EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 10
439-443
Year: 2020

FORMULATION AND EVALUATION OF FLUCONAZOLE BUCCAL TABLETS CONTAINING MICROPARTICULATE SYSTEM FOR CONTROLLED RELEASE

***Nagendra R., Charan C. S. and Hanumanhachar Joshi**

Nagendra R. Saradavilas College of Pharmacy Mysuru.

***Corresponding Author: Nagendra R.**
Nagendra R. Saradavilas College of Pharmacy Mysuru.

Article Received on 07/08/2020 **Article Revised on 28/08/2020** **Article Accepted on 18/09/2020**

ABSTRACT
The present study aimed at formulation and Evaluation of buccal tablets containing microparticulate system for controlled release of Fluconazole using blend of polymers in the treatment of candidiasis. The microparticles of Fluconazole were prepared by spray drying technique. The prepared microparticles were compressed into buccal tablets and evaluated for mucoadhesive properties, swelling index, *invitro* drug release studies. It was found that the Fluconazole release rate increased with a decreased amount of polymers. This can be adjusted by maintaining the concentration of the polymers. The formulation FC2 was found to be optimum formulation.

KEYWORDS: Fluconazole, Antifungal, Microparticles, Buccal Tablets, Controlled Release.

INTRODUCTION
The present research work involves the formulation of buccal drug delivery system. In recent years with the enhancement of life expectancy and the consequent increase in the number of patient's physical suffering from mucosal infections associated with immune compromised diseases, the search for formulations which reduce or minimize dose dumping and reduces the frequency of administration. Hence, increasing the effectiveness, safety, quality and expected a cost reduced medication.[1] Microencapsulation is a well-known method that is used to modify and delay drug release from pharmaceutical dosage forms. There number of microencapsulation techniques available for the formation of controlled and sustained release microparticulate drug delivery systems. Spray drying method is one of the popular methods for the encapsulation of drugs within water insoluble polymers.

Fluconazole, commonly known as *Diflucan*, is an antifungal drug used for the treatment of both systemic and superficial fungal infections in a variety of tissues. It was initially approved by the FDA in 1990. This drug is an *azole* antifungal, in the same drug family as Ketoconazole and Itraconazole. Fluconazole has many advantages over the other antifungal drugs including the option of oral administration. The side effect profile of this drug is minimal. It has been demonstrated as an efficacious treatment for vaginal yeast infections in one single dose.[2] Here an attempt was made to reduce the dosing frequency and to maintain the drug level at therapeutic concentration range, by formulating a Controlled drug delivery system in the form of microparticles using blend of hydrophilic and lipophilic polymers.

METHODS
Preparation of Microparticles
The microparticles were prepared by spray drying technique. Various formulations and process variables that could affect the preparation and properties of the microparticles were identified and optimized to get small, discrete and spherical microparticles. The formulation variables included concentration of drug: polymers ratio, amount of solvent used, types of excipients and its solubility. Different parameters such as temperature of inlet air, drying temperature, concentration of different polymers and drug, feed rate, inlet air pressure and aspiration were optimized during the process. Optimum drying conditions were employed for the process i.e,

Inlet temperature: 82°C
Feed-flow rate (ml/min); 5-6 ml/min
Compressed spray air flow: 10 L/min
Air pressure: 1.5 kg/cm^2

Table 1: Formulation chart of Fluconazole microparticles.

Formulation code	Chitosan (mg)	Carbopol 71G(mg)	Chitosan-carbopol 71G physical mixture (1:1) (mg)	IPEC (mg)
FA1	50	---	---	----
FA2	100	---	---	----
FB1	---	50	---	---
FB2	---	100	---	---
FC1	---	---	50	---
FC2	---	---	100	--
FD1	---	---	---	60
FD2	---	---	---	70

Compression of microparticles into tablets

Mucoadhesive tablets were fabricated by direct compression of prepared microparticles adding two percent of talc and microcrysaline cellulose. The blend was lubricated and then compressed into compacts by direct compression method using 8-mm flat-faced punches in KBr press (Technosearch, Mumbai, India) at one ton pressure with a dwell time of one.

***In vitro* mucoadhesive studies**

Mucoadhesive strength of the tablets was measured using modified physical balance. *In vitro* bioadhesion studies were carried out using sheep buccal mucosa and modified two-armed balance. The phosphate buffer pH 6.8 was used as the moistening fluid. A glass stopper was suspended by a fixed length of thread on one side of the balance and was counter balanced with the weights on the other side. Fresh sheep buccal mucosa was collected from the slaughter house. It was scrapped off from the connective tissues and a thin layer of buccal mucosa was separated and used for the bioadhesion study. A circular piece of sheep buccal mucosa was cut and fixed to the tissue holder and immersed in phosphate buffer pH 6.8 and the temperature was maintained at 37±1°C. Then the tablet was fixed to a glass stopper with the help of cyanoacrylate adhesive and placed on the buccal mucosa by using a preload of 50 gm and kept aside for 1 min to facilitate adhesion bonding. After preloading time, the preload was removed and the weights were added on the other side of the balance until tablet detaches from the sheep buccal mucosa. The weight required to detach tablet from buccal mucosa was noted.

Figure 1: Modified physical balance for mucoadhesive studies.

***In vitro* drug release studies**

Release of Fluconazole was determined using dissolution test apparatus USP type II at 100 rpm. The dissolution was studied using 100ml phosphate buffer 6.8.The temperature was maintained at 37±0.5°C. Aliquots (10 ml) of dissolution media were sampled at specified time intervals and replaced with fresh media immediately after sampling. Samples were analyzed for drug content by UV Visible spectroscopy.[2,3]

RESULTS AND DISCUSSION

Swelling studies

The dosage form planned for the buccal cavity, hence the swelling studies were carried out in buccal pH 6.8. In the initial stages, the swelling occurs very rapidly due to the entry of water via metastable pores in the tablets. This mechanism is known as hysteresis of the swelling that is followed by swelling as a result of diffusion processes. If an intact hydrated layer can be established over the period of study, diffusion may be the most important factor controlling the rate of drug release from the system diffusion. Drug release from hydrophilic matrix could occur by swelling-controlled mechanism.

Formulations containing chitosan (FA1 and FA2) alone exhibited least swelling index in phosphate buffer pH 6.8 FA1 and FA2 formulations have the ability to form the gel layer around the tablet in acidic pH, FB1 and FB2 formulation containing carbopol 71G exhibit swelling upto 8 hrs. The swelling property of carbopol 71G is directly influenced by the dissociation of carboxylic group that occur in neutral pH and basic pH. Hence the swelling index of carbopol 71G containing formulations is more in phosphate buffer pH 6.8. Formulations containing physical mixture of chitosan and carbopol 71G in FC1 and FC2 formulations exhibited varied swelling, due to the presence of both polymers that has the opposing swelling character in phosphate buffer pH 6.8.

Formulations containing only IPEC alone exhibited gradual increase in swelling. Increase in the concentration of IPEC in tablets, increases the swelling index which may be due to higher concentration of polymers that forms thicker gel layer around the tablet and a tighter polymeric network. Last three formulations containing IPEC with chitosan and carbopol 71G exhibit higher swelling.

These findings indicate the presence of only IPEC in matrix tablet exhibit slow uniform pH independent swelling degree and also the presence of chitosan and carbopol 71G in IPEC matrix tablets alters the swelling degree. Therefore the mechanism of drug release from IPEC matrix tablets was affected by the presence of chitosan and carbopol 71G.

Table 2: Swelling index data of fluconazole formulations in phosphate buffer pH 6.8.

Formulation Code	Swelling index Mean ± S.D*							
	Time in Hours							
	1 hour	2 hour	3 hour	4 hour	5 hour	6 hour	7 hour	8 hour
FA1	40 ±0.65	89 ±0.14	145 ±0.56	178 ±0.37	296 ±0.42	352 ±0.15	---	---
FA2	65 ±0.32	152 ±0.27	246 ±0.97	301 ±0.27	396 ±0.22	409 ±0.17	---	---
FB1	83 ±0.53	176 ±0.27	251 ±0.18	326 ±0.71	411 ±0.83	432 ±0.29	---	---
FB2	98 ±0.18	198 ±0.62	287 ±0.41	354 ±0.29	443 ±0.92	452 ±0.19	---	---
FC1	91 ±0.57	106 ±0.29	123 ±0.38	189 ±0.46	219 ±0.11	265 ±0.15	283 ±0.25	327 ±0.36
FC2	97 ±0.47	112 ±0.83	124 ±0.29	198 ±0.78	238 ±0.92	287 ±0.37	327 ±0.92	364 ±0.65
FD1	102 ±0.52	126 ±0.73	175 ±0.38	244 ±0.61	301 ±0.38	377 ±0.53	401 ±0.29	451 ±0.82
FD2	105 ±0.75	154 ±0.38	207 ±0.72	272 ±0.88	322 ±0.28	402 ±0.17	426 ±0.82	472 ±0.17

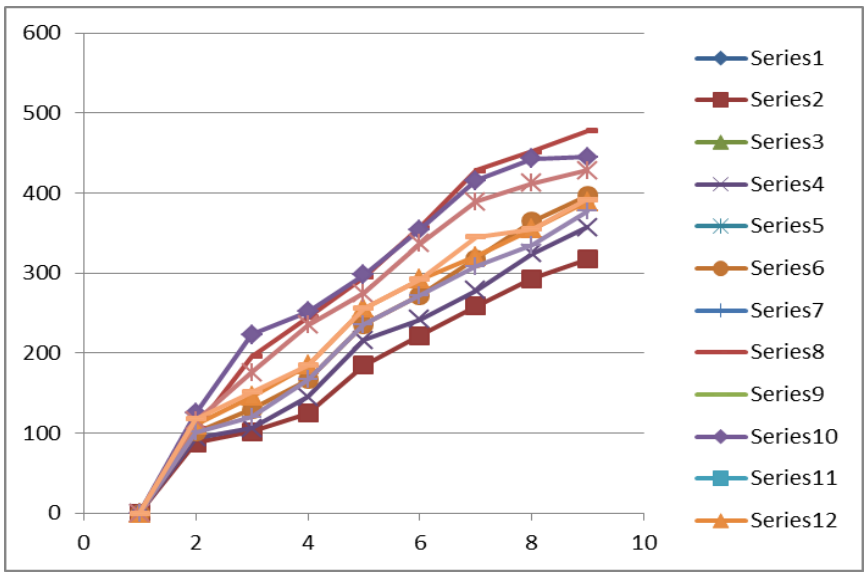

Figure 2: Swelling index profile for fluconazole formulations in phosphate.

Buffer pH 6.8

***In vitro* mucoadhesion studies**

Mucoadhesive strength for formulations is summarized in table 3. Based on the *in vitro* drug release profile, formulations were subjected for mucoadhesive studies. Three formulation containing IPEC exhibited the least mucoadhesive strength. The formed complex lacks the free functional groups which are involved in the complex formation; hence the satisfactory mucoadhesive strength was not evolved. Further increase in the concentration of IPEC, did not enhance mucoadhesive strength. The prepared complex lacks the strong binding but minor binding to the mucosal surfaces was observed which may be due to hydrogen bonding interactions.

Table 3: Mucoadhesive strength data of formulations.

Formulation code	Mucoadhesive strength(N/cm^2) Mean±SD*
FA1	0.020±0.006
FA2	0.03±0.007
FB1	0.031±0.007
FB2	0.031±0.008
FC1	0.07±0.01
FC2	0.08±0.01
FD1	0.10±0.01
FD2	0.08±0.01

*mean±SD, n=3

In- vitro drug dissolution

Release of Fluconazole was determined using dissolution test apparatus USP type II at 100 rpm. The dissolution was studied using 100 ml of phosphate buffer pH 6.8. The temperature was maintained at 37±0.5^{o}C. The sample were withdrawn at different time intervals 1,2,3,4,6,8,10 and 12 hrs filtered through whatman filter paper and replaced equal volume of dissolution medium. Sample was suitably diluted and analyzed for Fluconazole using UV-visible spectrophotometer. The percentage of Fluconazole release was calculated.

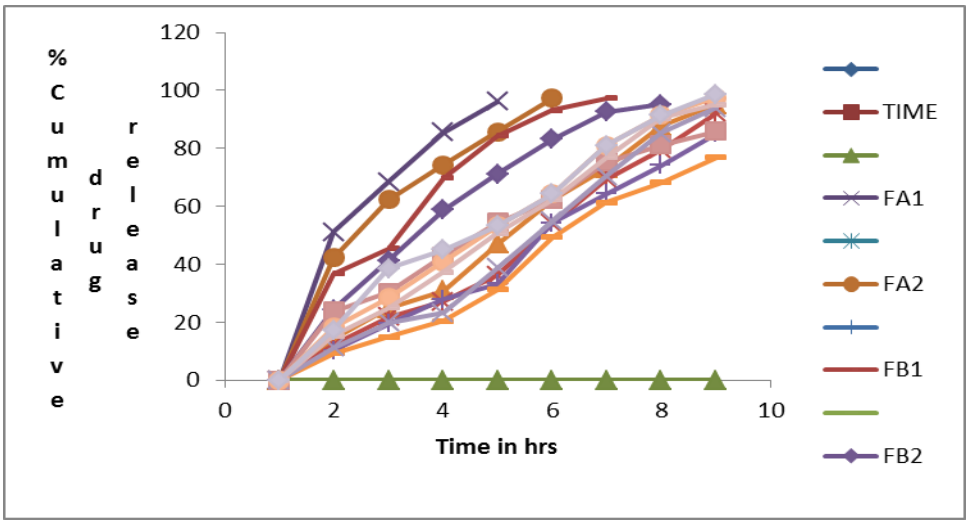

Figure 3: *In-vitro* drug release profile of the formulations.

CONCLUSION

The objective of this study was to formulate and evaluate buccal tablets containing microparticulate system for controlled release using different ratios of drug to polymers and prepared microparticles were characterized. There is strong prophylactic and clinical need to develop new solid dosage form for candidiasis with anticipated characteristics such as better therapeutic efficacy, retention for intended interval, patient flexibility with cost effective medication. The mucosal drug delivery system developed viz., interpolyelectrolyte complexes have demonstrated their dominance and suitability for buccal route for candidiasis Thus the study shows that the developed system have a pronounced appeal for the convenient treatment of candidiasis that may be explored in improving the limitations of existing drug delivery system.

IV. REFERENCES

1. Bakan J.A, Anderson J.L. Microencapsulation Part III, through Lachman. L, Lieberman H. A, Kanig J. L The Theory and Practice of Industrial Pharmacy, Varghese Publishing House, Bombay-14, 2nd edition., 1986; 428.
2. Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics a treaties, 2st ed, Vallabh prakashan, 2010; 397–515.
3. J.A, Bakan J.L.Anderson, “Microencapsulation Part III” through Lachman. L, Lieberman H. A, Kanig J. L. The Theory and Practice of Industrial Pharmacy, Varghese Publishing House, Bombay, 1986; 14: 428(2).
4. BK Kim, S J Hwang, Park JB and HJ Park. “Preparation and characterization of drug loaded polymethacrylate microspheres by an emulsion solvent evaporation method.” J microencapsulation, 2002; 811-22.
5. AA.Du Pasquier “Differential Scanning Calorimetry studies of lithium ion and the reactivity of carbon anodes in plastic lithium ion batteries.” J. Electrochem. Sci., 1998; 472-477; 145(2).
6. PB, Deasy Law MFL. “Use of extrusion spheronization to develop an improved oral dosage

form of indomethacin". Int. J. Pharm, 1997; 201-209.
7. XYan RA.Gemeinhart "Cisplatin delivery from Poly(acrylic acid-co-methyl methacrylate) microparticles," J. Control Release, 2005; 106: 198–208.
8. S. kumara, A.K sahaa and K.S Kumar "Preparation and characterization of indomethacin loaded ionically crosslinked microspheres using chitosan. "Scholars Research Library, 2012; 33-41: 4 (1).
9. S. Abreu1M. M. C. Forte 2, T. B. L. Kist3 L. P. Honaiser "Effect of the preparation method on the drug loading of alginate-chitosan microspheres" Express Polymer Letters, 2010; 456–464: 4(8).
10. K S Rangasamy, M Kugalur, G Natesan., "Formulation and evaluation of sustained release tablets of aceclofenac using hydrophilic matrix system". Int J PharmTech Res., 2010; 1775-80: 2(3).
11. Indian Pharmacopoeia, Government of India. Ministry of Health and Family Welfare. Delhi: The controller of Publications, 1996; 759.
12. Sobel JD, Faro S, Force RW, Foxman B, Ledger WJ, Nyirjesy PR, et al Vulvovaginal candidiasis: Epidemiologic, diagnostic and therapeutic considerations. Am J Obstet Gynecol, 1998; 178(2): 203-11.
13. Sobel JD, Brooker D, Stein GE, Thomason JL, Wermeling DP, Bradley B, et al Single oral dose Fluconazole compared with conventional Clotrimazole topical therapy of Candida vaginitis. Fluconazole Vaginitis Study Group. Am J Obstet Gynecol, 1995; 172:" 1263-8.