ELSEVIER

International Journal of Pharmaceutics 155 (1997) 191–199

international journal of pharmaceutics

A melt-extrusion process for manufacturing matrix drug delivery systems

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Received 20 October 1996; received in revised form 20 December 1996; accepted 16 May 1997

Abstract

A novel melt-extrusion process was developed to prepare matrix drug delivery systems. The disks contained drugs suspended in various polymers or polymer/additive combinations. Theophylline was incorporated into polyethylene (PE), polycaprolactone (PC), polyvinyl acetate (PVA), and cellulose acetate butyrate (CAB) at a 50% drug loading. There was an 8-fold difference in the effective diffusion coefficient (D_e) between the various polymers (from 1.17×10^{-12} to 7.63×10^{-12} cm^2/h). Increasing the theophylline load from 50 to 70% in PC and PE disks increased the D_e at least 10-fold. Disks with a solids content above 70% by weight could not be made. To modify the release, soluble particulate additives, that did not melt at the working temperature, were incorporated in the PE disks. The soluble, particulate additives reduced the D_e significantly, and decreased the ease with which the melted mass could be extruded. To improve the ease of manufacture, the particulate additives were replaced with polyethylene glycols that melted at the working temperatures. The D_e for the PC/PEG disks were approximately 10 times larger than those for the PC disks. In addition to theophylline, chlorpheniramine maleate and salicylic acid were also incorporated into PC disks. The release of the three drugs in water, a pH 1.2 buffer, and a pH 7.5 buffer was determined. The effects of drug type and media on the drug release rates were explained using the drug's solubility, mean particle size, and dissociation constant.

Keywords: Melt-extrusion; Polyethylene; Polycaprolactone; Drug release; Soluble additives; Polymer; Matrix; Diffusion; Percolation theory

1. Introduction

Many new drug delivery systems (DDS) are developed to deliver drugs with relatively short

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PII S0378-5173(97)00165-8

durations of action or narrow therapeutic indices at a controlled rate, which will maximize the pharmacological benefits, while minimizing the potential side effects. A new technology was developed that uses melt-extrusion to prepare polymer disks containing drug in a single in-line process.

A simple way to make matrix DDS is to compress polymer–drug mixtures into a compact to form the DDS without prior granulation. Alternatively, the drug can be granulated with a polymer, so the drug particles are coated with a layer of polymer that may retard the release of the drug. There are several ways by which drugs have been incorporated into granules: solvent evaporation (Said and Al-Shora, 1980), solvent granulation (Onay-Basaran and Olsen, 1985; deHaan and Lerk, 1986), polymer solution granulation (Agabeyoglu, 1985), fusion (Parab et al., 1980; Ahmed and Enever, 1981; Flanders et al., 1987), and sintering (McTaggart et al., 1984). The granulations are compressed into tablets, which depends greatly on the compaction properties of the polymer–drug granules. This limits the polymers that can be used and the amounts of drug that can be incorporated into each compact.

A logical extension of the matrix concept is a DDS design in which the drug particles are dispersed in a polymer, so that the release of the drug is controlled by the polymer and not by the porosity of the system. Fassihi and co-workers (Fassihi et al., 1985; Fassihi and Parker, 1986) dispersed the drug in the melted polymer, and cooled the dispersion in the required form. An alternative is to compress the polymer–drug mixture at the melting point of the polymer to form the solid compact containing the drug (Mulley et al., 1987).

Melt-extrusion offers two advantages over the previously described methods. The manufacture of the DDS does not depend on the compressibility of the polymer, but on the melting point and melt viscosity of the polymer. Secondly, the intense agitation during preparation causes deaggregation of the drug particles suspended in the melted polymer, resulting in a uniform dispersion of fine particles (Maxwell, 1972). Depending on the polymer's melt viscosity, the drug can constitute a large fraction of the DDS (Hashem and El-Dien, 1990; Prapaitrakul et al., 1990). Therefore, versatility is an important characteristic of the proposed technology.

The purpose of this investigation was to develop a melt-extrusion technology for preparing matrix drug delivery systems.

2. Methods and materials

The following materials were used as received without further purification: theophylline and chlorpheniramine maleate (Sigma Chemical Co., St. Louis, MO); polyethylene glycol 3400, 6000, 8000, 10 000 (Aldrich Chemical Co., Milwaukee, WI); polycaprolactone, polyethylene (nominal M_n 1400), polyvinyl acetate (Scientific Polymer Products Inc., Ontario, NY); sucrose, sodium chloride, hydrochloric acid, potassium phosphate, and sodium hydroxide (Fisher, Fairlawn, NJ); Pluronic F68 (BASF, Parsippany NJ); cellulose acetate butyrate 500-1 (FMC, Newark, DE).

2.1. Melt-extrusion

The polymer and drug powders were screened through a 250-μm sieve. Particles larger than 250 μm were comminuted in an analytical micro-mill (Chemical Rubber Co., Cleveland, OH) and passed through the 250-μm sieve. The drug was mixed with the polymer powder by geometric dilution using a spatula. If called for in the formulation, soluble additives were mixed with the polymer–drug mixture. Accurate samples of the powder mixture were weighed and placed in the cup (stator) of the melt-extruder (Mini-Max molder, Custom Scientific Instruments, Inc, Cedar Knolls, NJ). The temperature of the cup was maintained at desired temperature (see Table 1). The centrally positioned cylindrical rotating member (rotor) was lowered repeatedly into the cup while in motion to mix the melted polymer and the drug. After a preselected period (see Table 1) the mass was extruded into a disk mold (3×12 mm). After cooling the mold the polymer disk containing the drug was removed and stored in a desiccator. The weight of the disks was approximately 400 mg; the exact weight of the disks depended on their composition.

Table 1
Melt extrusion conditions

Polymer	%	Modifier	%	°C	Time (sec)	Comments
PVA	50			170	30	
CAB	50			195	30	
PE	50			105	30	
PE	30			110	30	
PE	20			120	30	Very difficult to extrude; the disks were very brittle
PE	30	Sucrose	20	115	30	
PE	30	NaCl	20	115	30	
PE	30	Pluronic F68	20	105	30	At 105°C the disk stuck to the mold
PC	50			60	30	
PC	30			70	30	Very difficult to extrude; the disks were very brittle
PC	30			80	30	Much more fluid; easier to extrude
PC	20			100	60	Did not extrude
PC	20	PEG 10 000	10	70	45	
PC	10	all PEGs	20	70	45	

2.2. Drug release studies

The release of drug from the polymer disks was determined using a Hanson dissolution apparatus. Three release media were used: distilled water, a HCl/NaCl buffer (pH 1.2; $\mu = 0.061$; $\beta = 0.21$), and a $NaOH/KH_2PO_4$ buffer (pH 7.5; $\mu = 0.119$; $\beta = 0.09$). All three media contained 0.02% w/v polyoxyethylene sorbitan monooleate to improve wetting, and were maintained at 37 ± 0.5°C. The paddle method was used at 100 rpm. The disks remained suspended in the dissolution media by the action of the paddles. The samples were assayed for drug using a Varian UV/VIS spectrophotometer at 260 nm for chlorpheniramine maleate, at 230 nm for salicylic acid, or at 272 nm for theophylline.

2.3. Release kinetics

The release of drug from the disks occurred through the two planar surfaces and the annular surface. The Higuchi (1963) equation for the release of drugs dispersed in matrix systems was developed based on the premise that drug is released through a single planar surface, so that the releasing surface area remains constant. Cobby et al. (1974) proposed the following equation for the three-dimensional release of solute from a matrix.

$$\frac{M_t}{M_\infty} = k^3 q t^{3/2} - k^2 t(2q+1) = k\sqrt{t}\,(q+2) \qquad (1)$$

where M_t is the amount of drug released at time t (g); M_∞ is the amount of drug released at time infinity (g); k is the release rate constant ($h^{-0.5}$); t is time (h) and

$$q = \frac{r_o}{h_o} \qquad (2)$$

where r_o is the radius of the disk (cm) and h_o is the half height of the disk (cm).

D_e, the effective diffusion coefficient (cm^2/h) is

$$D_e = D\frac{\epsilon}{\tau} = \frac{A^2 K^2 r_o^2}{C_s(2A - \epsilon C_s)} \qquad (3)$$

where A is the initial drug load (g/cm^3); C_s is the solubility of the drug in the dissolution fluid (g/cm^3); ϵ is the porosity of the matrix and τ is the tortuosity.

2.4. Drug distribution in the disks

Polycaprolactone/polyethylene glycol 10 000 M_w disks containing theophylline were used to demonstrate homogeneity of the drug distribution in the disks. Three disks were cut into four pieces and the drug content of each piece was determined separately. Each piece was weighed and placed in a 250-ml separatory funnel. Methylene chloride (25 ml) was added and the funnels were

shaken until all the polymer dissolved. After 12 h, 100 ml of 0.1 N HCl was added to dissolve theophylline. The funnels were left standing with intermittent agitation for another 24 h. The aqueous phases were sampled and assayed for their drug content using a UV/VIS spectrophotometer. Partitioning of theophylline between the phases was accounted for when determining the drug content. There was no significant difference in drug content between the disks ($p = 0.972$) or between the pieces ($p = 0.897$).

2.5. Physical testing of the disks

The hardness of the disks was determined on a Heberlein Hardness tester. The hardness of the disks was higher than 20 kg. The friability of the disks was determined using a Roche friabilator (Erweka) for 100 revolutions. The weight loss for all formulations was less than 0.05% of the original disk weight.

2.6. Drug characterization

The solubility of the drugs in the various media was determined. A known excess amount of drug was placed in a test tube and a known volume of release medium was added. After sealing the screw cap with parafilm, the test tubes were equilibrated in a water bath at 37°C for 3 days with agitation. The supernatant was filtered, diluted with the appropriate medium, and assayed for dissolved drug. This value of the dissolved drug concentration was taken as the solubility of the drug in that medium. These are relative solubilities since no attempt was made to maintain the pH of the media. These solubilities represent the drug concentration in the microenvironment in the pores of the disks and not the absolute solubilities.

The absolute density of the drugs was determined using a Micromeritics helium pycnometer. The particle size distribution was determined through microscopic observation of a dilute suspension of drug particles in liquid paraffin.

2.7. Statistical analysis

The data are reported as means ($\pm$ standard deviation) of three runs. To calculate the effective diffusion coefficient, the release data were fitted to Eq. (1) by minimizing the sums of squares residuals between the actual data and the data generated by Eq. (1). One-way and two-way analyses of variance were done to test for significant differences between treatment means (Minitab Statistical Software). The Dunnett's test ($\alpha = 0.05$) was used to contrast treatment means with a control mean. Tukey's multiple range test ($\alpha = 0.05$) was used to perform pairwise comparison between treatment means.

3. Results and discussion

3.1. Melt-extrusion

Melt-extrusion of powder blends consisting of polymer and drug is a relatively easy technique for preparing matrix drug delivery systems. In this method heat is used to make thermoplastic materials pliable enough to incorporate drug particles in the polymer matrix. Intensive mixing is achieved through the shear stress created by the shear rate used (Maxwell, 1972). The polymer–drug mass could be extruded at low pressures, provided the melt viscosity of the dispersion was low.

The operating temperature ranged from 60°C for PC to 195°C for cellulose acetate butyrate (CAB) (see Table 1). Polycaprolactone (PC) was the easiest to extrude and CAB required the greatest force to extrude. At a higher solids fraction, the operating temperature was increased slightly to maintain the ease of extrusion. At higher temperatures the melted polymer was more fluid, which aided in the extrusion process. In addition, at the lower temperatures the disks were very brittle and tended to break upon removal from the mold. The amount of solids in the melt was limited by the rapid rise in melt viscosity, which prevented extrusion of the mass. A practical upper limit of 70% was reached for polycaprolactone (PC) and polyethylene (PE).

3.2. Percolation theory

The major pathway for drug release was diffusion through pores created after dissolution; a minor pathway was diffusion through the polymer. To be released from the polymer disk, the drug particles must be connected to the surface through a network of adjacent particles. In general, the percolation theory deals with the properties and number of these networks or clusters (Stauffer, 1985). Several investigators have used percolation theory to describe the release of solutes from insoluble matrices (Saltzman and Langer, 1989; Siegel and Langer, 1989; Siegel et al., 1989; Hastedt and Wright, 1990).

Upon dissolution of soluble particles pores are created, which connect to form clusters. As the void fraction in the disk increases, the mean size of the clusters increase. At the critical porosity, the clusters combine to become an infinite network, spanning the thickness of the disk. The release of the drug occurs by porous diffusion through a network of interconnected pores generated by dissolution of drug and other soluble additives. Diffusion of the drug through the polymer is assumed minimal. Therefore retardation of drug diffusion compared to free diffusion in water is due to the physical restriction by the pore morphology. The rate and extent of drug release depends on the probability of forming an infinite or percolating pore cluster. At a low total soluble fraction (TSF) the probability of forming a percolating pore cluster is less, and release is, therefore, limited and slow. As the TSF increases the cluster size expands, increasing the extent and rate of release. The predominance of one release pathway over the other depends on the TSF. At high TSF diffusion through continuous pores (major pathway) dominate, but at low TSF diffusion through the polymer phase (minor pathway) dominates.

3.3. Effect of polymer type and drug loading

Typical release profiles of theophylline from matrix disks prepared with polycaprolactone (PC), polyethylene (PE), polyvinyl acetate (PVA), and cellulose acetate butyrate (CAB) at a 50% drug loading are depicted in Fig. 1. The release data fit well to Eq. (1). The slowest release was seen with CAB ($D_e = 1.17 \times 10^{-12} \pm 0.25 \times 10^{-12}$ cm^2/h) and the fastest release was seen with PVA ($D_e = 7.63 \times 10^{-12} \pm 1.52 \times 10^{-12}$ cm^2/h) (see Table 2).

Since the same drug powder was used in making the disks, the topology of the pore network in the disks after drug release should be similar. The effect of polymer type is, therefore, attributed to the difference in the chemical properties of the surfaces between the disks. For example, different contact angles between the media and the disk surface may cause dissimilar rates of media influx into the pore network, resulting in different release rates. Siegel et al. (1989) concluded that the mere presence or creation of pores does not guarantee release, and that the chemical nature of the surface (i.e. hydrophilic or hydrophobic) influences wetting and, therefore, drug release. At extremely low total soluble fraction (TSF) polymer characteristics will influence diffusion through the polymer phase.

When the theophylline loading was increased from 50 to 70% in disks made from polycaprolactone (PC) or polyethylene (PE), the D_e increased

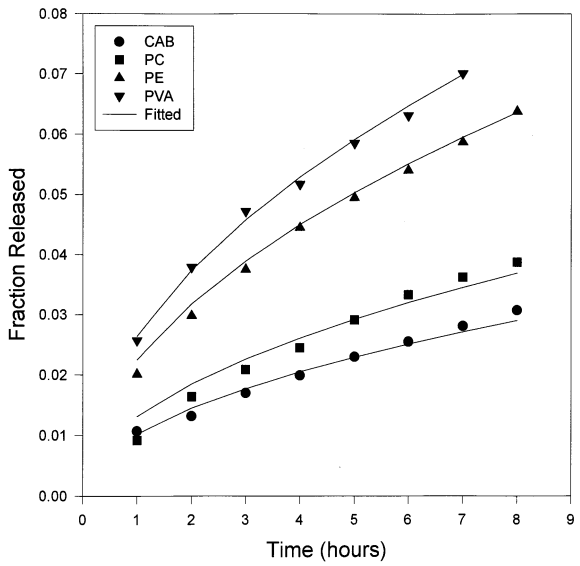

Fig. 1. Typical release profiles for theophylline from polyethylene, polycaprolactone, polyvinyl acetate, and cellulose acetate butyrate disks at a 50% drug loading. Symbols are actual data points; solid lines are fitted values from Eq. (1).

Table 2
Diffusion coefficients for the release of drug from the melt-extruded disks

Polymer	Modifier	Drug	Media	Batch	Diffusion coefficient $\times 10^{-10}$ cm^2/h		
					Mean	SD	CV
PC-30		THEO-70	Tween	2	5.98	1.95	32.60
PE-30		THEO-70	Tween	4	0.70	0.05	7.01
PC-50		THEO-50	Tween	1	0.02	0.00	13.52
PE-50		THEO-50	Tween	3	0.04	0.00	8.24
PVA-50		THEO-50	Tween	5	0.08	0.02	19.90
CAB-50		THEO-50	Tween	6	0.01	0.00	21.75
PE-30	F68-20	THEO-50	Tween	9	0.02	0.00	19.16
PE-30	NACL-20	THEO-50	Tween	8	0.07	0.01	8.50
PC-30	PEG10-20	THEO-50	Tween	10A	1.20	0.18	14.82
PC-30	PEG34-20	THEO-50	Tween	13A	1.22	0.09	7.12
PC-30	PEG6-20	THEO-50	Tween	12A	1.16	0.02	2.03
PC-30	PEG8-20	THEO-50	Tween	11A	1.12	0.03	2.74
PE-30	SUCR-20	THEO-50	Tween	7	0.29	0.02	6.94
PC-20	PEG10-10	THEO-70	Tween	14	47.29	8.63	18.25
PC-10	PEG10-20	THEO-70	Tween	10	47.66	6.01	12.61
PC-10	PEG34-20	THEO-70	Tween	13	7.73	0.21	2.65
PC-10	PEG6-20	THEO-70	Tween	12	10.49	0.30	2.83
PC-10	PEG8-20	THEO-70	Tween	11	7.95	0.22	2.77
PC-30		SA-70	Tween	28	0.74	0.00	0.40
PC-10	PEG10-20	SA-70	Tween	22	3.28	0.57	17.46
PC-30		CPM-70	Tween	25	193.65	50.79	26.23
PC-10	PEG10-20	CPM-70	Tween	19	3956.09	101.04	2.55
PC-30		THEO-70	pH 7.5	18	1.37	0.20	14.66
PC-10	PEG10-20	THEO-70	pH 7.5	16	108.83	0.83	0.76
PC-30		SA-70	pH 7.5	30	2.70	0.90	33.21
PC-10	PEG10-20	SA-70	pH 7.5	24	26.78	6.16	23.01
PC-30		CPM-70	pH 7.5	27	103.65	7.96	7.68
PC-10	PEG10-20	CPM-70	pH 7.5	21	5558.73	117.29	2.11
PC-30		THEO-70	pH 1.2	17	1.01	0.10	10.35
PC-10	PEG10-20	THEO-70	pH 1.2	15	9.87	0.24	2.44
PC-30		SA-70	pH 1.2	29	0.54	0.06	11.22
PC-10	PEG10-20	SA-70	pH 1.2	23	1.61	0.18	11.14
PC-30		CPM-70	pH 1.2	26	546.62	102.46	18.75
PC-10	PEG10-20	CPM-70	pH 1.2	20	5840.77	1233.36	21.12

approximately by one and two orders of magnitude ($p < 0.001$), respectively (see Table 2). The higher D_e at 70% drug loading is due to the much larger void fraction in the disk following drug release. The larger void fraction increased the probability of an infinite pore cluster, reducing the resistance to diffusion.

3.4. Effect of soluble additives

To increase the rate of theophylline release, 20% of the insoluble PE polymer was replaced with soluble, particulate additives. The total soluble fraction (TSF) in these disks was 70% (50% theophylline and 20% additive). Sucrose, NaCl and Pluronic F68 did not melt at the working temperatures and, therefore, remained intact as particles in the disks when extruded. Dissolution of these soluble additives increased the void fraction, raising the probability of forming a percolating pore continuous to the disk surface.

Dunnett's test ($\alpha = 0.05$) was used to contrast the treatment means with two controls that contained no additive, but had a total soluble frac-

tion (TSF) of 50 and 70% theophylline. Compared to the formulation containing 50% theophylline, addition of the soluble, particulate additives significantly increased the D_e. However, since the disks containing the soluble, particulate additives had a TSF of 70%, the D_e for these disks were compared to the D_e for polyethylene (PE) disks with 70% theophylline. In these contrasts, the D_e from formulations containing the soluble, particulate additives was significantly smaller ($p < 0.001$) than the D_e for PE disks with a 70% drug loading. Therefore, these soluble, particulate additives were not successful in increasing D_e beyond that expected based on total soluble fraction (TSF) alone.

The smaller than expected D_e upon adding these additives is explained as follows. The media in the pores created by the dissolution of the additive particles is saturated with these solutes. The solubility of theophylline in this microenvironment is less than in pure media. Therefore, the concentration gradient for theophylline diffusion is less in these pores. The viscosity of the fluid in these pores may be higher than in pores created by dissolution of the theophylline, which limits diffusion of the dissolved drug. The net result is a slower release of theophylline from these pores.

Polyethylene glycols of various molecular weights were incorporated into polycaprolactone (PC) disks. The various PEGs did melt at the working temperatures and, therefore, mixed intimately with the polymer and drug. A two-way ANOVA was used to analyze the effect on D_e of adding 20% PEG of varying molecular weights at a 70 and a 90% TSF.

An initial evaluation showed a significant main effect due to molecular weight ($p < 0.001$) and due to drug load ($p < 0.001$), and a significant interaction effect ($p < 0.001$). There was no significant effect due to molecular weight at the 70% TSF, but there was a significant effect at the 90% TSF. This, however, is only due to the high D_e seen with PEG 10 000. There was no significant effect due to PEG molecular weight below 10 000 Da. Dunnett's test ($\alpha = 0.05$) was used to contrast PEG added at the 50% drug load with 70% TSF. Addition of PEG did not increase D_e beyond that expected from the TSF. A similar comparison between PEG added at the 70% drug load and a control was not possible because we could not make a disk with a 90% drug loading.

When we compared the effect of total soluble fraction (TSF) at a constant drug load (70%) on D_e we found that D_e increased significantly ($p < 0.032$) as the TSF increased from 70% (no PEG) to 90% (20% PEG).

The fact that PEG as a group was more effective in increasing D_e than the particulate additives may be due to the resulting pore structure. In the case of the particulate additives the pores formed were larger than those formed by PEG, which melted at the working temperatures. However, unless the drug particle is connected to these larger pores, no release will occur. Since PEG melted during disk preparation, it seems logical that PEG provided greater access to the drug particles through a more prolific pore network, created when PEG dissolved. An additional explanation is the hydrophillic nature of PEG. Diffusion of the drug through the polymer phase would be faster through PEG than through PC, hence faster release from PEG/PC matrices compared to PC matrices.

3.5. Effect of drug type and release medium

The overall main effect due to drug type and due to release medium was significant ($p < 0.001$ and $p = 0.05$, respectively). In comparing the release of the three drugs, chlorpheniramine maleate had the fastest release rate and theophylline had the slowest release rate, with salicylic acid in between (see Table 2).

The solubilities determined for the three drugs (see Table 3) are relative because no effort was made to maintain the pH constant in the saturated solutions. The purpose was to determine the drug concentration of the saturated solution in the microenvironment found in the pores. It is probable that the pH of the media in the pores was different from the pH in the bulk of the solution. This influenced the solubility of the drugs in the microenvironment. A clear example of this is salicylic acid. With a pK_a of 2.97, its solubility at pH 7.5 should be approximately four orders of magnitude higher than its solubility at pH 1.2.

Table 3
Various properties of theophylline, chlorpheniramine maleate, and salicylic acid

Property	Drug		
	Theophylline	Chlorpheniramine maleate	Salicylic acid
Absolute density (g/ml)	1.61 ± 0.07	1.36 ± 0.103	2.19 ± 0.131
Mean particle size (μm)	142.47 ± 91.04	93.81 ± 71.96	65.24 ± 38.68
Tween solubility (g/l)	9.08 ± 0.12	510.34 ± 10.93	3.37 ± 0.03
pH 1.2 solubility (g/l)	10.69 ± 0.98	687.79 ± 40.63	2.79 ± 0.02
pH 7.5 solubility (g/l)	11.58 ± 0.65	684.08 ± 20.26	9.54 ± 0.01
D_e in Tween (cm^2/h)[a]	3.298×10^{-6}	2.505×10^{-4}	5.672×10^{-5}
D_e in pH 1.2 (cm^2/h)[a]	2.929×10^{-5}	8.553×10^{-4}	4.896×10^{-5}
D_e in pH 7.5 (cm^2/h)[a]	4.135×10^{-5}	1.129×10^{-4}	7.742×10^{-5}
Dissociation constant (pK_a)	13–14	9.2	2.97

[a] Release of drug from PC disks with a 70% drug loading.

The extremely high solubility of chlorpheniramine maleate compared to the other two drugs (see Table 3) provided a very large concentration gradient for diffusion. The solubility of chlorpheniramine maleate was approximately 60 times greater than that for theophylline and 100 times greater than that for salicylic acid. Because of its lower absolute density (see Table 3), the dissolution of chlorpheniramine maleate created a slightly larger pore volume. However, the D_e for chlorpheniramine maleate is only about 10 times larger than the D_e for the other two drugs. The less than anticipated increase in D_e may be due to the only slightly larger pore volume.

The solubility of theophylline is higher than that of salicylic acid in similar media (see Table 3). According their absolute densities (see Table 3), the volume of the disk occupied by theophylline is greater than that occupied by salicylic acid. This also represents the pore volume upon dissolution. The arithmetic mean particle size of theophylline is approximately twice that of salicylic acid (see Table 3). The higher solubility of theophylline favors its quicker release compared to salicylic acid. However, if one assumes spherical particles, then the same mass of salicylic acid will contain 1.64 times more particles than theophylline. This means that a disk containing 70% by weight salicylic acid will have more channels after drug release than a similar disk containing theophylline. The larger number of pores favors a more rapid drug release from disks containing salicylic acid. From the release data (see Table 3) it is clear that, in this case, the effect of pore numbers is greater than the solubility effect.

The D_e for theophylline in distilled water, pH 1.2 or pH 7.5, were similar. For salicylic acid, the highest release rate was obtained in pH 7.5 buffer and the lowest release rate was obtained in pH 1.2 buffer (see Table 2). The release rate for chlorpheniramine maleate was highest in pH 1.2 buffer and lowest in pH 7.5 buffer.

The lack of a significant media effect on the theophylline D_e was expected since the differences in theophylline solubility in the various media were small (see Table 3). The impact of media on the salicylic acid release rate was also predictable. At pH 1.2, salicylic acid is predominantly undissociated and at pH 7.5 it is predominantly dissociated. This resulted in the higher solubility of salicylic acid at higher pH and, indirectly, the larger D_e in pH 7.5 (see Tables 2 and 3). Similar arguments cannot be made for the effect of media on chlorpheniramine maleate D_e. The solubilities of chlorpheniramine maleate in the buffers were similar, and both were higher than the solubility in water. The higher solubilities are probably due to an ionic strength effect.

4. Conclusion

The melt-extrusion process developed for preparing sustained release matrix disks is a viable

alternative to current technologies for thermostable drugs. The process allows easy incorporation of drugs into polymers to yield hard disks with easily modified release rates.

Acknowledgements

The authors are grateful to the PMA foundation for their support, in part, with this project.

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