

Design of sustained release pellets of ferrous fumarate using cow ghee as hot-melt coating agent

Dinesh M Sakarkar, Avinash K Dorle, Nilesh Manoharrao Mahajan¹, Suresh Gendappa Sudke²

Departments of Pharmaceutics, Sudhakar Rao Naik Institute of Pharmacy, Pusad, Yawatmal, ¹IBSS College of Pharmacy, Malkapur, Buldana, ²SGSPS Institute of Pharmacy, Kaulkhed, Akola, Maharashtra, India

Abstract

Introduction: The objective of the present study was to design ferrous fumarate (FF) sustained release (SR) pellets using of cow ghee (CG) as an important hot-melt coating (HMC) agent. **Materials and Methods:** The pellets were coated by HMC technique using CG and ethyl cellulose composition by conventional coating pan without the use of spray system. FF formulated as pellets and characterized with regard to the drug content and physico-chemical properties. Stability studies were carried out on the optimized formulation for a period of 6 months at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ relative humidity. **Results:** Pellets with good surface morphology and smooth texture confirmed by stereo micrographs. HMC is easy, efficient, rapid and simple method since virtually no agglomeration seen during coating. In-vitro release from pellets at a given level of coating and for present pellet size was dependent upon the physico-chemical property of the drug and mostly aqueous solubility of the drug. The selection of optimized FF formulation was confirmed by comparing percent cumulative drug release with theoretical release profile. Formulation F2 had difference factor (f_1) and similarity factor (f_2) values was found to be 5 and 66 respectively. F2 showed SR of drug for 8 h with cumulative per cent release of $98.03 \pm 4.49\%$. Release kinetics indicates approximately zero order release pattern. HMC pellets were stable during the course of stability study. **Conclusions:** By means of HMC using CG and ethyl cellulose, SR pellets containing FF were successfully prepared.

Key words: Agglomeration, difference factor, similarity factor, theoretical release profile

INTRODUCTION

Coating is a vital stage in the formulation of pharmaceutical dosage form where ultimate objective is to modify drug release characteristics or to achieve superior aesthetic quality (like color, texture and taste) and superior physical and chemical protection. With the dramatic rise in the number of drugs requiring coating, increased cost of process time and compounds used. Technologists are now under growing pressure to increase yield, improve product quality and reduce process time.^[1] Historically, solutions of polymers and organic solvents have been used to produce the desired coatings.^[2-4] The coating

solution has been commonly applied onto the substrate with the aid of a high-pressure, pneumatic or ultrasonic nozzle. Several factors have contributed to search for alternatives to organic solvent systems. In 1970, the U.S. Environmental Protection Agency introduced the Clean Air act^[5] reducing the amount of atmospheric solvent emissions, thereby dictating the use of expensive recovery systems. The Occupational Safety and Health Administration in 1976^[6] implemented new worker restrictions on the amount and duration of worker exposure to many organic solvents. Finally, the corresponding increase in the cost of these solvents encouraged the pharmaceutical industry to seek alternative systems.^[2,3]

Address for correspondence:

Prof. Suresh Gendappa Sudke,
C/o K.S. Paulkar, Parivar Colony-4, Keshav Nagar,
Akola - 444 004, Maharashtra, India.
E-mail: sureshsudke@gmail.com

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Hot-melt coating (HMC) or solvent-free coating methods offer many advantages over current and conventional coating techniques,^[7,8] such as they do not require the use of costly organic solvents. Since there is no solvent to be evaporated, processing times are much shorter. Tedious process of solvent disposal, treatment or recovery associated with organic solvents is eliminated. Since no aqueous medium is used, no risk of bacteriological contamination and hydrolysis of drug, the process is environment friendly. The materials used for solvent-free coating techniques are generally waxes that are much cheaper as compared with costly polymers employed in solvent coatings. The great versatility of waxes in terms of their solubility and

Table 1: Composition of sustained release hot-melt coated FF pellet formulation

Formulation code	FF (mg)	Sucrose (mg)	Cow ghee (mg)	Ethyl cellulose (mg)	α -tocopherol (mg)
F1	200	40	24	00	01
F2	200	40	18	6	01
F3	200	40	9	9	01
F4	200	40	6	18	01
Total weight of pellets in each capsule				265 mg	

FF: Ferrous fumarate

Table 2: Process parameters for HMC of FF pellets

Process parameters	Settings
Pellet charge	500 g
Pellet size	16-20 mesh
Pan speed	24 rpm
Amount of coating solution	50 g
Core to coat ratio	10:1
Pellet bed temperature	60°C
Relative humidity	30-50%
Coating time	30 min
Curing conditions	30°C for 48 h

HMC: Hot-melt coating, FF: Ferrous fumarate

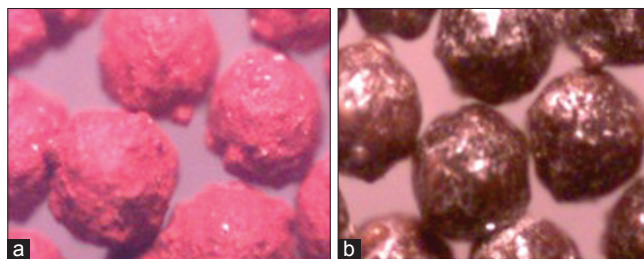
ability to solubilize other excipients make them useful in a variety of formulations for different purposes. Though few, whatever research that has been performed in HMC employed waxes such as beeswax, cetyl alcohol and lanolin, which have definite disadvantages such as the ability to demonstrate hypersensitivity or immunogenic responses in certain individuals. Very few studies ever employed cow ghee (CG) as an agent for HMC; although, it is an important component of our daily diet and absolutely free from the hypersensitivity skin and other reactions. Moreover, studies that employed the procedure for preparing sustained release (SR) drug pellets were normally carried out in coating pan and fluid-bed apparatus, which limits the technique as it involves sophistication.^[8,9]

The present study was demonstrated to check the suitability of CG as a SR HMC agent in conjunction with ethyl cellulose to achieve SR profile. To prevent the oxidation of CG, α -tocopherol was used as antioxidant in the coating composition. It is worthy of mentioning that for sustaining the release of water soluble drugs, the method is still advantageous in the sense that prior coating of pellets with this composition followed by final application of a SR film coating with ethyl cellulose or a suitable polymer would lead to faster processing and use of lesser polymer in comparison to formulations where release is primarily controlled by the application of polymeric membrane only.

MATERIALS AND METHODS

Materials

Ferrous fumarate (FF), sucrose, α -tocopherol and ethyl cellulose were procured from Zim Laboratories Ltd., Kalmeshwar MIDC, Nagpur, India. CG was obtained from Gourakshan center, Amravati, India. Solvents and all other reagents used were of

**Figure 1:** Stereo micrographs of ferrous fumarate pellets: (a) Uncoated pellets; (b) hot-melt coated pellets $\times 60$

analytical grade and were procured locally. Double distilled water was used throughout the study.

Preparation of pellets

FF and sugar syrup (33.3% w/v) were blended in a suitable bowl for 5 min and passed through 16 meshes to form extrudates. The wet extrudates charged into the rotary shaker pelletizer and the equipment was operated for 5 min at 200 rpm to produce drug pellets.^[10] Pellets were dried at 60°C for 3 h and then sifted to collect 16-20 mesh fractions. Undersize and oversize pellets were rejected. Pellets of fraction 16-20 mesh were coated with ghee-ethyl cellulose molten blend in a 12 inches diameter coating pan equipped with 4 radially arranged baffles and system to heat the pan. The HMC compositions were shown in Table 1. CG was heated to 80°C and ethyl cellulose was dissolved in the molten ghee with stirring at the same temperature. FF pellets were then rolled in the coating pan until a bed temperature of 60°C was attained. The molten coating mass was loaded onto the hot rolling drug pellets in a slow stream. After the complete application of coating mass, the pellets were allowed to roll further for 10 min during which time the bed temperature was allowed to gradually come down. The pellets were then removed and cured in a dryer for 48 h. The parameters employed for HMC of FF pellets in coating pan are given in Table 2.

EVALUATION OF PELLETS

Photomicrography

Micrographs of uncoated and HMC pellets were taken using Intel play digital microscope QX3 attached to a personal computer. The photographs were used to examine the uniformity of coating and surface of pellets after coating [Figure 1].^[11]

Table 3a: Characterization of physico-chemical parameters for coated ferrous fumarate pellets

Formulation code	Angle of repose* (°)	Bulk density* (g/cc)	Tapped density* (g/cc)	Hausner's ratio*	Carr's index* (%)
F1	26.75±0.03	0.69±0.003	0.76±0.003	1.11±0.005	9.63±0.038
F2	23.13±0.12	0.70±0.003	0.77±0.003	1.09±0.005	8.64±0.387
F3	22.34±0.03	0.71±0.002	0.77±0.003	1.08±0.006	8.05±0.530
F4	20.78±0.05	0.74±0.003	0.78±0.003	1.04±0.005	7.21±0.421

*Value (mean±standard deviation) when sample size is $n=3$ **Table 3b: Characterization of physicochemical parameters for coated ferrous fumarate pellets**

Formulation code	Mean particle size (μ)	Hardness* (kg/cm ²)	Friability* (%)	Drug content* (%)
F1	827-876	2.75±0.25	0.72±0.005	98.64±0.04
F2	886-949	3.15±0.10	0.64±0.011	99.16±0.06
F3	896-936	3.45±0.35	0.57±0.008	97.15±0.17
F4	904-955	3.75±0.15	0.53±0.004	98.35±0.33

*Value (mean ± standard deviation) when sample size is $n=3$

Angle of repose

Accurately weighed 50 g of HMC pellets were poured gently through glass funnel on the graph paper. The height of the pile and diameter were noted for determination of angle of repose by using the following formula. The values of angle of repose were recorded in Table 3a.^[12]

$$\text{Angle of repose } (\theta) = \tan^{-1}(h/r) \quad \dots(1)$$

Bulk density

Accurately weighed 25 g of HMC pellets of 16/20 mesh were poured gently through glass funnel into 100 ml calibrated measuring cylinder. The surface was carefully made smooth without application of pressure. The volume occupied by sample was recorded and bulk density (g/ml) was calculated and recorded in Table 3a.^[12]

$$\text{Bulk density} = \frac{\text{Weight of sample}}{\text{Bulk volume}} \quad \dots(2)$$

Tapped density

Tapped density was determined in a similar way to that of bulk density. However, final volume was measured after tapping the cylinder from 3 inches until constant volume was obtained using Electrolab tapped density apparatus. The volume occupied by sample was recorded and tapped density (g/ml) was calculated and recorded in Table 3a.^[12]

$$\text{Tapped density} = \frac{\text{Weight of sample}}{\text{Tapped volume}} \quad \dots(3)$$

Compressibility index

The morphology of pellets and total structure can change in any variation in formulation or material properties, affecting porosity, which is considered to have a great influence on coating, flow and packing during tablet or capsule filling. It also influences the rate of release of drug from pellets by affecting the capillary action of dissolved drug. From the bulk density and tapped density

data, the compressibility index was obtained using the following equation and recorded in Table 3a.^[12]

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \dots(4)$$

Hauser's ratio

From the bulk density and tapped density data Hauser's ratio was obtained. Hauser's ratio for the HMC pellets was carried out using the following equation and recorded in Table 3a.^[12]

$$\text{Hauser's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \dots(5)$$

Hardness and friability

The hardness or crushing strength of HMC pellets was examined by Veego digital dial type hardness tester (Veego Scientific, India) and noted [Table 3b]. For the friability study, accurately weighed 10.0 g of pellets (initial weight) were placed on sieve having 0.85 mm aperture with 25 glass beads of 3 mm diameter and then both were placed in Roche's friabilator (Veego Scientific, India) for 100 revolutions at 25 rpm speed. The pellets were collected and placed on the sieve with 0.85 mm aperture. The smaller particles were allowed to pass through the sieve and pellets were reweighed (Final weight). The friability was determined as percentage loss of mass of pellets after the test was recorded in Table 3b.^[13]

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad \dots(6)$$

Size distribution

The size distribution of pellets was carried out using sieve shaker and set of four active standard test method sieves (#14, #16, #18 and #20) for 5 min. The size distribution of pellets expresses the efficiency of the process of manufacture the uniform size pellets. The mean pellet size was calculated and recorded in Table 3b.^[14]

$$\text{Mean pelle size } (d_{\text{avg}}) = \frac{\sum \% \text{ retained} \times \text{Average Sieve Aperture}}{100} \quad \dots(7)$$

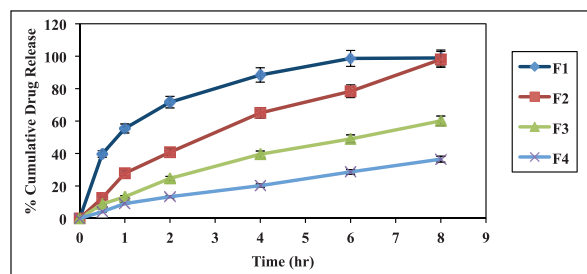


Figure 2: *In-vitro* release profile of ferrous fumarate from hot-melt coated pellets

Drug content

Accurately weighed 500 mg of hot-melt coated pellets were grind carefully in the mortar. A total of 50 mg of this powder was transferred carefully to 100 ml volumetric flask and add 30 ml of methanol and sonication was carried out using laboratory sonicator (ISP Technologies, India) for 15 min to extract the FF. Final volume was made with 0.1N hydrochloric acid. Aliquots of filtered samples (5 ml) were mixed with 5 ml of 10% w/v hydroxylamine HCl solution followed by 10 ml acetate buffer of pH 4.5 in a volumetric flask. The mixture was allowed to stand for 20 min following which 2 ml of 0.25% w/v solution of o-phenanthroline was added and the volume adjusted to 25 ml with distilled water. The solution was allowed to stand for 20 min. Absorbance was measured at 515 nm using UV-Visible Spectrophotometer (UV1800, Shimadzu, Japan) reagent blank. (Note: Standard solution of ferrous ammonium sulphate was used as blank reagent for comparison of results). Drug content was noted for all the formulations [Table 3b].

$$\text{Drug content (\%)} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times 100 \quad \dots(8)$$

Theoretical release profile (TRP)

For SR dosage form, drug release in 2, 4, 6 and 8 h should be 45, 60, 75 and greater than 90% respectively.

In-vitro drug release study

In-vitro release of FF pellets was carried out to evaluate the SR characteristics imparted by HMC with ghee formulations. Dissolution studies were performed using United States Pharmacopoeia (USP) XXV apparatus II (rotating paddle method), model Electrolab, 6 vessel assembly at 100 rpm. The dissolution medium consisted of 750 ml hydrochloric (pH 1.2) for 8 h. Temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Aliquots of 5 ml were withdrawn at predetermined intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots withdrawn were diluted suitably, filtered and analyzed. All release studies were conducted in triplicate and the mean values were plotted versus time with a standard deviation less than three indicating reproducibility of result. The percent cumulative drug release against time was plotted [Figure 2].

Analysis of FF in dissolution samples

Aliquots of filtered dissolution samples at different time intervals

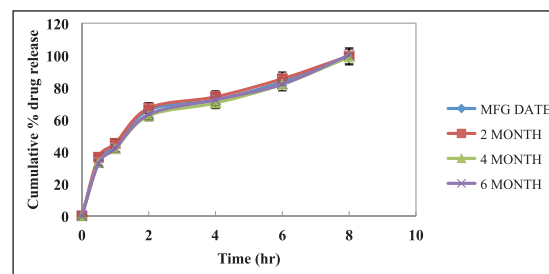


Figure 3: *In-vitro* release profile of ferrous fumarate from hot-melt coated pellets for stability study sample

(5 ml) were mixed with 5 ml of 10% w/v hydroxylamine hydrochloride solution followed by 10 ml acetate buffer of pH 4.5 in a volumetric flask. The mixture was allowed to stand for 20 min following which 2 ml of 0.25% w/v solution of o-phenanthroline was added and the volume adjusted to 25 ml with distilled water. The solution was allowed to stand for 20 min. Absorbance was measured at 515 nm using a reagent blank. Results were calculated by comparison.

Stability studies of pellet

The pellets filled hard gelatin capsule shells were placed in amber colored bottles and wrapped with aluminum foils. Then, they were stored at temperature $40 \pm 2^\circ\text{C}$ and relative humidity (RH) $75 \pm 5\%$ for 6 months in the stability chamber ([Remi Laboratory Instrument CHM-6S [GMP]]). The pellets were evaluated for any changes in physical appearance and percent cumulative drug release after 2, 4 and 6 months. Result obtained was compared with data obtained for zero time and room temperature ($28 \pm 2^\circ\text{C}$) and RH ($42 \pm 2\%$). The plot of percent cumulative drug releases against time in hours, manufacture day, after 2, 4 and 6 months for stability study were plotted [Figure 3].^[15,16]

RESULTS

Pellets with good surface morphology and smooth texture were produced as a result of HMC with ghee formulation. Stereo micrography confirmed uniformity of coating of pellets [Figure 1]. Coating could be performed with ease and in a very short period of time; thus, establishing the simplicity and rapidity of processing. Percent yield of coated pellets was excellent since virtually no agglomeration was observed during the coating. Such results were expected since the coating composition was non-tacky and the presence of ghee in fact facilitated free rolling of pellets. The evaluation parameters indicate that the pellets have good flow property with low friability and thus pass the tests as per USP limits. The drug content in the pellets was also found to be within pharmacopoeia limit as per USP.

The selection of optimized FF formulation was confirmed by comparing release profile of prepared formulation with TRP.^[17,18] Formulation F2 shows difference factor (f_1) and similarity factor (f_2) values was found to be 5 and 66 respectively. In the formulation F2, at a given level of coating and for a given pellet size, amount of drug released during the *in-vitro* study

Table 4: Kinetic parameters of formulations

Formulation code	Zero order model		First order model	
	Rate constant (k_0)	Correlation coefficient (R)	Rate constant (k)	Correlation coefficient (R)
F1	10.5031	0.9579	0.0752	0.9983
F2	8.3007	0.9768	0.0839	0.9978
F3	3.4952	0.9843	0.0220	0.9907
F4	4.9306	0.9905	0.0435	0.9983

k_0 : Zero order rate constant, k : First order rate constant

from hot-melt coated pellets was 98.03 ± 4.49 for 8 h [Figure 2].

Drug release from coated pellets was clearly observed to be a function of the physico-chemical property of the drug. More specifically, the release profile was a reflection of the drug's aqueous solubility. As the FF being more water soluble its lipid-coated pellets demonstrated more than 65% dissolution in just 4 h. Since the procedure adopted for HMC did not facilitate application of more than 10% coating composition, further retardation of FF release could not be achieved. The results of the significance calculation were also prognosticated by the rate constants. The kinetic parameter calculations demonstrated that the rate of dissolution of the iron (II) fumarate was of zero kinetic order, which means that the product stores iron as a depot and ensures its slow and uniform release [Table 4]. This is a very important requirement with a view to the prevention of gastric irritation.

The stability study revealed that, there was no significant change in physical characteristics and drug release pattern from pellets [Figure 3]. Thus, the pellets were stable at accelerated condition. The results of this study are in unison with studies conducted by different authors, but utilizing different lipid materials that are for a given wax-coating composition, ability to achieve or prepare SR drug pellets utilizing a given amount of the coating was a factor dependent upon the drugs solubility. Lower level of coating could SR of poor water soluble drugs such as theophylline, whereas very high amount of deposition of coating could retard release of freely soluble drugs like phenylephrine hydrochloride. Thus, the present composition of CG could be successfully employed as a SR HMC agent as any other waxy material like Compritol^[19] if the amount of coating deposited on the pellets could be controlled depending on the physico-chemical characteristics of the drug. Application of larger quantity of coating material could be made possible by use of more sophisticated equipments and procedures like fluid-bed coating.^[20]

CONCLUSIONS

The objective of this study was to design the SR hot-melt coated ferrous (II) fumarate pellets using CG in conjunction with ethyl cellulose as HMC agent. Since alone CG cannot provide physical strength and uniform thickness to the coating film. Ethyl cellulose along with CG provides the strength as well as stability in consistency of coat during storage so that there is no need to store the formulation at refrigerated conditions. The method employed

is simple, rapid, economical and did not require the use of toxic solvents. It is worthy of mentioning that for controlling the release of water soluble drugs, the method is still advantageous in the sense that prior coating of pellets with this composition followed by final application of a SR film coating with ethyl cellulose or a suitable polymer would lead to faster processing and use of lesser polymer in comparison to formulations where release is primarily controlled by the application of polymeric membrane only. The drug content study revealed uniform distribution of the drug in the pellets. The results of *in-vitro* drug release showed the order of formulation F1 > F2 > F3 > F4. The drug release rate varied among the formulations depending on the compositions of polymers used. The obtained dissolution data indicated that the drug release follows zero order profile.

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