Drug Development and Industrial Pharmacy

ISSN: 0363-9045 (Print) 1520-5762 (Online) Journal homepage: https://www.tandfonline.com/loi/iddi20

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To cite this article: Gulzar Muhammad, Muhammad Tahir Haseeb, Muhammad Ajaz Hussain, Muhammad Umer Ashraf, Muhammad Farid-ul-Haq & Muhammad Zaman (2020) Stimuli-responsive/smart tablet formulations (under simulated physiological conditions) for oral drug delivery system based on glucuronoxylan polysaccharide, Drug Development and Industrial Pharmacy, 46:1, 122-134, DOI: 10.1080/03639045.2019.1706551

To link to this article: https://doi.org/10.1080/03639045.2019.1706551

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY
2020, VOL. 46, NO. 1, 122–134
https://doi.org/10.1080/03639045.2019.1706551

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RESEARCH ARTICLE

Stimuli-responsive/smart tablet formulations (under simulated physiological conditions) for oral drug delivery system based on glucuronoxylan polysaccharide

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ABSTRACT

Objective: Development of stimuli-responsive intelligent drug delivery system (based on a polysaccharide, glucuronoxylan [GX]) with on-off switching properties under physiological conditions.

Significance: As GX exhibits high swelling index and stimuli-responsive swelling/de-swelling properties, therefore, this material appeared highly useful to design pH, solvent and ionic stress-sensitive oral tablet formulations, which offered on-off switching properties. In this way, we could design intelligent/smart drug delivery systems for levosulpiride (LS) and theophylline (TF) with valuable pharmaceutical properties.

Methods: GX-based tablet formulations were explored for stimuli-responsive, reversible swelling–deswelling behavior, dynamic swelling, and its kinetics. Tablet surface and channeling after swelling were observed using scanning electron microscopy (SEM). Drug release study was performed mimicking the physiological conditions like pH and transit time of gastrointestinal tract (GIT). Radiographic images of tablet path (*in vivo*) were recorded.

Results: GX-based formulations exhibited high swelling in deionized water (DW), pH 6.8 and 7.4 while negligible swelling at pH 1.2. SEM images discovered the presence of microcracks and nanopores on the surface of tablets and showed channeling after swelling of tablets in DW. Sustained drug release was observed and found directly proportional to the concentration of GX in the formulations with negligible release at pH 1.2. *In vivo* radiographic evaluation indicated the retention of tablets in GIT for 7 h. Hemocompatibility studies showed the non-thrombogenic and non-hemolytic nature of GX.

Conclusions: GX-based smart/stimuli-responsive formulations can control/sustain the release of drugs in GIT.

ARTICLE HISTORY
Received 21 July 2019
Revised 5 December 2019
Accepted 14 December 2019

KEYWORDS
Polymeric biomaterials; polymeric drug delivery system; pH; salts; controlled release; drug targeting

Introduction

Oral administration of the non-steroidal anti-inflammatory drugs (NSAIDs) using conventional delivery systems is associated with certain limitations such as uncontrolled rapid release, stomach pain, gastric bleeding, requirement of multiple doses owing to shorter half-lives, short exposure to targeted site, faster elimination from the body, changed pharmacokinetics, etc. [1]. These limitations can be controlled using polysaccharides-based intelligent drug delivery systems that help the drugs to bypass harsh stomach environment and provide sustained release in the intestine with better efficacy and patient compliance [2–4]. Such drug delivery systems especially based on naturally occurring water-swellable polysaccharides have fascinated the researchers because they provide controlled release of drugs owing to their distinct and reversible stimuli-responsive (temperature, pH, ionic concentration, and enzymes) nature [5–7]. In this context, arabinoxylans [8], rhamnogalacturonan [9], chitosan [10], alginate [11], carrageenan [12], starch [13], pectin [14], etc., have been widely investigated due to their biocompatible and biodegradable nature [15,16]. These smart hydrogels are considered promising candidates for the controlled release of drugs also due to their swelling de-swelling behavior at various physiological pH [17,18].

Besides huge medicinal applications of *Mimosa pudica* (*Mimosaceae*) [19–22], it is also a highly valuable plant as its seeds upon soaking in water extrude a mucilage which mainly consists upon glucuronoxylan (GX), a smart polysaccharide having a high swelling index and hydrogel in nature [17]. GX is a branched structure, which mainly composed of two main components. The major components which constitute the backbone of the GX are xylose, mannose, and glucuronic acid whereas, the minor components are arabinose, glucose, and galactose. These minor components are attached to the backbone and constitute the branches of the GX [23,24].

Our interest is to investigate the swelling behavior and stimuli-responsive nature of GX-based tablet formulations to ascertain the potential of GX even after passing through different stages of tablet preparation especially compression. Stimuli-responsive (under simulated physiological conditions) and sustained/controlled release tablet formulations will be developed and evaluated in detail for two different classes of drugs, i.e. theophylline (TF) and levosulpiride (LS). TF is mainly prescribed in respiratory diseases whereas, LS is an antipsychotic drug. Both drugs are selected for this study due to their different solubility profile/pH-dependent solubility. TF is soluble over a wide range of pH, therefore, such a

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Supplemental data for this article can be accessed here.

drug is potentially beneficial to evaluate the sustained release behavior of a new polymeric material. On the other hand, LS exhibits pH-dependent solubility, hence, it is used to evaluate the drug release pattern from GX-based matrix tablet at different pH simulated to the GIT environment.

The response of GX containing tablets to various stimuli such as pH, ionic concentrations and solvents is investigated here. Herein, we are thoroughly investigating GX tablet formulations for *in vitro* drug release and kinetics at simulated pH of GIT. The physical integrity of the tablets during the gastrointestinal tract (GIT) transit is studied in an animal model using X-ray analysis. We are also focused on hemocompatibility studies of GX in order to extend its possible biomedical applications.

Materials and methods

Materials

Seeds of *M. pudica* (MP) purchased from the local market were of 'Hem Zaden B.V. Netherlands.' After manual cleaning and grading, the seeds were stored at room temperature. Potassium dihydrogen phosphate, *n*-hexane, ethanol, KCl, isopropyl alcohol, NaCl, and HCl were purchased from Riedel-de Haën, Germany. Analytical grade sodium hydroxide (Merck Chemicals GmbH, Darmstadt, Germany) was standardized with oxalic acid before further use. Tragacanth, magnesium stearate, and microcrystalline cellulose used were obtained from Fluka (St. Gallen, Switzerland). All these chemicals were used without further purification. LS and TF were according to United States Pharmacopeia (USP) standard.

Isolation of hydrogel (glucuronoxylan)

GX was isolated according to the already reported method [17] with slight modification. Briefly, clean seeds of MP were soaked in water for 12 h and then warmed at 50 °C for 30 min. Seeds became swell and the hydrogel/mucilage came out from seed coat. This hydrogel was separated simply by filtering through clean cotton cloth. Extracted hydrogel/mucilage was washed with *n*-hexane thrice to remove lipophilic substances as well as with ethanol to remove polar impurities and then dried at 50 °C in a vacuum oven overnight. The dried hydrogel was kept in a vacuum desiccator after grinding and passing through 60 mesh sieve. The yield of GX was 9% (w/w) with respect to the total mass of dried seeds.

Formulation design for GX

Tablet formulations with various proportions of GX were designed to evaluate its stimuli-responsive and sustained release potential for the delivery of TF and LS.

Drug-excipient compatibility study

Purity of isolated GX and its compatibility with active ingredients and other excipients were evaluated through Fourier transform infrared (FTIR) spectroscopy. FTIR spectra of samples were recorded on IR-Prestige-21 (Shimadzu, Japan) spectrometer from 4000 to 400 cm^{-1}. KBr discs of samples were made and dried under vacuum for 30 min at 60 °C before analysis.

Tablets preparation

The evaluation of GX as stimuli-responsive and sustained release agent for oral (tablet) drug delivery systems was carried out using TF and LS as model drugs. Tablets were prepared according to the composition mentioned in Table 1 by the wet granulation method (Supplementary Material). Prepared granules and compressed tablets were passed through pre- and post-compression parameters (Supplementary Material).

Scanning electron microscopy

The surface morphology of the compressed tablet and water-swollen then freeze-dried tablet formulation were examined using FEI Nova, NanoSEM 450 operating at 10 KV, equipped with a low energy Everhart-Thornley detector (ETD) using secondary electrons.

Dynamic swelling and stimuli-responsive evaluation of formulations

Tablet formulations of GX were examined for their stimuli sensitive swelling and on-off switching (swelling de-swelling) properties.

pH-sensitive swelling of GX containing tablet formulations

Various tablet formulations (Table 1) were evaluated for their swelling behavior in buffer solutions of pH 1.2, 6.8, 7.4, and deionized water (DW) at 37 °C (mimicked body temperature) for 10 h [25,26]. Buffer solutions were prepared according to the standard procedure reported in USP 32. Tablets were enclosed in tea bags and placed in DW and buffer solutions of different pH. After fixed time intervals, tea bags were removed from the media and calculated the weight of the swollen tablets. Then, tea bags were again placed in their respective media for further swelling. The swelling study was carried out until no further swelling of the tablets was observed. The swelling capacity or swelling index (*g/g*) was determined using Equation (1).

$$\text{Swelling index } (g/g) = \frac{W_t - W_w - W_i}{W_i} \quad (1)$$

where, W_t is the weight of wet tea bag with swollen tablet, W_w is the weight of wet tea bag (empty) and W_i is the weight of the dry tablet.

Swelling kinetics

The values of normalized (Q_t) and equilibrium degree of swellings (Q_e) were used to find the second-order swelling kinetics (Supplementary Material).

Table 1. Composition of different formulations.

Formulation composition (mg/tablet)	GXF	TF1	TF2	TF3	LS1	LS2	LS3
GX	125	75	100	125	75	100	125
Theophylline	–	100	100	100	–	–	–
Levosulpiride	–	–	–	–	100	100	100
Microcrystalline cellulose	155	105	80	55	105	80	30
Tragacanth	15	15	15	15	15	15	15
Magnesium stearate	5	5	5	5	5	5	5
Total weight	300	300	300	300	300	300	300

Evaluation of salt solution responsive swelling

Tablets of different formulations were evaluated for swelling in different concentrations of NaCl and KCl solutions [26]. Drug release from a polymeric drug delivery system mainly depends upon the swelling behavior of the polymer in the surrounding media. Presence of salt in food may have some influence on the swelling of tablets and ultimately affect the drug release behavior when given concurrently. Molar solutions of NaCl and KCl (0.1, 0.2, 0.3, 0.4, 0.5, 1.0, 1.5, and 2.0 M) were prepared and accurately weighed tablets of different formulations were placed in these solutions. The swelling index was noted after 24 h (equilibrium swelling) using the same method which was previously applied for swelling study in the buffer of different pH.

Stimuli-responsive swelling de-swelling (on-off switching) behavior

Prepared tablets were evaluated for on-off switching in water-ethanol, water-normal saline, and buffer solutions of pH 7.4 and 1.2, respectively [27,28]. To evaluate the swelling behavior, a tablet of each formulation was placed in a Tea Bag and allowed to swell in respective swelling medium (DW and pH 7.4) for 1 h and weighed periodically. Then, tea bags containing swollen tablets were placed in their respective de-swelling medium (ethanol, normal saline and pH 1.2) for 1 h and again weighed. The swelling de-swelling cycles were performed three times and mean values have been plotted. The swelling index was calculated using Equation (1).

In vitro *drug release study of TF and LS*

The effect of GX on the release of TF and LS tablets was studied for 16 h at pH 1.2, 6.8, 7.4, and DW using USP dissolution apparatus II operated at 37 °C and 50rpm. The release of drugs from tablets was also monitored at pH 1.2 for 2 h, pH 6.8 for 8 h, and pH 7.4 for 6 h in order to mimic the pH and transit time of GIT. After fixed time intervals, sample (5 ml) was withdrawn, filtered, diluted (if necessary), and analyzed using UV/Vis spectrophotometer at λ_{max} 272 and 293 nm for TF and LS, respectively. Fresh dissolution media were added to make up the deficiency of withdrawn volume. The experiment was performed in triplicate and the cumulative percentage of drug release was expressed according to mean values.

Drug release kinetics and mechanism

Zero-order, first-order, Higuchi, and Hixson–Crowell models were applied on drug release data for the investigation of drug release kinetics. The drug release mechanism was determined by the Korsmeyer–Peppas model (Supplementary Material).

In vivo *X-ray study*

An X-ray study was performed to observe the *in vivo* behavior of tablet formulation. Barium Sulfate ($BaSO_4$) was used as an opaquant in tablet formulation. Formulation TF3 was selected for *in vivo* X-ray study and the composition of the tablet was the same as mentioned in Table 1 except that 25% TF was replaced with $BaSO_4$ [29]. It was also evaluated that post-compression parameters, i.e. hardness, friability, thickness and weight of tablet and drug release profile were fairly the same as of TF3.

Specimen collection and storage

Four healthy stray dogs (18 kg each) were selected for *in vivo* X-ray study [30]. The selection of animal model was made due to the large size and weight of the tablet. To observe the sustained release behavior of GX-based formulation, the tablet should swallow as a whole without chewing. Therefore, the dog was selected which was easy to administer the tablet without any swallowing complications. Experimental procedures were followed in accordance with the protocols issued by the National Institute of Health's Guidelines for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978). The study was approved vide letter No. IAEC-2016-15A dated 27.01.2016 by Institutional Animal Ethics Committee, The University of Lahore, Lahore. The animals were kept fast overnight but given free access to ordinary tap water. TF3 formulation containing 25% $BaSO_4$ was administered using a gavage tube to a stray dog followed by water (100 ml). During the whole study, dogs were only allowed to drink water and no food was given. A radiograph of the abdomen of dog was taken just before and after the administration of tablet to ensure the absence of any radiopaque material and presence of tablet in the stomach, respectively. X-ray study was carried out for 7 h and radiographic images were taken after different time intervals using the X-ray machine (Beam Limiting Device, Model TF-6TL-6, Toshiba Corporation, Tokyo, Japan).

Hemocompatibility studies of GX

GX is being evaluated as a sustained release material in oral drug delivery system, therefore, biocompatibility (especially, hemocompatibility) studies of the material will be beneficial for its potential biomedical applications. Hemocompatibility of GX was evaluated through thrombogenicity and hemolytic potential as described by International Standard Organization (ISO) (ISO10993-4, 1999).

Thrombogenecity evaluation

The thrombogenicity potential of GX was determined through the gravimetric method [31–33]. In this method, GX (500 mg) was suspended in phosphate buffer saline (PBS) and kept at 37 °C in an incubator for 24 h. Excess PBS was decanted, $CaCl_2$ (0.1 M, 0.2 ml) and citrate blood (2 ml) were added in swelled GX and kept aside for 45 min. Distilled water was added to the mixture to stop clotting. Formed clots were fixed with formaldehyde (36–38%, 5 ml), separated, dried, and weighed. The same procedure was adopted without blood (negative control) and without GX (positive control). Thrombose concentration was calculated using Equation (2).

$$Thrombose\ (\%) = \frac{mass\ of\ test\ sample - mass\ of\ (-)\ control}{mass\ of\ (+)\ control - mass\ of\ (-)\ control} \times 100 \quad (2)$$

Hemolysis analysis

Possible interaction of GX with blood was evaluated through hemolytic potential. American Society for Testing and Materials (ASTMs) has demonstrated the procedure for hemolysis analysis [34]. GX (500 mg) was soaked in PBS at 37 °C overnight. Swelled GX was mixed with the known concentration of citrate blood and PBS and incubated at 37 °C for 3 h. The supernatant was separated after centrifugation at 10^4 rpm for 15 min and optical density (OD) was determined at 540 nm through UV–Vis spectrophotometer. For positive and negative control, a known concentration of citrate blood incubated with distilled water and with PBS, respectively [33]. The

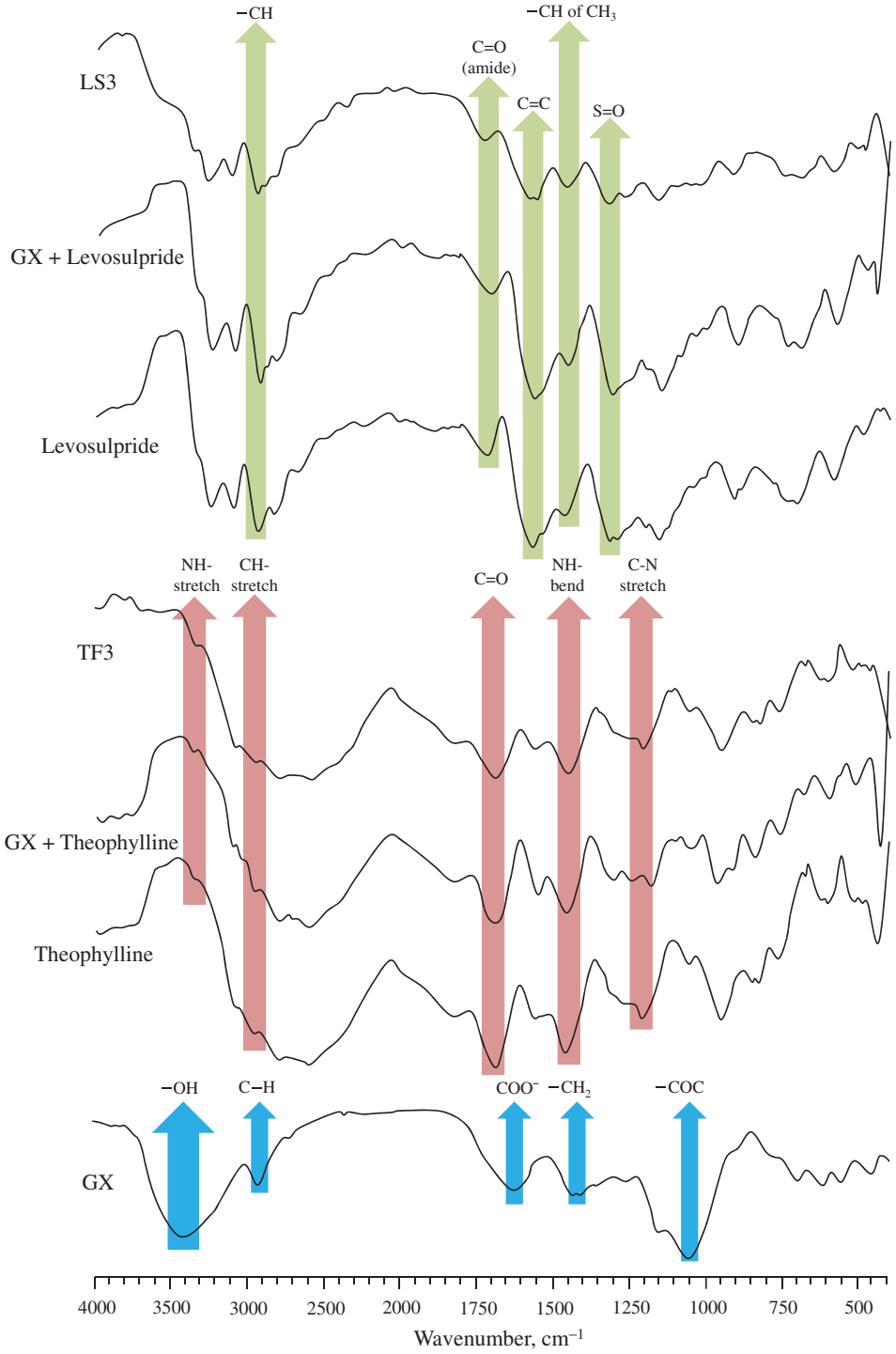

Figure 1. FTIR spectra of GX, theophylline, and levosulpiride; binary mixture of GX with theophylline and levosulpride and formulations TF3 and LS3.

hemolytic potential was determined using Equation (3).

$$\textit{Hemolytic index}\ (\%) = \frac{\textit{OD of test sample} - \textit{OD of}\ (-)\ \textit{control}}{\textit{OD of}\ (+)\ \textit{control} - \textit{OD of}\ (-)\ \textit{control}} \times 100 \quad (3)$$

Results

Drug-excipient compatibility studies

FTIR spectrum of GX has shown characteristic bands of –OH at 3400 cm^{-1}, $-CH_2$ at 2912 cm^{-1} and –COC at 1080 cm^{-1} which indicated the polysaccharidal nature of GX [35,36]. FTIR spectrum of TF produced characteristic bands of –NH stretch of secondary amines ranging from 3500 to 3300 cm^{-1} followed by peaks pertaining to –CH stretch at 3000–2800 cm^{-1} (Figure 1). The characteristic bands at 1670 and 1470 cm^{-1} indicated the presence of the C=O group and –NH bend in TF, respectively. Peaks appearing due to C–N stretch in aromatic amines are present at 1240 cm^{-1} [37]. FTIR spectrum of LS has shown characteristic bands at 2935 cm^{-1} for –CH, 1690 cm^{-1} for C=O of amide, 1455 cm^{-1} for C–H of the methyl group, 1560 cm^{-1} for C=C of cyclic alkene and 1342 cm^{-1} for S=O stretching [38].

Pre-compression parameters of various formulations

Wet granulation method was used to prepare granules of powder blend which improved its flowability and compressibility. Such parameters are evaluated through determination of the angle of repose, Hausner ratio and Carr's index. The values of loose and tapped bulk densities were investigated to be in the range of 0.637–0.811 and 0.672–0.852 g/cm^3, respectively (Table 2). Angle of repose, Hausner ratio, and Carr's index were found in the range of 24.71–26.13°, 1.022–1.056, and 2.10–5.30%, respectively.

Post-compression parameters of tablet formulations

The thickness and hardness of all tablet formulations were explored to be in the range of 4.05–4.19 mm and 7.87–8.34 kg/cm^2, respectively (Table 2). Similarly, the friability and weight of tablets were documented in the range of 0.69–0.91% and 300.4–305.7 mg, respectively. Drug contents in TF formulations (TF1, 98.91%; TF2, 99.08%; and TF3, 98.78%) and LS formulations (LS1, 98.49%; LS2, 99.42%; and LS3, 98.63%) were approximately the same.

Swelling response of GX formulations to different media

The swelling response of GX-based tablet formulations in different media is important to evaluate the swelling capacity in different media and to develop sustained/targeted drug delivery system.

Swelling behavior of GXF tablets in buffers and swelling kinetics

The results of swelling studies of GXF tablets (without drug) in DW and buffer of pH 1.2, 6.8, and 7.4 indicated that swelling of tablets was high in DW, pH 6.8 and 7.4 whereas, negligible swelling was observed at pH 1.2 (Figure 2(a)).

Various kinetics models were applied to the data obtained from swelling of GXF tablets in DW and buffers of different pH for the evaluation of swelling kinetics. The best fit model was investigated to be second-order because it gave an almost straight line between t/Q_t and t (Supplementary Figure S1).

Swelling behavior and swelling kinetics of TF and LS formulations

TF (TF1, TF2, and TF3) and LS (LS1, LS2, and LS3) formulations have shown a high swelling index in DW and at pH 6.8 and 7.4 as depicted in Figure 3. The swelling of these formulations in DW was high as compared to the swelling at pH 6.8 and 7.4. At pH 1.2, negligible swelling of these formulations was observed. It was also observed that swelling of these tablets is directly proportional to the concentration of GX in tablets. Swelling of TF and LS formulations followed second-order kinetics as expressed by straight lines between t/Q_t and t in all media (Supplementary Material, Figures S2 and S3).

Saline responsive swelling of various tablet formulations

Responsiveness of GXF tablets and selected formulations of TF and LS (i.e. TF3 and LS3) against different concentrations (0.1–2.0 M) of NaCl and KCl was evaluated and explored inverse relation between concentration of salt solutions and swelling indices (Figure 2(e,f)). It was also noted that TF3 and LS3 formulations exhibited slightly less swelling than GXF tablets. Moreover, swelling of all three tablet formulations (GXF, TF3, and LS3) was less in NaCl solution than the KCl solution.

Table 2. Pre-compression and post-compression parameters of theophylline (TH) and levosulpiride (LS) formulations (Mean ± SD).

	Pre-compression parameters (n = 3)					Post-compression parameters (n = 10)				
Formulation code	Angle of repose	Loose bulk density (g/cm^3)	Tapped bulk density (g/cm^3)	Hausner's ratio	Compressibility index (%)	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
TF1	25.21 ± 1.27	0.811 ± 0.05	0.852 ± 0.08	1.050 ± 0.07	4.80 ± 1.08	7.87 ± 0.23	4.09 ± 0.06	305.7 ± 3.24	0.76 ± 0.07	98.91 ± 0.38
TF2	25.90 ± 1.45	0.784 ± 0.11	0.801 ± 0.09	1.022 ± 0.12	2.10 ± 2.81	7.91 ± 0.14	4.13 ± 0.09	303.6 ± 3.93	0.91 ± 0.11	99.08 ± 0.72
TF3	26.13 ± 0.85	0.749 ± 0.21	0.766 ± 0.06	1.023 ± 0.21	2.20 ± 3.24	8.22 ± 0.09	4.17 ± 0.07	302.9 ± 4.65	0.71 ± 0.13	98.78 ± 0.67
LS1	24.71 ± 2.13	0.704 ± 0.08	0.734 ± 0.14	1.043 ± 0.19	4.10 ± 1.33	8.34 ± 0.18	4.12 ± 0.08	300.4 ± 5.33	0.84 ± 0.08	98.49 ± 0.72
LS2	25.44 ± 0.89	0.682 ± 0.10	0.720 ± 0.05	1.056 ± 0.14	5.30 ± 2.08	8.07 ± 0.06	4.05 ± 0.02	305.6 ± 4.96	0.74 ± 0.10	99.42 ± 0.39
LS3	25.78 ± 1.90	0.637 ± 0.09	0.672 ± 0.13	1.055 ± 0.06	5.20 ± 2.39	8.16 ± 0.12	4.19 ± 0.05	301.1 ± 4.46	0.69 ± 0.19	98.63 ± 0.81

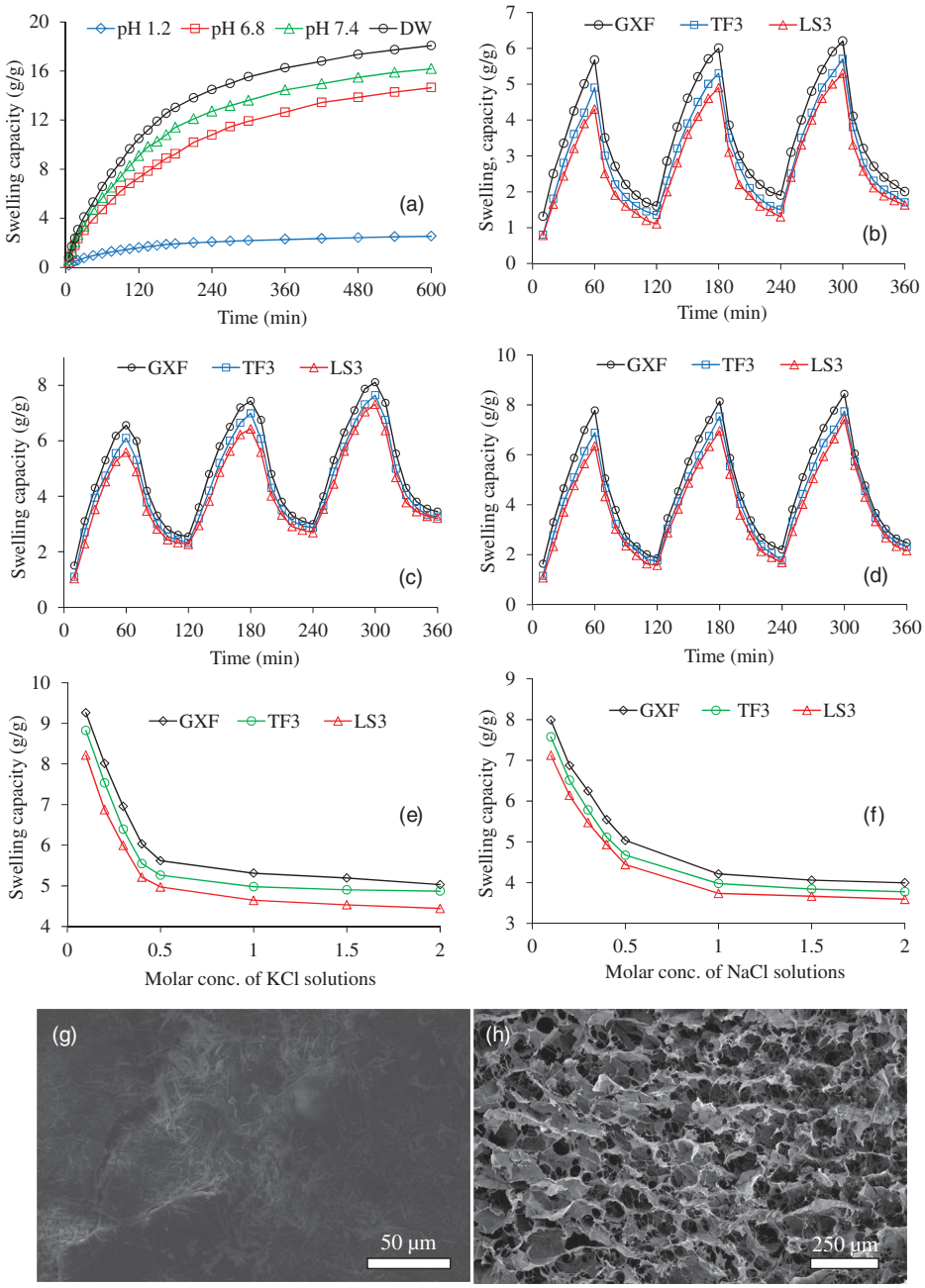

Figure 2. Swelling capacity of GXF tablets in buffer of pH 1.2, 6.8, 7.4, and in deionized water (DW) (a); swelling de-swelling behavior of GXF, TF3, and LS3 tablet formulations at pH 7.4 and 1.2 (b), DW and normal saline (c) and DW and ethanol (d); equilibrium swelling (after 24 h) of GXF, TF3 and LS3 tablet formulations in different molar concentrations of KCl (e) and NaCl solutions (f); SEM images of the surface of GXF tablet showing microcracks (g) and micro-channels of water-swollen then freeze-dried tablet (h).

Swelling de-swelling response of GX-based formulations to different stimuli

For the utilization of GX as polymer matrix in various formulations, swelling de-swelling behavior of different formulations (GXF, TF3, and LS3) was observed in water-normal saline, water-ethanol, and buffers of pH 7.4 and 1.2.

pH-responsive swelling de-swelling of tablets

Tablet formulations were exposed to the buffer of pH 7.4 for 1 h and swelling of all formulations was observed. On shifting and placing these swollen tablets for 1 h in a buffer of pH 1.2, a sharp de-swelling of these tablets can be seen. The swelling de-swelling cycle was observed for three times with similar behavior (Figure 2(b)).

Water-normal saline responsive swelling de-swelling of tablets

Tablets of three different formulations (GXF, TF3, and LS3) exhibited significant swelling on placing in DW and showed de-swelling on shifting to a normal saline solution (Figure 2(c)).

Water-ethanol responsive swelling de-swelling of tablets

Swelling de-swelling behavior of tablet formulations (GXF, TF3, and LS3) was examined alternately in water and ethanol for 1 h.

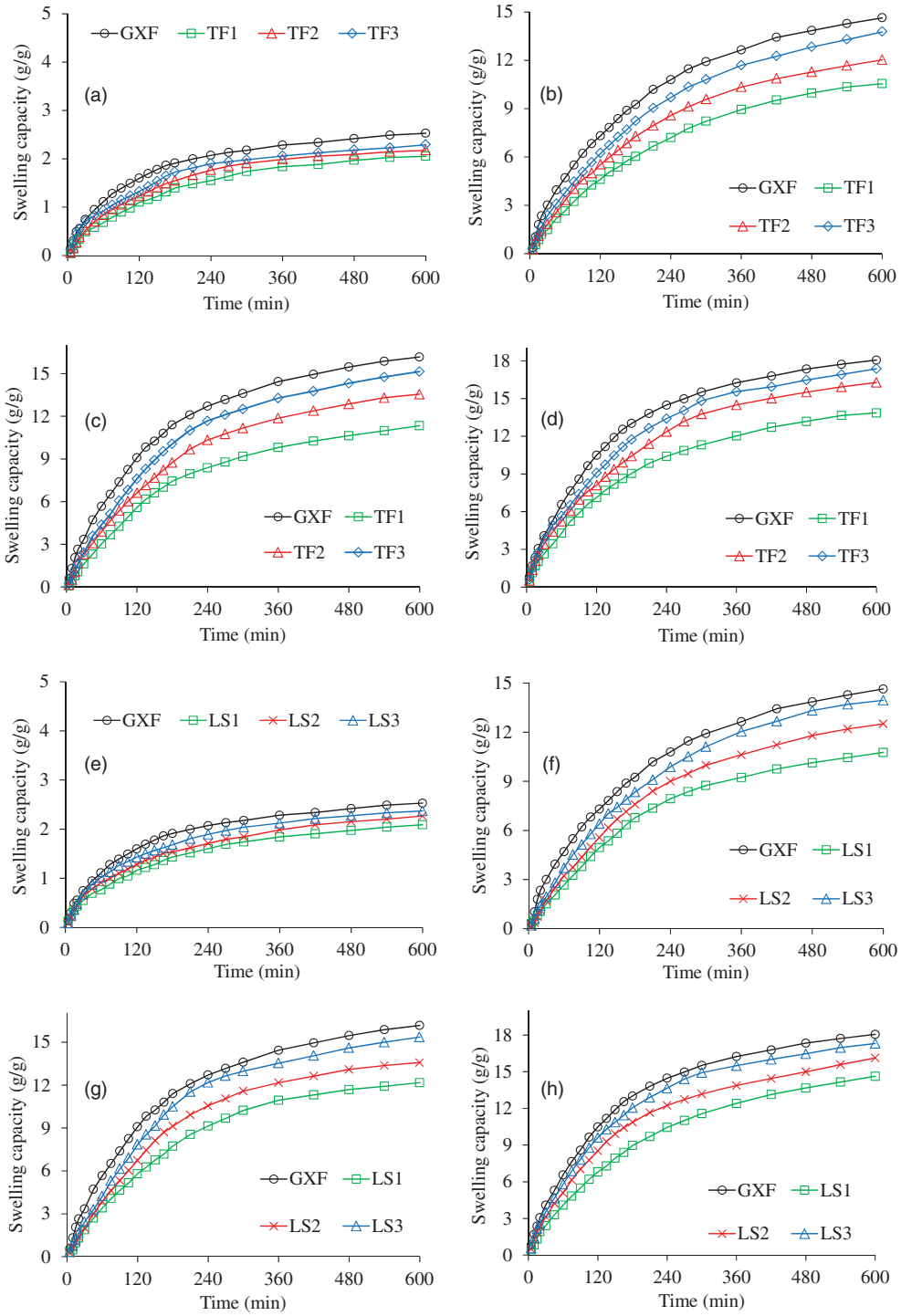

Figure 3. Swelling capacity of TF formulations (TF1, TF2, and TF3) and LS formulations (LS1, LS2, and LS3) in buffer of pH 1.2 (a,e), 6.8 (b,f), 7.4 (c,g), and deionized water (d,h), respectively.

It was discovered that swelling of tablet formulations diminished on shifting to ethanol and abrupt de-swelling was observed (Figure 2(d)) [28].

Scanning electron microscopy

The surface morphology of GXF tablet was examined using scanning electron microscopy (SEM). SEM revealed the presence of micro-cracks on the surface of GXF tablet (Figure 2(g)) and micro-channels on the surface of the swollen then freeze-dried GXF tablet (Figure 2(h)) [39].

In vitro *drug release studies*

Drug release studies from GX-based TF tablets

Drug release studies were carried out to evaluate the TF release pattern at pH 6.8, 7.4, and DW from GX-based TF tablet formulations. After 12 h, study at pH 6.8, the drug released from TF1, TF2, and TF3 was noted as 95.09%, 83.97%, and 73.21%, respectively

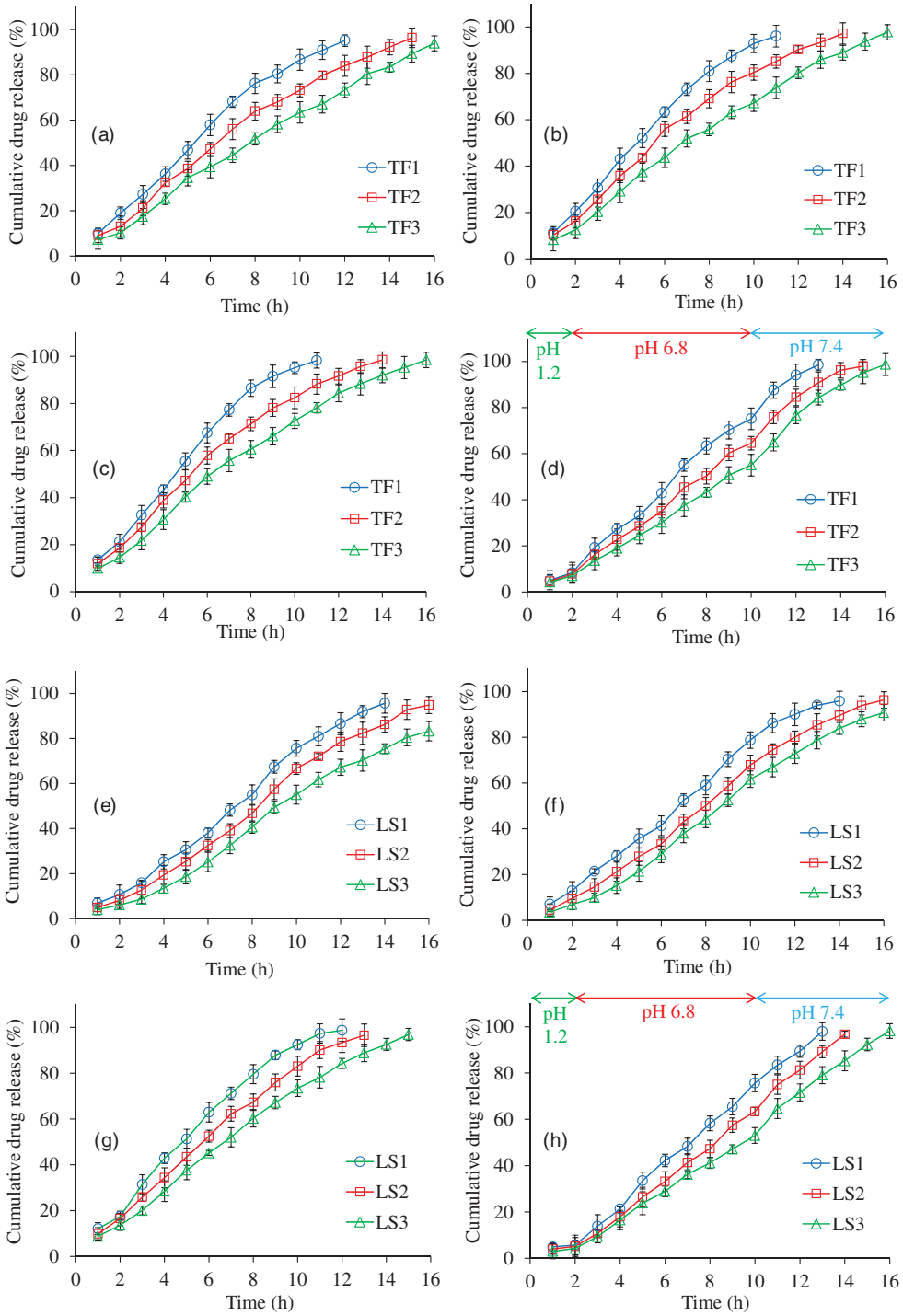

Figure 4. Drug release study from TF formulations (TF1, TF2, and TF3) and LS formulations (LS1, LS2, and LS3) in buffer solution of pH 6.8 (a,e), 7.4 (b,f), deionized water (c,g) and mimicking the pH and transit time of gastrointestinal tract (d,h), respectively.

(Figure 4(a)). Whereas, at pH 7.4 and DW, maximum drug (96.04% and 98.21%) was released after 11 h from TF1, respectively. Similarly, at pH 7.4 and in DW, 97.18% and 98.43% drug was released from TF2 after 14 h. More sustained and prolonged drug release was observed from TF3 formulation in which 16 h was taken by TF3 formulation to release 97.73% and 98.44% drug (Figure 4(b,c)).

Drug release study was carried out in simulated pH and transit time of GIT. The drug release at pH 1.2 and after 2 h was explored to be 8.33%, 7.78%, and 7.02% from TF1, TF2, and TF3, respectively (Figure 4(d)). On shifting to pH 6.8, a prolong and sustained drug release behavior was observed during the 8 h study. In this duration, 75.11%, 64.54%, and 55.02% drug was released from TF1, TF2, and TF3, respectively. In basic buffer (pH 7.4), almost complete drug release was observed within 4 h.

Drug release studies from GX-based LS tablets

During LS release study from tablet formulations, a sustained and prolonged release of LS was observed at pH 6.8, 7.4, and DW. However, slightly better-sustained release behavior can be seen at pH 6.8 than 7.4 (Figure 4(e,f)). After a 14 h drug release study at

Table 3. Mathematical data representing drug release kinetics models of GX based theophylline (TF) and levosulpiride (LS) tablet formulations.

		GX based TF formulations									GX based LS formulations								
		pH 6.8			pH 7.4			Deionized water			pH 6.8			pH 7.4			Deionized water		
		TF1	TF2	TF3	TF1	TF2	TF3	TF1	TF2	TF3	LS1	LS2	LS3	LS1	LS2	LS3	LS1	LS2	LS3
Zero order	R^2	0.9826	0.9771	0.9937	0.9873	0.9767	0.9899	0.9922	0.9648	0.9794	0.9863	0.9828	0.9748	0.9934	0.9867	0.9781	0.9880	0.9962	0.9896
	K_0	8.956	7.161	6.164	9.945	8.166	6.741	10.749	8.444	7.115	7.109	6.206	5.269	7.580	6.449	5.799	9.866	8.440	7.073
	MSC	3.8711	3.6318	4.9282	4.1683	3.5930	4.4531	4.6285	3.1805	3.7393	4.1386	3.9276	3.5572	4.8603	4.1802	3.6961	4.2242	5.4018	4.4275
First order	R^2	0.8556	0.8747	0.8540	0.8560	0.8834	0.8703	0.8272	0.9037	0.8840	0.7497	0.7577	0.8336	0.7533	0.7634	0.7847	0.8472	0.8335	0.8608
	K_1	0.164	0.133	0.107	0.186	0.155	0.121	0.204	0.161	0.134	0.128	0.113	0.089	0.139	0.120	0.101	0.188	0.155	0.129
	MSC	1.7132	1.8952	1.7421	1.6882	1.9491	1.8756	1.5057	2.1588	1.9872	1.1630	1.2177	1.5711	1.1775	1.2415	1.3358	1.6563	1.5706	1.7903
Higuchi	R^2	0.8510	0.8675	0.8456	0.8532	0.8672	0.8573	0.8368	0.8863	0.8740	0.7705	0.7661	0.7508	0.7891	0.7694	0.7574	0.8483	0.8403	0.8506
	K_H	24.470	22.022	19.495	25.967	23.323	20.672	26.634	24.203	21.894	20.724	19.355	16.906	21.335	19.463	18.623	25.740	22.991	21.669
	MSC	1.7219	1.8787	1.7351	1.7189	1.8223	1.8044	1.5903	2.0078	1.9286	1.3179	1.3197	1.2646	1.3898	1.3244	1.2913	1.6859	1.6526	1.7583
Hixson–Crowell	R^2	0.9701	0.9788	0.9738	0.9700	0.9805	0.9782	0.9599	0.9858	0.9812	0.9225	0.9205	0.9234	0.9364	0.9971	0.9164	0.9672	0.9691	0.9698
	K_{HC}	0.043	0.035	0.028	0.048	0.039	0.032	0.051	0.042	0.035	0.032	0.028	0.023	0.034	0.029	0.026	0.048	0.039	0.034
	MSC	3.3297	3.7103	3.5069	3.3067	3.7722	3.6841	2.9934	4.0887	3.8315	2.4034	2.3991	2.4438	2.5882	2.4752	2.3567	3.2187	3.2942	3.3580
Korsmeyer–Peppas	R^2	0.9884	0.9888	0.9958	0.9934	0.9891	0.9954	0.9939	0.9895	0.9929	0.9935	0.9897	0.9853	0.9961	0.9939	0.9869	0.9925	0.9979	0.9935
	K_{KP}	11.169	9.902	7.215	12.242	11.114	8.483	12.155	12.679	9.993	4.241	4.436	3.421	6.309	4.660	3.916	11.888	9.514	8.654
	n	0.895	0.861	0.934	0.897	0.859	0.902	0.936	0.814	0.854	1.246	1.139	1.174	1.084	1.138	1.158	0.907	0.943	0.914
	MSC	4.1980	4.2896	5.2691	4.7328	4.2787	5.1682	4.7825	4.3212	4.7416	4.7263	4.3834	4.0370	5.3157	4.8895	4.1514	4.6131	5.8931	4.8346

pH 6.8, the cumulative drug release (%) from formulations LS1, LS2, and LS3 was found to be 95.61%, 86.22%, and 75.44%, respectively (Figure 4(e)). Similarly, 95.88%, 89.54%, and 83.90% drug was released from LS1, LS2, and LS3, respectively, when the buffer of pH 7.4 was used as a drug release medium (Figure 4(f)). In DW, 98.76%, 93.32%, and 84.29% drug was released after 14 h study from LS1, LS2, and LS3, respectively (Figure 4(g)). In GIT mimicking conditions, drug release was negligible at pH 1.2 which was noted to be 5.72%, 5.17%, and 4.27% for LS1, LS2, and LS3, respectively, after 2 h (Figure 4(h)). The formulations were then shifted to phosphate buffer of pH 6.8 for 8 h where sustained drug release behavior of LS from tablet formulations was observed. From LS1, 97.88% drug was released after 3 h when shifted to pH 7.4. Similarly, 96.71% and 98.11% drug from LS2 and LS3 was released after 4 and 6 h study at pH 7.4, respectively.

Drug release kinetics and mechanism

The analysis of the mathematical data of drug release kinetics models revealed that the Korsmeyer–Peppas model and zero-order are the best fit model as the values of the regression coefficient (R^2) are highest (~1) for these two models. Furthermore, model selection criteria (MSC) is another way to find the most suitable drug release kinetic model and the highest value of MSC is considered the most suitable model. According to MSC values, Korysmeyer–Peppas and zero-order are the appropriate kinetics models. Diffusion coefficient (n) values calculated from the Korsmeyer–Peppas equation showed that drug is released from TF and LS formulations by super case II transport [40,41]. Data obtained from various kinetics models for LS and TF formulations are shown in Table 3.

In vivo *X-ray study*

Real-time behavior of GX-based sustained release tablet formulations was observed in dog GIT using radiographic imaging technique and these images after various time intervals are depicted in Figure 5. Radiographic images taken before and after administration of the tablet are expressed in Figure 5(a,b), respectively. In the image taken after 0.5 h, the whole tablet can be seen in the stomach of the animal. After 1.5 h, the bright and sharp edges of the tablet can still be seen which indicated that the tablet remains intact after passing through the stomach. Furthermore, the change in the position of the tablet from the stomach to the intestine and then colon is also evident in Figure 5(c,d,e), respectively. During the transit of the tablet from the stomach to the colon, the sharpness of the edges of the tablet disappears and also the size of the tablet is a bit large which indicated somewhat swelling of the tablet in GIT of the dog. The translucent layer around the tablet glassy core can also be seen. Additionally, due to the swelling and erosion of the tablet at this stage, the size of the tablet also reduced. After 7 h, the tablet was completely disintegrated as it is disappeared in Figure 5(f).

Hemocompatibility studies

Thrombogenecity potential of GX was evaluated by determining the weight of the clot and compared to the control. The weight of blood clot and thrombose (%) was found 0.30 ± 0.08 g and 92.22%±2.11%, respectively. In positive control, the weight of the blood clot was more than the sample. The value of the hemolytic index was calculated as 4.29%.

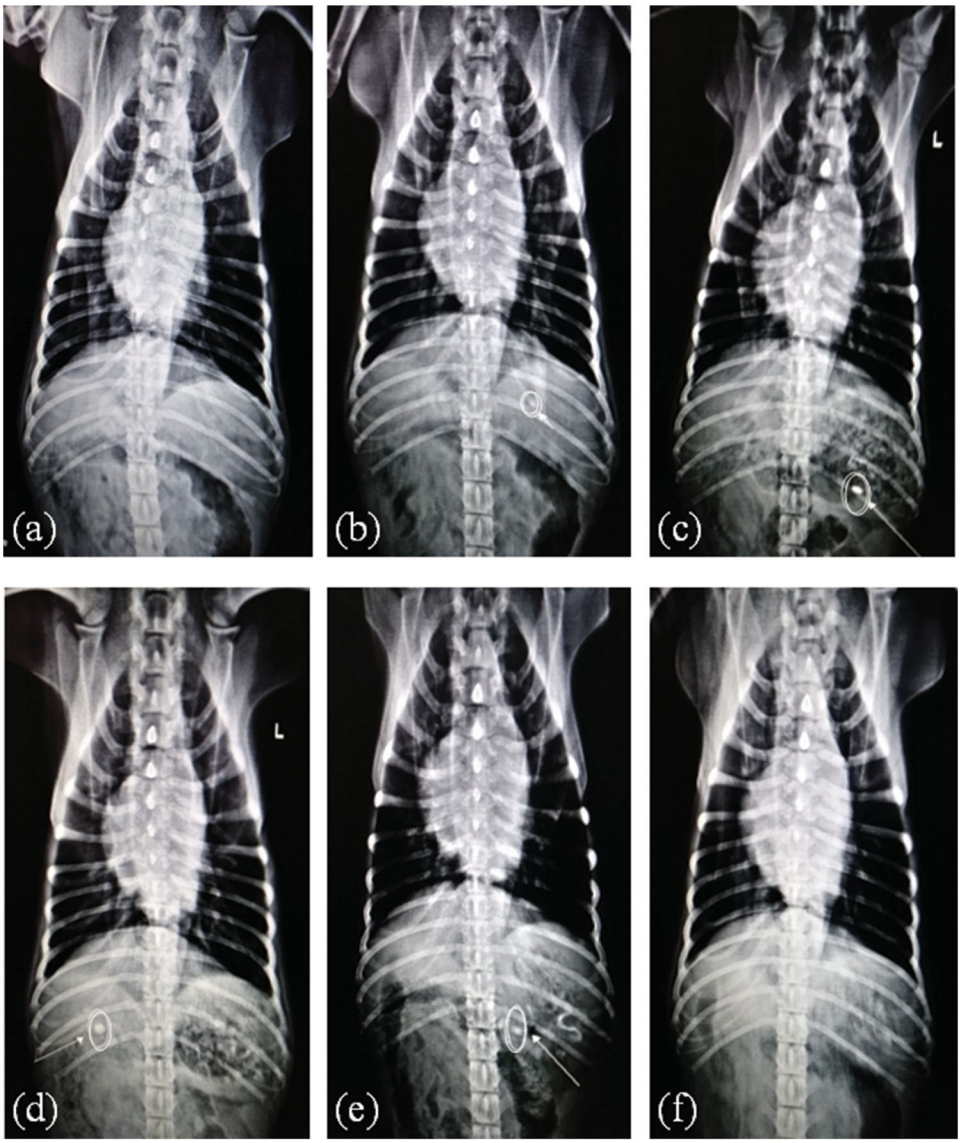

Figure 5. X-Ray photographs of TF3 after different time intervals, 0 h (a), 0.5 h (b), 1.5 h (c), 4.5 h (d), 5.5 h (e), and 7 h (f).

Discussion

GX was isolated using a hot water extraction method with reasonable yield and used to develop a sustained release drug delivery system for TF and LS. FTIR analysis of the physical blend of the active ingredient with excipients and formulations TF3 and LS3 confirmed the absence of any new band, which indicated the compatibility of these ingredients. The values of pre-compression parameters are within standard range, which indicated the suitability of granules for compression. Similarly, post-compression parameters confirmed the content uniformity of active ingredient and aptness of the prepared tablets for *in vitro* and *in vivo* evaluation [42–44].

The high swelling index of GXF tablet formulations was observed at pH 7.4, 6.8, and in DW. In phosphate buffer of pH 7.4, carboxylic groups present on polymeric (GX) chain ionized to carboxylate ions ($–COO^-$) which repelled each other. As a result, the polymeric chains are relaxed and the penetration of water in the matrix became easy. Hence, a high swelling index of these tablets was observed (Figure 2(a)). In an acidic environment, i.e. pH 1.2, carboxylic groups became protonated and the electrostatic repulsion between these anionic groups ($–COO^-$) diminished. Subsequently, the polymer chains came closer to each other which resulted in the shrinking of the polymer. Additionally, charge screening effect of excessive sodium ion (Na^+) in phosphate buffers decreased swelling at pH 6.8 and 7.4 than DW [45,27]. Therefore, less swelling was observed in phosphate buffer of pH 7.4 and 6.8 as compared to DW (Figure 2(a)). A similar swelling trend was observed in GX-based TF (TF1, TF2, and TF3) and LS (LS1, LS2, and LS3) formulations (Figure 3), i.e. high swelling in DW and at pH 7.4 and 6.8 whereas negligible swelling at pH 1.2. It was also noted that irrespective of the presence and nature of the active ingredient, the swelling of these formulations are only dependent on the concentration of GX in the formulation.

Less swelling ability of all tablet formulations in NaCl and KCl solutions is due to charge screening effect of excessive cations present in the media which diminished the electrostatic repulsions of carboxylate anions [9,46]. Additionally, less swelling is also due to a decrease in osmotic pressure between polymer chain and salt solutions, which in turn reduced diffusion of water into tablets (Figure 2(e,f). Moreover, swelling indices of tablets were less in NaCl solution than KCl solution owing to smaller size and greater charge density of sodium ions (Na^+).

Deprotonation of carboxylic groups present in the polymeric chain of GX in basic buffer solution resulted in the formation of carboxylate anions. The electrostatic repulsion generated as the result of anion–anion interaction relaxed the polymeric chains for more water penetration and increased the swelling (Figure 2(b)). Reverse process was observed in the acidic buffer where swelling decreased due to protonation of these carboxylate anions which strengthened the hydrogen bonding and shrunk the polymer chains [27]. Consequently, the de-swelling of GX-based tablets was observed.

The reason for the de-swelling of GX-based tablets in normal saline is the osmotic pressure difference between the internal and external environment of swollen tablets when placed in normal saline solution. The greater osmotic pressure of saline solution instigated the water to move out of swollen polymeric (GX) material and shrinking was evident (Figure 2(c)).

It was discovered that abrupt decrease in swelling of tablets in ethanol was due to its less affinity with GX [38]. Moreover, low polarity and dielectric constant of ethanol than water were also considered as the reason for the de-swelling of the GX-based tablets in ethanol (Figure 2(d)).

SEM analysis revealed the presence of microscopic cracks and pores on the surface of tablets that facilitates the easy penetration of swelling/dissolution media. Such microchannels supported the utilization of GX-based tablet formulations for sustained/controlled release of drugs [39].

A sustained and prolonged release of TF and LS was observed at pH 6.8, 7.4, and water which may be due to greater swelling of tablets in these media (Figure 4). At pH 6.8 (Figure 4(a)), the release of TF was more sustained and prolonged as compared to the release at pH 7.4 (Figure 4(b)) and DW (Figure 4(c)) which is beneficial for the development of site-specific drug delivery system. Similarly, the release of LS was more sustained and prolonged at pH 6.8 (Figure 4(e)) than pH 7.4 (Figure 4(f)), and DW (Figure 4(g)). These results indicated that the release of drugs is dependent on the concentration of GX in the tablets and independent on drugs' nature (neutral, acidic, or basic) as a more sustained release of both drugs was observed at pH 6.8. It was inferred that the release of drug from all formulations was inversely proportional to the concentration of GX which is due to high swelling and water holding capacity of the polymer. Drug release study mimicking the conditions of GIT also revealed that drug is completely released at intestinal pH while insignificant release of drug was observed at stomach pH, i.e. 1.2 (Figure 4(d,h)). Therefore, GX can be used to protect the stomach from the harmful effects of the drugs.

The swelling index of the polymeric matrix, solubility of drug, and polymer–drug interaction are the main factors that controlled the drug release from sustained drug delivery systems [39]. Korsmeyer–Peppas model and zero-order are considered the most suitable model which explained the TF and LS release kinetics from GX-based tablets. These models indicated that the release of drugs is independent of their concentration. Diffusion coefficient (n) values from the Korsmeyer–Peppas equation showed that drugs (TF and LS) are released from formulations by the erosion of polymeric matrix [40,41] and rate of drug release remains constant with the passage of time.

Radio-graphical images of GIT taken after various time intervals indicated that the tablet (TF3) remain intact in the stomach, in the small intestine and even in the colon during the 7 h study. The change in position of tablet and increase in the size of tablets is due to movement through GIT and swelling of the tablet in GIT media/environment, which is necessary for site-specific and sustained release of active ingredient.

Hemocompatibility studies of GX indicated the safety potential of GX. According to the safety standards of ISO document 10993-3 2002, any material having the hemolytic index $<5\%$ is considered safe for biomedical applications [47,48]. Therefore, due to less hemolytic index (4.29%) of GX, this polymeric material is considered safe and could be used for various biomedical applications.

Conclusion

The use of GX as tablet excipient and smart drug delivery material for LS and TF formulations has been established by pre- and post-compression parameters and found suitable for compression. The swelling capability of GX in DW and phosphate buffers (pH 6.8 and 7.4) was significant, however, insignificant swelling was observed in HCl buffer (pH 1.2). Responsiveness of GX to various stimuli such as pH, ionic concentration and solvents was prominent which leads to the development of site-specific drug delivery systems. It was also confirmed that GX protected the drugs from the acidic environment of the stomach and provided colon-targeted release due to high swelling ability at pH 6.8 and 7.4. The drug release mechanism was investigated to be super case transport II in which drug is released by erosion. It is evident from the SEM that surface of tablets is porous in nature and these nanopores contributed to the swelling of tablets and sustained release of the drug. Hemocompatibility studies also confirmed the non-thrombogenic and non-hemolytic nature of GX. Therefore, this study revealed that GX is a potential candidate for stimuli-responsive sustained release drug delivery systems.

Acknowledgments

G. Muhammad gratefully acknowledges the Higher Education Commission, Pakistan for funding under "HEC Indigenous 5000 Fellowships" scheme. We are grateful to Consolidated Chemical Laboratories (Pvt.) Ltd. for generously gifting the levosulpiride; Instruments Labs, University of Sargodha for extensive utilization of instruments; Prof. Dr. Irshad Hussain and Mr. Zajif Hussain for acquisition of SEM and X-ray technician and radiographer, and Mubarak Medical Complex, Sargodha, Pakistan for technical help and provision of X-ray facility.

Disclosure statement

The authors report no declaration of interest.

Funding

This study was supported by the Higher Education Commission, Pakistan under "HEC Indigenous 5000 Fellowships" scheme.

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