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FORMULATION AND EVALUATION OF BUCCOADHESIVE DISKS OF BENZOCAINE

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ABSTRACT

Buccoadhesive erodible disks of benzocaine were prepared using different bioadhesive polymers along with excipients like mannitol. The optimized disk containing 30.0 mg of benzocaine, 1.5 mg of sodium stearyl fumarate and 90.0 mg of mannitol along with carbopol 934P, 30mg was found to release the drug for a period of over 6.0 h without getting dislodged. Maximum in vitro drug release was found to be 60.0% in 6.0-h study. In situ release characteristics were evaluated using a 'flow-through assembly', which simulated the conditions of the human buccal cavity. The drug concentrations in the in situ samples were found to be above (10ug/ml) of the drug up to 6 hours. The physico chemical properties, bioadhesive performance and the surface pH of the disks were satisfactory.

KEYWORDS: Buccoadhesive, stearyl fumarate, mannitol, carbopol.

INTRODUCTION

Many Studies are been accomplished in order to describe the etiology of Dental phobia and most of them agreed that the local anesthesia injection is the most relevant reason.[1, 2] Lidocaine gel has been used as an alternative but it is not very effective because of salivary flow, that is why another solutions been searched.[3,4] Attempts have been realized by several researchers to find a solution and the anesthetic patch is been used ,but its efficacy was insufficient, it was not stable, and patients reported it as discomfortable.[5-8] Buccal bioadhesive sustained release disks might be a viable alternative. Bioadhesion as a term has appeared since 1980 and its application in the oral cavity is been described by several papers for the last ten years.[9-11] The utilization of a buccal mucoadhesive tablets or disks may be

one of the most successful way to treat buccal local pathologies. The sustained release of drugs in the oral cavity helps to overcome constant salivary secretion in the mouth.

Buccoadhesive disks or tablets are used as buccal delivery systems. Hydrogel-based bioadhesive tablets can adhere to the buccal mucosa or gum, and the drug is released upon hydration of the device, forming a hydrogel. The device should be fabricated so that the swelling rate of bioadhesive polymer is optimized to ensure a prolonged period of bioadhesion as well as a controlled or sustained drug release. Tablets of triamcinolone acetonide (Aftach), developed for local treatment of aphthous ulcers, consist of a bioadhesive hydroxypropyl cellulose/polycrylic acid layer and lactose non-adhesive backing layer.[12] Nicotine replacement therapy requires a fast release of nicotine followed by a prolonged release of nicotine for maximal efficacy. A bilayer buccal adhesion nicotine tablet provided a drug release pattern combining fast release and prolonged release profiles and resulted in improved smoking cessation rates.[13] Chlorhexidine-chitosan microsphere-based buccal tablets have shown enhanced antimicrobial activity and prolonged drug release in the oral cavity.[14]

Bioadhesive disks or tablets are usually prepared by direct compression. Drugs can also first be formulated in certain forms (e.g., micro spheres) for achieving some desirable properties before direct compression to produce tablets.

Because minor aphthous ulcers (canker sores not associated with systemic disease) affect nearly 20% of the population.[15] Cankermelts and Canker Cover both use “natural” active ingredients and both report research evidence for the efficacy of the products for pain relief and improvement in healing, although the published studies of Canker Cover were conducted with no controls.[16] Benzocaine is indicated to treat a variety of pain-related conditions. It may be used for Local anesthesia of oral and pharyngeal mucous membranes (sore throat, cold sores, canker sores, toothache, sore gums, denture irritation).[17]

The purpose of the study is to develop a new mucoadhesive form and to clarify its efficacy in performing topical anesthesia in dentistry. This new pharmaceutical form is the Mucoadhesive disks using various bioadhesive polymers. Disks will be charged with the anaesthetic drug benzocaine to assure a sustained local anaesthetic effect.

Physicomechanical properties, swelling behaviour, in vitro bio adhesion, and in vitro release of the prepared disks have been subjected to investigations. The most promising formulae were subjected to in situ release study.

EXPERIMENTAL

1. MATERIALS

Hydrxypropyl methyl cellulose (HPMC K4M) was purchased from Dow chemical company, Midland, Michigan48674, USA. Carbopol 934P, was supplied from Sorgan Co. Wiedelberg, Germany. Hydrooxypropyl cellulose (HPC), average M.wt 100,000, was obtained from Winlab Co. UK. Mannitol was obtained from Serva GmbH & Co., Heidelberg, Germany. Polyehylene glycol 6000 (PEG), was purchased from BDH Co., poole, England. Bezocaine (BZ), was supplied from winlab chemical Co., England. Sodium stearyl fumarate(SSF) was a gift from JRS Pharma , Spain. All other chemical used are of analytical grade.

METHODS

Preparation of buccal bioadhesive BZ disks.

List of formulations are shown in table (1). Components of each formula were mixed in turbula mixer (type S27, Erweka, Apparatebau, Germany) for 15 min and then directly compressed into tablets using a single punch tablet machine (type EKO, Erweka, Apparatebau, Germany) using 9.5 mm flat punches. Tablets hardness was kept within the range of 6-8 kp. and thickness of about 1.8-2.0 mm.

2- Evaluation of the prepared tablets

2.1- Construction of Benzocaine calibration curve.

Benzocaine was determined spectrophotometrically at λ 285 nm. Calibration curve was constructed. This was done by accurately weighing 10 mg of the drug and dissolving it in 100 ml of McIlvian phosphate buffer(pH 6.8). Dilutions were made to obtain different concentrations corresponding to 2.5, 5.0, 7.5, 10, 15, and,20 ug/ml of the drug. The absorbance was measured at 285 nm using the same solvent medium as a blank.

2.2. - Determination of actual Benzocaine content in the prepared Disks.

One powdered disk was dissolved in 300 ml of phosphate buffer (pH6.8). Then an aliquot was withdrawn and filtered through Millipore filter (0.45u). The filtrate was diluted and the concentration of the drug was spectrophotometrically at λ 285 nm.

2.3 -Determination of crushing strength and % friability of the prepared BZ disks.

For each formulation, 6 random selected disks were examined using Erewka hardness tester, and 20 disks for friability test according USP using Roche friabilator.

2.4- Determination of thickness of the prepared BZ disks.

Thickness was determined by means of micrometer (mean of 5 disks).

2.5- Measurement of water uptake of the prepared tablets.

Five Disks were soaked each in 50 ml of stimulated saliva solution (PH=6.75) adjusted at 37.0+0.5^{o}C. Disks were removed at different time intervals, weighed after drying the surface water by filter paper and returned to the medium. The percent increase in weight at different time intervals was calculated as:-

$$\% \text{ increase in weight} = \frac{\text{hydrated tablet wt- dry tablet wt.}}{\text{dry tablet wt.}} \text{ x100}$$

2.6 -Determination of surface pH of the prepared disks.

The surface pH of the prepared disks was determined after soaking each formula in (one disk in distilled water (1ml) for 15 minutes. After the time of soaking the pH of the wet surface was measured by placing the electrode in contact with the surface of the disk.

2.7- In-Vitro bioadhesion test of the prepared Films and Disks.

In vitro bioadhesion of the formulations was examined adopting a previously published method [18] using chicken pouch as a model mucosal membrane. The tissue was obtained from chicken after slaughter, removed from it's contents and surface fats, and stored frozen in simulated saliva solution (2.38 g Na2HPO4.2H2O , 0.19 g KH2 PO4 and 8.0 g NaCl/L , pH= 6.75). This membrane was thawed to room temperature before use. Rectangular piece (Surface area 4.0 cm^2) of the tissue was cut and glued with cyanoacrylate adhesive on the ground surface of the tissue holders made of Plexiglas.The tablet is directly fixed to the lower plexiglas holder and the tissue is glued only to the upper holder. The upper holder was allowed to hang on an iron stand with the help of an aluminum wire fastened with a hook provided on the backside of the holder. A pre weighed light weight polyethylene bag was attached the hook on the back side of the lower tissue holder with aluminium wire. After a pre-load time of 1.0 minute water was added to the polyethylene bag through an intravenous infusion set at a rate 2.0 drops per second until the lower holder detached by the heavy weight

of water infused. The water collected in the bag was measured and expressed, as weight (gram force) required for the detachment. Diagram of the instrument used is shown in Fig.1

2.8. In-vitro release studies

In each of the flasks of the USP apparatus 1 (Caleva Ltd., Model 85T) 1000 ml of phosphate buffer pH 6.8 were equilibrated to 37±0.5°C at 50 rpm using a continuous automated monitoring system. This system consists of an IBM computer PK8620 series and PU 8605/60 dissolution test software, Philips VIS/UV/NIR single beam eight-cell spectrophotometer Model PU 8620, Epson FX 850 printer, and Watson-Marlow peristaltic pump. An accurately weighed tablet of each of the prepared formulations was added to each flask. Samples were withdrawn at time intervals for 6 hours. For each formula, release runs were performed in triplicate and absorbance was recorded automatically at 285 nm. The cumulative percentage of drug released was determined as a function of time.

Analysis of the release data

The release data were kinetically analyzed using different Kinetic models (Zero order, first order and Higuchi diffusion model) to determine the mechanism of drug release from the different buccoadhesive formulations.

2.9 In – Situ Release Studies of Buccoadhesive tablet Formulations

The in-situ release of benzocaine from formulations was investigated using self designed open, continuous flow through cell. One disk is adhered to the plexiglas (5.0 cm diameter) . The disk was placed in the bottom of glass tube fitting the plexiglas diameter. Sixty ml. of pH 6.8 phosphate buffer was poured on the disk urface. The whole assembly was immersed in a water path maintained at 37 ^{o}C .the buffer solution was continuously circulated over the disk surface in an open circuit at a rate of 1.0 ml / minute (which simulate the flow of saliva in the oral cavity) using Watson- Marlow peristaltic pump. Fresh buffer was added in the same rate (1.0 ml / minute) using the same pump, so the volume of the buffer remains constant (60 ml). The drug release in the effluent buffer was monitored using automated monitoring system. For each formula, experiment was run in triplicate, absorbance at 285 nm was recorded automatically up to 6 hours and percentage of drug release was calculated and the mean of three readings was considered.

RESULTS AND DISCUSSION

1. Calibration curve of Benzocaine(BZ) in phosphate buffer pH 6.8 at 285 nm.

Results showed a linear relationship between the absorbance and the concentration of BZ in phosphate buffer pH 6.8 at 285 nm. ,in concentration range of 2.5-20 ug / ml. The linear equation was.

$Y= 0.1 X + 0.004$ and $R^2 = .9999$

2- Determination of actual Benzocaine content in the prepared Disks.

Actual BZ content in the prepared Disks was in the range of 95-105% of the clamed content. This indicates the stability of BZ in the used procedure for preparation as well as the even distribution of the drug in the prepared films and disks.

3-Mechanical evaluation of the prepared disks.

Table (1) shows the composition of the prepared disks. Three bioadhesive polymers were utilized in the preparation of benzocaine buccal disks, namely carpobol 934, HPMC, and HPC in two different drug: polymer ratio (1:1) and (1: 2). Table (1) shows the physico-mechanical properties of the prepared disks. It could be observed that all the prepared disks showed acceptable hardness and friability values.

4- Swelling properties of the prepared disks.

Fig.2 shows the effect of polymer type and ratio on the rate and extent of water uptake by the prepared disks presented as the percent increase in tablet weight versus time. Disks contain carbopol show higher rate of water uptake. The rate of water uptake is directly proportional to the carbopol content. As an anionic polymer, carbopol swill rapidly at pH 6.8. Disks prepared with HPC show slight increase in the first hour followed by a gradual decrease in weight mainly due to surface erosion. Disks contain HPMC show higher rate of water uptake than HPC but less than carbopol .

5- In vitro Bioadhesion of the prepared BZ disks.

There are several advantages in having bio/ muco adhesive drug delivery systems. As a result of such adhesion, the formulation stays longer time at the delivery site and this improves the bioavailability of the drug. Also the increased residence time will enhance and elongate the local effect whenever it is desired. So the bioadhesive force is an important physicochemical parameter for buccoadhesive dosage forms.

Adhesion occurs shortly after the beginning of hydration and swelling of the film. Various mechanisms have been proposed to explain the in vitro bioadhesion or mucoadhesion phenomena. These included hydrogen bonding, Vander Waals forces, hydrophobic bonding wetting, diffusion interpenetration physical entalgment and surface free energy.[19]

There are several studies using different techniques to measure the mucoadhesive force between the dosage form and mucosal membranes. In this study the bioadhesive force expressed as the detachment stress in dyne/cm^2, was determined from the minimal weights that detached the mucosal surface from the gel using the following equation.

Detachment stress (dyne/cm^2) = m.g/A.

Where

m= The weight of water infused at detachment.

g= Acceleration due to gravity considered as 980 cm/sec^2.

A=area of tissue exposed. (in cm^2)

Table (2) shows the results of bioadhesion test of the prepared disks.

From the results obtained, the following could be concluded

- The mucoadhesive polymers investigated could be arranged according to their mucoadhesive force as follows.
  Carbopol> HPMC> HPC
- Increasing polymer concentration leads an increase in the detachment stress and hence the mucoadhesion. However, addition of PEG 6000 resulted in decreased bioadhesion.

6- Benzocaine Release from the prepared disks.

Benzocaine release from formulae F1-F8 was studied at 37 ºC ± 0.5 ºC using phosphate buffer (PH 6.8) as the release medium.

BZ release profiles from the prepared disks are shown in Fig.3. The drug was gradually released from all formulations over a period of 6 hours. Therefore all the prepared disks could be adequately sustained. BZ was more rapidly released from formulations containing 1: 1 carbopol: BZ ratio (F4& F7). However, addition of PEG 6000 resulted in release enhancement (F4). Increasing carbopol: BZ ratio to 2:1 resulted in significant decrease in drug release (F1).

At polymer: drug ratio of 1:1, the rank order of release was carbopol> HPC > HPMC. Increasing polymer: drug ratio to 2:1 gave a similar pattern, with decrease in the amount of benzocaine released. Carpobol is acidic in nature, in the mean time, BZ is more soluble in acidic medium. This might be the reason for increased release of BZ from disks contain carbopol in comparison with other formulations contain the neutral non ionic polymers HPC and HPMC. Another reason for higher release rate from formulae contain carpobol is the rapid hydration and swelling as shown in Figure (2). The effect of carbopol concentration on drug release was observed in previous studies.[20,21]

4.5.2 Kinetic Assessment of the In-vitro Release of BZ from the Prepared Disks.

In order to determine the release model which best describes the pattern of drug release, the in-vitro release data were fitted to zero order, first order and diffusion controlled release mechanisms according to the simplified Higuchi model.

a- Zero-order Kinetic model: C=Co- Ko t.

b- First order Kinetic model: log C = log Co-Kt/2.303

c- Higuchi diffusion model: Q= 2 Co (Dt/π) ½

Where: -

Co= initial drug concentration

C= drug concentration (released) at time t.

T= time of release

Q= amount of drug released/unit area

Ko= zero order rate constant, K= first order rate constant and D=diffusion Coefficient and it was calculated according to the following equation.

D= (Slope/2Co)2 π

The preference of a certain mechanism was based on the correlation coefficient (r) for the parameters studied, where the highest correlation coefficient is preferred for the selection of mechanism of release.

Successive evidence of the relative validity of diffusion and first order models obtained by analyzing the data using the following equation[22]

$Mt/M/oo=K. t^{n}$

Where Mt/Moo is the fraction released by the drug at time t, K is a constant incorporating structural and geometric characteristic and n is the release exponent characteristic for the

drug transport mechanism. When n=0.5 fickian diffusion is observed and the release rate in dependent on t, while 0.5<n<1.0 indicate anamalous (non fickian) transport and when n=1, the release is zero order. In swellable systems, factors affecting the release kinetics are liquid diffusion rate and polymeric chain relaxation rate. When the liquid diffusion is slower than the relaxation rate of the polymeric chains, the diffusion is Fickian, whereas when the relaxation process is very slow compared with the diffusion rate, the case II transport occurs. When liquid diffusion rate and polymer relaxation rate are of the same order of magnitude, anomalous or non-fickian diffusion is observed[22]

Table (3) presents the results of kinetic modeling for the prepared disks. Formulas F2, F3, F4 and F8, show a non fickian release behavior of BZ, however formula F1 containing 2:1 carbopal: BZ show fickian release, while formulas F5 – F7 nearly approached zero order (case II transport) release.

7- In Situ release of selected formulations containing 30 mg Benzocaine.

The use of in situ release technique to predict in vivo release in the oral cavity was reported by many authors.[23-25] This actually resembles the release of the drug in the buccal cavity. Based on the results of swelling, bioadhesion, surface pH, and in vitro release, formula F7 chosen for in Situ release studies (better bioadhesion, and adequate release characteristics). The results of in situ release study are presented in Fig.4. The results revealed that, the concentration of BZ released was maintained well above (10 ug /ml) for a period of more than 6 hours. The duration of topical anesthesia might depend on the type and amount applied, so by such formulation containing an appropriate amount of the drug, a consistent concentration of the local anesthetic benzocaine could be maintained for hours.

Table 1: Formulations and Physico-Mechanical Properties of the prepared BZ disks.

Component	Formula No. and amounts in mg							
	F1	F2	F3	F4	F5	F6	F7	F8
BZ	30	30	30	30	30	30	30	30
Carpobol	60	-	-	30	-		30	15
HPMC	-	60	-	-	30	-	-	15
HPC	-	-	60	-	-	30		-
Mannitol	60	60	60	70	90	90	90	90
PEG 6000	-	-	-	20	-	-	-	-
SSF	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight(mg)	151.5	151.5	151.5	151.5	151.5	151.5	151.5	151.5
Hardness(KP)	8.5±1	6.2±0.6	7.1±0.6	8.8±0.8	7.1±0.5	7.4±0.8	8.3±0.8	7.8±0.6

Thickness (mm)	1.7±0.1	1.85±0.06	1.9±0.1	1.9±0.1	1.7±0.1	1.8±0.07	1.69±0.05	1.70±0.04
Friability (%)	0.18	0.31	0.23	0.16	0.25	0.27	0.20	0.22

Table (2): Detachment force and surface pH of the prepared disks

Formula No.	Detachment force dyne/cm^2 x10 -3	Surface pH
F1	36.4 ± 4.1	4.0 ± 0.2
F2	30.8 ± 3.1	6.2 ± 0.2
F3	27.7 ± 3.0	6.3 ± 0.3
F4	24.0 ± 2.7	4.6 ± 0.4
F5	21.0 ± 2.8	6.4 ± 0.3
F6	19.5 ± 1.8	6.4 ± 0.4
F7	35.0 ± 3.2	4.6 ± 0.2
F8	31.0 ± 2.9	5.4 ± 0.3

Table (3): Kinetic Modeling of BZ Release From The Prepared Disks

Release model		Formula No:-							
		F1	F2	F3	F4	F5	F6	F7	F8
Zero order	R	0.958	0.964	0.973	0.964	.976	0.988	0.998	0.994
	Ko	0.015	0.038	0.028	0.100	.047	0.053	0.097	0.057
First order	R	0.963	0.976	0.976	0.995	.986	0.994	0.988	0.996
	K1	0.150	0.420	0.290	1.620	.490	0.58	1.37	0.64
Highchi diffusion model	R	0.997	0.996	0.996	0.992	.987	0.983	0.966	0.977
	Kh	0.317	0.797	0.585	2.09	.96	1.08	1.9	1.14
Log M/mas Vis log t	R	0.980	0.992	0.997	0.968	.971	0.990	.998	0.998
	n	0.503	0.695	0.588	0.798	.968	0.928	0.961	0.823
Selected model		Fickian	Non-Fickian	Non-Fickian	Non-Fickian	Nearly approaching Zero order			Non-Fickian

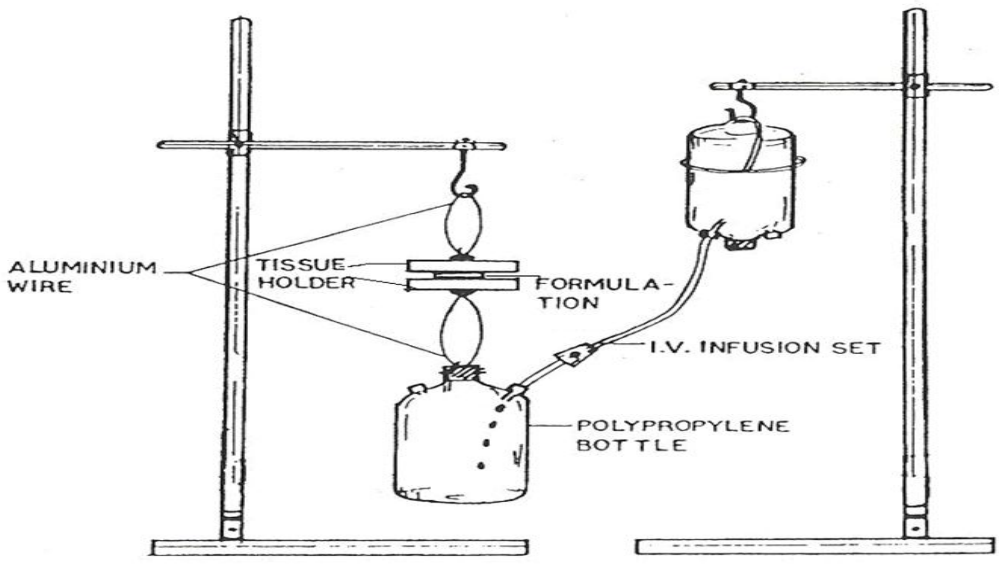


Fig (1): Modified apparatus for in vitro bioadhesion test.

Fig (2):Swelling behaviour of the prepared BZ disks

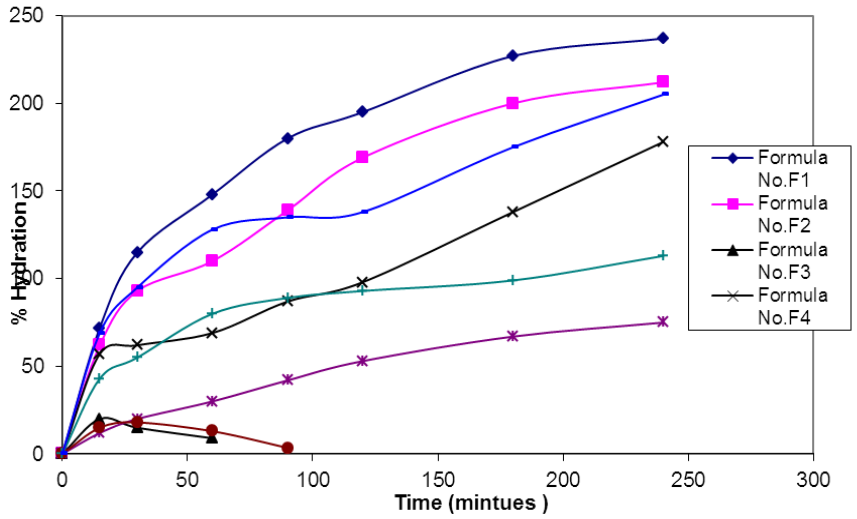


Fig (3):In-vitro Benzocaine(BZ) Release from the prepared disks

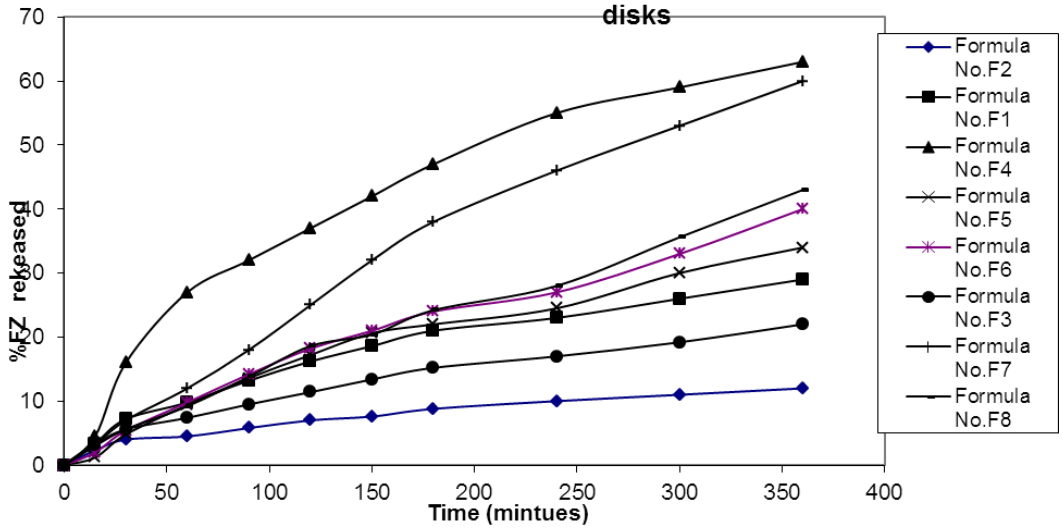
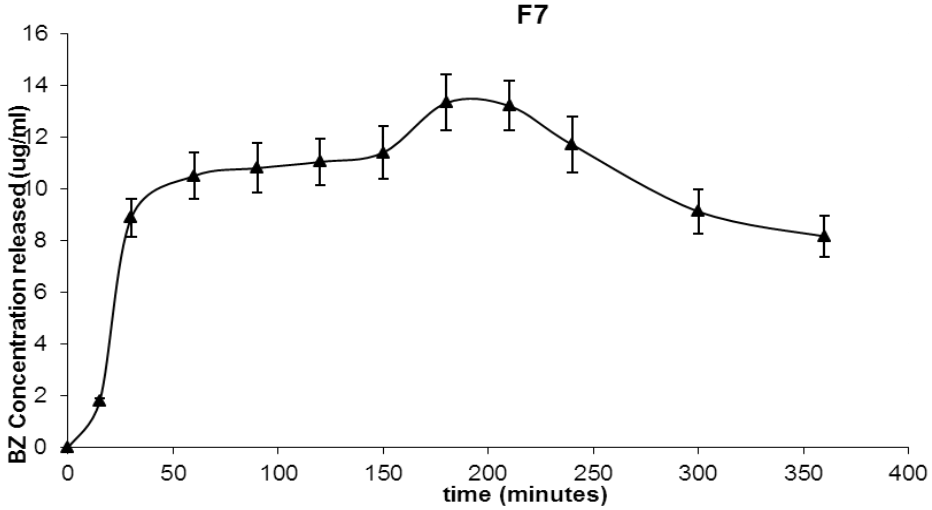


Fig (4):In situ release ofFluconazole (BZ) from disk formula F7



CONCLUSION

Buccoadhesive erodible disks of benzocaine were successfully prepared using different bioadhesive polymers. The physico chemical properties, bioadhesive performance and the surface pH of the disks were satisfactory. The optimized disk containing 30.0 mg of benzocaine, 1.5 mg of sodium stearyl fumarate and 90.0 mg of mannitol along with carbopol 934P, 30mg was found to release the drug for a period of over 6.0 h without getting dislodged. Maximum in vitro drug release was found to be 60.0% in 6.0h study. In situ release characteristics were evaluated using a 'flow-through assembly. The drug concentrations in the in situ samples were found to be above (10ug/ml) of the drug up to 6 hours. The prepared disks could be used successfully to sustain the effect of the local anesthetic effect of benzocaine.

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