Biocompatible hydroxy double salt tablet formulations

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ABSTRACT

Generally, commercial extended release tablets are core-based, which can cause problems for certain patients if they split them prior to ingestion. There is a need to develop non-core-based extended release tablets. We have previously reported the synthesis of two new biocompatible hydroxy double salts (HDSs), $[Mg_2Zn_3(OH)_8]$ $Cl_2 \cdot 3.4H_2O$ (MgZn–Cl) and $[Fe_{2.4}Zn_{2.6}(OH)_8]Cl_2 \cdot 2H_2O$ (FeZn–Cl) (J. Mater. Chem. B 2016, 4, 5789), and found them to be good candidates for the extended release of diclofenac (Dic), ibuprofen (SI) and valproate (Val) (Appl. Clay. Sci. 2022, 221, 106456). Here we build on these previous results and report scale-up synthesis of MgZn–Cl and FeZn–Cl loaded with Dic, SI, and Val. The scaled-up products were blended with excipients and formulated into non-core based tablets. The post-compression parameters of the HDS-based tablets were assessed against the pharmacopeia requirements (friability, weight, and dose uniformity) and all passed the tests. Drug release studies were carried out using the paddle method (USPII) in conditions representative of the gastrointestinal tract. The HDS tablets were found to meet the pharmacopeia requirements for modified release dosage forms and showed similar release profiles to current commercial formulations. It is thus possible to develop modified release non-core based tablets using HDSs. These have additional benefits over standard commercial tablets, because the presence of the essential elements Zn, Fe and/or Mg in the layers can compensate for deficiencies induced over long-term treatment, and enhance therapeutic efficacy in some cases. Furthermore, the buffering effect of the HDS layers has the potential to prevent the gastric irritation often associated with the use of non-steroidal anti-inflammatory drugs.

1. Introduction

Medicines administration can be achieved via a variety of routes, such as oral, inhalation, and injection. To achieve the oral delivery of medicines, tablets, capsules, or liquid formulations are commonly employed. Tablets are the most frequently used dosage form for oral delivery and occupy two thirds of the global drug market [1]. The oral route is preferred over other methods of applying medicines because it is the most simple and results in high levels of patient compliance [2]. However, a patient cannot simply take the drug (active pharmaceutical ingredient (API)) alone for various reasons. Thus, when drugs are processed into medicines such as tablets several additional inactive materials known as "excipients" are added, which are blended with an API to facilitate the delivery, manufacturability and stabilisation of the API in tablets or other pharmaceutical dosage forms [3]. They are sub-divided into various functional classifications such as diluents, disintegrants, binders and lubricants [4–7].

Tablets are made by compressing an API and excipients, and there

exist numerous compression techniques including wet granulation and direct compression (DC). DC is the simplest method for tablet manufacturing, and involves tablets being fabricated by directly compressing a blend of an API powder and excipients [8].

In order to ensure the required functional performance *in vivo*, a series of stringent quality requirements exists. The finished tablets need to possess certain properties that are determined by a pharmacopeia, with specific testing regimens for these mandated. Additional quality tests are implemented by manufacturers to ensure their product meets the required specifications. The first is a hardness test, where the load required to crush a tablet is measured, and it is crucial that a tablet is neither too hard nor too soft. The hardness for oral tablets is usually between 40 and 100 N for immediate release and 100–200 N for modified release [9]. The second test is a friability test; the mass loss in this test should be less than 1%, and after the test the tablets should not show any sign of breakage [10]. In addition, all pharmaceutical preparations are required to contain a constant dose of active ingredient, with small variations permitted within strict pharmacopeial limits. For each
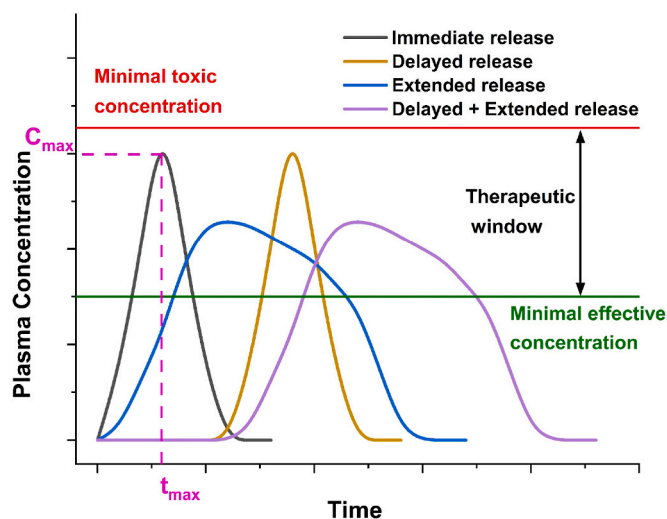
Fig. 1. The effect of the different tablet types on drug concentration *in vivo*.

Table 1
Details of the scale-up reaction conditions.

Material	Starting materials	Volume of water (mL)	Temperature (°C)	Time (days)
FeZn–Cl	ZnO (100 g), $FeCl_2 \cdot 4H_2O$ (240 g), KI (166 g)	2500	RT	3
MgZn–Cl	ZnO (200 g), $MgCl_2 \cdot 6H_2O$ (700 g)	1000	RT	3
FeZn-drug	FeZn–Cl (0.5 mol), drug (2 mol) KI (0.2 mol)	500	60	3
MgZn-drug	MgZn–Cl (0.5 mol), drug (2 mol)	500	60	3

batch of tablets prepared, the uniformity of active ingredient content is assayed in two separate tests: a uniformity of weight (mass) study and quantification of the uniformity of API amount per tablet [11]. Finally, the disintegration properties of the tablet (i.e., how easily it breaks up into small pieces) and its dissolution (rate of release of API into solution as a function of time) are quantified.

Tablets have proved to be a remarkably versatile dosage form, and there are many types of different drug delivery profile which can be provided using them. Tablets may for instance be immediate release, delayed release, or extended release (Fig. 1); in all cases, the excipients play an important role in controlling drug release [12].

It is established that a drug's efficacy can be improved and its side effects reduced if it is released in a sustained manner rather than through conventional (immediate) release [13,14]. Most commercial extended release tablets are API core-based, with a drug-loaded core covered by a coating material [15]. The drug release from those tablets is typically governed by water diffusion from the external milieu into the core via the coating and/or by dissolution of a pH-responsive coating. However, a common practice in paediatric and geriatric patients is to split (break) tablets before swallowing them. This will damage the integrity of the coating, compromising the modified release properties and leading to much faster release *in vivo* [16]. This could lead to a plasma concentration exceeding the maximum of the therapeutic window, resulting in a toxicity risk [17]. Hence, it is necessary to develop non-core based extended release tablets.

To develop non-core based extended-release tablets, drug delivery systems (DDSs) that can be blended easily with excipients and release APIs in controlled manner are required. Modern DDSs are usually polymer based [18,19]; much less attention has been paid to inorganic delivery systems, even though they have a number of promising features. The hydroxy double salts (HDSs) are auspicious as DDSs. They are made of two-dimensional metal hydroxide sheets which bear a positive charge. The metal ions in these sheets occupy both octahedral and tetrahedral sites (located above and below the sheets) in the molar ratio 3:2. The charge is balanced by anions present between the sheets, and these can be ion-exchanged out of the formulation (Supplementary Information, Fig. S1). The general formula for an HDS is $[(M^{2+}_{2-x}Me^{2+}_x)(OH)_{4-y}]X^{n-}_{y/n} \cdot zH_2O$, where M^{2+} and Me^{2+} are divalent metal ions (e.g., Zn^{2+}, Fe^{2+}, Mg^{2+}) and X^{n-} is an exchangeable interlayer anion (e.g., Cl^-).

The HDSs have many advantageous features: they are inexpensive and easy to synthesise; can be made with a wide range of metal ion combinations and interlayer anions; and, are stable and do not show any sign of degradation over period of five years. This has resulted in them

being exploited to develop materials for various applications (e.g. cosmetics, water treatment, catalysis, anticorrosion, and photocatalysis) [20–23]. In addition, HDSs can release an API loading in a sustained manner, improve API solubility, extend API shelf-lives, and can be easily mixed with excipients [24–29]. Thus, the HDSs have been explored as DDSs to deliver numerous APIs, such as antihistamines [30], antibiotics [31], anti-inflammatory APIs [32], and anticancer drugs [33]. Even though the HDSs constitute an excellent DDS, they still have certain limitations. For instance, only anionic APIs can be loaded into the HDSs, the loading process requires heat and tends to be slow, and the loading ratio is limited by the need for charge balance.

In our previous work, we showed that biocompatible HDS systems could offer desirable release properties, were cytocompatible, and can potentially increase API shelf-lives [28,34]. Here, we looked to extend our work by scaling up the production of intercalated systems, mixing these with excipients and formulating into non-core modified release tablets. A wide range of formulations were prepared, and the HDS tablets that showed similar release profiles to comparable commercial modified-release formulations are discussed here, since *in vitro/in vivo* correlation (IVIVC) has been already established by the manufacturers. The post-compression parameters of the prepared tablets were assessed according to pharmacopeia requirements [35]. Drug release studies from the HDS-based and commercial tablets were carried out under conditions that mimic the human gastrointestinal tract.

2. Experimental section

2.1. Materials

Materials were obtained as follows: Zinc oxide (ZnO) and magnesium chloride ($MgCl_2 \cdot 6H_2O$) (99%; Fisher Scientific, Waltham, MA, USA); iron chloride ($FeCl_2 \cdot 4H_2O$), potassium iodide (KI), ibuprofen sodium (SI), and valproate sodium, polyvinylpyrrolidone (PVP, MW ca. 44 000), microcrystalline cellulose (Avicel PH 101), magnesium stearate (Sigma-Aldrich; Gillingham, UK); diclofenac sodium (98%; Cambridge Bioscience, Cambridge, UK); spray dried mannitol (Pearlitol 200; a kind gift from Roquette-Pharma, Lestrem, France). All chemicals were used without further purification. Commercial tablets were sourced as follows: Diclofex 75 mg (Almus, Chessington, UK), Brufen Retard 800 mg (Abbott, Chicago, IL, USA), Rheumatac Retard 75 mg (Amdipharm Mercury, Oakville, Canada), Clofenac 100 mg (Squarepharma, Dhaka, Bangladesh) and Epilim Chrono 200 mg (Sanofi, Paris, France).

2.2. HDS synthesis and scale up

Recently we reported the synthesis of two HDSs ($[Mg_2Zn_3(OH)_8]Cl_2 \cdot 3.4H_2O$ (MgZn–Cl) and $[Fe_{2.4}Zn_{2.6}(OH)_8]Cl_2 \cdot 2H_2O$ (FeZn–Cl)) and the intercalation of three drugs (diclofenac sodium [Dic], sodium ibuprofen [SI], and sodium valproate [Val]) into both HDSs [28,34]. In order to have sufficient material for tablet making, scale-up syntheses and intercalation were performed in sealed Schlenk flasks fitted with

Table 2
The HDS tablet formulations. Avicel® and Pearlitol® act as a diluent/filler, while PVP is a binder and Mg stearate a lubricant.

	HDS-Guest (% w/w)	Avicel® PH 101 (% w/w)	PVP K44 (% w/w)	Pearlitol® 200 (% w/w)	Mg stearate (% w/w)	Tablet target weight (mg)	Total mass (g)	Compression settings
MgZn-Dic-Tab	70.5	17.4	0.9	10.2	1.0	187.7	14.5	28/42
FeZn-Dic-Tab	70.5	17.4	0.9	10.2	1.0	209.0	15.5	27/42
Fe$_{ox}$Zn-Dic-Tab	53.0	25.3	4.1	14.8	2.8	198.2	15.0	27/42
FeZn-Dic-Tab1	22.0	47.9	2.5	27.0	0.6	191.0	14.8	25/42
MgZn–SI-Tab	70.7	17.3	0.9	10.2	0.9	210.0	15.4	25/42
FeZn–SI-Tab	70.7	17.3	0.9	10.2	0.9	224.5	16.0	27/42
MgZn-Val-Tab	59.3	18.9	–	20.9	0.9	683.0	36.0	40/42
MgZn-Val-Tab1	59.3	18.9	–	20.9	0.9	683.0	36.0	50/42
MgZn-Val-Tab2	70.4	17.4	0.9	10.3	1.0	460.0	27.0	40/42

paddle stirrers. All experiments were performed under stirring in water for three days consecutively, at predetermined temperatures (at room temperature (RT) for MgZn–Cl and FeZn–Cl, and at 60 °C for intercalation reactions) and using reagent amounts as detailed in Table 1. For the FeZn–Cl and FeZn-drug systems, air was excluded from the reaction vessel by flushing with N$_2$. The products were recovered by vacuum filtration. For MgZn–Cl and MgZn-drug, the resultant white powder was rinsed with deionised water and ethanol, and then allowed to dry under vacuum at 40 °C. For FeZn–Cl and FeZn-drug, the materials tended to oxidise easily when in contact with air, and to minimise this, the water was rapidly drained from the preparation using a large filter funnel before the solid was washed with a small amount of deionised water and ethanol, with both processes performed under a N$_2$ flow. The products were then dried in a vacuum oven in the presence of silica gel at 40 °C and 0% relative humidity. To investigate the effect of oxidation, some of the FeZn-Dic was left to dry in a normal oven and denoted Fe$_{ox}$Zn-Dic.

2.3. Materials characterisation

Powder X-ray diffraction (XRD) patterns were recorded using a MiniFlex 600 diffractometer (Rigaku, Tokyo, Japan), with Cu Kα radiation at 40 kV and 15 mA, to confirm that the scaled-up products were the same as those prepared at the small scale in our previous work [28, 34]. A full characterisation of the various systems generated at small scale is reported in prior publications [28,34].

2.4. Tablet preparation

The HDS-drug intercalates were blended with excipients for tablet preparation. The recipe was based initially on a previous report by Taj and co-workers [29], with some variations in the excipient blend then introduced to explore the effect this had on drug release. The HDSs and excipients were sieved and mixed prior to compression. Various combinations were tried; only those that showed similar release profiles to commercial tablets and were found to pass pharmacopeial specifications are reported here. The compositions of the formulations prepared and forces used to compress them are detailed in Table 2. All the tablet formulations were compressed using a F3 tableting machine (Manestry, Liverpool, UK). In some formulations, the same HDS-API was combined with either different excipient ratios or tableted with varied compression forces (to investigate the latter effect). To distinguish between those tablets a numerical suffix was used.

2.5. Pharmacopoeial assessment

2.5.1. Friability

Batches of tablets (n = 10–35) were pre-weighed to approximately 6.5 g each and placed in a friability tester (TBH 200, Copley Scientific, Nottingham, UK). They were rotated 100 times, after which the tablets were recovered, any dust attached to them removed, and they were reweighed.

2.5.2. Hardness

The hardness of five tablets of each formulation was determined using a hardness tester (FR1000, Copley Scientific, Nottingham, UK).

2.5.3. Weight variation

Between 10 and 30 tablets were weighted individually, and the mean mass, standard deviation, and number of tablets lying outside the pharmacopeia specified ranges were calculated.

2.5.4. Drug content

As an extra test, an investigation was conducted to see if the API content in each tablet is correlated to its weight. Three tablets of the 10 used for the weight variation study were selected at random for each formulation and finely ground using a mortar and pestle. The powder was transferred into a volumetric flask containing an HCl solution (10–25 mL), shaken for 2 h at room temperature, the pH neutralised with NaOH, and the final volume adjusted to 250 mL with deionised water. The solution was filtered, suitable dilutions were made, and UV spectra recorded for Dic and SI (UV 1800 spectrometer, Shimadzu, Kyoto, Japan). For the Val the measurements were performed using high-performance liquid chromatography (HPLC; 1260 Infinity, 1260 Quat Pump VL, Agilent Technologies, Santa Clara, CA, USA). The stationary phase was a Supelco® Discovery® HS F5-5 HPLC Column (5 μm particle size, L × I.D. 15 cm × 4.6 mm) and the mobile phase was acetonitrile/phosphate buffered saline (pH 3.0) (60/40 v/v), with a flow rate of 0.9 mL/min and injection volume of 100 μL. The Val concentration was assayed at 210 nm and 40 °C.

2.5.5. Disintegration

Between 6 and 18 tablets were placed in the tubes of a ZT34 basket-rack assembly (Copley Scientific, Nottingham, UK). Two different immersion fluids were used (pH 1.0 and 6.8), the temperature was maintained at 37 ± 2 °C, and each experiment was run for 1 h.

2.6. Drug release

Drug release (dissolution) tests were carried out under experimental

Table 3
Summary of pharmacopeial test results for the HDS tablets.

Formulation	Drug	Weight variations (%) (±SD)	Hardness (N) (±SD)	Friability (weight loss) (%)	Drug content (%) (±SD)	Number of units outside the ranges (mass/dose)
MgZn-Dic-Tab	Dic	101.2 ± 2.6	101.2 ± 5.4	0.2	102.8 ± 3.8	0/0
FeZn-Dic-Tab	Dic	96.5 ± 1.6	123.5 ± 7.8	0.1	98.8 ± 2.5	0/0
FeZn-Dic-Tab1	Dic	99.5 ± 1.7	79.3 ± 3.7	0.2	92.6 ± 1.7	0/0
Fe$_{ox}$Zn-Dic-Tab	Dic	99.8 ± 1.0	115.3 ± 4.2	0.4	102.7 ± 2.3	0/0
MgZn–SI-Tab	SI	97.5 ± 2.0	43.0 ± 4.6	0.7	99.0 ± 1.2	0/0
FeZn–SI-Tab	SI	95.5 ± 2.2	53.0 ± 3.5	0.5	97.4 ± 3.3	0/0
MgZn-Val-Tab	Val	96.1 ± 0.7	77.0 ± 7.8	0.7	94.5 ± 3.0	0/0
MgZn-Val-Tab1-	Val	100.4 ± 0.6	93.0 ± 4.5	0.5	98.8 ± 2.7	0/0
MgZn-Val-Tab2	Val	95.8 ± 0.5	120.0 ± 5.2	0.3	100.2 ± 3.3	0/0

conditions as close as possible to the gastrointestinal tract and following US pharmacopeia requirements [36]. The USP-II test (a paddle method) was used, with a PTWS model instrument (PharmaTest, Hainburg, Germany) fitted with an inline spectrometer (CE 2500, Cecil, Cambridge, UK) being employed to perform these experiments. Drug release studies were performed initially in 750 mL of 0.1 M HCl in a vessel held at $37 \pm 0.5\,^{\circ}$C and stirred at 50 rpm. After 2 h of operation, the pH of the medium was adjusted to 6.80 ± 0.05 by adding 250 mL of 0.20 M tribasic sodium phosphate. Experiments were carried out for another 22 h at this pH. Dissolution tests were carried out in darkness and in triplicate. For Val formulations, the measurements were performed with aliquots removed periodically and analysed by HPLC as described in Section 2.5.4. All aliquots from the release experiments were filtered using 100 nm pore size dissolution filters prior to analysis.

3. Results and discussion

3.1. Tablet preparation

To prepare tablets in large batches of 0.5 kg, it was first necessary to scale up the HDS preparation process. This was achieved successfully and the scale up products showed similar XRD patterns to small batches previously reported [28,34], though the FeZn–SI, FeZn-Dic, and MgZn–SI showed some extra reflections related to metal oxide impurities (FeO or MgO) (Supplementary Information, Fig. S2 and Table S1). The HDS-drug intercalates were blended with excipients, and after some optimisation tablet preparation was successfully achieved. All the tablets manufactured had smooth surfaces, and some are depicted in Fig. S3. Some key pre- and post-compression parameters are summarised in Table S2.

3.2. Pharmacopoeial assessment

The US and British Pharmacopoeias set strict guidelines for the post-compression parameters that a tablet must have [37–39]. A summary of the key parameters evaluated and number of tablets used are given in Table 3 and Table S3. First, the mass and content uniformity of the tablets was explored. The HDS tablets had a target mass between 180 and 685 mg, depending on the drug. The targeted and observed masses can be seen in Tables 2 and 3. The relative standard deviation (RSD) weight variation of the HDS tablets was found to range between 0.5 and 2.6%, while measurements on commercially available tablets showed the RSDs on the masses to lie between 1 and 17.4% (data not shown). The pharmacopeia limit for percentage deviation of tablets of 80–250 mg is ±7.5% and above 250 mg is ±5.0%. Of the 20 tablets sampled, for a batch to pass the quality test no more than two tablets can deviate from the target weight by more than the allowable limit and none by more than twice that limit. Here, none of the HDS tablets assessed fell outside the 5% range and thus the formulation batches were found to pass according to the specifications given in the US and British Pharmacopoeias [37,38]. Moreover, the extra drug content uniformity test conducted on the HDS tablets, showed values ranging between 92.6 ± 1.7 and $102.8 \pm 3.8\%$ of the target content observed. These values lie within the USP and BP requirements of $100 \pm 15\%$. The pharmacopoeias stipulate that of 10 tablets assayed, the batch fails if more than one tablet is outside 85–115% of the mean, or any tablet lies outside 75–125% of the mean. All the formulations pass this test as well [37,38].

Tablets undergo repeated mechanical shocks or stress during their manufacturing, packing and transportation. This can cause attrition, capping or breakage of tablets. Thus, tablets are formulated to withstand such stress. To find out if the tablets have sufficient mechanical strength to withstand fracture, aberration and capping during the manufacture and handling process, hardness and friability were determined [40]. The
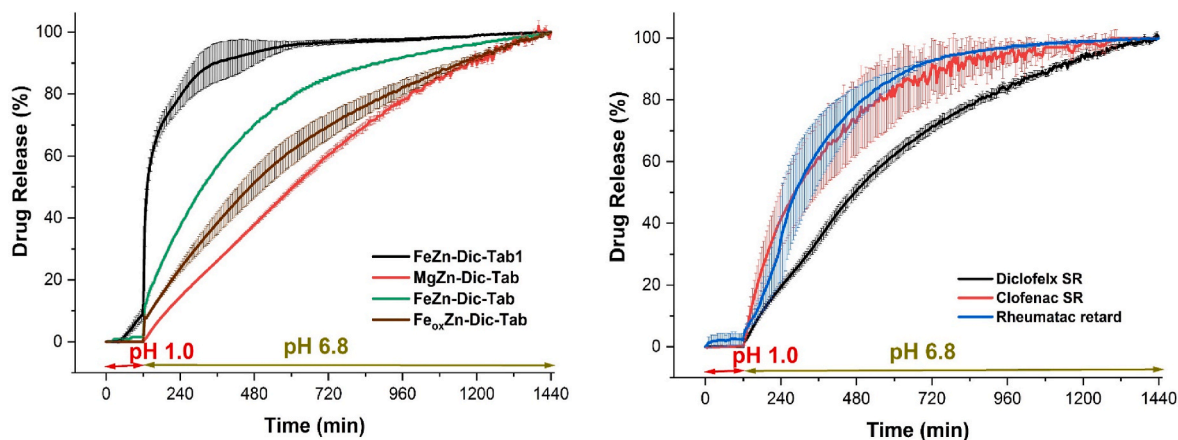

Fig. 2. Dic release from the different HDS-Dic tablets formulations and commercial tablets at pH 1 and pH 6.8 (mean ± S.D., n = 3). The error bars on FeZn-Dic-Tab are too small to see (<1%).

Table 4
Summary of Dic release from the different tablets.

	FeZn-Dic-Tab	FeZn-Dic-Tab1	Fe$_{ox}$Zn-Dic-Tab	MgZn-Dic-Tab	Rheumatec Retard	Dicloflex	Clofenac
After 2 h (%)	1.2 ± 0.0	9.0 ± 1.9	0.5 ± 0.1	0.1 ± 0.0	2.1 ± 2.2	0.1 ± 0.1	0.2 ± 0.1
After 24 h (%)	100 ± 0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0
t_{50}/min	317 ± 4.0	134 ± 5.0	472 ± 52.0	620 ± 18.0	290 ± 57.0	478 ± 18.0	301 ± 80.0
t_{90}/min	885 ± 1.0	360 ± 19.0	1143 ± 28.0	1202 ± 37.0	665 ± 42.0	1097 ± 29.0	686 ± 158.0

hardness values for the HDS tablets were found to be uniform and to range between 43 and 123.5 N. Friability values were found to be 0.7% or lower (Pharmacopeia requirement <1%). No sign of cracking, capping, or breaking were seen, which implies that the HDS tablets had appropriate strength. Thus, all the HDS tablets were found to meet the pharmacopeia requirements, as is evident from the results shown in Table 3.

Disintegration tests performed in an acidic immersion fluid (pH 1.0) showed no evidence of disintegration, cracking, or softening of the HDSs tablets after 1 h, except in the case of MgZn-Val-Tab, MgZn-Val-Tab1, and MgZn-Val-Tab2. The API solubility in an acidic media determines the fate of HDS-API here. We observed previously that both HDS-Dic and HDS-SI only partially dissolve in pH 1 conditions, and both Dic and SI acted as a "shield" to protect the layers, since both drugs are poorly soluble at this pH. However, Val is soluble in acidic media and HDS-Val dissolved very quickly. This might explain why only the Val tablets disintegrated in the acidic milieu [28]. In addition, tests carried out in a neutral immersion fluid (pH 6.8) showed that all tablets disintegrated within 1 h. This suggests that the Dic and SI tablets could be suitable for delayed release applications.

3.3. Drug release study

3.3.1. Diclofenac

Dissolution tests from MgZn-Dic-Tab, FeZn-Dic-Tab, FeZn-Dic-Tab1, Fe$_{ox}$Zn-Dic-Tab, and commercial extended release (ER) Dic tablets (Rheumatac Retard, Dicloflex and Clofenac) are presented in Fig. 2. All the tablets showed only small amounts of Dic release at pH 1, with FeZn-Dic-Tab1 releasing 9% of its loading and the other tablets between 0 and 5% during the first 2 h at this pH (these conditions mimic the stomach milieu and transit time). The higher amounts of release from FeZn-Dic-Tab1 may be caused by the destruction of some of the HDS layers; the tablets were observed to disintegrate before the pH was raised. The other tablets disintegrated only after the adjustment of the pH to 6.8. After 2 h, once the pH was adjusted to 6.8, the release rate from all the tablets increased. The time duration and drug release percentage are summarised in Table S4. This is triggered by anion exchange of the Dic located in the interlayer with phosphate anions in solution (see Table 4). The FeZn HDS remained green after the experiment, as can be seen in Fig. S4, indicating that oxidation of Fe^{2+} does not occur to any significant extent during the release process. In the FeZn-Dic-Tab1 formulation the excipients/HDS ratio is higher than the FeZn-Dic-Tab. It is known that mannitol (Pearlitol®) can lead to quicker disintegration and enhance the solubility of poorly soluble APIs [41]. In addition, microcrystalline cellulose (Avicel) can improve liquid media transport into the tablets interior, which also speeds up the disintegration time [42]. This explains why FeZn-Dic-Tab1 disintegrated within the first 2 h and showed higher Dic solubility in acidic media than FeZn-Dic powder (Fig. S5).

The release rate from FeZn-Dic-Tab and MgZn-Dic-Tab was consistent from tablet to tablet, with a standard deviation (SD) less than 1.8% throughout all the experiments, while the other systems were more variable, with SDs of up to 16%. FeZn-Dic-Tab and MgZn-Dic-Tab could therefore perform better than the commercial tablets in giving the same outcomes with every application, since they have very consistent rates [43].

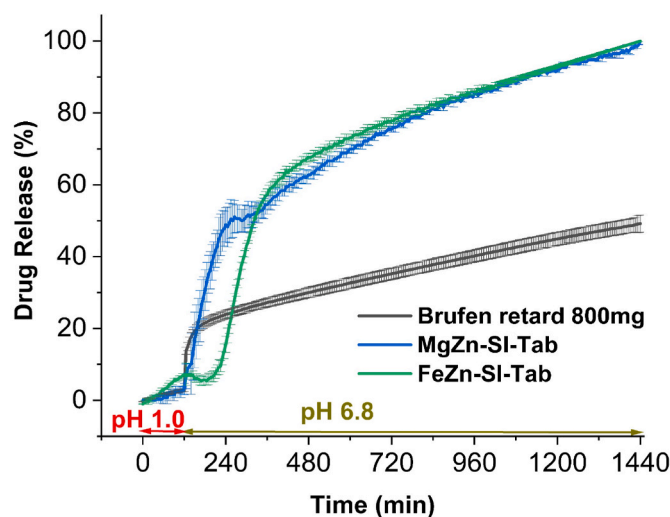The new HDS-non-steroidal anti-inflammatory drug (NSAID)

Fig. 3. SI release from FeZn–SI-Tab, MgZn–SI-Tab (n = 3, mean ± S.D), and Brufen Retard (n = 4, mean ± S.D) at pH 1 and pH 6.8.

formulations meet the pharmacopeia requirements for delayed-release dosage forms as well as extended release dosage forms: these specify that less than 10% of the incorporated drug should be released in the acidic media and the drug is freed at a slow rate over a prolonged duration of time, respectively [36,44]. In addition, all the drug loading was liberated within 24 h. By meeting the pharmacopeia delayed-release dosage form requirements, the new HDS tablets are expected to prevent the stomach irritation which can be caused by Dic. By meeting the other requirement, the HDS tablets may contribute to improved patient compliance. Each of FeZn-Dic-Tab, Fe$_{ox}$Zn-Dic-Tab and MgZn-Dic-Tab showed a similar release profile to the commercial tablets, thus they are expected to be suitable for patients with normal transit times (Fig. S5). FeZn-Dic-Tab1 disintegrated quickly and showed a faster release profile, and hence might be suitable for patients with faster transit times [45,46]. If the transit time is rapid and drug release too slow, the tablets can be excreted from the human body before freeing all their loading, which leads to a decrease in bioavailability [47,48]. Therefore, there is a risk that the drug level does not attain the therapeutic window, resulting in no pharmacological effect (in this case no pain relief).

3.3.2. Ibuprofen (SI)

Dissolution tests from HDS tablets (FeZn–SI-Tab, MgZn–SI-Tab) and commercial tablets (Brufen Retard) are displayed in Fig. 3. All the tablets showed minimal release at low pH, with FeZn–SI-Tab releasing less

Table 5
Summary of SI release from the different tablets.

	MgZn–SI-Tab	FeZn–SI-Tab	Brufen retard
After 2 h (%)	3.2 ± 1.1	7.1 ± 0.4	2.9 ± 0.4
After 24 h (%)	100 ± 0.0	100 ± 0.0	49.2 ± 2.0
t_{50}/min	255 ± 56.0	323 ± 3.0	1444 ± 44.0
t_{90}/min	1098 ± 26.0	1102 ± 20.0	–

than 8%, and the other two tablets 3% during the first 2 h at pH 1.0. Once the tablets were in a milieu mimicking the intestine (pH 6.8), there was a sharp burst of release from the MgZn–SI-Tab and Brufen Retard. The time duration and drug release percentage are summarised in Table S5. In contrast, the SI release from FeZn–SI-Tab remained flat for 75 min and then was followed by a sharp acceleration in release. The release rate from all the tablets slowed after that, and both HDS formulations behave similarly from 5 h until the end of the experiments (Table 5). After the initial burst release, drug was freed from the tablets in an almost linear fashion from all three types of tablets.

Only 50% of the SI content was released from the Brufen Retard tablet within 24 h (and 79% within 48 h). After 24 h, there is risk that the remains of the tablet will have been excreted from the human body or be enrobed inside human stools, and thus the remaining drug will not be freed. This is wasteful, since more drug is being used to make the medicine than is used in the body, and in addition the drug concentration may not be maintained within the therapeutic window with this type of formulation. The MgZn–SI-Tab and FeZn–SI-Tab showed a comparable solution drug concentration vs time profile to the commercial Brufen Retard tablet, but the HDS tablets free all their loading within 24 h; this is illustrated in Fig. S6.

The release of SI from HDS tablets was slower compared to its release from the HDS-SI powder (Fig. S7). SI release from $Zn_5(OH)_8$–SI HDS tablets has been reported by Taj *el al* [29] in similar conditions. These authors found that *ca.* 10% of the drug was released in an acidic media, and following transfer to neutral medium the rest of the drug was freed within 10 h. Shiyani and co-workers reported that LDH-SI tablets did not release in acidic milieu and all the SI was released after 10 h in the neutral medium [49]. In addition, Rojas and co-workers reported that LDH-SI tablets (compressed LDH-SI without additional excipients) did not release at pH 1.2 and only 16.5% was released after 24 h at pH 6.8 [50]. Most of the SI modified release tablets formulations reported in the literature showed only one-phase first order release [51–53], which make them less effective in bringing the SI plasma concentration quickly to the therapeutic window and maintaining it for longer period.

All data reported here, and previously by other scientists, showed a burst release of SI in a phosphate buffer (pH ≥ 6.8). Since it is known that the SI is absorbed quickly in the gastrointestinal tract of a healthy human being [54], this should bring the SI plasma concentration rapidly into the therapeutic window; the second, extended, part of the release profile should maintain it within this window for a prolonged period of time [55,56]. The MgZn–SI-Tab and FeZn–SI-Tab formulations meet the pharmacopeia requirements for both delayed-release dosage forms and extended release dosage forms. Therefore, they are expected to prevent damage to the stomach caused by drug release in this low pH environment, as well as improving patient compliance. They showed a similar release profile to a commercial tablet, and thus should be suitable for patients with normal transit times.

NSAIDs (e.g., SI and Dic) are mainly utilised in the treatment of pain and can cause undesirable side effects in the human gut [57]. New NSAID formulations are being sought that can surmount concerns linked with current medicines [58]. Mg salts can be used for pain management in combination with other drugs such as NSAIDs and clinical trials have showed that this can improve treatment efficacy with lower NSAID doses [59]. It can also lessen the lag time before a therapeutic effect is felt, leading to faster analgesia [60]. Zn^{2+} plays an important role in the human body and can act as an anti-inflammatory agent [61], and when ZnO is co-administered with NSAIDs it can minimise their side effects in the gastrointestinal tract and increase anti-inflammatory activity [62]. Further, prolonged use of NSAIDs can lead to a potential iron deficiency [63], and iron supplements are usually recommended. The new HDS-NSAID tablets could thus overcome concerns associated with commercial NSAID formulations, and in addition the presence of the metal ions should improve functional performance and compensate for iron depletion (Table S6).
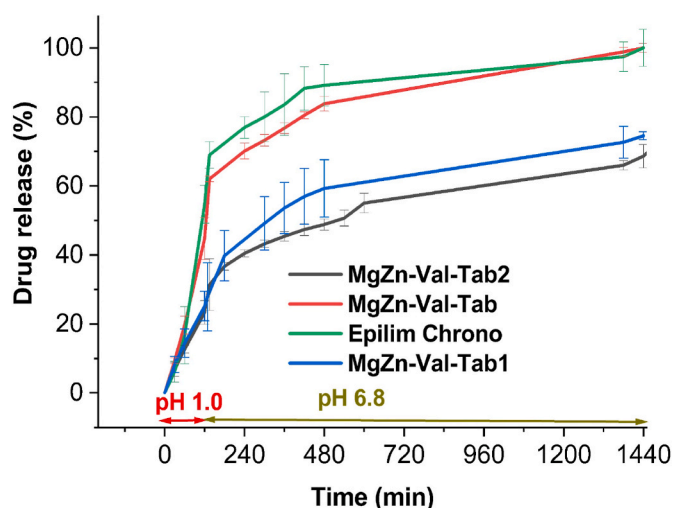

Fig. 4. Val release from the various MgZn-Val tablets and Epilim Chrono at pH 1 and pH 6.8 (n = 3, mean ± S.D).

Table 6
Summary of Val release from the different tablets.

	MgZn-Val-Tab	MgZn-Val-Tab1	MgZn-Val-Tab2	Epilim Chrono®
After 2 h (%)	44.8 ± 6.1	25.2 ± 4.3	22.7 ± 3.4	54.7 ± 5.5
After 24 h (%)	100 ± 0.0	74.6 ± 1.1	67.1 ± 4.0	100 ± 0.0
t_{50}/min	124 ± 4.0	317 ± 20.0	540 ± 42.0	110 ± 11.0
t_{90}/min	848 ± 79.0	1580 ± 33.0	1636 ± 13.0	625 ± 46.0

3.3.3. Valproate sodium (Val)

Dissolution test results from MgZn-Val-Tab, and commercial tablets (Epilim Chrono®) are shown in Fig. 4. The release of Val from HDS tablets was slower compared to its release from the HDS-Val powder (Fig. S8). In acidic media, the drug release was slower from MgZn-Val-Tab1 and Tab2 than MgZn-Val-Tab and Epilim Chrono (see Table 6). Once the pH was adjusted, the release rate slowed down from all four formulations. The time duration and drug release percentage are summarised in Table S7. Epilim Chrono and MgZn-Val-Tab released all their loading within 24 h, while MgZn-Val-Tab1 and MgZn-Val-Tab2 released only 74.6% and 68.6%, respectively. MgZn-Val-Tab and Epilim Chrono showed very similar release profiles. MgZn-Val-Tab and MgZn-Val-Tab1 have an identical composition and the only difference was the compaction pressure, which was higher in MgZn-Val-Tab1 (as reflected in the hardness test results). The same compaction pressure was used with MgZn-Val-Tab and MgZn-Val-Tab2, but MgZn-Val-Tab2 had greater hardness and a slower release rate. The HDS/excipients ratio in MgZn-Val-Tab2 was higher than MgZn-Val-Tab, thus the disintegration time is found to be longer and the rate of dissolution slower.

Val release in acidic conditions was much higher than the amount of drug release observed from the other HDS tablets, even though MgZn-Val-Tab contains the same excipients as the MgZn-Dic-Tab and MgZn–SI-Tab. This is however a positive observation. Val release in acidic media is required: a clinical trial showed that Epilim Chrono tablets (which release in the stomach) are more effective in the long-term treatment of epilepsy than enteric-coated sodium valproate tablets (which do not) [64]. The greater extent of release from the HDS-Val tablets can be attributed to the higher solubility of Val compared to the other drugs. The release rate difference between the three Val-loaded HDS tablets is thought to be due to porosity, which has an inverse correlation with hardness and a positive correlation with the release rate [65–70]. The hardness test showed that MgZn-Val-Tab2 was the most resistant to crushing, followed by MgZn-Val-Tab1 and finally

Table 7
Summary of kinetic models considered.

Model	Equation	References
Zero-order	$M_t = M_0 + k_0 t$	[86]
First-order	$\ln(M_t/M_\infty) = -k_1 t$	[87]
Bhaskar	$\ln(M_t/M_\infty) = k_B t^{0.65}$	[88]
Higuchi	$M_t/M_\infty = k_H t^{1/2}$	[89]
Korsmeyer-Peppas	$M_t/M_\infty = k_{KP} t^n$	[90]
Hixson-Crowell	$M_0^{1/3} - M_t^{1/3} = k_{HC} t$	[91]
Baker-Lonsdale	$\frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{2/3}\right] - \frac{M_t}{M_\infty} = k_{BL} t$	[92]

MgZn-Val-Tab (Table 3). The release mechanism is believed to be mainly due to weathering in acidic media. Once the pH was adjusted, there was a deceleration in the release rate, which suggested that a new release mechanism became dominant, ion exchange (which is highly dependent on the anions present).

The release rate could be tailored by varying the ratio of excipients or

the compressional force used to prepare the three HDS-Val tablets. It is known that antacids can increase the bioavailability of valproic acid [71–74], and since HDSs can act in an antacid role MgZn-Val-Tab may be able to generate the same effect as Epilim Chrono with a smaller dose. MgZn-Val-Tab is expected to be suitable for patients with normal transit time, while MgZn-Val-Tab1 and MgZn-Val-Tab2 might be useful for those with a longer transit time.

Epileptic children at the early stage are recommended Val as a first-line treatment [75]. It is known however that valproate therapy over long periods usually results in the depletion of essential elements such as Zn and Mg [76,77], so metal supplements are prescribed with the therapy. It can also lead to gastritis and antacids are usually prescribed as a preventive treatment [78]. The HDSs possess a buffering property and can also compensate the depleted elements. Thus, the HDS-Val tablets could fulfil both functions without any additional supplements or preventive medications and could improve patient compliance by delivering multiple functions in a single tablet (Table S6).

It proved impossible to precisely monitor drug release from the FeZn-
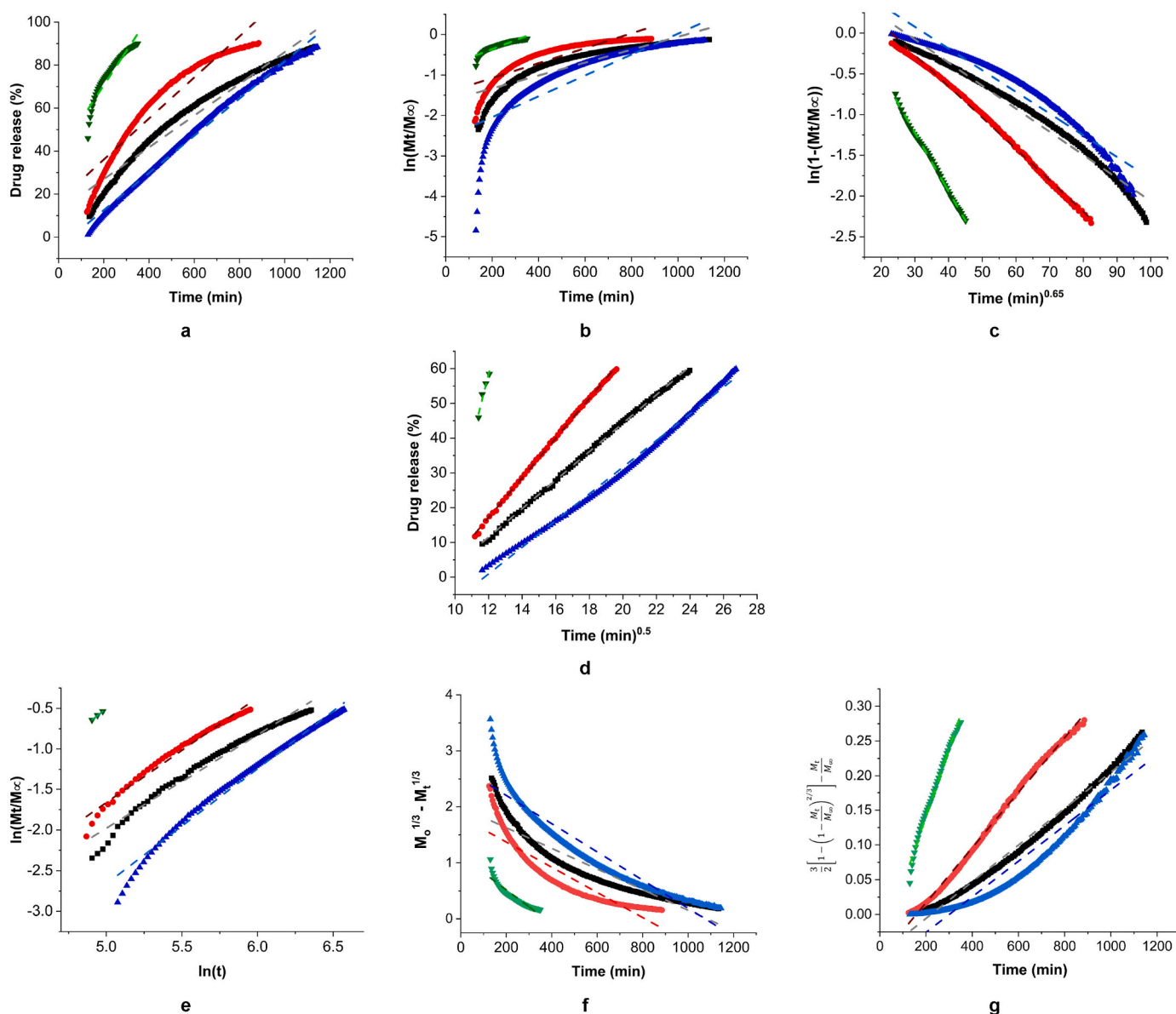

Fig. 5. Kinetic models fitted to the experimental release data at neutral pH for MgZn-Dic-Tab (▲); FeZn-Dic-Tab (●); Fe$_{ox}$Zn-Dic-Tab (■) and FeZn-Dic-Tab1 (▼): (**a**) zero order model; (**b**) first order model; (**c**) Bhaskar model; (**d**) Higuchi model; (**e**) Korsmeyer-Peppas model; (**f**) Hixson-Crowell model; and (**g**) Baker-Lonsdale model.

Val system as there was found to be interference with the UV/vis measurements, even though the aliquots were filtered (0.1 μm) prior to measurement. This could be due to the presence of Fe in solution [79–85].

3.4. Kinetics study

To gain more insight into the release mechanism from the HDS tablets, some widely used mathematical models were utilised. These models are summarised in Table 7, where M_t and M_∞ are the amount of drug released at time t and after an infinite amount of time; M_0 is the initial amount of drug present in solution (usually, $M_0 = 0$). k (the release constant) and n (the release exponent) are associated with the release mechanism underway.

Two kinds of mechanism were postulated during the investigation of drug release from HDS tablets: weathering or dissolution of HSDs layers in the acidic solution (pH $\geq$ 1.0) and an ion-exchange process in phosphate buffer (pH $\geq$ 6.8). The fits of the models to Dic release at pH $\geq$ 6.8 are given in Fig. 5, and the results are summarised in Table S8. It is clear that the first order model does not describe Dic release, reflected by the fact that data clearly do not lie on a straight line.

The Korsmeyer-Peppas and the Higuchi models are also not suitable to explain the release process from the HDS tablets,. This is not surprising given the complexity of the tablet composition and shape, and indeed it has been noted that it is generally not appropriate to use these models to analyse drug release kinetics from tablets [93].

In contrast, the Bhaskar model fits the release profiles much better ($R^2 > 0.99$), except for MgZn-Dic-Tab and Fe_{ox}Zn-Dic-Tab, indicating that the release mechanism from HDS tablets in most cases is controlled by ion exchange. The release of Dic from MgZn-Dic-Tab at neutral pH appears to be zero order for the first 80% of release ($R^2 > 0.99$), with the release data lying on a straight line ($R^2 > 0.998$). Usually, zero-order release systems are intricate, take time to develop, costly, and tough to manufacture. Zero-order release formulations are much sought after owing to their ability to release drug at a constant rate, leading to good control of plasma concentration [94]. The MgZn-Dic-Tab is easy, inexpensive, and quick to manufacture.

The fits of the models to SI and Val release at pH $\geq$ 6.8 are given in Figs. S9 and S10 and the fitting parameters listed in Table S8. It is clear that the Bhaskar model was the only model able to describe SI and Val release ($0.97 < R^2 < 0.99$). For SI, all the models indicate that there are two different segments of release, and thus fitting was carried out individually for each segment. The resultant analysis suggests that the SI release mechanism from HDS tablets is controlled by an ion exchange mechanism. The release of SI showed slightly different behaviour from Dic and Val which could result from a variety of factors such as the interactions of the guests with the layers or SI's physicochemical properties, since a similar pattern was observed from another system (Brufen Retard).

4. Conclusions

In this work, the MgZn–Cl and FeZn–Cl HDS synthesis was successfully scaled up, and the APIs Dic, SI and Val intercalated at scale. The API-loaded HDSs were formulated into non-core-based tablets, and these met the standard pharmacopeia requirements (weight consistency, hardness, friability, and drug content). Drug release from the HDS tablets was investigated in conditions that mimic the human gastrointestinal tract. All the loaded HDS tablets met the pharmacopeia extended release dosage form requirements. Release from the various HDS tablets was governed by a complex interplay of factors such as API solubility, the HDS/excipients ratio, and the compression force. Novel extended release non-core based HDSs tablets were prepared that showed similar release profiles to commercial formulations (Epilim Chrono®, Brufen Retard®, Rheumatac Retard®, Clofenac®). A kinetic analysis showed that API release from HDS tablets was largely governed by ion exchange

(Bhaskar model) while some had constant (zero order) release profiles. In addition to passing all relevant pharmacopoeial tests, the presence of essential elements (Mg, Fe, Zn) in the HDS tablets may have additional physiological benefits, potentially ameliorating some side-effects of standard treatments, which should be studied further in future work. They could thus provide an "all in one" treatment that could improve therapeutic effects and remove the need for other preventive medication.

Author statement

Conceptualization, A.Y.A.K., G.R.W.; methodology, A.Y.A.K.; validation, A.Y.A.K.; formal analysis, A.Y.A.K.; investigation, A.Y.A.K.; data curation, A.Y.A.K.; writing—original draft preparation, A.Y.A.K.; writing—review and editing, A.Y.A.K., G.R.W; visualization, A.Y.A.K.; supervision, G.R.W.; project administration, G.R.W. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2023.104989.

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