Sublingual Oxycodone

Physico-Chemical properties of oxycodone:

Oxycodone

![Chemical structure of oxycodone](image)

**Table 1: Comparison of oxycodone properties to Lipinski’s rule of 5**

<table>
<thead>
<tr>
<th></th>
<th>Oxycodone&lt;sup&gt;¹&lt;/sup&gt;</th>
<th>Lipinski’s Rule of 5&lt;sup&gt;¹&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>315.36</td>
<td>&lt;500</td>
</tr>
<tr>
<td>Hydrogen bond donors</td>
<td>1</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Hydrogen bond acceptors</td>
<td>5</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Log p</td>
<td>0.7</td>
<td>&lt;5</td>
</tr>
<tr>
<td>PSA</td>
<td>59</td>
<td>&lt;140</td>
</tr>
<tr>
<td>Rotatable bonds</td>
<td>1</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>
Oxycodone is a 315.36g/mol white crystalline powder\textsuperscript{1,2}. According to table 1, oxycodone does not break Lipinski’s rules of 5 thus, can be absorbed passively across cell membranes, resulting in oral bioavailability \textsuperscript{4}. Oxycodone is nearly insoluble in water and ether and melts between 215-220°C indicating a high energy crystalline solid state that may affect aqueous solubility \textsuperscript{1,5}. Therefore, it is formulated as oxycodone hydrochloride to improve solubility and consequently dissolution resulting in a decreased propensity for erratic absorption \textsuperscript{1}. Due to poor sublingual absorption, oxycodone is considered lipophobic \textsuperscript{6}. Oxycodone is a weak base with Pka 8.6. At low PH 4, it is ionised increasing aqueous solubility. At high PH it’s an unionised form dominates, hence solubility in n-octanol increases \textsuperscript{6}. However no significant statistical difference exists in membrane permeation at high or low PH due to oxycodone’s inherent low lipid solubility \textsuperscript{2}. A study showed the concentration of oxycodone lost was always below 4%, which is lower than the recommended 10%, signifying stability and a longer shelf life\textsuperscript{7}. The physicochemical properties of oxycodone result in a bioavailability of 60 to 80%\textsuperscript{1}. However oxycodone’s posology is primarily determined by pharmacological effects including tolerance \textsuperscript{1}.

**Formulation:**

Oxycodone is among the most commonly used opioid analgesics for relief of moderate to severe pain. Oxycodone is currently available mainly as rectal and oral formulations. Oral formulation is the preferred route of administration however in some cases the oral route may not be the best option for the patient owing to swallowing difficulties or when a faster onset of action is required such as in breakthrough pain \textsuperscript{8}. In such situations a parenteral formulation can be utilised however even it might not be suitable owing to decreased venous access in some patients. Another alternative to oral administration is the rectal and transdermal route \textsuperscript{8}. Rectal administration can result in greater variability compared with oral administration due to poorer blood supply to the rectum and smaller surface area, and while the transdermal route may result in minimal pre-systemic hepatic elimination, it may exhibit a slow onset of action \textsuperscript{8,9}.

The major problem associated with oral formulations is that oxycodone is subject to hepatic first-pass effects \textsuperscript{10}. Oxycodone is metabolised to the dominant non-active metabolite noroxycodone and oxymorphone \textsuperscript{10}. Oxymorphone accounts for only 10% of metabolites and although it is an extremely potent metabolite the small quantities generated result in an overall decrease of oxycodone activity via oral administration \textsuperscript{10}. Onset of action is another factor which needs to be considered when determining therapy for breakthrough pain. By means of the oral route pain relief can occur as early as 15 minutes and peak at approximately 1 hour after administration \textsuperscript{11}. As a result oral oxycodone is not ideal for the management of breakthrough pain.
This concern can be addressed by formulating oxycodone as a sublingual tablet where the drug can directly enter systemic circulation and bypass the hepatic first pass effect leading to faster more effective pain relief. However oxycodone in a sublingual formulation also has its limitations. A study conducted by Abeer.M et al looked at the development of a sublingual spray formulation of oxycodone with a secondary focus on the effects of pH on the sublingual absorption of oxycodone. The study establish that maximum plasma concentrations were reached in 20 minutes when using the sublingual preparation compared to immediate release tablets which required 1.3 hours to reach peak levels. Absorption of sublingual drugs is known to be dependent on pH and lipid solubility. Abeer.M et al observed increased oxycodone bioavailability with a formulation of higher pH (consisting of pH 9.0) compared with a formulation of lower pH (consisting of pH 4.0). This was due to the fact that in high pH oxycodone existed primarily in the unionized form which allows it to diffuse through the lipid bilayer of the oral mucosa. However the difference in bioavailability observed was not statistically significant. Thus it can be hypothesized that the very poor lipid solubility of both the ionized form and unionized form of oxycodone is the foremost contributing factor to the limited absorption of oxycodone in the sublingual formulation.

Physical and mechanical characteristics of a sublingual tablet affect its disintegration time which in turn also affects the drugs absorption. A smaller tablet with low hardness and high porosity disintegrates more rapidly than a larger harder tablet. However a tablet with high porosity and low hardness is more friable and this can present packaging problems. Ondansetron wafers are also fragile and so encounter the same packing problem. As a solution peel back foil blister packs are utilised to ensure the tablets are not accidently broken. This packaging system can also be utilised for oxycodone sublingual tablets to protect them from accidental damage by the administrator.

**Excipient function:**
Rapid sublingual absorption and hepatic metabolism bypass, increase bioavailability and reduce time to maximal plasma concentration.

**Taste**
Taste masking of tablets through sweeteners is important for compliance. Sugar based excipients like mannitol rapidly dissolve in saliva causing an endothermic heat of dissolution creating a pleasant taste.

**Size**
Given limited dissolution time and mucosal surface area, dissolution rate is enhanced by reducing size of active particle ingredient (API) thus increasing surface area. Maintaining an
API of less than 10 μ for opioids provides stability of crystalline structure and reproducible quality and performance\textsuperscript{3,18}.

**Absorption**
Including a suitable buffer whilst formulating an ionisable drug would result in domination of an unionised form hence increasing absorption \textsuperscript{16}. However, erratic absorption via swallowed drug in saliva leads to variability issues \textsuperscript{16}. Mixing fine drug particles with bioadhesive materials such as hydroxyethyl cellulose that have saliva swelling factors greater than 10 which are then attached to a rapidly dissolving mannitol carrier particle results in rapid disintegration and release of units that adhere to sublingual mucosa prolonging contact time, improving absorption and consequently reducing variability \textsuperscript{16,19}. Adding disintegrants for example microcrystalline cellulose into carrier particles will accelerate dispersion leading to faster dissolution \textsuperscript{13}.

**Disintegration**
Disintegrants such as Microcrystalline cellulose II (MCCII), Crospovidone and Croscarmellose sodium play a vital role in rapid dissolution \textsuperscript{20}. In a sublingual spironolactone study, MCCII which disintegrates by wicking exhibited the fastest disintegration rate \textsuperscript{20}. In another study, crospovidone and naphthalene showed greatest amount of drug released, 70.56% in 2 minutes. This is due to the fact that naphthalene facilitates the wicking mechanism of crospovidone by increasing porosity \textsuperscript{17}.

**Conclusion**
Our product, will microencapsulate oxycodone into PH sensitive \textsuperscript{15} hydroxyethyl cellulose (bioadhesive) attached to rapidly dissolving mannitol carrier incorporated with MCCII (disintegrant) to improve taste, decrease dissolution time, increase absorption and ultimately bioavailability. Given no altering of oxycodone’s structure, we assume elimination and metabolism of sublingual oxycodone to be similar to oral oxycodone.

**Manufacturing sublingual oxycodone:**
This formulation will be manufactured by direct compression which is inexpensive but effective, as it consist of easily mixed ingredients that can be compressed without the need for granulation beforehand \textsuperscript{16}.

Table 2: Formulation ingredients\textsuperscript{16,20}

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>Sweeter agent, Bulking agent, Dissolution agent</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>Buffer</td>
</tr>
<tr>
<td>Microcrystalline Cellulose II</td>
<td>Disintegrant, Binder</td>
</tr>
</tbody>
</table>
Dissolution agent

<table>
<thead>
<tr>
<th>Hydroxyethyl Cellulose</th>
<th>Bioadhesive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient:</td>
<td>Oxycodone</td>
</tr>
</tbody>
</table>

Figure 2: Direct Compression of sublingual tablets

Foil blister packs will be used to protect the tablet from moisture, light and oxygen. The hollow enclosure allows the patient to easily pop out the tablet without breaking it or sealed with a peelable sticker.

Figure 3: Foil blister packs

Biopharmaceutics of sublingual oxycodone:

Oxycodone sublingual tablets can typically be prescribed for the relief of breakthrough pain. They must be absorbed through the membrane under the tongue to alleviate pain in
the patient. This can benefit a sub-population of people who suffer acute and chronic pain in a community, hospital and a palliative care setting. Since pain is highly subjective, the duration of therapy depends on the patient and the disease.

Ultimately, this formulation is advantageous over Endone® tablets as the sublingual route provides faster absorption because it avoids first pass effect\textsuperscript{26}. This leads to a rapid onset of action which relieves the patient from breakthrough pain within a couple of minutes rather than hours.

The limiting step in this formulation largely revolves around increasing the absorption of drug across the membrane and maintaining its bioavailability to produce a therapeutic response\textsuperscript{16,26}. As we are changing oxycodone from a tablet form to a sublingual tablet, the ADME properties of drug will depend on the limiting step of absorption which was emphasised in the previous question.

As mentioned above, oxycodone is a highly hydrophilic drug which rejects any possible structural modifications to increase its lipophilicity and enhance absorption\textsuperscript{26}.

Therefore, we have decided to overcome this barrier by changing our formulation approach and optimise the use of excipients to improve absorption.

Table 3: Sublingual Formulation Considerations\textsuperscript{16}

<table>
<thead>
<tr>
<th>Sublingual Tablet Requirements</th>
<th>Explanation</th>
<th>Barriers</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log P 1-5</td>
<td>The drug must be lipophilic to partition across the membrane but not too lipophilic that the drug is lodged within the membrane</td>
<td>Oxycodone has a Log P of 0.7</td>
<td>Microencapsulating oxycodone to increase dissolution and absorption\textsuperscript{16}</td>
</tr>
<tr>
<td>Saliva solubility</td>
<td>The rate of drug absorption across the membrane follows the ‘diffusive model of absorption’ where the drug absorbed depends on the concentration gradient. The drug must be soluble in the saliva to increase drug absorption across the membrane</td>
<td></td>
<td>Hydroxyethyl cellulose is a bioadhesive agent which enhances dissolution in the saliva and in turn increase flux across the membrane\textsuperscript{16}</td>
</tr>
<tr>
<td>MW &lt; 500</td>
<td>This MW follows ‘Lipinski’s Rule of 5’\textsuperscript{1} as a greater MW may restrict the drug’s ability to permeate across the membrane</td>
<td>MW of Oxycodone is 315 g/mol</td>
<td>A small tablet with high porosity and low hardness is most suited for sublingual administration\textsuperscript{16}</td>
</tr>
<tr>
<td>pH 5.6-7.6</td>
<td>A narrower range compared to the gastrointestinal tract which changes the ionisation state of the drug and thus the drug’s absorption</td>
<td>Oxycodone is a weak base with a pKa of 8.6 which will exist in its unionised form in the mouth</td>
<td>This will most likely be formulated as a salt with a buffering agent of sodium bicarbonate to control the pH of the saliva</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Taste</td>
<td>Drugs delivered through the mucous membrane of the mouth, must be sweetened or flavoured to ensure compliance</td>
<td>Mannitol is used as a sweetener and a dissolution enhancer by producing endothermic heat</td>
<td></td>
</tr>
<tr>
<td>Short residing time</td>
<td>The tablet must rapidly disintegrate to release the drug in saliva and permeate across the membrane</td>
<td>Oxycodone is highly lipophilic</td>
<td>Mannitol and MCII aid in the dissolution and disintegration of the tablet to release oxycodone from the formulation instantly</td>
</tr>
</tbody>
</table>

**References:**


Legend:
Marilyn - Physicochemical properties and Excipients
Foram - Formulation
Laarni - Manufacturing and Biopharmaceutics