

Formulation of ferrous fumarate (combination) tablets by using a direct-compression method

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Abstract

Ferrous fumarate has poor flow properties which cause compression problems. When ferrous fumarate is manufactured in combination with folic acid, the same problem is encountered. Therefore, a wet-granulation method is used for tablet manufacturing, which is a time-consuming and energy-wasting process compared to a direct-compression method. In the present work, ferrous fumarate and folic acid (combination) tablets have been prepared using an optimized direct-compression technique that decreases the total manufacturing time of a batch (approx. 1.5 million tablets) from 24-28 h to only 2-3 h. The direct-compression technique is a simple and cost-effective method of manufacturing ferrous fumarate and folic acid (combination) tablets. Several formulations were developed using different proportions of avicel PH102, talcum, magnesium stearate, sodium lauryl sulfate, sugar, primojel, lactose, PVPK-30 and aerosil. Ten formulations were found to fulfill the specified criteria.

Keywords: Ferrous fumarate, folic acid, tablets, direct compression, combination.

Introduction

In most developing countries, the prevalence of malnutrition and micronutrient deficiencies is high among infants and young children aged 6 to 23 months (UNICEF, 2003). As they grow older, the energy and nutrient contribution from complementary food becomes increasingly important for meeting daily requirements (WHO, 1998; Gibson *et al.*, 1998; Nestel *et al.*, 2003). If daily food is not meeting the whole requirements then supplements should be taken to avoid deficiencies, which may cause diseases. Iron is one of the essential metals required by the body. We normally get iron from nutritious foods. In contrast, folic acid supplementation is required to reduce the risk of neural tube defects (MRC, 1991; Czeizel & Dudas, 1992; Daly *et al.*, 1995). Furthermore, emerging evidence suggests that folic acid-containing supplements are associated with reducing the risk of malformations and certain paediatric cancers (Botto *et al.*, 2004; Bailey & Berry, 2005; Goh *et al.*, 2006; 2007; Nguyen *et al.*, 2008). Ferrous fumarate and folic acid (combination) tablets are used to treat anaemia that is caused by an iron deficiency.

Ferrous fumarate has an iron content of 32.87% and is poorly soluble in water, soluble in dilute acid (such as gastric acid) and is well absorbed as ferrous sulphate (Hurrell *et al.*, 1989; 1991; 2000). In infants, iron absorption from ferrous fumarate is significantly higher than iron absorbed from ferric pyrophosphate (Davidsson *et al.*, 2000; Meredith *et al.*, 2003). According to the British pharmacopoeia, ferrous fumarate tablets have been manufactured alone or in combination with folic acid, usually ferrous fumarate 150-200 mg and folic acid

0.1-0.5 mg. The manufacturing methods used for tablet formulation (wet-granulation methods) are time consuming and multistep processes. However, the direct-compression method allows tablets to be compressed directly from mixtures of the drug and excipient without any preliminary treatment (British pharmacopoeia, 2004). A simple formula is composed of an active ingredient, diluent, binding agent and a lubricant (Martino *et al.*, 2004). A simple flow sheet diagram is shown in Fig. 1.

The direct-compression method has advantages over other manufacturing processes for tablets and provides high efficiency (Zhang *et al.*, 2003). Direct compression is simple and more economical by reducing the total time and manufacturing requirements. In contrast, wet granulation not only increases the cycle time but also has certain limits imposed by thermolability and moisture sensitivity of the active pharmaceutical ingredient(s). Therefore, the pharmaceutical industry is now focusing more on the direct-compression process (Beyer *et al.*, 2001; Yasmeen *et al.*, 2005). The unnecessary exposure of any drug to moisture and heat can never be justified (Shangraw, 1989). Tablets produced by the direct-compression method give lower microbial levels than those prepared by the wet-granulation method (Ibrahim & Olurinola, 1991).

Several formulations have been developed, including DC granules (Direct compression granules) of ferrous fumarate for the direct-compression method. DC granules have good compressibility characteristics because they are mixtures of ferrous fumarate with pre-gelatinised starch, gelatin and PVP or carboxymethyl cellulose; however, they are not pure ferrous fumarate according to

official monographs. Moreover, mixing problems with folic acid may arise due to the difference in particle size.

Materials and methods

Materials

Avicel PH 102 (Ming Tai- Taiwan), lactose (Fonterra Ltd Auckland-New Zealand), PVP K-30 (Shandong Dexiang-China), magnesium stearate (Peter Greven-Malaysia), aerosil (Degussa-Germany), Talcum (China),

Table 1. Percentage concentrations of variables for the selected trials.

Excipients	Level	
	Low	High
A ₁ = Amount of magnesium stearate	0.032	0.128
A ₂ = Amount of avicel PH 102	0.000	0.721
A ₃ = Amount of lactose	0.000	0.561
A ₄ = Amount of aerosil	0.000	0.064
A ₅ = Amount of sugar	0.000	0.401
A ₆ = Amount of PVP K-30	0.000	0.160
A ₇ = Amount of sodium lauryl sulphate	0.000	0.080
A ₈ = Amount of talcum	0.000	0.192
A ₉ = Amount of primojel	0.000	0.080

The amount of ferrous fumarate was fixed at 162 mg (equivalent to 150 mg of ferrous fumarate) and folic acid to 0.6 mg (equivalent to 0.5 mg of folic acid). The total amount of all excipients was fixed at 62.4 mg. $A_1+A_2+A_3+A_4+A_5+A_6+A_7+A_8+A_9 = 100\%$ of the formulation ($\Sigma A = 1$).

Table 2. Percent proportion of ingredients in the mixture of excipients.

Trial #	Magnesium Stearate	Avicel pH102	Lactose	Aerosil	Sugar	PVPk30	S.L.S	Talcum	Primojel
1	0.096	0.500	0.192	0.064	0.032	0.038	0.032	0.048	0.000
2	0.064	0.500	0.224	0.064	0.071	0.000	0.032	0.048	0.000
3	0.128	0.593	0.000	0.000	0.000	0.038	0.016	0.192	0.033
4	0.080	0.481	0.000	0.064	0.000	0.160	0.016	0.128	0.071
5	0.080	0.641	0.000	0.032	0.160	0.000	0.000	0.048	0.038
6	0.096	0.000	0.561	0.064	0.080	0.000	0.064	0.064	0.071
7	0.032	0.000	0.321	0.064	0.401	0.048	0.080	0.054	0.000
8	0.064	0.321	0.000	0.000	0.401	0.000	0.064	0.112	0.036
9	0.080	0.610	0.192	0.000	0.000	0.000	0.038	0.000	0.080
10	0.064	0.721	0.000	0.000	0.000	0.000	0.032	0.183	0.000

The amount of ferrous fumarate was fixed at 162 mg (equivalent to 150 mg of ferrous fumarate), and the amount of folic acid was set to 0.6 mg (equivalent to 0.5 mg of folic acid) to adjust the assay limits to 100 % of both the active pharmaceutical ingredients.

sodium lauryl sulphate (Stepan, Philippines), sugar (Pakistan), sodium starch Glycolate / Primojel (Yung Zip-Taiwan), ferrous fumarate (Mumbai-India) and folic acid (Changzhou jiangsu-China). All reagents used were analytical grade. Ferrous fumarate (B.P grade 93-101%) was used as the standard in quantitative analysis.

Preparation of ferrous fumarate and folic acid (Combination) tablets

Magnesium stearate (A₁), avicel PH 102 (A₂), lactose (A₃), aerosil (A₄), sugar (A₅), PVP K-30 (A₆), Sodium lauryl sulphate (A₇), talcum (A₈), and primojel (A₉) were mixed in different proportions according to the formulation procedure, which is illustrated in Table 1 and 2. Many formulations were developed, including ten formulations

used as trials and one optimised formulation are reported. In each formulation, all of the ingredients used were weighed carefully (Analytical balance, AY-220, Shimadzu Corporation Japan) and mixed in a bottle mixer (Pakistan) for 30 minutes. Different proportions of excipients were used in different trials as described in Table 1 and 2. The actual amount of all the ingredients for each trial is listed in Table 3. A compression machine (Zp -19 China) was used to produce the tablets with a compression force of 2500 to 2800 kg. Concave punches (dia. 7.5 mm) were used to produce the tablets because concave faced tablets are more easily coated.

Powder properties

The moisture content of the sample was determined using a moisture analyser (MA-45 Courio Pak.) The difference between the expected mass of the tablet and the actual mass of the tablet corresponds to the percent of moisture present in the sample. The flow properties of the powder can be determined by the angle of repose, which is a characteristic related to interparticulate friction or resistance to movement between particles. The results from angle of repose tests are reported to be dependent upon the method used (US Pharmacopoeia, 2007). Here the angle of repose was measured using a

fixed funnel method (Prista *et al.*, 1995). The end of a funnel was placed 2 cm above a flat base. Powder (around 2.5 g depending on the bulk density of the material) was poured into the funnel, so that after pouring the powder out of the funnel, the top of the resulting powder cone reached the end of the funnel. The angle of repose (α) was determined from the height of the cone (h) and the diameter at the base (d). Each result is a calculated average of three measurements.

$\tan \alpha = 2h/d$ or $\tan \alpha = \text{height}/0.5 \text{ base}$ (US Pharmacopoeia 30-NF25, 2007).

Where α is the angle of repose, h is the height of the cone formed by the powder (mm) and d is the diameter of the cone (mm).

Tablet specifications

All of the properties in the tablets were checked according to the specifications of the B.P. and U.S.P.

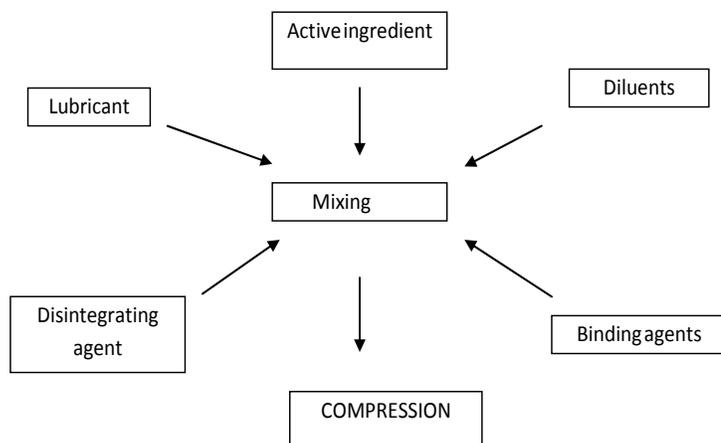
Weight variation test: Twenty tablets were weighed individually, and the average weight was calculated and compared with the individual tablet weight.

Hardness: The hardness of the tablets was checked using an electronic hardness tester (Curio Pak Pakistan). For each trial, tablet hardness was checked 10 times, and then the average was calculated and reported.

Friability: Twenty tablets were weighed before and after being placed in a Roche Friabilator (Curio Pak-Pakistan), and percent weight loss was calculated. The process was repeated thrice, and the average value was calculated and reported.

Disintegration test: Disintegration time of the tablets was checked using a disintegration time apparatus (Curio Pak-Pakistan). The process was repeated 5 times, and the average was calculated and reported.

Fig. 1. The direct-compression process of tablet manufacturing (Armstrong, 2002).



Assay: The percent content of ferrous fumarate and folic acid was analysed according to the official procedure given in B.P. 2007.

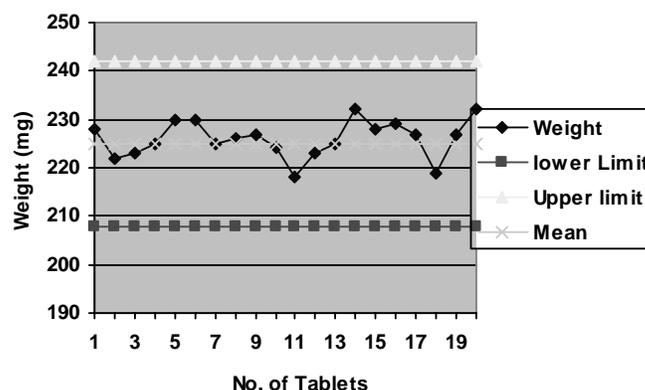
Dissolution test: Dissolution is another important parameter in quality control testing. The dissolution of ferrous fumarate and folic acid tablets (Combination) was checked according to the specifications given in the U.S.P 30-NF 25. Ferrous fumarate content of every sample (n=4) was checked using atomic absorption spectrometry (Analytic Jena AAS Vario 6) at a wavelength of 248.3 nm.

Analysis of the data: Each formulation was performed practically, and all of the steps during manufacturing of the tablets were supervised by qualified staff. The data was analysed by the quality control personnel from Genera Pharmaceuticals, I-9 Islamabad.

Results and discussion

The compression characteristics of a powder are highly dependent upon the flow of the powder (Hong-

Fig. 2. Tablets weight variation

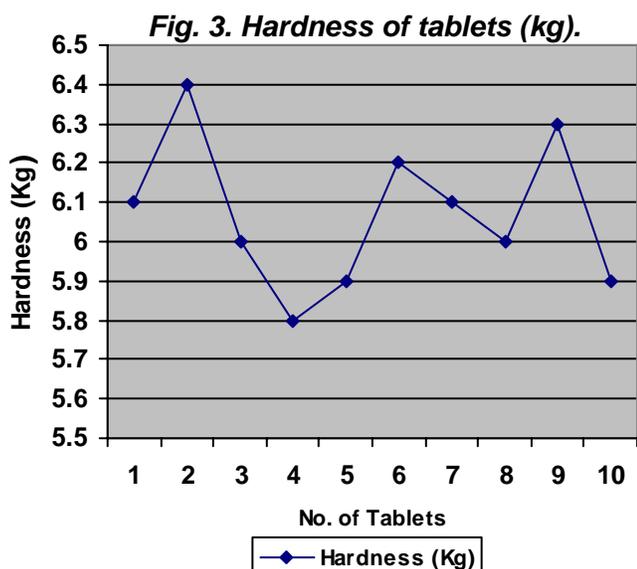


Guang & Ru-Hua, 1995; Prista *et al.*, 1995; Jivraj *et al.*, 2000). The flowability of a powder is highly dependent upon the angle of repose. During the trials we found that tablets produced from powder with a high value for the angle of repose were not produced according to specification i.e., they had poor flow and bad compressibility. Moisture content of the sample also plays an important role in the compressibility of a powder. It was observed that when the moisture content of the sample was low, the tablets showed signs of capping due to poor compression. When the moisture of the sample was high, there were problems of sticking and poor die filling. Therefore, it is very important to have the moisture at a specific level for the best results. For good compression of ferrous fumarate and folic acid tablets (combination), the moisture content should be between 3.2-3.8%. It was found that the actual moisture content of all of the ingredients collectively was 2.6%; therefore, external moisture was added to obtain the best results. Also, it was found that the order of mixing the excipients and the addition of moisture played an important role during the direct compression of ferrous fumarate and folic acid (Combination) tablets. The moisture content of the powder in each trial was determined using a moisture analyser (MA-45 Courio Pak.). The moisture content and angle of repose values are listed in Table 4.

Microcrystalline cellulose (avicel) is widely used in pharmaceuticals primarily as a binder/diluent in oral tablet and capsule formulations in both wet-granulation and direct-compression processes (Enezian, 1972; Lerk & Bolhuis, 1973; Lerk *et al.*, 1974; Lamberson & Raynor, 1976; Lerk *et al.*, 1979; Chilamkurti *et al.*, 1982; Wallace *et al.*, 1983). In addition to its use as a binder/diluent, microcrystalline

Table 3. Various trials for composition of tablets (mg).

Trial #	Mg. Stearate	Avicel pH102	Lactose	Aerosil	Sugar K30	PVP	S.L.S	Talcum	Primojel	Total wt. (mg)
1	6.00	31.00	12.00	4.00	2.00	2.40	2.00	3.00	0.00	225.00
2	4.00	31.00	14.00	4.00	4.40	0.00	2.00	3.00	0.00	225.00
3	8.00	37.00	0.00	0.00	0.00	2.40	1.00	12.00	2.06	225.06
4	5.00	30.00	0.00	4.00	0.00	13.00	1.00	8.00	1.40	225.02
5	5.00	40.00	0.00	2.00	10.00	0.00	0.00	3.00	2.40	225.00
6	6.00	0.00	35.00	4.00	5.00	0.00	4.00	4.00	4.40	225.00
7	2.00	0.00	20.00	4.00	25.00	3.00	5.00	3.40	0.00	225.02
8	4.00	20.00	0.00	0.00	25.00	0.00	4.00	7.00	2.26	224.86
9	5.00	38.00	12.00	0.00	0.00	0.00	2.40	0.00	5.00	225.02
10	4.00	45.00	0.00	0.00	0.00	0.00	2.00	11.40	0.00	225.02



cellulose also has some lubricant (Omray & Omray, 1986) and disintegrant properties that make it useful in tablet processing. Avicel is self-lubricating (Omray & Omray, 1986) and adds strength to tablets (Hernier & Teleman, 1997). For best results in pharmaceutical formulations, it should be used at a concentration of 5-20% (Lamberson & Raynor, 1976; Marshal & Sixsmith, 1974, 1975; Hollenbeck *et al.*, 1978; Lerk *et al.*, 1979; Wallace *et al.*, 1983).

Ferrous fumarate is a poorly flowable active pharmaceutical agent and causes friction with the punches and dies in the compression machine. The use of lubricating agent(s) is the way to overcome the friction problems with the compression machine. Talcum and magnesium stearate were selected as lubricating agents. Talcum is used as a lubricant and glidant (Grexa & Parmentier, 1979) at concentrations of 1-10%. Magnesium stearate is another very important lubricant, glidant and anti-adherent (Hanssen *et al.*, 1970; Pilpel, 1971). However, Magnesium stearate is hygroscopic and may retard the dissolution characteristics of the product (Butcher & Jones, 1972; Caldwell, 1974; Bilany, 1980). It can also increase tablet friability, therefore, magnesium stearate should be used in the lowest concentration possible (0.25-2%). The blending time with magnesium

stearate should also be carefully controlled (Bossert & Stamm, 1980; Sheikh-Salem & Fell, 1981; Tong *et al.*, 1982; Chowhan *et al.*, 1982; Garcia- Marquez *et al.*, 1992; Hussain *et al.*, 1992). In trials 3 and 6, we found that the tablets failed to meet the friability specifications due to a high concentration of Magnesium stearate and low moisture content (Bossert & Stamm, 1980; Bolhuis *et al.*, 1981).

Primojel (Sodium starch glycolate) was used as a disintegrating agent. For best results, it is used at a concentration of 2-10% (Khan & Rhodes, 1973; Bavitz *et al.*, 1974, 1975). We found that primojel in combination with sodium lauryl sulphate had very good disintegration times, which is obvious from trials 6 and 9. Sodium lauryl sulphate is a good disintegrating agent in the manufacturing of ferrous fumarate and folic acid (Combination) tablets. The best results are obtained when it was used at a concentration of 1-2% (Hand book of pharmaceutical excipients, 2006). However, we found that the optimal concentration of sodium lauryl sulphate varied when used in combination with other disintegrants, such as primojel. PVP K-30 was used as a binder in the formulations. It can also be used as diluent or coating agent at concentrations of 0.5-5% (Hand book of pharmaceutical excipients, 2006). We observed in trial 4 that by increasing the concentration of PVP K-30 (more than 5%), the disintegration time increased (Table 5).

The volumetric fill of the die cavity determines the weight of the compressed tablets. According to official books, the specified limit on weight variation for tablets lighter than 250 mg is $\pm 7.5\%$ (Remington, 2000). It was found that all the tablets passed the U.S.P and B.P specifications for weight variation. Weight variations for the optimised formulation are given in Table 6 and illustrated graphically in Fig. 2.

In the pharmaceutical industry, hardness of the tablets is an important parameter because pharmaceutical tablets must have sufficient ability to survive the handling forces during packaging and shipping. However, if the hardness exceeds a certain limit, it increases the disintegration time, which ultimately affects the bioavailability (Lachman *et al.*, 1976). In our trials, hardness varied from 4.5 kg to 11.2 kg. The average hardness for the optimised formulation was found to be

Table 4. Angle of repose & moisture content of the trials.

Trial #	Angle of repose (°)	Moisture content (%)
1	26.87	3.45
2	25.32	3.32
3	25.77	2.83
4	31.59	3.41
5	33.76	2.65
6	39.98	2.87
7	42.87	2.54
8	35.66	2.65
9	32.23	2.92
10	25.24	3.53

6.07 Kg. The hardness for the optimised formulation is given in Table 7 and illustrated graphically in Fig. 3.

Friability is another important parameter that is related to hardness. According to the U.S.P XXVIII, the allowed limit of friability is not more than 1% of weight Loss. In trials 1, 2, 4 and 10, friability was within the

the upper limit because of a low amount of disintegrating agent. In trials 4 and 5, tablets failed the disintegration test because of a high amount of binding agents, which increased the hardness. In trials 3 and 8 the disintegration time was within the specified limits set by the B.P and U.S.P (less than 15 min. for uncoated tablets). An optimised formulation was developed (Table 8), which fulfils all the requirements of official books (Table 9). Dissolution of the ferrous fumarate and folic acid (combination) tablets was found to be within the specified limits of U.S.P 30-NF 25 (not less than 75% in 45 min.) in all of the trials. The amount of active ingredient in the product was evaluated by the specified procedures given in the B.P i.e., titration method for

Table 5. Tablet specifications* of the trial formulations (1-10).

Formulation #	Weight (mg)	Hardness (kg)	Friability %	Disintegration time (min.)	Dissolution %	Ferrous Fumarate (%)	Folic acid (%)
1	227.5	7.80	0.37	12.6	90.0	102.50	103.50
2	226.2	8.40	0.25	13.7	88.40	103.50	105.30
3	229.5	4.50	1.15	3.4	93.50	102.70	106.40
4	225.4	9.70	0.28	17.0	89.70	99.80	103.80
5	223.1	11.10	1.02	16.2	92.30	100.80	112.20
6	230.2	03.60	1.50	2.7	91.60	103.50	111.50
7	220.6	03.20	1.62	1.8	95.00	99.80	113.00
8	227.0	05.30	1.14	2.5	89.60	102.30	109.70
9	230.3	04.00	1.08	2.1	94.10	103.50	110.80
10	227.4	05.80	0.21	14.6	91.20	100.70	107.40

*Average weight, hardness, friability, disintegration time, dissolution, and percent contents of active pharmaceutical ingredients of the trials. The tablets were not compressed properly in trials 6, 7 and 9 because of poor flow and less binding agents.

Table 6. Weight of 20 tablets (randomly selected) from the optimised formulation.

No. of tabs	1	2	3	4	5	6	7	8	9	10
Weight (mg)	228	222	223	225	230	231	225	226	227	224
No. of tabs	11	12	13	14	15	16	17	18	19	20
Weight (mg)	218	223	225	232	228	229	227	219	227	232

Table 7. Hardness of 10 tablets from the optimised formulation.

No. of tabs	1	2	3	4	5	6	7	8	9	10
Hardness (Kg)	6.1	6.4	6.0	5.8	5.9	6.2	6.1	6.0	6.3	5.9

specified limit. However, in the trials 3 and 5, the tablets failed to meet the specified limit of friability due to low moisture content. In trials 6, 7, 8 and 9, the tablets failed to meet the specified limit of friability due to less binding agent. As specified in U.S.P XVIII, complete disintegration is the state in which any residue of the tablet, except fragments of insoluble coating remaining on the screen, is a soft mass having no palpable firm core (Lachman *et al.*, 1976). In trials 1, 2 and 10, the disintegration time was near

Table 8. The optimised formulation that fulfils B.P and U.S.P specifications for ferrous fumarate and folic acid (combination) tablets.

Ingredient	mg/tablet
Ferrous fumarate	162.00
Folic acid	00.60
Avicel pH 102	42.40
Magnesium stearate	4.00
Talcum	12.00
Sodium lauryl sulfate	2.00
Primojel	2.00

ferrous fumarate and for folic acid and a HPLC method was adopted using a Shimadzu 120 A Isochromatic HPLC from Germany.

Conclusion

An optimised formulation of ferrous fumarate and folic acid (combination) tablets using a direct-compression method was formulated. The formulation contains more than 71% of the active pharmaceutical ingredient, which is usually manufactured using a wet-granulation method. Wet

Table 9. Expected and observed responses, including both physical and chemical characteristics for the optimised formulation of ferrous fumarate and folic acid (combination) tablets.

Test	Expected	Observed
Moisture content (%)	3.00	3.40
Angle of repose (%)	31.50	26.30
Hardness (kg)	7.00	6.07
Average weight (mg)	225.0	226.0
Friability (%)	0.68	0.36
Disintegration (min)	3.00	1.30
Dissolution (%)	90.00	94.80
Ferrous fumarate (%)	100.00	103.0
Folic acid (%)	100.00	108.50

granulation is a costly, time consuming, energy wasting and a complicated method of manufacturing. In the present work, an optimised formulation using a direct-compression method was found to be the best for use by the pharmaceutical industry because this method is time saving, cost effective and increases production capacity. The optimised formulation met all of the specifications of the B.P and U.S.P.

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