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(RESEARCH ARTICLE)

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Development of single layer osmotic controlled release tablet for low soluble drug: Single Core Osmotic Pump (SCOP)

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Abstract

A novel Single Core Osmotic Pump (SCOP) pill has been created to administer high doses of the low solubility medication Rifaximin using osmosis. The formulations were evaluated using six comparative parameters: Q24 (total release after 24 hours), Q12 (total release after 12 hours), TL (lag time), RSQzero12 (R square of the zero-order equation for drug release in 12 hours), RR12 (in vitro release rate for 12 hours), and T80% (time required to deliver 80% of the drug). The drug release profile from osmotic devices shows that the choice of polymer and its concentration in the core formulation can significantly impact the release of the drug. Augmenting the osmogent quantity to an optimal level resulted in a substantial enhancement of Q12 and a notable improvement in the zero-order release pattern of rifaximin. In order to improve the bioavailability of the core formulation, an additive called citric acid was included. Citric acid has several properties that contribute to this enhancement, such as increased solubility of the active ingredient, the creation of a difference in osmotic pressure, regulation of the flow of the active ingredient, and making the composition containing the active ingredient more water-loving. Consequently, TL and T80% experienced a decline, whereas Q12 and RR12 saw a rise. The concentration of PEG 4000 in the semipermeable membrane of the SCOP was found to have a significant impact on TL, T80%, Q12, Q24, and RR12. Specifically, increasing the concentration of PEG 4000 led to a decrease in TL and T80%, while increasing Q12, Q24, and RR12. The optimal aperture diameter for achieving a zero-order release pattern was found to be 850 µm. This study also demonstrated that optimizing the thickness of SPM is crucial for achieving zero order kinetics. The invented SCOP technology has the potential to create a single layer osmotic controlled release tablet of a water insoluble medication with a high dosage.

Keywords: Single Core Osmotic Pump; Water Swellable Polymer; Osmotic Agent; Rifaximin; Solubilizer; Coating and Drilling

1. Introduction

In the last five decades, there has been increased focus on the development of controlled-release delivery systems due to the acknowledgment of the therapeutic benefits they offer. Osmotic pumps are a significant technology in the development of controlled drug delivery systems. These devices utilize osmotic pressure as a power source to administer drugs at predefined zero-order rates over a prolonged duration. While other forms of oral osmotic systems

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have been documented, the most significant one is Theeuwes elementary osmotic pump. This system consists of an osmotic core that is enclosed by a semi-permeable membrane which has a medication delivery aperture. Upon contact with gastrointestinal fluids, this technology allows osmotically driven water to enter through a semi-permeable membrane, dissolve the soluble drugs, and escape through the delivery orifice. These systems utilize osmotic pressure to administer the active compound(s) in a regulated manner. As a result, the delivery rates are anticipated to remain unaffected by gastrointestinal conditions.

The medication release rate from osmotic pumps is determined by the combined solubility and osmotic pressure of the core. Consequently, medications that are not easily dissolved in water do not generate enough osmotic pressure and are administered at a slow pace. In order to address this issue, alternative osmotic pumps have been developed for drugs that are not easily soluble in water. Adding a solubility-modulating chemical to the core can sometimes solve this problem. Nevertheless, this method is inadequate when dealing with situations that require a substantial quantity of the modulator. Furthermore, if the modulator is rapidly depleted from the system, the device will release the medicine at uneven rates.

The literature study indicated that it is feasible to achieve single-layer osmotic drug administration for drugs with poor solubility. However, the review did not specify the constraints or the ideal formulation variables for such systems. The present study examines the variables that impact the effective release of low solubility active pharmaceutical ingredients (APIs) from a single-layer osmotic system.

The model drug chosen for the development of the single core osmotic pump (SCOP) was Rifaximin. Rifaximin is primarily given for the treatment of depressive illness, typically in a dosage range of 50-200 mg per day. Rifaximin exhibits limited solubility in water, especially at pH levels higher than 6 to 7. This can lead to reduced bioavailability. Patients are typically started on Rifaximin at a dosage of 50 mg/day or lower. Patients who do not exhibit a response to the 50 mg dosage are administered greater dosages. If it is deemed necessary to attain effectiveness, greater dosages can be achieved with gradual increments in dosage. Developing enhanced Rifaximin dosage forms with reduced occurrence and intensity of adverse reactions would be beneficial as it would enhance patient comfort and compliance. Additionally, it would allow for the administration of bigger initial dosages, beyond 50 mg, without the requirement for progressive increments. Commencing treatment with greater first doses could be beneficial since it may lead to a quicker onRifaximin of antidepressant effects. The present study utilized Rifaximin as the model drug.

Therefore, the development of an enhanced Rifaximin dosage form that allows for the administration of high doses of Rifaximin (e.g., 60 mg and above) orally, while minimizing side effects, would enable a broader use of Rifaximin therapy. This would result in a substantial enhancement in adherence to the prescribed dosage and convenience for patients. [1,2,3]

2. Materials and method

2.1. Materials

The compound Rifaximin was provided as a kind donation by Hetero Drugs Limited, a pharmaceutical company based in Hyderabad, India. Natrosol (250 H, 250 L) and Klucel (EXF, HF) were provided as gracious donations by DKSH India Pvt Ltd. located in Mumbai, India. The company Colorcon Asia Pvt Ltd. (located in Goa, India) gifted us with samples of PolyoxWSR Coagulant and Methocel. The Xanthan Gum was obtained as a complimentary sample from Ottochemi, a company based in Mumbai, India. We received a free sample of cellulose acetate from Eastman Chemical Co. (USA). The gift sample of Neosorb P 30/60 was received from Roquette Asia Pvt. Ltd, located in Mumbai. The gift sample of Xylitol was obtained from DaniscoIngradient, USA. Citric acid, Polyethylene glycol 4000, and Sodium lauryl sulphate were acquired from S. D. Fine Chemicals in Mumbai, India. The remaining compounds employed were of analytical grade.

2.2. Experimental Method

2.2.1. Drug-Excipients Compatibility Study

Evaluating potential incompatibilities between an active pharmaceutical ingredient and various excipients is a crucial step in the preformulation phase of dosage form development. The Differential Scanning Calorimeter (DSC TA-60WS) enables rapid assessment of potential incompatibilities by detecting alterations in physical properties, such as shifts in melting endotherms and exotherms, as well as changes in the associated enthalpies of reaction. The differential scanning calorimetry (DSC) thermograms were obtained for the following substances: the pure drug Rifaximin, the polymer Natrosol 250HX, the osmotic agent Neosorb P 30/50 DC, and a mixture of the drug with the polymer Natrosol 250HX

and the osmotic agent Neosorb P 30/50 DC. The mixture of the drug with all excipients, in a ratio of 1:1, as employed in the formulation, was also included in the recordings. The thermal analysis was conducted under a nitrogen environment with a consistent heating rate of 10˚C/min, spanning a temperature range of 40˚C to 300˚C. [4,5,6]

2.2.2. Drug Estimation

UV spectrophotometry was utilized to assess the homogeneity of drug content and to quantify the amount of Rifaximin throughout the dissolution test. The sample solution's reaction was measured at a wavelength of 274 nm. The quantities of Rifaximin in the sample solution were calculated by fitting the responses to the regression equation for Rifaximin. A calibration curve was constructed using concentrations ranging from 100 to 200 µg/ml.

2.2.3. Formulation Development and Optimization of Core Tablet

The core tablets were created by the process of direct compression. To choose a water swellable polymer, formulations were created utilizing 10% w/w core weight of Polyox Coagulant, Methocel K4M, Natrosol 250HX, Xanthan Gum, and Klucel HF. The impact of these polymers on release profiles was then assessed. The fundamental components are outlined in (Table-1). The Rifaximin was combined with a water-swellable polymer and left to mix for a duration of 10 minutes. After sieving the mixture through a 40-mesh screen, Neosorb P30/60 DC (an osmotic agent) and Klucel EXF (a binder) were added in geometric dilution. The mixing process was then continued for an additional 10 minutes. Sodium lauryl sulphate, a wetting agent, and Acryflow-L, a lubricant, were added to the mixture and stirred for an additional 5 minutes. The mixture was subsequently compacted into tablets weighing an average of 695 ± 10 mg using a rotary tablet machine (Rimek Mini Press-II) fitted with a 13 mm diameter round, smooth, and standard concave tooling. The mean hardness of compressed tablets was 6.5 ± 1.5 kg/cm2. [7]

Analyzed were a range of formulation and dissolving characteristics in order to optimize SCOP. Several parameters, including Q24 (amount of the drug released within 24 hours), Q12 (amount of the drug released within 12 hours), TL (delay time of the drug release from the device), RSQZERO 12 (R square value of release data for 12 hours fitted to the zero order equation), RR12 (in vitro release rate for 12 hours), and T80% (time required to deliver 80% of the drug), were utilized to compare various formulations. Formulations that met the criteria of having a Q24 value more than 70% and a Q12 value greater than 50% were selected for further tests. Out of the chosen formulations, those with a TL of 2 hours were not accepted. The remaining formulations were then compared based on their RSQzero, RR12, and T80%.

Table 1 Formulae of SCOP TABLET (mg tablet)

Ingredients (mg)	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**
Rifaximin	200	200	200	200	200	200
Polyox Coagulant		60				
HPMC K4M			60			
Natrosol 250 HX				60		
Xamthan Gum					60	
Klucel HF						60
Neosorb P30/60DC	346	286	286	286	286	286
Klucel EXF	30	30	30	30	30	30
Citric acid	105	105	105	105	105	105
SLS	18	18	18	18	18	18
Acryflow-L	6	6	6	6	6	6

2.3. Coating and Drilling

The core tablets underwent coating using a traditional laboratory coating pan. The coating solution was formulated by dissolving 16 grams of cellulose acetate CA 398-10 and 8 grams of polyethylene glycol 4000 in a solvent mixture consisting of 356 grams of acetone and 20 grams of water. The different constituents of the coating solution were

sequentially incorporated into the solvent mixture. The initial component was permitted to dissolve prior to the addition of the subsequent component. Prior to commencing the coating process, the tablets were heated to a temperature of 40 ± 5 0C for a duration of 10 minutes. Subsequently, the coating solution was administered at a consistent spray rate of 4-5 ml/min. A coating technique was applied to a batch of 100 tablets. The rotational speed of the pan was maintained at 20 revolutions per minute (rpm), and the temperature of the hot air input was kept at 40 ± 5 degrees Celsius. The coating process was repeated until the necessary percentage coat weight (10%) was achieved on the core tablets. To examine the impact of coating membrane properties, such as the quantity of plasticizer and thickness, on drug release, osmotic tablets were coated with various concentrations of plasticizer and different membrane thicknesses, as indicated in Table 2. [8,9,10]

The coated tablets were perforated on one side using conventional mechanical micro drills. In order to reduce the impact of orifice size on the release of the active ingredient, a hole with a diameter of 850μm was bored into the tablets.

Table 2 Coating membrane composition for SCOP

Batch No.	CA: PEG	%Weight Gain	Orifice Diameter	No. of Orifice
B31	6.5:3.5	10	850	1
				2
				4
B32	7.0:3.0	10	850	1
B33	7.5:2.5	10	850	1
B34	8.0:2.0	10	850	1
B35	6.5:3.5	10	350	1
B36	6.5:3.5	10	550	1
B37	6.5:3.5	10	650	1
B38	6.5:3.5	8	8501	1

2.4. *In Vitro* Release Studies

The release of various formulations was studied using the USP apparatus II, paddle method (Dissolution test equipment-TDT-06T, Electrolab, India). The paddle speed was consistently Rifaximin at 50 revolutions per minute (rpm), while 900 milliliters of Acetate Buffer with a pH of 4.5 was utilized as the dissolution medium. 10ml samples were collected at specific time intervals (1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours) and substituted with an equal volume of fresh medium. The substituted medium was filtered using a 0.45 μm filter and analyzed using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer at a wavelength of 274nm. The drug concentration was determined using a standard calibration plot and reported as the cumulative percentage of drug dissolved. [11,12]

2.5. Surface Morphology

In order to examine the alteration in the structure of the membrane, the surface of the coated tablets was analyzed using Scanning Electron Microscopy (SEM) both before and after conducting dissolving investigations. When a tablet is placed in the dissolution medium, the coated membrane absorbs water, resulting in the formation of pores through the leaching of water-soluble pore formers. The alterations in the visual characteristics of the coated membrane of SCOP during the dissolution process were examined using scanning electron microscopy (SEM).

2.6. Burst Strength

The burst strength of the depleted shells (n = 6), following 24 hours of dissolving, was assessed to ensure that the tablets would retain their structural integrity in the gastrointestinal tract (GIT). The burst strength was measured by determining the force needed to fracture or rupture the shells during dissolving studies. For this purpose, the texture analyzer used was Brookfield's Texture Analyzer - QTS, equipped with a 5 kg load cell and a 25mm aluminum cylindrical probe. A test speed of 0.8 mm/s was chosen, and the distance traveled was Rifaximin at 6 mm.

2.7. Accelerated Stability Studies

The SCOP formulation was efficiently packaged in aluminum strips that were coated with PVC. As per the ICH recommendation, the packaged formulations were kept in stability chambers (Cintex humidity oven; Cintex Industrial Corporation, Dadar, Mumbai) at a temperature of 40°C and a relative humidity of 75% for a duration of 3 months. Each month, samples were collected and analyzed for drug content and drug release rate using a UV spectrophotometer. [14]

3. Results and discussion

3.1. Drug-Excipients Compatibility Study

The DSC thermograms of the individual excipients, namely Rifaximin, Natrosol 250HX, and Neosorb P 30/60 DC, as well as the 1:1 mixture of Rifaximin, are presented in Figures 1A to 1F.Comparisons were made between Natrosol 250HX and Rifaximin:Neosorb P 30/60 DC, together with a medication and its excipients. The DSC thermogram of Rifaximin (Form II) (Figure 1A-1F) exhibits a minor endotherm at 188.44°C (ΔH = 7.75 J/g) with an on Rifaximin temperature of around 181.74°C. This endotherm indicates a transition from a solid state to Form III. The event that occurs after this is the melting of Form III. It starts at a temperature of 247.44 0C, reaches a strong peak at 250.93 0C (with a heat change of 67.66 J/g), and then recovers at 255.56 0C. This recovery temperature falls between the range of 246 – 251 0C. The third peak observed on the thermogram at a temperature of 295.86 degrees may indicate the degradation of the Rifaximin. Therefore, it may be inferred that the transition depicted on the graph corresponds to the melting point of the Rifaximin.

Figure-1B and 1C display a peak at a temperature of 237.01 0C, with a heat change of 12.48 J/g. The on Rifaximin temperature is 227.57 0C, and the recovery temperature is 243.06 0C. Additionally, there is a peak at a temperature of 103.77 0C, with a heat change of 113.39 J/g. The on Rifaximin temperature for this peak is 95.25 0C, and the recovery temperature is 110.92 0C. These observations are for the substances Natrosol 250HX and Neosorb P 30/60 DC, respectively.

The thermogram of the mixture of Rifaximin and Natrosol 250HX (Figure 1D) reveals a peak corresponding to Rifaximin. The on Rifaximin temperature is 252.37°C, with a maximum temperature of 253.39°C (ΔH = 69.25 J/g), and recovery occurs at 263.01°C. The thermogram of the Rifaximin alone has a distinct peak at 250.93 0C (with a heat change of 67.66 J/g), beginning at 247.74 0C and concluding at 255.56 0C. These results suggest that there was no alteration in the maximum peak value or enthalpy, indicating a lack of interaction between the drug and polymer.

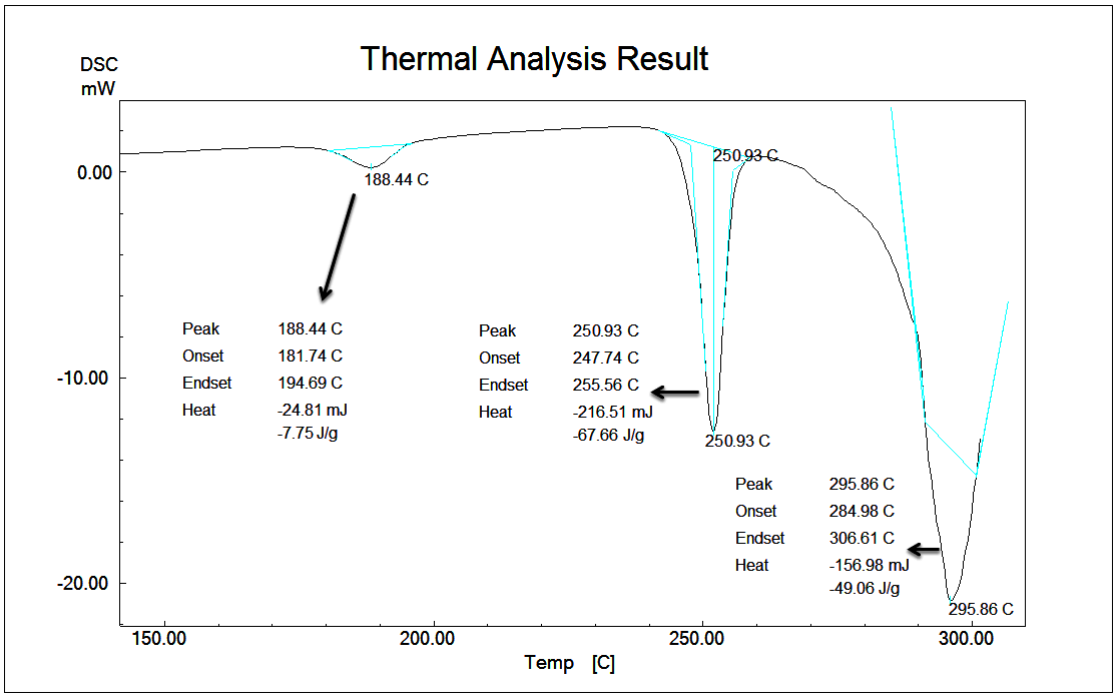

Figure 1A DSC curve of Rifaximin

The thermogram of Rifaximin and Neosorb P 30/60 DC (Figure-1E) reveals that the Rifaximin material exhibits a peak with an on Rifaximin temperature of 246.72°C, a maximum temperature of 253.98°C (with a heat change of 66.26 J/g), and a recovery temperature of 255.52°C. The thermogram of the Rifaximin alone exhibits a distinct peak at 250.93 0C (with a heat change of 67.66 J/g), with the on Rifaximin occurring at 247.74 0C and recovery at 255.56 0C. These results indicate that there were no alterations in the maximum peak intensity or enthalpy, suggesting that there was no interaction between the medication and osmogent.

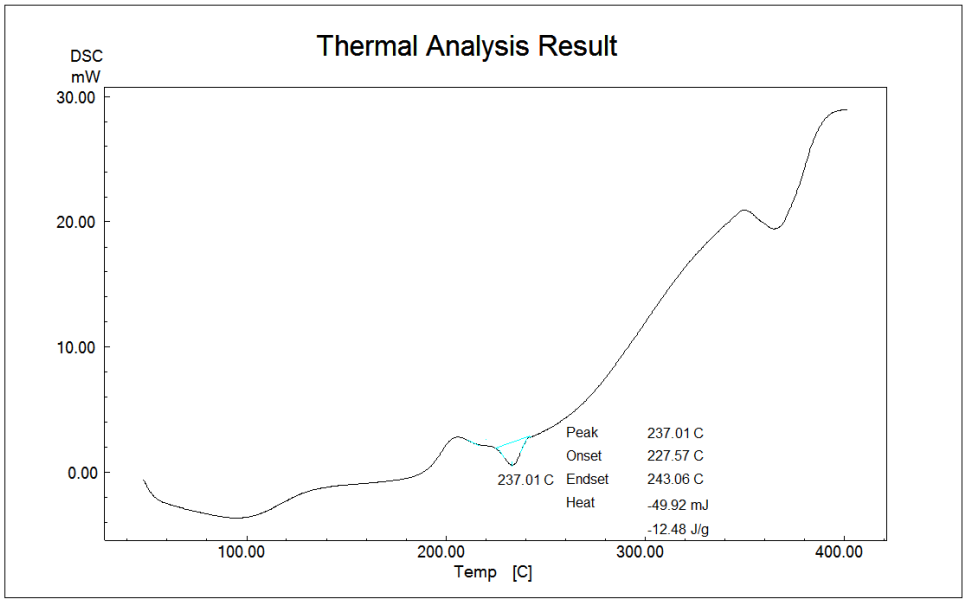

Figure 1B DSC curve of Natrosol 250 HX

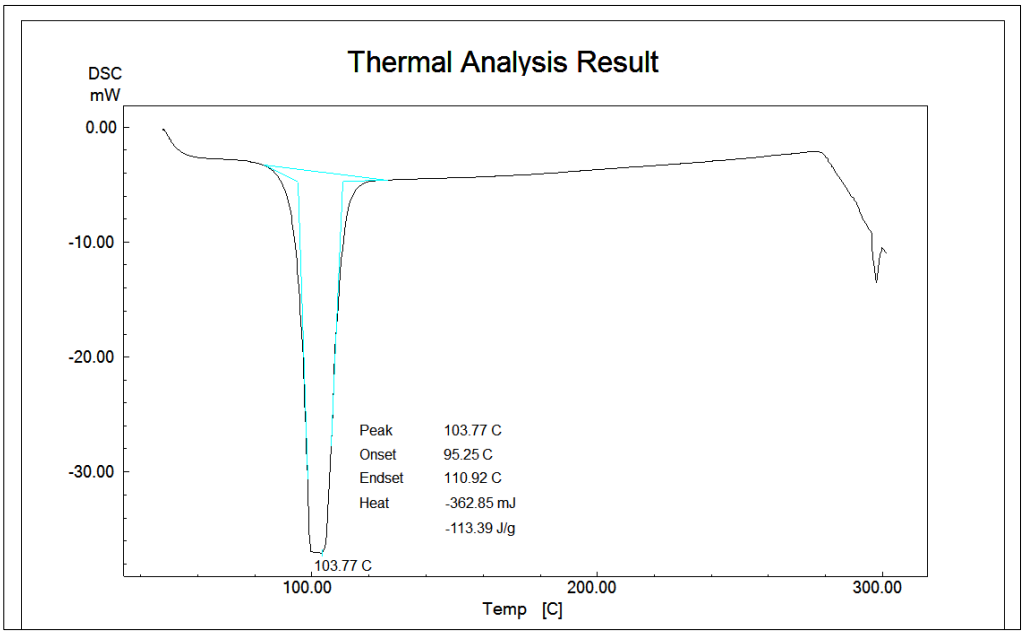

Figure 1C DSC curve of Neosorb P 30/60 DC

Figure 1F displays a thermogram of a Rifaximin (substance) with four different excipients: 1) Natrosol 250HX, 2) Neosorb P 30/60 DC, 3) Klucel EXF, and 4) SLS. The thermogram shows that there is no significant change in the peak maxima at 252.63 (ΔH = 69.25 J/g), the on Rifaximin temperature at 250.21, and the recovery temperature at 261.48, when compared to Figure 1A which represents the Rifaximin alone. In Figure 1A, the peak maxima is at 250.93 0C (ΔH = 67.66 J/g), the on Rifaximin temperature is at 247.74 0C, and the recovery temperature is at 255.56 0C. There were

no significant alterations observed in enthalpy, peak start, peak maxima, and recovery peak in all of these instances, suggesting that Rifaximin is compatible with the excipients utilized. [15]

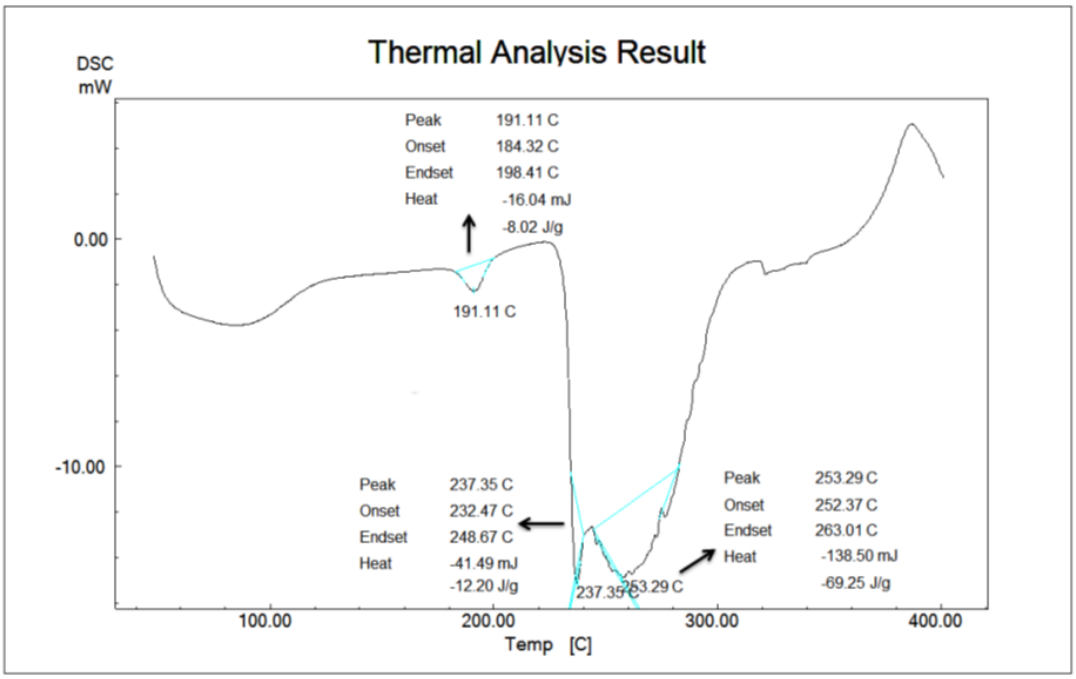

Figure 1D DSC curve of Rifaximin + Natrosol 250 HX

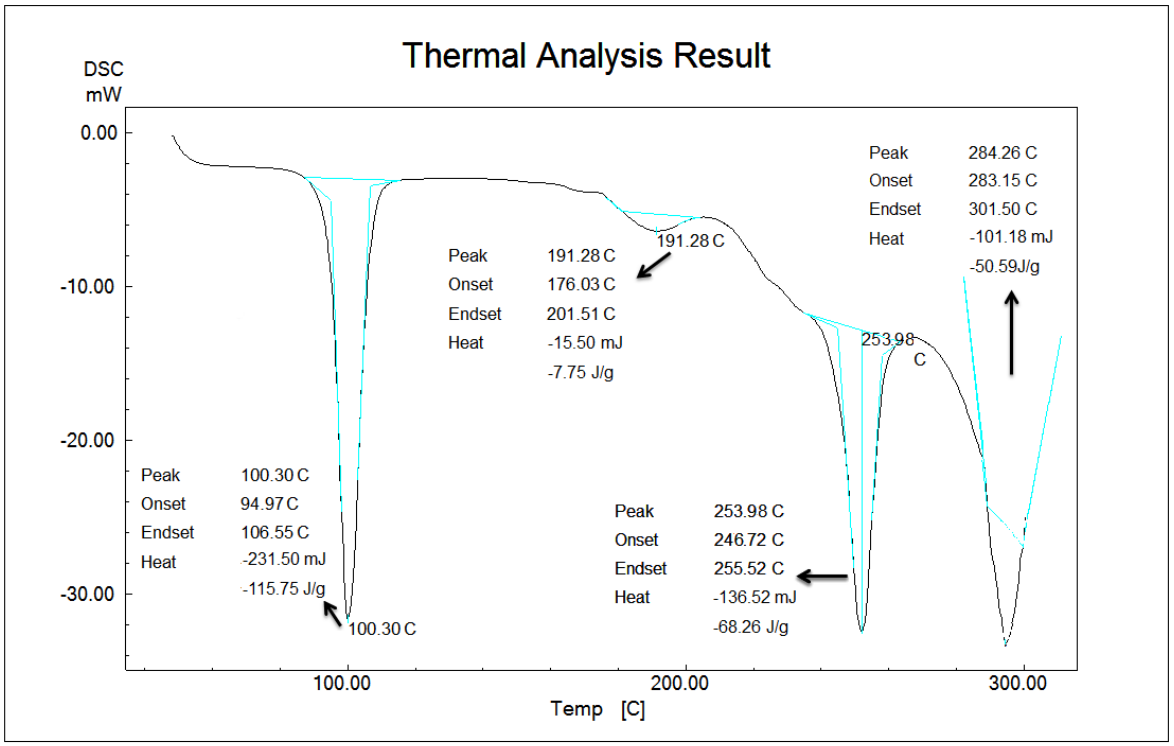

Figure 1E DSC curve of Rifaximin + Neosorb P 30/60 DC

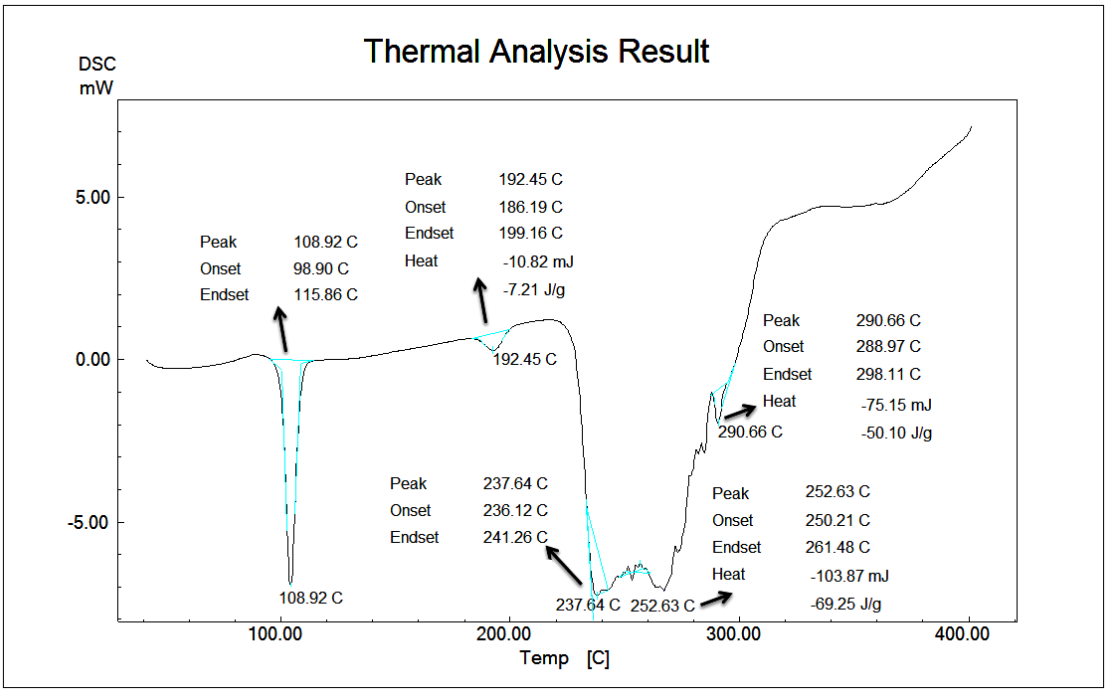

Figure 1F DSC curve of Rifaximin + Excipients

3.2. Drug Estimation

A linear association was shown by plotting peak regions against Rifaximin concentrations ranging from 100 to 200 µg/ml. The percentage recovery ranged from 98.43 ± 0.491 to 101.91 ± 0.6148, indicating the accuracy of the suggested technique. Each measurement was the mean of three replicates. The regression line had a slope of 0.0029, a y-intercept of 0.0331, and a correlation coefficient of 0.9997.

3.3. Formulation Development and Optimization of Core Tablet Influence of Water Swellable Polymer

This study involved creating various core formulations by using 10%w/w of Natrosol 250HX, Polyox WSR Coagulant, Xanthan Gum, Klucel HF, and HPMC K4M based on the weight of the core. The percentages for Q24 were 43.24%, 38.12%, and 39.80% for the osmotic device comprising Xanthan Gum, Klucel HF, and HPMC K4M, respectively. These polymers do not show any noticeable differences compared to the control (Q24 was 34.30%), which does not contain a water swellable polymer. Additionally, the RSQZERO12 values for the formulations comprising Klucel HF and HPMC K4M were 0.8506 and 0.9113 respectively, indicating that these polymers did not exhibit a satisfactory release profile. Nevertheless, the utilization of hydroxy ethyl cellulose (Natrosol 250HX) and PolyoxWSR coagulant seems to be highly efficient. These two polymers exhibit a favorable release profile. The formulation consists of 10% of the core weight of Natrosol 250HX and Polyox WSR Coagulant. The Q24 values for this formulation were 70.30% and 59.67%, the RSQZERO values were 0.9899 and 0.9852, and the RR12 values were 10.88 and 8.38, respectively. Figure 2 illustrates the impact of water swellable polymers on the release of drugs.

Nevertheless, the Natrosol 250HX is the optimal choice for the SCOP system due to its minimum lag time of 1.12 hours, favorable release rate of 10.88, and significant drug release of 59.34 within 12 hours. This selection ensures a zero-order release and a satisfactory amount of drug release during a 24-hour period.

At a specific extrusion pressure, the rate of extrusion generally decreases as the viscosity increases. Applicants have discovered that when high molecular weight hydroxyethyl cellulose (Natrosol 250HX) is combined with the drug particles, it forms solutions with water that have a high viscosity. However, these solutions can still be extruded from the tablets with a relatively modest amount of effort. The efficacy of HEC may be associated with its rheological characteristics and hydration rate. Furthermore, the swelling process did not result in the rupture of the system, despite the generated pressure. The findings also indicated that a consistent rate of expansion of the polymer guaranteed a steady release of the medication (RSQZERO 12: 0.9899). Based on the observed results, Natrosol 250HX was selected for further investigation.

3.4. Influence of Different Osmotic Agent

Several potential osmotic agents with varying osmotic pressures were investigated. Figure 3 displays the release characteristics of formulations that include Mannogem and Neosorb P30/60 DC. Pharmaburst 500 and Xylitab are both osmotically active agents. The data shows that the devices containing NeosorbP30/60 DC had the greatest Q12 value of 56.17 and the shortest TL value of 1.15h.The RSQZERO 12 values were compared for osmotic devices containing 262 mg of Mannogem, Neosorb P30/60 DC, Pharmaburst 500, and Xylitab. The device containing Neosorb P30/60 DC had the highest RSQZERO 12 value (0.9950), followed by Xylitab (0.9886), Mannogem (0.9205), and Pharmaburst 500 (0.9850). The value of Q24 for Xylitab was somewhat higher than that of Neosorb P30/60 DC. Nevertheless, the shortest TL (transition lag) and greater Q12 (dissolution efficiency), RR12 (relative release rate), and RSQZERO 12 (cumulative percentage release at 12 hours) values of Neosorb P30/60 DC indicate that it is the preferred option for the SCOP system in achieving zero order release and a satisfactory amount of drug release over a 24-hour period. Put simply, the osmotic pumps that contained Neosorb P30/60 DC as the osmotic agent exhibited a release pattern that matched zero order kinetics. The results indicated that the inclusion of Neosorb P30/60 DC significantly reduced the time required for drug release from the osmotic system (1.15 hours for Neosorb P30/60 DC compared to 1.3 hours, 3 hours, and 3.3 hours for Xylitab, Mannogem, and Pharmaburst 500, respectively, $p<0.05$). The formulation using Pharmaburst 500 as an osmotic agent had the lowest Q24 (54.64%) and the longest TL (3.3h). The devices containing Pharmaburst 500 may have a poor release rate, which could be attributed to a low osmotic activity. As a result, the formulation that contained 262mg of Neosorb P 30/60 DC was chosen for further testing. [1,16,17]

3.5. Influence of Solubilizer

When selecting an organic acid to utilize as a solubilizer using Rifaximin, there are several parameters that need to be taken into account. Citric acid is an organic acid that meets the specified characteristics. It has a water solubility of over 2000mg/ml, a high ratio of acid equivalents per gram (15.6 mEq/g), and a high osmotic pressure. Figure 4 displays the release curve of a composition with varying concentrations of citric acid. The values for Q12 were as follows: 61.68%, 62.45%, 62.17%, 68.42%, 69.98%, and 73.42%. These values correspond to citric acid concentrations of 0%, 3%, 6%, 9%, 12%, and 15% of the core weight. The data suggests that the release of the medication was enhanced as the concentration of citric acid was raised.

The formulations containing 0, 3, 6, 9, 12, and 15% of citric acid exhibited dissolution times of 24, 22, 22, 18, 18, and 16 hours, respectively. These results demonstrate that the quantity of citric acid significantly influenced the release profile of Rifaximin from osmotic systems. However, the TL and RR12 values were similar for formulations containing 9%, 12%, and 15% citric acid. The TL value was 0.45 for all three formulations, while the RR12 values were 12.77mg/h, 13.06mg/h, and 13.71mg/h, respectively ($p=0.03$). The formulation containing 15% citric acid was chosen as the most suitable due to its shortest T80% (16h) and higher correlation coefficient of zero-order kinetic (RSQZERO 12: 0.9948) compared to tablets containing 9% and 12% citric acid (TL: 18h and 18h and RSQZERO 12: 0.9913 and 0.9907, respectively). Further investigations were conducted on this formulation to analyze the impact of coating parameters, including the number and size of orifice, thickness of coating, and concentration of plasticizers. [1,18]

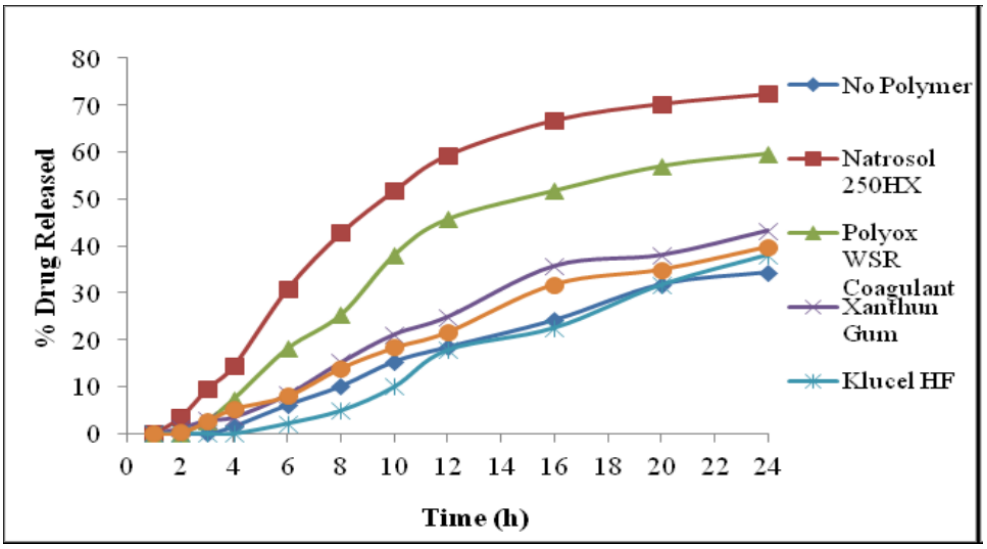

Figure 2 Influence of hydrophilic polymer on *in vitro* Rifaximin release

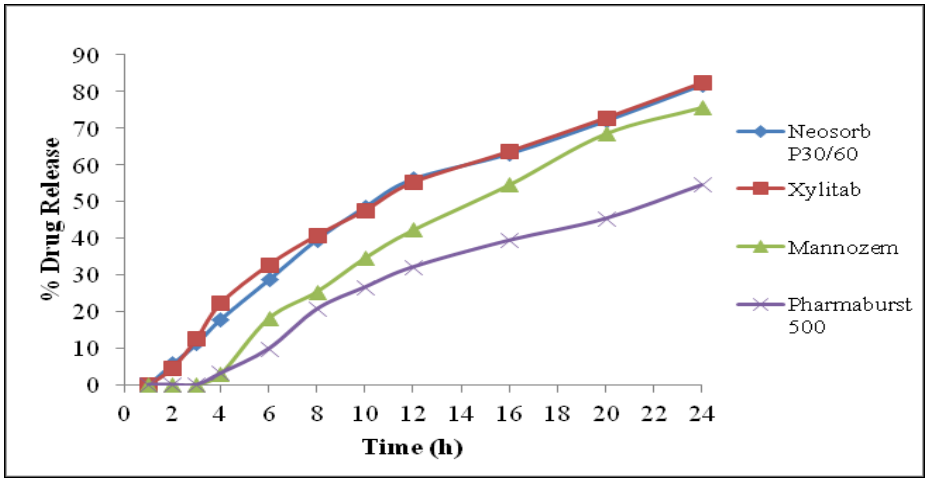

Figure 3 Influence of osmogent on in vitro Rifaximin release

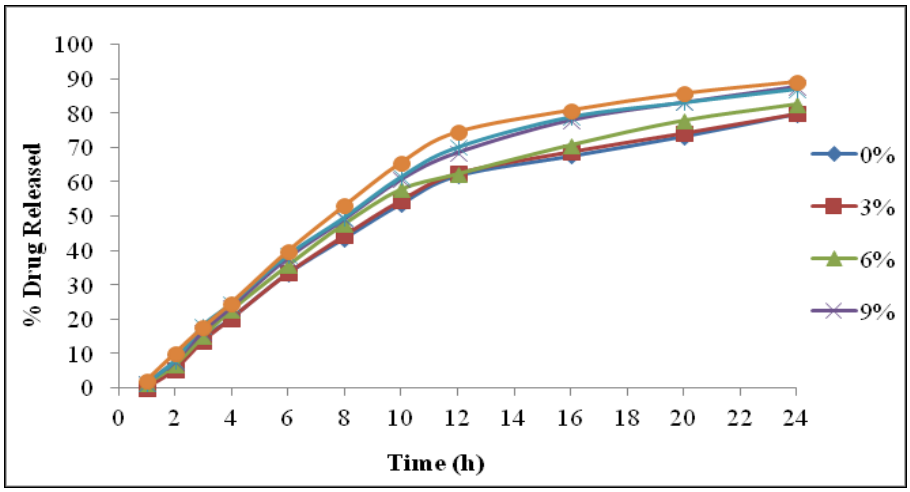

Figure 4 Influence of different concentration of citric acid on in vitro Rifaximin release

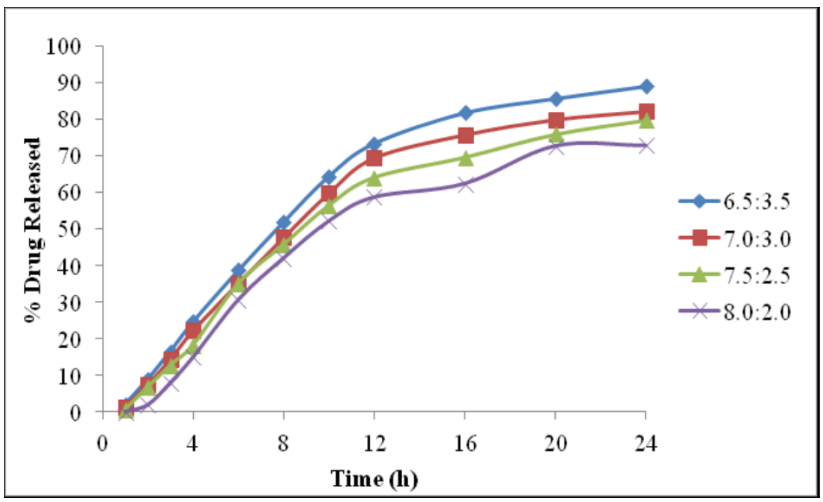

Figure 5 Release profile of Rifaximin from formulation containing different concentration of PEG 4000 in the SPM formulation

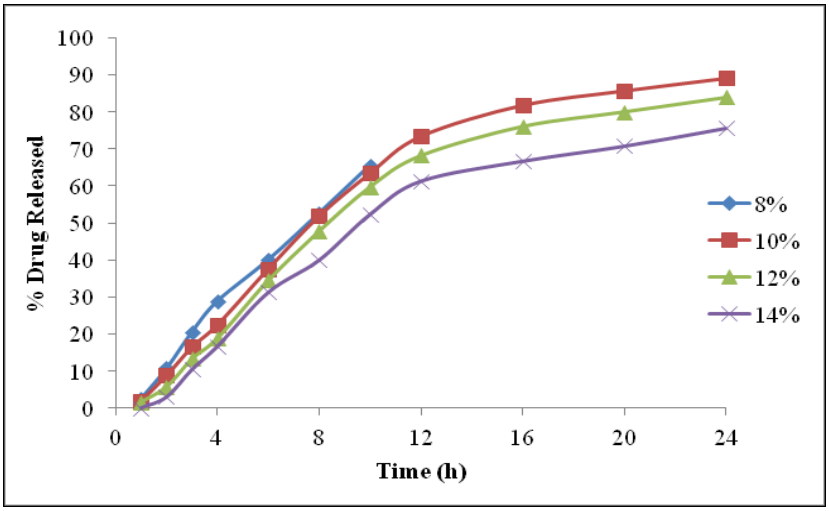

Figure 6 Release profile of Rifaximin from osmotic device with different SPM thicknesses

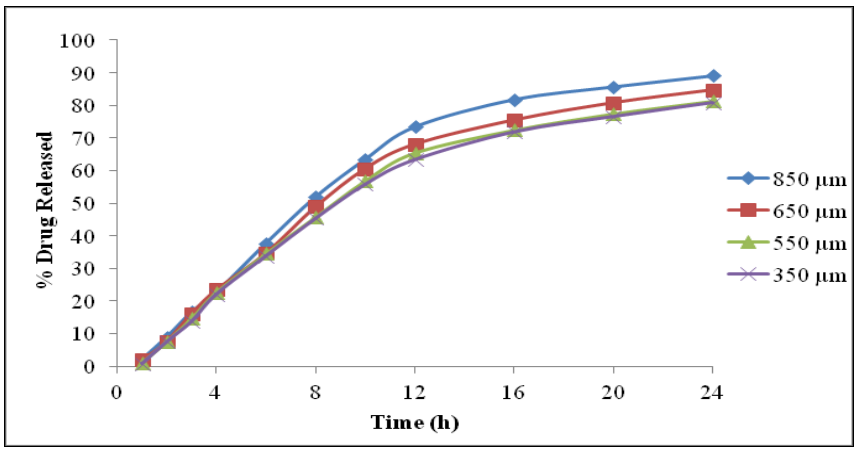

Figure 7 Release profiles of Rifaximin from osmotic devices with different orifice size

3.6. Influence of Coating and Drilling

Based on the aforementioned results, the improved tablet formulation B4 was selected for use in the subsequent trial. The membrane had a crucial role in determining the release profile of SCOP. Plasticizers are included into polymers to alter their physical properties and enhance their ability to form films. It is crucial to examine the impact of plasticizers on the release rate of drugs from osmotic devices, as they can also influence the permeability of polymer films. PEG, being a hydrophilic plasticizer, has the potential to be easily leached out, resulting in a completely porous structure. This, in turn, leads to an increase in membrane permeability and the rate at which drugs are released. The water permeability of the coating is influenced by the ratio of cellulose acetate to polyethylene glycol (CA: PEG) used in the formulation of the coating solution. In order to examine the impact of the quantity of PEG on drug release, the CA membranes were made more flexible by adding varying proportions of PEG. Figure 5 displays the release characteristics of formulations that contain varying quantities of plasticizer. The membrane containing CA: PEG ratios of 6.5:3.5, 7.0:3.0, 7.5:2.5, and 8.0:2.0 had permeabilities of 73.42%, 66.45%, 62.1%, and 58.63%, respectively. The results indicate that higher levels of PEG resulted in an elevated rate of medication release. Increasing the amount of PEG in the CA membrane leads to the formation of more empty space after leaching. Consequently, this results in a higher permeability of the membrane and a higher rate of drug release.

PEG 4000, a hydrophilic plasticizer, was added to the coating formulation to increase the hydrophilicity of the semipermeable membrane (SPM). This leads to an increase in the rate at which water can penetrate across the membrane, resulting in a decrease in the lag time of osmotic systems. The lag time values were 0.3, 0.3, 0.45, and 2.15 hours for membranes containing CA:PEG ratios of 6.5:3.5, 7:3, 7.5:2.5, and 8:2, respectively. Previous studies have also found similar findings on the correlation between water absorption and T80%. The permeability of the membrane with CA:PEG ratios of 6.5:3.5, 7:3, and 7.5:2.5 was 80% after 15, 20, and 24 hours, respectively. In contrast, a membrane with

a CA:PEG ratio of 8.0:2.0 did not exhibit drug release in 80% of cases. Achieving a suitable release profile with zero order kinetics requires a good hydrophilic/lipophilic balance in the structure of SPM. The figure indicates that membranes with a CA:PEG ratio of 6.5:3.5 are the most effective in the SPM formulation for achieving a zero-order release device for SCOP.

To alter the drug-release profile of the SCOP formulation, the most direct approach is to adjust the weight of the coating. Choosing and optimizing the thickness of the SPM is a highly effective method for ensuring a consistent rate of medication release from osmotic tablets. Figure 6 illustrates the release characteristics of osmotic devices that were created with varying thicknesses of SPM. The tablets were coated with the aim of achieving weight increases of 8%, 10%, 12%, and 14% relative to the weight of the core. The ratio of cellulose acetate (CA) to polyethylene glycol (PEG), specifically 6.5:3.5, remained consistent for all formulations. The tablet made of SPM saw a weight rise of 8% and then fractured and dissolved when exposed to the breakdown medium.

Figure 6 demonstrates that as the thickness of the membrane increases, the resistance of the membrane to the diffusion of the dissolving medium also increases. This leads to a decrease in the rate at which the tablet core dissolves, ultimately resulting in a reduced release rate of the medicine from the osmotic devices. The results indicate that increasing the coating weight from 10% to 14% resulted in a substantial increase in lag time and a significant drop in Q24. Specifically, the lag time increased from 0.3 hours to 1.3 hours, and Q24 declined from 89.08 to 75.68 for formulations comprising 10%, 12%, and 14% of coating weight, respectively ($p<0.05$). An analysis of the parameters associated with release kinetics indicated that the drug release from the formulation with a coating weight of 10% of the core weight followed zero-order kinetics (RSQZERO 12 = 0.9965), as opposed to the formulations with coating weights of 12% and 14% of the core weight (RSQZERO 12 = 0.9950 and 0.9952, respectively). The findings indicated that it is crucial to adjust the thickness of the SPM in order to prevent the system from rupturing due to the pressure generated during swelling. Additionally, this optimization ensures that the tablet is adequately moistened within an acceptable timeframe. The adjustment of the thickness of the SPM enhances the suitability of the osmotic system in terms of release rate, release kinetics, lag time, and other fundamental characteristics.

The aperture diameter is a crucial factor that affects the pace at which drugs are released, the time it takes for the release to begin, and the overall release pattern in osmotic drug delivery devices. Therefore, it is necessary to optimize the size of the delivery aperture in order to regulate the release of the drug from osmotic systems. Figure 7 displays the drug release profiles from formulations with varying aperture diameters. Orifices with diameters of 350, 550, 650, and 850 μm were mechanically drilled on both sides of the surface. There was no discernible disparity in the rate at which the medication was released when comparing orifice diameters ranging from 350 to 550 μm. Nevertheless, the results indicated notable alterations in certain release characteristics as a result of the modification in orifice size to 350 and 550 μm. The TL and RSQZERO 12 showed significant improvement ($p<0.05$) when the aperture diameter was increased from 350 to 550 μm. Specifically, TL increased from 1 to 0.45h, while RSQZERO 12 increased from 0.9923 to 0.9942 for orifice sizes of 350 and 550 μm, respectively. The orifice diameter was enlarged, resulting in a considerable decrease in system lag times and an increase in Q24. The Q24 percentage increased from 80.84% while using a 350 μm orifice size to 89.08% when using an 800 μm orifice size. The lag time was reduced from 1 hour to 0.3 hours when the orifice size was raised from 350 μm to 850 μm, respectively ($p<0.05$). These findings demonstrate the significance of the orifice diameter in regulating the release of drugs from the SCOP.

Out of all the formulations, the ones with an orifice size of 850μm exhibited the greatest Q24h and T80% values, and the smallest lag time (Q24h: 89.08%, T80%: 16h and TL: 0.3h, $p = 0.02$). The results suggest that the optimal aperture size in SCOP systems is significantly bigger than that in regular Elementary Osmotic Pump (EOP) systems, which are often utilized for delivering medicines with high to moderately water solubility [29]. The disparity likely arises from distinct mechanisms of drug release employed by these systems. End of pipeline (EOP) systems typically release the drug content in a soluble form, as indicated by reference. On the other hand, suspended solid particle forms are released concurrently with the drug in soluble form by SCOP.

3.7. SEM Study

Figure 8A depicts the structure of the membrane prior to breakdown. Initially, the surface of the coated tablets was even and without any imperfections when exposed to a watery environment, and the coatings seemed to be devoid of any flaws. Figure 8B displays the scanning electron microscope (SEM) image of the membrane's micro porosity structure following dissolution. The porosity of the membrane has significantly risen due to the leaching of a water-soluble component, specifically PEG 4000, during dissolution. This has subsequently led to an increase in the membrane's permeability.

3.8. Burst Strength

Following 24 hours of dissolution experiments, the depleted tablets were assessed for burst strength to ensure that they remain intact in the gastrointestinal tract and do not result in the sudden release of the entire dose. Figure 9 demonstrates the relationship between the burst strength of the exhausted shells and the thickness of the coating. Figure 10, on the other hand, illustrates the reliance of burst strength on the amount of plasticizer. Figure 9 illustrates the impact of coating thickness on burst strength. As the coating weight of the tablet increases, the thickness of the membrane also increases, resulting in an increase in burst strength. The burst strength was measured to be 3724g and 6913g for coating weights of 10% and 14%, respectively, with a statistically significant difference ($p<0.05$). Another factor that influences burst strength is the plasticizer content of the coated membrane. As the level of PEG-4000 increased, the membrane became more permeable when exposed to water, resulting in a drop in its strength. The burst strength was measured to be 3724 g and 4901 g for membranes with a CA:PEG ratio of 6.5:3.5 and 8.0:2.0, respectively. In every instance, the value surpasses the mechanical destructive forces in the gastrointestinal tract (GIT), ensuring that the formulations will remain intact in the GIT without any occurrence of dose dumping. When the coating weight growth was tuned at 10% and the ratio of CA to PEG was 6.5:3.5, the burst strength was measured to be 3724g (37.24N). This indicates that the SCOP remains intact in the gastrointestinal tract (GIT).

3.9. Accelerated Stability Studies

Table 3 Comparison of dissolution parameter after stability study

Time Point	Assay of Rifaximin	T_{LH}	$Q_{12\%}$	$Q_{24\%}$	RSQ_{ZERO12}
Initial	100±3.02	1.12	59.34	70.30%	0.9899
After 30 days	100±2.41	1.11	58.89	70.01%	0.9897
After 60 days	100±2.14	1.12	58.49	69.89%	0.9895
After 90 days	100±1.12	1.01	58.11	69.45%	0.9897

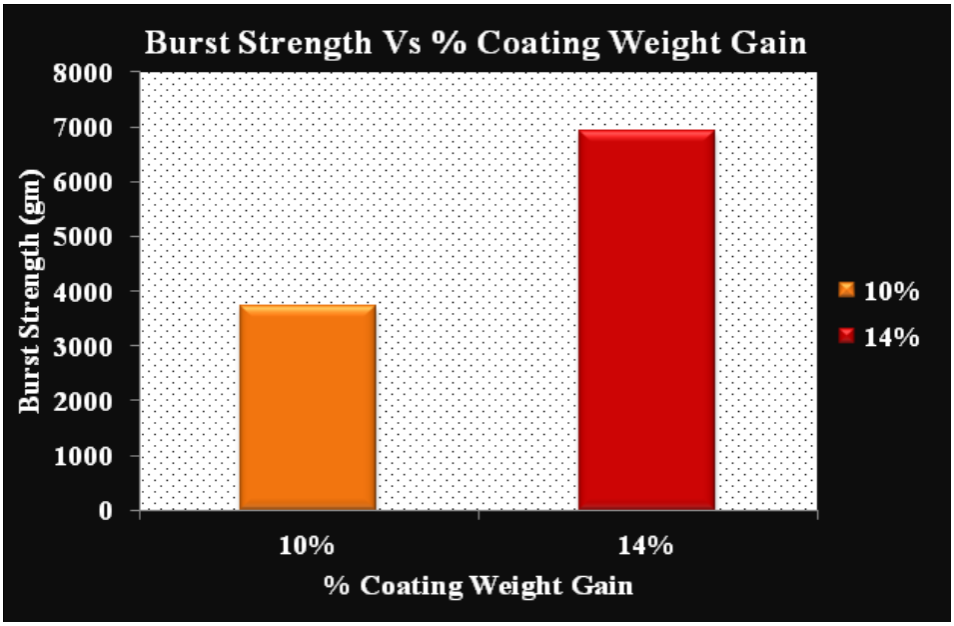

Figure 9 Effect of coating weight on burst strength

A pharmaceutical firm with ethical standards is dedicated to supplying consumers with medication goods that are effective and free from harm. To guarantee this, it is necessary to establish a program that examines the product's stability throughout its several stages of development and adheres to appropriate storage conditions and expiration dates under those parameters. In light of the current movement towards globalizing manufacturing processes, it is crucial that the end product is durable enough to be marketed internationally, taking into account various climatic conditions such as tropical, subtropical, and temperate regions. The enhanced formulation of SCOP, which includes Rifaximin, underwent accelerated stability testing using aluminum/aluminum strips as the most effective packaging

material. This packaging material was utilized in the current investigation. Batch number B4 was enclosed in an aluminum strip and exposed to short-term stability experiments at a temperature of 40 ± 2°C and a relative humidity of 75 ± 5% for a duration of 90 days.

Monthly samples exhibited no notable alterations in their physical attributes, drug composition, and in vitro drug release properties. The stability research confirmed that the formulations remained stable in terms of drug content and in vitro drug release. The tablets' in vitro drug release profiles were compared for various dissolution parameters, as given in Table 3, to determine the Rifaximin release. The analysis of several dissolving parameters indicated that there was no statistically significant distinction between the in vitro drug release profiles before and after stability experiments ($p<0.05$).

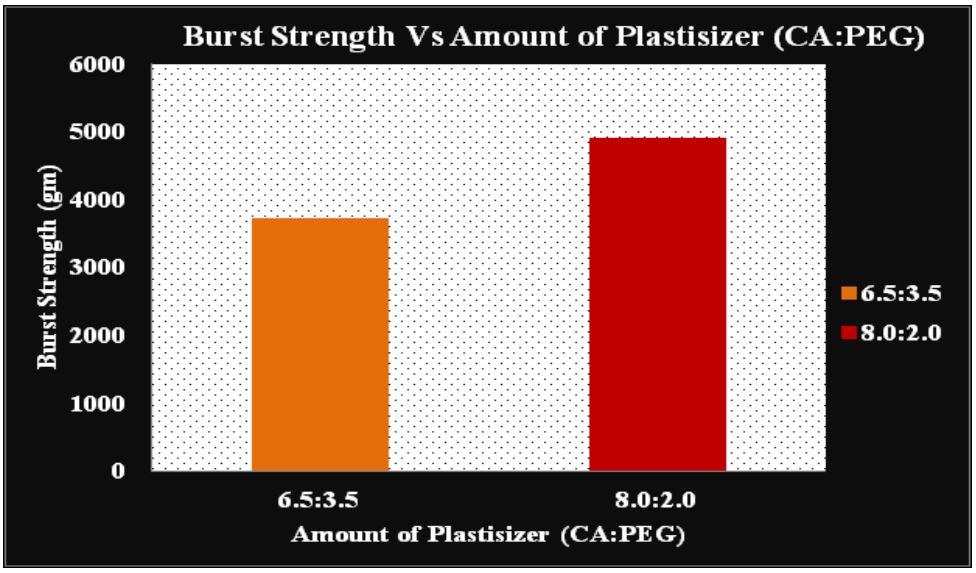

Figure 10 Effect of amount of plasticizer on burst strength

4. Conclusion

The objective of this project was to create an oral osmotic device, called SCOP, that could release the Rifaximin at a controlled pace for up to 24 hours. The core of the tablet consists of hydroxyethyl cellulose (Natrosol 250HX) and a sugar. The hydroxyethyl cellulose helps to trap the medication particles as they are pushed out through a hole in the coating. The sugar creates the osmotic pressure that drives the absorption of water. The Single Core Osmotic Pump (SCOP) is easy to make as it does not require a push compartment and is less complex in terms of orifice drilling compared to the push-pull osmotic tablet. A refined formulation was discovered to have the capability to provide the medicine at a nearly constant pace for up to 12 hours. The medication release rate from these tablets was found to be positively correlated with the concentrations of the osmogent and plasticizers, whereas it was negatively correlated with the thickness of the coating. This study also demonstrated the feasibility of developing a single-layer osmotic controlled release tablet with a high dosage of a water-insoluble medication.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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