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Original Article

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Design, development, and characterization of an oral push-pull osmotic pump for the controlled release delivery of norfloxacin.

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ABSTRACT

BACKGROUND & OBJECTIVE: Osmotic pumps are promising methods for controlled drug release. They are devices used for delivering drugs orally or through implantation. The primary aim of this research is to develop a Norfloxacin oral push-pull osmotic pump capable of providing a controlled drug release while ensuring that the release remains unaffected by the hydrodynamics and pH of the surrounding medium.

METHODOLOGY: The core tablet was fabricated using direct compression and subsequently coated with HPMC, PEG-400, sorbitol, and acetone as a solvent. Swelling polymers, specifically Guar Gum (Cyamopsis tetragonoloba), Xanthan Gum (polysaccharide B-1459), and Hydroxypropyl Methylcellulose were also included in the fabrication of the core tablet, with NaCl serving as the cosmogenic.

RESULTS: The formulations exhibited favorable flow properties. Friability, hardness, and weight variation testing yielded values within limits, indicating satisfactory outcomes. The drug content uniformity ranged from 98.00% to 99.67%, indicating uniform drug distribution within the formulations. Thermal analysis suggested that the sample was thermally stable. Dissolution studies revealed an in vitro dissolution rate of 98.5% over 15 hours. Release kinetics analysis using four models indicated controlled drug release, with the value of regression (R2) confirming this observation and the n exponent suggesting non-Fickian diffusion.

CONCLUSION: Osmotic pumps offer zero-order drug delivery, ensuring steady-state drug release to maintain therapeutic levels for a more extended period; thus, they minimize side effects and improve patient compliance.

KEYWORDS: Osmotic Drug Delivery, Antibacterial, Delayed-Action, Swelling Agents, Direct Compression, Non-Fickian, Push and Pull.

INTRODUCTION

Over the time, oral drug delivery has become the primary method for systemic drug administration. Conventional delivery systems typically release the drug immediately, lacking control over its release or the ability to sustain effective concentrations at the target site. Factors such as the presence of food, pH instability in the gastrointestinal tract, enzymatic degradation of gastrointestinal fluid, and changes in gastrointestinal motility contribute to the low bioavailability of certain drugs through conventional delivery methods. In contrast, controlled drug delivery systems can deliver drugs in a controlled pattern over an extended period. Osmotically controlled delivery systems deliver the drug to a significant extent, and the physiological factors of the gastrointestinal tract do not influence their delivery mechanism. These systems are suitable for both systemic and targeted drug delivery. Osmotically controlled oral drug delivery systems employ osmotic pressure to regulate the release of active agents [1].

These pumps comprise a central core encased in a semipermeable membrane that contains drugs and osmogen. This is an osmotic device that has the potential to deliver both poorly water-soluble and greatly water-soluble drugs at a constant rate. One of the layers contains the drug, a polymeric osmotic agent, and the other is the tablet excipient. They function by the concept of osmosis, which is the movement of a solvent from an area of lower solute concentration to an area of higher solute concentration across a semipermeable membrane.

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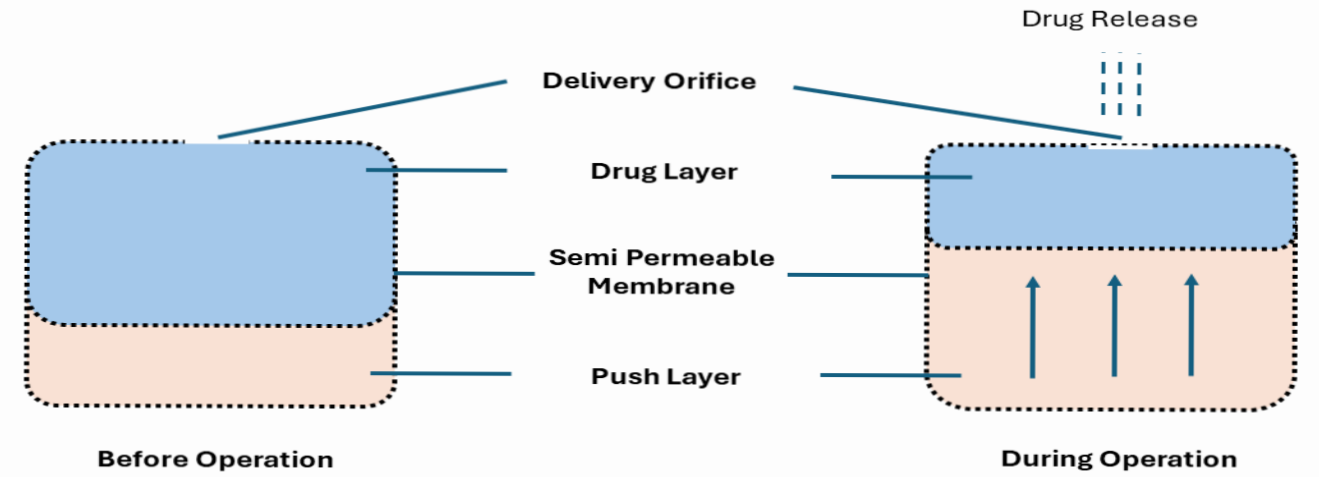
Exposure to an aqueous environment causes the osmotic polymer layer to swell, resulting in the development of osmotic pressure. This layer pushes the layer composed of the drug, upon which it releases the drug in the form of fine dispersion via the orifice. Figure-I displays a schematic illustration of push-pull osmotic pumps. Osmotic pumps are remarkable because they maintain consistent release rates regardless of factors such as pH or gastrointestinal conditions. The components of an osmotic pump include drugs, wicking agents, semipermeable membranes, pore-forming agents, coating solvents, and osmotic agents. Irrespective of being complex to manufacture, osmotic pumps are essential for optimizing therapeutic outcomes [2] .

Figure-I: Diagrammatic representation of push-pull osmotic pumps.



Despite the innovative nature and benefits of the osmotic drug delivery system, it does have its limitations, including the need for specialized equipment to create an opening in the system, the system's residence time in the body can fluctuate based on gastric motility and food intake and the release of the drug's saturated solution might lead to irritation or ulcers. However, considering the significant advantages of this system, these limitations can be overlooked. The benefits often outweigh the drawbacks, making the osmotic pump a valuable tool in drug delivery [3].

Norfloxacin is a fluoroquinolone. It is derived from nalidixic acid and treats various bacterial infections. It is commonly prescribed for urinary tract infections, prostate infections, and certain types of gastroenteritis. It functions by inhibiting the proliferation of bacteria. Its half-life is approximately 3 hours. This characteristic makes it an ideal candidate for osmotic systems, which are typically best suited for drugs with a biological half-life ranging from 1 to 6 hours [4].The study aims to develop a Norfloxacin push-pull osmotic pump for sustained drug delivery, achieving independence from pH and hydrodynamics variations. This innovative system offers zero-order kinetics, pulsed or delayed drug release, and is predictable and programmable.

The pump acts as an in-situ liquid dosage form, allowing for drugs with varying solubility patterns. The aim is to extend the half-life of Norfloxacin, enhancing its therapeutic efficacy and minimizing dosing frequency. The design and optimization of the osmotic pump system aim to improve patient compliance and treatment outcomes [5].

METHODOLOGY

The formulation contains various substances, such as swelling polymers like guar gum (Cyamopsis tetragonoloba), xanthan gum (polysaccharide B-1459), and Hydroxypropyl Methylcellulose (HPMC), as well as an osmogen (NaCl). Coating layers consist of acetone, PEG 400, HPMC, and sorbitol. Additionally, microcrystalline cellulose (MCC) is used as a bulking agent, and Norfloxacin as API. All the materials are sourced through Sigma Aldrich Pharmaceuticals Germany and used in their original state without further purification. Table-I lists the ingredients and their roles in the formulation.

Table- I: Ingredients and their role in formulation.

Ingredients	Role in formulation
Norfloxacin	Active Ingredient: It is derived from nalidixic acid, and it is used to treat various bacterial infections.
Guar gum	Guar gum's role in osmotic pumps is crucial for controlling drug release rate by forming a viscous gel, ensuring steady, controlled medication delivery over extended periods.
Xanthan gum	Xanthun gum acts as a swelling agent in osmotic pump systems, absorbing water and expanding to control drug release, ensuring consistent and sustained patient delivery.
Osmogen	It produces an increase in osmotic pressure within the pump, which forces the drug out of the pump through the delivery orifice.
HPMC	It's an osmogent, an organic polymer. It functions as a film-forming and thickening agent.
PEG 400	It acts as a flux regulator and enhances flux. These substances help in controlling the fluid permeability of the flow via the wall. Enhance the flow as a result.
Sorbitol	It is used as a vehicle in drug delivery.
Microcrystalline cellulose	Microcrystalline cellulose, used in osmotic pump systems, acts as a disintegrant and binder, regulating drug release rate and preserving tablet or capsule structural integrity.
Acetone	This solvent is used for coatings. An appropriate solvent was employed to develop the osmotic drug delivery device's wall.

Push-pull osmotic pumps were prepared using a direct compression process, followed by coating. The study was conducted over eight months, from August 21, 2023, to February 9, 2024. Ethical approval for the study was obtained from the Lahore University of Biological & Applied Sciences (UBAS), Lahore, Pakistan, with reference number (ref: RMEC/AM/09754).

This ensured compliance with ethical standards and guidelines. The method is referred from Nandi S et al. The core tablets were fabricated using the powder direct compression technique. Before tableting, each component of the drug layer and the push layer underwent thorough mixing. Subsequently, a ZP-17 tableting machine was employed to compress the push layer powder slightly before incorporating the drug layer powder. Twenty tablets were selected from each formulation. Tablet hardness was determined using an Erweka hardness tester. Each set of 20 tablets was weighed and positioned to contact the lower plunger of a barrel equipped with compressible springs. The crushing strength was measured in kg/cm² by applying pressure with the top plunger until the tablet fractured. The acceptable hardness range for sustained-release tablets is 10 to 20 kg/cm² as specified in United States Pharmacopeia and National Formulary (USP-NF). General Chapter <1217> Tablet Breaking Force. 42nd Edition. Rockville, MD: United States Pharmacopeial Convention; 2022.

PREFORMULATION EVALUATION

ORGANOLEPTIC EVALUATION

Evaluation by means of sense organs. It includes the macroscopic appearance, odor, taste, and color of Active Pharmaceutical Ingredient (Drug)[6].

Bulk Characterization

Bulk Density

Granules are weighed on the weighing balance, and their apparent density is measured by placing them in a calibrated measuring cylinder to find their volume. This volume measurement is referred to as the bulk volume[7].

Formula

The bulk density is calculated by following the formula;

Bulk density=(weight of powder)/(bulk volume)

Tapped Density

Granules were weighed on the weighing balance and then transferred to the calibrated measuring cylinder. The tapped density was measured by tapping the measuring cylinder for 200 time[7].

Formula

The following formula calculates the tapped density.

Tapped density=(weight of powder)/(volume tapped)

Carr's Ratio/Index

Carr's ratio estimates the flowability of the material and can be determined by measuring the bulk and the tapped density of the material[8].

Formula

Carr's index=(tapped density-bulk density)/(tapped density)*100

The tested tablets were deemed suitable as their hardness fell within this range, specifically between 10 and 14 kg/cm². The core tablets were coated with acetone solution, HPMC, PEG 400, and sorbitol using a traditional coating machine, which resulted in an 8–10% increase in the weight of the core tablet, which complied with the acceptance criteria for coating solution, i.e., 12%[5]. A spray pan coating machine with a hot air blower was employed, maintaining the plasticizer content at 400.25% (w/w).

The stainless-steel pan, 22 cm in diameter, rotated at 25 rpm while spraying at a rate of 4 ml/min. The coating membrane thickness was controlled within 475-550 µm, and the tablets were dried at 50°C for 12 hours. Post-coating, the tablets exhibited an average weight gain of 13.56 ± 1.46%, demonstrating the achievement of the desired characteristics for the coated tablets. A total of 100 tablets were prepared in each formulation, and 20 tablets were selected from each formulation and subjected to different testing techniques. Nine different formulations were developed using various combinations and concentrations of ingredients. These ingredients were selected based on information gathered from a literature review. The goal was to determine the optimal combination and concentration for achieving desired outcomes. By testing different formulations, we aimed to identify the advantages of specific ingredients and their quantities[6].

Hausner's Ratio

Hausner's Ratio is an indicator of the flowability of bulk solids. It exhibits the relation between the tapped density and bulk density, which the given formula can determine [9].

Formula

Hausner's ratio=(tapped density)/(bulk density)

Angle of Repose

Pour the material onto a flat surface to form a conical pile. Measure the radius (r) and height (h) of the pile. Calculate the angle of repose using the formula provided, where the angle (θ) can range from 0° to 90°. The variables h, r, and θ represent the height, radius, and angle of repose of the powder pile, respectively [10].

Formula

θ tan-1-h/r

Whereas h=height of the heap and r=radius of the heap

Solid State Testing

Ftir Analysis

Tablet ingredients were analyzed using Smart iTR™ ATR accessory and Nicolet iS10 FTIR spectrophotometer, recording spectra from 4000-650 cm−1 at 8 cm−1 resolution. Data was recorded in triplicate for quantitative analysis and compared to a reference database to identify specific components. Advanced software processing enhanced the accuracy of the quantitative analysis, providing a comprehensive understanding of the tablets' composition. This method ensures accurate and reliable analysis[11].

Solubility Studies

The solubility of norfloxacin is determined in water and different pH mediums. Samples were prepared by adding varied volumes of 5M HCl or 5M NaOH to achieve pH values between 2 and 8. The solutions were then shaken at 37°C until saturated, usually within 48 hours. The pH of the supernatant was measured, and UV spectrophotometry was used to analyze aliquots at 273 nm wavelength [12].

Stability Studies

In adherence to the International Conference on Harmonization (ICH) guidelines, the formulations were subjected to various storage conditions. They were stored at room temperature in an aluminum foil pouch and subjected to stability cabinet conditions of (18°C-33°C) and 40°C± 0.5°C with 75% relative humidity (RH) for six months. Subsequently, tablets were removed and assessed for physical characteristics, DSC, drug content, drug release assay, and other relevant factors [12].

POST FORMULATION EVALUATION

Friability

A dual drum, automatic tablet friabilator (Pharma Alliance Group Inc., Model F2, Santa Clarita, CA) was used to evaluate the tablet's friability. 20 tablets were selected from each formulation. It was run for four minutes at 25 rpm. Following the friability test and dedusting by USP protocol, the weight loss of each tablet and the batch was calculated as in United States Pharmacopeia and National Formulary (USP-NF), <1216> Friability. Rockville, MD: United States Pharmacopeial Convention; 2023. The following equation was used to compute the friability % [13].

Formula

%friability=F (1-final weight/known weight)*100

Weight Variation

For the weight variation test, 20 tablets were individually weighed, the average weight was calculated, and the individual tablet weights were compared to the average. A percentage weight deviation was determined and was assessed against the standards set by the United States Pharmacopeia and National Formulary (USP 43–NF 38). Rockville, MD: United States Pharmacopeial Convention; 2020. Section <905>: Uniformity of Dosage Units [13].

Hardness

Tablet hardness was measured using an Erweka hardness tester, with 20 tablets from each formulation subjected to force until they broke. A hardness of 3-5 kg/cm² is considered sufficient for uncoated tablets, and 8-11 kg/cm² for coated tablets [13].

Drug Content Uniformity

20 tablets from each formulation were weighed and powdered. The 100 mg drug equivalent was dissolved in 6.8 pH phosphate buffer in a 100 ml volumetric flask. One milliliter of the primary stock solution was further diluted with a 6.8 pH phosphate buffer to achieve a concentration of 1 µg/ml. Absorbance was then measured at 273 nm using a UV-Vis spectrophotometer [13].

Thickness

A Vernier caliper was employed to determine the diameter and thickness of the tablets. 20 tablets were selected from each formulation. Each tablet was positioned horizontally and vertically between the jaws of the caliper. The digital screen was adjusted until it touched the tablet's edge, and the measurements were recorded in millimeters. The maximum allowable thickness variance for each tablet was 5% [13].

Fourier transform infrared spectroscopy (FTIR)

FTIR will be used to ensure compatibility between components. Spectra of API, excipients, and physical mixtures were generated using spectral 100 FTIR ATR spectroscopy. Samples were evaluated for characteristic peaks, and an interferogram was produced. Interferogram analysis allows for the identification of specific functional groups present in the samples, aiding in the determination of chemical composition and potential interactions between components. By identifying particular functional groups in the samples, interferogram analysis helps determine the chemical makeup and possible interactions between constituents. This thorough examination provides significant information about the molecular structure and compatibility of the materials under investigation. The functional group region was scanned between 1400 and 600 cm1, while the fingerprint region was scanned between 4000 and 1400 cm1. The scanning range was 400 to 4000 cm1 [14].

Differential Scanning Calorimetry (DSC)

DSC tests were conducted using the selected tablet formulation. In an aluminum pan, samples weighing 3.4–5.6 mg were heated to a maximum temperature of 300°C at a rate of 10°C/min. Indium was utilized to calibrate the apparatus, and dry nitrogen was employed as the carrier gas at a flow rate of 25 milliliters per minute. To confirm, the test was run once again [15].

Thermogravimetric Analysis (TGA)

A furnace that has been configured to display a linear temperature increase over time and a precision balance are needed for the TGA. All physical events are covered, with the exception of crystalline transitions and fusions. Weighed and put into metal containers, a 5 mg sample was heated at 10ºC/min between 25 and 300ºC in a nitrogen environment [16].

In vitro Drug Dissolution

The dissolution process used a USP type I apparatus with 900ml of water at 37°C ± 0.5°C and 100 rpm stirring speed. Dissolution in a USP type III apparatus used water at 20 dips per minute for different agitation modes. Samples were taken at intervals, filtered through a 0.45 µm filter, and analyzed using a UV-Vis Spectrophotometer as described in United States Pharmacopeial Convention. United States Pharmacopeia and National Formulary (USP 43-NF 38). Chapter <711> Dissolution. Rockville, MD: United States Pharmacopeial Convention; 2023 [17].

In vitro Disintegration

Tablets are placed in the tubes of a USP type I apparatus and immersed in a beaker containing water, gastric fluid, or intestinal fluid at a temperature of 37°C ± 2°C. The test evaluates the time required for the tablet to dissolve completely. Successful disintegration occurs when all tablets break down and pass through a #10 mesh screen within the designated time limit as defined in United States Pharmacopeial Convention. United States Pharmacopeia and National Formulary (USP 43-NF 38). Chapter <701> Disintegration. Rockville, MD: United States Pharmacopeial Convention; 2023 [17].

RESULTS

Preformulation Studies

Organoleptic Evaluation

Norfloxacin is a white-colored powder, crystalline in nature, odorless, and slightly bitter.

In vitro Release Kinetics

Plots were used to analyze drug release kinetics from the optimized formulation. Models included zero-order (cumulative % release vs. time), first-order (log cumulative % remaining vs. time), and Higuchi (cumulative % release vs. square root of time). Equations used were Qt = k0 t (zero-order), Qt = Q0e^(-k1t) (first-order), and Qt = kH√t (Higuchi). The best model was selected based on goodness-of-fit (R^2) and sum of squared residuals (SSR) values, with the model showing the highest R^2 and lowest SSR considered the most suitable [18].

Bulk Characterization

A comprehensive analysis was undertaken to gauge the quality of the powder, taking into consideration various parameters as elucidated in Table- II.

Table- II: Bulk Characterization.

Formulation Codes	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)	Flowability
F1	0.512	0.611	15	1.14	31	Good
F2	0.532	0.623	12	1.14	33	Good
F3	0.515	0.632	13	1.16	34	Good
F4	0.523	0.621	15	1.14	32	Good
F5	0.519	0.620	14	1.13	32	Good
F6	0.513	0.611	11	1.12	34	Good
F7	0.516	0.610	12	1.11	35	Good
F8	0.518	0.615	11	1.14	31	Good
F9	0.516	0.514	14	1.15	35	Good

Solubility Studies

The solubility of norfloxacin was evaluated in different dissolution media. Table-III demonstrates the solubility of norfloxacin in water and solutions containing different pH values.

Table- III: Solubility results.

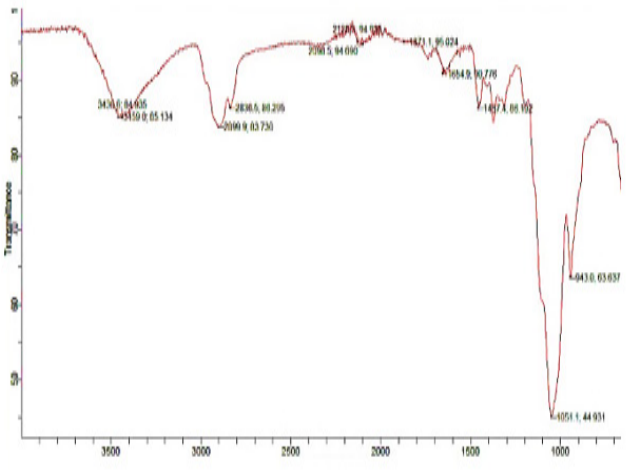
Medium	Water (Mean ± SD)	Phosphate buffer (pH=7) (Mean ± SD)	Phosphate buffer (pH=9) (Mean ± SD)
Solubility (µg/ml)	5±0.35	650±15.41	1380±22.78

Fourier transform infrared spectroscopy (FTIR)

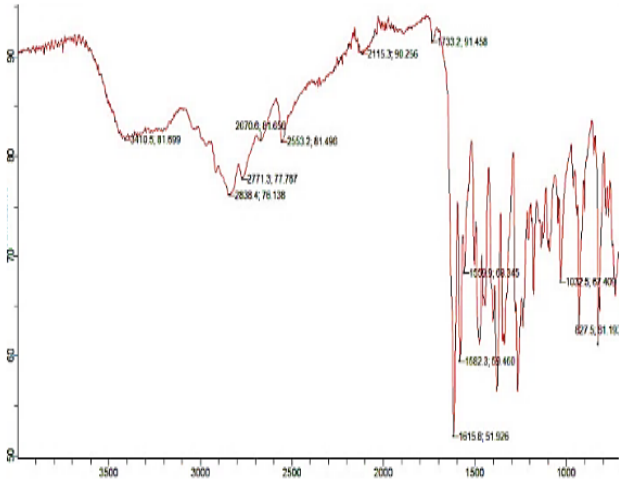
FTIR analysis of various compounds reveals distinctive peaks reflecting their chemical compositions. Norfloxacin exhibits peaks at 3400 cm^{-1}, 2800 cm^{-1}, 1680 cm^{-1}, and 1280 cm^{-1}, with notable features including N-H bending at 1645 cm^{-1} and C=C bonding at 1615 cm^{-1}. Guar gum displays peaks at 2912 cm^{-1}, 1636 cm^{-1}, 1375 cm^{-1}, 1146 cm^{-1}, 1023 cm^{-1}, and 659.7 cm^{-1}, representing CH_2 group stretching, ring stretching, and primary OH group characteristics. Xanthan gum showcases peaks at 3334 cm^{-1}, 2890 cm^{-1}, 1425 cm^{-1}, 1159 cm^{-1}, and 1105 cm^{-1}, with features such as aldehyde group presence and C-O group bending. HPMC exhibits peaks at 3494 cm^{-1}, 2890 cm^{-1}, 1456 cm^{-1}, 1170 cm^{-1}, and 1135 cm^{-1}, indicating alcoholic group presence and C-O group characteristics. Sorbitol demonstrates peaks at 2564 cm^{-1}, 2805 cm^{-1}, and 1105 cm^{-1}, representing aldehyde group presence and OH group bending. These distinct spectral features offer insights into the molecular structures and functional groups present within each compound analyzed using FTIR techniques. The spectra of all ingredients are shown in Figure-II.

Figure-II: FTIR graph of a) Norfloxacin b) Guar Gum c) Sorbitol d) HPMC e) Xanthan gum.

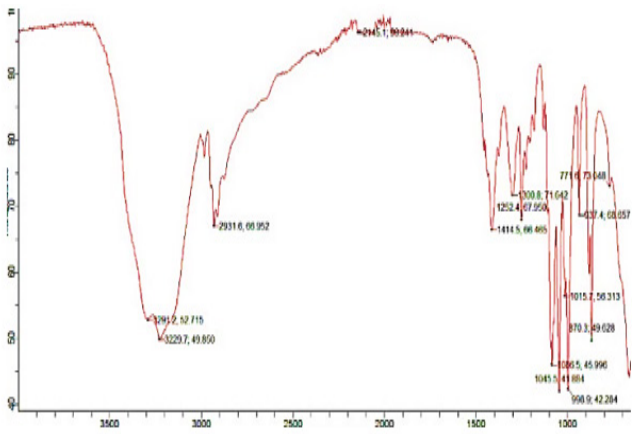
a)



b)



c)



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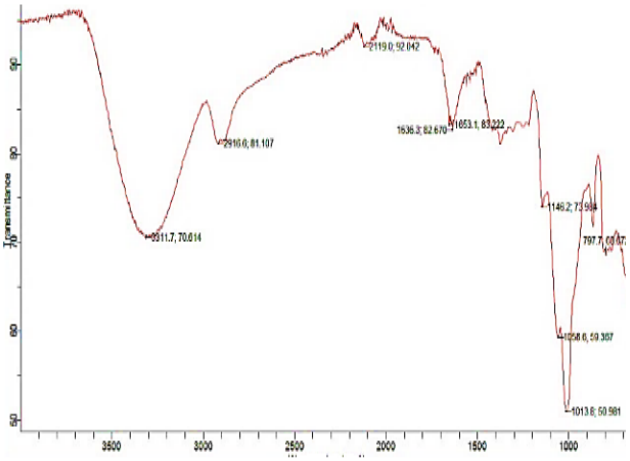
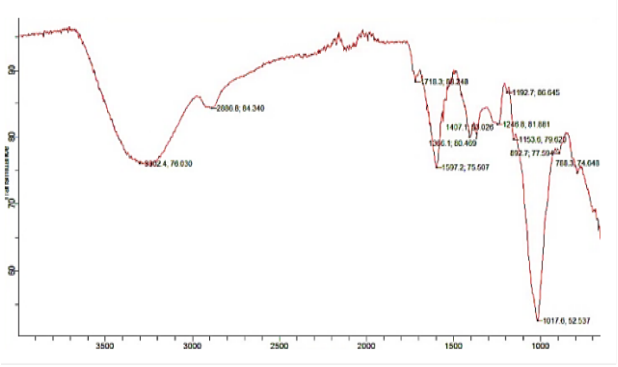


e)



Stability studies

The formulations' stability remained intact throughout the storage duration, and the results were deemed acceptable. No discernible changes were observed in the formulations' chemical and physical properties during this time frame.

POST FORMULATION STUDIES

Synthesis of formulation

We aimed to develop the push-pull osmotic pump using direct compression followed by coating. This resulted in the formation of a push-pull osmotic pump and the successful formulation development. The formulation tables for each of the nine formulations are shown in Table- IV.

Table- IV: Formulation table.

	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
API	Norfloxacin (mg)	400(mg)	400(mg)	400(mg)	400(mg)	400(mg)	400(mg)	400(mg)	400(mg)	400(mg)
Swelling polymer	Guar gum (mg)	50(mg)	75(mg)	100(mg)	---	---	---	20(mg)	30(mg)	35(mg)
	Xanthan gum (mg)	---	---	---	50(mg)	75(mg)	100(mg)	20(mg)	30(mg)	40(mg)
	HPMC (mg)	---	---	---	---	---	---	20(mg)	30(mg)	40(mg)
Osmogen	NaCl (mg)	40(mg)	40(mg)	40(mg)	40(mg)	60(mg)	60(mg)	60(mg)	80(mg)	80(mg)
Coating layer	HPMC (%)	70%	60%	50%	70%	60%	50%	60%	50%	40%
	Sorbitol	30%	40%	50%	---	---	---	20%	25%	30%
	PEG-400 (%)	---	---	---	30%	40%	50%	20%	25%	30%
Solvent	Acetone	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Weight makeup	Microcrystalline cellulose (mg)	105(mg)	80(mg)	55(mg)	105(mg)	60(mg)	35(mg)	75(mg)	25(mg)	---
Total	weight(mg)	595(mg)	595(mg)	595(mg)	595(mg)	595(mg)	595(mg)	595(mg)	595(mg)	595(mg)

Friability

The friability test results for formulations F1 to F9 consistently show values below 1% and typically within the 0.05-0.50% range, as outlined in Table- V, confirming the tablets' integrity.

Hardness

In the study, the hardness of formulations F1 to F9, as indicated in Table V ranges from 6-8 kg/cm² for uncoated tablets, while coated tablets exhibit hardness between 8.3-11 kg/cm². These findings comply with the official limits outlined in the US Pharmacopeia (USP) protocols, demonstrating satisfactory tablet strength.

Weight Variation

The average weight of uncoated tablets remains constant at 595mg across all formulations. However, after coating, the weight of the tablets varies due to the differing amounts of coating polymer present in each formulation. Notably, the average percentage deviation across all formulations complied with US Pharmacopeia (USP) standards, as shown in Table-V.

Thickness

Table V provides a comprehensive overview of the tablet thickness variations observed across formulations F1 to F9, ranging from 4.1 to 4.8 units.

Drug Content Uniformity

The test followed official methods, revealing excellent content uniformity across all batches, as in Table V, with values ranging from 98.00% to 99.67%.

Fourier transform infrared spectroscopy FTIR

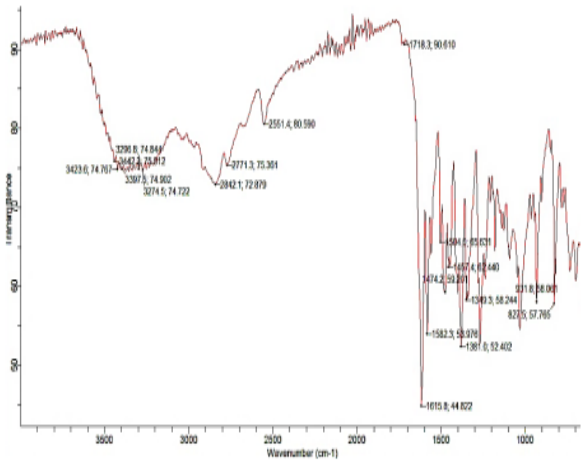
The optimized formulation was analyzed using FTIR spectroscopy to evaluate potential interactions between the drug and excipients. FTIR analysis of individual compounds reveals distinctive peaks corresponding to their chemical compositions. The FTIR spectrum of the formulation closely matched the drug spectrum of Norfloxacin, showing characteristic peaks at 3423 cm^{-1}, 2771 cm^{-1}, 1615 cm^{-1}, and 1380 cm^{-1}. Guar gum exhibited peaks identical to its preformulation FTIR at 2842 cm^{-1}, 1582 cm^{-1}, 1349 cm^{-1}, 1052 cm^{-1}, and 827 cm^{-1}, representing CH_2 group stretching, ring stretching, and primary OH group characteristics. Similarly, Xanthan gum displayed peaks at 3442 cm^{-1}, 3274 cm^{-1}, 1474 cm^{-1}, and 1059 cm^{-1}, indicating the presence of aldehyde groups and C-O bending.

HPMC showed characteristic peaks at 3397 cm^{-1}, 3296 cm^{-1}, and 1504 cm^{-1}, associated with alcoholic groups and C-O group features. Sorbitol exhibited peaks at 2551 cm^{-1} and 1718 cm^{-1}, corresponding to aldehyde groups and OH group bending. These distinct spectral features confirm the molecular structures and functional groups of each compound remain intact, with no evidence of peak shifting or interactions, indicating the stability of the formulation. The results are illustrated in Figure-III.

In vitro disintegration

Norfloxacin push-pull osmotic pumps provided controlled release without disintegration. Results are shown in Table-V.

Figure-III: FTIR graph of Norfloxacin Push Pull Osmotic Pump.



Differential Scanning Calorimetry (DSC)

The DSC results depicted in Figure 4 revealed a single peak exhibiting exothermic behavior at 365°C due to degradation.

Thermogravimetric Analysis (TGA)

In Figure-IV, the TGA results indicate that the sample's initial weight did not alter from 0°C to 90°C, indicating its stability within this temperature range. The degradation started at the onward temperature, and degradation was completed at 375°C.

Figure-IV: Thermogram of Push and pull Osmotic Pump.

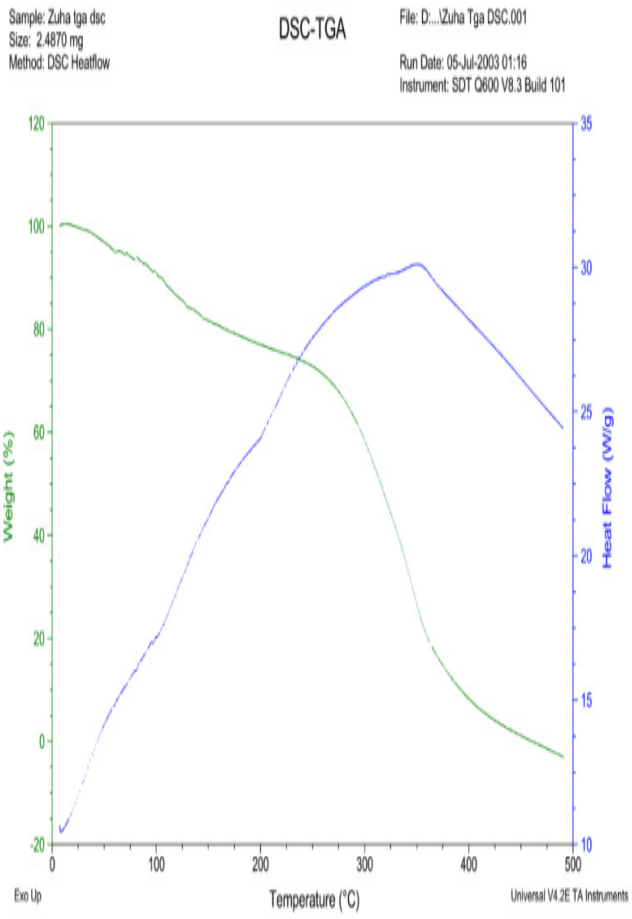


Table- V:Post -formulation Characterization results.

Formulation Codes	Friability (%)	Average Weight (mg)	Hardness (kg/cm²)	Thickness (mm)	Drug Content Uniformity (%) (mean ± SD)	In vitro disintegration (minutes)
F1	0.06	600.45	8.4	4.2	98.62±0.47	No disintegration
F2	0.45	599.56	9	4.3	99.24±0.21	No disintegration
F3	0.32	600.45	8.3	4.1	99.56±0.53	No disintegration
F4	0.26	601.78	10.5	4.2	98.45±0.58	No disintegration
F5	0.38	602.36	11	4.7	99.67±0.64	No disintegration
F6	0.30	600.45	9.7	4.6	98.78±0.25	No disintegration
F7	0.27	599.65	10.1	4.5	98.37±0.66	No disintegration
F8	0.22	598.99	8.6	4.7	99.01±0.02	No disintegration
F9	0.31	602	9.4	4.8	99.56±0.53	No disintegration

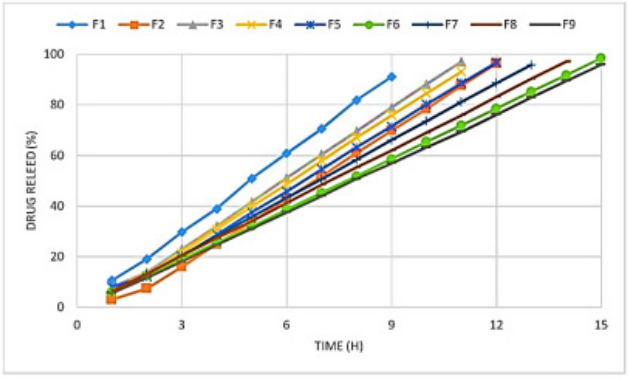
In vitro dissolution

Figure-V illustrates the in vitro release profiles of nine distinct formulations (F1-F9) of norfloxacin from push-pull osmotic pumps over 15 hours. Notably, F1 demonstrated an initial burst release, reaching 50% at the 5-hour mark, and achieved a peak release of 91.1% by the 9th hour. Drug release over time for nine formulations is shown in Table VI. With most formulations achieving 80% drug release within 10 hours, F9 exhibited a lower release rate of 69.4% within the same timeframe. F8 notably achieved 98.5% release by the 13th hour. Interestingly, F6 displayed the highest release, reaching 98.5% at the 15-hour mark.

Table-VI: % Drug release over a time.

Time	% Drug Dissolution								
(Hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	10.7	3	8.1	7.9	8.0	5.9	6.0	6.4	5.6
2	19.1	7.4	13.7	12.5	12.1	12.4	13.0	13.2	11.7
3	29.7	16	22.9	21.4	20.2	19.3	20.5	20.4	18.1
4	38.9	25	32	30.8	28.7	25.5	27.9	27.3	24.7
5	50.9	33.7	41.6	39.8	37.5	31.9	35.7	34.0	31.2
6	60.8	43.0	51.1	48.6	45.8	38.7	43.3	41.3	37.5
7	70.5	51.8	60.4	57.9	54.6	45.3	50.6	48.5	44.0
8	81.9	60.9	69.5	67.0	63.2	51.8	58.3	55.3	50.8
9	91.1	69.8	78.9	75.9	71.5	58.6	66.1	62.0	56.9
10		78.4	88.1	84.6	80.2	65.5	73.6	69.0	63.2
11		87.6	97.1	93.1	88.6	71.9	81.2	75.9	69.4
12		96.4			96.7	78.6	88.6	83.2	76.2
13						85.2	95.8	90.3	82.9
14						91.7		97.1	89.5
15						98.5			95.9

Figure-V: Percentage of drug release profile.



In Vitro Release Kinetics

The release of the drug was analyzed using four models: the zero-order model, the first-order model, the Higuchi diffusion model, and the Korsmeyer, and their regression analysis graphs are shown in Figures 6,7,8 and 9, respectively. Results presented in Table- VII indicate that the release pattern of the designed PPOP (Push-Pull Osmotic Pump) adheres more closely to the zero-order model, with a maximum R-square value of 0.9998 observed for formulations F1 to F9. The highest R-square value in the first-order model is 0.9098 for formulation F9. Additionally, the drug release in the Korsmeyer model falls within the range of n= 0.9976-1.0000, indicating a non-Fickian diffusion mechanism. Release kinetics are calculated with the DD Solver.

Table VII: Release kinetics profile.

Formulation	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	K0	R(Square)	K1	R(Square)	kH	R(Square)	kKP	n
F1	10.111	0.9991	0.16	0.9096	24.915	0.808	9.665	0.9994
F2	7.653	0.9787	0.117	0.8584	21.32	0.7394	4.583	0.9976
F3	8.666	0.9956	0.138	0.8842	23.380	0.7864	7.120	0.9994
F4	8.311	0.9945	0.130	0.8920	22.409	0.7826	6.696	0.9990
F5	7.905	0.9950	0.125	0.8853	22.227	0.7858	6.368	0.9992
F6	6.532	0.9998	0.107	0.9042	20.549	0.8177	6.204	1.0000
F7	7.322	0.9989	0.117	0.9030	21.462	0.8064	6.601	0.9998
F8	6.914	0.9998	0.112	0.9081	21.047	0.8191	6.601	0.9998
F9	6.346	0.9996	0.102	0.9098	19.954	0.8153	5.934	0.9999

Figure-VI: Zero-order regression analysis.

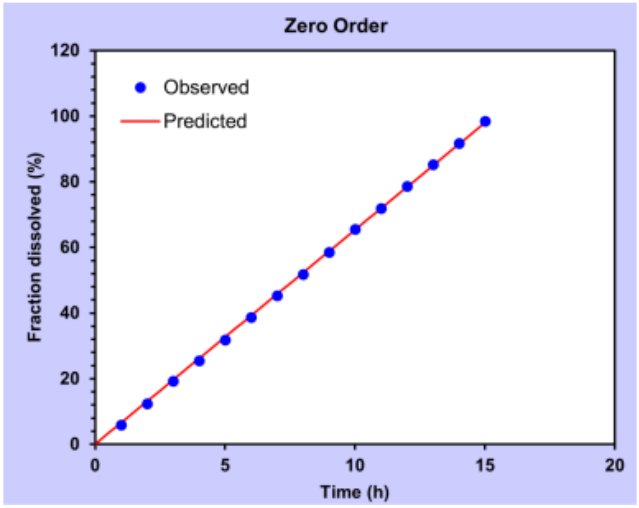


Figure-VII: First-order regression analysis.

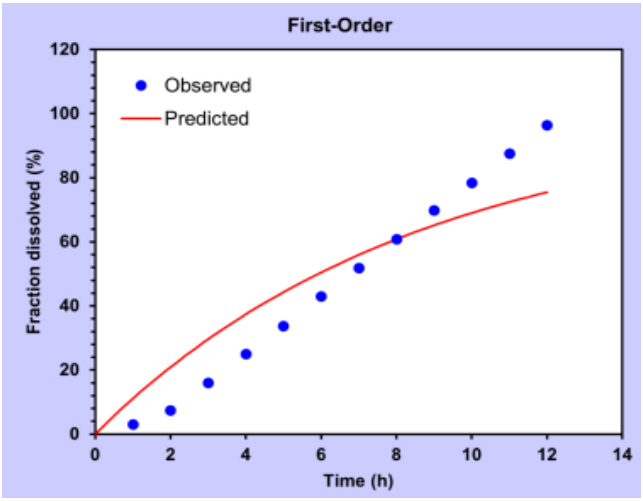


Figure-VIII: Higuchi regression analysis.

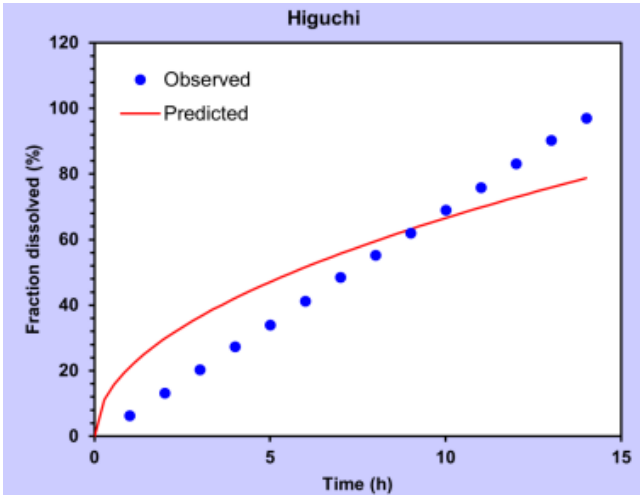
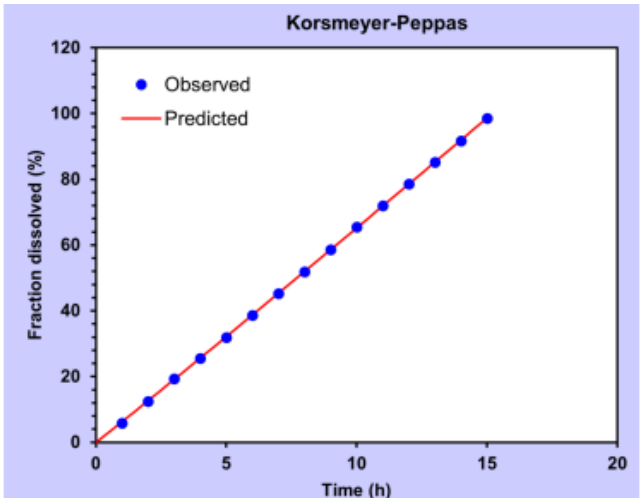


Figure-IX: Korsmeyer regression analysis.



DISCUSSION

This study investigated a novel approach to treating several kinds of bacterial infections by developing an oral push-pull osmotic pump that delivers norfloxacin at a controlled release. The powder direct compression method was used to produce the core tablets, which were subsequently coated with an appropriate coating solution to enable independence from changes in the surrounding medium's pH and hydrodynamics and, ultimately, enhance patient compliance and treatment results. Various tests, such as Fourier-Transform Infrared Spectroscopy (FTIR), Thermogravimetric Analysis (TGA), Hardness, Friability, Thickness, Weight Variation, and Differential Scanning Calorimetry (DSC), were used to evaluate the tablets' quality carefully. The Pre-formulation studies conducted on Norfloxacin provided invaluable insights into its physicochemical properties, which served as a cornerstone for the subsequent formulation development process.

The comprehensive bulk characterization not only ensured the powder's suitability for tablet manufacturing but also underscored the importance of fluidity and compressibility in maintaining uniform tablet quality. Carr's index and Hausner's ratio, which are used to measure powder compressibility and flowability, indicate good flow properties for norfloxacin powder. The study found that all formulations, with the exception of F1, which showed fair flowability, exhibit good flow properties for norfloxacin powder, with an angle of repose between 31 and 37 degrees. In their study, A Green Approach to Synthesize Ondansetron Oral Mucoadhesive Tablets by Using Natural Polymers and in vitro Characterization Mustafa et al. 2024 noted similar results [14].

Both bulk and tapped density fell within acceptable limits of less than 1, indicating good compaction properties for norfloxacin powder. Similar results of bulk and tapped density were observed by Hameed et al.,2024 during their studies, Comprehensive insights on treatment modalities with conventional and herbal drugs for the treatment of duodenal ulcers [19].

Norfloxacin demonstrated good solubility in different dissolving media, i.e., water and phosphate buffer with pH 7 and 9, ensuring adequate drug dissolution upon administration. Laracuente , et al. 2020 in their study, Zero-order drug delivery: State of the art and future prospects, demonstrated similar results [20]. Stability studies provided essential data on the formulations' robustness over time. No discernible changes were observed in the chemical and physical properties of the formulation during this time frame. Similar results on stability studies were reported by Hashem et al., in their study, Formulation and stability studies of metformin hydrochloride in a controlled porosity osmotic pump system [21].

The tablets successfully passed all quality control tests. The hardness of the tablets ranged between 8.3 to 11 kg/cm² as specified in United States Pharmacopeia and National Formulary (USP-NF). General Chapter <1217> Tablet Breaking Force. 42nd Edition. Rockville, MD: United States Pharmacopeial Convention; 2022. Similarly, the friability ranged between 0.06 to 0.38 as described in United States Pharmacopeia and National Formulary (USP-NF), <1216> Friability. Rockville, MD: United States Pharmacopeial Convention; 2023... the drug content uniformity ranges between 98.37±0.84 to 99.67±0.67.

After coating, the weight of the tablets varies due to the differing amounts of coating polymer present in each formulation. The concentrations of HPMC and PEG 400 in the coating solutions vary for each of the nine formulations. The thickness of the tablet ranges between 4.1 to 4.8, which significantly impacts drug dissolution and disintegration rates and ease of administration. All these quality control tests complied with the official limits and met the acceptance criteria. In their study on the Fabrication and in-vitro characterization of mucoadhesive tablets using a natural biocompatible polymer containing metformin HCl, Mustafa, et al., 2024 noted similar results of hardness, friability, weight variation, thickness, and content uniformity [22].

The FTIR analysis not only confirmed the chemical integrity of the active pharmaceutical ingredient (API) but also shed light on potential interactions between norfloxacin and various excipients, thereby guiding formulation optimization. Distinctive peaks corresponding to norfloxacin were observed at 3400 cm-1, 2800 cm-1, 1600 cm-1, and 1460.34 cm-1, and these were compared with the peaks observed in the osmotic push-pull pump formulation. Additionally, characteristic peaks related to Xanthan Gum, HPMC, and Guar Gum were identified at 3334 cm-1, 3494 cm-1, and 2912 cm-1. No significant peak-shifting phenomena were observed. Comparable results to the spectra obtained were followed by, Sahoo, et al., 2011 during their studies of FTIR-and-XRD-investigations-of-some-fluoroquinolones [8].

The single peak in the DSC graph peak corresponds to the phase transition of norfloxacin. At this temperature, norfloxacin initiates its melting process, transitioning into a liquid state while releasing energy into the surrounding environment. The absence of any discernible peak suggests the absence of endothermic behavior. In the TGA graph beyond 90°C, some degradation and weight variance were observed, yet the sample remained stable overall. As the temperature surpassed 280°C, a sharp deflection peak emerged, signifying the onset of sample degradation. This degradation process persisted as the temperature continued to increase. Thus, the sample exhibited stability until it reached 280°C. Similar results of DSC and TGA graph peaks were observed by Nunes et al., 2018 in their study of thermal, spectroscopic, and antimicrobial activity characterization of some norfloxacin complexes [23].

In vitro disintegration and dissolution studies elucidated the release profiles of norfloxacin from push-pull osmotic pumps, highlighting their potential for controlled drug delivery. Norfloxacin exhibited acceptable drug release profiles in an in vitro test. Nine norfloxacin formulations were tested in vitro over 15 hours. F1 showed a 50% burst release at five hours and a peak release of 91.1% by nine hours. Most formulations released at 80% in 10 hours, but F9 released at 69.4%. F8 reached 98.5% release by thirteen hours, and F6 showed the maximum release at 15 hours, reaching 98.5%. Norfloxacin tablets' in vitro dissolving rate pattern was examined using mathematical models in this work. With values near to 1, the findings showed that the tablets adhere to first-order release kinetics. Furthermore, for every formulation, the Korsemeyer-Pappas model verified first-order kinetics. Over a specific amount of time, a comparable pattern of drug release was noted by Zhao et al., 2022, in their study, Development of an Oral Push–Pull Osmotic Pump of Fenofibrate-Loaded Mesoporous Silica Nanoparticles [24].

The strength of this topic is the innovative approach to drug delivery that can improve patient compliance and reduce side effects. This technology has the potential to revolutionize the way antibiotics are administered, leading to more effective treatment outcomes. The oral push-pull

osmotic pump allows for precise control over drug release rates, ensuring optimal therapeutic levels of norfloxacin in the body. By combining osmotic principles with push-pull mechanisms, this pump offers a reliable and efficient method for sustained drug delivery. The limitation of this topic is the need for further research and testing to ensure safety and efficacy before widespread implementation. Additionally, regulatory approval may be a lengthy process that could delay the availability of this innovative drug delivery system to patients in need. Future prospects include exploring the potential application of this technology for other drugs and medical conditions, as well as optimizing the design to enhance drug release kinetics and overall performance. Furthermore, collaboration with pharmaceutical companies and regulatory agencies will be crucial in advancing this novel drug delivery system toward clinical use.

CONCLUSION

Through this research, it has been established that a push-pull osmotic pump can serve as an effective platform for the controlled release of norfloxacin. By utilizing a direct compression technique and coating with a cellulose acetate solution, a favorable controlled release pattern for norfloxacin has been realized. This innovative method has the potential to enhance patient compliance and therapeutic efficacy by providing sustained and predictable drug delivery, thus making valuable contributions to the advancement of pharmaceutical science in the realm of antibiotic therapy.

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Authors' Contribution:

Muhammad Abid Mustafa: Substantial contributions to the conception and design of the work.
Zuha Tariq: The acquisition of data for the work.
Obeda Asghar: Analysis of data for the work.
Umar Ali: Interpretation of data for the work.
Muntaha Gull Shahid: Drafting the work.
Rabia Zaka : Reviewing it critically for important intellectual content.
Muhammad Suffyan Butt: Final approval of the version to be published.
Muhammad Junaid Yaqoob: Design of the work.

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