doi.org/10.36721/PJPS.2026.39.12.337.1

Formulation, evaluation and characterization of fexofenadine IR and paracetamol SR multiparticulate drug delivery system

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Abstract: **Background**: Multiparticulate Drug Delivery (MDD) system are particularly considered as well suited systems for controlling oral preparations that have low risk of dose-dumping. **Objectives**: The current research work was aimed to prepare Fexofenadine HCl immediate release (IR) and Paracetamol sustained release (SR) pellets in a single dosage unit for the treatment of Allergic Rhinitis. Extrusion-spheronization was used to fabricate pellets. **Methods**: The formulations were analyzed for several parameters, including micromeritic studies, Friability, Weight variation test, Swelling, X-Ray Diffraction (XRD), Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscopy (SEM), *in-vitro* release and stability studies. **Results**: The results showed that the formulated pellets have an excellent flowability (23.01° to 25.23°), bulk density falls in the range of 1.23 g cm^{-3} to 1.42 g cm^{-3}, tapped density ranges 1.43 g/cm^3 1.58 g/cm^3, carr's compressibility index lie between 10.31 % to 15.17 %, Hausner's ratio ranges 1.11 to 1.18 which concluded pellets had good flow properties. Friability was less than 1%; the T6 formulation showed the maximum swelling of 99.28%. No interaction between excipient and drug was found. T6 showed a drug release of 99.08% in 24 hours. **Conclusion**: The research effectively demonstrated that preparing a single-unit dosage form of paracetamol and fexofenadine is a safe, simple and promising technique for SR of Paracetamol, thereby increasing patient compliance by reducing the dosage frequency.

Keywords: Extrusion-spheronization; Fexofenadine HCl; Multiparticulate drug delivery systems; Pellets; Paracetamol; Sustained release

Submitted on 17-10-2025 – Revised on 07-12-2025 – Accepted on 26-02-2026

INTRODUCTION

Pharmaceutical research and development are focusing primarily on delivery technologies that help patients achieve their therapeutic goals while reducing side effects. Recent trends suggest that Multiparticulate Drug Delivery (MDD) technologies are particularly well suited to producing controlled- or sustained-release oral preparations with low dose-dumping risk, blending flexibility to achieve varied release patterns and a repeatable, limited gastric residence time (Holm, Kokott *et al*., 2022). Pellets were manufactured by converting powder or granules together into spherical unit, subsequently by adding a granulating solution. Pellet sizes range from 0.5-1.5 micron. These are commonly used in sustained-release delivery systems due to their uniform spreadability and repeatable release kinetics (Farooq *et al*., 2019). Pellets can be prepared in a variety of ways (Wagh, Surawase *et al.*, 2020). Extrusion–spheronization is the most widely and effectively employed process for the continuous manufacture of pellets. The advantages of this approach include the ability to produce spherical pellets with minimal friability, excellent flow characteristics, size homogeneity and efficient drug absorption. Several formulation and process variables, such as the choice of extruder or spheronizer, the quantity and type of granulating fluids and the spheronization interval influence extrusion and spheronization processes. So, to maximise pellet yield, these factors must be carefully selected (Farooq *et al*., 2019; Ibrahim and Alshora, 2021;. Pelletized products are used to increase the safety and efficacy of therapeutic compounds, as well as provide flexibility in dosing form development and design (Patel, Gohel *et al.*, 2019).

Allergic rhinitis is characterized primarily as sinus hypersensitivity symptoms because of an immune-mediated (mostly IgE-dependent) swelling following exposure of allergen to the mucous membranes of nasal cavity. The common cold is a more prevalent disease and usually manifests as nasal stuffiness/secretion, coughing and sneezing. For the treatment of the common cold and allergic rhinitis, a combination of NSAIDs, nasal decongestants and antihistamines are effective. According to a clinical trial conducted in 2017, symptomatic relief and treatment of the common cold and allergic rhinitis can be achieved by combining Paracetamol 500 mg and Fexofenadine HCl 60 mg (Kiran and Pawaskar, 2017).

Fexofenadine belongs to selective H1 receptor blocker that has been on the market in the United States since 2000,

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with minimal sedative effects. Microcrystalline cellulose (MCC), particularly commercial-level Avicel PH-101, were regarded as an essential extrusion–spheronization excipient (Chaerunisaa, Sriwidodo *et al*., 2019, Soltani, Kamali *et al*., 2022). However, MCC preparations have some drawbacks, such as pellet non-disintegration, which leads to extended matrix-type dissolution (Soltani, Kamali *et al.*, 2022). This undesirable feature can be mitigated by using a significant amount of disintegrating agents (Xia, Shi *et al.*, 2018). Several additional excipients, such as crospovidone and polyvinyl pyrrolidine (PVP), have been used as extrusion–spheronization assistants with MCC in recent years (Grohn, Weis *et al*., 2020).

Paracetamol is a medication used as anti-pyretic and analgesic. The drug is often given in 500 mg to 1 g daily doses every 3–4 hours. For optimal analgesic activity, blood concentrations of 10–20 mg/mL must be attained via rapid and complete absorption from an oral dose form. It is rapidly absorbed from tablets and liquids, reaching peak concentration about 1 hour after intake (van der Heijden, Mian *et al.*, 2022). The dosing frequency suggests the need to design a sustained-release (SR) oral formulation (Sharma, Sarkar *et al.*, 2019). Hydroxypropyl methylcellulose (HPMC) is the most widely used hydrophilic polymer for sustained drug delivery systems due to its gel-forming ability, increased drug loading capacity, non-toxicity, pH-independent solubility and flexibility to achieve desired drug release profiles (Vlad, Pintea *et al*., 2025).

The current research work aimed to formulate a combination of immediate-release Fexofenadine and sustained-release Paracetamol in a single dosage unit to reduce dosing frequency and increase patient compliance. To the best of the author's knowledge, there are no commercially available FDCs, which combine an IR fexofenadine and a multiparticulate SR paracetamol to provide both antihistaminic and anti-pyretic effect with one dosage form. The current research work consequently fills this gap by formulating and characterizing a multiparticulate IR/SR dual-release system that (i) releases fexofenadine immediately, (ii) provides a controlled release of paracetamol to reduce dosing frequency. This distinguishes our developed formulation from existing FDCs (Kiran and Pawaskar, 2017).

MATERIALS AND METHODS

Materials

Paracetamol and Fexofenadine HCl were gifted as samples from Neutro Pharma; Crospovidone was obtained from Ashland, USA; HPMC K 100M, HPMC K-15 and Pregelatinised Starch were obtained from Colorcon, Germany; Microcrystalline cellulose and PVP K-30 were obtained from Hangzhou Zhongbao, China. All the chemicals used in the current research were of analytical grade.

Methods

Preparation of fexofenadine HCl IR pellets

All of the prepared pellets contained the same amount of the active (Fexofenadine HCl) and PVP K-30 (Table 1). The weighed amount of Fexofenadine HCl was mixed with Diluent (MCC 101, Lactose Monohydrate), Binder (PVP K-30) and Disintegrant (Crospovidone, Crosscarmellose sodium) and the mixture was screened through a 60-mesh screen. Sieved materials were mixed again. The granulating agent, distilled water, was added slowly to the blended materials and mixing was continued to obtain a damp mass of acceptable homogeneity. The wetted mass was passed through an Extruder and the extrudates were immediately introduced into a spheronizer. Pellets were then collected from the spheronizer and oven-dried at 60°C (Wang, Kan *et al.*, 2015).

Preparation of paracetamol SR pellets

The weighed amounts of Paracetamol, HPMC K 100M, Pregelatinized starch and HPMC K15 were sieved through a mesh no. 30 and blended to achieve uniform mixing. A binder solution was prepared by dissolving PVP K-30 in distilled water, then slowly adding it to the blended materials to obtain a wet mass of desired consistency. The wet mass was passed through the extruder and then into spheronizer. The formed pellets were dried at 60°C (Table 1).

Encapsulation of fexofenadine HCl IR and paracetamol SR pellets

Pellets in proportion of 12.90% Fexofenadine HCl IR pellets and 87.10% of Paracetamol SR pellets were mixed and encapsulated in empty hard gelatin capsule of size "00" with an average fill weight of 620 mg per capsule.

Characterization of pellets

Following parameters were assessed to evaluate the formulated pellets.

Micromeritic properties

Pellets were assessed for micromeritic analysis by calculating the angle of repose (equation 1), bulk density, Carr's index, Hausner's ratio and tapped density (Farooq *et al.*, 2019).

$$\theta = \tan\text{-}1\frac{h}{r} \quad (1)$$

Bulk density is defined as the weight-to-volume ratio of the pellets without tapping (equation 2)(Raval, Ramani *et al.*, 2013).

$$Bulk\ density\ (d\mathrm{b}) = \frac{M}{Vb} \quad (2)$$

Tapped density is the ratio of sample weight to volume after tapping a measuring cylinder 100 times from 2 inches above the bottom (equation 3) (Tumuluru, 2018).

$$Tapped\ density\ (dt) = \frac{M}{V\mathrm{t}} \quad (3)$$

The Carr's compressibility index was determined by multiplying with hundred, the ratio of the difference between tapped density and bulk density to tapped density (equation 4) (Farooq *et al.*, 2019).

$$Carr's\ Index = \frac{dt-db}{dt} \times 100 \quad (4)$$

The Hausner's ratio was evaluated using bulk density and tapped density (equation 5) (Farooq *et al.*, 2019).

$$Hausner's\ ratio = \frac{dt}{db} \quad (5)$$

Friability

A Roche friabilator was used to determine pellet friability. 10 g of pellets was placed in the friabilator, rotated for 10 minutes at 25rpm and then sieved through a mesh no. 250 µm. After dedusting, the initial and final weights of pellets were recorded and friability was determined using equation 6 (Farooq *et al.*, 2019).

$$Friability\ (\%) = \frac{Wi-Wf}{Wi} \times 100 \quad (6)$$

Weight variation test

Twenty capsules of the trial formulations are individually weighed on an electronic weighing balance (Shimadzu) to calculate the weight variation of all the formulations.

Swelling index

The weight of the formed Paracetamol SR pellets was measured after the process of pelletization. The swelling was calculated by immersing pellets (100 mg) at 37°C in an acidic buffer at pH 1.2 for 24 hours. The pellets were swollen in an acidic buffer solution; the swollen pellets were separated and the surplus fluid was removed with filter paper swabs. The weight of the pellets was determined again and the swelling was calculated (equation 7)(Farooq *et al.*, 2019).

$$Swelling\ Index\ (\%) = \frac{Ws-Wd}{Ws} \times 100 \quad (7)$$

"W_s" is the weight of swollen pellets and "W_d" represents the weight of dried pellets.

Fourier-transform infrared spectroscopy

FTIR spectroscopy was used to determine the compatibility of Fexofenadine HCl and Paracetamol with the excipients. Drug and excipient infrared spectra were recorded at a scanning range of 4000 to 500cm^{-1} (Farooq *et al.*, 2019).

Drug content analysis by reverse phase HPLC method

The fabricated pellets were evaluated for its percentage drug contents. The capsules were ground in a mortar and pestle. 155 mg of ground capsule pellets equivalent to 15 mg of Fexofenadine HCl and 124.90 mg Paracetamol were taken in a 25 mL volumetric flask containing diluent (pH 2.0 buffer and Acetonitrile, 7:13) 5 mL of this solution was taken into a 50mL volumetric flask and the volume was made up to mark with the diluent. Samples were evaluated using a C18 column at 25ºC, a flow rate of 1.0 mL/min and a detection wavelength of 220 nm (Shimadzu HPLC) (Shabbir *et al*., 2026).

Scanning electron microscope (SEM)

The diameter and surface characteristics of pellets were investigated by using SEM (Zeiss EVO LS10, Germany). Formulations were kept in the SEM's sample chamber and scanning was conducted at 20 kV at different magnifications (Farooq *et al.*, 2019).

X-ray diffractometer (XRD)

XRD provides data on how the actual structure differs from the idealized one due to internal stresses and defects, unlike phase identification. X-ray diffraction spectrum was obtained using a Bruker D8 Advance diffractometer at 298 K with 40 kV voltage and a scanning angle of 5 to 100 degrees (Farooq *et al.*, 2019).

In-vitro drug release study

An in-vitro study was carried out using the USP apparatus I (Basket); 900 mL of pH 1.2 HCl medium was added to each basket. The rotation speed was set to 50 revolutions per minute and each vessel was equilibrated to 37±0.5°C. One capsule content of the fabricated formulation was placed in each basket and dissolution was commenced. 10 mL sample was withdrawn after 45 minutes for the dissolution study of Fexofenadine HCl and 10 mL samples was taken out at the regular time intervals of 1, 2, 4, 8, 16 and 24 hours for the dissolution study of Paracetamol. The sample aliquot was filtered at each time point using Whatman filter paper No. 41. 5 mL of Paracetamol sample was taken, transferred into a 50 mL volumetric flask and the dissolution medium was used to make up the final volume. The samples were analyzed at a detection wavelength of 259 nm for Fexofenadine HCl and 280nm for Paracetamol.

Drug release kinetics

Several kinetic models such as the zero-order kinetic model (equation 8), first-order model (equation 9), Higuchi's model (equation 10), Hixson–Crowell (equation 11) and Korsmeyer-Peppas (equation 12) model were applied to the reults of *in-vitro* drug release results to understand the kinetics and drug release mechanisms better. Depending on the maximum correlation coefficient, the best-suited model was picked for additional review (Kasekar, Singh *et al.*, 2020).

Zero-order Kinetic

$$F = k0 \times t \quad (8)$$

First-order Kinetic

$$F = 100 \times [1 - Exp\ (-k1\ x\ t)] \quad (9)$$

Higuchi's Model

$$F = kH\ x\ t\text{^}0.5 \quad (10)$$

Hixson–Crowell Model

$$F = 100 \times [1 - (1 - kHC \times t)\text{^}3] \quad (11)$$

Korsmeyers Peppas Model

$$F = kKP \times t\text{^}n \quad (12)$$

Table 1: Formulations design of paracetamol SR and fexofenadine HCl IR pellets.

Serial. No.	Ingredients	T_1	T_2	T_3	T_4	T_5	T_6
Fexofenadine IR pellets							
1	Fexofenadine HCl	60.00	60.00	60.00	60.00	60.00	60.00
2	Croscarmellose Sodium	1.00	3.00	4.00	-	-	-
3	Crospovidone	-	-	-	1.00	3.00	5.00
4	Lactose Monohydrate	11.00	10.00	10.00	-	-	-
5	MCC	-	-	-	14.00	13.00	12.00
6	PVP K-30	8.00	7.00	6.00	5.00	4.00	3.00
Total (mg)		80.00	80.00	80.00	80.00	80.00	80.00
Paracetamol SR pellets							
1	Paracetamol	500.00	500.00	500.00	500.00	500.00	500.00
2	HPMC K 100M	-	2.68	5.55	8.66	10.54	15.43
3	PVP K-30	5.14	5.14	5.14	5.14	5.14	5.14
4	Pregelatinized Starch	24.63	27.58	24.11	19.90	17.02	11.20
5	HPMC K-15	10.23	4.60	5.20	6.30	7.30	8.23
Total (mg)		540.00	540.00	540.00	540.00	540.00	540.00

Table 2: Micromeritic evaluation of formulated pellets.

Trials	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Hausners ratio	Friability (%)
T1	23.01 ± 0.53	1.23 ± 0.06	1.45 ± 0.04	15.17 ± 0.85	1.18 ± 0.02	0.45 ± 0.10
T2	23.76 ± 0.59	1.35 ± 0.04	1.52 ± 0.05	11.18 ± 0.93	1.13 ± 0.01	0.61 ± 0.09
T3	24.13 ± 0.61	1.27 ± 0.08	1.43 ± 0.06	11.19 ± 0.84	1.13 ± 0.04	0.51 ± 0.16
T4	23.94 ± 0.58	1.36 ± 0.02	1.56 ± 0.04	12.82 ± 0.91	1.15 ± 0.02	0.39 ± 0.19
T5	25.23 ± 0.68	1.42 ± 0.09	1.58 ± 0.08	10.31 ± 0.93	1.11 ± 0.03	0.49 ± 0.16
T6	24.53 ± 0.72	1.26 ± 0.08	1.44 ± 0.07	12.50 ± 0.87	1.14 ± 0.02	0.26 ± 0.15

All the results are expressed mean ± SD of three replicates

Statistical analysis

Statistical study of the data was performed by using ANOVA. The data were represented as the mean ± standard deviation of three. A value of p less than 0.05 was declared significant.

Stability studies

The optimized batch's stability was studied by encapsulating the pellets, packing them into appropriate material and subjecting them to stability studies at 40°C and RH 75%, conditions as per ICH guidelines, for 6 months. Various parameters (e.g., physical appearance, shape, drug content analysis and dissolution,) were assessed to evaluate the encapsulated pellets (Gayke, Shukla *et al.*, 2021).

RESULTS

Micromeritic properties

The results concluded that the angle of repose ranged between 23.01° to 25.23°, the bulk density was in the range of 1.23 g cm^{-3} to 1.42 g cm^{-3}, tapped density lies within the range of 1.43 g cm^{-3} to 1.58 g cm^{-3}, carr's index lie between 10.31 % to 15.17 %, the results of Hausner's ratio were in the range of 1.11 to 1.18 which concluded that prepared pellets had "excellent" flow properties. The friability of the trial formulations was less than 1%. Results are represented in Table 2.

Weight variation test

The results showed that the weight of capsules lies between 573.50 mg and 666.50 mg; the percentage deviation limit is ±7.5 % as per the British Pharmacopeia.

Swelling index

Swelling index of paracetamol SR pellets

The swelling patterns of all six formulations were analyzed in acidic media (pH 1.2) at 24-hour intervals. The results concluded that paracetamol SR trial formulation of "T6" showed the maximum swelling percentage i.e., 99.28% (Fig. 1 and Fig. 2).

Swelling index of fexofenadine IR pellets

The swelling pattern of the formulations of Fexofenadine HCl IR pellets were analyzed in pH 1.2 buffer. The results showed that IR pellets did not swell and did not dissolve completely in the medium after 45 minutes.

Fourier-transform infrared spectroscopy (FTIR)

The chemical alteration occurs in prepared Fexofenadine IR pellets and Paracetamol SR pellets as a result of interaction of drugs with the polymers was studied through FTIR spectra. A separate spectrum of Fexofenadine, Paracetamol, all the excipients and polymers used and the prepared formulation was obtained using a Bruker Alpha 2 spectrometer (USA). The FTIR spectra (Fig. 3) of

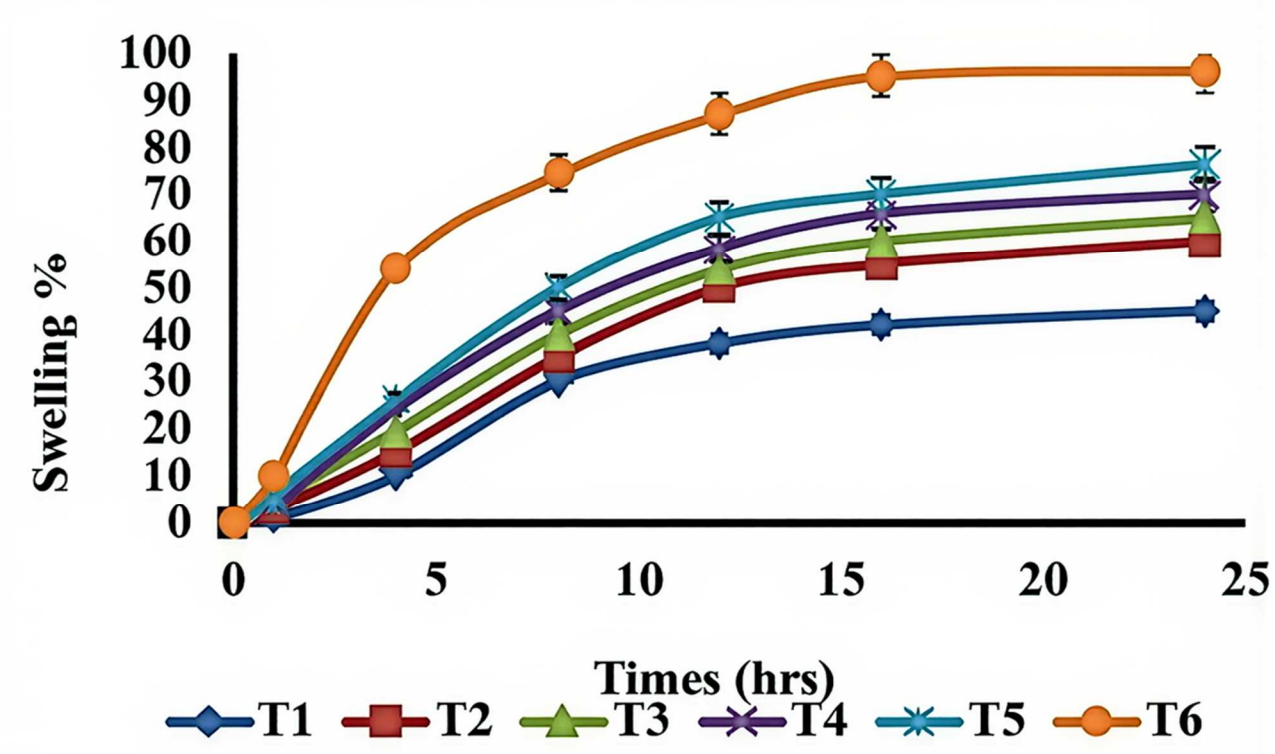

Fig.1: Swelling percentage of formulated paracetamol SR pellets

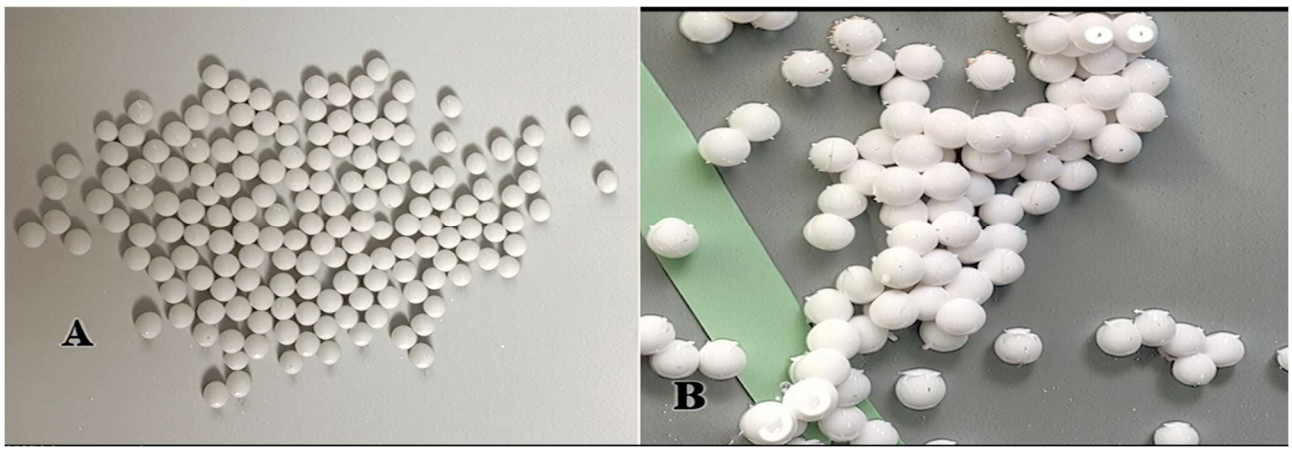

Fig. 2: Swelling study of paracetamol SR pellets, (A) Pellets at the initial stage, (B) Pellets after twelve hours study

Table 3: Drug content analysis of all the prepared formulations

Sr. No.	Trials	Results	
		Fexofenadine HCl pellets (%)	Paracetamol SR pellets (%)
1	T1	100.1 ± 0.011	99.2 ± 0.017
2	T2	99.8 ± 0.012	99.9 ± 0.016
3	T3	99.7 ± 0.015	100.0 ± 0.013
4	T4	99.1 ± 0.017	99.2 ± 0.012
5	T5	99.2 ± 0.010	99.0 ± 0.011
6	T6	99.2 ± 0.016	100.0 ± 0.010

All the results are expressed as mean ± SD of three replicates

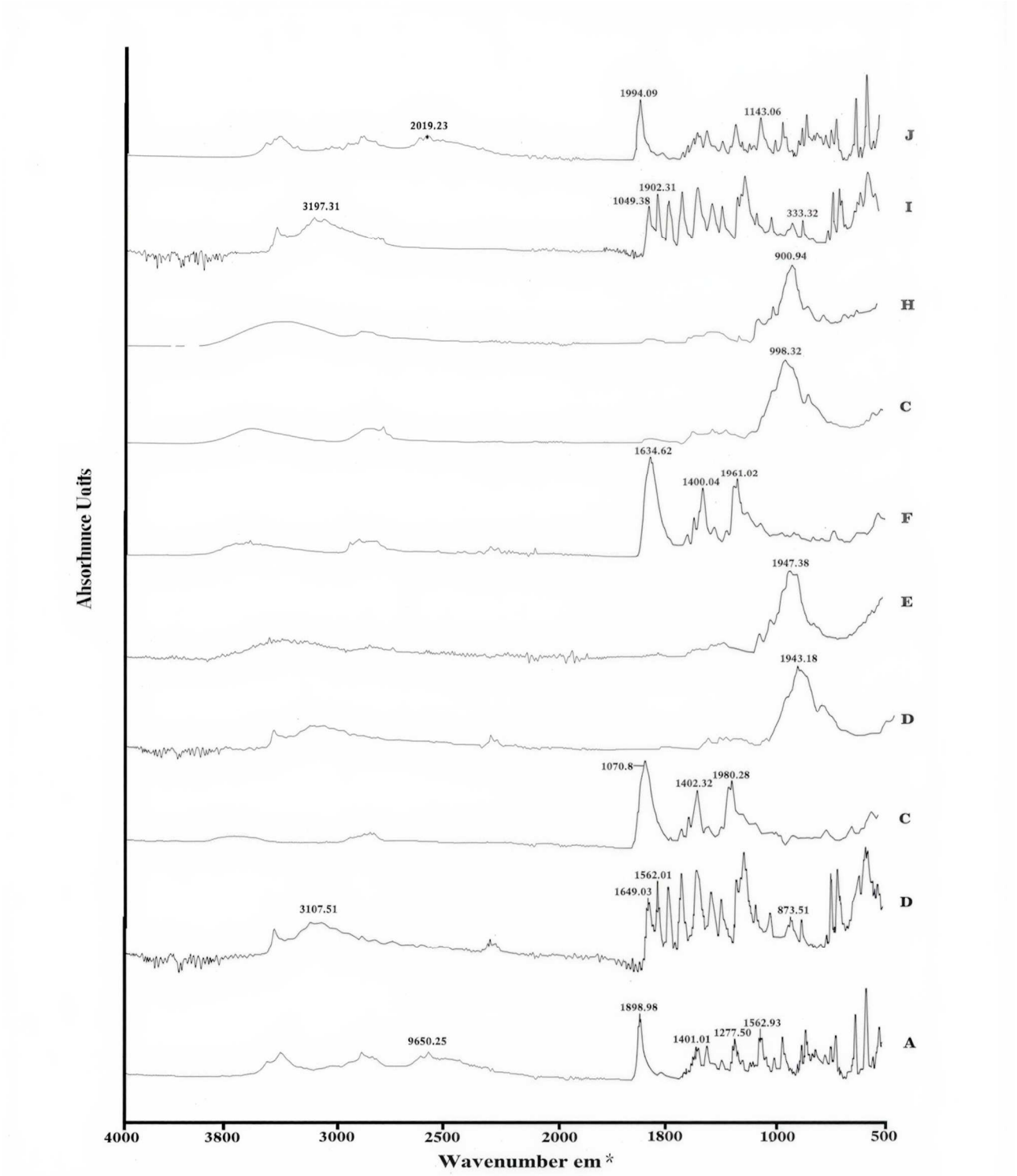

Fig. 3: FTIR spectra of all the materials used. (A) FTIR spectrum of Fexofenadine HCl pure drug; (B) FTIR spectrum of Paracetamol pure drug; (C) FTIR spectrum of Crospovidone; (D) FTIR spectrum of Microcrystalline cellulose; (E) FTIR spectrum of PVP K-30; (F) FTIR spectrum of HPMC K 100 M; (G) FTIR spectrum of Pregelatinized starch; (H) FTIR spectrum of HPMC K-15; (I) Spectrum of fabricated Paracetamol SR pellets; (J) Spectrum of prepared Fexofenadine HCl IR pellets.

Fexofenadine showed peak at 2638.23 cm^{-1} which is because of the stretching of OH group, peak at 1698.98 cm^{-1} is because of "CO" stretching, peak at 1401.89 cm^{-1} is of "C=C" stretching, peak at 1277.50 cm^{-1} is of amine "CN", peak at the wavelength of 1163.06 cm^{-1} is of "CO". The FTIR spectrum of Paracetamol showed that the peak at 3107.31 cm^{-1} is due to "CH3". The vibrational peaks at 1649.83 cm-1 and 1609.04 cm^{-1} correspond to "C=O" and "C=C" stretching, respectively. Peak at 1502.81 cm^{-1} and 1432.11 cm^{-1} is of "N H" stretching. Peaks at 835.53 cm^{-1} is assigned to "CN". The same peaks are observed in the spectra of Fexofenadine HCl IR pellets and Paracetamol SR pellets; the lack of new peaks in the Fexofenadine IR and Paracetamol SR spectra indicates that no polymorphic changes occurred in the drug product during pellet preparation.

Drug content analysis

The percentage release of Paracetamol and Fexofenadine HCl is within specified limit 90.0%-110% (Table 3). Drug contents of fexofenadine HCl Pellets ranges from minimum 99.1 ± 0.017% in T4 to maximum 100.1 ± 0.011% in T1. (Yadav, Salunkhe *et al.*, 2024).

Scanning electron microscope (SEM)

The formulation's success was confirmed using scanning electron microscopy. The SEM analysis was used to confirm the smoothness and spherical shape of the pellets. The SEM images of Paracetamol SR pellets and Fexofenadine IR pellets (Fig. 4 and Fig. 5)

X-ray diffraction (XRD)

The X-ray diffraction spectrum was determined using a Bruker D8 Advance X-ray diffractometer. The results of XRD graph of Paracetamol (11.0°, 20.40°, 20.79°, 21.16°, 32.5° and 40.0°) (Ibrahim, Tchouar *et al.*, 2025) and Fexofenadine HCl (10.0°, 15.0°, 30.7° and 40.0°) (Li, Wu *et al.*, 2021)

In-vitro drug release study

All the fabricated pellets were compared in simulated gastric fluid (TS) at regular intervals up to 24 hours for Paracetamol SR pellets and at a predetermined interval of 45 minutes for Fexofenadine HCl pellets. The results showed that the formulation "T6" performed best (Fig. 7).

Drug release kinetics

Table 4 shows the results of the drug release kinetics for all 14 formulations. All formulations were analyzed using different kinetic models, including the Higuchi model, first-order, Korsmeyer model (n value), Hixson-Crowell and zero-order kinetic models. All of the formulations followed Korsmeyer Peppas model. The value of n ranges from 0.438 to 0.862.

Statistical analysis

The analysis of variance results were tabulated in table 5.

Stability studies

Accelerated stability studies were performed on the Paracetamol SR and Fexofenadine IR pellets to evaluate their drug release, physical appearance and content of drug. No significant change in results were found after 1, 3 and 6 months which suggests that the formulations are stable at 40°C and RH 75%,

DISCUSSION

The current research is more focused towards optimization, to improve the desired outcomes and reduces adverse events. MDD have showed better results by sustaining drug release with minimum risk of dose dumping. Ultimately, these particulates played a major role in drug delivery and improves the quality of therapy. Formulations T1–T3, containing low concentrations of polymers, hence the formulated pellets exhibit good flowability, due to the low polymer content, resulting in decreased cohesion and friction between particles. When the concentration of the polymer is increased, there is a slight increase in bulk density, tapped density, angle of repose and Carr's compressibility index. Still formulations T4–T6 maintained good flow properties rather high polymer concentration. Although Carr's index, angle of repose, bulk and tapped density were slightly higher than those in T1–T3 (Yadav, Salunkhe *et al*., 2024). Generally, the flow properties of formulations do not raise any concerns regarding manufacturing of pellets (Lam and Nokhodchi, 2022). The addition of MCC pH 101 showed a significant positive impact, enhancing spheronization and reducing friability, as seen in formulations T4 and T6 (Chishti, Pathan *et al*., 2024).

Similarly, the drug content of paracetamol SR Pellets ranges from a minimum of 99.2 ± 0.017 % in T1 to a maximum of 100.0 ± 0.013 % in T3. The comparatively high drug content (fexofenadine and paracetamol) in T1, T2, T3 and T4 indicates that these preparations incorporated the maximum drug content with minimal loss during production. These fluctuations in drug content may arise due to differences in excipient interactions, processing conditions and formulation accuracy. The formulations, which contains a relatively lower concentration of polymer probably ensured that the drug is uniformly present within the granules (Yadav, Salunkhe *et al*., 2024).

XRD showed various diffraction peaks which indicated the crystalline nature of actives, while no diffraction peaks observed in the XRD graph of prepared formulation and this confirmed that the fabricated capsule containing Paracetamol SR and Fexofenadine HCl IR pellets existed in amorphous form (Fig. 6).

All of the IR formulations showed a 75-100% drug release within 45 minutes. While all SR formulations showed a continuously sustained release of drugs after 24 hours. This complies with the aim for our research work.

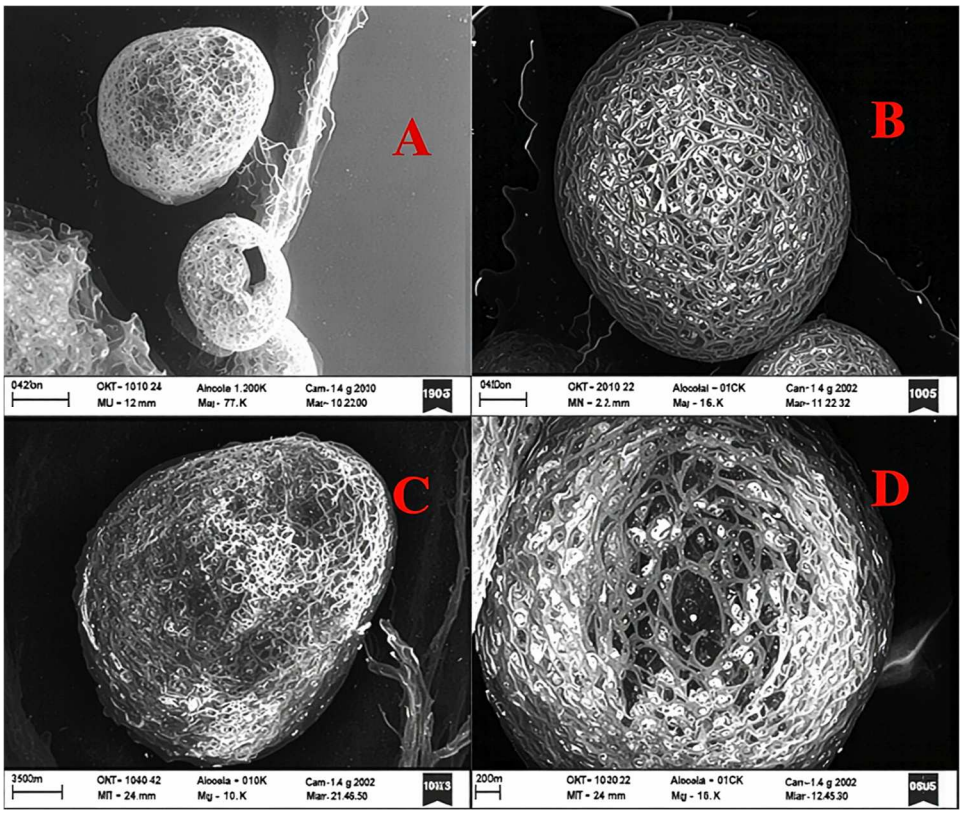

Fig. 4: SEM Analysis of paracetamol SR pellets. (A) Image captured at 179X; (B) Image captured at 282X; (C) Image captured at 313X; (D) Image captured at 492X.

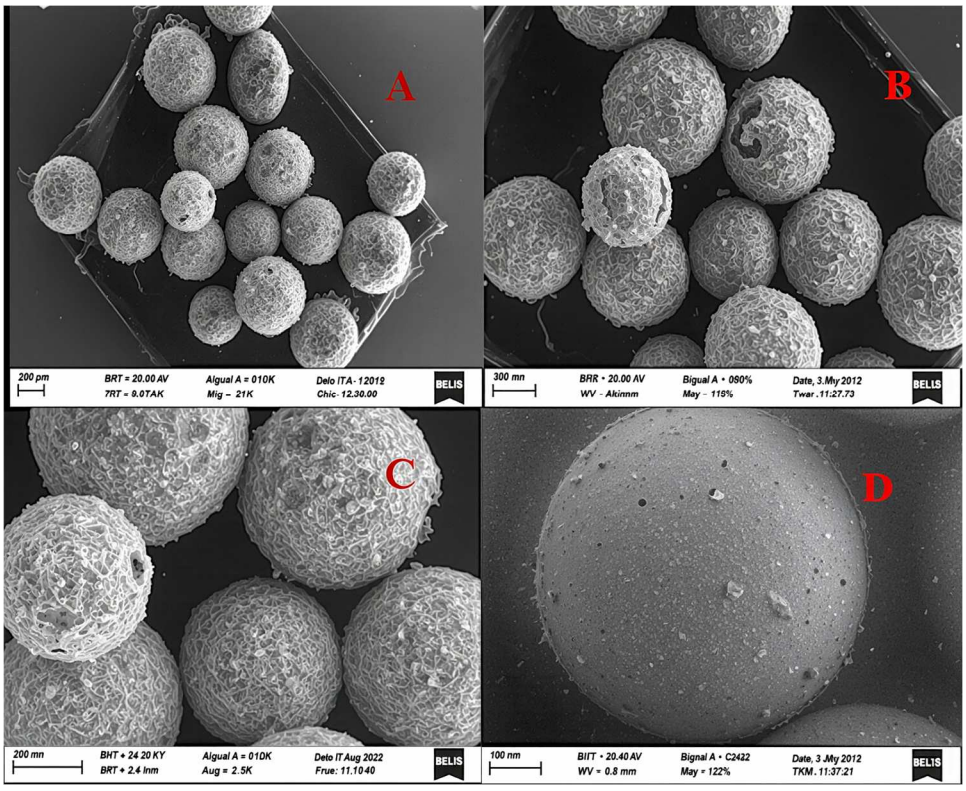

Fig. 5: SEM Analysis of fexofenadine HCl pellets at (A) Image captured at 81X; (B) Image captured at 133X; (C) Image captured at 215X; (D) Image captured at 320X.

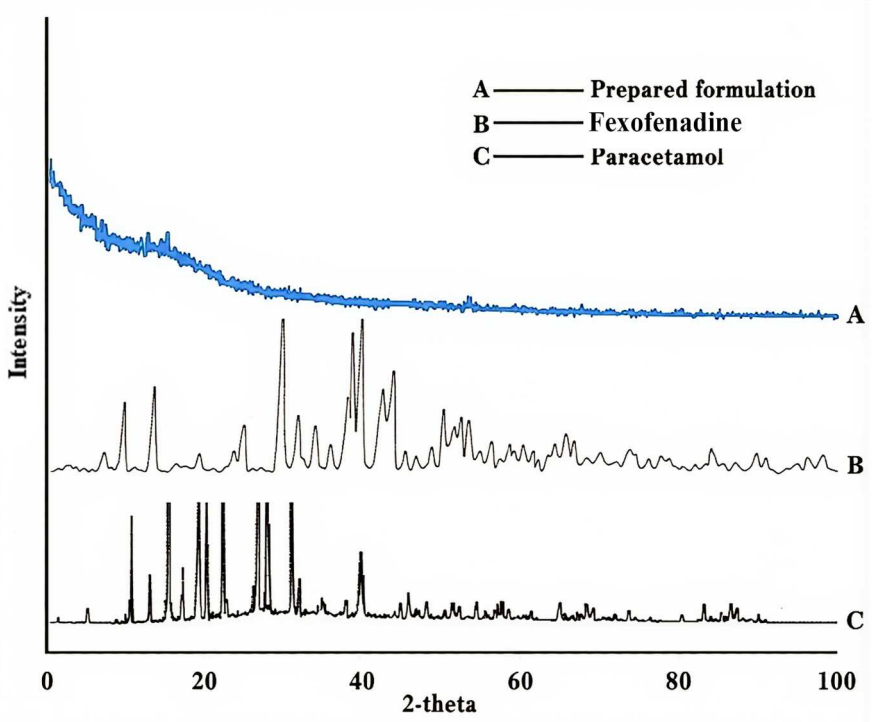

Fig. 6: X-ray diffractometer profile. (A) XRD pattern of formulated Fexofenadine HCl IR and Paracetamol SR capsule; (B) XRD pattern of pure Fexofenadine HCl; (C) XRD pattern of pure Paracetamol.

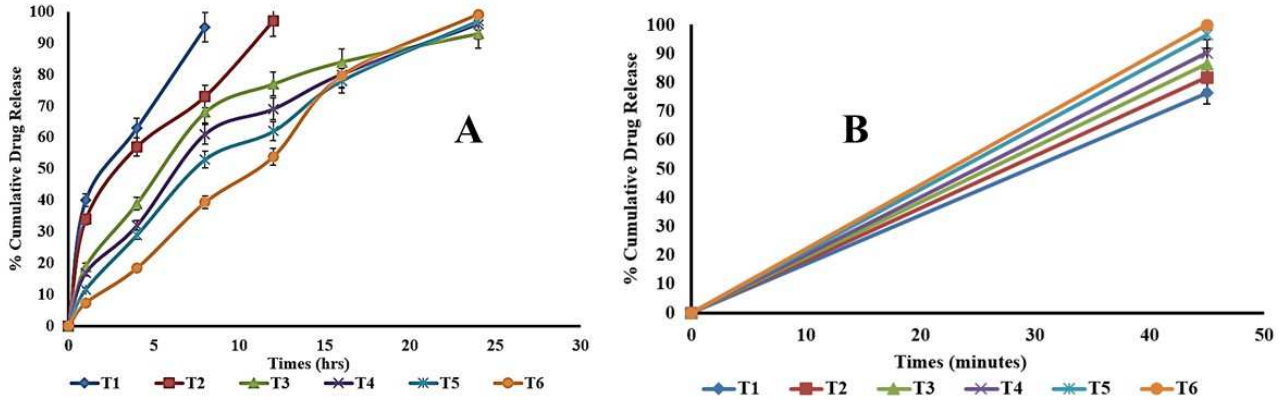

Fig. 7: Fig. 7A showed the % cumulative drug release from Paracetamol SR pellets, while Fig. 7B depicts the % cumulative drug release from Fexofenadine HCl IR pellets.

Table 0: Drug release kinetics were analyzed by applying Zero order, First order, Higuchi Model, Korsmeyers-Peppas Model and Hixson-Crowell Model.

Formulation	Zero order	First order	Higuchi model	Korsmeyer-peppas model	n	Hixson-crowell model
T1	0.8058	0.9476	0.9878	0.9913	0.442	0.9278
T2	0.7849	0.9423	0.9870	0.9915	0.438	0.9192
T3	0.6844	0.9890	0.9736	0.9779	0.448	0.9700
T4	0.8202	0.9871	0.9876	0.9890	0.534	0.9801
T5	0.9106	0.9867	0.9779	0.9957	0.634	0.9917
T6	0.9816	0.9466	0.9049	0.9900	0.862	0.9722

The results of kinetic analysis suggested that the Korsmeyers-Peppas Model was the best suitable model for prepared formulation. This model is applied on the basis of highest regression value.

Table 5: Analysis of variance (ANOVA)

ANOVA						
Source of variation	SS	df	MS	F	P-value	F crit
Between groups	5800.697	6	966.783	0.912	0.496	2.324
Within groups	44517.717	42	1059.946			
Total	50318.414	48				

The value of "F" in above table is close to the "1", it indicated that null hypothesis is true. Statistical analysis concluded that no significant difference indicated by the value of P that is greater than 0.05.

Table 6: Results of Accelerated stability studies of Fexofenadine HCl IR and Paracetamol SR pellet, after 1, 3 and 6 months.

Accelerated stability studies					
Assessment frequency (Months)			**1**	**3**	**6**
Tests (Physical, Chemical)	Acceptance criteria		April 2022	July 2022	Oct 2022
Physical Appearance					
Fexofenadine HCl IR pellets	White to off-white colored spherical shaped pellets		Complies	Complies	Complies
Paracetamol SR pellets	White to off- white colored spherical shaped pellets		Complies	Complies	Complies
Drug release					
Fexofenadine HCl	NLT 80% (Q) of the labeled amount of Fexofenadine HCl is dissolved in 45 minutes		99.69%	98.65%	97.73%
	Time intervals	Limits			
	1st hour	NMT 10%	7.32%	7.89%	6.92%
	4 hours	10% - 25%	20.32%	19.62%	19.86%
Paracetamol	8 hours	20% - 45%	35.96%	34.23%	34.01%
	12 hours	40% -60%	55.63%	53.10%	54.24%
	16 hours	NLT 70%	78.05%	77.63%	77.04%
	24 hours	NLT 80%	99.01%	98.23%	97.24%
Drug contents					
Fexofenadine HCl	90.0 % – 110.0 % of label claim.		100.0%	99.5%	98.9%
Paracetamol	90.0 % – 110.0 % of label claim.		99.2%	99.2%	99.0%

If the value of n is less than 0.5, it indicates that the formulation followed Quasi-Fickian diffusion. While a value of 0.5 indicates Fickian diffusion. Furthermore, whenever the value of n exceeds 0.5 but is less than 0.89, the release followed an anomalous or non-Fickian transport mechanism. This showed that our formulations followed both diffusion and swelling mechanism for drug release (CIMPOAE, Luca Liviu *et al*., 2021, Siddique, Zaman *et al*., 2022).

All 14 formulations were stored in an accelerated stability chamber bottle at 40°C and 75% RH for 6 months. After 1, 3 and 6 months, the % release of drug and drug content were calculated and the results revealed no significant change in pellets physical appearance, drug release and drug content (Table 6).

CONCLUSION

The SR Paracetamol and IR Fexofenadine pellets have been successfully prepared in this research, suggesting that Paracetamol pellets prepared with HPMC could be used as an oral SR drug delivery system. Excipients, solvents and polymers all contributed to the synthesis of an efficient MDDS. The release of Paracetamol from pellets was affected by input parameters such as a polymer (HPMC). XRD studies confirmed that the drug in the formulation is non-crystalline. *In-vitro* drug release analysis showed slow diffusion of dissolution media into the Paracetamol pellets due to the hydrophilicity and gelling properties of HPMC, resulting in SR for 24 hours. The Korsmeyer–Peppas model was the best fit and showed that the drug release mechanism is non-Fickian diffusion. The objective of the study has been successfully accomplished, as satisfactory

prompt release of Fexofenadine HCl and 24 hours SR of Paracetamol have been observed from the prepared optimized formulation. This method can be used to produce sustained-release formulations for other medications with a short half-life, a high risk of first-pass metabolism, frequent dosing and a high production cost.

Acknowledgment
Princess Nourah bint Abdulrahman University Researchers Supporting Project number (PNURSP2026R340), Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.

Authors' contributions
Conceptualization: M.Z, Methodology: S.N and W.S, Final drafting A.S and H.H, Review and editing by Y.A and J.A

Funding
The authors would like to thank Princess Nourah bint Abdulrahman University Researchers Supporting Project number (PNURSP2026R340), Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.

Data availability statement
All of the relevant data already incorporated in main manuscript file.

Ethical approval
Not applicable

Conflicts of interest
The authors declare no conflicts of interest.

REFERENCES

Brahim MT, Tchouar N, Ouadah K, Messaoudi M, Merah M and Messaoudi ZA (2025). Using PXRD and FT-IR to uncover the solid-state nature of paracetamol in panadol® powder: Crystalline stability and excipient interactions. *Lat. Am. J. Pharm.,* **44**(6): 503-509.

Chaerunisaa AY, Sriwidodo S and Abdassah M (2019). Microcrystalline cellulose as pharmaceutical excipient. *Pharmaceutical formulation design-recent practices*, IntechOpen, Published in London, UK, Chapter **3**: 41-62.

Chishti NA, Pathan I and Dehghan MH (2024). Formulation, optimization and evaluation of pellets loaded glipizide co amorphous mixture using central composite design to enhance solubility. *J. Res. Pharm.,* **28**(5): 1536-1549.

Cimpoae L, Luca Liviu R and Iovanov RI (2021). A study on the influence of the formulation factors on *In-vitro* release of ketoprofen from sustained release tablets. *Rom. J. Pharm. Pract,* **14**(1): 41-48.

Farooq M, Shoaib MH, Yousuf RI, Qazi F and Hanif Mjpb (2019). Development of extended release loxoprofen sodium multiparticulates using different hydrophobic polymers. *Polym. Bull.,* **76**(5): 2537-2558.

Gayke AU, Shukla K and Jain S (2021). Formulation development and evaluation of aqueous polymer dispersions (pellets) for extended release dosage forms of galantamine hydrobromide. *J. Adv. Sci. Res.,* **12**(03): 226-234.

Grohn P, Weis D, Thommes M, Heinrich S, Antonyuk SJCe and technology (2020). Contact behavior of microcrystalline cellulose pellets depending on their water content. *Chem. Eng. Technol.,* **43**(5): 887-895.

Holm TP, Kokott M, Knopp MM, Boyd BJ, Berthelsen R, Quodbach J, Lobmann KJEJoP and Biopharmaceutics (2022). Development of a multiparticulate drug delivery system for in situ amorphisation. *Eur J Pharm Biopharm.,* **180**(1): 170-180.

Ibrahim MA and Alshora DHJP (2021). Development and characterization of eudragit-RL-100-based aceclofenac sustained-release matrix pellets prepared via extrusion/spheronization. *Polymers,* **13**(22): 4034.

Kasekar NM, Singh S, Jadhav KR and Kadam VJ (2020). BCS class II drug loaded protein nanoparticles with enhanced oral bioavailability: *In-vitro* evaluation and *in-vivo* pharmacokinetic study in rats. *Drug Dev. Ind. Pharm.,* **46**(6): 955-962.

Kiran MD and Pawaskar LJ (2017). Safety and efficacy of a combination of paracetamol, phenylephrine and fexofenadine in adult patients of common cold and allergic rhinitis: Phase IV study. *World J. Pharm. Res.,* **6**(4): 1624-1634.

Lam M and Nokhodchi A (2022). The combination of liqui-mass system and pelletization to improve pharmaceutical properties of hydrochloro-thiazide. *Dissolution Technol,* **29**(3): 128-136.

Li S, Wu H, Zhao Y, Zhang R, Wang Z and Han J (2021). Solid form and phase tr ansformation properties of fexofenadine hydrochloride during wet granulation process. *Pharmaceutics.,* **13**(6): 802.

Patel H, Gohel Mukesh (2019). A review on enteric coated pellets composed of core pellets prepared by extrusion-spheronization. *Recent Pat Drug Deliv Formul.,* **13**(2): 83-90.

Raval MK, Ramani RV and Sheth N.R (2013). Formulation and evaluation of sustained release enteric-coated pellets of budesonide for intestinal delivery. *Int. J. Pharm. Investig.,* **3**(4): 203-211.

Shabbir N, Zaman M, Siddique W, Mudassir M, Alhuthali HM, Alzahrani AR, Rehman ZU and Imran M (2026). Development and validation of an RP-HPLC method for simultaneous estimation of atorvastatin calcium and ezetimibe. *Acta Chromatographica*, 1326-2025.

Sharma S, Sarkar G, Srestha B, Chattopadhyay D and Bhowmik M (2019). In-situ fast gelling formulation for oral sustained drug delivery of paracetamol to dysphagic patients. *Int J Biol Macromol*, **134**(2019): 864-868.

Siddique W, Zaman M, Sarfraz RM, Butt MH, Rehman AU, Fassih N, Albadrani GM, Bayram R, Alfaifi MY and Abdel-Daim MM (2022). The development of

eletriptan hydrobromide immediate release buccal films using central composite rotatable design: An *in-vivo* and *in-vitro* approach. *Polymers,* **14**(19): 3981.

Soltani F, Kamali H, Akhgari A, Garekani HA, Nokhodchi A and Sadeghi FJAPT (2022). Different trends for preparation of budesonide pellets with enhanced dissolution rate. *Adv. Powder Technol.,* **33**(8): 103684.

Tumuluru JS (2018). Effect of pellet die diameter on density and durability of pellets made from high moisture woody and herbaceous biomass. *Carbon Resour. Convers,* **1**(1): 44-54.

Van der Heijden L, Mian P, Hias J, de Winter B, Tournoy J, Van der Linden L, Tibboel D, Walgraeve K, Flamaing J, Koch BJD and Aging (2022). Highly variable paracetamol pharmacokinetics after multiple oral dosing in frail older people: A population pharmacokinetic analysis. *Drugs & Aging*., **39**(1): 83-95.

Vlad RA, Pintea A, Pintea C, Redai EM, Antonoaea P, Bîrsan M and Ciurba A (2025). Hydroxypropyl methylcellulose—A key excipient in pharmaceutical drug delivery systems. *Pharmaceutics,* **17**(6): 784.

Wagh MRA, Surawase RK (2020). Formulation and development of sustained release pellets of nifedipine by fluidized bed processor. *Res. J. Pharm. Technol.,* **13**(4): 1757-1761.

Wang J, Kan S, Chen T, Liu JJPd and technology (2015). Application of quality by design (QbD) to formulation and processing of naproxen pellets by extrusion–spheronization. *Pharm. Dev. Technol.,* **20**(2): 246-256.

Xia Y, Shi CY, Fang JG, Wang WQ (2018). Approaches to developing fast release pellets via wet extrusion-spheronization. *Pharm. Dev. Technol.,* **23**(5): 432-441.

Yadav VD, Salunkhe DS and Lokhande VY (2024). Multiparticulate drug delivery of losartan potassium via extrusion-spheronization: Formulation and dissolution comparisons. *BIO I,* **5**(33): 1-11.