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META-OPINION

A meta-opinion: cannabinoids delivered to oral mucosa by a spray for systemic absorption are rather ingested into gastro-intestinal tract: the influences of fed / fasting states

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ABSTRACT

Introduction: Sativex® spray is clinically utilized to deliver delta9-tetrahydrocannabinol and cannabidiol to oral mucosa for systemic absorption. We challenge the consensus that the mechanism of absorption following the oro-mucosal application occurs via the buccal tissue.

Areas covered: Correctness of the consensus of this absorption pathway arose when reviewing publications regarding the influence fed versus fasting states have on pharmacokinetics of these cannabinoids administered to the oral mucosa. This finding is more suitable for peroral administration, where stomach content affects the absorption profile. We hypothesize that these cannabinoids are ingested and absorbed in the gastrointestinal tract.

Expert opinion: Although clinical importance of Sativex® is not disputed, the wide acceptance of its being a successful example of drug delivery through oral mucosa is questionable. Sativex® acts as an example for other drugs delivered to oral mucosa for systemic absorption and unintentionally washed by the saliva flow into the gastrointestinal tract. Delivery of each medicine through oral mucosa should be validated *in-vivo* to ensure this route to be the predominant one. Revealing the underlying absorption mechanisms would enable predicting the impact of different physiological parameters such as saliva flow and fed/fasting states on the pharmacokinetics of the delivered medication.

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1. Introduction

Sativex® spray delivers cannabinoids delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD) to oral mucosa for systemic absorption. It is one of the very few preparations successfully utilized in clinical practice to deliver drugs to the systemic circulation through the oro-mucosal lining – either by administering it to the buccal mucosa or under the tongue [1]. Sativex® has been widely presented in the literature as a successful example of this kind of drug administration [2,3]. Yet, an emerging body of published data may prove this finding to be inaccurate.

Sativex® was developed and currently manufactured by GW Pharmaceuticals, Inc. (Carlsbad, CA, USA). It contains an extraction from the *cannabis sativa* plant [4] with ~70% 1:1 THC and CBD as active ingredients, 5% – other cannabinoids, and the rest – terpenoids, flavonoids, sterols, alkanes, and other chemicals. These substances dissolve in a solution of ethanol and propylene glycol with peppermint oil added as a flavoring agent. The spray is delivered to oral mucosa for systemic absorption. The idea behind the drug delivery is to circumvent the first pass metabolism in the enterocytes and the liver and other gastro-intestinal issues related to absorption of drugs [5]. Each actuation of the device releases the solution in the volume of 100 µl containing 2.7 mg THC and 2.5 mg CBD. Sativex® is used as a treatment for symptom improvement of moderate to severe spasticity in multiple sclerosis patients as well as for other medical conditions. The maximum daily dose is 12 actuations.

Delivery through oral mucosa possesses unique advantages over other modes of drug delivery, yet there is a challenge. A molecule must have specific physico-chemical characteristics to permeate through the oral mucosa. For example, it should not have extremely high lipophilicity, preferably with log P in the range of 1–3 [2]. Thus, Sativex® is an unusual pharmaceutical preparation due to the very high lipophilicity of THC and CBD molecules, with log P in the range of 6–7, administered to oral mucosa.

After reviewing the literature on the topic of pharmacokinetics (PK) of cannabinoids after delivery by Sativex® spray, we encountered an interesting discrepancy. It was clearly shown by Stott et al. [6] (authors affiliated with GW Pharmaceuticals) that PK of cannabinoids delivered by Sativex® is different when administered to fasting subjects compared to ones that were fed. This finding seems rather strange, as food intake before oro-mucosal administration of the medicine should not influence its PK. Yet, we did not find any reference to this issue in the literature [7].

2. Current evidence

In the abovementioned work, Sativex® was administered in a cross-over study to 12 male healthy volunteers either after

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10 h of fasting (with an additional 4 h fasting post-dose), or right after consumption of a high-fat meal. Water was not permitted from 1-h pre-dose until 2-h post-dose, with the exception of 240 ml of water administered at the time of dosing. A single dose of four actuations of the spray was administered either buccally or sublingually. In the fed group, a three- and five-fold higher AUC and two- and three-fold higher peak serum concentrations (Cmax) for THC and CBD, respectively, were obtained (Table 1). For both cannabinoids, the median time to reach Cmax (Tmax) was delayed in the fed group to 4 h relatively to 1.5 h in the fasting-group. Statistical analysis shows that there was a statistically significant effect of food on the PK parameters.

These findings are more appropriate for PK of substances ingested into the gastrointestinal tract rather than absorbed through oral mucosa. The authors suggest that perhaps at least a part of the dose administered is being swallowed. As a result, food may influence PK parameters via several possible mechanisms, such as: prolonged gastric residence time (and, consequently, delayed Tmax), improved mucosal permeability, and/or addition of lymphatic absorption pathway (both augmenting AUC and Cmax). While it may be valid that only part of the dose of Sativex® delivered to the oral mucosa is being swallowed, one cannot ignore the fact that the swallowed part is far greater than the one supposedly entering the blood circulation by permeating through the oral mucosa. The authors stipulate the differences in AUC and Cmax on the known high inter-subject variability of Sativex® PK, however without an explanation for the difference found in Tmax.

This group undertook another clinical trial [8] in which a dose of two sprays actuations or eight spray actuations was delivered to two groups of six healthy volunteers who fasted as previously described. A similar shorter Tmax of 1 h was obtained.

In an earlier work of developing Sativex® [9] Guy and Flint (both affiliated with GW Pharmaceuticals) published a clinical study using overnight-fasting by three male and three female healthy volunteers. In one of the treatments, volunteers received sublingual aerosol (GW-1009–01) of CBD and THC equal to eight spray actuations of Sativex®. Most PK parameters are similar or close to those obtained by Stott et al., under the same experimental conditions, except for AUC of THC, which was far lower. The median Tmax of both cannabinoids was 2.4 h.

In an additional study [10] Guy and Robson (both affiliated with GW Pharmaceuticals) administered Sativex® to 24 healthy male volunteers by four sublingual spray actuations. This time volunteers received a low-fat meal before dosing. The median Tmax of both cannabinoids was about 4 h, again similar to data obtained by Stott et al., under similar experimental conditions with fed volunteers and different from those obtained by Guy and Flint with fasting volunteers. However, AUC and Cmax of both cannabinoids were far lower than those obtained by Stott et al., although higher than in fasting volunteers. Although high inter-subject variability cannot be ignored, we can again speculate that the meal had an effect on the PK of cannabinoids administered by oro-mucosal spray. Perhaps a high-fat meal has an augmenting effect on the absorption of these lipophilic substances compared to a low-fat meal.

In another work by Guy and Robson [11] four actuations of Sativex® were administered to 12 volunteers after a light meal. Results were not conclusive. Although Cmax was similar to other works with fed volunteers, AUC was significantly lower and median Tmax was around 2.5 h. The results, which cannot be associated with either fed or with fasting groups, may be due to the fact that the subjects were allowed to eat only snacks. The caloric composition of the meal has a direct influence on the gastric emptying time. As gastric emptying time may directly affect Tmax, it can explain why a light meal only slightly affects the PK of THC and CBD compared to results obtained after a high-fat meal. Nevertheless, another interesting finding of this work is that PK profiles, although very variable, are similar in all four types of administration modes: buccal, sublingual and oro-pharyngeal sprays as well as per oral delivery in a capsule. Once again, this raises a question regarding the validity of the consensus of Sativex® delivery of the cannabinoids through the oral mucosa and not by per oral ingestion.

Karschner et al. [12] administered buccally and sublingually two or six Sativex® actuations to nine male and female cannabis smokers in a cross-over study. Participants were provided with a standard breakfast the morning of each study session prior to dosing. The assumption of the study was that all participants might have smoked cannabis before and during the study (except right before the dosing of Sativex®). This was confirmed by the presence of THC and CBD in plasma at baseline sampling before dosing. Therefore, AUC and Cmax are relatively high and cannot be compared with other reports. However, Tmax should not be influenced greatly in this setup. Once again, as was mentioned in the case of fed volunteers, the median Tmax of both cannabinoids was around 3.5–4 h. Another interesting finding in this paper derives from the PK data obtained after peroral administration of the same doses of synthetic THC in an oil base to the same participants. All the PK parameters were the same as with Sativex®.

Cherniakov et al. [13] administered four actuations of Sativex® to the buccal and sublingual mucosa of nine fasting (8 h) healthy male volunteers. Atsmon et al. [14] made a similar experiment using 14 male healthy volunteers following an overnight fast of at least 10 h and a standard high-fat meal within 30 min prior to Sativex® administration. Both experimental setups are similar to those conducted by Stott et al. AUC and Cmax in both works were significantly lower than those reported by Stott et al. In the work by Cherniakov et al. (fasting volunteers), the median Tmax of THC was 2 h and of CBD – three (although a plateau type shape was obtained for CBD without a definite peak). In the work by Atsmon et al. (fed volunteers), median Tmax was 3.5 h for both cannabinoids, results that corroborate the corresponding findings mention above.

Viewing all the reports collectively makes one wonder if the cannabinoids delivered by Sativex® indeed reach systemic circulation by permeating the oral mucosa. Instead, it may be surmised that following application of the spray to the

Table 1. Human pharmacokinetic studies of THC and CBD delivered by spray to oral mucosa.

				THC			CBD		
Reference	Number of volunteers	Fed/ fasted	Dose in Sativex® actuations	Tmax median (range) (h)	Cmax mean (SD) (ng/ml)	AUCinf or *AUClast mean (SD) (h x ng/ml)	Tmax median (range) (h)	Cmax mean (SD) (ng/ml)	AUCinf *AUClast mean (SD) (h x ng/ml)
Stott et al. [6]	12	fasted	4	1.50 (0.75–2.00)	3.98 (2.28)	12.51 (7.32)	1.39 (0.75–2.25)	1.15 (0.74)	5.64 (4.09)
	12	fed high fat	4	4 (2.00–4.08)	6.48 (4.10)	34.99 (16.41)	4 (3.02–9.02)	3.66 (2.28)	23.13 (9.29)
Stott et al. [8]	6	fasted	2	1 (0.75–1.50)	1.48 (0.53)	3.46 (1.79)	1 (0.75–1.50)	0.39 (0.08)	1.66 (0.51)
	6	fasted	8	1 (0.75–1.50)	5.4 (2.41)	24.69 (20.67)	1 (0.75–1.75)	2.17 (1.23)	13.28 (12.86)
Guy and Flint [9]	6	fasted	8	2.17 (1.0–3.0)	3.69 (0.88)	12.9 (4.96)	2.35 (0.75–6)	2.6 (1.38)	13.53 (3.64)
Guy and Robson [10]	24	fed low fat	4	4.38	4.9	15.31	4.22	3.33	11.97
Guy and Robson [11]	12	fed low fat	4	2.4 (1–4.5)	6.14 (5.367)	12.84 (7.12)	2.8 (1–4.5)	3.02 (3.15)	6.8 (4.46)
Karschner et al. [12]	9	fed low fat	2	3.3 (1.2–4.5)	5.1 (3)	*32.3 (21.3)	3.6 (1.0–5.5)	1.6 (1.2)	*4.5 (2.4)
	9	fed low fat	6	4.0 (1.2–5.6)	15.3 (10.2)	*58.8 (29.1)	4.5 (1.2–5.6)	6.7 (6)	*18.1 (10.8)
Cherniakov et al. [13]	9	fasted	4	2 (1–4)	1.8 (0.6)	*8 (3)	3 (1–5)	0.5 (0.3)	*3.1 (1.2)
Atsmon et al. [14]	14	fed high fat	4	3.50 (1.50–4.00)	5.21 (2.64)	18.01 (6.68)	3.50 (1.0–5.0)	2.05 (1.10)	7.81 (2.81)

THC – delta9-tetrahydrocannabinol, CBD – cannabidiol, SD – standard deviation, Tmax time to Cmax, Cmax maximum-observed plasma concentration, AUCinf area under the plasma concentration–time curve from time zero to infinity, AUClast area under the plasma concentration–time curve from time zero to the last measurable concentration

cheek, the liquid content is washed by saliva flow and subsequently swallowed. Thereafter, the cannabinoids are absorbed from the intestinal tract. When a solution with a content resembling the one in Sativex® was administered by swallowing, the PK profile obtained was similar to that of Marinol®, an oral lipid formulation of THC approved for clinical use [15].

There are additional cases of drugs administered to oral mucosa and ingested, at least partially, and absorbed from the intestine. For example, Kharasch et al. [16] describe oral transmucosal fentanyl lozenge placed between the cheek and lower gum. By this administration mode, only 25% undergoes absorption through the oral lining, while the rest is ingested and subsequently absorbed from the intestine. Additional reports describe that different molecules after being delivered to buccal mucosa continue to remain in tested saliva for several hours. This explained by a mechanism in which a molecule enters the buccal mucosa, accumulates in the tissue and is subsequently released back into the oral cavity and washed by the saliva flow [17–23].

The question at what rate cannabinoids permeate buccal mucosa if at all should be experimentally investigated to fully understand the described phenomenon.

3. Expert opinion

There is no dispute regarding the importance of Sativex® as a part of the therapeutic arsenal for various medical conditions, due to its successful clinical utilization. However, perhaps the wide acceptance of its being an important example of a medicine that permeates oral mucosa with clinically relevant blood levels is misleading and should be re-examined. Moreover, as one of the major adverse effects of chronic use of Sativex® is ulcerations of oral lining, its ingestion, when possible, may be a more appropriate mode of administration and should be considered.

Although there is a substantial amount of data regarding systemic drug delivery via oral mucosa, only a few products are currently on the market. Several explanations may be given to this phenomenon. There should be an unequivocal reason to prefer oral-mucosal delivery over other modes of administration, specifically the peroral route. The reason can be a circumvention of harsh conditions in the gastrointestinal tract, first-pass metabolism, inability to swallow, or other related considerations. The substance administered through oral mucosa should be highly potent, as there is limited place in the oral cavity for drug delivery. It should also possess specific physicochemical properties, enabling its high and fast permeability through the oral mucosa.

Since the majority of published works regarding the research of permeation through oral mucosa is *in vitro*, it may cause deviation in our understanding of these processes from the results obtained from clinical setup. As with the example of Sativex®, the need for delivery to oral mucosa is questioned. Although this administration route has great potential, appropriate drug candidates should be chosen, and their suitability to this mode of administration should be validated *in vivo*. Furthermore, as the saliva flow is still an under-estimated issue it must be taken into consideration in the development of oro-mucosal delivery devices.

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Declaration of interest

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