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Formulation development and in-vitro comparative study of extended-release paracetamol tablets

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Abstract

This study focuses on developing simple, robust methods to prepare extended release paracetamol 665 mg hydrophilic matrix tablets using hydroxypropyl methylcellulose (HPMC) as the principal matrix former and binder in a wet granulation process. Nonionic cellulose ethers such as HPMC are widely used in oral extended release systems because they hydrate to form a viscous gel layer that controls drug diffusion and matrix erosion, thereby sustaining drug release over an extended period. In this work, paracetamol–HPMC matrix tablets were produced by wet granulation using water as the granulating fluid, providing a solvent free, industry relevant manufacturing approach. Two granule populations were designed: "fast release" granules containing the super disintegrant croscarmellose sodium, and "slow release" granules without disintegrant to enhance gel formation and retard release. These granules were blended at different ratios before compression on a tablet press to obtain biphasic and sustained release profiles tailored to match existing modified release paracetamol products. The optimized formulation was benchmarked against leading extended release paracetamol brands marketed in the USA and Europe by comparing 12 hours dissolution profiles, which demonstrated that the in vitro drug release behavior of the developed tablets was comparable to that of the reference products, indicating their potential as cost effective alternatives in the kingdom of Saudi Arabia.

Keywords: Extended release, Paracetamol, Rheumatoid arthritis.

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1. Introduction

Paracetamol is one of the most widely used over-the-counter analgesic and antipyretic drugs, and in many settings, it is taken without prior medical consultation or close therapeutic monitoring. It is effective in relieving a broad spectrum of mild-to-moderate pain and in reducing fever and is particularly valuable in elderly patients with degenerative joint and musculoskeletal disorders who may not tolerate non-steroidal anti-inflammatory drugs (NSAIDs) well. Because the elimination half-life of paracetamol is relatively short, typically about 1–3 hours in adults, conventional immediate-release formulations require multiple doses throughout the day to maintain adequate symptom control. This frequent dosing increases the risk of dosing errors and unintentional overdosing, and long-term use of high total daily doses is associated with dose-dependent hepatotoxicity and, in susceptible patients, acute kidney injury due to cumulative exposure [1, 2].

For these reasons, prolonged- or extended-release dosage forms of paracetamol have been developed to maintain therapeutic plasma concentrations over an extended period, thereby decreasing the number of daily doses required and potentially improving adherence in patients with chronic pain. These formulations release paracetamol more slowly, leading to a flatter concentration–time profile with fewer peaks and troughs, which may also help reduce peak-related adverse effects while still providing sustained analgesia. In the symptomatic management of rheumatoid arthritis (RA), extended-release paracetamol is generally considered when NSAIDs are contraindicated or poorly tolerated, functioning mainly as an adjunct for mild-to-moderate pain rather than as a first-line or disease-modifying agent. Its prolonged action makes it particularly attractive for nighttime or background pain control in chronic inflammatory and degenerative joint diseases, where continuous relief is desirable [3-7].

Globally, joint disorders represent a major public health burden: osteoarthritis alone affected an estimated hundreds of millions of individuals in 2019, with prevalence rising in ageing and obese populations. In such patients, paracetamol is often perceived as a safer long-term option than NSAIDs, but the need for repeated dosing with standard tablets means that total daily intake can approach or exceed recommended limits, especially when patients combine prescription products with multiple over-the-counter cold or flu remedies that also contain paracetamol. Because paracetamol toxicity is clearly dose-dependent, both in terms of single acute overdoses and cumulative chronic exposure, strategies that reduce total daily dose and frequency while preserving efficacy are clinically attractive. Extended-release formulations can help by offering 8–12 hours of symptom relief per tablet, potentially lowering the number of tablets taken per day and simplifying regimens, which in turn may enhance adherence and reduce the risk of inadvertent overdose [8, 9].

Despite this clinical rationale, the availability of extended-release paracetamol products can be limited and varies between countries and markets. In many regions, patients and clinicians still rely predominantly on immediate-release tablets, caplets or syrups, and may be unaware of modified-release alternatives. In the Kingdom of Saudi Arabia, only a single extended-release paracetamol product, Panadol Extend (manufactured in the Ireland), is currently marketed, which restricts therapeutic choice and cost competition. This creates an opportunity and a clear need for the development of additional extended-release paracetamol formulations that are safe, effective, and pharmaceutically equivalent or superior to existing brands, in order to broaden access for patients with chronic pain conditions such as osteoarthritis and RA, and to support rational analgesic use that minimizes the risk of hepatotoxicity and other dose-related adverse effects [10-12].

1.1. Research Aims

As only one exported brand is available on the Saudi official market, we aim to make and evaluate new formulas of extended-release paracetamol tablets to be as good as reference brands Tylenol arthritis (650mg, Johnson & Jhonson, USA) and Panadol Extend (665mg, GSK, Irland), as there is no generic manufactured extended-release paracetamol tablets available in KSA.

We compared our new formulations from the point of physiochemical characteristics and dissolution profiles with sustained release brands Panadol Extend (Irland) and Tylenol Arthritis (USA).

2. Materials and Methods

For the development of the two formulations, we made 2 types of granules by wet granulation technique:

A. Granules containing paracetamol 660 mg (sigma Aldrich, Germany), HPMC 3% as a binder & disintegrant Sodium Starch Glycolate 3% (fast granules).

B. Granules containing paracetamol & HPMC 3% binder without disintegrant (slow granules).

Other tablets' ingredients:

- Aerosol, to improve powder flow for compression tableting and enhance dissolution
- Mg stearate, as a lubricant and flow agent to prevent ingredients from sticking during compression process.
- Avicel, to improve compressibility and flowability.

Then we made two formulas containing different percentages of slow and fast granules as shown in Fig. 1., like the paracetamol composition of the 2 brands (Tylenol Arthritis, USA and Panadol extended release, Ireland).

2.1. Preparation of Tablets

This section describes the preparation of extended-release paracetamol matrix tablets and the subsequent quality control and dissolution testing performed according to current pharmacopoeial standards.

The required quantity of paracetamol powder was accurately weighed and passed through a 100-mesh sieve to ensure a uniform, fine particle size suitable for wet granulation. The sieved paracetamol and starch were mixed thoroughly in a mortar and pestle to obtain a homogeneous dry blend before granulation. A hydrophilic polymer binder solution was

prepared by dispersing hydroxypropyl methylcellulose (HPMC) in boiling water with continuous stirring until a translucent, lump-free paste was formed, indicating complete hydration of the polymer. This hot HPMC paste was gradually incorporated into the paracetamol–starch mixture in a planetary mixer (Kenwood) over 30 minutes to produce a cohesive wet mass of suitable plasticity for granulation.

The wet mass was then passed through a 12-mesh granulating screen, and the wet granules were collected on stainless-steel trays. Initial drying was carried out in a hot-air oven at 50 °C for 30 minutes. Approximately half-dried granules were subsequently sieved through a 16-mesh screen to narrow the particle-size distribution and improve flow and compressibility, then returned to the oven and dried for an additional 30 minutes or until a constant weight was obtained. The final granules were weighed to determine yield and then blended with the remaining excipients (such as diluents, glidants and lubricants) in a polyethylene bag using a tumbling motion to ensure uniform distribution. The lubricated granules were compressed into tablets on a single-punch tablet press (Erweka, Germany) at a compression force of about 3500 psi, adjusting tooling and dwell time to obtain intact tablets with acceptable hardness.

2.2. Standard Curve

For calibration of the analytical method, a standard curve of paracetamol in 0.1 N HCl was prepared. An accurately weighed 250 mg of reference paracetamol was dissolved in 100 mL of 0.1 N HCl and sonicated for 20 minutes to ensure complete dissolution, producing a clear stock solution. Serial dilutions were prepared from this stock to cover the expected concentration range of dissolution samples. The absorbance of each standard solution was measured at 243 nm using a UV–visible spectrophotometer (Shimadzu UV-1800, Japan), with appropriately diluted 0.1 N HCl as the blank. A calibration curve of absorbance versus concentration was constructed and used for quantitative analysis of paracetamol in subsequent studies.

Physical characterization of the compressed tablets was carried out in line with USP–NF 2023 requirements.

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2.3. Weight Variation

For weight-variation testing, twenty tablets from each batch were individually weighed on an analytical balance (A&D Company Ltd., Tokyo, Japan). The mean tablet weight, standard deviation and percentage deviation from the mean were calculated to assess compliance with pharmacopoeia limits.

2.4. Hardness

Tablet hardness was evaluated using a tablet hardness tester (EBT-2PRL, Electrolab). Six tablets were placed individually between the machine's jaws and the force required to fracture each tablet was recorded; the average crushing strength provided an indication of mechanical robustness.

2.5. Thickness

Tablet thickness was measured for the same six units using the gauge on the hardness tester, and the mean thickness was reported to monitor consistency of compression. This test is important to be sure of uniform and reproducible tablets of the same dimensions.

2.6. Friability

Friability testing was performed using a friabilator (Erweka, Germany). Twenty pre-weighed, dedusted tablets were placed in the drum, which was rotated at 25 rpm for 4 minutes, corresponding to 100 revolutions. The tablets were then removed, dedusted and reweighed. Percentage weight loss was calculated and compared with USP acceptance criteria to ensure that the tablets could withstand mechanical stress during handling and transportation. The test repeated 3 times for each sample.

2.7. Disintegration

Disintegration testing was carried out on six tablets per batch using a basket-rack assembly disintegration tester (PharmaTest, Germany). Three tablets were tested with discs and three without discs in 900 mL of 0.1 N HCl maintained at 37 ± 2 °C, and the time taken for each tablet to disintegrate completely was recorded.

2.8. Preparation of pH 5.8 Phosphate Buffer (USP)

A pH 5.8 phosphate buffer was prepared according to USP guidelines for use as a dissolution medium in method development and comparative profiling. First, a 0.2 M monobasic potassium phosphate solution was prepared by dissolving 27.22 g of KH_2PO_4 in purified water and diluting to 1000 mL. A 0.2 M sodium hydroxide solution was prepared separately by dissolving 8 g of NaOH pellets in water and making up to 1000 mL. To obtain the buffer, 250 mL of the KH_2PO_4 solution was mixed with 18 mL of the NaOH solution and diluted to 1000 mL with water, yielding a buffer of pH 5.8 after verification with a calibrated pH meter.

2.9. Dissolution

Dissolution testing of the formulated tablets and reference products was performed using USP Apparatus II (paddle) (Electrolab, India) in accordance with USP 32 recommendations. Six tablets from each batch were placed in 900 mL of phosphate buffer pH 6.8, maintained at 37 ± 0.5 °C, with the paddles rotating at 100 rpm. At predetermined time intervals (15 and 30 minutes, and 1, 3, 5, 7, 9 and 12 hours), 10 mL aliquots of the dissolution medium were withdrawn and

immediately replaced with an equal volume of pre-warmed fresh buffer to maintain sink conditions and constant volume. Samples were filtered through 0.45 µm syringe filters (Millipore) to remove undissolved particles, and the filtrates were suitably diluted with buffer when necessary. The absorbance of each dissolution sample was measured at 243 nm using the UV spectrophotometer against phosphate buffer as the blank. Drug concentrations were determined from the standard calibration curve, and the cumulative percentage of paracetamol released at each time point was calculated and plotted as a function of time. All tests used for tablet characterization and performance evaluation, including weight variation, hardness, thickness, friability, disintegration and dissolution, were conducted in compliance with the relevant United States Pharmacopeia–National Formulary (USP–NF).

3. Results

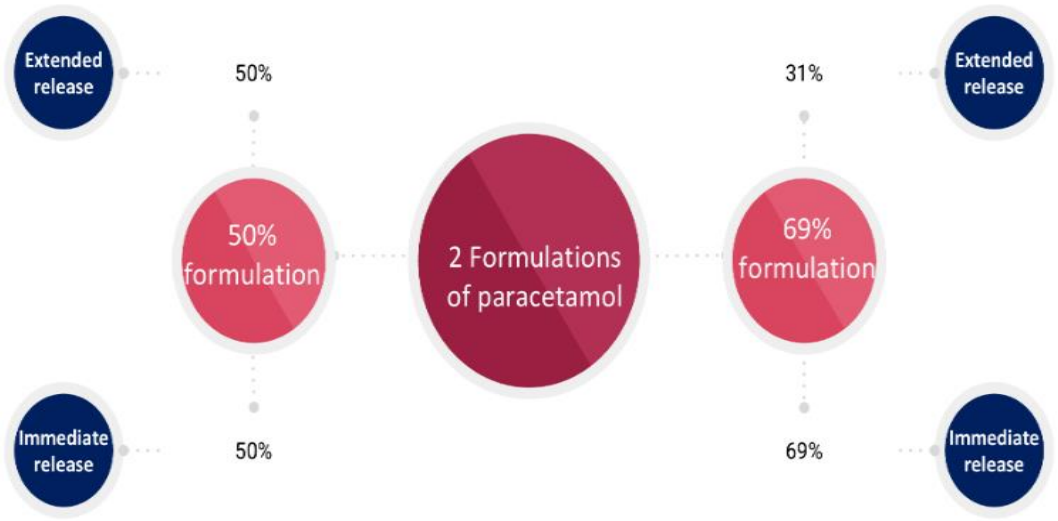

Figure 1.
Formulations composition.

F1: 50% of extended-release granules and 50% of fast release granules.
F2: 31% of extended-release granules and 69% of fast release granules.

Table 1.
Average values hardness, thickness, friability, weight variation, and disintegration time.

Drug name	Hardness (N)	Thickness (mm)	Friability %	Weight (mg)	disintegration time (mins)
Panadol Extend	270.67	6.21	0.02	712.41	165
Tylenol Arthritis	285.33	6.12	0.05	786.86	67
F1 50/50 %	123.91	4.14	0.49	654.51	94
F2 69/31 %	136.29	4.30	0.18	685.50	106

As shown in Table 1, all formulations have an acceptable hardness value. All formulations friability is within expected limit which is <1%. Disintegration time: longest disintegration time is Panadol extended followed by F2, F1 and finally Tylenol.

3.1. Dissolution Profile

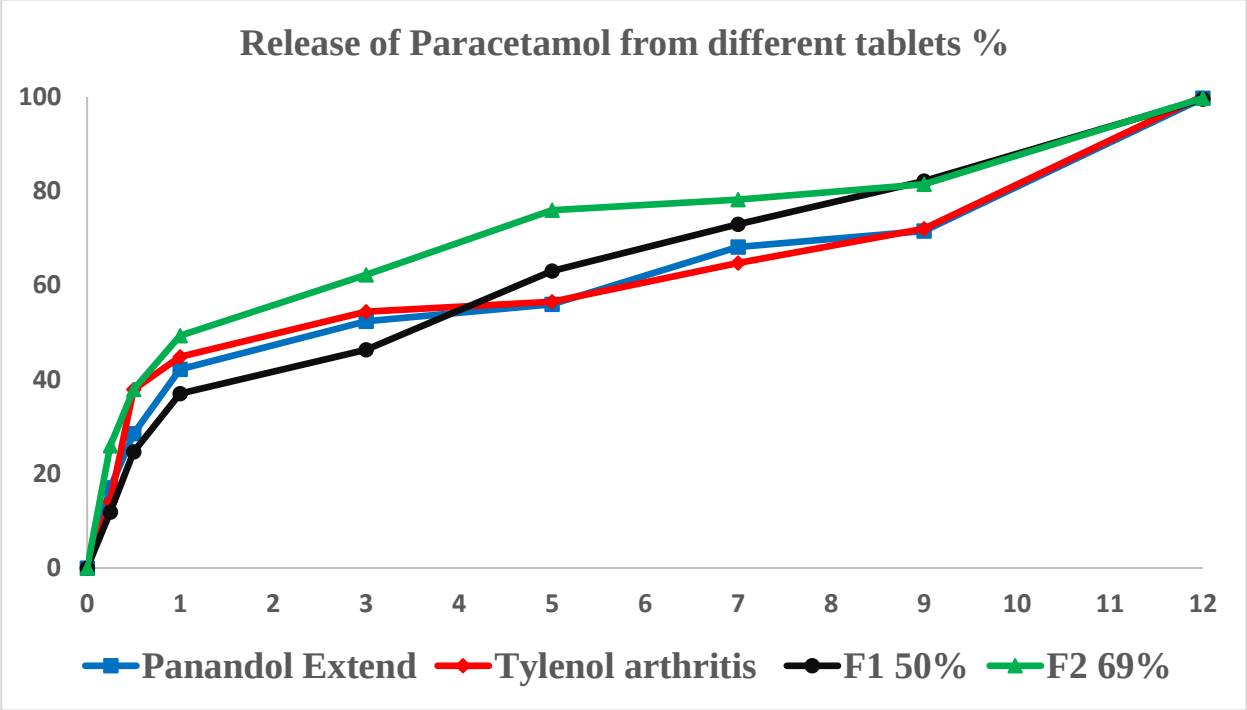

Figure 2.
Dissolution profiles as percentage of drug release.

As illustrated in Figure 2 the in-vitro release profiles of paracetamol from the experimental formulations closely follow those of the commercial extended-release brands Panadol Extend and Tylenol Arthritis across the 12-hour testing period. During the initial phase, formulation F2 shows the most rapid onset, achieving 50% drug release (T50%) within approximately 1 hour, whereas Tylenol Arthritis and Panadol Extend reach 50% release at about 3 hours, and F1, which contains a higher proportion of slow-release granules, attains T50% at around 5 hours, reflecting its more retarded release pattern. This early behavior indicates that the proportion of fast-release granules in F2 confers a quicker rise in paracetamol concentration that may be advantageous for prompt pain relief, while F1 more closely mimics a purely sustained-release system, with slower initial liberation of the drug.

In the middle and late phases of the dissolution test, the four profiles remain broadly parallel, confirming that all products ultimately provide extended drug delivery throughout the 12-hour window. At 8 hours, Tylenol Arthritis and Panadol Extend have released about 67% and 70% of their paracetamol content, respectively, whereas F1 and F2 show slightly higher release of roughly 78% and 80%, suggesting a marginally faster approach to near-complete release for the test formulations without compromising their prolonged-release nature. By 12 hours, all tablets, including the two reference brands and both experimental batches, reach essentially 100% cumulative drug release, demonstrating that the hydrophilic HPMC matrix and the fast/slow granule strategy can reproduce the overall extent of release obtained from established market products while offering flexibility to fine-tune onset and mid-phase release characteristics

4. Discussion

There is currently no locally manufactured extended-release paracetamol tablet available in the Kingdom of Saudi Arabia; the only product accessible to patients and prescribers is the imported brand Panadol Extend. This reliance on a single imported product limits competition, may impact on cost, and creates potential vulnerability in the supply chain. The present work therefore aimed to explore a simple, wet-granulation approach to produce extended-release paracetamol tablets using HPMC hydrophilic matrices and to evaluate whether such formulations could achieve in-vitro performance comparable to established reference brands. By systematically varying the proportions of fast- and slow-release granules, it was possible to tailor the release profile and generate products that fulfilled pharmacopoeia quality tests and provided sustained drug release over 12 hours.

The results of physicochemical characterization showed that both experimental formulations (F1 and F2) exhibited acceptable hardness, thickness, friability and weight variation, all within USP limits, indicating that the granulation and compression conditions yielded mechanically robust and uniform tablets. The disintegration pattern reflected the different proportions of fast and slow granules: Panadol Extend showed the longest disintegration time, followed by F2, F1 and Tylenol Arthritis, suggesting a gradation in matrix integrity consistent with their respective compositions. These findings support the concept that manipulating the ratio of HPMC-rich slow-release granules to disintegrant-containing fast-release granules can modulate tablet erosion, gel formation and liquid penetration, and thus control the overall release rate.

With respect to dissolution behavior, the comparative profiles over 12 hours demonstrated that the developed formulations could closely mimic the release of reference brands. F2, which contained a higher proportion of

immediate-release granules (69%), released 50% of its paracetamol content within 1 hour, indicating a faster onset of action similar to that desired for acute pain relief. In contrast, F1 with a 50:50 ratio of fast to slow granules displayed a more gradual release, with 50% of the drug released at around 5 hours, more closely approximating a predominantly sustained-release profile. At intermediate time points, particularly at 8 hours, both F1 and F2 showed slightly higher percentages of drug released compared with Panadol Extend and Tylenol Arthritis, which may translate into marginally earlier attainment of near-complete exposure while still maintaining the extended-release character [13-15].

By 12 hours, all formulations, including the reference brands, achieved essentially complete drug release (approximately 100%), fulfilling the typical design goal for twice-daily modified-release paracetamol products. Taken together, these findings indicate that relatively simple adjustments in the ratio of fast and slow granules enable close emulation of the biphasic release behavior of Tylenol Arthritis and Panadol Extend. From a pharmaceutical-technology perspective, the wet-granulation process using HPMC as binder and matrix former, combined with conventional excipients such as disintegrants, glidants and lubricants, appears robust and readily scalable. Clinically, such formulations could offer effective 12-hour pain control with reduced dosing frequency, potentially improving adherence in patients with osteoarthritis or rheumatoid arthritis who require long-term paracetamol therapy and are unsuitable for NSAIDs. Overall, the data support the feasibility of producing high-quality extended-release paracetamol tablets within KSA, which could enhance local manufacturing capacity and broaden therapeutic options for chronic pain management [16-19].

5. Conclusion

This study demonstrates that extended-release paracetamol tablets prepared by a straightforward wet-granulation method with HPMC as a hydrophilic matrix former can achieve physicochemical properties and in-vitro dissolution characteristics comparable to the leading commercial products Panadol Extend and Tylenol Arthritis. By optimizing the relative proportions of fast- and slow-release granules, the developed formulations were able to deliver controlled drug release over a 12-hour period, with complete release by the end of the test and dissolution curves that closely paralleled those of the reference brands. The tablets met key quality attributes, including hardness, friability, weight uniformity and disintegration behavior, confirming that the selected process parameters and excipient system are suitable for robust tablet manufacture.

From a practical standpoint, these findings indicate that locally produced extended-release paracetamol tablets could represent a viable alternative to imported brands, helping to address the current gap in the Saudi market where only one modified-release product is available. Such formulations may support better symptom control and adherence in patients with chronic musculoskeletal and arthritic pain, particularly those in whom NSAIDs are contraindicated or poorly tolerated. Future work should include scale-up, stability studies, and in-vivo bioequivalence or pharmacokinetic evaluations to confirm therapeutic equivalence and to satisfy regulatory requirements for generic registration. If these further steps are successful, the approach described here could contribute to the establishment of cost-effective, high-quality extended-release paracetamol products manufactured within KSA, thereby strengthening national pharmaceutical self-sufficiency and improving access to optimized analgesic therapy for patients with chronic pain conditions.

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