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Application of instrumental evaluation of color for the pre-formulation and formulation of rabeprazole

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Abstract

The aims of this study were to fast screen the compatibility of rabeprazole and excipients using a spectrocolorimeter and to examine the relationship between the color change value and drug contents/drug degradation products in solid dosage forms. The color change values of rabeprazole-excipient mixtures were measured using a spectrocolorimeter, with six tablet formulations compressed using a single-punch instrumental tablet press. The rabeprazole and degradation products contents in the tablets were analyzed using an HPLC method, with the color change values of the tablets measured using spectrocolorimetery for 4 weeks. These experiments indicated that the instrumental evaluation of color was a speedy, simple and useful tool in the determination of the interaction between the drug and excipients, as well as in the formulation of solid dosage forms. The relationships of the % reduced drug contents versus the color change value, and those of the % drug degradation products versus the color change value were exponentially increased in formulations containing zinc stearate. On stress testing, the color change value of rabeprazole was inconsistent with previous reports, as the degradation of rabeprazole can be greatly influenced by humidity as well as temperature. Consequently, these results highlight the potential of color formation in the application of pre-formulation and formulation of drugs.

Keywords: CIELAB; Discoloration; Pre-formulation; Formulation; Chemical stability; Rabeprazole

1. Introduction

Color is a basic visual feature of any solid pharmaceutical dosage form. The Food and Drug Administration Guidelines for stability testing of solid-state pharmaceuticals include the appearance/color as an important characteristic of stability (USP, 2006). Because visual observations and subjective assessments lack precision and objectivity, the quantitation of the color change value in solid-state pharmaceuticals during stability testing has received only limited attention. A way of overcoming this deficit, at least for solid surfaces, is to evaluate the color and color differences using reflectance spectroscopy. Instrumental color evaluations as the stability test for drugs in the various formulations have been described in the literature (Kitamura et al., 1989; Stark et al., 1996; Berberich et al., 2002). However, there have been few reports on the application of pre-formulation, such as screening of drug-excipient interactions, using color change value evaluations or application of formulation, to reveal the relationship between a drug degradation product and the color change value in solid dosage forms.

Rabeprazole is a potent gastric proton pump inhibitor, which causes dose dependent acid secretion (Langtry and Markham, 1999). It has a faster onset of action and lower potential for drug interaction compared to omeprazole. Rabeprazole is indicated in the treatment of erosive or ulcerative gastro esophageal reflux disease, the healing of duodenal ulcers and treatment of pathological hypersecretory conditions, including Zollinger Ellison syndrome. Rabeprazole is an acid labile drug, which is commercially available as enteric-coated tablets (Pariet®, 1998). Moreover, rabeprazole, which is similar to omeprazole, has been reported to be chemo- and thermo-labile, and rapidly degraded and discolored when exposed to acidic

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media and warm temperatures (Aciphex®, 1999; Chan et al., 2001).

The aims of this study were to fast screen the compatibility of rabeprazole and excipients using a spectrocolorimeter and to examine the relationships between the color change value and drug contents/drug degradation products in solid dosage forms. Of particular concern is whether color formation is useful in the application of pre-formulation and formulation of drugs.

2. Materials and methods

2.1. Materials

The following materials were used as received, without further purification: rabeprazole sodium was obtained from Lee Pharma, Ltd. (Andhra Pradesh, India). HPLC grade methanol was obtained from Fisher Scientific (Fair Lawn, NJ, USA). Phosphoric acid, potassium phosphate monobasic, sodium phosphate dibasic (Shinyo Pure Chemicals Co., Japan) and other excipients were of reagent grade. Water was purified using reverse osmosis and filtered in house.

2.2. Color measurement

The CIELAB color system has been included in the general chapter of the United States Pharmacopoeia since 1985. The tristimulus transformation of the reflectance spectrophotometer used in this study is described in the USP. The CIELAB color system gives an exact numerical specification of human color vision. The system defines the conditions for perceiving color by (a) specifying the relative spectral energy distributions of various illuminants, known as CIELAB Standard Illuminants, (b) dictating that the modification of an illuminant by interaction with an object be measured with a reflectance spectrocolorimeter conforming to the CIELAB recommendations and (c) quantifying the nature of human color vision in terms of three color matching functions; $\bar{x}$, $\bar{y}$ and $\bar{z}$, whose numerical values are available in published tables, and known collectively as a CIELAB Standard Observer. Three functions are required as color vision has been found to be trichromatic, i.e. a single perceived color results from the effect of three separate stimuli on the visual cortex.

The tristimulus values are used to calculate the 1976 CIE L^*, a^* and b^* (CIELAB) color space values, which enable colors to be regarded as existing in an approximately uniform three dimensional space. Each particular color has a unique location, as defined by its Cartesian coordinates with respect to a^* (red–green axis), b^* (yellow–blue axis) and L^* (lightness axis) for the brightness in the Cartesian coordinates system (Fig. 1).

The L^* coordinate serves as the psychometric correlation of perceived lightness, which covers a range from white (1 0 0) to black (0) along a grey scale. The a^* and b^* coordinates are related to Hering's opponent color theory, and give the locations of the various hues on red versus green (a^*) and yellow versus blue (b^*) scales. If both a^* and b^* are zero, the color lies on the L^* axis, and is termed achromatic. The color difference (ΔE) is calculated using coordinate geometry, as the length of the line joining the two color positions: $\Delta E = \sqrt{(\Delta L*)^2 + (\Delta a*)^2 + (\Delta b*)^2}$

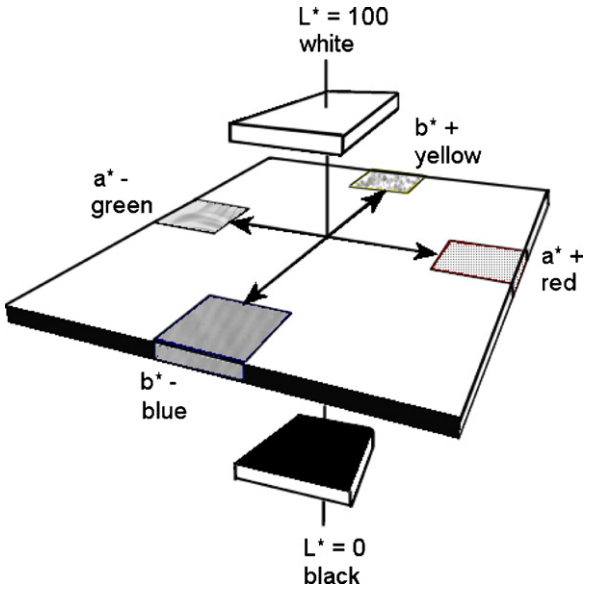

Fig. 1. CIELAB color space diagram.

A change or difference in color, corresponding to a value of $\Delta E > 1.5$, can be perceived by the human eye (Stark et al., 1996).

A spectrocolorimeter, CR-241 (Minolta, Japan), using 0° illumination and 45° viewing geometry, with the spectral component excluded, was used in this study. The equipment was calibrated daily using the same diaphragm, against the white reference and darkness, prior to any measurements being conducted. Usually, one sample is measured with 10 units. The mean values of L^*, a^* and b^* of these 10 units are calculated, with the color change value (ΔE) calculated using these mean values.

2.3. Screening of the rabeprazole-excipient compatibility

The color changes of rabeprazole-excipient mixtures were measured (at initial and 3 days) using a spectrocolorimeter. Five gram of rabeprazole was added to 5 g of each excipient, with the powder then transferred to 30 mL vials and the mouths sealed with a cap. Each rabeprazole-excipient mixture was then placed under the accelerated condition in (1) at 40 ± 2 °C and 75% ± 5 RH and the stress condition in (2) at 60 ± 2 °C in a stability chamber (Labfine Instrument, Korea). Each vial was vortex mixed for over 1 min prior to being placed over the viewing port of the reflectance spectrocolorimeter.

2.4. Formulations of rabeprazole tablets and chemical stability

From the rabeprazole-excipient compatibility results, the promising excipients were selected, and the stability of six tablet formulations containing 20 mg rabeprazole examined. The six tablet formulations are described in Table 1. Normally convex, 7 mm tablets, with a target weight of 140 mg, were compressed using a single-punch instrumented tablet press (Caver press,

Table 1
Compositions of the rabeprazole uncoated tablet formulations

	Components	A	B	C	D	E	F
Drug	Rabeprazole sodium (mg)	20	20	20	20	20	20
Stabilizer	Aluminum stearate (mg)	60	60	60	–	–	–
	Zinc stearate (mg)	–	–	–	40	40	40
Disintegrant	Crospovidone (mg)	40	40	40	40	40	40
Filler	Lactose anhydrous (mg)	20	–	–	40	–	–
	Al Mg silicate (mg)	–	20	–	–	40	–
	Mannitol (mg)	–	–	20	–	–	40
	Total (mg)	140	140	140	140	140	140

USA). Each formulation was placed in an open containers under the accelerated condition in (1) at 40 ± 2 °C and 75% ± 5 RH and the stress condition in (2) at 60 ± 2 °C in a stability chamber (Labfine Instrument). During the stability test, the rabeprazole and degradation products contents in the tablets were obtained after the first, second, third and the fourth weeks, using a stability-indicating HPLC method for rabeprazole. The rabeprazole contents are converted to the reduced drug contents (%). The reduced drug contents (%) after each week were calculated from the initial drug content (%) minus the drug contents remaining (%) after each week. The color change values of the tablets were also measured after the first, second, third and the fourth weeks, using a spectrocolorimeter.

2.5. Analytical procedures and HPLC conditions

The rabeprazole and degradation products contents of the tablets were analyzed using an HPLC method. The HPLC procedures were fully validated prior to their routine use, with the area under the peak values used for the calculations. The validation tests included system suitability, accuracy, reproducibility, linearity and ruggedness.

The HPLC system (Agilent 1100, USA) consisted of a Model G1311A pump, a Model G1311A autosampler, a Model G1311A column oven and a Model G1311A diode array detector, operated at 290 nm. The data station was an Agilent Chemstation. The column used was a Luna C_{18} column

Table 2
Accuracy and precision of HPLC method for rabeprazole analysis

Standard conc. (μg/mL)	Interday			Intraday		
	Recovered conc. (μg/mL)	|% Deviation|	% CV	Recovered conc. (μg/mL)	|% Deviation|	% CV
	4.30[a]	13.92		4.79[b]	4.19	
5	5.52[c]	10.45	12.59	5.07[d]	1.31	2.79
	4.79[b]	4.19		4.93[e]	1.37	
	9.51	4.90		9.58	4.22	
10	10.45	4.48	5.32	9.61	3.91	0.18
	9.58	4.22		9.61	3.93	
	19.70	1.49		19.51	2.45	
20	19.53	2.35	0.54	19.27	3.65	0.62
	19.51	2.45		19.39	3.06	
	51.03	2.05		51.42	2.85	
50	49.87	0.27	1.59	51.73	3.45	0.29
	51.42	2.85		51.58	3.16	
	101.33	1.33		99.98	0.02	
100	99.19	0.81	1.08	99.38	0.62	0.30
	99.98	0.02		99.65	0.35	
	199.13	0.44		199.72	0.14	
200	200.44	0.22	0.33	199.95	0.03	0.06
	199.72	0.14		199.85	0.08	
Mean		3.14	3.57		2.15	0.71

[a] Day 1: conc. = 65.2466 × peak area − 0.9385 (r = 0.99992).
[b] Day 3 (first analysis): conc. = 67.4472 × peak area − 0.4052 (r = 0.99995).
[c] Day 2: conc. = 73.5333 × peak area + 0.6009 (r = 0.99997).
[d] Second analysis: conc. = 77.8100 × peak area + 0.0608 (r = 0.99993).
[e] Third analysis: conc. = 72.3907 × peak area − 0.1595 (r = 0.99994).

(5 mm, 250 mm × 4.6 mm i.d.; 5 μm; Phenomenex, CA, USA) operated 30 °C. The analytical mobile phase, consisting of 0.05 mol/L phosphate buffer (pH adjusted to 7.0 with dilute phosphoric acid) and methanol, in a 60:40 (v/v) ratio, was continuously passed through the analytical column, at a flow rate of 1.0 mL/min. A 10 μL sample was injected into the column.

3. Results

3.1. Validation of rabeprazole analysis method using HPLC

A slight modification of a previous reported HPLC assay was used to determine the content of rabeprazole (Ramakrishna et al., 2005).

Fig. 2 shows a typical chromatogram of rabeprazole. The peak for rabeprazole was sharp and the retention time was approximately 6.3 min. The calibration curves for rabeprazole were linear at concentrations ranging from 5 to 200 μg/mL ($r > 0.9999$). In order to validate the rabeprazole analysis method using HPLC, the accuracy and precision were determined as the absolute % deviation and coefficient of variation (% CV), respectively. Table 2 shows the interday mean accuracy of 3.14%

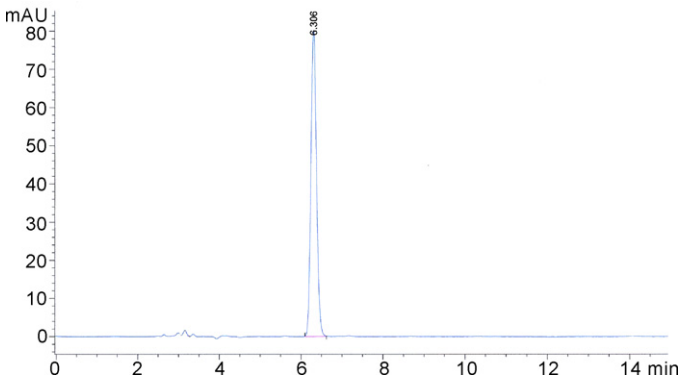

Fig. 2. Representative chromatogram of rabeprazole.

Table 3
The CIELAB color space values and ΔE for rabeprazole-excipient mixtures stored under: (1) at 40 °C and 75% RH and (2) at 60 °C conditions for 3 days

Excipients	Initial			After 3 days at 40 ± 2 °C and 75% ± 5 RH				After 3 days at 60 ± 2 °C			
	L^*	a^*	b^*	L^*	a^*	b^*	ΔE	L^*	a^*	b^*	ΔE
Al stearate	58.50	0.46	5.10	57.45	−0.24	3.56	2.01	53.78	0.56	7.84	5.46
Crospovidone	58.22	−0.27	5.85	60.85	−0.23	15.05	9.58	58.35	−0.22	12.42	6.59
Ca stearate	71.33	0.16	2.79	60.13	−0.38	7.81	12.29	65.13	−0.56	7.42	7.77
$CaSO_4$	54.40	0.52	5.55	24.50	0.02	6.91	29.93	58.65	−0.08	12.13	7.86
Lactose anhydrous	88.46	0.26	7.60	36.09	−0.55	4.49	52.47	82.63	0.02	15.92	10.16
Al Mg silicate	93.07	−0.23	4.98	64.15	−1.15	11.75	29.71	87.66	−0.86	13.66	10.24
Mannitol	87.62	0.71	9.55	43.92	1.06	15.66	44.13	82.86	0.46	19.15	10.72
Zn stearate	66.86	0.13	2.93	56.12	−0.25	6.50	11.32	55.72	−0.20	7.12	11.90
Hypromellose	91.34	0.13	7.51	61.11	0.26	20.73	33.00	81.64	−0.04	14.57	12.00
Meglumine	59.15	0.45	7.01	40.13	−1.56	31.01	30.69	53.32	−0.63	17.64	12.18
Cyclodextrin	58.45	−0.64	4.36	14.08	−0.16	−0.37	44.62	52.48	0.32	15.59	12.78
Hydroxypropyl cellulose	57.41	−0.54	5.15	36.32	1.39	15.95	23.78	51.32	0.81	16.38	12.85
Ca silicate	64.40	0.09	3.25	44.02	−0.04	6.21	20.59	52.51	0.42	11.24	14.33
Povidone	89.30	0.26	8.57	51.13	3.70	24.28	41.42	78.38	0.33	17.98	14.42
Eudragit RLPO	58.21	−0.44	5.68	26.96	1.94	14.80	32.64	51.35	1.49	18.92	15.06
Arginine	56.99	0.59	5.48	14.18	0.35	5.19	42.81	50.91	1.56	21.53	17.33
Ca carboxymethylcellulose	90.11	0.10	7.63	37.33	0.96	9.12	52.81	75.18	0.22	17.44	17.87
Sugar	57.29	−0.11	6.13	13.42	0.70	3.80	43.94	46.42	2.06	20.62	18.24
Sodium starch glycolate	58.32	−0.44	5.68	31.24	1.73	14.05	28.43	43.56	1.66	16.70	18.54
L-HPC	58.62	−0.27	5.97	31.83	3.07	11.41	27.54	42.54	4.36	15.37	19.19
$CaHPO_4$	55.06	0.60	5.55	20.80	1.45	5.49	34.27	35.12	2.73	9.53	20.45
Na_2SO_4	57.79	0.53	5.88	17.20	1.49	10.16	40.83	40.18	1.68	17.06	20.89
Sodium lauryl sulfate	55.54	0.07	7.54	44.05	0.47	13.02	12.74	37.47	5.10	17.45	21.22
$AlCl_3$	58.38	0.53	5.68	39.20	19.17	32.48	37.86	58.61	3.12	27.74	22.25
Polyvinyl alcohol	56.63	−0.08	6.15	23.08	1.98	12.37	34.18	40.23	4.26	21.43	22.87
Na carboxymethyl cellulose	58.34	0.39	5.18	23.67	1.87	12.25	35.41	38.92	2.51	18.28	23.52
Corn starch	58.46	0.53	5.68	29.65	1.02	8.86	28.99	36.63	4.60	16.68	24.80
Microcrystalline cellulose	90.25	−0.07	7.39	74.60	1.63	16.33	43.61	66.76	1.13	16.55	25.24
Glyceryl behenate	56.77	0.13	7.54	41.09	0.48	14.05	16.99	29.72	2.52	7.89	27.15
Na_2HPO_4	58.34	0.39	5.33	7.83	0.39	0.48	50.74	32.57	1.88	15.90	27.89
KOH	58.46	0.54	4.66	44.87	1.09	11.98	15.45	30.46	5.24	13.16	29.64
Dextran	59.43	0.69	6.43	37.60	1.85	15.95	23.86	29.29	3.71	12.74	30.96
$AlK(SO_4)_2$	58.31	0.68	5.56	21.86	1.93	9.56	36.69	24.86	3.65	12.24	34.24
Emcompress	90.80	0.04	6.13	40.20	0.06	2.88	50.70	52.46	1.72	8.36	38.44
K_2CO_3	58.79	0.46	5.10	32.78	3.12	16.95	28.71	20.06	4.35	14.16	39.96
KH_2PO_4	54.31	0.70	5.55	23.71	0.25	−0.66	31.22	11.45	0.49	−0.10	43.23
$CaCl_2$	56.63	−0.08	6.15	16.45	−0.09	2.98	40.30	12.40	0.31	−0.55	44.73
Poloxamer 407	59.43	0.69	5.65	33.44	1.82	13.43	27.16	9.44	1.40	0.32	50.28

ranging from 0.02 to 13.92% and the intraday mean accuracy of 2.15% ranging from 0.02 to 4.22%. The interday mean precision of the HPLC method was 3.57% ranging from 0.33 to 12.59% and the intraday mean precision of the HPLC method was 0.71% ranging from 0.06 to 2.79%.

The analysis method was found to be precise, selective and reproducible (Ramakrishna et al., 2005).

3.2. Fast screening of the interaction between rabeprazole and excipients

Stability testing has emerged in the field of pharmaceuticals as being very important to maintain the efficacy of a drug, as it provides measurements of the storage capacity of a drug, as well as demonstrates the safety of the drug products. Also, stability testing is a requirement for the regulatory approval during product marketing, and is a vital component of the overall quality control program. Rabeprazole is an acid labile drug, and has been reported to be chemo- and thermo-labile, and rapidly degraded and discolored when exposed to acidic media and warm temperatures. Therefore, in order to rapidly screen the interaction between rabeprazole and its excipients, the color change value of the drug-excipient mixture can be measured using a spectrocolorimeter.

In the ICH stability guideline Q1A(R2) (2003), accelerated storage condition for drug substances is suggested the following condition: at 40 ± 2 °C and 75% ± 5 RH. Moreover, stress testing is likely to be carried out and it should include the effect of temperatures (in 10 °C increments (e.g., 50, 60 °C, etc.) above that for accelerated testing). Therefore, many stress studies in 60 °C have been reported in the literature for bulk drugs (Rao et al., 2005a,b,c; Singh et al., 2006; Breton et al., 2006; Rao et al., 2006) or finished products (Mohammadi et al., 2006; Sekiya et al., 2007).

The CIELAB color space values and ΔE for drug-excipient mixtures stored under: (1) at 40 ± 2 °C and 75% ± 5 RH and (2) at 60 ± 2 °C conditions are shown in Table 3. Of the 38 excipients, aluminum stearate, crospovidone and zinc stearate showed minimum color change values at 40 ± 2 °C and 75% ± 5 RH. At 60 ± 2 °C, aluminum stearate, crospovidone and calcium stearate showed minimum color changes; lactose anhydrous, aluminum magnesium silicate and mannitol, which act as fillers, also showed good compatibility with the drug. These results show that the instrumental evaluation of the color of drug-

Table 4
The CIELAB color space values and ΔE for the six rabeprazole formulation uncoated tablets stored under: (1) at 40 °C and 75% RH and (2) at 60 °C conditions for 4 weeks

Formulations	Day	At 40 ± 2 °C and 75% ± 5 RH				At 60 ± 2 °C			
		L^*	a^*	b^*	ΔE[a]	L^*	a^*	b^*	ΔE
A	0	94.95	−0.30	3.34	–	94.95	−0.30	3.34	–
	7	73.31	−0.30	5.52	21.75 ± 0.12	79.85	0.57	13.50	18.22 ± 0.01
	14	71.13	−0.25	6.36	24.02 ± 0.04	75.57	0.98	11.17	20.94 ± 0.01
	21	72.03	−0.10	8.02	23.39 ± 0.59	74.57	0.12	9.64	21.34 ± 0.19
	28	73.84	0.28	8.30	21.70 ± 0.00	74.92	0.42	8.64	20.74 ± 0.00
B	0	95.07	−0.27	3.22	–	95.07	−0.27	3.22	–
	7	75.26	−0.21	6.32	20.05 ± 0.09	81.19	0.50	14.01	17.60 ± 0.07
	14	71.98	−0.24	6.33	23.30 ± 0.03	77.25	1.61	12.88	20.35 ± 0.00
	21	70.57	−0.29	7.04	24.80 ± 0.48	76.09	0.85	10.61	20.40 ± 0.04
	28	72.99	0.40	8.31	22.67 ± 0.01	75.94	0.87	9.56	20.18 ± 0.01
C	0	94.78	−0.30	3.14	–	94.78	−0.30	3.14	–
	7	72.16	−0.30	5.63	22.75 ± 0.19	79.68	0.52	13.31	18.22 ± 0.11
	14	70.98	−0.28	6.55	24.04 ± 0.01	75.81	0.97	11.06	20.59 ± 0.00
	21	70.92	−0.08	8.29	24.40 ± 0.38	73.91	0.07	9.13	21.71 ± 0.19
	28	72.99	0.27	8.58	22.46 ± 0.01	74.25	0.35	8.32	21.18 ± 0.01
D	0	94.11	−0.16	3.78	–	94.11	−0.16	3.78	–
	7	76.92	−0.31	7.59	17.60 ± 0.02	86.61	0.14	13.01	11.89 ± 0.00
	14	73.56	0.31	6.76	20.77 ± 0.09	80.44	2.00	13.07	16.67 ± 0.00
	21	71.69	−0.02	6.71	22.61 ± 0.34	76.56	1.80	10.89	19.03 ± 0.01
	28	71.02	0.45	6.67	23.28 ± 0.01	74.97	1.82	9.58	20.10 ± 0.01
E	0	94.60	−0.22	3.07	–	94.60	−0.22	3.07	–
	7	79.32	0.03	6.76	15.72 ± 0.07	89.09	0.27	7.97	8.54 ± 2.37
	14	75.78	0.38	5.99	19.05 ± 0.04	82.95	2.15	10.72	14.13 ± 0.02
	21	73.38	0.02	5.93	21.41 ± 0.03	78.45	2.25	9.54	17.57 ± 0.03
	28	72.71	0.45	6.06	22.10 ± 0.03	77.21	2.48	8.18	18.32 ± 0.03
F	0	93.67	−0.14	3.81	–	93.67	−0.14	3.81	–
	7	75.45	−0.02	7.42	18.57 ± 0.08	86.30	0.22	12.76	11.60 ± 0.11
	14	72.67	0.34	6.43	21.16 ± 0.03	80.50	1.94	12.89	16.13 ± 0.05
	21	70.94	−0.07	6.46	22.88 ± 0.28	75.73	1.78	10.71	19.31 ± 0.35
	28	70.49	0.37	6.59	23.35 ± 0.04	74.61	1.87	9.73	20.05 ± 0.05

[a] $N = 3$, mean ± S.D.

excipient mixtures is a fast and simple tool for the determination of the interactions between a drug and its excipients.

3.3. Color change values and chemical stability of rabeprazole uncoated tablet

The CIELAB color space and ΔE values for the six rabeprazole formulation uncoated tablets, stored under (1) at $40 \pm 2\,^{\circ}C$ and $75\% \pm 5$ RH and (2) at $60 \pm 2\,^{\circ}C$ conditions, are shown in Table 4. Of the six formulations, those containing zinc stearate showed less color change than formulations containing aluminum stearate after 3 weeks, although the ΔE of the formulations containing aluminum stearate decreased under conditions of at $40\,^{\circ}C/75\%$ RH after 4 weeks.

In the formulations A, B and C, over a quarter of drug were decomposed after 2 weeks. Since one of the purposes for our studies was the rapid detection of drug degradation, we discontinued the HPLC analysis of formulations A, B and C. Therefore, we also discontinued the analysis of formulations D, E and F after 4 weeks. The results of the reduced drug contents and degradation products for the six formulations stored under stress conditions are shown in Tables 5 and 6. As shown in Tables 5 and 6, compared to the formulations containing zinc stearate, the drug contents and degradation products were largely changed in formulations containing aluminum stearate, which was consistent with the ΔE results of the uncoated tablets.

Table 5
% Reduced drug contents for the six rabeprazole formulation uncoated tablets stored under: (1) at $40\,^{\circ}C$ and 75% RH and (2) at $60\,^{\circ}C$ conditions

Formulations	Days	At $40 \pm 2\,^{\circ}C$ and $75\% \pm 5$ RH	At $60 \pm 2\,^{\circ}C$
A	0	0.00 ± 1.03[a]	0.00 ± 1.03
	7	−3.38 ± 1.49	8.31 ± 3.30
	14	26.62 ± 2.10	33.06 ± 0.50
B	0	0.00 ± 0.85	0.00 ± 0.85
	7	8.12 ± 1.20	10.09 ± 1.60
	14	27.74 ± 0.90	25.35 ± 1.40
C	0	0.00 ± 0.88	0.00 ± 0.88
	7	5.95 ± 1.30	14.33 ± 2.00
	14	30.31 ± 0.80	34.44 ± 0.90
D	0	0.00 ± 1.13	0.00 ± 1.13
	7	0.78 ± 0.90	−0.31 ± 1.00
	14	13.16 ± 1.60	7.11 ± 2.80
	21	21.29 ± 2.31	23.21 ± 3.49
	28	32.90 ± 1.9	25.20 ± 0.80
E	0	0.00 ± 0.94	0.00 ± 0.94
	7	2.91 ± 1.40	0.84 ± 2.60
	14	21.35 ± 2.50	11.61 ± 1.70
	21	45.38 ± 1.01	32.94 ± 1.76
	28	48.97 ± 1.05	37.37 ± 1.02
F	0	0.00 ± 1.01	0.00 ± 1.01
	7	6.29 ± 2.80	4.21 ± 2.70
	14	18.57 ± 3.50	13.65 ± 2.00
	21	45.11 ± 0.53	29.90 ± 1.40
	28	48.53 ± 1.17	34.82 ± 0.57

[a] $N = 3$, mean ± S.D.

Table 6
% Degradation products for the six rabeprazole formulation uncoated tablets stored under: (1) at $40\,^{\circ}C$ and 75% RH and (2) at $60\,^{\circ}C$ conditions

Formulations	Days	At $40 \pm 2\,^{\circ}C$ and $75\% \pm 5$ RH	At $60 \pm 2\,^{\circ}C$
A	0	0.84 ± 0.01[a]	0.84 ± 0.01
	7	2.85 ± 0.02	7.77 ± 0.44
	14	15.92 ± 0.70	30.85 ± 1.63
B	0	0.94 ± 0.01	0.94 ± 0.01
	7	2.89 ± 0.02	7.45 ± 0.45
	14	17.59 ± 0.62	28.23 ± 0.65
C	0	0.97 ± 0.01	0.97 ± 0.01
	7	2.77 ± 0.15	7.63 ± 0.37
	14	19.66 ± 0.94	30.59 ± 1.13
D	0	0.99 ± 0.05	0.99 ± 0.05
	7	0.96 ± 0.06	2.01 ± 0.04
	14	6.58 ± 0.46	10.07 ± 0.62
	21	17.04 ± 0.17	22.36 ± 1.34
	28	21.51 ± 1.11	25.57 ± 0.74
E	0	0.91 ± 0.08	0.91 ± 0.08
	7	2.14 ± 0.02	4.75 ± 0.26
	14	12.89 ± 0.95	20.05 ± 0.68
	21	23.32 ± 0.79	32.51 ± 1.60
	28	29.91 ± 0.60	34.57 ± 1.38
F	0	0.82 ± 0.00	0.82 ± 0.00
	7	1.57 ± 0.08	2.77 ± 0.36
	14	12.48 ± 0.56	14.32 ± 1.26
	21	23.90 ± 0.99	26.00 ± 1.67
	28	29.37 ± 0.55	31.27 ± 0.73

[a] $N = 3$, mean ± S.D.

These results showed that the instrumental evaluation of the color of uncoated tablet is a speedy and useful tool in the formulation of solid dosage forms.

4. Discussion

Color testing for screening of the interactions between rabeprazole and its excipients was shown to give fast, simple and reliable results for the pre-formulation of rabeprazole. The relationship between the reduced drug content and ΔE value of formulations containing zinc stearate is shown in Fig. 3, with the results showing exponential relationships between increasing reduced drug contents and increasing ΔE values. The relationship between the degradation products and ΔE of formulations containing zinc stearate is shown in Fig. 4, with the results also showing exponential relationships between increasing degradation products and increasing ΔE values. The correlation coefficients in all case were >0.97 (Table 7). When we examined the relationship between the color change value and drug degradation products, the color value changed abruptly (great scale) in spite of a little amount of drug degradation in the initial stage. As time passed, drug degradation increased greatly, however, the color value changed a little amount. These results correlated with the exponential relationship between the color change value and drug degradation products. Therefore, we can suggest that the instrumental evaluation of the color is a useful skill to detect the drug stability because color change is sensitive indication when the drug starts to decompose.

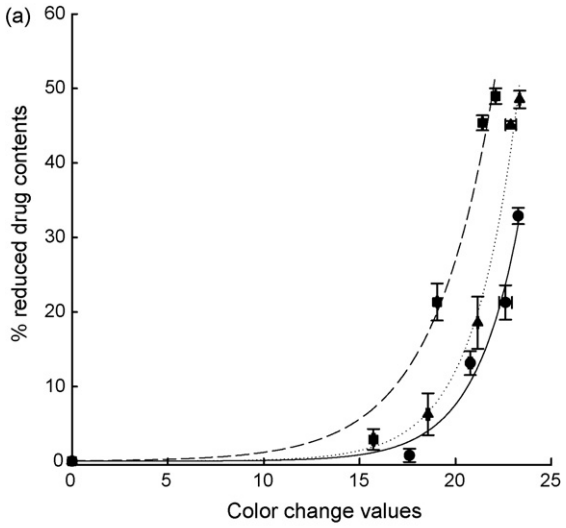

Fig. 3. Correlation of color change value (ΔE) and % reduce rabeprazole contents for the rabeprazole formulation uncoated tablets containing zinc stearate stored under: (a) at 40 °C and 75% RH and (b) at 60 °C conditions ($N = 3$, mean ± S.D.). Key: formulation D (●); formulation E (■); formulation F (▲).

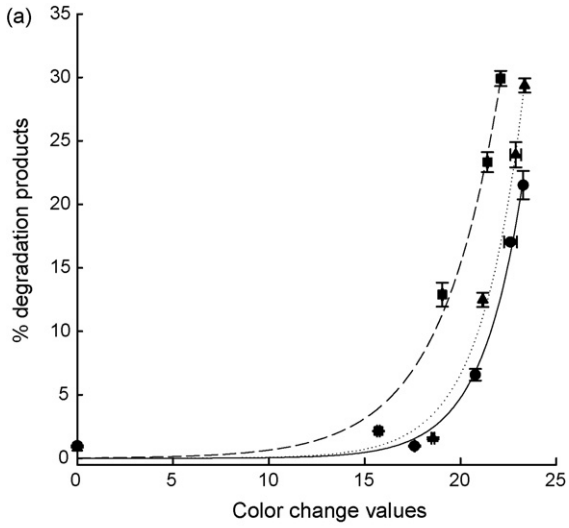

Fig. 4. Correlation of color change value (ΔE) and % degradation products for the rabeprazole formulation uncoated tablets containing zinc stearate stored under: (a) at 40 °C and 75% RH and (b) at 60 °C conditions ($N = 3$, mean ± S.D.). Key: formulation D (●); formulation E (■); formulation F (▲).

The exponential relationship between the color change value and drug degradation products differs from those reported by Stark et al. (1996), which showed linear relationships between the ΔE values and drug contents for three formulations. Moreover, Kitamura et al. (1989), Stark et al. (1996) and Berberich et al. (2002) reported that although the rate of color formation was different for each product, and does not always reflect the decomposition of the active drug, it appears that the color change value obeys the Arrhenius Law on stress testing. However, in the case of rabeprazole, the ΔE values under conditions of at 40 °C/75% RH are greater than at 60 °C, which is inconsistent with the previous reports of Kitamura et al. (1989), Stark et al. (1996) and

Table 7
Correlation coefficients and parameters between color change values and % reduced drug contents and between color change values and % degradation products of rabeprazole uncoated tablets

Formulations	At 40 °C and 75% RH						At 60 °C					
	% Reduced drug contents			% Degradation products			% Reduced drug contents			% Degradation products		
	r[a]	a[b]	b	r	a	b	r	a	b	r	a	b
D	0.9889	0.0012	0.4368	0.9965	0.0004	0.4677	0.9771	0.0353	0.3311	0.9918	0.1251	0.2671
E	0.9904	0.0521	0.3123	0.9947	0.0268	0.3173	0.9971	0.2075	0.2853	0.9931	1.6984	0.1665
F	0.9951	0.0023	0.4286	0.9953	0.0009	0.4477	0.9997	0.2720	0.2425	0.9960	0.3298	0.2270

[a] Correlation coefficient.
[b] $y = a \times e^{bx}$.

Berberich et al. (2002), as the degradation of rabeprazole can be greatly influenced by humidity as well as temperature.

The color change value of rabeprazole can arise due to temperature, humidity or the interaction between the drug and its excipients. Whatever the source of the color change value during the screening of excipients and the short term stability testing of solid dosage forms, the fact it can be quantified using CIELAB color values suggests that color may be a useful tool in the pre-formulation and formulation of the drug. The methods using instrumental measurement of color change are already widely used in the field of food and dye industries. However, there have been few reports on application of instrumental evaluation of color for pre-formulation or formulation. Therefore, more researches are demanded to other drugs and other pharmaceutical application. Prior to attempting the first formulation with a new drug, most research groups carry out compatibility testing. The principle is to make up reasonably rationed mixtures of drug and excipient, to ascertain which excipients may be reasonably used with the drug. The methods used nowadays have followed in step with analytical developments and are (a) chemical assay, (b) thin layer chromatography, (c) HPLC, (d) differential scanning calorimetric method and (e) microcalorimetric methods (Carstensen and Rhodes, 2000). However, in order to use these methods, costs for instruments are relatively expensive and sample preparations are complicated to treat a large amount of samples. The instrumental color measurement method is cheaper and speedier than other methods. It has advantages over the other methods to screen a large amount of samples quicker, easier and more convenient. Consequently, these results highlight the potential of the color formation in the application of pre-formulation and formulation of drugs. However, comparative absolute L^*, a^* and b^* values depend on the instrument being used. Therefore, the CIELAB and ΔE values are only comparable when all measurements are performed with comparable or correlated instruments (Berberich et al., 2002).

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