ZERO-ORDER CONTROLLED-RELEASE KINETICS THROUGH POLYMER MATRICES

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ABSTRACT

Controlled-release technology involves the diffusion of molecules into an environment at a constant rate. A zero-order control-release prototype utilizing vapor pressure equilibrium was developed by placing liquid organic substances into a petri dish covered with a polymer membrane. Three organic substances with differing polarities (ethyl acetate, hexane, and 2-pentanol) were each tested through three different polymer membranes (polyethylene, 10% ethylene-vinyl acetate, and 12% ethylene-vinyl acetate). The release rates of these various molecule-polymer combinations were measured and compared to the predictions of established solubility parameters. The results of the experiment demonstrated a constant rate of release and indicated that polarity had a significant effect on rate. However, other factors such as the crystallinity of the polymer membranes, vapor pressure, and molecule-polymer affinity may have influenced the results as well. The research provided the groundwork for further studies in zero-order release mechanisms.

INTRODUCTION

Controlled-Release

Controlled-release technology deals with the release of chemicals into an environment at a rate that remains constant even as the concentration of the chemical decreases. This growing field is an increasingly important “scientific activity concerned with the control . . . of the biological effects of therapeutic agents in . . . health, and of other active agents in environmental, consumer, and industrial applications” (1). This field is particularly important in the fields of agriculture, zoology, cosmetics, medicine, and therapy. Products that utilize this technology seek to keep the rate of release of a substance independent of the concentration of substance to be released (1). For example, in agriculture, controlled-release technology allows for the continued fertilization of crops as the fertilizer is released into the soil at a constant rate. Without controlled-release, a chemical must be administered at repeated intervals in order to maintain the desired concentration. As the substance enters into a system, there is a spike in the rate of release (or in the rate of absorption if the substance is diffusing through a vessel like a pill) (Fig. 1). This rate decreases in proportion to the concentration of drug that has not yet been absorbed. If the pill were to have a constant release rate, the concentration of the drug could be maintained at the desired level so drugs could be effective for longer periods of time with fewer risks of side effects.
The most common controlled-release mechanisms involve the diffusion of a chemical through a polymer delivery system. In a homogeneous system, the chemical to be released is embedded into the polymer matrix and then slowly diffuses into the environment (Fig. 2). For this model, the rate remains relatively stable but does decrease over time as the remaining chemical has to travel greater distances during diffusion. Another more effective method is the reservoir system (Fig. 2), in which the chemical diffuses out through a polymer membrane surrounding it. In this mechanism, the rate remains largely constant because the polymer membrane has a uniform composition throughout the device and a uniform thickness over time (2). The type of polymer used for the membrane is the key to creating this diffusion-based controlled-release system.

Figure 1: Concentration of substance vs. time. This figure shows the large fluctuations in concentration leading to side effects or ineffectiveness. Controlled-release, meanwhile, seeks to keep the concentration at the effective level.

Figure 2: Comparison of chemical embedded in a polymer matrix (far left) and a reservoir system. This figure shows two different mechanisms seeking to achieve controlled-release. The reservoir system maintains a release rate closer to zero-order because the polymer acts as a uniform membrane surrounding the molecule (2).
Polymers

A polymer is a macromolecule consisting of a series of chemically bonded monomer units. They can be either natural or synthetic, and most are in the solid state due to strong intermolecular forces such as hydrogen-bonding. The morphology of different polymers largely accounts for their observed diverse properties (3). Important characteristics include their molecular size, strength of their intermolecular forces, entanglement, crystallinity, and cross-linking.

The structure of polymers has substantial effects on properties such as strength and flexibility. They can have linear, branched, or ring-shaped architecture. Linear polymers consist of a long chain of monomers without any branching and allow easy packing of the monomers. Branched polymers contain “side chains” that extend off of the backbone unit. They increase the intermolecular forces and decrease the flexibility of the polymer. Ring-shaped polymers, like their name suggests, have chains arranged in a ring structure (4).

The structure of solid polymers contains intertwining crystalline and amorphous regions (Fig. 4). The orderly crystalline regions contribute to a polymer’s rigidity and opaqueness, and do not allow molecules to pass through. In contrast to these areas, the tangled amorphous regions contribute to a polymer’s flexibility and transparency, and allow for diffusion of molecules (4). The crystallinity is determined by the distribution of the atoms relative to each other. For example, chain length, chain branching, and inter-chain bonding help determine the ratio of crystalline to amorphous regions. Intermolecular forces also help a structure form a crystal – polar and hydrogen bonds, for example, hold polymers very tightly together. A polymer that has a long chain, few branches, and inter-chain bonding will be more crystalline in structure. This tightly-packed crystalline shape allows for less diffusion through the membrane (4).

Cross-linking, on the other hand, within a structure strengthens the polymer by bridging polymer chains and tying them together. Once cross-linking has taken place, the object has a rigid shape because all the polymer chains are covalently bonded (5). Similar to crystallinity, the less flexible structure of a cross-linked polymer allows for less diffusion across the membrane (5).

Generally, in order to modify the release rate of a chemical, the shape or composition of the chemical is changed (6). For many industries, the substance to be released is unique and hard to replace, like expensive drugs or rare fertilizers. A more viable means of changing the rate would be altering some characteristic of the polymer-based delivery system. For a chemical to pass through a polymer without pores, it must first dissolve into the polymer. The different
structural characteristics of the polymer influence how quickly the chemical can pass through the polymer chains. For example, a very polar chemical would very slowly dissolve across a highly non-polar polymer, producing a very slow release rate. The chemical to be released interacts with the long chains of the polymer as it dissolves and is then driven by a concentration or chemical potential gradient to diffuse through. Therefore, different polymers with varying properties were tested in this experiment to determine which would lead to a more ideal rate of release.

Polyethylene and EVA

Polyethylene and ethylene-vinyl acetate (EVA) were chosen as the polymers for this experiment.

Polyethylene (Fig. 5) is a common polymer used in packaging materials. It consists of ethylene monomers, which are composed of two methylene units connected by a double bond between the two carbon atoms (CH2=CH2). The polymer polyethylene forms when the double bonds are broken and the monomers connect to create a long chain of ethylene monomers. Catalysts can quicken the polymerization process and cause branching or elongation of a linear chain. Branched molecules are referred to as low-density polyethylene (LDPE) and linear low-density polyethylene (LLDPE), while linear molecules are referred to as high-density polyethylene (HDPE) and ultrahigh-molecular-weight polyethylene (UHMWPE) (7). The branches allow the molecule to retain a high degree of flexibility because the molecule does not have a tightly packed structure, allowing for a higher rate of release.

Polyethylene is a non-polar polymer. However, its regular structure causes it to form more crystalline regions than a more polar polymer.

Using free-radical catalysts, ethylene can be copolymerized with vinyl acetate to form ethylene-vinyl acetate copolymer (EVA) (Fig. 6). This is another polymer commonly used in the packaging industry for films, adhesives, toys, tubing, and wire coatings. EVA copolymers are more permeable to gases and moisture than polyethylene (7). EVA can be made with differing ratios of vinyl-acetate to ethylene. Due to the non-polar structure of ethylene and the polar carboxyl group on vinyl acetate, the composition ratio can be altered to synthesize EVA copolymers of various polarities, which will affect the rate of diffusion.
By utilizing these membranes to create a controlled-release mechanism, the reaction rate had to be analyzed through the application of diffusion kinetics.

Diffusion Kinetics

Chemical kinetics is the study of how quickly a reaction progresses (8). Chemical reactions can be described by differential rate laws that relate the concentration of reactants to the rate of the reaction. Most processes are experimentally confirmed to be either first-order or second-order. Depending on the reaction mechanism, a series of elementary chemical steps, the particular process will be modeled as a differential rate law with one or multiple initial reactant concentrations. In this experiment, a physical process occurred instead of a chemical reaction. In order for molecules to evaporate through a particular polymer matrix, they must first dissolve into the polymer and then physically pass through by diffusion.

In a first-order process, the rate of diffusion is directly proportional to concentration of a particular substance. The differential rate law takes the form $Rate = k[A]$, where $k$ is a rate constant whose units vary depending on the rate order and $[A]$ is the concentration of substance “A.” This first-order rate law indicates that as the physical process progresses and the contained concentration is consumed, the diffusion rate decreases with the drop in molecular concentration (Fig. 6). In a second-order process, the rate of diffusion is directly proportional to the squared concentration of a substance. The differential rate law $Rate = k[A]^2$ shows that as the reactants are consumed, the rate decreases more rapidly than the drop in reactant concentration (Fig. 6). In a zero-order process, the rate of diffusion is constant. The differential rate law would take the form $Rate = k$. This characteristic indicates that the process progresses at the same speed regardless of the concentration of substance present until the substance is completely consumed (Fig. 6). Zero-order kinetics is difficult to achieve but diffusion at a constant rate is the ultimate goal of all controlled-release mechanisms.

Figure 6. Reaction Rate vs. Concentration and Concentration vs. Time graphs for first-order (green), second-order (blue) and zero-order (red) reactions. Zero-order will achieve a constant rate of release (8).
Solubility Parameters

It is important to predict the solubility of the substance moving across the polymer. Experimental evidence can provide this information, but performing numerous combinations of substances and polymers in order to obtain a desired rate of release would be impractical. Instead, mathematical models can predict the degree of solubility of certain substances. One model is solubility parameters, which provide both graphical and mathematical representations of different solubility levels. The first model was Hildebrand’s solubility parameter (9). In 1936, Hildebrand proposed that the cohesive energy, or the energy of Van der Waals forces holding a substance together, could be used to predict miscibility of two compounds. Hildebrand’s equation, which accounted for the molecular volume and heat of vaporization, was fitting for non-polar substances (9). However, since deviations arose when it was used to predict the solubility parameters of polar substances, a new equation was proposed by Charles M. Hansen (9). Hansen used four variables, the dispersion force bond energies (δd), dipole force bond energies (δp), hydrogen bond energies (δh), and the interaction radius, a three-dimensional approximation of the other two-dimensional parameters (R0). The differences between the first three parameters are used to calculate the Hansen distance (Ra) (10). While making the solutions on different graphs, Hansen’s solubility parameters increased the accuracy of predicting the solvency of two substances. However, Hansen parameters are difficult to use due to their temperature dependency and the limitations of three-dimensional graphing. Finally, solubility parameters have mainly been previously used to determine if polymers would dissolve in a liquid rather than the other way around, meaning their value as a predictor of rates is probably limited (9).

Table 1. Solubility parameters for the polymers and liquids to be used.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Dispersion (δd)</th>
<th>Polarity (δp)</th>
<th>Hydrogen bonding (δh)</th>
<th>Molar volume</th>
<th>R0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene</td>
<td>16.3</td>
<td>5.9</td>
<td>4.1</td>
<td>-----</td>
<td>8.20</td>
</tr>
<tr>
<td>EVA 10%</td>
<td>16.43</td>
<td>6.09</td>
<td>4.03</td>
<td>-----</td>
<td>8.20</td>
</tr>
<tr>
<td>EVA 12%</td>
<td>16.46</td>
<td>6.13</td>
<td>4.02</td>
<td>-----</td>
<td>8.20</td>
</tr>
<tr>
<td>PVAC</td>
<td>17.6</td>
<td>7.8</td>
<td>3.4</td>
<td>-----</td>
<td>8.20</td>
</tr>
<tr>
<td><strong>Liquids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>15.8</td>
<td>5.3</td>
<td>7.2</td>
<td>98.5</td>
<td>----</td>
</tr>
<tr>
<td>Hexane</td>
<td>14.9</td>
<td>0</td>
<td>0</td>
<td>131.6</td>
<td>----</td>
</tr>
<tr>
<td>2-pentanol</td>
<td>15.6</td>
<td>6.4</td>
<td>13.3</td>
<td>109.6</td>
<td>----</td>
</tr>
</tbody>
</table>

[5-6]
Hansen’s solubility parameter equation:

\[
(Ra)^2 = 4(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2
\]

\[
Ra/R_0 = RED
\]

The relative energy difference (RED) value of this ratio predicts solubility. If it is less than one, the two substances are very soluble. If it equals one, the two are slightly soluble. If it is greater than one, they are likely to insoluble.

Table 2. RED ratios for several combinations to be used

<table>
<thead>
<tr>
<th></th>
<th>RED&gt;1</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PE w/2-P</td>
<td>9.32/8.20</td>
<td>1.137</td>
<td>Insoluble</td>
<td></td>
</tr>
<tr>
<td>EVA 10 w/2-P</td>
<td>9.42/7.75</td>
<td>1.215</td>
<td>Insoluble</td>
<td></td>
</tr>
<tr>
<td>EVA 12 w/2-P</td>
<td>9.44/8.20</td>
<td>1.151</td>
<td>Insoluble</td>
<td></td>
</tr>
<tr>
<td>PE w/EA</td>
<td>3.31/8.20</td>
<td>0.404</td>
<td>Soluble</td>
<td></td>
</tr>
<tr>
<td>EVA 10 w/EA</td>
<td>3.50/7.75</td>
<td>0.452</td>
<td>Soluble</td>
<td></td>
</tr>
<tr>
<td>EVA 12 w/EA</td>
<td>3.40/8.20</td>
<td>0.414</td>
<td>Soluble</td>
<td></td>
</tr>
<tr>
<td>PE w/H</td>
<td>7.71/8.20</td>
<td>0.940</td>
<td>Soluble</td>
<td></td>
</tr>
<tr>
<td>EVA 10 w/H</td>
<td>7.92/8.20</td>
<td>0.966</td>
<td>Soluble</td>
<td></td>
</tr>
<tr>
<td>EVA 12 w/H</td>
<td>7.97/8.20</td>
<td>0.972</td>
<td>Soluble</td>
<td></td>
</tr>
</tbody>
</table>

Development of Experiment

*Utilizing Vapor Pressure Equilibrium*

The apparatus used for the experiment was a petri dish containing the specified liquid with a polymer covering, which established the vapor-pressure equilibrium. For every substance there is a given vapor pressure: the amount of the chemical that will evaporate before equilibrium is established between the gas and liquid phases. At equilibrium, the rate of liquid substance that evaporates and the rate of vapor that condenses are the same, but if some vapor is
removed, more of the liquid must evaporate to maintain that equilibrium. This occurrence is 
based on Le Chatelier’s Principle, and forms the underpinning of this apparatus. As some of the 
vapor diffuses through the membrane, it is replaced by evaporating liquid. This means the 
concentration of vapor in the air inside the apparatus is constant, and should achieve relatively 
constant release. By rate laws, diffusion is a first-order reaction so Rate = k[X], where k is a 
constant and [X] is the concentration of the vapor. The concentration should not change under 
this apparatus, yielding a constant rate and effectively creating a zero-order diffusion (11).

**Molecule Selection**

The three liquids chosen as molecules to diffuse across the polymers were ethyl acetate, 
2-pentanol, and n-hexane. Ethyl acetate was selected because it was a widely available volatile 
molecule. Its low boiling point, 77°C, would ease the experiment by giving it a higher vapor 
pressure and thus a faster rate of evaporation. It was also slightly polar, allowing it to interact 
with both polar and non-polar membranes (12). To minimize variables within the experiment, the 
other three molecules were chosen so that they would have similar properties, such as molar 
mass and shape, excluding polarity, which was to be the focus of the study. Hexane and 2-
pentanol were chosen because their molar masses are within four grams of ethyl acetate, but each 
has different polarities and intermolecular forces. Hexane is completely non-polar and interacts 
with London dispersion forces (12). Ethyl acetate is slightly more polar and has a carbon-oxygen 
double bond. 2-pentanol is more polar than ethyl acetate and has limited capabilities for 
hydrogen bonding.

**HYPOTHESIS**

The goal of this experiment is to develop an apparatus that can achieve zero-order 
release. Various methods can be used to affect and control of the rate of release such as polarity, 
density, crystallinity, and cross-linking (4, 5). The experiment seeks to test the effects of varying 
polarity on the rate of release, and whether Hansen parameters can be used to predict the 
interactions between release molecules and polymers (10). Based on Le Chateliers principle, the 
liquid reservoir will maintain constant vapor concentration, resulting in a constant release rate 
(11). Using solubility parameters as guidance, a molecule with the most similar polarity 
compared to a polymer film will diffuse the most quickly, and increasing the difference will 
reduce the rate. This research will be used to help develop a correlation model that can relate 
differences in polarity with rates of release.

**METHODS AND MATERIALS**

The setup for each trial of this experiment was 10 milliliters of liquid in an 8.91 cm 
diameter pyrex dish that was covered with a polymer film (Fig. 7). In the first trial, four set-ups 
were used each with a different liquid: hexane, glycerol, 2-pentanol, or ethyl acetate; and no 
polymer film. The initial mass of each dish and liquid was recorded on a tared balance. 
Periodically after that, the mass of each petri dish and liquid was recorded and the mass that had 
been evaporated was calculated. These uncovered set ups served a controls for the experiment.
Figure 7. Apparatus. This shows a petri dish covered with a polymer membrane (left) as well as a scale and stopwatch used to take mass and time measurements.

In the next trial, the same four liquids were each matched with three polymer films, A&P plastic wrap, Dura-seal, or Parafilm. The dishes were massed before and after the liquid had been put in, and the masses were recorded and attached to the dishes. The samples were left, covered by polymers, in a fume hood over a three day period. The purpose of this was to make sure the solvents would noticeably diffuse through the polymers that were available. Based on the results of this trial, the apparatus was slightly modified and the main experiment was initiated. In the main experiment, the solvents used were hexane, 2-pentanol, and ethyl acetate. The polymers used as films were Polyethylene, Ethylene Vinyl Acetate (EVA) with 10% Vinyl Acetate, and EVA with 12% Vinyl Acetate. All of the possible liquid and polymer combinations were tested three times, giving a total of twenty seven set ups.

This procedure was repeated in three trials in order to guarantee consistent results. The initial mass was recorded, and then new masses for each trial were taken periodically. These trials continued for several days, with measurements being taken every few hours. Zero order kinetics made the length of time between measurements insignificant; as long as there was liquid left un-evaporated, the rate would be constant and on the same line when graphed.
RESULTS

Hexane

Figure 8. Diffusion rates of hexane through polymer matrices. Zero-order release was achieved by hexane through all three polymer membranes except for one trial of polyethylene, which was excluded from statistical analysis.

Hexane proved to have the fastest average rate of release through EVA 12%, followed by EVA 10%, and then polyethylene. The average rates are very linear, except for polyethylene where there were fluctuating trials with much lower R-squared values that were excluded from statistical analysis (Fig. 8).
Ethyl Acetate

Figure 9. Diffusion rates of ethyl acetate through polymer matrices. Zero-order release was achieved by ethyl acetate through all three polymer membranes.

Ethyl acetate had the fastest rate of release EVA 10%, followed by EVA 12%. Polyethylene had a much lower rate of release. The average rates were very linear with $R^2$ values all above .977 (Fig. 9).
2-Pentanol

Diffusion Rates of 2-Pentanol through Polymer Matrices

Figure 10. Diffusion rates of 2-pentanol through polymer matrices. Zero-order release was achieved by 2-pentanol through all three polymer membranes except for one trial of EVA 10%, which was excluded from statistical analysis.

2-pentanol had nearly equal rates of release through EVA 10% and EVA 12%, with a much lower value in polyethylene. The average rates were fairly linear with $R^2$ values all above .915 (Fig. 10).
Figure 11. Average rates of diffusion for all molecule-polymer combinations. Ethyl acetate, hexane, and 2-pentanol all diffused faster through more polar matrices, though ethyl acetate diffused most quickly through the less polar EVA 10%.

Hexane flowed the most quickly through all three membranes, followed by ethyl acetate, while 2-pentanol had much lower rates of release through all three membranes (Fig. 11).

Statistical Analysis

First, an ANOVA test was conducted for each molecule released using the mechanism, with highly significant P-values that were several orders of magnitude less than the alpha value, 0.05. Thus, this indicates that there was indeed a significant difference between the data sets.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Hexane</th>
<th>2-Pentanol</th>
<th>Ethyl Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>0.001</td>
<td>0.00004</td>
<td>0.00007</td>
</tr>
</tbody>
</table>

Then, individual t-tests (one-tailed, two-sample assuming unequal variances) were conducted for each type of polymer membrane for each molecule. These tests showed that there was a significant difference between PE and both of the EVA’s but not between the two EVA’s, as also shown in the graph above.
Table 4. Comparison p-values of hexane

<table>
<thead>
<tr>
<th>Comparison</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA 10% vs. EVA 12%</td>
<td>0.081</td>
</tr>
<tr>
<td>EVA 12% vs. PE</td>
<td>0.017</td>
</tr>
<tr>
<td>PE vs. EVA 10%</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Table 5. Comparison p-values of ethyl acetate

<table>
<thead>
<tr>
<th>Comparison</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA 10% vs. EVA 12%</td>
<td>0.11</td>
</tr>
<tr>
<td>EVA 12% vs. PE</td>
<td>0.00000033</td>
</tr>
<tr>
<td>PE vs. EVA 10%</td>
<td>0.0060</td>
</tr>
</tbody>
</table>

Table 6. Comparison p-values of 2-pentanol

<table>
<thead>
<tr>
<th>Comparison</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA 10% vs. EVA 12%</td>
<td>0.43</td>
</tr>
<tr>
<td>EVA 12% vs. PE</td>
<td>0.00065</td>
</tr>
<tr>
<td>PE vs. EVA 10%</td>
<td>0.0048</td>
</tr>
</tbody>
</table>

DISCUSSION

The results prove that zero-order release can be achieved through the use of vapor-pressure equilibrium, under certain conditions.

Equilibrium

The trials did not immediately establish zero-order release. At time=0, the amount of vapor in the apparatus would also be 0. Some of the molecule would have first had to evaporate to establish a constant vapor pressure. Next, the molecule would have to dissolve into the polymer membrane, travel across the membrane, and finally diffuse into the atmosphere. All of these processes led to inconsistent results in the first few minutes until equilibrium was established (Fig. 8, 9, 10). This period of inconsistency seemed to be greatest in the 2-pentanol trials which required several hours to fully saturate in the apparatus as opposed to ethyl acetate and hexane which achieved zero order kinetics after approximately 30 and 5 minutes, respectively. This reflects the lower volatility of 2-pentanol compared to the other molecules (13).

Hexane

For hexane, the results contradicted not only the predictions of the solubility parameters but the hypothesis of the effects of polarity. It had been thought that non-polar hexane would flow most easily through non-polar polyethylene. Unexpectedly, the rate increased with more vinyl acetate (Fig. 11). This result is most likely due to differences in polymer crystallinity rather than polarity. Polyethylene, because its structure is very simple and regular, is more likely to contain dense crystalline regions (4). EVA, because it is a copolymer containing a mixture of
polar and non-polar elements, is much more likely to have amorphous regions, particularly as the percentage of vinyl acetate increases. Amorphous regions, since they are looser and constantly in motion, are more likely to allow for the diffusion of hexane.

Another possible explanation for the failure of hexane to diffuse across a non-polar membrane most quickly is the solution process itself. The hypothesis rested on the idea that molecules of similar polarities to a polymer would dissolve into that polymer. However, there is the possibility that, once dissolved, the molecule has difficulty exiting the matrix into the atmosphere. Hexane may have quickly dissolved into the polyethylene membrane but did not quickly diffuse out because the two non-polar compounds tend to remain dissolved in each other. (Fig. 11)

Future experiments seeking to control for this unforeseen variable could use a differential scanning calorimeter to find the heat of crystallization of a polymer and compare it to standard polyethylene to find the level of crystallinity (14). Other groups could compare the effects of polarity and crystallinity to determine which influences the rate of release to a greater extent.

Hexane did pass through each polymer more rapidly than ethyl acetate and 2-pentanol, due to either its higher vapor pressure increasing the frequency of interactions with the polymer, or its lower polarity combined with less polar membranes (Fig. 11).

Ethyl acetate

For ethyl acetate, polarity proved to be a major factor in the rate of diffusion through the membrane and the results matched the predictions according to the solubility parameter. According to the parameters, EVA 10% would have the highest release rate, EVA 12% would have the next highest, and polyethylene would have a slightly lower rate, and the results reflected this (Table 2). However, pure polyethylene allowed for only 10% of the transmission rate of EVA 12% (Table 4), much larger than the difference predicted by the parameters. Meanwhile the release rate of EVA 10% was 82% of that of EVA 12% (Table 4), a much smaller difference than the parameters predicted. These results indicate that Hansen solubility parameters offer at best a vague approximation of the effects of polarity on diffusion.

Based on this data, the optimal polarity for release of ethyl acetate would be slightly less than EVA 10%. Figure 12 shows one possible model (a quadratic correlation) for the relationship between polarity and rate based on these trials. More data would be needed to test and revise this relationship, and to determine how large a role crystallinity played in the results compared to polarity.
Figure 12. Rates of Diffusion of Ethyl Acetate. This shows one possible model for the correlation between polarity and release rate for ethyl acetate. Since it is based on only three release rates, more data is needed to verify, adjust, or disprove it.

2-Pentanol

2-pentanol was the most polar of the molecules used in the experiment (13). It therefore took a much longer time to stabilize, and had a much slower release rate than the other molecules. 2-pentanol’s polarity made it the most inconsistent molecule in the experiment, most likely due to its ability to form hydrogen bonds with the polymer, leading to a more irregular release. All 2-pentanol trials except for two outliers achieved zero-order release (Fig. 10), and the data became more consistent as the mass was measured over a longer time-frame. This means that a wide variety of molecules can achieve zero-order release from this apparatus despite complicating reactions with the membrane.

Future experiments involving 2-pentanol may seek to use much more polar membranes and observe whether the polarity similarity creates a more consistent rate or whether increased hydrogen bonding decreases the rate.

Sources of Error

There are several possible sources of error in this experiment. First, there could have been holes in the membrane that would have been too small for us to notice, or the rubber band may not have established a full seal. In addition, several of the scales fluctuated wildly, either due to slight air movement in the lab, objects nearby the scale, or technical difficulties such as the polymer film bearing some of the weight against the balance. Finally, the polymers were of slightly different thicknesses. Both EVA polymers were 1.5 millimeters thick, but the polyethylene was 1.8 millimeters thick, which may have affected the rate of release.

Future Studies
One experiment to build on this work would be to use one of the molecules and test its release rates with a number of EVA polymers of known concentrations. This type of experiment would better explore the correlation between polarity and rate. The ultimate goal would be the creation of a formula or a refined solubility parameter that would be able to predict the release rate of a molecule through a film given their polarities. As the results show, other factors, such as crystallinity, vapor pressure, and solute molecules failing to diffuse out of the solvent polymer due to their affinity for each other (Fig. 11). This would allow industrial applications of control-release to more accurately adjust the rate to their needs.

Another topic future experiments can explore is using a mixture of different substances. One possible application of zero-order kinetics, air fresheners, would require a variety of molecules, some polar and some non-polar, to pass through a single membrane in consistent proportions. Future experiments could test how the rate of release of two different molecules is related to their individual release rates, if an interaction between the molecules causes a different effect, or if a mixture can even still achieve zero-order release. Mixing two polar molecules, two non-polar molecules, and a polar and non-polar molecule would allow for a better understanding of how interactions between the compounds themselves affect their interactions with the polymer.

Many applications of zero-order release would seek to use solids or non-volatile liquids as their release molecule. Now that it is clear that Le Chatelier’s Principle can be used to maintain constant concentration in gases, other groups may want to develop an apparatus using other equilibria. Another apparatus that had been considered, for example, was dissolving a solid molecule in a liquid. In this setup, the film would be stretched across the bottom and the solid would diffuse across into a chamber below.

Conclusion

This apparatus yielded a number of trials with zero-order release. However, it is difficult to draw conclusions about the effects of polarity due to other variables such as crystallinity, vapor pressure, and the possibility that molecules encountered difficulty desorbing out of the membrane. Hansen Solubility Parameters ignored these subtleties, limiting their usefulness for our purposes. These findings lay the groundwork for vapor pressure-based release mechanisms, though the finer points of controlling the constant rate remain unresolved. Before a similar apparatus can be implemented for agricultural or pharmaceutical applications, a more refined method of controlling the rate of release is needed. Still, this experiment was successful in proving that zero-order release can be achieved without expensive or labor-intensive methods.

REFERENCES

[5-17]
11. Vapor Pressure [Internet]. Purdue University; [cited 2010 July 26]. Available from: http://www.chem.purdue.edu/gchelp/liquids/vpress.html

APPENDICES [5-18]
Appendix A. Hexane rates of release for all trials.

<table>
<thead>
<tr>
<th>Hexane</th>
<th>EVA 10% - 1</th>
<th>2</th>
<th>3</th>
<th>EVA 12% -1</th>
<th>2</th>
<th>3</th>
<th>PE - 1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of release (g/s ( \cdot ) m2)</td>
<td>0.009</td>
<td>0.010</td>
<td>0.011</td>
<td>0.012</td>
<td>0.016</td>
<td>0.012</td>
<td>-0.004</td>
<td>0.004</td>
<td>0.005</td>
</tr>
<tr>
<td>R(^2) Value</td>
<td>0.992</td>
<td>0.978</td>
<td>0.971</td>
<td>0.999</td>
<td>0.954</td>
<td>0.998</td>
<td>-2.504</td>
<td>0.749</td>
<td>0.300</td>
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</tbody>
</table>

Appendix B. Ethyl acetate rates of release for all trials.

<table>
<thead>
<tr>
<th>Ethyl Acetate</th>
<th>EVA 10% - 1</th>
<th>2</th>
<th>3</th>
<th>EVA 12% -1</th>
<th>2</th>
<th>3</th>
<th>PE - 1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of release (g/s ( \cdot ) m2)</td>
<td>0.010</td>
<td>0.007</td>
<td>0.009</td>
<td>0.007</td>
<td>0.007</td>
<td>0.007</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>R(^2) Value</td>
<td>0.965</td>
<td>0.900</td>
<td>0.975</td>
<td>0.967</td>
<td>0.961</td>
<td>0.998</td>
<td>0.997</td>
<td>0.995</td>
<td>0.998</td>
</tr>
</tbody>
</table>

Appendix C. 2-Pentanol rates of release for all trials.

<table>
<thead>
<tr>
<th>2-Pentanol</th>
<th>EVA 10% - 1</th>
<th>2</th>
<th>3</th>
<th>EVA 12% -1</th>
<th>2</th>
<th>3</th>
<th>PE - 1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of evaporation (g/s ( \cdot ) m2)</td>
<td>0.00031</td>
<td>0.00031</td>
<td>0.00024</td>
<td>0.00027</td>
<td>0.00030</td>
<td>0.00029</td>
<td>0.00005</td>
<td>0.00005</td>
<td>0.00006</td>
</tr>
<tr>
<td>R(^2) Value</td>
<td>0.919</td>
<td>0.985</td>
<td>0.981</td>
<td>0.063</td>
<td>0.831</td>
<td>0.752</td>
<td>0.989</td>
<td>0.986</td>
<td>0.978</td>
</tr>
</tbody>
</table>