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**ORIGINAL ARTICLE**

# Swelling, erosion and drug release characteristics of salbutamol sulfate from hydroxypropyl methylcellulose-based matrix tablets

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**Abstract**

*Background*: Hydrophilic matrix formulations are important and simple technologies that are used to manufacture sustained release dosage forms. *Method*: Hydroxypropyl methylcellulose-based matrix tablets, with and without additives, were manufactured to investigate the rate of hydration, rate of erosion, and rate and mechanism of drug release. Scanning electron microscopy was used to assess changes in the microstructure of the tablets during drug release testing and whether these changes could be related to the rate of drug release from the formulations. *Results*: The results revealed that the rate of hydration and erosion was dependent on the polymer combination(s) used, which in turn affected the rate and mechanism of drug release from these formulations. It was also apparent that changes in the microstructure of matrix tablets could be related to the different rates of drug release that were observed from the test formulations. *Conclusion*: The use of scanning electron microscopy provides useful information to further understand drug release mechanisms from matrix tablets.

**Key words:** *Carbopol®; drug release; erosion; hydrophilic matrix tablets; hydroxypropyl methylcellulose; salbutamol sulfate; sodium carboxymethylcellulose; swelling*

## Introduction

Hydrophilic monolithic matrix devices are commonly used as sustained release (SR) dosage forms because of their ease of manufacture and the nature of this relatively well-understood technology. The rate of drug release from monolithic devices can be modulated by the level and type of polymer or combinations of polymers that are used to manufacture a formulation. The inclusion of polymeric adjuvants changes the microscopic porosity and tortuosity of matrices thereby affecting both the rate and mechanism of drug release[1].

Following immersion of hydrophilic matrix tablets into aqueous media, the polymer hydrates, and tablets swell and increase in size after which the matrix dissolves and/or erodes with time[2,3]. Swelling is a complex phenomenon that is governed by diffusion of the solute throughout the matrix structure, polymer stress relaxation, and inconsistent swelling. These processes are dependent on the composition and structure of the polymeric matrices that are used when manufacturing SR formulations[4].

Polymer erosion from the matrix involves two processes, namely, disentanglement of individual molecules at the matrix surface and subsequent transport of these molecules from the surface of the matrix to the bulk solution[5,6]. Physical entanglement of the polymer chains hinders dissolution of the polymer; however, at the outer surface of a matrix tablet the polymer is diluted by the bulk medium to a point where the polymer no longer has structural integrity. This phenomenon results in polymeric disentanglement at the surface of the tablet, which results in the polymer layer eroding and eventually the tablet disappears[4,7]. Furthermore, chain entanglement affects the rate of polymer erosion in hydrophilic matrices and depends on the molecular weight and concentration of the polymer used in formulations[4].

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Early studies have shown that drug release from swellable hydrophilic matrices is dependent on the thickness of the hydrated gel layer that is formed during the swelling phase of polymer hydration[2,3]. The degree of swelling determines the diffusional path length of a drug, and the thicker the gel layer the slower the rate of drug release from a matrix[8]. The thickness of the gel layer increases during the swelling phase and then remains constant in what is known as the synchronization phase (i.e., where the rates of swelling and erosion are equal) and eventually decreases as polymer erosion becomes dominant[7].

The rate of hydration and viscosity of a polymeric matrix, polymer swelling, and erosion are important attributes that influence the rate of drug release from hydrophilic matrix formulations. Specifically a rate-controlling polymer must swell rapidly when immersed in aqueous medium so as to prevent formulation components, including the active pharmaceutical ingredient and other water-soluble excipients from leaching into the bulk medium. In addition, an increase in viscosity of the resultant gelatinous layer means that there is a greater impediment to drug liberation and greater resistance to polymer erosion[6,9].

Cellulose ethers including hydroxypropyl methylcellulose (HPMC) are commonly included in hydrophilic matrices that are used to manufacture oral SR formulations because of their low toxicity and wide regulatory acceptance. Furthermore dosage form performance and product quality of these formulations are not significantly affected by manufacturing process variables[10]. HPMC has been the polymer of choice for the manufacture of several SR formulations and its use and applications are well documented[1,11–16]. Other polymers that have the potential for use as matrix-forming materials include Carbopol®[17–19] and sodium carboxymethylcellulose (SCMC)[14,20] and these were investigated as possible adjuvants to modulate both the rate and mechanism of drug release of the low-dose and water-soluble drug, salbutamol sulfate (SBS).

The swelling and erosion of polymeric matrices has been reported and the relative importance of these processes in governing the mechanism of drug release was studied[4,21–23]. The gravimetric method is commonly used to determine the extent of polymer erosion from hydrophilic matrix tablets over time[22–24], although the amount of dissolved polymer in the dissolution medium during a dissolution test has been quantified using size exclusion chromatography[4,21]. The relationship between swelling process and drug release kinetics has also been reported and the mechanism of release was dependent on the swelling and erosion characteristics of polymeric matrices[11,25–28].

Scanning electron microscopy (SEM) has been used to describe the tablet surface and cross sections of hydrophilic matrix formulations which revealed the changes in the matrix structure[26]. However, there is no direct link between polymer swelling and progressive changes that occur in the polymer microstructure during the course of the dissolution test. Lee et al.[29] described the surface and cross-sectional morphology of uncoated HPMC tablets, but the relationship between the surface and cross-sectional characteristics and the in vitro drug release characteristics of the polymer and how this changes during the course of a dissolution test were not evaluated. The microstructure and hydration properties of HPMC matrices of different molecular weights have been studied using electron paramagnetic resonance, nuclear magnetic resonance, and differential scanning calorimetry[30]. Although the study revealed the complex interrelationships between the viscosity grade of HPMC, in vitro dissolution rate of a water-soluble salt and the free base, water absorption capacity of polymers and polymer swelling, there was no apparent link between these aspects and the mechanism of drug release and the microstructure of polymeric matrices during the course of dissolution testing.

Although there is extensive information regarding the relationship between swelling and erosion of matrices and drug release kinetics, there is limited information about the link between drug release kinetics and microstructural changes within matrices during dissolution testing. The use of SEM may prove useful for understanding the impact of tablet porosity and tortuosity on drug release rates which may offer insight into the effect of changing polymer combinations and the impact thereof on drug release kinetics. Furthermore, there has been limited investigation, if any, into changes that occur within polymeric matrices at different stages of dissolution testing, that is, early, middle, and later stages, and how these relate to different rates of drug release that are observed when different polymeric combinations are used to manufacture SR formulations.

The objective of this study was to investigate the interrelationship between swelling and erosion behavior of tablet matrices manufactured using HPMC-based matrices and drug release kinetics with the microstructure of manufactured matrices at predetermined intervals during dissolution testing. Furthermore, the impact of additional polymer inclusion, specifically Carbopol® 71G and SCMC, on drug release rates and kinetics and changes in the microstructure were also investigated.

## Materials

SBS was donated by Aspen-Pharmacare (Port Elizabeth, Eastern Cape, South Africa). Methocel® K100M and Methocel® K4M (HPMC) (Dow Chemical Company, Midland, MI, USA), Avicel® PH101 (FMC BioPolymer, Philadelphia, PA, USA), SCMC (Aspen-Pharmacare, Port Elizabeth,

Eastern Cape, South Africa), Carbopol® 71G (Lubrizol, Wickliffe, OH, USA), magnesium stearate (Aspen-Pharmacare, Port Elizabeth, Eastern Cape, South Africa), and colloidal silica (Aspen-Pharmacare, Port Elizabeth, Eastern Cape, South Africa) were donated by the relevant suppliers and used as received. All other reagents were at least of analytical reagent grade and used as received.

## Methods

### *Tablet manufacture*

Hydrophilic matrix tablets were manufactured using direct compression, and batch sizes of 1000 tablets were produced for each formulation that was manufactured. The SBS, Methocel® K100M, additional polymers where required and Avicel® PH101 were dry blended using a Saral® Rapid Mixer and Granulator (Saral Engineering Company, Mumbai, Maharashtra, India) in a 5 L bowl using a speed of 100 rpm for the main impeller for 15 minutes. Thereafter 1% (w/w) magnesium stearate and 0.5% (w/w) colloidal silica were added and the blend mixed at the same speed for a further 3 minutes. The blend was transferred to a feed hopper and tablets were compressed on a Manesty® F3 single punch tablet press tooled with 7 mm flat-faced round punches to a uniform weight of 140 mg. A summary of the unit composition of the batches that were manufactured is shown in Table 1.

### *Weight, hardness, and thickness*

Twenty tablets of each formulation were tested for weight uniformity using a Mettler-Toledo Model AG135 electronic balance (Mettler-Toledo, Inc., Columbus, OH, USA). Tablet diameter, thickness, and hardness were measured using a PTB 311 Automated Tablet Testing Instrument (Pharma Test Apparatebau, Hainburg, Hesse, Germany) and the results reported as the mean ± SD.

### *Tablet analysis*

Twenty tablets were collectively weighed and ground using a mortar and pestle to form a homogenous powder.

**Table 1.** SBS tablet formula.

| | SBS-01 (mg) | SBS-02 (mg) | SBS-03 (mg) |
|---|---|---|---|
| SBS | 9.6 | 9.6 | 9.6 |
| Methocel® K100M | 70 | 70 | 70 |
| Carbopol® 71G | — | 28 | — |
| SCMC | — | — | 28 |
| Colloidal silica | 0.7 | 0.7 | 0.7 |
| Magnesium stearate | 1.4 | 1.4 | 1.4 |
| Avicel® PH101 | 58.3 | 30.3 | 30.3 |

An accurately weighed portion of the pooled sample, equivalent to the weight of one tablet (approximately 9.6 mg of SBS), was transferred to another mortar and mixed with approximately 70 mL of high–performance liquid chromatography (HPLC)-grade water to form a paste. The paste was quantitatively transferred to a 100 mL volumetric flask and sonicated for 15 minutes, and the resultant solution was made up to volume with water to produce a solution of approximately 96 µg/mL of SBS. A 5 mL aliquot of the solution was then transferred to a 20 mL A-grade volumetric flask and mixed with the internal standard, terbutaline sulfate, to produce a solution in which the concentration of internal standard was approximately 25 µg/mL. A 2 mL aliquot of this solution was filtered through a 0.45 µm Millipore® (Millipore, Bedford, MA, USA) filter prior to analysis by HPLC. Tablet analysis was performed in triplicate ($n$ = 3) and the results are expressed as the mean ± SD.

### *HPLC analysis*

A modular HPLC system was used to collect data and consisted of a Model P100 dual piston pump (Thermo Separation Products, San Jose, CA, USA), a Model AS100 autosampler (Thermo Separation Products), which was equipped with a Rheodyne® Model 7010 injector (Rheodyne, Reno, NV, USA) fitted with a 20 µL fixed volume loop and a 250 µL GASTIGHT® Model 1725 syringe (Hamilton Co., Reno, NV, USA), a Linear UV/VIS-500 Model 6200-9060 detector (Linear Instrument Co., Irvine, CA, USA), and a Spectra Physics SP 4600 integrator (Thermo Separation Products). A Phenomenex® Hyperclone® column, 5 µm, 150 × 4.6 mm (Phenomenex, Torrance, CA, USA), was used at ambient temperature (22°C) and the isocratic separation was achieved using a mobile phase consisting of 20% (v/v) ACN in 18 mM phosphate buffer at pH = 4, containing 15 mM sodium octane sulfonate with UV detection at 220 nm. The volume of injection was 20 µL and a flow rate of 1.0 mL/min was used for the separation.

### *In vitro dissolution studies*

A VanKel® Bio-Dis dissolution tester (VanKel Industries, Edison, NJ, USA) was used for the assessment of in vitro release of these formulations. A model VK 750D digitally controlled water circulation/heater (VanKel Industries) was used to maintain the temperature of the dissolution medium at 37 ± 0.5°C. A mesh of pore size 177 µm was used to retain the dosage form in the inner tubes and a dip speed of 10 dpm was used as the agitation rate. The duration of dosage form exposure to buffers of different pH is summarized in Table 2.

A 2 mL aliquot of the dissolution medium was removed and filtered through a 0.45 µm Millipore® filter

**Table 2.** Dissolution test conditions.

| pH | Duration of exposure (minutes) |
|---|---|
| 1.2 | 60 |
| 4.5 | 90 |
| 6.0 | 240 |
| 6.8 | 360 |
| 6.8 | 480 |
| 6.8 | 720 |

(Millipore). Thereafter a 1.5 mL aliquot was carefully placed in a sampling vial and 100 µL of terbutaline sulfate solution (400 µg/mL) was added to the vial such that the final concentration of the internal standard was approximately 25 µg/mL. The samples were analyzed using a validated HPLC method and the percent of drug released at different stages of the dissolution test was calculated.

### *Polymer swelling and erosion*

The rate of dissolution medium uptake by the tablets and polymer erosion was determined by equilibrium or gravimetric analysis methods[24,31,32]. The study was conducted using USP Apparatus 3 (VanKel Industries). Dry matrix tablets were accurately weighed using a Mettler-Toledo AG135 electronic balance (Mettler-Toledo, Inc.) and placed in a reciprocating cylinder prior to immersion in dissolution media of different pH maintained at 37 ± 0.5°C (Table 2) and agitated at 10 dpm. Tablets were removed at 60, 90, 240, 360, 480, and 720 minutes following exposure to the dissolution medium and lightly blotted with 125 mm filter paper (41 ashless Whatman® filter paper) to remove excess water. The swollen tablets were weighed to determine the extent of water uptake and were subsequently dried in a convection oven at 40°C. After 12 hours the tablets were cooled to ambient temperature and then weighed until a constant weight had been achieved and this was termed the dried weight. All studies were conducted in triplicate. The percent increase in tablet weight that can be attributed to the uptake or absorption of water was calculated at each time point using Equation (1):

$$\%\text{Water uptake} = \frac{W_s - W_i}{W_i} \times 100\%, \quad (1)$$

where $W_s$ = weight of swollen samples at sampling times and $W_i$ = initial weight of tablet matrices.

The percent matrix erosion was estimated at each time point using Equation (2):

$$\text{Matrix erosion} = \frac{W_i - W_t}{W_i} \times 100\%, \quad (2)$$

where $W_t$ = weight of dried matrices at sampling times and $W_i$ = initial weight of tablet matrices.

### *Modeling of dissolution profiles*

The mechanism and kinetics of drug release were deduced by fitting dissolution curves to the zero-order (Equation 3), Higuchi[33,34] (Equation 4), and Korsmeyer–Peppas[35] (Equation 5) models using the Curve-Fitting Toolbox of Matlab® (MathWorks Inc., Natick, MA, USA). The goodness of fit was established using the adjusted coefficient of determination $R^2_{\text{adj}}$ where the closer the value is to 1, the better the data fit to the model used to describe drug release patterns.

$$Q_t = k_0 t, \quad (3)$$

$$Q_t = k_{\text{H}} t^{\frac{1}{2}}, \quad (4)$$

$$\frac{M_t}{M_\infty} = kt^n, \quad (5)$$

where $Q_t$ = amount of drug released at time $t$; $M_t/M_\infty$ = fraction of drug released at time $t$; $k_0$, $k_{\text{H}}$, $k$ = kinetic constants for zero-order, Higuchi, and Korsmeyer–Peppas models, respectively; and $n$ = diffusional exponent the value of which is dependent on the mechanism of drug release and geometrical shape of the matrix that is being tested or assessed.

### *Scanning electron microscopy*

The surface and cross-sectional morphology of the matrix tablets prior to and during in vitro dissolution tests were analyzed using a Model TS 5136LM Vega® Tescan SEM (Tescan USA, Cranberry Twp, PA, USA). After each exposure interval, dosage forms at different time points were carefully removed from the dissolution apparatus and dried to constant weight in a convection oven at 40°C. Each dosage unit was cross-sectioned before mounting on a graphite plate and metallized with gold under vacuum. Tablet matrices were visualized under an accelerated voltage of 20 kV using different magnification to assess the structural changes in matrix structure during in vitro dissolution test conditions.

## Results and discussion

### *Physical properties of tablets*

Small smooth white tablets with no evidence of capping, chipping, or cracking were manufactured. The

**Table 3.** Physical properties of tablets.

| | SBS-01 | SBS-02 | SBS-03 |
|---|---|---|---|
| Weight (mg) | 141.01 ± 2.53 | 141.11 ± 1.21 | 140.68 ± 1.74 |
| Thickness (mm) | 2.99 ± 0.06 | 3.03 ± 0.03 | 3.17 ± 0.08 |
| Diameter (mm) | 7.16 ± 0.01 | 7.16 ± 0.01 | 7.22 ± 0.01 |
| Hardness (N) | 81.82 ± 4.41 | 123.64 ± 5.63 | 55.16 ± 5.80 |
| Assay (mg) | 9.64 ± 0.09 | 9.58 ± 0.23 | 9.62 ± 0.12 |

tablet weight and thickness, friability, and hardness of batches of tablets manufactured in these studies are summarized in Table 3.

The tablet weight, thickness, and diameter ranged from approximately 140 to 142 mg, 2.95 to 3.15 mm, and 7.15 to 7.22 mm, respectively, for the batches tested. The tablets remained intact for the duration of the study, with no visible signs of tablet fracture, chipping, or capping.

Tablet hardness was consistent for each of the batches manufactured although the hardness for each batch was formulation specific. It is apparent that the inclusion of Carbopol® (SBS-02) resulted in the manufacture of the hardest tablets compared to tablets from batch SBS-01, whereas adding SCMC (SBS-03) resulted in the production of relatively weak tablets compared to SBS-01. The low standard deviations of measurements indicate that the tablets showed little variability and it can be concluded that the method of manufacture of the formulations is appropriate for the production of quality SR matrix tablets of SBS.

### *Polymer swelling*

Visual and tactile evaluation of the matrix formulations confirmed that the dosage forms had developed a viscous gel on the surface following exposure to dissolution medium. The tablets were slippery to the touch, and the swelling increased initially and eventually decreased over the course of the dissolution test. The swelling behavior of the polymer over the course of a 720-minute dissolution test is shown in Figure 1.

Previous studies have suggested that polymer swelling such as that observed in this research occurs as a result of osmotic stress exerted at the moving front that is located between the dry glassy core and the outer rubbery gel layer[36]. When a water-soluble drug is incorporated into a hydrophilic matrix such as that manufactured using HPMC (SBS-01), there is an increase in the osmotic stress within the polymer matrix which results in water penetrating into the interior of the matrix with consequent polymer swelling and formation of microcavities that promote drug release[36].

The maximum liquid uptake and swelling of tablets of SBS-01 was achieved after 480 minutes after which the average tablet weight decreased because of matrix

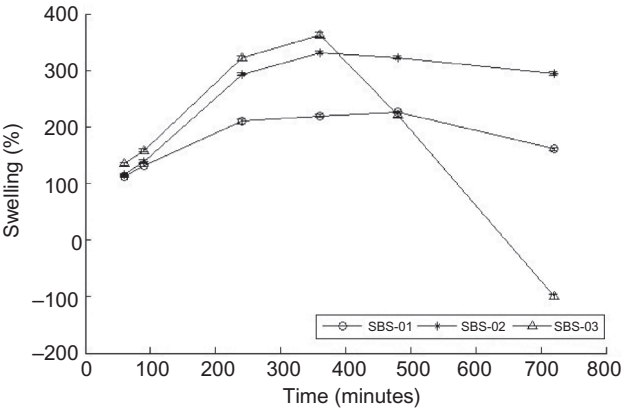


**Figure 1.** Plot of percent swelling (water uptake) as a function of time (mean ± SD, $n = 3$).

erosion. Tablets of batches SBS-02 and SBS-03 both reached maximum swelling after 360 minutes but the rate of polymer erosion of SBS-03 was higher than that observed for SBS-02. The decline in tablet weight of SBS-02 indicates that erosion of the polymer is not as rapid as that observed for the formulation containing SCMC (SBS-03) and is discussed later. Batches SBS-02 and SBS-03 also show higher levels of overall swelling of the tablet matrix suggesting that there is an increase in the diffusional distance through which drug molecules must pass prior to release from the inner matrix into the dissolution medium. The gel layer that is formed acts as a barrier to diffusion of the drug from the dosage form and it would therefore be expected that the rate of drug release from matrices that contain additional Carbopol® and SCMC would be lower than that for matrices that do not contain the additional polymer.

The water uptake data were analyzed using the Vergnaud model[37] to determine the rate and mechanism of water uptake into the polymeric matrices. The generalized form of the Vergnaud model used is shown in Equation (6)[24,32]:

$$M_t = kt^n, \tag{6}$$

where $M_t$ = amount of liquid transferred at time $t$; $k$ = swelling constant which depends on the amount of liquid transferred over an infinite time; and $n$ = mechanism of water uptake.

The model was only applied to the swelling phase of the test (0–360 minutes) as at least one of the formulations started to erode at that time (Figure 1). The Vergnaud plot for hydrophilic matrix formulations is shown in Figure 2 and the characteristics of tablet matrices that describe the rate and mechanism of water penetration are summarized in Table 4. In general, the $R^2$ values

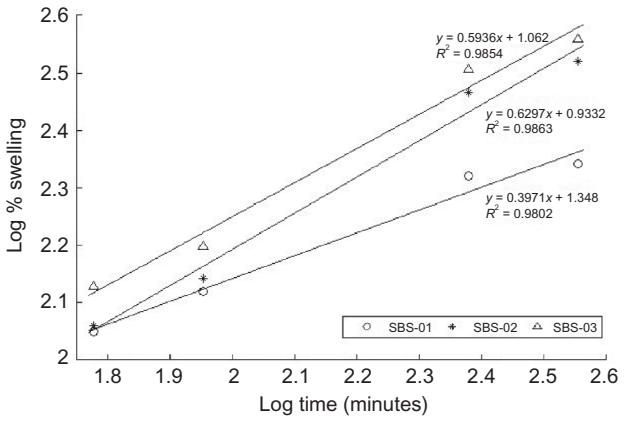


**Figure 2.** Vergnaud plot of log percent swelling (water uptake) as a function of time.

**Table 4.** Kinetic parameters according to the Vergnaud model computed using Equation (6).

| | $n$ | $k$ | $R^2$ |
|---|---|---|---|
| SBS-01 | 0.3971 | 22.284 | 0.9802 |
| SBS-02 | 0.6297 | 8.574 | 0.9863 |
| SBS-03 | 0.5963 | 11.534 | 0.9854 |

indicate that the data can be well described by this model ($R^2 > 0.98$ for all data sets).

The rate of polymer hydration is an important aspect in controlling the rate of drug release from polymeric matrices and was therefore measured to determine if a correlation between the rate of polymer hydration and drug release rates from matrix formulations existed. The swelling constant derived from the Vergnaud model depends on the porosity of the matrix and diffusivity of water in the matrix[32] and is an indicator of the rate of polymer hydration. The results summarized in Table 4 suggest that the rate of water penetration is considerably higher for tablets of batch SBS-01 than that observed for the tablets that contained additional polymers Carbopol® 71G and SCMC. The high swelling exponent suggests that burst swelling occurs when matrices manufactured using HPMC are immersed in an aqueous medium and results in controlled drug release from these formulations.

The rate of polymer hydration is dependent on the structure of the polymer or polymer combinations used in formulations in addition to the degree of interaction of functional groups within polymeric matrices with water. The better the interaction between a polymer surface and water, the faster the polymer hydrates because the first layer of adsorbed water molecules enables easier adsorption of additional water molecules[38]. The presence of the methyl substituent of HPMC suggests that the polymer backbone has medium polarity and permits interaction of the molecule with water[38], thereby promoting hydration and consequent swelling such as that observed.

The addition of Carbopol® 71G, which is composed of allyl ethers of pentaerythritol, to the primary formulation changes the interaction of water molecules with the surface of the polymer and results in a lower rate of hydration compared to that observed for the HPMC formulation. The swelling of Carbopol® is dependent on the pH of the medium to which it is exposed to during dissolution testing. When Carbopol® comes into contact with water, the glass transition temperature drops dramatically, and plasticization of the polymer chains by water commences gyration of the molecules. A relaxational response by the polymer chains because of stresses introduced by the presence of the dissolution medium is observed. As the radius of gyration increases, the end-to-end distance between the polymer chains increases and the polymer is seen to swell[10,39]. The $pK_a$ of Carbopol is $6 \pm 0.5$, and at acidic pH because of the low degree of ionization, hydration is limited and becomes increasingly greater as the pH increases. At a pH of 4.5, the polymer starts to ionize, becoming more hydrated, and starts to swell[39]. This is evident from the lower rate of polymer hydration observed following fitting of data to the Vergnaud model. It is evident from the Vergnaud plot in Figure 2 that the most rapid swelling for the polymer occurs between 90 and 240 minutes when the pH of the dissolution medium is changed from pH 4.5 to 6.0, and a corresponding large increase in the water uptake is observed. The slow rate of polymer hydration or polymer swelling during the initial stages of dissolution testing is also evident in Figure 1, where it is clear that the rate of water uptake increases significantly after pH 4.5 (or 90 minutes) resulting in increasing water hydration.

When SCMC, which is a cellulose derivative with carboxymethyl groups bound to some of the hydroxyl groups of the glucopyranose monomers that make up the cellulose backbone, is immersed in aqueous medium water does not interact readily with the surface of the polymer and results in a slower rate of hydration compared to that observed when HPMC alone is used. The combination of anionic SCMC and nonionic HPMC results in the formation of hydrogen bonds between the carboxyl groups of SCMC and the hydroxyl groups of HPMC, leading to stronger physical entanglement of the polymer chains compared to either pure polymers[40]. It is likely that the stronger physical entanglements that are formed result in a reduced rate of water penetration and a lower rate of polymer hydration according to the Vergnaud model.

The data summarized in Table 4 also reveal that the rate of hydration of tablet matrices that contain mixtures of HPMC and Carbopol® 71G is slower than that observed when SCMC is used as an adjuvant. This is

due to the lower hydrophilicity of Carbopol® polymers compared to SCMC and poorer interaction of water molecules with the surface and consequent lower rates of polymer hydration.

Polymer swelling kinetics may be inferred from the value of the exponent that is obtained from the Vergnaud equation. According to Ebube et al.[41] when $n < 0.5$ polymer swelling is determined or controlled by diffusion of the dissolution medium into the matrix because the rate of diffusion of liquid is considerably less than the rate of relaxation of the polymer segment. However, when $n = 1$, water diffuses through the matrix at a constant velocity showing an advancing liquid front marking the limit of liquid penetration into the matrix. A value of $0.45 < n < 1$ indicates an anomalous or complex behavior in which the rate of water diffusion and polymer relaxation in the tablet matrix are of the same magnitude. The mechanism of polymer hydration by HPMC matrices ($n = 0.397$) under the conditions that were evaluated follows a diffusion-controlled mechanism where the rate of polymer relaxation is greater than the rate of water penetration into the matrix. The inclusion of polymeric adjuvants results in a change in the mechanism of polymer hydration or swelling as indicated by the value of $n > 0.5$ for both formulations, which suggests that an anomalous or complex mechanism of release exists. The addition of the polymeric adjuvant clearly results in a change in the properties of the matrix and its behavior in an aqueous medium. Both polymers used have ionizable functional groups that result in a different interaction with water molecules compared to the HPMC matrix. Carbopol® shows pH-dependent swelling kinetics, and although water is not ionizable, water molecules are able to form stronger hydrogen bonds with ionizable functional groups, especially at pH > 4.5 where the polymer starts to ionize. This results in polymer chain relaxation and therefore a complex mechanism of swelling kinetics that may be attributed to both diffusion of water and polymer swelling as the polymeric chains start to gyrate. Similarly, SCMC is ionizable and results in the formation of hydrogen bonds with water, and polymer relaxation and movement of a gel front occur thus resulting in an anomalous mechanism of polymer swelling.

### *Polymer erosion*

Hydrophilic matrix formulations eventually undergo erosion as polymers dissolve following immersion in aqueous media. The rates of polymer erosion for the different hydrophilic matrices that were evaluated are shown in Figure 3.

The formulation prepared using HPMC (SBS-01) shows the slowest rate of polymer erosion, compared to

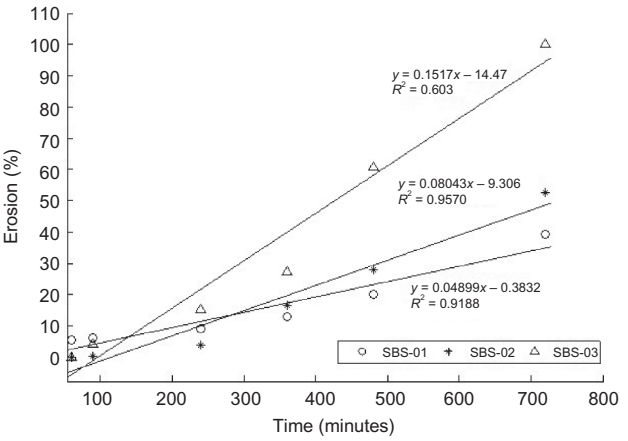


**Figure 3.** Plot of percent erosion of tablets versus time.

formulations that contain additional polymer. A moderate rate of polymer erosion is observed for the Carbopol®-containing (SBS-02) preparations suggesting that they have a greater resistance to erosion compared to tablets of batch SBS-03 which exhibited the highest rate of polymer erosion.

HPMC is water soluble and when water penetrates the cellulose matrix, the polymer chains become hydrated and these eventually disentangle from the matrix because HPMC contains linear hydrophilic polymeric chains which do not cross-link but instead form a gelatinous layer on the surface of the tablets that is susceptible to erosion. At high polymer concentrations, the linear polymer chains entangle to form what may be considered 'virtual cross-linking' which eventually erodes, resulting in drug liberation[17,39]. However, the rate of polymer erosion is dependent on the viscosity of the HPMC grade that is used in the formulation and Methocel® K100M has a high molecular weight and is of high viscosity grade and is therefore relatively resistant to polymer erosion compared to the low molecular weight and low viscosity grades.

When Carbopol® matrices are placed in water, the cross-linked nature of the polymeric chains results in the formation of water-insoluble discrete microgels in which the drug is dispersed. These do not dissolve or erode in aqueous medium in contrast to the erosion observed in linear polymers. However, when the polymer is fully hydrated, osmotic pressure from within the networks disrupts the structure, sloughing off discrete microgels from the surface of the polymer. The microgels remain intact after being removed from the surface of the polymer and drug release of water-soluble drugs continues to occur by diffusion from the interior of the microgels[17,39]. The combination of HPMC and Carbopol® in a formulation means that there is a combination of discrete microgels and linear polymers in the gel layer and therefore the dissolution of the linear matrix

and sloughing off of the microgels occurs simultaneously in this system. This is a likely reason why the rate of polymer erosion from batch SBS-02 is faster than that observed from SBS-01.

The rate of erosion of batch SBS-03 is higher than that observed for batch SBS-01 and this is in agreement with earlier studies where it was reported that the combination of nonionic and ionic polymers results in a faster rate of erosion compared to formulations that only contain a nonionic polymer such as HPMC[10,16]. The optimization of the ratio of ionic : nonionic polymer suggests that the rate of advancement of the swelling front into the glassy polymer and the attrition of the rubbery state polymer are synchronized, such that the diffusional path through which the drug must move remains nearly constant and independent of time[10,16]. This would result in a zero-order release pattern from hydrophilic matrix systems. However, the limitation of this theory is that it does not account for the incidences when the size of the matrix is smaller than the original size. It has therefore been proposed that as the rate of water penetration into the tablet matrix increases with time and the erosion rate of the matrix is nearly constant for these systems, the diffusional path changes with time. As a consequence drug release rate per unit area of the matrix also changes with time and the net effect of this is that the cumulative amount of drug that is released from the dosage form is linear until the entire dose is released from a dosage form[10].

### *In vitro release studies*

The in vitro release profiles for formulations in which Methocel® K100M was the primary matrix-forming polymer are depicted in Figure 4. Batch SBS-01 contains 50% (w/w) Methocel® K100M and was used as the reference formulation against which the other formulations were compared.

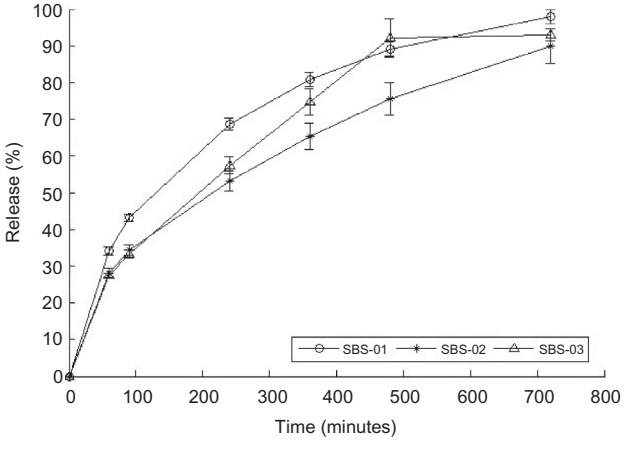


**Figure 4.** Dissolution rate profiles of SBS from tablets of batches SBS-01, SBS-02, and SBS-03.

The dissolution profile for tablets from batch SBS-01 reveals that SBS is released rapidly from the formulation and that approximately 35% of the dose is liberated within an hour of the commencement of testing. This is a typical characteristic of SR hydrophilic matrix dosage forms in which water-soluble drugs are included. Hydrophilic matrices generally exhibit an initial burst release followed by a gradual decreasing rate of release over the course of dissolution testing[20]. The in vitro release profile also reveals that the release of SBS from the matrices is almost complete after 12 hours and the inclusion of additional polymers may result in a reduction in both the burst and overall release rate of SBS.

The inclusion of Carbopol® 71G (SBS-02) to the primary formulation (SBS-01) resulted in a decrease in both the burst and overall release rate of SBS from the formulations as shown in Figure 1. Carbopol® polymers are high molecular weight cross-linked synthetic polymers of acrylic acid that are insoluble in water, although they readily absorb water and swell. This property makes them ideal candidates for inclusion in the formulation of hydrophilic devices for oral SR delivery[17,39]. On hydration Carbopol® polymers form a gelatinous layer that has a significantly different structure to that formed by HPMC described previously. The cross-linked nature of the network results in the entrapment of drugs in the hydrogel domains thereby hindering drug diffusion from these matrices. The addition of Carbopol® polymers therefore results in a reduction in drug release[17] as observed in Figure 4. The pH-dependent swelling kinetics of Carbopol® polymers that are shown in Figure 1 have important implications when designing SR formulations because pH-dependent swelling kinetics present a means of controlling the initial burst release observed for water-soluble compounds during the early stages of dissolution testing.

Batch SBS-03 was formulated with SCMC as an additional excipient and the results reveal that there is an initial burst, equivalent to approximately 25% of the dose that is released within an hour of commencement of dissolution testing. The amount of drug released as a result of the burst for this formulation is lower than that observed for batch SBS-01, which is congruent with other reports[40]. The combination of an anionic polymer such as SCMC with nonionic polymer such as HPMC has been shown to result in a synergistic increase in viscosity of the gel layer that is formed on hydration and therefore a greater barrier to drug diffusion with a consequent decrease in burst release. The change in release is attributed to the formation of hydrogen bonds between the carboxyl groups of SCMC and the hydroxyl groups of HPMC, leading to stronger physical entanglement of the polymer chains compared to either pure

polymers[40]. It is also apparent that the release rate between 1 and 8 hours of the dissolution test is linear compared with the release pattern that is observed for batch SBS-01. The linear pattern observed indicates that drug release follows zero-order release kinetics.

### *Salbutamol sulfate release rate and mechanism of release*

The relative contribution of polymer erosion and drug diffusion to the drug release processes is dependent on the specific polymer combinations and ratios that are used in formulating an SR dosage form. If a durable and viscous matrix-forming polymer is used to manufacture SR formulations, then water-soluble drugs such as SBS are released primarily by diffusion-controlled kinetic processes and drug release rates decrease over time. In cases where an erodible polymer combination is used in a formulation, polymer erosion will contribute significantly to the mechanism of release and active pharmaceutical ingredient (API) release rates remain constant throughout the period of use of the delivery system.

Mathematical models including the zero-order, Higuchi, and Korsmeyer–Peppas models are useful when attempting to elucidate and understand the mechanism of drug release from matrix formulations and their use is well documented[42–45]. When dissolution data are fitted to these empirical models, a high $R^2_{adj}$ value indicates the appropriateness of the model to describing the possible mechanism of drug release. When the Korsmeyer–Peppas model is used the value of the exponent $n$ is used to infer the drug release mechanism. The dissolution data shown in Figure 1 were used to determine the mechanism of release for the batches under investigation for a percent SBS released <60% for the Korsmeyer–Peppas model and complete drug release for the other models. The resultant parameters generated following modeling of the data using these models are summarized in Table 5.

The results summarized indicate that drug release from the matrices manufactured in this research cannot be attributed to a zero-order mechanism and that it may be better described by the Higuchi model, indicating that diffusion is likely to be the primary mechanism governing drug release. This may be inferred from the higher values of $R^2_{adj}$ when the Higuchi model is fitted to the dissolution data. The Korsmeyer–Peppas model is more comprehensive and describes drug release patterns that range from diffusion-controlled mechanisms and zero-order release. According to the model, drug diffusion through polymeric matrices can be described by three types of release mechanism, namely, Fickian, anomalous, and/or swelling-controlled diffusion[46]. The numerical value of the exponent $n$ describes the mechanism of drug release from a dosage form and is specific for a particular geometry. For a cylinder such as the matrix tablets that were manufactured in this study, when $n = 0.45$, the mechanism of release is considered to be governed by Fickian diffusion and is termed Case I transport. When $0.45 < n < 0.89$ then mass transfer of an API from the matrix is considered to follow an anomalous transport mechanism that is a function of both drug diffusion and polymer relaxation. When the exponent $n > 0.89$ the release mechanism is considered to be swelling-controlled and is referred to as Case II transport.

**Table 5.** Drug release parameters for manufactured formulations.

| | SBS-01 | SBS-02 | SBS-03 |
|---|---|---|---|
| $k$ | 0.04573 | 0.03469 | 0.02917 |
| $n$ | 0.4946 | 0.5193 | 0.5434 |
| $R^2_{adj}$ | 0.9994 | 0.9998 | 0.9996 |

The value of the exponent obtained following modeling the dissolution profiles generated after testing of HPMC matrices was 0.4946, indicating that drug release is primarily controlled by a diffusion mechanism and that drug transport is dependent on the concentration gradient that exists between the tablet matrix and the aqueous dissolution medium. The drug moves from a region of high concentration in the tablet matrix to a region of low concentration in the bulk aqueous medium. These results are in agreement with those previously reported[6,47] in which it was shown that the liberation of water-soluble drugs from hydrophilic matrices is primarily diffusion controlled.

Diffusion of a drug through the gelatinous layer and erosion of the polymeric matrix may both contribute to drug release mechanisms from hydrophilic matrices, although one process will often be dominant[32]. The relative contribution of these mechanisms is dependent on the specific polymer combinations and ratios that are used in the formulation of SR dosage forms. If a durable and viscous matrix former is used to prepare SR formulations, then water-soluble drugs such as SBS are liberated primarily by diffusion-controlled kinetics and the rate of drug release decreases with time. Whereas if an erodible polymer combination is used in formulation, then polymer erosion will be a significant contributor to the mechanism of drug release.

The release of drug from Carbopol® matrices has been reported to exhibit both diffusion-controlled[48] and zero-order release profiles[18,19,49]. The inclusion of Carbopol® to matrix formulations that contain HPMC results in a shift in the mechanism of drug release as was observed for batch SBS-04. The value of $n$ increased from 0.4946 to 0.5193 when Carbopol® was added to the HPMC-containing formulation. This is indicative that an anomalous mechanism of drug release that may be attributed to both polymer relaxation and diffusion is

occurring, although diffusion is still the primary mechanism of drug release.

The dissolution profile for batch SBS-03 revealed that linear release kinetics occurs between 1 and 8 hours indicating that drug release is directly proportional to time. The combination of HPMC and SCMC has previously been reported to result in zero-order release patterns of drug molecules from matrix formulations[16,40,50]. The exponent $n$ in this case was 0.5434 indicating that an anomalous transport process predominates because of both diffusion and polymer relaxation, although diffusion is still a significant contributor to the release process. The low dose and high aqueous solubility of SBS resulted in rapid drug release during the initial stages of dissolution testing and therefore a deviation from a true zero-order release pattern was observed. By altering the ratio of HPMC : SCMC it is possible to achieve true zero-order release formulations as has been previously reported[50].

### *Scanning electron microscopy*

#### Surface morphology

The change in surface morphology of matrix tablets at different stages of the dissolution test was observed using SEM. The effect of adding Carbopol® and SCMC on the surface morphology was also evaluated. Figure 5 portrays the surface morphology of dry tablets that had not been exposed to dissolution medium. The surface is smooth with no evidence of grooves or unevenness on the surface. The cross section shows that the tablet matrices that are prepared are likely to be homogenous; it also shows the well-compressed nature of the dry glassy core.

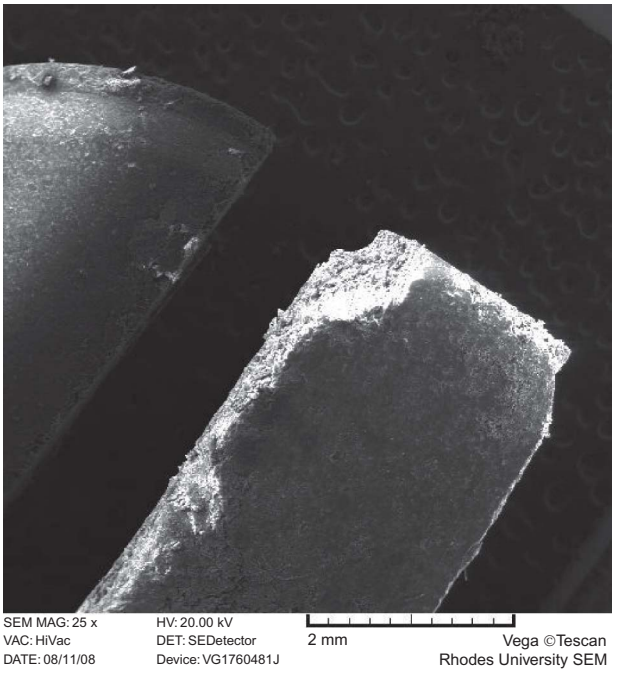


**Figure 5.** Cross-sectional and surface morphology of untreated tablets viewed at 25× magnification.

Figure 6 shows the impact of dissolution test medium on the surface morphology of formulations that had been exposed to the dissolution medium at different stages of the dissolution test, that is, in the early (60 minutes), middle (360 minutes), and later (720 minutes) stages of the dissolution test.

The micrographs showed that the surface of the matrix tablets is of a rubbery and viscous nature. Even though diffusion is the major contributor of the drug release mechanism, it is evident from looking at the micrographs and considering gravimetric analysis that erosion of the matrix occurs during the course of the dissolution test. The percent polymer eroded increases during the dissolution test and this is evident from observing the surface structure which shows a greater eroded surface at the end of the dissolution test and is in agreement with the observations depicted in Figure 3. The magnified surfaces show that polymer strands had formed compact structures during the dissolution tests and these became increasingly so during the course of the dissolution test. Water penetrates the tablet matrices and causes polymer disentanglement on the surface for all formulations, which appears as grooves on the surface. At the end of the dissolution test, it is evident that SBS-01 and SBS-02 have undergone polymer erosion, and SBS-03 has completely eroded.

There are differences in the matrix microstructure in the different formulations, which also related to the rate and mechanism of release that was described earlier. The surface structure of SBS-02 appears more compact compared to that of SBS-01, particularly in the early stage of the dissolution test. This is due to the ionic nature of the polymer, which is not ionized at low pH and remains compact and reduces the rate of water penetration into the matrix, with a corresponding decrease in the rate of drug release. During the later stages of the dissolution test, the polymer strands of Carbopol® become ionized and the microstructure becomes less compact and results in increased swelling that is evident from the gravimetric analysis (Figure 1).

The surface of SBS-03 shows that the surface structure is more compact compared to that of SBS-01, showing more grooves on the surface and closer packing of structure. This corresponds with the lowering of the initial rate of drug release that is observed for this formulation in Figure 4. The increase in compactness corresponds to the theory of increasing viscosity because of the synergistic relationship between the ionic and nonionic polymers[40].

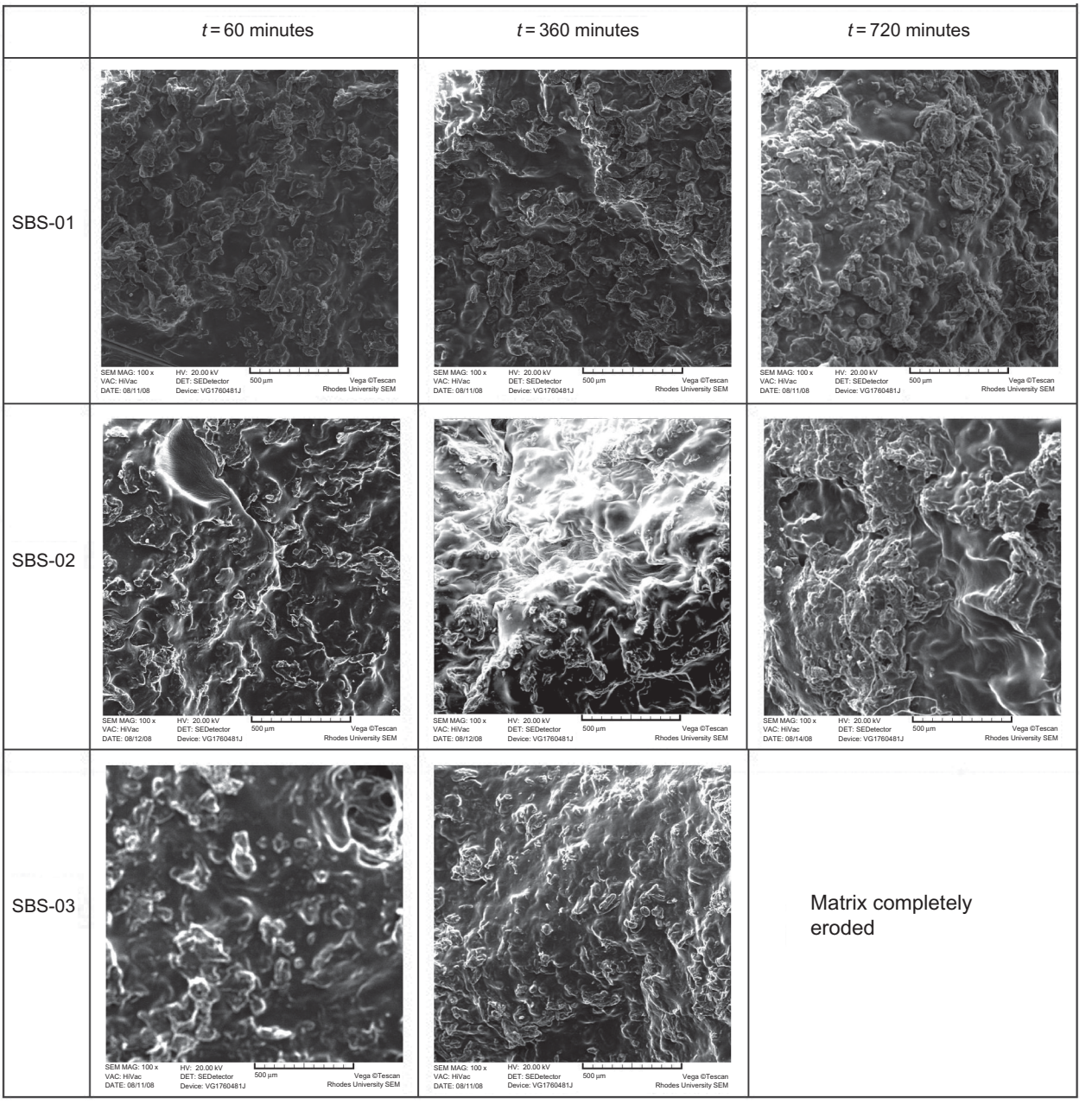


**Figure 6.** SEM showing surface of matrix tablets during tablet dissolution.

**Cross-sectional views**

Cross-sectional views of the matrix tablets were taken at different stages of the dissolution test to determine the changes in matrix structure during the dissolution test. Figure 7 is a depiction of the typical cross-sectional view of the prepared tablets before the dissolution test.

The presence of microcavities within the polymeric matrices is evident from the SEM study which shows that channels formed as a result of polymer swelling are likely to promote drug release from these polymeric matrices.

When HPMC is used as a matrix former, there is a change in the matrix structure as the dissolution test proceeds. After 90 minutes, the tablet was swollen and there was an increase in the number of water channels visible in the microstructure. The matrix tablet continued to increase in size for the duration of the dissolution test, with increases in the radial and axial dimensions of the hydrated tablets until the end of the test. Therefore, although erosion of the tablets became evident in the later stages of the dissolution test (Figure 3), there was

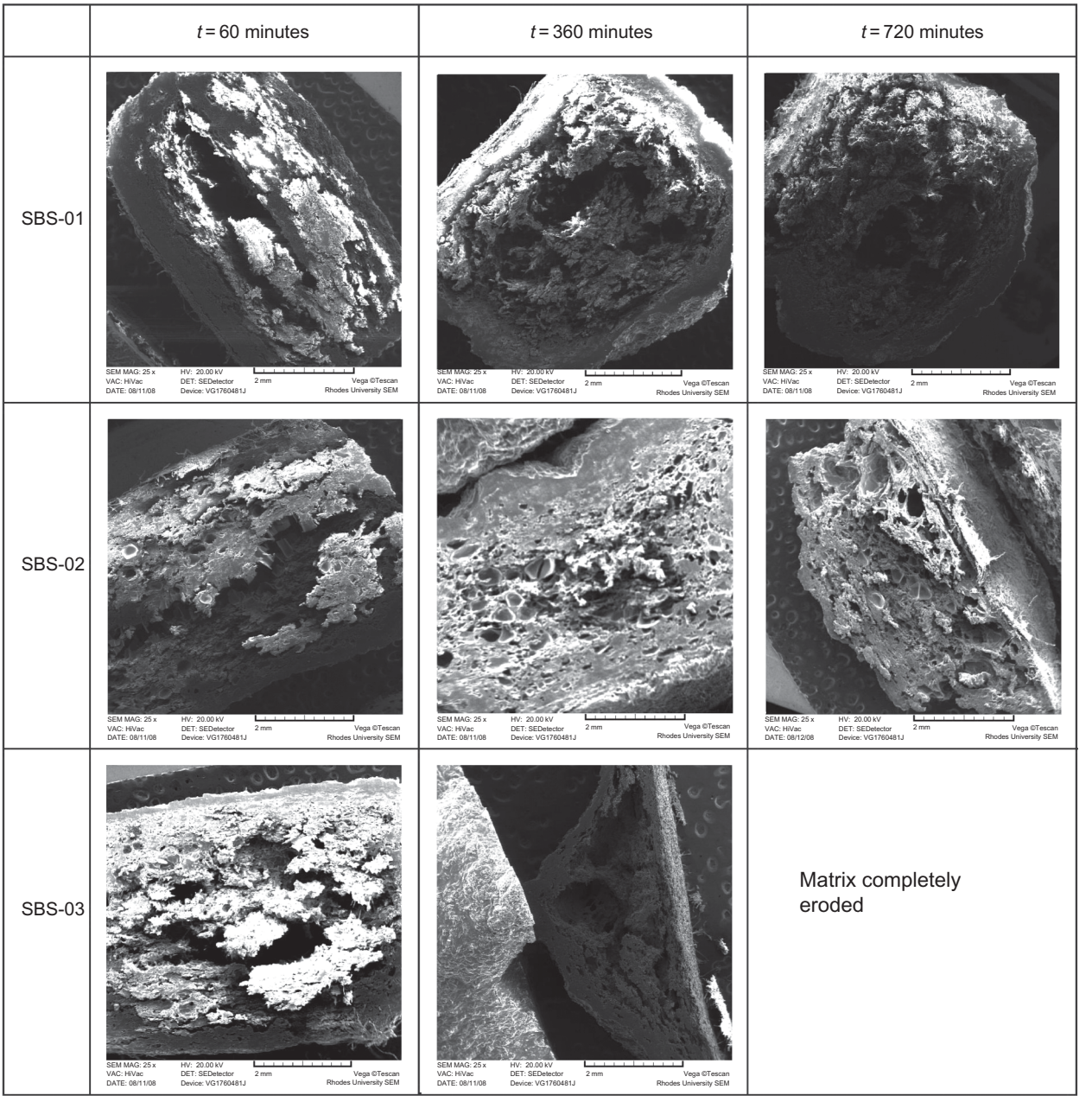


**Figure 7.** Cross-sectional views of tablet matrices prepared from SBS-01, SBS-02, and SBS-03 during the course of the dissolution test.

an increase in physical size because of the presence of microcavities within the matrix structure.

The addition of additional polymer resulted in a change in matrix structure that was related to changes in the swollen and erosion rates and the mechanism of drug release from the formulations. The addition of Carbopol® to the formulation resulted in a more compact structure compared to the HPMC formulation and resulted in a consequent decrease in the rate of drug release from the formulation compared to SBS-01.

The inclusion of SCMC also resulted in a change in matrix structure that is observed in the early stages of the dissolution test, where the increase in viscosity because of the combination of polymers results in a more compact structure with a consequent reduction in the drug release rate. However, after 360 minutes, the matrix was most eroded and had large cavities in the structure. The rate of drug release in the latter regions of the dissolution test is also higher compared to the HPMC formulation.

## Conclusions

Water uptake and erosion studies when hydrophilic matrix tablets were exposed to aqueous medium for a period of 12 hours were undertaken. Both the drug release rate and kinetics from polymeric matrices are influenced by the rate of water penetration into the interior of the matrix, extent of polymer swelling, drug diffusion from the interior of tablet matrices, and polymer erosion. The current studies revealed that polymer swelling occurs significantly in matrices that are based on HPMC, although it is evident that the inclusion of adjuvants, Carbopol® and SCMC, results in changes in the rate of water penetration, polymer swelling, and rate of erosion. The changes in polymer swelling and erosion that were observed when polymeric adjuvants were added also resulted in changes in both the rate and mechanism of drug release from manufactured matrices. It is evident that the use of different polymer combinations results in changes in the surface properties, tortuosity, and porosity of hydrophilic matrices, which impact the burst release and rate of dissolution in the later stages of the dissolution test. Understanding the changes in these properties using a visualizing tool such as SEM provides insight into how the microstructure and microcavities change during the dissolution test and how these impact the rate of drug dissolution from hydrophilic matrices. Additionally, the changes in microstructure in these formulations are also a function of the polymer combinations that are used to manufacture formulations as is evident from the current study. Information from swelling and erosion studies in conjunction with SEM provides a useful strategy for understanding formulation behavior and ultimately optimization of pharmaceutical products.

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## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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