In Vitro Release Mechanism of Acetylsalicylic Acid from Melt-Extrusion Granules of Dika Wax

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ABSTRACT
Dika wax obtained from the seed of tropical plant, Irvingia gabonensis, was used to prepare extrusion granules for controlled release of acetylsalicylic acid. The high capillary melting temperature of the wax (38 ºC – 40 ºC) was taken into consideration, realizing that the drug would not be freely released from the unblended wax under conditions that mimic the average haemostatic temperature of the body. To overcome this setback, the melting temperature of the wax was modified by blending with a non-congealing vegetable oil on the one hand and an emulsifying agent on the other. Evidence obtained from the results showed that the specific material used in modifying the melting temperature of the wax has considerable influence on the rate of drug release from the extrusion granules, but not necessarily on the mechanism of release. The batches with emulsifying agent released faster than those with vegetable oil, while both systems conformed to the Higuchi’s model of drug release in a diffusion-controlled mechanism.

KEYWORDS: Melt-extrusion, dika wax, release mechanism, acetylsalicylic acid, granules.

INTRODUCTION
The efficacy of a drug can be significantly influenced by the method by which the drug is delivered [1]. Granulation (a process in which primary powder particles are made to adhere to form larger multi-particle entities) renders the materials free flowing, results in uniform mixtures that do not segregate or separate, improves the compression characteristics of the drug, controls the rate of drug release, reduces dust and improves the appearance of the final product [2, 3]. In the wax melt granulation approach, the drug powder is triturated with the melted wax followed by screening a solid dispersion of the drug in the wax [4, 5]. Based on their proven safety and efficacy, lipid-based carriers provides the desired alternative drug carriers to hydrolysable polymers [6]. These carriers allow for either hydrophilic or hydrophobic drugs to be incorporated [7], provide protection of incorporated active compounds against degradation as well as offer the possibility of improved bioavailability, controlled drug release and drug targeting [8]. Melt-granulation employs the use of lipophilic materials as matrix carriers to enhance the stability, mask the unpleasant taste, improve the dissolution rate and bioavailability as well as achieve sustained, controlled/modified release of incorporated drug(s) [9, 10].

Homolipids are esters of fatty acids with various alcohols [6]. Several studies have been carried out on the possible applications of a homolipid based on dika wax (a dry free flowing, non-caking solid lipid extracted from the kernels of Irvingia gabonensis) in the formulation of drug delivery systems, where it offered improved physicochemical and functional properties of the incorporated drugs [3, 11-13]. Aspirin [(2-acetoxy)-benzoic acid], also known as acetylsalicylic acid (ASA), is a member of the non-steriodal anti-inflammatory drugs (NSAIDs) that act by inhibition of cyclo-oxygenase [14]. It also has antiplatelet effect inhibiting the production of thromboxane and is believed to prevent stroke. Pharmacologically, aspirin is an analgesic used to relieve minor aches and pains, an anti-inflammatory medication, used in the management of migraine, episodic tension headache; dull and throbbing, joint, post-surgery and menstrual pains. It is also valuable...
in the treatment of pericarditis, coronary artery disease and acute myocardial infarction. It has been recommended, at low doses, for prophylaxis of cardiovascular diseases (CVDs) [15]. Aspirin, with a half-life of 4-9 hours, is rapidly and completely absorbed following oral administration achieving peak plasma concentration within 1-2 hours. Previous studies have shown that dika wax enhanced the stability, and modified the rates of release of aspirin from various sustained-release formulations of the drug [16, 17]. In this study, a dika wax-based melt-extrusion granules were formulated in an attempt to modulate the drug release. The exact mechanism by which drug release was modulated has been proposed. This is important for proper appreciation of the mode of administration of this important drug, especially to the elderly patients, who require it as a cardioprotective agent.

EXPERIMENTAL
Materials
Distilled water, soy bean oil (Gino vegetable oil), Hydrochloric acid (M & B Ltd., England) Aspirin crystals (Whitehall, England), Calcium carbonate (Merck, Darmstadt, Germany), Dika wax, Emulsified ointment BP, Ferric chloride solution.

Preparation of melt-granulations
An oil/wax baseline blend was prepared by melting dika wax and Gino vegetable oil in the ratio of 3:1 over a thermostatic water bath. The melted mixture was thoroughly mixed together using a glass stirrer. It was then allowed to solidify at room temperature. This formed homogenous solid base for melt granulation. The base was used to prepare various batches of the granules as shown in Table 1. The base was heated over a thermostatic water bath until it melted. Acetylsalicylic acid was dispersed in the molten base and stirred to achieve a uniform mixture. An appropriate amount of calcium carbonate was added and also mixed thoroughly with the base-aspirin combination. The entire formulation was allowed to cool at room temperature. It was then passed through a sieve of 0.8 mm. Capsules containing 500 mg of granules were produced from each batch by manual filling of empty gelatin capsule shells. The capsules were stored in air tight containers and labeled properly. The entire procedure was repeated using emulsifying ointment BP in place of Gino vegetable oil.

Characterization of granules
Each batch of the granules was characterized based on flow rate, angle of repose, bulk density, tapped density, true density, Carr’s compressibility index, Hausner’s ratio and porosity.

Flow rate: A quantity (100 g) of the granules was accurately weighed in a digital analytical balance. The granules were allowed to flow through a funnel and the time taken for the granules to completely flow through the funnel was taken. The flow rate was obtained by dividing the mass of the granules by the time of flow. Thus flow rate was calculated as

\[
\text{Flow rate} = \frac{\text{Mass of granules (grams)}}{\text{Time of flow (seconds)}}
\]  

Angle of Repose: This was obtained using the fixed cone method [2]. A circular base of known diameter was used as the base while the granules flowed from a funnel onto the base. The height of the cone formed was taken and the angle of repose was calculated as follows:

\[
\tan \alpha = \frac{H}{D}
\] or

\[
\alpha = \arctan \left( \frac{H}{D} \right)
\]

where \( H \) = height of the granules, \( D \) = diameter of the granule, \( \alpha \) = angle of repose.

Table 1: Ratio of components of aspirin melt-extrusion granules

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Lipid or wax base</th>
<th>Aspirin</th>
<th>Calcium carbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>V</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Bulk Density: The granules of known mass were poured into a measuring cylinder while ensuring that the surface of the granule bed was level. The volume of granules in the measuring cylinder was noted. The bulk density was obtained as:

\[
\rho_b = \frac{M}{V_b}
\]

where \( \rho_b \) = bulk density, \( V_b \) = volume of granules and \( M \) = mass of granules.

Tapped Density: The tapped density was obtained by gently tapping the measuring cylinder containing the granules on a flat, level surface, until no further reduction in volume was noted. The tapped density was obtained with the expression,
**True Density:** This was obtained using a 50-ml pycnometer. The intrusion fluid used was benzene. The pycnometer was filled with benzene and weighed accurately. One gram of granules was added. The new weight of pycnometer and its contents was determined. The true density was calculated using the formula:

\[ D = \frac{w_2 \times w_4}{V(w_2 + w_3 - w_4)} \quad \text{Eq. 6} \]

where \( w_1 = \) weight of empty pycnometer; \( w_2 = \) weight of benzene needed to fill the pycnometer; \( w_3 = \) weight of pycnometer and its contents (benzene and granules); \( w_4 = \) weight of granules; \( V = \) volume of pycnometer.

**Carr’s Index (C.I.):** This was calculated from the density data thus:

\[ \text{C.I.} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100 \quad \text{Eq. 7} \]

**Hausner’s Quotient (H.Q):** This was calculated from the expression,

\[ H.Q = \frac{\text{Tapped density}}{\text{True density}} \quad \text{Eq. 8} \]

**Porosity (\( \varepsilon \)):** This was calculated using the formula:

\[ \varepsilon = 1 - \frac{\text{Bulk density}}{\text{True density}} \times 100 \quad \text{Eq. 9} \]

**In vitro drug release studies**

Each granule-filled capsule was placed in a stainless wire mesh basket, connected to a metal perpendicular holder. The set-up was suspended in 900 ml of 0.1M HCl which served as the dissolution medium. The dissolution medium, maintained at 37 ± 1 °C, was stirred continuously with the magnetic stirrer at 100 rpm. For the wax/oil-based granules, 10 ml samples of the drug solution were withdrawn every 10 min for 2 h, while for ointment/wax-based granules, samples were withdrawn at intervals of 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50 and 60 min. Withdrawn samples were replaced with equal volume of plain dissolution medium. The sample drug was complexed with a solution of 0.1 % Ferric chloride, diluted appropriately, and then analyzed spectrophotometrically with an EL digital colorimeter at a wavelength of 420 nm. At least two replicate release profiles were taken on each batch and average values were used. The amount of acetylsalicylic acid released (Q) was determined from the absorbance values, using a calibration correlation, which was found to conform with the Beer’s law (Fig. 1).

The drug release mechanisms were investigated by subjecting the data to graphical analyses as follows:

- **Zero order release:** \( Q \) vs time.
- **Diffusion-controlled release (Higuchi model):** \( Q \) vs \( T^{1/2} \).
- **First order release (Schwartz model):** \( Q/t \) vs \( Q \).
- **Diffusion-controlled release (Schwartz model):** \( Q/t \) vs \( 1/Q \).

**RESULTS AND DISCUSSION**

Results obtained for the various parameters tested were used in assessing the physical and flow properties of granules (Table 2). The granules produced in batch 1 were sticky and could not flow. Thus, their flow rates could not be measured. Also batches 4 and 5 produced particles that were too fine in size, and so could not flow. The flow properties of those batches could not be measured. Only the flow rates of granules of batches 2 and 3 were measurable. In each case, flow rates increased with decrease in amount of dika wax incorporated. All other physical properties of the granules were similar in accordance with their blending patterns. There was, however, an exception in the porosity values. Porosities of wax/ointment blends were generally higher than those of wax/oil blends. Obviously, the wax/oil
blends were more homogenous than the counterpart wax/ointment blends. The Emulsifying ointment BP, by its nature, is a heterogenous formulation consisting of materials such as soft paraffin, liquid paraffin, sodium lauryl sulphate, etc. This composition readily contrasts with the vegetable oil that is a single triglyceride. This contrasting nature of the blends would possibly account for this obvious differences in the porosity of the resulting granules.

Rates of drug release from the wax/ointment base were higher than those of wax/oil base. For that reason, samples are withdrawn at shorter intervals of time in the dissolution study, than in the case of wax/vegetable oil base. It was observed that while the rate of drug release reduced with increase in amount of wax/oil base, the pattern was irregular with wax/ointment base. It is probable that the presence of a highly surface active agent, sodium lauryl sulphate, in the wax/ointment base is responsible for the divergent release behaviours recorded. The solubilizing effect of surfactants is a well-known physicochemical phenomenon, that modifies the solubility and release of drugs [12].

<table>
<thead>
<tr>
<th>Lipid base</th>
<th>S/N</th>
<th>Granule property</th>
<th>Batch code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Dika wax/oil</td>
<td>1</td>
<td>Flow rate (g/sec)</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Repose angle (degrees)</td>
<td>41.28</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Bulk density (g/ml)</td>
<td>0.437</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Tapped density (g/ml)</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>True density (g/ml)</td>
<td>1.327</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Carr’s index (%)</td>
<td>30.32</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Hausner’s quotient</td>
<td>1.435</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Porosity (%)</td>
<td>67.45</td>
</tr>
</tbody>
</table>

| Dika wax/ointment | 1   | Flow rate (g/sec) | *          | 2.65       | 3.52       | *           | *           |
|                  | 2   | Repose angle (degrees) | 42.83 | 39.65 | 36.20 | 34.30 | 45.67       |
|                  | 3   | Bulk density (g/ml)  | 0.45      | 0.50      | 0.673      | 0.472       | 0.404       |
|                  | 4   | Tapped density (g/ml) | 0.505 | 0.618 | 0.826 | 0.598 | 0.474       |
|                  | 5   | True density (g/ml)  | 1.603     | 2.348     | 1.686      | 1.264       | 0.948       |
|                  | 6   | Carr’s index (%)     | 23.00     | 19.00     | 18.50      | 21.00       | 14.80       |
|                  | 7   | Hausner’s quotient   | 1.3       | 1.236     | 1.227      | 1.266       | 1.174       |
|                  | 8   | Porosity (%)         | 71.93     | 78.71     | 61.9       | 62.66       | 57.44       |

* Granules in these batches did not flow.

To determine the mechanism of drug release, the zero order, first order, Higuchi and diffusion controlled release models were applied. The plots that showed linearity would indicate that drug release followed a particular release pattern or mechanism. The graph of Q (quantity of drug released) against time was plotted (Figs. 2 and 3). There was no linearity in the two plots, indicating absence of zero order kinetics. To determine whether the release pattern would follow a first order, a plot of Q/t against Q was applied. A linear relationship was obtained in the granules of wax/oil base (Fig. 4). For granules with wax/ointment base no linear relationship was obtained (Fig. 5). The Higuchi plot of Q versus the square root of time showed linearity in both bases (Figs. 6 and 7), indicating that a diffusion controlled mechanism of drug release may be applicable. To verify this, the plot of Q/t versus 1/Q was used and a straight line graph was obtained (Figs. 8 and 9). This confirmed that the release of acetylsalicylic acid from melt-extrusion granules followed a diffusion controlled mechanism. Since the discrete granular particles were non-disintegrating because of the dominance of lipid materials in the formulations, the only logical process of drug release would be by diffusion. This is accentuated by the fact that the granules did not swell, and so drug release would not be by gel-erosion. In the formulations containing emulsifying ointment, the surface active agent would be expected to influence the pattern of drug release. Clearly, the presence of the emulsifying ointment caused a shift of drug release kinetics from the first order pattern exhibited in granules made with wax/oil base. This overriding influence of the solubilizer was not noticed in the drug release
mechanism. This indicates that drug release mechanisms are independent of drug release kinetics. Drug release mechanisms generally relate to the interactions between component ingredients in a formulation, and this includes the possible interactions between active ingredients and excipients.

Fig. 2 Plot of Q versus time for granules made with wax/vegetable oil blend = Batch 1 = Batch 2 = Batch 3 = Batch 4 = Batch 5

Fig. 3 The plot of amount of aspirin released vs time for granules made with blends of dila wax and emulsifying ointment BP. ○ = Batch 1 □ = Batch 2 ▲ = Batch 3 ● = Batch 4 ■ = Batch 5

Q (µg)

Fig. 4 Plot of Q/t vs Q for granules made with wax/oil blends. ○ = Batch 1 □ = Batch 2 ▲ = Batch 3 ● = Batch 4 ■ = Batch 5

Q (µg)

Fig. 5 Plot of Q/t vs Q for granules made with wax/emulsifying ointment blends. ○ = Batch 1 □ = Batch 2 ▲ = Batch 3 ● = Batch 4 ■ = Batch 5
Fig. 6 Plot of $Q$ vs square root of time for granules made with blends of wax and vegetable oil.
- $\circ = $ Batch 1
- $\square = $ Batch 2
- $\triangle = $ Batch 3
- $\bullet = $ Batch 4
- $\blacksquare = $ Batch 5

Fig. 7 Plot of $Q$ vs square root of time for granules made with blends of wax and vegetable oil.
- $\circ = $ Batch 1
- $\square = $ Batch 2
- $\triangle = $ Batch 3
- $\bullet = $ Batch 4
- $\blacksquare = $ Batch 5

Fig. 8 Plot of $Qt$ vs $Q$ for granules made with blends of wax and vegetable oil.
- $\circ = $ Batch 1
- $\square = $ Batch 2
- $\triangle = $ Batch 3
- $\bullet = $ Batch 4
- $\blacksquare = $ Batch 5

Fig. 9 Plot of $Qt$ vs $1/Q$ for granules made with blends of wax and emulsifying ointment.
- $\circ = $ Batch 1
- $\square = $ Batch 2
- $\triangle = $ Batch 3
- $\bullet = $ Batch 4
- $\blacksquare = $ Batch 5
Obviously, the two sets of melt-extrusion granules examined in the present study would be pertinent in different clinical situations. When a rapid onset of action of the drug is required, such as in the management of pairs of various aetiologies, formulations such as those made with wax/ointment would be applied. On the other hand, when slow and sustained drug release is desirable, such as in cardio-protective regimens, the formulations based on wax/oil blends would be desirable. Furthermore, due to the lipid nature of the bases, the formulations would be suitable for stability of a drug, such as acetylsalicylic acid, which readily undergoes hydrolysis in the presence of moisture.

CONCLUSIONS
This study has shown that the specific material (Gino vegetable oil or emulsifying agent) used in modifying the melting temperature of dika wax has considerable influence on the rate of drug release from the extrusion granules, but not necessarily on the mechanism of release. The batches with emulsifying agent released faster than those with vegetable oil, while both systems conformed to the Higuchi’s model of drug release in a diffusion-controlled mechanism.

REFERENCES

