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Controlled Release by Permeability Alteration of Cationic Ammonio Methacrylate Copolymers Using Ionic Interactions

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ABSTRACT A multiparticulate drug delivery system was studied in which the drug release of a model drug theophylline could be modulated by interactions of ammonio methacrylate polymer and anions. The system consisted of a EUDRAGIT® NE coated anionic core, layered with drug and further layered with EUDRAGIT® RS. The effects of different anions like chloride, succinate, citrate, and acetate as well as the thickness of the polymer layers on the in vitro drug release were studied. It was seen that succinate and acetate anions had permeability enhancing effects and citrate and chloride anions had permeability retarding effects on the polymer. The results indicate that changing these variables would enable us to get a desired release profile and hence the proposed system could be a viable alternative to existing technologies for the development of a controlled drug delivery system.

KEYWORDS Theophylline, Ionic interaction, EUDRAGIT® RS, Controlled drug release

INTRODUCTION

In the last decade, considerable attention has been focused on the development of novel drug delivery systems and among the various types of systems emerging, oral controlled-release systems hold a major market share because of their obvious advantages of ease of administration and better patient compliance (Verma et al., 2002). A number of design options are available for the preparation of controlled-release delivery systems, including polymer-based matrix systems, reservoir type systems, bilayered tablets and gastric retention systems (Chang & Hsiao, 1989; Gillian & Wan, 1991; Lee, 1992; Peppas, 1998; Narasimhan & Langer, 1997; Conte & Maggi, 2000; Peppas & Sahlin, 1989; Lee, 1985; Talukder & Fassihi, 2004) but the challenge lies in developing systems which would be flexible to enable drug delivery based on the therapeutic requirement, i.e., the kind of release desired – such as pulsed (Narisawa et al., 1994; Narisawa et al., 1996; Narisawa et al, 1995; Beckert et al., 1999; Petereit et al., 2000) quick slow (Maggi et al., 1997), zero order

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(Chidambaram et al. 1998) and accelerated release (Ravishankar & Renner, 2005).

Some of the marketed delivery systems available based on the above techniques are OROS® (Chandrasekaran et al., 1978; Verma et al, 2000), TIMERx® (Bryan, 2005), DIFFUCAPS (Youan, 2004), CONTIN® (Arkinstall, 1988), CODAS® (Smith et al., 2001). A flexible technology among them is the osmotic drug delivery system (OROS®) where the principle of osmotic pressure is used for the delivery of drugs, making it to a large extent independent of pH and other physiological parameters(Santus & Baker, 1995). Two compartments (Theeuwes, 1978), two-layer pull-push systems, (Costese & Theeuwes, 1982) and three-layer osmotic systems (Stephens & Wong, 1989) are some of the delivery devices based on this technology. However, these systems have a common disadvantage of a need for sophisticated production procedures (Lu et al., 2003) and hence development of novel drug delivery systems using conventional manufacturing processes is a subject of ongoing research in the industry.

The objective of this study was to develop a multi-unit drug delivery system based on the ionic interactions of ammonio methacrylate polymers and anions that would be flexible to be manipulated to give a desired release profile. The developed system, using theophylline as a model drug, consisted of pellets with a EUDRAGIT® NE coated inner core of anions in the form of a salt, layered with drug and further coated with EUDRAGIT® RS (Fig. 1). The manufacturing of the system, the influence of different anions and the effect of the polymer layers on the drug release profiles have been presented.

MATERIALS

Theophylline USP grade (Kores India Pvt Ltd, B. No. TAM/2003/224) was used as a model drug.

The following chemicals were obtained from commercial suppliers and used as received: sodium acetate, sodium chloride, tri-sodium citrate, sodium succinate (all of guaranteed reagent grade from Merck), Vivapur PH101 (microcrystalline cellulose, J. Rettenmaier & Sohne GmbH.+Co.), Kollidon 30 (polyvinyl pyrrolidone, BASF Corporation, USA), Aerosil-200 (colloidal silicon dioxide, Degussa AG, Germany), Imwitor 900 (glyceryl monostearate, SASOL, Germany GmbH), Tween 80 (polysorbate 80, Merck), talc (Luzenac, Italy), triethyl citrate (Morflex, Inc. USA), EUDRAGIT® NE30D (polyacrylate Dispertion 30 Per Cent EP, Roehm GmbH & Co. KG), EUDRAGIT® RS30D (ammonio methacrylate copolymer (EP- Type B), Roehm GmbH & Co. KG). Purified water BP was used for all practical purposes. Before use, the materials were stored at constant relative humidity (about 40–50%) and room temperature (22°C–25°C).

METHODS

Controlled-release pellets were prepared by multiple layering on salt cores. Figure 1 represents the

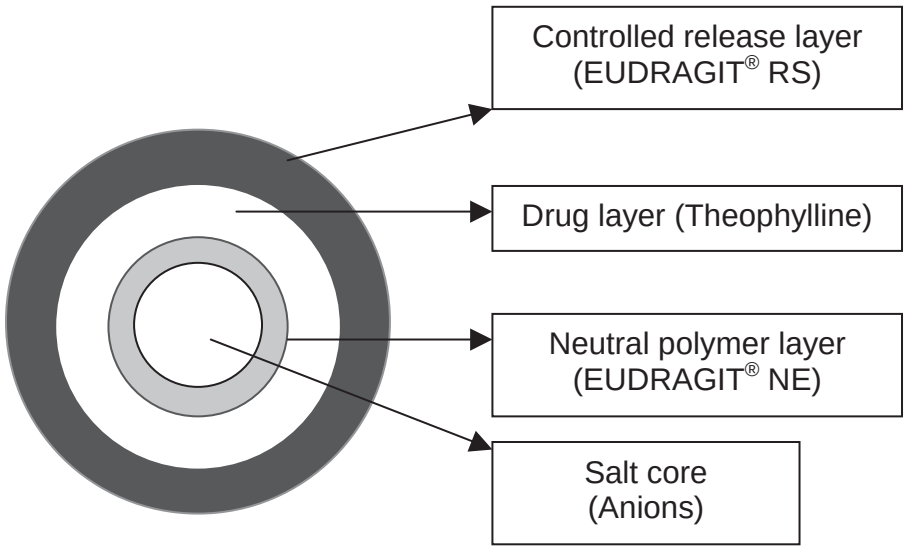

FIGURE 1 **Schematic Representation of Structure of the Pellets with the Proposed Technique.**

schematic structure of the pellet with the proposed technique. Different salts, sodium acetate, sodium chloride, tri-sodium citrate and sodium succinate were used. Trials were carried out using the model drug Theophylline (Solubility: 1 gm in 100 – 1000 mL of water (British Pharmacopoeia, 2002).

Preparation of Controlled-Release Pellets

Sizing of Salt Cores

Commercially available salts were milled (multimill at medium speed, Clit Multimill, Model – CPMMMM), sifted (vibratory sifter, Model- CPMVS-10") and the fractions between 425–850 μm (70% of the pellets in the size range of 600–850 μm) were taken for the coating trials.

Coating of Neutral Polymer (EUDRAGIT® NE) on the Salt Cores

The coating of the salt cores with EUDRAGIT® NE 30 D was done at a 20% (w/w) level. Table 1 describes the formulation details. Tween 80 at 2%w/w of polymer was used as plasticizer and glyceryl mono-stearate at 5%w/w of polymer was used as a glidant for optimum film formation (Petereit et al., 1995). The coating was done in a fluid bed processor (Gansons FBP, Model-GFBC-1- nozzle diameter 1.0 mm /schlick), using top spray. The processing parameters were as follows: atomizing air pressure 2.0 bar; inlet air temperature, 30–34°C; product temperature, 23–27°C; rate of solution spray, 3–5 g/min; air flow rate 50 m^3/h. After processing, the EUDRAGIT® NE coated cores were cured at 40°C for 2 h in a drying oven.

The cores were screened and a size fraction between 425–850 μm (70% of the pellets in the size range of 710 – 850 μm) was used for further processing (Fig. 2).

Theophylline Layering on the EUDRAGIT® NE Coated Cores

This process involved the deposition of successive layers of dry powder of theophylline along with the excipients on the EUDRAGIT® NE coated salt cores with the help of a binding solution (4% w/w solution of Kollidon 30 in water) in a conventional stainless-steel coating pan (Gansons Ltd, Model-CP-450 GMP).

TABLE 1 **Formulation Details for the Different Stages of Processing**

STAGE 1- Formula for EUDRAGIT® NE 30 D (20% w/w) coating on salt cores (500 g)			
Ingredients	Quantity	Solid content (g)	% w.r.t. dry polymer
EUDRAGIT® NE30 D	333 g	100	-
Tween 80	2 g	2	2.0
Imwitor 900 (GMS)	5 g	5	5.0
Purified water	373 g	-	-
Total	**713** g	**107**	-
STAGE 2- Formula (powder blend) for theophylline layering on EUDRAGIT® NE coated salt cores (500 g)			
Ingredients	Quantity	% in the blend	
Theophylline USP	945 g	94.92	
Aerosil 200	4.6 g	0.4	
Kollidon 30	46 g	4.0	
Binder solution (4%w/w Kollidon 30)	150 g	-	
STAGE 3- Formula for EUDRAGIT® RS 30 D (20% w/w) coating on theophylline layered pellets (500 g)			
Ingredients	Quantity	Solid content (g)	% w.r.t. dry polymer
EUDRAGIT® RS 30 D	333 g	100	-
Talc	50 g	50	50.0
Triethyl citrate	20 g	20	20.0
Purified water	447 g	-	-
Total	**850 g**	**170**	-

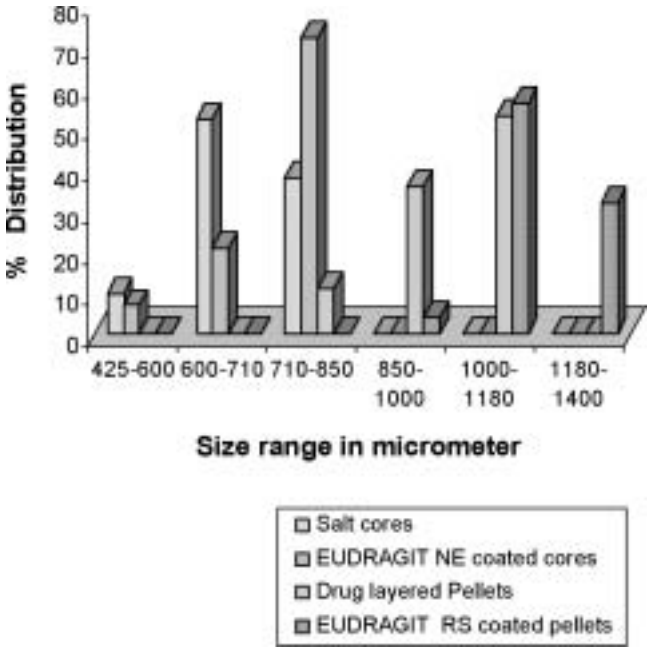

FIGURE 2 **Size Distribution of Pellets after Different Stages of Processing.**

Table 1 details the formula for a representative batch prepared. Cores were taken in the coating pan and intermittently treated with a nebulized binder solution applied by spray gun and uniformly dispersed drug powder blend. At the end of each cycle of wetting and powder application, the pellet bed was dried partially. The processing parameters were as follows: nozzle bore (coating gun), 1.00 mm; atomizing pressure, 1 bar; pan (18 in. diameter) speed, 26 rpm; spray rate, 0.4 g/min. The drug-loaded pellets obtained were dried at 40°C for 12 h in a drying oven.

The pellets were screened and pellets in the size fraction of 710–1180 μm (70% in the size range of 850–1180 μm) were used for further processing.

Coating of Controlled Release Polymer (EUDRAGIT® RS) on the Theophylline Layered Pellets

Theophylline layered pellets were coated with EUDRAGIT® RS30 D at different coating levels; 20%, 25% and 30% (w/w) level. Talc at 50%w/w of polymer and tri-ethyl citrate at 20%w/w of polymer were used as glidant and plasticizer, respectively (refer to Table 1). The coating was done in a fluid bed processor (Gansons FBP, Model- GFBC-1- nozzle diameter 1.0 mm/schlick), using top spray. The processing parameters were as follows: atomizing air pressure, 2.0 bar; inlet air temperature, 30–34°C; product temperature, 26–30°C; rate of solution spray, 6–8 g/min; air flow rate, 50 m^3/h. After processing, the EUDRAGIT® RS coated pellets were cured at 40°C for 24 h in a drying oven. About 1% Aerosil 200 was added to the coated pellets while curing, as the polymer film exhibit a tendency to agglomerate during curing.

Preparation of Controlled-Release Pellets Using Microcrystalline Cellulose as a Core

Microcrystalline cellulose cores were prepared in a rapid mixer granulator (Clit rapid mixer granulator-model-CPMRMG-10) using 10% Kollidon 30 solution as a binder. Granules in the size fraction of 425–850 μm (70% in the range of 600–710 μm) were used for further preparation of the pellets as described in the previous sections.

Scanning Electron Microscopy

The surface morphology and film thickness of the pellets were examined by scanning electron microscopy (SEM) (Phillips XL30, Courtesy: CIRCOT, Mumbai, India). Samples were gold-coated using sputter coater and examined at 10 kv with tilted edges of 45°. To evaluate the film thickness, pellets ($n = 3$) were radially sectioned before the sputter coating and the thickness was evaluated at 3 points (RSD $< 6\%$).

Theophylline Release Studies

In vitro dissolution tests were carried out in USP I Apparatus (Electrolab- model TDT-8L) at 37°C ($n = 6$) at a rotation speed, set at 100 rpm using 900 mL water as the medium. At each time point, 10 mL of solutions were withdrawn and the quantitation of sample solutions was done spectrophotometrically at a wavelength of 271 nm (Shimadzu 1601 spectrophotometer) against standard solutions of theophylline. The cumulative amounts of drug dissolved were plotted versus time as percent dissolved drug. The release studies for one of the formulations were also carried out in different media (with different ionic strengths) including solutions of sodium chloride, sodium succinate, sodium citrate and sodium acetate under the above conditions to correlate the effect of the anions.

RESULTS AND DISCUSSION

Manufacturing Process

A manufacturing procedure for the production of pellets using different salts was successfully developed. Near-spherical pellets with salts as cores could be obtained using conventional processes of aqueous coating in a fluid bed processor. There were no problems observed with the core generation and subsequent drug layering with Theophylline. The concentration of the cores (salts) in the pellet was around 19–22% (w/w) at a 20% (w/w) of EUDRAGIT® RS coating.

The yield obtained after EUDRAGIT® NE coating was 83 to 92%. The time required for processing a 500 g batch in the fluid bed processor was 4–5 h. The SEM of the cross section of the core revealing an uniform coating on the salt core is presented in Fig. 3a. The neutral EUDRAGIT® NE polymer layer at 20%w/w coating level gave a thickness of about 15–30 microns ($n = 9$ RSD $< 6\%$) which acted as an insoluble permeable membrane. This layer helps in the physical separation of the salt and drug layer. Sodium succinate crystals were found to be friable and had a tendency to break up during coating. Hence, care was exercised during the coating trials in the fluid bed processor.

The process of theophylline layering onto the EUDRAGIT® NE coated cores could be optimized by considering loading capacity to get near-spherical pellets (Fig. 3b) and the yield obtained during the process was 85 to 90%. The total time required for the processing was 2–3 h. The analyses of drug content on random samples were performed ($n = 6$, RSD $< 2\%$) before proceeding for the next step, i.e., EUDRAGIT® RS coating. Other alternative processes, which could be used for drug

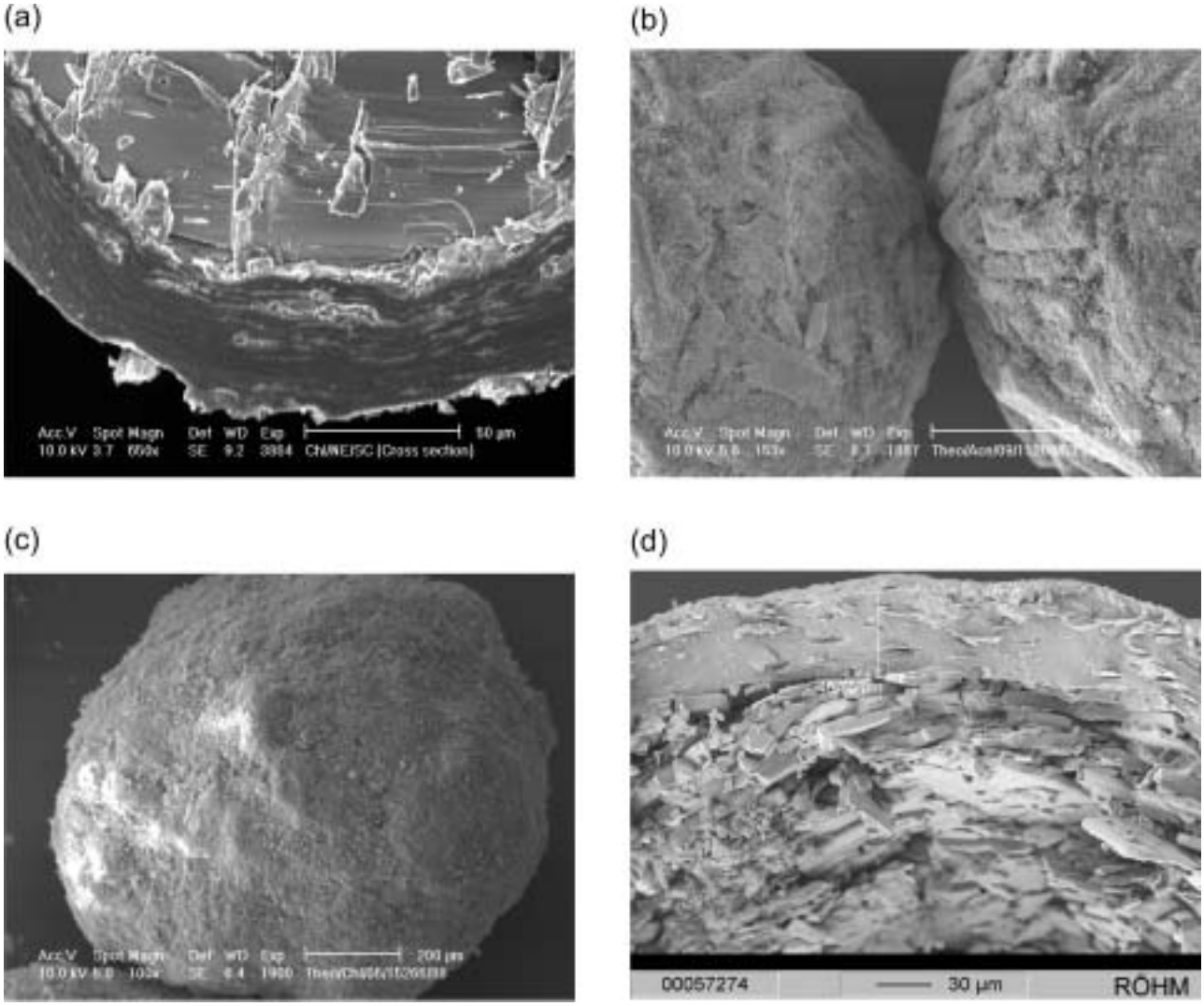

FIGURE 3 SEM Pictures of Pellets (a) Cross-Section of EUDRAGIT® NE Coated Salt Core (b) Theophylline Layered Pellet (c) EUDRAGIT® RS Coated Pellet (d) Cross-Section of EUDRAGIT® RS Coated Pellet.

layering are tangential spray using rotor technology for insoluble drugs and bottom spray for partially soluble or soluble drugs. Upon EUDRAGIT® RS coating of the pellets, a smooth outer surface without any crevices and a uniform polymer layer could be obtained (Fig. 3c and 3d). The pellets were in the size range of 1000–1400 µm. The yield of pellets obtained after EUDRAGIT® RS coating was 80 to 86%. The coating process was completed in 5–6 h. The size distribution of the pellets after the different stages of processing is given in Fig. 1.

Effect of Anions in the Dissolution Medium

Theophylline release from pellets prepared using sodium chloride cores were studied in dissolution media containing different anions; chloride, citrate, acetate and succinate. The effect of the ionic strengths of each of these salts on the drug release was also studied in order to compare their influence.

Figure 4 demonstrates the comparative effect of the anions (0.2 M solutions) on the drug release. The results revealed that the drug dissolution rate gets increased or decreased in the presence of these anions. Chloride and citrate ions decreased the release of the drug while acetate and succinate enhanced the drug release. The results are explained by the differences in the hydration effects of the anions. Chloride and citrate reduce the hydration of the film after interacting with the quaternary ammonium group of the EUDRAGIT® RS and thus lowers the release. The effect with succinate and acetate anions is the reverse of this and thus results in increased permeability of the film and a faster drug release (Bodmeier et al., 1996).

Figures 5a and 5b demonstrate the effect of different ionic concentrations on the drug release profiles ($T_{50\%}$). At a 0.01 M concentration of the ions in the dissolution medium, there is no significant permeability altering effect. This could be probably because of not enough concentration of the ions being available in the medium to affect an interaction with the cationic polymer. Increasing ionic strengths (0.05 M to 0.2 M) increased the drug release in case of media with succinate and acetate ions and decreased the drug release in case of media with citrate and chloride ions.

Effect of Anions in the Pellet Cores

When the anions were used as cores, the release of theophylline from the pellets was enhanced or

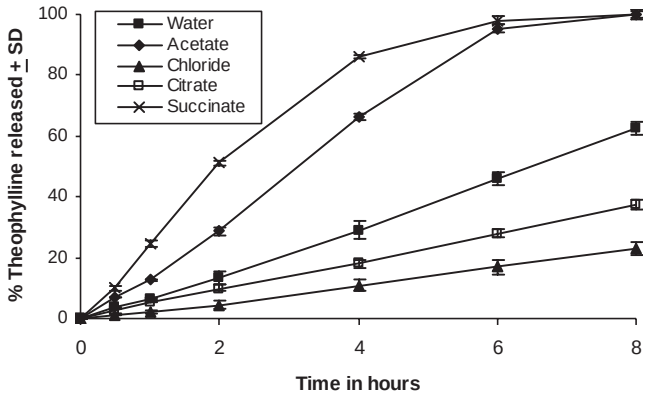

FIGURE 4 **Effect of Anions on Release of Theophylline from Pellets: Pellets Containing Sodium Chloride Core with EUDRAGIT® RS (20%w/w) Subjected to Dissolution in Solutions Containing Different Anions.**

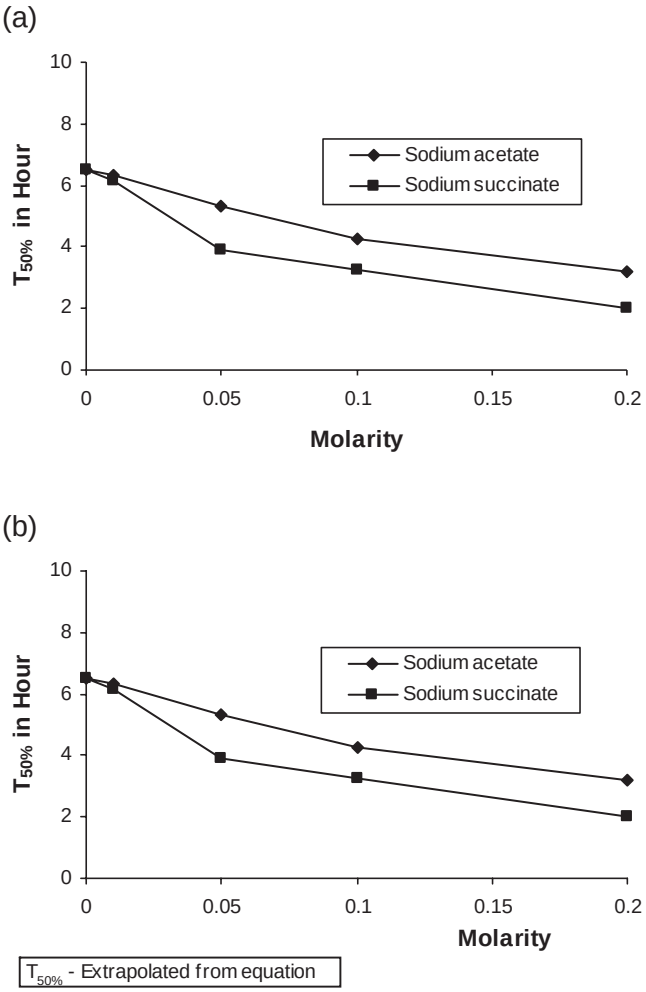

FIGURE 5 **Effect on Different Ionic Strengths on $T_{50\%}$ Values of Theophylline Pellets (a) Effect of Permeability Enhancing Anions (b) Effect of Permeability Retarding Anions.**

retarded depending on the type of anion used, in comparison to pellets having cellulose cores. Similar to the effect exhibited by the anions when used in the dissolution media, the release was retarded in case of pellets with sodium chloride and sodium citrate cores and enhanced with sodium succinate and sodium acetate cores (Fig. 6). Sodium chloride had maximum retarding effect on the drug release and sodium succinate had maximum release enhancing effect on drug release.

The effects of the anions on the drug release are due to the occurrence of ion-exchange between the anion and quaternary ammonium group of the controlled release polymer, i.e., EUDRAGIT® RS which contains 33 moles of quaternary ammonium groups per mole of polymer (Okar, 1982). The dissociation of these quaternary ammonium groups in aqueous media is responsible for the hydration and swelling of the film. This quaternary ammonium group has chloride ions as anionic counterions. The rate of drug release depends on the extent of electrostatic interaction of the anion with the quaternary ammonium group i. e. substitution of the chloride counterion with the anion (Wagner & McGinity, 2002).

$$\text{Resin}---\text{N}^{+}(\text{CH}_3)_3\text{Cl}^{-} + \text{RCOO}^{-} \Rightarrow$$
$$\text{Resin}---\text{N}^{+}(\text{CH}_3)_3\text{RCOO}^{-} + \text{Cl}^{-}$$

From the results obtained in the current study, it was seen that the order of drug release from the pellet was succinate > acetate > citrate > chloride. Thus, chloride ions inhibit the hydration of EUDRAGIT® film, thus controlling the drug release. Similarly, succinate ions after getting exchanged with the chloride counterions increases the permeability of the film by increasing its hydration. Hence, it can be concluded that the interaction is governed by the selectivity of the anions (Narisawa et al., 1994; Bodmeier et al., 1996) which in turn influences the film hydration.

Effect of EUDRAGIT® Layers

The effect of thickness of the neutral polymer layer (EUDRAGIT® NE) was studied for the pellets and results obtained with succinate and citrate cores are represented in Fig. 7. The release profiles revealed that increase in the thickness of EUDRAGIT® NE layer slows the rate of drug release for pellets with succinate cores and increases the rate of drug release for pellets with citrate cores. Since the modulating layer surrounds the salt core, a higher thickness would prolong the presence of the anion in the microenvironment and in turn the flux of the anions from the core to the EUDRAGIT® RS film. Studies are ongoing in the laboratory for predicting the exact mechanism and rate of the flux of the anions through the EUDRAGIT® NE polymer film.

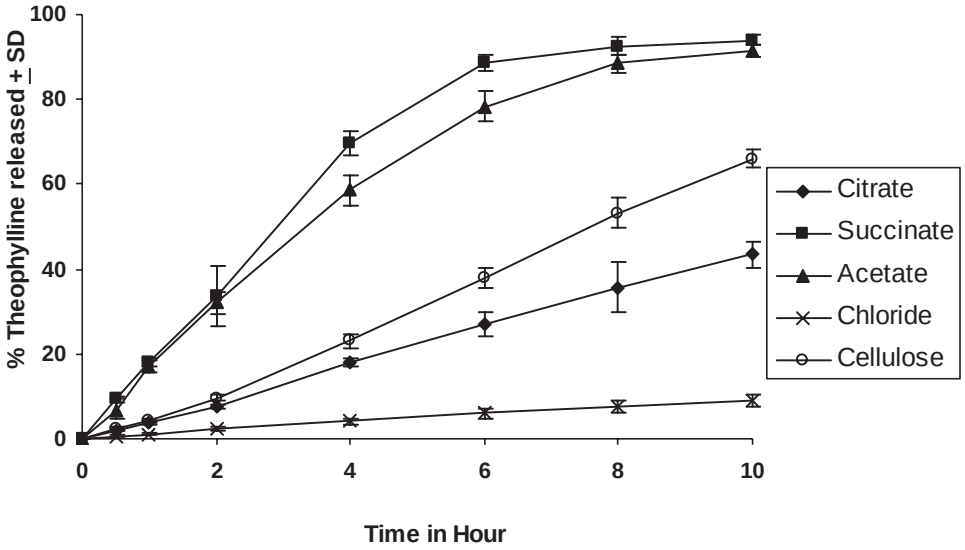

FIGURE 6 **Theophylline Release from Pellets with Different Anionic Cores: Pellets Containing Different Salts as Cores and Coated with EUDRAGIT® RS as the Controlled Release Layer (20%w/w).**

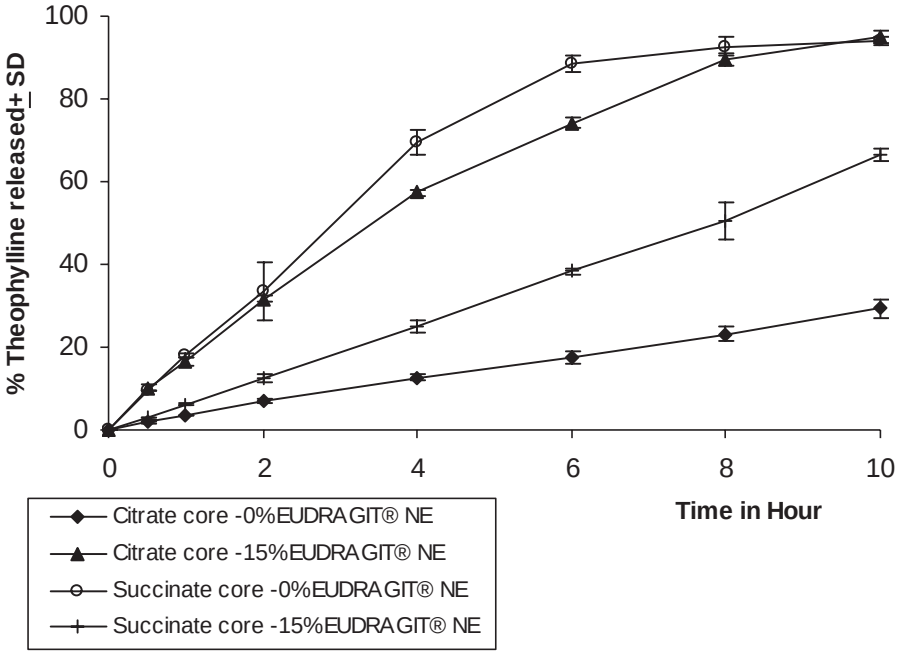

FIGURE 7 **Effect on Release of Theophylline from Pellets Coated with Different EUDRAGIT® NE Levels: Pellets Containing Sodium Citrate (EUDRAGIT® RS- 8%w/w) and Sodium Succinate (EUDRAGIT® RS- 20%w/w) as Cores.**

With increasing thickness of the controlled release layer (EUDRAGIT® RS), the slope of drug release was decreased indicating that controlling the thickness of the layer would change the release profiles (Fig. 8). Similar results were obtained with pellets using other anions.

When instead of the EUDRAGIT® RS as a controlled release layer, EUDRAGIT® NE was used, there was no change in the drug release profile of the pellets in different ionic medium, thus clearly confirming that the ionic interaction with salts is caused by the cationic polymer in the system (Fig. 9).

The mechanism of drug release through the pellets prepared as per the system is diffusion controlled. During dissolution, the initial release of the drug from the pellets is through simple diffusion of the drug

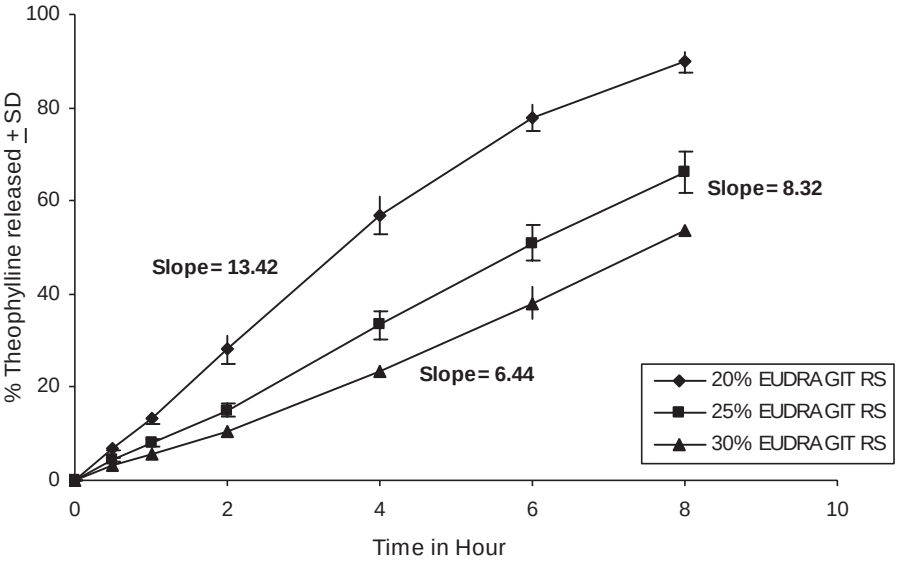

FIGURE 8 **Release Profile of Theophylline from Pellets Coated with Different EUDRAGIT® RS Levels: Pellets Containing Sodium Succinate Core.**

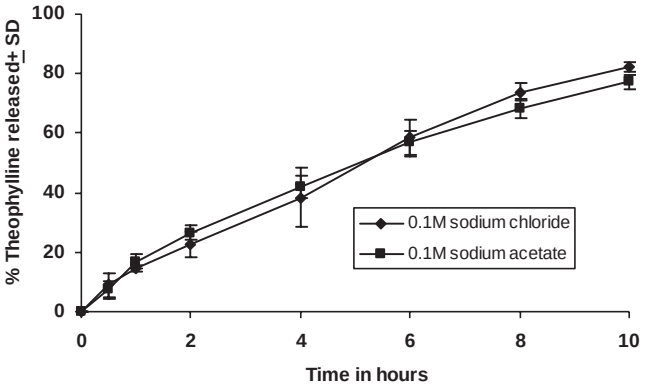

FIGURE 9 **Effect of Anions on Release of Theophylline from Pellets (Acetate Core) Coated with EUDRAGIT® NE (Both as Inner and Controlled Release Layer-20%w/w).**

through the EUDRAGIT® RS layer. After the medium or water penetrates further into the pellets, across the inner neutral polymer layer, it dissolves the salt and results in the dissociation of the anions which interact with the cations of the EUDRAGIT® RS film. Thus, the two polymer layers help in providing flexibility to this technology to change the release pattern as desired.

CONCLUSION

The present research proposes a method of preparation of multiparticulate drug delivery system, where the rate of release was controlled by ionic interactions. It was found that the release of the drug from the pellets could be enhanced or retarded with the use of different salts as a core material. The preferred salts could be sodium chloride, sodium succinate and sodium citrate, as they have significant effect on drug release. The manufacturing process of the pellets involves conventional pharmaceutical processes and equipment and the use of aqueous EUDRAGIT® polymer dispersions along with other pharmaceutical excipients. These pellets can be filled into capsules or can be further compressed to disintegrating tablets as the final dosage forms.

Different rates of drug release could be achieved using different salts. The slope of the line could be further controlled by altering the thickness of EUDRAGIT® NE and EUDRAGIT® RS layers. Thus by changing these factors, i.e., the anion cores and EUDRAGIT® film thickness, a desired release profile can be achieved. Moreover, considering the fact that it is a multi-unit dosage forms, it would have the advantages of rapid dispersion in the GI tract, maximized drug absorption, and reduced peak plasma fluctuations. The study indicates that the technology behind the system would provide a good alternative to existing technologies for design of controlled drug delivery systems.

REFERENCES

Arkinstall, W. W. (1988) Review of the North American experience with evening administration of Uniphyl tablets, a once daily theophylline preparation, in the treatment of nocturnal asthma. *Am. J. Med., 85*, 60–63.

Beckert, T.E., Pogarell, K., Hack, I., & Petereit, H.-U. (1999) Pulsed drug release with film coating of EUDRAGIT® & Mac 226; RS30D In *Proc. Int. Symp. Control. Release Bioact. Mater.*, 533–534.

Bodmeier, R., Guo, X., Sarabia, R. E., & Scullery, P. F. (1996) The influence of buffer species and strength on Diltiazem HCl release from beads coated with the aqueous cationic polymer dispersions, EUDRAGIT® RS, RL 30D. Pharm. Res., *13* (1), 52–56.

British Pharmacopoeia. (2002) Published by British Pharmacopoeial Commission office, Vol. 1, 1673.

Bryan, J. (2005) Development of drug delivery systems that match the circadian rhythm., *J. Pharm., 274*, 90–91.

Chandrasekaran, S. K., Benson, H., & Urquhart, J. (1978) Methods to achieve controlled drug delivery: The biomedical engineering approach. In *Sustained and Controlled Release Drug Delivery Systems*; Robinson, J. R., Ed. New York: Marcel Dekker, Inc. 557–593.

Chang, R. K., & Hsiao, C. (1989) EUDRAGIT® RL and RS pseudolatices: properties and performance in pharmaceutical coating as a controlled release membrane for Theophylline pellets. Drug Dev. Ind. Pharm., *15* (2), 187–196.

Chidambaram, N., Porter, W., Flood, K., & Qiu, Y. (1998) Formulation and charachterization of new layered diffusion metrices for zero-order sustained-release. *J. Control. Release, 52*, 149–158.

Conte, U., & Maggi, M. (2000) A flexible technology for the linear, pulsatile and delayed release of drugs, allowing for easy accommodation of difficult in vitro targets. *J. Control. Release, 64*, 263–268.

Cortese, R., Theeuwes, F. (1982) Osmotic device with hydrogel driving member. U. S. Patent 4,327,725, May 4, 1982.

Gillian, C. A., & Wan, P. A. L. (1991) Factors affecting drug release from a pellet system coated with an aqueous colloidal dispersion. *Int. J. Pharm., 73*, 51–68.

Lee, L. (1992) Diffusion-controlled Matrix systems. In *Treatise on controlled drug delivery*; Kydonicus, A., Ed. New York: Marcel Dekker Inc. 115–198.

Lee, P. I. (1985) Kinetics of drug release from the hydrogel metrices. *J. Control. Release, 2*, 277–288.

Lu, E., Jiang, Z., Zhang, Q., & Jiang, X. (2003) A water-insoluble drug monolithic osmotic tablet system utilizing gum arabic as an osmotic, suspending and expanding agent. *J. Control. Release, 92*, 375–382.

Maggi, L., Shepard, T., Rochdi, M., Grenier, P., Halbeisen, S., Zimmer, R., & Conte, U. (1997) A simulation approach for effective development of a naproxen Geomatrix Quick/Slow formulation. Proc. Of the 24th Int. Symp. Control. Release Bioact. Mater. Stockholm, Sweden, June 15–19, 1997, 327–328.

Narasimhan, B., & Langer, R. (1997) Zero-order release of micro and macromolecules from polymeric devices: the role of the burst effect. *J. Control. Release, 47*, 13–20.

Narisawa, S., Nagata, M., Danyoshi, C., Yoshino, H., Murata, K., Hirakawa, Y., & Noda, K. (1994) An organic acid-induced sigmoidal release system for oral controlled release preparations. *Pharm. Res., 11*(1), 111–116.

Narisawa, S., Nagata, M., Hirakawa, Y., Kobayashi, M., & Yoshino, H. (1996) An organic acid- induced sigmoidal release system for oral controlled release preparations permeability enhancement of EUDRAGIT® RS coating led by the physicochemical interactions with organic acid. *J. Pharm. Sci., 85* (2), 184–188.

Narisawa, S., Nagata, M., Ito, T., Yoshino, H., Hirakawa, Y., & Noda, K. (1995) Drug release behaviour in gastrointestinal tract of beagle dogs from multiple unit type rate controlled or time controlled release preparations coated with insoluble polymer based films. *J. Control. Release, 33*, 253–260.

Okar, R. S. (1982) Effect of polymer cation content on certain film properties. *J. Pharm. Pharmacol., 34*, 88–92.

Peppas, N. A. (1998) Hydrogels in Medicine and Pharmacy. Vols I, II and III. Boca Raton, FL: CRC Press.

Peppas, N. A., & Sahlin, J. J. (1989) A simple equation for the description of the solute release: III. Coupling of diffusion and relaxation. *Int. J. Pharm., 57*, 169–172.

Petereit, H.-U., Assmus, M., & Lehman, K. (1995) Glycerol Monostearate as a glidant in aqueous film-coating formulations. *Eur. J. Pharm. & Biopharm., 41* (4), 219–228.

Petereit, H. U., Beckert, T., & Lynenskjolt, E. (2000) Coated medicament forms with controlled active substance release. W O Patent 0019984, April 13, 2000.

Ravishankar, H., & Renner, G. (2005) In-vivo evaluation of EUDRAMODE™: A novel diffusion controlled multiple unit drug delivery system. Transactions of 32nd Annual Meeting and Exposition of Controlled Release Society, Miami, FL, June 18–22, 2005, 161.

Santus, G., & Baker, R. W. (1995) Osmotic drug delivery: A review of the patent literature. *J. Control. Release, 35*, 1–21.

Smith, D. H., Neutel, J. M., & Weber, M. A. (2001) A new chronotherapeutic oral drug absorption system for verapamil optimizes blood pressure control in the morning. *Am. J. Hypertens., 14*, 14–19.

Stephens, S. I., & Wong, P. S. L. (1989) Dosage form with improved delivery capability, U. S. Patent 4,863,456, September 5, 1989.

Talukder, R., & Fassihi, R. (2004) Gastroretentive Delivery systems: A mini review. *Drug Dev. Ind. Pharm., 30* (10), 1019–1028.

Theeuwes, F. (1978) Osmotic system for the controlled and delivery of agent over time. U. S. Patent 4,111,202, September 5, 1978.

Verma, R. K., Krishna, D. M., & Garg, S. (2002) Formulation aspects in the development of osmotically controlled oral drug delivery systems. *J. Control. Release, 79*, 7–27.

Verma, R. K., Mishra, B., & Garg, S. (2000) Osmotically controlled oral drug delivery. *Drug Dev. Ind. Pharm., 26* (7), 695–708.

Wagner K. G., & McGinity J. W. (2002) Influence of chloride ion exchange on the permeability and drug release of EUDRAGIT® RS30D films. *J. Control. Release, 82* (2), 385–397.

Youan, B. (2004) Chronotherapeutics: gimmick or clinically relevant approach to drug delivery? *J. Control. Release, 98*, 337–353.