Effect of a Dispersant on the Dissolution of Ferrous Fumarate from Capsule Formulations

S. DURGA PRASAD*, G. CHANGALA REDDY, P. S. S. PRASAD[1] AND K. MUKKANTI[2]
Famy Care Limited, Plot No: 1608 and 1609, G. I. D. C., Sarigam-396 155.
[1]Drugs Control Laboratory, Drugs Control Administration,
Vengalarao Nagar, Hyderabad-500 038.
[2]Centre for Environment, I. P. G. S. R., J. N. T. University, Hyderabad-500 028.

Accepted 7 August 2003
Revised 6 June 2003
Received 16 June 2003

The effect of sodium starch glycollate, a dispersant on the dissolution of ferrous fumarate capsules was studied. Ferrous fumarate was formulated into capsules with sodium starch glycollate and the capsules were evaluated (immediately after preparation and after storage at exaggerated conditions of temperature and relative humidity) for physical parameters, disintegration, drug content, and dissolution rate. Marked increase in the dissolution of ferrous fumarate was observed when sodium starch glycollate was included in the capsule formulation. This formulation gave fast and rapid dissolution of ferrous fumarate fulfilling the BP 1999 dissolution requirement.

The poor dissolution characteristic of relatively insoluble drugs has long been a problem to the pharmaceutical industry. When an insoluble or sparingly soluble drug is administered orally, the rate and extent of absorption are controlled by the dissolution rate in the gastrointestinal fluids. Techniques like solid dispersion and use of hydrophilic matrix, prodrug approach, complex formation and use of selected polymorphic forms, buffering agents and surfactants have been reported[1-3] to enhance the dissolution and bioavailability of poorly soluble drugs.

Ferrous fumarate, a potent haematinic drug, is slightly soluble in water and aqueous fluids and its oral absorption is dissolution rate limited. BP 1999 has prescribed a dissolution rate test specification for ferrous fumarate capsules[4]. Sodium starch glycollate (SSG) is the sodium salt of carboxymethyl ether of starch. It is official in USP 23-NF 18, BP 1993 and IP 1996. It is used as a disintegrant in tablets. SSG has been used earlier to increase the dissolution rate of piroxicam[5], chloramphenicol[6], acetaminophen[7] and indomethacin[8] from capsule formulations. The effect of SSG on the dissolution of ferrous fumarate from tablet formulations has been studied earlier[9]. The effect of SSG on the dissolution of ferrous fumarate from capsule formulation was not studied earlier. Ferrous fumarate capsules are official in BP and not in IP[10] and USP[11]. No commercial marketed ferrous fumarate capsules BP were available in Indian market.

***For correspondence**
E-mail: sprasad@famycare.com

In the present investigation, SSG is tried as a dispersant in ferrous fumarate capsule formulation. The prepared products (with SSG) have been compared with the products made with starch and polysorbate 80.

Ferrous fumarate IP/BP was obtained from Eagle Chem., Vapi, Starch IP/BP was purchased from Universal Starch, Dhule, Polysorbate 80 IP/BP was obtained from ICI, Mumbai, Sodium starch glycollate IP/BP was purchased from Ascot, Nandesari, Magnesium stearate IP/BP was obtained from Harihar Organics, Vapi, Colloidal silicon dioxide IP/BP was obtained from Degussa, Origin China, Hard gelatin capsule shells were purchased from Universal Capsules Limited, Aswe. Starch was used as a diluent. Magnesium stearate and colloidal silicon dioxide were used as lubricants.

Capsules each containing 200 mg (added about 8% excess to compensate the assay of raw material to 100%) of ferrous fumarate were prepared as per the formula given in Table 1. In each case 2.15 kg of ferrous fumarate, which was passed through sieve no 40, and the other additives (previously dried and the required amounts as per the formula, Table 1) which were passed through sieve no 80, were

TABLE 1: FORMULATION OF FERROUS FUMARATE CAPSULES (SIZE 2).

Ingredient	Weight (mg) / Capsule				
	F1	F2	F3	F4	F5
Ferrous fumarate (200 mg per capsule; equivalent to Fe (II) 65 mg per capsule)	215*	215*	215*	215*	215*
Starch	80	78.5	77	30	-
Polysorbate 80	-	1.5	3.0	-	-
SSG	-	-	-	50	80
Magnesium stearate	3	3	3	3	3
Colloidal silicon dioxide	2	2	2	2	2

Compositions of various formulations (F1, F2, F3, F4 and F5). *Added about 8% excess to compensate the assay of raw material to 100%.

mixed thoroughly by geometric dilution technique. The powder mixture was then filled into hard gelatin capsule shells (size 2) using Scorpio semi automatic capsule filling machine. In each case the theoretical batch size of capsules was 10 000 capsules. The practical yield (batch size) obtained in each case was between 95 to 98%. Temperature and relative humidity of the filling room between 20 to 25° and 45 to 55%, respectively. The prepared capsules were evaluated (immediately after preparation and after storage at exaggerated conditions of temperature and relative humidity) for physical parameters, disintegration, drug content, and dissolution rate.

All physical parameters were found within the standard limits for all formulations F1, F2, F3, F4 and F5 (initial and accelerated stability study capsules). Disintegration time's were determined using Veego tablet disintegration test machine USP standard using distilled water as the fluid and the results are given in Table 2. The ferrous fumarate content of the capsule was determined by titration method as per BP 1999, ferrous fumarate assay method and the results are given in Table 3.

Dissolution of ferrous fumarate from prepared capsules (formulations F1 to F5) was studied in a tablet dissolution tester of Electrolab, Model TDT-06 N (USP XXI/XXII) apparatus as per the BP 1999 dissolution rate test (apparatus 2) prescribed for ferrous fumarate capsules.

In each test, 900 ml of 0.1 M hydrochloric acid, one capsule, a speed of 50 rpm and a temperature of 37±0.3° were employed. A 100 ml aliquot of dissolution medium was withdrawn at different time intervals, filtered and assayed for ferrous fumarate content by titration with 0.01 M ammonium cerium (IV) sulphate VS using ferroin solution as indicator. Content of Fe (II) in the medium was calculated taking each ml of 0.01 M ammonium cerium (IV) sulphate VS to be equivalent to 0.5585 mg of Fe (II). The percent of ferrous fumarate dissolved at various times was calculated. T_{50} (time taken for 50% dissolution), T_{75} values and percent dissolved in 45 min. were recorded. The results are given in Table 3.

Capsules prepared (formulation F1 to F5) were stored

TABLE 2: DISINTEGRATION TIME OF PREPARED CAPSULES.

Batch Code	Disintegration Time (+/-S.D) (min*) (Initial prepared capsules)	Disintegration Time (+/-S.D) (min*) (Accelerated stability study capsules)
F1	6.0 (+/-0.64)	6.8 (+/-0.78)
F2	6.6 (+/-0.55)	7.0 (+/-0.66)
F3	7.0 (+/-0.72)	7.2 (+/-0.89)
F4	5.7 (+/-0.67)	6.0 (+/-0.56)
F5	5.2 (+/-0.55)	5.8 (+/-0.72)

Compositions of various formulations (F1, F2, F3, F4 and F5). Disintegration limits as per IP and BP: Not more than 30 Min.* Mean of six trials. (+/-S.D.) Standard Deviation.

TABLE 3: DISSOLUTION CHARACTERISTICS OF FERROUS FUMARATE CAPSULES.

Capsule Formulation	Fe (II) content (mg per capsule)	T_{50}	T_{75}	Percent dissolved in 45 min*
F1	64.4	32	40	59.2
F2	64.2	36	48	45.6
F3	64.0	34	45	52.3
F4	64.8	26	38	72.4
F5	64.4	20	30	99.0

Compositions of various formulations (F1, F2, F3, F4 and F5) - initial prepared capsules. T_{50} and T_{75} (time taken for 50% and 75% dissolution). *Mean of 6 trials (36 capsules)

TABLE 4: DISSOLUTION CHARACTERISTICS OF FERROUS FUMARATE CAPSULES.

Capsule Formulation	Fe (II) content (mg per capsule)	T_{50}	T_{75}	Percent dissolved in 45 min*
F1	64.2	34	42	58.6
F2	64.0	37	48	46.1
F3	64.0	35	46	50.2
F4	64.5	27	38	72.6
F5	64.3	21	31	98.6

Compositions of various formulations (F1, F2, F3, F4 and F5) - Accelerated Stability Study Capsules. T_{50} and T_{75} (time taken for 50% and 75% dissolution). *Mean of 6 trials (36 capsules).

for six under exaggerated condition of temperature (40±2º) with relative humidity (75±5%). The stored capsules were evaluated (at the end of sixth month) for physical parameters, disintegration, drug content and dissolution rate as per the method used for initial prepared capsules. The results are given in Table 4.

All capsules prepared were found to contain ferrous fumarate within 95 to 105% of the labeled claim fulfilling the requirement of BP. All capsules prepared with and without sodium starch glycollate disintegrated within 30 min. fulfilling the official (IP and BP) requirement for disintegration of capsules. The disintegration times for all samples (original and accelerated study) were within seven min. Formulations contained a physical mixture of ferrous fumarate and other additives as starch, polysorbate 80, magnesium stearate and colloidal silicon dioxide. The dissolution of ferrous fumarate from capsules with additives as starch (F1), and polysorbate 80 (F2 and F3), was slow and spread over a period of 90 min. T_{50} and T_{75} values were recorded. Capsules of formulations F1, F2 and F3 prepared with starch and polysorbate 80 did not comply with the dissolution test as per BP (not less than 70% in 45 min). Whereas when SSG was included the dissolution of ferrous fumarate was very fast and rapid and was complete within 40 min. T_{50} values were found to be decreased several times indicating the rapid dissolution of the drug with SSG as its strength was increased. The rapid dispersal of the capsule contents might have resulted in the rapid dissolution of the drug. Capsule formulation F3 and F4 fulfilled the official BP 1999 dissolution requirement as not less than 70% of the labeled amount of the drug dissolved in 45 min. All capsules prepared were found stable in respect of physical parameters, disintegration, drug content and dissolution rate even after stored at exaggerated temperature 40±2° and relative humidity 75±5%. Thus sodium starch glycollate was found to increase the dissolution of ferrous fumarate from capsule formulations.

REFERENCES

1. Notari, R.E., Eds., In; Biopharmaceutics and Pharmacokinetics, 2nd Edn., Marcel Decker Inc., New York, 1975, 12.

2. Choudhary, K.P.R. and Rajyalakshmi, Y., **Eastern Pharmacist,** 1987, 51.
3. Misra, A.N. and Baweja J.M. **Indian Drugs,** 1997, 34, 216.
4. British Pharmacopoeia, Her Majestry's Stationary Office, London, 1999, 1829.
5. Choudhary, K.P.R. and Madhusudhan, P., **Eastern Pharmacist,** 1990, 143.
6. Durga Prasad, S., **Indian J. Pharm Sci.,** 1996, 58, 86.
7. Durga Prasad, S, **Indian Drugs,** 1998, 35, 434.
8. Durga Prasad, S., **Indian Drugs,** 1999, 36, 651.
9. Durga Prasad, S., Changala Reddy, G., Prasad, P.S.S and Mukkanti, K., **Indian Drugs**, 2002, 39, 350.
10. Pharmacopoeia of India, The Controller of Publications, Delhi 1996, 313 and Addendum 2000, 850.
11. United States Pharmacopoeia, 24, United States Pharmacopoeial Convention, 2000, 711.