



Fabrication and Assessment of fast Dissolving Buccal Films of Labetalol Hydrochloride for Hypertension

**Jagadesh Kumar Yadav Kalluri*¹, R. Rajalakshmi¹, EM. Ramya Sudha¹,
Kiran kumar reddy B¹, Bhagyasree. Y¹, Mohan Kumar Atluri¹, Subbarayudu.B²**

¹Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, A.Rangampet, Tirupati, A.P

²Department of Pharmaceutics, Sreenivasa College of Pharmacy, Proddature, Kadapa, A.P, India.

Abstract

Labetalol hydrochloride is used as prevention of hypertension. It is having low bioavailability and high hepatic first pass metabolism. In the present work was Fast dissolving buccal films of Labetalol hydrochloride were prepared by solvent casting method with objective to improve the bioavailability, Patient compliance and Onset of action by using water soluble polymers like HPMC E-15(Hydroxypropyl methylcellulose), PVP K-30(Polyvinyl pyrrolidone) with the combination of PEG-400 (Polyethylene Glycol) as a plasticizer and glycerine used as sweetening agent.before the formulation the drug and polymer interaction was studied by FT-IR Analysis. The prepared films were evaluated for weight variation, surface pH, folding endurance, drug content uniformity, dissolving time, disintegration time, *in-vitro* drug release studies. From the evaluation study F3 formulation containing drug and polymer (1:3 ratio) showing good folding endurance and as well as increased controlled release of drug 94.35%. The present study concluded that fast dissolving buccal film formulation for poorly water soluble drugs for promising drug release and onset of action.

Keywords: Labetalol hydrochloride, HPMC E-15, Buccal films, *in-vitro* studies, PEG 400.

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***Corresponding author**

Jagadesh Kumar Yadav Kalluri
E-mail: venkatdvk23@gmail.com
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1. Introduction

For the last two decades, there has been an enhanced demand for more patient- compliance dosage forms to achieve onset of action in order to treat acute diseases like anti-hypertensive agents, anti-ulcer and NSAID'S formulated as oral drug delivery system formulations. Oral drug delivery systems still need some advancement to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage

forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. In the Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral fast dissolving films (OFDFs). (1-5)

These Fast dissolving buccal films improve the bioavailability of the drug by bypassing the first pass effects and avoiding the pre-systemic elimination of the drug within the GIT Tract. The active substance is may be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa respectively. According to literature, API can be added from 5%-25% w/w of total weight of polymer. For the effective formulation, dose of drug should be in mgs (less than 20 mg/day). The drugs which are potent, show high first pass metabolism and patient non-compliant are best candidates for fast dissolving buccal films.

Labetalol hydrochloride is a selective alpha-1 and non-selective beta adrenergic blocker used to treat high blood pressure (Anti-hypertensive agent).it has the low bioavailability (60-70%) due to hepatic first pas metabolism. Hence to improve the therapeutic index and bioavailability of the drug may administered by buccal route through buccal films. the present study deals with the formulation and evaluation of fast dissolving buccal films of Labetalol hydrochloride using water soluble polymers like HPMC E-15 and PVP K-30 in combination with PEG 400 as plasticizer and Glycerine as sweetening agent by solvent casting method. (6-11)

2. Experimental

Materials

Labetalol hydrochloride was gift sample (A-Z Pharmaceuticals ltd, Chennai), and other ingredients used were of analytical grade.

Methods

FT-IR Analysis

FT-IR Analysis of Labetalol hydrochloride, HPMC E-15, Physical Mixture of Labetalol Hydrochloride with HPMC E-15 and Labetalol hydrochloride formulations were analysis. The peaks produced by pure drug were with physical mixture and formulation.

Preparation of fast dissolving buccal films of Labetalol hydrochloride (12-14)

Buccal films of Labetalol hydrochloride F₁ were prepared by solvent casting technique using film forming polymers. Required amount of HPMC E-15 and PVP K-30 according to the formulation table No.1 was weighed accurately and soaked aside for 1hour for swelling of polymer. Required amount of water was added to the above polymer solution and dispersion was stirred. Simultaneously Labetalol hydrochloride was weighed accurately and dissolved in 5 ml of distilled water in another beaker. Then drug solution was added to the polymer solution and polyethylene glycol was added as plasticizer and glycerine as sweetener and was mixed thoroughly with the help of magnetic stirrer. The above solution was sonication for 20 min for removal of air bubbles .The glass mould 16 cm² (4 × 4) was placed over a flat surface and the resulting 5 ml solution containing 50 mg drug with the help of measuring cylinder was transferred into glass mould slowly drop by drop and was spread uniformly. The glass mould containing polymeric solution of drug was kept for 24 hours at 60⁰ c temperature for drying. After drying the films were removed from moulds then they were cut into required 4 cm² (2 × 2) sizes i.e., 12.5 mg. Similarly formulations F₂, F₃, F₄, F₅, F₆ were prepared.

Table.1 Formulation of Labetalol hydrochloride fast dissolving films

S.No	Formulation	Labetalol Hydrochloride(mg)	HPMC E-15(mg)	PVP K-30(mg)	PEG (ml)	Glycerine (ml)	Distilled Water(ml)
1	F ₁	50	100	-	2	0.5	5
2	F ₂	50	200	-	2	0.5	5
3	F ₃	50	300	-	2	0.5	5
4	F ₄	50	100	200	2	0.5	5
5	F ₅	50	200	150	2	0.5	5
6	F ₆	50	300	100	2	0.5	5

Methods of Evaluation (15-21)

Weight variation

For weight variation three films of every formulation were taken weighed individually on digital balance then average weight was calculated.

Surface pH

The film to be tested was placed in a petridish and was moistened with 0.5 ml of distilled water and kept for 1 h. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and kept for 1 min to allow equilibrium condition.

Folding endurance

The folding endurance was determined by repeatedly folding one patch at the same place till it break. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Disintegrating time

The dissolving time was determined by placing the film in a beaker containing 50 ml of phosphate buffer (pH 6.8). Time required by the film to dissolve completely was noted.

Content Uniformity

A film of 2 X 2 was cut and placed in a beaker. 10 ml of phosphate buffer solution (pH6.8) was placed. The contents were stirred in magnetic stirrer to dissolve the film. The contents were transferred to a volumetric flask (10 ml). The absorbance of the solution was measured against the corresponding blank solution at 284 nm. The experiments were carried out in triplicate and average value was calculated.

In-vitro dissolution studies

A buccal film was attached to the wall of the dissolution vessel such as a 1000 ml beaker, midway from the bottom with instant adhesive. After 2 min, the vessel was filled with 900 ml of phosphate buffer of pH 6.8. The temperature of the dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. Samples of 3ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through $0.45 \mu\text{N}$ Whatmann filter paper and after appropriate dilutions with phosphate buffer pH (6.8) absorbance was measured at 284 nm. Drug release was calculated and the cumulative percentage drug released was determined.

3. Results and Discussion

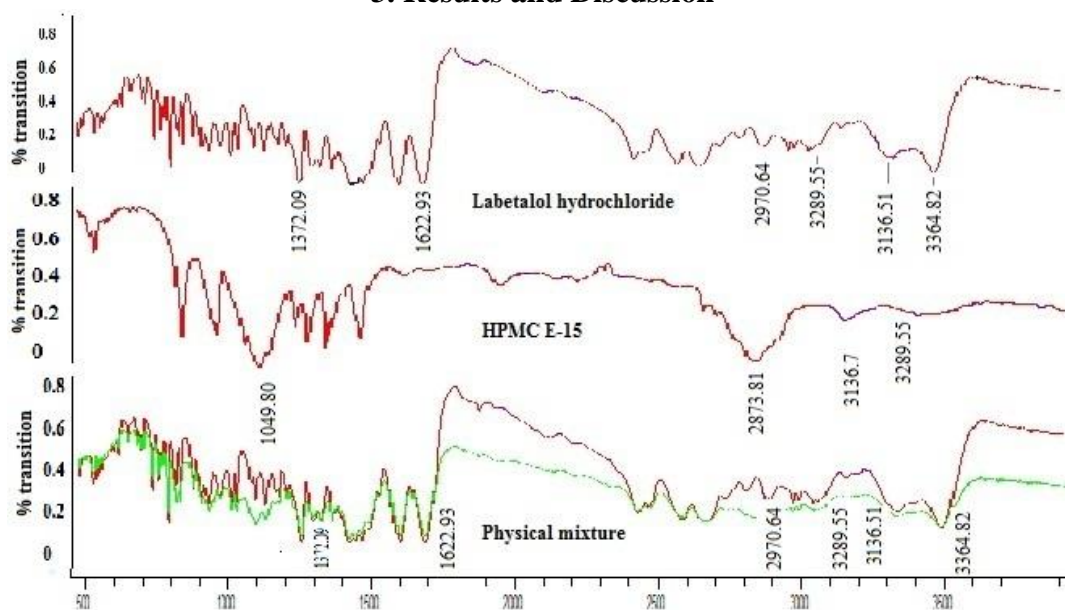


Figure.1 FT-IR Spectra of Labetalol HCl and physical mixture of Labetalol hydrochloride and HPMCE-15

Fast-dissolving (or) buccal films of Labetalol hydrochloride were prepared by using the water soluble polymers like HPMC E-15 (Hydroxypropylmethylcellulose) and PVP K-30(Polyvinylpyrrolidone). Before the formulation preformulation studies were conducted like FT-IR of Labetalol hydrochloride. FT-IR studies were used to find out the interaction between the drug and polymers. Figure No. 1 containing a Labetalol hydrochloride and mixture of Labetalol hydrochloride and HPMC E-15. The corresponding peaks of physical mixture, it is indicating there is no interaction between the drug and polymer. It is consisting that stability of Labetalol hydrochloride. Peaks of N-H Stretching at 3364.82 cm^{-1} , C-N Stretching at 1622.93 cm^{-1} , aromatic C-H Stretching at 2970.64 cm^{-1} which were present in Labetalol hydrochloride as well as found in physical mixture indicating that there is no interaction between drug and polymer. The prepared films were characterized for their release rates, surface pH, folding endurance, drug content uniformity and disintegration time. From the casted films, they were cut into required $4 \text{ cm}^2(2 \times 2)$ size. And each film contains 12.5 mg of Labetalol hydrochloride weight variation was observed in good range of 56 mg to 63 mg, disintegration time found to be in the range of 12(F1) to 23(F6) seconds.

Folding endurance was found by folding the film repeatedly at a point till they broke. The folding endurance of film was measured to be in the range of 123 to 158. The results of films are used for the drug content determination. The drug content was found to be 7.361mg(F4) to 10.9 mg(F3). The film pH was found to be 6.32 to 6.59. pH imbalance may cause for irritation to buccal mucosa, affect the drug release and degree of hydration of polymers like HPMC, PVPK-30. *In-vitro* drug release (dissolution rate) of all the formulations were performed by using pH 6.8 phosphate buffer as dissolution medium. The concentration of drug was found to be at 284 nm. the order of drug release was measured to be $F_3 > F_2 > F_1 > F_4 > F_5 > F_6$. F_4 to F_6 were lower the drug release because films containing PVP K-30, because of HPMC allowing the easy drug release of Labetalol hydrochloride as compared to PVP K-30. HPMC have the loosely bounded polymer in this films were readily disintegrated but PVPK-30 will takes more time to disintegration.

Table.2 Evaluation tests for Labetalol hydrochloride fast dissolving films

S.No	Evaluation parameters	Formulations					
		F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
1	Weight variation (%)	56	57	63	61	58	62
2	Surface pH	6.32	6.37	6.59	6.45	6.43	6.48
3	Folding endurance	123	135	158	122	138	148
4	Drug content (%)	71.8	68.04	86.59	58.89	64.89	67.2
5	Dissolving time(sec)	38	33	26	37	34	32
6	Disintegration time(sec)	16	17	15	17	19	23

Table.3 *In-vitro* drug release profiles of fast dissolving films

S.No	Time(sec)	% Drug release					
		F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
1	0	0	0	0	0	0	0
2	60	27.06	31.94	34.57	35.78	28.92	23.59
3	120	61.63	51.86	62.66	55.63	40.46	38.65
4	180	79.63	72.16	81.93	64.93	69.13	74.39
5	240	85.03	87.69	92.03	86.81	79.72	79.07
6	300	91.32	93.54	94.35	92.34	81.65	82.65

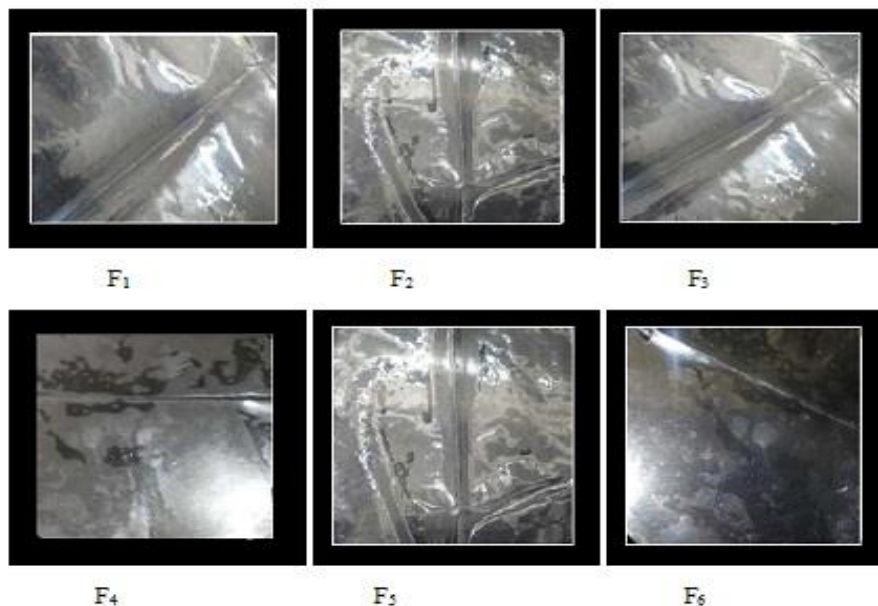


Figure.2 Photos of films

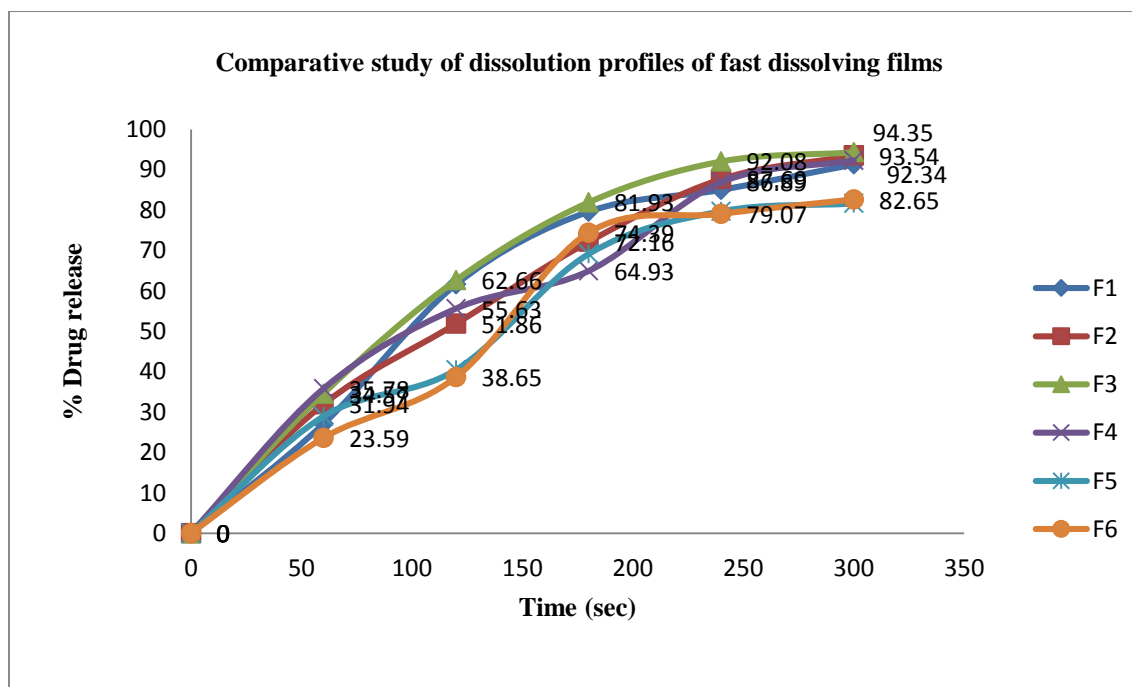


Figure.3 In-vitro drug release profiles of Labetalol hydrochloride fast dissolving films

4. Conclusion

The present study was concluded that F₁-F₃ (containing HPMC) and F₄-F₆ (containing HPMC with PVP K-30) as compared to F₃ (HPMC) has the erodible fast dissolving films containing Labetalol hydrochloride releases drug in very promising effective doses to systemic circulation. The drug release order of Labetalol hydrochloride buccal films prepared by solvent casting method as found to be F₃>F₂>F₁>F₄>F₅>F₆. It can be concluded that F₃ is optimum formulation and showed onset of action.

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