Table I. Components of Direct Compression Platforms

ODT platform	PEARLITOL®Flash	Ludiflash®	PROSOLV®ODT	F-Melt®
Excipients	Mannitol Maize starch	Mannitol Kollidon CL-SF Kollicoat SR 30D Kollidon 30	Microcrystalline cellulose Colloidal silicon dioxide Mannitol Fructose Crospovidone	Mannitol Xylitol Microcrystalline cellulose Crospovidone Magnesium aluminosilicate Dibasic calcium phosphate anhydrous

manufacturers and used as received (Table I). The ODTs were formulated with 6% benzocaine, 1.5% magnesium stearate, and 92.5% of the respective ODT platform. Briefly, benzocaine was added to each platform and mixed for 10 min in a Turbula mixer. Magnesium stearate, a lubricant, was mixed with the powder for 5 min. Each formulation was tableted at 500 mg using 10 mm diameter concave punches on a Korsh XP1 research tableting machine under two conditions. The tablets in the first group were produced at different compression force depending on platform compressibility to create tablets with an average hardness of 100 N. The tablets in the second group were made under a constant compression force of 20 kN, which resulted in tablets with varying hardness. Tablets were evaluated in accordance with US Pharmacopoeia methods for hardness (Schleuniger Pharmatron Tablet Hardness Tester), friability (VanKel Friability Tester), and *in vitro* disintegration time (Schleuniger Pharmatron Disintegration Tester, Model DTG 2000).

Benzocaine Stability and Sample Preparation

Tablets were placed under International Conference on Harmonization (ICH) stability conditions (8,9) in humidity chambers at 25°C and 60% relative humidity (RH) or under accelerated conditions, 40°C and 75% RH, for up to 6 months in open pans. Following storage under the various conditions, tablets were photographed and their diameter measured using a caliper.

Two tablets, each containing 30 mg benzocaine, were ground using a mortar and pestle and dissolved in 10 mL methanol. The mixture was vortexed and undissolved excipient residue was removed by centrifuging at 1,000 rpm for 5 min. Samples (50 μg/mL) were prepared for liquid chromatography–mass spectrometry (LC-MS) analysis. To force degradation, benzocaine (12 mg/mL) was subjected to 2 N HCl (acidic stress) or 30% H_2O_2 (oxidative stress) aqueous solutions and stored at room temperature for 10 days. Samples (50 μg/mL) were prepared for LC-MS analysis.

Table II. ODT Evaluation

Platform	Properties	Disintegration time (s)	Friability
PEARLITOL®Flash	H, 100 N	60	Passed
	Fc, 20 kN	68	Passed
Ludiflash®	H, 100 N	65	Passed
	Fc, 20 kN	150	Passed
PROSOLV®ODT	H, 100 N	420	Passed
	Fc, 20 kN	600	Passed
F-Melt®	H, 100 N	65	Passed
	Fc, 20 kN	150	Passed

H hardness, *Fc* compression force

LC-MS Conditions

LC-MS was performed on an Agilent 6410 Triple Quadrupole system with LC detection at 254 nm and operated in the selective ion monitoring (SIM) mode at specific mass to charge (m/z) ratios: 94, 120, 122, 137, 138, 139, 165, 166, 167, 178, 179, 180, 181, 182, 190, 193, 194, 195, 203. With this method, only the selected m/z values are detected in the analysis. The masses correspond to expected benzocaine decomposition products (7,10). Chromatographic separation of samples (10 μL) was achieved at a flow rate of 200 μL/min using a X-Bridge C8 column (2.1×50 mm i.d., 3.5 μm particle size) and an initial mobile phase consisting of a mixture of

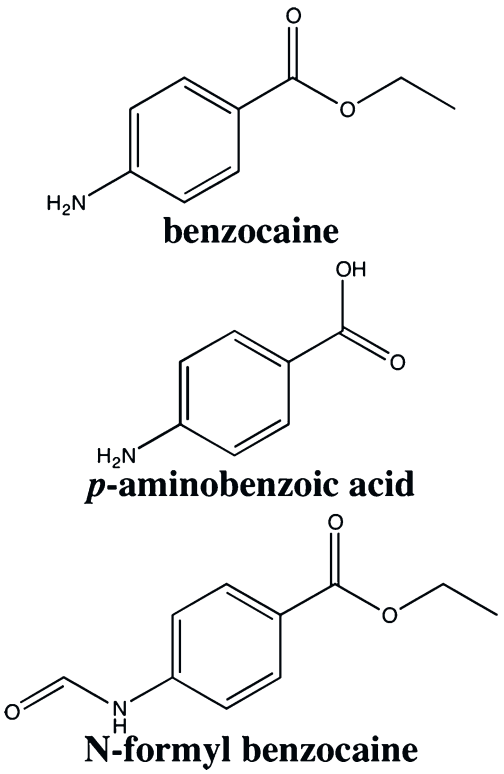

Fig. 1. Structure of benzocaine and its primary degradation products, *p*-aminobenzoic acid, and *N*-formylbenzocaine

water (5%) and methanol (95%) acidified with 0.1% formic acid. After an isocratic hold for 1 min, the sample was then eluted with linear gradient from 95 to 5% methanol acidified with 0.1% formic acid over a period of 8 min before returning to the initial isocratic condition for 5 min. To determine the molecular formula of the detected degradation, product mass spectrometry on a Shimadzu LC-MS IT-TOF was conducted.

RESULTS AND DISCUSSION

Tablet Production and Characterization

Tablets were easily formed with each of the commercially available platforms. All tablets were white and pharmaceutically acceptable when produced at constant pressure (20 kN) and constant hardness (100 N). All tablets produced passed the friability test and were reproducible in weight. The constant pressure condition was a pressure that was above the pressure needed to compress the tablets to the desired hardness. Due to this, the disintegration time for the constant pressure tablets was consistently higher than the constant hardness tablet disintegration time (Table II). The *in vitro* disintegration test in a basket dissolution apparatus was conducted in water as immersion fluid to compare the different formulations. In this test, the disintegration times were above the 30-s guideline described by the NIH, but the NIH guideline defines oral disintegration time and saliva is used as immersion fluid instead of water. Dissolution times can be used to compare the preparations but does not match the conditions for the NIH definition.

LC-MS Method Development

To validate if the LC-MS method can differentiate between benzocaine and potential degradation products, we generated degradants by subjecting benzocaine to acid hydrolysis and oxidation. Benzocaine (Fig. 1), or *p*-aminobenzoic acid ester (molecular formula $C_9H_{11}NO_2$, molecular weight 165.189 g/mol), is a local anesthetic used primarily to relieve pain or irritations on the skin and mucosal surfaces. Benzocaine degradation is both acid and base catalyzed (11). Under acidic stress conditions, a peak with a retention time of 2.1 min appeared in addition to the benzocaine peak at 8.8 min (Fig. 2a). According to the SIM chromatogram (Fig. 2b), the UV peak at 2.1 min corresponds to *p*-aminobenzoic acid (PABA, MW 138 g/mol). PABA is the primary degradation product of benzocaine resulting from ester hydrolysis. The SIM chromatogram at *m*/*z* 138 also matches with the UV peak at 8.8 min that corresponds to benzocaine (Fig. 2d). This is most likely due to the generation of fragment ions during the mass spectrometry process. Although no corresponding UV peak was apparent, ions with a *m*/*z* of 194.2 were also identified in the SIM mode of samples that underwent acid hydrolysis. This can be explained by the increased sensitivity of the SIM mode where the mass spectrometer only collects data for specified masses rather than scanning for masses over a wide range. Following oxidation

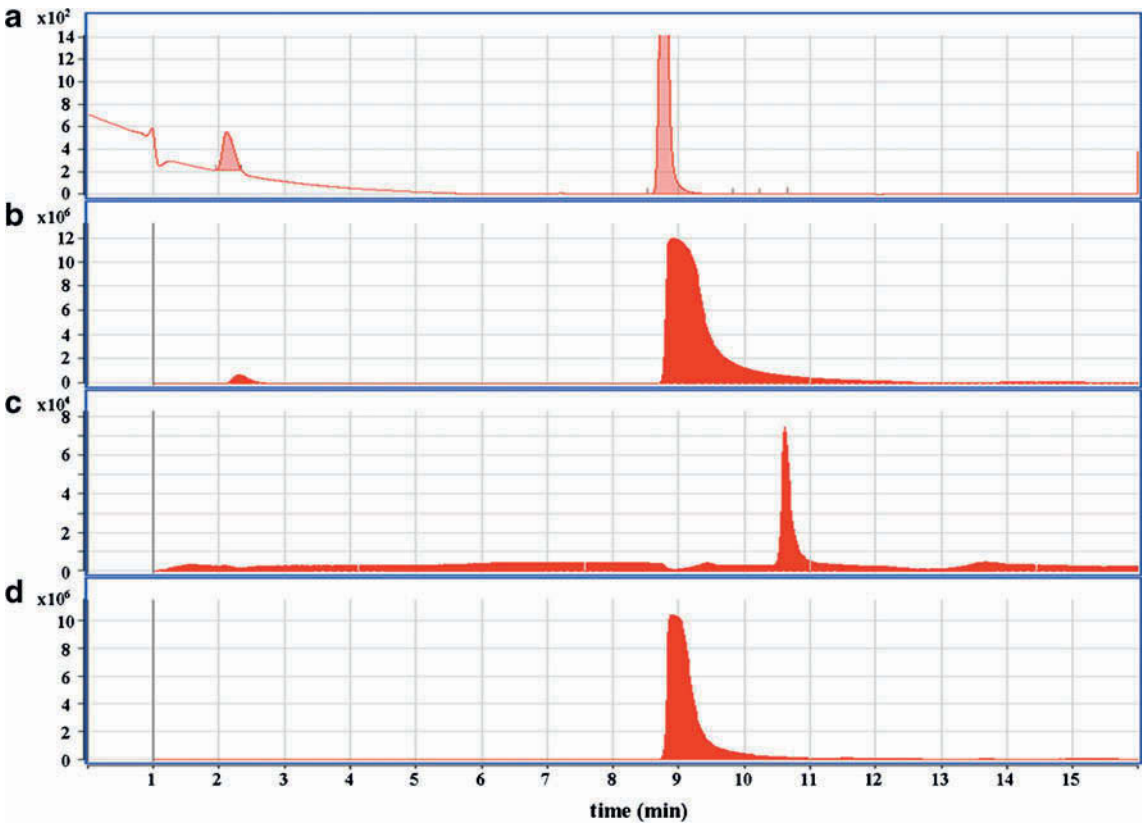

Fig. 2. Degradation under acid conditions. **a** UV and **b–d** SIM mode MS chromatograms observed following degradation of benzocaine under acid stress. The SIM MS chromatograms of **b** *p*-aminobenzoic acid, **c** *N*-formylbenzocaine, and **d** benzocaine are presented

stress, degradation products eluted at 7.9 and 10.2 min (Fig. 3a) with corresponding ions at m/z=181 and m/z= 194.3, respectively (Fig. 3b, d). It is clear from these results that the method can delineate between the parent compound and degradation products generated during acidic and oxidizing stress. Operating the LC-MS in the SIM mode further allowed us to match the retention data from UV/vis and mass spectra, which essentially gives us the molecular weight of the detected degradation product.

Effect of Different ODT Platforms on Benzocaine Stability

The stability of benzocaine in four commercially available ODT platforms for direct compression was investigated under ICH conditions (8): 25°C and 60% RH and 40°C and 75% RH, for up to 6 months. No degradation of benzocaine was observed in the tablets that were exposed to subtropical conditions (25°C and 60% RH) for the entire study period of 6 months (Table III). Under accelerated degradation conditions, benzocaine decomposition was identified in Prosolv®ODT tablets (Table III). A degradation product was detected in the liquid chromatogram at 9.4 min in addition to the benzocaine peak at 8.8 min (Fig. 4). The molecular formula of the degradation product was determined to be $C_{10}H_{11}NO_3$ from IT-TOF, which proposes *N*-formylbenzocaine as the major degradation product. The amount of degradant increased linear over time (Table III). In the forced degradation study, *N*-formylbenzocaine eluted at 10.2 min. This minor deviation in elution time might be explained by the absence of excipients in the forced degradation study and, hence, different column interactions or due to another product with the same molecular formula being present. In either case, it is clear that benzocaine is degrading in these formulations. Benzocaine degradation was dependent upon temperature and relative humidity, but the compression force did not affect drug stability (Table III).

Drug–excipient interactions or interactions between drug and reactive impurities in excipients lead to chemical or physical interactions that adversely affect the quality of the end product. *N*-formylbenzocaine (Fig. 1) is most likely formed in the tablets by the reaction with formic acid. Organic acids, such as formic acid, are common impurities in poly(ethylene glycol) (PEG), hydroxypropyl methylcellulose (HPMC), povidone, and polyvinyl alcohol (6,12). Often, excipients with formaldehyde impurities also contain some formic acid due to oxidation of formaldehyde to formic acid by atmospheric oxygen. Formaldehyde contaminations exist in microcrystalline cellulose (MCC), starch, pre-gelatinized starch, crospovidone, HPMC, PEG, and lactose (6). The PROSOLV®ODT platform contains silicified MCC and crospovidone (Table I) that could be potential sources of organic acid and aldehyde impurities. The formyl and acetyl species can cause degradation of amine drugs. Similar to our observation, degradation of the smoking cessation drug varenicline was observed in tablet formulations. *N*-Formylation and *N*-methylation of the secondary amine of varenicline was attributed to the

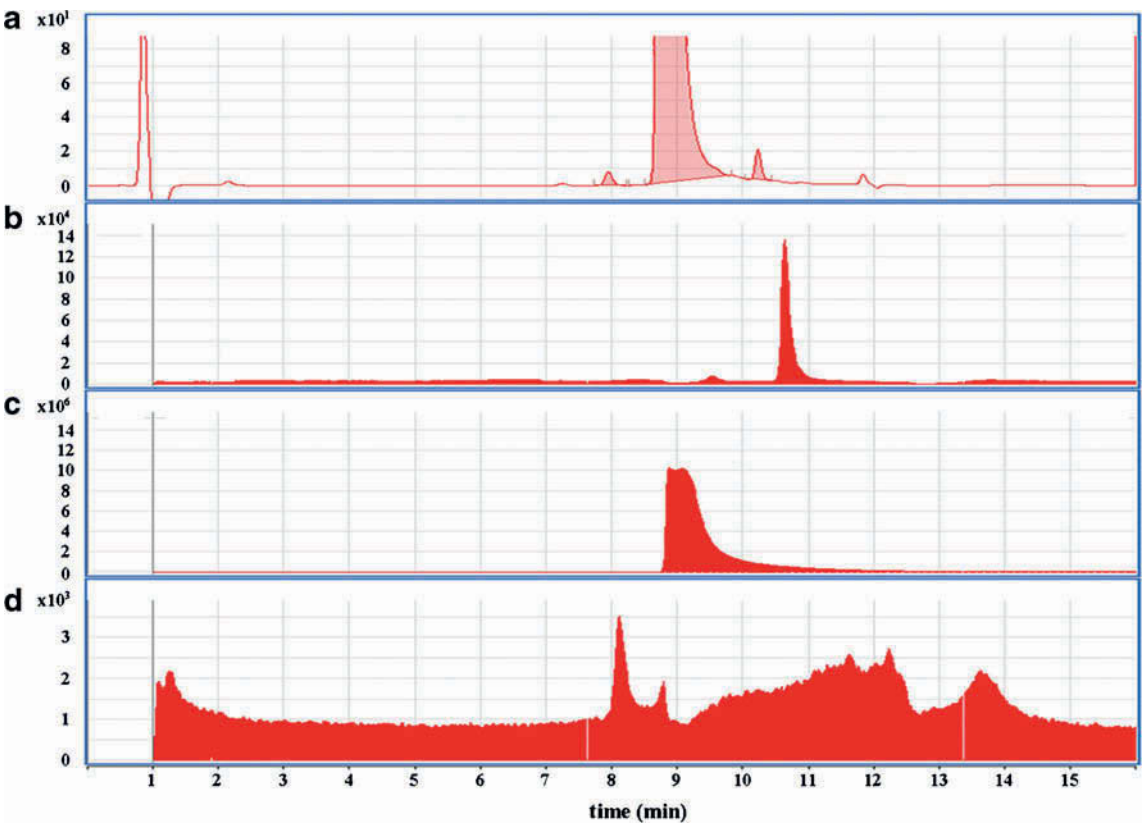

Fig. 3. Degradation under oxidative conditions. **a** UV and **b–d** SIM mode MS chromatograms observed following degradation of benzocaine under oxidative stress. The SIM MS chromatograms of **b** *N*-formylbenzocaine, **c** benzocaine, and **d** degradation product with m/z of 181 are presented

Table III. Amount of Degradation Product Within Tablets Stored Under Ambient and Accelerated Conditions. Only *N*-Formylbenzocaine Was Observed in Tablets. Values Are Presented as Mean±Standard Deviation (Three Independent Samples)

			N-Formylbenzocaine (%)[a]			
Time (days)	Condition	Properties	PEARLITOL®Flash	Ludiflash®	PROSOLV®ODT	F-Melt®
0		H, 100 N	ND	ND	ND	ND
		Fc, 20 kN	ND	ND	ND	ND
30	25°C/60%RH	H, 100 N	ND	ND	ND	ND
		Fc, 20 kN	ND	ND	ND	ND
	40°C/75%RH	H, 100 N	ND	ND	0.65±0.16	ND
		Fc, 20 kN	ND	ND	0.38±0.04	ND
60	25°C/60%RH	H, 100 N	ND	ND	ND	ND
		Fc, 20 kN	ND	ND	ND	ND
	40°C/75%RH	H, 100 N	ND	ND	1.00±0.14	ND
		Fc, 20 kN	ND	ND	1.07±0.13	ND
90	25°C/60%RH	H, 100 N	ND	ND	ND	ND
		Fc, 20 kN	ND	ND	ND	ND
	40°C/75%RH	H, 100 N	ND	ND	1.22±0.22	ND
		Fc, 20 kN	ND	ND	1.38±0.51	ND
120	25°C/60%RH	H, 100 N	ND	ND	ND	ND
		Fc, 20 kN	ND	ND	ND	ND
	40°C/75%RH	H, 100 N	ND	ND	2.35±0.56	ND
		Fc, 20 kN	ND	ND	2.09±0.63	ND
150	25°C/60%RH	H, 100 N	ND	ND	ND	ND
		Fc, 20 kN	ND	ND	ND	ND
	40°C/75%RH	H, 100 N	ND	ND	2.94±1.52	ND
		Fc, 20 kN	ND	ND	3.01±1.52	ND
180	25°C/60%RH	H, 100 N	ND	ND	ND	ND
		Fc, 20 kN	ND	ND	ND	ND
	40°C/75%RH	H, 100 N	ND	ND	3.15±1.96	ND
		Fc, 20 kN	ND	ND	2.82±1.69	ND

ND not detected, *H* hardness, *Fc* compression force, *RH* relative humidity
[a] The amount of degradant (in percent) was determined from the UV spectra as follows: $degradant(\%) = \frac{AUC_{N\text{-}formylbenzocaine}}{AUC_{benzocaine}} \times 100\%$

decomposition of PEG, a component of osmotic tablets, to formaldehyde and formic acid (13).

Benzocaine degradation was only observed under high relative humidity and temperature, indicating that the degradation may be related to the adsorbed water by the excipients of the formulation. When the relative humidity exceeds the excipient's critical relative humidity (CRH), it gains moisture from that environment. The CRH of fructose, a component of the PROSOLV®ODT platform, is 64% when stored at 40°C and was thus surpassed under accelerated conditions (14). The observed degradation may be due to migration of the impurities present at high humidity conditions. This is supported for both conditions when the gross morphology of the tablets is considered.

Physical Appearance of Tablets

Although degradation of benzocaine was only detected in one platform, the physical appearance of the tablets varied greatly between the different ODT platforms, especially under accelerated conditions (Fig. 5). Mannitol, the main component of the platforms, is not hygroscopic and does not absorb water even under accelerated conditions. The disintegrants are proposed to cause the tablet's shape changes due to their propensity to absorb water. Tablets made with PEARLITOL® Flash, Ludiflash®, and F-Melt® maintained a shiny and relatively smooth surface for the entire study period of 6 months under subtropical conditions (25°C/ 60% RH) that exist in the USA, Japan, and Southern Europe. However, after storage under accelerated degradation conditions (40°C/75% RH) for 6 months, tablets containing PROSOLV®ODT and F-Melt® were esthetically unacceptable. We did not, however, examine the physical appearance of the different formulations in the absence of the API. It is, therefore, possible that the diminished appearance of the tablets occurs without the presence of the API. It is, therefore, not possible to draw a causal relationship between the browning of the tablets and degradation of the API. However, even if the two events are mutually exclusive, they suggest that the Prosolv®ODT platform is not appropriate for the given API.

The diameter of F-Melt® tablets increased 2 and 1 mm for tablets that were compressed to a hardness of 100 N or at a compression force of 20 kN, respectively, after 6 months under accelerated conditions (Table IV). PROSOLV®ODT and F-Melt® contain crospovidone that acts as a tablet disintegrant and swells upon contact with water. Benzocaine degradation detected in PROSOLV®ODT and swelling of tablets containing F-Melt® might also partially be attributed to the increased water uptake by crospovidone under the humid conditions. Aspirin degradation has been shown to be accelerated by the adsorbed water from urea and povidone in the respective formulation (15).

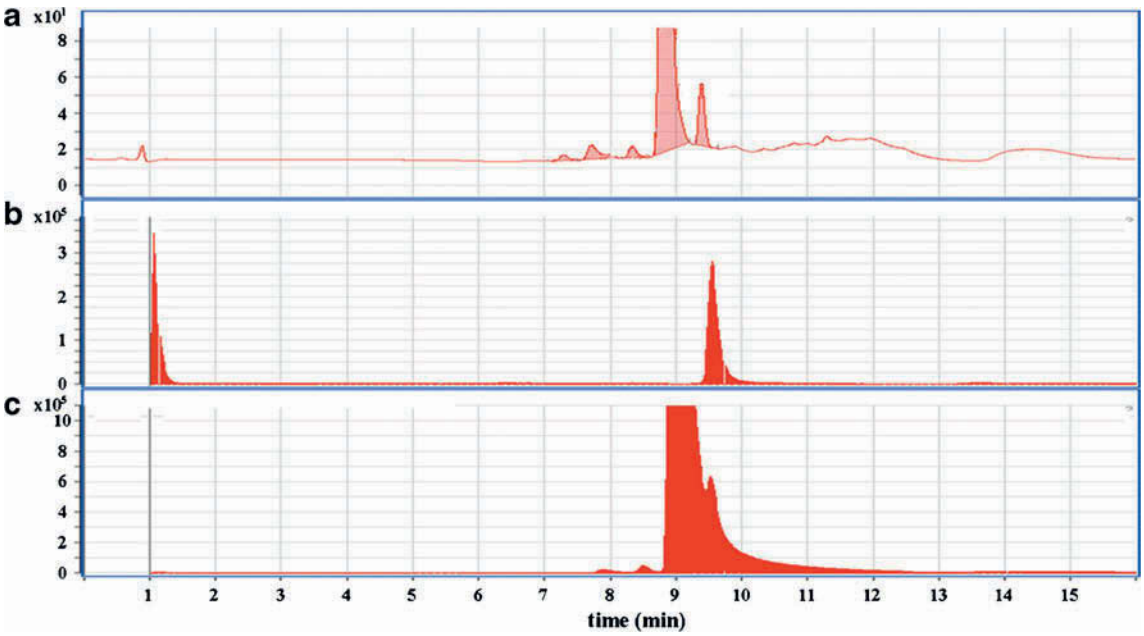

Fig. 4. Degradation products in platform P3. Representative **a** UV spectrum and **b**–**c** SIM chromatograms of benzocaine degradation in tablets prepared with PROSOLV® ODT. The SIM MS chromatograms of **b** *N*-formylbenzocaine and **c** benzocaine are presented

Regardless of the compression condition, tablets with PROSOLV® ODT changed shape and turned yellow at 40°C and 75% RH. The discoloration of the tablets is indicative of the Maillard reaction that can occur between

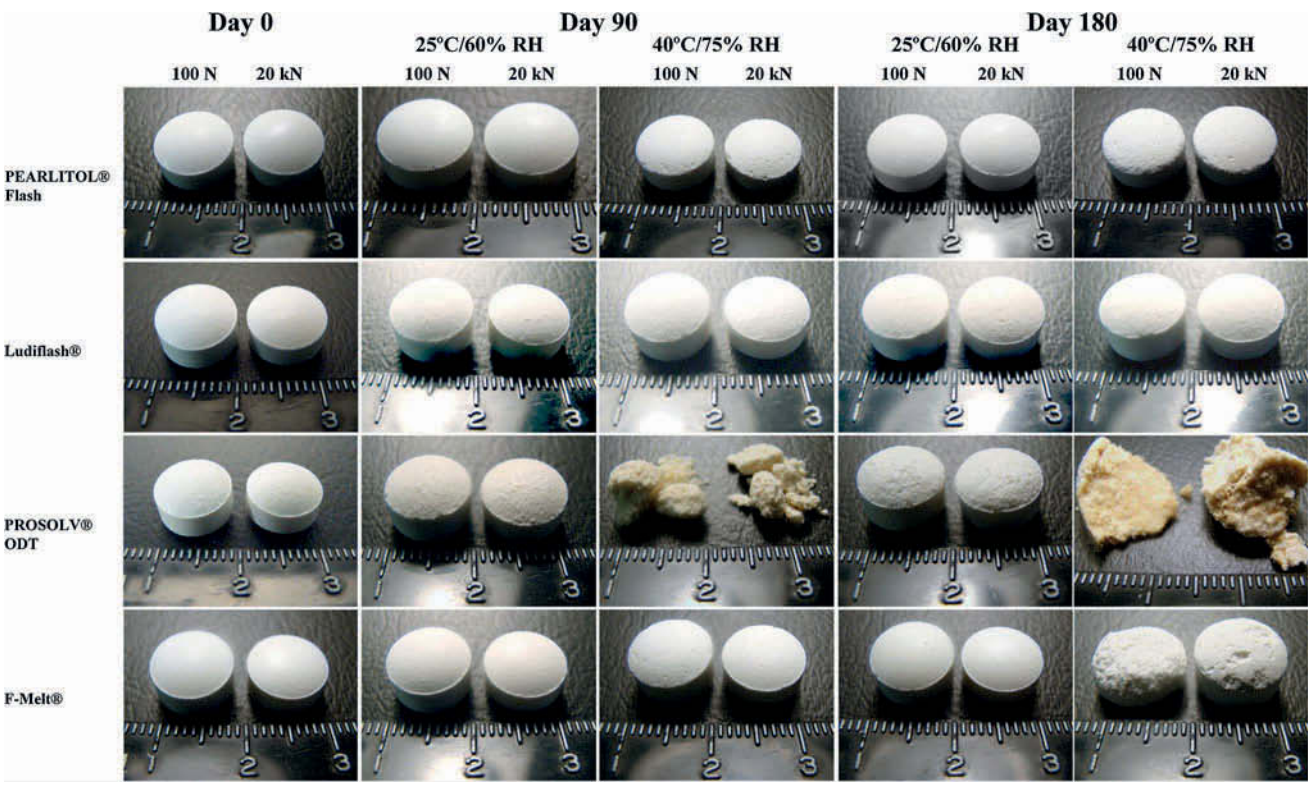

Fig. 5. Tablet size, shape, and color. Representative photographs of the benzocaine tablets at days 0, 90, and 180 under storage (25°C/60% RH) and accelerated conditions (40°C/75% RH)

Table IV. Diameter of Tablets (in Millimeter)

Time (day)	Storage	Compression	Diameter (mm) Platform			
			PEARLITOL® Flash	Ludiflash®	PROSOLV® ODT	F-Melt®
0	N/A	H, 100 N	10.09	10.34	10.24	10.14
		Fc, 20 kN	10.07	10.22	10.18	10.08
90	25°C/60% RH	H, 100 N	10.09	10.35	10.46	10.14
		Fc, 20 kN	10.07	10.22	10.45	10.08
	40°C/75% RH	H, 100 N	10.15	10.37	N/A	10.34
		Fc, 20 kN	10.14	10.28	N/A	10.23
180	25°C/60% RH	H, 100 N	10.09	10.35	10.89	10.14
		Fc, 20 kN	10.09	10.22	10.75	10.08
	40°C/75% RH	H, 100 N	10.40	10.46	N/A	12.05
		Fc, 20 kN	10.36	10.41	N/A	11.13

H hardness, *Fc* compression force, *RH* relative humidity

fructose and the primary amino group of benzocaine. Drug molecules with primary or secondary amine groups readily react with reducing sugars (16). Benzocaine may also be unstable in the presence of other reducing sugars such as glucose or lactose. The browning of vigabatrin tablets was associated with the incompatibility of the primary amine drug and a glucose impurity from MCC (17). Excipients such as MCC, starch, mannitol, and sucrose may also contain low levels of reducing sugars (6).

CONCLUSIONS

Benzocaine, a primary amine containing API, was stable in tablets that were stored at 25°C and 60% RH for the entire study period of 6 months. Degradation of benzocaine in PROSOLV®ODT tablets, which contained silicified microcrystalline cellulose, mannitol, fructose, and crospovidone, was observed under high temperature and humidity conditions (40°C and 75% RH). It is clear that ODT excipient mixtures play a significant role in the success of these formulations. When chosen wrongly, the excipient can lead to compromised stability of the API and reduced shelf life of the end product. Considering the excipient as a potential source of reactive impurities and understanding its impact on the active ingredient are essential in designing new formulations. We tested four direct compression platforms that all contained at least two different excipients. Although the excipient manufacturer strives to keep impurities low, it is also the responsibility of the user to understand the incompatibility potential between an excipient or its residues and the API, especially in those multicomponent materials. Impurities that may be problematic for a particular drug molecule might not affect other drugs. The type of dosage form (liquid or solid) and environmental factors such as temperature, humidity, and pH will affect the molecular mobility of reactive species and will thus also influence drug stability. Except PROSOLV®ODT, all the other platforms (PEARLITOL® Flash, Ludiflash®, and F-Melt®) showed chemical inertness towards benzocaine. Combining the chemical stability and physical appearance, PEARLITOL® Flash and Ludiflash® appear to have superior properties while F-Melt® was not pharmaceutically elegant and PROSOLV®ODT was an unacceptable platform for benzocaine.

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