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Fast-disintegrating Sublingual Tablets: Effect of Epinephrine Load on Tablet Characteristics

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ABSTRACT

The aim of this study was to evaluate the effect of increasing epinephrine load on the characteristics of fast-disintegrating sublingual tablets for the potential emergency treatment of anaphylaxis. Four tablet formulations, A, B, C, and D, containing 0%, 6%, 12%, and 24% of epinephrine bitartrate, respectively, and microcrystalline cellulose:low-substituted hydroxypropyl cellulose (9:1), were prepared by direct compression, at a range of compression forces. Tablet weight variation, content uniformity, hardness, disintegration time, wetting time, and friability were measured for each formulation at each compression force. All 4 tablet formulations at each compression force were within the *United States Pharmacopeia (USP)* limits for weight variation and content uniformity. A linear increase in compression force resulted in an exponential increase in hardness for all formulations, a linear increase in disintegration and wetting times of A, and an exponential increase in disintegration and wetting times of B, C, and D. At a mean ± SD hardness of ≥2.3 ± 0.2 kg, all tablet formulations passed the *USP* friability test. At a mean ± SD hardness of ≤3.1 ± 0.2 kg, all tablet formulations resulted in disintegration and wetting times of <10 seconds and <30 seconds, respectively. Tablets with drug loads from 0% to 24% epinephrine can be formulated with hardness, disintegration times, and wetting times suitable for sublingual administration.

KEYWORDS: sublingual, transmucosal drug delivery, fast-disintegrating tablets, epinephrine, anaphylaxis.

INTRODUCTION

Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes.[1-3]

Epinephrine is the drug of choice for the treatment of anaphylaxis worldwide.[4-6] It is available as an injectable dosage form in ampules or in autoinjectors. In aqueous solutions, epinephrine is unstable in the presence of light, oxygen, heat, and neutral or alkaline pH values.[7] Feasibility studies in humans[8] and animals[9] have shown that epinephrine can be absorbed sublingually. The optimal sublingual epinephrine dose for the treatment of anaphylaxis is unknown. Epinephrine is available as very water-soluble hydrochloride and bitartrate salts. Epinephrine bitartrate was used in this study because it was readily obtainable as the pure L-isomer, the pharmacologically active form.

Various techniques can be used to formulate rapidly-disintegrating or dissolving tablets.[10,11] Direct compression, one of these techniques, requires the incorporation of a superdisintegrant into the formulation, or the use of highly water-soluble excipients to achieve fast tablet disintegration. Direct compression does not require the use of water or heat during the formulation procedure and is the ideal method for moisture- and heat-labile medications. However, the direct compression method is very sensitive to changes in the type and proportion of excipients and in the compression forces, when used to achieve tablets of suitable hardness without compromising the rapid disintegration characteristics. Unique packaging methods such as strip-packaging, could be used to compensate for the problem of extreme friability of rapidly disintegrating tablets. Watanabe et al[12] and Bi et al[13] were the first to evaluate the ideal excipient proportions and other related parameters using a superdisintegrant in order to formulate durable

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fast-disintegrating tablets for oral administration. The effect of a wide range of microcrystalline cellulose:low-substituted hydroxypropyl cellulose ratios on the tablet characteristics was studied. A ratio of 9:1 and 8:2 resulted in greater tablet hardness in association with shorter disintegration and wetting times. Based on the results obtained by Watanabe et al and Bi et al, a microcrystalline cellulose:low-substituted hydroxypropyl cellulose ratio of 9:1 was selected as the optimal ratio to formulate and test the development of epinephrine tablets for sublingual administration. Extremely fast tablet disintegration would be required to enhance the release of epinephrine from tablets for rapid absorption by the sublingual mucosa blood vessels.

It was hypothesized that epinephrine could be formulated into fast-disintegrating tablets for sublingual administration as potential emergency treatment of anaphylaxis. This could be achieved by selecting the appropriate pharmaceutical excipients in the correct proportion, in combination with optimal manufacturing techniques and compression parameters. The aim of this study was to evaluate the effect of increasing epinephrine bitartrate load on the hardness, disintegration time, and wetting time of a fast-disintegrating tablet formulation.

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). 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

Four tablet formulations, A, B, C, and D, containing 0%, 6%, 12%, and 24% of epinephrine bitartrate, equivalent to 0, 5, 10, and 20 mg of epinephrine, respectively, 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 precalculated weight of epinephrine bitartrate with the total quantity of microcrystalline cellulose and two thirds of the quantity of low-substituted hydroxypropyl cellulose by using a 3-dimensional manual mixer (Inversina, Bioengineering AG, Wald, Switzerland). The microcrystalline cellulose:low-substituted hydroxypropyl cellulose ratio in each of the final tablet formulations was always maintained at 9:1.[12-15] All of the magnesium stearate and the remaining one third of the quantity of low-substituted hydroxypropyl cellulose were added immediately before the end of mixing.

Table 1. Composition of the 4 Tablet Formulations of Epinephrine*

	Tablet Formulations			
Ingredient %	A	B	C	D
Epinephrine bitartrate	-	6	12	24
Microcrystalline cellulose (PH-301)	88.2	82.8	77.4	66.6
Low-substituted hydroxypropyl cellulose (LH11)	9.8	9.2	8.6	7.4
Magnesium stearate	2	2	2	2

*Tablet weight was 150 mg.

Each tablet formulation was compressed at a preselected range of forces. An 11/32-inch die with a flat, scored face, bevel-edge upper punch and a flat, bevel-edge lower punch were selected based on results from a previous study.[16] The flat-scored tablets 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, drug content uniformity, and friability were measured using the *USP* methods and criteria.[17,18] Drug content was analyzed using a high-performance liquid chromatography system with ultraviolet detection (Waters Corp, Milford, MA) and tablet friability was measured using *USP* Friability instrument (Pharma Test Apparatebau GmbH, Hainburg, Germany). Five tablets were selected randomly from each formulation batch and tested for tablet hardness, disintegration time, and wetting time. The mean ± SD and percentage of coefficient of variation (CV%) were calculated.

- *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 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 tablets.
- *Wetting Time (WT):* Tablet WT was measured by a procedure modified from that reported by Bi et al.[13] The tablet was placed at the center of 2 layers of absorbent paper fitted into a rectangular plastic dish (11 cm × 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 using a stopwatch.

Data Analysis and Curve Fitting

All results were reported as mean ± SD (n = 5) and analyzed by plotting H, DT, and WT versus compression force (CF); DT and WT versus H and WT versus DT. The relationships were fitted to appropriate equations using Axum 5.0C (MathSoft Inc, Cambridge, MA) and NCSS (NCSS, Kaysville, Utah) software. The constants of each equation and the correlation of fit (R^2) were calculated using NCSS and Excel 2000 (Microsoft Corp, Redmond, WA) software.

Results and Discussion

The powders for all 4 formulations resulted in good mixing, flowability, and compressibility characteristics. Tablets manufactured from each formulation were within *USP* specifications for weight variation and drug content uniformity.[17] All formulations passed the *USP* friability test[18] at the following tablet H values: Formulation A ≥ 1.9 ± 0.1 kg, Formulation B ≥ 1.8 ± 0.1 kg, Formulation C ≥ 2.3 ± 0.2 kg, and Formulation D ≥ 2.0 ± 0.2 kg.

Hardness

The H results for increasing CFs for each formulation are reported in Table 2 and plotted in Figure 1. A linear increase in the CF resulted in an exponential increase in the tablet H for all 4 different formulations. Increases in CF possibly reduced the tablet porosity owing to a closer rearrangement and compaction of the particles resulting in a harder tablet.[13,14,19] The exponential increase in the tablet H can be described by Equation 1, where X is CF and Y is H. The equation constants (a and b) for the 4 formulations are reported in Table 3. Constant b can be used to predict characteristics for tablets prepared with >24% epinephrine. This constant could include factors such as degree of porosity and extent of hydrogen bond formation, but the individual contribution for such factors was not evaluated in this study.

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

As epinephrine bitartrate load increased, higher CF was required to maintain the range of H values recorded for formulation A (0% epinephrine bitartrate). This may be because of the poor compressibility of epinephrine bitartrate, which can interfere with, and reduce the formation of, hydrogen bonds between the cellulose particles.[13] Increasing epinephrine bitartrate loads results in a greater interference with

Table 2. The Effect of Increasing Compression Force on the Tablet Hardness, Disintegration Time, and Wetting Time*

	A						B						C						D					
CF	H	CV	DT	CV	WT	CV	H	CV	DT	CV	WT	CV	H	CV	DT	CV	WT	CV	H	CV	DT	CV	WT	CV
21.5	1.9	4.5	2.2	20.3	8.2	5.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22.0	2.5	6.6	3.2	14.0	11.4	7.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22.5	3.6	5.9	5.2	8.6	13.4	17.2	1.8	4.7	2.8	16.0	7.2	6.2	-	-	-	-	-	-	-	-	-	-	-	-
23.0	4.7	8.5	6.8	21.8	14.0	14.3	2.5	7.3	3.8	11.8	8.8	9.5	-	-	-	-	-	-	-	-	-	-	-	-
23.5	7.2	4.5	8.0	8.8	15.8	13.7	4.1	5.1	6.2	13.5	11.0	6.4	1.5	5.5	4.6	11.9	8.6	10.3	1.2	9.8	4.6	11.9	9.0	7.9
24.0	12.0	3.0	37.2	5.8	86.0	18.7	4.9	11.4	9.0	11.1	20.8	10.4	2.3	10	5.8	7.7	16.6	10.9	2.0	8.1	5.6	9.8	16.4	7.0
24.5	-	-	-	-	-	-	10.3	4.6	120.0	6.6	102.4	21.1	4.0	7.7	7.6	11.8	24.4	6.9	3.1	6.6	9.4	9.5	27.2	12.6
25.0	-	-	-	-	-	-	-	-	-	-	-	-	6.5	3.4	14.0	10.1	75.6	15.8	4.5	2.9	26.0	24.8	83.6	38.0
25.5	-	-	-	-	-	-	-	-	-	-	-	-	9.0	12.9	>120	-	>120	-	9.1	1.4	>120	-	>120	-

*CF indicates compression force (kN); H, tablet hardness (kg); CV, coefficient of variation (%); DT, disintegration time (sec); and WT, wetting time (sec).

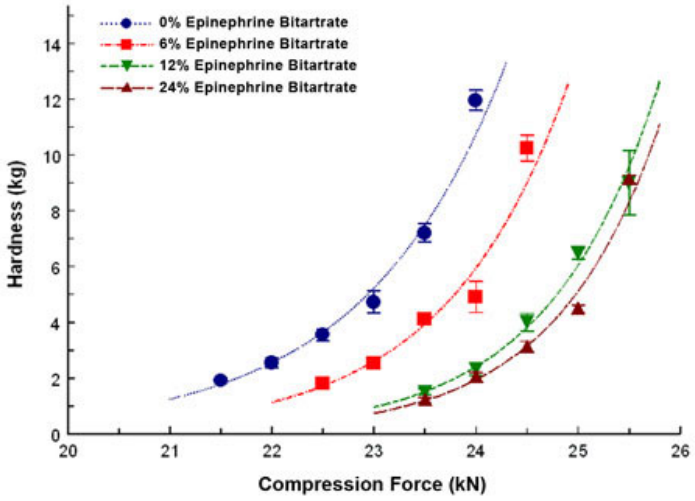

Figure 1. Effect of increasing compression force on tablet hardness of 0%, 6%, 12%, and 24% epinephrine bitartrate tablet formulations. Data are represented as mean ± SD (n = 5). R^2 is ≥0.97 in all formulations.

the interparticle hydrogen bonds formation requiring a higher CF to increase the contact points between the excipient powder particles in order to maintain the desired range of tablet H. Similar results have been reported by Watanabe et al,[12] Bi et al,[13,14] Ishikawa et al,[15] Sugimoto et al,[20] and Schiermeier et al[21] for other medications.

Disintegration and Wetting Time

In the *USP* disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks,[22] and 2 minutes is specified as the acceptable time limit for tablet disintegration.[23] The *USP* apparatus and specifications for the disintegration of sublingual tablets were not suitable for these formulations because the sublingual epinephrine tablets disintegrate so rapidly that differences in DT cannot be measured using them.

An alternative apparatus to detect the differences in oral tablet DT was designed by Bi et al.[13] The speed of the apparatus paddle was 100 rpm and the volume of the immersion fluid was 900 ml. These conditions do not reflect the in vivo sublingual cavity conditions, where a very limited volume (0.35-1.0 mL/min) of saliva is available under normal conditions, with a maximum of 5 to 7 mL/min after stimulation.[24] Also, the agitation in the immersion fluid created by the paddle rotation, which would not exist in the sublingual cavity, could enhance tablet disintegration, resulting in a shorter DT compared with what might be expected in the sublingual cavity. More complicated methods have been used to predict the DT of fast-disintegrating or dissolving tablets by using a texture analyzer.[25-27]

A relatively simple method, as previously described, was therefore developed to evaluate the DT of these fast-disintegrating sublingual tablets. In this method, the diameter (1.5 cm) of the test tube used is smaller than the diameter of sublingual area in humans (~3-4 cm). The larger sublingual area in humans might actually enhance rather than reduce tablet disintegration. The 1.5-cm diameter of the 10-mL test tube does compare with the sublingual cavity in small laboratory animals such as rabbits, which have been used to date for in vivo studies and are being considered for future studies.[9] The small volume of water (2 mL) used for tablet disintegration evaluation approximates the volume of saliva secreted under normal conditions. This in vitro DT simulates the relatively small sublingual area, the small volume of saliva, and the relatively static environment under the human tongue.

Although a wetting test is not a *USP* standard test, it is useful for quality control and provides supportive evaluation of these sublingual tablets. Unlike the disintegration test, the wetting test uses minimal water, which may be more representative of the quantity of moisture available sublingually. Using this test, the time required for moisture to penetrate the tablet completely is measured and possibly represents the time required to release epinephrine in the presence of minute volumes of saliva. The wetting test designed by Bi et al[13] compares favorably with the conditions in the sublingual area of humans and animals. This test was modified with regard to the dimensions of the dish and the volume of water used, as previously described.

The results of the disintegration and wetting tests for each formulation resulting from a range of increasing CF values are reported in Table 2 and plotted in Figures 2 and 3. Formulation A demonstrated an initial linear increase in the DT and WT (Figures 2 and 3) despite the exponential increase

Table 3. Correlation Constants, a and b, for the 4 Tablet Formulations*

	A		B		C		D	
Constants for	a	b	a	b	a	b	a	b
CF vs H	3×10^{-07}	0.72	1×10^{-08}	0.83	7×10^{-10}	0.92	1×10^{-10}	0.98
CF vs DT	63.32†	3.04†	4×10^{-08}	0.80	2×10^{-07}	0.72	8×10^{-12}	1.14
CF vs WT	67.54†	3.56†	1×10^{-6}	0.68	6×10^{-14}	1.38	2×10^{-14}	1.44
DT vs WT†	–1.26	2.26	2.44	2.70	26.25	7.19	4.71	3.40

*CF indicates compression force (kN); H, hardness (kg); DT, disintegration time (sec); WT, wetting time (sec).

†Constants derived using equation 2 (all other constants derived using equation 1).

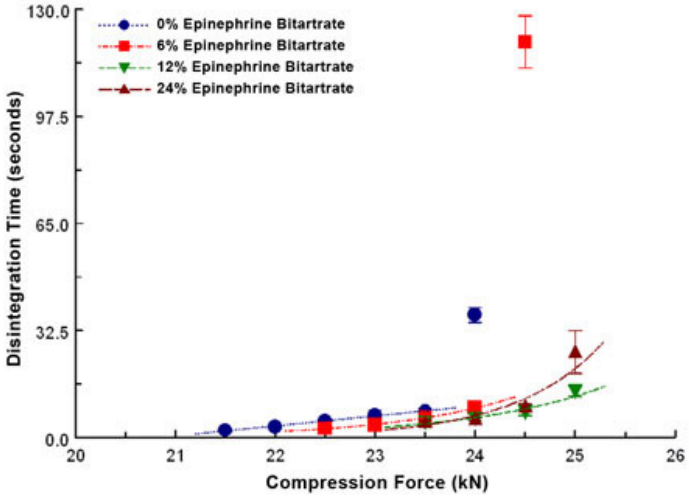

Figure 2. Effect of increasing compression force on tablet disintegration time of 0%, 6%, 12%, and 24% epinephrine bitartrate tablet formulations. Data are represented as mean ± SD (n = 5). R^2 is ≥0.91 in all formulations.

in tablet H. When CF was greater than 23.5 kilonewton (kN), dramatic nonlinear increases in DT and WT occurred. Below CF 23.5 kN the linear increase in tablet DT and WT can be described by Equation 2, where X is CF and Y is DT or WT. The equation constants (a and b) for Formulation A are recorded in Table 3.

$$Y = bX - a \qquad (2)$$

When the epinephrine bitartrate load was increased for Formulations B, C, and D, an exponential increase in the DT and WT resulted from the linear increase in the CF up to 24 kN for Formulation B and 25 kN for Formulations C and D (Figures 2 and 3). The DT increased dramatically and nonexponentially when CF was greater than 24 kN for Formulation B. Formulations C and D resulted in incomplete disintegration and wetting when CF was greater than 25 kN. The exponential increase in tablet DT and WT for Formulations B, C, and D can be described by Equation 1, where X is CF and Y is DT or WT. The equation constants (a and b) for Formulations B, C, and D are reported in Table 3.

Increasing CF probably results in increased particle contact and reduced tablet porosity. The degree of tablet porosity plays an important role in tablet wetting and disintegration. The pores form capillary pathways that allow rapid water penetration throughout the tablet.[12,13,28] When moistened, the superdisintegrant expands and swells to cause rupture and complete the disintegration of the tablet. The relationship between CF and tablet porosity and its effect on tablet disintegration and wetting have been previously described.[12-14,20,21]

The degree of bond deformation during compaction also affects tablet disintegration and wetting. Microcrystalline cellulose exhibits both elastic and plastic deformation.[19] Initially, the main type of deformation with increasing CF would be elastic deformation, with particles rearranging to form a compact. When CF exceeds the elastic deformation force, plastic deformation would become the main type of deformation causing closer and irreversible particle rearrangement. When exposed to small quantities of water, tablets experiencing elastic deformation will demonstrate short DT and WT because the massive expansion of the superdisintegrant will be able to break the bonds formed during compression. Conversely, tablets experiencing plastic deformation will demonstrate longer or incomplete DT and WT. This occurs because the closer particle arrangement possibly results in the formation of numerous, stronger interparticle bonds. In addition, reduced tablet porosity retards water penetration and delays or even inhibits the role of the superdisintegrant at high CF.

In the current study, tablets from all formulations demonstrated initial rapid DT and WT (Figures 2 and 3), despite the initial exponential increase in H with increasing CF, possibly owing to elastic deformation (Figure 1). The dramatic increase in DT and WT (Figures 2 and 3), as the CF exceeds certain critical values, probably represents changes from elastic to plastic deformation.

The range of tablet H (Table 2) of Formulations C (1.5 ± 0.1 to 6.5 ± 0.2 kg) and D (1.2 ± 0.1 to 4.5 ± 0.1 kg) resulting in complete tablet disintegration and wetting was smaller than for Formulations A (1.9 ± 0.1 to 12.0 ± 0.4 kg) and B (1.8 ± 0.1 to 10.3 ± 0.5 kg). Increasing the epinephrine bitartrate load increased tablet H dramatically at higher CF resulting in longer DT and WT, possibly owing to the reduction in the capillary action as a result of lower porosity

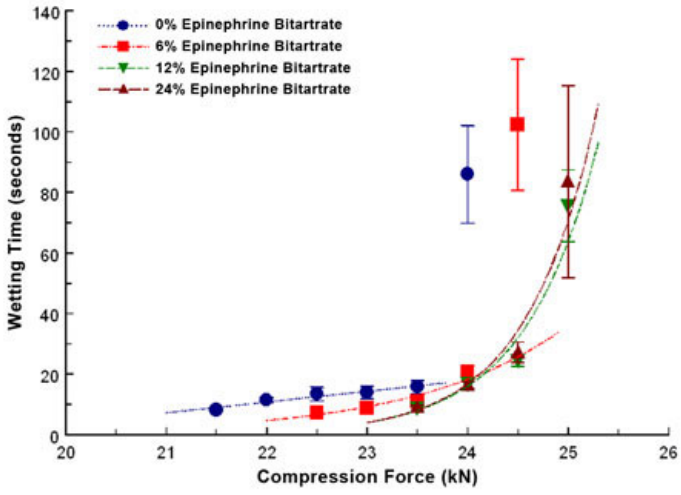

Figure 3. Effect of increasing compression force on tablet wetting time of 0%, 6%, 12%, and 24% epinephrine bitartrate tablet formulations. Data are represented as mean ± SD (n = 5). R^2 is ≥0.91 in all formulations.

of the compacted epinephrine bitartrate, and the higher CF required to form a satisfactory tablet compact. At lower CF, the increasing epinephrine bitartrate load in Formulations B, C, and D was less compacted and resulted in shorter DT and WT, comparable to those of Formulation A at a given CF (Table 2).

Relationship Between Hardness and Disintegration/ Wetting Time

The relationship between tablet H and the resulting DT and WT for each formulation is plotted in Figures 4 and 5.

The DT of Formulation A was maintained <10 seconds (6.8 ± 0.4 seconds) when the tablet H was ≤7.2 ± 0.3 kg (Figure 4), despite the exponential increase in tablet H. This small increase in DT as the tablet H was increased in Formulation A makes it an ideal candidate to be loaded with increasing doses of epinephrine bitartrate.

Loading Formulation A with increasing epinephrine bitartrate loads in Formulations B, C, and D resulted in lower tablet H and shorter DT at given CF values (Table 2). The DT was maintained below 10 seconds at tablet H for Formulations B ≤ 4.9 ± 0.6 kg, C ≤ 4.0 ± 0.3 kg, and D ≤ 3.1 ± 0.2 kg (Table 2). Further increases in tablet H up to 6.5 ± 0.2 kg for Formulation C and 4.5 ± 0.1 kg for Formulation D, still resulted in short DT values of 14.0 ± 1.4 seconds for Formulation C and 26.0 ± 6.4 seconds for Formulation D. Formulations B, C, and D retained short tablet DTs (Figure 4) without compromising tablet H and friability. Based on the *USP* friability criteria,[18] these tablet formulations can withstand shipping and handling when tablet H is maintained at least ≥2.3 ± 0.2 kg.

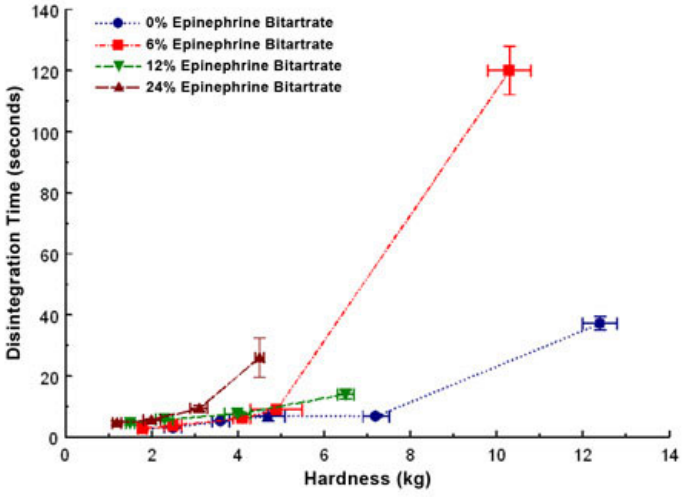

Figure 4. Relationship between tablet hardness and disintegration time of 0%, 6%, 12%, and 24% epinephrine bitartrate tablet formulations. Data are represented as mean ± SD (n = 5).

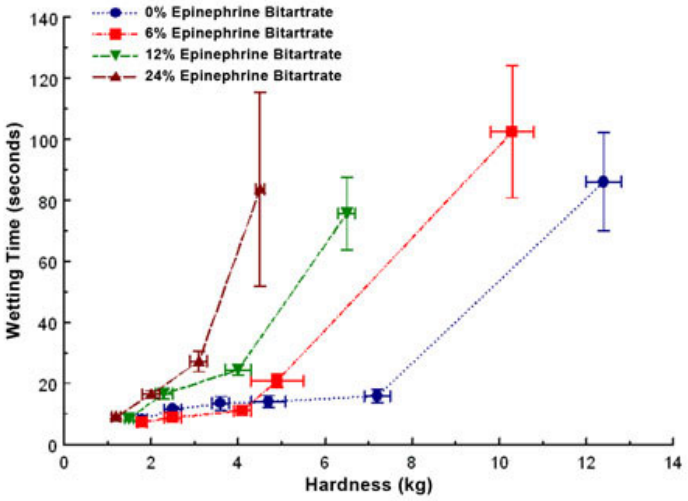

Figure 5. Relationship between tablet hardness and wetting time of 0%, 6%, 12%, and 24% epinephrine bitartrate tablet formulations. Data are represented as mean ± SD (n = 5).

Similar results were obtained by plotting tablet WT against H for each formulation. The WT of Formulation A was maintained <30 seconds, despite the exponential increase in the tablet H up to 7.2 ± 0.3 kg (Figure 5). In contrast, with increasing epinephrine bitartrate loads for the other formulations, a rapid WT (<30 seconds) required that tablet H be maintained for Formulations B ≤ 4.9 ± 0.6 kg, C ≤ 4.0 ± 0.3 kg, and D ≤ 3.1 ± 0.2 kg (Table 2).

The correlation between the DT and WT of different formulations results in a linear relationship between DT and WT (Figure 6), as previously reported by Bi et al[13] and Aly et al,[29] where the degree of tablet porosity appears to be the common factor. The data fitted to Equation 2 supports this

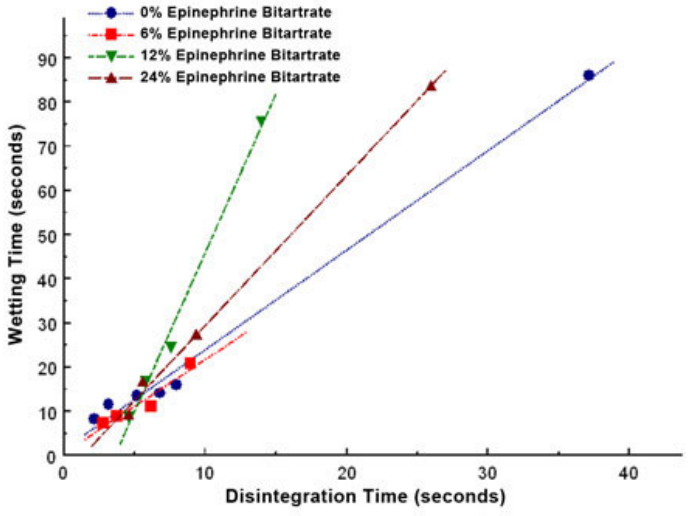

Figure 6. Correlation between tablet disintegration time and wetting time of 0% 6%, 12%, and 24% epinephrine bitartrate tablet formulations. Data are represented as mean ± SD (n = 5). R^2 is ≥ 0.98 in all formulations.

correlation (where X is DT and Y is WT), and the equation constants (a and b) for the 4 formulations are reported in Table 3.

CONCLUSION

Tablets with drug loads from 0% to 24% epinephrine can be formulated with hardness, disintegration times, and wetting times suitable for sublingual administration and might be potentially useful for the emergency treatment of anaphylaxis. The sublingual bioavailability of epinephrine from Formulations B, C, and D are being evaluated in a validated rabbit model.

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