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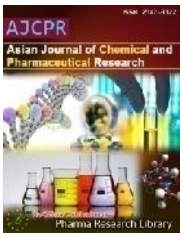

**Research Article** **Open Access**

# Design and Characterisation of Rifamiximin Multiparticulate Colon Targeted Drug Delivery

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**A B S T R A C T**

Aim of present work was design and develop consistent and optimized formulations of Rifaximin multiparticulate targeted drug delivery to colon with the following objectives.,explore multiparticulate CDDS to achieve localized effect and evaluate the pH- sensitive polymers such as Eudragit S 100 and L100 on Rifaximin, by reducing release of drug in pH conditions of upper GI tract while enhancing the release of formulations in alkaline surroundings of the colon. Also to optimize and evaluate in-vitro release and organ distribution of dosage forms in rat model, statistical assessment of polymer ratio's and percentage coating level interactions on drug release lag time and carry out accelerated stability studies of finalized formulations.

**Keywords:** Rifaximin, Multiparticulate, cdds

**A R T I C L E I N F O**

**CONTENTS**



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## 1. Introduction

**Types of Irritable bowel syndrome (IBS)**

IBS can be grouped as either constipation-predominant (IBS-C), with alternating stool pattern (IBS-A) and diarrhoea-predominant (IBS-D).IBS-D is categorized by bloating, persistent abdominal pain and modification of bowel habits. It wasinitiated with infectious unhealthiest fever, diarrhoea, and affirmative stool culture or vomiting. Later one has subsequently been termed "post-infectious IBS (IBS-PI) 68-69. The diagnostic algorithm identifies the patient's sign like diarrhoea, abdominal pain, and constipation. As an example, the declaration "50% of recurringtravellers had functional diarrhoea while 25% had

developed IBS" would mean that half the travellers had diarrhoea with abdominal pain. The Survey found residents back from international travel in United States were of IBS and relentlessdiarrhoea that developed throughout travel and persisted upon come back70.

Key factors in developing modified release pellets

Irrespective of the type polymer used for coating the key parameters for the success of pellet coating are as follows92.

Rate of release should beaccomplished in a repeatable manner for indented formulation.

- The small changes in coating recipe or process conditions should not impact the discharge pattern.
- Coating Processes should friendly and easy toscale-up from the bench scale to production.
- 4. Finished dosagemust be firm and,meticulous; changes in drug release uniqueness should devoid of significant time-dependent.
- Coating ingredient and method must be cost-effective.
- Science base process should selected, so as to endure the authoritarian challenge that leads preface of any pharmaceutical product.

## 2. Materials and Methods

**Materials**

Sugar spheres, Rifaximin, Povidone (kollidone K 30), HPMC E5, PEG 6000, Talc, Eudragit s100, Eudragit L100, Triethyl citrate, Red oxide of iron.

**Methods**

**Pre-Formulation Studiesofaceclofenac and Refaximin**

Pre-formulation studies were carried out to understand pH dependent solubility, active pharmaceutical ingredient and polymers compatibility in the formulation and the methods to conduct the same.

**Formulation Manufacturing Procedure**

**Preparation of Aceclofenac colon targeted delayed release pellets:** The Aceclofenac colon targeted release pellets formulation involves three different steps which includes drug absorption to sugar spheres by dissolving Aceclofenac and HPMC E5 in acetone. Hydroxypropyl Cellulose was used in swelling polymer covering of drug pellets and functional coating with ethyl cellulose 7cps at different concentrations.

**Characterization of Rifaximin CDDS**

**Bulk and tapped Density**

BD of prepared pellets was found out by three-tap method. Pellets were weighed then carefully transferred in to a 100mL graduatedcylinder. It was dropped to a solid wood plane 3 times to a height of 2.6 cm at an interval of 2sec. TD is the ratio of weight of dry to its tapped volume. From the above weighed quantity of granules was placed on tapped density tester (Electro lab Model: ETD-1020) and subjected to USP –Type II method (250 drops per minute and drop height is 3 mm ± 10%). The volume of pellet weight is measured after increment of 250 drops until the difference of last two values mean is zero.

$$\text{Bulk Density} = \frac{\text{Wt of the pellets (g)}}{\text{Untapped volume (ml)}}$$

$$\text{Tapped Density} = \frac{\text{ratio of dry Weight (g)}}{\text{Final tap volume (ml)}}$$

Compressibility Index (%) and Hauser's Ratio were calculated by using the following formulas.

$$\text{CI (\%)} = \frac{(\text{Tap Den} - \text{Bulk Den})}{\text{Tapped Density}} \times 100$$

$$\text{Hanser's Ratio} = \frac{\text{TD}}{\text{BD}}$$

**Sieve analysis**

Particle size distribution study was carried out by sieve analyser (Retsch AS 200) using standard screens of aperture size 16, 18, 20 and 24. 100 gm pellets weighed and transferred to sieve shaker then allow for shaking 50 Amplitude per 10 min. The sieve analysis shows enteric coated pellets are well distributed between 20- 24# screen. It indicates pellets were uniform, spherical and followed efficient process.

**Morphology of pellets by scanning electron microscopy (SEM):** The external structure and snappy section of beads of optimum formulation was checkedby means of scanning electron microscope. This was carried out to find the uniformity and thickness of coating, which is determining factor for evaluation of physical parameters.

**Statistical Optimization of Rifaximin Formulation Variables**

A central composite design with two factors, i.e., ratio of Eudragit L100 and S100 and % of functional coat (B) was exercised using statistical software (design expert version 9, India) to explore the effect of the investigated factors on the drug release from coated pellets. Drug release at the end of 2nd h dissolution in pH 6.8 (Y1) and at the end of 8th hr in pH 6.8 were designated as response variables.

## 3. Results and Discussion

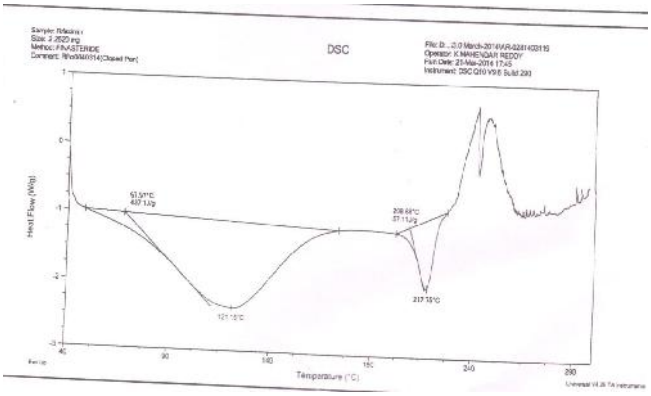


**Figure1:** DSC of Rifaximin

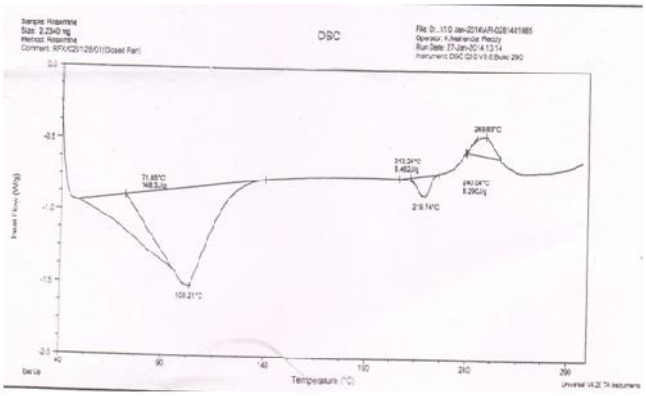


**Figure 2:** DSC of Rifaximin-excipients physical mixer

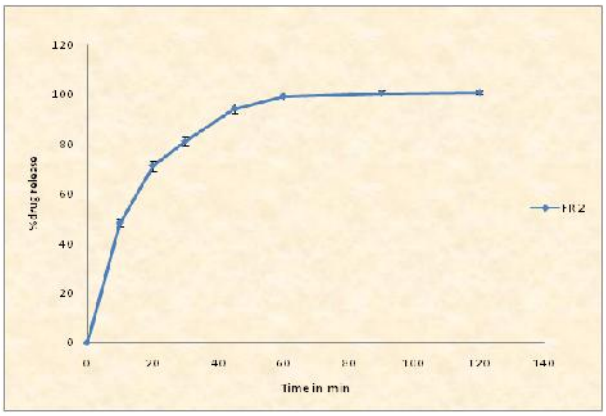


**Figure 3:** Dissolution profiles of drug pellets at pH 7.4 sodium phosphate buffer

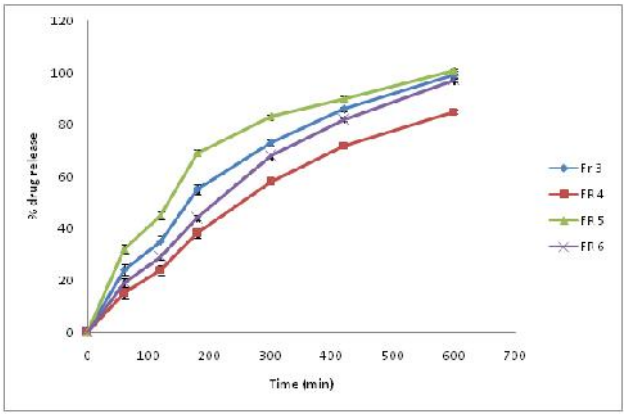


**Figure 4:** Dissolution profiles of drug pellets at pH 6.5 sodium phosphate buffer

**Stability Study Reports**

**Rifaximin stability studies:** The stability studies were conducted on the selected formulation F17 at 40°C/75% RH for 3 months. The pellets were evaluated for Description, Assay and Dissolution. The result is plotted in are shown in table 5.47**.**

## 4. Conclusion

The conclusion is summarized for the research work carried out on design of colon targeted drug delivery systems Rifaximin. Multi-unit dosage from selected to target drug for site specific action because of its advantage to bypass the dose dumping over single unit. Two different type of design approach exploited in this thesis, one with time dependent outer coating and swelling layer formation coating on inner layer which can impart sustained release of drug at colon; and other with combination of pH- dependent polymers in typical ratio's which can release fast or immediate manner at the physiological environment of colon.

Rifaximin a drug exerts local action than absorption systemically, indicated for traveller's diarrhoea by E.Coli and IBD. The formulation is designed to burst release at colon for faster local action to suppress the bacterial growth and to prevent inflammation of bowel. Rifaximin exhibit low solubility, hence it's a right candidate to formulate delayed release colon targeted multiple release units. In the present investigation, polymer combination that is pH dependent polymers Eudragit S 100 and L 100 for Rifaximin were used in the coating formulation that amend drug liberate with a suitable pause time at diverse physiological medias.

Novelmove towards CDDS was made using numerous coatings of combination of pH dependent poly methacrylates on API layered pellets. The deliverance arrangement might prove victorious for delivery of drug to the site with an immediate or burst release.RSM plot enabled formulation of Rifaximin with Eudragit polymers gave desired release profile. The optimized formulation demonstrates let go profiles for colonic delivery were close to envisaged formulation of Eudragit L100: Eudragit S 100 in ratio of 3.3 at 15.4% coating level.

**Table 1:** Composition of Rifaximin along with excipient's at for compatibility studies

| S.No. | Name of the Binary Mixture | Composition Ratio |
|---|---|---|
| 1 | Rifaximin | Not Applicable |
| 2 | Rifaximin + Sugar Spheres | 1 : 5 |
| 3 | Rifaximin + Povidon K30 | 1 : 1 |
| 4 | Rifaximin + HPMC E5 | 1 : 1 |
| 5 | Rifaximin + Polyethylglycol 6000 | 1 : 0.5 |
| 6 | Rifaximin + Talc | 1 : 0.5 |
| 7 | Rifaximin + Eudragit S100 | 1 : 5 |
| 8 | Rifaximin + Eudragit L100 | 1 : 5 |
| 9 | Rifaximin + Triethyl citrate | 1 : 0.5 |
| 10 | Rifaximin + Red iron oxide | 1 : 0.5 |
| 11 | Rifaximin + Povidon K30 + Eudragit S100 + Eudragit L100 | 1:1:5:5 |

**Table 2:** Compatibility of Rifaximin alone and with ingredient's at different ratios

| S.No. | Name of the Binary Mixture | Composition Ratio | Physical Observations |
|---|---|---|---|
| 1 | Rifaximin | | No colour change |
| 2 | Rifaximin + Sugar Spheres | 1 : 5 | No colour change |
| 3 | Rifaximin + Povidon K30 | 1 : 1 | No colour change |

| | | | |
|---|---|---|---|
| 4 | Rifaximin + HPMC E5 | 1 : 1 | No colour change |
| 5 | Rifaximin + Polyethylglycol 6000 | 1 : 0.5 | No colour change |
| 6 | Rifaximin + Talc | 1 : 0.5 | No colour change |
| 7 | Rifaximin + Eudragit S100 | 1 : 5 | No colour change |
| 8 | Rifaximin + Eudragit L100 | 1 : 5 | No colour change |
| 9 | Rifaximin + Triethyl citrate | 1 : 0.5 | No colour change |
| 10 | Rifaximin + Red iron oxide | 1 : 0.5 | No colour change |
| 11 | ximin + Povidon K30 + Eudragit S100 + Eudragit L | 1:1:5:5 | No colour change |

**Table 3:** Drug loading process parameters in coating pan (Ideal cure make)

| Parameter | Pan size | In let temp | Bed temp | Pan speed | Spray rate | Atomization pressure |
|---|---|---|---|---|---|---|
| Range | 6 inch | 55 – 60$^0$c | 55 – 40$^0$c | 22 – 30 rpm | 2– 3 m/min | 1-2 bar |

**Table 4:** Bottom spray coating process parameter (Wurster)

| Process parameters | Seal coating range | Polymer coating Range |
|---|---|---|
| Batch size (kg) | 0.5 | 0.5 |
| Equipment capacity | 2.4 | 2.4 |
| Fluid bed insert | 3.5''wurster | 3.5''wurster |
| Partition height (cm) | 8 | 10 |
| Distribution plate | C plate | C plate |
| Nozzle tip diameter (mm) | 1.0 | 1.0 |
| Inlet temperature $^0$c | 50-60 | 42-44 |
| Product temperature $^0$c | 35-40 | 28-33 |
| Spray rate (gm/min) | 4-8 | 3-8 |
| Atomization air pressure (bar) | 0.8 | 0.8-1.0 |
| Air flow (cfm) | 50-60 | 55-65 |

**Table 5A:** Physical evaluation of Rifaximin CDD DR pellets

| Characteristics | FR5 | FR6 | FR7 | FR8 | FR9 |
|---|---|---|---|---|---|
| Bulk density (g/ml) | 0.756 | 0.762 | 0.767 | 0.757 | 0.748 |
| Tapped density (g/ml) | 0.798 | 0.801 | 0.798 | 0.804 | 0.798 |
| Angle of repose (°) | 32 | 33 | 32.5 | 33.4 | 33 |
| Hausner's ratio | 1.05 | 1.05 | 1.04 | 1.06 | 1.06 |
| Carr's index (%) | 5.26 | 4.87 | 3.98 | 5.84 | 6.26 |

**Table 5B:** Physical evaluation of Rifaximin CDD DR pellets

| Characteristics | FR10 | FR11 | FR12 | FR13 | FR14 | FR15 | FR16 | FR17 |
|---|---|---|---|---|---|---|---|---|
| Bulk density (g/ml) | 0.760 | 0.746 | 0.759 | 0.763 | 0.757 | 0.761 | 0.765 | 0.762 |
| Tapped density (g/ml) | 0.788 | 0.796 | 0.809 | 0.810 | 0.785 | 0.793 | 0.795 | 0.811 |
| Angle of repose (°) | 32.7 | 33.4 | 33.5 | 33.2 | 33 | 33.4 | 33.1 | 32.7 |
| Hausner's ratio | 1.03 | 1.06 | 1.06 | 1.06 | 1.03 | 1.04 | 1.03 | 1.06 |
| Carr's index (%) | 3.55 | 6.28 | 6.55 | 5.8 | 3.56 | 4.03 | 3.8 | 6.0 |

**Table 6A:** Cumulative percentage retain of Rifaximin pellets

| Screen aperture size | FR5 | FR6 | FR7 | FR8 | FR9 | FR10 |
|---|---|---|---|---|---|---|
| #16 | 1.65 | 1.45 | 1.56 | 1.36 | 1.55 | 2.05 |
| #18 | 4.33 | 4.13 | 4.4 | 4.5 | 5.2 | 5.3 |
| #20 | 29.67 | 28.93 | 28.34 | 28.18 | 28.56 | 28.93 |
| #24 | 99.42 | 98.47 | 99.13 | 99.09 | 98.42 | 99.42 |
| Pan | 100 | 100 | 100 | 100 | 100 | 100 |

**Table 6B:** Cumulative percentage retain of Rifaximin pellets

| Screen aperture size | FR11 | FR12 | FR13 | FR14 | FR15 | FR16 | FR17 |
|---|---|---|---|---|---|---|---|
| #16 | 1.55 | 1.23 | 2.11 | 1.25 | 2.32 | 2.15 | 2.22 |
| #18 | 4.3 | 3.98 | 5.32 | 4.0 | 5.30 | 4.8 | 4.45 |
| #20 | 27.98 | 28.48 | 28.90 | 29.33 | 28.03 | 28.90 | 28.19 |
| #24 | 98.23 | 99.87 | 98.67 | 97.89 | 98.24 | 98.30 | 99.42 |
| Pan | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

**Table 7:** Dissolution profiles of drug pellets at pH 7.4 sodium phosphate buffer

| Time in min | 0 | 10 | 20 | 30 | 45 | 60 | 90 | 120 |
|---|---|---|---|---|---|---|---|---|
| % drug dissolved | 0 | 48.2 ±1.05 | 71.33 ±0.94 | 81.33 ±0.86 | 94.33 ±0.77 | 99.21 ±0.69 | 100.5 ±0.78 | 100.77 ±0.38 |

**Table 8:** Dissolution profiles of drug pellets at pH 6.5 sodium phosphate buffer

| Time min | FR3 | FR4 | FR5 | FR6 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 60 | 24.4±1.67 | 15.25±2.12 | 32.76±1.77 | 19.26±1.69 |
| 120 | 35.36±1.02 | 24.43±2.01 | 45.68±1.34 | 29.33±1.05 |
| 180 | 55.66±0.89 | 38.46±1.78 | 69.77±1.35 | 44.34±1.06 |
| 300 | 73.8±0.93 | 58.76±1.02 | 83.58±0.95 | 68.47±0.87 |
| 420 | 86.5±0.79 | 72.68±0.89 | 90.58±0.77 | 82.55±0.59 |
| 600 | 99.77±0.99 | 85.78±0.79 | 101.44±0.48 | 97.56±0.55 |

**Table 9:** Stability study values

| Parameters | Time period | | | |
|---|---|---|---|---|
| | Initial | 1 Month | 2 Month | 3 Month |
| Description | Complies | Complies | Complies | Complies |
| Drug content (%) | 99.8 | 98.4 | 101.3 | 97.9 |
| Cumulative % Drug Release | | | | |
| 0 | 0 | 0 | 0 | 0 |
| 120 | 0 | 0 | 0 | 0 |
| 180 | 0 | 0 | 0 | 0 |
| 240 | 0 | 0 | 0 | 0 |
| 300 | 4.21±1.28 | 4.5±.1.11 | 4.3±1.22 | 4.8±1.20 |
| 360 | 15.23±1.39 | 15.2±1.02 | 14.6±1.20 | 15.6±1.98 |
| 420 | 30.23±1.08 | 29.6±0.39 | 30.2±1.02 | 30.9±1.29 |
| 480 | 75.22±0.33 | 76.2±0.43 | 75.6±1.24 | 76.2±1.32 |
| 540 | 83.21±0.39 | 84.2±0.38 | 83.6±1.45 | 84.2±1.35 |
| 600 | 90.19±0.49 | 91.2±0.29 | 90.6±0.93 | 91.3±1.25 |
| 700 | 100.3±0.39 | 99.5±0.33 | 99.8±0.49 | 100±1.54 |

## 5. References


[1] He, W.; *Du,Q.;Cao,D.Y.;* Xiang, B.; and Fan, L.F.; International Journal of Pharmaceutics, 348, 2008, 35-45.

[2] Zahirul,M.; Khan.I.; Prebeg. Z.; Kurjakovic.N.; Journal Control Release, 58, 1999, 215-222.

[3] Remunan-Lopez,C.; Lorenzo-Lamosa,M.L.; Vila-Jato,J.L.; and Alonso,M.J.; European Journal of Pharmaceutics and Biopharmaceutics, 45, 1998, 49-56.

[4] Peter,J.W.; and Abdul,W.B.;International Journal of Pharmaceutics, 300, 2005, 89-94.

[5] Bose, A.; Elyagoby, T.W.; and Wong, International Journal of Pharmaceutics, 468, 2014, 178–186.

[6] Maria, M.; Friciu,; Tien, C.L.; Pompilia, I.; Mircea, and Alexandru.M.; European Journal of Pharmaceutics and Biopharmaceutics,85, 2013, 521–530.

[7] Amol,P.; Awesh,K.; Yadav, Gopal,R.; Sunil,J.; Shyam,S.; Pancholi, and Govind, P.A.; AAPS PharmSciTech, 8 (1), 2007, E1-E7.

[8] Das,S.; and Ng, K.Y.; J Pharm Sci. 99(12), 2010, 4903-16.

[9] Laila, F.A.A.; Chetan,B.C.; and Sajeev,C.; AAPS PharmSciTech, 10 (2), 2009, 418-429.

[10] Das, S.; and Ng, K.Y.; Int J Pharm. 29, 2010, 385(1-2):20-8.

[11] Xu, M.;Sun, M.;Qiao, H.;Ping, Q.; andElamin, E.S.;Int J Pharm.;468(1-2), 2014,165-71.

[12] Varshosaz, J.;Emami, J.;Tavakoli, N.;Minaiyan, M.; Rahmani,N.;Dorkoosh, F.;and Mahzouni. P.; Acta Pharm. 62(3), 2012, 341-56.

[13] Kulthe, S.S.;Bahekar, J.K.;Godhani, C.C.;Choudhari, Y.M.;Inamdar, N.N.;and Mourya, V.K.;Drug Dev Ind Pharm.39(1), 2013, 138-45.

[14] Rabišková, M,;Bautzová, T.;Gajdziok, J.;Dvořáčková, K.;Lamprecht, A.;Pellequer,Y.;and Spilková. J. Int J Pharm. 422(1-2), 2012, 151-9.

[15] Fu, J,;Wang, X.;Xu, L.;Meng, J.;Weng, Y.;Li, G.;He, H.;and Tang, X.; Int J Pharm. 406(1-2) 2011, 84-90.

[16] Wycliffe,S.O.; Rama,M.; Brenda,L.V.; and Steven,H.N.; International Journal of Pharmaceutics, 441, 2013, 343– 351.

[17] Sadeghi, F.; Akhgari, A.; and Afrasiabi, G.H.; International Journal of Pharmaceutics, 320, 2006 137-142.

[18] Pallab,R.; and Aliasgar, S.; European Journal Pharmaceutical Science, 37, 2009,363-369.

[19] Akhgari, A.; F., Sadeghi,H.; and Afrasiabi, G.H;European Journal of Pharmaceutics and Biopharmaceutics, 320, 2006, 137-142.
[20] Kampanart,H.; Pornsak,S.; Manee,L.; Sontaya, L.; Satit, Lee-Yong,L.; Katsuhide,T.; and Jurairat,N.; Eurupean Journal Pharmaceutical Science, 50, 2013, 303–311.