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In Vitro and *In Vivo* Studies of Oral Thin Films Containing Bisoprolol Fumarate

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The aim of the study is to prepare oral thin films (OTF) containing bisoprolol fumarate and to evaluate their dissolution and pharmacokinetic behaviour. Oral thin films were prepared using core polymers hydroxypropyl methylcellulose, kollicoat SR 30 D and poly(vinyl alcohol). Both the films were characterized by content uniformity, disintegration and *in vitro* dissolution studies to compare their release behaviours. Both the films showed a rapid disintegration property that was > 1 min after insertion into the medium. The formulations have good cumulative percentage drug release suitable for both immediate and controlled release. The oral thin films have excellent stability for a period of 8 weeks. The pharmacokinetic results suggest that oral thin films containing bisoprolol fumarate have potential use, in controlling hypertension and also in the treatment of cardiac diseases in geriatric patients, as an alternative to the present formulations in the market with better patient compliance.

Key Words: Oral thin films, Bisoprolol fumarate, Controlled release, Stability, Content uniformity.

INTRODUCTION

High blood pressure is a clear and modifiable risk factor for cardiovascular diseases[1,2]. High blood pressure increases the risk of heart attack, stroke, failure and kidney disease[3,4]. Bisoprolol fumarate has shown beneficial cardiac effects in patients with hypertension[5,6]. Studies have shown that bisoprolol fumarate is more effective in controlling high blood pressure when compared to propranolol, atenolol and metoprolol[7]. Oral thin film, a new drug delivery system for the oral delivery of drugs, typically consists of a thin oral biopolymer strips that release loaded active ingredients immediately after uptake. Oral thin films can be produced with a manufacturing process that is cost competitive over conventional tablets oral thin films begin to dissolve as soon as they are placed in the oral cavity, unlike conventional solid dosage forms such as immediate release tablets. Oral thin films, therefore, possess the major advantage over the difficulties caused from swallowing tablets[8]. The main objective of the present study is therefore to develop a controlled release bisoprolol fumarate thin film.

EXPERIMENTAL

Bisoprolol fumarate was obtained from Unichem Laboratories Ltd., Raigad, India. Hydroxypropyl methyl cellulose (HPMC, grade: METHOCEL™ E3Premium, 3cps) and Kollicoat SR 30 D were obtained as a gift sample from Signet Chemicals, Mumbai, India. Triethyl citrate (TEC), poly(vinyl alcohol), glycerol and aspartame were procured from Sigma Aldrich. Mango flavour was procured from Roton International Co. Ltd., China. Distilled and deionized water using a 'Milli-Q' system (Millipore Corp.) was used.

Preparation of oral thin films: The materials used to prepare oral thin films are given in the Table-1. Films were prepared by mixing poly(vinyl alcohol), HPMC, triethyl citrate, glycerol, Kollicoat SR 30 D, aspartame and mango flavour in water. Ultrasonic defoaming apparatus was used to remove the air bubbles in the solution. The mixture was then coated onto the glass plates to prepare the thin films using the coating apparatus fabricated locally. The obtained film with the basic glass plate was cut without lopping the glass plate into 2 cm × 2 cm in size, containing 5 mg of the drug. The films were then removed from the glass plates.

Mechanical properties

Film thickness: Precise film thickness measurements were carried out using NIKON DigiMicro encoders/gauges (Nanowave Inc. MA 01590 USA, MF501-50 mm travel range along with TC-101).

Tensile strength: The force at tearing and elongation was measured during tensile test by a universal testing apparatus.

TABLE-1
COMPOSITION OF THE OPTIMIZED FILM SOLUTIONS

Formulations	F1 (% w/w)	F2 (% w/w)
HPMC	2	–
Poly(vinyl alcohol)	2	1
Kollicoat SR 30 D	–	3
Triethyl citrate	–	0.09
Glycerol	0.8	–
Aspartame	0.2	0.2
Mango flavor	0.05	0.05
Drug (bisoprolol fumarate)	0.05	0.05
Water	94.90	95.61

The test sample was clamped between the tensioning tools. The drawing rate was 50 mm/min and no preload was used. The tensile stress at break (MPa) was calculated.

Content uniformity of the preparations: The dosage uniformity of the oral thin films were tested using 10 preparations and the content of bisoprolol fumarate was determined by HPLC. The contents of the preparations were 85 and 115 % and the relative standard deviation was less than or equal to 6.0 %. The acceptance value of the preparation is less than 15 %, according to the JP15.

Disintegration test: Disintegration times were measured *in vitro* for six samples by the standard United States Pharmacopeia (USP) disintegration method in artificial saliva at 37 ºC using the disintegration apparatus (Electro Lab, ED-2L, Mumbai, India).

Dissolution test: *In vitro* dissolution test was carried out according to the USP II paddle dissolution apparatus. The test solution was 900 mL of freshly deionized water at 37 ± 0.5 ºC and the rotation rate of 75 rpm. 10 mL aliquots of samples were taken at regular intervals and the same volume of fresh test solution was replenished and the concentration of bisoprolol fumarate was calculated using HPLC method.

Stability test: Oral thin film pieces cut from both the formulations were stored in an aluminum package in a chamber controlled at 40 ºC and 75 % in humidity for 4-8 weeks. The content of bisoprolol fumarate was then determined using HPLC. The film samples were also subjected to disintegration and dissolution tests.

***In vivo* studies:** The objective of this study is to determine the plasma concentration profile of bisoprolol fumarate The experiments were approved by the animal ethical committee at VIT University, Vellore, Tamilnadu, India. (CPCSEA Reg. No-1333/c/10CPCSEA, New Delhi, INDIA) The study was carried out on New Zealand white rabbits. Both the formulations (F1 and F2) were applied to the buccal cavity bilaterally. Blood samples were collected from marginal ear vein at regular intervals in a heparinized centrifuge tubes and centrifuged immediately and the plasma separated were stored at -20 ºC till the time of analysis. The drug was estimated at 273 nm.

RESULTS AND DISCUSSION

Mechanical properties and content uniformity of the preparation: Physico-chemical properties obtained for the films were in acceptable range and given in the Table-2. The values were between 86.3, 97.5, 86.7 and 100.7 % for the F1 and F2, respectively. Further, acceptance value of F1 and F2 was found to be 13.7 and 14.3 %, respectively and are thus within the limit (15 %) of content uniformity as per JP 15.

TABLE-2
PHYSICO-CHEMICAL PROPERTIES OF THE FILM FORMULATIONS

Properties	n	F1	F2
Film thickness (μm)	5	45 ± 7	90 ± 5
Tensile strength (MPa)	5	7.79 ± 0.05	9.73 ± 0.03
Content uniformity (%)	5	94.5 ± 4.5	96.7 ± 3.7
Disintegration	5	10 ± 2 s	52 ± 4 s

Disintegration test: The disintegration time for F1 and F2 was found to be 10 ± 2 and 52 ± 4 s, respectively. As F1 contains poly(vinyl alcohol) and HPMC that are water soluble and readily absorb water it disintegrates much faster when compared to F2 which contains Kollicoat SR 30 D.

Dissolution test: The *in vitro* release profiles of both the formulations are given in Fig. 1. The data reveal that F1 shows immediate release and F2 shows controlled release behaviour. The hydrophilic polymers, HPMC and poly(vinyl alcohol) present in F1 absorb water quickly and swell up thus releasing the drug immediately from the matrix. The release of the drug from F2 is slow when compared to F1 because F2 containing Kollicoat SR 30 D which is 30 % aqueous dispersion of poly(vinyl acetate) stabilized with poly(vinyl pyrrolidone). When the film comes into contact with the dissolution media, poly(vinyl pyrrolidone) dissolves and acts as a pore-forming agent. The drug, therefore, dissolves and diffuses out through the pores at a controlled rate. Thus formulation F2 shows controlled release behaviour.

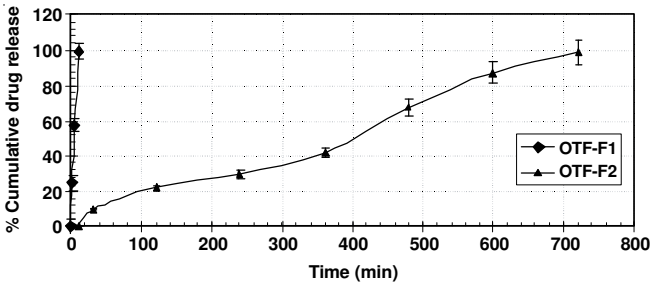

Fig. 1. Cumulative (%) drug release of F1 and F2 formulations

Stability: Fig. 2 reveals that the drug content is almost similar to that of initial samples and is constant for up to 8 weeks regardless of the storage conditions. The films, stored in aluminum packages at 40 ºC and 75 % in humidity for 4-8 weeks thus show no observable changes in all physical characteristics and there is no significant change in the rate of dissolution is observed till the 8th week compared to that of initial samples.

***In vivo* studies:** The drug concentrations in rabbit plasma were evaluated by HPLC. Fig. 3 shows the time course of changes in the drug concentrations after oral administration to rabbits. The pattern of changes for plasma concentrations is different for the two groups with slightly but not significantly higher in F2 group. Table-3 shows that there are significant differences in pharmacokinetic parameters, T_{max}, C_{max}, $AUC_{(0-\infty)}$, K_e and $t_{1/2}$, between the two groups. From the *in vivo* studies it may be concluded that C_{max} for F1 is high when compared to F2 and more over the $t_{1/2}$ of the F2 is higher when compared to

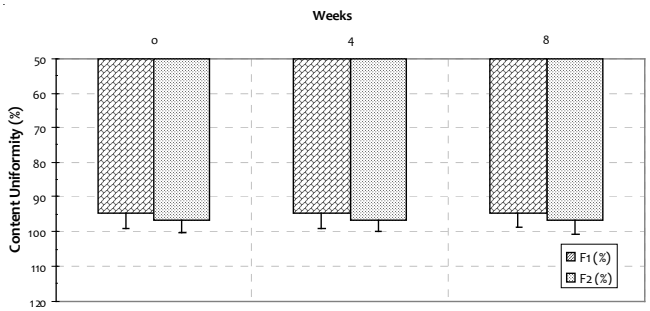

Fig. 2. Content uniformity of formulations under stability studies

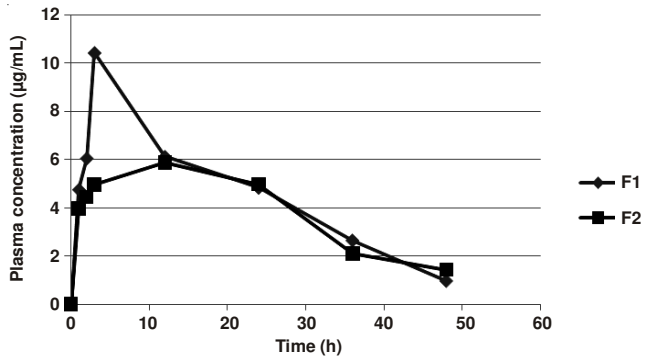

Fig. 3. Comparison of time course changes in plasma concentration of bisoprolol fumarate (F1 and F2)

TABLE-3
COMPARISON OF PHARMACOKINETICS PARAMETERS

Parameters	F1	F2
T_{max} (h)	12	12
C_{max} (µg/mL)	6.12	5.87
$AUC_{(0-\infty)}$ (µg/mL h)	222.8	188.15
K_e (h^{-1})	0.066	0.052
$T_{1/2}$ (h)	10.35	13.35

F1. These findings show that F2 formulation has good controlled release behaviour when compared to that of the F1 formulation.

Conclusion

In this paper, drug release behaviour for oral thin film formulations loaded with bisoprolol fumarate (5 mg) is reported. The content uniformity, dissolution, stability tests performed, reveals that the formulations are stable for 8 weeks. Both the films meet the criteria of acceptance value in the dosage uniformity test for JP15 and USP27. Moreover, the films show faster disintegration with good stability. The plasma concentration of bisoprolol in rabbits is more in F1 compared to F2. F2 thus shows controlled release behaviour compared to F1. Pharmacokinetic parameters were significantly different for the two formulations.

REFERENCES

1. S. Lewington, R. Clarke, N. Qizilbash and R. Peto, *The Lancet*, **360**, 1903 (2002).
2. P. Dinakar, C. Varalakshmi1, P.K. Prakash Reddy and S. Mohanlakshmi, *J. Pharm. Res*., **3**, 1955 (2009).
3. J.G. Wang, J.A. Staessen, S.S. Franklin, R. Fagard and F. Gueyffier, *Hypertension*, **45**, 907 (2005).
4. A.V. Chobanian, G.L. Bakris, H.R. Black and W.C. Cushman, *J. Am. Med. Assoc*., **289**, 2560 (2003).
5. T.F. Llgenli, F. Kilicaslan, A. Kirilmaz and M. Uzun, *Cardiology*, **106**, 127 (2006).
6. J.K. McGavin and G.M. Keating, *Drugs*, **62**, 2677 (2002).
7. G. Leopold, W. Ungethum, J. Pabst, Z. Simane, K.U. Buhring and H. Wiemann, *Brit. J. Clin. Pharmacol*., **22**, 293 (1986).
8. V. Ulrike and G. Paolo, Drug Delivery Report, Spring/Summer, 64 (2006).