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Review

Can currently available drugs for erectile dysfunction be re-formulated to achieve rapid effect?

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ABSTRACT

Currently available drugs (sildenafil, tadalafil, vardenafil) for erectile dysfunction (ED) are only approved for oral administration. The time to achieve maximum plasma drug concentration (Tmax) and onset of effect following the oral administrations is usually around 30–60 min. Sublingual/intranasal administration can offer convenient and more rapid Tmax. The present article provides a review of the chemical/physical properties of the 3 drugs as well as anatomical and physiological characteristics relevant to sublingual/intranasal drug delivery. In addition, new formulations reported in the literature for such delivery are assessed for suitability to human administration. Based on our review, we believe that intranasal delivery of these drugs is more likely to be successful due to the large surface area of absorption mucosa as well as amount of drug needed to achieve therapeutic effect. An appropriate solubilizing vehicle as well as a pH of 4–7 that can allow rapid absorption will be crucial for rapid intranasal delivery of these drugs.

Key words: sublingual, intranasal, phosphodiesterase inhibitors, erectile dysfunction

1. Background on pharmacokinetics and dosing of currently FDA approved drug for erectile dysfunction

Sildenafil, tadalafil, and vardenafil are currently FDA-approved drugs for the treatment of erectile dysfunction (ED). These drugs are characterized as type 5 phosphodiesterase (PDE_5) inhibitors, which selectively and competitively inhibit PDE_5 on smooth muscle cells in the penis and pulmonary vasculature (Huang and Lie, 2013).

For the biochemical events relating to ED, PDE_5 plays an important role and is present in the smooth muscle of the corpus cavernosum, where nitric oxide is released from endothelial cells during sexual arousal. Nitric oxide also plays an important role in a prolonged erection as it activates guanylate cyclase to convert guanosine triphosphate to cGMP. As cGMP accumulates, the smooth muscle in the corpus cavernosum relaxes and causes an increase in blood flow to the penis. PDE_5 cleaves and degrades cGMP to 5'-GMP, while PDE_5 inhibitors prevent cGMP hydrolysis and increase nitric oxide. The enhanced nitric oxide then leads to an increase in cGMP. However, PDE_5 inhibitors are not directly responsible for an immediate erection. Therefore, sexual stimulation is still necessary after the drug is administered (Huang and Lie, 2013).

Sildenafil (Viagra) is the first commercially available ED drug in USA. Sildenafil is available in tablet form and is taken orally (FDA, 2010, 2017). Its effective dosage can range from 25–100 mg once daily. Its active ingredient is sildenafil citrate. The time to reach its maximum plasma concentration (Tmax) is about 60 min (range 30–90 min). Its absolute bioavailability is about 41%. The drug is mostly metabolized by cytochrome P450 3A4 (CYP3A4), with a half-life of about 4 h (FDA, 2017). Sildenafil has a volume of distribution of 105 L, which suggests "extensive tissue binding" given that sildenafil has a plasma protein binding of about 96%.

Tadalafil (Cialis) was approved by FDA in 2008. Its recommended dose for erectile dysfunction is 10 mg as needed and can increase up to a maximum of 20mg as needed (FDA, 2018). Tadalafil can also be taken once daily with an initial dose of 2.5–5 mg. Following a single oral administration, its Tmax is between 30 min and 6 hours with a median time of 2 h. The bioavailability of tadalafil after oral dosing has been shown to be either 36% or 80%, depending on the study conducted (Elbardisy et al., 2019). Tadalafil undergoes hepatic metabolism mainly through CYP3A4 to

catechol metabolites which then undergoes methylation and glucuronidation. In healthy individuals tadalafil has a mean terminal half-life of 17.5 hrs and is mainly excreted as metabolites (61% in feces and 36% in urine) (FDA, 2018). Food does not influence the rate and extent of absorption, hence tadalafil can be taken with or without food. Tadalafilis greatly distributed in tissues with a volume of distribution of 63L and is 94% plasma protein bound at therapeutic concentrations (FDA, 2018).

Vardenafil (Levitra) was approved by FDA in 2003. Its recommended dose is 10 mg tablet taken once a day as needed (FDA, 2014). The effective dosage can range from 5–20 mg. The active ingredient is vardenafil hydrochloride trihydrate. The Tmax is about 60 min (30 min–2 h), and its absolute bioavailability after oral administration is about 15%. (This low bioavailability is most likely due to liver first pass metabolism and poor solubility). The drug is mostly metabolized by CYP3A4 and the M1metabolite accounts for about 7% of total pharmacologic activity. The terminal half-life of vardenafil or the M1 metabolite is about 4–5 h (FDA, 2014).

In summary, each of these three drugs for erectile dysfunction has a Tmax about 60 minutes or longer, with an early Tmax about 30 min. This corresponds to the onset of action about 30 min or later with maximum effect at about 1 h. In general, such delayed onset of effect from the oral dose is not preferred as compared to a more rapid acting formulation. Thus, formulations that can improve the onset of effect are desirable.

2. Potential advantage of sublingual/sublingual formulations to achieve rapid effect for ED drugs

The route of drug administration that can provide the most rapid onset of effect is intravenous injection. Such route of administration however is inconvenient and possibly dangerous. Alternatively, sublingual or intranasal administration may provide a convenient choice to achieve a rapid effect. Moreover, there are potential advantages with such drug administration compared to oral administration (Behl et al., 1998; Chhajed et al., 2011; Fortuna et al., 2014; Khan et al., 2017; Narang and Sharma, 2011). The main advantage is related to the high permeability and vascularized structure of the sublingual/nasal mucosa. When a drug is administered through sublingually/intranasally, the thin membrane and abundant vasculature present can lead to rapid permeation or absorption as well as avoiding the gastrointestinal tract where these drugs will undergo hepatic first-pass metabolism. Thus, there is a rapid onset of action from fast absorption as well as a lower dose of the drug required for therapeutic effect, leading to potentially better safety (Behl et al., 1998; Chhajed et al., 2011; Fortuna et al., 2014; Khan et al., 2017; Narang and Sharma, 2011).

While both intranasal and sublingual administration can offer similar rapid drug absorption without first pass metabolism there are several important differences between these 2 routes of administration: (a) The surface area for absorption is very different, although both type of mucosa are quite thin. The sublingual surface area is only 26 cm^2 whereas the nasal cavity area is 120–180 cm^2 or 96 m^2 if microvilli are included (Beule, 2010; Gizurarson, 2012; Kraan et al., 2014). Thus, the amount of drug that can be potentially absorbed sublingually is very limited compare to that intranasally when considering the total surface area at these two sites. (b) Saliva is generated continuously at the sublingual site and together with the tongues can enable rapid disintegration and dissolution of small tablets. On the other hand, tablet formulation is not suitable for intranasal administration. However, powder formulation is suitable for intranasal administration due to its relatively large surface area. (c) The enzymes and transporters present at the sublingual and nasal site are different. They may be important considerations for specific dosing of specific drugs, although such research is not adequately studied at present. (d) A nasal spray is required for intranasal administration of solution or powder. Sublingually either solution by spray or tablet formulation can be administered.

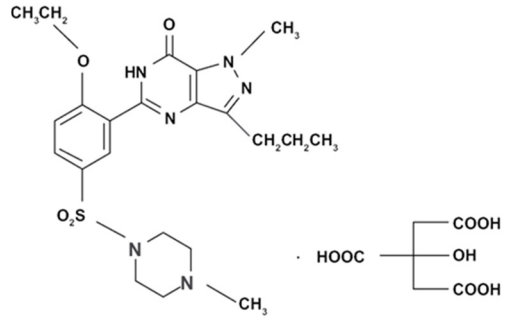
Of differences described above, from the perspective of rapid drug absorption, the total surface area for absorption and good solubility relevant to the therapeutic dose of the drug are the most important factors for consideration. In relevance to sublingual versus intranasal administration, for the same therapeutic dose (e.g. in mg quantity) needed to be absorbed to achieve a rapid effect, intranasal administration is likely to be more suitable due to the larger surface area for absorption.

3. Chemical/physical properties of sildenafil, tadalafil, and vardenafil and relevance to sublingual/sublingual formulation

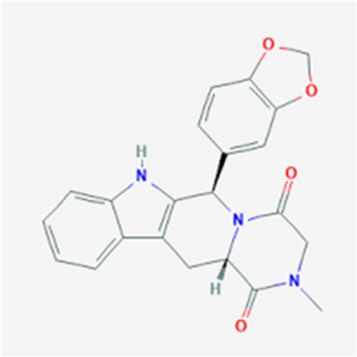
For effective transmucosal (sublingually/intranasally) drug delivery, certain physicochemical properties of the drug are desirable. These include good lipophilicity or good membrane partition coefficient (with a good log P), low molecular weight, pKa of the drug that would lead to a favorable ionization at the pH of the sublingual and nasal epithelium, and good solubility (Beule, 2010; Chhajed et al. 2011; Gizurarson, 2012; Kraan et al., 2014). Additionally, the drug and vehicle must cause minimal local irritation and possessing a pleasant taste and odor together with a small dose to achieve a therapeutic effect (Abhang et al., 2014; Bitter et al., 2011)

Sildenafil citrate is a weakly basic drug. Its white crystalline powder has a molecular weight of 666.70, and a solubility of 3.5 mg/ml in water (National Center for Biotechnology Information, Sildenafil, 2019; Pranitha and Lakshmi, 2018). Its structure is shown in Figure 1a. Since its

(a) Sildenafil Citrate



(b) Tadalafil



(c) Vardenafil Hcl trihydrate

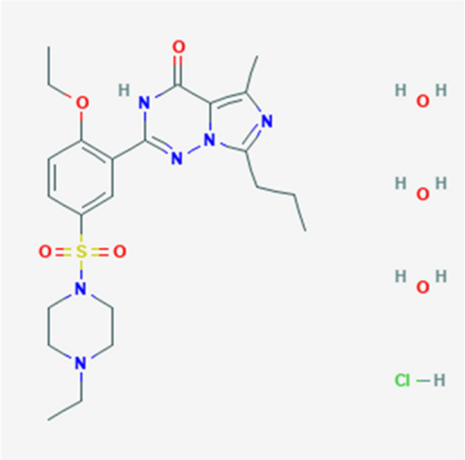


Figure 1

usual effective oral dose is about 50–100 mg, the amount of drug that can be rapidly absorbed from the sublingual/nasal sites is likely to be inadequate based on aqueous solubility of 3.5 mg/ml. Thus, the high molecular weight and low aqueous solubility of sildenafil citrate might not be suitable for sublingual/intranasal drug delivery in aqueous medium. However, sildenafil citrate has a pKa of 7.2, which is around the pH range of 4.0 to 7.0 for nasal and sublingual sites, and a log P of 2.7, which could allow for sufficient drug absorption when administered sublingually/intranasally using new technology (Al-Ghananaeem, 2013; Elshafeey et al., 2009; Lu et al. 2011; Sheu et al., 2016).

Tadalafil is a lipophilic water insoluble drug with a molecular weight of 389.411, pKa of 15.17 and water solubility of only about 0.2 mg/ml at 25ºC (National Center for Biotechnology Information, Tadalafil 2019). Its molecular structure is shown in Figure 1b. Tadalafil has a high permeability with poor solubility, resulting in a reduced gastrointestinal dissolution and consequently leading to variable bioavailability. In comparison to the other PDE_5 inhibitors, it has the slowest absorption rate among the 3 drugs for ED, with a mean of 2h to reach maximum concentration. In order to enhance bioavailability of tadalafil, various formulations are being designed such as sublingual and intranasal sprays, solid dispersion, micronization and lipid-based formulations (Baek and Cho, 2016; Elbardisy et al., 2019; Kim et al., 2018; Sharma et al., 2018; Teymouri et al., 2019).

Vardenafil HCI trihydrate has a molecular weight of 579.1 (FDA, 2014). Its molecular structure is shown in Figure 1c. The vardenafil base has a pKa = 7.15 (mostly basic) and 9.86 (mostly acidic), and logP = 3.64. Its solubility is pH dependent and is about 8.8, 1.6, 0.16 and 0.09 mg/ml at pH 1, 3, 5 and 6 respectively. The solubility of the active pharmaceutical ingredient (API), vardenafil HCI trihydrate, in water is much higher, about 14 and 1.4 mg/ml at pH 3.9 and 4.4 respectively (unpublished data by the author). While the solubility of the API in water appears to be better than the base form, the API solubility in water is still low and is rapidly decreasing with increasing pH (from pH 4–7). Thus, despite excellent membrane partition coefficient (logP = 3.64) of the vardenafil base, sublingual or intranasal administration using aqueous vardenafil solution will not yield an advantage in bioavailability compared to oral administration.

Vardenafil, however, can achieve an improved solubility in certain solvents, e.g. alcohol or other organism-aqueous mixture solvents (Berry et al., 2016; Pranitha and Lakshmi, 2018). Pure alcoholic solution of vardenafil is a concern due to potential membrane irritation and damage. Thus, an alcoholic-aqueous mixture or other organic-aqueous mixtures that are relatively safe (or well tolerated by human subjects) at low concentrations as under the “generally regarded as safe” or “GRAS” category should be used (Wang et al., 2008).

4. New formulation for sublingual/intranasal administration

Since their aqueous solubility at pH 4.0–7 (close to physiologic pH range at nasal and sublingual membranes) is low, sildenafil, tadalafil, and vardenafil are not suitable for administration as an aqueous solution when administered sublingually or intranasally to achieve a rapid effect. The low aqueous solubility of the three phosphodiesterase inhibitors is a major obstacle for efficient permeation and/or absorption

Table 1. In vivo studies of PDE_5.

Name+ (ref.#)	Animal	Dose mg	Route	Cmax µg/ml	Tmax h	$AUC_{0-\infty}$ µg.h/ml
Sildenafil (Elshafeey et al., 2009)	Rabbit	5 (mg/kg)	Intranasal (nasal microemulsion)	0.713 ± 0.023	0.75 ± 0.00 (h)	1.412 ± 0.026
Sildenafil (Sheu et al., 2016)	Rabbit	0.7	Sublingual spray: propylene glycol	0.089 ± 0.012	0.29 ± 0.24	0.135 ± 0.019
Sildenafil (Lu et al., 2011)	Rabbit	4.9	Intranasal microemulsion: Tween 20:Ethanol (4:1) and water:oleic acid (1:3)	0.015	0.08	0.041
Sildenafil (Lu et al., 2011)	Rabbit	10.0	Intranasal microemulsion: Tween 20:Ethanol (1:4) and water:oleic acid (1:5)	0.187	0.78	0.497
Sildenafil (Lu et al., 2011)	Rabbit	7.5	Intranasal microemulsion: Tween 20:Propanol (4:1) and water:oleic acid (1:3)	0.070	0.83	0.087
Sildenafil (Lu et al., 2011)	Rabbit	10.0	Intranasal microemulsion: Tween 20:Ethanol (1:4) and water:oleic acid (1:4)	0.090	0.56	0.249
Sildenafil (Lu et al., 2011)	Rabbit	4.6	Intranasal microemulsion: Tween 20:PEG 600 (4:1)	0.008	0.33	0.011
Sildenafil (Lu et al., 2011)	Rabbit	4.4	Intranasal microemulsion: Tween 20:PEG 600 (1:4)	0.151	0.50	0.146
Sildenafil (Lu et al., 2011)	Rabbit	4.0	Intranasal microemulsion: Tween 20:Propylene Glycol (4:1)	0.212	1.50	0.364
Sildenafil (Lu et al., 2011)	Rabbit	3.6	Intranasal microemulsion: Tween 80:Ethanol (4:1) and water:oleic acid (1:3)	0.097	0.33	0.104
Sildenafil (Lu et al., 2011)	Rabbit	10.0	Intranasal microemulsion: Tween 80:Ethanol (1:4) and water:oleic acid (1:5)	0.444	0.45	0.814
Sildenafil (Lu et al., 2011)	Rabbit	3.2	Intranasal microemulsion: Tween 80:Propanol (4:1) and water:oleic acid (1:3)	0.045	1.08	0.111
Sildenafil (Lu et al., 2011)	Rabbit	10.0	Intranasal microemulsion: Tween 80:Propanol (1:4) and water:oleic acid (1:4)	0.414	0.39	0.535
Sildenafil (Lu et al., 2011)	Rabbit	3.9	Intranasal microemulsion: Tween 80:PEG 600 (4:1)	0.030	3.03	0.375
Sildenafil (Lu et al., 2011)	Rabbit	4.5	Intranasal microemulsion: Tween 80:PEG 600 (1:4)	0.027	1.25	0.079
Sildenafil (Lu et al. 2011)	Rabbit	3.8	Intranasal microemulsion: Tween 80:Propylene Glycol (4:1)	0.291	0.08	0.103
Tadalafil (Kim et al., 2018)	Male Beagle dogs	5.0	Intranasal	0.07645 ± 0.01207 (µg/ml)	1.50 ± 0.41	0.790 ± 0.225
			Oral	0.05949 ± 0.00922 (µg/ml)	1.71 ± 0.39	0.479 ± 0.103
Tadalafil (Teymouri et al., 2019)	Male wistar rats	10 mg/kg	Inhalation	0.281032867 ± 0.0866034 (µg/ml)	19.7 ± 6.7	11.900 ± 3.200
			Oral	0.2170148 ± 0.08442279 (µg/ml)	5.3 ± 1.0	6.600 ± 2.700
Tadalafil (Elbardisy et al., 2019)	Rat	0.108	Intranasal Capmul-MCM-EP, Labrasol:trascutol, nanoemulsion	3/6 rats rated effective*	0.5	—
		0.270	Intranasal	4/6 rats rated effective*	0.5	—
		0.540	Oral	2/6 effective*	0.5	—

+ Sildenafil citrate with molecular weight of 666.7 and tadalafil with molecular weight of 389.4 are used for conversion calculations.
*erection instead of concentration.

at sublingual/nasal sites. To optimize mucosal permeation and/or absorption via the sublingual/intranasal routes of administration, a suitable solvent (such as an organic-aqueous mixture) that can improve solubility as well as permeability at suitable pH is needed. This is especially important for intranasal drug administration since special ciliated cells are present at nasal cavity to clear inhaled drug to the throat.

Various mixtures of solubilizing agents to enhance solubility and permeability of the ED drugs have been reported and tested in vivo (see Table 1). Majority of these formulations could not achieve rapid absorption or achieve short Tmax (less than 15 min) or adequate concentration (equivalent to that achieved orally in human subjects). The combination of oils, surfactants and co-surfactants or co-solvents have been found to enhance solubility and shortened Tmax for sildenafil and tadalafil, although the safety of these formulations requires further safety. Although alcoholic formulation of vardenafil administered as nebulizer has been found to rapidly achieve effective plasma concentration compared to oral administration in human subjects, nebulizer however is inconvenient and further research to develop sublingual/intranasal delivery will improve convenience.

5. Conclusion

Improvement to achieving an earlier Tmax than that from oral therapy is desirable for the currently available ED drugs. In view of the low aqueous solubility of the 3 available drugs, sildenafil, tadalafil and vardenafil, use of suitable co-solvents will be important for achieving an early Tmax in addition to demonstration of human safety. Since a new concept based on pH solubility to enhance mucosal membrane permeation as well as a pharmacokinetic model to predict absorption of mucosal (sublingual) delivery have been recently described, the use of these concepts could further improve future sublingual/intranasal delivery (Li et al., 1999; Wang et al., 2008, 2010, 2013) especially if they can be combined with surfactant/co-solvent model when applying to low aqueous soluble compounds such as phosphodiesterase inhibitors (Li et al., 1999).

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