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Epinephrine for the Treatment of Anaphylaxis: Do All 40 mg Sublingual Epinephrine Tablet Formulations with Similar *In Vitro* Characteristics Have the Same Bioavailability?

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ABSTRACT: Epinephrine autoinjectors are underutilized in the first aid emergency treatment of anaphylaxis in the community; so non-invasive sublingual epinephrine administration is being proposed. In order to determine the effect of changing excipients on the bioavailability of sublingual epinephrine, four distinct fast-disintegrating epinephrine 40 mg tablet formulations, A, B, C and D, were manufactured using direct compression. All formulations were evaluated for tablet hardness (H), disintegration time (DT) and wetting time (WT). In a prospective 5-way crossover study, four sublingual formulations and epinephrine 0.3 mg i.m. as a control were tested sequentially in a validated rabbit model. Blood samples were collected before dosing and at intervals afterwards. Epinephrine plasma concentrations were measured using HPLC-EC. All tablet formulations met USP standards for weight variation and content uniformity, and resulted in similar mean H, DT and WT ($n = 6$). The area under the curve (*AUC*), maximum concentration (C_{max}) and time at which C_{max} was achieved (T_{max}) did not differ significantly after the sublingual administration of formulation A and epinephrine 0.3 mg i.m. The *AUC* after B, C and D were significantly lower ($p < 0.05$) than after epinephrine 0.3 mg i.m. These results suggest that the selection of excipients used in these tablet formulations can affect the bioavailability of sublingually administered epinephrine. Copyright © 2006 John Wiley & Sons, Ltd.

Key words: epinephrine; adrenaline; fast-disintegrating tablet; sublingual absorption; EpiPen; anaphylaxis

Introduction

Epinephrine is the recommended drug of choice for the treatment of anaphylaxis. A dose of 0.3–0.5 mg in adults and 0.01 mg/kg to a maximum of 0.3 mg, in children, given by intramuscular injection in the thigh is often recommended [1–4]. Most anaphylactic reactions occur unexpectedly in the community [1–3] and for out-of-hospital emergency treatment of anaphylaxis, epinephrine autoinjectors such as EpiPen®, EpiPen Jr® (Dey LP, Nappa, CA), Twinject 0.3 mg® and Twinject 0.15® (Verus Pharmaceuticals, Inc., San Diego, CA) are prescribed. These autoinjectors are underutilized when anaphylaxis occurs [5,6] due to high cost, which limits availability worldwide [7], limitations if multiple doses are required [8], anxiety associated with the use of

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needles [3] and errors due to incorrect administration technique [6,9]. It is impossible to give accurate doses to infants, or to children weighing <15 kg, or between 20 and 25 kg, using the 0.15 and 0.3 mg epinephrine autoinjectors, and alternative methods, such as epinephrine ampules/syringes/needles [10] or epinephrine metered-dose inhalers [11] are impractical [3].

The readily accessible, convenient sublingual route of administration has long been used to administer medications such as nitroglycerine and was also used in the 1970's for the administration of isoproterenol. Sublingual administration is a promising non-invasive alternative route for epinephrine administration [12]. Drugs administered sublingually bypass potential metabolic conversion in the gastrointestinal tract and hepatic first-pass metabolism, and reach the systemic circulation in a pharmacologically active form [13–15]. Lipophilic drugs with a low molecular weight such as epinephrine are likely absorbed across the sublingual mucosa into the venous circulation by transcellular diffusion [16], a mechanism driven by the concentration gradient [12].

Tablet formulations that disintegrate or dissolve rapidly in the sublingual cavity are required in order to enhance the availability of epinephrine for rapid absorption into the blood vessels in the sublingual mucosa. Using a novel fast-disintegrating tablet formulation, the sublingual epinephrine dose required to achieve plasma epinephrine concentrations similar to those obtained after the intramuscular injection of 0.3 mg epinephrine from an EpiPen® was determined to be 40 mg [12]. The effect of changing tablet excipients (non-medicinal ingredients) on the bioavailability of epinephrine sublingual tablets has not yet been described.

The aim of this study was to evaluate the effect of changing excipients on the epinephrine sublingual bioavailability from four different tablet formulations which have similar *in vitro* tablet characteristics, in comparison with epinephrine 0.3 mg by intramuscular injection in the thigh, using a validated rabbit model. This model has been used previously to compare the rate and extent of epinephrine absorption after epinephrine administration by several different routes, such as intravenous, intramuscular, subcutaneous, pulmonary and sublingual routes [12,17].

Materials and Methods

Materials

(−)-Epinephrine (+) bitartrate, (−)-3,4-dihydroxy-α-[(methylamino)methyl]benzyl alcohol (+)-tartrate (1:1) salt, was purchased from Sigma-Aldrich (St Louis, MO). The following excipients were kindly supplied by the manufacturers and used as received: Ceolus® (microcrystalline cellulose), type PH-301, PH-M-06 and KG-802 (Asahi Kasei Chemicals Corp, Tokyo, Japan), RxCipient® (calcium silicate), type FM1000 (Huber Engineered Materials, Havre de Grace, MD) and Pearlitol® (mannitol), type 400 DC (Roquette America, Inc., Keokuk, IA), as fillers; low-substituted hydroxypropyl cellulose, type LH11 (Shin-Etsu Chemical Co, Tokyo, Japan) and Polyplasdone® (crospovidone), type XL-10 (ISP Technologies, Inc., Wayne, NJ), as superdisintegrants; Pharmaburst® (patent formula), as a ready to use formula for fast-disintegrating tablets (SPI Pharma, New Castle, DE); RxCipient® (silicon dioxide), type GL200 (Huber Engineered Materials, Havre de Grace, Maryland), as a glidant; PRUV® (sodium stearyl fumarate) by JRS Pharma LP (Patterson, NY), and magnesium stearate purchased from Mallinckrodt Baker (Phillipsburg, NJ) as lubricants.

Preparation of tablets

Four tablet formulations, A, B, C and D containing 48.5% of epinephrine bitartrate, equivalent to 40 mg of epinephrine, were prepared by direct compression (Table 1). The total weight of the compressed tablets was maintained at 150 mg. These tablets were prepared by mixing the pre-weighed excipients and epinephrine using a three dimensional manual mixer (Inversina®, Bioengineering AG, Switzerland). The microcrystalline cellulose: low-substituted hydroxypropyl cellulose ratio in formulations A and B was 9:1 [18,19]. All of the magnesium stearate and sodium stearyl fumerate were added just before the end of mixing.

Each tablet formulation was compressed using an 11/32 inch die, a flat, scored face, bevel edge upper punch, and a flat, bevel edge lower punch. The tablets were pressed at a pre-selected compression force based on results from our

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Table 1. Composition of the four tablet formulations of epinephrine[a]

Ingredient %	Tablet formulation			
	A	B	C	D
Epinephrine bitartrate	48.51	48.51	48.51	48.51
Microcrystalline cellulose (PH-301)	44.54	—	—	—
Microcrystalline cellulose (PH-M-06)	—	22.27	—	—
Microcrystalline cellulose (KG-802)	—	—	12.87	—
Calcium silicate	—	—	10.55	
Pharmaburst®	—	—	—	49.49
Low-substituted hydroxypropyl cellulose (LH11)	4.95	2.47	—	—
Crospovidone		—	1.3	—
Mannitol	—	24.74	26.00	—
Silicon dioxide	—	—	0.26	—
Magnesium stearate	2.00	2.00	0.51	—
Sodium stearyl fumarate	—	—	—	2.00

[a] Tablet weight was 150 mg.

previous study [20] using a Manesty®—F3 single-punch tablet press machine (Liverpool, UK). All tablets were formulated in the manufacturing laboratory of the Faculty of Pharmacy at the University of Manitoba.

In vitro evaluation of tablet characteristics

Each batch of 200 tablets was collected into a stainless steel beaker. Tablet weight variation, drug content uniformity and friability were measured using USP methods and criteria [21,22]. The drug content was analysed using a high performance liquid chromatography (HPLC) system with ultraviolet (UV) detection (Waters Corp., Milford, MA) and tablet friability was measured using a USP Friability instrument (Pharma Test Apparatebau GmbH, Hainburg, Germany). Six tablets were selected randomly from each formulation batch and tested for tablet hardness, disintegration time and wetting time. The mean $\pm$ standard error (SEM) and percentage of coefficient of variation (CV %) were calculated.

Hardness (*H*): The H or the crushing tolerance of tablets was measured by an Erweka® hardness tester (Heusenstamm, Germany).

Disintegration time (*DT*): A novel, relatively simple method with rigorous requirements was developed to evaluate the DT of rapidly disintegrating tablets, as described previously [20].

Wetting time (*WT*): Tablet WT was measured by a procedure similar to that reported by Bi *et al* [18] with slight modifications described previously [20].

Effect of water-soluble excipients on epinephrine solubility. The dissolution of 7.3 mg of epinephrine bitartrate was evaluated in 100 µl of water and 100 µl of a saturated solution of mannitol, equivalent to 40 mg of epinephrine dissolving in 1 ml of saliva (1 ml saliva volume was based on the normal salivary secretion in humans, 0.2 ml/min [23], over 5 min). Dissolution was monitored over 5 min using a microscope ($10^{4\times}$ power) (Nikon YS100, Nikon Canada Inc., ON, Canada) equipped with a digital camera (Sony 3-CCD, DXC-390P, Sony Electronics Inc., NJ) using Northern Eclipse V6.0 software (Empix Imaging, Inc., ON, Canada).

Animal studies

All animal studies were conducted according to current guidelines published by the Canadian Council on Animal Care [24] and were approved by the University of Manitoba Protocol Management and Review Committee.

In a prospective, controlled, 5-way crossover sequential study, five New Zealand white rabbits (mean weight $\pm$ SEM, 4.7 $\pm$ 0.1 kg) were investigated on five different days at least 4 weeks apart, using a protocol described previously [17]. Each rabbit received an

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epinephrine 40 mg sublingual tablet using each formulation, and epinephrine 0.3 mg intramuscular in the right thigh using an EpiPen® with the same lot number. The method of sublingual epinephrine tablet administration to rabbits was described previously [12].

After epinephrine intramuscular, the solution remaining in the EpiPen® autoinjector was evacuated into a polystyrene test tube, sealed and frozen at −20°C, to be analysed for epinephrine content using HPLC system with UV detection (Waters Corp., Milford, MA).

Measurement of plasma epinephrine concentrations

An indwelling catheter (OPTIVA* 22G 1″, Johnson & Johnson Medical, Arlington, TX) was inserted into an ear artery 30 min before dosing. A 2 ml blood sample was obtained immediately before dosing and at 5, 10, 15, 20, 30, 40, 60, 90, 120, 150 and 180 min afterward.

Blood samples were refrigerated within 1 h of sampling and centrifuged at 4°C. The plasma was frozen at −20°C. Before analysis, the plasma was thawed at room temperature and epinephrine was extracted by a solid–liquid extraction process, with an efficiency of 84%. Epinephrine concentrations were measured using an HPLC system with electrochemical detection (Waters Corp., Milford, MA) [25,26]. Two calibration curves with two different epinephrine concentration ranges were prepared. The low-range calibration curve was linear over the range 0.1–1.0 ng/ml, with a coefficient of variation of 0.8% at 0.1 ng/ml and 1.5% at 1.0 ng/ml. The high-range calibration curve was linear over the range 1.0–10.0 ng/ml, with a coefficient of variation of 5.0% at 1.0 ng/ml and 1.2% at 10.0 ng/ml.

Data analysis

Mean (±SEM) maximum plasma epinephrine concentrations (C_{max}), the times at which C_{max} was achieved (T_{max}) and the area under the plasma concentration versus time curves (*AUC*) were calculated from the plasma epinephrine concentration versus time plots of each individual rabbit using WinNonlin® 5.0 (Pharsight, Mountain View, CA). The *AUC*, C_{max} and T_{max} values for each rabbit were compared by using repeated-measures ANOVA, Tukey-Kramer tests and paired Students' *t*-test using NCSS Statistical Analysis Software (NCSS, Kaysville, UT). Differences were considered to be significant at $p < 0.05$.

Results

In vitro results

The powders from all four formulations had good mixing, flowability and compressibility characteristics. Tablets manufactured from each formulation were within USP specifications for weight variation and drug content uniformity [21].

The mean (±SEM) hardness, disintegration time and wetting time results of the four tablet formulations are summarized in Table 2. Tablet hardness was similar for all four formulations and ranged from 1.5 ± 0.1 kg to 2.6 ± 0.1 kg. The disintegration and wetting times were less than 15 s and 60 s, respectively, for all four tablet formulations. Tablets from formulations A and

Table 2. The hardness, disintegration time, wetting time and friability of the four tablet formulations[a]

	In vitro tablet characteristic						
Formulation	H	CV	DT	CV	WT	CV	F
A	2.4 ± 0.1	12.4	13.5 ± 0.2	4.1	26.2 ± 1.8	17.0	0.6
B	1.5 ± 0.1	16.9	13.2 ± 0.8	14.7	47.3 ± 3.3	16.9	13.4
C	2.4 ± 0.1	7.5	9.3 ± 0.5	13.0	14.3 ± 0.6	9.5	0.3
D	2.6 ± 0.1	4.3	8.3 ± 0.3	9.8	26.5 ± 2.0	18.2	6.5

H indicates tablet hardness (kg); CV, coefficient of variation (%); DT, disintegration time (s); WT, wetting time (s); F: friability (%) (USP limits ⩽1%).
[a]mean ± SEM ($n = 6$).

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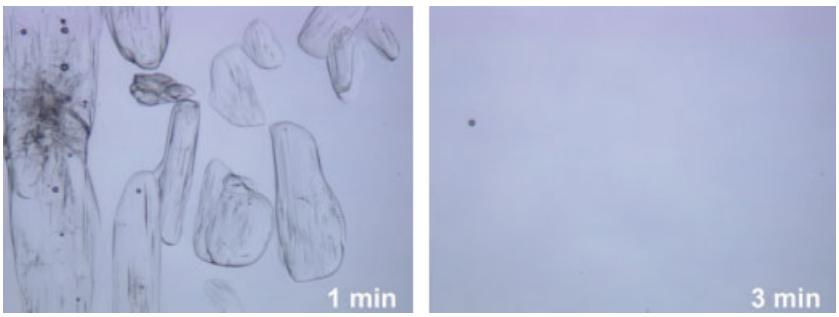

Figure 1. Photomicrograph of the dissolution of epinephrine bitartrate crystals in water over 3 min

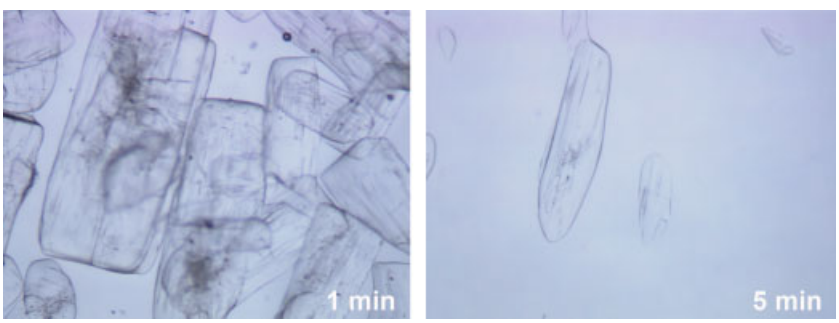

Figure 2. Photomicrograph of the dissolution of epinephrine bitartrate crystals in a saturated solution of mannitol over 5 min

C, but not from formulations B and D met the USP standards for tablet friability [22] (Table 2).

The dissolution of 7.3 mg of epinephrine bitartrate in 100 µl of water, the control, was complete in less than 3 min (Figure 1) when compared with dissolution of 7.3 mg of epinephrine bitartrate in 100 µl of a saturated solution of mannitol, which was incomplete after 5 min (Figure 2).

In vivo results

The mean epinephrine dose injected using EpiPen® autoinjectors was 0.34 mg, calculated by multiplying the mean epinephrine concentration, measured in the evacuated EpiPen® solutions, by the stated injected volume (0.3 ml). Mean epinephrine tablet doses were 38.15 ± 0.51, 35.79 ± 0.30, 39.20 ± 0.29 and 39.34 ± 0.28 mg for formulations A, B, C and D, respectively, measured using the USP content uniformity standard test (Table 3).

Mean (±SEM) plasma epinephrine concentration versus time plots after the administration of epinephrine 40 mg sublingual tablets from each formulation and epinephrine 0.3 mg by intramuscular injection are shown in Figure 3. Mean (±SEM) *AUC*, $C_{baseline}$ (endogenous), C_{max} and T_{max} values after the administration of epinephrine 40 mg sublingual tablets of each formulation and epinephrine 0.3 mg by intramuscular injection are shown in Table 3. No adverse effects were observed.

Mean (±SEM) *AUC* after the administration of epinephrine 40 mg sublingual tablets of formulation A (1861 ± 537 ng/ml/min) and epinephrine 0.3 mg by intramuscular injection (2 431 ± 386 ng/ml/min) did not differ significantly. The mean *AUC* after the administration of epinephrine 40 mg of formulation B (615 ± 87 ng/ml/min), formulation C (606 ± 149 ng/ml/min), and formulation D (646 ± 202 ng/ml/min) sublingual tablets were significantly lower than after epinephrine 0.3 mg by

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Table 3. Epinephrine bioavailability after 40 mg sublingual epinephrine administration from four different tablet formulations and epinephrine 0.3 mg intramuscular (i.m.) injection in the thigh

	Sublingual tablet				i.m. injection
Mean ± SEM[a]	A	B	C	D	EpiPen®
Epinephrine dose (mg)	38.15 ± 0.51	35.79 ± 0.30	39.20 ± 0.29	39.34 ± 0.28	0.34
$AUC_{0-3\,h}$ (ng/ml/min)	1861 ± 537	615 ± 87[b]	606 ± 149[b]	646 ± 202[b]	2431 ± 386
$C_{baseline}$ (ng/ml)	15.4 ± 3.2	4.2 ± 0.7	11.2 ± 7.5	3.5 ± 1.4	9.6 ± 3.5
C_{max} (ng/ml)	31.0 ± 13.0	6.0 ± 0.9[b]	7.1 ± 1.6[b]	6.7 ± 3.2[b]	50.0 ± 17.0
T_{max} (min)	9 ± 2	28 ± 10	27 ± 9	16 ± 4	21 ± 5

AUC, area under the plasma concentration versus time curve; $C_{baseline}$, baseline plasma concentration (endogenous epinephrine); C_{max}, maximum plasma concentration (mean ± SEM of individual C_{max} values from each rabbit, regardless of the time at which C_{max} was achieved); T_{max}, time at which maximum plasma epinephrine concentration was achieved (mean ± SEM of individual T_{max} values from each rabbit).
[a] $n = 5$.
[b] $p < 0.05$ compared with i.m. injection.

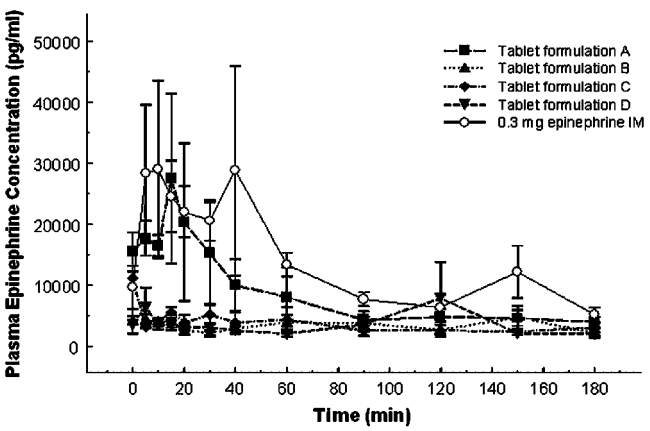

Figure 3. Plasma epinephrine concentration versus time plots after administration of epinephrine sublingually from four different tablet formulations, and after epinephrine intramuscular injection (i.m.)

intramuscular injection (2431 ± 386 mg/ml/min).

Mean (±SEM) C_{max} values after epinephrine 40 mg sublingual tablets of formulation A (31.0 ± 13.1 ng/ml) and epinephrine 0.3 mg by intramuscular injection (50.3 ± 17.1 ng/ml) did not differ significantly. Mean C_{max} values after epinephrine 40 mg of formulation B (6.0 ± 0.9 ng/ml), formulation C (7.1 ± 1.6 ng/ml) and formulation D (6.7 ± 3.2 ng/ml) sublingual tablets were significantly lower than after epinephrine 0.3 mg by intramuscular injection (50.3 ± 17.1 ng/ml).

Mean (± SEM) T_{max} after the administration of epinephrine 40 mg of formulation A (9 ± 4 min), formulation B (28 ± 10 min), formulation C (27 ± 9 min) and formulation D (16 ± 4 min) sublingual tablets, and epinephrine 0.3 mg by intramuscular injection (21 ± 11 min) did not differ significantly.

Discussion

Interest in the sublingual route as a readily accessible and non-invasive route of administration has been increasing recently for a wide range of medications [13–15,27–30]. The high vascularity of the sublingual mucosa facilitates rapid drug absorption directly into the venous circulation through the sublingual and frenular veins, bypassing the gastrointestinal tract, the hepatic portal circulation and hepatic first-pass

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metabolism. In comparison to the extremely limited range of doses currently available in epinephrine autoinjectors, sublingual tablets can be formulated in a wide range of epinephrine doses to provide accurate doses for individuals over a wide range of ages and body weights [12]. Tablets are easy to carry and unobtrusive to self-administer sublingually. Multiple doses could be readily available. Tablets should be less expensive to produce than the autoinjector units, and, unlike autoinjectors, are easy to dispose of in a safe and ecologically acceptable manner.

It has been demonstrated for the first time that the bioavailability of epinephrine following the sublingual administration of a 40 mg dose from different fast-disintegrating tablet formulations might be affected considerably by the composition of the excipients in the tablets. All four tablet formulations met the USP standards for content and weight variation and resulted in similar disintegration and wetting times. However, only formulation A resulted in *AUC*, C_{max} and T_{max} values that did not differ significantly from those obtained after a mean dose of 0.34 mg epinephrine by intramuscular injection. Although the T_{max} values obtained after the sublingual administration of formulation A did not differ significantly from those after the administration of 0.34 mg epinephrine by intramuscular injection, there was evidence of a shorter and more desirable T_{max} after the administration of formulation A when compared with the intramuscular injections. Tablets from formulations A and C passed the USP friability test. Although tablets from formulations B and D did not pass this friability test, they had sufficient hardness for handling during the sublingual administration in the animal model.

In this study, the differences in the epinephrine bioavailability from the four tablet formulations are a result of the type of excipients used in these formulations. The rate-limiting step for epinephrine absorption following sublingual administration is the rate of dissolution. The epinephrine bitartrate crystals used in these tablet formulations are very water-soluble (1 g in 3 ml of water [31]). Dissolution occurred rapidly and was complete in less than 3 min (Figure 1). The rate of dissolution of epinephrine bitartrate can be influenced by the presence of other water-soluble excipients. Mannitol, a highly water-soluble excipient (1 g in 5.5 ml of water [32]), was used in formulation B at 24.74% and in formulation C at 26.0% of tablet weight. Epinephrine bitartrate dissolution in a saturated solution of mannitol was slow and incomplete at the end of 5 min (Figure 2), the length of time for which the tablet was held under the rabbit's tongue. The mannitol in formulations B and C might reduce the epinephrine bitartrate rate and extent of dissolution, especially in the limited saliva volumes available in the sublingual cavity, and therefore might reduce epinephrine bioavailability from these formulations. Formulation D was prepared using a patented excipient of unknown composition.

The *AUC* and C_{max} values after the 40 mg sublingual epinephrine dose in formulations B, C and D were significantly lower than those following a mean dose of 0.34 mg epinephrine injected intramuscularly. They were of the same order as the values after a 20 mg sublingual epinephrine dose of formulation A (801 ± 160 ng/ml/min and 6.6 ± 1.4 ng/ml, respectively) which was used in our previous study [12]. Lower *AUC* and C_{max} values indicate that epinephrine bitartrate dissolution might have been decreased by the presence of mannitol in formulations B and C.

It is unlikely that epinephrine diffusion across the sublingual epithelial mucosa into the venous circulation is influenced by any of the excipients used in these four tablet formulations. Monosaccharides are absorbed by a secondary active transport utilizing sodium cotransporters [33] and should not interfere with epinephrine transcellular passive absorption [16]. Water-insoluble excipients will not be absorbed because they do not dissolve in saliva.

The formulations containing highly water-soluble excipients, such as mannitol and other sugars, could possibly delay the dissolution of epinephrine bitartrate and reduce the sublingual bioavailability of epinephrine. The sublingual administration of 40 mg of epinephrine from the novel water-insoluble, rapidly disintegrating tablet, formulation A resulted in plasma epinephrine concentrations similar to those obtained after epinephrine 0.34 mg by intramuscular injection in the thigh. These tablets should be

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developed further for the potential first-aid emergency treatment of anaphylaxis in humans.

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