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Transdermal Delivery Controlled by a Chitosan Membrane

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ABSTRACT

The release of a drug from a transdermal delivery system with a rate controlling chitosan membrane was analyzed in vitro and in vivo. Lidocaine hydrochloride, a local anesthetic, was used as the model drug. The in vitro permeability of various chitosan membranes for the drug was investigated using a Franz diffusion cell. Drug release was slower through chitosan membranes with a higher degree of deacetylation (% DD) and with a larger thickness. A transdermal chitosan patch was developed using a chitosan membrane for rate control and a chitosan hydrogel as a drug reservoir. The most prolonged release in vitro was obtained with a 95% DD chitosan rate controlling membrane. The transport mechanism was found to be non-Fickian. The functionality of this transdermal patch was studied on the forearm of human volunteers by assessing the anesthetic effect. Patches with 70% and 95% DD membranes delayed the anesthetic effect, increasing the delay with increasing % DD. It was concluded that a combination of chitosan membrane and chitosan hydrogel is a good transparent system for controlled drug delivery and that the release kinetics in vitro at least for lidocaine have a predictive value for its anesthetic effect in vivo. The demonstration of a direct relationship between in vitro drug membrane permeability and its physiological effect might be considered as quite unique.

Key Words: Chitosan; Transdermal drug delivery; Rate controlling membrane.

INTRODUCTION

Recent findings in pharmacokinetic research have opened new opportunities for transdermal drug delivery systems.[1] Transdermal delivery, if possible, has many advantages over conventional oral application: gastrointestinal decomposition and hepatic first pass biotransformation are circumvented, drugs can be given at lower dosages during a larger period of time, and drug delivery can be terminated quickly at any time. Polymeric membranes are commonly used to control the rate of drug release in transdermal delivery

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systems.[2] Natural and synthetic polymers have been studied for this purpose and some have been successfully commercialized. The natural biopolymer chitosan is a copolymer of *N*-acetyl D-glucosamine and D-glucosamine and is produced from crustacean sources.[3] Because of their high biocompatibility, biodegradability, and nonantigenicity, chitosan membranes and hydrogels are interesting candidates for many biomedical applications.[4] Skin irritation, a common problem in the application of transdermal patches, can be minimal when chitosan is used as contact membrane in the fabrication of the transdermal system.[5]

Chitosan hydrogels have been investigated for the development of controlled and prolonged release of drugs in various physical forms, such as microparticles,[6] microspheres,[7] nanospheres,[8] gels,[5,9] and membranes.[10] Different forms of chitosan membranes[10] including cross-linked membrane[5] and interpenetrating networks with other polymers[11] have been investigated. Permeation through a chitosan membrane can be controlled by varying the degree of deacetylation, the molecular weight, and the chain flexibility of the chitosan used for the casting of the membranes.[12]

In most release studies using chitosan membranes, the mixture of drug and chitosan solution was allowed to co-cast to form a drug-loaded membrane. The chitosan membrane formed in this way might be affected in its micro architecture by the presence of the drug. This will not only hold for membranes with a high drug content but even at lower drug concentrations, since during the casting nearly all solvent evaporates and the drug concentration in the semi-solid phase becomes very high. Membranes formed in the presence of a drug have been shown to be more crystalline and to be influenced in their drug release behavior.[13] Therefore, it seems appropriate to apply chitosan twice: chitosan as a membrane that controls only the rate of permeation of the drug, but does not contain any drug, and chitosan as a hydrogel matrix containing the drug, acting as a reservoir from which the drug can be diffused, basically unhindered.

Lidocaine HCl is a water-soluble drug and a local anesthetic successfully used in patients undergoing superficial surgical procedures to relieve pain. A few lidocaine transdermal patches are available commercially and are used for relief of pain associated with postherpetic neuralgia.[14] The EMLA® patch, an eutectic emulsion of lidocaine and prilocaine, is used as an anesthetic for biopsy[15] or for intramuscular injection in children.[16] The anesthetic effect in the skin can be measured by assessment of pain using the Visual Analogue Scale,[15] the Faces Pain Scale,[16] or by investigation of warm sensation, cool sensation, and hot pain.[17]

In this study, an in vitro release profile of the model drug lidocaine HCl through various chitosan membranes was investigated in a Franz diffusion cell. A transdermal lidocaine HCl delivery system was developed using chitosan membranes with different % degree of deacetylation (DD) as a rate controlling membrane and chitosan hydrogel as the drug reservoir. The release profiles analyzed in vitro were compared with the in vivo anesthetic effect.

MATERIALS AND METHODS

Materials

Three chitosan samples obtained from shrimp shells[3] were provided internally by the Bioprocess Technology Laboratory, Asian Institute of Technology, Bangkok, Thailand. The chitosans had a degree of deacetylation of 70%, 88%, and 95% DD but the same molecular weight of 800 kDa. Lidocaine HCl was purchased from Sigma. Tegaderm® (a pressure sensitive adhesive) and ethylene vinyl acetate film (backing layer) were obtained from the 3M Company, Bangkok, Thailand. All other chemicals used in this study were of analytical grade.

Preparation of Rate Controlling Chitosan Membranes

Chitosan solution (1% w/v) in 1% (v/v) acetic acid was prepared by shaking overnight. The solution was filtered, degassed, and the appropriate amount was poured into a plastic petri plate. The chitosan membrane was formed by drying at 40°C for 48 hours. Chitosan membranes were soaked in 4% (w/v) NaOH to neutralize the acetic acid, washed several times with distilled water, and dried. Membranes were prepared using different amounts of 70%, 88%, and 95% DD chitosan solution to get a thickness of 10, 20, or 40 μm. They were kept in a closed container above water at relative humidity of 80% for 72 hours to obtain a uniform moisture content.

Designing a Chitosan Transdermal Delivery System

A transdermal delivery system with lidocaine as the model drug was developed consisting of a rate

controlling chitosan membrane, a drug-loaded chitosan hydrogel, and a backing layer of ethylene vinyl acetate covered by a film of Tegaderm for skin adhesion. To prepare the reservoir, chitosan 70% DD (2% w/v) was dissolved in 0.5% (v/v) acetic acid by shaking overnight. A mixture was prepared of 56 mL chitosan solution, 7 mL of 50% propylene glycol, and 10 mL lidocaine HCl stock solution (250 mg/mL). The mixture was poured onto a flat plate and allowed to cast at 40°C for 24 hours. After discarding about 15 cm^2 at the edges, a hydrogel of 110 cm^2 was obtained.

The resultant hydrogel layer was cut with a circular knife into 5-cm^2 pieces. These pieces were used as a drug reservoir for in vitro release studies and contained 100 mg of the drug. The rate controlling membranes were 70%, 88%, and 95% DD chitosan membranes with 20 μm thickness. For the in vivo study, a drug reservoir containing about 16 mg of the drug lidocaine was prepared by cutting a circular hydrogel of 0.8 cm^2. The reservoir was placed on a 20-μm thick rate controlling membrane of 70% DD or 95% DD and covered with the backing layer and Tegaderm.

Assessment of In Vitro Lidocaine Release

The in vitro release behavior of lidocaine HCl through chitosan membranes was assessed using a Franz diffusion cell (5 cm^2 effective area of diffusion) at 30±2°C. Chitosan membranes of different thicknesses and different % DD were used to test for their permeability for the drug. The chitosan membrane was soaked in distilled water for 30 min, mounted between donor and receptor compartments of the diffusion cell, and fastened with a rigid clamp. The donor compartment was filled with 5 mL of lidocaine HCl (20 mg/mL) in phosphate buffer 0.01 M pH 7.4; the receptor compartment was filled with phosphate buffer and stirred with a teflon-coated magnetic stirrer. The amount of drug released was determined by withdrawing 200-μL aliquots from the side arm of the diffusion cell receptor compartment at predetermined times. The volume withdrawn was replaced with an equal volume of buffer. Samples were analyzed using an ultraviolet (UV) spectrophotometer (Unicam, Cambridge, UK) at λ_{max} of 263 nm.

Release of lidocaine HCl from the transdermal patch was studied in the same way in the Franz diffusion cell. The rate controlling membrane (20 μm thick, various % DD) was mounted as described above. The drug reservoir containing 100 mg lidocaine HCl loaded in 5 cm^2 of 70% DD chitosan hydrogel was placed on the donor side of the rate controlling membrane and covered with a backing layer. A thin layer of gauze was used to study the drug release from hydrogel without a rate controlling membrane.

Quantification of the Anesthetic Effect in Human Volunteers

Twenty volunteers, between 25 and 32 years old, of both sexes, with no history of drug allergy or dermatological disease, participated in this study. Different patches with drug reservoir only, or drug reservoir with rate controlling membrane of 70% DD or 95% DD were used to study their anesthetic effect on skin. Patches were randomly applied on the ventral forearm of volunteers approximately 8 cm from the wrist with a space between patches of 1–1.5 cm. The patch was covered with a backing layer to prevent loss of drug or solvent at the outer side of the reservoir. Tegaderm was used to stick the patch to the surrounding skin. Volunteers were instructed not to touch the application sites during the study. Anesthetic effect was measured by assessment of warm sensation, cool sensation, and sharp pain. A system with 12 metal bars in a holder was developed for warm and cool sensation assessment, and it was kept in a water bath at 50°C for testing warm sensation and in melted ice for testing cool sensation. A sharp object was used to test sharp pain sensation. A screen in front of the eyes of volunteers prevented them from observing what sensation was being tested.

A verbal report score was used for the assessment. Scores for warm sensation were given as follows: 0=no temperature noted, 1=mildly warm, 2=moderately warm, and 3=very warm. For cool sensation: 0=no temperature noted, 1=mildly cool, 2=moderately cool, and 3=very cool. For sharp pain sensation: 0=no touch sensation noted, 1=not sharp at all or dull, 2=mildly sharp, 3=moderately sharp, and 4=very sharp. Total scores for warm, cool, and pain sensations were calculated by addition (maximum 3+3+4=10) and recorded at 0.5, 1, 2, 4, and 6 hours after the application of the patch. The skin was inspected for itchiness, redness, and edema during application and after removal of the patch, but no side-effects had been observed in volunteers.

Data Analysis

Results are expressed as the mean of at least three replicates±SD. Statistical analysis was performed using one-way analysis of variance (ANOVA).

RESULTS AND DISCUSSION

In Vitro Release of Lidocaine Through Chitosan Membranes

Chitosan preparations with the same molecular weight but with different % DD were used to prepare membranes of various thicknesses. Drug release was remarkably dependent on the type of membrane. The diffusion equation, $M_t/M_\infty = Kt^{0.5}$, proposed by Higuchi[18,19] was applied to analyze the kinetics of drug release. In this equation, the rate constant of drug release K is a drug-specific constant dependent on the structural and geometrical properties of the chitosan membrane and can be determined from the slope of the plot of M_t/M_∞ vs. $t^{0.5}$. M_t is the amount of lidocaine released at time t, and M_∞ is the total amount of the drug released at infinite time. An initial straight-line behavior and later deviation from linearity was observed. This indicates that the initial portion of the curve follows a Higuchi release mechanism.

Since many release processes can be represented by a coupling of a Fickian and a non-Fickian mechanism, Ritger and Peppas[20] introduced the power law equation $M_t/M_\infty = Kt^n$ to characterize the controlled release behavior of a drug from polymeric matrixes.[18] In this equation, the same M_t/M_∞ ratio and the same value for the rate constant of drug release K are used. The exponent n is dependent on the mechanism of drug release. Both equations are applicable only to the first 60% of the release.[13,20,21] The values of n can be calculated from the slope of ln M_t/M_∞ vs. ln t. Generally, for a thin film or slab, n=0.5 is indicative of Fickian release and 0.5>n>1 indicates anomalous transport due to swelling.

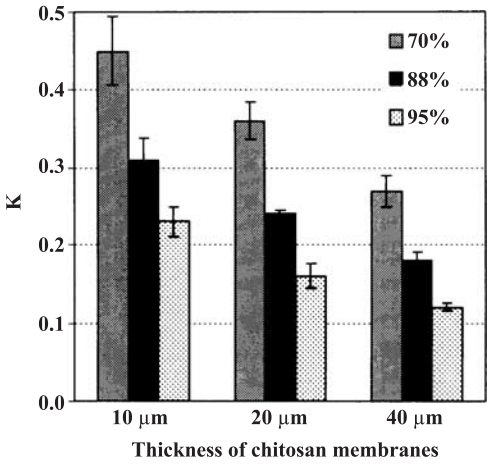

Figure 1. Release of lidocaine HCl through chitosan membranes of various % DD and thickness. Value of K±SD for drug release was calculated according to Higuchi's equation.

Table 1. Release of lidocaine HCl through chitosan membranes of 70%, 88%, and 95% DD and 10, 20, and 40 μm thickness.

Rate controlling chitosan membrane	Higuchi ($M_t/M_\infty = Kt^{0.5}$)		Power law ($M_t/M_\infty = Kt^n$)	
	K	r^2	n	r^2
70% DD				
10 μm	0.45	0.987	0.70	0.990
20 μm	0.36	0.987	0.62	0.996
40 μm	0.27	0.981	0.66	0.996
88% DD				
10 μm	0.31	0.973	0.70	0.992
20 μm	0.24	0.981	0.67	0.999
40 μm	0.18	0.967	0.67	0.990
95% DD				
10 μm	0.23	0.985	0.54	0.990
20 μm	0.16	0.985	0.72	0.992
40 μm	0.12	0.970	0.76	0.995

Mean value of K and n for the release of drug was calculated according to Higuchi's equation and power law equation, respectively. The correlation coefficient is r^2.

As shown in Fig. 1, the rate of drug release was dependent on % DD and the thickness of the chitosan membranes. K and n have been calculated according to the Higuchi and power law equations, respectively. The higher the % DD or the thicker the membrane, the smaller the value of K, which indicates the prolonged release of the drug. By preparing thicker and higher % DD chitosan membranes, slower release of lidocaine HCl can be attained. The rate of drug release through chitosan membranes with different degrees of deacetylation and the same thickness is significantly different ($P<0.05$). This is in line with the conclusion of Miyajima et al.[21] that the charge of the matrix affects the microstructure of the membrane and the release profile of a drug. Swelling indexes of chitosan membranes with 70%, 88%, and 95% DD were 315±17, 110±4, and 99±5% respectively. It is tempting to postulate that the faster drug release from the 70% DD chitosan membrane is caused by the high swelling properties of that membrane. The release of lidocaine HCl through different % DD chitosan membranes does fit the power law ($r^2>0.99$) equation better than the Higuchi model ($0.967<r^2<0.987$) (Table 1). All values of n appear to be higher than 0.5 and therefore the release mechanism is controlled by a combination of diffusion and swelling of the polymer matrix. In other words, lidocaine HCl is

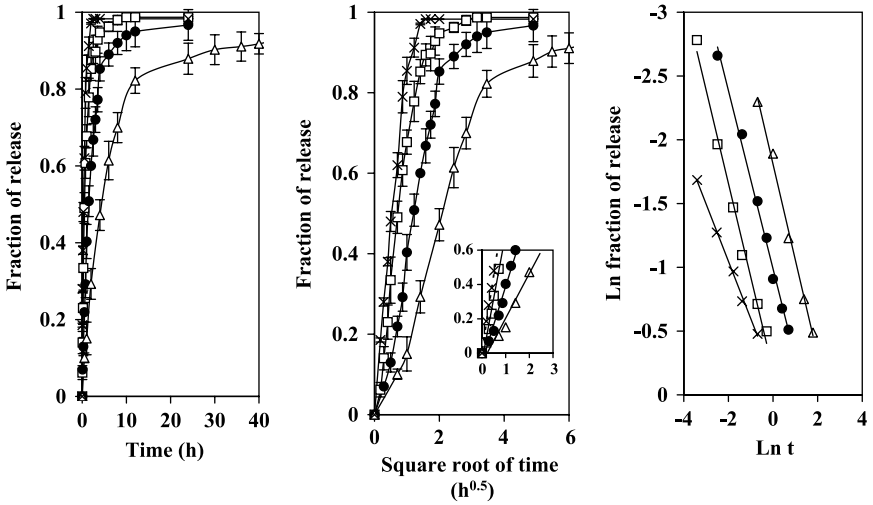

Figure 2. The release of lidocaine HCl from a transdermal chitosan patch. (a): The fraction of release of the drug from patches with 70%, 88%, or 95% DD chitosan membranes or no membrane as a function of time. (b): The fraction of release plotted against the square root of time (Higuchi's equation). Inset: release profile up to the release of ~60% of lidocaine HCl. (c): The same data plotted against ln t according to the power law. -×-, No membrane; -□-, 70% DD; -●-, 88% DD; and -△-, 95% DD. SD calculated from 3–5 replicates.

transported in different % DD chitosan membranes for a considerable part by a non-Fickian diffusion process.

In Vitro Release of Lidocaine from Chitosan Patches

The chitosan-based transdermal delivery patch was composed of three parts: the rate controlling chitosan membrane, the chitosan hydrogel drug reservoir, and the backing layer. The drug reservoir consisted of a 70% DD chitosan hydrogel holding 100-mg/5 cm^2 of the drug and had a nearly unaltered transparency at a moisture content of 65–70%. The in vitro release of lidocaine HCl from this patch was found to be dependent on the % DD of the chitosan membrane (Fig. 2). The release of the drug was slower with chitosan membranes of higher % DD. Drug release from hydrogel without a rate controlling membrane was very fast. K values for these three patches were significantly different ($P<0.05$) (Table 2). The drug release from the patch with a 95% DD chitosan membrane was clearly more prolonged than that of 70% and 88% DD. Thus, chitosan membranes with different % DD can be used to control the drug release from the drug reservoir. The release kinetics observed in the Franz cell for the lidocaine patch are similar to those observed for the lidocaine solution in the permeation experiments. Also, in this case, the chitosan transdermal delivery system fitted better the power law equation (Table 2). The release exponent, n, shows non-Fickian polymer interacting diffusion of the drug through the membranes. Drug release from chitosan hydrogel alone was found to obey Fick's law.

Table 2. Release of lidocaine HCl from transdermal chitosan patches with 20 μm thick 70%, 88%, or 95% DD Rate Controlling Chitosan Membranes.

Chitosan transdermal delivery system	Higuchi ($M_t/M_\infty = Kt^{0.5}$)		Power law ($M_t/M_\infty = Kt^n$)	
	K	r^2	n	r^2
Drug reservoir + a thin layer of gauze	0.88	0.994	0.45	0.997
Drug reservoir + 70% DD	0.74	0.985	0.73	0.991
Drug reservoir + 88% DD	0.44	0.973	0.70	0.994
Drug reservoir + 95% DD	0.26	0.970	0.75	0.995

Mean value of K and n for the release of the drug was calculated according to Higuchi's equation and power law equation, respectively. The correlation coefficient is r^2.

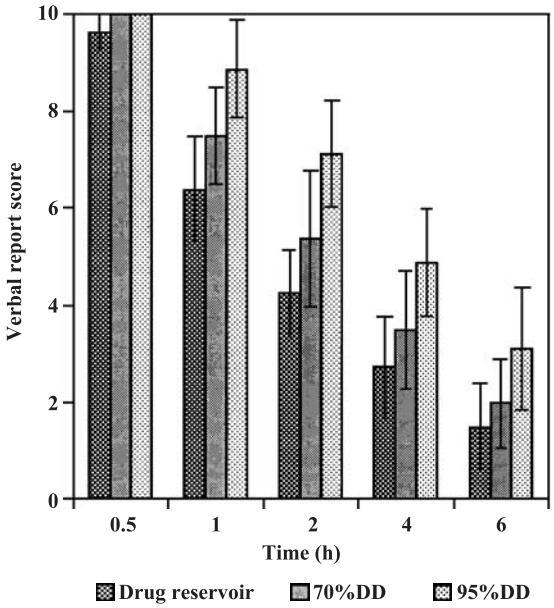

Figure 3. Verbal response by human volunteers after application of the lidocaine patch. Responses for warm sensation (max 3), cool sensation (max 3), and sharp pain (max 4) were added. Maximum verbal score is 10. Patch consists of drug reservoir only. Patch consists of drug reservoir+70% DD chitosan membrane. Patch consists of drug reservoir+95% DD chitosan membrane.

In Vivo Release Study with Human Volunteers

For a study of the quantification of the in vivo release of lidocaine and its control by chitosan membranes, the anesthetic effect has been assessed directly in human volunteers. There is no need to measure the uptake of lidocaine in stratum corneum or in isolated skin. In the volunteer study, the following patches were applied to the skin: drug reservoir only and drug reservoir with rate controlling membranes of 70% DD and 95% DD. The patches made good contact with skin as their moisture content was well controlled. A backing layer and Tegaderm were used to cover the top of the patch and to affix the patch to the skin, respectively. The surface of the skin could be observed clearly through the Tegaderm and patch, as the chitosan delivery system is transparent. The anesthetic effect of the lidocaine-chitosan patch on the skin was assessed by recording the warm, cool, and sharp pain sensations, verbally expressed by the volunteers (Fig. 3). The anesthetic effect was dependent on the type of rate controlling membrane. The fastest effect was obtained with the drug reservoir in the absence of a rate controlling membrane. The verbal response decreased slowly when the patches were applied with rate controlling membranes. The system with 95% DD chitosan membrane gave a more delayed anesthetic effect than that of 70% DD.

The verbal report of the volunteers is in good agreement with the in vitro release profile of the chitosan membrane for lidocaine. Both the rate of in vitro release and the onset of the anesthetic effect decrease in the following order: no rate limiting membrane, 70% DD membrane, and 95% DD membrane. Especially, the kinetics observed with the 95% DD membrane were strikingly similar (Fig. 4). This also shows that in this condition, lidocaine penetration through the skin is not a rate limiting step. It can be concluded that percutaneous release of lidocaine can be effectively controlled in humans, using chitosan membranes. The demonstration

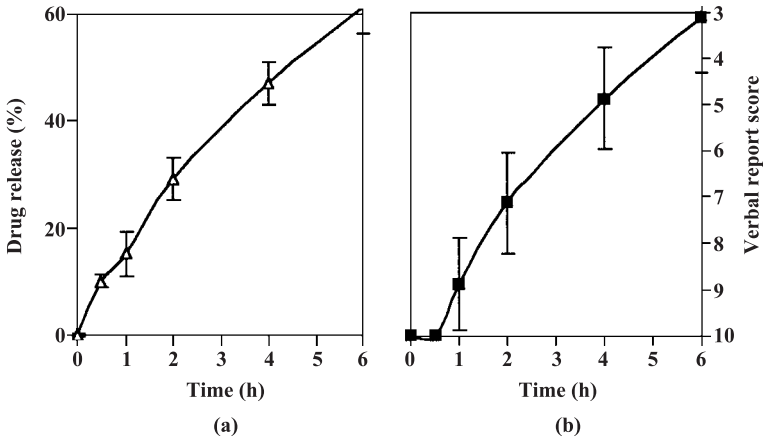

Figure 4. Comparison between in vitro lidocaine release (a) and onset of anesthetic effect in volunteers (b) by a transdermal chitosan patch with 95% DD rate controlling chitosan membrane.

of a direct relationship between in vitro drug membrane permeability and its physiological effect might be considered as quite unique.

CONCLUSION

The data presented in this paper concern the combination of lidocaine HCl as the model drug and chitosan as the rate controlling membrane. The data confirm that the assessment of drug release in vitro has a predictive value for the anesthetic effect of a chitosan-based lidocaine skin patch. The use of chitosan in a transdermal patch is attractive due to its biocompatibility and biodegradability as well as opportunities to modify the charge density and molecular chain length of the chitosan in the membranes, without changing its status as a natural biopolymer. Further prolonging of the drug release might be achieved by using thicker membranes of (nearly) completely deacetylated chitosan. The knowledge on the use of chitosan to control drug release in transdermal delivery systems might be applicable to other transdermal drug delivery systems as well.

It should be noted that the present system using lidocaine HCl as the model drug offers a unique opportunity to correlate in vitro and in vivo behavior of a transdermally acting drug, since only a small number of drugs can be applied through the skin. Of these drugs, only a very limited number exert their effects topically and can be assessed in volunteers by a verbal response and/or by a noninvasive technique. Further studies with this model drug will address the effect of various pretreatment of skin and the quantification of the effect of enhancers on the improvement of transdermal uptake.

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REFERENCES

1. Chein, Y.W. Transdermal drug delivery and delivery systems. In *Novel Drug Delivery Systems*, 2nd Ed.; Marcel Dekker, Inc.: New York, 1992; Vol. 1, 301–380.
2. Sugibayashi, K.; Morimoto, Y. Polymers for transdermal drug delivery systems. J. Control. Release **1994**, *29*, 177–185.
3. Stevens, W.F. Production of chitin and chitosan: refinement and sustainability of chemical and biological processing. In *Chitin and Chitosan,* Proceedings of the Eighth International Chitin and Chitosan Conference, Yamaguchi, Japan, Sept 21–23, 2000; Uragami, T., Kurita, K., Fukamizo, T., Eds.; Kodansha Scientific Ltd.: Japan, 2001; 293–300.
4. Hirano, S. Chitin biotechnology application. In *Biotechnology Annual Review*; El-Gowely, M.R., Ed.; Elsevier Science: Amsterdam, 1996; Vol. 2, 237–258.
5. Thacharodi, D.; Rao, K.P. Development and in vitro evaluation of chitosan–based transdermal drug delivery systems for the controlled delivery of propranolol hydrochloride. Biomaterials **1995**, *16*, 145–148.
6. van der Lubben, I.M.; Verhoef, J.C.; van Aelst, A.C.; Borchard, G.; Junginger, H.E. Chitosan microparticles for oral vaccination: preparation, characterization and preliminary in vivo uptake studies in Murine Peyer's patches. Biomaterials **2001**, *22*, 687–694.
7. Genta, I.; Perugini, P.; Pavanetto, F. Different molecular weight chitosan microspheres: influence on drug loading and drug release. Drug Dev. Ind. Pharm. **1998**, *24* (8), 779–784.
8. Ohya, Y.; Cai, R.; Nishizawa, H.; Hara, K.; Ouchi, T. Preparation of PEG-grafted chitosan nanoparticles as peptide drug carriers. STP Pharma Sci. **2000**, *10* (1), 77–82.
9. Kristl, J.; Smid-Korbar, J.; Struc, E.; Schara, M.; Rupprecht, H. Hydrocolloids and gels of chitosans as drug carriers. Int. J. Pharm. **1993**, *99*, 13–19.
10. Rocha, A.N.L.; Dantas, T.N.C.; Fonseca, J.L.C.; Pereira, M.R. Permeation of drugs in chitosan membranes. J. Appl. Polym. Sci. **2002**, *84*, 44–49.
11. Thacharodi, D.; Rao, K.P. Collagen-chitosan composite membranes controlled transdermal delivery of nifedipine and propranolol hydrochloride. Int. J. Pharm. **1996**, *134*, 239–241.
12. Chen, R.H.; Tsaih, M.L. Effect of preparation method and characteristics of chitosan on the mechanical and release properties of the prepared capsule. J. Appl. Polym. Sci. **1997**, *66*, 161–169.
13. Puttipipatkhachorn, S.; Nunthanid, J.; Yamamoto, K.; Peck, G.E. Drug physical state and drug-polymer interaction on drug release from chitosan

matrix films. J. Control. Release **2001**, *75*, 143–153.
14. Rowbotham, M.C.; Davies, P.S.; Verkempinck, C. Lidcaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. Pain **1996**, *65*, 39–44.
15. De Waard-van der Spek, F.B.; Mulder, P.G.H.; Oranje, A.P. Prilocaine/lidocaine patch as a local premedication for skin biopsy in children. J. Am. Acad. Dermatol. **1997**, *37*, 418–421.
16. Cassidy, K.L.; Reid, G.J.; McGrath, P.J.; Smith, D.J.; Brown, T.L.; Finley, G.A. A randomized double-blind, placebo-controlled trial of the EMLA® patch for the reduction of pain associated with intramuscular injection in four to six-year-old children. Acta Paediatr. **2001**, *90*, 1329–1336.
17. Wallace, M.S.; Ridgeway, B.; Jun, E.; Schulteis, G.; Rabussay, D.; Zhang, L. Topical delivery of lidocaine in healthy volunteers by electroporation, electroincorporation, or iontophoresis: an evaluation of skin anesthesia. Reg. Anesth. Pain Med. **2001**, *26* (3), 229–238.
18. Roseman, T.J.; Higuchi, W.I. Release of medroxyprogesterone acetate from a silicone polymer. J. Pharm. Sci. **1970**, *59* (3), 353–357.
19. Otsuka, M.; Matsuda, Y.; Suwa, Y.; Fox, J.L.; Higuchi, W.I. A novel skeletal drug delivery system using self-setting calcium phosphate cement. 2. Physiochemical properties and drug release rate of the cement-containing indomethacin. J. Pharm. Sci. **1994**, *83*, 611–615.
20. Ritger, P.L.; Peppas, N.A. A simple equation for description of solute release I. Fickian and non-Fickian release form non-swellable devices in the form of slabs, spheres, cylinders or discs. J. Control. Release **1987**, *5*, 23–36.
21. Miyajima, M.; Koshika, A.; Okada, J.; Ikeda, M. Effect of polymer/basic drug interactions on the two-stage diffusion-controlled release from a poly (L-lactic acid) matrix. J. Control. Release **1999**, *61*, 295–304.

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