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Study of Effect of Various-Natural Polymers in the Formulation Development of Mucoadhesive Buccal Tablets of Labetalol HCl

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A B S T R A C T

Labetalol was formulated as buccal tablets to improve its bioavailability by avoiding first pass metabolism. HPMC K4M, HPMC K15M and HPMC K100M were selected as polymers and various formulations were prepared by using these polymers. The pre-compression blend of Labetalol buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio and all the results indicated that the blend was having good flow nature and better compression properties. The swelling studies were performed for the formulations which were shown desired drug release. The formulations prepared with HPMC K100M in the concentration of 20 mg (F7) was showing better result 98.23% drug release. The swelling studies were performed for the formulations which were shown desired drug release and the value was found to be 68.5 % in 12 hours. Ex-vivo residence time, Moisture absorption, surface pH, Bioadhesion strength values for selected formulations were found to be good.

Keywords: Labetalol, HPMC K4M, HPMC K15M, HPMC K100M, Buccal tablets.

A R T I C L E I N F O

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1. Introduction

Buccoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. The medicament is placed between the cheek and the gum. The barrier to drug absorption from this route is the epithelium of oral mucosa. Passive diffusion is the major mechanism for absorption of drugs. Drugs with short biological half-lives, requiring a

sustained effect, poor permeability, sensitivity to enzymatic degradation and poor solubility may be successfully delivered via bioadhesive buccal delivery systems [1-3].

Labetalol is an antihypertensive drug that blocks alpha and beta adrenergic receptors of the sympathetic nervous system which leads to decrease in blood pressure [4]. Present research was focused on formulation of labetalol buccal tablets in order to decrease the dosage frequency and to increase the patient compliance. Nine formulations were prepared using different grades of hydroxyl propyl methyl cellulose and all the formulations were evaluated for pre and post compressional parameters.

2. Materials and Methods

Labetalol is obtained from Natco Pharma, Hydroxy Propyl Methyl Cellulose K4M, Hydroxy Propyl Methyl Cellulose K15M, Hydroxy Propyl Methyl Cellulose K100M was procured from SD fine chemicals Pvt Ltd. Magnesium stearate from Himedia, Talc from Nice chemicals and MCC from Nihar traders PVT Ltd. All the other chemicals used were of analytical grade.

Method

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. HPMCK4M, HPMCK15M, HPMCK100M are the mucoadhesive and biodegradable polymers used in this preparation of buccal mucoadhesive drug delivery systems. Labetalol was mixed manually with different ratios of HPMC K4M, HPMC K15M, HPMC K100M and Microcrystalline Cellulose as diluent for 10 min. In every formulation constant amount of PVPK30 was added as binding agent.

The blend was mixed with talc and magnesium stearate for 3-5 min. Then the powder blend was compressed into tablets by the direct compression method using 8 mm flat faced punches. The tablets were compressed using 8 station Cemach rotary tablet-punching machine. The weight of the tablets was determined using a digital balance and thickness with digital screw gauge. Composition of the prepared bioadhesive buccal tablet formulations of Labetalol were given in Table no 1.

Evaluation of Buccal Tablets

Pre Compression Blend [5-9]:

A. Angle of repose:

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$, h = Height of the cone,

r = Radius of the cone base

B. Bulk density: 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read. The bulk density was calculated using the formula:

Bulk Density = M / V_o

Where, M = weight of sample, V_o = apparent volume of powder

C. Tapped density: After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$Tap = M / V$$

Where, Tap= Tapped Density, M = Weight of sample, V= Tapped volume of powder

D. Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = $[(tap - b) / tap] \times 100$

Where, b = Bulk Density, Tap = Tapped Density

Post Compression Blend [10-14]:

The prepared Labetalol buccal tablets were studied for their post compression blend like weight variation, hardness, thickness, friability and drug content.

A. Weight variation:

The weight variation test is done by taking 20 tablets randomly and weighed accurately. The composite weight divided by 20 provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by 10 % and none should deviate by more than twice that percentage. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula:

% Deviation = (Individual weight – Average weight / Average weight) X 100

The average weight of tablets in each formulation was calculated and presented with standard deviation.

B. Tablet Thickness:

The thickness and diameter of the tablets was determined using a Digital Vernier caliper. Ten tablets from each formulation were used and average values were calculated. The average thickness for tablets is calculated and presented with standard deviation.

C. Tablet Hardness:

Six tablets were taken from each formulation and hardness was determined using Monsanto hardness tester and the average was calculated. It is expressed in Kg/cm^2.

D. Friability:

A sample of pre weighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as

$F (\%) = [Wo-W/W_O] X100$

Where, W_0 is the initial weight of the tablets before the test and W is the final weight of the tablets after test.

E. Assay:

Six tablets of each formulation were taken and amount of drug present in each tablet was determined. Powder equivalent to one tablet was taken and added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 272 nm using pH6.8 phosphate buffer.

***In-vitro* release studies:**

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. Tablets were supposed to release the drug from tablets which placed in the dissolution apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 12 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 272nm.

Release kinetics:

Data of *in-vitro* release was fit into different equations to explain the release kinetics of labetalol release from buccal tablets. The kinetic equations used were zero – order and first order equations.

3. Results and Discussion

Labetalol was formulated as buccal tablets to improve its bioavailability by avoiding first pass metabolism. HPMC K4M, HPMC K15M, HPMC K100M were selected as polymers and various formulations were prepared by using these polymers and evaluated.

Compatibility studies (FT-IR):

FT-IR spectrum of the pure drug by which the compatability of drug to all other excipients can be known by the wave numbers which are present and found that there is no incompatibity between drug and excipients. Results are shown in Fig no-1,2.

Solubility Studies:

The solubility of Labetalol in phosphate buffer solution pH 6.8 was determined by phase equilibrium method. An excess amount of drug was taken into 20 ml vials containing 10 ml of phosphate buffers (pH 6.8, pH 7.4 and water). Vials were closed with rubber caps and constantly agitated at room temperature for 24 hr using rotary shaker. After 24 hr, the solution was filtered through 0.2µm Whatmann's filter paper. The amount of drug solubilized was then estimated by measuring the absorbance at 272 nm using a UV spectrophotometer. Results are shown in table no-2.

Characterization of Precompression Blend:

The precompression blend of Labetalol Buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 28^0, Carr's index values were less than 11 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties. Results are shown in table no-3.

Physical Evaluation of Labetalol Buccal tablets:

The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 4.5. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 3.6 to 5 kg/cm^2 and the friability values were less than 0.561% indicating that the buccal tablets were compact and hard. The thickness of the tablets ranged from 3.71-3.91cm. All the formulations satisfied the content of the drug as they contained 98-100% of Labetalol and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits. Results are shown in table no-4.

***In vitro* release studies:**

From the results it was evident that, HPMC K100M in the concentration of 20mg (F7) showed better result 98.23% drug release. Results are shown in table no-5 and fig no 3-5.

Release kinetics:

kinetics revealed that the formulation followed zero order kinetics with regression value of 0.986 with non fickian diffusion mechanism. Results are shown in table no-6.

Swelling Studies:

The swelling studies were performed for the optimized formulation which was shown desired drug release. Swelling behavior of a buccal system was essential for uniform and prolonged release of drug and proper bioadhesion. The formulation containing HPMC K100M was shown good swelling index. Results are shown in table no-7 and fig no-6.

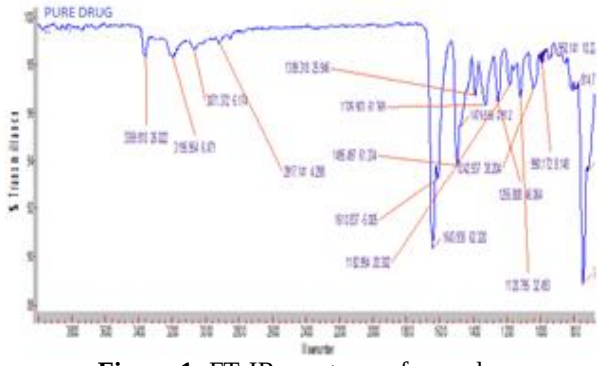

Figure 1: FT-IR spectrum of pure drug

Figure 2: FT-IR spectrum of optimized formulation

Table 1: Composition of buccal tablets

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Drug	100	100	100	100	100	100	100	100	100
HPMC K4M	30	60	90	-	-	-	-	-	-
HPMC K15M	-	-	-	30	60	90	-	-	-
HPMC K 100M	-	-	-	-	-	-	30	60	90
MCC pH 102	161	131	101	161	131	101	161	131	101
Mg. Stearate	3	3	3	3	3	3	3	3	3
Aerosil	6	6	6	6	6	6	6	6	6
Total Weight (mg)	300	300	300	300	300	300	300	300	300

Table 2: Solubility studies

S.No	**Medium**	**Concentration (µg/ml)**
1	Phosphate 6.8 buffer	14.5
2	Phosphate 7.4 buffer	13.8
3	Water	12.4

Table 3: Physical properties of precompression blend

Formulation Code	**Angle of repose (Θ)**	**Bulk density (gm/cm^3)**	**Tapped density (gm/cm^3)**	**Carr's Index (%)**	**Hausner's ratio**
F1	25.10°	0.53±0.01	0.59±0.01	9.43±0.12	1.09±0.02
F2	25.43°	0.54±0.03	0.60±0.02	9.40±0.13	1.10±0.01
F3	25.41°	0.54±0.02	0.58±0.03	10.01±0.19	1.13±0.06
F4	26.40°	0.51±0.01	0.61±0.06	10.11±0.02	1.16±0.01
F5	27.12°	0.58±0.03	0.63±0.03	10.34±0.13	1.17±0.03
F6	25.31°	0.59±0.03	0.64±0.04	10.12±0.34	1.11±0.06
F7	26.11°	0.56±0.01	0.63±0.01	9.93±0.11	1.13±0.03
F8	26.15°	0.53±0.03	0.58±0.03	10.13±0.02	1.12±0.01
F9	25.43°	0.54±0.03	0.60±0.02	9.40±0.13	1.10±0.01

All the values represent mean ± Standard deviation (SD), n=3

Table 4: Physical properties of post compression blend

Formulation code	**Weight variation (mg)**	**Thickness (cm)**	**Diameter**	**Hardness (Kg/cm^2)**	**Friability (%)**	**Content uniformity (%)**
F1	303.20	3.76±0.01	8.12±0.01	4.5±0.7	0.420	99±0.12
F2	304.30	3.74±0.04	8.14±0.02	4.2±0.5	0.341	99±0.3
F3	301.10	3.71±0.01	8.01±0.01	3.6±0.6	0.363	100±0.1
F4	304.20	3.80±0.06	8.03±0.03	4.8±0.5	0.561	100±0.3
F5	305.22	3.81±0.04	8.04±0.04	3.8±0.4	0.482	99±0.6
F6	304.12	3.74±0.05	8.09±0.05	4.4±0.6	0.513	99±0.4
F7	299.33	3.76±0.03	8.11±0.03	5 ± 0.1	0.412	98±0.9
F8	300.22	3.71±0.04	8.09±0.06	4.6±0.2	0.432	99±0.1
F9	300.10	3.73±0.03	8.03±0.02	4.0±0.3	0.512	100±0.1

Table 5: *In vitro* dissolution data for formulations F1 - F3 by using HPMC K4M Polymer.

Time (hrs)	**% Drug release**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
0.5	26.73	16.73	9.4	14.23	12.56	7.73	24.4	16.56	11.06
1	31.06	20.4	13.23	20.9	16.57	11.56	35.56	26.23	16.73
2	44.9	25.9	20.4	32.73	18.9	16.56	49.9	35.56	21.06
3	57.06	35.56	29.9	42.9	27.73	18.9	61.06	44.23	34.4
4	75.56	44.9	33.23	50.4	42.4	22.73	70.73	50.56	41.06
6	81.06	54.4	38.73	57.73	47.9	28.23	81.73	66.56	46.56

8	94.9	66.56	46.56	68.56	54.4	36.06	93.73	78.23	52.4
10	99.56	79.9	49.9	83.73	66.56	48.4	98.4	89.4	60.73
12	-	87.73	59.56	90.9	72.73	60.4	98.23	92.06	70.4

Table 6: Kinetic Studies

Formulation code	**Mathematical models (Release Kinetics)**				
	Zero order	**First order**	**Higuchi**	**Korsmeyer-Peppas**	
	R^2	**R^2**	**R^2**	**R^2**	**n value**
F7	0.986	0.9119	0.9348	0.9427	0.6177

Table 7: Swelling index of optimized formulation (F7)

Time (hrs)	**Swelling Index (%)**
	F7
0	0
0.5	11.1
1	18.3
2	24.3
3	25.3
4	31.11
5	42.2
6	51.3
7	63.4
8	68.5

Each value represents the mean±SD (n=3)

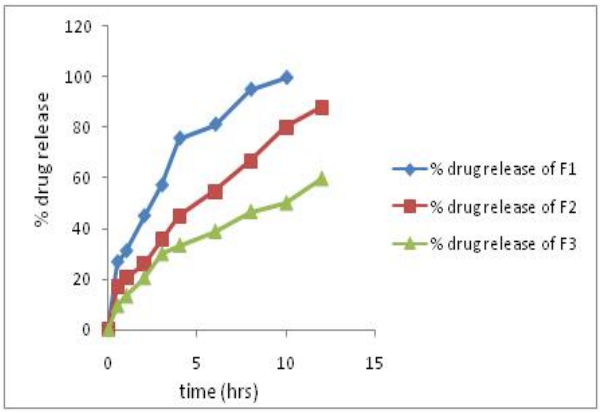

Figure 3: *In-vitro* dissolution data for formulations F1 - F3 by using HPMC K4M polymer

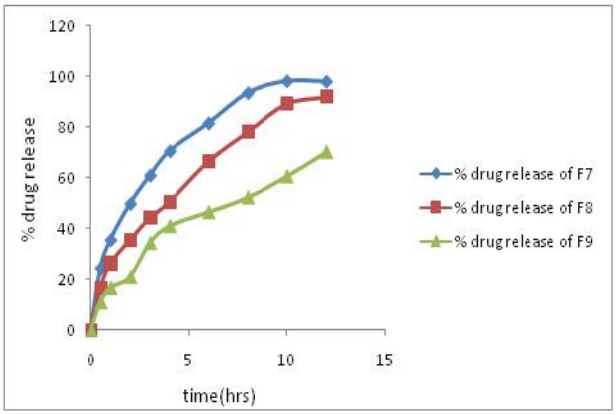

Figure 5: *In-vitro* dissolution data for formulations F7 – F9 by using HPMC K100M Polymer

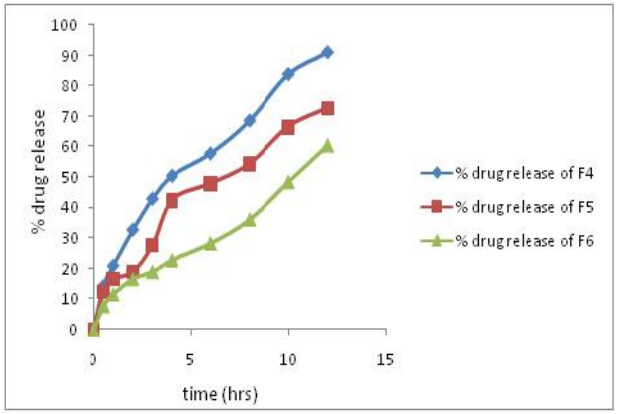

Figure 4: *In-vitro* dissolution data for formulations F4 - F6 by using HPMC K15 M Polymer

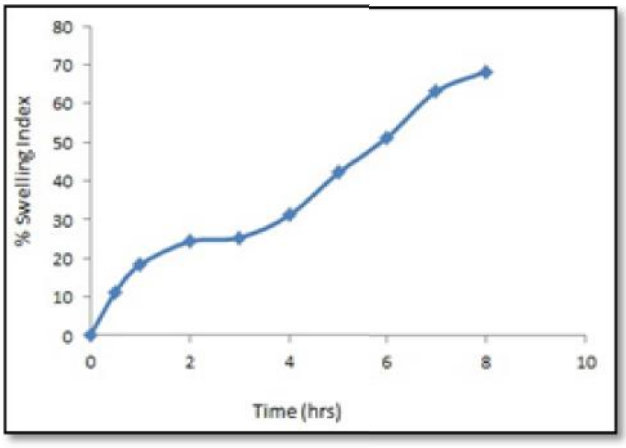

Figure 6: Graph Showing Swelling Index Values

4. Conclusion

From the results it was concluded that the blend was having good flow nature and better compression properties. The swelling studies were performed for the formulations which were shown desired drug release. The formulations prepared with HPMC K100M in the concentration of 20 mg (F7) was showing better result 98.23% drug release. The swelling studies were performed for the formulations which were shown desired drug release and the value was found to be 68.5 % in 8 hours.

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