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Research Article

Design of Buccal Dosage Form of PropafenoneHCl: Study the Effect of Polymers and Diluents on Drug Release

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ABSTRACT

The objective of this study was to develop effective bioadhesive buccal bilayered tablets comprising of drug containing bioadhesive layer and drug free backing layer, expected to release the drug in unidirectional for extended period of time. Tablets of Propafenone HCl were prepared by direct compression method using bioadhesive polymers like Carbopol 934P, Hydroxy propyl cellulose in different combinations and concentrations with backing layer of ethyl cellulose. Buccal tablets were evaluated by different parameters such as thickness, hardness, weight uniformity, content uniformity, swelling index, surface pH, *ex vivo* bioadhesive strength, *ex vivo* residence time, *in vitro* drug release, *ex vivo* drug permeation, stability studies in human saliva, *in vivo* mucoadhesive performance studies and FTIR studies. The drug release rate of formulations prepared with HPC (Max.86.2±0.7%) was retarded due to the high viscosity of the polymer andformation of complex matrix network when compared to the other polymers.The optimized formula (PH4) followed non-fickian release mechanism with zero order kinetics. The present study concludes that buccal delivery of Propafenone HCl tablets can be good way to bypass the first pass metabolism.

Keywords*: Bioadhesive buccal bilayered tablets, Directcompression, PropafenoneHCl.*

INTRODUCTION

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets and capsules are the most popular dosage forms.The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity [1]. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption. Other routes, such as nasal, ocular, pulmonary, rectal, and vaginal drug administration, have provided excellent opportunities for the delivery of a variety of compounds. However, the mucosal lining of the oral cavity offers some distinct advantages [2]. The aim of the research study is to prepare the bilayered buccal tablets by using carbopol-934 as primary mucoadhesive polymer and HPC as matrix forming (Secondary) polymers with different diluents like Mannitol, spray dried lactose and MCC by direct compression method [3]. Propafenone HCl (PH) is a Class 1C antiarrhythmic drug which is having direct stabilizing action on myocardial membrane as well as a local anesthetic effect. It is mainly used in the treatment of supraventricular Tachyarrhythmia is. PH has a short half-life i.e. about 2-10 hrs and low bioavailability. It is also having a narrow absorption window. Because of this the drug has to be taken frequently. The usual dose is 150 mg to taken three times a day or 300 mg twice a day. Moreover absorption site of PH is a GI tract. In the treatment of cardiac arrhythmias, angina and hypertension, a loading

as well as maintenance dose is required [4]. The main objective is to study the effect of these polymers and different diluents on drug release, to perform various quality control evaluation parameters for the prepared tablets.

MATERIALS AND METHODS

Propafenone HCl was obtained as a gift sample from Aurobindo Ltd., (Hyderabad). Hydroxy Propyl Cellulose (HPC) (Rohm Pharma GmbH, Germany), Carbopol (CP) were used as polymers. Mannitol, Spray dried lactose Micro Crystalline Cellulose (SD Fine Chemicals) served as diluents. Aspartame, Magnesium stearate is obtained from SD Fine Chemicals.

Preparation of bilayered buccal tablets

Bilayered buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100, except lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min. After sufficient mixing lubricant was added and again mixed for additional 2-3 min. Preparation involves two steps, first the mixture is compressed using 8 mm flat faced punch on 16 stages rotary tablet compress machine.Then upper punch is raised and the backing layer of ethyl cellulose is placed on above compact then two layers are compressed again to get bilayered buccal tablet [5]. Composition of the prepared bioadhesive buccal tablet formulations of Propafenone HCl were given in Table. The ratios indicating that the ratio of CP and HPC.

Table.1: Formulation table containing CP: HPCwith different diluents

Formulation code	PH1	PH2	PH3	PH4	PH5	PH6	PH7	PH8	PH9	PH10	PH11	PH12
Propafenone HCl	150	150	150	150	150	150	150	150	150	150	150	150
Carbopol-934	30	20	40	45	30	20	40	45	30	20	40	45
HPC	30	40	20	15	30	40	20	15	30	40	20	15
Mannitol	30	30	30	30	-	-	-	-	-	-	-	-
Spray dried lactose	-	-	-	-	30	30	30	30	-	-	-	-
MCC	-	-	-	-	-	-	-	-	30	30	30	30
Aspartame	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Ethyl cellulose (backing layer)	50	50	50	50	50	50	50	50	50	50	50	50

HPP: Hydroxy Propyl Cellulose, **MCC:** Micro Crystalline Cellulose

Evaluation of mucoadhesive buccal tablets

Compatibility Studies: The drug excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR). Infra-red spectra of pure drug and optimized formulation were recorded [6].

Selection of wavelength for analysis ofPropafenone HCl: the prepared concentration of 10 µg/ml and it was used for initial spectral scan in the UV range of 200-400 nm to detect maximum wavelength and further dilutions for linearity were prepared from the stock solution by allegation method [7, 8].

Pre-compression parameters: The blends for mucoadhesivebuccal tablets were characterizedwith respect to angle of repose, bulk density, tappeddensity, Carr's index, and Hausner's ratio[9].

Post compression parameters Thickness: The thickness of the tablets was measured by micrometer and it is expressed in mm[10].

Hardness: Tablets require strength or hardness to withstand mechanical shocks of handling in manufacture, packing and shipping. Tablet hardness was measured by Monsanto hardness tester and results are expressed in Kg/cm^2[11].

Weight variation test: 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight[12].

Friability: It was performed in Rochefriabilator[13].

Determination of drug content (assay):twenty tablets were taken and triturated well. The quantity equivalent to 100mg of Propafenone HClwas dissolved in 100ml of phosphatebufferpH 6.8 solutions on rotary shaker overnight[14].

Surface pH study: The tablets were allowed to swell for 2 hours in 2ml of pH 6.8 PBS and measured by using pH meter[15].

Swellingindex: Each tablet was weighed (W1) and placed in petridish with 5ml of phosphate buffer pH 6.8. After placing the formulation for specified time, the tablets were wiped off to remove excess of surface water by using filter paper and again reweighed (W2). Where, W1=Initial weight of the tablet. W2= Weight of tablet after swelling time interval[16].

Determination of the *Ex- vivo* residence time:The *Ex- vivo* residence time was found using a locally modified USP disintegration apparatus. The disintegration medium was composed of 800 ml pH 6.8phosphatebuffer maintained at 37°C. The sheep buccal tissue was tied with thread to the central stand[17].

***In vitro* drug release study:** *In vitro* drug release study of mucoadhesivetablets were performed using standard USP dissolution apparatus type II. For each time interval 5ml sample was withdrawal and replacement of fresh medium at predetermined time interval. The samples were analyzed for drug content using double beam UV spectrophotometer at 238nm[18].

RESULTS AND DISCUSSION

Compatibility study:

From the FT-IR study, the drug was found to be compatible with all the excipients, as shown in Figure 1&2.

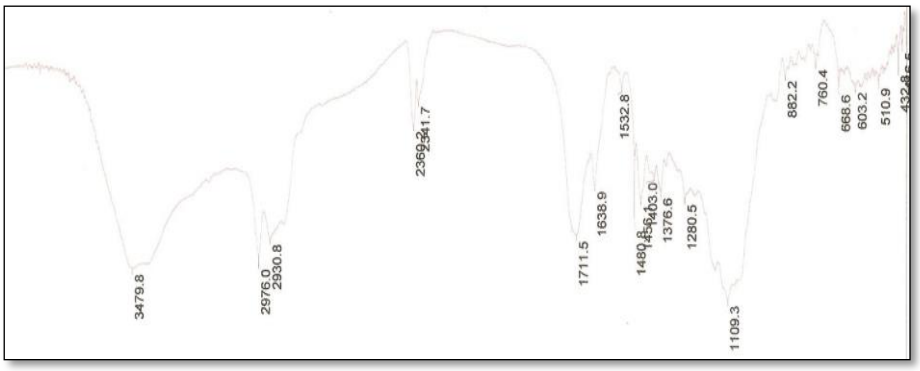

Figure 1. FTIR spectrum of Propafenone HCl pure drug

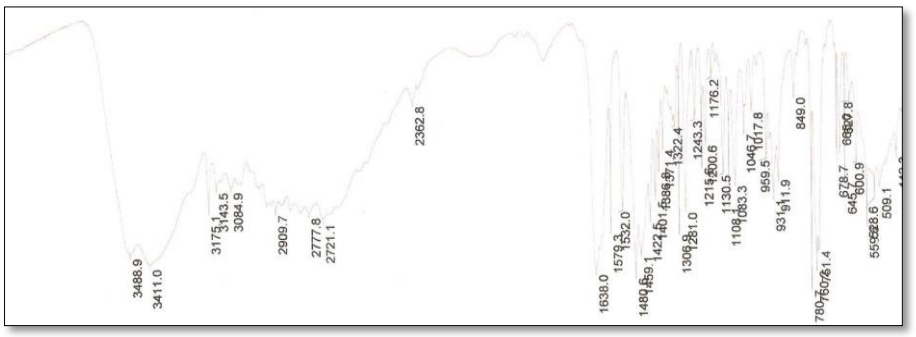

Figure 2. FTIR spectrum of optimized formulation (PH4)

Table 2. Standard graph of PropafenoneHCl in phosphate buffer pH 6.8.

Sl. No.	Concentration (mcg/mL)	Absorbance
1	4	0.164
2	8	0.307
3	12	0.473
4	16	0.597
5	20	0.726
6	24	0.934

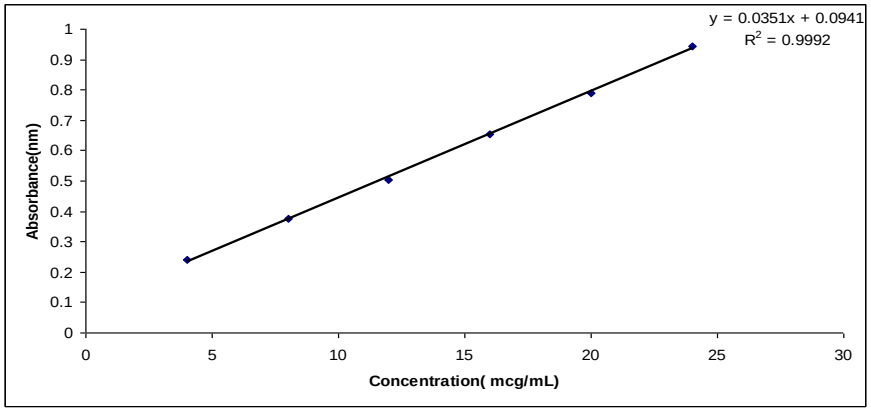

Figure 3. Standard graph in phosphate buffer pH 6.8.

Flow properties of batches were evaluated by measuring the angleofrepose, Carr's index and Hausner's ratio. Thus, angle of repose and compressibility index are indicates of good flow properties of powder blend mucoadhesive buccal tablets of Propafenone HCl.

Table3: Physico-chemical parameters of formulations containing HPC

Batch code	Thickness (mm)	Weight Variation (mg)	Friability (%)	Hardness (Kg/cm^2)	% Drug content
PH1	3.43±0.010	292.6±0.20	0.09	4.3±0.13	98.74
PH2	3.26±0.020	296.0±0.24	0.17	4.8±0.33	101.17
PH3	3.73±0.035	291.9±0.15	0.08	5.3±0.13	99.69
PH4	3.64±0.010	295.2±0.70	0.07	6.6±0.10	99.04
PH5	3.64±0.040	299.0±0.50	0.24	4.6±0.10	99.58
PH6	3.71±0.030	296.3±0.20	0.31	5.1±0.05	100.39
PH7	3.70±0.010	299.9±0.25	0.42	5.5±0.05	99.57
PH8	3.64±0.030	297.3±0.60	0.08	6.7±0.05	99.07
PH9	3.71±0.042	297.9±0.50	0.08	3.9±0.09	99.40
PH10	3.38±0.057	292.9±0.48	0.42	4.9±0.15	99.37
PH11	3.56±0.023	294.4±0.20	0.08	4.7±0.21	99.38
PH12	3.55±0.010	293.1±0.47	0.46	5.6±0.10	101.03

The weight of the tablets passed within the limit as per IP standards, the thickness was found to be in the range of 3.26±0.020 to 3.73±0.035mm. The hardness of the tablets was in the range of 3.9±0.09to 6.7±0.05kg/cm², and the friability was in the range of 0.07 to 0.46. All these parameters were within acceptable limits. The drug content of all formulated found to be an average of 98.74 to 101.17 %.All 12 formulations were tested for physical parameters like weight variation, thickness, hardness, friability and found to be within pharmacopoeia limits.

Table 4: Bioadhesive strength, *Ex vivo*residences time andSurface pH values of formulations with HPC

Formulation Code	Bio adhesion Strength (gm)	*Ex vivo* ResidenceTime (hr)	Surface pH
PH1	21.2±0.09	3.62±0.10	5.10±0.024
PH2	16.1±0.07	4.41±0.15	6.40±0.515
PH3	31.1±0.16	6.52±0.25	6.21±0.015
PH4	40.8±0.07	11.3±0.15	6.66±0.515
PH5	19.4±0.15	3.73±0.10	6.13±0.010
PH6	21.0±0.21	5.15±0.35	6.85±0.015
PH7	29.3±0.06	6.74±0.14	6.81±0.035
PH8	41.1±0.27	10.7±0.25	6.85±0.005
PH9	18.5±0.06	4.13±0.35	6.75±0.010
PH10	20.3±0.31	4.35±0.27	6.91±0.040
PH11	25.5±0.07	7.26±0.31	6.63±0.050
PH12	39.1±0.16	9.45±0.16	6.92±0.015

The *ex-vivo* mucoadhesion time for the prepared buccal tablets varies from 5 h to more than 6 h. The difference between the values of the *ex-vivo* mucoadhesion time for buccal tablets can be attributed to the combination of the various amounts of the polymer which affect the mucoadhesion. Moreover, Carbopoland HPC owing to its solubility in water and the observed high swelling rate and extent, resulted in lower mucoadhesion time. The surface pH of the formulations was found to be 5. 10±0.24 to 6.92±0.015, and the pH was found to be near to the neutral. These results recommended that the formulation is suitable for oral application and they were not irritant to the buccal mucosa. Surface pH values for all the formulations are shown in Table 4. According to the IP, buccal tablet should disintegrate within 4 h.

Table 5. Swelling index profile of formulations containing CP: HPC

Time (hr)	PH1	PH2	PH3	PH4	PH5	PH6	PH7	PH8	PH9	PH10	PH11	PH12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	0.11	0.18	0.31	0.31	0.08	0.26	0.30	0.40	0.15	0.24	0.25	0.43
2	0.36	0.73	0.51	0.57	0.37	0.83	0.57	1.02	0.41	0.57	0.74	1.05
3	0.73	1.15	1.01	1.10	0.72	1.25	1.08	1.74	0.66	1.16	1.08	1.57
4	1.08	1.36	1.41	1.52	1.14	1.44	1.51	2.26	0.92	1.52	1.45	2.11
5	1.36	1.5	1.68	1.96	1.44	1.75	1.84	2.60	1.11	1.68	2.03	2.66
6	1.60	1.77	2.02	2.62	1.68	2.02	2.26	3.44	1.30	1.82	2.54	2.92
7	1.73	1.63	2.42	3.18	2.06	2.37	2.59	3.22	1.52	1.39	2.35	2.73
8	1.85	1.53	2.69	2.94	1.98	2.14	2.80	3.02	1.43	1.17	2.05	2.50

Appropriate swelling property of a buccal device is essential for uniform and prolonged release of drugs and proper bioadhesion. The mucoadhesive polymers (HPC with Carbopol) used in the study were hydrogel that swelled upon contact with water and retained a large amount of water.

Table 6: *In vitro* cumulative drug release profile of formulationswith HPC

Time (hr)	PH1	PH2	PH3	PH4	PH5	PH6	PH7	PH8	PH9	PH10	PH11	PH12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	4.9± 0.8	2.4± 0.9	4.8± 0.9	4.4± 0.6	2.2± 0.2	1.2± 0.2	2.8± 0.09	2.0± 0.1	1.13± 0.1	0.2± 0.1	1.2± 0.1	2.0± 0.1
2	12.9± 0.4	4.4± 0.5	12.1± 0.8	10.2± 0.8	7.8± 0.6	4.1± 0.7	7.9± 0.1	8.5± 0.3	3.8± 0.1	2.1± 0.1	4.1± 0.2	7.9± 0.2
3	16.5± 0.2	6.8± 0.6	20.0± 0.5	17.9± 0.7	16.5± 0.8	8.0± 0.6	15.5± 0.2	15.2± 0.2	7.3± 0.2	5.2± 0.2	8.0± 0.1	15.5± 0.3
4	20.7± 0.3	10.8± 0.2	26.1± 0.4	25.2± 0.6	22.5± 0.9	10.9± 0.2	24.4± 0.4	23.8± 0.3	11.1± 0.1	8.4± 0.1	17.8± 0.3	23.7± 0.1
5	24.4± 0.3	14.9± 0.5	32.6± 0.6	34.7± 0.8	28.7± 0.2	15.1± 0.3	32.3± 0.8	32.3± 0.4	16.6± 0.3	13.1± 0.3	25.2± 0.5	31.5± 0.2
6	30.6± 0.4	20.0± 0.4	40.0± 0.4	43.3± 0.7	32.9± 0.3	23.3± 0.7	40.0± 0.6	42.2± 0.6	23.3± 0.7	16.3± 0.5	30.9± 0.7	40.0± 0.7
7	38.4± 0.5	25.4± 0.3	49.9± 0.8	54.6± 0.7	38.4± 0.6	29.4± 0.6	47.0± 0.8	51.9± 0.4	29.4± 0.4	22.3± 0.6	37.7± 0.1	47.0± 0.7
8	46.9± 0.6	30.5± 0.7	58.2± 0.9	86.2± 0.7	46.1± 0.5	36.8± 0.7	55.8± 0.3	62.7± 0.3	35.8± 0.6	28.7± 0.5	44.0± 0.6	52.2± 0.8

In-vitro drug release studies were conducted in phosphate buffer pH 6.8, and the studies revealed that the release of Propafenone HClfrom different formulations varies with characteristics and composition of polymers, as shown in Table 6.The *in vitro* drug release profile of the optimized formulation (PH4) was 86.2±0.7% of the drug in 8 hrs. It means the release of drug from optimized formulation was sustained release.

Table7: Release kinetics and mechanism of optimized formulation

Batch code	Mathematical models (Kinetics)				
	Zero order	First order	Higuchi	Peppas model	
	r^2	r^2	r^2	N	r^2
PH4	0.9978	0.9454	0.9016	1.0518	0.9955

The *in vitro* dissolution data for best formulation PH4 were fitted in different kinetic models i.e, zero order, first order, Higuchi and Korsmeyer-Peppas equation. Optimized formulation PH4 shows R^2value 0.9978. As its value nearer to the

'1' it is confirmed as it follows the zero order release. The mechanism of drug release is further confirmed by the Korsemeyer and peppas plot, if n = 1.0518 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport. The mechanism of release is anomalous, that is both diffusion and erosion are involved and the data was shown in the table 7.

CONCLUSION

The physico-chemicalproperties of all the formulations prepared with different polymers like Carbopol 934P, HPC was shown to be within the limits. Maximum Bioadhesion strength and *ex vivo* residence time values were found for formulations prepared with Carbopol 934P (45 g). The drug release rate of formulations prepared with Carbopol 934P (Max.86.2±0.7%) was retarded due to the high viscosity of the polymer andformation of complex matrix network when compared to the other polymers. The rate of drug release of the formulations prepared with MCC as diluents was less due to its water insoluble nature compared to water soluble diluents like spray dried lactose and mannitol. The marketed product released the drug within 10 min. Release profile of the optimized formulation (PH4) was compared with conventional marketed products.

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