J Mater Sci: Mater Med (2010) 21:583–588
DOI 10.1007/s10856-009-3899-6

In vitro drug release study of methacrylate polymer blend system: effect of polymer blend composition, drug loading and solubilizing surfactants on drug release

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Received: 17 August 2007 / Accepted: 5 October 2009 / Published online: 24 October 2009

Abstract The application of polymers as the drug delivery systems for treating oral infections is a relatively new area of research. The present study was to test the release of the antibacterial drug chlorhexidine diacetate (CHDA), the antifungal drug Nystatin (NYS) and the antiviral drug acyclovir (ACY) from polymer blends of poly(ethyl methacrylate) and poly(*n*-hexyl methacrylate) of different compositions. The effects of polymer blend composition, drug loading and solubilizing surfactants on the release of the drugs have been studied. Measurements of the in vitro rate of drug release showed a sustained release of drug over extended periods of time. Drug release rates decreased with increasing PEMA content in polymer blends. CHDA release rates increased steadily with increasing drug load. The drug release rates increased with the addition of surfactants. This study demonstrates that the three therapeutic agents show a sustained rate of drug release from polymer blends of PEMA and PHMA over extended periods of time. By varying polymer blend compositions as well as the drug concentration (loading), it is possible to control the drug release rates to a desired value. The drug release rate is enhanced by addition of surfactants that solubilize drugs in the polymer blends.

Dr. Siddugari ('Sid') Kalachandra, Research Professor in the University of North Carolina's School of Dentistry, died on March 14, 2008.

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1 Introduction

The application of polymers as the new drug delivery systems for the release of antibacterial, antifungal and antiviral drugs for treating oral infections is an ongoing area of translational research. Certain types of composite filling materials, the so-called 'compomers' [1, 2], some orthodontic adhesive resins [3], and methacrylate-based copolymers have been reported as matrices for the release of fluoride ions [4].

In dentistry, drug loaded polymeric materials are being used in the control of *candida albicans* to avoid repeated mouth washes [5, 6]. The sustaining effect of poly(lactide-co-glycolide) and PMMA to control the release of chlorhexidine digluconate for the treatment of oral canal disinfection [7] and an implantable copolymer of lactic and glycolic acid as an antimicrobial delivery device for the treatment of periodontal disease [8] have also been reported.

Drug carriers using methacrylate-based systems for intra-oral drug release have also been studied. It was reported that tetrahydrofurfuryl methacrylate/poly(ethyl methacrylate) (THFMA/PEM), a cold cure polymer system, was used as a delivery vehicle for chlorhexidine diacetate (CHDA) and other drugs for the treatment of chronic *candidal* infections in immune suppressed or palliative care patients [9–11]. A copolymer of methyl methacrylate and 2-hydroxy ethyl methacrylate (HEMA) has been studied as an intra-oral device for releasing drugs [12, 13]. In another study, chlorhexidine-releasing HEMA based composites were produced through addition of hydrophobic dimethacrylates and the factors affecting

chlorhexidine release rates are discussed [14]. The use of HEMA in biomedical applications is reported in the literature [15–18].

Nystatin (NYS) is an antifungal drug that is widely used for treating oral infections. It has low solubility in water and saliva [19]. Studies have shown that the solubility of sparingly water-soluble drugs can be increased through the addition of surfactants [20–23]. The addition of surfactants promoted a much higher release of NYS from a chewing gum formulation used as a drug delivery device [24]. The surfactants used in this study were non-ionic surfactants Tween 60 (polyoxyethylene sorbitan mono stearate), Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) and Panodan AB 90 (diacetyl tartaric acid esters of mono and diglycerides of vegetable fats). The effect of surfactant on the release of certain drugs was also demonstrated recently by the research from our group [25]. There are other reports of enhanced drug release due to the addition of surfactants [26–29].

Polymer blending is a simple yet attractive method to combine and optimize physical and mechanical properties of polymers. One advantage of using polymer blends over the synthesis of new polymers is that the composition of the polymer blend is easy to control and change according to the experimental requirements. Polymer blends can also provide effective control of release kinetics for pharmaceuticals and offer significant advantages over traditional drug delivery methods. For example, by altering the composition of the polymer blend, one can effectively "customize" the release profiles to meet the desired delivery needs.

Blending concepts have been used for a long time in drug delivery [30–37]. It was reported that release rates of several hydrophilic compounds and proteins were proportional to the water content in hydrated blends of poly(vinyl alcohol)/poly(glycolic acid-co-lactic acid) (PVA/PGLA) [30]. Park et al. [31] obtained controlled release of bovine serum albumin from blends composed of poly(lactic acid)/poly(ethylene oxide-co-propylene oxide-co-ethylene oxide) (PLA/PEO-PPO-PEO). The authors explained their results in terms of entanglement of the triblock copolymer surfactant with the PLA amorphous phase. Another report showed examples of well controlled drug release with a miscible blend composed of poly(D,L-lactic acid) (PDLLA) and poly(1,5-dioxepan-2-one) (PDXO) [32]. Uniform adjustment of release rates was also obtained in other polymer blends [36, 37]. However, complicated release has been reported in some papers by changing the experimental conditions [33–35].

Obviously, more systematic studies would be necessary to fully understand the relationships between the miscibility, morphology, and controlled release behavior of polymer blends. The use of methacrylate materials in dentistry is well established and it would be of interest to study the drug release properties from polymer blend system of poly(ethyl methacrylate) (PEMA) and poly(*n*-hexyl methacrylate) (PHMA).

In this report, polymer blends of poly(ethyl methacrylate) and poly(*n*-hexyl methacrylate) of different compositions were used to study the release of the antimicrobial agent CHDA, the antifungal agent NYS and the antiviral agent acyclovir (ACY). The effects of blend composition, surfactants and drug loading on drug release have been investigated.

2 Materials and methods

The materials used in this study are detailed in Table 1.

2.1 Preparation of drug loaded films

Drug loaded films were prepared as previously reported [25, 38, 39]. Polymer blend casting solutions were prepared by dissolving the polymers in different composition with the drug in dichloromethane stirring in a stoppered conical flask for 24 h at room temperature. The 10 and 20% content of PEMA in polymer blends were chosen due to the thermomechanical requirements of the drug-loaded films.

For the experiment studying the effect of the composition of the polymer blends, the concentration of the drug was 2.5 wt%. Polymer blends with 10% PEMA were used in the studies involving the effect of drug loading and surfactant concentrations on the drug release. Drug concentrations of 1.0, 2.5, 5.0 and 7.5 wt% were used in the study of drug loading effect. Drug loaded samples with surfactants Tween and Cremophor were prepared similarly in drug to surfactant ratios of (1:1), (1:2) and (1:3). For the experiments involving the effect of surfactants on drug release, 2.5 wt% drug loaded polymer films were used.

Table 1 Materials and suppliers

Material	Supplier
Chlorhexidine diacetate	Sigma–Aldrich[a]
Nystatin	Sigma–Aldrich
Acyclovir	Sigma–Aldrich
PEMA (M_w = 515, 000)	Sigma–Aldrich
PHMA (M_w = 400, 000)	Scientific Polymer Products, Inc.[b]
Dichloromethane	Mallinckrodt Baker Inc.[c]
Tween 60 (Tween)	Sigma–Aldrich
Cremophor RH 40 (Cremophor)	Sigma–Aldrich

[a] St. Louis, MO, USA

[b] Ontario, NY, USA

[c] Phillipsburg, NJ, USA

2.2 Determination of release rate

Three drug loaded polymer square films (2 cm × 2 cm × 0.07 cm) were cut from each dry film to follow the kinetics of drug release at 37°C. 10 ml of distilled water was used as the extracting medium. Fresh 10 ml samples of the media were used daily for 12–15 days and the extracts were analyzed monitoring the drug concentration by measuring the optical density (OD) spectrophotometrically (Hitachi U-2810 Spectrophotometer) at wavelengths (λ_{max}) where the maximum absorption occurred. The λ_{max} values were 257.5, 253 and 306 nm for CHDA, ACY and NYS, respectively. Using standard plots of OD versus concentration, the drug concentration was determined each day. Average drug release rate was determined by the accumulative drug release divided by the time (in days).

UV spectral measurements were made for the two surfactants Tween and Cremophor. The surfactants did not exhibit any absorbance in the region 200–400 nm and did not interfere with the determination of absorbance values for NYS. Additionally, the standard plots of NYS were similar with and without the addition of surfactants. Similar observation was made with reference to our previous study involving the same two surfactants incorporated into EVA (ethylene vinyl acetate) copolymers [25].

2.3 Statistical analysis

For each study, one-way analysis of variance was applied to the drug release rates transformed to a log scale to achieve approximate normality and variance homogeneity.

3 Results

3.1 Effect of polymer blend composition on the drug release

The release of ACY and CHDA from the polymer blends are presented in Figs. 1 and 2. As the PEMA content of the blend increased from 10 to 20%, the release rate of ACY decreased from 3.19 to 2.82 μg/cm^2 day (t test P value = 0.031) while the release rate of CHDA decreased from 2.56 to 2.08 μg/cm^2 day (t test P value = 0.002), as shown in Table 2. All release studies exhibited an initial burst effect followed by a slow release.

3.2 Effect of drug loading on drug release

Figure 3 shows the CHDA release from polymer blends with 10% PEMA with increasing drug loads in water at 37°C.

Table 3 summarizes the data on the effect of loading of CHDA ranging from 1.0 to 7.5 wt% in polymer blends on the release rate of the drugs. The release rate increased as the drug load increased (overall and pair wise ANOVA, $P < 0.0001$).

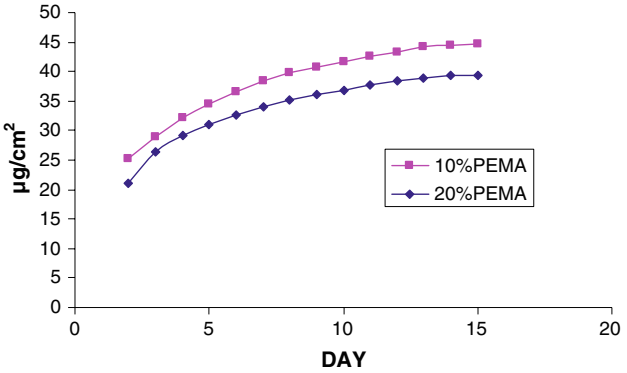

Fig. 1 Effect of blend composition on the release of ACY from polymer blend with 10 or 20% PEMA at 37°C

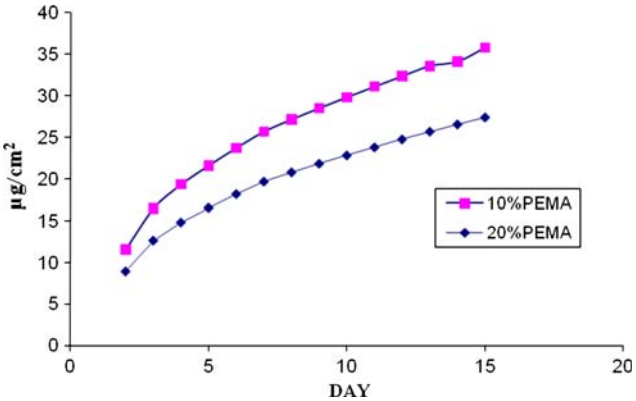

Fig. 2 Effect of blend composition on the release of CHDA from polymer blend with 10 or 20% PEMA at 37°C

Table 2 Release rate (standard deviation) of ACY and CHDA from polymer blends of different composition

	ACY (μg/cm^2 day)	CHDA (μg/cm^2 day)
10% PEMA	3.19 (0.19)	2.56 (0.02)
20% PEMA	2.82 (0.05)	2.08 (0.11)

3.3 Effect of surfactant on drug release

Table 4 shows the release rates of NYS alone and with surfactants in water at 37°C. The effect of surfactant content on NYS release was studied in water (Figs. 4, 5). Analysis of the data shows that the release rate of NYS alone is 0.62 μg/cm^2 day. Generally, addition of surfactants resulted in an increase in the release rate of NYS. The increase in surfactant content resulted in a 1.2–3.1 times higher NYS release rate with the addition of Tween (ANOVA, $P < 0.0001$) and a 2.1–3.0 times higher release rate with the

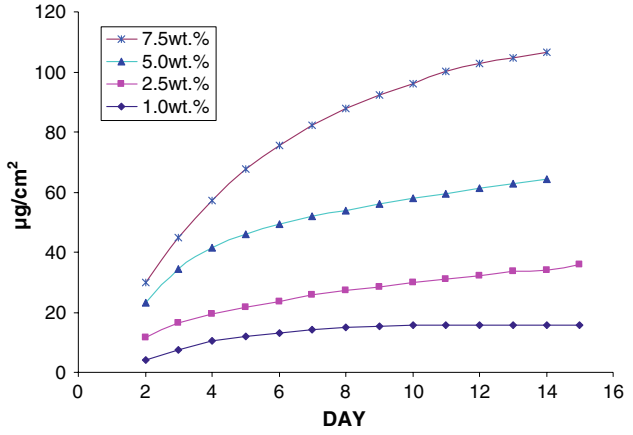

Fig. 3 Effect of drug load on the release of CHDA from polymer blend with 10% PEMA at 37°C

Table 3 Release rate (standard deviation) of CHDA with increase in drug load in water

Drug loading (wt%)	Rate of drug release in water (µg/cm^2 day)
1.0	1.19 (0.11)
2.5	2.56 (0.15)
5.0	4.96 (0.05)
7.5	8.19 (0.06)

Table 4 Release rate (standard deviation) of NYS and NYS with addition of surfactants in water

Drug with/without surfactant	Release rate in water (µg/cm^2 day)
NYS alone	0.62 (0.04)
NYS + Tween (1:1)	0.72 (0.07)
NYS + Tween (1:2)	1.52 (0.06)
NYS + Tween (1:3)	1.94 (0.04)
NYS + Cremophor (1:1)	1.31 (0.03)
NYS + Cremophor (1:2)	1.66 (0.03)
NYS + Cremophor (1:3)	1.83 (0.06)

addition of Cremophor (ANOVA, $P < 0.0001$). At comparable ratios, addition of Tween did not result in a significantly different release rate than addition of Cremophor for ratios of 1:2 and 1:3 after adjustment for multiple pairwise comparisons (P values $> 0.05/21 = 0.0024$), but Tween did result in a significantly lower rate than Cremophor for the 1:1 ratio (P value < 0.0001).

4 Discussion

The two polymers used, PEMA and PHMA, are thermodynamically miscible. Their solubility parameters are very close: 17.7 and 17.0 (MPa)$^{1/2}$, respectively [40]. That

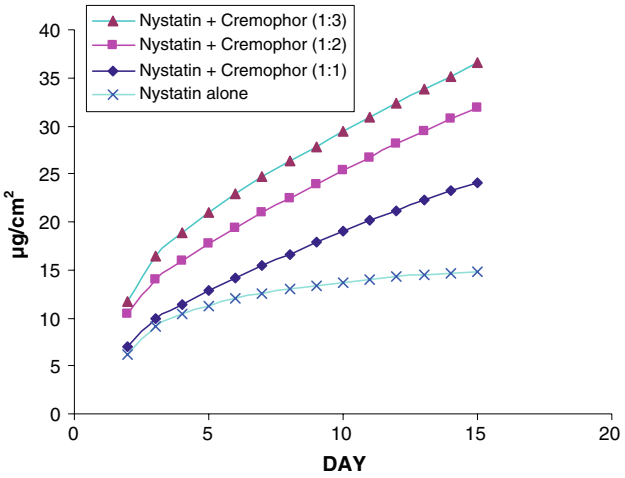

Fig. 4 Effect of increase in concentration of Cremophor on the release of NYS from polymer blend with 10% PEMA at 37°C

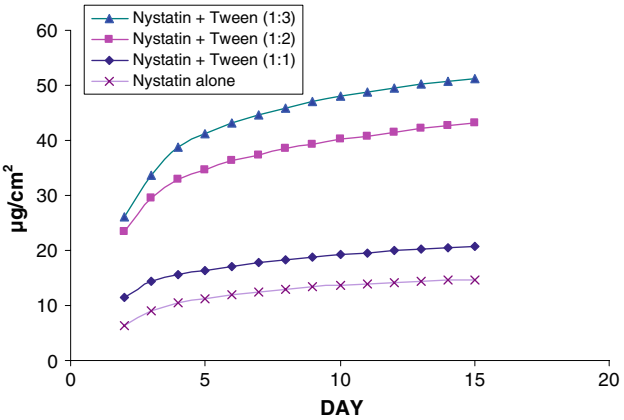

Fig. 5 Effect of increase in concentration of Tween on the release of NYS from polymer blend with 10% PEMA at 37°C

means that there are no phase separated regions (micro- or macro) and the polymers are "mutually soluble".

The 10 and 20% content of PEMA in polymer blends were chosen because this range was found to have optimal thermomechanical characteristics suitable for the preparation of drug-loaded films that can be potentially used as the form of mouth guard to deliver drugs in dentistry, which is one objective of this study. With higher PEMA content, polymer blends were unsuitably brittle and would not allow this kind of application. The glass transition temperature (T_g) of PEMA is 47–70°C and that of PHMA is −5°C [41].

4.1 Effect of polymer blend composition

The polymer blends of different compositions incorporated with CHDA and ACY have shown some interesting drug release profiles. It is known that an increase in overall rigidity of the polymer reduces the diffusivity of the

polymer [42]. As the content of PEMA decreases, the polymer blend becomes more rubbery and permeable. This permits an enhanced diffusion of drug molecules through the polymer matrix resulting in an increased drug release. Varying the composition of the polymer blend for drug delivery thus appears to offer an effective means of controlling the drug release rate.

4.2 Effect of drug loading

The significance of drug loading dose on drug release from polymer blend systems was investigated. The release rate of CHDA increased with increasing drug proportions in the polymer matrix as shown in Table 3. Increase in loading of the drug affecting the release kinetics has been reported earlier [43]. Water diffuses into the matrix through the dispersed phase to dissolve the drug upon contact. The drug particles, once dissolved, leave behind pores in the polymer matrix. The drug molecules can then diffuse out through the interconnecting pores [38, 43]. As the drug loading increases, the pores created by occupied drug molecules would be larger and/or greater in number and the release rate of the drug would be faster.

4.3 Effect of solubilizing agents on the rate of NYS release

The study showed very clearly that the addition of surfactant will increase the release rate of NYS.

When surfactant molecules are dissolved in water at concentrations above the critical micelle concentrations (CMC), they form aggregates known as micelles. The formation of micelles can increase the solubility of sparingly soluble substances in water. Release rate of NYS increased with addition of surfactants owing to the micellar formation by surfactants that solubilize the poorly soluble NYS in aqueous environments. Also, it is possible that the surfactant lowers the interfacial tension between the polymer matrix and the dissolution medium; hence it will increase the dispersability of the polymer matrix containing the drug and will also increase the release rate. Perhaps the surfactant acts as a wicking agent, causing the fluid to enter the matrix, the surfactant may then aid in dissolving the drug and forming channels from which the drug may be released [25, 28].

As the concentration of surfactant was increased, the release rate of NYS increased. This may be explained due to the increase of micelle numbers, as a result of the increased surfactant proportion. The increase in micelle numbers enhances the solubilization of the drug. We also speculate that increasing amounts of surfactants in the polymer blend system together with the drug increase the porosity facilitating the enhanced diffusion of drug molecules through the channels present in the matrix (polymer blend matrix), leading to an increase in the rate of drug release.

5 Conclusions

Polymer blends of poly(ethyl methacrylate) and poly (*n*-hexyl methacrylate) of different compositions incorporated with CHDA, NYS and ACY were prepared. In vitro rate measurements showed sustained release rates over extended periods of time. Blend composition has a significant influence on the release rates of CHDA and ACY. Drug release rate decreases with increase in PEMA content. Also the increase in drug concentration in polymer blend was studied. Drug release rates increased steadily with increase in drug load. The release rate of NYS in water increased with the addition of surfactants. Furthermore, increasing surfactant concentrations resulted in increased drug release rates. Thus, the release rates of drugs from the polymer blends can be altered by varying the blend composition, by changing the drug concentration and by the addition of surfactants.

Acknowledgements This work was supported by NIH-NIDCR Grant R01 DE 15267. The authors wish to thank Dr. Anton Schindler, Principal Scientist, Research Triangle Institute, Research Triangle Park, North Carolina, USA, for his valuable suggestions. We also thank Dr. John S. Preisser, Associate Professor, Department of Biostatistics, University of North Carolina, Chapel Hill for his help with the statistical analysis.

References

1. Ahrends J, Ruben J. Fluoride release from a composite resin. Quintessence Int. 1988;9:513–4.
2. Behrend B, Geurtsen W. Long-term effects of four extraction media on the fluoride release from our polyacid-modified composite resins (compomer) and one resin-modified glass-ionomer cement. J Biomed Mater Res. 2001;58:631–7.
3. Rothwell M, Anstice HM, Pearson GJ. The uptake and release of fluoride by ion-leaching cements after exposure to toothpaste. J Dent. 1998;26:591–7.
4. Patel MP, Pearson GJ, Braden M, Mirza MA. Fluoride ion release from two methacrylate polymer systems. Biomater. 1998;19: 1911–7.
5. Addy M, Handley R. The effects of the incorporation of chlorhexidine acetate on some physical properties of polymerized and plasticized acrylics. J Oral Rehabil. 1981;8:155–63.
6. Wilson SJ, Wilson HJ. The release of chlorhexidine from modified dental acrylic resin. J Oral Rehabil. 1993;20:311–9.
7. Lee DY, Spangberg LSW, Bok YB, Lee CY, Lee KY. The sustaining effect of three polymers on the release of chlorhexidine from a controlled release drug device for root canal disinfection. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100:105–11.
8. Yue IC, Poff J, Cortes ME. A novel polymeric chlorhexidine delivery device for the treatment of periodontal disease. Biomater. 2004;25:3743–50.

9. Patel MP, Braden M, Downer S. Heterocyclic methacrylate based drug release polymer system. J Mater Sci: Mater Med. 1994;5: 793–7.
10. Parker S, Patel MP, Tibald J, Braden M. Two methacrylate based materials for intra-oral drug delivery. Plast Rubber Compos Process Appl. 1997;26:298–302.
11. Patel MP, Cruchley AT, Coleman DC, Swai H, Braden M, Williams DM. A polymeric system for the intra-oral delivery of an anti-fungal agent. Biomater. 2001;22:2319–24.
12. Sipos TT, Lebanon NJ. Intra-oral device containing 2-hydroxyethyl methacrylate-methyl methacrylate copolymer for slow medicament release. European Patent No. 569797, 861993.
13. Nerurkar MJ, Zenter GM, Rytting JH. Effect of chloride on the release of chlorhexidine salts from methyl methacrylate-2-hydroxyethyl methacrylate copolymer reservoir devices. J Control Rel. 1995;33:357–63.
14. Leung D, Spratt DA, Pratten J, Gulabivala K, Mordan NJ, Young AM. Chlorhexidine-releasing methacrylate dental composite materials. Biomater. 2005;26:7145–53.
15. Veleva AN, Khan SA, Cooper SL. Oxidative and hydrolytic stability of a novel terpolymer for biomedical applications. J Biomed Mater Res. 2005;74A:117–23.
16. Fussell GW, Cooper SL. Synthesis and characterization of acrylic terpolymers with RGD peptides for biomedical applications. Biomater. 2004;25:2971–8.
17. Udipi K, Cheng P, Chen M, Lyu SP. Biocompatible controlled released coatings for medical devices and related methods. US Patent No. 2005084515, 2005.
18. Mir GN, Lawrence WH, Autian J. Toxicology and pharmacological actions of methacrylate monomers. I. Effects on isolated, perfused rabbit heart. J Pharm Sci. 1973;62:778–82.
19. Reynolds J. Martindale the extra pharmacopoeia. 28th ed. London: The Pharmaceutical Press; 1982. p. 729.
20. Rangel-Yagui CO, Pessoa A Jr, Tavares LC. Micellar solubilization of drugs. J Pharm Pharm Sci. 2005;8:147–63.
21. Lawrence MJ. Surfactant systems: their use in drug delivery. Chem Soc Rev. 1994;23:417–24.
22. Attwood D, Florence AT. Surfactant systems: their chemistry, pharmacy and biology. London: Chapman and Hall; 1983.
23. Florence AT. Drug solubilization in surfactant systems. In: Yalkowsky SH, editor. Techniques of solubilization of drugs. New York: Marcel Dekker Inc.; 1981.
24. Andersen T, Gram-Hansen M, Pedersen M, Rassing MR. Chewing gum as a drug delivery system for nystatin influence of solubilising agents upon the release of water insoluble drugs. Drug Dev Ind Pharm. 1990;16:1985–94.
25. Padmavathy T, Randall MK, Khin LT, Preisser JS, Kalachandra S. Effects of solubilizing surfactants and loading of antiviral antimicrobial, and antifungal drugs on their release rates from ethylene vinyl acetate copolymer. Dent Mater. 2007;23:977–82.
26. Hanaee J, Javadzadeh Y, Taftachi S, Farid D, Nokhodchi A. The role of various surfactants on the release of salbutamol from suppositories. IL Farmaco. 2004;59:903–6.
27. Buckton G, Efentakis M, Al-Hmoud H, Rajan Z. The influence of surfactants on drug release from acrylic matrices. Int J Pharm. 1991;74:169–74.
28. Efentakis M, Al-Hmoud H, Buckton G, Rajan Z. The influence of surfactants on drug release from a hydrophobic matrix. Int J Pharm. 1991;70:153–8.
29. Schott H, Chong KL, Feldman S. The role of surfactants in the release of very slightly soluble drugs from tablets. J Pharm Sci. 1982;71:1038–45.
30. Pitt C, Cha Y, Shah S, Zhu K. Blends of PVA and PGLA: control of the permeability and degradability of hydrogels by blending. J Control Rel. 1992;19:189–99.
31. Park T, Cohen S, Langer R. Poly(L-lactic acid)/pluronic blends: characterization of phase separation behavior degradation, and morphology and use as protein-releasing matrixes. Macromolecules. 1992;25:116–22.
32. Edlund U, Albertsson A-C. Microspheres from poly(D, L-lactide)/poly(1, 5-dioxepan-2-one) miscible blends for controlled drug delivery. J Bioactive Compatible Polym. 2000;15:214–29.
33. Lecomte F, Siepmann J, Walther M, Macrae R, Bodmeier R. Blends of enteric and GIT-insoluble polymers used for film coating: physicochemical characterization and drug release patterns. J Control Rel. 2003;89:457–71.
34. Mi F, Shyu S, Lin Y, Wu Y, Peng C, Tsai Y. Chitin/PLGA blend microspheres as a biodegradable drug delivery system: a new delivery system for protein. Biomater. 2003;24:5023–36.
35. Kenawy E, Bowlin G, Mansfiel K, Layman J, Simpson D, Sanders E, et al. Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid) and a blend. J Control Rel. 2002;81:57–64.
36. Shen Y, Sun W, Zhu K, Shen Z. Regulation of biodegradability and drug release behavior of aliphatic polyesters by blending. J Biomed Mater Res. 2000;50:528–35.
37. Thomas P, Padmaja T, Kulkarni M. Polyanhydride blend microspheres: novel carriers for the controlled release of macromolecular drugs. J Control Rel. 1997;43:273–81.
38. Lin DM, Kalachandra S, Valiyaparambil J, Offenbacher S. A polymeric device for delivery of anti-microbial and anti-fungal drugs in the oral environment: effect of temperature and medium on the rate of drug release. Dent Mater. 2003;19:589–96.
39. Padmavathy T, Alimohammadi N, Kalachandra S. Poly(ethylene-co-vinyl acetate) copolymer matrix for delivery of chlorhexidine and acyclovir drugs for use in the oral environment: effect of drug combination copolymer composition and coating on the drug release rate. Dent Mater. 2007;23:404–9.
40. Bicerano J. Prediction of polymer properties. New York: Marcel Dekker, Inc; 1993.
41. Brandrup J, Immergut EH. Polymer handbook. 3rd ed. New York: Wiley; 1989.
42. Donbrow M, Friedman M. Enhancement of permeability of ethyl cellulose films for drug penetration. J Pharm Pharmacol. 1975;27:633–46.
43. Hsu TTP, Langer R. Polymers for the controlled release of macromolecules: effect of molecular weight of ethylene-vinyl acetate copolymer. J Biomed Mater Res. 1985;19:445–60.