Celanese
The chemistry inside innovation™

POTENTIAL USE OF ETHYLENE VINYL ACETATE COPOLYMER EXCIPIENT IN ORAL CONTROLLED RELEASE APPLICATIONS: A LITERATURE REVIEW

BIN ZHANG, SENIOR CHEMIST
CELANESE, INC., IRVING, TX, 75039, USA

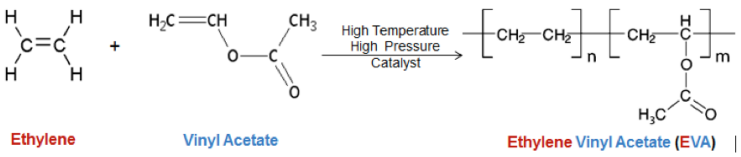
ABSTRACT

Ethylene vinyl acetate copolymer (EVA) has a successful commercial history in the pharmaceutical industry as a controlled release excipient. The usage covers a wide spectrum of parenteral applications ranging from transdermal drug delivery, contraceptive insertions, subcutaneous implants and mucosal contact forms. The importance and prominence of EVA in parenteral applications has inspired researchers to study EVA-based controlled release systems in other areas. This paper summarizes the recent developments of EVA-based oral controlled release drug delivery systems. In these studies, the EVA-based drug delivery systems were mostly prepared by hot melt extrusion (HME). The results have showed that the in vitro/in vivo drug release profiles of EVA-based systems can be readily tuned to be suitable for oral administration with the addition of a secondary functional component. The biocompatibility and oral toxicity studies on EVA are also summarized. Results in Simulator of the Human Intestinal Microbial Ecosystem (SHIME) evaluation indicate that EVA does not enzymatically or chemically interact with the simulated intestinal fluid. EVA-based systems have shown great potential in controlled release of drugs for oral administration.

INTRODUCTION

ETHYLENE VINYL ACETATE COPOLYMER

Ethylene vinyl acetate (EVA) is a copolymer of ethylene monomer and vinyl acetate (VA) monomer, as illustrated in Scheme 1. The polymer is made by free radical polymerization under high pressure conditions.



Scheme 1. Reaction scheme of ethylene vinyl acetate copolymer polymerization

EVAs are commonly available up to 40% vinyl acetate (VA). Since the reactivity ratio between ethylene and VA is close to 1, VA monomers are almost randomly distributed on the polymer backbone [1]. VA monomers distributed across the backbone impact the polymer's melting point, percentage of crystallinity, and optical properties. The stiffness and hardness of the polymer decrease as crystallinity decreases. The addition of the VA monomer also increases the polarity of the polyethylene backbone and thus affects the solubility/diffusivity of small molecules within EVA and compatibility of EVA with other polymers. These property variations can be used to influence the drug release properties in pharmaceutical applications where EVA is used.

USE OF EVA IN PARENTERAL CONTROLLED RELEASE DRUG DELIVERY SYSTEM

EVA has a long and successful history in the pharmaceutical industry. It not only has been widely used in parenteral drug delivery systems as an excipient for R&D purposes but also has numerous successes in commercial products. Selected commercial parenteral drug delivery products using EVA are listed in Table 1 [2]. EVAs have successfully enabled the controlled release of parenteral active pharmaceutical ingredients (APIs) in intravaginal rings/intrauterine devices [3-7], subcutaneous implants [8-12], ocular implants [13-17], dental products [18-22] and biological deliveries [23-27]. In these applications, EVA serves as an excipient where APIs are dissolved and/or dispersed and the release rate is controlled by diffusion. It is also widely reported that EVA has been used in transdermal drug delivery as a rate-controlling membrane, as well as other functional components [28-32]. These applications of EVA in drug delivery systems have been comprehensively reviewed in a previous white paper by Celanese [2].

Table 1. Commercial parenteral drug delivery products using EVA [2]

Trade Name	Manufacturer	Active Ingredient	Indication/Application
Ocusert	Alza	Pilocarpine	Glaucoma
Progestesert	Alza	Progesterone	Intrauterine device
Implanon®	Merck	Etonogestrel	Contraceptive implant
NuvaRing®	Merck	Etonogestrel/Ethinylestradiol	Contraceptive intravaginal ring
Actisite®	Alza/J & J	Tetracycline	Periodontitis
Cypher®	Cordis/J&J	Sirolimus	Vascular restenosis
Vitrasert®	Bausch & Lomb	Gancyclovir	CMV retinitis
Bravo™ Matrix	Surmodics	Varies	Stent coatings; intravitreal implants

Table 1. Commercial parenteral drug delivery products using EVA [2]

HOT MELT EXTRUSION

Hot melt extrusion (HME) is one of the most widely used processing technologies for the use of EVA in the pharmaceutical industry [33-36]. There are other processing technologies such as coacervation and spray drying, however HME has been reported the most in the literature. The rapid growth of HME in recent pharmaceutical development has been seen and well-reviewed by the industry [33, 37-41]. In the HME process, an extruder is used to process a formulated polymer-containing mixture including binders, excipients, APIs, processing aids and other components in the molten state of the polymer. The extrudates then are obtained after the die by using a series of downstream processing equipment such as a conveyor belt, a cooling water bath, a pelletizer, or a calender. In the absence of solvent, HME offers a robust continuous process that enables high API loading, a fast processing rate, great homogeneity, and solid-in-solid dispersion. In the process, all the materials will experience heat and shear. Low temperature processing in HME is usually preferred in pharmaceutical manufacturing due to concern about the thermal and shear stability of the formulation ingredients, most significantly the APIs.

EVA IN ORAL DRUG DELIVERY

The successful applications of EVA in parenteral systems have triggered studies in other drug delivery areas. Oral administration is one of the most important drug delivery routes, and EVA has received significant attention in this area [33, 34, 42-45].

The use of polymers for oral drug delivery has been long adapted by the pharmaceutical industry on both academia level and commercial level [41, 46, 47]. It is well known that the human gastrointestinal system is extremely complex and presents challenges to oral administration, such as a harsh chemical environment (pH ~2 in the stomach to close to neutral in the ileum or colon) and an enzymatic burden. Many polymers have been successfully introduced to oral formulations to help provide different functions with controlled release being one of them. The current research of EVA oral drug delivery has been focused on the controlled release of water soluble APIs with low pharmacological potency, relatively short biological half-life and good thermal stability. Examples are metoprolol tartrate (MPT) and diltiazem hydrochloride (DTZ) [33, 34, 42-45].

STABILITY AND PROCESSABILITY OF EVA

In some early studies using EVA with drugs targeting oral administration reported by Follonier and coworkers, a series of common controlled release polymers were compared

with a 40 wt% EVA [42]. Formulations were prepared by HME. Because of the potential for high temperature exposure during HME, the thermal stability of each polymer was first evaluated by thermogravimetric analysis (Table 2). EVA showed better thermal stability than the other polymer excipients as indicated by the decomposition temperatures. Further evaluation on the extrusion processibility of the same group of materials is listed in Table 3. It is clear that the EVA sample used can be processed at a much lower temperature (80 oC) than all the other polymeric excipients. Plasticizers and a drying step were not needed to process EVA while, they were required for all the other polymers for the reported extrusion process. The combination of a high decomposition temperature, a low processing temperature, and ease of processing offers EVA a wide processing window, great processing flexibility, and simplified processing. A study on the long term storage stability and treatment stability of the same EVA system indicated that the EVA-based system is robust during processing and storage. Table 4 shows the calculated percentage of VA of the reported EVA after the treatment of grinding, extrusion, and storage. The results indicated that after a sequential of grinding, extrusion, and 2-year storage there was no evidence of significant thermal stability issues or compositional changes on the EVA samples [42].

Table 2. Thermogravimetric analysis of the reported controlled release polymeric excipients [42]

Polymer	Onset dec. temp. (°C)	% Weight loss at 200 °C	Discoloration
Ethyl cellulose (EC)	190	2.1	Browning from 205 °C
Hydroxyl propyl methylcellulose	185	3.0	Yellowing from 190 °C
Cellulose acetate butyrate (CAB)	230	-	Browning from 230 °C
Poly(vinyl chloride)	210	-	Browning from 170 °C
Poly(vinyl chloride-co-vinyl acetate)	220	-	Browning from 160 °C
EVA (EVA with 40 wt% VA)	300	-	Yellowing from 300 °C
Poly(ethyl acrylate/methyl methacrylate/trimethyl ammonio ethyl methacrylate chloride)	185	0.7	Yellowing from 200 °C

Table 2. Thermogravimetric analysis of the reported controlled release polymeric excipients [42]

Table 3. Extrusion parameters of the reported controlled release polymeric excipients [42]

Polymer	Plasticizer	Plasticizer wt%	Initial drying	Extrusion temp (°C)	Plasticization time (min)
Ethyl cellulose (EC)	Diethyl phthalate	5	2 h at 80 °C	120	10
Cellulose acetate butyrate (CAB)	Triacetin	5	2 h at 80 °C	160	5
Hydroxyl propyl methylcellulose	PEG 400	3-10	12 h at 80 °C	140-180	5-15
Poly(vinyl chloride)	Dioctyl phthalate	10	2 h at 80 °C	150	5
Poly(vinyl chloride-co-vinyl acetate)	Diethyl phthalate	10	2 h at 80 °C	110-120	5
EVA (EVA with 40 wt% VA)	-	-		80	10
Poly(ethyl acrylate/methyl methacrylate/trimethyl ammonio ethyl methacrylate chloride)	Triacetin	5	2 h at 80 °C	110	5

Table 3. Extrusion parameters of the reported controlled release polymeric excipients [42]

Table 4. Percentage of weight loss and VA content of the reported EVA samples after various treatments [42]

Treatment			Calculated wt% Vinyl acetate
Grinding	Extrusion	2-year storage	
-	-	-	39.6
+	-	-	40.6
+	+	-	39.9
+	+	+	39.3

Table 4. Percentage of weight loss and VA content of the reported EVA samples after various treatments [42]

CONTRIBUTING FACTORS OF EVA DRUG RELEASE PROFILE

The in vitro drug release profile of the EVA-based system in comparison with selected polymeric excipients is shown in Figure 1 [42]. Diltiazem hydrochloride was the studied API. Under the same API to polymer ratio, the EVA-based system exhibited a significantly lower cumulative drug release than the ethyl cellulose (EC) and the poly(ethyl acrylate) derivative systems. In the time span of the first 8 h, the total percentage of released drug from the EVA system was about 20 wt% in a pH 7.0 phosphate buffer at 37 oC. This slow release characteristic with low total drug released illustrates the potential of a controlled release system with very high drug loading [42]. Further studies have suggested that the EVA drug release profile can be influenced by many other EVA properties and can be tuned by modifications.

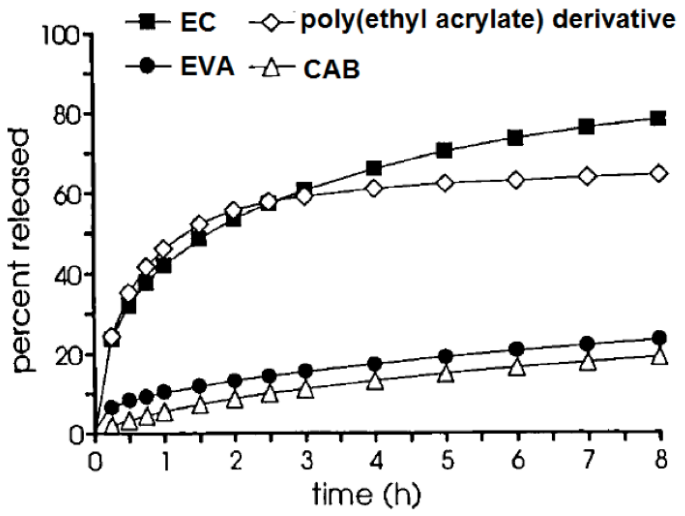


Figure 1. Release profiles of diltiazem hydrochloride from extruded pellets based on various polymers (polymer/drug ratio 1:1, size 2x2 mm) [42]

There are many other factors affecting the drug release properties for EVA-based oral controlled release system. In a separate study by Almeida and coworkers [34], it was found that the VA content of the polymer, the drug loading, and the processing temperature can significantly affect the in vitro drug release behavior. Figures 2, 3, and 4 showed the results of cumulative drug release properties of the reported EVA/ metoprolol tartrate (MPT) system with the stated variables in demineralized water at 37 oC [34]. When an EVA sample with 15 wt% VA (EVA15) was used, a cumulative drug release >80 % was obtained within the first 12 h. This was more than double the total drug release obtained from EVA 40.

As shown in Figure 3, increasing the drug loading increased the cumulative drug release. In the EVA40/MPT system, a significant total drug release increase was observed at a drug loading of 50 wt% over lower drug loadings [34]. With an extra 10% drug loading (from 40 wt% (x) to 50 wt% (■) in Figure 3), the cumulative dry release increased from 20 % to 40 % in the first 12h. Similar results on the drug loading also have been reported on an EVA/DTZ system [43].

In this specific study, the processing temperature was also identified as an important factor. A low processing temperature had shown negative impact on the release properties (Figure 4). The total drug release increased from about 25% to about 40% as the processing temperature increased from 60 oC to 80 oC. This reported processing temperature dependency may be due to the influence of processing temperature on the drug crystallinity in the EVA matrix. The percentages of crystallinity of MPT in the EVA/ MPT extrudates were found to decrease with the increase of processing temperature based on the reported DSC data [34]. Other contributing factors such as pellet size and porosity have also been reported.

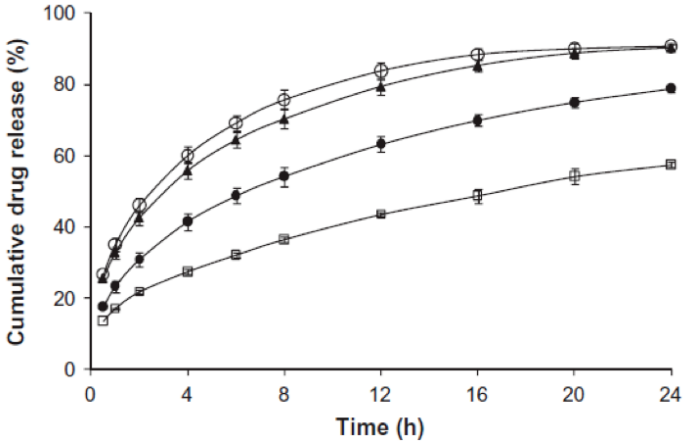


Figure 2. Cumulative drug release of MPT from EVA40 (□), EVA28 (□), EVA15 (□), and EVA9 (□) matrices (EVA/MPT, w/w, 50/50) [34]

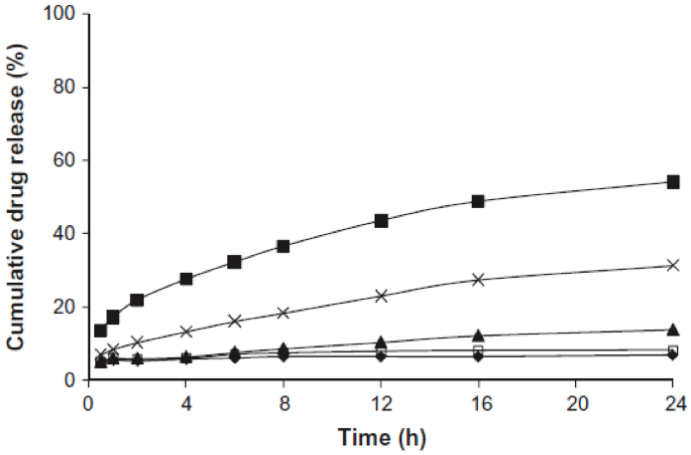


Figure 3. Cumulative drug release of MPT from EVA40/MPT matrices containing different drug loadings: 10 wt% (□), 20 wt% (□), 30 wt% (□), 40 wt% (x) and 50 wt% (□) [34]

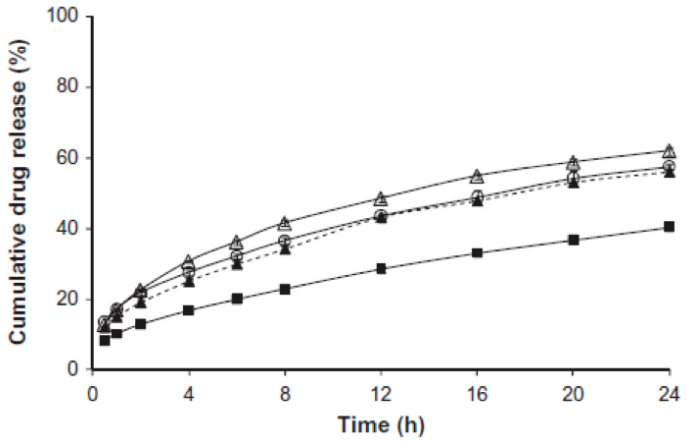


Figure 4. Cumulative drug release of MPT from EVA40/MPT matrices (50/50, w/w) processed at 60 oC (□), 80 oC (□), 90 oC (□), and 100 oC (Δ) [34]

MODIFICATIONS OF EVA FOR DRUG RELEASE PROFILE TUNING

An important way to tune the drug release profile is to modify the EVA/drug systems with additional components. The results here are based on the work of several research groups, and illustrate the manipulation of the EVA drug release profile of water soluble APIs by using additives [42-45].

It was reported in a later publication by Follonier and coworkers that the addition of non-ionic hydrophilic polymers can significantly accelerate the drug release [43]. Polyvinylpyrrolidone (PVP) and polyvinyl alcohol (PVOH) are shown as two examples in the non-ionic hydrophilic polymer category. In Figure 5, PVP and PVOH were used at a loading of 20 wt%. From a baseline ~20 % (EVA with no additives), both PVP and PVOH enhanced the drug release of the EVA-based system to about 60 % and 90 % respectively in 12h at a pH of 7.0 for the EVA/MPT system. The difference in the enhancement was attributed to the difference in the hydration power of the additives. Similarly, other non-ionic hydrophilic polymers have also been reported to have the same acceleration effect. These polymers include polyethylene oxide, cellulose acetate phthalate, and hydroxylpropylmethylcellulose phthalate [43, 44].

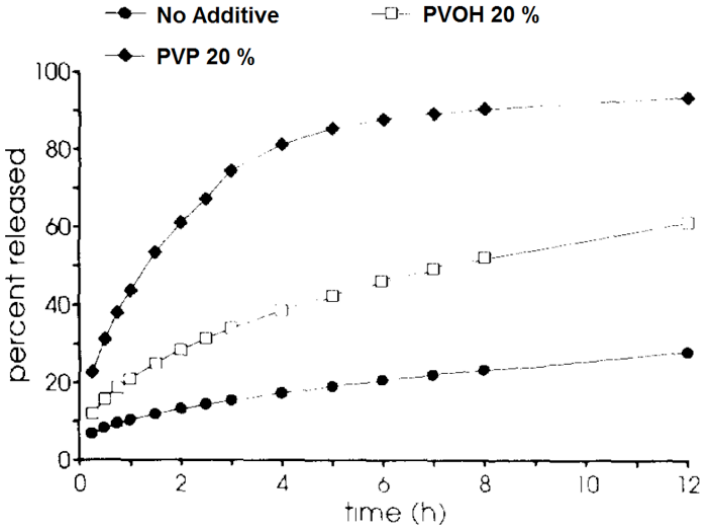


Figure 5. Release profiles of diltiazem hydrochloride from EVA-based pellets with non-ionic hydrophilic polymer additives at pH 7.0 [43]

When ionic hydrophilic polymers were added to the EVA-based drug release system, both a significant increase in total drug release and a pH response occurred [43]. Figure 6 illustrates use of chitosan lactate and methoxyl pectin at a 20 wt% loading on the EVA/MPT system. The total drug release was clearly enhanced by the additives. Within the first 12 h, the cumulative drug release was about 90 % for the chitosan modified systems and 80 % for the pectin modified systems. For both additives, the release rate at pH 7.0 showed a smaller increase when compared with the increase at pH 1.0. This is due to the proposed mechanism that at pH 7.0, both additives presented a water-insoluble barrier layer on the surface and in the pores of the EVA matrix [43].

Some swelling agents were also studied as additives in EVA-based controlled release systems. In studies showed in Figure 7 [43], croscarmellose sodium, low-substituted hydroxylpropylcellulose (L-HPC), crospovidone, and sodium starch glycolate were evaluated. Without the initial burst effect, pronounced increase in drug release rate was observed from all the swelling agent modified EVA/MPT systems. Among all the systems in Figure 7, the sodium starch glycolate modified system showed the highest total release of about 95 % within the first 12 h at a loading of 20 wt%. It was later reported that the swelling agent effect was still valid at a much lower concentration in an EVA-based microparticle system synthesized by a coacervation method [45]. Figure 8 shows the cumulative drug release of the EVA microparticle system modified by 2.00 wt% of sodium starch glycolate in the simulated gastric fluid and the intestinal fluids at different pH values.

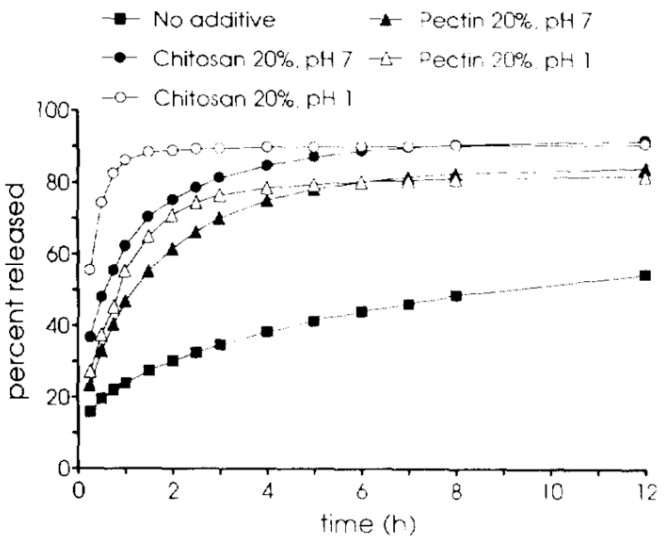


Figure 6. Release profiles of diltiazem hydrochloride from EVA-based pellets with cationic polymer additives at pH 1.0 and 7.0 [43]

Independent of the pH of the medium, the modified EVA system provided a very constant release rate and a total drug release of about 75 % in the span of 12 h. The drug release rate of this modified system was then compared with a commercial formulation (Cardizem® CD). The sodium starch glycolate-containing EVA system exhibited a controlled release rate with better consistency than the Cardizem® CD system in the in vitro study, as demonstrated in Figure 9 [45]. The in vivo study of the two systems in rabbits suggested that the modified EVA system showed equivalent drug plasma concentration to Cardizem® CD but with less subject variability indicated by smaller coefficient of variation. Similar equivalency in drug plasma concentration was reported in a PEO modified EVA/MPT drug delivery system when compared to the Slow-Lopressor® 200 Dvitabs® in the in vivo study in dogs [44].

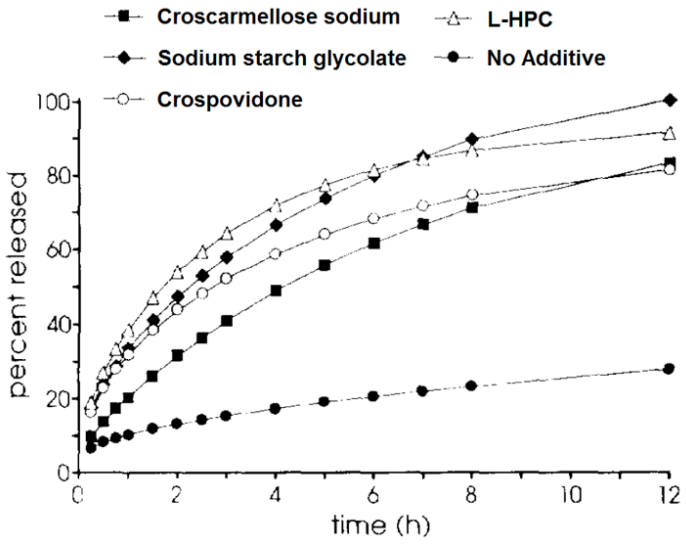


Figure 7. Release profiles of diltiazem hydrochloride from EVA-based pellets with swelling agents at pH 7.0 [43]

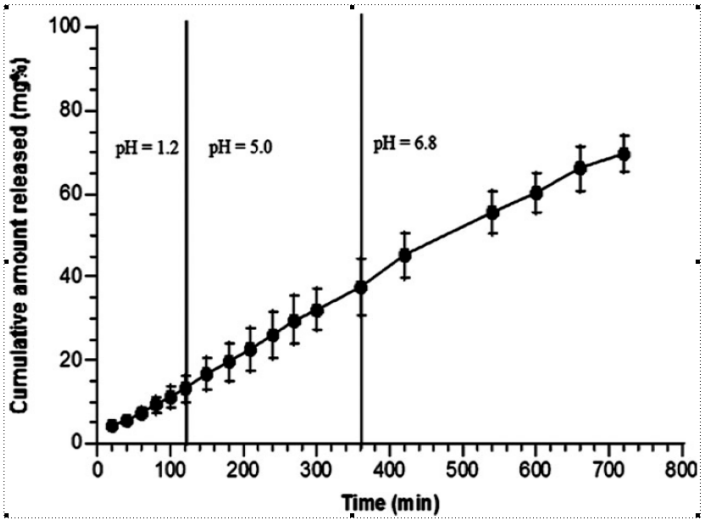


Figure 8. Cumulative amount of diltiazem HCl released (mean ± SD) from treated microparticles containing 2.00% w/w sodium starch glycolate into 900 mL simulated gastric fluid pH 1.2 (0–120 min), simulated intestinal fluid pH 5.0 (120–360 min) and simulated intestinal fluid pH 6.8 (360–720 min), at 37 oC and 100 rpm (n = 2) [45]

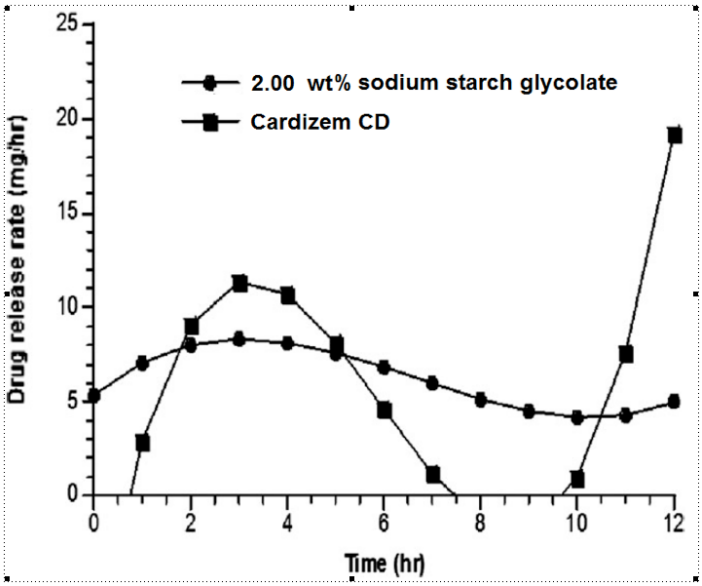


Figure 9. Diltiazem HCl release rates from the new controlled release formulation and Cardizem® CD into 900 mL water at 37 °C and 100 rpm [45]

ORAL TOXICITY OF EVA

As the parenteral pharmaceutical usage of EVA is well established, the toxicology study in the area has been well investigated. Biocompatibility data including cytotoxicity, sensitization, irritation, intracutaneous toxicity, acute systemic toxicity, implantation, and genotoxicity are readily available. EVA is also approved for FDA indirect contact and is on the FDA inactive ingredient list for approved non-oral drug products in many categories [48, 49].

The oral toxicity of EVA was evaluated by Simulator of the Human Intestinal Microbial Ecosystem (SHIME) by a group of

researchers [34]. Table 5 summarizes the results of the control group where no EVA was used and the treatment group, which was treated with 40 wt% VA EVA at the concentration of 2 g/L. The EVA samples after the treatment were characterized by DSC, X-ray diffraction, SEM, and Raman spectroscopy. No significant evidence was observed that EVA was enzymatically or chemically altered by the simulated GI tract fluids. Data in Table 5 also suggests that the simulated intestinal fluid was not significantly changed in composition by the EVA treatment.

Table 5. Results (pH, bacterial group, ammonium and fatty acid concentration) of the SHIME experiments after exposure of EVA40 to simulated intestinal fluid [34]

	Control	Treatment
Bacterial groups concentration [log (CFU ml^{-1})]		
Lactobacillus sp.	3.77 ± 0.22	3.53 ± 0.41
Clostridium sp.	7.11 ± 0.36	7.12 ± 0.12
Total aerobes*	7.74 ± 0.15	6.77 ± 0.24
Total anaerobes	7.95 ± 0.25	7.88 ± 0.07
Bifidobacterium	7.06 ± 0.27	6.84 ± 0.38
pH	6.45 ± 0.04	6.48 ± 0.08
Ammonium (mg NH_4^+ -H/L)	158.31 ± 7.46	162.98 ± 4.94
Fatty acids (mmol/l)		
Acetate	1.32 ± 0.09	1.27 ± 0.09
Proprionate	6.55 ± 0.21	6.62 ± 0.20
Butyrate	4.62 ± 0.83	5.05 ± 0.12
Total SCFA	15.60 ± 1.08	16.11 ± 0.04
BSCFA	3.11 ± 0.14	3.16 ± 0.04

Table 5. Results (pH, bacterial group, ammonium and fatty acid concentration) of the SHIME experiments after exposure of EVA40 to simulated intestinal fluid [34]

The EVA concentration was 2 g/L in the treatment group; no EVA was used in the control group.

** Indicated a significant difference between the control and the treatment group ($p < 0.01$, $a = 5\%$), with a mean difference of 9.46 CFU ml-1 for total aerobes.*

The oral toxicity of some EVA structural or compositional analogs such as polyvinyl acetate and vinyl acetate is also available from many sources [49, 50]. Table 6 shows the animal (rat and mouse) oral toxicity data of polyvinyl acetate which is a polymeric structural analog of EVA [49]. The data suggest that polyvinyl acetate presents a very low oral toxicity with LD50 > 25 mg/Kg.

Table 6. Oral toxicity of polyvinyl acetate [49]

Route/Organism	Dose
Oral, Mouse	Lethal dose: > 25 mg/Kg
Oral, Rat	Lethal dose: > 25 mg/Kg
Oral, Rat	LD50: > 25 mg/Kg

Table 6. Oral toxicity of polyvinyl acetate [49]

CONCLUSION

Ethylene vinyl acetate (EVA) copolymers have shown excellent stability, processability, and versatility in the controlled release of selected oral administrated drugs via hot melt extrusion (HME). For the drug systems discussed in this paper, desired release profiles can be achieved with proper modifications. Promising results have been reported in both in vitro drug release studies, as well as through in vivo studies in comparison with commercial drug products. EVA-based systems have shown great potential in controlled release of drugs for oral administration.

REFERENCES

1. Malpass DB. Introduction to Industrial Polyethylene: Properties, Catalysts, and Processes: John Wiley & Sons, Dec 17, 2010.
2. Applications of Ethylene Vinyl Acetate Copolymers (EVA) in Drug Delivery Systems. Celanese White Paper.
3. Kerns J and Darney P. Vaginal ring contraception Contraception 2011;83(2):107-115.
4. Ballagh SA. Vaginal ring hormone delivery systems in contraception and menopause Clin Obstet Gynecol 2001;44(1):106-113.
5. Novak A, de la Loge C, Abetz L, and van der Meulen EA. The combined contraceptive vaginal ring, NuvaRing: an international study of user acceptability Contraception 2003;67(3):187-194.
6. Roumen FJ and Dieben TO. Clinical acceptability of an ethylene-vinyl-acetate nonmedicated vaginal ring Contraception 1999;59(1):59-62.
7. Gokhale A, McConnell J, Loxley A, and Mitchnick M. Combination devices to protect women from sexual transmission of HIV Drug Delivery Technol. 2009;9(3):18-21.
8. Croxatto HB. Clinical profile of Implanon: a single-rod etonogestrel contraceptive implant Eur J Contracept Reprod Health Care 2000;5 Suppl 2:21-28.
9. Lesser GJ, Grossman SA, Leong KW, Lo H, and Eller S. In vitro and in vivo studies of subcutaneous hydromorphone implants designed for the treatment of cancer pain Pain 1996;65(2-3):265-272.
10. Costantini LC, Kleppner SR, McDonough J, Azar MR, and Patel R. Implantable technology for long-term delivery of nalmefene for treatment of alcoholism Int. J. Pharm. 2004;283(1-2):35-44.
11. Sabel BA, Dominiak P, Haeuser W, During MJ, and Freese A. Extended levodopa release from a subcutaneously implanted polymer matrix in rats Ann. Neurol. 1990;28(5):714-717.
12. Ling W, Casadonte P, Bigelow G, Kampman KM, Patkar A, Bailey GL, Rosenthal RN, and Beebe KL. Buprenorphine implants for treatment of opioid dependence. A randomized controlled trial JAMA, J. Am. Med. Assoc. 2010;304(14):1576-1583.
13. Bourges JL, Bloquel C, Thomas A, Froussart F, Bochot A, Azan F, Gurny R, BenEzra D, and Behar-Cohen F. Intraocular implants for extended drug delivery: Therapeutic applications Adv. Drug Delivery Rev. 2006;58(11):1182-1202.
14. Langer R, Brem H, and Tapper D. Biocompatibility of polymeric delivery systems for macromolecules J Biomed Mater Res 1981;15(2):267-277.
15. Pearson PA, Jaffe GJ, Martin DF, Cordahi GJ, Grossniklaus H, Schmeisser ET, and Ashton P. Evaluation of a delivery system providing long-term release of cyclosporine Arch. Ophthalmol. (Chicago) 1996;114(3):311-317.
16. Okabe K, Kimura H, Okabe J, Kato A, Kunou N, and Ogura Y. Intraocular tissue distribution of betamethasone after intrascleral administration using a non-biodegradable sustained drug delivery device Invest Ophthalmol Vis Sci 2003;44(6):2702-2707.
17. Beeley NRF, Stewart JM, Tano R, Lawin LR, Chappa RA, Qiu G, Anderson AB, de Juan E, and Varner SE. Development, implantation, in vivo elution, and retrieval of a biocompatible,

sustained release subretinal drug delivery system J. Biomed. Mater. Res., Part A 2006;76A(4):690-698.

18. Tonetti M, Cugini MA, and Goodson JM. Zero-order delivery with periodontal placement of tetracycline-loaded ethylene vinyl acetate fibers J. Periodontal Res. 1990;25(4):243-249.

19. Sanders EH, Kloefkorn R, Bowlin GL, Simpson DG, and Wnek GE. Two-Phase Electrospinning from a Single Electrified Jet: Microencapsulation of Aqueous Reservoirs in Poly(ethylene-co-vinyl acetate) Fibers Macromolecules 2003;36(11):3803-3805.

20. Kalachandra S, Lin D, and Offenbacher S. Controlled drug release for oral condition by a novel device based on ethylene-vinyl acetate (EVA) copolymer J. Mater. Sci. Mater. Med. 2002;13(1):53-58.

21. Kalachandra S, Takamata T, Lin DM, Snyder EA, and Webster-Cyriaque J. Stability and release of antiviral drugs from ethylene vinyl acetate (EVA) copolymer J. Mater. Sci. Mater. Med. 2006;17(12):1227-1236.

22. Tallury P, Randall MK, Thaw KL, Preisser JS, and 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(8):977-982.

23. Langer R and Folkman J. Polymers for the sustained release of proteins and other macromolecules Nature (London) 1976;263(5580):797-800.

24. Preis I and Langer RS. A single-step immunization by sustained antigen release J Immunol Methods 1979;28(1-2):193-197.

25. Creque HM, Langer R, and Folkman J. One month of sustained release of insulin from a polymer implant Diabetes 1980;29(1):37-40.

26. Rhine WD, Hsieh DST, and Langer R. Polymers for sustained macromolecule release: procedures to fabricate reproducible systems and control release kinetics J. Pharm. Sci. 1980;69(3):265-270.

27. Brown LR, Wei CL, and Langer R. In vivo and in vitro release of macromolecules from polymeric drug delivery systems J. Pharm. Sci. 1983;72(10):1181-1185.

28. Tiwary AK, Sapra B, and Jain S. Innovations in transdermal drug delivery: formulations and techniques Recent Pat. Drug Delivery Formulation 2007;1(1):23-36.

29. Aggarwal G and Dhawan S. Development, fabrication and evaluation of transdermal drug delivery system - a review Pharm. Rev. 2009;7(5):No pp given.

30. Cho C-W, Choi J-S, and Shin S-C. Controlled release of furosemide from the ethylene-vinyl acetate matrix Int. J. Pharm. 2005;299(1-2):127-133.

31. Shin S-C and Byun S-Y. Controlled release of ethinylestradiol from ethylene-vinyl acetate membrane Int. J. Pharm. 1996;137(1):95-102.

32. Cho C-W, Kim S-J, Yang K-H, Song J-H, Jeong H-J, and Shin S-C. Enhanced Controlled Release of Loratadine From the Ethylene-vinyl Acetate Matrix Containing Plasticizer Drug Delivery 2008;15(7):423-428.

33. Almeida A, Claeys B, Remon JP, and Vervaet C. Hot-melt extrusion developments in the pharmaceutical industry Hot-melt Extrusion 2012:43-69,, 41 plate.

34. Almeida A, Possemiers S, Boone MN, De Beer T, Quinten T, Van Hoorebeke L, Remon JP, and Vervaet C. Ethylene vinyl acetate as matrix for oral sustained release dosage forms produced via hot-melt extrusion Eur. J. Pharm. Biopharm. 2011;77(2):297-305.

35. Bhatnagar P, Dhote V, Mahajan Suresh C, Mishra Pradyumna K, and Mishra Dinesh K. Solid dispersion in pharmaceutical drug development: from basics to clinical applications Curr Drug

Deliv 2014;11(2):155-171.

36. DiNunzio JC. Hot-melt extrusion for drug delivery Abstracts of Papers, 244th ACS National Meeting & Exposition, Philadelphia, PA, United States, August 19-23, 2012 2012:MEDI-246.

37. Crowley Michael M, Zhang F, Repka Michael A, Thumma S, Upadhye Sampada B, Battu Sunil K, McGinity James W, and Martin C. Pharmaceutical applications of hot-melt extrusion: part I Drug Dev Ind Pharm 2007;33(9):909-926.

38. Repka Michael A, Battu Sunil K, Upadhye Sampada B, Thumma S, Crowley Michael M, Zhang F, Martin C, and McGinity James W. Pharmaceutical applications of hot-melt extrusion: Part II Drug Dev Ind Pharm 2007;33(10):1043-1057.

39. Kolhe SR, Chaudhari PD, and More DM. Recent advances in hot melt extrusion technology Int. J. Pharm. Sci. Res. 2012;3(12):4658-4669.

40. Maniruzzaman M, Boateng JS, Snowden MJ, and Douroumis D. A review of hot-melt extrusion: process technology to pharmaceutical products ISRN Pharm. 2012:436763, 436769 pp.

41. Lee Thomas WY, Boersen Nathan A, Hui HW, Chow SF, Wan KY, and Chow Albert HL. Delivery of poorly soluble compounds by amorphous solid dispersions Curr Pharm Des 2014;20(3):303-324.

42. Follonier N, Doelker E, and Cole ET. Evaluation of hot-melt extrusion as a new technique for the production of polymer-based pellets for sustained-release capsules containing high loadings of freely soluble drugs Drug Dev. Ind. Pharm. 1994;20(8):1323-1339.

43. Follonier N, Doelker E, and Cole ET. Various ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained-release pellets prepared using polymeric materials J. Controlled Release 1995;36(3):243-250.

44. Almeida A, Brabant L, Siepmann F, De Beer T, Bouquet W, Van Hoorebeke L, Siepmann J, Remon JP, and Vervaet C. Sustained release from hot-melt extruded matrices based on ethylene vinyl acetate and polyethylene oxide Eur. J. Pharm. Biopharm. 2012;82(3):526-533.

45. Al-Nimry SS, Alkhamis KA, Ibrahim HG, and Salem MS. Development and evaluation of a novel dosage form of diltiazem HCl using ethylene vinyl acetate copolymer and sodium starch glycolate (in vitro/in vivo study) J. Appl. Polym. Sci. 2013;127(5):4138-4149.

46. Siegel RA, Kost J, and Langer R. Mechanistic studies of macromolecular drug release from macroporous polymers. I. Experiments and preliminary theory concerning completeness of drug release J. Controlled Release 1989;8(3):223-236.

47. Siegel RA and Langer R. Mechanistic studies of macromolecular drug release from macroporous polymers. II. Models for the slow kinetics of drug release J. Controlled Release 1990;14(2):153-167.

48. 21 CFR. (2013) Code of Federal Regulations. Reg Nos. 175.105; 175.300; 176.180; 177.1200; 177.1210; 177.1350; 177.1390; 178.1005; 179.45.

49. RTECS. (2013). Polyvinyl acetate – CAS No. 9003-20-7. Registry of Toxic Effects of Chemical Substances.

50. Journal of the American College of Toxicology 1982-1993;1-12(11):465.

Celanese

The chemistry inside innovation™

Celanese EVA Polymers

celanese.com/eva-polymers
vitaldose.com

CELANESE EVA POLYMERS

222 W. Las Colinas Blvd.
Suite 900N
Irving, TX 75039

CUSTOMER SERVICE

t: 1-800-661-3663
e: orderseva@celanese.com

MANUFACTURING

Edmonton, Alberta Canada

TECHNOLOGY AND PRODUCT STEWARDSHIP

8040 Dixie Highway
Florence, KY 41042
t: 1-859-525-4740
e: eva.techservice@celanese.com

EVA-004_EVAinOralControlledRelease_WP_Global_EN_1214