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Comparative analysis of mechanical and dissolution properties of single- and multicomponent folic acid supplements

Jelena Đuriš[a,*], Bojan Čalija[a], Bojana Vidović[b], Vladimir Dobričić[c], Jela Milić[a], Svetlana Ibrić[a]

[a] Department of Pharmaceutical Technology and Cosmetology, University of Belgrade—Faculty of Pharmacy, Vojvode Stepe 450, 11221 Belgrade, Serbia
[b] Department of Bromatology, University of Belgrade—Faculty of Pharmacy, Vojvode Stepe 450, 11221 Belgrade, Serbia
[c] Department of Pharmaceutical Chemistry, University of Belgrade—Faculty of Pharmacy, Vojvode Stepe 450, 11221 Belgrade, Serbia

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ABSTRACT

Previous reports revealed several concerns related to the quality of marketed folic acid dietary supplements with potential influence on their efficacy, such as underdosages of the folic acid content, complexity of composition and the failure to meet the disintegration and/or dissolution requirements.

This study was aimed to compare various marketed folic acid supplements, formulated as single- or multicomponent products, by testing their weight variation, friability, hardness, disintegration and dissolution properties according to the compendial requirements; accompanied with the investigation of influence of composition on the dosage form properties.

The obtained results revealed significant differences in mechanical and dissolution properties between the tested supplements, especially between the single- and multicomponent products, where most of the multicomponent products failed to meet the compendial requirements for either dissolution or disintegration. These findings indicate the need for harmonized and strict regulatory requirements for the quality of multicomponent dietary supplements.

1. Introduction

Folic acid is a synthetic form of vitamin B9 used in dietary supplements and processed food. Intake of folic acid during pregnancy significantly reduces the risk of *spina bifida* or other neural tube defects (Milunsky et al., 1989). At least 85% of folic acid is estimated to be bioavailable from processed food or dietary supplements, whereas only about 50% of folate naturally present in food is bioavailable (Dietary Supplement Fact Sheet, 2016). Women of populations in which adverse pregnancy outcomes are prevalent often consume diets low in vitamins and minerals, including folate (Scholl and Johnson, 2000). Folic acid is available in multivitamins and prenatal vitamins, in supplements containing other B-complex vitamins and/or minerals, and as a single supplement (with the folic acid content ranging from 200 to 600 μg, and most frequently being 400 μg) (Dietary Supplement Fact Sheet, 2016). These products come in the common solid dosage forms, such as tablets and capsules.

Requirements for quality of dietary supplements are still not harmonized worldwide, making it possible to have products on the market which do not contain sufficient amounts of the active ingredient(s) or those active ingredient(s) are not released appropriately from the dosage form, with the possible absence of the expected outcome. Quality control for multivitamin and multimineral dietary supplements may include determination of sources and contents of formulated vitamins and minerals, as well as testing of properties related to the dosage form, such as hardness, friability, disintegration, dissolution, *etc*. United States Pharmacopoeia (USP 39–NF 34) has included chapters ⟨2040⟩ and ⟨2091⟩ on testing of disintegration and dissolution, and weight variation of dietary supplements, respectively (USP 39-NF 34, 2016). Since dietary supplements are formulated and manufactured using the same technology as drugs, *in vitro* dissolution requirement, as a surrogate for *in vivo* absorption, is considered appropriate for oral solid dosage forms of multivitamin and multimineral products (Srinivasan, 2001). A mandatory

* Corresponding author.
E-mail address: jelena.djuris@pharmacy.bg.ac.rs (J. Đuriš).

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dissolution requirement has been set by the USP for folic acid present in multivitamin-mineral combination products (Srinivasan, 2001).

According to the literature data, over- and underdosages of vitamins and/or minerals content in dietary supplements on the United States and Canadian markets have been reported (Yetley, 2007). Typically, folic acid overdosages range from 10 to 40% (Sarheed et al., 2015), whereby inclusion of overdosages may serve to overcome issues related to poor dissolution and/or stability of folic acid. In addition, failure of the folic acid dietary supplements to meet the disintegration or dissolution requirements has been reported (Stout et al., 1996; Hoag et al., 1996; Giebe and Counts, 2000; Sculthorpe et al., 2001; Younis et al., 2009). Folic acid absorption is maximal at the proximal jejunum and poor in the distal jejunum (Younis et al., 2009), so the slow and incomplete disintegration of the supplements along with slow dissolution of folic acid may cause low bioavailability.

Folic acid shows an increase in solubility with rise in pH, from 8.8 μg/ml (at pH 1.2) to 4.3 mg/ml (at pH 6.8), at 37 °C (Bellavinha et al., 2015). According to the equation for the Dose Number (Do)

Table 1
Composition and dosage forms of investigated folic acid dietary supplements.

code	single-or multi-component	active(s)	declared folic acid content (μg)	dosage form	excipients	country of origin
SC1	single component	**folic acid**	400	hard capsules	maltodextrin	Serbia
SC2		**folic acid**	400	uncoated tablets	dicalcium phosphate, microcrystalline cellulose, stearic acid, silica dioxide, cellulose gum	USA
SC3		**folic acid**	400	uncoated tablets	dicalcium phosphate, cellulose, stearic acid	USA
SC4		**folic acid**	400	uncoated tablets	cellulose, dicalcium phosphate, modified cellulose gum, magnesium stearate	Canada
SC5		**folic acid**	400	film tablets	maize starch, microcrystalline cellulose, croscarmellose sodium, talc, silica dioxide, hypromellose, magnesium stearate, macrogol 400, colors: titanium dioxide, riboflavin, cochineal	Serbia
SC6		**folic acid**	400	film tablets	lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, talc, yellow iron oxide, titanium dioxide	Macedonia
SC7		**folic acid**	400	film tablets	microcrystalline cellulose, calcium hydrogen phosphate anhydrous, pregelatinized starch, croscarmellose sodium, magnesium stearate	Serbia
MC1	multi-component	**folic acid**,vitamin B1, vitamin B2, vitamin B6, vitamin B12, zinc, selenium	400	uncoated tablets	lactose monohydrate, maize starch, stearic acid, polyethylene glycol 4000	Serbia
MC2		beer yeast, **folic acid**, vitamin B6	200	uncoated tablets	maize starch, microcrystalline cellulose, silica dioxide, magnesium stearate, cacao powder, flavorings	Serbia
MC3		**folic acid**, vitamin B12	400	uncoated tablets	maize starch, microcrystalline cellulose, magnesium stearate, colloidal silica dioxide, sorbitol, flavorings	Serbia
MC4		vitamin D3, vitamin E, vitamin B1, vitamin B2, vitamin B6, niacin, **folic acid**, pantothenic acid, biotin, vitamin B12, vitamin A, vitamin C, calcium, zinc, copper, iodine, iron, manganese, selenium, chromium, molybdenum	400	film tablets	microcrystalline cellulose, acacia gum, croscarmellose, hypromellose, polydextrose, triglyceride, magnesium oxide; talc; magnesium stearate; silica dioxide; titanium dioxide, iron-oxide, red	Germany
MC5		vitamin A, vitamin D3, vitamin E, vitamin B1, vitamin B2, niacin, vitamin B6, pantothenic acid, vitamin B12, **folic acid**, biotin, vitamin C, calcium, iron, selenium, zinc, copper, manganese, iodine	400	film tablets	magnesium oxide, sodium starch glycolate, crosslinked carboxymethylcellulose, magnesium stearate, polyvinylpyrrolidone, shellac, talc, hydroxypropylcellulose, hypromellose, colors: cochineal, titanium dioxide, iron oxides	Serbia
MC6		beta-carotene, vitamin B1, vitamin B2, vitamin B3, vitamin B5, vitamin B6, vitamin B12, **folic acid** vitamin C, vitamin D3, vitamin E, biotin, iron, magnesium, manganese, zinc, copper, iodine, selenium chrome, molybdenum, *Lactobacillus rhamnosus*,*Zingiber officinale*	400	film tablets	microcrystalline cellulose, calcium phosphate; magnesium oxide, hypromellose; polyvinylpyrrolidone, ethylcellulose, magnesium stearate, silica dioxide, stearic acid, titanium dioxide, carmine indigo, iron-oxide	Belgium
MC7		vitamin E, vitamin C, pantothenic acid, vitamin B1, vitamin B2, niacin, vitamin B6, **folic acid**, biotin, vitamin B12, calcium, magnesium, iron, zinc, manganese, copper, chrome, iodine, selenium, molybdenum	400	film tablets	calcium phosphate, microcrystalline cellulose, hypromellose, maltodextrin, polyethylene glycol, magnesium stearate, silica dioxide, stearic acid, titanium dioxide, red iron oxide	Poland
MC8		calcium, vitamin C, niacin, vitamin E, zinc, iron, pantothenic acid, vitamin B6, vitamin B1, vitamin B2, copper, **folic acid,** selenium, biotin, vitamin D, vitamin B12	600	film tablets	microcrystalline cellulose, magnesium stearate, silica dioxide, stearic acid, hypromellose, titanium dioxide, red iron oxide	Italy
MC9		vitamin D, vitamin E, vitamin C, vitamin B1, vitamin B2, vitamin B3, vitamin B6, **folic acid**, vitamin B12, biotin, pantothenic acid, vitamin K, natural mixture of carotenoids, iron, magnesium, zinc, iodine, copper, selenium	400	film tablets	microcrystalline cellulose, hypromellose, magnesium oxide, dibasic calcium phosphate, hydroxypropylcellulose, titanium dioxide, iron-oxide, stearic acid, magnesium stearate, silica dioxide, crosslinked sodium, carmellose	United Kingdom
MC10		omega-3 fatty acids, **folic acid**, vitamin E, vitamin D3, iodine	400	soft capsules	fish oil, fish gelatin, rape oil, glycerol, soy lecithin, silica dioxide	Monaco