



Formulation Development and Optimization of Multiparticulate System by Extrusion Spheronization Method

Aney Joice Samuel ^{a*} and Kiran Bhise ^a

^a Department of Pharmaceutics, M.C.E Society's Allana College of Pharmacy, Pune, Maharashtra-411001, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2022/v34i52B7216

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/93169>

Original Research Article

Received 19 August 2022

Accepted 25 October 2022

Published 28 October 2022

ABSTRACT

Aim: This study aimed at formulating and optimizing the multiparticulate system of Rifaximin by adopting 32 factorial designs with independent variables X1 and X2 as concentrations of two excipients.

Methodology: The pellets were prepared by the Extrusion Spheronization method and evaluated for percentage yield, flow property, percentage drug content, friability, and in-vitro percentage cumulative drug release.

Results: The optimized batch (OR7) displayed excellent flow properties, 0.15±0.03% friability, and 97.85±0.22% drug content with a cumulative drug release of 93.24±0.95%.

Conclusion: The results confirm the usefulness of factorial design to identify the effect of variables on pellet characteristics. The optimized batch can further be coated with different polymers to obtain targeted drug delivery.

Place of Study: Department of Pharmaceutics, M. C. E. Society's Allana College of Pharmacy, Pune.

Keywords: *Extrusion spheronization; In-vitro release; microcrystalline cellulose; sodium starch glycollate.*

1. INTRODUCTION

“Rifaximin, a BCS class IV drug, is a nonsystemic structural analog of rifampin that inhibits the synthesis of bacterial RNA by binding to the β subunit of bacterial DNA-dependent RNA polymerase. Rifaximin’s additional pyrido imidazole ring makes it virtually nonabsorbable enabling it to achieve a high concentration in the gastrointestinal tract and to be active against enteric infection or abnormal floral states. It is used clinically to treat a variety of gastrointestinal disorders including traveler’s diarrhea, hepatic encephalopathy, irritable bowel syndrome, and inflammatory bowel diseases” [1,2].

“Pellets as a drug delivery system offer not only therapeutic advantages but also technological advantages, for example, better flow properties, less friable dosage form, narrow particle size distribution, ease of coating and uniform packing. The reproducibility of the drug blood levels is an additional advantage to the use of a pellet formulation” [3,4]. Various methods for obtaining pellets include agitation, layering, cryopelletization, extrusion spheronization, spray drying, balling, melt agglomeration and hot melt extrusion. The widely used method for producing pellets is by extrusion spheronization technique [5,6]. “The main objective of extrusion spheronization is to provide pellets of uniform size with high drug loading capacity. It is a composite process of wet mass extrusion followed by spheronization to produce uniform-sized spherical particles called spheroids/pellets/beads/matrix depending upon the process of spheronization” [7,8]. Most of the pellet formulations for extrusion/spheronization include microcrystalline cellulose as the main excipient, which has the proper rheological properties, cohesiveness, and plasticity to produce spherical particles.

“The most preferable route of administering the drug is by oral route and Rifaximin is available in the market as 200mg and 550mg tablets. The dose regimens vary depending on the disease: for Irritable Bowel Syndrome with Diarrhea (IBS-D), the suggested dose is 400 mg thrice or 550 mg twice daily for two weeks, 200 mg thrice daily is given for three days in traveler’s diarrhea, Hepatic encephalopathy requires a dose of 550 mg twice or three times daily and Pouchitis patients may need doses of 400 to even 800 mg twice daily. The half-life of rifaximin reported in healthy subjects at steady-state plasma concentration was 5.6 hours and was 6 hours in

IBS-D patients. In a study conducted on healthy volunteers, of the 96.94% total recovery, 96.62% of the orally administered radioactivity was recovered in feces largely as the unchanged drug” [9]. To increase the residence time at the required site of action an effort has been taken to develop a multiparticulate drug delivery system of Rifaximin. Although few multiparticulate systems by spray drying and drug layering have been reported, no literature was found that supports the spheronization of Rifaximin with extrusion technique. Therefore, formulation of Rifaximin pellets by extrusion spheronization technique has been attempted in the present work by using microcrystalline cellulose (MCC), sodium carboxy methyl cellulose (SCMC), sodium starch glycolate (SSG) as diluent, binder and disintegrant respectively.

2. MATERIALS AND METHODS

2.1 Materials

Rifaximin was received as a gift sample from Lupin Pharmaceuticals Ltd, Aurangabad, India. Sodium starch glycolate, microcrystalline cellulose, and the sodium salt of carboxymethyl cellulose were purchased from the Research lab, fine chem Industries, Mumbai, India. All the ingredients used in the study were of analytical grade.

2.2 Methods

2.2.1 Flow property study

The drug was characterized via flow properties such as angle of repose and compressibility index.

2.2.2 Angle of repose [10]

The angle of repose has been defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. The angle of repose was determined by the fixed funnel method. The angle of repose was calculated by the following equation:

$$\tan\theta = \frac{h}{r} \quad \text{Therefore;}$$

$$\theta = \tan^{-1} \frac{h}{r}$$

2.2.3 Carr’s index [11]

The bulk density and tapped density of the drug were determined using bulk density apparatus.

The percentage compressibility or Carr's index (CI) was calculated according to the equation:

$$\% \text{ compressibility} = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

where, ρ_t = tapped density and ρ_b = bulk density

2.2.4 Formulation development of pellets [12,13]

Rifaximin pellets were prepared by the Extrusion spheronization technique (Extruder and Mini Spheronizer, Cronimach). In this dry mixing of Rifaximin, microcrystalline cellulose and SSG were done for 5 min and added SCMC solution to make a damp mass. This mass was then passed through the extruder, using a sieve screen size of 0.87 mm. The extrudates were spheronized at appropriate speed and time. Final pellets were collected and dried at 70°C for 10 min. The dried pellets were passed through a set of sieves of size 600 μm (30#), 710 μm (25#), 1190 μm (16#), and 2360 μm (8#).

Table 1. Full factorial experimental design layout

Formulation	Variable in coded form	
	X_1	X_2
OR1	-1	-1
OR2	0	-1
OR3	1	-1
OR4	-1	0
OR5	0	0
OR6	1	0
OR7	-1	1
OR8	0	1
OR9	1	1

2.2.5 Experimental design [14,15,16,17]

In the existing observe, a 32 full factorial layout changed in to hired to observe the impact of unbiased variables i.e. attention of SCMC (X_1) and attention of SSG (X_2) at the based variable, i.e. cumulative % drug release (CPR). Optimization of the formulation development process was performed using a statistical experimental design with a trial version of the software DESIGN EXPERT®. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. A statistical model (equation below) incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_1^2X_1^2 + b_2^2X_2^2$$

Where, Y is the established variable, b_0 is the mathematics imply reaction of the 9 runs, b_1 is the envisioned coefficient for the thing X_1 and the b_2 is envisioned coefficient for the thing X_2 , the principle effects (X_1 and X_2) constitute the common end result of converting one thing at a time from its low to excessive fee and its correlated coefficient is b_{12} , the interplay terms (X_1X_2) display how the reaction modifications whilst elements are concurrently modified and the polynomial terms (X_{12} and X_{22}) are covered to research non-linearity.

2.3 Characterization of Pellets

2.3.1 Flow property of pellets [18]

Pellets were characterized for their flow properties such as the angle of repose and compressibility index. The procedure is the same as described earlier.

2.3.2 Percentage usable yield [19,20,21]

The yield of the batch turned into calculated in terms of percent usable yield as according to the quantity of pellets acquired in the scale variety of 710 μm (25#) to 1190 μm (16#) with the aid of using the subsequent equation.

$$\% \text{ usable yield} = \frac{\text{wt of pellets in the size range}}{\text{wt of practically obtained total yield}} \times 100$$

2.3.3 Friability test [22]

Friability check for pellets changed into performed in Roche Friabilator. About five gm of pellets within side the usable yield length range (710 μm -1190 μm) have been taken and circled for one hundred revolutions. The pellets have been collected, byskip them via 25# sieve and weighed out retained pellets. The % weight reduction changed into calculated from the preliminary weight and weight of pellets after the check.

2.3.4 Drug content [23]

The % drug loading was calculated with the help of UV spectroscopic method. The crushed pellets in powder form equivalent to 100mg of Rifaximin was taken in volumetric flask of 100 ml and dissolved in 70 ml of 6.8 pH phosphate buffer. After a 30-min ultrasonic extraction, the solution was diluted with buffer again to 100 ml and then filtered through a 0.45 μm membrane. 0.2 ml of

this solution was transferred to a 100-ml volumetric flask and buffer was added to give a volume of 100 ml and the absorbance was measured at 437nm. The drug content was then calculated from the absorbance of the standard.

2.3.5 *In vitro* dissolution study [24,25]

The drug release study was supported out using Dissolution test apparatus USP type I, Basket at temperature of $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and rotation of 100 rpm by filling 900 ml of Phosphate buffer (pH-6.8) and 10ml of 1.5%SLS of as dissolution medium. Pellets equal to 100mg of dose were occupied into a capsule and dissolution study performed. 10 ml of tester solution was withdrawn at predetermined time intervals by filtering through a $0.45 \mu\text{m}$ membrane filter, by diluted suitably and spectrophotometrically analyzed at 437 nm. An equivalent volume of fresh dissolution medium was substituted immediately after the removal of the test sample. The readings were taken in triplicate. The drug content and CPR are shown in Fig. 2.

3. RESULTS AND DISCUSSION

The multi-unit particulate system (pellets) of Rifaximin was successfully developed and characterized using MCC by extrusion and spheronization method. The result of the characterization of pellets such as particle size, friability, Carr's Index and angle of repose was found satisfactory. Carr index was found to be 11-20% when compared with the values given in Pharmacopoeia; it was found that all batches were showing good to excellent flow properties. Angle repose of the pellets showed less than 40° which confirms good to excellent flow properties. The drug content of pellets was found to be between $92.13 \pm 0.35\%$ and $97.85 \pm 0.22\%$. Friability of pellets helps in determining their hardness and strength of pellets. Rifaximin pellets produced by the extrusion spheronization method using MCC showed an acceptable friability of less than 1%. The optimized pellet formulation (OR7) displayed excellent flow properties, low friability, and high drug content

with a cumulative drug release of $93.24 \pm 0.95\%$. These pellets can be incorporated into a hard gelatin capsule to improve patient compliance.

Regression analysis of 3^2 full factorial design was employed to study the effect of variables, i.e., the concentration of SCMC (X_1) and concentration of SSG (X_2) on the dependent variable, % drug. The results as summarized in the below table. The results indicate that the dependent variable is strongly dependent on the selected independent variables as they show a wide variation among the nine batches. The polynomial equation may be accustomed conclude when considering the magnitude of the constant and therefore the mathematical sign it carries, i.e., positive or negative. Polynomial equations generated by style skilled code are explained hereby for its interpretation of the impact on response parameters.

$$\begin{aligned} \text{CPR} &= 73.09 + 3.01(X_1) + 19.75(X_2) + 3.07(X_1^2) + \\ &0.587(X_2^2) - 0.6925(X_1)(X_2) \\ (R^2 &= 0.9971) \end{aligned}$$

The CPR for all batches R1 to R9 shows a good correlation coefficient of 0.9971. Variables that have a p-value less than 0.05, significantly affect the release profile. From the regression analysis, the p-value for factors X_1 & X_2 is less than 0.05. So factor X_1 means the concentration of SCMC & X_2 means the concentration of SSG are the dominant variables for the release profile. The relationship between the independent variables and the response can be further explained by using contour plots and surface plots. The data were subjected to determine the effect of polymers SCMC (X_1) and SSG (X_2) on the dependent variable. It is already known that SCMC and SSG in the concentrations used here are more responsible for the release of drug from pellets. Fig. 3 reveals the highlighted area at which all the dependent parameters crossed over; which in turn shows the best combination of SCMC and SSG for drug release. The selection of the optimized batch was based on the overlay section area of the graph which is 0.5gm of SCMC and 3gm of SSG.

Table 2. Actual and coded values of the independent factors

Code	Binder (SCMC) (X_1)	Disintegrant (SSG) (X_2)
-1	0.5	2
0	1	2.5
1	1.5	3

Table 3. Formulation of 3² full factorial design

Batches	Rifaximin (%)	SSG (%)	SCMC (%)	MCC (%)
OR1	30	2	0.5	50
OR2	30	2	1	50
OR3	30	2	1.5	50
OR4	30	2.5	0.5	50
OR5	30	2.5	1	50
OR6	30	2.5	1.5	50
OR7	30	3	0.5	50
OR8	30	3	1	50
OR9	30	3	1.5	50

Table 4. Results of pellets characterization

Sample	Carr's Index (%)	Angle of repose (°)	% usable yield	Friability (%)	Drug Content(%)
OR1	16.54±0.75	28.15±0.82	78±0.64	0.32±0.02	92.13±0.35
OR2	18.28±0.67	30.12±0.41	72±0.84	0.66±0.02	94.15±0.96
OR3	19.36±0.68	30.45±0.62	81±0.55	0.32±0.03	92.85±0.88
OR4	12.22±0.23	26.30±0.82	79±0.74	0.51±0.01	93.35±0.25
OR5	11.36±0.16	38.26±0.54	79±0.24	0.66±0.01	94.05±1.04
OR6	20.56±0.29	37.16±0.34	81±0.84	0.16±0.02	93.65±0.38
OR7	12.14±0.67	26.52±0.72	84±0.34	0.15±0.03	97.85±0.22
OR8	20.04±0.73	22.81±0.52	76±0.72	0.52±0.01	96.89±0.16
OR9	11.11±0.24	25.48±0.42	73±0.50	0.52±0.02	94.60±0.24

All values are expressed as mean of n=3± standard deviation (SD)

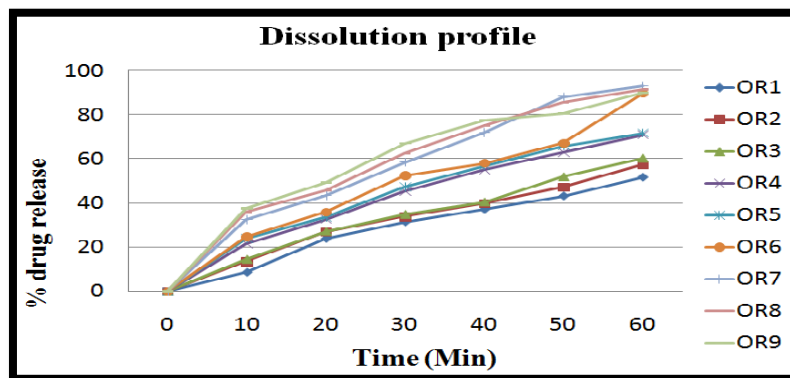


Fig .1. The release profile of Rifaximin pellets (data is presented in mean±SD (n=3))

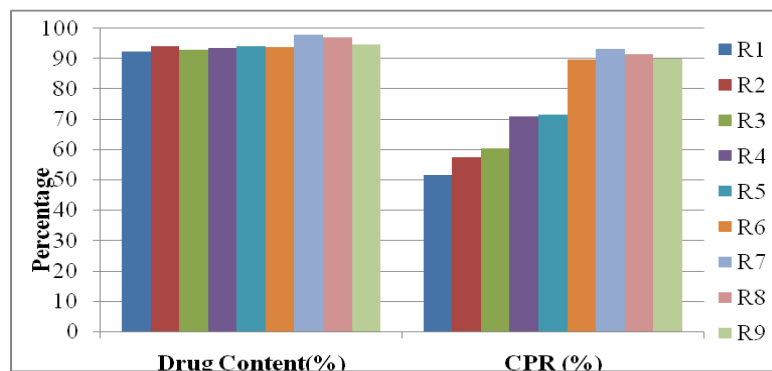


Fig. 2. Percentage drug content and Cumulative percent drug release of Rifaximin pellets, n=3±SD

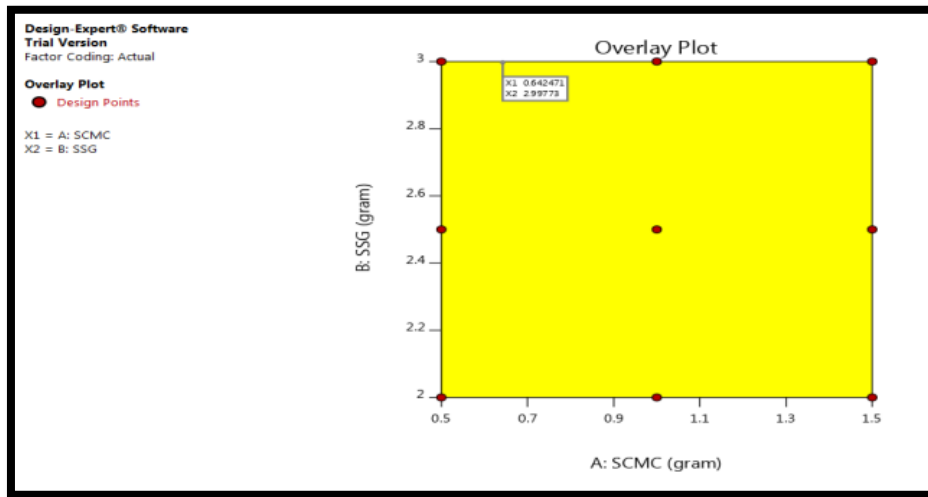


Fig. 3. Response surface plot

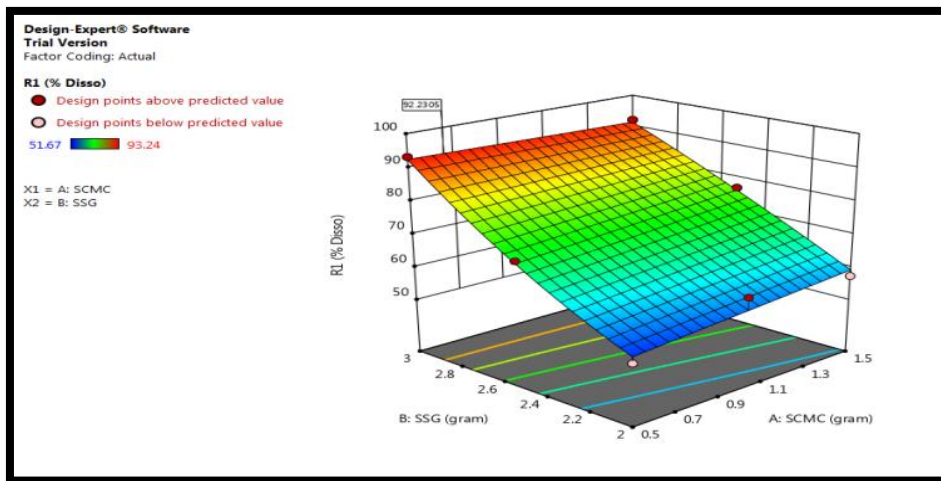


Fig. 4. Response Surface Plot (3D Surface Plot) rate

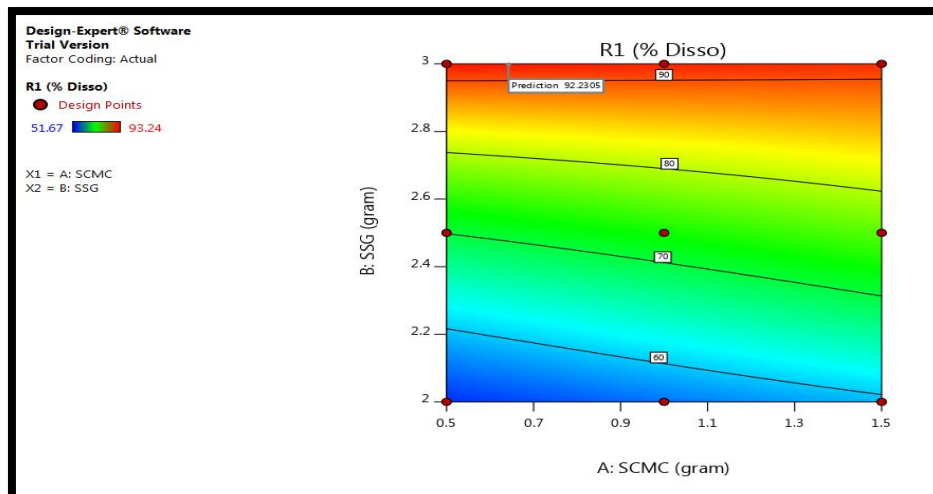
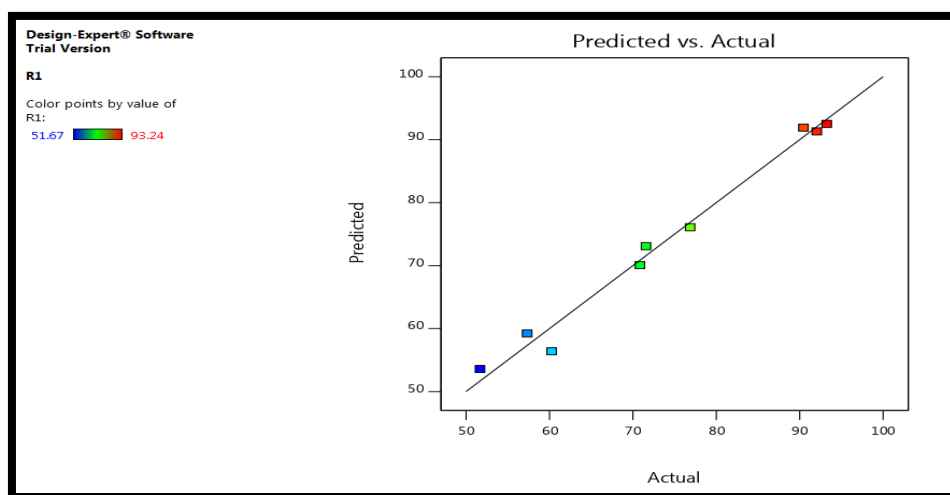


Fig. 5. 2D contour plots showing the prediction for % dissolution rate of Rifaximin pellets

Table 5. Comparison between predicted vs. actual values of cumulative percentage release for optimized batch

Dependent variables	Values obtained	
	Experimental values	Predicted values
CPR	93.24%	92.23%

**Fig. 6. Predicted vs Actual value of cumulative percentage release for the optimized batch of Rifaximin pellets**

4. CONCLUSION

In the present study, efforts were made to develop and optimize Rifaximin loaded pellets as a multiparticulate drug delivery system. Extrusion-spheronization technique was adopted for formulating pellets based on literature study. The formulated pellets were characterized for flow properties, friability, drug loading and % *In vitro* drug release. The trial batches were optimized for polymers SCMC and SSG. The influence of selected excipients on the dissolution profile of the pellets was studied. It was observed based on the design that batch OR7 with 0.5gm of SCMC and 3gm of SSG could be used to prepare Rifaximin pellets by extrusion spheronization with more than 90% drug release. Correlation of independent and dependent variables can be done using the polynomial equations obtained from the statistical evaluation of results. Thus it is concluded that Rifaximin used in the form of pellets provides desired drug concentration at the targeted site.

ACKNOWLEDGEMENTS

Authors are grateful to Lupin Pharmaceuticals Ltd, Aurangabad, India for providing a gift sample of Rifaximin API.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

- Jiang ZD, Ke S, Palazzini E, Riopel L, DuPont H. In vitro activity and fecal concentration of rifaximin after oral administration. *Antimicrob Agents Chemother.* 2000;44:2205–6. DOI: 10.1128/AAC.44.8.2205-2206.2000
- Hirota SA. Understanding the Molecular Mechanisms of Rifaximin in the Treatment of Gastrointestinal Disorders – A Focus on the Modulation of Host Tissue Function. *Mini Rev Med Chem.* 2015;16(3):206-17. DOI:10.2174/1389557515666150722105705.
- Shelar VS, Shirolkar SV, Kale RN. Formulation optimization of promethazine theoclate immediate release pellets by using extrusion-spheronization technique *Int. J. App Pharm.* 2018; 10(1):30-35. DOI:https://doi.org/10.22159/ijap.2018v10i1.20350.
- Vervaeet C, Baert L, Remon JP. Extrusion-spheronisation A literature review. *Int. J. Pharm.* 1995; 116:131–146.

- Available: [https://doi.org/10.1016/0378-5173\(94\)00311-R](https://doi.org/10.1016/0378-5173(94)00311-R)
5. Dhandapani NV, Shrestha A, Shrestha N, Thapa A, Goti S, Sharma RB. Pelletization by Extrusion-Spheronization- A detailed review. *All Res. J. Biol.* 2012;3:10-23.
 6. Muley S, Nandgude T, Poddar S. Extrusion-spheronization a promising pelletization technique: In-depth review. *Asian journal of Pharmaceutical Sciences.* 2016;11:684-699.
Available: <https://doi.org/10.1016/j.ajps.2016.08.001>
 7. Zhang L, Jiang P, Liu J. Novel Sustained-Release of Propafenone through Pellets: Preparation and in Vitro/in Vivo Evaluation. *Int. J. Mol. Sci.* 2014;15:15503-15511.
DOI: 10.3390/ijms150915503.
 8. Veena MC, Senthilkumar SK Extrusion-spheronisation technique - A review. *International Journal of Pharmacy.* 2013;3(1):20-25.
 9. Robertson KD, Nagalli S. Rifaximin, National library of medicine National center for biotechnology information; 2022, Bookshelf ID: NBK562329
PMID: 32966000.
Available: <https://www.ncbi.nlm.nih.gov/books/NBK562329/>
 10. Lachman L, Liberman HA, Kanig JL. *The Theory and Practise of Industrial Pharmacy.* 3rd edition. Varghese Publishing House. 1987;296.
 11. Chan LW, Chan WY, Heng PWS, An improved method for the measurement of colour uniformity in pellet coating, *International Journal of Pharmaceutics.* 2001;213:63-74.
DOI: 10.1016/S0378-5173(00)00619-0
 12. Sureshkumar R, Munikumar M, Ganesh GN, Jawahar N, Nagasamyvenkatesh D, Senthil V, et al. Formulation and evaluation of pectin-hydroxypropyl methylcellulose coated curcumin pellets for colon delivery. *Asian J Pharm.* 2014;3(2):138-142.
DOI: <https://doi.org/10.22377/ajp.v3i2.255>.
 13. Barthelemy P, Lafor JP, Farah N., Joachim J., Compritol® 888 ATO: An innovative hot-melt coating agent for prolonged-release drug formulations, *European Journal Pharm. Biopharm.* 1999; 47(1):87-90.
DOI: 10.1016/s0939-6411(98)00088-5.
 14. Panwar MS, Tanwar YS. Factorial design approach for optimization of floating microspheres of diltiazem hydrochloride. *Asian J. Pharm.* 2015;9:206-12.
DOI:10.4103/0973-8398.160318.
 15. Prathap. M et al. Application of factorial design and optimization of glimepiride sustained release matrix tablets. *Asian Journal of Research in Biological and Pharmaceutical Sciences.* 2016;4(1):1-12.
 16. Sen SO, Devbhuti P, Sen KK, Ghosh A. Development, and evaluation of sustain release microparticles of metoprolol succinate. *Int J. App Pharm.* 2019;11(5):166-172.
DOI: <https://doi.org/10.22159/ijap.2019v11i5.31664>.
 17. Miléna Lengyel, Nikolett Kállai-Szabó, Vince Antal, András József Laki and István Antal. Microparticles, Microspheres, and Microcapsules for Advanced Drug Delivery. *Sci. Pharm.* 2019; 87(3): 20.
Available: <https://doi.org/10.3390/scipharm87030020>.
 18. Mehta S, De Beer T, Remon JP, Vervaet C. Effect of disintegrants on the properties of multiparticulate tablets comprising starch pellets and excipient granules. *International journal of pharmaceutics.* 2012;422(1-2):310-17.
DOI: 10.1016/j.ijpharm.2011.11.017
 19. Pund S, Joshi A, Vasu K, Nivsarkar M, Shishoo C. Gastroretentive delivery of rifampicin: *In vitro* mucoadhesion and in vivo gamma scintigraphy. *IntJ Pharm.* 2011;411(1-2):106-12.
DOI: 10.1016/j.ijpharm.2011.03.048.
 20. Sinha VR, Agrawal MK, Kumria R. Influence of formulation and excipient variables on the pellet properties prepared by extrusion spheronization. *Current Drug Delivery.* 2005;2(1):1-8.
DOI: 10.2174/1567201052772898.
 21. Hileman GA, Upadrashta SM, Neau SH. Drug solubility effects on predicting optimum conditions for extrusion and spheronization of pellets. *Pharmaceutical development and Technology.* 1997; 2(1):43-52.
DOI: 10.3109/10837459709022608.
 22. Akhgari A, Abbaspour MR, Pirmoradi S. Preparation and evaluation of pellets using acacia and tragacanth by extrusion-spheronization. *DARU Journal of Pharmaceutical Sciences.* 2011;19(6):417.
 23. Ozturk AG, Ozturk SS, Palsson BO, Wheatley TA, Dressman JB. Mechanism of release from pellets coated with an ethylcellulose-based film. *Journal of Controlled Release.* 1990;14(3):203-213.
DOI:10.1016/0168-3659(90)90160-U.

24. Patel AH, Patel R, Patel BN et al. Preparation and evaluation of multiple unit pellet system of metronidazole for colon targeting. World J. Pharm. Pharm. Sci. 2014;3(5):1505-9.
25. Son YJ, Horng M, Copley M, McConville JT. Optimization of an in vitro dissolution test method for inhalation formulations. Dissolution Technologies. 2010;17(2):6-13.

© 2022 Samuel and Bhise; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:

<https://www.sdiarticle5.com/review-history/93169>