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Relative Effectiveness Coefficient: A Quality Characteristic of Toothpastes Containing Active Components

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It has been proposed that the parameter of relative effectiveness coefficient (*REC*) be used for the qualitative assessment of toothpastes containing active ingredients. *REC* is the ratio between the concentration of the active component in water eluates obtained after three minutes and adequately prolonged (up to the reaching of equilibrium state) dispersion of the toothpaste in distilled water at a 1 : 4 ratio (condition simulating the use of toothpaste in the oral cavity). The change in *REC* after storage following its production, as well as testing the toothpaste stability at high and low temperatures, provides an evidence for deviations in its quality. *REC* was applied for the assessment of toothpastes containing 0.5% zinc citrate as an active ingredient.

Key words toothpaste; quality assessment; relative effectiveness coefficient; zinc citrate

The routine chemical analysis of toothpastes provides information about their qualitative and quantitative composition.[1,2] This evaluation is adequate only for hygiene toothpastes, but not for therapeutical ones. The latter contain different active ingredients, due to which they have various effects: anticaries, disinfection, inhibition of plaque formation, strengthening of gums, *etc.* The active components are released in the oral cavity during the brushing of teeth. Therefore, it is necessary to determine not only their total, but also the water soluble amount—the quantity of the active component obtained in the aqueous eluate of the toothpaste under the proven maximum elution degree of the component. It is possible, regardless of the high water soluble content of the active component, that only a small portion of it is evolved into the oral cavity, if the evolution process is slow. Our studies provide evidence that no relationship exists between the degree and the rate of elution of the active component from the toothpaste mass.[3] Maximum elution degree may be reached early, during the first minute of dispersion of the paste, but its value still be far away from the effective one. That is why it is important, when the chemical analysis of therapeutical toothpastes is carried out, to determine the effective, truly utilized part of the active ingredient. Therefore, the assessment of therapeutical toothpastes must include a criterion related with the separation dynamics of the active component, investigated under fixed standard conditions.

In the present paper we propose to use a criterion we call relative effectiveness coefficient (*REC*) to achieve this goal. *REC* is a dimensionless magnitude, having a value of less than or up to unity, and is defined by the term: $REC = C_3/C_e$; C_3 is the concentration of the active component in the water eluate obtained after 3 min dispersion of the toothpaste in distilled water, and C_e is the concentration of the active component in the water eluate, obtained after dispersing the toothpaste in distilled water and until it reaches equilibrium (maximum, independent of dispersion time, concentration of the active component in the water eluate). C_3 and C_e are expressed in identical units and are determined under the same conditions: equal quantities of the samples subjected to analysis (one part) and distilled water (four parts), identical stirring, and the same analytical methods and calibration.

Experimental

Procedure In a 100 ml beaker, weighted with an analytical scale 4.0 + 0.05 g of toothpaste was added, and distilled water was added up to 20.00 g. The mixture was stirred with an electromagnetic stirrer and spinned in a centrifuge. The concentration of the active component in the eluate was determined. Three samples were tested. The first was stirred for 3 min (C_3 is determined). The two other samples were dispersed at different durations (longer than 3 min) to achieve identical concentrations of the active component in the supernatant layer of both samples (C_e is determined). The ratio $C_3/C_e = REC$ was calculated.

Data described in the present paper were obtained at a stirring rate of 800 rpm. The zinc ion concentration in the aqueous eluates was determined by atomic absorption methods and EDTA titration.

Results and Discussion

Table 1 describes data for the eluation dynamics of zinc ions in different media. When the paste was dispersed in artificial saliva[4] or a mixture of artificial saliva and distilled water, zinc ions were eluated slower than in water, but after a certain period of time, equilibrium was reached. It is not convenient to use artificial saliva or a mixture of saliva and distilled water as a standard phase, since it is impossible to achieve accurate reproducibility of these

Table 1. C_i/C_e Values for Zinc Ions

Dispersion time (min)	C_i/C_e	Distilled water	Artificial saliva	Artificial saliva and water mixture (1 : 4)
1	C_1/C_e	0.28 ± 0.03	0.15 ± 0.05	0.20 ± 0.04
2	C_2/C_e	0.58 ± 0.04	0.33 ± 0.06	0.37 ± 0.05
3	C_3/C_e	0.81 ± 0.03	0.49 ± 0.06	0.53 ± 0.05
4	C_4/C_e	0.99 ± 0.04	0.66 ± 0.05	0.68 ± 0.05
5	C_5/C_e	1.00 ± 0.04	0.82 ± 0.05	0.83 ± 0.05
6	C_6/C_e	1.00 ± 0.03	0.98 ± 0.06	0.99 ± 0.05
10	C_{10}/C_e	1.00 ± 0.04	0.99 ± 0.06	1.00 ± 0.05
15	C_{15}/C_e	1.00 ± 0.03	1.00 ± 0.06	1.00 ± 0.05
	C_e value (mol/l)	$(1.76 \pm 0.06) \times 10^{-3}$	$(9.80 \pm 0.09) \times 10^{-4}$	$(1.74 \pm 0.09) \times 10^{-3}$

4 g toothpaste containing 0.5% zinc citrate is dispersed in 16 ml liquid media; mean from 5 values, 95% confidence level.

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Table 2. *REC* Values (with Respect to Zinc) for Toothpastes Containing 0.5% Zinc Citrate and Different Abrasives (Calcium Carbonate, Calcium Phosphate Dihydrate, Alumina and Silica)

Composition	Time for reaching C_e (min)	C_3 (μg/ml)	C_e (μg/ml)	*REC*	C_3/C_e°	C_e^* (μg/ml)
I	20	86±3	159±3	0.54±0.02	0.28	46
II	20	90±3	150±3	0.60±0.03	0.29	42
III	20	88±3	142±3	0.62±0.03	0.28	40
IV	20	78±3	134±3	0.58±0.03	0.25	43
V	20	72±3	141±3	0.51±0.02	0.23	49
VI	5	111±4	128±4	0.87±0.04	0.36	29
VII	5	62±2	77±3	0.81±0.03	0.20	31
VIII	5	79±3	105±3	0.75±0.03	0.25	33
IX	5	39±2	65±2	0.60±0.02	0.13	42
X	3	100±4	100±3	1.00±0.04	0.32	25
XI	4	92±3	114±4	0.81±0.03	0.30	31
XII	5	80±3	111±3	0.72±0.03	0.26	35
XIII	5	91±3	107±3	0.85±0.03	0.29	29
XIV	5	22±2	37±1	0.60±0.02	0.07	42
XV	4	151±4	152±3	0.99±0.04	0.48	25
XVI	1	180±4	207±3	0.87±0.04	0.58	29

Mean from 5 values, 95% confidence level; I—X-laboratory formulations and XI—XVI-commercially available brands; 4 g toothpaste is dispersed in 16 ml distilled water; C_e° = total zinc quantity in 4 g toothpaste/(4 + 16); $C_e^* = 25/REC$ (25 μg/ml is the therapeutical concentration of zinc ions).

media in different laboratories. The shortest time required for enabling the dispersion to achieve reproducible *REC* results is 3 min. When the duration of the dispersion is equal to or longer than 3 min, the stirring velocity and type of electromagnetic stirrer do not substantially affect the concentration of the active component in the water eluate. As can be seen from the data summarized in Table 2, the maximum value of *REC* does not correspond to the maximum value of C_3/C_e°, or to the maximum value of C_3 or C_e. It is not suitable, instead of *REC*, to use the "3 min yield" (C_3/C_e^0) of an active ingredient, calculated with respect to its total amount, since it is not possible to determine C_3 and C_e^0 by an identical analytical method. This would affect the overall rate of error. The determination of C_e alone does not provide adequate information about toothpaste quality, because a relationship between the equilibrium (C_e) and truly existing (C_3) concentration of the active component in the water eluate during the washing of the teeth does not exist. In order to obtain a useful effect, the substantial factor is the C_3 value, but if the ratio of two magnitudes determined by an identical method can be used, then the admitted systematic error may be eliminated. The values of the concentrations C_3 and C_e depend on the structure of the toothpaste, of the total and water soluble amounts of the active component. The *REC* value depends only on the structure of the toothpaste and can provide information about its quality and stability. It is important to ensure an adequately high concentration of the active component in the oral cavity with the least possible content of the component in the paste. For example, the effective concentration of zinc ions for ensuring a therapeutical effect is 25 μg/ml.[5,6] As can be seen in Table 2, this can be achieved at different theoretical equilibrium zinc concentration (C_e^*) values, depending on *REC*. A good toothpaste must be able to retain, without any changes during the declared shelf-life, not only the values of the total and water soluble amounts of the active ingredient, but also the respective *REC* value of this component. For example, the *REC* value of the toothpaste composition XI (Table 2), after 3 months exposure in a thermostat at 42 °C, changed from 0.81 to 0.58. The C_e value was altered slightly, from 114 to 105 μg/ml, but the C_3 value (the effective concentration of zinc ions) decreased from 92 to 61 μg/ml.

In conclusion, the concept of *REC* can be a useful quality characteristic in formulating new therapeutical toothpastes, in their comparative assessment, and in evaluating their shelf-life.

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