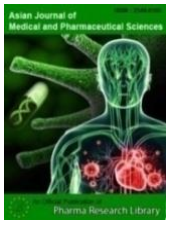

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Formulation and In-Vitro Evaluation of Pindolol Tablets for Buccal Drug Delivery System

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A B S T R A C T
Pindolol is a nonselective beta blocker which is used in the treatment of hypertension. It is also an antagonist of the serotonin 5-HT1A receptor, preferentially blocking inhibitory 5-HT1A auto receptors, and has been researched as an add-on therapy to selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression. The aim of the present study was to develop buccal formulation of Pindolol to maintain constant therapeutic levels of the drug for over 12 hrs. HPMCK15M, Locust bean gum and Xanthan gum were employed as polymers. Pindolol dose was fixed as 10 mg. Total weight of the tablet was considered as 60 mg. Polymers were used in the concentration of 10 mg, 20 mg and 30 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F4) showed better and desired drug release pattern i.e.,98.53 % in 12 hours. It followed zero order release kinetics mechanism.

Keywords: Pindolol, Buccal Tablets, HPMCK15M, Locust bean gum and Xanthan gum.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Buccal administration refers to a enteral route of administration by which drugs diffuse through the oral mucosa (tissues which line the mouth) and enter directly into the bloodstream. Buccal administration may provide better bioavailability of some drugs and a more rapid onset of action compared to oral administration because the medication does not pass through the digestive system and thereby avoids first pass metabolism [1]. As of May 2014, buccal forms of the psychiatric drug, asenapine; the opioid drugs buprenorphine, naloxone, and fentanyl; the cardiovascular drug nitroglycerin; the nausea medication Prochlorperazine; the hormone replacement therapy testosterone, and nicotine as a smoking cessation aid, were commercially available in buccal forms, as was midazolam, an anticonvulsant, used to treat acute epileptic seizures. Buccal administration of vaccines has been studied, but there are challenges to this approach due to immune tolerance mechanisms that prevent the body from over-reacting to immunogens encountered in the course of daily life. Within the oral mucosal cavity, delivery of drugs is classified into three categories, Sublingual delivery: which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth[2]. Buccal delivery: which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and Local delivery: which is drug delivery into the oral cavity It is richly vascularized and more accessible for the administration and removal of a dosage form. Buccal drug delivery has a high patient acceptability compared to other non-oral routes of drug administration. Harsh

environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery. Moreover, rapid cellular recovery and achievement of a localized site on the smooth surface of the buccal mucosa Low permeability of the buccal membrane: specifically, when compared to the sublingual membrane[3].

The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm2 represents non-keratinized tissues, including the buccal membrane. The continuous secretion of saliva (0.5–2 l/day) leads to subsequent dilution of the drug. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form. The present work is aimed at formulating buccal delivery of Pindolol using various polymers and to study the effect of Drug polymer ratio or concentration of polymer on drug release [4].

2. Materials and Methods

Materials

Materials and methods: Materials-Pindolol (NATCO LABS), Methocel K100M (Signet Chemical Corporation, Mumbai, India), Xanthan gum, Magnesium stearate (SD fine chemicals, Mumbai, India), Locust bean gum, MCC pH 102, Talc (Merck Specialties Pvt Ltd, Mumbai, India).

1. Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 1.The tablets were prepared as per the procedure given below and aim is to prolong the release of Pindolol. Total weight of the tablet was considered as 60mg.[5, 6]

Procedure:

- Pindolol and all other ingredients were individually passed through sieve no ≠ 60.
- All the ingredients were mixed thoroughly by triturating up to 15 min.
- The powder mixture was lubricated with talc.
- The tablets were prepared by using direct compression method.

Evaluation of Pindolol Buccal Tablets

Preformulation parameters: The powder blend was subjected for the following studies [7]

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio

Angle of repose:

The angle of repose of powders was determined by the funnel method. Accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was calculated by using the given formula. The results were tabulated in Table 2.

$$\tan\theta = \frac{h}{r}$$

Where,

h = height of the powder cone

r = radius of the powder cone

Bulk density and tapped density:

A quantity of 10gms of powder from each formula was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was tapped continuously until no further change in volume was observed. Then bulk density (BD) and tapped density (TD) were calculated by using the given formula and the results were tabulated in Table 2.

$$BD = \frac{\text{Weight of the powder}}{\text{Initial volume}}$$

$$TD = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

Carr's index:

The Compressibility of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which it is packed. The formula for carr's Index is given below and the results were tabulated in Table 2.

$$\text{Carr}'\text{s index } (\%) = \frac{TD - BD}{TD} \times 100$$

Hausner's ratio:

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material. It is calculated by using the given formula. The results were tabulated in Table 2.

$$\text{Hausner}'\text{s ratio} = \frac{TD}{BD}$$

Post compression studies[8]

Thickness:

Tablet thickness can be measured using digital vernier calipers. 3 tablets were taken and their thickness was measured and the average thickness for each tablet was calculated. The results were tabulated in Table 3.

Hardness:

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using monsanto hardness tester. An average of three observations is reported. The results were tabulated in Table 3.

Friability test: Friability of the tablets was determined using Roche friability. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Conventional tablets that lose less than 1% of their weight are acceptable. The results were tabulated in Table 3.

$$\%Friability = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Weight variation:

The weight variation test is done by weighing 20 tablets individually, calculating average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The results were tabulated in Table 3.

$$\%\ \text{Weight variation} = \frac{\text{Average weight - Initial weight}}{\text{Average weight}} \times 100$$

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Determination of drug content:

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Pindolol were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

Dissolution parameters:

Apparatus -- USP-II, Paddle Method
Dissolution Medium -- 6.8 ph phosphate buffer
RPM -- 50
Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature -- 37°c ± 0.5°c

Procedure:

900ml 0f 6.8 phosphate buffer was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated 6.8 ph phosphate buffer was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 261 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

3. Results and Discussion

The present study was aimed to developing buccal tablets of Pindolol using various polymers. All the formulations were evaluated for physicochemical properties and in-vitro drug release studies.

Analytical Method: It was found that the estimation of Pindolol by UV spectrophotometric method at λ_{max}261 nm in pH 6.8 Phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 10- 60µg/ml. The regression equation generated was y = 0.1351x + 0.0148, R^2 = 0.997.

Pre-formulation parameters of powder blend

The data's were shown in Table 8.2.The values for angle of repose were found in the range of 22°-25°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.51 to 0.54 (gm/cc) and 0.52 to 0.55 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.92% to 15.67%. The Hausner ration fall in range of 1.03 to 1.12. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Quality Control Parameters For tablets: Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the formulation of tablet.

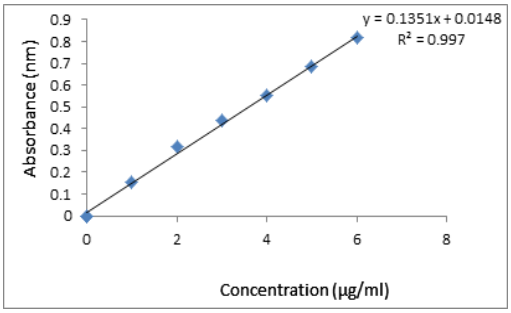

Fig 1: Standard graph of Pindolol in pH 6.8 phosphate buffer (261 nm)

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 8.3. The average weight of the tablet is approximately in range of 59 to 63mg, so the permissible limit is ±10% (=60mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test: Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data's were shown in Table 8.3. The results showed that the hardness of the tablets is in range of 4.4 to 4.6 kg/cm^2,which was within IP limits.

Thickness: Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-8.3 .The result showed that thickness of the tablet is raging from 1.4 to 1.6.

Friability: Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 8.3. The average friability of all the formulations lies in the

range of 0.53 to 0.56% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.09 -98.64%.

***In-Vitro* Drug Release Studies**

In-vitro Dissolution studies: In-vitro dissolution studies were carried out by using 900ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 12 hrs.

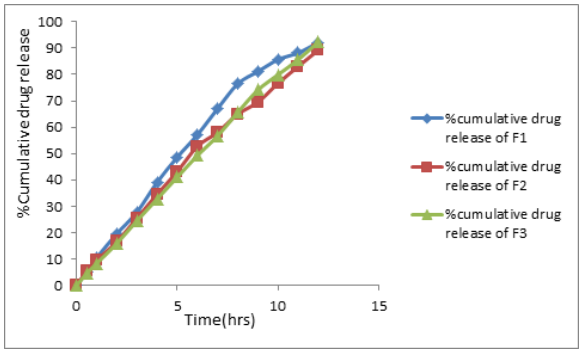

Fig 2: Dissolution profile of Pindolol (F1, F2, F3 formulations)

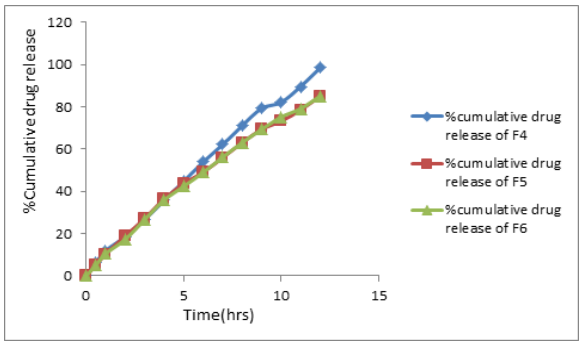

Fig 3. Dissolution profile of Pindolol (F4, F5, F6 formulations)

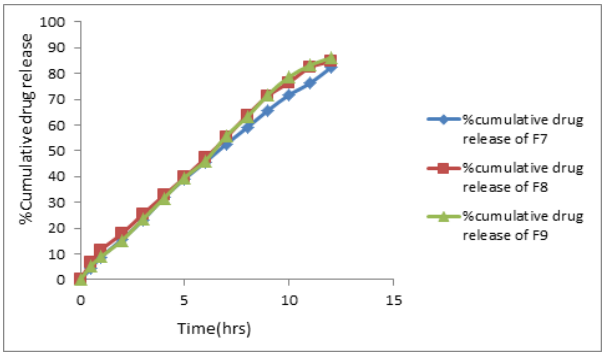

Fig 4: Dissolution profile of Pindolol (F7, F8, F9 formulations)

From the figures 2-4 it was evident that the formulations prepared with super disintegrant Locust bean gum showed maximum % drug release in 8 min i.e.98.53% (F4 formulations and the concentration of super disintegrant was 10 mg). So the principle of super disintegrants was found to be useful to produce sublingual tablets. F4 formulation was considered as optimized formulation.

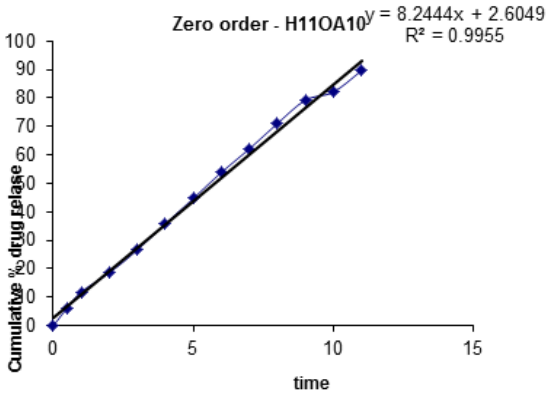

Fig 5 : Zero order release kinetics graph

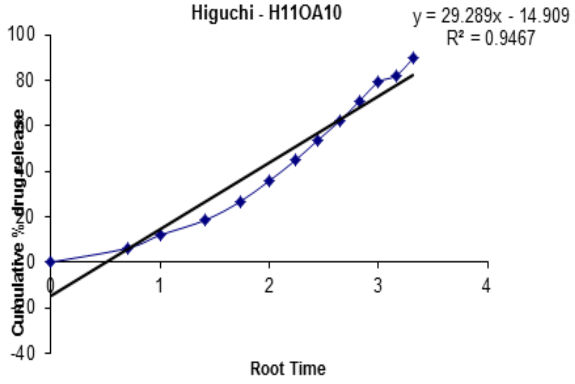

Fig 6 : Higuchi release kinetics graph

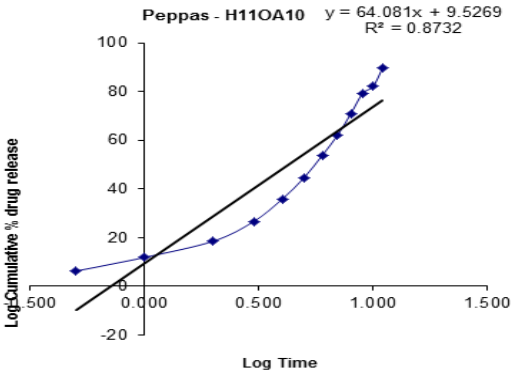

Fig 7: Kars Mayer peppas graph

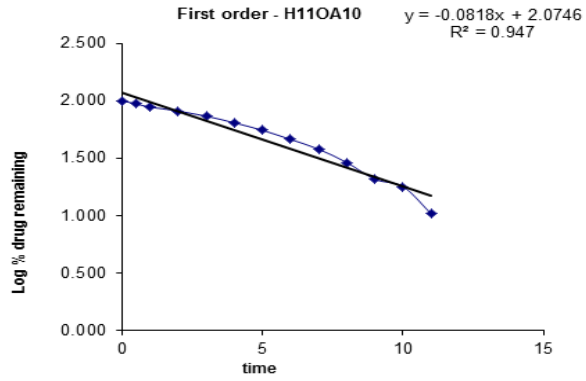

Fig 8: First order release kinetics graph

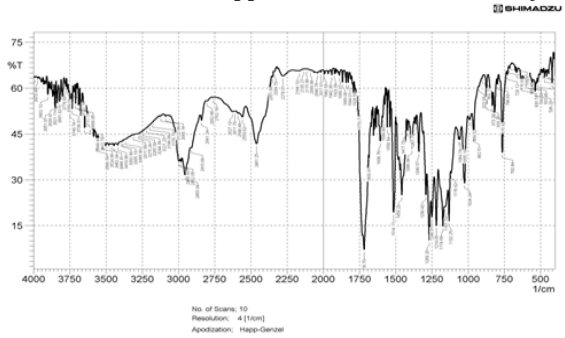

Fig 9: FTIR spectrum of pure drug

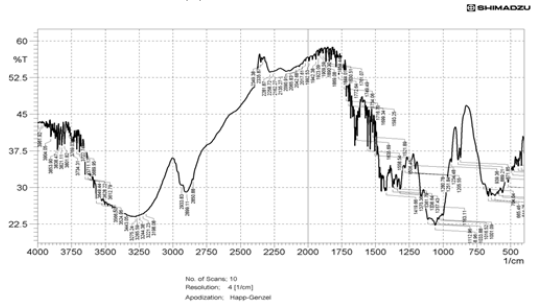

Fig 10: FTIR spectrum of optimised formulation

Table 1: Formulation composition for tablets

Formulation No	Pindolol	HPMCK 15M	Locust bean gum	Xanthan gum	Mag. Stearate	Talc	MCC pH 102
F1	10	10	-	-	3	3	QS
F2	10	20	-	-	3	3	QS
F3	10	30	-	-	3	3	QS
F4	10	-	10	-	3	3	QS
F5	10	-	20	-	3	3	QS
F6	10	-	30	-	3	3	QS
F7	10	-	-	10	3	3	QS
F8	10	-	-	20	3	3	QS
F9	10	-	-	30	3	3	QS

All the quantities were in mg

Table 2: Pre-formulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	22.13	0.52	0.53	14.36	1.08
F2	23.05	0.53	0.52	13.92	1.06
F3	22.68	0.51	0.54	14.25	1.05
F4	22.41	0.54	0.55	14.08	1.03
F5	23.73	0.53	0.53	15.12	1.11
F6	22.17	0.53	0.53	14.73	1.12
F7	23.36	0.52	0.54	14.12	1.08
F8	22.18	0.53	0.53	15.67	1.09
F9	24.35	0.52	0.55	14.32	1.11

Table 3: Post compression parameters

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	62	4.5	0.54	1.5	97.09
F2	63	4.4	0.53	1.4	98.15
F3	59	4.5	0.54	1.6	97.24
F4	61	4.5	0.55	1.5	98.36
F5	62	4.6	0.56	1.5	98.64
F6	60	4.5	0.54	1.4	97.12
F7	63	4.4	0.56	1.4	98.67
F8	62	4.5	0.55	1.5	97.16
F9	59	4.5	0.54	1.5	98.12

4. Conclusion

The aim of the present study was to develop buccal formulation of Pindolol to maintain constant therapeutic levels of the drug for over 12 hrs. HPMCK15M, Locust bean gum and Xanthan gum were employed as polymers. Pindolol dose was fixed as 10 mg. Total weight of the tablet was considered as 60 mg. Polymers were used in the concentration of 10 mg, 20 mg and 30 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F4) showed better and desired drug

release pattern i.e.,98.53 % in 12 hours. It followed zero order release kinetics mechanism.

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