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RESEARCH ARTICLE

Development and *In Vitro* Characterization of a Sustained-Release Pirfenidone Matrix Tablet Using Hydrophilic and Hydrophobic Polymers

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Abstract: Pirfenidone, a primary therapeutic agent for Idiopathic Pulmonary Fibrosis (IPF), has a short biological half-life that requires frequent daily dosing, often leading to non-adherence and adverse effects. This work is focused on the development of a matrix-based sustained-release (SR) tablet to prolong drug release over 12 hours. Tablets were prepared by direct compression, utilizing different concentrations of hydrophilic polymers (HPMC K15M, HPMC K4M) and a hydrophobic polymer (Eudragit RS 100) as release-retarding agents. Nine formulations (F1-F9) were systematically developed. Pre-compression evaluations confirmed that all powder blends exhibited good to excellent flow properties. Post-compression analysis showed that all tablet formulations complied with pharmacopoeial standards for weight variation, hardness, friability, and drug content uniformity. Drug-excipient compatibility was confirmed via Fourier Transform Infrared (FTIR) spectroscopy. *In vitro* dissolution studies, conducted in sequential pH media (0.1N HCl followed by pH 6.8 phosphate buffer), revealed distinct polymer-dependent release profiles. HPMC K4M, a low-viscosity grade, failed to sustain release, whereas Eudragit RS 100 provided significant retardation, resulting in incomplete release at higher concentrations. Formulation F1, containing HPMC K15M, achieved the target release profile, liberating 94.98% of the drug over 12 hours. The release kinetics for F1 were best described by the Higuchi model, indicating a diffusion-controlled mechanism. This formulation presents a viable platform for a reduced-dosing regimen of pirfenidone, offering potential for improved patient compliance.

Keywords: Pirfenidone; Sustained Release; Matrix Tablet; HPMC; Eudragit RS 100

1. Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive, and fibrosing interstitial lung disease with a poor prognosis [1]. Pirfenidone, an anti-fibrotic and anti-inflammatory agent, is one of the standard-of-care treatments approved for IPF, having been shown to slow the decline in lung function [2]. Although it is therapeutically efficient, the clinical use of Pirfenidone is compromised by its pharmacokinetic profile. It possesses a short biological half-life of approximately 2.5 to 3 hours, necessitating a frequent dosing schedule, typically 801 mg administered three times daily [3]. This regimen can lead to significant fluctuations in plasma drug concentration, creating peaks associated with adverse effects (such as nausea, dyspepsia, and photosensitivity) and troughs that may compromise efficacy. Such demanding schedules are often a barrier to patient adherence [4].

Modified-release drug delivery systems, particularly oral sustained-release (SR) formulations, offer a well-established strategy to overcome these limitations. By modulating the rate of drug release, SR systems can maintain therapeutic plasma concentrations for an extended duration, reduce the frequency of administration, minimize side effects related to high peak concentrations, and improve overall patient compliance [5].

Among the various SR techniques, polymer-based matrix tablets are frequently employed due to their formulation simplicity, low manufacturing cost, and suitability for high-speed production via direct compression or granulation [6]. These systems function by dispersing the active pharmaceutical ingredient (API) within a porous polymer scaffold. The release mechanism is then controlled by the properties of this matrix. Hydrophilic matrix systems, commonly utilizing cellulose derivatives like Hydroxypropyl Methylcellulose (HPMC), are widely popular. Upon contact with gastrointestinal fluids, HPMC hydrates to form a viscous, gelatinous layer on the tablet surface. This gel layer acts as a diffusional barrier; the drug is released through a combination of

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diffusion through the gel and erosion of the matrix itself [7]. The viscosity grade of HPMC is a critical parameter; higher viscosity grades (e.g., K15M) form a stronger, more resilient gel layer, leading to more prolonged release compared to lower viscosity grades (e.g., K4M) [8]. Alternatively, hydrophobic or water-insoluble polymers can be used to create inert matrix systems. Polymethacrylates, such as Eudragit RS 100 (poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride)), form a pH-independent, water-insoluble matrix. This polymer swells minimally, and drug release is governed almost exclusively by the diffusion of the drug through the network of pores and channels within the inert scaffold [9].

The present work was focused on the design, development, and *in vitro* characterization of sustained-release matrix tablets of pirfenidone. This research work evaluated the impact of two different viscosity grades of HPMC (K15M and K4M) and a hydrophobic polymer (Eudragit RS 100) at various concentrations on the drug release profile to identify an optimized formulation suitable for a 12-hour release duration.

2. Materials and Methods

2.1. Materials

Pirfenidone was obtained as a gift sample from Cipla Ltd. (Mumbai, India). HPMC K15M, HPMC K4M, and Eudragit RS 100 were procured from Yarrow Chem Products (Mumbai, India). Microcrystalline cellulose (Avicel) and colloidal silicon dioxide (Aerosil) were also from Yarrow Chem Products. Talc was obtained from Loba Chem (Mumbai, India), and Magnesium Stearate was from Alembic Ltd. (Baroda, India). Disodium hydrogen phosphate and other reagents were of analytical grade and obtained from Qualigens Fine Chemicals (Mumbai, India).

2.2. Methods

2.2.1. Analytical Method Development

A stock solution of pirfenidone (1000 µg/mL) was prepared in methanol. This was further diluted with 0.1 N HCl and pH 6.8 phosphate buffer to create working standards (100 µg/mL) in each medium. From these, serial dilutions were prepared to yield concentrations ranging from 5 to 20 µg/mL. The absorbance of these solutions was measured using a UV-Visible double beam spectrophotometer against their respective blanks. The wavelengths of maximum absorbance λmax were determined to be 205 nm in 0.1 N HCl and 207 nm in pH 6.8 phosphate buffer. Calibration curves were generated by plotting absorbance versus concentration to establish linearity.

2.2.2. Drug-Excipient Compatibility Studies

Fourier Transform Infrared (FTIR) spectroscopy was employed to assess potential physicochemical interactions between pirfenidone and the selected excipients. Spectra were recorded for the pure drug, physical mixtures of the drug with each polymer (HPMC K15M, HPMC K4M, Eudragit RS 100), and the optimized formulation blend. Samples were prepared using the KBr pellet method, and spectra were scanned over the range of 4000–400 cm^{-1} [10]. The spectra were analyzed for the appearance or disappearance of characteristic peaks or significant shifts, which would indicate an interaction.

2.2.3. Formulation of Sustained-Release Matrix Tablets

Nine tablet formulations (F1–F9) were developed, as detailed in Table 1.

Table 1. Formulation Composition of Pirfenidone Matrix Tablets (All weights in mg)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pirfenidone	320	320	320	320	320	320	320	320	320
HPMC K15M	33	56	67	-	-	-	-	-	-
HPMC K4M	-	-	-	33	56	67	-	-	-
Eudragit RS 100	-	-	-	-	-	-	33	56	67
Avicel	76	53	42	76	53	42	76	53	42
Aerosil	10	10	10	10	10	10	10	10	10
Talc	7	7	7	7	7	7	7	7	7
Magnesium stearate	4	4	4	4	4	4	4	4	4
Total	450	450	450	450	450	450	450	450	450

The tablets were prepared using the direct compression method. Pirfenidone, the respective matrix-forming polymer (HPMC K15M, HPMC K4M, or Eudragit RS 100), and Avicel were individually passed through a #40 mesh sieve. The ingredients were thoroughly blended in a mortar and pestle using geometric mixing. The blend was then lubricated with sieved Aerosil and Talc, followed by the addition of Magnesium Stearate, which was mixed for 2-3 minutes. The final powder blend, with a target tablet weight of 450 mg, was manually fed into the die of an eight-station rotary tablet machine and compressed.

2.2.4. Evaluation of Pre-Compression Parameters

The powder blends for all nine formulations were characterized for their flow and compressibility properties.

- Bulk Density (BD): A weighed quantity of the powder blend (m) was gently poured into a graduated cylinder, and the unsettled volume (V_0) was recorded. Bulk density was calculated as m/V_0 [11].
- Tapped Density (TD): The same cylinder was subjected to a fixed number of taps (100) using a tap density tester until a constant volume was achieved. The final tapped volume (Vf) was recorded. Tapped density was calculated as m/Vf [12].
- Compressibility Index (Carr's Index): This was calculated from the bulk and tapped densities using the formula: Carr's Index (%) = [(TD – BD) / TD] × 100 [13].
- Hausner Ratio: This was calculated as the ratio of tapped density to bulk density: Hausner Ratio = TD / BD [13].
- Angle of Repose (θ): The fixed-funnel method was used. The blend was allowed to flow through a funnel, fixed at a height (h) of 2.5 cm, onto a horizontal surface. The radius (r) of the base of the resulting conical pile was measured, and the angle was calculated as $\theta = \tan^{-1}(h/r)$ [14].

2.2.5. Evaluation of Post-Compression Parameters

The compressed tablets from all batches were evaluated for their physicochemical properties according to standard pharmacopoeial methods.

- Weight Variation: Twenty tablets from each batch were randomly selected and weighed individually. The average weight and percent deviation were calculated to assess compliance with Indian Pharmacopoeia (IP) specifications [11].
- Hardness: The crushing strength of 6-10 tablets from each batch was measured using a Monsanto hardness tester. The force required to fracture the tablet diametrically was recorded in kg/cm² [13].
- Thickness: The thickness of 20 randomly selected tablets was measured using Vernier calipers, and the average value was recorded [11].
- Friability: Twenty tablets were accurately weighed (W_1) and subjected to abrasion in a Roche friabilator at 25 rpm for 4 minutes. The tablets were then de-dusted and re-weighed (W_2). The percentage weight loss was calculated as: Friability (%) = $[(W_1 - W_2) / W_1] \times 100$. A value of less than 1% is considered acceptable [15].
- Drug Content Uniformity (Assay): Ten tablets from each batch were weighed and finely powdered. A quantity of powder equivalent to the average tablet weight was accurately weighed, dissolved in suitable media, and diluted volumetrically. The solution was filtered, and the filtrate was analyzed using the UV spectrophotometer at the predetermined λmax. The drug content was calculated and compared against the IP specification (95–105%) [15].

2.2.6. In Vitro Drug Release Study

The *in vitro* release of pirfenidone from the matrix tablets was assessed using a USP Type II (Paddle) dissolution apparatus. The study was performed at 37 ± 0.5°C with a paddle rotation speed of 50 rpm. A sequential pH change was used to simulate gastrointestinal transit: the tablets were first placed in 900 mL of 0.1N HCl for 2 hours, after which the medium was replaced with 900 mL of pH 6.8 phosphate buffer for the subsequent 10 hours. Aliquots of the dissolution medium were withdrawn at specified intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours) and replaced with an equal volume of fresh, pre-warmed medium to maintain sink conditions. The samples were analyzed by UV spectrophotometry at 205 nm (for 0.1N HCl) and 207 nm (for pH 6.8 buffer). The cumulative percentage of drug release was calculated and plotted against time [16].

2.2.7. Drug Release Kinetics and Mechanism

To elucidate the mechanism of drug release from the matrix, the dissolution data of the optimized formulation (F1) was fitted to several mathematical models: Zero-order (cumulative % release vs. time), First-order (log cumulative % remaining vs. time), and the Higuchi model (cumulative % release vs. square root of time). The coefficient of determination (R^2) for each model was calculated to identify the best-fit model. The data was also fitted to the Korsmeyer-Peppas model (log cumulative % release vs. log

time) to characterize the release mechanism, where the release exponent 'n' provides insight into the mode of transport (e.g., Fickian diffusion, anomalous transport, or Case II transport) [17].

3. Results and Discussion

3.1. Analytical Method

The calibration curves for pirfenidone in both 0.1 N HCl λmax 205 nm) and pH 6.8 phosphate buffer (λmax 207 nm) showed excellent linearity over the concentration range of 5–20 µg/mL. The coefficient of determination (R^2) for both curves was found to be greater than 0.999, confirming the suitability of the analytical method for the assay and dissolution studies.

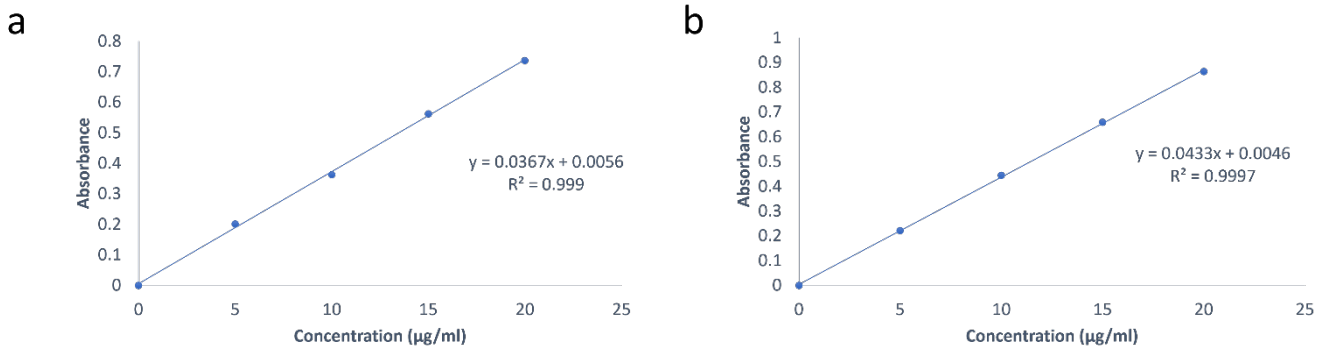

Figure 1. Standard Calibration Curve of Pirfenidone in a. 0.1 N HCl and pH 6.8 Phosphate Buffer

3.2. Drug-Excipient Compatibility (FTIR)

The FTIR spectra for pure pirfenidone and its physical mixtures with the polymers are presented in Figures 2. The spectrum of pure pirfenidone (Figure 2a) displayed its characteristic peaks, including those corresponding to C=O stretching (carbonyl) and C-N stretching. The spectra of the physical mixtures (Figures 2b) and the final optimized tablet blend showed the retention of all principal peaks of pirfenidone without any significant shifts, broadening, or the appearance of new peaks. This spectral evidence confirms the absence of any significant physicochemical interactions between the drug and the polymers (HPMC K15M, HPMC K4M, Eudragit RS 100), indicating their compatibility for use in the formulation.

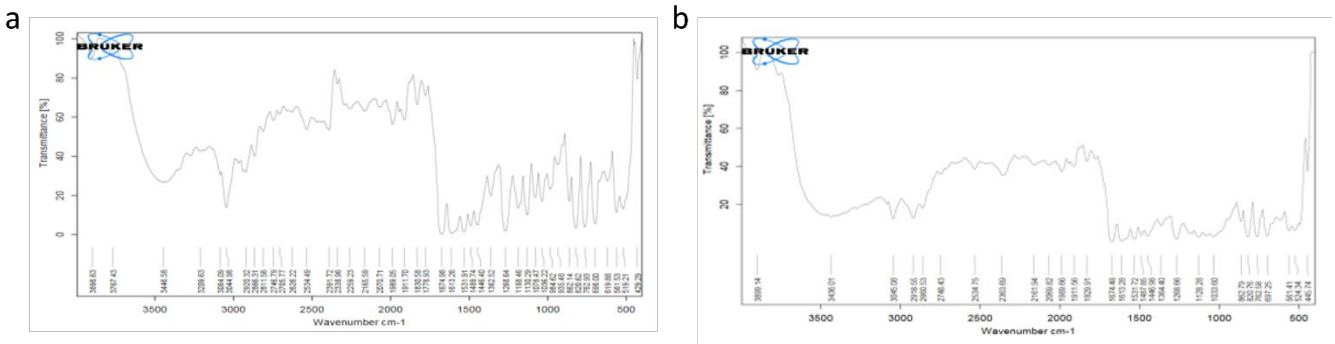

Figure 2. FTIR spectrum of a. Pure Drug and b. Pure Drug + All Excipients Mixture

3.3. Pre-Compression Properties of Powder Blends

The micromeritic properties of the powder blends for all nine formulations are summarized in Table 2. The angle of repose for all blends was found to be in the range of 25°–28°, which is indicative of good to excellent flow properties. Furthermore, the Carr's Index values ranged from 6.67% to 18.37%, and the Hausner Ratio ranged from 1.07 to 1.21. Values for Carr's Index below 20% and Hausner Ratio below 1.25 are generally considered to represent good flowability and compressibility [13]. These results, collectively, suggest that all powder blends were suitable for the direct compression manufacturing process, which relies on consistent powder flow into the die cavity.

Table 2. Pre-Compression Parameters of Formulation Blends (Mean ± SD)

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose (°)	Carr's index (%)	Hausner ratio
F1	0.40 ± 0.02	0.46 ± 0.01	27 ± 0.2	13.04 ± 0.03	1.15 ± 0.05
F2	0.42 ± 0.01	0.49 ± 0.02	25 ± 0.3	14.29 ± 0.03	1.17 ± 0.03
F3	0.41 ± 0.02	0.46 ± 0.01	26 ± 0.4	10.87 ± 0.01	1.12 ± 0.06
F4	0.42 ± 0.03	0.45 ± 0.01	26 ± 0.5	6.67 ± 0.03	1.07 ± 0.04
F5	0.40 ± 0.01	0.48 ± 0.01	27 ± 0.6	16.67 ± 0.02	1.20 ± 0.05
F6	0.41 ± 0.02	0.49 ± 0.03	28 ± 0.1	16.33 ± 0.02	1.20 ± 0.06
F7	0.44 ± 0.01	0.53 ± 0.01	25 ± 0.5	16.98 ± 0.03	1.20 ± 0.06
F8	0.42 ± 0.02	0.51 ± 0.01	26 ± 0.3	17.65 ± 0.02	1.21 ± 0.03
F9	0.40 ± 0.03	0.49 ± 0.03	27 ± 0.2	18.37 ± 0.03	1.21 ± 0.05

3.4. Post-Compression Tablet Evaluation

The physicochemical properties of the compressed pirfenidone matrix tablets are presented in Table 3.

Table 3. Physicochemical Characterization of Pirfenidone Tablets (Mean ± SD)

Formulation	Weight variation (mg)	Tablet hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	449 ± 0.64	5.2 ± 0.25	4.26 ± 0.5	0.31 ± 0.02	99.11 ± 0.18
F2	450 ± 0.54	5.9 ± 0.5	4.31 ± 0.25	0.42 ± 0.04	98.25 ± 0.11
F3	450 ± 0.42	4.7 ± 0.5	4.17 ± 0.7	0.48 ± 0.02	99.25 ± 0.22
F4	450 ± 0.55	5.8 ± 0.5	4.21 ± 0.6	0.50 ± 0.01	98.84 ± 0.17
F5	450 ± 0.41	4.7 ± 0.22	4.44 ± 0.11	0.58 ± 0.02	97.93 ± 1.04
F6	449 ± 0.45	5.7 ± 0.8	4.32 ± 0.15	0.56 ± 0.03	99.13 ± 0.15
F7	449 ± 0.51	5.8 ± 0.26	4.15 ± 0.14	0.49 ± 0.03	98.53 ± 0.8
F8	450 ± 0.68	5.5 ± 0.72	4.32 ± 0.11	0.44 ± 0.01	98.35 ± 1.37
F9	450 ± 0.41	5.7 ± 0.22	4.21 ± 0.12	0.45 ± 0.02	99.76 ± 0.7

All tablet formulations complied with the IP specifications for uniformity of weight (within ±5% of the 450 mg target). The tablet hardness for all batches was found to be in the range of 4.7–5.9 kg/cm^2, ensuring adequate mechanical integrity for handling and transportation. Friability was well below the 1% pharmacopoeial limit for all formulations, further confirming their mechanical strength. The drug content uniformity was excellent, with assay values ranging from 97.93% to 99.76%, well within the acceptable IP limits of 95–105%. These results indicate that the direct compression process successfully produced robust tablets with uniform drug distribution.

3.5. *In Vitro* Drug Release and Formulation Discussion

The *in vitro* cumulative drug release profiles for all nine formulations are presented in Figure 3. The results indicate that the drug release rate was significantly influenced by both the type and concentration of the matrix-forming polymer. The impact of HPMC viscosity was immediately apparent. Formulations F4-F6, prepared with the lower viscosity grade HPMC K4M (nominal viscosity 4,000 cP), exhibited rapid drug release. Formulation F4 (lowest K4M concentration) released 95.01% of its drug load in only 6 hours, and F5 released 97.22% in 8 hours.

This indicates that the gel layer formed by HPMC K4M was not sufficiently strong or viscous to retard the diffusion of a soluble drug like pirfenidone for the 12-hour target period [8]. In contrast, formulations F1-F3, prepared with the high viscosity grade HPMC K15M (nominal viscosity 15,000 cP), provided significantly more prolonged release. The higher viscosity and molecular weight of HPMC K15M allow it to form a more robust and durable gel layer upon hydration, which increases the diffusional path length and effectively slows drug release [7].

A clear concentration-dependent effect was observed within all polymer groups. As the concentration of the polymer increased, the drug release rate decreased. For the HPMC K15M series, the 12-hour release decreased from 94.98% (F1, 33 mg) to 81.23% (F3, 67 mg). This is because a higher polymer content creates a more concentrated and tortuous gel matrix, further impeding drug diffusion.

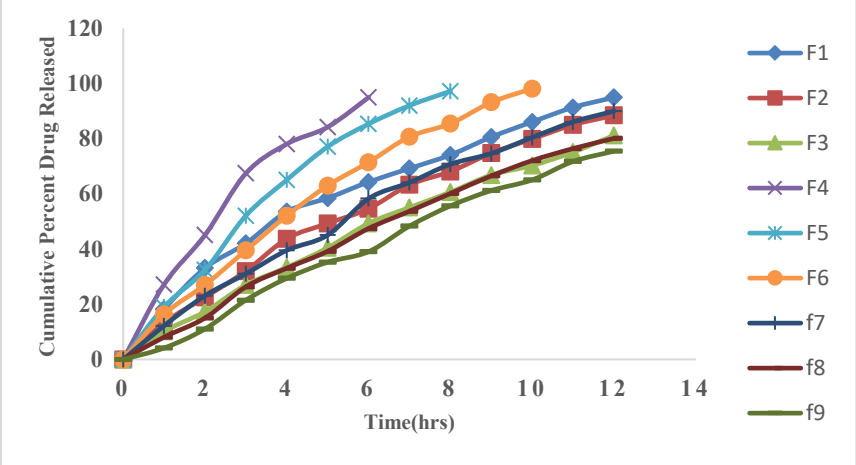

Figure 3. *In Vitro* Cumulative Percentage Drug Release

Similarly, formulations F7-F9, made with the hydrophobic polymer Eudragit RS 100, showed a strong concentration-dependent retardation. F7 (33 mg) released 90.01% at 12 hours, while F9 (67 mg) released only 75.49%. Eudragit RS 100 is water-insoluble and forms a rigid, non-eroding matrix. Drug release occurs via diffusion through the pores and channels of this matrix. A higher polymer load results in a less porous, more rigid structure, thus slowing diffusion significantly [9]. The incomplete release seen in F8 and F9 suggests that at these concentrations, the matrix is too dense to permit full drug liberation in 12 hours.

Based on these results, formulation F1 was identified as the optimized formulation. It provided the most desirable release profile, with a controlled release approaching completion (94.98%) at the 12-hour time point, avoiding the rapid release of the K4M group and the incomplete release of the higher-concentration Eudragit group.

3.6. Drug Release Kinetics

The *in vitro* dissolution data for the optimized formulation (F1) was fitted to various kinetic models to determine the release mechanism (Figure 4).

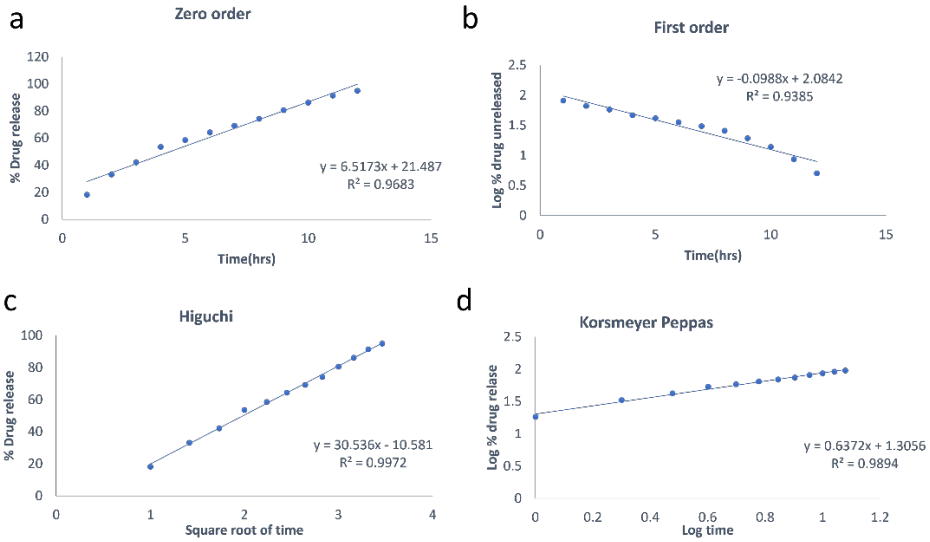

Figure 4. Drug Release Kinetics a. Zero Order b. First Order c. Higuchi and d. Korsmeyer Peppas

The coefficient of determination (R^2) values were calculated for each model. The Higuchi model yielded the highest R^2 value (0.9972), indicating the best fit. This suggests that the release of pirfenidone from the F1 matrix is diffusion-controlled, where the rate of release is proportional to the square root of time. This is a characteristic finding for drug release from a non-eroding, swelling hydrophilic matrix where diffusion through the hydrated gel layer is the rate-limiting step [17].

4. Conclusion

Sustained-release matrix tablets of pirfenidone were successfully developed and formulated using the direct compression method with HPMC and Eudragit polymers. All nine prepared formulations showed acceptable pre-compression flow properties and complied with all pharmacopoeial standards for post-compression parameters, including weight variation, hardness, friability, and drug content. The *in vitro* release studies confirmed that the polymer type (hydrophilic vs. hydrophobic) and its concentration are critical variables that significantly dictate the rate and extent of drug release. HPMC K4M failed to sustain release for 12 hours, while higher concentrations of Eudragit RS 100 resulted in incomplete release. Formulation F1, composed of 320 mg pirfenidone and 33 mg of the high-viscosity polymer HPMC K15M, was identified as the optimal formulation. It exhibited a controlled and near-complete release of 94.98% over a 12-hour period. The release kinetics of F1 were best described by the Higuchi model, confirming that the release mechanism is predominantly diffusion-controlled. This optimized formulation presents a promising platform for a reduced-dosing regimen of pirfenidone, which could enhance patient adherence and improve therapeutic outcomes in the long-term management of idiopathic pulmonary fibrosis.

References

[1] Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011 Mar 15;183(6):788-824.

[2] King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014 May 29;370(22):2083-92.

[3] Genentech, Inc. ESBRIET® (pirfenidone) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2019.

[4] Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011 May 21;377(9779):1760-9.

[5] Bhowmik D, Gopinath H, Kumar BP, Duraivel S, Kumar KPS. Controlled release drug delivery systems- a review. The Pharma Innovation. 2012;1(10):24-32.

[6] Alhalmi A, Altowairi M, Saeed O, Alzubaidi N, Almoiliqy M, Abdulmalik W. Sustained release matrix system: an overview. World J Pharm Pharm Sci. 2018;7(6):1470-86.

[7] Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev. 2012 Mar;64(Suppl):163-74.

[8] Maderuelo C, Lanao JM, Zarzuelo A. The effect of HPMC viscosity grade on drug release from matrix tablets. Int J Pharm. 2011;411(1-2):137-45.

[9] Thakral S, Thakral NK, Majumdar DK. Eudragit®: a technology platform for controlled oral drug delivery. Int J Pharm. 2013;457(2):486-98.

[10] Devi R, Komala M, Jayanthi B. Studies on drug compatibility with different pharmaceutical excipients in nanoparticle formulation. Res J Pharm Technol. 2022;15(8):3443-6.

[11] Indian Pharmacopoeia Commission. Indian Pharmacopoeia 2018. Ghaziabad: Indian Pharmacopoeia Commission; 2018.

[12] United States Pharmacopeia and National Formulary (USP 43-NF 38). Rockville, MD: United States Pharmacopeial Convention; 2020. Chapter <616> Bulk Density and Tapped Density of Powders.

[13] Shah RB, Tawde SA, Kabadi M. Significance of bulk density, tapped density, and Hausner ratio in blend and granule characterization. Pharm Tech. 2017;41(10):42-45.

[14] United States Pharmacopeia and National Formulary (USP 43-NF 38). Rockville, MD: United States Pharmacopeial Convention; 2020. Chapter <1174> Powder Flow.

[15] Pavani J, Deepika B, Nagaraju K, Regupathi T, Rao KN, Dutt KR. Formulation development and *in vitro* evaluation of sustained release matrix tablets of tramadol hydrochloride. Innovat International Journal of Medical & Pharmaceutical Sciences. 2017;2(6):28-38.

[16] Bawankar RD, Mandekar PS, Kediya A, Mundhada DR. Formulation, Characterization and Evaluation of Sustained Release Matrix Tablet of Antiemetic Agent. Pakistan J Sci Ind Res Ser A: Phys Sci. 2025 Jul 8;68(2):169-77.

[17] Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13(2):123-33.