Folic Acid in Human Nutrition

- **Folic acid is a water soluble B vitamin widely distributed in foods. Deficiencies lead to impaired cell division and altered protein synthesis.**
- **Newborn children of women receiving adequate folic acid in their diet show a lower incidence of spina bifida and anencephaly, neural tube defects that affect 2,500 newborns annually.**
- **In 1992 the US Public Health Service recommended that women of child-bearing age consume 400mcg/day of folic acid.**
- **The FDA required folic acid fortification of breads and enriched cereal grain products beginning in January of 1998.**
- **The crystalline synthetic form of folic acid commonly found in dietary supplements is twice as bioavailable as natural folate found in leafy, dark green vegetables such as broccoli and spinach.**

History of USP Dissolution Standards

- **November 1992 – Preliminary nutritional monographs (disintegration requirement only).**
- **May 1993 – First dissolution standard established incorporating "index" vitamins and minerals. Reported as "% assay".**
- **January 1995 – Folic acid dissolution test added (when folate related neural tube defect claims are made). Reported as "% assay".**
- **May 1997 – Folic acid dissolution now reported as "% label".**
- **November 1998 – Folic acid dissolution testing required regardless of claims.**
- **January 2000 – All dissolution test reporting changed to "% label". Alternate 0.05M pH 6.0 citrate buffer media added due to difficulties with dissolution in water.**

The Problem – Folic Acid Dissolution

- **1997 – Hoag, et.al. reported on high USP dissolution failure rate of folic acid-containing prenatal products (J. Am. Pharm. Assoc. 1997)**
- **May 1998 – FDA courtesy letter to industry regarding potential for similar failures in dietary supplements.**
- **Possible causes elucidated**
  - **Particle size of folic acid raw material**
  - **Insufficient or non-uniform blending**
  - **Formulation issues (insoluble carriers)**
  - **Complexation with minerals (Fe^{+2}, Cu^{+2})**
  - **Test methodology issues – citrate buffer proposed**

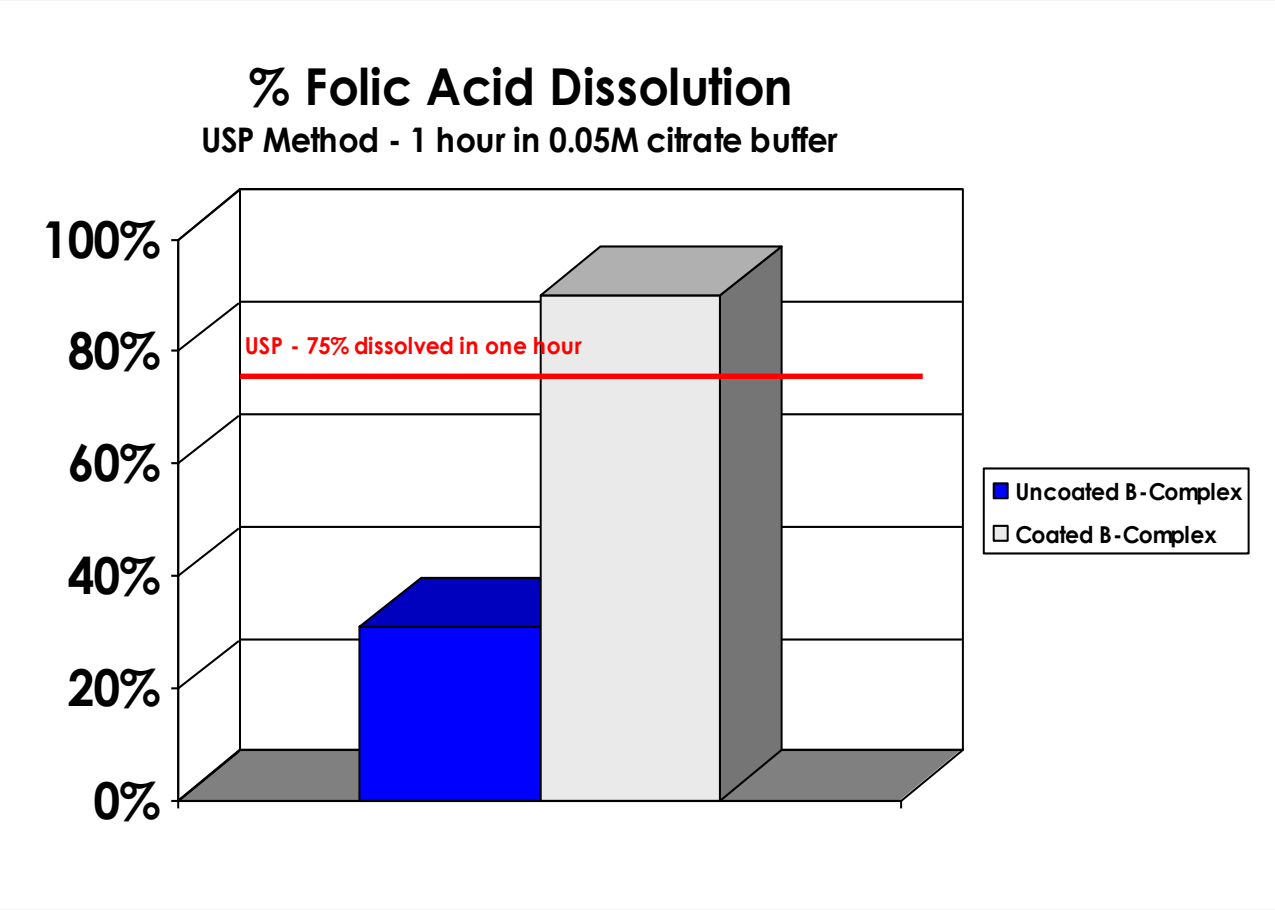
A Solution – Enhanced Bioavailability
Folic Acid Coating

- **Crystalline folic acid is dispersed in a water soluble film forming polymer, such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose, acrylic polymer or soluble starch.**
- **An appropriate plasticizer, such as glycerine, propylene glycol or hydroxylated soy lecithin is added.**
- **Optional coloring and/or flavoring agents can be added.**
- **The resulting dispersion is applied utilizing conventional aqueous film coating techniques to tablet cores containing the remaining dietary ingredients (vitamins, minerals, botanicals, amino acids, etc.).**
- **Added benefits include taste masking and ease of swallowing.**
- **Excellent process and product stability.**
- **Patent pending.**

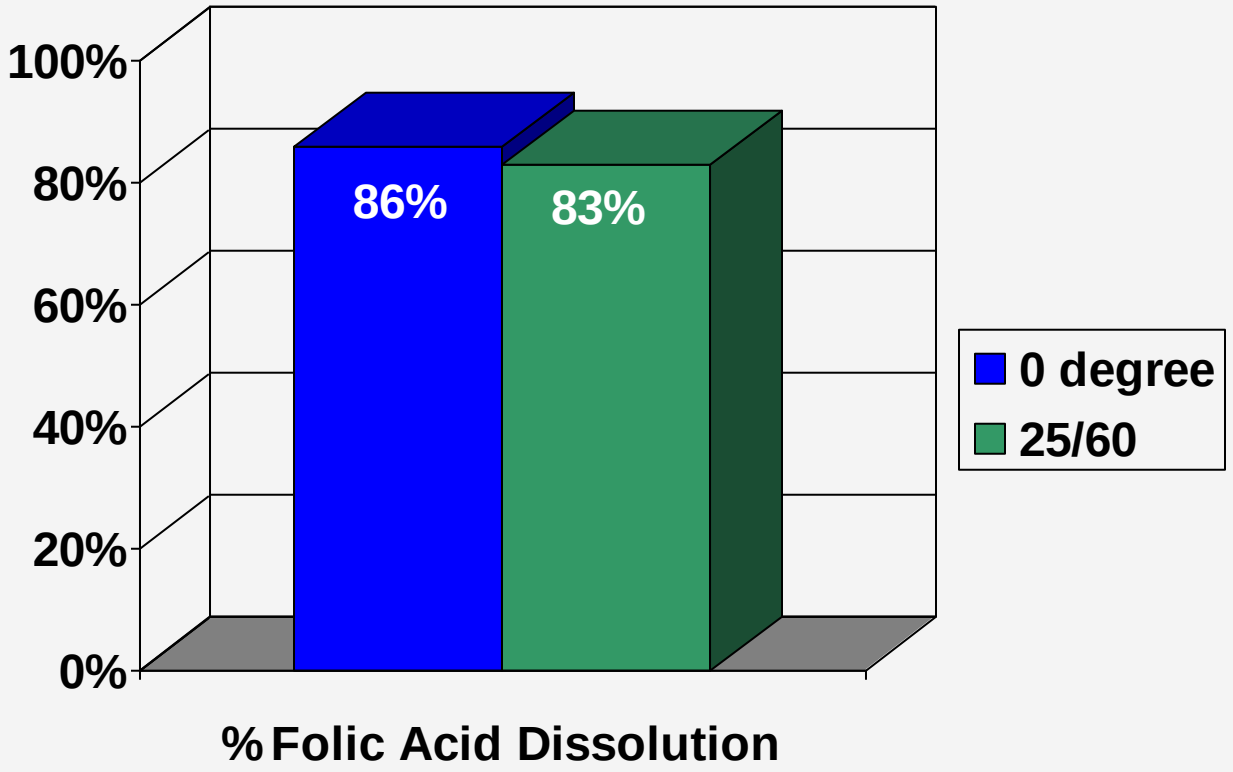
Analytical Determination of Folic Acid

- **Standard USP dissolution apparatus (75 RPM paddle speed, shielded from light due to folic acid light instability)**
- **Dissolution media: Water or 0.05M citrate buffer at 37°C. .**
- **A total of 6 tablets are tested. Withdraw solution aliquots after 60 minutes and pool samples. Filter pooled sample.**
- **Inject filtered sample in reverse-phase C18 HPLC**

Folic acid dissolution – Uncoated vs. Coated B-Complex tablets



12 Month Ambient Stability Data (25°C/60% RH)



Conclusion

- **Coating multivitamin or multivitamin-multimineral tablets with a folic acid coating offers a simple way of enhancing folic acid dissolution performance and improving bioavailability.**
- **Process is simple, cost effective and stable.**
- **Performance may vary depending on each particular formulation.**

Enhancement of Folic Acid Dissolution in Solid Dosage Forms of Dietary Supplements

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