

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Research Article

Design and Evaluation of Time Dependent Delayed-Release Diclofenac Sodium Tablets for Chronopharmaceutical Drug Delivery

J. Sackey^{1*}, A. K. Olowosulu¹, A. Abdulsamad¹, S. Gwary¹

¹Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria

ARTICLE INFO

Received: 06/07/2019
Revised: 25/12/2019
Accepted: 21/02/2020

*Corresponding author.
Tel.: +234 8063969143

E-mail:
phinieplus@gmail.com

KEYWORDS: Diclofenac sodium, Press-coated tablets, Chronotherapy, Rheumatoid arthritis.

ABSTRACT

This research was aimed at formulating and evaluating time dependent delayed-release diclofenac tablets for chronopharmaceutical drug delivery using press-coating technology. Rapid disintegrating diclofenac core tablets were initially formulated using the direct compression method. Coats of powdered tragacanth or xanthan gum alone, and in combination in various mixing ratios of 25:75, 40:60, 50:50 and 75:25 were compressed around the core tablet to form 3- layered tablets. The press-coated tablets were evaluated for post compression parameters such as weight variation, crushing strength, friability as well as, swelling index, lag time and *in vitro* release studies in three different simulated gastro-intestinal fluids. The result revealed that the core and compression coated tablet formulations were within the official specified limits. The release profile of the press coated tablets exhibited lag times depending upon the type, amount and polymer combination ratio in the tablet coat. Optimization was done using analysis of variance (ANOVA). The optimized batch F6 which consisted of 40% xanthan and 60% tragacanth gave a lag time of 6 h followed with burst release and complete drug release of 98.51%. This research shows that press-coated diclofenac tablets with 40:60% xanthan and tragacanth gum coat can be exploited in chronopharmaceutical delivery of diclofenac sodium.

©BY 4.0 Open Access 2019 – University of Huddersfield Press

INTRODUCTION

The oral route remains the most frequently used route for drug administration because of the low cost of the therapy, ease of administration and high levels of patient compliance (Peter, 2013). However, some disadvantages still exist which include possible inactivation of the drug by the gastrointestinal tract enzymes, poor bioavailability with poorly soluble drugs e.g. griseofulvin and extensive metabolism (first-pass effect) of certain drugs like propranolol, may occur via this route (Verma et al., 2010). This has led to the development of the modified-release or non-conventional release systems.

A modified-release drug delivery system simply means that the release of the drug from the dosage form has been modified or manipulated in a way with respect to an immediate-release delivery of the same drug, with the specific aim of delivering the active pharmaceutical ingredient at desired rates, pre-

defined time points, or specific sites along the gastrointestinal tract and has led to improved patient compliance and reduced side effects of the drugs (McConnel and Basit, 2013).

A classic example of the modified release system is the chronopharmaceutical drug delivery system (ChrDDS) which releases a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy (Wal et al., 2009). To achieve a chronopharmaceutical pattern of drug delivery, development of delayed release tablets is one of the promising time specific delivery systems that release the drug after a predetermined lag time, such that upon administration of the drug by 10 pm, the release is delayed by 6 h followed by a burst release (immediate release) of the drug between 4 and 6 am to coincide with the time of peak symptom manifestation of the disease. The lag time of the delayed release tablets which is the period of no drug release or less than 10% drug release depends on the

nature of therapeutic application, type and amount of polymer coat and the core to coat ratio of the tablets. Press-coating is becoming a technique of great interest in the formulation of delayed release tablets due to its advantages over liquid coating and other solid dosage forms (Pawar et al., 2014).

The ChrDDS is required especially for the treatment of diseases with established circadian rhythm in their pathogenesis, such as bronchial asthma, cardiovascular diseases, duodenal ulcer and arthritis with mainly night or early morning symptoms (Belgamwar et al., 2008). Rheumatoid arthritis exhibits variation in symptoms, with patients experiencing exacerbated pain and joint stiffness in the early morning (Ingpen, 1968). This correlates with an early morning rise in circulating levels of pro-inflammatory cytokines, such as interleukin-6, -1 and tumor necrosis factor (Arvidson et al., 1994). Chronotherapy for all forms of arthritis can be achieved using non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac sodium and should be timed to ensure that the peak blood levels of the drug coincide with peak pain.

The objective of this research is to explore the use of powdered tragacanth or xanthan gums alone and in combination as press coats over diclofenac core tablets. The ability of the formulations to retard drug release in the upper gastrointestinal tract and give a burst release after a predetermined lag time of 6 h was evaluated.

MATERIALS AND METHODS

Materials

Diclofenac sodium powder BP (D/428/15, Unilab Chemical & Pharmaceuticals, India), ludipress®, sodium starch glycolate, sodium lauryl sulphate, tragacanth gum, xanthan gum. All other chemicals used were of analytical grade.

Methods

Drug-excipient compatibility studies

Fourier transform infra-red (FT-IR) studies

Sample of the pure drug (diclofenac sodium) and the physical mixture of the polymer blend (xanthan and tragacanth) and drug were mixed with IR grade potassium bromide and converted into transparent pellets (1 ton/cm²) with a hydraulic press and scanned from 4000 to 650 cm⁻¹ using a Shimadzu instrument (Model FTIR-8300S, Tokyo, Japan). The resultant FT-IR spectra scan was examined for the presence of characteristic and diagnostic peaks of drug, shifting of drug peaks, and the generation of

new peaks as a result of drug-excipient interaction (Mohire and Yadav, 2010).

Compression of diclofenac core tablet

The core tablets were prepared by the direct compression method (Table 1). Diclofenac sodium (50%) was geometrically mixed with ludipress, sodium starch glycolate (6%) and sodium lauryl sulphate (0.75%) for 5 min in a glass jar. Magnesium stearate (0.25%) was added to the powder blend and mixed for 3 min to get a homogenous blend. The powder mix (200 mg total tablet weight) was compressed into tablets at a 7.0 MN/m² compression pressure on the single stroke tablet press (Erweka AR 400 Germany) equipped with the 8 mm punch and die assembly.

Table 1. Formula for preparing diclofenac core tablets

Ingredients	Per tab (mg)
Diclofenac (50%)	100
Ludipress (43%)	86
S.S.G (6%)	12
S.L.S (0.75%)	1.5
Mag. Stearate (0.25%)	0.5
Tablet weight	200

*Key: S.L.S - Sodium lauryl sulphate, S.S.G - Sodium starch glycolate

Evaluation of diclofenac core tablets

The weight variation of 20 core tablets was determined on an electronic balance (Digital Balance top loading HF 2000 (USA) followed by the calculation of the mean. The average thickness and diameter of 10 core tablets were measured using the Digital Vernier Calliper (USA) TOH-700K (USA). The mean hardness of 5 core tablets was determined using the Monsanto hardness tester (Phillips Harris Ltd, England). The average friability of 10 core tablets was determined in the Erweka friabilator Type A3R, (Germany). The mean disintegration time of 6 core tablets was determined in the Erweka Disintegration apparatus (Type ZT3, Germany) while the dissolution study was performed using the Multipurpose DGN Dissolution Apparatus (Shanghai China). All the evaluations were carried out in triplicate.

Compression-coating of diclofenac core tablets

A sample of 200 mg diclofenac core tablet was coated as shown in Table 2. The appropriate quantity of the single polymer or mixture of polymers was geometrically mixed with microcrystalline cellulose (diluent), talc (glidant) and magnesium stearate (lubricant). 50% w/w of the calculated polymer coat was placed into the 12 mm die cavity; the core tablet was centrally placed carefully and the die cavity filled

with the remaining quantity (50% w/w) of coat and finally compressed into tablets using the single stroke

tablet press (Erweka AR 400 Germany) at 6.0 MN/m² compression pressure.

Table 2. Formula for preparing diclofenac sodium compression-coated tablet

Materials	F1	F2	F3	F4	F5	F6	F7	F8
Xanthan	348.0	-	304.5	-	76.13	121.80	152.25	228.38
Tragacanth	-	348.0	-	304.5	228.38	182.70	152.25	76.13
MCC	40	40	35	35	35	35	35	35
Talc	8	8	7	7	7	7	7	7
Mag.St	4	4	3.5	3.5	3.5	3.5	3.5	3.5
Total (mg)	400	400	350	350	350	350	350	350

*Key: MCC – Microcrystalline cellulose, F1 -Diclofenac sodium tablet compression coated with xanthan powder (400mg), F2 - Diclofenac sodium tablet compression coated with tragacanth powder (400mg), F3 -Diclofenac sodium tablet compression coated with xanthan powder (350mg), F4 -Diclofenac sodium tablet compression coated with tragacanth powder (350mg), F5 - Diclofenac sodium tablet compression coated with binary mixture of Xan:Trag (25:75) 350mg, F6 -Diclofenac sodium tablet compression coated with binary mixture of Xan:Trag (40:60) 350mg, F7 -Diclofenac sodium tablet compression coated with binary mixture of Xan:Trag (50:50) 350mg, F8 -Diclofenac sodium tablet compression coated with binary mixture of Xan:Trag (75:25) 350mg

Evaluation of compression-coated tablets

The formulated compression-coated tablets were evaluated for average weight, thickness, diameter, hardness, friability and drug content as per same procedure followed by core tablet. In addition, the following parameters were evaluated;

Swelling studies

A modification of the method of Singh et al., 2012b was adapted. One (1) tablet from each batch was randomly selected, weighted (M_o) and placed in a petri dish containing 10 ml of 0.1 N HCL (pH 1.2 buffer) for the first 2 h and followed by phosphate buffer (pH 7.4) for 8 h. The tablet was removed after every hour and blotted with a tissue paper to remove the excess fluid then weighed again (M_t). This procedure was repeated 9 times that is for 10 h. The % water uptake was calculated as thus;

$$\text{Swelling index (\%)} = \frac{M_t - M_o}{M_o} \times 100 \dots\dots\dots(1)$$

Where M_t = weight of tablets at time t , M_o = initial weight of tablet

In-vitro drug release studies

The *in-vitro* drug release studies were carried out using the basket method in the DGN multipurpose, dissolution rate test apparatus at $37 \pm 1^\circ\text{C}$ and 100 rpm under sink condition. The dissolution was started in 900 ml of acidic buffer of pH 1.2 (simulated gastric fluid; SGF) for the first 2 h; simulating the average gastric residence time, then continued in phosphate

buffer pH 7.4 (simulated intestinal fluid; SIF) for the next 3 h; representing the average intestinal residence time. The media was then replaced with phosphate buffer pH 6.8 (simulated colonic fluid; SCF) until the end of the experiment. At predetermined time intervals (every hour until the end of the experiment), one (1) ml of sample was withdrawn and replaced with the same volume of the specified medium after each withdrawal. The withdrawn sample was diluted to 10 times its volume and analysed at 276 nm using a UV Spectrophotometer. The amount of diclofenac sodium released from the tablet was determined using the calibration curve.

Lag time determination

The lag time is the period of no drug release or less than 10% drug release. The lag time (t_{10}) and release time (t_{80-100}) represent the times in hr of 10 % and 80-100% drug release, respectively. The lag time for the different batches was determined using the data from the *in-vitro* dissolution study of the compression coated tablets.

Similarity factor determination

The method of Shah et al., 1998 was adopted.

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \dots\dots\dots(2)$$

Where R_t = cumulative percentage of reference product dissolved at time t , T_t = cumulative percentage of test product dissolved at time t , n = number of time points.

Kinetic modeling

Data obtained from the *in-vitro* dissolution studies were inserted into different kinetic models including zero order, first order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas; the equations from Harris-Shoab et al., (2006) were adapted.

Statistical analysis and data presentation

Analysis of variance (one-way ANOVA) was used to compare the tablet properties across different categories of data sets using SPSS software. Differences were considered significant for *p* values <0.05. The results obtained were presented as Mean, Standard error of the mean (SEM) and Percentages (%) in tables and figures.

RESULTS AND DISCUSSION

Drug-excipient compatibility studies

The FT-IR spectra data of pure diclofenac sodium (figure 1) show principal characteristic peaks at 3388 cm⁻¹, 3257 cm⁻¹, 1572 cm⁻¹, 1304 cm⁻¹ and 745 cm⁻¹ corresponding to the functional groups N-H stretch, O-H stretch, C=O stretch, C-N stretch, and C-Cl stretching. The characteristic peaks between 3257 cm⁻¹ – 1572 cm⁻¹ indicate stretching frequency as a result of the carboxylic groups present. It also serves as a diagnostic peak for carbonyl groups of organic acids and the major functional group of diclofenac sodium which belongs to the anthranilates group of non-steroidal anti-inflammatory drugs. The spectra data from the combination of diclofenac sodium and the polymers (xanthan and tragacanth) show all the principal characteristic and diagnostic peaks related to pure diclofenac sodium with their positions remaining unchanged. This usually confirms the absence of interaction between the drug and the different polymers (Vyas et al., 2009).

Evaluation of diclofenac core tablets

The average weight of the core tablets (table 3) conformed to the USP and BP specification of weight variation which states that the allowed tablet weight variation for an average of 200 mg is $\pm 7.5\%$ indicating uniform filling of the die due to good flow of the powder. The core tablets showed uniform thickness and diameter as shown in table 3. The hardness and friability of the core tablets were found to be within the pharmacopeia limits indicating that the tablets were compact and hard. The disintegration time was fast (3.3 min) and conformed to the EP specification for rapid disintegrating tablets (E.P, 2007). This can be as a result of the high concentration of superdisintegrant (6% w/w) in the formulation. Drug

release from the core tablet was fast and showed more than 90 % release within 5 min (figure 3) and can be attributed to the presence of the wetting agent (SLS 0.75 %) incorporated in the formulation. The core tablets were designed to release the active ingredient very fast so as to achieve fast and complete drug release in the colon after a lag phase of 6 h. The drug content of core tablet was found to be within the pharmacopeia limits as shown in Table 3.

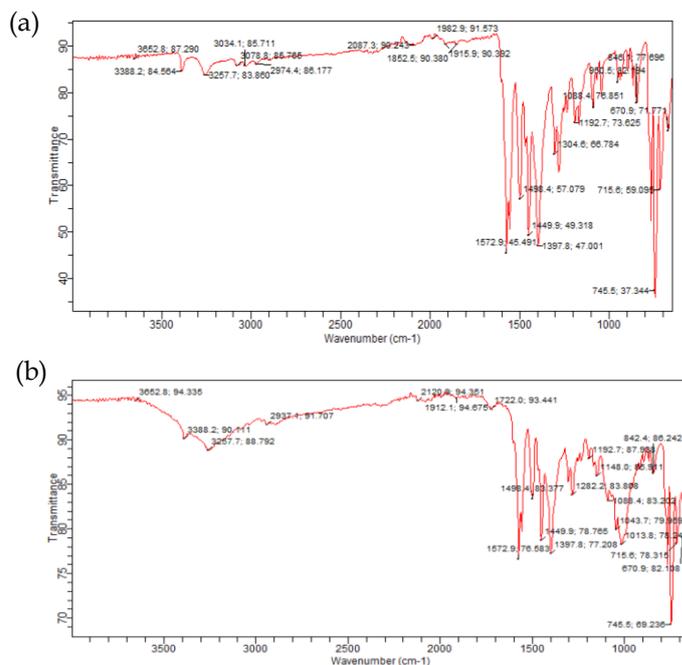


Fig. 1. FT-IR spectra of (A) pure drug, (B) physical mixture of drug and excipients

Evaluation of compression-coated diclofenac tablets

All the batches of coated tablets had tablet weight variation within the range of the allowed deviation of $\pm 5\%$ of the total tablet weight as specified by the B.P (2002). The thickness of the coated tablets were much higher than the core as a result of the coat applied unto the core. The thickness and diameter of the formulations coated with 350 mg coat (F3 – F4) were significantly lower at *p* < 0.05 than formulations coated with 400 mg coat (F1 – F2) as a result of the higher concentration of polymer used to coat the latter (Table 3). The thickness and diameter of tablets coated with 350 mg coat weight (F3 – F8) were also significantly different at *p* < 0.05 across the different polymers and their combinations; this could be attributed to differences in the densities of the different polymers and their combinations. The crushing strength of all the coated tablets were much higher than the core tablet and can be attributed to the

formation of strong inter-particulate bonds around the core (Prabhu et al., 2010). The crushing strengths of all the coated formulations were similar irrespective of the type or combination of polymers used for coating. The friability values of the coated formulations were less than 1 %, indicating that the polymers conferred sufficient mechanical strength unto the tablets making them resistant to shock and abrasion. All the coated formulations have drug content values within the official limit of 95 - 105 % (USP, 2007).

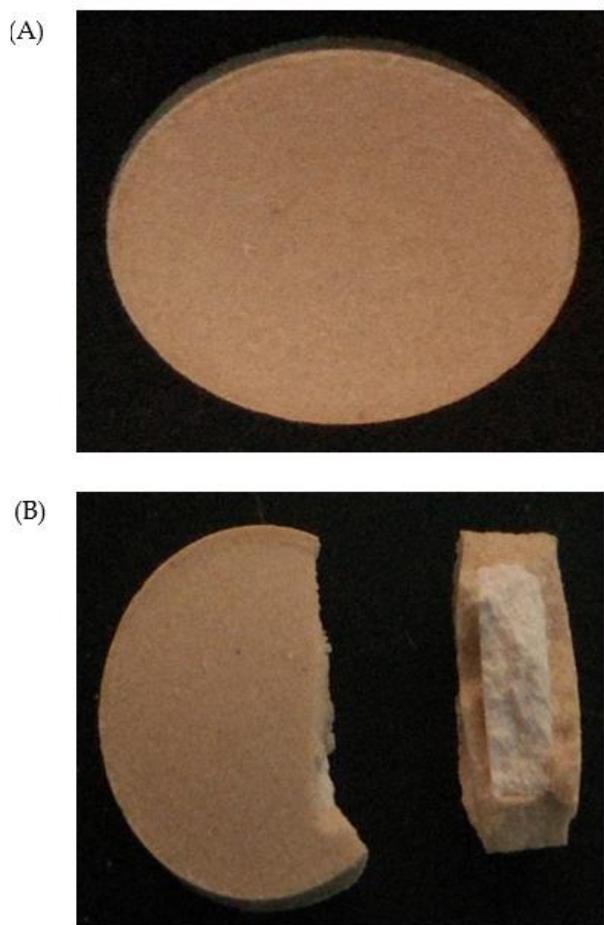


Fig. 2. A) Transverse view and B) Longitudinal view of compression-coated tablets.

Effect of polymer-coating on swelling of diclofenac tablets

The amount and type of polymer used as coating agents influence the degree of thickness of the hydrated gel layer which in turn determines the diffusion pathlength the drug molecules require to transverse through the polymer mass into the dissolution medium. In addition, variation of pH of the buffer could influence hydration, swelling, erosion and drug release profiles of ionic polymers

(Perez-Marcos et al., 1996). The coated tablets showed significant difference ($p < 0.05$) in their swelling capacities.

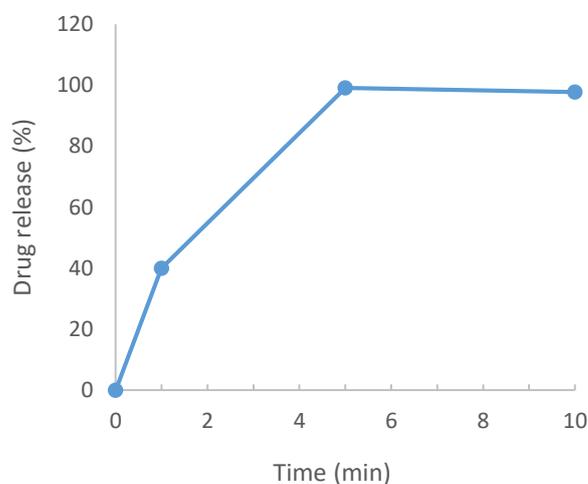


Fig. 3. Drug release (%) versus time (min) of diclofenac core tablets in phosphate buffer 6.8

On exposure of tablets to the aqueous buffer, the formulations containing 400 mg polymer coat (F1 - F2) showed greater water uptake in comparison to formulations coated with 350 mg polymer coat (F3 - F4) (Figure 4). This could be attributable to the presence of greater amount of polymer chains necessary for bonding in the former than the latter and will enable the production of more stable viscous gel layer around the tablet and maintain tablet integrity for a longer time (Omidan and park, 2008).

Formulations F1 and F3 coated with 400 mg and 350 mg xanthan gum powder exhibited an initial low swelling in SGF followed by rapid swelling and increase in tablet weight in SIF and required more than 10 h to achieve maximum swelling. This could be attributable to the higher solubility, viscosity and swelling ability of xanthan gum at higher pH in addition to small degree of erosion due to polymer relaxation (Jagdale and Pawar, 2014). This confirms the report by Singh et al., (2012b) with the use of xanthan gum.

Conversely, formulations F2 and F4 coated with 400 mg and 350 mg tragacanth gum powder exhibited rapid swelling and increase in weight in the first 2 h in the SGF to a greater extent than those coated with xanthan, indicating greater gel formation around the tablets in the SGF and will eventually influence drug

Table 3. Physical properties of diclofenac core and compression-coated tablets. Values in parentheses represent standard error of mean (n=3)

Parameters	Core	F1	F2	F3	F4	F5	F6	F7	F8
Mean weight (mg)	199 (0.33)	601 (0.33)	600 (0.57)	552 (0.57)	551 (0.57)	550 (0.00)	550 (0.01)	550 (0.01)	551 (0.57)
Diameter (mm)	8.06 (0.01)	12.25 (0.01)	12.15 (0.01)	12.15 (0.01)	12.06 (0.01)	12.06 (0.00)	12.01 (0.01)	12.11 (0.00)	12.12 (0.00)
Thickness (mm)	4.05 (0.12)	4.51 (0.03)	4.35 (0.04)	4.42 (0.01)	4.27 (0.01)	4.32 (0.01)	4.34 (0.01)	4.35 (0.01)	4.37 (0.01)
Crushing strength (kgf)	6	20	20	20	20	20	20	20	20
Content uniformity (%)	100.34	100.96	100.46	99.46	101.45	100.31	102.45	101.95	99.96
Friability (%)	0.97	0.00	0.00	0.00	0.36	0.30	0.29	0.27	0.18
Disintegration time (min)	3.3	ND							

*Key: ND - not determined, F1 -Diclofenac sodium tablet compression coated with xanthan powder (400mg), F2 - Diclofenac sodium tablet compression coated with tragacanth powder (400mg), F3 - Diclofenac sodium tablet compression coated with xanthan powder (350mg), F4 -Diclofenac sodium tablet compression coated with tragacanth powder (350mg), F5 -Diclofenac sodium tablet compression coated with binary mixture of xan: trag (25:75) 350mg, F6 - Diclofenac sodium tablet compression coated with binary mixture of xan: trag (40:60) 350mg, F7 - Diclofenac sodium tablet compression coated with binary mixture of xan: trag (50:50) 350mg, F8 - Diclofenac sodium tablet compression coated with binary mixture of xan: trag (75:25) 350mg.

transport in the SGF; this was followed by a sudden decrease in weight gained after about 5 and 4 h respectively indicating the onset of erosion after maximum swelling in the SIF, implying that swelling index is dependent on pH of the medium and amount of polymer in the coating material. This predominant effect on swelling in the SGF can be attributable to the higher solubility, viscosity and swelling ability of tragacanth at lower pH (Weller, 2009).

The formulations coated with the combination of xanthan and tragacanth (F5 – F8) however exhibited moderate swelling which was lower than the tablets coated with xanthan alone but higher than those coated with tragacanth alone (Figure 5). As the concentration of xanthan in the press-coated tablets increased (F5 – F8), a reciprocal increase in the swelling index of the tablets was observed.

Conversely, as the tragacanth concentration increased in the press-coated tablets (F5 – F8) the water uptake capacity of the tablets decreased in the SIF. The effect of xanthan here is evident in retarding erosion due to the presence of tragacanth and shows an improvement of the combination over the formulations coated with tragacanth alone.

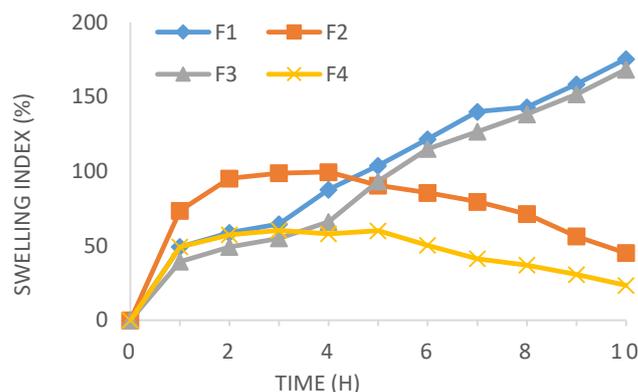


Fig. 4. Weight gain (%) Versus time (h) of diclofenac tablets press-coated with XAN alone and TRAG alone in the simulated GI fluids.

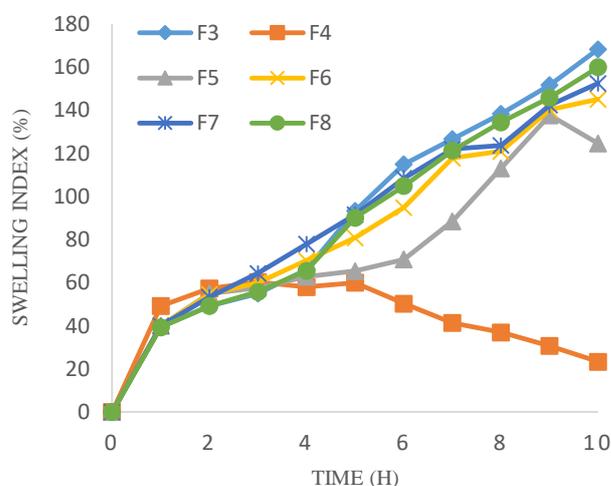


Fig. 5. Weight gain (%) Versus time (h) of diclofenac tablets press-coated with XAN alone, TRAG alone and XAN + TRAG combination in the simulated GI fluids.

Effect of polymer-coating on drug release

A successful drug delivery system for chronotherapy of rheumatoid arthritis is expected to retard drug release for 6 h in the upper GIT (simulated gastric fluid and simulated intestinal fluid) or allow only minimal drug release of less than 10 % in the upper GIT but release the drug promptly after a predetermined lag phase of 6 h.

Hydrophilic polymers have been reported to rapidly form a surface “gel” layer on exposure to aqueous media; undergo hydration followed by a progressive plasticization of the polymer leading to swelling and as the chains uncoil and extend, more locations become available for hydrogen bonding and further molecular entanglements (Reddy et al., 2016). The overall result is an increase in the thickness of the gel layer surrounding the tablet, which serves as a barrier to influx of dissolution media into the core and increases the diffusion path length for transport of the dissolved drug into the dissolution media, which consequently retards rate of drug release.

A direct correlation can be observed between the type of polymer, amount of polymer, swelling capacity, dissolution medium and lag time of the coated tablets. No drug release was observed from formulations F1 and F3 coated with xanthan alone in the SGF, 0.008 % and 2 % respectively was released after 6 h and complete release was achieved at 14 and 12 h respectively showing slower release than observed for other formulations. This can be attributed to the ability of xanthan to form thick and stable gelatinous layer around the tablet core causing an increase in the diffusion path length for transportation of dissolved drug and retarding the rate at which the drug is released. These findings conform to the report by Mor and Nanda, (2011) in the evaluation of guar and xanthan gum in the formulation of ibuprofen colon drug delivery.

Drug release from formulations F2 and F4 containing tragacanth alone was 0.08 % and 0.5 % respectively in the SGF, 68 % and 100 % respectively in the SIF (Figure 6) and complete release was achieved at 6 and 5 h respectively which shows faster release than observed in formulations coated with xanthan and may be due to the inability of tragacanth to maintain the integrity of the tablet at higher pH. The low release in SGF correlates with the result of higher swelling in SGF.

Formulations coated with tragacanth exhibited better ability to offer barrier to drug release in the upper GIT (SGF) but failed at retarding drug release for 6 h and may be attributed to the higher viscosity of tragacanth at low pH resulting in the formation of stable gelatinous layer that acts as a barrier around the tablet core hence preventing release in the SGF. However, the viscosity of tragacanth decreases with increase in pH which eventually supports the dissolution of the gelatinous barrier at higher pH resulting in faster drug release.

In the formulations containing xanthan and tragacanth gum coating mixtures (F5, F6, F7 and F8), no release was observed in the SGF and 63 %, 11 %, 8% and 4% respectively was released after 6h (Figure 6). The result shows the ability of batches F6, F7 and F8 to retard drug release by 6 h in the upper GIT and shows a direct correlation with the result of the swelling profile. Complete release was achieved at the 8 h, 8 h, 9 h and 11 h respectively. This indicated an improvement of the combination polymers over the single polymer coated tablets because the looser gels formed with tragacanth at higher pH are more susceptible to matrix erosion and lead to faster drug release and are therefore unable to retard drug release by 6 h, while the stronger gels formed with xanthan, though they successfully retard drug release by more than 6 h are unable to provide prompt and complete release after the desired lag phase. However, a combination of the polymers produced a suitable gel on swelling which resulted in better control over drug release. The coated tablets showed significant difference ($p < 0.05$) in their drug release profiles.

All the coated formulations exhibited “burst-release” at different times in the simulated fluids indicating the onset of erosion of part or most of the outer hydrophilic polymer layer. When the hydrophilic polymer layer swelled adequately, it allowed influx of sufficient dissolution medium into the core tablet. The synergy between the wetting agent (SLS) and the superdisintegrant (SSG) present in the core allowed rapid penetration of dissolution medium into the core tablet followed with extensive swelling of the core tablet which exerted pressure on the outer layer resulting in burst release of the drug (Khadabadi et al., 2013). The “burst-release” from the optimized formulation F6 was between 6 and 8 h with 11 – 100 %

release, which was more rapid than the burst observed from the other coated formulations.

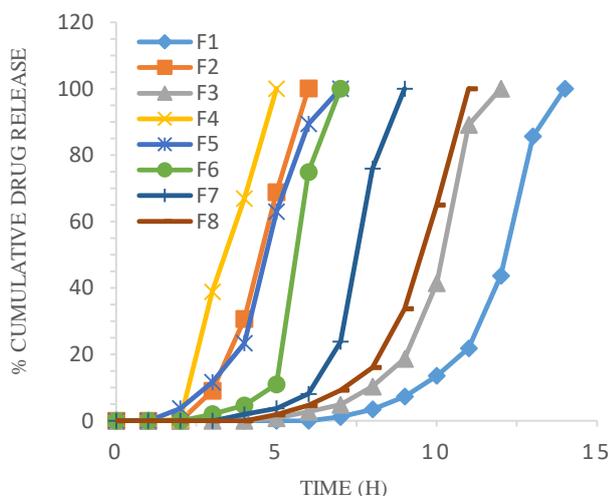


Fig. 6. Drug release profile of press-coated diclofenac tablets in the simulated GI fluids.

Effect of polymer-coating on lag time

From the *in vitro* dissolution profile of the press coated tablets (Fig. 6), it is evident that a lag phase was allowed before rapid release of the drug. All the batches exhibited variable lag times and showed a direct correlation between the type of polymer, amount of polymer, polymer combination and swelling capacity of the coated tablets. Batches F1 and F3 produced tablets with the highest lag times of 9 and 7 h respectively, while F2 and F4 produced tablets with lag times of 3 and 2 h respectively showing a direct relationship with the amount of polymer and swelling capacity. Noticeably, the lag times of tablets coated with tragacanth were significantly shorter than those coated with xanthan because of the lower viscosity and the hydrogel strength of tragacanth in comparison with xanthan at higher pH.

Batches F5 – F8 produced tablets with variable lag times and exhibited a direct correlation with the swelling index. The tablets showed moderate lag times which were lower than the tablets coated with xanthan alone but higher than those coated with tragacanth alone with the range between 3 and 7 h.

Comparison of dissolution profile of compression-coated tablets

Data from the similarity factor determination (table 5) show that the dissolution profile of formulations F3 and F8 as well as F6 and F7 are similar. This implies that the dissolution profiles of all the other

formulations are significantly different from the formulations containing only xanthan at the corresponding concentration and suggest that the formulations F6 or F7 can be successfully used for chronotherapeutic delivery of diclofenac sodium.

Table 4. Parameters derived from dissolution profile of compression-coated tablets.

Formulations	Lag time (h)	Time for complete drug release (h)
F1	9	14
F2	3	6
F3	7	12
F4	2	5
F5	3	8
F6	5	8
F7	6	9
F8	7	11

Table 5. Comparison of dissolution profile of compression-coated tablets

Batches	Similarity factor (<i>f</i> ₂)	Inference
F1 and F2	35	NS
F3 and F4	20	NS
F3 and F5	18	NS
F3 and F6	22	NS
F3 and F7	24	NS
F3 and F8	50	S
F6 and F7	55	S

*Key: S = similar; NS = not similar

Kinetics and mechanism of drug release from compression-coated tablets

All the coated formulations except F2 and F4 (coated with 400 mg and 350 mg tragacanth powder) showed linearity to the Hixson-Crowell model (table 6) which describes the drug release by dissolution with changes in surface area and diameter of the particles of the tablet. While batches F2 and F4 showed linearity to zero order kinetics implying that drug release was independent of time or initial concentration. The mechanism of drug release was analysed using the Korsmeyer-Peppas model. The '*n*' values of all the formulations except F1 were between 1.65 and 2.58, and indicates swelling-controlled release also known as super case II transport. This value implies that the drug release from the prepared formulations was due to both diffusion and polymeric chain relaxation. While batch F1 with '*n*' value of 0.58 signifies that

anomalous or non-fickian diffusion was the mechanism for drug release.

Table 6. Kinetics and Mechanism of drug release from compression-coated tablets

Kinetics	F1	F2	F3	F4	F5	F6	F7	F8
Zero order, r^2	0.6814	0.823	0.7390	0.8751	0.8354	0.5832	0.8499	0.6062
First order, r^2	0.4708	0.0324	0.5055	0.6329	0.6339	0.4014	0.7015	0.5792
Higuchi model, r^2	0.5328	0.5860	0.4279	0.6415	0.6108	0.3802	0.6293	0.4113
Hixson-crowell model, r^2	0.9017	0.0058	0.8811	0.8722	0.9661	0.9212	0.952	0.9168
Korsemeyer-peppa's model, r^2	0.6872	0.7032	0.6459	0.4216	0.9072	0.3543	0.6322	0.6890
n	0.5888	2.097	1.6508	2.019	2.581	2.4754	2.0666	1.763
Predominate kinetics	HC	ZO	HC	ZO	HC	HC	HC	HC

CONCLUSION

A chronopharmaceutical drug delivery system was designed by press coating technique and evaluated in accordance with the pharmacopoeia specifications. The results from this investigation revealed that the formulation F6 comprising of 40: 60 xanthan: tragacanth combination achieved a burst release of drug in the simulated colonic fluid after a lag time of 6 h with very minimal release in the simulated upper gastro intestinal tract and can therefore be exploited as press-coating agent for chronotherapeutic delivery of diclofenac sodium in the management of rheumatoid arthritis.

REFERENCES

Arvidson, N. G., Gudbjornsson, B., Elfman, L., Ryden, A. C., Totterman, T. H. and Hallgren, R., 1994. Circadian rhythm of serum interleukin-6 in rheumatoid arthritis. *Ann Rheum Dis*, 53:521-524.

Belgamwar, V. S., Gaikwad, M. V., Patil, G. B., and Surana, S., 2008. Pulsatile drug delivery system. *Asian Journal of Pharmaceutics*, 141-145.

British Pharmacopoeia (BP) 2002. Her Majesty's stationary office, university, press, Cambridge, London. 1 and 2.

European Pharmacopoeia, 6th edition, Council of Europe, Strasbourg 2007.

Harris-Shoaib, M., Jaweria, T., Merchant, M. H. And Yousof, R. I., 2006. Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. *Pakistan Journal of Pharmaceutical Science*, 19(2), 119-124.

Ingpen, M. L., 1968. The quantitative measurement of joint changes in rheumatoid arthritis. *Ann Phys Med*, 9:322-327.

Jagdale, S. C., and Pawar, C. R., 2014. Application of design of experiment for polyox and xanthan gum coated floating pulsatile delivery of sumatriptan

succinate in migraine treatment. *BioMed Research International*, pp 1-10.

Khadabadi, S. S., Chishti, N. H., Khan, F. M., and Tadvee, A. A., 2013. Formulation and evaluation of press coated tablet of ketoprofen - a chronotherapeutic approach. *International Journal of Pharmacy and Pharmaceutical Sciences*, 5(3), 733-740.

McConnel, E. L., and Basit, A. W., 2013. Modified-release oral drug delivery. In M. E. Aulton & K. M. G. Taylor (Eds.), *Aulton's pharmaceutics: the design and manufacture of medicines* (pp. 7-19). Edinburgh: Churchill Livingstone Elsevier.

Mohire, N. C., and Yadav, A. V., 2010. "Novel approach to formulate β - cyclodextrin complexed mouth dissolving tablet of metronidazole and its in-vitro evaluation. *Journal of Pharmacy Research*, 3(3), 662-667.

Mor, J., and Nanda, A., 2011. Formulation and Evaluation of a Colon Targeted Drug Delivery System Using Ibuprofen as a Model Drug. *The Pharmaceutical Research*, 5(1), 176-183.

Omidian, H., and Park, K., 2008. Advances in superporous hydrogels. *Journal of Controlled Release*, 102, 3-12.

Pawar, R., Jaimini, M., Chauhan, B. and Shamar, S., 2014. Compression coated tablets as drug delivery systems (tablet in tablet); A review. *International Journal of Pharmaceutical Research and Development*, 6(1), 21-33.

Peter, Y., 2013. Design of dosage forms. In M. E. Aulton & K. M. G. Taylor (Eds.), *Aulton's pharmaceutics: the design and manufacture of medicines* (pp. 7-19). Edinburgh: Churchill Livingstone Elsevier.

Perez-Marcos, B., Ford, J. L., Armstrong, D. J., Elliot, P. N., Rostron, C., and Hogan, J. E., 1996. Influence of pH on the release of propranolol hydrochloride from matrices containing hydroxypropyl methylcellulose K4M and Carbopol 974. *Journal of Pharmaceutical Science*, 85, 330-334.

- Prabhu, P., Nissara, A., Harish, N. M., Mohd, G. A., Narayanacharyulu, D. S., and Evs, S., 2010. Investigation and comparison of colon specificity of novel polymer khaya gum with guar gum. *Pakistan Journal of Pharmaceutical Sciences*, 23(3), 259-265.
- Reddy, M. N. K., Bandari, S., and Jaswanth, A., 2016. Development and Characterization of Press Coated Tablet of Flurbiprofen: A Chronotherapeutic Approach. *Asian Journal of Pharmaceutics*, 10(4), S727-S735.
- Shah, V. P., Tsong, Y., Sathe, P., and Liu, J. P., 1998. *In-vitro* dissolution profile comparison-statistics and analysis of the similarity factor, f₂. *Pharmaceutical Research*, 15, 889-896.
- Singh, P. K., Shukla, T. S., Easwari, T. S., Kumar, S. and Chudhary, R., 2012^b. formulation, development and evaluation of mucoadhesive oral dosage form containing clarithromycin using different mucoadhesive polymers. *International Journal of Pharmaceutical Science and Health Care*, 2(2), 159-171.
- United States Pharmacopoeia., 2007. Diclofenac sodium delayed release tablet, pp.30-25.
- Verma, P., Thakur, A. S., Deshmukh, K., Jha, A. K. and Verma, S., 2010. Routes of drug administration. *International Journal of Pharmaceutical Studies and Research*, 1, 54-59.
- Vyas, V., Sancheti, P. and Karekar, P. (2009). Physicochemical characterization of solid dispersion systems of tadalafil with poloxamer 407. *Acta pharmaceutica*, 59, 453-461.
- Wal, P., Wal, A., Rai, A. K. and Saxena, A., 2009. *Journal of Pharmaceutical Science and Technology*, 1(2), 59-62.
- Weller, P. J., 2009. Tragacanth. In; Handbook of Pharmaceutical Excipients, 6th edition, pharmaceutical press, London: pp 744-746.