In vitro and in vivo evaluation of a new sublingual tablet system for rapid oromucosal absorption using fentanyl citrate as the active substance

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Abstract

Oromucosal delivery of drugs promotes rapid absorption and high bioavailability, with subsequent almost immediate onset of pharmacological effect. However, many oromucosal delivery systems are compromised by the possibility of the patient swallowing the active substance before it has been released and absorbed locally into the systemic circulation. This paper introduces a new tablet system for sublingual administration. The tablet is based on interactive mixtures of components, consisting of carrier particles partially covered by fine dry particles of the drug, in this case fentanyl citrate. In the interests of increasing retention of the drug at the site of absorption in the oral cavity, a bioadhesive component was also added to the carrier particles. Tablets containing 100, 200 and 400 μg of fentanyl were tested both in vitro and in vivo. The tablets disintegrated rapidly and dissolution tests revealed that fentanyl citrate was dissolved from the formulation almost instantly. Plasma concentrations of fentanyl were obtained within 10 min, with no second peak. These results indicated that the bioadhesive component prevented the fentanyl from being swallowed (the fraction swallowed was considered smaller compared to other mucosal delivery systems), without hindering its release and absorption. This new sublingual tablet formulation may also hold potential for other substances where a rapid onset of effect is desirable.

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Keywords: Sublingual tablet; Fentanyl; Oromucosal delivery; Interactive mixture; Ordered mixture; Bioadhesion

1. Introduction

1.1. Background

A rapid onset of pharmacological effect is often desired from drugs, especially in the treatment of acute disorders. This can effectively be achieved by parenteral administration, but this method may not always be convenient for the patient. Therefore, there is growing interest in developing new, non-parenteral, reliable and convenient dosage forms using administration routes where a rapidly dissolved drug is immediately absorbed into the systemic circulation. Tablet formulations are generally the first choice for drug administration because of the relative ease of both production and usage. However, for acute disorders, the time to onset of action for a conventional oral tablet is generally not acceptable; this is usually attributable to gastric emptying causing a highly variable lag time between drug administration and onset of intestinal absorption.

Oromucosal delivery, especially that utilising the buccal and sublingual mucosa as absorption site, is a promising drug delivery route which promotes rapid absorption and high bioavailability, with subsequent almost immediate onset of pharmacological effect. These advantages are the result of the highly vascularised oral mucosa through which drugs enter the systemic circulation directly, bypassing the gastrointestinal tract and the first pass effect in the liver (Moffat, 1971). Among the most important characteristics of tablet formulations used for oromucosal delivery are a short disintegration and dissolution time. However, in order to achieve optimal oromucosal delivery, properties of the active compound and other properties of the formulation have...
also to be considered. The parent compound has to be sol-
uble, stable and able to easily permeate the mucosal barrier
at the administration site. Further, the dosage form has to
be rapidly dissolved while retaining a sufficiently long con-
tact time at the administration site. If dissolution of the drug
is incomplete, contact time is short, and/or permeation too
low, part of the dose will not be absorbed through the seal
mucosa and will be swallowed, with subsequent effects on
bioavailability.

The main prerequisites for rapid dissolution of drugs in-
clude a large surface area of the drug exposed to the dis-
solving liquid and the lack of thick, stagnant hydrodynamic
boundary layers around the drug particles that hinder drug
dissolution by slowing diffusional transport (e.g. Noyes and
Whitney, 1897; Nyström et al., 1985; Birat et al., 1992). While
the drug surface area effectively in contact with the dis-
solving fluid can be enlarged by using very finely divided
grades of drug, the added excipients should not hinder dis-
solution by separating the dissolving liquid from the drug
particles. The use of water-soluble excipients is the most
common approach in this context. Freeze-drying the dosage
form is an expensive but effective way of obtaining highly
porous tablets, which promote rapid exposure of the drug
phase and thus rapid drug dissolution (e.g. Corveleyn and
Remon, 1998). Another, more simple, method of improv-
ing drug exposure is to use so-called ordered or interactive
mixtures (Westerberg, 1992). These are achieved by mix-
ing coarse carrier particles with a fine drug component for
a relatively long time so that the fine drug particles adhere
to the surface of the carrier particle by adhesion forces, and
are optimally exposed to the dissolving fluid (Nyström and
Westerberg, 1986).

1.2. The new sublingual tablet concept

This paper outlines a new formulating system for rapidly
absorbed sublingual tablets. The new concept is based on
the use of ordered mixtures of fine drug particles attached
to coarser excipient carrier particles. These ordered units
(each unit comprises a well defined carrier particle coated
with drug particles) offer several formulation advantages:
(a) they potentially facilitate the design of rapidly disinte-
grating tablets, (b) they provide optimal drug exposure and
(c) they have the potential to provide immediate drug disso-
lution. Certain factors are required to achieve an interactive
mixture containing a low proportion of drug and high ho-
mogeneity of dose. Obviously, the drug should be able to
form strong adhesive interactions with the carrier particles.
Previous studies have indicated that the drug particle size
should not exceed 5 μm in diameter and should preferably
have a narrow size distribution (Nyström and Malmaqvist,
1980; Sundell-Bredenberg and Nyström, 2001). It is also ap-
parent that high dose homogeneity can be obtained by dry
mixing micronised drugs in proportions as low as 0.015%
(w/w) (Sundell-Bredenberg and Nyström, 2001). Westerberg
and Nyström (1993) found that the use of ordered mix-
tures with a low surface area coverage of the carrier parti-
cle resulted in drug dissolution rates even faster than those
from well-dispersed suspensions. These studies thus sug-
gest that a finely divided potent drug mixed with a coarse
water-soluble material ought to result in both a high unifor-
nity of drug content and rapid drug dissolution. Further, the
use of this dry mixing technique allows direct compression
of the tablets, with associated economical advantages over
the classic wet granulation technique.

One problem associated with sublingual tablet formula-
tions is the potential for the patient to swallow parts of the
dose before the active substance has been released and ab-
sorbed locally into the systemic circulation. Addition of a
bioadhesive component to the formulation is a well-known
approach of increasing the probability of a more site-specific
drug release. However, because this concept is normally
applied to non-disintegrating tablets or discs in order to extend
the release of the active substance, such a system may not
be suitable for an immediate-release formulation. A new ap-
proach to the problem has been suggested by Bredenberg
and Nyström (2003), who found that by dry mixing, carrier
particles could be partially covered with fine dry particles
of a bioadhesive material to form an interactive mixture.
These small, bioadhesive units could then replace the large,
bioadhesive, single unit (tablet or disc). It is then theoreti-
cally possible to add the active substance to the surface of
these carrier particles, resulting in ordered units comprising
coarse particles carrying both bioadhesive component and
drug. After compression, tablets composed of these units
would have the potential to rapidly disintegrate and release
the units to adhere to the sublingual mucosa. Provided the
drug is instantly dissolved and able to permeate the mucous
membranes easily, it will be rapidly absorbed at the admin-
istration site before there is a chance of it being swallowed.

Patients with cancer often suffer from chronic pain and
require round the clock opioid therapy. However, break-
through pain frequently appears despite this analgesic ther-
apy, and supplemental opioid doses are required (Portenoy
and Hagen, 1990). Then, administering oral morphine, the
onset of action is often delayed up to 60 min (Hanks et al.,
1998). Parenteral therapy would provide instant relief from
this pain, but this route is not particularly convenient for the
patient. In this context, a specially designed tablet formu-
lation would have the potential to be both therapeutically
effective and easy for the patient to use.

Fentanyl is a potent synthetic opioid, which is used in
the treatment of breakthrough pain (Portenoy and Lesage,
1999). As the citrate salt, fentanyl is sparingly soluble in
water and highly lipophilic, and is expected to be rapidly
absorbed after complete dissolution because of its ease of
permeation through mucous membranes (McClain and Hug,
1980; Dollery et al., 1991). An existing product in the form
of a lollipop containing fentanyl citrate was designed to
allow rapid absorption of the drug from the oral cavity (Mock
et al., 1986; Ashburn et al., 1989). The active compound
was incorporated into a dissolvable candy matrix and placed
on a stick. The patient holds the lollipop against the buccal mucosa and licks it. However, it is documented that a large proportion of the active substance is swallowed using this delivery system (Zhang et al., 2002). This results in highly variable bioavailability, since fentanyl citrate undergoes extensive cytochrome P450 (CYP)-3A4-mediated metabolism in both the intestine and the liver (Streisand et al., 1991; Labroo et al., 1997). The absorption (Weinberg et al., 1988) and efficacy (Zeppetella, 2001) of fentanyl delivered as a solution to the sublingual mucosa has also been investigated. In a study by Zeppetella (2001), a solution of fentanyl citrate (maximum 3 ml, corresponding to 150 mg fentanyl base) was placed under the patient’s tongue; for most patients (82%), an analgesic effect was obtained after 10–15 min. However, some patients found it difficult to retain the solution under the tongue and swallowed it. Weinberg et al. (1988) used a solution of fentanyl with a pH of 6.5, which is the natural pH of saliva. The solution (1 ml corresponding to 50 mg fentanyl base) was held under the tongue for 10 min without swallowing, at which point the solution was expectorated and analysed. The mean amount absorbed was calculated to be 51% of the fentanyl dose, higher than the 22% calculated for morphine.

Considering the shortcomings of the approaches currently available for administration of fentanyl to patients suffering breakthrough pain, it was felt that a new sublingual solid dosage form that provided a rapid and reproducible onset of action and was also convenient for the patient was a desirable aim. This dosage form should also encourage retention of the active substance under the tongue, so as to increase contact time at the absorption site and avoid the potential intra- and interindividual variability resulting from swallowing it. The studies described in this paper were designed to evaluate a new sublingual tablet system using low doses of fentanyl citrate (Rapinyl®). In this system, water-soluble carrier particles are covered with fentanyl citrate and a bioadhesive material during dry mixing. In principle, the tablet quickly disintegrates into the ordered units consisting of carrier, fentanyl citrate and bioadhesive component (Fig. 1). These units initially adhere to the mucosa. The water-soluble carrier particles gradually dissolve and fentanyl citrate dissolves along with them. With this approach, optimal exposure of active substance to the dissolving fluids is combined with bioadhesive retention of the drug in the oral cavity.

2. Materials and methods

2.1. Materials

Fentanyl citrate (Diosynth, The Netherlands) was milled by hand in a mortar. Fentanyl citrate is sparingly soluble in water (1:40), has a pKa of 8.43, a partition coefficient in octanol/water of 955 and a dose-dependent plasma half life of 1–6 h (Dollery et al., 1991). Granulated mannitol (Roquette, France) was used as carrier material, cross-linked polyvinylpyrrolidone (Kollidon CL, BASF, Germany) was used as the disintegrant and bioadhesive component, silified microcrystalline cellulose (ProSolv SMCC® 90, Penwest Pharmaceuticals Co., USA; referred to hereafter as SMCC) was used as the binder and magnesium stearate (Petter Greven, Fett-Chemie GmbH & Co., KG, Germany) was used as the lubricant; all were used as supplied.

2.2. Methods

2.2.1. Primary characterisation of test materials

The apparent particle density (B.S. 2955, 1958) of the materials (n = 3) was measured using a helium pycnometer (AccuPyc 1330 Pycnometer, Micromeritics, USA). The external specific surface area of mannitol was determined using Friedrich permeametry (Eriksson et al., 1990). Blaine permeametry (Kaye, 1967) was used to determine the external specific surface area of all other powders (except magnesium stearate); the surface areas were corrected for slip flow because of the small particle size (Alderborn et al., 1985).

2.2.2. Preparation of mixtures

Coarse mannitol particles were covered with fentanyl citrate by dry mixing (Fig. 2). The materials were mixed in a Teflonized metal jar in a tumbling mixer (Tubula mixer T2F, W.A. Bachofen AG, Switzerland) at 90 rpm for 48h. However, for the lowest drug proportion (100 µg base drug per tablet), the mixing time was increased to 72h (Sundell-Bredenberg and Nyström, 2001). Kollidon CL and SMCC were added to the interactive mixture and mixed at 30 rpm for an additional 30 min (Fig. 2).

![Fig. 1. Schematic model of the disintegration, bioadhesion and drug dissolution of the new sublingual tablet system.](image_url)
2.2.3. Compaction of tablets
Prior to compaction, all tablet masses were mixed with magnesium stearate (0.5% (w/w)) in the tumbling mixer at 30 rpm for 2 min. Tablets were made in a single punch press (Korsch EK0, Germany) using 6 mm flat bevel edged punches; the powder was filled into the die with a feed shoe. The tablets contained fentanyl citrate corresponding to 100 μg, 200 μg or 400 μg of fentanyl base. Each batch comprised 1000 tablets.

2.2.4. Characterisation of tablets

2.2.4.1. Porosity. The tablet porosity was calculated from the dimensions and weight of the tablet and the apparent particle density of the mixture, which was calculated according to Jerwanska et al. (1995).

2.2.4.2. Tensile strength. A diametral compression test (Kraemer HC97, Kraemer Elektronik GmbH, Germany) was performed according to European Pharmacopoeia (1997) method 2.9.8 (resistance to crushing of tablets) (n = 35).

2.2.4.3. Friability. The friability of the tablets was measured according to European Pharmacopoeia (1997) method 2.9.7 (friability of uncoated tablets), i.e. using the Roche friability apparatus for 4 min with the drum rotating at a speed of 25 rpm. Twenty tablets were weighed before and after the measurement and the weight loss was calculated (n = 1).

2.2.4.4. Disintegration time. The disintegration time of the tablets was measured in water according to European Pharmacopoeia (1997) method 2.9.1 (disintegration of tablets and capsules, test A) (Kraemer DES-1, Kraemer Elektronik GmbH, Germany). In this study, the disintegration time was recorded both with and without the use of discs.

2.2.4.5. Assay of fentanyl. The content of fentanyl in ten tablets was analysed using reversed-phase high-performance liquid chromatography (RP-HPLC) with UV detection. The mobile phase consisted of phosphate buffer (pH 2.8) with 35% acetonitrile. The analyses were performed according to the European Pharmacopoeia and by Quintiles AB, Sweden.

2.2.4.6. Drug dissolution. Dissolution tests were performed according to a modified European Pharmacopoeia paddle method (Prolabo dissolutest, Germany). The paddle rotation rate was 50 rpm and the dissolution medium was water (volume: 300 ml; temperature 37 °C). Samples were collected after 1, 3, 5, 7 and 10 min. The amount of fentanyl was determined using liquid chromatography (LC) with Shimadzu SPD-10A vp detector. The mobile phase consisted of 65% phosphate buffer (pH 2.8) and 35% acetonitrile. The LC system was equipped with a Aquasil C18 column (250 mm × 4.6 mm, 5 μm). The analysis was performed by Mikro Kem AB, Sweden. The percentage of dissolved drug was calculated in relation to the maximum amount detected (≥100%) and the data were presented in the dissolution rate profiles as a function of time.

2.3. Clinical study

2.3.1. Study design
After giving written informed consent to participate in the study, one patient (62 years male) with cancer (myeloma) received fentanyl doses of 100, 200 and 400 μg, respectively, as a single dose in the form of a sublingual tablet. The doses were given in random order and were separated by wash-out periods of at least 3 days. Blood samples (n = 16, 7 ml each) for determination of fentanyl in plasma were collected at 0-600 min. Tolerability parameters such as blood pressure, heart rate and oxygen saturation were followed during the complete study day. Adverse events were continuously monitored throughout the study. A safety follow-up, including physical examination, routine haematology and clinical chemistry was performed 2–5 days after the last dose. This paper presents results from one patient.
which was included in a study with eight patients with cancer (Lennemäa et al., submitted for publication). The study was approved by the ethics committee of Gothenburg University.

2.3.2. Sample analysis
Fentanyl was separated from plasma samples by liquid/liquid extraction, using n-heptane containing 3% 2-butanol at pH >12. After evaporation, the residue was dissolved in 5 mM formic acid solution. The amount of fentanyl was determined using RP-HPLC with LC–MS/MS detection. The mobile phase consisted of acetonitrile:water (18:82) containing 5 mM formic acid. The analysis was performed by Quintiles AB, Sweden.

3. Results and discussion
3.1. The formulation of the fentanyl tablets
The materials used and composition of the tablets in this study are presented in Table 1 and Fig. 2. In interactive mixtures consisting of close to identical ordered units, the drug dissolution rate is affected by the particle size of both the drug and the carrier as well as by the physicochemical properties of the carrier (Westberg, 1992). Westerberg et al. (1986) found that the carrier particle is required to be highly soluble for rapid drug dissolution. In this study, the surface area coverage of mannitol with fentanyl citrate particles was 7% (100 µg), 14% (200 µg) and 27% (400 µg). Bredenberg and Nyström (2003) have shown that highly water-soluble carrier materials are less bioadhesive than insoluble carriers, probably because the tensile fracture goes through the partly dissolved carrier particles rather than through the mucosa or between the mucosa and the bioadhesive material. However, it is not always desirable to concentrate only on optimal bioadhesion and the choice of carrier for these fentanyl tablets involved consideration of both a high dissolution rate to optimise absorption of fentanyl over the sublingual mucosa and adequate bioadhesive properties to minimise swallowing of the substance. Since mannitol fulfils both these criteria (Westberg, 1992; Bredenberg and Nyström, 2003) it was chosen as the carrier material. Kollidon CL also has bioadhesive properties (Bredenberg and Nyström, 2003) and was therefore expected to prolong the residence time of the ordered units at the sublingual mucosa. Kollidon CL also has the advantage of being a very effective disintegrant (e.g. Kornblum and Stoopak, 1973; Shangraw et al., 1980). Addition of a highly deformable binder (Mattson and Nyström, 2001) is a moderately deformable binder (Mattson and Nyström, 2001) and is unlikely to significantly impair the disintegration process.

Table 1
Primary characteristics of test materials and composition of the fentanyl tablets

<table>
<thead>
<tr>
<th>Material</th>
<th>Apparent particle density (g/cm³)</th>
<th>External specific surface area (m²/g)</th>
<th>Test materials corresponding to Placebo (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>100 µg (mg)</td>
</tr>
<tr>
<td>Fentanyl citrate</td>
<td>1.282 (±0.001)</td>
<td>2.3⁴</td>
<td>0.159⁶</td>
</tr>
<tr>
<td>Mannitol</td>
<td>1.486 (±0.000)</td>
<td>0.024 (±0.004)</td>
<td>59.4</td>
</tr>
<tr>
<td>SMCC</td>
<td>1.578 (±0.003)</td>
<td>0.35 (±0.00)</td>
<td>7.00</td>
</tr>
<tr>
<td>Kollidon CL</td>
<td>1.224 (±0.001)</td>
<td>0.42 (±0.025)</td>
<td>3.00</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.071 (±0.004)</td>
<td>0.400</td>
<td>0.400</td>
</tr>
<tr>
<td>Tablet weight³</td>
<td>70.0</td>
<td>70.0</td>
<td>70.0</td>
</tr>
</tbody>
</table>

⁴ Measured with a helium pycnometer (Accupyc 1330 Pycnometer, Micromeritics, USA). Mean values (±S.D.), n = 3.
⁵ Measured with a Friedelmann permeameter (Eriksson et al., 1990) or Blaine permeameter (Kaye, 1967; Alderborn et al., 1985). Mean values (±S.D.), n = 3.
⁶ Corresponding to 100 µg fentanyl base.
⁷ Corresponding to 200 µg fentanyl base.
⁸ Corresponding to 400 µg fentanyl base.
⁹ Not determined
¹⁰ Nominal value.
400 (±0.78) 0.44 12.1 (±1.38) 95 91.0–101.4 50 <10
200 70.0 (±0.59) 0.74 11.3 (±1.69) 95 87.7–105 33 <10
400 60.3 (±0.73) 0.64 11.7 (±2.27) 96 88.2–94.4 45 <10

Table 2

Technical properties and drug content of fentanyl tablets

Tablets (μg fentanyl) | Weighta (mg) | Frailtyb (%) | Crushing strength (%) | Average contentd (%) | Uniformity of content (minimum–maximum) (%) | Disintegration time
| With discsf (s) | Without discsf (s)
---|---|---|---|---|---|---
100 | 70.2 (±0.76) | 0.44 | 12.1 (±1.38) | 95 | 91.0–101.4 | 50 <10
200 | 70.0 (±0.59) | 0.74 | 11.3 (±1.69) | 95 | 87.7–105 | 33 <10
400 | 60.3 (±0.73) | 0.64 | 11.7 (±2.27) | 96 | 88.2–94.4 | 45 <10

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3.2. Primary characteristics of the fentanyl tablets in vitro

3.2.1. Tablet strength, weight, friability and porosity

The tablets were characterised regarding weight, tablet strength and friability (Table 2). The weight and friability results were within the limits specified in the European Pharmacopoeia (1997). Both tablet strength and disintegration time were affected by tablet porosity. The porosity of the tablet may affect the efficacy of the disintegrant. A relatively low porosity was most effective for the action of a disintegrant in some studies (Shangraw et al., 1980; Ferrari et al., 1995). However, no general relationship between porosity and disintegration time was seen in the study by Mattsson et al. (2001) and it was concluded that the material properties of the tablet components, such as solubility and bonding ability, would also affect disintegration time. The aim of this study was to achieve high tablet tensile strength and fast tablet disintegration. The tablet porosity was approximately 25% for all three batches, which appears adequate considering the results for tablet strength (Table 2).

3.2.2. Average drug content and content uniformity

Since the amount of active substance in the tablets was relatively low and dry mixing was applied to obtain the ordered units, it was essential to document the average drug content and uniformity of the tablets. With a mean tablet weight of approximately 70 mg (Table 2), the corresponding content of fentanyl citrate was 0.22% (w/w) (100 μg), 0.45% (w/w) (200 μg), and 0.90% (w/w) (400 μg). Since a small amount of drug is mixed with a large amount of a coarse excipient, it is important to have an adequate number of drug particles present (Sundell-Bredenberg and Nyström, 2001). This was achieved by using a small particle size (<5 μm in diameter) (Nystrom and Malmqvist, 1980; Sundell-Bredenberg and Nyström, 2001). Thereby, the possibility of the statistical probability to find a sufficient number of drug particles on each carrier particle is increased. In this study, the particle size of fentanyl citrate was not determined directly; however, the specific surface area was used as a surrogate measure. The surface area, at 2.3 m²/g, was considered to indicate sufficiently small particles. This was confirmed by the tests of average drug content and content uniformity, which showed that only minor segregation had occurred during tablet processing (i.e. mixing and tableting) (Table 2).

3.2.3. Tablet disintegration

In principle, the tablets should disintegrate rapidly, to instantly generate many ordered units consisting of mannitol, fentanyl citrate and Kollidon CL (Fig. 1). The disintegration time of the three batches of tablets containing fentanyl citrate corresponding to 100, 200 and 400 μg fentanyl base was 33–50 s using discs and less than 10 s without discs (Table 2). The higher value with discs was probably caused by adhesion of the tablets to the discs (because of the addition of bioadhesive), which fudged the endpoint. It seems reasonable from these results that the tablet will adhere to the mucosa in the mouth. The in vitro data obtained with discs probably better reflects the disintegration time in vivo into ordered units. However, the peristaltic movements that occur in the mouth may contribute to the disintegration of the tablets.

3.2.4. Drug dissolution

The dissolution tests revealed that fentanyl was dissolved almost instantly from the tablets. Data for the amount of dissolved fentanyl as a function of time are presented in Fig. 3. For tablets of 100 and 200 μg fentanyl, roughly 75% of the substance was dissolved from the tablet within 1 min, and more than 95% within 3 min. Drug dissolution from tablets containing 400 μg was slightly slower: 75% within 2 min and 95% within 5 min. The dissolution profiles for all tablets are comparable with those obtained for ordered mixtures by Westerberg and Nyström (1991), i.e. compaction of the ordered units did not negatively influence the dissolution rate. After initially rapid disintegration, ordered units are quickly exposed to the solvent and drug dissolution starts more or less instantly. The somewhat lower dissolution rate for tablets containing 400 μg fentanyl was thus not due to retardation by the disintegration process, but was probably due to the higher surface area coverage of the hydrophobic drug (Westerberg and Nyström, 1993).
In these in vitro dissolution studies, a large amount of dissolution medium was used (300 ml, pH 7.3). However, the volume of fluid used in vivo was much smaller. Since the solubility of fentanyl citrate is 25 mg/ml in water (Dollery et al., 1991), approximately 0.025 ml fluid would theoretically be required to dissolve a dose of fentanyl citrate corresponding to 400 mg fentanyl base. The fentanyl base has a solubility of 0.74 mg/ml in buffered aqueous media at pH 7.04 (Roy and Flynn, 1989), and the corresponding volume required for complete dissolution using this measurement is 0.54 ml.

3.3. Pharmacokinetic study

After single dose administration, plasma concentrations of fentanyl were obtained within 10 min, with no second peak corresponding to possible gastrointestinal absorption (Fig. 4). It therefore appears that the bioadhesive component (Kollidon CL) promoted the retention of the ordered units under the tongue without hindering the release and local absorption of fentanyl. It appears that the fraction of the fentanyl dose that was swallowed was smaller compared to other mucosal delivery systems (Streisand et al., 1998). This was further supported by calculating the area under the plasma concentration–time curves (AUC) and comparing them with pharmacokinetic data from intravenous administration (data from the literature; Mather et al., 1998). Based on this comparison, at least 70% of the doses administered, reached the systemic circulation (Lennernäs et al., submitted for publication).

The fast-acting sublingual tablet described in this paper has potential to be a valuable addition to the arsenal of drugs for breakthrough pain. The technique could also be useful for substances other than fentanyl where a rapid onset of effect is desirable. However, the new sublingual tablet system would probably be less useful for hydrophilic drug molecules, since this group of drugs will not undergo sufficiently rapid absorption across the sublingual mucosa to effectively utilise the advantages of rapid disintegration and drug dissolution that are built into this system.

4. Conclusions

With this new sublingual tablet system, an optimal exposure of active substance to the dissolving fluids in the mouth is combined with bioadhesive retention of the drug in the oral cavity, resulting in rapid sublingual absorption where intestinal absorption is thus essentially avoided. The possibility to attain a rapid absorption into the systemic circulation give promises of a new approach to treat breakthrough pain.

The new sublingual tablet system could also be useful for substances other than fentanyl where a rapid onset of effect is desirable.

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