

## Original Research Article

# Evaluation of sustained-release metformin hydrochloride matrix tablets using blends of chitosan and xanthan

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## Abstract

**Purpose:** To develop sustained-release metformin matrix tablets using chitosan and xanthan, and to compare their performance with hydroxypropyl methylcellulose (HPMC; K100M) matrix and a commercial sustained-release (SR) product.

**Method:** Metformin matrix tablet formulations were prepared by direct compression of chitosan-xanthan blends at ratios of 1:0 to 0:1, developed based on a 3x2-factorial design (polymer levels 25 – 35 % w/w). A formulation based on HPMC K100M (30 % w/w) and a commercial product were used as controls. Formulated tablets were tested for pre- and post-compression characteristics, swelling/erosion, in vitro dissolution, release kinetics and accelerated stability.

**Results:** All blends showed fair to good flow (angle of repose 27.9 – 33.8°, Hausner ratio ≤ 1.24), friability (< 0.6 %) and content uniformity (98.1 – 101.3 %). Increasing polymer level and xanthan proportion slowed metformin release. Optimised 30 % chitosan: xanthan (1:1) matrix released 95.2 % metformin content after 12 h, closely matching HPMC formulation (96.0 %), and commercial SR product ( $f_2 = 67$ ). The optimized product (F5) release fitted Higuchi/Korsmeyer-Peppas models ( $R^2 \geq 0.99$ ;  $n = 0.63$ ), indicating anomalous diffusion. Stability testing showed no significant changes in all parameters tested ( $p > 0.05$ ).

**Conclusion:** Chitosan-xanthan matrices, especially the 1:1 mixture at 30 % w/w, produce stable metformin SR tablets with dissolution behaviour equal to those of HPMC and a commercially available SR metformin product, suggesting their use as alternatives to synthetic/semi-synthetic polymers in once-daily metformin dosage forms.

**Keywords:** Chitosan, Hydrophilic matrix, Metformin hydrochloride, Natural polymers, Sustained-release tablets, Xanthan gum

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## INTRODUCTION

Metformin hydrochloride is the main oral biguanide used for the management of type 2 diabetes mellitus (T2DM). It is prescribed as the first-line treatment due to its effectiveness, cardiovascular safety profile, and low risk of hypoglycaemia [1,2]. The drug is highly soluble in

water and has low permeability, and population pharmacokinetics (PKs) reveal that the absolute oral bioavailability is approximately 50 - 60 %. These properties make metformin a class III substance based on the Biopharmaceutics Classification System (BCS) [3]. Metformin formulated into immediate release (IR) tablets is well absorbed from the gastrointestinal fluid and

is typically given two or three times daily up to a total dosage of 2 - 3 g to achieve glycaemic control [2].

The need to take this drug frequently is due to its relatively low half-life of 4 - 8 hours [3]. These regimens are not patient-friendly, because patients with T2DM usually need lifelong therapy and often take multiple concomitant drugs, and thus, multi-dose regimens are not the most optimal to use in routine practice [4]. Furthermore, IR metformin has high early peak plasma concentrations with a comparatively steep fall prior to the subsequent dose, causing significant rises and falls in blood glucose levels. These peaks are directly correlated with dose-related gastrointestinal adverse events, including diarrhoea, nausea, abdominal pain and bloating, which are some of the leading reasons to discontinue the treatment or reduce the dose [5]. A decrease in the intestinal luminal appearance rate of metformin is thus a significant technique of enhancing tolerability.

Extended-release or sustained-release (SR) formulations are aimed at releasing metformin slowly over long periods, which levels off the concentration-time curve and minimizes fluctuations. Clinical evidence shows that once-daily or twice-daily SR metformin is capable of achieving the same level of glycaemic control as IR formulations and is linked to fewer gastrointestinal adverse events and greater patient-reported satisfaction with treatment, most notably due to the simplified dosing schedule [4]. Some studies have reported sustained-release metformin preparations using individual natural polymers, such as xanthan gum, chitosan and other polysaccharides, and mixtures of natural gums with hydroxypropyl methylcellulose (HPMC) [6,7]. Nevertheless, existing data are uneven in terms of drug loading, polymer ratios, production processes and dissolution, which makes it hard to make conclusive findings, as regards comparison of the relative performance of natural and synthetic matrices [8]. Chitosan and xanthan gum are natural polysaccharides that have been used as excipients in various drug delivery efforts [9,10]. It would be necessary to carry out a systematic comparison of these natural-polymer matrices against an HPMC-based matrix tablet and compare their physicochemical characteristics, *in vitro* dissolution testing and kinetic modelling, in order to establish whether these polymers can serve as robust, economical and patient-friendly substitutes in sustained-release metformin formulations. This study aims to develop sustained-release matrix tablets of metformin HCl based on natural polymers and to compare

their performance with a conventional HPMC matrix system.

## EXPERIMENTAL

### Materials

Metformin hydrochloride (USP grade; assay 99.0 %). Chitosan (medium molecular weight, degree of deacetylation; 85 %) and xanthan gum (pharmaceutical grade), HPMC K100M, Microcrystalline cellulose (MCC PH-102) was and colloidal silicon dioxide, Magnesium stearate and talc. All other chemicals that were used were of analytical-grade, and preparation of solutions was done in double-distilled water.

Metformin hydrochloride (500 mg) sustained-release tablet (once-daily product) was purchased from a local pharmacy. The brand name is not released to avoid a promotional bias.

### Design

To examine the effect of polymer level (X1) and chitosan: xanthan ratio (X2) on metformin matrix tablets performance, a design of 3x2 full factorial was used. Factor levels were identified by preliminary screening trials in order to allow satisfactory tablet manufacturability and target release in a time range of 12 h. The concentration of total polymer (X1) was measured using 25, 30 and 35 % of the weight of the core tablet, coded -1, 0, and +1, respectively. The ratios of chitosan: xanthan (X2) were determined as 1:0, 1:1, and 0:1, coded as -1, 0, and +1, respectively.

There were a total of nine trial formulations (F1 - F9) of all combinations of factors having been prepared. Synthetic-polymer comparator; HPMC K100M was included as a 30 %w/w tenth formulation (F10), and the commercial sustained-release product (external) was used as control. The major dependent variables were percentage drug release at 2 h (Q2), 6 h (Q6), and 12 h (Q12); time for 50 % of metformin release (t50); mean dissolution time (MDT); and release exponent Korsmeyer-Peppas (n). Other responses were physical properties of tablets (hardness, friability, and drug content).

The formulation procedures of batches were held constant, while polymer levels and types were varied. Tablet weights were adjusted to target 750 mg, each containing an equivalent of 500 mg metformin hydrochloride. Table 1 summarises the composition and Table 2 is the factorial design matrix.

**Table 1:** Composition of metformin HCl matrix tablets (per 750-mg tablet)

| Component                 | Function                | Quantity (mg)* |
|---------------------------|-------------------------|----------------|
| Metformin HCl             | Active ingredient       | 500            |
| Chitosan / Xanthan / HPMC | Matrix former           | 187.5–262.5    |
| MCC PH-102                | Diluent                 | q.s. to 750    |
| Colloidal silicon dioxide | Glidant                 | 5              |
| Talc                      | Lubricant/anti-adherent | 5              |
| Magnesium stearate        | Lubricant               | 5              |

\*Exact polymer and MCC quantities varied according to the factorial design. MCC: Microcrystalline cellulose

**Table 2:** 3<sup>2</sup> factorial design for natural-polymer matrix tablets

| Formulation | X <sub>1</sub> : Polymer level (% w/w) | X <sub>2</sub> : Chitosan: xanthan ratio | Coded levels (X <sub>1</sub> , X <sub>2</sub> ) |
|-------------|----------------------------------------|------------------------------------------|-------------------------------------------------|
| F1          | 25                                     | 1:0                                      | (-1, -1)                                        |
| F2          | 25                                     | 1:1                                      | (-1, 0)                                         |
| F3          | 25                                     | 0:1                                      | (-1, +1)                                        |
| F4          | 30                                     | 1:0                                      | (0, -1)                                         |
| F5          | 30                                     | 1:1                                      | (0, 0)                                          |
| F6          | 30                                     | 0:1                                      | (0, +1)                                         |
| F7          | 35                                     | 1:0                                      | (+1, -1)                                        |
| F8          | 35                                     | 1:1                                      | (+1, 0)                                         |
| F9          | 35                                     | 0:1                                      | (+1, +1)                                        |

Formulation F10 consisted of metformin HCl 500 mg, HPMC K100M 30% w/w, and the same quantities of MCC and other excipients as seen in Table 1

### Preparation of sustained-release matrix tablets

Direct compression was used to prepare all the batches. Metformin HCl and polymer(s) were calculated in relation to the per-tablet composition to determine the quantities required. Metformin, chitosan, xanthan gum, or HPMC and MCC were sieved using a 40-mesh sieve to disaggregate. The sieved powders (without lubricants and glidants) were put into a cone-shaped blender and stirred for 10 min at 15 rpm to achieve a homogeneous mixture. Colloidal silicon dioxide was added next and mixing was done for 5 min to enhance flow. Lastly, talc and

magnesium stearate were added and blended further after 3 min to reduce the chances of excessive lubrication. A lubricated blend was pressed in a rotary tablet press equipped with 12 mm flat-faced punches. The compression force was set to achieve tablets that were hard with 80 - 100 N without capping or laminating. When compressing, the weight of the tablets and their hardness were periodically monitored and compression parameters were adjusted as necessary. Prepared tablets (Figure 1) were placed in high-density polyethylene sealed containers at room temperature, awaiting further examination.



**Figure 1:** Photograph of chitosan and xanthan-based as well as HPMC-based sustained-release tablets and commercial sample

## Pre-compression evaluation of powder blends

Prior to compression, each formulation blend was characterised for flow and density because such parameters are known to influence die filling and weight uniformity. Angle of repose was determined using the fixed-funnel method. Approximately 50 g of powder was allowed to flow through a funnel with a 10 mm orifice onto a flat surface, forming a conical heap. The height (h) and radius (r) of the pile were measured, and the angle of repose ( $\theta$ ) was calculated using Eq 1.

$$\tan \theta = \frac{h}{r} \dots\dots\dots (1)$$

Bulk density ( $\rho_b$ ) was measured by gently pouring a known mass of powder into a 100-mL graduated cylinder and recording the unsettled volume. Tapped density ( $\rho_t$ ) was obtained after subjecting the cylinder to 250 taps on a tapped-density apparatus or until the volume change was < 1 mL. From these densities, Carr's compressibility index (CI) and Hausner ratio (HR) were computed using Eq 2 and Eq 3. Flow properties were interpreted according to established criteria for pharmaceutical powders.

$$CI(\%) = \left\{ \frac{\rho_t - \rho_b}{\rho_t} \right\} 100 \dots\dots\dots (2)$$

$$HR = \frac{\rho_t}{\rho_b} \dots\dots\dots (3)$$

## Post-compression evaluation of tablets

Finished tablets were evaluated in accordance with pharmacopeial recommendations for uncoated tablets.

### Appearance and dimensions

Twenty tablets from each batch were visually inspected for surface defects. Tablet thickness and diameter were measured using a digital Vernier calliper, and mean values were calculated.

### Weight variation

Twenty tablets were individually weighed on an analytical balance. The mean weight and percentage deviation for each tablet were determined and compared with pharmacopeial acceptance limits for tablets of this size.

### Hardness

Ten tablets per batch were tested using a digital hardness tester, and results were expressed as

mean  $\pm$  standard deviation (SD). Target hardness was 80 – 100 N.

### Friability

A sample of ten tablets was placed in a friabilator and tumbled at 25 rpm for 4 min (100 revolutions). Tablets were dedusted and reweighed; friability was calculated as the percentage mass loss. Values not exceeding 1.0 % were considered acceptable.

### Drug content and uniformity

Ten tablets were individually assayed. Each tablet was powdered, and an amount equivalent to 100 mg metformin was transferred to a volumetric flask, sonicated with phosphate buffer at pH 6.8, and diluted appropriately. After filtration through a 0.45- $\mu$ m membrane, absorbance was measured at 233 nm using a UV-visible spectrophotometer. Calibration curves were constructed over the concentration range 5 – 25  $\mu$ g/mL and were linear with correlation coefficients ( $R^2$ )  $\geq$  0.999. Intra-day precision was assessed at three concentration levels (n = 6) with relative standard deviation (RSD) < 2 %. Individual tablet contents were expressed as percentage of label claim.

### Swelling and erosion studies

Swelling and matrix erosion were evaluated for selected formulations to better understand the hydration behaviour of the polymer network. Tablets were weighed ( $W_0$ ), placed in wire baskets and immersed in 900 mL of phosphate buffer (pH 6.8) at  $37 \pm 0.5$  °C in the dissolution apparatus without rotation. At predetermined times (1, 2, 4, 6, 8 and 12 h), baskets were withdrawn, gently blotted with tissue paper to remove surface moisture and reweighed ( $W_s$ ). Swelling index (SI) was calculated using Eq 4.

$$SI(\%) = \left\{ \frac{W_s - W_0}{W_0} \right\} 100 \dots\dots\dots (4)$$

For erosion studies, the swollen tablets were dried at 40 °C to constant weight ( $W_d$ ). Percentage erosion (E) was determined as shown in Eq 5. Swelling and erosion profiles were plotted as a function of time for qualitative comparison between formulations.

$$E(\%) = \left\{ \frac{W_0 - W_d}{W_0} \right\} 100 \dots\dots\dots (5)$$

### In vitro drug release study

*In vitro* metformin release from formulated tablets were evaluated using USP type II Apparatus

(paddle method) at  $37 \pm 0.5$  °C and 50 rpm. Dissolution medium in each vessel was 900 mL, and 0.1 N hydrochloric acid (HCl; pH 1.2) was used during the first 2 h. Phosphate buffer (pH 6.8) was added thereafter to complete the next 10 h of the test to make the overall duration of the test 12 h. A 5 mL sample was withdrawn at predetermined time intervals (0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h) and filtered instantly using 0.45 µm membranes, followed by the addition of the same volume of fresh medium to maintain sink conditions. After the proper dilution and blank correction, the concentration of metformin was measured spectrophotometrically at 233 nm. Six replicate tablets were used to test each of the formulations (n = 6). The cumulative percent of drug released was determined based on 500 mg of metformin. Dissolution test on HPMC-based formulation (F10) and commercial sustained-release preparation was done under the same conditions to enable comparison.

### Drug release kinetics and mechanism

To elucidate release mechanisms, dissolution data for formulations achieving sustained release without dose dumping were fitted to several kinetic models widely used for matrix systems (zero-order, first-order, Higuchi, Korsmeyer–Peppas and Hixson–Crowell).

The following equations were applied.

#### Zero-order model

$$Q_t = Q_0 + k_0 t \dots\dots\dots (6)$$

Where  $Q_t$  is the cumulative amount of drug released at time?  $t$ ,  $Q_0$  is the initial amount of drug in the solution (usually zero), and  $k_0$  is the zero-order release constant.

#### First-order model

$$\ln(Q_0 - Q_t) = \ln Q_0 - k_1 t \dots\dots\dots (7)$$

#### Higuchi model

$$Q_t = k_H t^{1/2} \dots\dots\dots (8)$$

#### Korsmeyer–Peppas model (for the initial 60% of release)

$$\frac{Q_t}{Q_{\infty}} = k_{KP} t^n \dots\dots\dots (9)$$

#### Hixson–Crowell model

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t \dots\dots\dots (10)$$

The non-linear regression run on GraphPad Prism (version X) was used for curve fitting and checked in Microsoft Excel. The coefficient of determination ( $R^2$ ), adjusted  $R^2$ , and sum of squared resistance were used to evaluate the goodness of fit. Akaike Information Criterion (AIC) and model selection criteria outlined by Dash *et al* [3] were used, where needed, to select one out of competing models. In the case of Korsmeyer–Peppas model, the release exponent (n) was used to deduce the main mechanism of metformin release (Fickian diffusion, anomalous transport, or case-II transport).

## RESULTS

### Pre-compression properties

The flow and packing characteristics of all powder blends are summarised in Table 3. Angles of repose ranged from 27.9° to 33.8°, while Carr's index values varied between 12.3 % and 19.6 %. Hausner ratios were between 1.14 and 1.24. Blends containing the highest total polymer level and xanthan-dominant compositions (F7 – F9) showed slightly higher angles of repose and compressibility indices, indicating more cohesive behaviour, but all values still fell within the range generally considered acceptable for direct compression. Overall, the blends exhibited fair to good flow and were suitable for rotary tableting without additional granulation steps.

### Post-compression properties

All batches produced mechanically robust tablets with uniform appearance and no visible defects such as capping, lamination, or picking. Table 4 presents the key post-compression parameters. Mean tablet weights were within 1.1 % of the nominal 750 mg target for every formulation, and individual weight variations complied with pharmacopeial limits for uncoated tablets of this size. Hardness values ranged from 82.4 to 95.7 N, indicating adequate mechanical strength for further handling and packaging. Friability remained below 0.6 % for all batches, confirming good abrasion resistance. Thickness values were consistent ( $\approx$  5.2 – 5.4 mm), reflecting uniform die fill. Drug content ranged from 98.1 to 101.3 % of the label claim, with relative standard deviations below 2 %, demonstrating good dosage uniformity. There were differences in physical parameters observed between tablets containing natural polymers and HPMC reference formulation.

**Table 3:** Pre-compression properties of powder blends (n = 3)

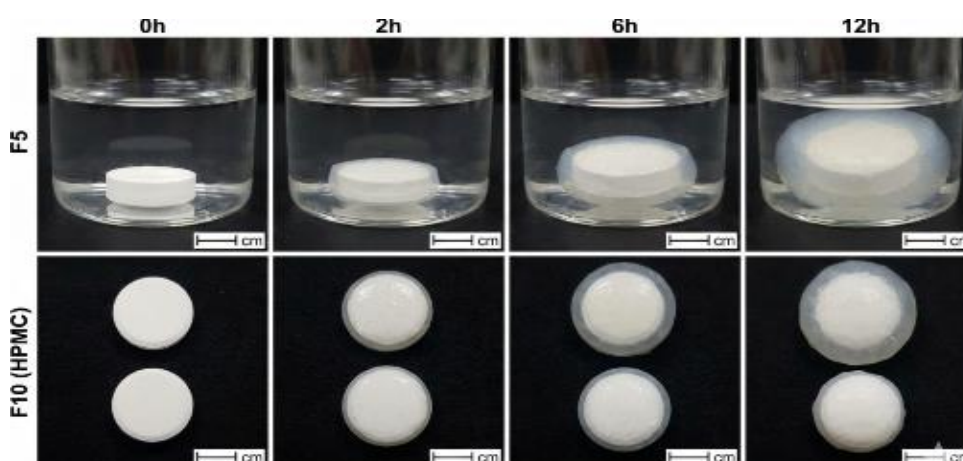
| Formulation | Angle of repose (°) | Bulk density (g/mL) | Tapped density (g/mL) | Carr's index (%) | Hausner ratio |
|-------------|---------------------|---------------------|-----------------------|------------------|---------------|
| F1          | 30.1                | 0.47                | 0.55                  | 14.5             | 1.17          |
| F2          | 28.5                | 0.48                | 0.55                  | 12.7             | 1.15          |
| F3          | 32.4                | 0.46                | 0.56                  | 17.9             | 1.22          |
| F4          | 29.8                | 0.49                | 0.57                  | 14.0             | 1.16          |
| F5          | 27.9                | 0.50                | 0.57                  | 12.3             | 1.14          |
| F6          | 31.5                | 0.48                | 0.58                  | 17.2             | 1.21          |
| F7          | 32.7                | 0.46                | 0.57                  | 19.3             | 1.24          |
| F8          | 30.9                | 0.47                | 0.57                  | 17.5             | 1.21          |
| F9          | 33.8                | 0.45                | 0.56                  | 19.6             | 1.24          |
| F10 (HPMC)  | 29.2                | 0.49                | 0.57                  | 14.0             | 1.16          |

**Table 4:** Post-compression properties of metformin matrix tablets (mean ± SD)

| Formulation | Weight (mg, n=20) | Thickness (mm, n=10) | Hardness (N, n=10) | Friability (%) | Drug content (% label, n=10) |
|-------------|-------------------|----------------------|--------------------|----------------|------------------------------|
| F1          | 751.2±3.8         | 5.23±0.04            | 84.5±4.2           | 0.48           | 99.2±1.1                     |
| F2          | 749.6±4.1         | 5.22±0.05            | 86.3±3.9           | 0.44           | 100.3±1.4                    |
| F3          | 752.5±3.6         | 5.24±0.04            | 82.4±4.7           | 0.53           | 98.7±1.5                     |
| F4          | 750.7±4.3         | 5.26±0.05            | 88.9±4.0           | 0.41           | 99.8±1.2                     |
| F5          | 748.9±3.9         | 5.25±0.04            | 88.1±3.8           | 0.39           | 99.6±1.0                     |
| F6          | 751.6±4.0         | 5.27±0.05            | 90.3±4.1           | 0.37           | 100.7±1.3                    |
| F7          | 749.8±3.7         | 5.31±0.05            | 92.4±4.5           | 0.35           | 98.1±1.6                     |
| F8          | 752.1±4.2         | 5.32±0.04            | 95.7±3.9           | 0.32           | 99.4±1.3                     |
| F9          | 750.3±3.5         | 5.33±0.05            | 94.8±4.2           | 0.34           | 99.0±1.4                     |
| F10 (HPMC)  | 749.5±3.8         | 5.24±0.04            | 90.5±3.7           | 0.37           | 100.1±1.2                    |

**Table 5:** Swelling index and erosion of selected formulations (mean ± SD, n = 3)

| Formulation       | Swelling index 2 h (%) | Swelling index 6 h (%) | Swelling index 12 h (%) | Erosion 12 h (%) |
|-------------------|------------------------|------------------------|-------------------------|------------------|
| F4 (Chitosan 1:0) | 82.3±4.1               | 141.7±6.3              | 165.4±7.2               | 35.1±2.4         |
| F5 (1:1 mix)      | 73.6±3.8               | 145.2±5.9              | 180.3±6.7               | 30.2±2.1         |
| F6 (Xanthan 0:1)  | 61.5±3.3               | 152.8±7.0              | 193.6±7.5               | 27.6±2.0         |
| F10 (HPMC)        | 56.8±3.1               | 132.4±5.6              | 161.2±6.1               | 22.4±1.8         |



**Figure 2:** Swollen matrix tablets at different time points

### Swelling and erosion behaviour

Swelling and erosion studies were performed on the three 30 % polymer formulations (F4–F6) and HPMC reference (F10) to characterise the hydration behaviour of the different matrices (Figure 2). Table 5 summarises the swelling

indices at 2, 6, and 12 h and the percentage erosion after 12 h. All matrices exhibited rapid initial hydration followed by progressive swelling. Xanthan-rich F6 showed the highest swelling index at 12 h, reflecting the strong water-uptake capacity and gel-forming ability of xanthan gum. The chitosan-only matrix (F4) displayed more

pronounced erosion, particularly in the later phase of the test, consistent with gradual loss of hydrated polymer from the tablet surface. The 1:1 chitosan: xanthan formulation (F5) showed intermediate swelling with moderate erosion, suggesting a balanced contribution of diffusion and erosion processes to drug release. HPMC tablets swelled more slowly and eroded least, in line with the formation of a relatively dense, persistent gel layer.

### ***In vitro* drug release profiles**

Dissolution testing demonstrated that all matrix formulations were capable of sustaining metformin release over 12 h, although the rate and pattern of release were strongly influenced by polymer level and composition. Table 6 summarises the percentage of drug released at 2, 6 and 12 h for each formulation, while Table 7 presents the derived  $t_{50}\%$ ,  $t_{90}\%$  and mean dissolution time (MDT) values.

Formulations with the lowest polymer level (25 %, F1 – F3) showed faster release, with approximately 75 – 82 % of drug released by 6 h and almost complete release by 12 h. Increasing total polymer content to 35 % (F7 – F9) substantially retarded release, particularly in xanthan-rich F9, which released only 88.2 % of

drug by 12 h. The intermediate polymer level (30 %) produced profiles that more closely resembled the commercial sustained-release product. Among these, F5 (30 % polymer, 1:1 chitosan: xanthan) and F6 (30 % polymer, xanthan-dominant) displayed cumulative releases at 2, 6 and 12 h that were very similar to both HPMC-based F10 and the commercial preparation.

The analysis of variance on the values of MDT showed that the total polymer level and chitosan: xanthan ratio significantly affected the rate of release ( $p < 0.01$ ), with the higher the polymer loads and the higher the xanthan ratios, the longer the MDT and the higher the  $t_{90}$ . F5 and F10 have MDT and  $t_{50}\%$  values nearest to those of the commercial product, no indication of initial burst release, and thus were viewed as promising candidates for sustained-release.

### **Kinetic modelling**

Dissolution data for all formulations were fitted to several kinetic models to elucidate the mechanism of drug release. Table 8 summarises the determination coefficients ( $R^2$ ) for the zero-order, first-order, Higuchi and Korsmeyer–Peppas models, together with the Peppas release exponent ( $n$ ).

**Table 6:** Cumulative metformin release at selected time points (mean  $\pm$  SD,  $n = 6$ )

| Formulation   | $Q_2$ (% at 2 h) | $Q_6$ (% at 6 h) | $Q_{12}$ (% at 12 h) |
|---------------|------------------|------------------|----------------------|
| F1            | 38.1 $\pm$ 2.3   | 82.4 $\pm$ 3.1   | 99.1 $\pm$ 2.0       |
| F2            | 34.3 $\pm$ 2.0   | 78.2 $\pm$ 2.7   | 98.2 $\pm$ 1.9       |
| F3            | 30.2 $\pm$ 1.9   | 74.1 $\pm$ 2.6   | 97.0 $\pm$ 2.1       |
| F4            | 29.1 $\pm$ 1.8   | 68.0 $\pm$ 2.5   | 96.3 $\pm$ 1.8       |
| F5            | 25.4 $\pm$ 1.7   | 56.3 $\pm$ 2.2   | 95.2 $\pm$ 1.7       |
| F6            | 22.1 $\pm$ 1.5   | 54.0 $\pm$ 2.1   | 94.1 $\pm$ 1.8       |
| F7            | 20.0 $\pm$ 1.4   | 51.2 $\pm$ 2.0   | 92.4 $\pm$ 2.0       |
| F8            | 18.2 $\pm$ 1.3   | 46.0 $\pm$ 1.9   | 90.1 $\pm$ 2.1       |
| F9            | 16.4 $\pm$ 1.3   | 42.1 $\pm$ 1.8   | 88.2 $\pm$ 2.3       |
| F10 (HPMC)    | 24.0 $\pm$ 1.6   | 58.0 $\pm$ 2.2   | 96.0 $\pm$ 1.6       |
| Commercial SR | 23.1 $\pm$ 1.5   | 55.1 $\pm$ 2.1   | 94.0 $\pm$ 1.9       |

**Table 7:** Release-profile descriptors for all formulations (mean of  $n = 6$ )

| Formulation   | $t_{50}\%$ (h) | $t_{90}\%$ (h) | MDT (h) |
|---------------|----------------|----------------|---------|
| F1            | 3.1            | 7.9            | 5.4     |
| F2            | 3.3            | 8.2            | 5.7     |
| F3            | 3.5            | 8.5            | 5.9     |
| F4            | 3.8            | 9.0            | 6.3     |
| F5            | 4.3            | 10.8           | 7.1     |
| F6            | 4.6            | 11.2           | 7.4     |
| F7            | 4.9            | 11.6           | 7.7     |
| F8            | 5.4            | 12.5           | 8.3     |
| F9            | 5.8            | 13.2           | 8.8     |
| F10 (HPMC)    | 4.2            | 10.6           | 7.0     |
| Commercial SR | 4.4            | 11.1           | 7.3     |

**Table 8:** Kinetic parameters for metformin release from matrix tablets

| Formulation | R <sup>2</sup> |             |         |                  | n (Peppas) |
|-------------|----------------|-------------|---------|------------------|------------|
|             | Zero-order     | First-order | Higuchi | Korsmeyer-Peppas |            |
| F1          | 0.983          | 0.970       | 0.994   | 0.995            | 0.57       |
| F2          | 0.985          | 0.969       | 0.995   | 0.996            | 0.58       |
| F3          | 0.986          | 0.968       | 0.995   | 0.996            | 0.59       |
| F4          | 0.987          | 0.967       | 0.996   | 0.997            | 0.61       |
| F5          | 0.991          | 0.972       | 0.996   | 0.997            | 0.63       |
| F6          | 0.989          | 0.970       | 0.995   | 0.996            | 0.65       |
| F7          | 0.988          | 0.967       | 0.994   | 0.995            | 0.67       |
| F8          | 0.987          | 0.965       | 0.993   | 0.994            | 0.70       |
| F9          | 0.987          | 0.966       | 0.992   | 0.993            | 0.72       |
| F10 (HPMC)  | 0.989          | 0.971       | 0.995   | 0.996            | 0.61       |

In all formulations, Higuchi and Korsmeyer-Peppas models gave the best R<sup>2</sup> values, which indicated that diffusion in a hydrated matrix was the most prevailing factor that determined drug release. Peppas exponents (n) ranged from 0.57 to 0.72, which is in line with non-Fickian (anomalous) transport, which is a composite of diffusion and polymer relaxation/erosion. Small increases in n values of high-polymer, xanthan-rich formulations (F8, F9) indicate the increased role of gel relaxation and erosion in the release mechanism.

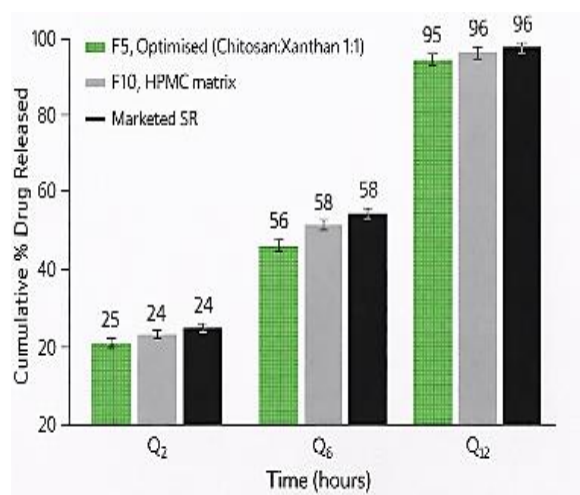
### Optimised formulation and stability

The optimised natural-polymer formulation was 30 % polymer 1:1 chitosan: xanthan matrix (F5) based on parameters of dissolution and similarity to the commercial product. F5 had a balanced release profile (Q<sub>2</sub>, 25 %; Q<sub>6</sub>, 56 %; Q<sub>12</sub>, 95 %), MDT and t<sub>50</sub> % was similar to the release profile of HPMC reference formulation (F10) and commercial sustained-release tablet. Similarity factors (f<sub>2</sub>) obtained by comparing F5 and F10 with commercial product were 67 and 69, respectively, which proves that the two formulations had dissolution profiles similar to the commercial product. Three-month accelerated stability testing of F5 and F10 at 40 °C/75 % RH showed no apparent visual change and only slight changes in either physical or release property (Table 9). After storage, there was a slight increase in hardness, which is consistent with the further consolidation of the matrix, but friability was not more than 0.5 %. The values of drug content were within 2 percent of starting values, showing the stability of metformin and the

polymers at test conditions. Three-month dissolution profiles were similar to the original profiles, with the f<sub>2</sub> values of both F5 and F10 of over 60, indicating they were equal and no significant change in release behaviour had occurred (Figure 3).

### DISCUSSION

The pre-compression data indicated that all the powder mixes were of fair to good flow with angles of repose less than 35° and Hausner ratios less than 1.24 and therefore recommended that the compositions could be direct compression without prior granulation.



**Figure 3:** Comparative dissolution profiles of optimised formulation, HPMC matrix and commercial product

**Table 9:** Stability data for optimised formulations under accelerated conditions (mean ± SD)

| Formulation | Time (months) | Hardness (N, n=10) | Friability (%) | Drug content (% label, n=10) | Q <sub>12</sub> (% released, n=6) | f <sub>2</sub> vs initial |
|-------------|---------------|--------------------|----------------|------------------------------|-----------------------------------|---------------------------|
| F5          | 0             | 88.1±3.8           | 0.39           | 99.6±1.0                     | 95.2±1.7                          | —                         |
| F5          | 3             | 92.3±4.1           | 0.41           | 98.9±1.1                     | 94.7±1.9                          | 66                        |
| F10 (HPMC)  | 0             | 90.5±3.7           | 0.37           | 100.1±1.2                    | 96.0±1.6                          | —                         |
| F10 (HPMC)  | 3             | 94.2±4.0           | 0.40           | 99.2±1.2                     | 95.6±1.8                          | 64                        |

The above findings are supported by reports that well-blended polymer-MCC mixtures have acceptable flow despite comparatively high polymer charges [11]. In this positive trend, a rise in polymer content and in the percentage of xanthan gum was also likely to lead to minimal increase in compressibility index, which is an outcome of the fact that hydrated gums are naturally more cohesive than MCC. However, after compression testing, it was found that all formulations matched pharmacopeial requirements of weight variation, friability, and content uniformity, and neither type of polymer nor concentration was harmful to the manufacturability of tablets.

Polymer composition had a very strong impact on drug release compared to physical properties. At a constant drug concentration of 500 mg, a continuous increase in total polymer concentration to 25 then 35 % gradually reduced the rate of metformin release as indicated by increasing  $t_{50}$ ,  $t_{90}$  and mean dissolution time. Hydrophilic matrices are supposed to exhibit this behaviour; the more the polymer concentration, the greater the gel layer thickness and tortuosity, which increases the length of the diffusional path of the drug molecules [11]. Xanthan gum introduction yielded higher sustained discharge in relation to chitosan at later time points at every polymer degree; this is due to the elevated capacity to bind water and the high viscosity of xanthan gels [8].

The higher percentages of erosion and a slight increase in the rate of release were observed with chitosan-rich formulations and particularly after 6 h, probably because chitosan becomes partially soluble in acidic conditions and can be eroded in agitators [13]. In comparison, xanthan-dominant systems yielded more coherent, slowly eroding gel layers that retained the integrity of the matrix during the period of dissolution. The 1:1 chitosan: xanthan mixture at 30 %w/w (F5) presented an intermediate performance, where hydration and swelling were quick at the beginning, and gel strength was high enough to ensure that the dose was not dumped. Its performance profile was quite comparable with that of HPMC K100M matrix and the commercialised sustained-release product, indicating that a suitable optimised natural-polymer blend could be used to achieve the functionality of the long-established platform HPMC [11].

Kinetic analysis showed that Higuchi and Korsmeyer-Peppas models provided the most appropriate description of dissolution data of all the formulations, with  $R^2$  values generally being

above 0.99. The higher fit to Higuchi model would explain the opinion that diffusion through a hydrated polymeric net is the major release process of metformin in such matrices in accordance with the classical description of water-penetrating, gel-forming networks [3]. Nevertheless, Peppas exponents (0.57 - 0.72) were always larger than the limit of pure Fickian diffusion in cylindrical matrices and were in a range of values related to non-Fickian, or anomalous, transport, suggesting that the polymer relaxation and erosion processes had a major contribution [3].

These interpretations are supplemented by the swelling-erosion data. Tablets made of chitosan at high concentrations showed greater percentage of erosion after 12 h, especially at intermediate and high levels of polymer, which is in line with a matrix where water uptake is accompanied by a progressive loss of hydrated polymer from the surface. The erosion of the diffusion front by diffusion through the gel controls the release of drugs in such systems and the diffusion front is continuously renewed. Xanthan-dominant matrices swelled more but eroded less, suggesting that polymer relaxation instead of mass loss is a more significant factor in the gel structure. The chitosan: xanthan 1:1 mix exhibited intermediate swelling and fair erosion, which is consistent with a mixed mechanism whereby both diffusion is regulated by gel relaxation and erosion on the surface.

Swelling and erosion rates were lower in HPMC matrix compared to the natural-polymer systems, which indicates the formation of a dense and cohesive gel layer typical of high viscosity HPMC grades [11]. However, the fact that the exponents of Peppas are similar and that both natural-polymer and HPMC tablets fit well into diffusion-based models indicates that when the tablets become moist, then the chitosan-xanthan matrices can be regarded as acting in a mechanistic manner that is very much similar to that of conventional HPMC hydrophilic matrices.

Data on dissolution profiles align with the published information on sustained-release metformin tablets using synthetic hydrophilic polymers. HPMC matrices reported by Wadher *et al* [6] showed that about 25 - 30 % of metformin was released at the 2<sup>nd</sup> hour and 90 - 95 % at the 12<sup>th</sup> hour, which is quite similar to the behaviour of F10 and the commercially available product in the current study. Other HPMC-based metformin systems also showed similar MDT and  $t_{50\%}$  values and release best characterized by Higuchi and Korsmeyer-Peppas models with exponents indicating an anomalous transport [7]. The fact

that our HPMC data aligns with these reports facilitates the validity of the dissolution methodology and gives us a good benchmark on which to gauge the performance of the natural-polymer matrices.

In reference to natural polymers, some authors have reported that the use of xanthan gum to prolong the release of metformin is a possibility, although most of these formulations either used a lower drug load or omitted a direct comparison between HPMC and natural polymers [7]. Investigations with individual gums or chitosan tended to have a longer release, but also indicated that the release rate was more sensitive to medium pH and hydrodynamic conditions, which is more characteristic of the more complex hydration behaviour of natural polysaccharides [8,13]. Conversely, the 1:1 chitosan: xanthan mixture at 30 % w/w in the current study yielded a release profile that was comparable to HPMC and a commercial sustained-release formulation, even with the relatively large dose of metformin 500 mg.

The main originality of this study is in the systematic factorial comparison of chitosan-xanthan blends on various overall polymer concentrations with HPMC reference under harmonised formulation and testing conditions. The work offers substantially more evidence than had been previously available that natural matrices are viable alternatives to semi-synthetic cellulose ethers, as f2 similarity factors above 60 was obtained with an optimised natural-polymer blend in comparison to a commercial sustained-release product. Besides, the swelling-erosion characterisation and kinetic modelling provide understanding of the mechanisms by which particularly chitosan: xanthan ratios control gel structure and release behaviour, which can be used to design future sustained-release systems with plentiful, possibly cost-effective natural excipients.

## CONCLUSION

Chitosan and xanthan gum have been used to develop sustained-release metformin HCl tablets that are stable and met formulation standard comparable to HPMC-based formulation. All formulations made by direct compression satisfied pharmacopeial requirements and tablet quality criteria, to establish the manufacturability of high-dose (500 mg) metformin with these excipients. Chitosan-based systems demonstrated greater erosion and a slightly higher rate of release. A 1:1 chitosan: xanthan mix at 30 %w/w was optimised to have an equivalent release profile, MDT and kinetic

behaviour with an HPMC K100M matrix and a commercial sustained-release product, and the similarity between the matrix and the product had a similarity factor of virtually identical dissolution performance. Kinetic modelling and swelling-erosion information verified that the release of drugs in both the natural-polymer and HPMC matrices was anomalous and diffusion-controlled. Transitory accelerated stability investigations also indicated that the natural-polymer formulation was physically intact with drug content and release profiles within three months thereby justifying the use of chitosan-xanthan matrices as potential naturally available alternatives to HPMC in sustained-release metformin tablet preparation.

## DECLARATIONS

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None.

### Ethical approval

None provided.

### Use of Artificial intelligence/Large language models

The authors confirm that AI-based tools were used solely for language editing and manuscript polishing purposes (e.g., grammar, phrasing, and clarity). No AI tools were used to generate content, interpret data, or influence study design, results, or conclusions. All intellectual contributions, study analyses, and interpretations reported in the manuscript are the original work of the authors.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Conflict of interest

No conflict of interest is associated with this work.

### Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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