

Preparation and Quality Evaluation of Ferrous Fumarate and Folic Acid Oral Dispersible Tablets

Lei LUO ^{1#}, Qi CHEN ^{# 2}, Yonghuang LUO ^{2*} & Nadia BOURKAIB ³

¹ *Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, UK*

² *College of Pharmaceutical Sciences, Southwest University, Chongqing, 400715, China*

³ *Department of Pharmaceutics, China Pharmaceutical University, Nanjing 210009, China*

SUMMARY. The aim of this study was to develop a method for the preparation of ferrous fumarate and folic acid oral dispersible tablets and their quality evaluation through HPLC and spectrophotometry. The formulation was optimized with dissolubility and dispersed uniformity as reference parameters by single-factor and orthogonal experiments. The results exhibited that the optimal formulation contained: 182 mg ferrous fumarate, 0.4 mg folic acid, 101 mg microcrystalline cellulose, 27 mg crosslinking polyvinylpyrrolidone, 5 mg sodium dodecyl sulfate, 13.5 mg 2% povidone-K₃₀, 3.4 mg micronized silica gel, 1.7 mg magnesium stearate, and 3.4 mg steviosin with exterior and interior addition. The disintegration time was approximately 50 s or less, and more than 80% of folic acid and ferrous fumarate were dissolved within 10 min. Consequently, the formulation design is reasonable; the process of preparation is feasible.

INTRODUCTION

Folic acid (also known as vitamin Bc or folacin), is the water-soluble form of vitamin B9. It is essential to numerous bodily functions. The human body needs folate to synthesize DNA, repair DNA, and methylate DNA. In addition, it acts as a cofactor in biological reactions ^{1,2}. It was found that folic acid plays a role in preventing and treating certain anemias, particularly during pregnancy ³. High folate intake during pregnancy is now strongly recommended because of its essential role in brain development. Multiple clinical trials have shown that folate supplementation can markedly reduce the occurrence of spina bifida and anencephaly in babies, as well as helping prevent many other birth defects ⁴⁻⁶. In addition, menstruation bleeding (classics bleeding preceding conception) causes iron deficiency during pregnancy. If the intake of iron is insufficient, it will be easy for pregnant woman's iron deficiency anemia to occur ⁷⁻¹¹. It appears important and urgent for pregnant women to replenish iron and folate si-

multaneously to prevent iron deficiency anemia (IDA), megaloblastic anemia (MGA) and neural tube defect ¹².

Oral dispersible tablets when placed in the oral cavity rapidly dissolve or disintegrate without water and therefore are a valuable tool to treat patients, which have problems taking normal tablets ¹³. The tablets can be taken without or with a small amount of water. They disintegrate fast in the mouth. They are also a good choice for medicines, which have to be taken when people are, for example, travelling and water for swallowing a normal tablet is not available ¹⁴.

Our group prepared a new formulation which combines the ferrous fumarate and folic acid in dispersible tablets, for treating anemia. The patents for the ferrous fumarate and folic acid dispersible tablets have been issued in China with patent number, ZL 2009 10191130.7 ¹⁵. In this preparation, the ratio of ferrous fumarate and folic acid (150:1) is recommended by the World Health Organization ¹⁶.

KEY WORDS: Dispersible tablets, Ferrous fumarate, Folic acid, Formulation, Quality evaluation.

* Author to whom correspondence should be addressed. *E-mail:* luoyonghuang@126.com

These authors contributed equally to this work.

MATERIALS AND METHODS

Equipment

Jingtian Electronic Analytical Balance FA2004A (Electric Instrument Co., Ltd. Shanghai, China); TDP-5 single-punch tablet press (Taizhou Aurora Medicinal Machinery Co. Ltd, Jiangsu, China); RCZ-6B2 Drug dissolution instrument, CJY-300B Tablets friability Tester, YPD-200C Hardness Tester (Huanghai Medicine Checking Instrument Co. Ltd, Shanghai, China).

Chromatographic analysis was performed by using a Elite HPLC system (Elite Analytical Instruments Co. Ltd, Dalian, China) ,which consisted of a P200 pump, a 6-way valve sampler (GJ605), a chromatogram workstation (WDL-85), and an UV200 detector. A Shim-pack VP-ODS C₁₈ (250 × 4.6 mm, 5 μm) column was used.

Materials and reagents

Folic acid reference standard (91.1 % purity, Lot 100074-200913) was obtained from National Institute for Food and Drug Control (China). Ferrous fumarate was purchased from Anji Hoosun Pharmaceutical Co., Ltd., Zhejiang, China. Folic acid was obtained from Hebei Jiheng Pharmaceutical Co., Ltd. Hebei, China). Microcrystalline Cellulose (MCC) and sodium dodecyl sulfate (SLS) were obtained from Shanhe Medicinal Auxiliary Materials Co., Ltd (Anhui, China). Mannitol was purchased from Guangzhou Tianguan Food Additive Co., Ltd (China), L-HPC, lactose, o-phenanthroline, povidone K₃₀, magnesium stearate, micronized silica gel steviosin, and crosslinking polyvinylpyrrolidone (PVPP) were obtained from Xi'an Huian Cellulose Chemical Industries Co., Ltd. (China), Changzhou LangSheng biological engineering Co., Ltd. (China), Shanghai YongYe Biological Engineering Co., Ltd. (China), Nanhang Pharmaceutical, Hainan (China), Ehua Pharmaceutical Co., Ltd., Shandong (China), Joinway Pharmaceutical Co., Ltd., Zhejiang (China), and Tianan Stevia Products Co., Ltd. (China), respectively.

Dosage of ferrous fumarate and folic acid

In this preparation, the used ratio of ferrous fumarate and folic acid (150:1) was the same as recommended by the World Health Organization. The dosage of ferrous fumarate was 182 mg and the dosage of folic acid was 0.4 mg in each tablet.

Disintegration

According to the disintegration test method described in BP 2009¹⁷, one tablet was put in a beaker containing 200 mL of water R at 15-25

°C; numerous bubbles of gas were evolved. When the evolution of gas around the tablet or its fragments ceases the tablet has disintegrated, being either dissolved or dispersed in the water so that no agglomerates of particles remain. The operation was repeated on five other tablets. The tablets comply with the test if each of the 6 tablets used disintegrates in the manner described above within 3 min. Moreover fineness of dispersion should be also evaluated. In addition, two tablets were placed in 100 mL of water R and stirred until completely dispersed. A smooth dispersion was produced, then passed through a sieve screen with a nominal mesh aperture of 710 μm.

Dissolution Method

Dissolution of FA was conducted using CH.P2010 (Vol II, Method 3, small glass method) apparatus at a speed of 75 rpm 18. The diluent (pH 7.2), 0.2 mol/L potassium dihydrogen phosphate buffer was used at a volume of 200 mL and maintained at 37 ± 0.5 °C. Two mL of the dissolution media were collected at 5, 10, 15, 20, 30, and 45 min, respectively and then quickly filtered through 0.45 μm membrane. 2 mL of fresh media at the same temperature were added to the basket after the withdrawal of each sample simultaneously. Finally, 20 μl of filtrate was injected into the column, the content of folic acid was detected according to the method of HPLC described by Chen *et al.*¹⁹.

After that, *in vitro* dissolution tests of ferrous fumarate we carried out using CH.P 2010 (Vol II, method 1, rotating basket method) apparatus speed was set at 75 rpm²⁰. The diluent (pH 1.2), 0.1 mol/L hydrochloric acid was used at a volume of 900 mL and maintained at 37 ± 0.5 °C. Two mL of the dissolution media were collected at 5, 10, 15, 20, 30, and 45 min, respectively and then quickly filtered through 0.45 μm membrane. Finally, the content of ferrous fumarate was measured based on the method described in CH.P 2010 (Appendix IV A, UV spectrophotometry) through the reaction between o-phenanthroline and ferrous ion²¹.

Single-factor test

According to the basic formulation of the tablets, 182 mg ferrous fumarate, 0.4nmg folic acid, 125 mg filling agent, 28 mg disintegrant, 8 mg surfactant, 4 mg lubricants and appropriate povidone K₃₀ were mixed. The appearance, disintegration, dissolution and the suspensibility were investigated.

On the basis of the preliminary experiment,

the bulking agent which accounted for 25% of the total tablet, was sieved from MCC, mannitol and lactose with disintegration time and homogeneity for target. PVPP, CCNa and L-HPC were tested to screen the most suitable disintegrants for the formulation. The results showed that tablets fully disintegrated within 40 sec when PVPP was used, as shown in Table 1. For further studies, three methods including exterior addition, interior addition, exterior and interior addition, were all investigated for dissolution. According to the above prescription, starch, HPMC, PVP-K₃₀ were evaluated taking the hardness and the disintegrating time of tablet as indices.

Orthogonal test

According to the single factor test results, the content of MCC (A), PVPP (B), SLS (C) and PVP-K₃₀ (D) were selected as the four factors. Every factor had three levels, which as follows A(%): 25.30.35; B(%): 5,8,11; C(%): 0.5,1.0,1.5; D (%):2,4,6. The formula and preparation technology of dispersible tablets were optimized in terms of disintegration time, dispersible uniformity and the surface finish by orthogonal experiment L9 (3⁴).

Formulation and production technology of ferrous fumarate and folic acid dispersible tablets

The optimal formulation contained: 182 mg ferrous fumarate, 0.4 mg folic acid, 101 mg MCC, 27 mg PVPP, 5 mg SLS, 13.5 mg2% PVP-K₃₀, 3.4 mg micronized silica gel, 1.7 mg magnesium stearate, and 3.4 mg steviosin.

Three batches (20111207, 20111209 and 20111214) of dispersible tablets were prepared with the wet granulation techniques. The manufacturing process was as follows: Both main drug and excipients were micronized and then sifted through a #100 mesh sieve. The main drug, MCC, 2/3 PVPP, SLS and micronized silica gel were added gradually with equal quantity and well mixed to obtain a powder mixture.

Then appropriate amount of 2% ethanol was slowly added to form a wet mass through #24 mesh sieve. The wet mass was dried at 50°C for about 1h and then passed through #24 mesh

sieve again. Lastly, the dried granules were blended with magnesium stearate, steviosin and the remaining PVPP, and compressed to form tablets having an average weight of 338 mg using the tableting machine.

RESULTS

Comparison of dissolution

The common tablets were made by our group, which contained the same content of FA and ferrous fumarate. Also they were qualified by the method of HPLC and UV. The dissolution of dispersible tablets and common tablets were compared via the same paddle method. As shown in Fig. 1, within the first 10 min, ODTs accumulated dissolution percent of ferrous fumarate was more than 90% and FA exceeded 78%, while the accumulated dissolution percents of common tablets of FA and ferrous fumarate were only 44.1 and 54.3%, respectively. Therefore, ferrous fumarate and folic acid dispersible tablets was a rapid-release solid preparation.

Single-factor test

From the results in Tables 2 and 3, a preliminary formulation was prepared, which consisted of the main drug, MCC, PVPP, PVP-K₃₀, SLS, steviosin, micronized silica gel, magnesium stearate and so on. Furthermore, exterior and interior addition was determined to be the way to add disintegrants.

Orthogonal test

With orthogonal design and extreme difference analysis method, the influence of the four following factors on the tablets: amount of PVPP, concentration of PVP-K₃₀, amount of MCC and SLS and through comprehensive analysis, the optimal prescription of the dispersible tablets was determined as follows: A2B2C3D1, which means that the content of PVCC was 8%, MCC was 30%, SLS was 1.5%, and the concentration of PVP-K₃₀ was 2%.

Quality Evaluation

The preliminary assessment of the appearance, tablet weight variation (TWV) of the dispersible tablets were conducted under the demand of Appendix IA of CH.P2010 (Vol II) ²².

Disintegrants	PVPP	L-HPC	CCNa
Disintegration time (s)	25 ± 5	167 ± 6	50 ± 5
Dispersible uniformity	Qualified	Unqualified	Qualified

Table 1. Effects of different disintegrants on disintegration time and dispersible uniformity.

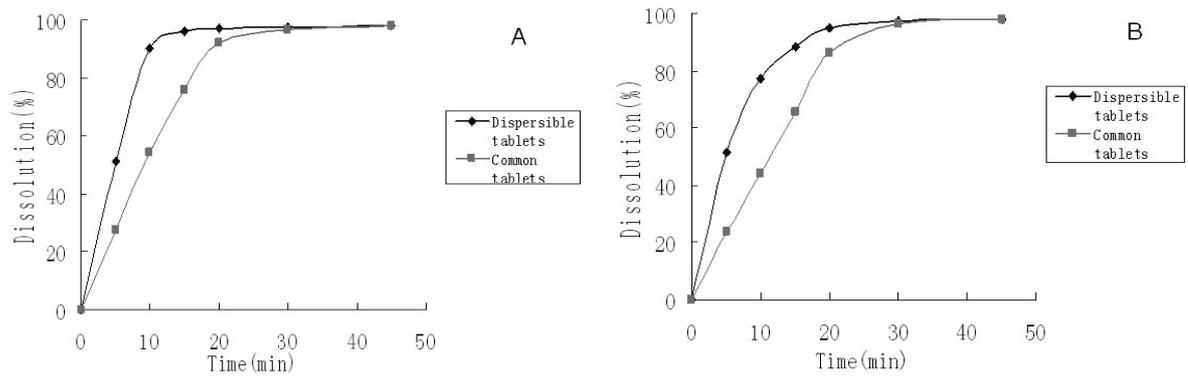


Figure 1. Dissolution curves of dispersible tablets and common tablets. **A.** Folic acid, **B.** Ferrous fumarate.

Bulking agents	MCC	lactose	mannitol
Disintegration time (s)	46 ± 3	99 ± 5	142 ± 8
Dispersible uniformity	Qualified	Qualified	Qualified

Table 2. Effects of different bulking agents on disintegration time and dispersible uniformity.

Bonding agents	starch slurry	HPMC	PVP-K30
DT(s)	163 ± 8	158 ± 7	55 ± 4
Friability	Qualified	Unqualified	Qualified

Table 3. Effects of different bonding agents on disintegration time and friability.

Levels	Factors			
	A(MCC)	B(PVPP)	C(SLS)	D(PVP-K30)
1	25%	5%	0.50%	2%
2	30%	8%	1.00%	4%
3	35%	11%	1.50%	6%

Table 4. Factors and levels of orthogonal test.

Disintegrating time (DT) was analyzed according to the requirements in BP 2009¹⁷. Dissolution was carried out with the method described by the reference. The mobile phase consisted of phosphate buffer (containing 0.05 mol/L potassium dihydrogen phosphate and 0.1 mol/L potassium hydroxide) and methanol (80:20, v/v), the pH was adjusted to 6.3. The flow rate was 1.0 mL/min and the injection volume was 20 µl. The column temperature was maintained at 30 °C and the detection wavelength was fixed at 277 nm. Besides, the mobile phase was degassed and filtered through 0.22 µm membrane filter prior to use. The results are shown in Table 4. They all fit the demands of SFDA.

DISCUSSION

For ease of molding and unit-dose, both water-soluble bulking agents such as lactose, mannitol, sucrose and insoluble ones like compressible starch, calcium sulfate, MCC can be chosen to increase the weight and volume of tablets. Different bulking agents have a significant impact on disintegration time and dispersed uniformity. As a naturally occurring substance, Microcrystalline Cellulose chosen in this experiment has proven to be stable, safe and physiologically inert. It revolutionized tableting because of its unique compressibility and carrying capacity. It compacts well under minimum compression pressures, has high binding capability, and creates tablets that are extremely hard, stable, but yet disintegrate rapidly. Other advantages include low friability, inherent lubricity, and the highest dilution potential of all binders²³⁻²⁶.

Types and properties of disintegrants are one of the key factors that affect the quality of dispersible tablets. PVPP was able to absorb water into tablets because of its high capillary activity. The tablet almost disintegrates instantly due to the internal pressure (swelling pressure) went

over its own strength²⁷. In addition, folded molecular chain in the cross-links extended to separate when water or aqueous solutions came in suddenly²⁸. The results of expansion consisted in the increase of volume (approximately two times larger in 5 min), which was corroborated by the tablets including PVPP that immediately collapsed. For ensuring the property of PVPP, exterior and interior addition was chosen after carefully sifting three adding methods. Hence, this method not only ensures rapidly disintegrating, but also is in favor of further dispersion.

PVP-K₃₀ was a kind of hydrophilic binding agents, which increased compressibility and hydrophilicity of tablets at the same time. Both ferrous fumarate and folic acid were poorly soluble in water. Using PVP-K₃₀ was conducive for main drug to dissolve out.

In wet granulation, granules are formed by the addition of a granulation liquid onto a powder bed which is under the influence of an impeller. When PVPP and a solvent/water are mixed with powders, PVPP forms a bond with the powders during the process, and the solvent/water dries. Once the solvent/water has been dried and the powders have formed a more densely held mass, then the granulation is milled. This process results in the formation of granules. Wet granulation has many advantages over the traditional way, such as beautiful appearance, good flowability of powders and good property.

CONCLUSION

In this research, the preparation techniques and the formula of Ferrous Fumarate and Folic Acid Dispersible Tablets were optimized, with an in-vitro disintegration time of approximately 50 s. We have also demonstrated that these dispersible tablets released more rapidly and completely than common ones.

Acknowledgements. This project was supported and funded by Science and Technology Research Project of Chongqing (CSTC2012gg-yyjs80005), Science and Technology Innovative Capacity construction Program of Chongqing (CSTC, 2009CB1010), Chongqing Engineering Research Center for Pharmaceutical Process and Quality Control.

REFERENCES

- Kim, Y.I. (2004) *Environ. Mol. Mutagen.* **44**: 10-25.
- Harris, H.R, D.W Cramer, A.F Vitonis, M. De-
pari & K.L. Terry (2012) *Int. J. Cancer* **131**:
E518-29.
- Ayfer, A., N. Yusuf, A. Murat & N. Yasemin
(2010) *Afr. J. Biotechnol.* **34**: 5605-10.
- Czeizel, A.E.(2004) *Int. J. Med. Sci.* **1**: 50-61.
- Czeizel, A.E. (1995) *J. Pediatr. Gastroenterol.
Nutr.* **2**: 4-16.
- Wilson, R.D., Davies G., Desileta V., G.J. Reid,
A. Summers, P. Wyatt, *et al.* (2003) *J. Obstet.
Gynaecol. Can.* **25**: 959-73.
- Ece, A., B.S. Uyanik, A. Iscan, P. Ertan & M.R.
Yigitoglu (2006) *Biol. Trace Elem. Res.* **12**: 31-
9.
- Beard, J. & R. Stoltzfus (2000) *Belmont Conf.
Nutr.* **131**: 563-701.
- Arnold, D.L., Williams M.A., Miller R.S., C. Qiu
& T.K. Sorensen (2009) *J. Obstet. Gynaecol.
Res.* **35**: 446-52.
- Mukhopadhyay, A., N. Bhatla, A. Kriplani,
R.M. Pandey & R. Saxena (2004) *J. Obstet. Gy-
naecol. Res.* **30**: 409-17.
- Friel, J.K., K. Aziz, W.L. Andrews, S.V. Hard-
ing, M.L. Courage & R.J. Adams (2003) *J. Pedi-
atr.* **143**: 582-6.
- Ma, A.G., E.G. Schouten, F.Z. Zhang, F.J. Kok,
F. Yang, D.C. Jiang, *et al* (2008) *J. Nutr.* **138**:
1946-50.
- Charoo, N.A., A.A.A. Shamsher, A.S. Zidan &
Z. Rahman (2012) *Int. J. Pharm.* **423**: 167-78
- Kasliwal, N., J.S. Negi, V. Jugran & R. Jain
(2011) *Arch. Pharm. Res.* **34**: 1691-700.
- Luo, Y.H. (2009) *China: ZL 2009 10191130.7*.
- WHO/UNCIF/UNU (2001) World Health Orga-
nization Geneva, (WHO/NHD01.3).
- British Pharmacopoeia (2009) The British Phar-
macopoeia Commission. BP 2009. *Dispersible
tablets [S]*. ISBN 978 0 11 322799 0. London:
The Stationery Office Vol III:6583.
- Chinese Pharmacopoeia (2010). Appendix X C.
p. 87.
- Chinese Pharmacopoeia (2010) Appendix X C.
p. 86.
- Chinese Pharmacopoeia (2010) Appendix IV
A. p. 23
- Chinese Pharmacopoeia (2010) Appendix IA. p. 5.
- Chen, Q., Y.L. Liu, Y.H. Luo, Y. Luo & L.Y.
Luo (2012) *Lat. Am. J. Pharm.* **31**: 555-60.
- Holman, L. & T. Trenktrog (2011) *Dispersible
bosentan tablet [P]*. Official Gazette of the
United States Patent and Trademark Office
Patents.
- Zhao, P., L.L. Li, X.Y. Yang & H.S. Jiao (2010)
J. Chin. Med. Mater. **33**: 988-90.
- Liu, C.Z., X.G. Liu, J.M. Tong, D.W. Chen &
K.S. Bi (2009) *Pharm. Dev. Technol.* **14**: 506-15.
- Wu, Z.F., W. He & Y Li. (2008) *Journal Chin.
Med. Mater.* **31**: 1557-9.
- Sun, G.N. & Q. Ren (2008) *China Pharm.* **19**:
2458-60.
- Guo, S.R. (1999) *China Pharm. J.* **34**: 384-6.