In Vitro-In Vivo Evaluation of a Controlled Release Buccal Bioadhesive Device for Oral Drug Delivery

Deepak Tiwari,[1,3,4] David Goldman,[2] Chris Town,[2] Robert Sause,[1] and Parshotam L. Madan[1]

Received April 30, 1999; accepted August 4, 1999

Purpose. To investigate the use of buccal bioadhesive device in targeting controlled drug delivery to the gastrointestinal tract.

Methods. A three-leg crossover study was designed to evaluate the application of buccal bioadhesive device for providing controlled drug delivery to the gastrointestinal tract of a model drug cyanocobalamin in four healthy adult male beagle dogs.

Results. In vitro dissolution studies using deionized water as the medium indicated that 100% of the drug was released within 15 min from a immediate release oral capsule formulation, whereas 90% of the drug was released within a period of 18 hrs from a buccal bioadhesive device formulation. Drug release from the buccal bioadhesive devices appeared to follow Higuchi's square root of time dependent model. The terminal half-life of the drug following I.V. administration in four dogs was found to be 16.4 ± 2.4 hrs. Following immediate release oral capsule administration of the drug C_{max}, t_{max} and bioavailability were 2333 ± 1469 ng/L, 2.5 ± 1.0 hrs and 14.1 ± 7.9%, respectively. Following buccal bioadhesive device administration of the drug C_{max}, t_{max} and bioavailability were 4154 ± 1096 ng/L, 11 ± 1.2 hrs and 35.8 ± 4.1%, respectively. Significantly higher bioavailability of the drug was observed with the buccal bioadhesive device administration when compared to the immediate release oral capsule.

Conclusions. The buccal bioadhesive device appears to improve the oral bioavailability of cyanocobalamin by providing controlled delivery of the drug to the gastrointestinal tract.

KEY WORDS: Polyox®; buccal; bioadhesive; vitamin B_{12}; polyethyleneoxide; bioavailability.

INTRODUCTION

The oral cavity forms a convenient and easily accessible site for the delivery of therapeutic agents (1). Advances in bioadhesive and controlled release technology have caused a renewal of interest in delivery of drugs to the oral cavity from buccal bioadhesive devices (2). The proposed uses of buccal bioadhesive devices have so far been limited to targeting the delivery of drugs to the environment of oral cavity, either for treating local oral conditions by maintaining high drug concentrations in the oral cavity or for systemic effects of the drugs by requiring drug absorption across the oral mucosa (3–9). The objective of this study was to investigate the application of buccal bioadhesive device in targeting drug delivery to the gastrointestinal tract. The requirements for the buccal bioadhesive device formulation employed here were to act as a reservoir to control drug delivery to the upper gastrointestinal tract while maintaining the appropriate buccal bioadhesive characteristics. This delivery system was envisaged to maximize the time of drug exposure at its absorption site in the gastrointestinal tract and thereby improve its oral bioavailability. The delivery of drug from buccal bioadhesive devices to the gastrointestinal tract was hypothesized to be accomplished by the release of drug into the saliva, which is then inadvertently swallowed periodically. High molecular weight polyoxyethylene polymer have been shown to be safe and effective in providing good buccal bioadhesive characteristics in human volunteers (10–12). One such commercially available polymer (Polyox® 303) was used in this study for the formulation of buccal bioadhesive devices. Cyanocobalamin, a slightly water-soluble drug known to exhibit poor and erratic oral bioavailability, was used as a model marker drug (13–17). The effect of the delivery approaches on the drug bioavailability was measured by comparing AUC's from buccal bioadhesive devices to immediate release oral capsules. An I.V. bolus dose of the drug was given for determination of the absolute bioavailability.

MATERIALS AND METHODS

Materials

Polyoxyethylene (Polyox® 303) was donated by Union Carbide (Danbury, CT, USA). Cyanocobalamin USP was purchased from Spectrum (Gardena, CA, USA). HPLC grade water and acetonitrile were purchased from Fisher Scientific (Springfield, NJ, USA). Sorbitol NF/FCC was purchased from Archer Daniel Midland Company (Decatur, IL, USA).

Preparation of Cyanocobalamin Buccal Bioadhesive Device

An accurately weighed 70 mg quantity of the premixed Polyox 303 and cyanocobalamin mixture (97:3) was filled into the tablet die having a 7 mm standard cup lower punch. The mixture was gently hand compressed using a 7 mm flat upper punch. An accurately weighed 30 mg quantity of premixed sorbitol and magnesium stearate mixture (95.5:0.5) was poured on top of the above compressed mixture into the same die and then this two-layered device was directly compressed at room temperature using Carver® press (Carver Inc., Wabash, IN, USA), under a 1000 Kg force for 6 seconds. The mean thickness of all the prepared devices were in the range 1.5 ± 0.3 mm.

Preparation of Oral Capsule

An accurately weighed 250 mg quantity of the premixed anhydrous lactose and cyanocobalamin mixture (99.6:0.4) was hand filled in size 0 capsules.

Preparation of I.V. Solution

An accurately weighed quantity of cyanocobalamin was dissolved in normal saline to achieve a 0.5 mg/mL concentration. The solution was then filtered through a pre-sterilized 0.2 μm filter and stored in a sterile container.

[1] St. John's University, College of Pharmacy & Allied Health Professions, Jamaica, New York 11439.

[2] Bayer Corporation, Pharmaceutical Division, West Haven, Connecticut 06516.

[3] Present Address: Bayer, Corporation, Pharmaceutical Division, 400 Morgan Lane, West Haven, Connecticut 06516.

[4] To whom correspondence should be addressed. (e-mail: deepak.tiwari.b@bayer.com)

0724-8741/99/1100-1775$16.00/0

Drug Assay

The assay for cyanocobalamin was performed using a reverse phase HPLC-UV method using Spectra System-P4000/AS3500 (Finnigan Corp., Piscataway, NJ, USA). An 85:15 mixture of water and acetonitrile (adjusted to pH 2.5 with phosphoric acid) was used as mobile phase at 1.0 mL/min flow rate. A sample volume of 100 μL was injected onto a 4.6 mm × 250 mm Spherisorb ODS-2.5 μm Altima column (Sigma-Aldrich, St. Louis, MO, USA) and eluents were analyzed at 230 nm.

Drug Release Kinetics

Drug release from the prepared buccal bioadhesive devices and oral capsules were evaluated using a standard USP dissolution apparatus I (Vankel Industries Inc., Edison, NJ, USA) at 100 rpm. Deionized water (900 mL) at 37 ± 0.5°C was used as the dissolution medium for buccal bioadhesive devices. Drug release from the oral capsules was evaluated using both 0.1 N HCl and deionized water as dissolution medium. Ten-mL aliquots of dissolution medium were collected at predetermined time intervals and replaced with an equal volume of fresh dissolution medium. The samples were filtered through a 0.45 μm filter and assayed for drug content.

Residual Drug Content

The bioadhesive devices removed from dogs were analyzed for the residual drug content by completely dissolving the device in deionized water under constant stirring for 24 hrs. All samples were diluted quantitatively and assayed for drug content.

Pharmacokinetic Evaluation

A three-leg crossover trial was designed to evaluate the bioavailability of cyanocobalamin from the two dosage forms: buccal bioadhesive device and immediate release oral capsules for comparison to the I.V. solution. This study was performed on four healthy adult male beagle dogs, 4 years of age, and having weights in the range of 14 to 17 Kg. The research adhered to the "Principles of Laboratory Animal Care" (NIH publication #85-23, revised 1985).

In the first leg of the study, dogs were dosed with buccal bioadhesive device formulation, which was placed in the oral cavity, on the gingival mucosa adjacent to upper canine tooth. The devices were adhered to the mucosa by maintaining a gentle fingertip pressure for 1 minute. Devices were left in place for a maximum of 12 hrs. All used devices were collected and stored for later analysis of residual drug levels. In the second leg of the study, dogs were dosed with the oral capsule formulation. The capsule was inserted deep into the mouth of the dogs and the mouth was kept closed for 1 minute. In the third leg of the study, dogs were dosed by injecting 1 mL of the prepared 0.5 mg/mL drug solution. A minimum of ten day period was used between each leg of the study for drug washout.

Following dosing, dogs were housed in stainless steel cages and fasted for 12 hrs. Blood samples (4.0 mL) were collected into heparinized plain, red top vacutainer tubes from canula implanted in the right cephalic vein at specified times post dosing. The time points for blood collections were 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 24 and 48 hr after dosing. Additional samples were collected at 5 and 15 min post dosing by the I.V. route. After collection of each blood sample, the canula was flushed with approximately 0.2 mL of a 10% v/v heparin/normal saline solution to keep the canula patent. All samples were immediately placed on ice upon collection and centrifuged at 3000 rpm for 15 min to obtain serum. Aliquots were stored at −80°C, pending analysis. The serum samples were analyzed at a contract research organization (Ani Lytics, Gaithersburg, MD), where a commercial radioassay kit (Diagnostic Products Corporation, Los Angeles, CA) was used as described in the product literature for the quantitative determination of cyanocobalamin.

RESULTS

Drug Release Kinetics

The release profile of the drug from the prepared buccal bioadhesive device formulation is shown in Fig. 1. The results indicated that 50% of the drug was released in 6 hrs and 90% of the drug was released in 18 hrs from the prepared buccal bioadhesive devices. The data points were fitted to Higuchi's square root of time equation for drug release from polymer matrices. A good correlation (r^2 = 0.9906) was observed indicating that the drug release from the buccal bioadhesive devices followed Higuchi's square root of time dependent model. The results of the dissolution study with prepared oral capsules using 0.1N HCl and deionized water as the medium indicated that irrespective of the dissolution medium used almost 100% of the drug was released from the capsule formulation in 15 minutes.

Animal Studies

Pharmacokinetic evaluation of the drug delivered from I.V. solution, immediate release oral capsules, and the buccal

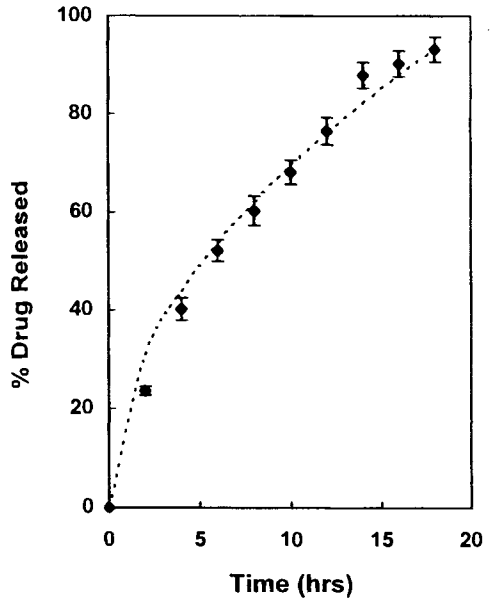

Fig. 1. Drug release profile of buccal bioadhesive device in deionized water. (---------)-Higuchi's square root of time dependent model, r^2 = 0.9906.

bioadhesive device was accomplished using four adult healthy male beagle dogs. All serum concentration time profiles were plotted in semilogarithmic fashion and were subjected to compartment-model independent analysis (18–19). The serum concentration data was normalized to base levels by subtracting the intrinsic concentrations of cyanocobalamin at time zero. The area under the concentration versus time curve from t = 0 to the time of the last blood sample was determined by the linear trapezoidal rule (20). For estimating the remaining area, the last blood concentration was divided by the terminal rate constant, obtained from the I.V. study (21). The last two points on the concentration-time profiles after drug administration via the I.V. route were used to calculate the terminal elimination rate constant. The percent bioavailability was calculated as the ratio of the total areas under the concentration-time curve ($AUC_{0-\infty}$), after I.V. and test formulation (capsule or buccal bioadhesive device) administration and was corrected for the administered dose.

Pharmacokinetics of Cyanocobalamin Following I.V. Administration

The serum concentration-time profiles of all four dogs after a single bolus I.V. dose of 0.5 mg are shown in Fig. 2. All four dogs appeared to show similar concentration-time profiles indicating low variability of the results. The calculated Mean ± SD values of terminal half-life ($t_{1/2}$), AUC_{0-48} and $AUC_{0-\infty}$ following I.V. bolus administration of 0.5 mg dose in the four dogs were 16.4 ± 2.4 hrs, 180.1 ± 6.7 μg-hrs/L and 188.5 ± 8.5 μg-hrs/L, respectively.

Pharmacokinetics of Cyanocobalamin Following Oral Capsule Administration

Figure 3 represents the plots of serum cyanocobalamin concentration versus time following drug administration via immediate release oral capsules. Dogs 1, 2 and 4 appeared to show similar concentration-time profiles, indicating the low variability among these three dogs. However, the profile of dog 3 appeared to be atypical. The observed C_{max} for the dogs 1, 2, 3 and 4 were 1614, 1590, 4536 and 1592 ng/L, respectively. The C_{max} of dog 3 was approximately 3 times higher than dogs 1, 2 and 4. The observed t_{max} for the dogs 1, 2 and 4 were 2 hrs, whereas, dog 3 showed a t_{max} of 4 hrs. The percent bioavailability for dogs 1, 2 and 4 were 7.5, 10.3 and 13.2, respectively. A significantly higher percent bioavailability of 25.4 was observed for the dog 3.

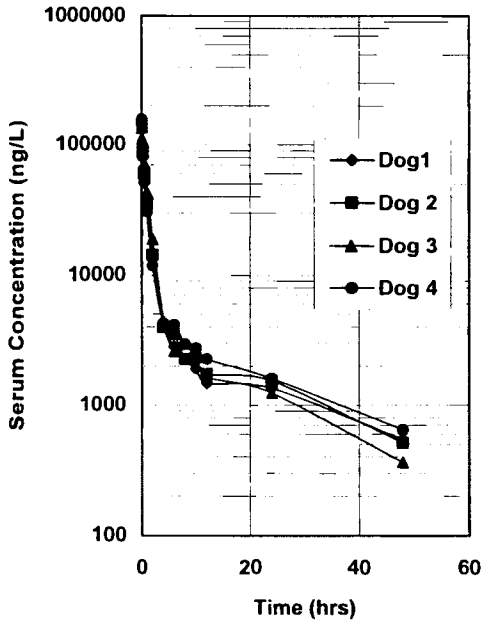

Fig. 2. Cyanocobalamin pharamacokinetics following I.V. administration.

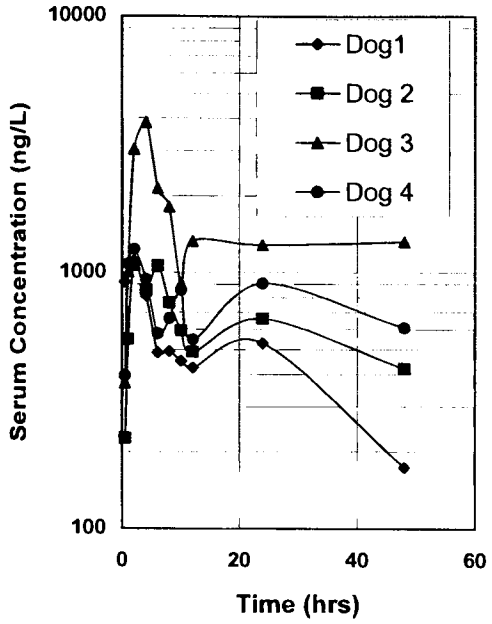

Fig. 3. Cyanocobalamin pharamacokinetics following oral capsule administration.

The concentration-time profiles of all four dogs showed sporadic multiple secondary peaks of absorption. Cyanocobalamin is absorbed by intrinsic factor mediated and a non-intrinsic factor mediated transport mechanism and is reported to exhibit enterohepatic-recycling (13–17). Therefore, it appears that the sporadic appearance of secondary peaks in the concentration-time profiles is probably due to the multiple absorption mechanisms and/or the enterohepatic recirculation of the drug (22).

Pharmacokinetics of Cyanocobalamin Following Buccal Bioadhesive Device Administration

Figure 4 represents the serum concentration-time profile of all four dogs following drug administration via buccal bioadhesive device. A lower device adhesion time (i.e., when device failed to remain in place) of 6–8 hrs was observed in dog 4, compared to the device adhesion time of 10–12 hrs in the other three dogs. Consequently, as indicated by the residual drug content analysis of the removed devices only 0.5 mg of the dose was delivered in dog 4 in comparison to the 1.0 mg of the delivered dose in dogs 2 and 3. The amount of the delivered dose could not be determined in the dog 1, where the device was lost between 10–12 hrs of the study period. However, for

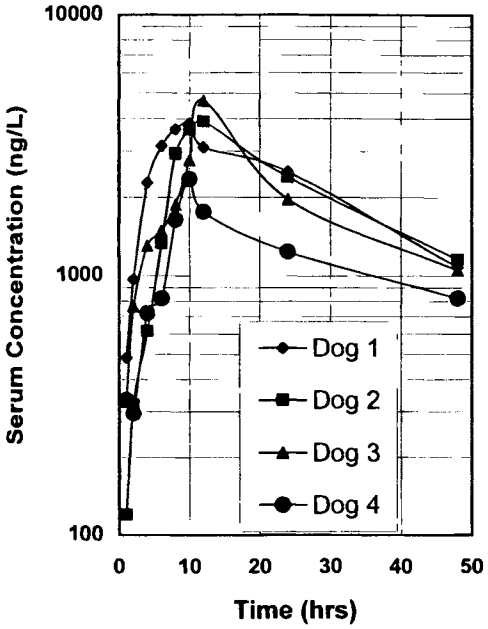

Fig. 4. Cyanocobalamin pharamacokinetics following buccal bioadhesive device administration.

the purpose of calculating the percent bioavailability the amount of delivered dose for dog 1 was assumed to be 1.0 mg. Accordingly, the percent bioavailability of the dogs 1, 2, 3 and 4 were 38.2, 34.4, 30.7 and 39.9, respectively. The observed t_{max} for dogs 1 and 4 was 12 hrs, while dogs 2 and 3 showed t_{max} of 10 hrs. The C_{max} of dogs 1, 2 and 3 were 4267, 4536 and 5197 ng/L, respectively. A lower C_{max} of 2617 ng/L was observed for dog 4. The observed low adhesion time and consequently the less amount of the delivered dose appeared to be the reason for observing a lower C_{max} in the dog 4.

Figure 5 represents the comparative concentration-time profiles of all four dogs following I.V., immediate release oral capsules and buccal bioadhesive device administration. An improvement in the bioavailablity is observed for all four dogs when cyanocobalamin was administered via the buccal bioadhesive device in comparison to the immediate release oral dosage form. The percent bioavailability of the drug administered via buccal bioadhesive device in three typical dogs 1, 2 and 4 were 3.5 to 5 times higher when compared to the immediate release oral capsule. The percent bioavailability of the drug administered via buccal bioadhesive device in the atypical dog 3 exhibiting high absorption of the drug from oral capsule also showed the improvement, but was only 1.2 times higher than the immediate release oral capsule dosage form. Similarly, the C_{max} of the drug in dogs 1, 2 and 4 were significantly higher when the drug was administered via buccal bioadhesive device in comparison to the immediate release oral capsules. However, the C_{max} was marginally higher for dog 3 when drug was administered via buccal bioadhesive device compared to the immediate release oral capsules. However, t_{max} was significantly longer for all the four dogs when drug was administered via buccal bioadhesive device (10–12 hrs) compared to the immediate release oral capsules (2–4 hrs).

DISCUSSION

The pharmacokinetic parameters (Mean ± SD) following administration of cyanocobalamin from immediate release oral capsules and buccal bioadhesive devices are shown in Table I. The mean values of t_{max}, $AUC_{0-\infty}$, and percent bioavailability were significantly higher (paired t-test, $P < 0.05$) for drug administration from buccal bioadhesive devices than from immediate release oral capsules. The mean value of C_{max} was also higher for drug administration from buccal bioadhesive devices than from immediate release oral capsules, but failed to demonstrate statistical significance. A significantly higher amount of dose (~35%) was absorbed by normal healthy dogs when drug was administered via buccal bioadhesive devices than when drug was administered via immediate release oral capsules (~14%).

Cyanocobalamin is known to exhibit poor, erratic oral bioavailability and it is absorbed by two different mechanisms (13–17). An active transport mechanism is mediated by the "intrinsic factor" which is secreted by the parietal cells in the gastric mucosa. A cobalamin-intrinsic-factor-complex is formed and attached to a specific ileal receptor protein on the luminal surface of the ileal mucosa. After its uptake into the enterocyte cyanocobalamin is released from the complex, binds to transcobalamin II and is transferred into the portal blood. This active uptake mechanism takes place in ileum and is of importance in the absorption of physiological doses of cyanocobalamin (<10 μg). In addition, cyanocobalamin is taken up by the passive diffusion, which is independent from the "intrinsic factor" and takes place along the entire small intestine. This mechanism is important for the absorption of pharmacological doses of cyanocobalamin (>10 μg). Since, the dose (0.5 to 1.0 mg) administered in this study via immediate release oral capsules and buccal bioadhesive devices was much higher than the physiological dose (~10 μg) the major mechanism of cyanocobalamin absorption is expected to be by passive diffusion.

The drug from buccal bioadhesive devices is first released into the environment of the oral cavity (saliva) and then inadvertently delivered to gastrointestinal tract by periodic swallowing of the saliva. Because, the drug is first exposed to oral cavity, some absorption across the oral mucosa is possible. However, given the relatively larger size of the cyanocobalamin molecule (molecular weight ~ 1355 daltons), its highly hydrophilic characteristic with partition coefficient less than 0.05, the existence of predominantly ionized species in the oral cavity (pKa ~ 3.3) and the absence of a permeability enhancer in the formulation, absorption across the oral mucosa is expected to be of an insignificant magnitude.

The drug is delivered to the gastrointestinal tract from both buccal bioadhesive devices and oral capsules. However, the drug from buccal bioadhesive devices is released in a controlled manner providing for a sustained exposure of the drug at its gastrointestinal absorption site. Whereas, a rapid instantaneous release of drug from immediate release oral capsules results in dumping of dose, this in turn provides for a limited time of drug exposure at its gastrointestinal absorption sites. Therefore, it appears that in the case of dose dumping from immediate release oral capsules absorption is the rate limiting step and bioavailability of the drug is significantly improved from buccal bioadhesive devices by controlling the rate of drug delivery to

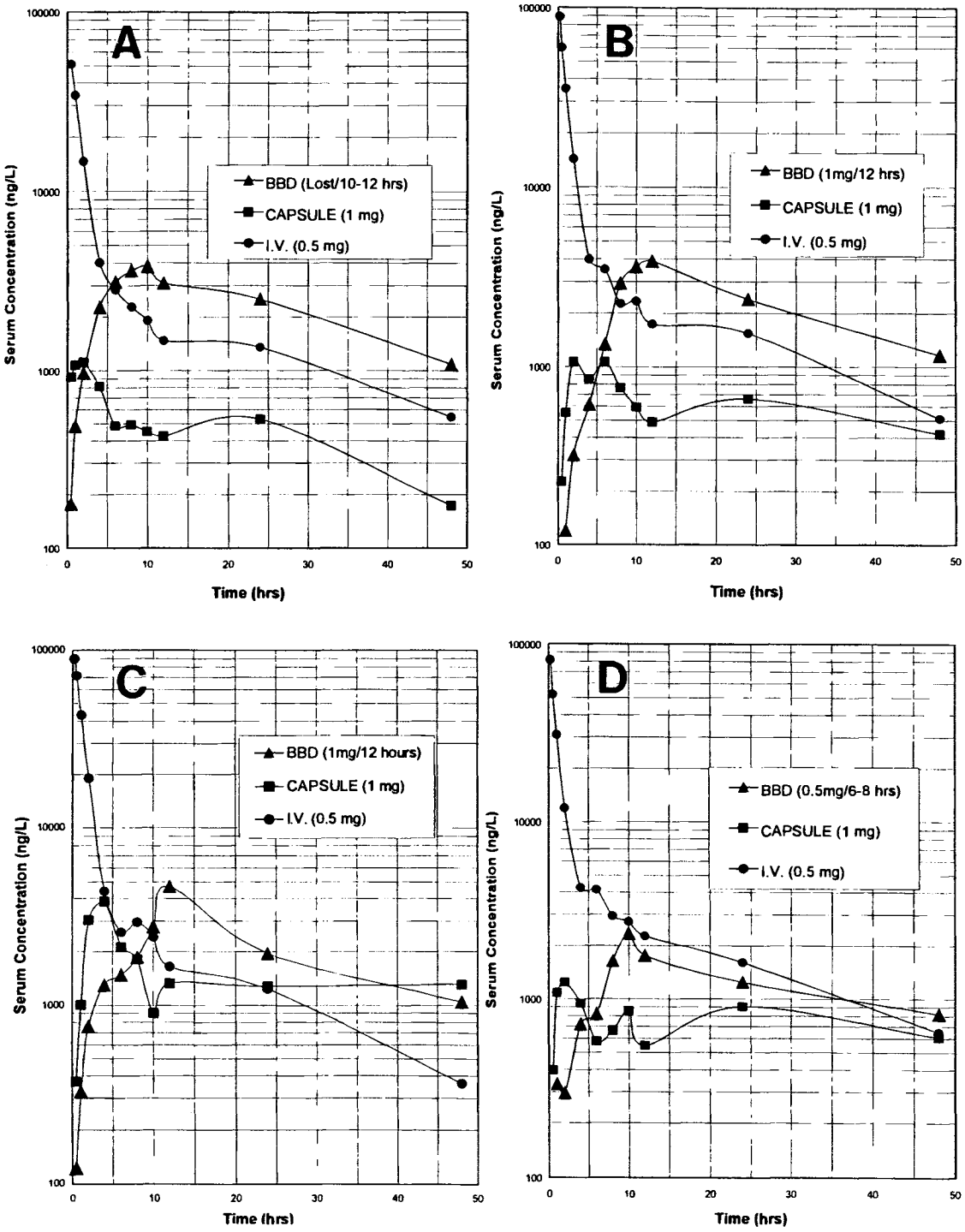

Fig. 5. Comparative cyanocobalamin pharamacokinetics following I.V., oral capsule and buccal bioadhesive device (BBD) administration. A, Dog 1; B, Dog 2; C, Dog 3; and D, Dog 4.

its gastrointestinal absorption sites. Ideally, optimum exposure of drug at its gastrointestinal absorption site could be provided by a bioadhesive system, which after oral administration would remain in contact with the gastrointestinal mucosa at or above its absorption site. The use of such oral bioadhesive drug delivery systems that are known to increase gastrointestinal transit time of the drugs have been proposed to achieve optimum drug exposure time and thereby improve drug bioavailability (23). However, the success of these systems in humans has been disappointing due to the high luminal mucus turnover rates (24). The controlled drug release to gastrointestinal tract from buccal bioadhesive devices may also be useful in increasing the transit time of drugs for the duration of its oral mucosal adhesion time.

Table I. Cyanocobalamin Pharmacokinetic Parameters Following Oral Capsule and Buccal Bioadhesive Device Administration

	C_{max} (ng/L)	t_{max} (hrs)	$AUC_{0-\infty hrs}$[a] (μg-hrs/L)	% Bioavailability[a]
Oral Capsule	2333 ± 1469	2.5 ± 1.0	53.6 ± 30.8	14.1 ± 7.9
BBD Device	4154 ± 1096	11 ± 1.1[b]	134.4 ± 16.5[b]	35.8 ± 4.1[b]

Note: All values are expressed as Mean ± SD.
[a] Data normalized to 1 mg dose.
[b] Significantly different from oral capsule (paired t-test, $P < 0.05$).

CONCLUSIONS

The rapid and instantaneous drug release from oral capsule may result in an efficient absorption of cyanocobalamin due to dose dumping. The buccal bioadhesive device formulation by providing controlled release behavior appears to increase the duration of drug exposure at its gastrointestinal absorption sites resulting in significantly enhanced oral bioavailability of cyanocobalamin.

REFERENCES

1. M. M. Veillard, M. A. Longer, T. W. Martens, and J. R. Robinson. Preliminary studies of oral mucosal delivery of peptide drugs. *J. Contr. Rel.* **6**:123–131 (1987).
2. G. Ponchel. Formulation of oral mucosal drug delivery systems for the systemic delivery of bioactive materials. *Adv. Drug Del. Rev.* **13**:75–87 (1994).
3. T. Nagai and Y. Machida. Buccal delivery systems using hydrogels. *Adv. Drug Del. Rev.* **11**:179–191 (1993).
4. S. J. Pimlott and M. Addy. Evaluation of a method to study uptake of prednisolone sodium phosphate from different oral mucosal sites. *Oral Surg. Oral Med. Oral Pathol.* **60**:35–37 (1985).
5. M. Ishida, N. Nambu, and T. Nagai. Mucosal dosage form of lidocaine for toothache using hydroxypropyl cellulose and carbopol. *Chem. Pharm. Bull.* **30**:980–989 (1982).
6. T. Nagai and R. Konishi. Buccal/gingival drug delivery systems. *J. Contr. Rel.* **6**:353–360 (1987).
7. T. Nagai, Y. Machida, and R. Konishi. Bioadhesive dosage forms for buccal/gingival administration. In V. Lenaerts and R. Gurny (eds.), *Bioadhesive Drug Delivery Systems*, CRC press, Florida, 1990, pp. 142.
8. Y. Nozaki, M. Kakumoto, M. Ohta, K. Yukimutsu, and Y. W. Chien. A new transmucosal therapeutic system. *Drug Dev. Ind. Pharm.* **19**:221–275 (1993).
9. N. A. Peppas and J. R. Robinson. Bioadhesives for optimization of drug delivery. *J. Drug Target.* **3**:183–184 (1995).
10. P. Bottenberg, R. Cleymae, C. Muynck, J. P. Remon, D. Coomans, Y. Michotte, and D. Slop. Development and testing of bioadhesive fluoride-containing slow-release tablets for oral use. *J. Pharm. Pharmacol.* **43**:457–464 (1991).
11. P. Bottenberg, R. Cleymae, C. Muynck, J. P. Remon, D. Coomans, and D. Slop. Comparison of salivary fluoride concentrations after administration of a bioadhesive slow-release tablet and a conventional fluoride tablet. *J. Pharm. Pharmacol.* **44**:684–686 (1992).
12. D. Tiwari, D. Goldman, R. Sause, and P. L. Madan. Evaluation of polyoxyethylene homopolymers for buccal bioadhesive drug delivery device formulations. *Pharm. Res.* **14**:S–151 (1997)
13. L. B. Bailey. Vitamin chart no. 12. *Nutr. Support Serv.* **11**:24 (1986).
14. K. Schumann, H. G. Classen, M. Hages, R. Prinz-Langenohl, K. Pietrzik, and H. K. Biesalski. Bioavailability of oral vitamins, minerals, and trace elements in perspective. *Arzneim. Forsch.* **47**:369–380 (1997).
15. J. M. Scott. Bioavailability of vitamin B_{12}. *Eur. J. Clin. Nutr.* **51**:S49–S53 (1997).
16. A. Doscherholmen and P. S. Hagen. A dual mechanism of Vitamin B_{12} plasma absorption. *J. Clin. Invest.* **36**:1551–1557 (1957).
17. E. L. Smith. Absorption, excretion, & distribution in the body. In R. Peter and F. G. Young (eds.), *Methuen's Monographs on Biochemical Subjects*, John Wiley & Sons, New York, 1965, pp. 132–133.
18. C. L. Cheng, S. H. Gehrke, and W. A. Ritschel. Development of an azopolymer based colonic release capsule for delivering proteins/macromolecules. *Methods Find Exp. Clin. Pharmacol.* **16**:271–278 (1994).
19. G. Geisslinger, S. Menzel, O. Zoller, Zh. Cheng, and K. Brune. Absorption and distribution of ibuprofen and acetylsalicyic acid formulations. *Drug Invest.* **7**:52–55 (1994).
20. M. Gibaldi and P. Perrier, Estimation of Areas—Appendix D. In J. Swarbick (ed.), *Pharmacokinetics*, Marcel Dekker, New York, 1982, pp. 445–449.
21. C. Li, P. P. Bhatt, and T. P. Johnston. Transmucosal delivery of oxytocin to rabbits using a mucoadhesive buccal patch. *Pharm. Dev. Technol.* **2**:265–274 (1997).
22. K. C. Kwan, M. R. Dobrinska, J. D. Rogers, A. E. Till, and K. C. Yeh. Bioapharamceutics. In L. Lachman, H. A. Lieberman, and J. L. Kanig (eds.), *The Theory and Practice of Industrial Pharmacy*, Lea & Febiger, Pennsylvania, 1986, pp. 215–216.
23. M. Helliwell. The use of bioadhesives in targeted delivery within the gastrointestinal tract. *Adv. Drug Del. Rev.* **11**:221–251 (1993).
24. A. Rubinstein and B. Tirosh. Mucus gel thickness and turnover in the gastrointestinal tract of the rat: response to cholinergic stimulus and implication for mucoadhesion. *Pharm. Res.* **11**:794–799 (1994)