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Fast-Disintegrating Sublingual Epinephrine Tablets: Effect of Tablet Dimensions on Tablet Characteristics

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ABSTRACT The purpose of this study was to evaluate the effect of changing dimensions on the hardness (H), disintegration time (DT), and wetting time (WT) of fast-disintegrating epinephrine tablets for sublingual administration as potential first aid treatment for anaphylaxis. Tablet formulations I and II, containing 0% and 10% epinephrine bitartrate, respectively, and weighing 150 mg were prepared by direct compression. Formulations were compressed at a range of forces using an 8/32″ die with concave punches (CP); a 10/32″ and an 11/32″ die with CP and flat punches (FP). Tablet weight variation, content uniformity, thickness, H, DT, and WT were measured. The 8/32″, 10/32″, and 11/32″ dies resulted in tablet thickness of ranges 0.25–0.19″, 0.17–0.1″, and 0.16–0.08″, respectively. The DT and WT using the 8/32″ die were ≤10 and ≤30 sec, respectively, at H ≤5.4 ± 0.2 kg for formulation I, and H ≤5.4 ± 0.3 kg for formulation II. The DT and WT were ≤10 and ≤30 sec, respectively, using 10/32″ die/CP, 10/32″ die/FP, 11/32″ die/CP, and 11/32″ die/FP at H ≤6.2 ± 0.6 kg, ≤6.8 ± 0.4 kg, ≤4.9 ± 0.1 kg, and ≤7.2 ± 0.3 kg, respectively, for formulation I. For formulation II, the DT and WT were ≤10 sec and ≤30 sec, respectively, when H < 4 kg. No difference in DT and WT was observed between concave and flat tablets. The 11/32″ and 10/32″ dies resulted in more ideal tablet dimensions for sublingual administration, but H must be maintained <4 kg to ensure rapid DT and WT.

KEYWORDS Sublingual, Fast-disintegrating tablets, Epinephrine, Anaphylaxis

INTRODUCTION

Fast-disintegrating and fast-dissolving tablets are becoming popular as novel delivery systems for drug administration. They are more convenient for children, elderly patients, patients with swallowing difficulties, and in the absence of potable liquids (Allen, 2003; Fu et al., 2004). In addition, sublingual administration of drugs formulated as tablets can result in a faster pharmacological response than using oral tablets (Bredenberg et al., 2003; Cunningham et al., 1994; Kroboth et al., 1995; Price et al., 1997) and bypass the gastrointestinal and hepatic first pass metabolic processes (Lefkowitz et al., 1996). Such tablets

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could be good candidates for the treatment of emergency conditions via the sublingual route of administration, especially for drugs that are extensively metabolized following oral administration.

Epinephrine, the drug of choice for the emergency treatment of anaphylaxis, is available only as injectable dosage forms (Lieberman, 2003; McLean-Tooke et al., 2003; Sampson et al., 2006; Simons, 2004). It is extensively metabolized after oral administration by catechol-*o*-methyltransferase in the gastrointestinal tract and by monoamine oxidase in the gastrointestinal tract and in the liver (Lefkowitz et al., 1996). In aqueous solutions, epinephrine is unstable in the presence of light, oxygen, heat, and neutral or alkaline pH values (Connors et al., 1986). Feasibility studies in humans (Simons & Simons, 2004) and animals (Rawas-Qalaji et al., 2006a) have shown that epinephrine can be absorbed sublingually. Epinephrine is available as very water-soluble hydrochloride and bitartrate salts.

Extremely fast tablet disintegration is required to expedite the availability of epinephrine for rapid absorption by the sublingual mucosa blood vessels. Various techniques can be used to formulate fast-disintegrating or dissolving tablets (Allen, 2003; Fu et al., 2004). In this study, direct compression was used to manufacture fast-disintegrating sublingual epinephrine tablets containing a superdisintegrant in order to circumvent the use of heat or moisture during the manufacturing processes. The appropriate tablet dimension and shape that demonstrates an ideal fast-disintegrating tablet's characteristics is required for manufacturing epinephrine tablets for sublingual administration as potential first aid treatment of anaphylaxis.

Tablets intended for sublingual administration may require dimensions different from those tablets for oral administration. Sublingual tablets should have either very small dimensions such as nitroglycerin tablets, or be thin and flat in order to fit comfortably into the sublingual cavity. In contrast to tablets for oral administration, changes in sublingual tablet dimensions could affect the disintegration and wetting times as the excipients (nonmedicinal ingredients) are replaced with increasing percentages of medication.

The aim of this study was to evaluate the effect of changing tablet dimensions, by modifying diameter, thickness, and shape, on tablet hardness, disintegration time, and wetting time while retaining constant tablet weight, but adjusting medication: excipients ratios.

MATERIALS AND METHODS

Materials

(–)–Epinephrine (+)bitartrate was purchased from Sigma-Aldrich (St. Louis, MO). It was used because it was readily obtainable as the pure L-isomer, the pharmacologically active form. Ceolus® PH-301 (microcrystalline cellulose) with a mean particle size of 50 μm was supplied by Asahi Kasei Chemicals Corp (Tokyo, Japan) and low-substituted hydroxypropyl cellulose (LH11) with a mean particle size of 50 μm was supplied by Shin-Etsu Chemical Co. (Tokyo, Japan). Magnesium stearate was purchased from Mallinckrodt Baker (Phillipsburg, NJ).

Preparation of Tablets

Two tablet formulations I and II, containing 0% and 10% (15 mg) of epinephrine bitartrate respectively, were prepared by direct compression (Table 1). The total weight of the compressed tablets was maintained at 150 mg. Tablet formulations were prepared by mixing the precalculated weight of epinephrine bitartrate with the total quantity of microcrystalline cellulose and two-thirds of the quantity of low-substituted hydroxypropyl cellulose for 4 min using a three dimensional manual mixer (Inversina®, Bioengineering AG, Switzerland). The microcrystalline cellulose : low-substituted hydroxypropyl cellulose ratio in each of the final tablet formulations was always maintained at 9:1 (Bi et al., 1996, 1999; Ishikawa et al., 2001; Watanabe et al., 1995). All of the magnesium stearate and the remaining one-third of the quantity of low-substituted hydroxypropyl cellulose were added to

TABLE 1 **Composition of Tablet Formulations I and II***

	Tablet formulations	
Ingredient %	I	II
Epinephrine bitartrate	0	10%
Microcrystalline cellulose (PH-301)	88.2%	79.2%
Low-substituted hydroxypropyl cellulose (LH11)	9.8%	8.8%
Magnesium stearate	2%	2%

*Tablet weight was 150 mg.

the powder and mixed for 30 sec, as a running powder, to achieve external positioning of the low-substituted hydroxypropyl cellulose and the magnesium stearate. In order to achieve rapid and complete tablet disintegration, it is very important that the low-substituted hydroxypropyl cellulose is positioned both internally and externally (Sheth et al., 1980).

Each tablet formulation was assessed for flowability by measuring the angle of repose and then compressed at a preselected range of compression forces (CF). An 8/32, 10/32, and 11/32″ die with concave upper and lower punches (CP) and flat, scored face, bevel edge upper punch and a bevel edge lower punch (FP) were used during compression of the tablet formulations. The various tablet shapes and dimensions were compressed using a Manesty®–F3 single-punch tablet press machine (Liverpool, UK).

Evaluation of Tablet Characteristics

Each batch of 200 tablets was collected into a stainless steel beaker. Tablet weight variation and drug content uniformity was measured using USP methods and criteria (USP/NF, 2003). Six tablets were selected randomly from each formulation batch and tested for tablet hardness, disintegration time, and wetting time. The mean ± standard deviation (SD) and percentage of coefficient of variation (CV%) were calculated.

Thickness (T): The T of both concave and flat tablets was measured at the center of the tablet using a dial caliper (Hempe Manufacturing Co., Inc., New Berlin, WI).

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

Disintegration Time (DT): A relatively simple method with rigorous conditions was developed (Rawas-Qalaji et al., 2006b) to evaluate the DT of rapidly disintegrating tablets. Each individual tablet was dropped into a 10 mL glass test tube (1.5 cm diameter) containing 2 mL distilled water, and the time required for complete tablet disintegration was observed visually and recorded using a stopwatch. The visual inspection was enhanced by gently rotating the test tube at a 45° angle, without agitation, to distribute any tablet particles that might mask any remaining undisintegrated portion of the tablet.

Wetting Time (WT): Tablet WT was measured by a procedure modified from that reported by Bi et al. (1996). The tablet was placed at the center of two layers of absorbent paper fitted into a rectangular plastic dish (11 × 7.5 cm). After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded by using a stopwatch.

Data Analysis and Curve Fitting

All results were reported as mean ± SD ($n = 6$) and analyzed by plotting H vs. CF; DT and WT vs. H. The relationships were fitted to appropriate equations using Axum 5.0C (MathSoft, Inc.) and NCSS (NCSS, Kaysville, Utah) softwares. The constants of each equation and the correlation of fit (R^2) were calculated using NCSS and Excel 2000 (Microsoft Corporation) softwares.

RESULTS AND DISCUSSION

The powders from both formulations I and II resulted in very good mixing, flowability, and compressibility characteristics. The angles of repose for formulation I and II were 30° and 40°, respectively (Wadke & Jacobson, 1980). Tablets manufactured from each formulation were within USP specifications for weight variation and drug content uniformity (USP/NF, 2003).

Hardness

The H values of the compressed tablets resulting from a series of linearly increasing CF using different die's sizes and punches' shapes for formulations I and II are illustrated in Fig. 1. It was shown previously that a linear increase in the CF resulted in an exponential increase in the tablet H (Rawas-Qalaji et al., 2006b). At lower CF, elastic deformation would be the main form of microcrystalline cellulose particles rearrangement. Once the CF exceeded the elastic deformation forces, plastic deformation would be the more dominant form of microcrystalline cellulose particles rearrangement (Marshall, 1986). This would result in a low tablet porosity and harder tablet compact that would affect or even limit tablet disintegration and wetting

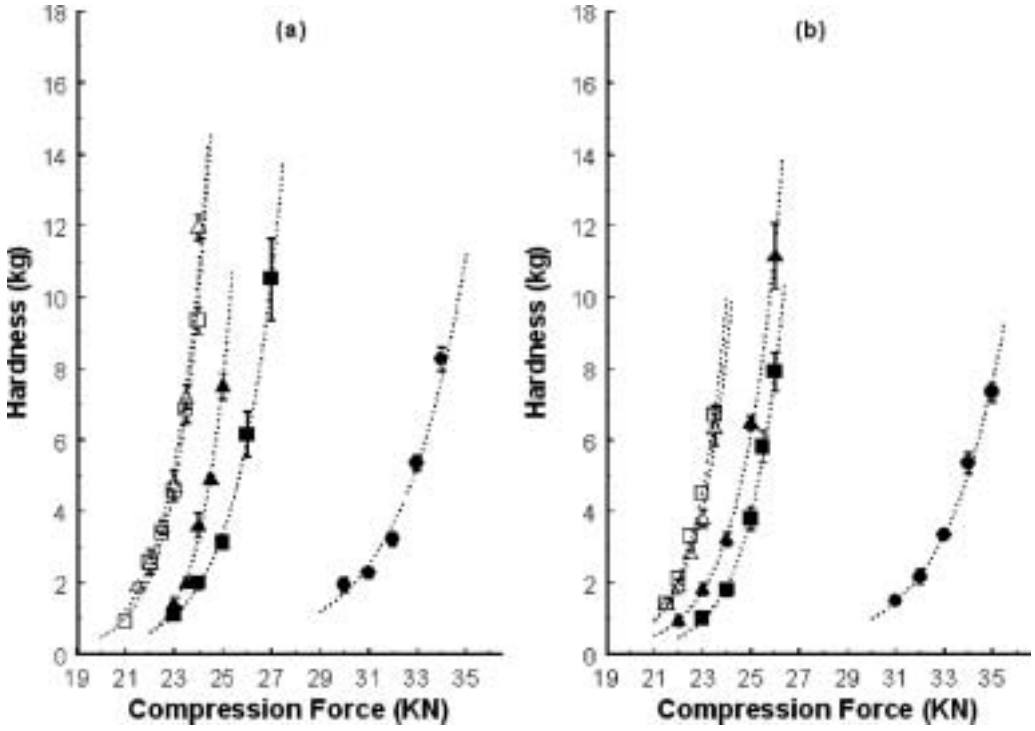

FIGURE 1 **Effect of increasing compression force on tablet hardness for formulation I (panel a) and II (panel b). Symbols: closed: concave punches, open: flat punches; circle: 8/32″ die; square: 10/32″ die; triangle: 11/32″ die. Data are represented as mean ± SD (n = 6). R^2 is ≥ 0.97 in all formulations.**

(Bi et al., 1999; Bi et al., 1996; Sugimoto et al., 2001; Watanabe et al., 1995). Similar results were obtained in this study, using the three different die sizes, with both concave and flat-scored punches. The correlation between CF and H can be described by Equation 1, where X is CF and Y is H. The equation constants (a and b) for the different tablet dimensions and shapes of both formulations are shown in Table 2.

$$Y = ae^{bX} \quad (1)$$

As the die size was increased to produce thinner, larger diameter tablets, lower CF were required to achieve a comparable range of H (mean ± SD, 0.9 ± 0.1–12.0 ± 0.4). Using dies with larger diameters would increase the contact points between the powder surface and the punches, and result in a thinner powder layer in the die, requiring lower CF. Also, tablets compressed using CP required higher CF than FP to achieve a comparable range of H, as more force may be required at the perimeter of the tablets to form the concave shape.

The exponential increase in the tablet H following the linear increase in the CF was more dramatic with the use of dies of larger diameters, 10/32″ and 11/32″, resulting in thinner tablets. This dramatic increase in the tablet H, despite the lower CF required when compared to the 8/32″ die, was shown by the increment of the slope (b) values (Table 2), and the smaller range of

TABLE 2 **Correlation Constants a and b for Formulations I and II***

	CP						FP			
	8/32″		10/32″		11/32″		10/32″		11/32″	
Constants for	a	b	a	b	a	b	a	b	a	b
I	2×10^{-5}	0.37	2×10^{-6}	0.57	1×10^{-8}	0.82	1×10^{-7}	0.77	3×10^{-7}	0.72
II	5×10^{-6}	0.41	1×10^{-7}	0.70	1×10^{-6}	0.62	7×10^{-8}	0.78	2×10^{-7}	0.74

*CP indicates concave punches; FP, flat-scored punches.

CF required to compress these tablets as shown in Fig. 1. The thinner powder layer resulted in fewer particles to be compacted and fewer void spaces available for particles rearrangement per a unit range of the tablet diameter, which resulted in more plastic deformation than elastic deformation.

The resulting tablet thickness for a series of increasing CF values using the 8/32″, 10/32″, and 11/32″ dies ranged from 0.25 to 0.19″, 0.17 to 0.1″, and 0.16 to 0.08″, respectively. Tablets compressed using 8/32″ die were considered to be too thick for use as sublingual tablets. The dimensions of tablets compressed using the 10/32″ and 11/32″ dies were deemed to be more ideal for sublingual administration.

Disintegration and Wetting Time

For fast-disintegrating or fast-dissolving tablets, the standard apparatus and procedure specified in the USP (USP/NF, 1990a,b) cannot be used to measure the differences in the disintegration times accurately. Instead, a relatively simple method was used in this study as previously described, to evaluate the DT of fast-disintegrating tablets intended for the sublingual administration (Rawas-Qalaji et al., 2006b).

Salivary secretions in humans can vary between 0.35–1.0 mL/min under normal conditions. These salivary volumes are very small in comparison with the large volume of solution (900 mL) used in the USP disintegration test (USP/NF, 1990b). It was determined that the volumes of solution used in the wetting test of Bi et al. (1996) compared favorably with sublingual salivary volumes and sublingual conditions in vivo. While not an official USP test, it can predict the tablet wettability in the presence of minimal amounts of liquid, and more ideally represents the conditions of epinephrine tablet disintegration in the sublingual cavity.

The DT and WT values vs. H, for both formulations with different diameters and shapes, are shown in Figs. 2 and 3, respectively. The maximum H for both formulations that resulted in DT ≤ 10 sec and WT ≤ 30 sec are shown in Table 3.

For formulation I, all tablets with different shapes and dimensions resulted in short DT (≤10 sec) and WT (≤30 sec) at a wide range of H (Figs. 2a and 3a, respectively). The maximum H ± SD at which the various tablets resulted in rapid disintegration and wetting was relatively similar and ranged between 4.9 ± 0.1 kg and 7.2 ± 0.3 kg (Table 3).

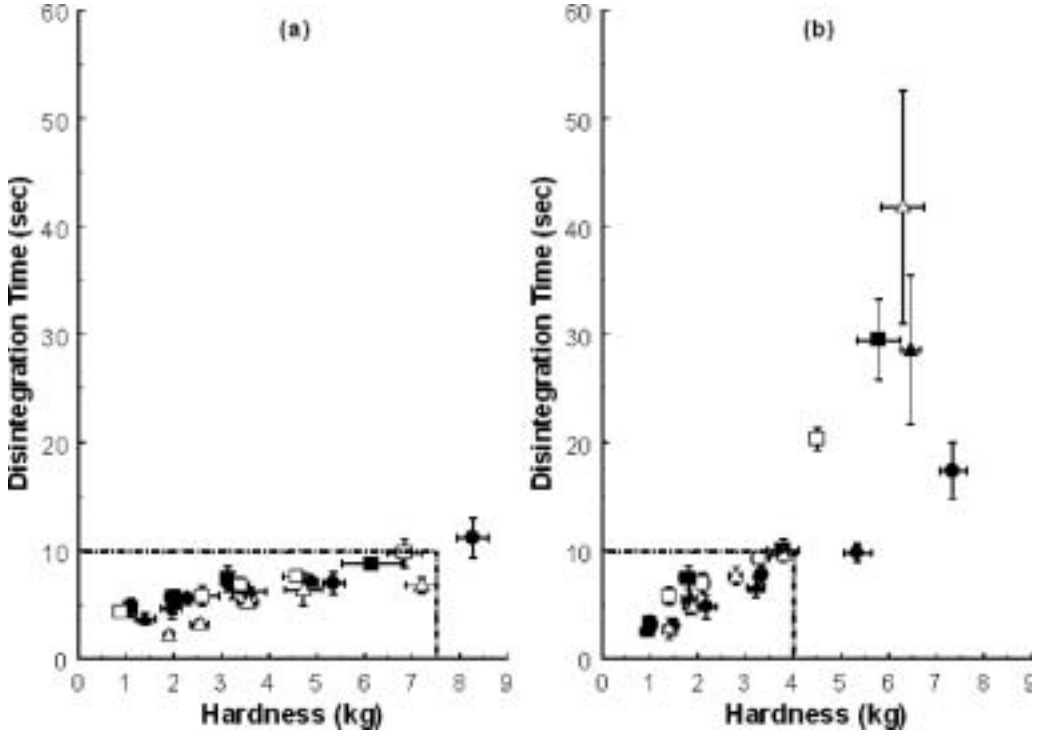

FIGURE 2 **Relationship between tablet hardness and disintegration time for formulation I (panel a) and II (panel b). Symbols: closed: concave punches, open: flat punches; circle: 8/32″ die; square: 10/32″ die; triangle: 11/32″ die. Data are represented as mean ± SD (*n* = 6).**

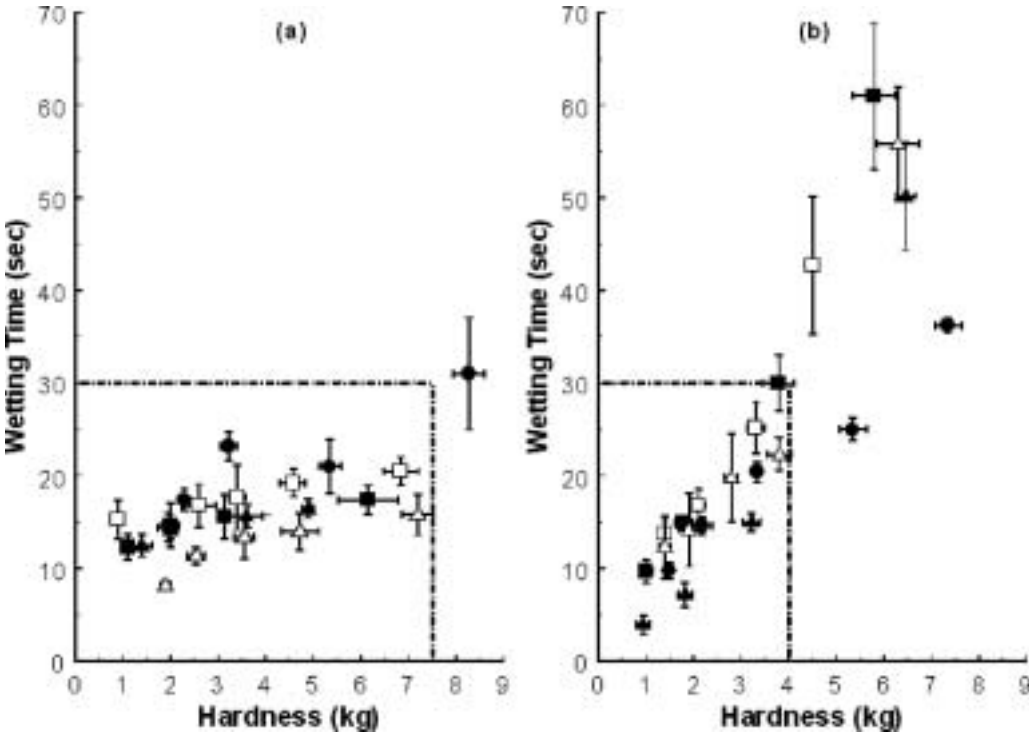

FIGURE 3 **Relationship between tablet hardness and wetting time for formulation I (panel a) and II (panel b). Symbols: closed: concave punches, open: flat punches; circle: 8/32″ die; square: 10/32″ die; triangle: 11/32″ die. Data are represented as mean ± SD (*n* = 6).**

TABLE 3 **The Maximum Hardness at which Tablets from Formulations I and II Resulted in Disintegration Time ≤10 sec and Wetting Time ≤30 sec***

	CP						FP			
	8/32″		10/32″		11/32″		10/32″		11/32″	
Formulation	H	CV	H	CV	H	CV	H	CV	H	CV
I	5.4 ± 0.2	4.2	6.2 ± 0.6	10.3	4.9 ± 0.1	2.5	6.8 ± 0.4	2.2	7.2 ± 0.3	4.5
II	5.4 ± 0.3	5.3	3.8 ± 0.3	8.7	3.2 ± 0.2	5.5	3.3 ± 0.2	2.2	3.8 ± 0.3	6.6

*CP indicates concave punches; FP, flat-scored punches; H, mean ± SD tablet hardness (kg); CV, coefficient of variation (%).

For formulation II, the tablets with 8/32″ diameter also resulted in DT ≤ 10 sec and WT ≤ 30 sec at a wide range of H (Figs. 2b and 3b), and the maximum H at which these tablets resulted in rapid disintegration and wetting was similar to formulation I (Table 3). Although there was no major difference in the DT and WT between formulations I and II, these tablets were considered less suitable for sublingual administration than 10/32″ and 11/32″ diameter-tablets.

The DT and WT for formulation II tablets with 10/32″ and 11/32″ diameters increased dramatically at higher H, so to retain the same DT and WT, less CF resulting in lower H should be used (Table 3). The difference in the DT and WT between 10/32″ and 11/32″ diameter-tablets and 8/32″ diameter-tablets at higher H in the presence of an epinephrine bitartrate load in the formulation is possibly due to the effect of a higher number of bonds formed during compaction of these thinner 10/32″ and 11/32″ diameter-tablets, which would affect the type of deformation. A closer particle arrangement during the compaction occurred, due to fewer particles and fewer void spaces available for compaction per unit range of the tablet diameter as the powder load in the cavity becomes thinner. The low compressibility of epinephrine bitartrate leads to the formation of more irreversible bonds between particles, so plastic deformation was probably more dominant, resulting in longer DT and WT for these tablets. In addition, the significant decrease in the tablet porosity, due to the incorporation of epinephrine bitartrate (Rawas-Qalaji

et al., 2006b) and the fewer spaces available between particles as described previously, would also adversely affect the DT and WT. These results indicate that loading epinephrine bitartrate into formulation II resulted in a greater negative impact on the DT and WT of 10/32″ and 11/32″ diameter-tablets than on the 8/32″ diameter-tablets at H > 4 kg (Figs. 2b and 3b, respectively).

There was a general increase in the DT and WT of tablets from formulation II when compared to formulation I, especially when the H was >4 kg. The delay was more dramatic with larger diameter-tablets. The effect of loading epinephrine bitartrate in formulation II on the tablets characteristics has been reported previously (Rawas-Qalaji et al., 2006b).

For 10/32″ and 11/32″ dies, changing from concave punches to flat punches had no effect on DT and WT. This could be due to the small difference in the tablet surface area and dimensions between the 10/32″ and 11/32″ diameter-tablets.

CONCLUSION

Tablets containing epinephrine bitartrate with dimensions and shapes suitable for sublingual administration can be formulated without adversely affecting fast disintegration and wetting times, and could have the potential for the first aid treatment of anaphylaxis. The sublingual bioavailability of epinephrine from this tablet formulation is being evaluated in a validated rabbit model.

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