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Evaluation and Comparison of Five Matrix Excipients for the Controlled Release of Acrivastine and Pseudoephedrine

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ABSTRACT

For treatment of allergic rhinitis, acrivastine with pseudoephedrine in Semprex®-D conventional capsules requires dosing every 6–8 hours. This study was designed to develop a controlled release matrix tablet of acrivastine and pseudoephedrine and evaluate 5 different matrix excipients for their in vitro controlled-release profiles. Compritol® 888ATO, Eudragit® RS, Methocel® K100M, Polyox® WSR301 and Precirol® ATO5 were used alone or in varying combinations for the formulation of controlled release matrix tablets. In vitro drug dissolution and mathematical modeling were used to characterize drug release rate and extent. All tablet formulations yielded quality matrix preparations with satisfactory tableting properties. Due to the aqueous solubility of pseudoephedrine and the size of the dose, none of the matrix excipients used alone prolonged drug release significantly to meet the desired twice-daily administration frequency. The use of two excipients in combination, however, significantly decreased the dissolution rate of both active ingredients. A combined lipid-based Compritol® and hydrophilic Methocel® produced optimal controlled drug release for longer than 8 hours for both acrivastine and pseudoephedrine.

Key Words: Acrivastine; Pseudoephedrine; Controlled release matrix tablet; Dissolution; Mathematical modeling.

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INTRODUCTION

Acrivastine, [(E)-3-(6-[3-pyrrolidino-1-(4-tolyl)-prop-1E-enyl]-2-pyridyl)-acrylic acid], is a second-generation, non-sedating H_1-antihistamine that was derived from the first-generation antihistamine triprolidine.[1] It has specific antihistaminic activity for the treatment of allergic rhinitis with reduced potential for the sedative side effects that characterize triprolidine and other first-generation antihistamines.[2] Semprex®-D capsules contain 8 mg of acrivastine and 60 mg of the decongestant pseudoephedrine hydrochloride, a commonly used antihistamine-decongestant combination that relieves rhinorrhea, sneezing, itching, and nasal congestion.

Frequent dosing, 3–4 times daily, is normally required for acrivastine, as the compound has a relatively short plasma elimination half-life of 1.5–2 hours.[3] This contrasts unfavorably with the other second-generation, non-sedating antihistamines such as fexofenadine and loratadine that are taken no more than once or twice daily, due mainly to their long half-lives.[3–5] A controlled release formulation of acrivastine and pseudoephedrine would maintain effective plasma concentrations of both active ingredients for longer than 8 hours, subsequently reducing drug administration to a twice or even once daily regimen.

Both acrivastine and pseudoephedrine are appropriate candidates for controlled release preparations, because controlled release approaches are able to considerably improve in vivo performance and reduce administration frequency for both compounds. While extended release or controlled release dosage forms of pseudoephedrine have been available for years,[6,7] formulating a relatively simple and straightforward solid controlled release formulation for acrivastine and pseudoephedrine still presents several technical challenges. Concurrent presence of two active ingredients in the formulation increases the complexity and difficulty in formulation development and drug dissolution. Optimization of drug release rates of both acrivastine and pseudoephedrine from the same preparation to achieve a satisfactory overall controlled release pattern will be solely dependent on the formulation techniques and the excipient selections. In addition, physicochemical properties of acrivastine are distinctly different from those of pseudoephedrine. Acrivastine is relatively insoluble in most pharmaceutical solvents, but pseudoephedrine is readily soluble in almost all solvents. There are also specific treatment requirements for each medication. As a decongestant, pseudoephedrine is required to produce a prompt relief to the nasal congestion and maintain its pharmacological action over a prolonged period of time. Acrivastine as an antihistamine should produce constant antihistaminic activity over the complete dose interval. It will therefore require special formulation technology to coordinate drug release profiles of the active ingredients to achieve the most optimal therapeutic goals.

The extensive availability of synthetic, biocompatible and biodegradable pharmaceutical excipients as tablet additives and the successful application of highly sophisticated techniques to produce various controlled release tablets have been well documented and established both in laboratory research and in industrial manufacture.[8–10] These technologies exhibit many advantages over traditional tableting processing, yielding high production efficiency and versatility, ease of automation and cost-saving benefits. Matrix tablets are one of the most widely used dosage forms within controlled release techniques in pharmaceutical manufacturing standards, as drug release rates are controlled mainly by the type and proportion of excipients used in the preparations, and no complex production procedures such as coating and pelletization are required.

We hypothesized that, by selecting appropriate pharmaceutical excipients and manufacturing techniques, it would be possible to modify drug release profiles for both acrivastine and pseudoephedrine from the same matrix tablet formulation and achieve sustained drug release for up to 8–12 hours. This projected dissolution rate will enable a twice daily dosing regimen in vivo. To test this hypothesis, we developed controlled release matrix tablet formulations of acrivastine and pseudoephedrine using 5 different types of matrix excipients, and evaluated in vitro controlled release characteristics using dissolution method and mathematical modeling.

MATERIALS AND METHODS

The pharmaceutical excipients used in the study were received as gifts from various sources. They were the water-soluble, hydrophilic polymers Methocel® K100M (hydroxypropyl methylcellulose, The Dow Chemical Company, Midland, MI, USA) and Polyox® WSR301 (polyethelene oxide, Union Carbride Corporation, Danbury, CT, USA), the water-insoluble, acrylic resin Eudragit® RS (methacrylic acid esters, Röhm Pharm, Darmstadt, Germany), and the water-insoluble, lipid-based excipients Compritol® 888ATO (glyceryl behenate NF, Gattefossé s.a., Lyon, France) and Precirol®

ATO5 (glyceryl palmitostearate, Gattefossé s.a., Lyon, France). Acrivastine was received as a gift from Celltech Pharmaceuticals (Rochester, NY, USA), and pseudoephedrine was purchased from Medisca Pharmaceutique Inc. (Montreal, QC, Canada). Other tablet additives used included magnesium stearate and ethanol (Fisher Scientific, Fair Lawn, NJ, USA).

Each tablet formulation contained 20 mg of acrivastine and 150 mg of pseudoephedrine, with the projected administration frequency of once every 12 hours. The compositions of the matrix tablet formulations are listed in Table 1. Some formulations contained one single matrix excipient to control drug release, while other formulations contained a combination of two matrix excipients as controlled release mechanisms. Wet granulation with ethanol was used to prepare the granules, which were passed through a No. 20 sieve to obtain size uniformity. They were then placed in a drying oven (45°C) for 2 hours. All granules were weighed before and after the drying process to control residual humidity below 5%.

Tablets were prepared by using a Manesty® single-punch tablet press (Liverpool, UK). A set of 7/16 punches and die was used for the tableting and the compression force was set at 50 kg for all tablet formulations. Tablet hardness was measured using an Erweka® hardness tester (Heusenstamm, Germany), and all tablet batches produced a hardness ranging 8–10 kg.

In vitro dissolution tests were carried out on a VanKel® 600 Dissolution Apparatus (Palo Alto, CA, USA) using USP Apparatus I. The dissolution medium was distilled water. The dissolution temperature was maintained at 37±0.5°C and the rotation speed was set at 50 rpm. Samples were collected from the dissolution medium every 30 minutes for up to 8 hours. Each sample volume removed was replaced by an equal volume of fresh dissolution medium. Six replicates were tested for each batch of the tablet formulations. Dissolution samples were filtered and diluted to appropriate concentrations for drug analysis.

Concentrations of acrivastine and pseudoephedrine were simultaneously measured using an HPLC assay developed in our laboratory.[11] In brief, a Waters® HPLC system (Milford, MA, USA) comprised of a 600S Controller, a 616 Solvent Delivery Pump, a 717 Autosampler, and a 996 Photodiode Array Detector was used with a C_{18} Nova-Pak® column (4 μm, 3.9×150 mm). The mobile phase was composed of acetate buffer (pH 4.0):acetonitrile:methanol (45:47:8) and was delivered at a flow rate of 0.8 mL/min. The detection wavelength for both compounds was 214 nm. Under these HPLC conditions, pseudoephedrine and acrivastine were eluted from the column at 2.0 and 2.5 minutes respectively. The detection limit was 5 ng for acrivastine and 10 ng for pseudoephedrine respectively, and no interference was found from any tablet excipients or additives.

Mathematical modeling of drug release characterization used two well-known equations from Hixson-Crowell[12,13] and Peppas-Ritger.[14,15] The Hixson-Crowell Cube Root Kinetics Equation describes the relationship between drug release and dissolution time using Eq. 1,

$$\left[\frac{W_d}{W_i}\right]^{1/3} = 1 - k_1 t \quad (1)$$

where W_d is dry weight of the tablet at designated times after immersion in the dissolution medium, W_i is initial dry weight of the tablet, k_1 is the erosion rate constant of the tablet, and t is the dissolution time.

Table 1. Matrix tablet formulations of acrivastine and pseudoephedrine.

	Formulation (mg/tablet)						
Excipients	A	B	C	D	E	F	G
Acrivastine	20	20	20	20	20	20	20
Pseudoephedrine	150	150	150	150	150	150	150
Eudragit® RS	75	–	–	–	–	–	–
Compritol® 888ATO	–	75	–	–	–	40	130
Precirol® ATO5	–	–	75	–	–	–	–
Methocel® K100M	–	–	–	75	–	140	200
Polyox® WSR301	–	–	–	–	75	–	–
Magnesium stearate	5	5	5	5	5	5	5
Total weight	250	250	250	250	250	355	505

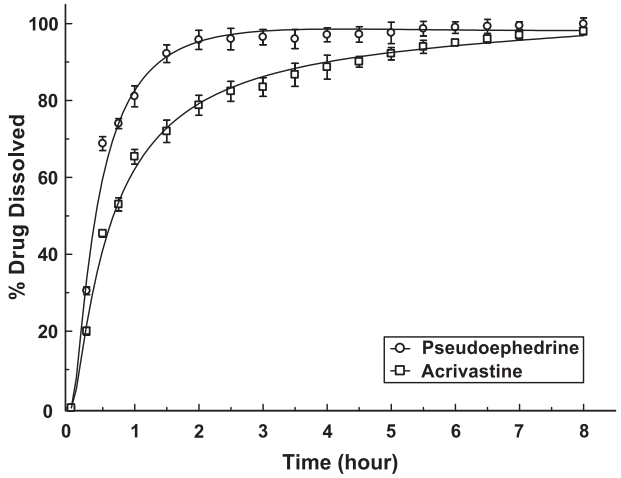

Figure 1. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula A (Eudragit® RS).

When drug dissolution is considerably slower than tablet erosion, a modified Hixson-Crowell Equation could be used, which more accurately correlates the drug dissolution profile,

$$\left[1 - \frac{Q_d}{A}\right]^{1/3} = 1 - k_2 t \tag{2}$$

where Q_d is dissolved drug amount at time t, A is the total drug amount in the matrix, and k_2 is apparent rate constant of drug dissolution. Dissolution data from dissolution studies were fitted linearly using Eq. 2.

The Peppas-Ritger Equation was developed to describe the influence of polymeric hydration and swelling on drug release rate. The equation has been modified by Korsmeyer et al.[16] to simplify the relationship between drug diffusion from the matrix tablet and the dissolution time through Eqs. 3 and 4,

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

$$\log\left[\frac{M_t}{M_\infty}\right] = \log k + n \log t \tag{4}$$

where M_t/M_∞ is the fraction of drug release, k is a release rate constant, n is the diffusional release exponent indicative of the drug release mechanism, and t is the dissolution time. Dissolution data of the study ($M_t/M_\infty \leq 0.6$) were correlated linearly using Eq. 4.

The time required for 50% of the drug to be released ($DT_{50\%}$, hours) and dissolution efficiency (DE, %)[17,18] of the formulations were also obtained to compare differences in drug release rate and extent. $DT_{50\%}$ was obtained directly from the dissolution-time curves. Dissolution efficiency was calculated from the following equation,

$$\mathrm{DE}(\%) = \frac{AUC_{dissolution(0\rightarrow 8\ hr)}}{100\% \times 8\ hr} \times 100 \tag{5}$$

RESULTS

All tablet formulations tested possessed satisfactory tableting properties such as good mixing/granulating characteristics, flowability and compressibility. Tablets were manufactured from each tablet formula that complied with specifications for weight variation, hardness and drug content. The manufacturing process was simple and straightforward with conventional granulation and mixing procedures. No complex processing was required for the production of matrix tablets of acrivastine and pseudoephedrine.

Figure 1 shows drug release from Tablet Formula A that was composed of 30% Eudragit®. Dissolution of pseudoephedrine was slightly retarded for up to 2 hours, while dissolution of acrivastine was prolonged for 5 hours. Figure 2 shows drug release from Tablet Formula B that was composed of 30% Compritol®. Drug release was extended to 4 hours and 8 hours for pseudoephedrine and acrivastine respectively. Figure 3 shows drug release from Tablet Formula D that was composed of 30% Methocel®. Dissolution of pseudoephedrine and acrivastine was prolonged for up to 7 and 8 hours respectively. Figure 4 shows drug release from

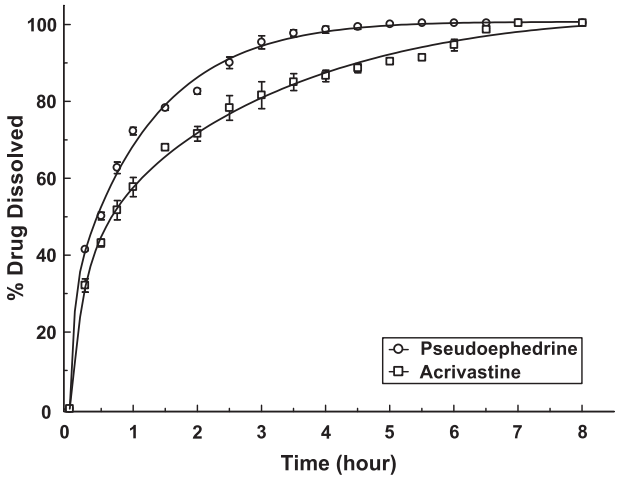

Figure 2. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula B (Compritol® 888ATO).

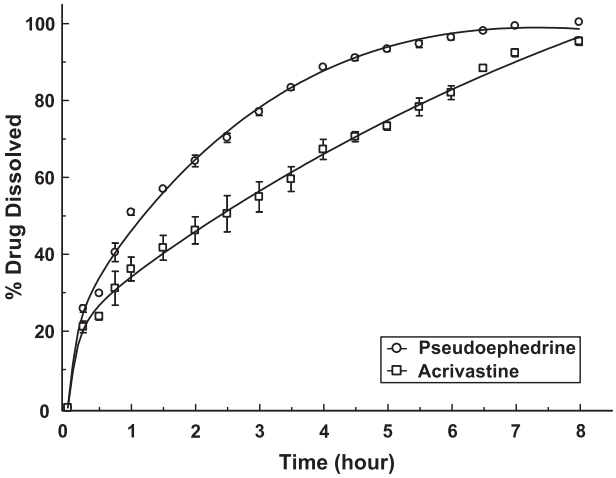

Figure 3. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula D (Methocel® K100M).

Tablet Formula E that was composed of 30% Polyox®, which had sustained dissolution profiles of pseudoephedrine and acrivastine for up to 6 and 8 hours respectively. Drug dissolution data from Tablet Formula C (Precirol®, dissolution figure not shown) were similar to that of Formula B, as they are both lipid-based matrix excipients. None of the above formulations was able to sustain the dissolution of both active ingredients to the extent that met the designed objective of drug administration once every 12 hours. Dissolution of pseudoephedrine was routinely faster than that of acrivastine, mainly due to its greater aqueous solubility.

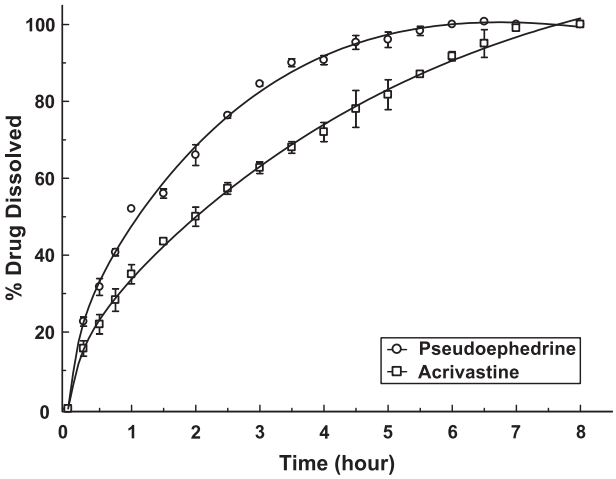

Figure 4. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula E (Polyox® WSR301).

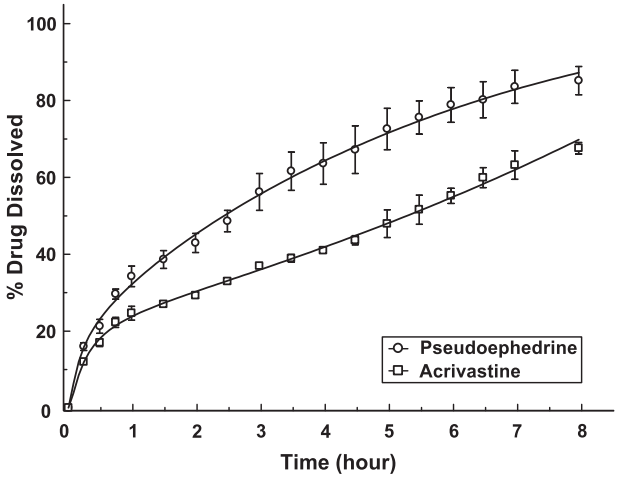

Figure 5. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula F (Compritol® 888ATO+ Methocel® K100M, I).

Figures 5 and 6 show drug release from Tablet Formulas F and G respectively that were composed of lipophilic Compritol® and hydrophilic Methocel® in various proportions. Drug release was significantly prolonged for both acrivastine and pseudoephedrine. Formula F appeared to achieve our design objectives in terms of drug release. At 8 hours, the overall drug dissolution was 68% for acrivastine and 85% for pseudoephedrine respectively.

Table 2 lists dissolution parameters of acrivastine and pseudoephedrine from various tablet formulations

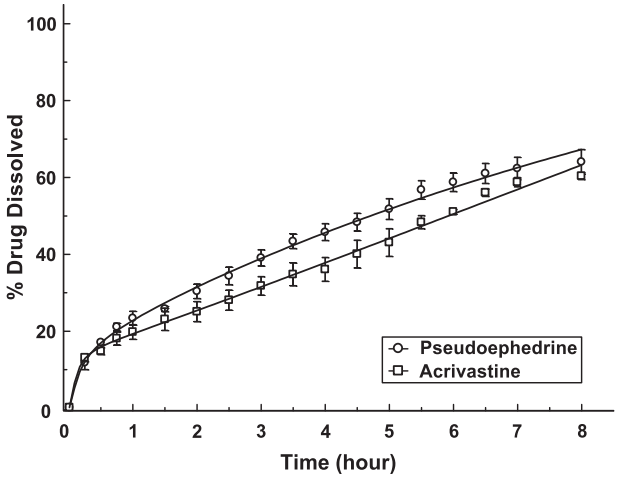

Figure 6. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula G (Compritol® 888ATO+ Methocel® K100M, II).

Table 2. Results of linear regression of acrivastine and pseudoephedrine release using the Hixson-Crowell Cube Root Kinetics Equation (Eq. 2).

	Acrivastine			Pseudoephedrine		
Formulation	k_2 (1/h)	y-intercept	R^2	k_2 (1/h)	y-intercept	r^2
Formula A	0.074	0.806	0.928	0.283	0.875	0.931
Formula B	0.090	0.864	0.963	0.106	0.762	0.960
Formula C	0.089	0.848	0.965	0.145	0.831	0.986
Formula D	0.068	0.954	0.980	0.102	0.921	0.992
Formula E	0.101	1.003	0.950	0.114	0.912	0.990
Formula F	0.033	0.956	0.986	0.055	0.935	0.991
Formula G	0.029	0.965	0.987	0.033	0.952	0.988

Table 3. Results of linear regression of acrivastine and pseudoephedrine release using the Peppas-Ritger Equation (Eq. 4).

	Acrivastine			Pseudoephedrine		
Formulation	n	k	R^2	n	k	r^2
Formula A	0.843	0.693	0.956	0.846	1.049	0.913
Formula B	0.426	0.578	0.999	0.401	0.699	0.972
Formula C	0.449	0.570	0.995	0.417	0.709	0.973
Formula D	0.409	0.348	0.985	0.480	0.469	0.943
Formula E	0.569	0.339	0.998	0.535	0.475	0.978
Formula F	0.454	0.231	0.983	0.499	0.321	0.988
Formula G	0.464	0.205	0.959	0.495	0.230	0.991

Table 4. Dissolution parameters of the formulations.

	Acrivastine		Pseudoephedrine	
Formulation	$DT_{50\%}$ (hr)	DE (%)	$DT_{50\%}$ (hr)	DE (%)
Formula A	0.88	81.95	0.47	91.38
Formula B	0.65	80.38	0.35	88.72
Formula C	0.80	81.60	0.50	89.05
Formula D	2.25	62.98	1.13	77.81
Formula E	2.00	68.42	1.06	80.48
Formula F	5.25	41.99	2.44	59.82
Formula G	6.00	37.67	4.88	43.40

using the Hixson-Crowell Cube Root Kinetics Equation (Eq. 2). Table 3 lists dissolution parameters of acrivastine and pseudoephedrine from various tablet formulations using the modified Peppas-Ritger Equation (Eq. 4). Table 4 lists $DT_{50\%}$ and DE of both acrivastine and pseudoephedrine from various tablet formulations. Rankings in dissolution parameters from mathematical modeling were variable among Formulations A–E. However, rankings of dissolution rate from Formula F and Formula G were identical in all calculations.

DISCUSSION

The prevalence of allergic disorders has been increasing dramatically throughout the world for the past several decades. Approximately 30–40% of

individuals in the US and Canada have been reported to suffer from various allergies. Natural environmental allergens, air pollutants, stress, and xenobiotics have all been implicated in the genesis of these disorders. Antihistamines, particularly the non-sedating, second-generation compounds, have been one of the major drug categories used extensively for the treatment of allergic rhinitis. The availability of new dosage forms of acrivastine and pseudoephedrine could provide more competitive therapeutic choices for the treatment of this disorder.

The extreme aqueous solubility of pseudoephedrine compared to that of acrivastine was one of the major factors to be considered in controlling release of the medications from the matrix tablets. Since the proportion of pseudoephedrine, 150 mg, in the formulation is significantly larger than that of acrivastine, 20 mg, and pseudoephedrine is readily soluble as a hydrochloride salt, selecting appropriate matrix excipient in the formulation is critical to the success of the formulation development. Both water-soluble and water-insoluble matrix excipients were investigated in the study, with the goal of finding the optimal excipient type and amount that would be able to modify the overall drug release rate consistent with the design objectives.

Of the five matrix excipients evaluated in this study, Methocel® and Polyox® are hydrophilic, gel-swelling polymers that regulate water penetration to control release of the medications. Drug release is mainly dependent upon the rate and extent of water penetration into the tablet matrix and the relative aqueous solubility of both the matrix material and the drug compounds embedded in the matrix. Eudragit® is an insoluble resin that allows slow permeation of water into the matrix and drug diffusion out of the matrix. Compritol® and Precirol® are lipid-based insoluble wax excipients that control drug release by slow matrix erosion and drug diffusion. Drug release from these insoluble matrix materials is mainly dependent upon the rate and extent of water permeation and aqueous solubility of the drug compounds that are embedded in the matrix. Different drug release mechanisms were involved in controlling drug dissolution from these selected tablet formulations, depending on the type and ratio of the matrix material in the formulations. They included diffusion, dissolution and a combination of both diffusion and dissolution.

The apparent dissolution rate constant (k_2) from various tablet formulations ranged 0.029–0.101 hr^{-1} for acrivastine and 0.033–0.283 hr^{-1} for pseudoephedrine respectively (Table 2). The linear correlation (r^2) was larger than 0.95 for all formulations except Formula A, indicating satisfactory curve fitting of the dissolution data. Differences in this rate constant resulted from the use of different types of matrix excipients. The dissolution rate constant from Polyox® was larger than that of Methocel®, suggesting that water permeability and gel relaxation of Polyox® are more significant. For insoluble matrix materials tested in the study, drug dissolution appeared to be mainly dependent upon the aqueous solubility of the active ingredients. Tablets made of Eudragit® as a matrix excipient had a significantly larger rate constant for pseudoephedrine than lipid-based matrix Compritol® and Precirol®, indicating its larger water permeability and weaker bonding with water-soluble components. Li et al.[19] evaluated the controlled release of pseudoephedrine using Eudragit® resin as either matrix or coating excipient. Dissolution of pseudoephedrine from sustained release formulations was mostly prolonged for up to 6 hours. Williams et al.[20] also reported dissolution results for the controlled release of alprazolam from Methocel® matrix tablets. The study concluded that the hydrated gel layers were more permeable for alprazolam release when the tablets contained soluble excipients, resulting in faster rates of dissolution. Dissolution of pseudoephedrine in our study facilitated the penetration of water into the matrix interior, promoting diffusion of acrivastine from the tablets. This might be the main reason why no single excipient was able to prolong drug dissolution of both acrivastine and pseudoephedrine significantly and meet our design objectives.

According to the Peppas-Ritger Equation, the value of diffusional release exponent n dictates the drug dissolution mechanism. Drug release in zero-order, non-Fickian (anomalous) diffusion and Fickian diffusion is represented by $0.89 < n < 1.0$, $0.45 < n < 0.89$ and $n = 0.45$, respectively. The n values from various tablet formulations ranged 0.409–0.843 for acrivastine and 0.401–0.846 for pseudoephedrine respectively (Table 3). The linear correlation (r^2) was mostly larger than 0.95, representing satisfactory curve fitting of the dissolution data. Dissolution of acrivastine from Formula C, F and G appeared to observe a Fickian diffusion mechanism, as n values were very close to 0.45. Dissolution of acrivastine from other formulations and dissolution of pseudoephedrine from all formulations indicated combined mechanisms of anomalous diffusion and matrix relaxation/erosion. Rankings in dissolution rate constants for both active ingredients from this modeling were very similar, Formulas A, B, C > Formulas D, E > Formulas F, G. Zhang and Schwartz,[21] and Barthelemy et al.[22] studied dissolution of various compounds with Compritol® as matrix

material for controlled release formulations. Their results suggested that drug release from Compritol® matrix followed the Fickian diffusion mechanism, which was consistent with what we have found in formulations C, F and G that contained the lipid-based matrix excipients Compritol® or Precirol®.

Combined use of lipid-based Compretol® and hydrophilic Methocel® sustained drug release significantly compared to any formulation that was composed of only single matrix excipients. The dissolution profiles were characterized from dissolution rate constants obtained from Eqs. 2 and 4, and dissolution parameters $DT_{50\%}$ and DE. Formula F and Formula G had the lowest values among all test formulations. Dissolution of the highly soluble pseudoephedrine was well prolonged with the combined use of two different types of matrix excipients. In addition, increase in the proportions of matrix materials in the formulation further retarded the drug release rate and extent. Hydrophilic polymers such as Methocel® rely on water absorption to produce gel swelling and matrix relaxation, which subsequently facilitate drug dissolution and diffusion from the matrix. When a lipid-based excipient is concurrently present in the same matrix, its lipophilicity is able to reduce water uptake rate by the matrix. Consequently, drug dissolution and diffusion from tablet matrix is reduced to produce a sustained release pattern for a prolonged period of time. This formulation strategy worked satisfactorily for pseudoephedrine, even when there was a large amount of pseudoephedrine embedded in the tablet matrix. The combination of lipophilic and hydrophilic matrix materials in the formulation did not appear to significantly affect the dissolution characteristics of acrivastine, due probably to its lower aqueous solubility. Dissolution of acrivastine itself might have a similar rate profile as that of matrix hydration and erosion, resulting in satisfactory controlled release of acrivastine for up to 8 hours. Tiwari et al.[23] studied controlled release of tramadol hydrochloride using both hydrophilic (hydroxypropyl methylcellulose) and hydrophobic (hydrogenated castor oil) matrix excipients. Their study found that combined use of hydrophilic and hydrophobic excipients was not desirable because immediate tablet disintegration and drug dissolution took place. We did not observe such phenomena in our dissolution studies.

CONCLUSION

To achieve controlled release dissolution for both the antihistamine acrivastine and the decongestant pseudoephedrine that would be suitable for a twice daily administration regimen, no single water-soluble or water-insoluble matrix excipient studied was able to achieve the required drug release rate profiles in vitro, mainly due to large proportion of pseudoephedrine present in the matrix and its high aqueous solubility. However, the combination of lipid-based Compritol® 888ATO and hydrophilic Methocel® K100M in the formulation achieved the dissolution profiles that met the formulation objectives in terms of controlled drug release over 8–12 hours. This formulation will be further tested in vivo in an animal model for its pharmacokinetic and pharmacodynamic characteristics.

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