Influence of different formulations and granulation techniques on dissolution of folic acid in film coated tablets

Ljiljana Krsteska*, Dejan Kostovski, Ksenija Brzilova, Suzan M.Sejfulah, Sonja Ugarkovic

*Research and Development, ALKALOID AD, Aleksandar Makedonski 12,
1000 Skopje, Republic of Macedonia*

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Abstract

The vitamin folic acid has received considerable attention because of its role in decreasing risk of neural tube birth defects, and its potential role in reducing risks of cardiovascular and psychiatric diseases. We evaluated compositions of 5 different formulations in terms of meeting the USP standard for dissolution and disintegration. However all the examined formulations had met the disintegration test but only 3 formulations had met the dissolution requirements to release 75 % of the active ingredient in 45 minutes. The maximum value of dissolution of 97.52 % in S5 composition was achieved by combination of certain excipients (combination of hydrophilic and hydrophobic filler and suitable wetting agent) and wet high shear mixing granulation technique, resulting with optimized release of the active substance.

Key words: solubility, dissolution, tablets, vitamins, folic acid.

Introduction

Folic acid is a B complex vitamin, used for prevention and treatment of vitamin B deficiency, and it can be isolated from green leafy vegetables, liver, yeast and fruits. Synthetic folic acid is also commercially available. According to the European Pharmacopoeia, the substance is characterized as yellowish or orange crystalline powder, practically insoluble in water and in most organic solvents, but it dissolves in dilute acids and in alkaline solutions. Folic acid obtained from preparations is more bioavailable than dietary folate, since up to half of dietary folate is lost in the cooking process and requires hydrolysis for absorption (Suitor and Bailey, 2000). The failure of folic acid supplements to meet several pharmacopoeial requirements for disintegration has been reported earlier (Stout et al., 1996). Monograph for folic acid tablets in the current edition of US Pharmacopoeia (The United States Pharmacopoeia Con-

vention, 2010) declare that not less than 75 % of the labeled amount should be released and dissolved in the time period of 45 minutes.

Because of the historical experience of certain folic acid tablet failures and current demands of the US Pharmacopoeia, as well as because retaining the policy of quality and safety of the products, the development of future vitamin formulation should be made in a systematic way.

During the development of a medical product a dissolution test is used as a tool to identify formulation factors that influence on the dissolution rates of the active substance and may have a crucial effect on the bioavailability of the drug. As soon as composition and the manufacturing process is defined dissolution test is used in quality control of scale up and of production batches to ensure both batch-batch-consistency in certain instances a dissolution test can be used to waive a bioequivalence study (EMA, 2006). The aim of this study was to develop Folic acid film-coated tablets formulation that will release not less than 90 % of the labeled amount of folic acid into the dissolution media. For this purpose, several formulations with

* lkrstevska@alkaloid.com.mk

different excipients were evaluated, as well as two technological approaches of producing the tablets.

Materials and Methods

For the purpose of determining the optimal formulation, several combinations of fillers, disintegrants and binders were evaluated, as well as two preparing techniques wet granulation by high-shear mixer (HS) and dry mixing (DM) for direct compression were used. The complete overview can be seen in Table 2. Folic acid was obtained from manufacturer BASF GmbH Germany, Lactose monohydrate from Meggle, Wasserburg GmbH&Co, Microcrystalline cellulose from FMC Bio Polymer Wallingstown, Little Island Co Work, Ireland, Dicalcium phosphate from Budenheim, Germany, Silicon dioxide from Evonik Deggusa.

The particle size distribution of the active ingredient was measured on Morphologi - G3S, Malvern Instruments. The United States Pharmacopeial Convention, general chapter <776> optical microscopy. The dissolution test was performed according to dissolution method described in The United States Pharmacopeial Convention, general chapter <711> dissolution, using Apparatus II – paddle, paddle speed 50 rpm. Determination was made with HPLC system equipped with UV/VIS detector. Dissolution specification was NLT 75 % (Q) of released and dissolved Folic acid for time period of 45 min.

Desintegration of film-coated tablets was performed on Erweka desintegration tester type ZT 302. The disintegration test was performed according to disintegration method described in The United States Pharmacopeial Convention, general chapter <701> disintegration. Bulk and tapped density, compressibility index of granulates and mixtures for direct compression were tested on Tapped volumeter SVM100. The United States Pharmacopeial Convention, general chapter <616> bulk density and tapped density of

powders. Loss on drying (LOD) of granulates and mixtures for direct compression were tested on Mettler Toledo HG 63. The disintegration test was performed according to disintegration method described in The United States Pharmacopeial Convention, general chapter <731> loss on drying. Different formulations of tablet cores were produced on a rotary tablet press, with punch diameter of 7 mm and average mass of 110 mg. Tablet cores were coated in a conventional coating pan with PVA (Polyvinyl Acetate) based film coating until total mass of 115 mg was gained.

Results and discussion

API characterization

The particle size distribution of API plays important role in the dissolution rate of tablets. When API is insoluble, micronized active ingredient is a rational approach in the formulation (Amiji and Sandman, 2003). The particle size distribution of folic acid has D[0.9] below 50 μm , which complies micronized compounds.

The particle size distribution of Folic acid is presented in Table 1 and Fig. 1.

Table 1. Particle size analysis of folic acid from manufacturer BASF GmbH

FOLIC ACID / manufacturer BASF GmbH / Batch. No.HMNB913		
Sieve size	Results	
10 μm <	2.0 %	
20 μm <	34.7 %	
30 μm <	98.0 %	
D [0.9]	D [0.2]	D [0.1]
98.0	34.7	2.0

Fig. 1. Graphical presentation of the particle size distribution of the analyzed sample from manufacturer BASF GMBH.

Determination of physical parameters of granulates of different formulations (S1-S5)

All process control parameters bulk and tapped density, compressibility index, flow ability and LOD for all examined formulations were within prescribed range of the United States Pharmacopeial Convention., 2010 (Table 2) confirming the physical preferences of the granulates. Results from process control parameters carried out on the fine blends of examined formulations are displayed in Table 2.

Disintegration

When the tablet disintegrates it is broken down into small particles, which offers a greater surface area to the

dissolving media resulting in improvement of the dissolution rate of the drug. However, disintegration test offer no assurance that formulation will release the drug, even in the form of small particles, since a drug must normally be in solution before absorption can take place. Results from process control parameter of disintegration time carried out on the film coated tablets of examined formulations has been tested on each five examined composition and are displayed in Table 3.

All the tested products met European Pharmacopoeia requirements for disintegration time (Table 3). The longer disintegration time of formulation S2 can be explained with the addition of dicalcium phosphate, water insoluble filler. The rest of the formulations disintegrated in not more than 3 min.

Table 2. Process control of examined compositions

Parameters	Bulk density (g/ml)	Tapped density (g/ml)	Index of compressibility (%)	Flowability (s/100g)	LOD (%)
Formulation					
S1	0.500	0.617	18.96	9.8	1.97
S2	0.442	0.549	19.48	11.5	3.10
S3	0.515	0.602	14.45	11.9	2.65
S4	0.388	0.481	19.33	10.9	2.49
S5	0.543	0.658	17.48	11.9	3.30

Table 3. Process control of disintegration time of film coated tablets

Disintegration time (sec.)	Formulation				
	S1	S2	S3	S4	S5
	180	360	150	145	160

Table 4. Composition of examined formulations

Excipient	Formulation				
	S1	S2	S3	S4	S5
Folic acid	x	x	x	x	x
Lactose monohydrate	x		x	x	x
Microcrystalline cellulose	x	x	x	x	x
Dicalcium phosphate		x			
Silicon dioxide	x				
Sodium lauryl sulphate		x	x		x
Disintegration agent		x	x	x	x
Binder agent		x	x	x	x
Lubricant	x	x	x	x	x
Film coat /mg/	x	x	x	x	x
Total mass /mg/	115	115	115	115	115
Preparing technique	dry mixing	dry mixing	dry mixing	wet granulation	wet granulation

Dissolution

Orally administered tablets have their drugs dissolved in the gastrointestinal tract fluids before the absorption can occur. Often, the drug absorption rate is determined by the drug dissolution from the tablets (The United States Pharmacopeia Convention., 2010) Therefore the dissolution rate had shown influenced to the efficacy of the tablet products so it's bioavailability at all (EMA, 2006).

The most direct assessment of the drug's release would be *in vivo* bioavailability tests. However, there are several reasons that restrict the use of *in vivo* studies: length of time required, low precision of the measurements, correlation with the diseased state might have to be made with healthy human subjects or with animals, est. Because of above mentioned facts *in vitro* studies were used in this research.

The composition of five different formulations, using various fillers and excipients, applied in different ratios and prepared by two different technological procedures are presented in Table 4.

Dissolution rate of five different formulations are presented in Table 5 and Fig 2.

All the tested products didn't met requirements of Folic acid dissolution rate. The dissolution range was 47.50 – 99.87 %. It is obvious that partial solubility was obtained in compositions of formulation S1 and S2. In formulation S1, a combination of hydrophilic and hydrophobic filler was used prepared by dry mixing. However, the dissolution rate did not fulfill the requirements. In order to improve the dissolution rate, another filler (dicalcium phosphate) in combination with wetting agent, prepared by same technolog-

Table 5. Dissolution rate (%) of folic acid (in single entity folic acid film-coated tablets) in distillated water

		Formulation				
No.		S1	S2	S3	S4	S5
Percent released in 45 min of single six tablets						
1.		51.84	68.18	84.49	92.31	99.84
2.		60.35	76.90	84.28	94.57	97.54
3.		59.49	77.72	86.77	93.56	95.30
4.		51.18	65.14	88.16	92.55	96.90
5.		53.70	75.82	84.31	93.13	97.20
6.		47.46	53.18	84.24	87.92	98.30
Decsriptive statistics						
n = 6	Min.	47.46	53.08	84.24	87.92	95.30
	Max.	60.35	77.72	88.06	94.57	99.84
	Average	53.97	67.56	85.55	92.06	97.52
	STDEV	5.111	10.175	1.650	2.514	1.647

Fig. 2. Dissolution rate of folic acid in film-coated tablets in examined compositions

ical procedure as in case of S1 formulation was used. This approach did not turn satisfying results, again (Table 5). Therefore in formulation S3, dry mixing was used in combination with fillers (the same from formulation S1) and wetting agent (the same from formulation S2). It is obvious that the chosen combination was plausible in terms increasing the dissolution rate (Table 5). In formulation S4 and S5 dry mixing has been changed by wet high shear mixing technique and at least 90% dissolution was achieved (The United States Pharmacopeial Convention, 2010). The obtained dissolution rates of both formulations were within prescribed specification. The only difference between the formulations S4 and S5 is the percentage ratio of chosen combination of fillers. In S4 formulation hydrophilic/hydrophobic filler ratio was 1:1, while S5 formulation the same ratio was set to 2:1. The differences in the formulations are correlating with the observed differences in the dissolution rate of the active substance (Table 2, Fig. 2)

Conclusion

Poor dissolution of commercially available folic acid preparations in simulated gastric fluids could significantly affect product efficacy. In order to increase the dissolution rate several compositions of formulations by two granulation techniques were examined. The optimal formulation which released average of 97.52% of active substance was formulated by combination of hydrophilic and hydrophobic filler in ratio 2:1 and addition of 1.0 % (w/w) wetting agent by wet high shear mixing.

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Резиме

Влијание на различни формулации и техники на гранулација на растворливост на Фолна киселина во Фолна киселина филм обложени таблети

Љиљана Крстеска*, Дејан Костовски, Ксенија Брзилова, Сузан М. Сејфулах, Соња Угарковиќ

Развој и истражување, Алкалоид АД, Александар Македонски 12, 1000 Скопје

Клучни зборови: растворливост, таблети, витамини, фолна киселина

Витамин фолна киселина има добиено значително внимание поради улогата во намалување на ризикот од дефекти на невралната туба кај новороденчиња, и потенцијална улога во намалувањето на ризикот од кардиоваскуларни и психијатриски болести. Ние истражувавме композиции од 5 различни формулации во однос на исполнувањето на USP стандарди за хемискиот параметар растворливост и физициот параметар распадливост на активна компонента. Сите испитани формулации одговараат на пропишаната спецификација на тестот за распаѓање, но само 3 формулации одговараат на спецификационите барања за растворливост т.е. ослободување на 75% од активната компонента за 45 минути. Максималната вредност на раствориливост од 97,52% во формулацијата C5, беше постигната со комбинација на одредени експииенси (комбинација на хидрофилен и хидрофобен наполнител и соодветно квасечко средство) и техника на влажна гранулација со мешалка со голема брзина, што резултира со оптимално ослободување на активната супстанца.