Commerically available folic acid supplements and their compliance with the British Pharmacopoeia test for dissolution

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Summary
A recent report suggested that some folic acid preparations available in the United States failed to meet the specifications for dissolution specified by the US Pharmacopoeia (USP), of 70 per cent drug release in the first hour of testing. The Teratology Society recommends that women of child-bearing age should take a daily supplement of 400 μg folic acid when they are trying to conceive, to reduce the risk of foetal neural tube defects. The consequence of this failure to meet the USP requirements may be that an inadequate dose of folate may be absorbed and thus the expected level of protection against neural tube defects not afforded. The purpose of the present study was to examine a number of brands of folic acid (400 μg), available commercially in the United Kingdom, for compliance with the British Pharmacopoeia (BP) test for dissolution. Ten tablets (or capsules) from each of 11 brands were tested using dissolution apparatus compliant with BP requirements, using 0.1 M sodium hydroxide as the dissolution medium. The results indicated that four of the brands failed to release 70 per cent of the nominal drug content in the first hour of test and thus did not comply with the test. Two of the seven brands that passed the test went on to release more than 150 per cent of the nominal 400 μg drug content. These results highlight the problems of dose uniformity and the potential health risks of slow dissolution and under-dosing in commercially available folic acid dosage forms.

Keywords: folic acid, neural tube defects, dissolusive properties

Introduction
It has been reported that a daily supplement of 400 μg of folic acid can reduce the incidence of neural tube defect (NTD) affected births by 75 per cent. The mechanism by which folic acid provides protection from NTD is thought to involve enhanced methyl group donation, as the principal function of the folate coenzymes is the transfer of single carbon atoms. This also means it is vital for the metabolism of the endotoxic amino-acid homocysteine, a strong risk factor for coronary heart disease (CHD). For this reason, population-wide increases in folate intake have been suggested to reduce CHD.

The present study sought to investigate whether commercially available oral folic acid supplements available in the United Kingdom met the criteria of the British Pharmacopoeia (BP) test for dissolution. The requirements of this test are that for tablets and capsules the amount of active ingredient in solution should not be less than 70 per cent of the stated amount. Although it is recognized that none of the formulations under test were included in the BP and as such they do not have to comply with its requirements, the BP test is considered the gold standard, and achieving the parameters of the BP test indicates that a dosage form will release a suitable amount of active ingredient before the absorption window has been passed.

A single blind protocol was used. The products were purchased in Cardiff and tested in Liverpool. Personnel performing the dissolution test were not aware of the identity of the samples being tested.

Materials and methods
All tested brands had a labelled dose of 400 μg of folic acid and a sample of 10 tablets was randomly chosen from each packet.

A standard calibration curve of folic acid (Aldrich Chemical Company, USA, Lot 17028BK) in 0.1 M sodium hydroxide (BDH, UK, Lot 1546710L) was prepared to facilitate quantification of the amount of folic acid in solution. The dissolution apparatus (Model 7ST, G.B. Caleva, UK) used was compliant
with British Pharmacopoeia requirements and was used in accordance with stated guidelines. The absorbance of folic acid solutions was measured at 256 nm using a Philips PU 8625 UV–VIS spectrophotometer.

**Testing schedule**

One litre of the dissolution media was introduced into each dissolution flask and allowed to equilibrate to the test temperature (37°C). Samples were introduced into the dissolution flask and allowed to settle to the bottom (an inert wire collar was used to facilitate capsules sinking to the bottom). The apparatus was switched on so that the paddles rotated at 100 r.p.m. Aliquots (10 ml) of dissolution medium were removed (from each dissolution flask) immediately and then at 15 min intervals for up to 180 min. Samples of dissolution medium were filtered through a cellulose ester membrane filter (pore size 0.45 μm) immediately upon removal from the dissolution vessel and the absorbance of the filtrate at 256 nm was determined.

**Results**

Six of the 11 formulations tested (1, 3, 4, 8, 10 and 11) passed the BP test for dissolution; four failed (2, 5, 6 and 7) and another (formulation 9) was formulated with an excipient that interfered with the assay. Further testing revealed an average of 46 per cent of the labelled dose (46 ± 9 per cent). Formulations 1, 3, 4, 8 and 11 contained amounts of folic acid significantly in excess of the stated 400 μg. Formulations 2, 6, 7 and 9 contained amounts of folic acid significantly below the stated amount. Formulation 5 failed to disintegrate and release its active ingredient. Thus only one formulation (number 10) contained an amount of active ingredient within 10 per cent of that stated.

The dissolution profiles showing the mean solute concentration for each sample of tablets are shown in the Figure. The threshold line of 70 per cent (of 400 μg) dissolution is indicated. The figure graphically illustrates that the drug content of all except one (formulation 10) product fails to comply with the stated amount.

**Discussion**

The results of this study raise a number of concerns about medicaments sold as health supplements but not subject to the rigorous compendial requirements as ethical medicines. Six of the 11 samples passed the BP test for dissolution; however, five of those six contained amounts of folic acid significantly in excess of the stated amount.
excess of that stated (up to 250 per cent). Although there are no pathologies related to excess folic acid and toxicity is rare, excess folic acid may mask cobalamin deficiency and interfere with some drugs used to treat epilepsy.7

Four formulations failed the test, and four contained amounts of folic acid significantly below their stated dose. Sample 9 contained an agent that interfered with the assay, therefore only total folic acid was calculated, and was found to be on average 46 per cent of the stated dose (46 ± 9 per cent). This suggests that if the total content of sample 9 disintegrated before 1 h it would still not release 70 per cent of the labelled dose.

Carrying mediated membrane transport systems located in the first third of the small intestine (proximal jejunum) are responsible for the uptake of hydrophilic micronutrients such as folic acid. Any folic acid supplement that does not disintegrate and dissolve sufficiently before reaching the proximal jejunum will not present folic acid free for intestinal uptake. The BP guidelines state that 70 per cent of the total folic acid in any preparation should be available for uptake inside 1 h.

The Medical Research Council (MRC)1 advises a supplement of 400 μg of folic acid per day for prenatal and perinatal women to help reduce the risk of neural tube defects. It was because of these recommendations that preparations of 400 women to help reduce the risk of neural tube defects. It was Firth folic acid to fully reduce the risk of spina bifida and other NTDs.ment, certain women may not be receiving adequate amounts of folic acid. Any folic acid supplement that does not disintegrate and dissolve sufficiently before reaching the proximal jejunum will not present folic acid free for intestinal uptake. The BP guidelines state that 70 per cent of the total folic acid in any preparation should be available for uptake inside 1 h.

The Medical Research Council (MRC)1 advises a supplement of 400 μg of folic acid per day for prenatal and perinatal women to help reduce the risk of neural tube defects. It was because of these recommendations that preparations of 400 μg per tablet were used in this study. These results indicate that despite following MRC advice and taking a daily 400 μg supplement, certain women may not be receiving adequate amounts of folic acid to fully reduce the risk of spina bifida and other NTDs. Firth et al.5 reported that the average dietary folate intake in women of childbearing age is 288 ± 195 μg. If this is the case, then the large standard deviation means that some of the supplements tested would not bring the daily folate levels of women in the lower percentiles up to 400 μg/day. In addition, Brown et al.10 demonstrated that only a quarter of women of childbearing age had red blood cell folate levels high enough to reduce the risk of folate responsive NTDs, and one woman in eight had a negative folate balance. Boushey et al.11 emphasized the need for increased folic acid intake in the general population, possibly utilizing tablet supplementation, and more recently Abramsky et al.12 identified a lack of reduction of NTD-affected births over the last 10 years despite increases in public information. This, taken in conjunction with the present findings, suggests that manufacturers should be more aware of the dissolutive requirements of supplements, for maximum benefit to be maintained.

References

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