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Extended-Release Diclofenac Sodium and Punicic Acid Matrix Tablets: Formulation and In Vitro Evaluation

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Abstract

Background: Chronic inflammatory pain needs analgesia that is steady over the day, but immediate-release diclofenac sodium causes peaks and troughs in plasma concentration and requires frequent dosing. **Aim:** To formulate and evaluate extended-release (ER) matrix tablets containing diclofenac sodium (75 mg) and punicic acid (25 mg), an anti-inflammatory conjugated fatty acid of pomegranate seed oil, for anti-inflammatory pain management. **Methods:** Six batches (F1–F6, 250 mg per tablet) were prepared by wet granulation using hypromellose (HPMC) K4M and K15M as release-retarding polymers. The active ingredient blend was characterised by angle of repose, bulk and tapped density, compressibility index and Hausner's ratio; drug–excipient compatibility was tested by physical observation and FTIR. Dissolution was run for 12 h and compared with a specification of <30% at 2 h, 30–70% at 6 h and ≥85% at 12 h. Release data were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models, and profiles were compared by the similarity factor (f2), dissolution efficiency (DE) and mean dissolution time (MDT). **Results:** The active blend showed excellent flow (angle of repose 22.5°, Carr's index 3.71%, Hausner's ratio 1.04) and no incompatibility with the excipients. F2, F5 and F6 met the release specification. F5, containing 40 mg of HPMC K15M and no CMC sodium, released 14%, 44% and 92% of diclofenac sodium at 2, 6 and 12 h with near-linear kinetics (zero-order R^2 = 0.9996; Korsmeyer–Peppas R^2 = 0.9999, n = 1.05), consistent with swelling- and relaxation-controlled release. The reproducibility batch F6 was similar to F5 (f2 = 76). **Conclusion:** F5 is a promising 12 h ER matrix tablet of diclofenac sodium and punicic acid. All release data refer to diclofenac sodium; punicic acid release was not quantified separately and needs its own assay (HPLC or GC).

Keywords: diclofenac sodium; punicic acid; extended release; HPMC matrix tablet; wet granulation; release kinetics

I. Introduction

1.1 Inflammation and pain

Inflammation is the protective response of the body to infection, tissue injury and other harmful stimuli. In its acute form it is self-limiting: blood flow and vascular permeability increase, leukocytes reach the damaged tissue, the cause is removed and the tissue is repaired [1]. When the stimulus persists or the resolution mechanisms fail, inflammation becomes chronic and contributes to the development of many diseases, including arthritis, cardiovascular disease, metabolic disorders and cancer [2]. The cardinal signs of inflammation are redness, heat, swelling, pain and loss of function, and pain is usually the symptom that drives patients to seek treatment.

At the molecular level, inflammation is coordinated by chemical mediators such as prostaglandins, histamine, bradykinin and cytokines, which are released by activated immune and tissue cells [3,4]. The release of these mediators is controlled by intracellular signalling pathways, notably nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPK) and the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway [5–7]. Prostaglandins formed by the cyclooxygenase (COX) enzymes sensitise peripheral nerve endings and amplify the perception of pain, which is why inhibition of this enzyme system is the basis of most analgesic and anti-inflammatory therapy [8]. Persistent inflammatory pain is a major cause of reduced quality of life, and it requires treatment that is effective throughout the day and over long periods [9].

International Journal of Pharmaceutical research and Applications
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1.2 Diclofenac sodium and the need for extended release

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used drugs for inflammatory pain. They act mainly by inhibiting COX enzymes and thereby reducing prostaglandin synthesis [8]. Their long-term use, however, is limited by adverse effects, particularly serious gastrointestinal events such as ulceration and bleeding, which increase with the duration of exposure and with the peak drug concentration [11,12]. Diclofenac sodium is one of the most commonly prescribed NSAIDs and is used in rheumatoid arthritis, osteoarthritis, musculoskeletal injuries and post-operative pain [13,14]. It is well absorbed from the gastrointestinal tract, but its plasma half-life is short, about 1–2 h, so an immediate-release tablet must be taken two to four times a day to maintain the effect. Frequent dosing causes peaks and troughs in plasma concentration: the peaks increase the risk of adverse effects, and the troughs allow the pain to return. Complex regimens also lower adherence, which is a well-recognised problem in the treatment of chronic conditions [10].

Extended-release (ER) dosage forms are designed to release the drug slowly and at a controlled rate over many hours. They maintain the plasma concentration within the therapeutic range, reduce the dosing frequency, improve patient compliance and may lower the incidence of concentration-related adverse effects [15–17]. Several technologies are available, including matrix systems, osmotic pumps, reservoir systems, coated multiparticulates and ion-exchange complexes. Among them, hydrophilic matrix tablets are the most widely used because they are simple to manufacture on conventional equipment, cost-effective, robust and suitable for high drug loads [18,19]. Matrix tablets of diclofenac sodium have been studied extensively, and they are an established approach for converting the drug into a twice-daily or once-daily product [13,18].

1.3 HPMC matrices

Hypromellose (hydroxypropyl methylcellulose, HPMC) is the polymer most often chosen for hydrophilic matrices. When the tablet contacts water, the polymer at the surface hydrates and swells into a viscous gel layer. The drug then leaves the tablet by diffusion through this gel and by erosion of the outer layer, while the dry core recedes as water penetrates inwards [20]. The viscosity grade and the amount of HPMC are the main variables controlling the rate of release: higher-viscosity grades such as K15M form a stronger and more slowly eroding gel than lower-viscosity grades such as K4M. Release from such matrices is described by empirical and semi-empirical models (zero-order, first-order, Higuchi and Korsmeyer–Peppas), and the release exponent of the Korsmeyer–Peppas model helps to identify whether diffusion, polymer relaxation or both govern the process [20,23]. Wet granulation is commonly used to prepare such tablets because it improves the flow and compressibility of fine polymer and filler powders and gives a uniform distribution of the drug.

1.4 Punicic acid and rationale for the combination

Punicic acid (18:3 cis-9, trans-11, cis-13) is a conjugated linolenic acid with three conjugated double bonds, and it is the principal fatty acid of pomegranate seed oil. It has been reported to have anti-inflammatory, antioxidant and metabolic effects, which appear to act largely by suppressing the expression of pro-inflammatory cytokines and by enhancing endogenous antioxidant defences, rather than through the classical COX pathway of NSAIDs [21,22]. Because its mechanism differs from that of diclofenac, punicic acid is of interest as a complementary agent: the two compounds act on different parts of the inflammatory cascade, and the combination may therefore give a broader anti-inflammatory effect than diclofenac alone, possibly at a lower diclofenac exposure. Punicic acid is, however, a lipophilic fatty acid with a limited duration of action in the body, and it would also benefit from a sustained delivery system. An ER matrix tablet that delivers both ingredients gradually would therefore be a rational dosage form for long-term inflammatory pain.

1.5 Aim of the study

The aim of this work was to design and prepare ER matrix tablets containing diclofenac sodium (75 mg) and punicic acid (25 mg) using HPMC K4M and K15M as release-retarding polymers; to characterise the active blend by pre-formulation and drug–excipient compatibility studies; to evaluate the tablets; and to analyse the in vitro release pattern, release kinetics and reproducibility of the formulations against a 12 h release specification.

International Journal of Pharmaceutical research and Applications
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II. Materials and Methods

2.1 Materials and equipment

The materials, their grades and their functions are listed in Table 1. Instacoat Yellow (a ready-mix film-coating system) was used for the coating of batches F4–F6, and purified water was used as the granulating and coating solvent.

Table 1. Materials used and their functions

Material	Grade	Function
Diclofenac sodium	IP	Active ingredient (NSAID)
Punicic acid	Pharma	Active ingredient (anti-inflammatory fatty acid)
HPMC K4M	USP/NF	Matrix-forming, release-retarding polymer
HPMC K15M	USP/NF	Matrix-forming, release-retarding polymer (high viscosity)
CMC sodium	IP	Release modifier (F1–F3 only)
Lactose monohydrate	USP	Diluent
Povidone K30	USP	Binder
Colloidal silicon dioxide	USP	Glidant
Magnesium stearate	USP	Lubricant
Instacoat Yellow	–	Film coat (F4–F6)

The equipment used was a rapid mixer granulator, fluid-bed dryer, multimill, octagonal blender, 8-station tablet compression machine, Pfizer-type hardness tester, friabilator, electronic balance, hot-air oven, sonicator, melting point apparatus, UV-visible spectrophotometer (Shimadzu 1900, Japan), FTIR spectrometer (Bruker, Germany) and USP dissolution test apparatus (Prolab, India).

2.2 Pre-formulation studies of the active blend

The colour, odour and physical form of the active ingredient blend were observed visually. The melting point was determined by the capillary method. Solubility was assessed by adding 100 mg of the blend to 100 mL of each solvent (water, methanol, chloroform, acetonitrile, acetic acid and triethylamine) with shaking, and was expressed in the descriptive terms of the pharmacopoeia. Loss on drying (LOD) was determined by drying about 1 g at 105 °C to constant weight, and assay was done by UV spectrophotometry.

For the flow properties, the bulk density (weight W divided by the untapped volume V_0) and the tapped density (W divided by the volume V_t after tapping to a constant volume) were measured in a graduated cylinder. Carr's compressibility index and Hausner's ratio were calculated from these densities, and the angle of repose was calculated from the height h and the radius r of the cone formed by the powder poured through a funnel onto a flat surface:

$$\textit{Carr's index (\%)} = [(\text{Tapped density} - \text{Bulk density}) / \text{Tapped density}] \times 100$$

$$\textit{Hausner's ratio} = \text{Tapped density} / \text{Bulk density}$$

$$\textit{Angle of repose, } \theta = \tan^{-1}(h / r)$$

$$\textit{Loss on drying (\%)} = [(\text{Initial weight} - \text{Dried weight}) / \text{Initial weight}] \times 100$$

The results were interpreted with the standard flow scale (Table 2).

Table 2. Flow properties and the corresponding flow description

Flow description	Carr's index (%)	Hausner's ratio	Angle of repose (°)
Excellent	≤10	1.00–1.11	≤30
Good	11–15	1.12–1.18	31–35
Fair	16–20	1.19–1.25	36–40
Passable	21–25	1.26–1.34	41–45
Poor	26–31	1.35–1.45	46–55
Very poor	32–37	1.46–1.59	56–65
Very, very poor	>38	>1.60	>66

International Journal of Pharmaceutical research and Applications
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2.3 Standard calibration curve

A stock solution of diclofenac sodium was prepared in phosphate buffer (pH 6.8) and diluted serially to give concentrations within the Beer–Lambert range. The absorbance of each dilution was measured at the wavelength of maximum absorbance (about 276 nm), and absorbance was plotted against concentration. The calibration curve was used to calculate the drug content and the amount of drug released.

2.4 Drug–excipient compatibility

The active blend was mixed with each excipient in a fixed ratio (1:1 with HPMC K4M and CMC sodium; 1:0.5 with HPMC K15M and povidone; 1:0.1 with colloidal silicon dioxide; 1:0.25 with magnesium stearate; 1:5 with lactose monohydrate). The mixtures were sifted through a #40 sieve, sealed in 10 mL glass vials with aluminium seals and rubber stoppers, and stored at 25 °C/60% RH, together with the active blend alone as a control. The samples were examined for colour change, caking and liquefaction on days 15 and 30. FTIR spectra of the active blend with HPMC K4M, HPMC K15M, lactose monohydrate and povidone were also recorded to check for shifts or loss of characteristic peaks.

2.5 Formulation design

Six batches (F1–F6) of 100 tablets each (250 mg per tablet) were designed to study the effect of the polymer grade and amount on the release (Table 3). Each tablet contained 75 mg of diclofenac sodium and 25 mg of punicic acid. Batches F1–F3 contained mainly the low-viscosity HPMC K4M (40–41 mg including the extragranular portion), 10–15 mg of HPMC K15M and 10–12 mg of CMC sodium. Batches F4–F6 contained 40 mg of the high-viscosity HPMC K15M (30 mg intragranular and 10 mg extragranular) and no CMC sodium, and were film-coated. F6 was prepared with the composition of F5 to test reproducibility.

Table 3. Composition of the tablets (mg per tablet)

Ingredient	F1	F2	F3	F4	F5	F6
Diclofenac sodium	75	75	75	75	75	75
Punicic acid	25	25	25	25	25	25
HPMC K15M (intragranular)	15	15	10	30	30	30
HPMC K4M (intragranular)	30	31	30.5	21	11.5	11
CMC sodium	12	10	12	–	–	–
Lactose monohydrate	75	76	79.5	81	90.5	91
Povidone K30	5	5	5	5	5	5
Colloidal silicon dioxide	1	1	1	1	1	1
HPMC K15M (extragranular)	–	–	–	10	10	10
HPMC K4M (extragranular)	10	10	10	–	–	–
Magnesium stearate	2	2	2	2	2	2
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	250	250	250	250	250	250

2.6 Manufacturing process

The tablets were prepared by wet granulation, because the fine HPMC and lactose powders flow poorly and segregate, and granulation improves flow, compressibility and uniformity of drug content. The process is summarised in Figure 1 and was carried out as follows.

International Journal of Pharmaceutical research and Applications
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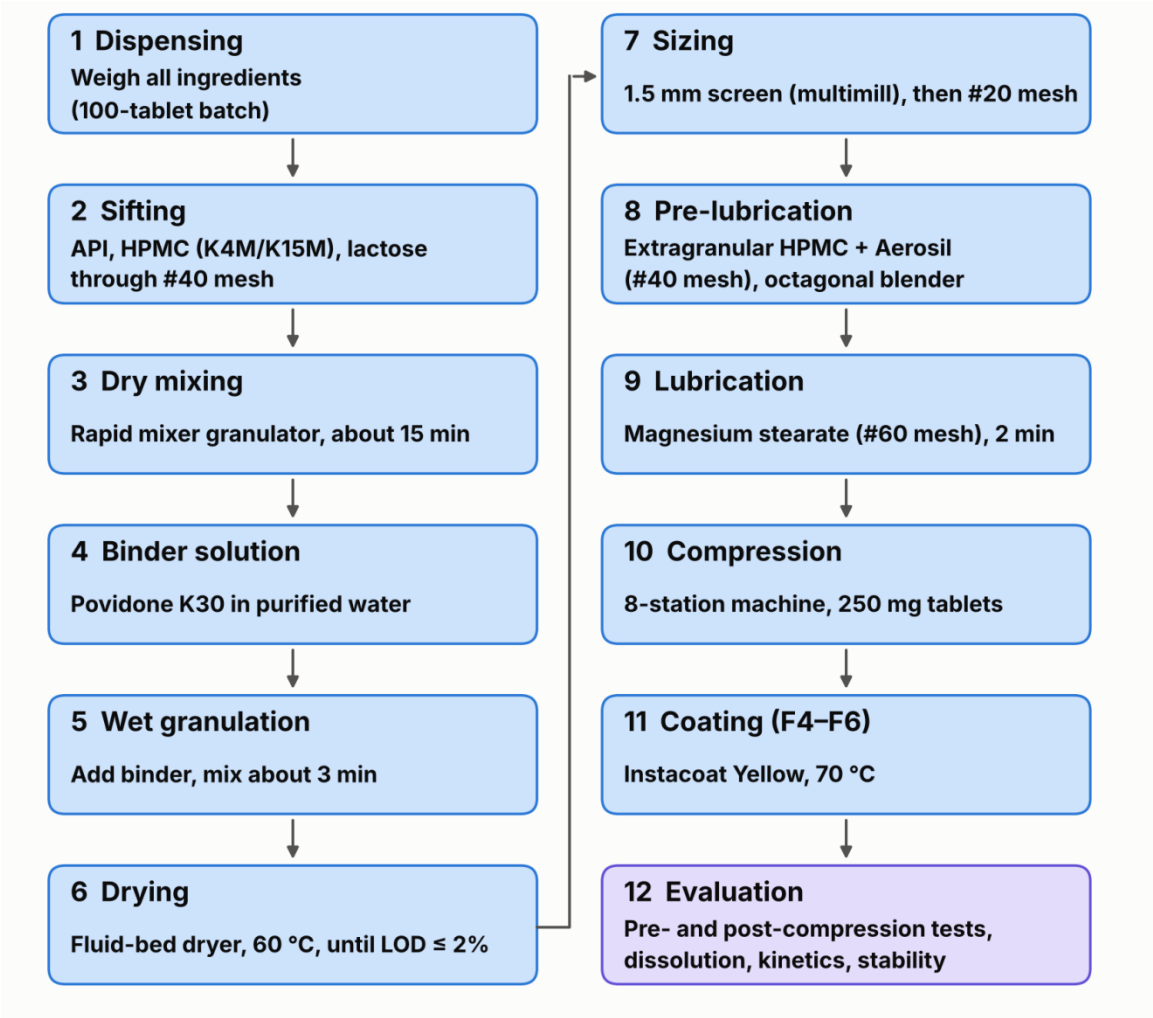

Figure 1. Flow chart of the manufacturing process of the extended-release tablets.

1. **Dispensing:** all ingredients were weighed accurately as per Table 3 and labelled.
2. **Sifting:** diclofenac sodium and punicic acid were mixed to form the active blend; the blend, the intragranular HPMC and lactose monohydrate were sifted through a #40 sieve.
3. **Dry mixing:** the sifted materials were mixed in a rapid mixer granulator for about 15 min.
4. **Binder solution:** povidone K30 was dissolved in a sufficient quantity of purified water.
5. **Granulation:** the binder solution was added slowly to the dry mix, and mixing was continued at high speed for about 3 min to form granules.
6. **Drying:** the wet granules were dried in a fluid-bed dryer at 60 °C to a loss on drying of not more than 2%.
7. **Sizing:** the dried granules were milled through a 1.5 mm screen in a multimill and passed through a #20 sieve.
8. **Pre-lubrication:** the extragranular HPMC and colloidal silicon dioxide, sifted through a #40 sieve, were blended with the sized granules in an octagonal blender.
9. **Lubrication:** magnesium stearate, sifted through a #60 sieve, was added and mixed for 2 min.
10. **Compression:** the blend was compressed into 250 mg tablets on an 8-station machine, and weight, hardness and thickness were checked during compression.

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1021-1031 www.ijprajournal.com ISSN:2456-4494

11. **Coating (F4–F6):** the tablets were coated at 70 °C with a suspension of 25 g Instacoat Yellow in 250 mL of purified water, stirred for about 20 min.

2.7 Evaluation of the tablets

The appearance, diameter and thickness of the tablets were recorded. Hardness was measured with a hardness tester. Friability was determined in a friabilator on a sample of tablets that were weighed before (W_0) and after (W) tumbling, and was calculated as shown below; a loss of not more than 1% is acceptable. For weight variation, 20 tablets were weighed individually and compared with their average weight; for tablets weighing 130–324 mg the pharmacopoeial limit is ±7.5%. For drug content, 20 tablets were weighed and powdered, a quantity equivalent to the labelled diclofenac sodium was dissolved in phosphate buffer (pH 6.8) with the aid of a sonicator, filtered and diluted, and the absorbance was read at about 276 nm against the calibration curve.

$$\textit{Friability (\%)} = [(W_0 - W) / W_0] \times 100$$

$$\textit{Weight variation (\%)} = [(\text{Individual weight} - \text{Average weight}) / \text{Average weight}] \times 100$$

2.8 In vitro dissolution

Release was studied in the USP dissolution apparatus at 37 ± 0.5 °C and 50 rpm. The medium was simulated gastric fluid (pH 1.2) for the first 2 h and simulated intestinal fluid (pH 6.8) up to 12 h. Samples were withdrawn at 2, 6 and 12 h, replaced with an equal volume of fresh medium, filtered and analysed by UV spectrophotometry, and the cumulative percentage released was calculated. The release was compared with the specification of less than 30% at 2 h, 30–70% at 6 h and not less than 85% at 12 h. Diclofenac sodium was the marker drug: the UV maximum of punicic acid (about 270 nm, conjugated triene) overlaps with that of diclofenac sodium (about 276 nm), so punicic acid could not be quantified separately by this method.

2.9 Analysis of the release data

The release data were fitted by linear regression to four models (Q is the cumulative percentage released at time t, and k is the rate constant of each model), and the model with the highest coefficient of determination (R^2) was taken as the best fit:

$$\textit{Zero-order: } Q = k_0 t$$

$$\textit{First-order: } \log(100 - Q) = \log 100 - (k_1 t / 2.303)$$

$$\textit{Higuchi: } Q = k_H \sqrt{t}$$

$$\textit{Korsmeyer–Peppas: } \log Q = \log k + n \log t$$

The release exponent n was obtained from the slope of the Korsmeyer–Peppas plot [23,24]. For a cylindrical tablet, $n \leq 0.45$ indicates Fickian diffusion, $0.45 < n < 0.89$ anomalous (non-Fickian) transport, $n = 0.89$ case-II transport and $n > 0.89$ super case-II transport, in which polymer relaxation and erosion dominate [23].

The profiles were compared by three model-independent parameters. The similarity factor f2 compares a test profile with a reference (Rt and Tt are the percentages released by the reference and the test at time t, and n is the number of time points), and a value of 50–100 means that the profiles are similar [25]. The dissolution efficiency (DE) is the area under the release curve up to 12 h, calculated by the trapezoidal rule, expressed as a percentage of the rectangle of 100% release over the same time [26]. The mean dissolution time (MDT) is the weighted mean time at which the drug is released (t_{mid} is the mid-point of each sampling interval and ΔQ the amount released in it):

$$f_2 = 50 \times \log\{[1 + (1/n) \Sigma (Rt - Tt)^2]^{(-0.5)} \times 100\}$$

$$\textit{DE (\%)} = [\text{Area under the release curve up to 12 h} / (100 \times 12)] \times 100$$

$$\textit{MDT} = \Sigma (t_{mid} \times \Delta Q) / \Sigma \Delta Q$$

III. Results and Discussion

3.1 Pre-formulation studies

The flow properties of the active blend were excellent on all three measures (Table 4): the angle of repose was 22.5°, Carr's index was 3.71% (from a bulk density of 0.545 g/cm³ and a tapped density of 0.566 g/cm³) and Hausner's ratio was 1.04. All three fall in the "excellent" class of the flow scale (Table 2). Loss on drying (1.65%) and assay (96.82%) met the required standards. These values describe the active blend alone. The final powder blend also contains fine HPMC and lactose, which flow poorly and tend to segregate, so wet granulation remained necessary to obtain good flow, compressibility and content uniformity during compression.

Table 4. Pre-formulation results of the active blend

Parameter	Result
Angle of repose	22.5°
Bulk density	0.545 g/cm³
Tapped density	0.566 g/cm³
Carr's index	3.71%
Hausner's ratio	1.04
Loss on drying	1.65%
Assay	96.82%

International Journal of Pharmaceutical research and Applications
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3.2 Drug–excipient compatibility

The physical observation of the active blend with each excipient (ratios in Section 2.4, 25 °C/60% RH) after 15 and 30 days and the FTIR spectra of the blend with HPMC K4M, HPMC K15M, lactose monohydrate and povidone gave satisfactory results. No incompatibility was found, so all the excipients were accepted for the formulation.

3.3 In vitro release and compliance with the specification

The in vitro release of the six batches is shown in Table 5 and Figure 2. At 2 h all batches released less than 30% (12–20%), so none showed a burst release. At 6 h, F1 (74%) was above the upper limit of 70%, F3 (70%) was at the limit, and F2 (66%) was close to it, whereas F5 (44%) and F6 (42%) were well inside the 30–70% window and F4 (30%) was at the lower limit. At 12 h, F1 (82%), F3 (84%) and F4 (78%) did not reach the required 85%, whereas F2 (87%), F5 (92%) and F6 (88%) did. F2, F5 and F6 therefore met the specification at all three time points. F2 had already released 66% at 6 h and then levelled off, whereas F5 and F6 released almost linearly over the whole 12 h.

Table 5. Cumulative release of diclofenac sodium (%)

Time	F1	F2	F3	F4	F5	F6	Specification
2 h	20	15	16	15	14	12	<30%
6 h	74	66	70	30	44	42	30–70%
12 h	82	87	84	78	92	88	≥85%

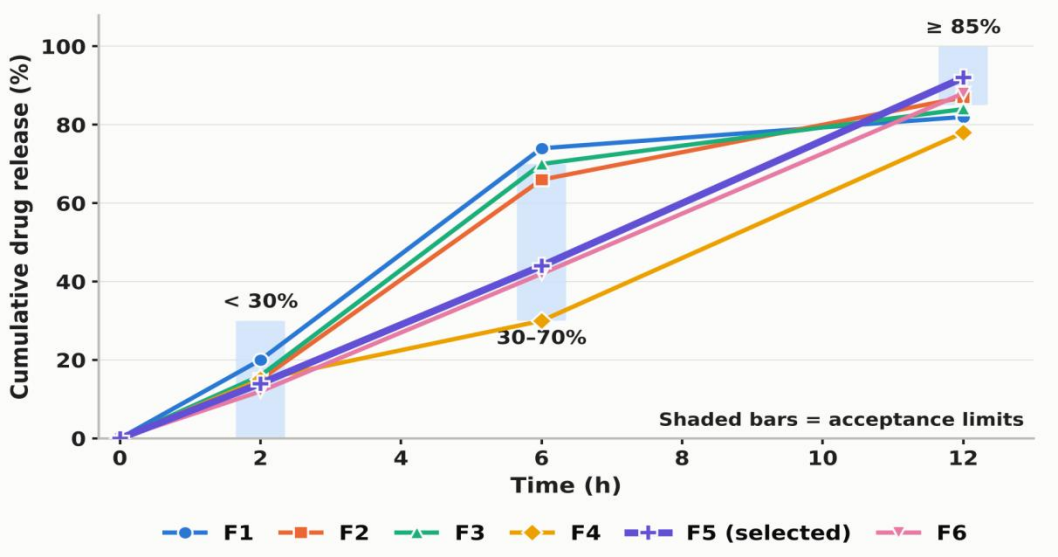

Figure 2. Release profiles of F1–F6 against the acceptance limits (shaded bars).

3.4 Effect of the formulation variables

The grade and amount of HPMC were the main factors controlling the release (Table 6). F1–F3 contained 40–41 mg of the low-viscosity HPMC K4M (including the extragranular portion) and only 10–15 mg of HPMC K15M. They released 66–74% within 6 h and then levelled off, which is the falling-rate pattern of a weak gel layer. When 40 mg of the high-viscosity K15M was used (F4–F6), the 6 h release fell to 30–44%, because a more viscous gel layer forms a stronger barrier to water penetration and to diffusion of the drug [20]. F4 retarded the release too strongly and failed the 12 h limit, mainly because it contained the largest total amount of HPMC (61 mg, against 51.5 mg in F5 and 51 mg in F6). F5 and F6, with a moderate total amount of polymer and a high proportion of K15M, gave the desired profile. In F1–F3 the water-soluble CMC sodium (10–12 mg) may also have opened the gel structure and accelerated the release. F4–F6 were additionally film-coated and free of CMC sodium, so the effect of the polymer grade cannot be separated completely from these two factors; a design in which only one variable is changed at a time would be needed to do so.

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1021-1031 www.ijprajournal.com ISSN:2456-4494

Table 6. Formulation variables and release of the batches

Batch	HPMC K4M (mg)	HPMC K15M (mg)	Total HPMC (mg)	CMC sodium (mg)	Coated	Release at 6 h (%)	Release at 12 h (%)	Specification met
F1	40	15	55	12	No	74	82	No
F2	41	15	56	10	No	66	87	Yes
F3	40.5	10	50.5	12	No	70	84	No
F4	21	40	61	–	Yes	30	78	No
F5	11.5	40	51.5	–	Yes	44	92	Yes
F6	11	40	51	–	Yes	42	88	Yes

3.5 Release kinetics and mechanism

F5 was selected for the kinetic analysis because its profile best matched the specification. It followed the Korsmeyer–Peppas model (R^2 = 0.9999) and the zero-order model (R^2 = 0.9996) best, followed by the Higuchi model (0.981); the first-order model gave the poorest fit (0.944) (Figure 3). The release exponent was n = 1.05, which is above 0.89 for a cylindrical tablet and indicates super case-II transport: release is controlled by swelling and relaxation of the polymer chains and by erosion of the gel layer, together with diffusion [20,23]. In a hydrated HPMC matrix the swelling front moves inwards, the diffusion front lies in the gel, and the erosion front moves at the outer surface; when the movement of the fronts is balanced, an almost constant release rate results. Similar anomalous release has been reported for other HPMC- and Methocel-based matrix systems that were analysed with the same models [27,28].

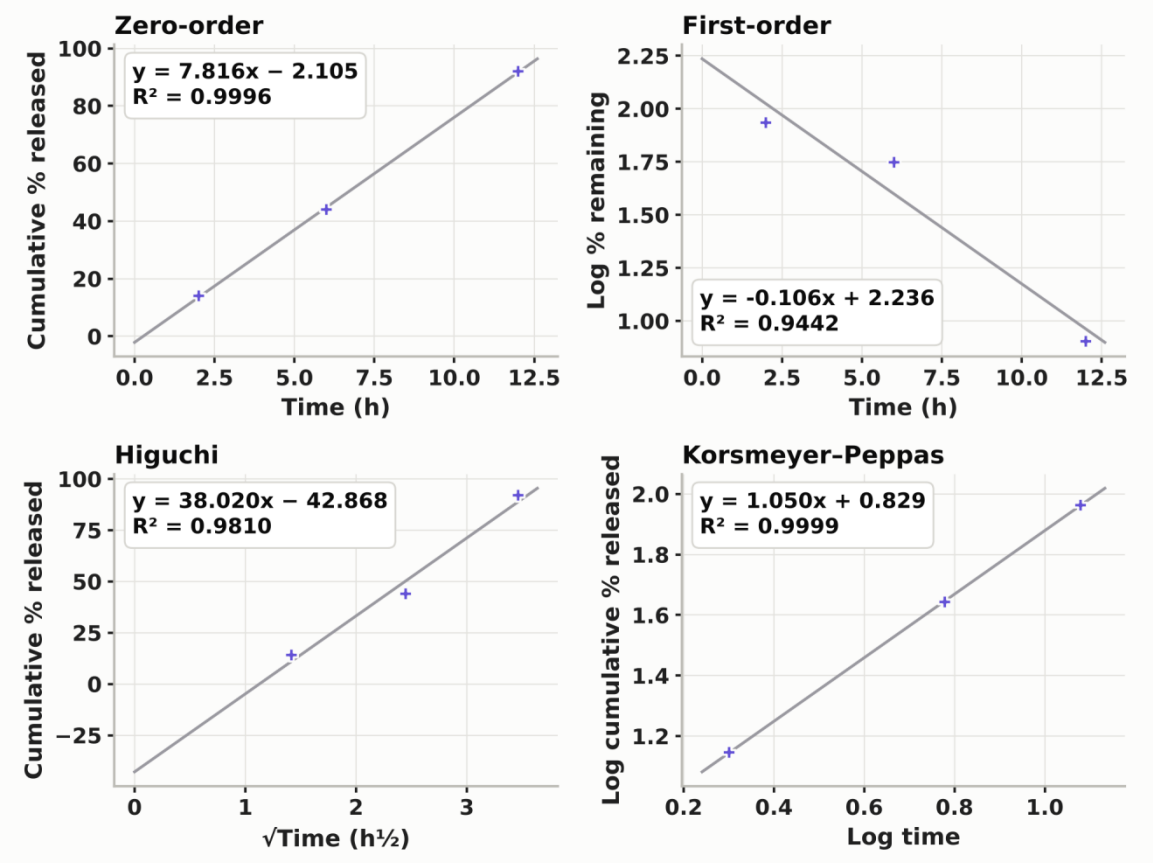

Figure 3. Release kinetics of the selected batch F5: zero-order, first-order, Higuchi and Korsmeyer–Peppas plots.

International Journal of Pharmaceutical research and Applications
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The same four models were then fitted to all six batches (Table 7). F2 and F3 were best described by the first-order model, F1 by the Korsmeyer–Peppas model and F4 by the zero-order model, whereas F5 and F6 showed near-linear release (zero-order R^2 above 0.999) with n = 1.05 and 1.11. The change from first-order behaviour in the K4M-rich batches to zero-order behaviour in the K15M batches shows that the stronger gel layer of the high-viscosity grade shifted the mechanism from diffusion through a weak gel to a swelling- and erosion-controlled process.

Table 7. Regression coefficients (R^2) and release exponent (n)

Batch	Zero-order	First-order	Higuchi	Korsmeyer–Peppas	n	Best fit
F1	0.7533	0.8485	0.8491	0.8959	0.82	Korsmeyer–Peppas
F2	0.8817	0.9898	0.9479	0.9402	1.01	First-order
F3	0.8167	0.9370	0.9001	0.9164	0.96	First-order
F4	0.9683	0.9260	0.9129	0.9517	0.89	Zero-order
F5	0.9996	0.9442	0.9810	0.9999	1.05	Korsmeyer–Peppas
F6	0.9999	0.9569	0.9840	0.9996	1.11	Zero-order

3.6 Model-independent comparison and reproducibility

The similarity factor between F5 and F6 was 76, so the two profiles are similar and the process is reproducible (Table 8, Figure 4). All the other batches gave f2 values of 37–47 and are therefore different from F5. F5 had a longer MDT (6.2 h) and a lower DE (44.8%) than F1–F3 (MDT 3.8–4.7 h; DE 53.0–56.3%), which confirms that its release is slower and more prolonged. F4 released most slowly (MDT 6.5 h; DE 35.8%) but did not reach the 12 h limit, so slow release alone is not sufficient: the release must also be complete within the dosing interval.

Table 8. Dissolution efficiency, mean dissolution time and similarity factor

Batch	DE 12 h (%)	MDT (h)	f2 vs F5	Similar to F5
F1	56.3	3.8	37	No
F2	53.0	4.7	44	No
F3	54.2	4.3	40	No
F4	35.8	6.5	47	No
F5	44.8	6.2	–	Reference
F6	42.5	6.2	76	Yes

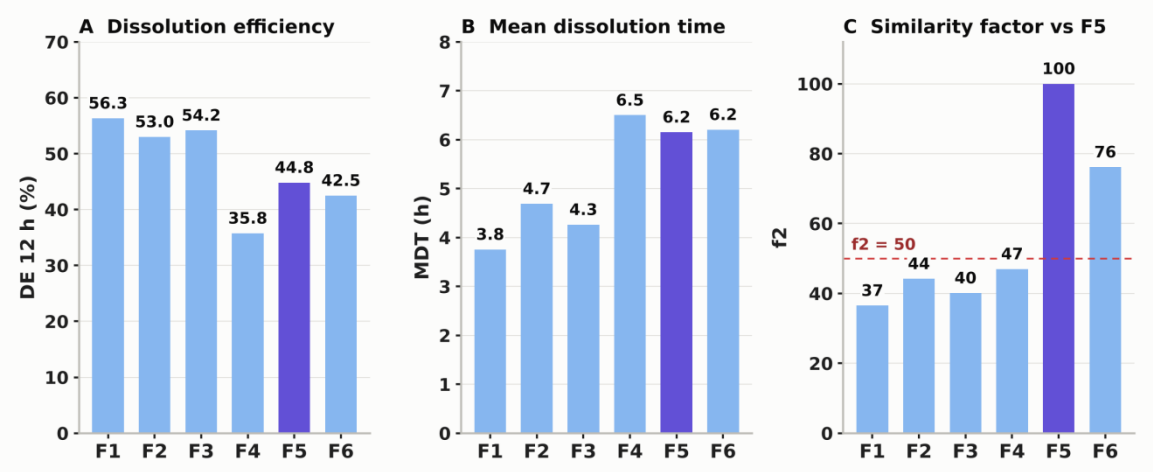

Figure 4. Dissolution efficiency (A), mean dissolution time (B) and similarity factor f2 versus F5 (C).

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3.7 Selection of the optimized batch

F5 was selected as the optimised formulation for four reasons: it met the release specification at all three time points; it released at an almost constant rate (zero-order R^2 = 0.9996) and reached the highest release at 12 h (92%); its profile was reproduced by F6 (f2 = 76); and its slow, complete release (MDT 6.2 h) matches the aim of an ER tablet, which is to avoid sharp peaks in drug concentration while maintaining the therapeutic level for 12 h. F2 also met the numerical limits, but it released 66% at 6 h, close to the upper limit, followed by a plateau, and its profile was different from that of F5 (f2 = 44).

IV. Conclusion

Extended-release matrix tablets of diclofenac sodium (75 mg) and punicic acid (25 mg) were prepared by wet granulation with HPMC K4M and K15M. The grade and amount of HPMC controlled the release: batches rich in K4M released 66–74% within 6 h and levelled off, while 40 mg of K15M lowered the 6 h release to 30–44%. F5 (14%, 44% and 92% at 2, 6 and 12 h) and its reproducibility batch F6 (12%, 42% and 88%) met the specification at every time point and were similar (f2 = 76). F5 released at a nearly constant rate (zero-order R^2 = 0.9996) and followed the Korsmeyer–Peppas model (R^2 = 0.9999, n = 1.05), indicating swelling- and relaxation-controlled release.

F5 therefore achieved the intended 12 h sustained release of diclofenac sodium in vitro and is a promising candidate for reducing dosing frequency and plasma fluctuations. These conclusions rest on three sampling times and apply to diclofenac sodium only. Future work should add more time points with replicates, quantify punicic acid release separately (HPLC or GC), complete stability studies and test the combination in vivo.

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