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RESEARCH ARTICLE

Effect of Different Carriers on *In Vitro* and *In Vivo* Drug Release Behavior of Aceclofenac Proniosomes

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Abstract: ***Background*:** Improved bioavailability of Aceclofenac (ACE) may be achieved through proniosomes, which are considered as one of the most effective drug delivery systems and are expected to represent a valuable approach for the development of better oral dosage form as compared to the existing product. However, the carrier in this system plays a vital role in controlling the drug release and modulating drug dissolution. Accordingly, a comparative study on different carriers can give a clear idea about the selection of carriers to prepare ACE proniosomes.

***Objective*:** This study aims to evaluate the role of maltodextrin, glucose, and mannitol as carriers for *in vitro* and *in vivo* performance of Aceclofenac (ACE) proniosomes.

***Methods*:** Three formulations of proniosomes were prepared by the slurry method using the 100 mg ACE, 500 mg span 60, 250 mg cholesterol with 1300mg of different carriers, *i.e*., glucose (FN1), maltodextrin (FN2), and mannitol (FN3). *In vitro* drug release studies were conducted by the USP paddle method, while *in vivo* studies were performed in albino rats. Pure ACE was used as a reference in all the tests. Lastly, the results were analyzed using the High-Pressure Liquid Chromatography (HPLC) method, and data were evaluated using further kinetic and statistical tools.

***Results*:** No significant differences ($p > 0.05$) in entrapment efficiency (%EE) of FN1, FN2, and FN3 (82 ± 0.5%, 84 ± 0.66%, and 84 ± 0.34% respectively) were observed and formulations were used for further *in vitro* and *in vivo* evaluations. During *in vitro* drug release studies, the dissolved drug was found to be 42% for the pure drug, while 70%, 17%, and 30% for FN1, FN2, and FN3, respectively, at 15 min. After 24 hrs, the pure drug showed a maximum of 50% release while 94%, 80%, and 79% drug release were observed after 24 hr for FN1, FN2, and FN3, respectively. The *in vivo* study conducted on albino rats showed a higher C_{max} and AUC of FN1 and FN2 in comparison with the pure ACE. Moreover, the relative oral bioavailability of proniosomes with maltodextrin and glucose as carriers compared to the pure drug was 183% and 112%, respectively. Mannitol-based formulation exhibited low bioavailability (53.7%) that may be attributed to its osmotic behavior.

***Conclusion*:** These findings confirm that a carrier plays a significant role in determining *in vitro* and *in vivo* performance of proniosomes and careful selection of carrier is an important aspect of proniosomes optimization.

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1. INTRODUCTION

With the advancement in formulation research, new strategies are being employed to overcome the challenges associated with the poor bioavailability of drugs. Multiple drugs have shown significant enhancement of bioavailability when formulated into vesicular systems. Proniosomes and niosomes are used to enhance the oral bioavailability of poorly water-soluble drugs [1-3], and they can facilitate the absorption and solve the bioavailability issues [4, 5]. Earlier findings suggest the role of niosomes in the enhancement of oral bioavailability of different drugs that belong to different

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Biopharmaceutical Classification System (BCS) classes such as Ganciclovir (BCS class III) niosomes [4], Carvedilol (BCS class IV)niosomes [5], and Paclitaxel BCS class IV proniosomes [6].

ACE is a BCS class II drug indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis [7]. However, the low bioavailability of ACE has limited its uses as compared to other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [7]. The water solubility of ACE is reported to be 0.088 $mg.mL^{-1}$, with approximately 15% oral bioavailability [8].

Proniosomes are dry, free-flowing formulations of the surfactant-coated carrier, efficiently rehydrated by brief agitation in hot water to form a multi-lamellar niosomes suspension suitable for administration by oral or other routes. Proniosomes can enhance the bioavailability of the drugs, either hydrophilic, amphiphilic, or lipophilic [3]. Proniosomes are also considered as one of the most straightforward strategies that can be easily scaled up for the large-scale manufacture of novel pharmaceutical delivery systems [9]. Proniosomes are processed to make beads, tablets, or capsules, which make their use easy [10].

The results of ACE proniosomes characterizations and optimization using Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), powder X-Ray Diffractometry (XRD), Scanning Electron Microscopy (SEM), drug entrapment, and micrometric properties are reported earlier [11]. The carrier in this system plays a vital role in controlling the drug release and modulate drug dissolution. Accordingly, a comparative study on different carriers, including proniosomes, can give clear ideas about the selection of carriers to prepare ACE proniosomes. This manuscript examines the role of three different carriers (glucose, maltodextrin, and mannitol) for *in vitro* and *in vivo* performance of ACE proniosomes.

2. MATERIALS

ACE (COS Grade) was received as a gift sample from MEDA PHARMA (Dubai, United Arab Emirates); glucose (D) and D-(-)- mannitol were purchased from VWR Chemicals BDH® (London, England); maltodextrin (reducing sugar (dextrose equivalent): <= 20.00%) was purchased from Himedia Laboratories (Mumbai, India); cholesterol was from MP Biomedicals; and LLC, Span 60, chloroform and methanol were from Merck (Darmstadt, Germany). HPLC grade acetonitrile was purchased from Fisher Scientific (UK). Disodium hydrogen phosphate, potassium dihydrogen phosphate, and sodium chloride were procured from Fluka Analytical (Seelze, Germany). All chemicals used in the study were of analytical grade.

3. METHODS

Preparation of proniosomes was done by using the slurry method as described in our earlier publication [11]. First, 100mg ACE, 500 mg Span 60, and 250 mg cholesterol were added to a 50 mL (1: 1) chloroform to methanol. Second, All the above ingredients were dissolved completely. Then, the different carriers (glucose, maltodextrin, and mannitol) were weighed accurately and placed in a 250 mL round bottom flask. After that, the above mixture was placed in the 250 mL round bottom flask containing the various amounts of the carrier as described in Table **1**. Afterward, solvent evaporation was carried out by a rotary evaporator (IKA, HB 10 Basic) under vacuum for 40 minutes at 40 ºC at 80 rpm. Finally, the prepared proniosomes were dried overnight by placing them in a room temperature incubator (37 ºC). The obtained proniosomes were stored in a tightly closed container at room temperature for further studies [12].

Proniosomes were hydrated using 50 ml of warmed distilled water (80º C) with gentle handshaking for 5 minutes. The procedure for the proniosomes hydration was similar to what Song *et al*. applied with little modifications [2].

3.1. *In vitro* Drug Release

The *in vitro* drug release of the optimized proniosomes was carried out using USP Type II Apparatus (Paddle method) [13]. Where the apparatus was adjusted to 100 rpm at 37 ± 0.2 in a 900 mL of fresh phosphate buffer (pH 6.8) as a dissolution medium. 50 mL of hydrated proniosomes were added (equivalent to 100 mg ACE). The pure drug was added to the medium as a fine powder (100 mg). Aliquots (4 mL) were withdrawn at definite intervals of 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours. The volume of the withdrawn samples was replaced by phosphate buffer. Each sample was filtered through a 0.45 µm membrane filter and analyzed by a validated HPLC method.

An HPLC system (Shimadzu Prominence model CTO - 10AS VP) with a UV detector was used for the analysis. A Hypersil Gold C18 column of 250 * 4.6 mm (length * dia) and the particle size of 5 µm (Thermo scientific) was used as a stationary phase. The chromatographic conditions used [14] are as follows; mobile phase: phosphate buffer (pH 5.0): acetonitrile in a ratio of 60:40 (v/v), the wavelength of detection 275 nm, flow rate: $1.0mL.min^{-1}$, and temperature: room temperature.

Table 1. Formulation and characterization parameters of ACE proniosomes [11].

Formulation Parameters						Characterization Parameters*			
Formula code	ACE (mg)	Span 60	Cholesterol (mg)	Solvent (mL)	Carrier	EE (%)	Z-Average (d.nm)	PDI	Zeta Potential (mV)
FN1	100	500	250	50	1300 mg glucose	82 ± 0.5	5240 ±128	0.575	- 46.3 ± 5.96
FN2					1300 mg of maltodextrin	84 ± 0.66	6403 ±25	0.701	- 45.2 ± 5.14
FN3					1300 mg of mannitol	84 ± 0.34	4669 ± 20	1.000	- 48.5 ± 5.06

* Data are means ± SD (n = 3).

ACE concentrations in aliquots and the percentage of drug dissolved were calculated by the standard curve developed by the HPLC method. A dissolution curve representing the concentration versus the time was plotted. The data of drug release was evaluated kinetically in comparison with the pure drug of ACE. Model-dependent methods were conducted to describe the dissolution profiles based on different mathematical models, including zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixon Crowell models [13].

A menu-driven add-in program for Microsoft Excel called DD Solver [15] was used to derive the different models. Minitab version 17 is the software used for statistical analysis of derived data.

3.2. *In Vivo* Drug Release

The animal study on rats began after obtaining the approval of the Institutional Animal Care and Use Committee; International Islamic University Malaysia (IACUC IIIUM), IIUM/IACUC. Approval/ 2018/29.

Sprague Dawley Albino rats of either gender with 175-200 g body weight at the time of the study aged 2-3 months old were used in this study. Rats were procured before 2 weeks of study, and they were acclimatized by keeping a controlled environment (24 ± 2 °C; 55 ± 10% relative humidity) as per other reported studies [16]. Rats were divided into five groups of six rats in each group. A single oral dose was used in the study. All groups were fed a similar 10 $mg.kg^{-1}$ of the rat body weight dose of ACE. The dose was calculated according to the Human Equivalent Dose (HED) and No Observed Adverse Effect Level (NOAEL), according to the following equation (1) [17].

$$HED\ (mg.kg^{-1}) = Animal\ NOAEL\ (mg.kg^{-1}) \times \frac{weight\ of\ animal\ (kg)}{weight\ of\ human\ (kg)} \quad (1)$$

Group 1 received a placebo, while group 2 received ACE pure powders. Group 3, 4, and 5 received three different formulas containing maltodextrin, glucose, and mannitol, respectively. Capillary tubes were used to collect blood samples (around 0.5 mL) from the retro-orbital sinus into heparinized tubes at 0.5, 1, 1.15, 1.30, 2, 4, 6, 8, and 12 h following the dose. The timing of the blood sampling was adjusted after a small pilot study on 2 rats only to ensure the proper time of sampling.

The plasma samples were prepared for HPLC analysis through the following steps: 90µL of plasma was added to a 1.5 mL centrifuge tube. A 10 µL of internal standard (Carbamazepine solution 500 $\mu g.mL^{-1}$) was added and vortexed for 10 seconds by semi-automated vortex equipment (VELP Scientifica vortex). Then, 200 µL of acetonitrile was added and again vortexed for another 10 seconds. The above mixture was centrifuged at 10000 rpm for 10 minutes. Then, the supernatants were taken and diluted with mobile phase to 1 mL in 2 mL HPLC vial insert. The samples were filtered using a 0.22 µm nylon membrane filter (Thermo scientific) and were analyzed by HPLC. The vial inserts were used with HPLC vials to give effective measurements due to the small volume.

3.3. Pharmacokinetics and Statistical Analysis

Using the HPLC plasma standard curve, the plasma concentration of ACE at different time intervals was subjected to pharmacokinetics (PK) analysis. Accordingly, the following PK parameters were calculated: Maximum plasma concentration (C_{max}) and time to reach maximum concentration (T_{max}) that were found directly from the plasma concentration profile. The area under the plasma concentration curve ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$), $AUC_{0\text{-}t}$ was calculated using the trapezoidal method (t is the last measurable concentration), while $AUC_{0\text{-}\infty}$ was calculated using the following equation, where C_t is the concentration of drug in solution at time t, and Kel is the elimination rate constant (Eq. 2):

$$AUC_{0-\infty}\ (\mu g.hr.mL^{-1}) = AUC_{0-t}\ (\mu g.hr.mL^{-1}) + \frac{C_t\ (\mu g.mL^{-1})}{k_{el}\ (hr^{-1})} \quad (2)$$

The elimination rate constant (K_{el}) was determined from the slope of the logarithm of plasma concentration and time (after multiplying with 2.303), while the half-life ($t_{1/2}$) was calculated by the following equations 3 and 4:

$$t_{\frac{1}{2}}\ (hr) = \frac{0.693}{k_{el}\ (hr^{-1})} \quad (3)$$

Lastly, the relative bioavailability F (%) was determined by:

$$F\ (\%) = \frac{AUC_{0-\infty\ sample}\ (\mu g.hr.mL^{-1})}{AUC_{0-\infty\ pure\ drug}\ (\mu g.hr.mL^{-1})} \times 100 \quad (4)$$

F (%) means the relative bioavailability.

Pharmacokinetics parameters were derived using Microsoft Excel and DD Solver. Data were analyzed statistically using Minitab 17.

4. RESULTS AND DISCUSSION

Carriers are an integral part of proniosomes composition. They permit the flexibility in the ratio of surfactant and other components incorporated and also increase the surface area and enhance drug loading. Different carriers can be used in the preparation of proniosomes. Maltodextrin is one of the preferred carriers in the formulation of other drug delivery systems [9]. At the same time, mannitol is an organic crystalline compound formed from the reduction of sugar. Glucose is also considered an important carrier; however, it is not used widely in the formulation of a novel drug delivery system [18]. Hence, maltodextrin, mannitol, and glucose were selected to prepare ACE proniosomes to study the effect of different carriers on such a system.

The optimized proniosomal formulations that have been concluded earlier by Rana *et al*. [11] were used for further *in vitro* and *in vivo* evaluations. Proniosomes were prepared by the slurry method, and niosomes derived from proniosomes exhibited good stability, high entrapment efficiency, and drug content Table **1**. The optimized formulations were consisted of 100 mg ACE, 500 mg Span 60, 250 mg cholesterol with different carriers, *i.e*., glucose (FN1), maltodextrin (FN2), and mannitol (FN3) with entrapment efficiency (%)

of 82±0.5%, 84±0.66%, and 84±0.34% respectively and were used as such.

4.1. *In vitro* Drug Release

The results of the *in vitro* drug release by the paddle method were analyzed using different techniques, such as graphical presentation, model-dependent method, and statistical analysis. At 15 minutes time point, significant differences ($p < 0.05$) in drug release were observed between the different formulations Fig. (**1**). The drug release for ACE pure drug was 42%, FN1 was 70%, FN2 was 17%, and for FN3, it was 30% at 15 min. Physicochemical characterization of the prepared proniosomes concluded non-significant differences in terms of entrapment efficiency, vesicle size, and content uniformity, as reported earlier [11]. Therefore, these differences may be attributed to the physical characteristics of the carrier used. Glucose presented in FN1 is considered a crystalline substance [18] and may destabilize the noisome membrane resulting in the fast and burst effect in the niosomes. Mannitol is also considered a crystalline substance, but there was no burst effect in FN3. This may be defended by the high osmosis capacity of mannitol [19]. Maltodextrin showed no characteristic crystalline peaks indicating its amorphous nature [20]. Amorphous particles are exhibiting fast-dissolving characters, which can lead to a fast dissolution but without burst effect as in glucose.

The pure drug showed a maximum of 50% release during the test period of 24 hrs which is attributed to the poor water solubility of the drug. ACE niosomes showed the release of 94%, 80%, and 79% after 24 hr for FN1, FN2, and FN3, respectively. These findings are in agreement with the findings of a study on candesartan cilexetil proniosomes that also used the paddle method for *in vitro* release [21]. According to the ACE proniosomes (FN1, FN2, and FN3) findings and other research works that have been done previously [13], proniosomes exhibit drug release promptly after administration and reaching the maximum within 4 hours with the absence of an extended-release mechanism. In the case of valsartan proniosomes with maltodextrin as a carrier, the results illustrated 60% drug release after 1 hr, then reached around 70% after 2 hr [12]. Similarly, FN2, which has maltodextrin as a carrier, shown 74% and 80% drug release after 1 hr and 2 hr, respectively. The *in vitro* drug release of celecoxib proniosomes with sorbitol as a carrier was also conducted by the paddle method, and the results revealed 48% of the drug released after 1 hr and 75% within 4 hrs [13].

The purpose of release models is to explain the kinetics of a drug released from the dosage form. Release models can be either mechanistic or empirical. The following is a brief review of some release models. Zero-order release kinetics is a release process where the drug is constantly released from a drug delivery device regardless of the concentration. It is expressed by osmotic pump systems, transdermal systems, matrix tablets with low soluble drugs, and coated forms [22]. In comparison, the first-order equation determines the release from a system when the release rate is dependent on concentration [22].

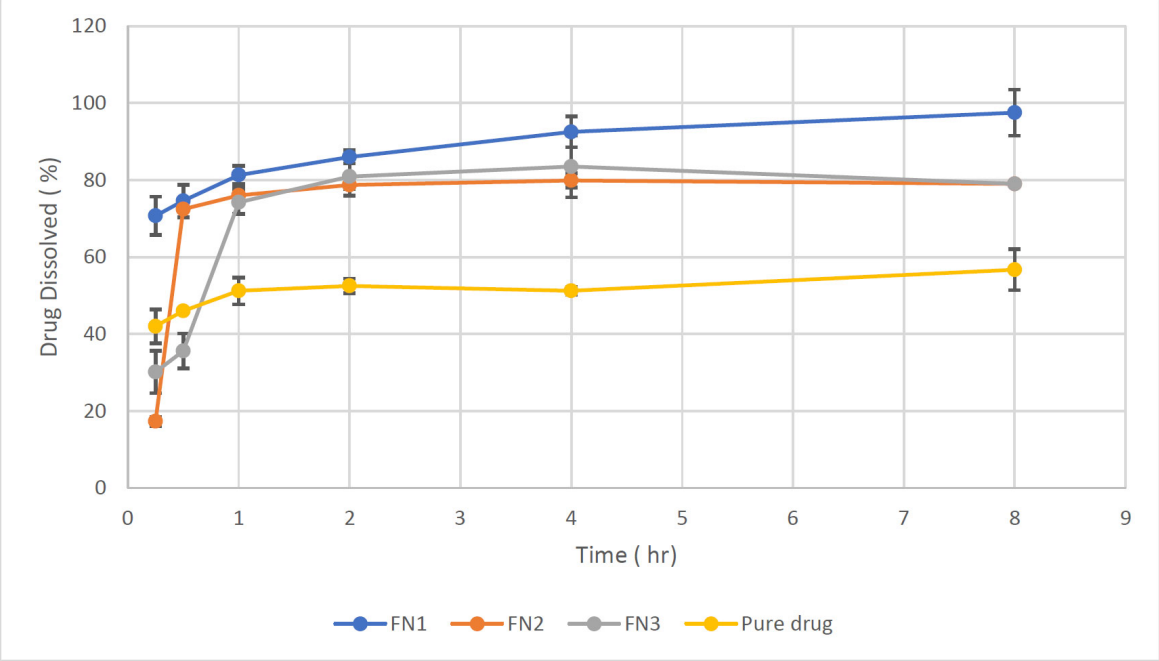

Fig. (1). Dissolution profiles of FN1, FN2, FN3 and pure ACE by the paddle method (mean ± SD; n=3). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The Higuchi model is useful for examining the release of water-soluble and low-soluble drugs included in semisolid and solid matrices. The simplified Higuchi model explains the release of drugs from the insoluble matrix as a square root of a time-dependent process based on a Fickian diffusion equation [23]. The most important advantage of this model is that it enables device optimization and makes it possible to understand the underlying drug release mechanisms better. The Higuchi and zero-order models are used to determine the limits for transport and drug release [23].

While the Hixson-Crowell cube root law describes the drug release from systems when the surface area and the diameter of particles or tablets change if there is no change in the shape as the suspended solid dissolves. It is usually used for a drug powder consisting of uniformly sized particles. This model depends on the assumption that the release rate is limited by the drug particles' dissolution rate and not by diffusion [24].

Lastly, the Korsmeyer-Peppas model is an empirical equation to examine the Fickian and non-Fickian release of drugs from swelling and non-swelling polymeric delivery systems [25].

The above-mentioned mathematical models were used for the parametric representation of the dissolution data. The following models: zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixon Crowell [2], were applied and compared, as shown in Table **2**. The correlation coefficient (r) value was used as the model selection criteria with a value closest to 1.

Referring to the Korsmeyer-Peppas model, the n value of FN1, FN2, and FN3 was n <0.5 that complies with the previous findings of FN1 and with other research works that have confirmed the diffusion mechanism as the mechanism of the drug release in the niosomal formulations [23]. FN1 illustrated the highest k and the lowest n value as an indicator of a burst effect in the prepared system. Both FN2 and FN3 fitted to the first-order model. Moreover, the first-order model explains the release of poorly water-soluble drugs from their water-soluble carrier [2]. Also, the first-order model is the best fitting model for ACE dissolution as a Class II drug [26].

4.2. *In vivo* Drug Release

The *in vivo* drug release results obtained after the single oral dose (equivalent to 10mg ACE.kg^{-1} of the animal weight) of FN1, FN2, FN3, and the ACE pure drug are illustrated in Fig. (**2**). According to Fig. (**2**), ACE proniosomes showed improved rate and extent of drug absorption where the plasma drug concentrations were detected from 1st sampling point (0.5 hr), reaching C_{max} within one hour, whereas no plasma drug concentrations were detected for the pure drug until 1.5 hours with maximum concentration was 0.66 µg.mL^{-1}at 3 hr. The C_{max} of FN1, FN2, and FN3 were significantly higher ($p<0.05$) than the C_{max} of the pure ACE. Among proniosomes, FN2 exhibited the highest plasma concentration (10.39 µg.mL^{-1}) followed by FN1 (4.10 µg.mL^{-1}) and the least with FN3 (2.89 µg.mL^{-1}). However, the $t_{1/2}$ was decreased while the K_{el} increased from 0.667 hr^{-1} for the pure drug to 0.985, 1.05, and 1.76 hr^{-1} for FN1, FN2, and FN3, respectively. The fast absorption and elimination of ACE entrapped niosomal formulation might be due to the enhanced solubility of the active agent in the gastrointestinal system [6].

As summarised in Table **3**, the C_{max} of pure ACE was 0.66 µg.mL^{-1} with an AUC_{0-t} of 4.851 µg.hr.mL^{-1}. These results were analogous with earlier pharmacokinetics studies of ACE tablets on Wistar rats using the same dose (10mg.kg^{-1}) in which the C_{max} was found as 0.96 µg.mL^{-1}, and the AUC_{0-t} was 3.11 µg.hr.mL^{-1} [27]. AUC_{0-t} of 4.851 µg.hr.mL^{-1} for the pure drug was increased to 5.175 µg.hr.mL^{-1} and 10.693 µg.hr.mL^{-1} with a corresponding increase in relative bioavailability of 183% and 112% for FN2 and FN1 respectively. Even though FN3 showed a high C_{max} compared to the pure drug, it was eliminated fast and thus led to a reduced $AUC_{0\rightarrow\infty}$ compared to the pure drug.

These results are comparable to earlier studies. ACE nanocrystals have been prepared in an attempt to enhance the ACE bioavailability. The results revealed increased C_{max} from 1.96 µg.mL^{-1} with the pure drug to 3.75 µg.mL^{-1} in the prepared nanocrystals, while the time to peak concentration (T_{max}) was 1 hr and the K_{el} increased from 0.202 hr^{-1} (pure drug) to 0.267 hr^{-1} (ACE nanocrystals) [28]. As well, $AUC_{0\rightarrow12}$ has been increased from 5.8 to 9 µg.h.mL^{-1} in the ACE nanocrystals. In another study, co-crystals of ACE by using the chitosan also suggested an increase in C_{max} and K_{el} with a decrease in half-life [8].

In general, niosomes are believed to enhance the oral bioavailability of BCS class II drugs; the biopharmaceutical characteristics of which are poor aqueous solubility and high permeability. The niosomal formulation of ganciclovir also exhibited a five-time increment in the bioavailability of ganciclovir after oral administration as compared with the tablet [4]. Moreover, tenofovir disoproxil niosomal formulation exhibited a more than twofold increase in oral bioavailability [29]. In the case of proniosomes, the carrier is used in greater quantities compared to niosomal components (*i.e.*, surfactant and cholesterol), and niosomal components are coated on the carrier; the dissolution behavior of the carrier can significantly affect the rate of niosome formation and release of the drug from the niosomes. In our formulations, 1300 mg of different carriers were used. FN2 that has maltodextrin as a carrier exhibited the fastest absorption with the highest C_{max}. Maltodextrin has been used widely in the preparation of fast dissolving tablets or film. It consists of linear amylase, branched amylopectin, and a relatively small amount of dextrose and maltose, which is responsible for its high solubility, and thus, it was always selected in fast-dissolving dosage forms [20]. Also, it was found to be the less crystalline carrier according to the previous studies done on the characterization of the proniosomes and niosomes earlier [11]. The less crystallinity of maltodextrin could be another

reason for its fast solubility and thus enhanced dissolution and bioavailability. The least C_{max} and F (%) was with the proniosomes prepared with mannitol as a carrier. Mannitol is known to be an osmotic substance that holds water in the small bowel lumen, thereby causing the net flux of water to be into the small bowel rather than the normal outward direction into plasma [30]. This may be the reason for the poor diffusion rate and low oral bioavailability compared to other formulations.

Table 2. Drug release kinetics (model dependent).

Batch	Zero Order		First Order		Higuchi		Korsmeyer-Peppas			Hixon Crowell	
	-	r	k_l	r	k_h	r	*n*	k	r	k_{hc}	r
Pure Drug	17.6	0.616	0.358	0.748	34.3	0.749	**0.071**	48.5	**0.856**	0.093	0.703
FN 1	31.82	0.946	3.57	0.864	61.4	0.986	**0.098**	80.64	**0.998**	0.374	0.989
FN 2	27.85	0.557	1.50	**0.836**	52.5	0.662	**0.249**	63.3	0.720	0.326	0.783
FN 3	27.9	0.783	1.06	**0.957**	51.07	0.868	**0.331**	58.13	0.893	0.293	0.953

k is the zero-order release constant, k_l is the first-order release constant, k_h is the Higuchi release constant, k is the Korsmeyer-Peppas release constant, n is the release exponent, k_{hc} is the Hixon Crowell release constant, and r is the correlation coefficient.

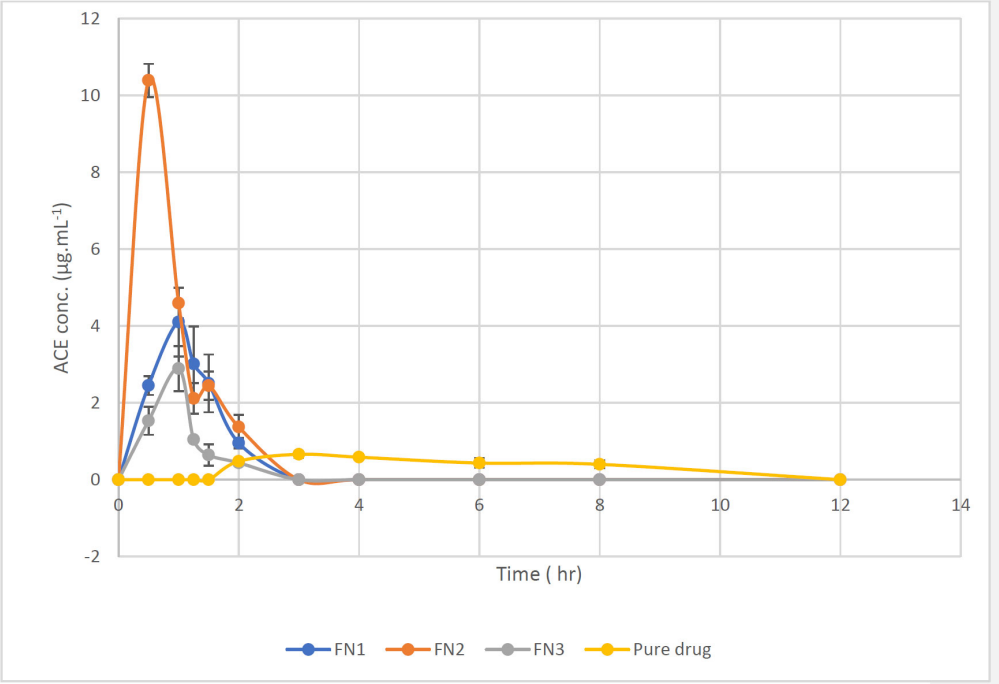

Fig. (2). Plasma concentration profile for different proniosomal formulations and pure drug (values expressed as mean ± SD of six animals each). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 3. Pharmacokinetic parameters obtained after the *in vivo* study (n=6).

Parameters	FN1	FN2	FN3	Pure Drug
C_{max} (µg.mL^{-1})	4.10±0.8	10.39±0.9	2.89±0.7	0.66±0.03
T_{max} (hr)	1±0.1	0.5±0.1	1±0.1	3±0.2
AUC_{0-t} (µg.hr.mL^{-1})	5.18±0.4	9.39±0.7	2.68±0.3	4.85±0.6
$AUC_{0-\infty}$ (µg.hr.mL^{-1})	6.14±0.5	10.69±0.8	2.93±0.4	5.45±0.7
k_{el} (hr^{-1})	0.99±0.01	1.05±0.01	1.76±0.02	0.67±0.01
$t_{1/2}$ (hr)	0.7±0.01	0.66±0.01	0.39±0.01	1.03±0.01
F%	112.8±2.3	183.5±2.4	53.7±1.9	-

CONCLUSION

Three proniosomal formulations were prepared using the slurry method. They consisted of 100 mg ACE, 500 mg Span 60, 250 mg cholesterol with different carriers, *i.e*., glucose (FN1), maltodextrin (FN2), and mannitol (FN3), and were assessed for *in vitro* and *in vivo* drug release. *In vitro* drug release concluded an average of 80% ACE released from niosomes in comparison to 50% released from pure powder, and the ACE dissolution was best fitted to the first-order model. *In vivo* drug release exhibited a fast and complete absorption of ACE from niosomes prepared with glucose and maltodextrin, while mannitol failed to give a complete absorption profile. ACE plasma concentrations were significantly different in the different proniosomal formulations. Significantly, the physical characterization of the carriers used played a vital role in the release and absorption of the drug from the niosomal preparations. The maltodextrin-based formulation was highlighted with its fast absorption and elimination with almost 183% relative bioavailability in comparison with the pure drug. Similarly, the glucose-based formulation also has an average of 112% relative bioavailability. Such improvement leads to the enhanced bioavailability of ACE by the use of proniosomes and niosomes. Mannitol-based formulation exhibited low plasma concentration and low absorbed percentage after oral administration, which led to its meagre chance to be used as a carrier for such novel systems. Based on these findings, glucose and maltodextrin could be considered as suitable carriers for proniosomes preparation and can be used for the preparation of proniosomes with other low bioavailable drugs.

AUTHOR CONTRIBUTIONS

All authors played essential roles in this article; R.M.F.S. initiated the idea, did the methodology, and original draft preparation; B.C. was responsible for data curation while M.T. contributed tothe conceptualization of the research work and results of the investigation; M.S. was responsible for the validation of the methods used, and writing,review and editing; all the work has been done under the full supervision of A.S.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The animal study on rats began after obtaining the approval of the Institutional Animal Care and Use Committee; International Islamic University Malaysia (IACUC IIIUM), IIUM/IACUC. Approval/ 2018/29.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All the necessary data and materials are included in the manuscript.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Jadon, P.S.; Gajbhiye, V.; Jadon, R.S.; Gajbhiye, K.R.; Ganesh, N. Enhanced oral bioavailability of griseofulvin via niosomes. *AAPS PharmSciTech,* **2009**, *10*(4), 1186-1192. http://dx.doi.org/10.1208/s12249-009-9325-z PMID: 19856107

[2] Song, S.; Tian, B.; Chen, F.; Zhang, W.; Pan, Y.; Zhang, Q.; Yang, X.; Pan, W. Potentials of proniosomes for improving the oral bioavailability of poorly water-soluble drugs. *Drug Dev. Ind. Pharm.,* **2015**, *41*(1), 51-62. http://dx.doi.org/10.3109/03639045.2013.845841 PMID: 24111828

[3] Yasam, V.R.; Jakki, S.L.; Natarajan, J.; Kuppusamy, G. A review on novel vesicular drug delivery: proniosomes. *Drug Deliv.,* **2014**, *21*(4), 243-249. http://dx.doi.org/10.3109/10717544.2013.841783 PMID: 24128089

[4] Akhter, S.; Kushwaha, S.; Warsi, M.H.; Anwar, M.; Ahmad, M.Z.; Ahmad, I.; Talegaonkar, S.; Khan, Z.I.; Khar, R.K.; Ahmad, F.J. Development and evaluation of nanosized niosomal dispersion for oral delivery of Ganciclovir. *Drug Dev. Ind. Pharm.,* **2012**, *38*(1), 84-92. http://dx.doi.org/10.3109/03639045.2011.592529 PMID: 21726136

[5] Arzani, G.; Haeri, A.; Daeihamed, M.; Bakhtiari-Kaboutaraki, H.; Dadashzadeh, S. Niosomal carriers enhance oral bioavailability of carvedilol: effects of bile salt-enriched vesicles and carrier surface charge. *Int. J. Nanomedicine,* **2015**, *10*, 4797-4813. http://dx.doi.org/10.2147/IJN.S84703 PMID: 26251598

[6] Bayindir, Z.S.; Yuksel, N. Characterization of niosomes prepared with various nonionic surfactants for paclitaxel oral delivery. *J. Pharm. Sci.,* **2010**, *99*(4), 2049-2060. http://dx.doi.org/10.1002/jps.21944 PMID: 19780133

[7] Dooley, M.; Spencer, C.M.; Dunn, C.J. Aceclofenac: a reappraisal of its use in the management of pain and rheumatic disease. *Drugs,* **2001**, *61*(9), 1351-1378. http://dx.doi.org/10.2165/00003495-200161090-00012 PMID: 11511027

[8] Mutalik, S.; Anju, P.; Manoj, K.; Usha, A.N. Enhancement of dissolution rate and bioavailability of aceclofenac: a chitosan-based solvent change approach. *Int. J. Pharm.,* **2008**, *350*(1-2), 279-290. http://dx.doi.org/10.1016/j.ijpharm.2007.09.006 PMID: 17945447

[9] Blazek-Welsh, A.I.; Rhodes, D.G. Maltodextrin-based proniosomes. *AAPS PharmSci,* **2001**, *3*(1), E1. http://dx.doi.org/10.1208/ps030101 PMID: 11741252

[10] Hu, C.; Rhodes, D.G. Proniosomes: a novel drug carrier preparation. *Int. J. Pharm.,* **1999**, *185*(1), 23-35. http://dx.doi.org/10.1016/S0378-5173(99)00122-2 PMID: 10425362

[11] Sammour, R.M.F.; Taher, M.; Chatterjee, B.; Shahiwala, A.; Mahmood, S. Optimization of Aceclofenac Proniosomes by Using Different Carriers, Part 1: Development and Characterization. *Pharmaceutics,* **2019**, *11*(7), 350.

http://dx.doi.org/10.3390/pharmaceutics11070350 PMID: 31323799

[12] Gurrapu, A.; Jukanti, R.; Bobbala, S.R.; Kanuganti, S.; Jeevana, J.B. Improved Oral Delivery of Valsartan from Maltodextrin Based Proniosome Powders. *Adv. Powder Technol.,* **2012**, *23*(5), 583-590. http://dx.doi.org/10.1016/j.apt.2011.06.005

[13] Nasr, M. *In vitro* and *in vivo* evaluation of proniosomes containing celecoxib for oral administration. *AAPS PharmSciTech,* **2010**, *11*(1), 85-89. http://dx.doi.org/10.1208/s12249-009-9364-5 PMID: 20058106

[14] Chandra, P.; Rathore, A.S.; Lohidasan, S.; Mahadik, K.R. Application of HPLC for the simultaneous determination of aceclofenac, paracetamol and tramadol hydrochloride in pharmaceutical dosage form. *Sci. Pharm.,* **2012**, *80*(2), 337-351. http://dx.doi.org/10.3797/scipharm.1108-04 PMID: 22896821

[15] Zhang, Y.; Huo, M.; Zhou, J.; Zou, A.; Li, W.; Yao, C.; Xie, S. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. *AAPS J.,* **2010**, *12*(3), 263-271. http://dx.doi.org/10.1208/s12248-010-9185-1 PMID: 20373062

[16] Sengupta, P.; Chatterjee, B.; Pal, T.K. Assessment of preclinical pharmacokinetics and acute toxicity of pioglitazone and telmisartan combination. *Regul. Toxicol. Pharmacol.,* **2017**, *91*, 151-158. http://dx.doi.org/10.1016/j.yrtph.2017.10.029 PMID: 29107617

[17] Crist, B. FDA Guidance for Industry: Dissolution Testing and Specification Setting for BCS Class 1 and 3 Drugs. **2015**, 15.

[18] Takagaki, A.; Tagusagawa, C.; Domen, K. Glucose production from saccharides using layered transition metal oxide and exfoliated nanosheets as a water-tolerant solid acid catalyst. *Chem. Commun. (Camb.),* **2008**, (42), 5363-5365. http://dx.doi.org/10.1039/b810346a PMID: 18985211

[19] Nunes, C.; Suryanarayanan, R.; Botez, C.E.; Stephens, P.W. Characterization and crystal structure of D-mannitol hemihydrate. *J. Pharm. Sci.,* **2004**, *93*(11), 2800-2809. http://dx.doi.org/10.1002/jps.20185 PMID: 15368529

[20] Lai, F.; Franceschini, I.; Corrias, F.; Sala, M.C.; Cilurzo, F.; Sinico, C.; Pini, E. Maltodextrin fast dissolving films for quercetin nanocrystal delivery. A feasibility study. *Carbohydr. Polym.,* **2015**, *121*, 217-223. http://dx.doi.org/10.1016/j.carbpol.2014.11.070 PMID: 25659692

[21] Yuksel, N.; Bayindir, Z.S.; Aksakal, E.; Ozcelikay, A.T. In situ niosome forming maltodextrin proniosomes of candesartan cilexetil: *In vitro* and *in vivo* evaluations. *Int. J. Biol. Macromol.,* **2016**, *82*, 453-463. http://dx.doi.org/10.1016/j.ijbiomac.2015.10.019 PMID: 26455402

[22] Cascone, S. Modeling and comparison of release profiles: Effect of the dissolution method. *Eur. J. Pharm. Sci.,* **2017**, *106*, 352-361. http://dx.doi.org/10.1016/j.ejps.2017.06.021 PMID: 28627469

[23] Flynn, E. Pharmacokinetic Parameters. *XPharm Compr. Pharmacol. Ref.,* **2007**, *1-3* http://dx.doi.org/10.1016/b978-008055232-3.60034-0

[24] Hixson, A.W.; Crowell, J.H. Dependence of Reaction Velocity upon Surface and Agitation. *Ind. Eng. Chem.,* **1931**, *23*(8), 923-931. http://dx.doi.org/10.1021/ie50260a018

[25] Peppas, N.A.; Sahlin, J.J. A Simple Equation for the Description of Solute Release. III. Coupling of Diffusion and Relaxation. *Int. J. Pharm.,* **1989**, *57*(2), 169-172. http://dx.doi.org/10.1016/0378-5173(89)90306-2

[26] Aigner, Z.; Heinrich, R.; Sipos, E.; Farkas, G.; Ciurba, A.; Berkesi, O.; Szabó-Révész, P. Compatibility Studies of Aceclofenac with Retard Tablet Excipients by Means of Thermal and FT-IR Spectroscopic Methods. *J. Therm. Anal. Calorim.,* **2011**, *104*(1), 265-271. http://dx.doi.org/10.1007/s10973-010-1105-1

[27] Dahiya, S.; Kaushik, A.; Pathak, K. Improved Pharmacokinetics of Aceclofenac Immediate Release Tablets Incorporating its Inclusion Complex with Hydroxypropyl-β-Cyclodextrin. *Sci. Pharm.,* **2015**, *83*(3), 501-510. http://dx.doi.org/10.3797/scipharm.1409-07 PMID: 26839834

[28] Dash, S.; Murthy, P.N.; Nath, L.; Chowdhury, P. Kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol. Pharm.,* **2010**, *67*(3), 217-223. PMID: 20524422

[29] Kamboj, S.; Saini, V.; Bala, S. Formulation and Characterization of Drug Loaded Nonionic Surfactant Vesicles (Niosomes) for Oral Bioavailability Enhancement. https://www.hindawi.com/journals/tswj/2014/959741/abs/

[30] Adkin, D.A.; Davis, S.S.; Sparrow, R.A.; Huckle, P.D.; Wilding, I.R. The effect of mannitol on the oral bioavailability of cimetidine. *J. Pharm. Sci.,* **1995**, *84*(12), 1405-1409. http://dx.doi.org/10.1002/jps.2600841205 PMID: 8748321