International Journal of Pharmacy and Biological Sciences-IJPBS™ (2019) 9 (3): 124-132
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Biological Sciences | Open Access | MCI Approved
UGC Approved Journal

Formulation and Evaluation of Buccoadhesive Drug Delivery System of Acebutolol Hydrochloride

Swapnali Zore*, Bhaskar Bangar and Akshay Shingate
Gourishankar Institute of Pharmaceutical Research Limb, Satara

Received: 10 Mar 2019 / Accepted: 9 Apr 2019 / Published online: 1 Jul 2019
Corresponding Author Email: kanishk.kala@gmail.com

Abstract
The main aim of this work was to formulate and study buccoadhesive buccal tablet of acebutolol using various suitable bioadhesive polymers such as Carbopol 934, HPMC K4M. Backing layer of ethyl cellulose was used by direct compression method. The prepared tablet where characterized by bioadhesive properties in vitro dissolution studies. In the last two head decades bucoadhesive drug delivery system has taken a huge life from the research laboratories to the hands of patients this dosage forms gain attention B'coz of their non-invasive administration. Rapid onset of effect good bioavailability elimination of hepatic first pass metabolism reduce amount of administered dose and dose related side effect this are available as tablet patches films vapours and semisolids like gels and ointment such formulations must be of convenient size and geometry and should other tightly or alternatively should erode completely duration of the application. The purpose of this research was to formulate and evaluate bioadhesive buccal tablets of acebutolol using HPMC K4M as a sustained release polymer, as ethyl cellulose as an impermeable backing layer. The tablets were evaluated for weight variation, thickness, hardness, friability.

Keywords
HPMC, Bioadhesive buccal Tablet, Acebutolol Hydrochloride

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INTRODUCTION

Novel Drug Delivery:

Over the last few decades Pharmaceutical scientists throughout the world are trying to explore transdermal and transmucosal routes as an alternative to injections. Buccal delivery of the desired drug using mucoadhesive polymers has been the subject of interest since the early 1980s[1]. Drug actions can be improved by developing new drug delivery systems, such as the mucoadhesive system. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to a bioavailability increase and both local and systemic effects. Owing to the ease of the administration, the oral cavity is an attractive site for the delivery of drugs. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation[3]. Treatment of an acute disease or a chronic illness has been mostly accomplished by delivering drugs using various pharmaceutical dosage forms, including tablets, capsules, pills,

suppositories, creams, ointments, liquids, aerosols, and injectables as carriers. Amongst various routes of drug delivery, oral route is perhaps the most preferred by the patient.

Buccal Drug Delivery:

Buccal delivery involves the administration of a drug via buccal mucosa (the lining of cheek) to the systemic circulation. The buccal mucosa is considerably less permeable than sublingual area and is generally not able to provide rapid absorption and good bioavailability seen with sublingual administration. Mucoadhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the buccal mucosa. Mucoadhesive drug delivery systems are those which utilize the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is of biological nature, are held together by means of interfacial forces. The attachment could be between an artificial material and a biological substrate, such as adhesion between a polymer and a biological membrane. To avoid disadvantages, various mucoadhesive dosage forms are given by different routes other than oral one. e.g. buccal, nasal, vaginal etc.Various newer researches are carried out in these sections. Antihypertensive, anti-anginal, analgesic, anti-inflammatory, anti-asthmatic, anti-infective, anti-neoplastic, hormonal and ophthalmic drugs are tried by these routes.

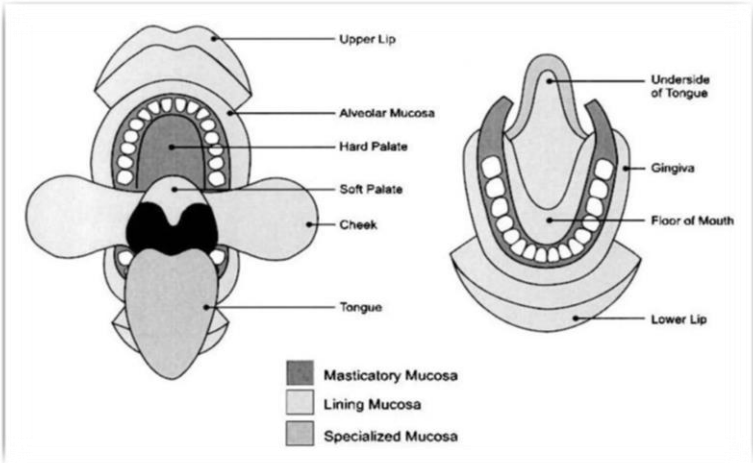
The oral cavity is lined by a relatively thick, dense and multilayered mucous membrane of a highly vascularized nature. Drug penetrating into the membrane can find access to the systemic circulation via net of capillaries and arteries lying underneath[3].

1. The mucus-secreting regions consisting of the soft palate, the floor of the mouth, the underside of the tongue, and the labial and buccal mucosa, which have a normally non-keratinized epithelium.
2. The hard palate and the gingival are the regions of the masticator mucosa and have a normally keratinized epidermis.
3. Specialized zone consisting of the borders of the lips and the dorsal surface of the tongue with its highly selective keratinization.

Oral mucosa:

Structure:

The total area of the oral cavity is about 100 cm. Out of this about one third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness. The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth (Figure 1). The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue accounts for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells.



Schematic representation of the different lining of in mouth.

Table no.1: Formulations of buccoadhesive tablets of acebutolol hydrochloride

Ingredients	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Acebutolol HCl	200	200	200	200	200	200	200	200	200
Carbopol – 934P	22.5	22.5	22.5	45	45	45	67.5	67.5	67.5
HPMC K4M	67.5	90	112.5	67.5	90	112.5	67.5	90	112.5
Spray dried lactose	50	50	50	50	50	50	50	50	50
Avicel pH 102	99	76.5	54	76.5	54	31.5	54	31.5	09
Magnesium stearate	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Talc	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Total	450	450	450	450	450	450	450	450	450

MATERIALS AND METHODS:

Table no.2: Backing layer for formulation of buccoadhesive tablets of acebutolol hydrochloride

Sr.No	Name of Chemical	Name of the Supplier
1	Acebutolol	Medispray Lab.Pvt.Ltd.Satara.
2	Carbapol-934P	S.D.LAB CHEM MUMBAI
3	Avicel pH 102	S.D.Lab Chem MUMBAI.
4	HPMC K4M	S.D.LAB CHEM MUMBAI.
5	Spray Dried lactose	S.D.LAB CHEM MUMBAI
8	Magnessium Stearate	S.D.LAB CHEM MUMBAI.
9	Talc	S.D.LAB CHEM MUMBAI.

RESULTS AND DISCUSSION:

1. Characterization of drug:

1.1. Description: The sample of acebutolol HCl was found to be a white crystalline and odorless substance.

1.2. Melting point:

Sr. No	Parameters	Acebutolol HCl
1	Melting point (°C) (Test sample)	140-142
2	Melting point (°C) (Reference)	141-144

Melting point of acebutolol HCl

Melting point of acebutolol HCl was found to be in the range of 141-143°C, while in the standard literature it is reported in the range of 141-144°C. So, it can be concluded that acebutolol HCl was in pure state.

2. UV spectroscopy:

2.1. λmax determination

The optimal absorbance 0.5763 was found at 233 nm. Thus, λ_{max} of acebutolol HCl was found to be at 233 nm in phosphate buffer of pH 6.8.

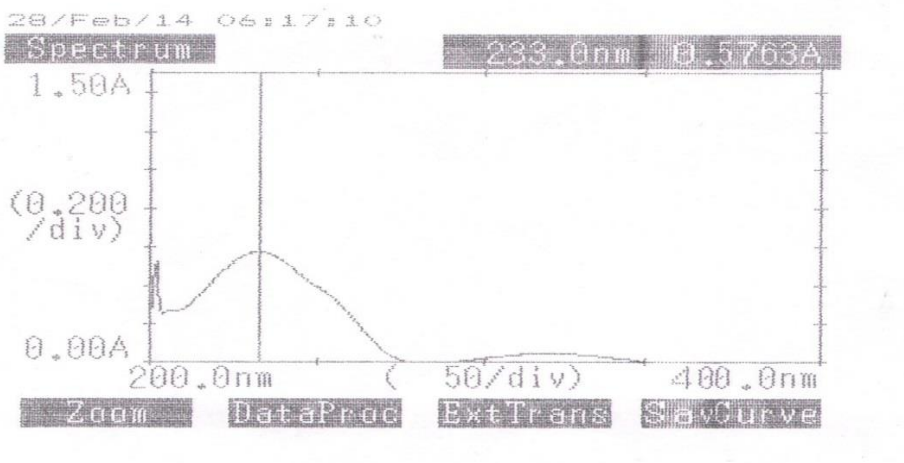


Figure: 1. UV spectrum of acebutolol HCl

2.2. Calibration curve of acebutolol HCl in phosphate buffer of pH 6.8

The results of absorbance shown at various concentrations of acebutolol HCl in pH 6.8 Phosphate buffer are given in table No.3

Sr. No.	Concentration (µg/ml)	Absorbance
2	5	0.2916
3	10	0.5763
4	15	0.8932
5	20	1.1657
6	25	1.4436

Absorbance value at various concentration of acebutolol HCl

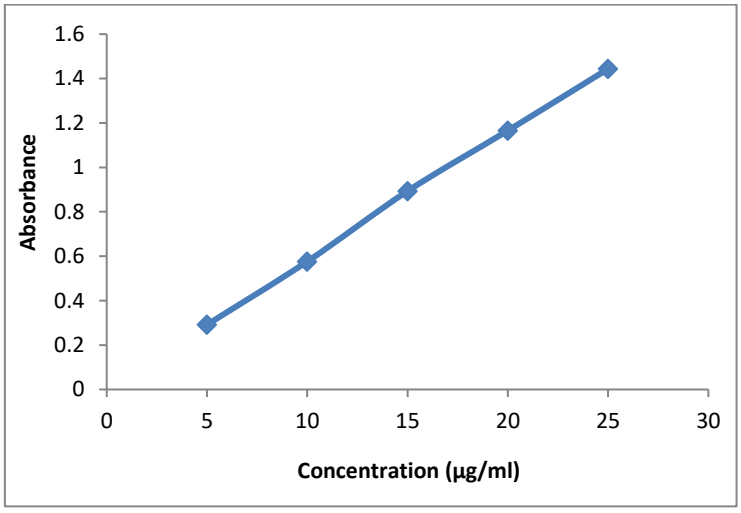


Figure 2: Calibration curve of acebutolol HCl in pH 6.8 phosphate buffer

The calibration curve exhibited good coefficient of correlation as shown in table.

Table no.4: Standard curve statistics

Sr. No	Parameters	Observations
1	Absorbance Maximum	233 nm
2	Slope	0.0580
3	Intercept	0.0028
4	Correlation Coefficient(R^2)	0.9993

3. Purity of drug:

3.1. Differential scanning calorimetry (DSC)

One of the most classic applications of DSC analysis is the determination of purity of drug sample. Figure 9. illustrates DSC thermogram of Acebutolol HCl.

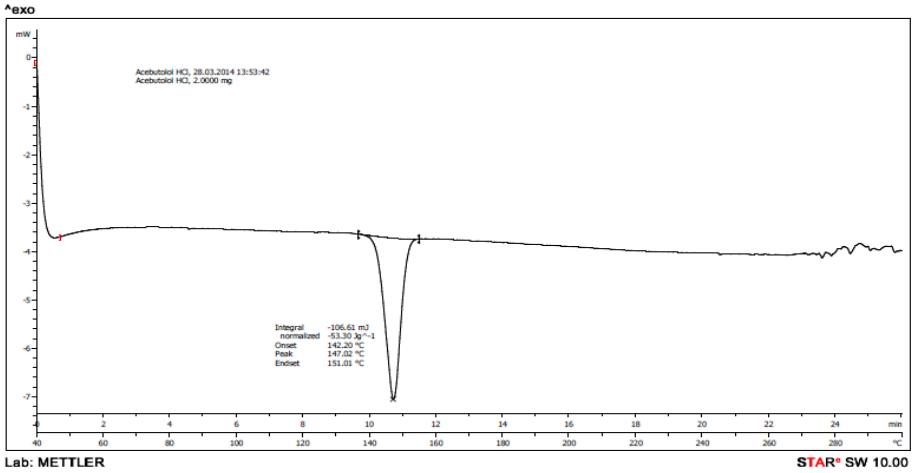


Figure 3: DSC thermogram of acebutolol HCl

The DSC thermogram of acebutolol HCl shows a sharp endothermic peak at 147.02°C corresponding to the melting transition temperature and decomposition of acebutolol HCl. Such sharp endothermic peak signifies that acebutolol HCl used was in pure state.

Table no.5: Parameters of thin layer chromatography of acebutolol HCl

Sr. No.	Parameters	Magnitudes
1.	Distance traveled by solvent front	4 cm
2.	Distance traveled by solute	1.8 cm
3.	Stationary phase used	silica gel G
4.	Mobile phase used	Methanol: Water (60:40)
5.	Rf value calculated	0.45
6.	Rf value reference	0.48

Calculated R_f value is nearly equal to reference Rf value, hence acebutolol HCl sample passes the test of purity.

3.3. FTIR Spectrum

An FTIR spectrum of acebutolol HCl and FTIR spectrum of formulation 2 (F2) is shown in Figure 10-11. FTIR peaks of acebutolol HCl are given in Table 20.

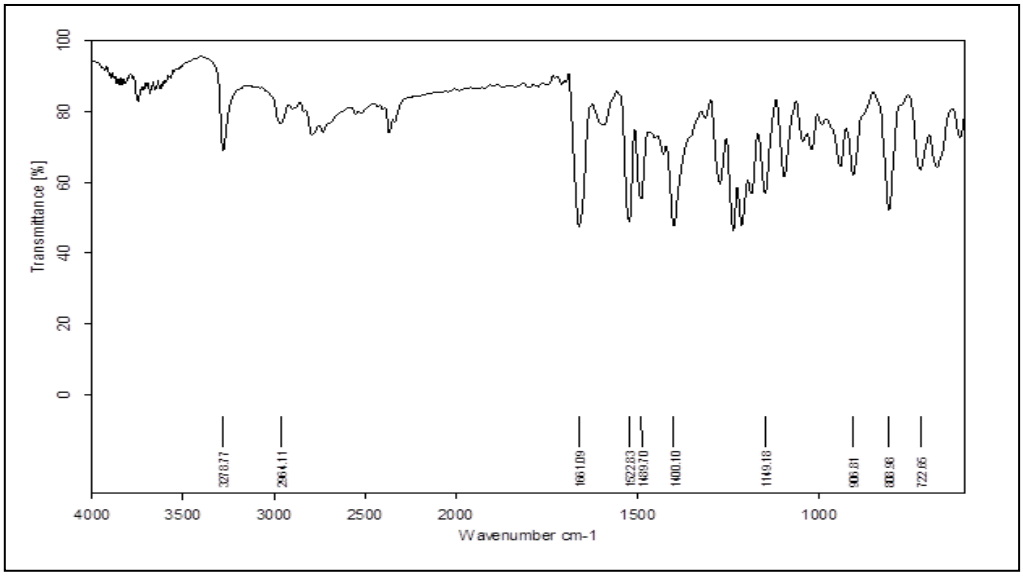


Figure 4. FTIR spectrum of acebutolol HCl

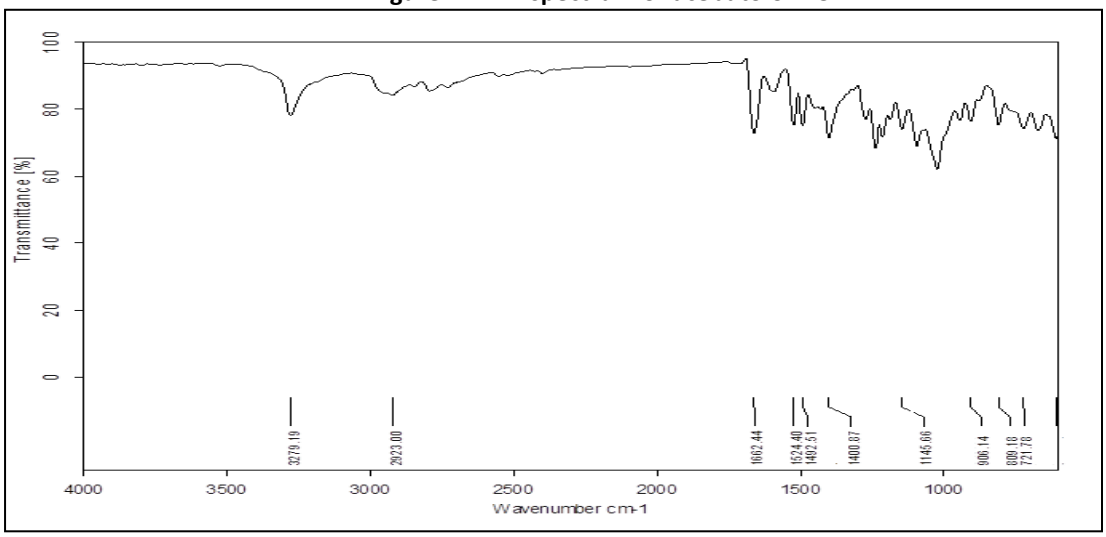


Figure 5: FTIR spectrum of formulation 2 (F2)

Table no.6: Characteristic peaks of FTIR spectrum of acebutolol HCl and formulation F2

Sr. No.	Wave number (cm^{-1})		Assignment
	Drug	F2	
1	3278.77	3279.19	C-H Stretch
2	2964.11	2923.00	N-H Stretch
3	1661.09	1662.44	C=O Stretch
4	1522.83	1524.40	N-H Bending
5	1489.70	1492.51	O-H Bending
6	1400.10	1400.87	C-H Bending In Plane
7	0906.81	0906.14	C-O Stretch
8	0808.98	0809.18	C-C Stretch
9	0722.65	0721.78	C-H Rocking

4. Powder characterization:

Powder characterization of each formulation was carried out and results obtained are as shown in Table 7.

Table No 7: Flow properties of formulation powder

Formulation Code	Angle of Repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's Ratio
F1	29.31±0.26	0.45±0.008	0.55±0.011	18.18±1.231	1.22±0.018
F2	29.50±0.11	0.40±0.006	0.49±0.015	18.18±1.432	1.22±0.019
F3	29.06±0.38	0.39±0.004	0.48±0.013	18.18±1.396	1.22±0.018
F4	29.39±0.20	0.41±0.007	0.51±0.011	18.19±1.274	1.22±0.018
F5	29.78±0.44	0.40±0.009	0.49±0.005	18.18±0.976	1.22±0.017
F6	29.35±0.35	0.40±0.005	0.49±0.007	18.18±0.823	1.22±0.019
F7	30.12±1.02	0.40±0.003	0.48±0.0007	18.16±0.879	1.22±0.019
F8	30.10±0.18	0.40±0.006	0.49±0.006	18.18±1.192	1.22±0.018
F9	29.31±0.13	0.40±0.009	0.49±0.009	18.18±0.839	1.22±0.016
Backing Layer	28.17±0.16	0.40±0.003	0.51±0.003	21.04±0.856	1.26±0.009

All values are expressed as mean± SD, n=3

Evaluation of tablets:

Tablet thickness and Diameter:

Thickness of Tablet was determined by using micrometer screw gauge. The thickness of the prepared tablets was found to be between 4.065±0.0009 to 4.066±0.0110 mm and diameter of tablets was found in the range of 12.0047±0.0087 to 12.0067±0.0009 mm.

There was no marked variation in the thickness of tablet within each formulation indicating uniform behavior of powder throughout the compression process. The result of measured thickness and diameter of each formulation was as shown in the table 9.

Tablet thickness and Diameter:

Table no.9: The result of measured thickness and diameter of each formulation

Formulations	Tablet thickness (mm)	Tablet Diameter (mm)
F1	4.066±0.011	12.0052±0.0016
F2	4.065±0.019	12.0061±0.0011
F3	4.066±0.0018	12.0051±0.0018
F4	4.066±0.0018	12.0064±0.0017
F5	4.065±0.0012	12.0058±0.0018
F6	4.065±0.0011	12.0055±0.0018
F7	4.066±0.0012	12.0047±0.0087
F8	4.065±0.0019	12.0067±0.0019
F9	4.066±0.0012	12.0064±0.0014

All values are expressed as mean± SD, n=3

Tablet hardness was determined by using Monsanto hardness tester. Hardness values of the formulation ranged from 5.27±0.008 to 6.32±0.016 kg/cm^2, which indicate good strength of tablet. The measured hardness of each formulation was as shown in the table no.10

Table no.10: The measured hardness of each formulation

Formulations	Hardness (kg/cm^2)
F1	5.27±0.008
F2	5.29±0.0013
F3	4.30±0.02
F4	5.50±0.013
F5	4.55±0.018
F6	5.58±0.019
F7	6.21±0.019
F8	5.29±0.013
F9	5.32±0.016

All values are expressed as mean± SD, n=10

Friability:

Tablet friability was determined by Roche friabilator and weight loss was calculated and represented in the terms of % friability. Friability values of all the formulation were less than 1%, indicating good strength of table.

Table no .11: The measured Friability of each formulation

Formulations	Friability (%)
F1	0.60
F2	0.52
F3	0.70
F4	0.67
F5	0.69
F6	0.65
F7	0.60
F8	0.54
F9	0.60

All values are expressed as mean± SD, n=10

Weight variation test:

The weight variation test carried out showed that all the formulation fell within the range of ± 7.5%. The average weight of tablet within each formulation was found to be uniform. This indicated uniform filling of the die cavity during tablet compression.

The prepared tablet of all formulations exhibited weight in the range of 548.2±0.79 to 549.9±1.38 mg. This indicated that the tablets of all the formulations passed the weight variation test. Table no.12.

Table no.12: Average weight of tablets

Formulations	Weight variation (Average weight, mg)
F1	548.2±0.79
F2	548.4±1.15
F3	549.1±1.13
F4	549.9±1.38
F5	548.9±0.56
F6	548.7±0.67
F7	548.8±0.64
F8	548.6±0.76
F9	548.8±0.70

All values are expressed as mean± SD, n=20

Determination of drug content:

The drug content was found to be uniform among all formulations and ranged from 96.00±0.14% to 101.68±0.18%. The content of active ingredient in each formulation was as shown in the table 13

Table no.13: The content of active ingredient in each formulation

Formulations	Drug content (%)
F1	101.48±0.18
F2	101.01±0.10
F3	99.42±0.14
F4	96.03±0.23
F5	98.02±0.86
F6	99.62±0.47
F7	96.03±0.14
F8	97.16±0.34
F9	98.29±0.63

All values are expressed as mean± SD, n=3

Flow properties of formulation F1 to F2 & Backing layer

Thickness of Tablet was determined by using micrometer screw gauge. The thickness of the prepared tablets was found to be between 4.065±0.0009 to 4.066±0.0110 mm and diameter of tablets was found in the range of 12.0047±0.0087 to 12.0067±0.0009 mm.

There was no marked variation in the thickness of tablet within each formulation indicating uniform behavior of powder throughout the compression process. The result of measured thickness and diameter of each formulation was as shown in the table.

Table no.14: The result of measured thickness and diameter of each formulation

Formulations	Tablet thickness (mm)	Tablet Diameter (mm)
F1	4.066±0.0110	12.0052±0.0006
F2	4.065±0.0009	12.0061±0.0011
F3	4.066±0.0008	12.0051±0.0008
F4	4.066±0.0018	12.0064±0.0007
F5	4.065±0.0012	12.0058±0.0008
F6	4.065±0.0011	12.0055±0.0008
F7	4.066±0.0012	12.0047±0.0087
F8	4.065±0.0009	12.0067±0.0009
F9	4.066±0.0012	12.0064±0.0014

All values are expressed as mean± SD, n=3

Hardness:

Tablet hardness was determined by using Monsanto hardness tester. Hardness values of the formulation ranged from 5.27±0.008 to 6.32±0.016 kg/cm^2, which indicate good strength of tablet.

Weight variation test:

The weight variation test carried out showed that all the formulation fell within the range of ± 7.5%. The average weight of tablet within each formulation was found to be uniform. This indicated uniform filling of the die cavity during tablet compression.

The prepared tablet of all formulations exhibited weight in the range of 548.2±0.79 to 549.9±1.38 mg. This indicated that the tablets of all the formulations passed the weight variation test.

***In vitro* drug release studies:**

For CP and HPMC K4M combination containing tablets, it was observed that with the increase in polymer content in tablets there was a decrease in rate of drug release. This behavior could be due to the increase in matrices viscosity and decrease in matrices porosity. This is probably due to the fact that CP is more hydrophilic and swellable than HPMC and promotes liquid entry and entrapment in the HPMC network. In addition, combination of anionic polymer (CP) with non-ionic HPMC produces a synergistic increase in viscosity (Najafi R et al 2005).

The release profile of formulations F1-F9, are illustrated in Table 29-38 and Figure 16-36. In the current study, the values of release exponent (n) were calculated as per Korsmeyer - Peppas equation (Power law equation).

Rate of drug release was found to decrease with increase in the content of either CP or HPMC. This is in agreement with literature findings that the viscosity of the gel layer around the tablet increases

with increase in the hydrogel concentration, thus limiting the release of active ingredient. As the carboxyl groups of CP dissociate highly at pH above their pK_a (i.e. 6.0 ± 0.5), The highest value of t_{50}% i.e. 9.1 h. was observed for the formulation (F9) containing carbopol 934 P 67.5 mg and HPMC K4M 112.5 mg. The lowest value of t_{50}% i.e. 5.2 h. was observed for the formulation (F7) containing carbopol 934 P 67.5 mg and HPMC K4M 67.5 mg. These observations indicate that formulation (F9) shows more release retardant properties than other formulations whereas formulation (F7) released the drug more rapidly than other formulations.

CONCLUSION

The mucoadhesive buccal tablets of acebutolol hydrochloride may be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of acebutolol hydrochloride through buccalmucosa. From amongst the different hydrogels known for their mucoadhesiveness and matrix integrity, Carbopol 934P and HPMC K4M were selected and buccoadhesive tablets of acebutolol hydrochloride were prepared successfully by direct compression method. This study revealed successful application of 3 full factorial design for the formulation of buccoadhesive drag delivery.

The evaluation parameters of prepared tablets were within the prescribed limits. Surface pH study of tablets indicated that the all formulations are suitable for buccal environment. In the present study a 3^2 full factorial design was used. The variables CP and HPMC K4M evaluated in this study exhibited significant effect on the responses ƒ, $t_{50\%}$and $reli_{12}$ h of the formulations. However, the CP markedly affected the mucoadhesion strength, while the HPMC K4M affected the release profile.

This formulated system will have better patient compliance because of decrease in the dose frequency of drug administration. The designed drug system holds promise

Mucoadhesive strength and drag release was found to be a function of concentration of polymers. As concentration of polymers increases mucoadhesive strength increases and drag release decreases. to further study i.e. permeability and in vivo studies leading to IVIVC for com

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