Drug Development and Industrial Pharmacy, 25(6), 701–709 (1999)

RESEARCH PAPER

Design, Development, and Biopharmaceutical Properties of Buccoadhesive Compacts of Pentazocine

Varsha Agarwal and B. Mishra*

Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi–221 005, India

ABSTRACT

Buccoadhesive compacts (BCs) of pentazocine (PZ) were prepared by the direct compression method using polymers like carbopol 974P (CP 974P) and hydroxypropyl methylcellulose (HPMC K4M) in ratios of 1:0 (batch B_1), 1:1 (B_2), 1:2 (B_3), 1:4 (B_4), and 0:1 (B_5). The compacts were evaluated for thickness uniformity, weight variation, drug content uniformity, and swelling index. Swelling was increased with an increase in HMPC K4M content in the compacts. An in vitro assembly was developed to measure and compare the bioadhesive strength of compacts. The maximum bioadhesive strength was observed in compacts formulated with a combination of CP 974P and HPMC K4M. The compacts were evaluated in vitro for 24 hr in pH 6.6 phosphate buffer using a standardized dissolution apparatus. The data were evaluated by a simple power equation ($M_t/M_\infty = Kt^n$); it was observed that all the compacts followed non-Fickian release kinetics. Some of the buccoadhesive compacts were evaluated in vivo in rabbits. The compacts gave controlled blood level profiles with a twofold to threefold increase in area-under-the-curve (AUC) values in comparison to oral administration of aqueous drug solution.

INTRODUCTION

Pentazocine (PZ), having both agonistic and weak opioid antagonistic activity, is used as a potent analgesic for chronic pain, such as that experienced with cancer, trauma, and postoperatively. As per the guidelines of the World Health Organization (WHO) for cancer pain management, analgesics like PZ are the drugs of choice (1). Pain prevention in chronic cancer is possible only with time-contingent dosing. Agonist/antagonist opiates, due to their ceiling effects and some associated side effects due to fluctuations in blood level and the like, cause

* To whom correspondence should be addressed.

many problems for administration in conventional dosage forms. These drawbacks can be overcome by designing a suitable buccoadhesive drug delivery system. The physicochemical and pharmacokinetic properties of PZ (short biological half-life of 2–3 hr, requirement for frequent dosing, and high first-pass metabolism) make it a suitable candidate for buccal administration. Long-term delivery of PZ at a controlled rate is thus needed in the body for chronic pain management.

Therefore, the aim of the present study was to design and develop a buccoadhesive compact (BC) of PZ using some selective bioadhesive polymers like hydroxypropyl methylcellulose K4M (HPMC K4M) and carbopol 974P (CP 974P). Such formulations are expected to perform therapeutically much better because of the improved bioavailability of drug due to avoidance of first-pass metabolism and fewer side effects due to controlled blood levels with minimum fluctuations compared to conventional formulations of PZ.

EXPERIMENTAL

Materials

Pentazocine (Ranbaxy Labs Ltd., Delhi, India), CP 974P (B.F. Goodrich, Cleveland, OH), HPMC K4M (Dow Chemicals, Midland, MI), potassium dihydrogen orthophosphate, sodium bicarbonate, and sodium carbonate anhydrous (Glaxo India Ltd., Mumbai) sodium hydroxide, hydrochloric acid (E. Merck India Ltd., Mumbai), benzene (Ranbaxy Labs. Ltd., SAS Najar, India) sodium lauryl sulfate (SLS) (Sisco Research Labs, Mumbai, India), pentobarbitone sodium (Loba Chemie, Mumbai, India), heparin injection (Biological E. Ltd., Hyderabad, India), and Superwiz® [Loctite India (P) Ltd., Mumbai], and double-distilled water were used. All the chemicals used were analytical reagent grade.

Methods

Preparation of Buccoadhesive Compacts

Buccoadhesive compacts were fabricated by the direct compression method using the formula shown in Table 1. All the ingredients of the compacts were passed through a no. 85 sieve and were blended in mortar with a pestle to obtain uniform mixing. Blending was done separately for the core and peripheral and backing layers. The blended powder of the core layer was lightly compressed on a 7-mm flat-faced punch and die set (Manesty Tabletting machine, England) at a pressure of 6 units, which gave a Monsanto hardness of 4 kg/cm^2. The core was then removed and placed in the center of a 12-mm die and filled with mixed ingredients of the peripheral layer. It was then slightly compressed. The upper punch was removed, and mixed ingredients of the backing layer were added over it and finally compressed at a pressure of 14 units, which gave a Monsanto hardness of 13 kg/cm^2. A schematic illustration of the BC is shown in Fig. 1.

Evaluation of Buccoadhesive Compacts

Thickness Uniformity

The thickness of 10 randomly selected BCs were measured, and the average thickness was computed.

Table 1

Formula for the Preparation of Buccoadhesive Compacts of Pentazocine

	Quantity in Each Compact (mg)				
Ingredients	B_1	B_2	B_3	B_4	B_5
Core					
Pentazocine	20.0	20.0	20.0	20.0	20.0
CP 974P	20.0	10.0	6.7	4.0	—
HPMC K4M	—	10.0	13.3	16.0	20.0
SLS	0.8	0.8	0.8	0.8	0.8
Peripheral layer					
CP 974P	40.0	40.0	40.0	40.0	40.0
HPMC K4M	40.0	40.0	40.0	40.0	40.0
Backing layer					
Magnesium stearate	25.0	25.0	25.0	25.0	25.0
CP 974P	12.1	12.1	12.1	12.1	12.1
HPMC K4M	12.1	12.1	12.1	12.1	12.1

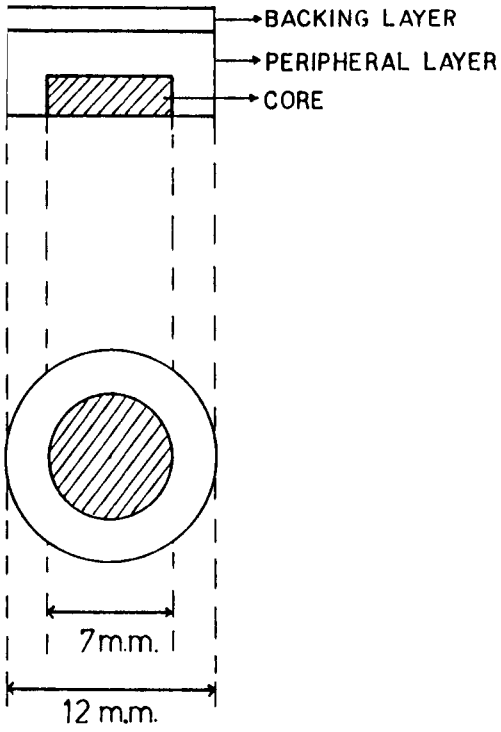

Figure 1. Schematic illustration of buccoadhesive compacts of pentazocine.

Weight Uniformity

The weight of each of 10 randomly selected BCs was determined by placing the sample on an electronic balance; the average weight of each batch was calculated.

Drug Content Uniformity

From each batch, 10 randomly selected BCs were weighed accurately and powdered. Powder equivalent to 20 mg of drug was transferred into a 100-ml volumetric flask containing 50 ml of phosphate buffer (pH 6.6) and was stirred continuously for 8 hr on a magnetic stirrer. The volume was made up to 100 ml with phosphate buffer, and absorbances were measured in an ultraviolet (UV) spectrophotometer (Shimadzu, Tokyo, Japan) at 278 nm. The concentrations were noted from the standard calibration curve, and the average values were calculated.

Swelling Studies of Buccoadhesive Compacts

The swelling rate of BCs was evaluated using a 1% w/v agar gel plate (2); 28 compacts were weighed, and the average weight of each 4 compacts was calculated (W_1). The compacts were placed with the core facing the gel surface in 7 petri dishes (each containing 4 compacts), which were placed in an incubator at 37°C ± 0.1°C. Four compacts were removed at time intervals of 0.5, 1, 2, 3, 4, 5, and 6 hr, excess water on the surface was carefully absorbed using filter paper, and swollen compacts were weighed. The average weight W_2 was calculated, and then the swelling index was calculated by the formula

$$(W_2 - W_1)/W_1$$

In Vitro Bioadhesion Test

In vitro bioadhesion of the compacts was examined by the modified procedure of Parodi et al. (3) (Fig. 2) using the peritoneum of healthy albino rats (CF strain) weighing 200–300 g; the peritoneum was removed under sodium pentobarbitone (30 mg/kg) anesthesia. The peritoneum was washed with saline solution and was kept in phosphate buffer (pH 6.6) prior to use. A circular piece (surface area 2 cm^2) of peritoneum was cut and glued with cyanoacrylate adhesive on the ground surface of a tissue holder made of plexiglass. Similarly, the compact was glued to another tissue holder of the same size. Thereafter, the tissue holders with peritoneum and compact were put in contact with each other with uniform and constant pressure for 5 min (preload time) to facilitate adhesion bonding. The tissue holder with peritoneum was allowed to hang on an iron stand with the help of an aluminum wire fastened with the hook provided on the back side of the holder. A preweighed lightweight polypropylene bottle was attached to the hook on the back

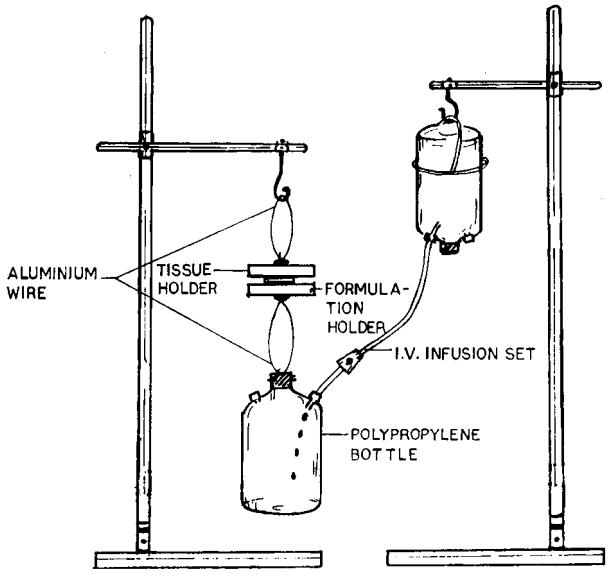

Figure 2. Modified apparatus for in vitro bioadhesion test.

side of the formulation holder with aluminum wire. After a preload time of 5 min, water was added to the polypropylene bottle through an intravenous infusion set at a rate of 1 drop/sec until the compact detached from the peritoneum. The water collected in the bottle was measured and expressed as weight (g) required for the detachment.

In Vitro Drug Release Study

In vitro drug release studies of BCs were conducted, in triplicate, on a simple standardized and modified dissolution apparatus (Fig. 3). The dissolution apparatus consists of a 1-L beaker used as the receptor compartment; this is covered with a perspex sheet with three holes, one for a thermometer, a second for a sampling tube, and a third for a donor tube. The donor tube is a glass rod attached with a grounded glass disk of 2 cm diameter; the backing layer side of the compact was attached at the bottom with the help of a cyanoacrylate instant adhesive (Superwiz). The glass rod containing the BC was attached to another glass rod bent at 90°, which was fixed to an iron stand.

Before starting the in vitro study, the donor tube attached with the BC was introduced into the receptor compartment containing 500 ml of deaerated, prewarmed (37°C ± 0.1°C) phosphate buffer (pH 6.6) in such a way that the compact's releasing surface remained 4 inches above the bottom of the beaker. The temperature was maintained at 37°C ± 0.1°C with an energy-controlled hot plate with a magnetic stirrer. Dissolution fluid was stirred at a constant speed of 100 rpm using a Teflon®-coated iron bead. Aliquots (5 ml each) were withdrawn at preset times (0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 9 hr) with the help of a sampling tube attached with a sintered glass filter at the bottom of the tube. The same volume of prewarmed (37°C ± 0.1°C) phosphate buffer was introduced into the receptor compartment after each withdrawal. All collected samples were assayed on a UV spectrophotometer at 278 nm. Released drug contents were determined from the calibration curve.

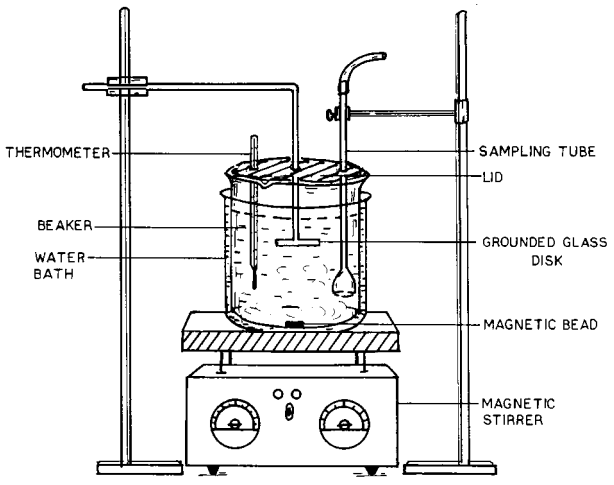

Figure 3. Modified dissolution apparatus used for in vitro release study of compacts.

In Vivo Studies

Based on their in vitro performance, three BCs were selected and were evaluated in vivo in rabbits to compare the blood level profiles of PZ with the profiles obtained after oral intubation of an aqueous solution of PZ to rabbits.

Five healthy albino rabbits of either sex weighing 2.0 ± 0.2 kg were selected for the in vivo evaluation of each formulation. They were fed with commercially available pellet diet and green vegetables and kept in normal housing conditions. Food was withdrawn 12 hr prior to the in vivo study with water ad libitum. There was a washout period of 1 week prior to in vivo evaluation of the next formulation.

The rabbits were first anesthetized with an intraperitoneal injection of sodium pentobarbitone (40 mg/kg) using a 26-gauge needle and syringe. The anesthesia was maintained by injecting 20 mg/kg sodium pentobarbitone intraperitoneally at regular intervals of 1 hr. Due to ease of buccal application, compacts (10 mg/kg) were cut in two, and their sides were coated with hydrophobic adhesive to prevent the leakage of the drug. Each half was attached to the buccal mucosa of rabbits by pressing it for 30 sec. Blood samples (2 ml) were withdrawn at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 24 hr from the middle ear vein using a 26-gauge needle and syringe and were collected in heparinized vials and stored at −10°C until assayed.

Aqueous drug solution (X), 10 mg/kg, (PZ dissolved in 4 ml phosphate buffer of pH 5.8) was administered orally to rabbits through an intragastric tube, and blood samples were collected and stored as above.

Assay of Pentazocine in Blood

All blood samples were analyzed using a slightly modified (4) spectrophotofluorometric (Jasco FP-777, Tokyo, Japan) method of El-Mazati and Way (5) at the excitation and emission maxima of 278 and 310 nm, respectively. Bioavailability parameters C_{max}, T_{max}, and area under the curve (AUC) were computed after calculation of drug concentration at different times of blood sampling from the calibration curve prepared as reported earlier (4).

Table 2

Physical Characteristics of Prepared Buccoadhesive Compacts of Pentazocine

Serial No.	Batch No.	Thickness[a] (mm)	Drug Content[a] (mg)	Weight Uniformity[a] (mg)
1	B_1	1.09 ± 0.04	20.21 ± 0.02	167.48 ± 4.58
2	B_2	1.11 ± 0.25	20.11 ± 0.19	169.66 ± 1.38
3	B_3	1.15 ± 0.19	19.89 ± 0.04	168.54 ± 0.29
4	B_4	1.19 ± 0.04	19.92 ± 0.07	168.10 ± 2.21
5	B_5	1.12 ± 0.21	19.56 ± 0.12	169.23 ± 0.79

[a] Mean ± SD, $n = 10$.

RESULTS AND DISCUSSION

Buccoadhesive polymer CP 974P grade was selected as it is a newer and safer analogue of CP 934P polymerized in ethyl acetate. Studies involving CP 974P have indicated it has a mild irritation effect to the buccal mucosa in higher concentrations (6).

The prepared BCs of PZ were evaluated for physical characteristics; the results are shown in Table 2. The BCs showed uniform thickness throughout, in the range 1.09–1.19 mm. Weight uniformity data for all formulations indicated no significant difference in the weight of individual formulations from the average value, and variations were found to be within limits. The drug contents in the BCs were also found to be within the limit of 100% ± 5%.

Swelling Index Studies

In this study, an agar plate was chosen as the simple model of the mucosa as it can keep an amount of water that resembles the secreting fluid in and around the buccal mucosa required for bioadhesion and subsequent swelling of the formulation to provide adequate release of drug. The swelling index of the prepared buccoadhesive compacts showed swelling rates in the order $B_5 > B_4 > B_1 > B_3 > B_2$ (Table 3 and Fig. 4). Batch B_5 (CP:HPMC 0:1) showed faster swelling compared to other formulations.

The maximum swelling was attained in 5 hr, after which polymer started eroding slowly in the medium. The high initial uptake of water may be due to the faster hydration rate of HPMC K4M. It was also observed that the swelling rate increased with an increase in HPMC K4M content of the compacts, except batch B_1, which contained CP only and initially showed less swelling than other batches. However, after 2 hr, batch B_1 exhibited a higher swelling rate than B_2 and B_3, with a greater increase in swelling between 5 and 6 hours; this is attributed to the property of carbopol to retain water and form a thick swollen mass.

In Vitro Bioadhesion Study

The mucoadhesive property of BCs of PZ containing varying proportions of CP 974P and HPMC K4M was

Table 3

Swelling Index Studies of Prepared Buccoadhesive Compacts of Pentazocine

Serial No.	Time (hr)	Swelling Index (Mean[a] ± SEM)				
		B_1	B_2	B_3	B_4	B_5
1	0.5	0.26 ± 0.05	0.25 ± 0.01	0.35 ± 0.03	0.55 ± 0.06	0.64 ± 0.08
2	1.5	0.41 ± 0.03	0.35 ± 0.02	0.51 ± 0.10	0.96 ± 0.07	1.13 ± 0.01
3	2.0	0.80 ± 0.12	0.60 ± 0.04	0.85 ± 0.08	1.55 ± 0.01	1.75 ± 0.09
4	3.0	1.33 ± 0.09	0.85 ± 0.15	1.10 ± 0.03	1.84 ± 0.02	2.05 ± 0.01
5	4.0	1.63 ± 0.04	0.99 ± 0.08	1.30 ± 0.03	2.12 ± 0.07	2.32 ± 0.08
6	5.0	1.91 ± 0.01	1.15 ± 0.07	1.51 ± 0.01	2.32 ± 0.12	2.51 ± 0.07
7	6.0	2.35 ± 0.02	1.25 ± 0.01	1.64 ± 0.08	2.51 ± 0.09	2.58 ± 0.08

[a] Mean of four readings.

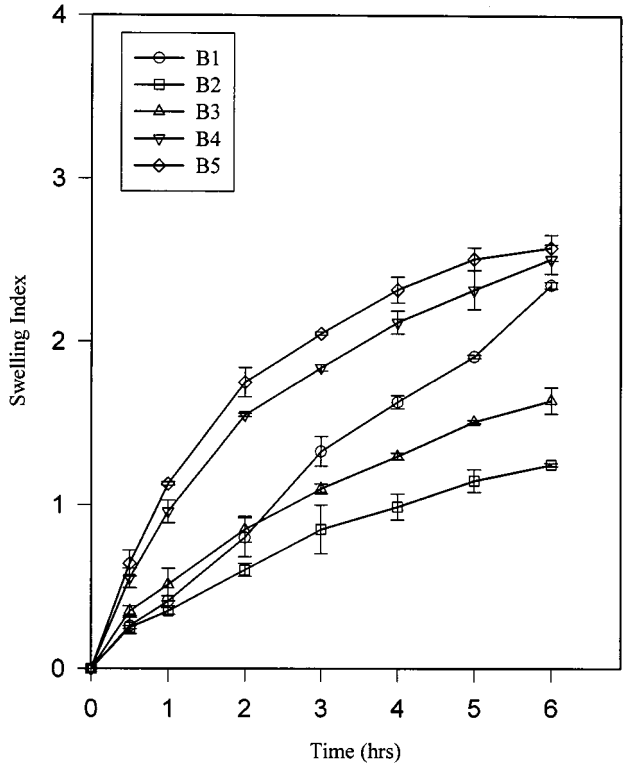

Figure 4. Swelling index studies of buccoadhesive compacts (values are expressed as mean ± SEM).

determined with a view to develop a compact with good adhesiveness without any irritation and other problems; the results are shown in Table 4. The maximum bioadhesive strength was observed in compacts containing CP 974P and HPMC K4M in a ratio of 1:1 (batch B_2) followed by ratios of 1:4 (B_4), 1:2 (B_2), and 0:1 (B_5) and least 1:0 (B_1).

Table 4

In Vitro Bioadhesion Study of Prepared Buccoadhesive Compacts of Pentazocine

Serial No.	Batch No.	Bioadhesive Strength[a] (g)
1	B_1	248 ± 9.0
2	B_2	450 ± 12.0
3	B_3	389 ± 8.0
4	B_4	412 ± 13.0
5	B_5	381 ± 8.8

[a] Mean ± SEM, $n = 3$.

Several studies have demonstrated that the bioadhesiveness of compacts depends on the rate of swelling, pH, applied strength, initial contact time, and selection of the model substrate surface (7). The bioadhesive property of carbopol is known to decrease at pH beyond 6 due to loss of hydrogen bonding. The pH of the buffer used in the present study was kept at 6.6, which presumably could have decreased the bioadhesive strength of the compact with carbopol alone (batch B_1) due to loss of hydrogen bonding. On the contrary, Gupta et al. (8) reported maximum bioadhesive strength of tablets of carbopol 934 alone. However, these workers used a different model mucosal substrate and different grade of carbopol, which may possibly have contributed to such contradictory observations.

In Vitro Release Study

The in vitro drug release profiles of PZ from BCs are shown in Fig. 5. The BC of batch B_1 provided maximum drug release (68.2%), followed by compacts B_5 (55.2%), B_2 (48%), B_4 (45.6%), and B_3 (40.7%) in 9 hr. The maxi-

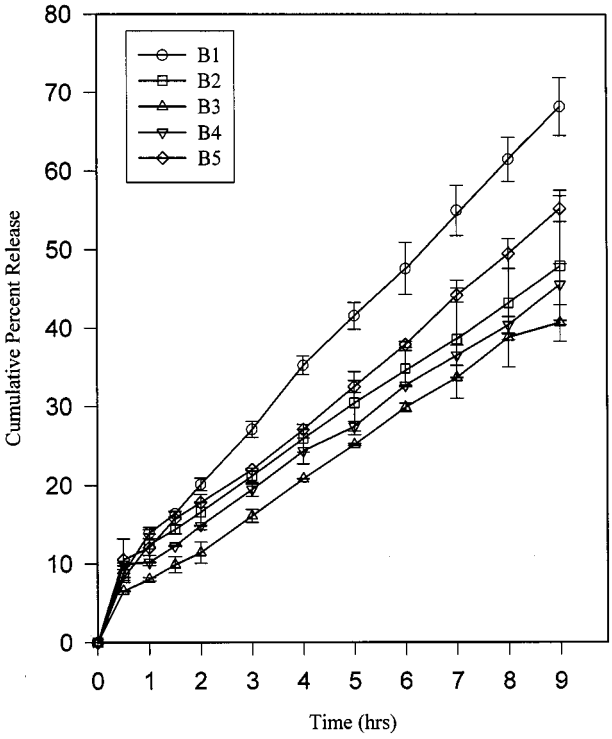

Figure 5. In vitro release profiles of pentazocine from different buccoadhesive compacts in phosphate buffer of pH 6.6 (values are expressed as mean ± SEM).

Table 5

Kinetic Constant (K), Diffusional Exponent (n), and Correlation Coefficient (r^2) Following Linear Regression of Log (M_t/M_∞) versus Log (t) of Buccoadhesive Compacts

Serial No.	Batch No.	*n*	*K*	r^2
1	B_1	0.723	0.133	0.999
2	B_2	0.598	0.117	0.994
3	B_3	0.687	0.084	0.984
4	B_4	0.604	0.110	0.981
5	B_5	0.603	0.129	0.979

mum cumulative percentage release of the PZ from batch B_1 could be attributed to ionization of CP 974P at pH 6.6, a pH environment higher than its pK_a value of 6 (9). Ionization of carbopol leads to the development of negative charges along the backbone of the polymer. Repulsion of like charges uncoils the polymer into an extended structure. The counterion diffusion inside the gel creates an additional osmotic pressure difference across the gel, leading to high water uptake. This water uptake leads to the considerable swelling of the polymer. The continued swelling of the polymer matrix causes the drug to diffuse from the formulation at a faster rate (10). Khanna, Agarwal, and Ahuja (11) have also reported a similar pattern of increased drug release from compacts containing a higher proportion of carbopol 974P.

However, compacts B_5, which contain only HPMC K4M, exhibited less drug release compared to batch B_1. This may be attributed to the stability of HPMC polymer over a wide range of acid and alkaline conditions. The compacts released the drug at a controlled rate, controlled by the swelling of the polymer, followed by drug diffusion through swelled polymer, and then further followed by slow erosion of the polymer. Further, the rate and extent of drug release did not differ significantly among batches B_3, B_4, and B_5.

To examine further the release mechanism of PZ form compacts, the results were analyzed according to the following equation (12):

$$M_t/M_\infty = Kt^n$$

where M_t/M_∞ is the fractional release of the drug, *t* denotes the release time, *K* represents a constant incorporating structural and geometrical characteristics of the device, and *n* is the diffusional exponent and characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the *n* value falls between 0.5 and 1.0, while in case of Fickian diffusion, $n = 0.5$; for zero-order release (case II transport), $n = 1$, and for supercase II transport, $n > 1$.

The values of *n* as estimated by linear regression of log (M_t/M_∞) versus log (*t*) of different formulations are shown in Table 5. The obtained values of *n* lie between 0.5 and 1.0 in all formulations for the release of PZ, indicating non-Fickian release kinetics, which is indicative

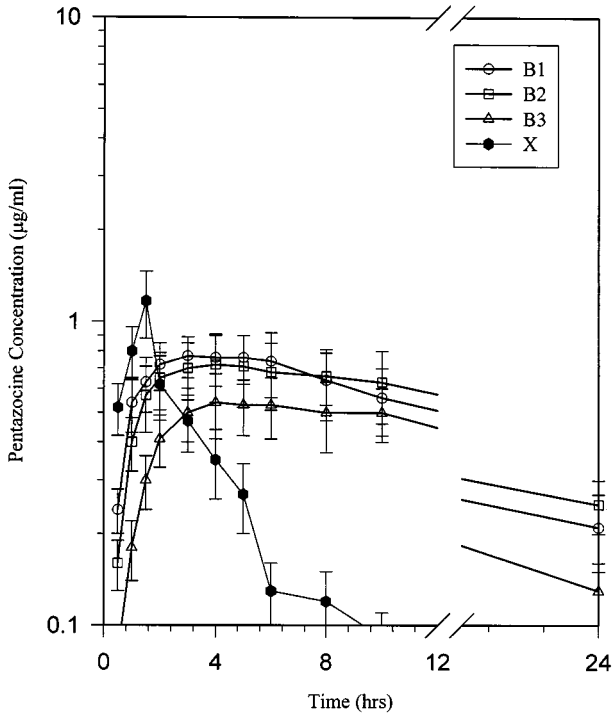

Figure 6. Profiles of average blood concentration of pentazocine versus time from different buccoadhesive compacts and aqueous drug solution in rabbits ($n = 5$) (values are expressed as mean ± SEM).

Table 6

*Pharmacokinetic Characteristics of Pentazocine After Oral Administration of Drug Solution and Application of Buccoadhesive Compacts in Rabbits (*n = *5, Mean ± SEM)*

Formulation	C_{max} (μg/ml)	T_{max} (hr)	AUC (0–24 hr) (μg/hr/ml)
Oral solution (*X*)	1.17 ± 0.29	1.5	4.26 ± 0.63
Buccoadhesive compacts			
B_1	0.77 ± 0.15	3.0	11.89 ± 1.78
B_2	0.72 ± 0.18	4.0	12.27 ± 1.72
B_3	0.54 ± 0.13	4.0	8.85 ± 1.33

of drug release mechanisms involving a combination of both diffusion and chain relaxation mechanisms (13).

Results clearly indicate that buccoadhesive compacts gave controlled and prolonged in vitro release of PZ for at least 9 hr.

In Vivo Studies

The blood level profile versus time of orally administered aqueous solution of PZ and of three compacts (B_1, B_2, and B_3) are shown in Fig. 6, and bioavailability parameters are presented in Table 6. Blood level profiles exhibited a sharp peak for the solution, with a faster decline in blood levels, but exhibited an absence of sharp peaks and more sustained blood levels, at least until 12 hr, for all three compacts. Moreover, compacts exhibited higher drug levels in the blood at the end of 24 hr compared to the drug solution.

C_{max} values of 0.77, 0.72, and 0.54 μg/ml and T_{max} values of 3, 4, and 4 hr were observed for compacts B_1, B_2, and B_3, respectively, compared to a C_{max} of 1.17 μg/ml and a T_{max} of 1.5 hr for the solution. It has been observed that, with the increase in HPMC K4M content in the compacts (batch B_3), the reason the mean maximum blood concentration C_{max} was decreased may be due to nonionization of polymer in salivary conditions and lower hydration and less water uptake of HPMC K4M polymer, causing slow drug delivery.

The AUC values of compacts B_1, B_2, and B_3 were 11.89, 12.27, and 8.85 μg/hr/ml, respectively, much higher than the AUC of the drug solution (4.26 μg/hr/ml). These observations clearly indicate that the bioavailability of PZ through buccoadhesive compacts is significantly improved (approximately two- to threefold) over the bioavailability observed after oral administration of drug solution; this is attributed to avoidance of the first-pass metabolism through the buccal route. Further, delayed T_{max} and lower C_{max} values from the compacts compared to drug solution, followed by less fluctuation in blood levels from compacts (i.e., absence of sharp peak and sharp fall in blood levels) and maintenance of higher blood levels until 24 hr from the compacts than from the drug solution clearly indicate that the buccoadhesive dosage forms (compacts) not only improved the bioavailability of the drug PZ, but also gave prolonged and controlled blood level profiles of PZ.

CONCLUSION

Thus, the present investigation established the usefulness of buccoadhesive compacts as potential controlled- and prolonged-release formulations of PZ, with imporved bioavailability of drugs such as PZ that undergo extensive first-pass metabolism when administered orally.

ACKNOWLEDGMENT

Varsha Agarwal is grateful to the University Grants Commission, New Delhi, India, for financial assistance to carry out this work.

REFERENCES

1. A. G. Lipman, Medical Times, 116, 25 (1988).
2. Y. Machida, H. Masuda, N. Fujiyama, S. Ito, M. Iwata, and T. Nagai, Chem. Pharm. Bull., 27(1), 93 (1979).
3. B. Parodi, E. Russo, G. Caviglioli, S. Cafaggi, and G. Bignardi, Drug Dev. Ind. Pharm., 22, 445 (1996).
4. B. Mishra and J. K. Pandit, Drug Dev. Ind. Pharm., 15, 1217 (1989).
5. A. M. El-Mazati and E. L. Way, J. Pharmacol. Exp. Ther., 177, 332 (1971).

6. P. Bottenberg, R. Cleymaet, C. D. Myunck, J. P. Remon, D. Coomans, Y. Michotte, and D. Slop, J. Pharm. Pharmacol., 43, 457 (1991).
7. A. Ahuja, R. K. Khar, and J. Ali, Drug Dev. Ind. Pharm., 23, 489 (1997).
8. A. Gupta, S. Garg, and R. K. Khar, Indian Drugs, 30, 152 (1993).
9. N. A. Peppas and A. R. Khare, Adv. Drug Delivery Rev., 11, 1 (1991).
10. M. Mandel, in *Encyclopedia of Polymer Science and Technology*, Vol. 11 (H. Mark and J. I. Kroschwitz, Eds.), Wiley, New York, 1985, p. 739.
11. R. Khanna, S. P. Agarwal, and A. Ahuja, Drug Dev. Ind. Pharm., 23, 831 (1997).
12. R. W. Krosmeyer, R. Gurny, E. Doelkar, P. Buri, and N. A. Peppas, Int. J. Pharm., 72, 25 (1983).
13. G. Ponchel, F. Touchard, D. Wouessidjewe, D. Duchene, and N. A. Peppas, Int. J. Pharm., 38, 65 (1987).