvedilol buccal tablets was shown in figure 5.

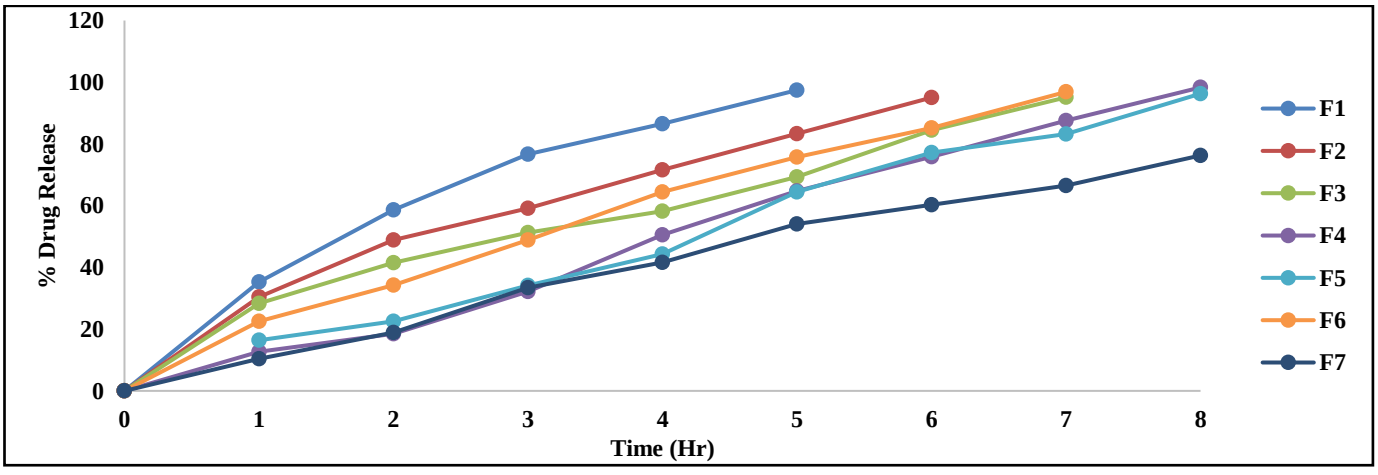

Figure 5: In Vitro Release Profile of Carvedilol buccal tablets (F1 to F7)

Stability studies

Optimized buccal tablets formulation F4 was selected for stability studies. According to ICH guidelines, optimized formulations F4 were stored at 40^{0}C temperature and 75% relative humidity (RH) for a period of 3 months. Formulation was evaluated for hardness, drug content and % drug release at the end of 3 months. No significant difference was observed in hardness, drug content and % drug release. From the stability study it was concluded that solid dispersion formulation F4 was found to be stable. Details of stability study data are shown in table 4

Table 4: Stability data optimized formulation F4

Formulation Code	Parameter	Before storage (0 month)	After storage (3 month)
F4	Hardness (kg/cm^2)	5.0±0.21	5.2±0.18
	% Drug content (%)	99.12±0.18	98.30±0.31%
	% Drug release	98.32±1.55	97.26±1.48

CONCLUSION

From the present study following conclusion were observed. The buccal tablets of carvedilol can be prepared successfully by direct compression technique by combination of polymer HPMC and Xanthan gum. All the prepared formulations were showed optimum mucoadhesive strength and % swelling index. FTIR-spectroscopic studies indicate no drug- excipient interaction in formulation. The in vitro dissolution profile showed that HPMC and xanthan gum had a potential to sustain the delivery of drug for the extended period of time. Among the all formulation F4 was consider as the ideal formulation which showed sustained release of carvedilol over a period of 8 hrs. From this study, it was concluded that the buccal tablets of carvedilol prepared using direct compression technique is a good approach of enhancing the bioavailability of carvedilol via buccal route in the management of hypertension Future detailed investigation is required to established in vivo efficiency of buccal tablets of carvedilol and the long term stability study need to be confirm the stability of buccal tablets of carvedilol.

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