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FORMULATION, EVALUATION, AND OPTIMIZATION OF GLIMEPIRIDE NANOSUSPENSION BY USING ANTISOLVENT EVAPORATION TECHNIQUE

Dattatraya Manohar Shinkar[1]*, Sonal Sanjay Jadhav[1], Prashant Laxman Pingale[1], Sahebrao Sampat Boraste[1], Sunil Vishvnath Amrutkar[2]

1. *Department of Pharmaceutics, GES's Sir Dr. M. S. Gosavi College of Pharmaceutical Education & Research, Nashik-422005, MS, India.*
2. *Department of Pharmaceutical Chemistry, GES's Sir Dr. M. S. Gosavi College of Pharmaceutical Education and Research, Nashik-422005, MS, India.*

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ABSTRACT

Recent work aimed to prepare nanosuspension of glimepiride by using antisolvent evaporation followed by sonication technique. As glimepiride belongs to BCS class II, thus it has less solubility and high permeability. Hence to enhance the solubility of glimepiride, it was formulated into nanosuspension. Different polymers were used to prepare stable nanosuspension by taking several trial batches. After getting the results from trial batches, the combination of Pluronic F68 and PEG 400 was selected for the preparation of glimepiride nanosuspension by using a 3^2 full factorial design. After evaluation of nine formulation batches, batch FG8 showed the highest %Entrapment efficiency of 85.3 ± 0.73 %. In comparison to other batches, the FG8 batch showed a percent total drug content of 96.40 ± 0.4 % which was the highest one. All batches of nanosuspension were evaluated for different parameters; in that batch, FG8 showed the minimum particle size of 177.1 ± 0.08 nm, low polydispersity index of 0.142 ± 0.01, and highest zeta potential of 33.0 mV respectively. In comparison to the release of pure drug glimepiride, an *in-vitro* dissolution study showed that batch FG8 had a maximum release of 97.6% at 60 minutes. The optimization was carried out mostly using a linear model. Following the study and collecting the ANOVA results, it was revealed that the FG8 batch was an optimized batch by using the combination of Pluronic F68 and PEG 400 a stable nanosuspension was formulated which enhanced the solubility followed by dissolution of pure glimepiride drug.

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Introduction

Nanotechnology is a subset of nano-science, which is one of the most promising, hard, and exciting research fields in today's scientific landscape [1]. It is the study of fine particles with distinctive aspects that changes as the particle's shape changes. More than 40% of medicines identified through high-throughput screening are water insoluble. Poorly water-soluble substances present plenty of challenges when it comes to putting them into traditional dosage forms. Low bioavailability and absorption are two major issues with poorly soluble drugs. Micronization, solubilization with co-solvents, usage of permeation enhancers, oily solutions, surfactant dispersions, salt creation, and precipitation procedures are some of the formulation techniques used to overcome the problems of poor solubility and poor bioavailability. These solubility increase systems have some restrictions, and so have partial utility in solubility improvement [2, 3]. Nanotechnology allows for a more tailored approach as well as increased bioavailability. It can also be employed with both lipophilic and hydrophilic agents. Pharmaceutical delivery techniques usually nanoformulations are a popular means of improving the pharmacokinetic features of drug compounds. Nanosuspension, nanoemulsion, polymeric nanoparticles, liposomes, and dendrimers are a few examples [4]. Nanosuspension is a sub-micron colloidal dispersion of drug particles that are stabilized by surfactants, polymers, or a mixture of both. They can also be called a biphasic system composed of pure drug particles in an aqueous vehicle with a particle diameter of fewer than 1 μm, with an average particle size ranging between 200 and 600 nm [5, 6]. Diabetes mellitus (DM) is a long-term

Corresponding Author: Dattatraya Manohar Shinkar; Department of Pharmaceutics, GES's Sir Dr. M. S. Gosavi College of Pharmaceutical Education & Research, Nashik-422005, MS, India. E-mail: dattashinkar@gmail.com.

endocrine and metabolic illness caused by a problem with insulin production and activity. Hyperglycemia can also be caused by the excess supply of other factors such as glucagon, adrenal hormones, or insulinase excitability. For medical applications, glucose level changes during the day, and two kinds of readings are commonly used. The usual fasting blood sugar level is ≥ 126 milligrams per deciliter, or ≥ 200 milligrams per deciliter two hours following ingesting 75 g of the glucose load [7, 8]. Oral anti-diabetic medications are oral drugs that help patients reduce their blood glucose levels. Glimepiride is a sulfonylurea derivative that is taken orally to treat type 2 diabetes [9, 10]. Sulfonylurea is also known as K_{ATP} Channel blockers. Sulfonylureas each have the same pharmacology composition, with the only function of reducing glucose levels in healthy people and type 2 diabetics, and not in type 1 diabetics. Sulfonylureas bind to ATP-Activated potassium channel complex (sulfonylurea receptor, SUR1). This binding reduces the outward flow of K+ ions across the cell membrane thus leading to the closure of the channel. This depolarizes the membranes and triggers the opening of Ca++ channels, leading to the rapid influx of Ca. Which increases intracellular Ca++ and causes alteration in the cytoskeleton. This stimulates the translocation of insulin-containing secretory granules to the plasma membrane and the release of insulin [11, 12]. Nanosuspension is a sub-micron colloidal dispersion of drug particles that are stabilized by surfactants, polymers, or a mixture of both. They can also be called a biphasic system composed of pure drug particles in an aqueous vehicle with a particle diameter of less than 1µm. Solid particles in nanosuspensions generally have a particle size distribution of less than one micron, with an average particle size ranging between 200 and 600 nm [13, 14]. A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration [15-17]. Mainly BCS class II drugs which are having low solubility and high permeability as well as BCS class IV drugs having low solubility and low permeability are generally formulated as nanosuspension [18, 19]. Nanosuspension can improve the solubility of drugs that are low soluble in both water and lipid environments. The rate and extent of drug dissolution can be accelerated by decreasing the particle size of the drug. The size of a drug particle has a strong influence on its solubility. When drug particles become smaller, they have more contact with the solvent, which increases the solubility [20-22].

Materials and Methods

Glimepiride has been acquired as a gift specimen from Ajanta Pharmaceutical Pvt. Ltd, Kandivali West, Mumbai, Polyvinyl Pyrrolidone K30, Pluronic F60, and PEG 400 were procured from Modern Industries, Nashik. All other reagents including organic solvents used for analytical purposes were of analytical grade obtained from Thermo Fisher Scientific India Pvt. Ltd.

Method for the Preparation of Nanosuspension

Nanosuspension was formulated by antisolvent evaporation followed by the sonication technique. An appropriate amount of the drug was dissolved in an organic solvent (Solution 1). Polymers and surfactants were incorporated in an aqueous solvent (Solution 2). 1 ml of solution 1 of the drug was injected drop-wise in an aqueous solution 2 with rapid stirring at 1200 rpm. Homogenization for a sufficient time, followed by intense sonication.

Formulation of Trial Batches

Several polymers were used for formulation purposes such as Pluronic F68, PEG 400, and PVP K30 as a stabilizer along with sodium lauryl sulfate as a surfactant. A preformulation study was conducted before the formation of nanosuspension to assess the drug for its organoleptic qualities, melting point determination, solubility study, determination of absorbance maxima (λ_{max}), FT-IR analysis, and drug-excipient compatibility study. For the selection of a combination of stabilizers, PVP K30, PEG 400, and Pluronic F68 were used as common stabilizers at different ratios in trial batches as shown in **Table 1**.

Table 1. Formulation of Trial Batches

Batch code	Glimepiride (mg)	PVP K30 (mg)	PEG 400 (mg)	Pluronic F68 (mg)	SLS (mg)	Acetone (ml)	Water (ml)	Homogenization speed (rpm)
T1	1	10	-	-	04	02	40	1200
T2	1	20	-	-	04	02	40	1200
T3	1	30	-	-	04	02	40	1200
T4	1	-	10	-	04	02	40	1200
T5	1	-	20	-	04	02	40	1200
T6	1	-	30	-	04	02	40	1200
T7	1	-	-	10	04	02	40	1200
T8	1	-	-	20	04	02	40	1200
T9	1	-	-	30	04	02	40	1200
T10	1	05	-	05	04	02	40	1200
T11	1	-	10	10	04	02	40	1200
T12	1	15	15	-	04	02	40	1200

Formulation of Nanospension by using 3^2 Full Factorial Design

3^2 full factorial design was used for the formulation of nanosuspension of Glimepiride. From the result of % Entrapment efficiency, the combination of Pluronic F68 and PEG 400 in the ratio of 10:10 along with glimepiride was selected to prepare factorial design batches. The nine glimepiride nanosuspension batches illustrated in **Table 2** was prepared by using a combination of Pluronic F68 (X1) and PEG 400 (X2) at three levels as low, medium, and high with sodium lauryl sulfate as the surfactant, acetone as organic solvent and water as a vehicle with homogenization speed of 1200 rpm.

Table 2. Formulation of Glimepiride Nanosuspension

Batch code	Glimepiride (mg)	Pluronic F68 (mg) (X1)	PEG 400 (mg) (X2)	SLS (mg)	Acetone (ml)	Water (ml)	Homogenization speed (rpm)
FG1	1	10	10	04	02	40	1200
FG2	1	10	20	04	02	40	1200
FG3	1	10	30	04	02	40	1200
FG4	1	20	10	04	02	40	1200
FG5	1	20	20	04	02	40	1200
FG6	1	20	30	04	02	40	1200
FG7	1	30	10	04	02	40	1200
FG8	1	30	20	04	02	40	1200
FG9	1	30	30	04	02	40	1200

Optimization Data Analysis

The variables in this study were optimized using a 3^2 full factorial strategy. The study plan and response surface plot were created using Stat-Ease 360, a design expert software that was utilized to analyze data from all of the formulations. The software was used to select a general linear model for all of the response variables. A linear model's objective is to describe or predict a quantitatively dependent variable using a set of independent variables, which can be categorical or quantitative.

Drug Entrapment Efficiency

The unentrapped glimepiride was estimated to evaluate the entrapment effectiveness of glimepiride nanosuspension. To summarize, the amount of unentrapped drug was removed from nanosuspension by centrifugation at 20,000 rpm for 30 minutes at 4 ± 0.5 ˚C in a cool ultracentrifuge, and the supernatant was spectrophotometrically (Shimadzu UV1800) examined at wavelength 228nm (n=3) [23]. The % entrapment efficiency (%EE) was determined by using the following equation:

$$\%\text{Entrapment efficiency (\%EE)} = \frac{(\text{Total drug taken} - \text{Drug in supernatant liquid})}{\text{Total drug taken}} \times 100 \quad (1)$$

Total Drug Content

A sample of 0.5 ml was evaporated until it was completely dry. After that, the remainder was dissolved in acetone and filtered through 0.45-micron filter paper. A UV spectrophotometer with a maximum wavelength of 228 nm was used to examine the samples. Total drug content (TDC) and % TDC were determined by following equations 2 and 3.

$$TDC = \frac{\text{Vol. total}}{\text{Vol. Aliquot}} \times \text{Drug amount in aliquot} \times 100 \quad (2)$$

$$\%\ \text{TDC} = \frac{\text{TDC}}{\text{TAD}} \times 100 \quad (3)$$

Where, Vol. total/ Vol. Aliquots are the ratio of total nanosuspension volume to the volume of aliquots taken and the total amount of drug (TAD) taken for the formulation of nanosuspension [24].

Particle Size Analysis

The HORIBA Scientific SZ 100 V2 Analyzer was used to estimate the average particle size and polydispersity index of nanosuspension formulations. For scanning, water was employed as a dispersion medium. The particle size was determined by scanning the sample 100 times.

Zeta Potential

The HORIBA Scientific SZ 100 V2 Zetasizer was used to measure the zeta potential of nanosuspension compositions. Before analysis, the samples were diluted using a suitable solvent. Zeta potential of at least ±30 mV is necessary for physically stable nanosuspensions sustained by electrostatic repulsion. The absolute value of zeta potential of about ±20 mV is adequate to

properly stabilize the nanosuspension formulation in the case of combined electrostatic or steric stabilization [25].

Differential Scanning Calorimetry
The current assets of the drug Glimepiride and one of the optimized batches were characterized by Differential Scanning Calorimeter (DSC 3 /500 / 3297, METTLER TOLEDO). Both the samples i.e. the drug and an optimized batch of 1.2000mg and 1.5000mg respectively used for scanning purposes.

In vitro Drug Release Studies
Using a USP type II dissolution device (Electrolab Dissolution Tester USP EDT 08L) with a speed of 50 revolutions per minute and saline PBS pH 6.8 as the dissolution medium at 37 ± 0.5 degree Celsius, drug release profiles of nanosuspensions produced using various procedures were studied. A sample of 5 mL was taken at various times ranging from 5 to 60 minutes. The fresh dissolution medium was added to the same volume. At ʎmax 228 nm (n = 3), the amount of emitted Glimepiride was measured spectrophotometrically (Shimadzu UV1800) [26-28].

Stability Study
The stability study of nanosuspension is done for 3 months as per the guidelines of ICH. The optimized batch FG8 is placed at 40 degrees Celcius ± 2 degrees Celcius, 75% Relative Humidity ± 5% Relative Humidity. The nanosuspension was filled into the vial and properly placed into the stability chamber for 3 months [29, 30].

Results and Discussion

Formulation of Trial Batches
Twelve trial batches were prepared to find out the best combination of polymers to use as a stabilizer for the preparation of nanosuspension, with the first nine batches including a 1:10, 1:20, and 1:30 drug and single polymer combination, respectively. The last three batches were made using a drug and two polymer combinations in the proportions of 1:5:5, 1:10:10, and 1:15:15. In the study of trial batches, the combinations of Glimepiride and Pluronic F68 in a 1:10 ratio (batch T7) and Glimepiride, Pluronic F68, and PEG 400 in a 1:10:10 ratio (batch T11) showed the highest percent Entrapment effectiveness of 83.60.08 and 81.40.34%, respectively. Based on the % Entrapment efficiency of trial batches, 3^2 full factorial designs with three levels of the low, medium, and high, and two factors of Pluronic F68 (X1) and PEG 400 (X2) were used to create nine nanosuspension batches.

Formulation of Nanosuspension by Using 3^2 Full Factorial Design
From the result of % Entrapment efficiency of trial batches, the combination of Pluronic F68 and PEG 400 shows the highest % entrapment efficiency. Thus by using a combination of Pluronic F68 and PEG 400 further nine batches were formulated and evaluated in different ratios of polymers.

Drug Entrapment Efficiency
The prepared final batches of glimepiride nanosuspension were evaluated for % Entrapment efficiency. The result obtained shown that the batch FG8 in a combination of glimepiride with Pluronic F68 and PEG 400 in the ratio of 1:30:20 have highest % Entrapment efficiency of 85.3±0.73 %.

%Total Drug Content
The % Total drug content of final batches of nanosuspension was obtained in the range of 84.10±0.65 to 96.4±0.04 %, which shows that there is minimum loss of drug during the formulation process of nanosuspension. The batch FG8 in the combination of glimepiride along with Pluronic F68 and PEG 400 shows the highest % total Drug Content of 96.4±0.04 %.

Particle Size Analysis
The particle size and PDI of the nanosuspension batches FG1 to FG8 were determined by using the HORIBA Scientific nanoparticle analyzer SZ-100V2. The average particle size and polydispersity index of nanosuspension batches were found to be between 177.1±0.08 to 525.2±0.15 nm and 0.142±0.01 to 0.781±0.37 respectively. PDI values greater than 0.5 tend to congregate and have huge size dispersion. The nearer the PDI value is to zero, the more homogeneous nanosuspension is created. According to the result, batch FG8 shows the minimum particle size and pdi of 177.1 ± 0.08 nm and 0.142 ± 0.01.

Zeta Potential
The electrophoretic flexibility of particles in an electric field was measured by using the same equipment to calculate the zeta potential of nanosuspension batches FG1 to FG9. The zeta potential result is provided in the table below. The zeta potential is a measurement of the electric charge on a particle's surface which assures the physical stability of fabric-based nanosuspensions. According to the result obtained, the zeta potential was found between 17.30 to 33.0 mV. Generally, a zeta potential of ± 30 millivolts is needed in case of electrostatic repulsion whereas a zeta potential of ± 20 millivolts is needed for combined electrostatic or steric stabilization. Of the nine batches, the FG8 batch shows the highest zeta potential of 33.0 mV.

Differential Scanning Calorimetry

The DSC of Glimepiride and an optimized batch of nanosuspension were taken between 0-350˚C at a heating rate of 20 degrees per min. In the DSC graph of Glimepiride, a sharp peak was obtained at 212.37˚C due to the melting point of glimepiride. While in the DSC thermogram of the optimized batch the peaks are obtained due to the polymers like Pluronic F68 and PEG 400 at their respective melting point. From the obtained graph it was observed that there was no interaction between drug and excipients as shown below in the **Figure 1** and **Figure 2** respectively.

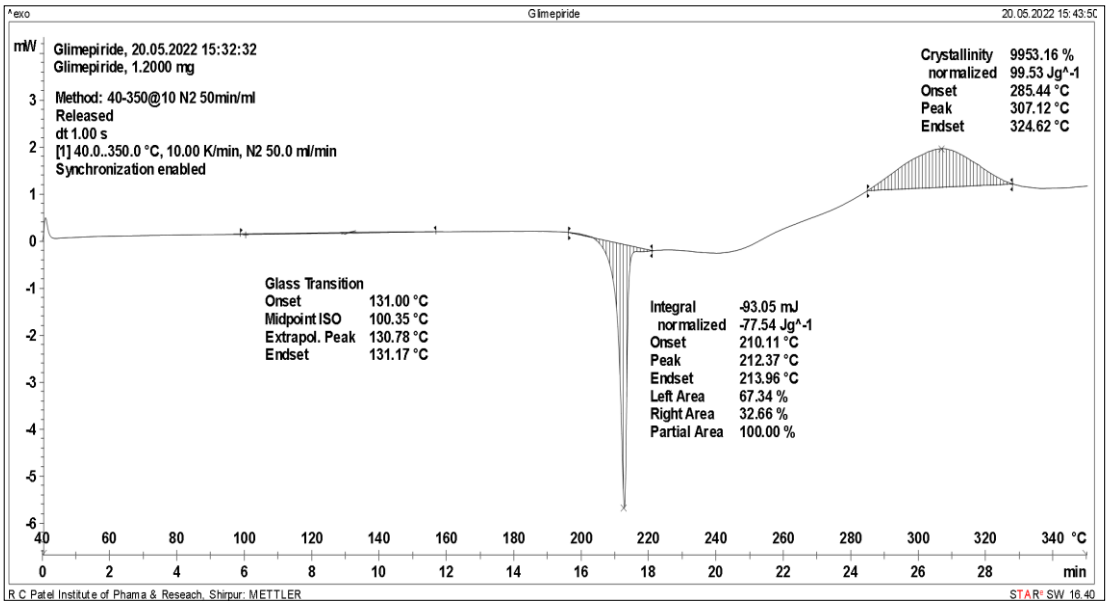


Figure 1. DSC Thermogram of pure drug Glimepiride

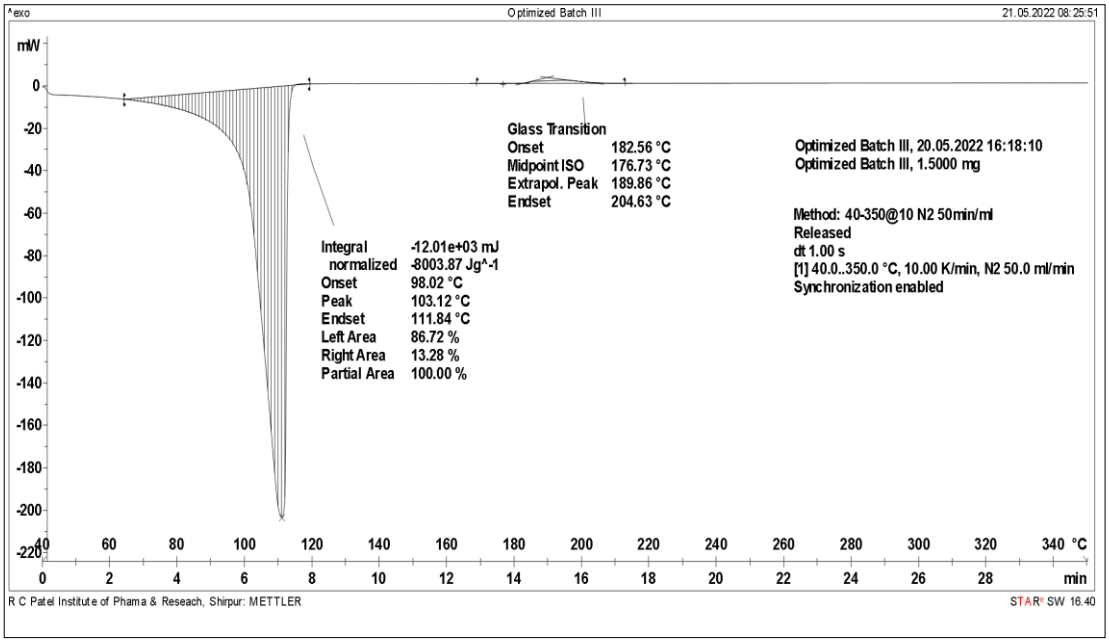


Figure 2. DSC Thermogram of Optimized Batch of Glimepiride Nanosuspension

Optimization Data Analysis

A 3^2 full factorial strategy was used to carry out optimization. Stat-Ease 360, is a design expert software that was utilized to analyze data from all of the formulations. Here two factors were selected as factor A: Pluronic F68 (X1) and Factor B: PEG 400 (X2) along with three levels as low, medium, and high by using Response 1: % CDR at 60 min (Y1), Response 2: % EE (Y2), Response 3: Particle size (Y3) and Response 4: Zeta potential (Y4) respectively. The data from all of the formulations were analyzed using the software Stat-Ease 360 for optimization. The optimization was carried out mostly using a linear model. Here, 2 independent (X1 and X2) and four dependent factors (Y1, Y2, Y3, and Y4) were considered as factors and responses respectively to carry out the optimization process. The concentration of Pluronic F68 (X1) and concentration of PEG 400 (X2) were the two factors used including three levels such as low, medium, and high along with %CDR 60 min (Response 1),

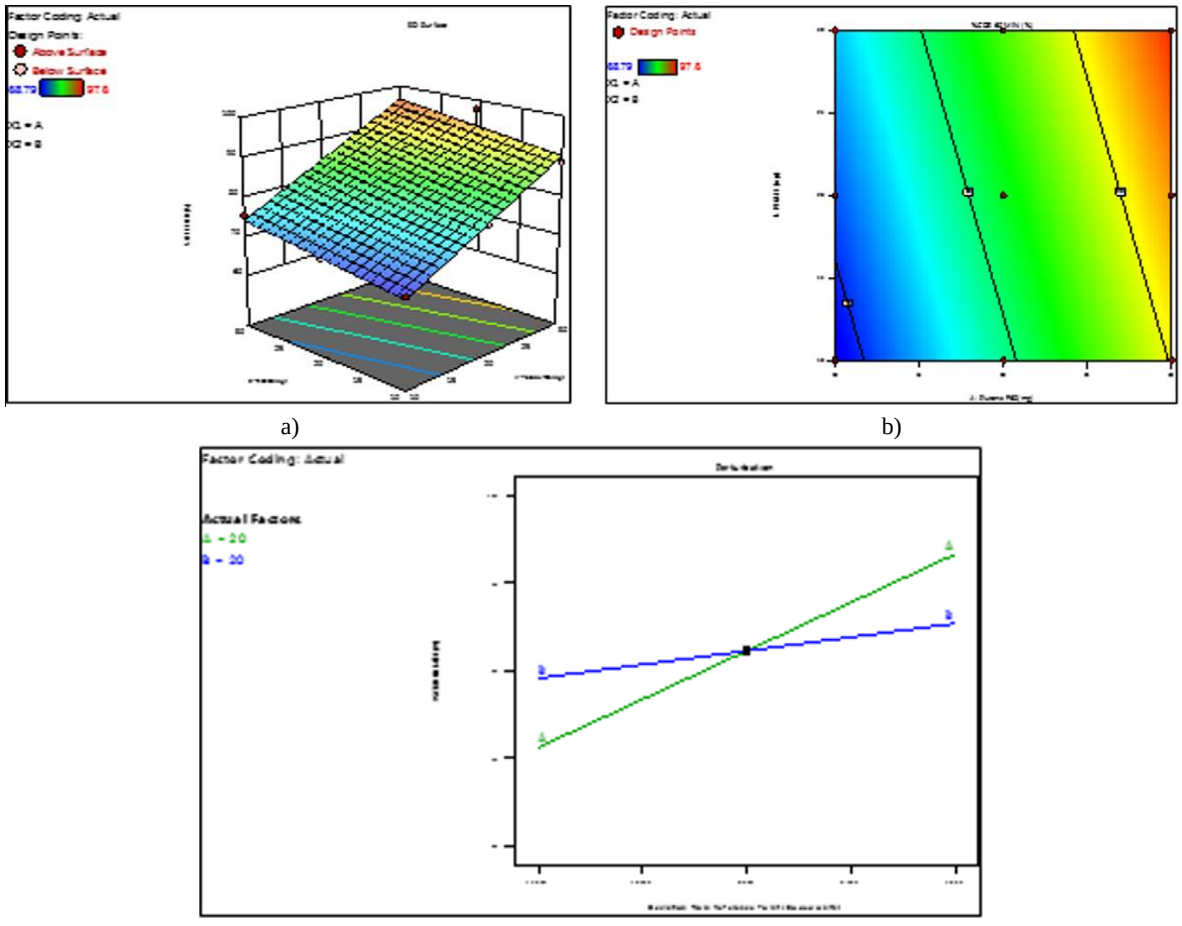
%Entrapment efficiency (Response 2), Particle size (Response 3) and Zeta potential (Response 4) respectively. Factor 1 containing the concentration of Pluronic F68 for all nine batches was chosen as a continuous factor, while factor 2 containing the concentration of PEG 400 for all nine batches was chosen as a discrete factor, and the analysis was run to obtain the ANOVA result, which included the confirmation denoting the optimized batch. Following the study and collecting the ANOVA results, it was revealed that the FG8 batch was optimized.

ANOVA

ANOVA the Analysis of Variance is used for a comparison of two models. It is generally helpful for testing two or more variables. To compare the mean response values at different levels of factors generally, ANOVA is used.

ANOVA for Linear Model

Response 1: %CDR 60 MIN



a) b)

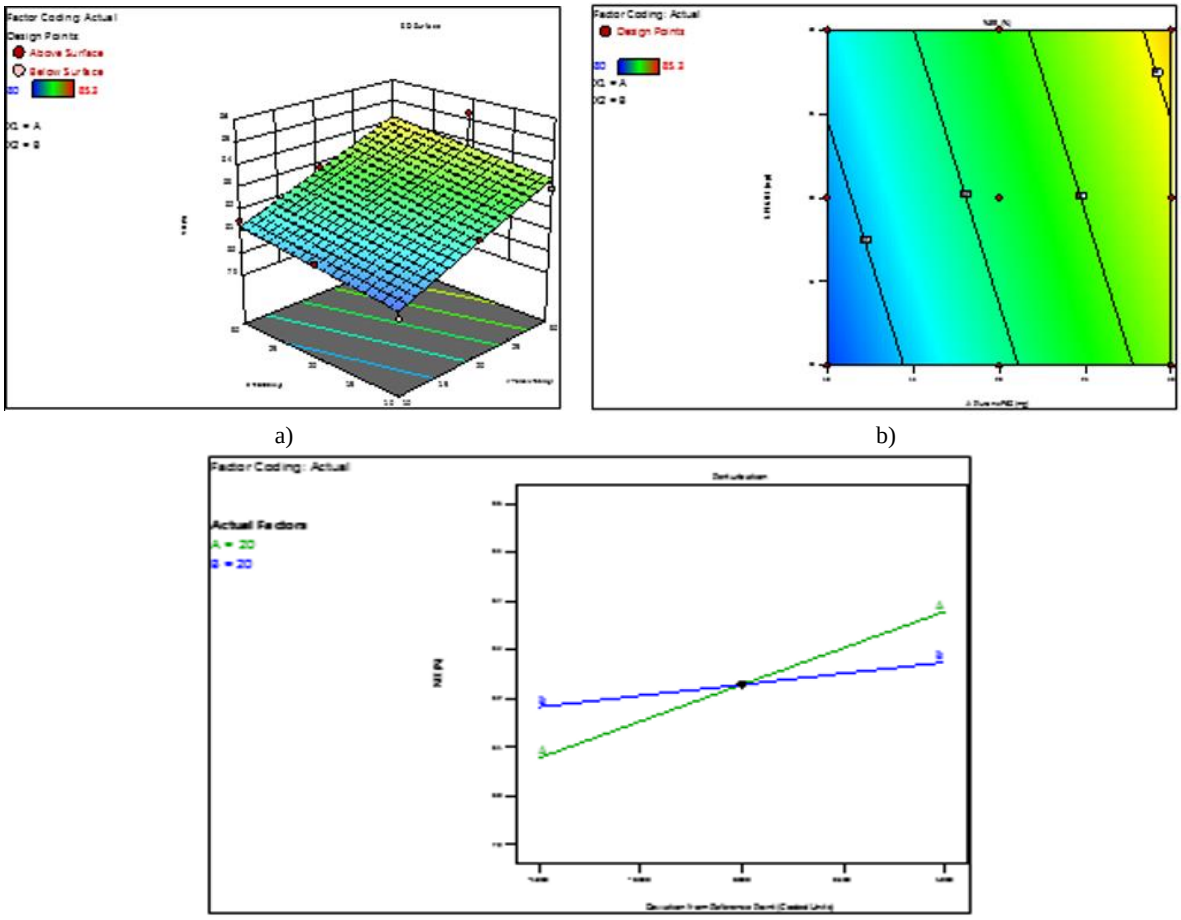
c)

Figure 3. a) 3D surface graph of drug release at 60 min, b) Contour graph of drug release at 60 min, c) Perturbation graph of drug release at 60 min.

In the case of the 3D surface plot and contour plot **(Figure 3)**, the green color portion indicates the effect of Pluronic F68 and the blue color indicates the effect of PEG 400 on percent cumulative drug release at 60 MIN. Here the plot indicates that an increase in the concentration of polymer indicates there was a rise in the release of the drug. Also for the perturbation plot green color line indicates factor A i.e. Pluronic F68 and the blue color line indicates factor B i.e. PEG 400. Here green line appeared more interactively as compared to the blue line thus, it indicates that Pluronic F68 has more effect on drug release as compared to PEG 400.

In the case of desirability it should be less than 1 which was obtained as per the required standard and assisted to identify the optimized formulation in the study.

Response 2: %EE



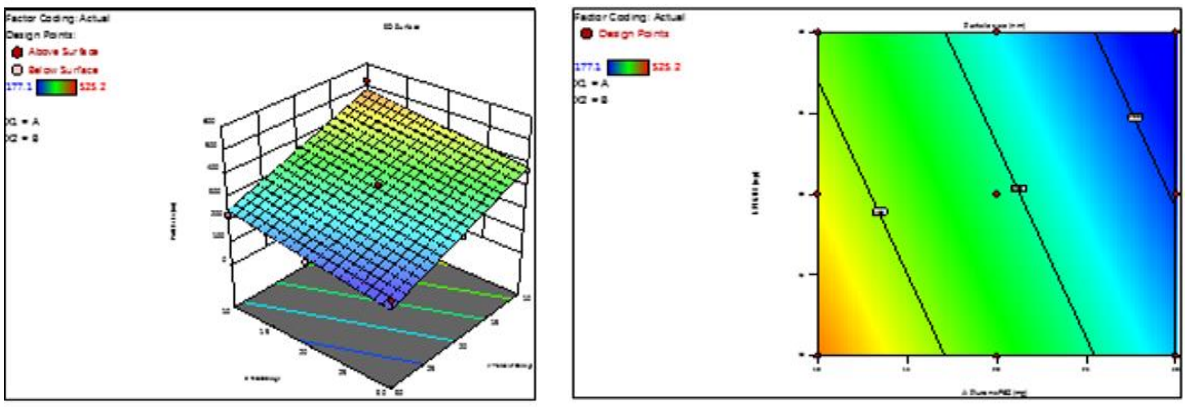
a) b)

c)

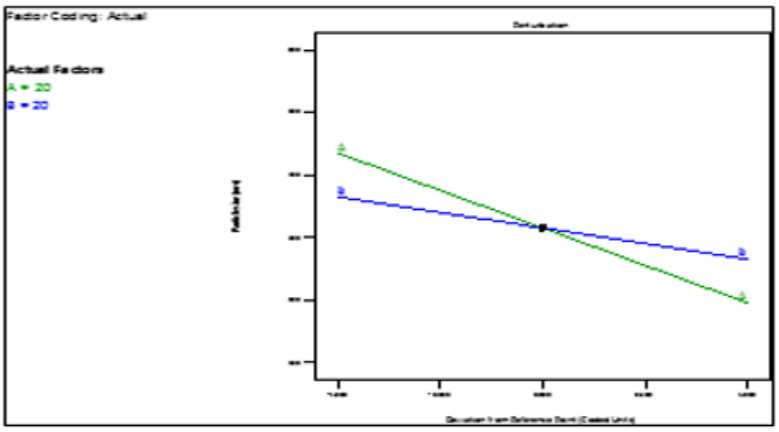
Figure 4. a) 3D surface graph of %EE, b) Contour graph of %EE, c) Perturbation graph of %EE

Here in the case of the 3D surface plot and contour plot **(Figure 4)**, the green color appeared in the major portion as compared to the blue color which indicated that Pluronic F68 has more effect on % Entrapment efficiency as compared to PEG 400. Also in the case of perturbation plot, the green color line of Factor A i.e. Pluronic F68 appeared more interactively as compared to the blue line of Factor B i.e. PEG 400 thus, it shows that Pluronic F68 has more effect on %Entrapment efficiency as compared to PEG 400.

Response 3: Particle Size



a) b)

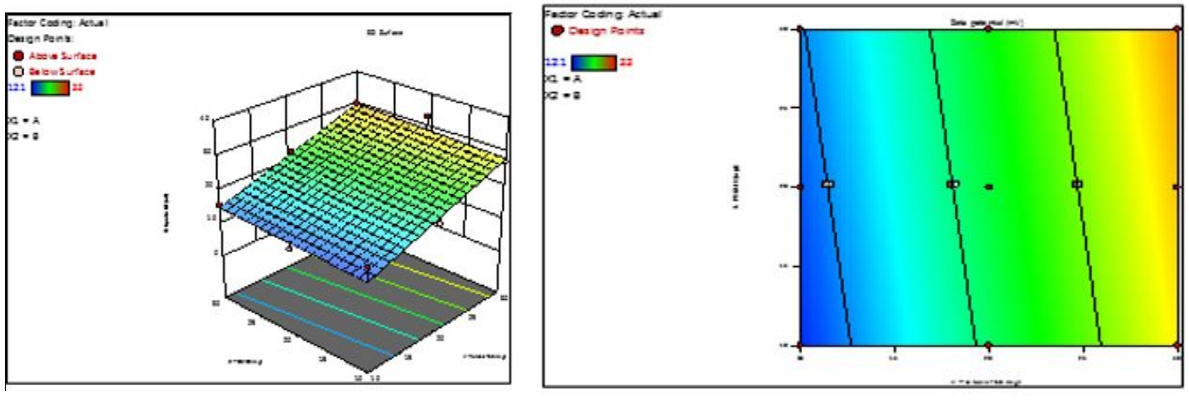


c)

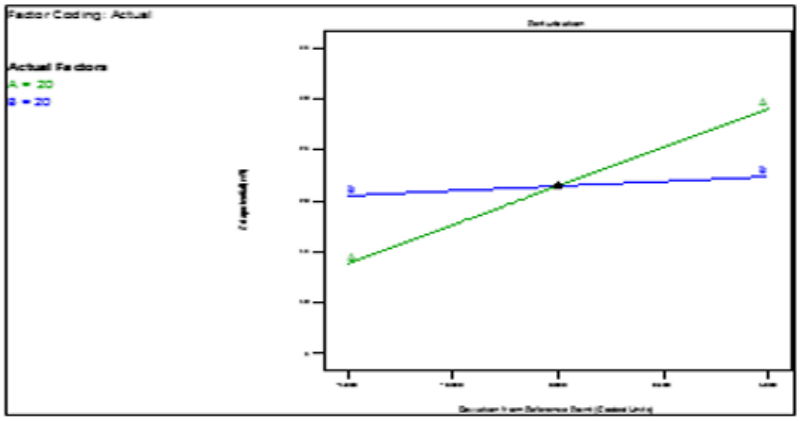
Figure 5. a) 3D surface graph of Particle size, b) Contour graph of Particle size, c) Perturbation graph of Particle size

Here in the case of the 3D surface plot and contour plot **(Figure 5)**, green color and blue color appeared in equal portion this indicated that Pluronic F68 and PEG 400 has an equal effect on particle effect. Also in the case of the perturbation plot both the line appeared interactively across each other, this indicated that both the polymer i.e. Pluronic F68 and PEG 400 has an equal effect on particle size.

Response 4: Zeta Potential



a) b)



c)

Figure 6. a) 3D surface graph of Zeta potential, b) Contour graph of Zeta potential, c) Perturbation graph of Zeta potential

Here, in the case of the 3D surface plot and contour plot **(Figure 6)**, the green color appeared in the major portion which indicated that Pluronic F68 has more effect on zeta potential as compared to PEG 400. Also in the case of perturbation plot green color line of Factor A i.e. Pluronic F68 appeared as more interactive while the blue line of Factor B i.e. PEG 400 appeared as parallel, thus it indicated that Pluronic F68 has more effect on zeta potential as compared to PEG 400. Thus from the result obtained through the ANOVA study, it was concluded that Batch FG8 (Pluronic F68 30 mg and PEG 400 20 mg) was found to be an optimized batch.

In vitro Drug Release Studies

From the results obtained, an optimized batch FG8 shows more drug release of 97.6% as compared to pure drug glimepiride which shows drug release of 32.17% at a time of 60 minutes represented in **Figure 7**.

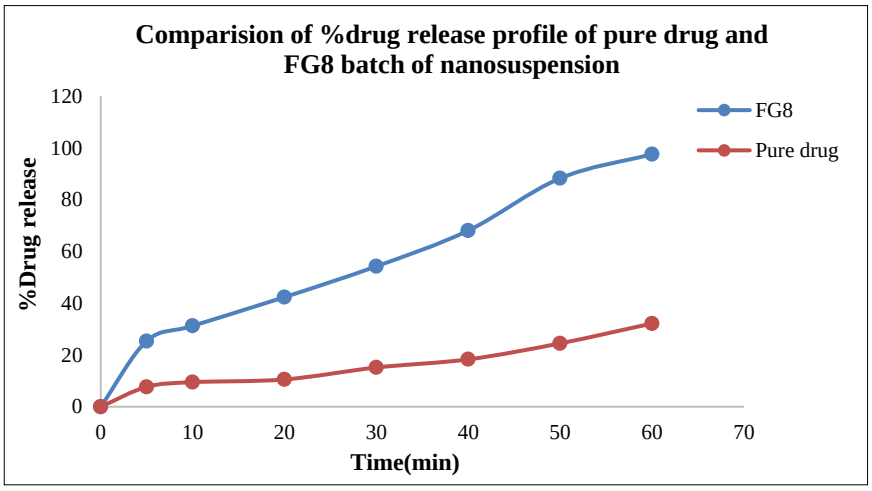


Figure 7. Graphical representation of a comparison of % drug release profile of the pure drug and FG8 batch of nanosuspension

Stability Studies

The outcome of the stability study was obtained after an accelerated term: 40˚C ± 2˚C, 75% RH ± 5% RH for 3 months. There is no measurable difference in the parameters evaluated were % Entrapment efficiency, % Totoal Drug content and *in vitro* drug release in three months. Thus it was determined that the drug is compatible with polymers.

Conclusion

Antisolvent evaporation followed by the sonication technique was utilized in the fabrication of glimepiride nanosuspension. Following the study and collecting the ANOVA results, it was revealed that the FG8 batch containing Pluronic F68 30 mg and PEG 20 mg was an optimized glimepiride nanosuspension. The *in-vitro* dissolution and bioavailability of glimepiride can be significantly improved if taken orally, by effectively lowering the particle size to an appropriate level. The study findings suggest that glimepiride nanosuspension may be a promising approach for enhancing the therapeutic action of the drug in human volunteers and that it may be important for the clinical assessment of nanosuspension in the future.

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Ethics statement: None

References

1. Mishra DK, Shandilya R, Mishra PK. Lipid-based nanocarriers: a translational perspective. Nanomed Nanotechnol Biol Med. 2018;14(7):2023-50. doi:10.1016/j.nano.2018.05.021
2. Patel M, Shah A, Patel NM, Patel MR, Patel KR. Nanosuspension: A novel approach for drug delivery system. J Pharm Sci Res. 2011;1(1):1-10.
3. Soumya M. In-vitro study of formulation and evaluation of glimepiride nanosuspension by precipitation method. World J Pharm Res. 2020;9(14):1239-63.
4. Gaur PK. Nanosuspension of flavonoid-rich fraction from Psidium guajava Linn for improved type 2-diabetes potential. J Drug Deliv Sci Technol. 2021;62:102358.
5. Kumar A, Sahoo SK, Padhee K, Kochar PS, Sathapathy A, Pathak N. Review on solubility enhancement techniques for hydrophobic drugs. Pharm Glob. 2011;3(3):001-7. doi:10.1016/j.jddst.2021.102358

6. Ahad HA, Chinthaginjala H, Bitraganti SR, Dasari RR, Musa GBM, Jyothi VN. Optimization of Lamivudine Solid Dispersions by Central Composite Design. Int J Pharm Phytopharmacol Res. 2021;11(4):18-23. doi:10.51847/1KVQAZGWqU
7. Sudhakar K, Mishra V, Hemani V, Verma A, Jain A, Jain S, et al. Reverse pharmacology of phytoconstituents of food and plant in the management of diabetes: Current status and perspectives. Trends Food Sci Technol. 2021;110:594-610. doi:10.1016/j.tifs.2020.10.024
8. Mishra V, Yadav N, Saraogi GK, Tambuwala MM, Giri N. Dendrimer based nanoarchitectures in diabetes management: An overview. Curr Pharm Des. 2019;25(23):2569-83. doi:10.2174/1381612825666190716125332
9. Kilor V, Sapkal N, Daud A, Humne S, Gupta T. Development of stable nanosuspension loaded oral films of glimepiride with improved bioavailability. Int J Appl Pharm. 2017;9(2):28-33. doi:10.22159/ijap.2017v9i2.16714
10. Park H, Seo HJ, Hong SH, Ha ES, Lee S, Kim JS, et al. Characterization and therapeutic efficacy evaluation of glimepiride and L-arginine co-amorphous formulation prepared by supercritical antisolvent process: Influence of molar ratio and preparation methods. Int J Pharm. 2020;581:119232. doi:10.1016/j.ijpharm.2020.119232
11. Ferrar JA, Sellers BD, Chan C, Leung DH. Towards an improved understanding of drug excipient interactions to enable rapid optimization of nanosuspension formulations. Int J Pharm. 2020;578:119094. doi:10.1016/j.ijpharm.2020.119094
12. Nayak BS, Mohanty B, Roy H, Patnaik A. Nanosuspension: bioavailability enhancing novel approach. Int J Pharma Bio Sci. 2018;8(2):540-54.
13. Rahim H, Sadiq A, Khan S, Amin F, Ullah R, Shahat AA, et al. Fabrication and characterization of glimepiride nanosuspension by ultrasonication-assisted precipitation for improvement of oral bioavailability and in vitro α-glucosidase inhibition. Int J Nanomedicine. 2019;14:6287. doi:10.2147/IJN.S210548
14. Sumathi R, Tamizharasi S, Sivakumar T. Formulation and evaluation of polymeric nanosuspension of naringenin. Int J App Pharm. 2017;9(6):60-70.
15. Geetha G, Poojitha U, Khan KAA. Various techniques for preparation of nanosuspension-A Review. Int J Pharm Sci Rev Res. 2014;3(9):30-7.
16. Khandbahale SV. A review-Nanosuspension technology in drug delivery system. Asian J Pharm Res. 2019;9(2):130-8. doi:10.5958/2231-5691.2019.00021.2
17. Guan W, Ma Y, Ding S, Liu Y, Song Z, Liu X, et al. The technology for improving stability of nanosuspensions in drug delivery. J Nanopart Res. 2022;24(1):1-38. doi:10.1007/s11051-022-05403-9
18. Jayaprakash R, Krishnakumar K, Dineshkumar B, Jose R, Nair SK. Nanosuspension in drug delivery-A review. Sch Acad J Pharm. 2016;5:138-41.
19. Shid RL, Dhole SN, Kulkarni N, Shid SL. Nanosuspension: a review. Int J Pharm Sci Rev Res. 2013;22(1):98-106.
20. Chaudhary A, Nagaich U, Gulati N, Sharma VK, Khosa RL, Partapur MU. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. J Adv Pharm Res. 2012;2(1):32-67.
21. Mudgil M, Gupta N, Nagpal M, Pawar P. Nanotechnology: a new approach for ocular drug delivery system. Int J Pharm Pharm Sci. 2012;4(2):105-12.
22. Nangare KA, Powar SD, Kate VK, Patwekar SR, Payghan SA. Therapeutics Applications of Nanosuspension in Topical/Mucosal Drug Delivery. J Nanomed Res. 2018;7(1). doi:10.15406/jnmr.2018.07.00170
23. Lu Y, Wang ZH, Li T, McNally H, Park K, Sturek M. Development and evaluation of transferrin-stabilized paclitaxel nanocrystal formulation. J Control Release. 2014;176:76-85. doi:10.1016/j.jconrel.2013.12.018
24. Chorny M, Fishbein I, Danenberg HD, Golomb G. Lipophilic drug loaded nanospheres prepared by nanoprecipitation: effect of formulation variables on size, drug recovery, and release kinetics. J Control Release. 2002;83(3):389-400. doi:10.1016/S0168-3659(02)00211-0
25. Goel S, Sachdeva M, Agarwal V. Nanosuspension technology: recent patents on drug delivery and their characterizations. Recent Pat Drug Deliv Formul. 2019;13(2):91-104. doi:10.2174/1872211313666190614151615
26. Kumar P, Chandrasekhar KB. Formulation and in-vitro and in-vivo characterization of nifedipine stabilized nanosuspension by nanoprecipitation method. Int J Res Pharm Sci. 2017;8(4):759-66.
27. Prajapati SK, Maurya SD, Das MK, Tilak VK, Verma KK, Dhakar RC. Dendrimers in drug delivery, diagnosis, and therapy: basics and potential applications. J Drug Deliv Ther. 2016;6(1):67-92. doi:10.22270/jddt.v6i1.1190
28. Tian Y, Wang S, Yu Y, Sun W, Fan R, Shi J, et al. Review of nanosuspension formulation and process analysis in wet media milling using microhydrodynamic model and emerging characterization methods. Int J Pharm. 2022:121862. doi:10.1016/j.ijpharm.2022.121862
29. Salem HF, Kharshoum RM. Nanoprecipitation technique for preparation of sterically stabilized risperidone nanosuspension: in vitro and in vivo study. Int J Pharm Pharm Sci. 2016;8(5):136-42.
30. Azimullah S, Sudhakar CK, Kumar P, Patil A, Usman MRM, Usman MZS, et al. Nanosuspensions as a promising approach to enhance bioavailability of poorly soluble drugs: An update. J Drug Deliv Ther. 2019;9(2):574-82. doi:10.22270/jddt.v9i2.2436