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Optimization of Extrusion-Spheronization Process Parameters Affecting Micromeritics of Dried Ferrous Sulphate Pellets

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Optimization of Extrusion-Spheronization Process Parameters Affecting Micromeritics of Dried Ferrous Sulphate Pellets **J Pharm Sci Bioscientific Res**. 2023. 11(6): 173-182

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ABSTRACT:

Purpose: This study aimed to prepare Dried Ferrous Sulphate pellets as an oral iron supplement. Pellets were prepared by the extrusion-spheronization process. Optimization of the process parameters was done to get the desired micromeritic properties of the pellets.Results: The formulation composition of the T4 batch was found suitable based on the ease of preparation, extrusion time, % product yield, pellet appearance, and average pellet size. This formulation was selected for the screening and optimization of extrusion-spheronization process parameters using 3 level 2 factor factorial design (Design expert 10.0.1). Spheronization speed and time as significant process parameters were optimized at 2000 RPM and 15 minutes (Batch F5) based on the desired values of average pellet size(617 µm), pellet roundness(0.85), and product (16 - 30 # pellets) yield (90 %) found as response variables. For the F5 batch, an immediate and complete In vitro drug dissolution (98.99± 3.5 % SD (n=3)) was found in 0.1 N HCl at 1 hr.Conclusion: Formulation composition and extrusion-spheronization process parameters significantly affected the pellet size and shape. Spheronization parameters were optimized using experimental design. The developed pellet dosage form is a multi-unit dosage form, it facilitates dosage adjustment as the biggest advantage (Iron doses vary based on the iron deficiency level). This formulation contains only iron salt so other minerals like zinc would not compete with iron absorption. The developed product in this study would be a potential alternative to immediate-release single-unit oral iron supplements.

KEYWORDS: Dried Ferrous Sulphate, Extrusion-spheronization, Gelucire 43/01, Iron, Roundness

1. INTRODUCTION

Iron as a micronutrient is an essential element[1]. An untreated Iron deficiency may result in severe condition of iron deficiency anemia, the predominant cause of anemia[2,3].

Iron deficiency treatment with balanced nutrition alone is important but not adequate. It is difficult to follow an iron-rich diet strictly and usually, it is not followed. Iron deficiency treated with iron supplementation improves haemoglobin better than multiple micronutrient supplementations[4–6]. As there is no active means of iron excretion from the body, its absorption from the duodenum through carrier protein, divalent metal transporter 1(DMT1) is tightly regulated[7]. The other divalent minerals like zinc, if present in iron supplements also compete for absorption by the same carrier pathway and affect iron absorption so these types of marketed formulations are considered as irrational ones [8]. Iron alone in supplements was found more efficacious than supplements with other mineral-multivitamins for improving haemoglobin levels, in a clinical study on nonpregnant anemic women[6].

Different types of Ferrous (sulphate, ascorbate, fumarate, gluconate, glycine-sulphate) or Ferric iron products are available for the treatment of iron deficiency. Ferrous products are preferred over ferric as Ferrous iron is more bioavailable due to its higher solubility than ferric iron. Iron also gets absorbed in ferrous form, not ferric form. Dried

Ferrous Sulphate is the preferable salt to other ferrous salts, based on the research studies [9].

The oral solid dosage forms can be classified into single-unit, non-divided dosage forms like tablets and capsules, and multiple-unit dosage forms, which include pellets, granules, and mini-tablets, these are divided formulations[10].

Multiple-unit dosage forms are advantageous over single-unit dosage forms in terms of the higher degree of dispersion in the gastrointestinal tract and therefore reduced risk of high localized concentration which is important specifically for an irritant drug[10]. They can be divided for the required dose without changing the formulation or process[11].

Amongst the multiple-unit dosage forms, pellets offer both industrial and clinical benefits. Pellets are spherical particles with a smooth surface, ideal size ranges from 0.7 to 1.4 mm. Pellets offer manufacturing privileges like excellent flow ability due to round shape, low friability, and narrow size distribution which are required for high coating efficiency, and uniform packing[12]. Pellets offer flexibility in the selection of sachet, capsule, tablet, or suspension as the final dosage form. Pellets can provide different release profiles at the same or different sites in the gastrointestinal tract (timed release). Pellets of different active ingredients can be blended to minimize multimedication or to accommodate incompatible actives[11].

Pelletization is the process that agglomerates fine bulk powders into free-flowing, small, semi-spherical, or spherical units, called pellets. This process can be done by different techniques like compression which involves extrusion and spheronization, agitation, layering, and globulation.

The extrusion-spheronization is a popular technique for pelletization. This technique involves wet mixing or melt dispersion of dry ingredients in the first step. The wet mass is extruded into cylinders (extrudates). These extrudates are broken into pieces and turned into spheres (spheronization) which are dried in a final step to yield pellets[13]. These steps must be understood well to understand the effect of different factors related to formulation (granulating liquid, excipients), machine (mixer, extruder with screen, spheronizer with a friction plate, dryer), and process (extrusion speed, spheronization time, and speed, material loading, drying method) which can influence the end quality of the pellets (properties include uniform size and spherical shape with smooth surface, good flow properties) and are to be considered during formulation optimization[12,14].

This research work aimed to develop pellets of Dried Ferrous Sulphate by extrusion spheronization technique.

2. MATERIALS AND METHODS

2.1 MATERIALS

Dried Ferrous Sulphate (Qualikems Fine Chem Pvt. Ltd, India), MCC-Microcrystalline cellulose (Avicel®) PH 102 (ACS Chemicals, India), 1, 10-Phenanthroline monohydrate (Merck Life Sciences Pvt. Ltd., India) were purchased. Gelucire® 43/01 was received as a gift sample by Gattefosse India Pvt. Ltd., India. HPMC K4M was gifted by Colorcon Asia Pvt. Ltd., India. Isopropyl alcohol (IPA) and all other chemicals used were of analytical grade.

2.2 METHODS

2.2.1 Spectrum analysis and Calibration curve of Dried Ferrous Sulphate

Accurately weighed Dried Ferrous Sulphate powder was dissolved in 0.1 N HCl to get a standard stock solution of 400 µg per ml. Standard drug dilutions of 4, 6, 8, 10, and 12 µg per ml were prepared by mixing 1, 1.5, 2, 2.5, and 3 ml of stock solutions individually with 2 ml Sodium acetate trihydrate (2 M) solution and 8 ml 1, 10-Phenanthroline reagent (0.25%), and diluted immediately with 0.1N HCl to 100 ml.

Spectrum was run of 4 µg/ml concentration from 400 to 800 wavelengths to confirm λ_{max} and was selected for calibration curve preparation[15](Figure 1).

The absorbance of each standard drug dilution was measured within 1 minute of dilution, using a UV/visible Spectrophotometer (SHIMADZU UV-1800 240W) at $\lambda_{max.}$, found from spectrum analysis.

2.2.2 A) Drug Characterization and Drug-excipient Incompatibility Study by Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectrum of pure drug was checked for the peaks of its characteristic functional groups. The drug-excipient incompatibility was checked through a comparison of FTIR spectra of pure drug and mixture of drug with excipients (Drug: Gelucire: HPMC K4M mixture in 1:1:1 ratio was packed and stored for 1 month at 25°C±5°C temperature and 60±5 % relative humidity before FTIR study). FTIR spectra (Figure 2) were generated in a range of 4000 to 400 cm^{-1} wavelength (model no. 112, FTIR, SHIMADZU Japan, Affinity-15 based on Attenuated total reflection technique[16].

2.2.2 B) Drug-excipient Incompatibility Study by drug content analysis

The compatibility of Dried Ferrous Sulphate in the presence of Gelucire 43/01 and HPMC K4M was checked and confirmed based on drug content analysis.

Dried Ferrous Sulphate and HPMC K4M were mixed in melted Gelucire (1:1:1 weight ratio) and the solidified mixture was packed and stored for 1 month at 25˚C±5˚C temperature and 60±5 % relative humidity. The mixture was analyzed after 1 month for its drug content (A mixture containing an amount of dried Ferrous Sulphate equivalent to 150 mg was dispersed in deionized water and stirred on a magnetic stirrer for 6 hours, filtered (0.45 µm membrane filter), and diluted. It was analyzed at λ_{max} 510 nm as per the procedure used for calibration curve development). The drug content of pure drug was compared with its equivalent amount in the mixture to indicate the drug's compatibility with excipients[17].

2.2.3 Preparation and optimization of Dried Ferrous Sulphate pellets by extrusion spheronization.

2.2.3 A) Formulation selection for screening of process parameters

The four trial batches as per Table 1 were prepared to select the best one for further screening of pelletization process parameters. Pellets were prepared using a laboratory scale basket-sieve type extruder (volume capacity of 314 cm^3) and spheronizer (volume capacity of 1074 cm^3) (Cronimach, India).

Table 1: Preliminary trial batches for formulation selection

	Quantity (%)						
Batch No.	Dried Ferrous Sulphate	Gelucire 43/01	HPMC K4M	MCC	IPA(70%v/v)	Deionized water	IPA(70%v/v): Deionized water (1:1)
T1*	30	45	15	10	-	-	-
T2	30	30	30	10	50#	-	-
T3	30	30	30	10	-	50#	-
T4	30	30	30	10	-	-	50#

*Melt extrusion procedure for T1 batch and wet mixing procedure for other batches

Solvent quantity added 50% to total weight of other ingredients

For the pellets preparation, all dry powder ingredients, Dried Ferrous Sulphate, HPMC K4M, and MCC were passed through an 80 # standard sieve and were weighed accurately. These ingredients were mixed thoroughly in a polybag for 10 minutes. The required amount of Gelucire® 43/01 was taken into a clean and dry mortar and melted at 43^0C on a thermostatic heating mantle. A dry mix from the previous step was then added to the melted Gelucire® 43/01 and kneaded for 5 minutes (the mixture was kept warm to avoid hard lump formation). At this point, the trial T1 batch (without solvent) mixture was ready for extrusion (melt extrusion)[18]. For other batches that involved solvent, the measured amount of wetting solvent was added slowly to the above lipid mixture and kneaded continuously for 5 minutes to get the soft wet mass ready for the extrusion. All batches were formulated for 20 g total bulk.

The soft mass was extruded at high speed (120 RPM) through a 16# (average aperture size of 1.0 mm) radial extrusion metal screen. Extrudates were collected and spheronized at a 2000 RPM speed, for 15 minutes using a friction plate 1 (Cross-hatched, 12 cm diameter with a grid height: width; 1:1 mm, and groove width of 2 mm). The spheronized pellets were collected on a paper sheet, in a tray, and air dried for 3 hours (at 30 ^{0}C room temp). The dried pellets were stored in an airtight plastic bottle and analyzed for evaluation parameters like pellet appearance, average pellet size, and process loss based on product yield. The mass extrudability and extrusion time were noted during extrusion (Table 2). All four batches were compared based on these qualitative and quantitative parameters.

2.2.3 B) Preliminary screening of process parameters to select significant parameters

Trial batch T4 formulation composition was selected and kept constant for the preliminary screening of extrusion speed, spheronization speed, and time as pelletization process parameters. Spheronizer friction plate was also included as one machine parameter. These batches (P1 to P12) were prepared at different spheronization speeds (800 RPM, 1500 RPM, 2000 RPM, 2500 RPM), at different spheronization times (5, 10, 15, and 20 minutes), at different extrusion speeds (Medium speed-70 RPM, High speed-120 RPM), and using two friction plates[12](Table 3). Trials were univariate type(only one factor varied at different levels for the comparison).

The effect of these process parameters was checked and compared based on the evaluation of the pellet's micromeritic properties which included average pellet size and pellet roundness as a shape parameter. Pellet's flow rate, angle of repose, bulk density, tapped density, and % carr's index as derived properties were also evaluated. The

significant process parameters were selected based on the comparison for further optimization.

2.2.3 C) Optimization of significant process parameters

Spheronization speed and time were found and selected as the significant process parameters to achieve the desired pellet properties of the selected T4 formulation composition. These parameters were optimized using an experimental design. Response surface randomized, factorial (3 levels, 2 factors) design was applied using Design of Expert 10.0.1, Software.

A spheronization speed of 2000 RPM and a spheronization time of 15 minutes were selected as central values. The software generated the design matrix of 10 batches (with repeat center point) (F1-F10) as per Table 4.

The Design matrix included spheronization speed (RPM), at 1750 (-1), 2000(0), and 2250 (+1) levels. It included spheronization time (minutes), at 12 (-1), 15 (0), and 18 (+1) levels.

For all these batches extrusion was done at 120 RPM and using friction plate 1 of spheronizer. Optimization was done based on the three desired pellet characteristics as response variables, R1:R2:R3; Average pellet size: pellet roundness: pellet product (16-30#) yield.

2.2.4 Characterization of pellets

Pellets were characterized for the following properties.

Average pellet size A standard sieving method was used to measure pellet average pellet size using a vibratory sieve shaker ((Singhla Scientific Industries, India) and a sieve set of 16,22,30,44, and 60 sieve numbers (10 g loading samples, shaken for 1 min). The weight of the pellets in each size fraction was determined. From these data average pellet size was calculated[19].

Pellets shape Roundness (reciprocal of Aspect ratio) as the pellet's shape(roundness ranges from 0 to 1, 1 is for spherical particle), indicating parameter was measured using a microscope with calibrated eyepiece micrometer scale ((OLYMPUS, CX33, Japan). Fifty pellets (retained on 22# and 30#), on a clean glass slide were observed to calculate average roundness[12]. Roundness of the pellet was calculated by dividing the measured inscribed (smallest) diameter by the circumscribed (largest) diameter of the pellet[20][21]. SAMSUNG GALAXY M30 mobile camera was used to take photographic images of Pellets (Figure 3).

Flow rate and angle of repose The Flow rate of pellets was calculated based on the time taken for the 10 g pellets to pass through a glass funnel (2 cm diameter). An angle of repose was measured by the fixed funnel method.

Bulk density, Tapped density, and % Carr's Index These were measured as per the standard procedure.[19]

Drug content To check the uniform mixing of a drug in pellets, the drug content of an optimized batch (F5) was checked as per the procedure mentioned in the "Drug-excipient Incompatibility Study by drug content" analysis section.

***In-vitro* dissolution study** The pellets (22#) of an optimized batch (F5) were evaluated for % drug dissolution, in 0.1 N HCl dissolution media (37^0C±0.5^0C temperature), at 50 RPM paddle speed (USP type 2 paddle dissolution apparatus (VEEGO, VDA-8D)). Pellets with a dose equivalent to 150 mg of Dried Ferrous Sulphate were added to the dissolution medium for the study. After 1 hr, a 5 ml sample was withdrawn, filtered (0.45 µm membrane filter), and diluted with 0.1 N HCl. The diluted samples were analyzed as per the procedure used for the drug calibration curve.

All characterization data are presented as a mean of triplicate results with standard deviation.

2.2.5 Statistical analysis

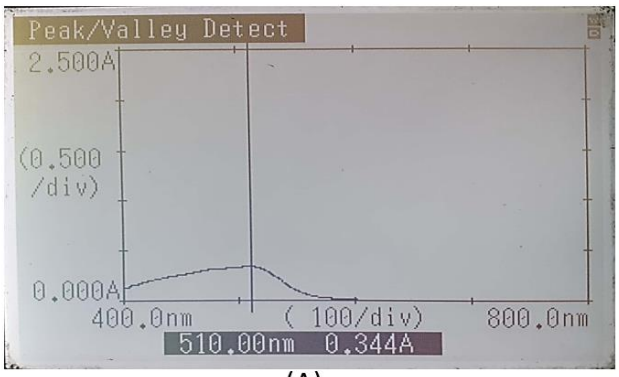
Statistical analysis of the input data of factorial batches was done using the design expert 10.0.1 software (Stat-Ease, USA) by applying the Quadratic polynomial model and the Analysis of variance (ANOVA) method. 3D response surface curves were generated. Regression analysis was done at a 0.05 level of significance to generate polynomial equations of the response variables.

3. RESULTS AND DISCUSSION

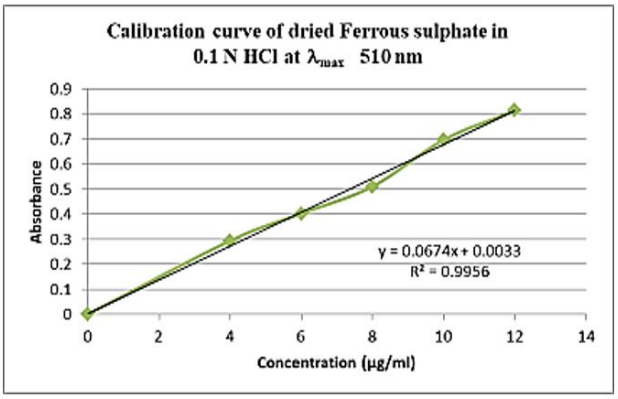
3.1 Spectrum analysis and Calibration curve of Dried Ferrous Sulphate

The UV-visible spectrum of a drug (Figure 1A) indicated λ_{max} (maximum absorbance wavelength) at 510 nm. A standard calibration curve of Dried Ferrous Sulphate in 0.1 N HCl at 510 nm wavelength was generated as per Figure 1B. The drug followed Beer Lambert's law with $R^2 = 0.9956$ and the regression equation was generated as $y = 0.0674x + 0.0033$.

Spectrophotometric analysis of metallic ferrous ions depends on its complexation with 1, 10-Phenanthroline (ligand) which results in a stable red color complex. This complex absorbs visible light of 510 nm wavelength (maximum). The intensity (absorbance) of the color increases linearly with increased concentration of ferrous ions in the solution which was confirmed by near to 1 value of R^2 hence this colorimetric estimation is useful to identify drug content and % dissolved drug using regression equation[15].



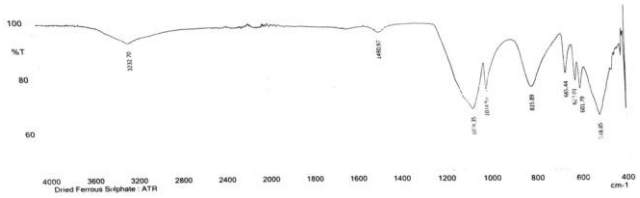
(A)



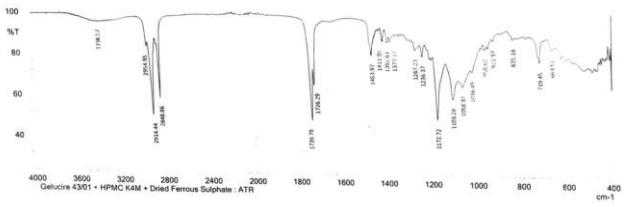
(B)

Figure 1 (A) Spectrum analysis of Dried Ferrous Sulphate (B) Standard Calibration Curve of Dried Ferrous Sulphate in 0.1 N HCl

3.2 A) Drug Characterization and Drug-excipient Incompatibility Study by FTIR



(A)



(B)

Figure 2 (A) FTIR spectrum of Dried Ferrous Sulphate (B) FTIR spectrum of a mixture of Drug and polymers

FTIR spectrum of pure Dried Ferrous Sulphate (Figure 2A) showed peaks at 3232 cm^{-1} (matches with reference peak 3410 cm^{-1}due to OH stretching of HSO_4 group), 1074 $cm^{-1}$and 1014cm^{-1} (similar to reference peaks from 1060 $cm^{-1}$to 1170cm^{-1} of S=0 stretching). The FTIR spectrum of the mixture of drug and polymers (Figure 2B) indicated retention of drug characteristic peaks at 3398 cm^{-1}, 1058 cm^{-1}, and 1016 cm^{-1} without significant shifting in their position. FTIR spectroscopy is a useful analytical tool to confirm the molecular structure of the drugs based on the identification of the peaks specific to functional groups present in the drug molecule. Significant shifting of peak position can be used to understand the incompatibility of a drug in the presence of other molecules. The spectra comparisons suggested compatibility between the drug and polymers used during the study[16].

3.2 B) Drug-excipient Incompatibility Study by drug content analysis

An average % Drug content, in a mixture, was observed at 98± 2 % (n=3) which was not significantly different than the 101± 1.3 % (n=3) drug content of the drug alone in a sample.

Drug content analysis of a mixture of excipients with the drug indicates the drug's compatibility with excipients[17]. There was no significant deviation observed in the drug content data of pure drug and drug in a mixture which confirmed the compatibility of Dried Ferrous Sulphate with Gelucire 43/01 and HPMC K4M.

3.3 Preparation and optimization of Dried Ferrous Sulphate pellets by extrusion spheronization.

3.3 A) Formulation selection for screening of process parameters

A comparison of qualitative and quantitative parameters (Table 2) of all four trial batches was done. Gelucire was selected as it works as a lipid binder and may yield a lubricating effect. It also provides high resistance to fracture because of the plasticity of lipid agglomerates[22]. HPMC K4M was selected as a hydrophilic binder and filler. MCC was selected to facilitate pelletization based on the literature[23].

The T1 batch was soft enough without solvent for the extrusion due to the higher amount of Gelucire and the pellets produced were spherical. As it is a low melting lipid, sticking to the metal surfaces of the extruder and spheronizer caused difficulty during processing and product loss. The other three batches differed only in the type of solvent used which significantly affected all the parameters. Solvent addition was required, to make the mass soft and extrudable[14]. As formulations contained both hydrophobic (Gelucire) and hydrophilic (Drug, MCC, and HPMC K4M) material, the addition of only organic solvent (IPA) or deionized water could not wet and bind the entire mass effectively. Poor binding in mass resulted in

Table 2 Qualitative and quantitative analysis of trial batches for formulation selection

Trial Batch	Extrudability	Extrusion time (minutes) mean±SD (n=3)	Pellet appearance	Average pellet /granule size (µm) mean±SD (n=3)	%Product yield±SD (n=3)
T1	Yes*	4±0.2	Uniform-size spherical pellets	1700±72	35±1.72
T2	Yes*	8±0.3	Irregular granules and powder aggregates.	346±15	34±1.65
T3	Yes	5±0.5	Irregular granules and powder aggregates.	804±38	42.5±2.05
T4	Yes	3±0.2	Pellets with normal size distribution	620±25	92.5±3.92

*Intermittent scrapping of the screen was required during extrusion due to the sticking of wet mass over the extrusion screen

fragmentation which affected size, shape, and product loss due to the sticking of rubbery mass (nonsolvent effect) to the machine surfaces. The T4 batch with an equal ratio of organic and aqueous solvent effectively activated the binding effect of Gelucire and HPMC and the lubricating effect of Gelucire significantly improved all the parameters in the desired range. The trial batch T4 formulation composition was selected as the best one among the other formulations and was selected for further trials on screening of process parameters.

3.3 B) Preliminary screening of process parameters to select significant parameters

Micromeritic properties of pellets prepared with T4 formulation composition at different process parameters(Table 3) were compared.

Table 3 Micromeritic evaluation of pellets at different Spheronization speeds, time, friction plate, and extrusion speed

Batch	Spheronizer Speed (RPM)	Spheronizer Time(minutes)	Average pellet size (µm)±SD (n=3)	Roundness±SD(n=50)	Flow rate g/sec±SD (n=3)	Angle of repose Θ°±SD (n=3)	Bulk density (g/cc) ±SD (n=3)	Tapped density (g/cc) ±SD (n=3)	% Carr's Index ±SD (n=3)
P1	800	15	689.19±29	0.53±0.03	4.80±0.09	31.0±1.2	0.71±0.02	0.74±0.02	4±0.1
P2	1000	15	620.23±24	0.65±0.03	4.80±0.1	31.0±1.3	0.71±0.02	0.74±0.02	4±0.1
P3	1500	15	691.90±27	0.73±0.02	4.50±0.9	28.6±1.2	0.71±0.02	0.74±0.02	4±0.1
P4	2000	15	620.47±25	0.90±0.02	6.34±0.08	23.4±1.2	0.71±0.02	0.74±0.02	4±0.1
P5	2500	15	570.48±21	0.92±0.03	6.11±0.09	23.4±1.0	0.67±0.02	0.71±0.02	6±0.3
P6	2500	10	616.45±15	0.90±0.05	6.34±0.08	23.4±1.2	0.71±0.02	0.74±0.02	4±0.1
P7	2500	5	563.13±28	0.85±0.11	6.11±0.04	23.4±1.2	0.71±0.02	0.74±0.02	4±0.1
P8	2000	10	586.84±23	0.80±0.09	6.34±0.09	23.4±1.2	0.71±0.02	0.74±0.02	4±0.1
P9	2000	20	592.20±26	0.93±0.03	6.66±0.08	23.4±1.2	0.67±0.03	0.71±0.03	6±0.3
P10	1500	20	625.31±28	0.81±0.13	4.51±0.06	28.6±1.3	0.71±0.03	0.74±0.03	4±0.1
P11	2000*	15	640.43±27	0.90±0.02	6.40±0.10	24.57±1.2	0.71±0.02	0.74±0.02	4±0.1
P12	2000#	15	468.30± 15	Aggregate	-	-	-	-	-

*Friction plate 2 was used (Cross hatched, 12 cm diameter. Grid height: width; 1:2 mm, groove width 4 mm)
#Pelletization at medium extrusion speed (70 RPM) with friction plate 1

Comparison of P1 to P5 data indicated the significant effect of spheronization speed on the pellet roundness (Shape). An increased spheronization speed improved the roundness (sphericity) of the pellets (Figure 3 (A)). Almost spherical pellets were found in the P4 and P5 batches. Increased spheronization time (Figure 3 (B)) at the same spheronization speed also improved pellet roundness (P5:P6:P7; P3:P10; P4:P8). This observation confirmed the reported effect on the spheronization of these parameters[24].

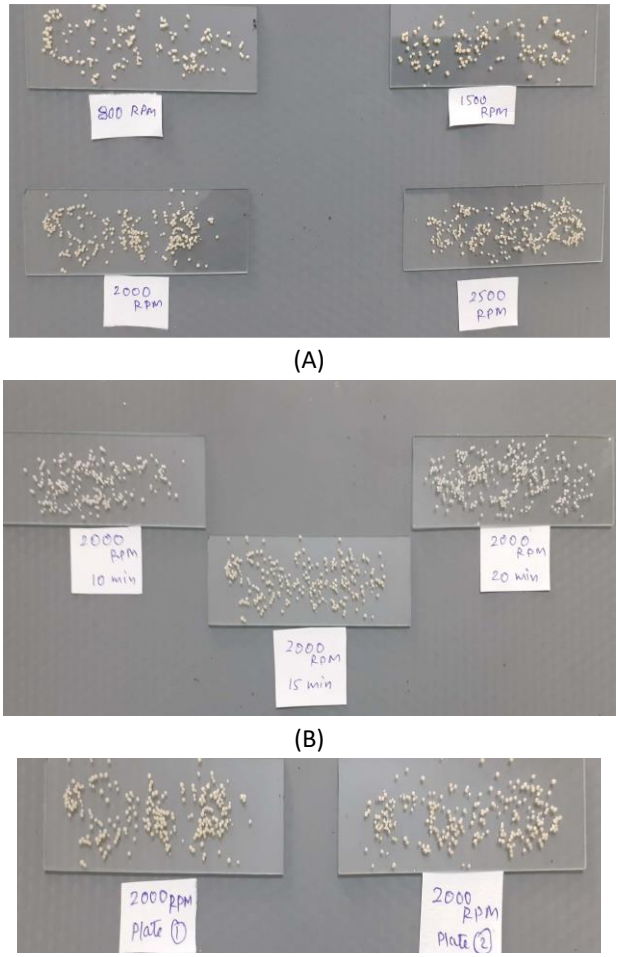


Figure 3 Effect of spheronization (A) Speed on pellet size and roundness (B) Time on pellet roundness (C) Friction plate on pellet size and roundness

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The effect of these parameters on pellet size was different. Pellet size increased from low to medium speed but decreased at high speed(P2-P5) A similar effect was observed with time parameters (P4:P8:P9; P5:P6:P7). This may be related to the friability of pellets occurring due to the high attrition of pellets with each other or with the spheronizer surface during the process at high speed and or for a prolonged time.

Pellet properties found were similar to pelletization with both friction plates 1 and 2 (P4 and P11), and friction plate 1 was selected for further optimization which was found with slightly better pellet roundness (Figure 3 (C)) and lower pellet size (friction plate 1 with smaller dimensions than friction plate 2 may have produced smaller pellet size[12]).

Batch P12 was prepared, at the medium extrusion speed. It resulted in high product loss (33%) which may occurred due to the solidification of Gelucire during extrusion (friction heat generated is low with slow speed and keeps low temperature environment [25]). The low speed may have affected the density and hence hardness of extrudates which resulted in powder aggregates during spheronization. Comparison of other properties was meaningless, hence were not analyzed.

At and after 2000 RPM spheronization speed, change in other process parameters did not affect significantly the other properties (derived properties). The pellet shape observed in batch P4 was similar to that found in batch P5, and batch P9.

Based on these observations, spheronization speed and time were considered as the significant process parameters for the optimization. These process parameters significantly affected pellet size and shape which were considered as desired response variables. The product yield of the pellet in size range (undersize to 16# and oversize to 30#) was also included as the response variable which indicated uniformity in the size of the pellets produced.

3.3 C) Optimization of significant process parameters

Table 4 Batches with response data as per 3^2 Factorial Design

Batch	Factor 1 A: Spheronization Speed RPM	Factor 2 B: Spheronization Time Minutes	Response 1 R1:Mean pellet size (µm) Mean± SD (n=3)	Response 2 R2:Pellet roundness Mean±SD (n=50)	Response 3 Product(16-30#) yield (%) Mean±SD (n=50)
F1	1750	12	619±23	0.65±0.03	94±2
F2	2000	12	616±18	0.78±0.03	93±3
F3	2250	12	589±27	0.82±0.02	86±2

F4	1750	15	624±30	0.75±0.03	92±3
F5	2000	15	618±20	0.84±0.03	90±2
F6	2250	15	600±20	0.91±0.02	85±4
F7	1750	18	615±21	0.68±0.04	90±5
F8	2000	18	609±25	0.73±0.04	89±4
F9	2250	18	590±27	0.9±0.02	84±3
F10	2000	15	617±23	0.85±0.03	90±3

3^2 Full factorial design was selected to create design space and to understand the effect of individual factors and their interactive effect on the response variables[13]. Increased speed and time improved pellet roundness but reduced pellet size and product yield. The results confirmed the effect of these process parameters, observed during a screening of parameters. Design space was generated based on the desired response criteria (R1:R2:R3; 610-620 µm:0.85 to 1: 90% and above). Considering all the response variables, batch F5 was considered as an optimized batch. Batch F5 contained % of Drug: Gelucire 43/01: HPMC K4M; 30:30:30, with 50 % wetting solvent (IPA(70%v/v): Deionized water;1:1). This batch was extruded at 120 RPM through 16# radial screen. It was spheronized at 2000 RPM for 15 minutes using friction plate 1. The resultant mean pellet size, pellet roundness, and product yield were 617 µm, 0.85, and 90% respectively.

3.4 Characterization of pellets

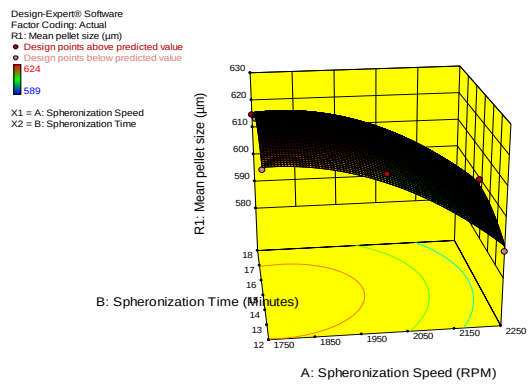
The average drug content of batch F5 observed was 99.54 %± 4.3 SD (n=3). This indicated uniformity of drug mixing in the bulk formulation. An average *in-vitro* % drug dissolution in 0.1 N HCl at 1 hour was 98.99± 3.5 SD (n=3) indicating that the total drug dissolved within 1 hr. The amount of Gelucire 43/01 and HPMC K4M, used in the formulation of batch F5 allowed immediate drug release. The pellets floated within 15 minutes in the dissolution media and then turned into a soft gel layer followed by dispersion. This optimized multi-particulate, pellet dosage form of Dried Ferrous Sulphate would be a potential alternative to oral immediate-release iron supplements with the advantages of multi-unit dosage forms.

3.5 Statistical analysis

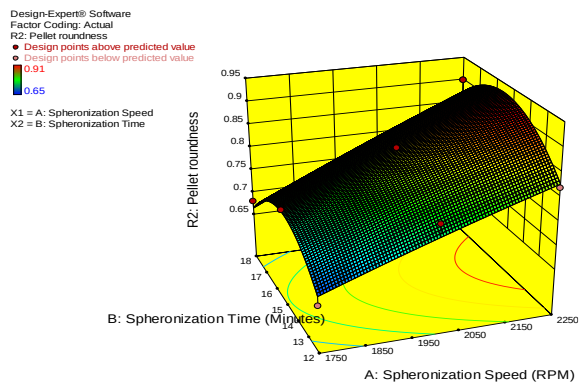
The statistical analysis generated 3D response surface curves for all three response variables.

The 3D graphical presentation facilitated a quick understanding of the significant effect of spheronization speed and time, observed on mean pellet size in Figure 4 (A), pellet roundness in Figure (B), and % product (16-30#) yield in Figure 4 (C).

A yellow region is the design space[26], in the overlay plot (Figure 4 (C)) which was generated based on the desired criteria input data. The checkpoint batch suggested in this region (at 2032 RPM speed for 14.5 minutes) was prepared and evaluated. The actual response variables obtained were compared with the predicted values by the model. The design model was found valid for its use as there were no significant differences between actual and predicted values.



(A)



(B)

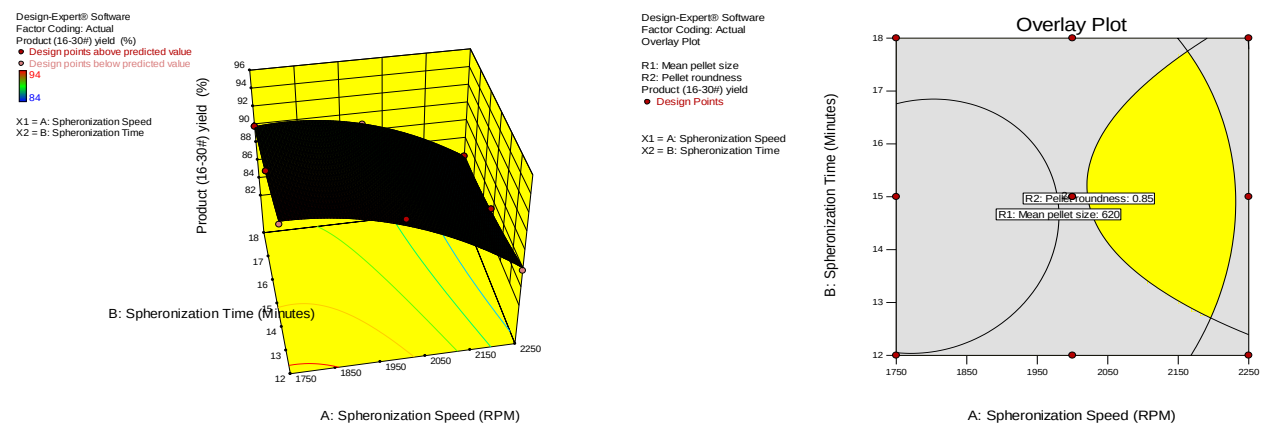


Figure 4 3D response surface curves indicating an effect of spheronization speed and time on response variables (A) R1: Mean Pellet size (B) R2: Pellet roundness (C) R3: % product (16-30#) yield (D) Overlay plot (Yellow design space) of two process parameter for the desired criteria of all response variables

The polynomial equations (with only significant terms based on p-value less than 0.05) with coefficient values for each factor were generated for each response variable as R1 = 618.9-13.17A-7.86A^2-7.38B^2, R2 = 0.84+0.092A-0.079B^2, and R3 = 90.29-3.5A-1.67B-2.07A^2, where factor A is spheronization speed and B is spheronization time.

A positive coefficient value in the equation indicates an increased value of the response variable for an increased value of the particular factor. A negative coefficient value in the equation indicates a decreased value of the response variable for an increased value of the particular factor. The interactive effect of the two factors was found insignificant. Polynomial equations are useful to get the desired values of response variables.

4. CONCLUSION

Based on the result data, it was concluded that formulation composition and extrusion-spheronization process parameters significantly influenced the micromeritic properties of the Dried Ferrous Sulphate pellets, specifically pellet size, and shape. These parameters were successfully optimized by a 3-level, 2-factor factorial design, based on mean pellet size, pellet roundness, and product yield. The batch F5 was concluded as an optimized batch. This optimized pellet dosage form of Dried Ferrous Sulphate would be a potential alternative to immediate-release oral iron supplement with all the advantages of a multi-particulate dosage form.

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6. CONFLICT OF INTEREST

The authors of this research study declared no conflict of interest in publishing the work.

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