

Original Research Article

Encapsulation of aceclofenac hydrogel-based solid dispersion for sustained delivery

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Sent for review: 4 March 2025

Revised accepted: 14 June 2025

Abstract

Purpose: To develop aceclofenac hydrogel-based solid dispersions (AC-HSDs) encapsulated in two modified gelatin capsules (MGCs as MGX1 and MGX2) for sustained drug delivery.

Methods: The AC-HSDs were prepared with Eudragit L 100 (EL1 – EL5) and hydroxypropyl methylcellulose acetate succinate (HP1 – HP5) at various drug: carrier ratios (1:1, 1:2, 2:1, 1:3, using solvent evaporation technique and characterized by percentage encapsulation efficiency (EE%), scanning electron microscopy (SEM), differential scanning calorimetry (DSC). In vitro drug release of 10 mg (AC-HSDs) was investigated using USP Type I and in vivo anti-inflammatory study of (AC-HSDs; test), pure aceclofenac, and aceclofenac tablet (positive control; administered orally at 10 mg/kg body) was evaluated using the rat paw edema method.

Result: Eudragit-based solid dispersions showed significantly higher entrapment efficiency compared to hydroxypropyl methylcellulose acetate succinate-based formulation ($p < 0.05$). The DSC and SEM of both batches revealed discrete particle sizes and shapes with decreased crystallinity. The AC-HSDs encapsulated in MGX1 showed significantly prolonged drug release compared to MGX2 ($p < 0.05$). Furthermore, HP-SDs showed significantly higher edema inhibition (86 %) compared to pure aceclofenac and commercial aceclofenac tablets ($p < 0.05$).

Conclusion: Aceclofenac hydrogel-based solid dispersions (AC-HSDs) encapsulated in MGCs show sustained release effects as an alternative technology to deliver aceclofenac.

Keywords: Aceclofenac, Sustained drug release, Modified gelatin capsules (MGCs), Solid dispersions, Anti-inflammatory

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INTRODUCTION

Sustained release drug delivery (SRDD) provides prolonged release of drugs over a long period, thereby achieving good patient-friendly administration with enhanced bioavailability. The basic concept behind SRDD is to improve patient compliance by increasing the bioavailability and effectiveness of the drug substance [1]. This drug delivery is an efficient

approach to delivering drugs with short half-lives, particularly when there is need for repetitive dosing. Some merits of SRDD include localized drug effect which reduces dosing frequency, ensuring uniform drug distribution, reducing side effects, stable drug absorption levels in blood and plasma, and patient compliance [2].

Recent studies have focused on the design of SRDD systems for lipophilic drugs [3]. However,

when designing such a drug delivery system, some factors must be considered which include half-life and pharmacological effect of the drug. Considering the shortfalls of conventional drug dosing systems (repeated dosing), SRDD achieves uniform drug release over prolonged period, reduced side effects, and favourable therapeutic drug blood levels. Conventional drug delivery methods may be easier and more preferred to deliver some drugs. However, frequent dosing may have several challenges such as poor adherence, low bioavailability, instability, toxicity, and others. Thus, an SRDD aims to maintain drug plasma levels and achieve a steady state.

There are previous works on sustained-release drug delivery (SRDD) using different methods. A sustained solid dispersion of metformin has been prepared to enhance poor permeability across biological membranes and half-life [4]. Hyaluronic acid (HA) sustained release was prepared for wound healing by mixing methacrylate and dopamine to produce a complex which was bonded with arginine derived substance to form hydrogels [5]. Poly (lactic-co-glycolic acid) microsphere was prepared with Doxorubicin-hyaluronate (DOX-HA) micelles to exhibit good sustained release characteristics compared to DOX alone [6]. Also, sustained release was obtained by complexing plasmid DNA with quaternary ammonium chain via electrostatic interaction and slow hydrolysis of ester bond that exposed negatively charged carboxyl groups [7].

Aceclofenac (AC) is a phenylacetic acid derivative group of nonsteroidal anti-inflammatory drugs. It is a class II agent in biopharmaceutical classification systems with poor solubility challenges. It has a poor water solubility of about 60 $\mu\text{g/mL}$ [8]. The substance has a biological half-life of < 4 h, which necessitates numerous daily doses. To maintain its therapeutic effect, the recommended dose ranges from 100 to 200 mg [9]. This is associated with gastrointestinal tract (GIT) disorders when administered orally [10].

The physicochemical challenges associated with aceclofenac (AC) have led to research aimed at finding solutions. Solid dispersions of aceclofenac with subsequent encapsulation in modified gelatin capsules (MGCs) were investigated to enhance its poor aqueous nature, short residence time, and improve its low bioavailability. Therefore, this study investigated aceclofenac hydrogel-based solid dispersions (AC-HSDs) using solvent evaporation technique and encapsulated in two 3-h modified gelatin

capsules (MGX1 and MGX2) for prolonged and sustained drug delivery.

EXPERIMENTAL

Materials

Aceclofenac (Jagmag Pharm, India), Eudragit® L 100 powder (Evonik, Darmstadt, Germany), Hydroxypropyl methylcellulose acetate succinate (Shin-Etsu, Chem company, Japan), Cremophor® RH 40 (BASF Ludwigshafen, Germany), dialysis membrane (6000 - 8000 Da). All other chemicals are of analytical grade and used as supplied.

Formulation of aceclofenac-hydrogel solid dispersion

Aceclofenac hydrogel-based solid dispersions (AC-HSDs) were prepared using solvent evaporation technique with Eudragit® L 100 (EL1 – EL5) and hydroxypropyl methylcellulose acetate succinate (HP; HP1 – HP5) in methanol (98 %) at various drug-carrier ratios (1:1, 1:2, 2:1, 1:3, and 3:1) [11]. The drug (10 mg) in each formulation was incorporated in a 250 mL beaker and dispersed with 30 mL methanol. The formulation was mixed with one carrier (EL or HP) and 0.5 mL Cremophor® RH 40 was incorporated and the beaker was set on a magnetic stirrer assembled at 800 rpm with no heat and stirred for about 60 min to give a uniform solution and improve solvent evaporation. The solid dispersions (SDs) formed were air-dried, weighed, and pulverized in a mortar and sieved (sieve no. 52). Same procedure was repeated with other ratios using the other carrier (EL or HP). The SDs were stored in airtight containers and kept in desiccators until further use.

Encapsulation efficiency (EE %) and drug loading capacity

The sample (10 mg) from AC-HSDs was transferred into a calibrated beaker and dispersed in 1 mL methanol and phosphate buffer (pH, 7.4) to the 10 mL mark [13]. The obtained mixture was separated with a centrifuge (SM800B, Uniscope, England) for 30 mins at 6000 rpm. The supernatant was analyzed with a spectrophotometer (Spectrum lab 752, Netherlands) at 290 nm. The blank was prepared using 10 mL of methanol and phosphate buffer in a ratio of 1:9. The samples were analyzed in triplicate. Loading capacity (LC) conveys the proportion between the encapsulated AC formulation and the entire quantity of the carrier,

with the theoretical quantity of AC contained in the solid dispersions.

Micromeritics properties of the solid dispersions

Densities

Samples (10 g) were placed inside the measuring cylinder and bulk volume (V_1) was recorded. The samples were subjected to 100 taps and tapped volume (V_2), was recorded. Bulk, tapped densities Hausner's ratio and Carr's index were calculated using Eq 1 – Eq 4.

Bulk density (BD) = weight of powder / bulk volume (V_1) (1)

Tapped density (TD) = weight of powder / tapped volume (V_2) (2)

Hausner's ratio = TD/BD (3)

Carr's index = $\{(TD-BD)/TD\}100$ (4)

Angle of repose

A clean glass funnel was clamped to a retort stand such that the distance from the tip of the funnel to the horizontal base was 5 cm. The funnel orifice was opened and the flow rate and angle of repose (θ) were determined in triplicate using Eq 5 and Eq 6.

Flow rate = w/t (5)

$\theta = \tan^{-1} 2 \cdot h/d$ (6)

Where w is the weight of powder, t is the flow time in seconds, h is the height of the heap of powder, and d is the diameter of the powder heap formed [12].

Scanning electron microscopy (SEM)

Morphological properties of selected SDs were evaluated by SEM machine (JEOL, JSM-6100) [13]. Samples were freeze-fractured in SEM holder at 50 °C. At 15 kV, surface morphology was determined, and the image was captured using an in-built digital camera, transferred and recorded using a scanning electron microscope.

Differential scanning calorimetry (DSC)

Melting transitions and changes in heat capacity of the AC-HSDs, pure aceclofenac, Eudragit® L 100, and Hydroxypropyl methylcellulose acetate succinate were determined using a differential scanning calorimeter (Netzsch DSC 204 F1,

Gerätebau, GmbH, selb, Germany). Each sample weighing between 3 - 5 mg was transferred into an aluminum pan, hermetically sealed and thermal characteristics were obtained within 20 - 400 °C at a heating rate of 10 K/min under a 20 mL min nitrogen flux [11].

In vitro drug release study of AC-HSDs

The *in vitro* AC release from the AC-HSDs encapsulated in modified gelatin capsules (MGCs) was carried out using an adopted method with little modification [13]. The two MGCs (MGX1 containing a chemically modified cap gelatin body with needle puncture at both ends with seals) and MGX2 (containing a chemically modified body and an unmodified cap sealed from the joint) were employed. This test was carried out with the optimized AC-HSDs selected based on the highest % EE from batches EL-SDs (EL1, containing drug: carrier 1:1) and HP-SDs (HP2, containing drug: carrier 1:2). The aceclofenac hydrogel-based solid dispersions (10 mg AC in AC-HSDs) was transferred into a three-hour chemically modified gelatin capsule (MGCs) selected based on a good swelling index, and poor aqueous dispersibility of the treated capsules [13]. Each encapsulated AC-HSD was lowered into a beaker containing 900 mL of simulated gastric fluid (SGF; pH, 1.2) for 2 h and then in simulated intestinal fluid (SIF; pH, 6.8) till the end. At 2, 5, 6 to 24 intervals, 5 mL aliquots of each medium were withdrawn and the percentage of AC released was determined at 290 nm spectrophotometrically (Spectrum lab, 752s, Netherlands). The % AC release was determined and the average was plotted against each time.

Animals

Adult female Wistar rats, weighing between 100 - 125 g, were procured from the Department of Veterinary Medicine, University of Nigeria, Nsukka (UNN). The animals were kept in animal cages under standard conditions (12 h light/dark cycle, room temperature, humidity 50 – 60 %) to acclimatize for one week with unrestricted access to feed and water *ad libitum* prior to the commencement of the experiment. The experiment was approved by the institutional Animal Ethics Committee, (approval no. FPSRE/UNN/19/00031) before commencement.

Anti-inflammatory studies

In vivo anti-inflammatory test of AC-HSDs was carried out using the rat paw edema protocol. A fresh undiluted egg albumin was used to induce edema. The animals were randomly assigned to

6 groups (n = 6). Groups 1, 2, 3, 4, 5, and 6 received AC-HSDs, pure aceclofenac, aceclofenac tablet, no treatment after inflammation, neither inflamed nor treated, and normal saline respectively. The animals were fasted for about 12 h prior to commencement of the test to enable consistent hydration with no difference in edematous reaction. The AC-HSDs (10 mg/kg/bw) were reconstituted with normal saline (0.9 %) and administered once orally to group 1 via a 1 mL syringe. Groups 2 and 3 received 10 mg/kg equivalent of aceclofenac once. Group 4 received no drug after inflammation. Group 5 was neither inflamed nor treated. A 1 mL normal saline was orally administered once to group 3 (placebo group). Thereafter, 0.1 mL phlogistic substance (fresh undiluted egg albumin) was administered into the sub-plantar tissue of the right hind paw of the rats 30 min after drug administration. The volume of distilled water displaced by the treated right hind paws of the rats was measured using a plethysmometer before drug administration and at 0.5 - 5 h after treatment. Variation in the aqueous displacement of the injected paw ($a - b$) was determined each period. Percent edema inhibition was calculated using Eq 7 [13].

$$\text{Inhibition (\%)} = \{1 - (a - b) / (c - d)\} 100 \dots\dots (7)$$

where a is the mean paw volume of treated rats after egg albumin injection, b is the mean paw volume of treated rats before egg albumin injection, c is the mean paw volume of control rats after egg albumin injection and d is the mean paw volume of control rats before egg albumin injection.

Statistical analysis

Data was analyzed using GraphPad InStat Demo (USA). Results were expressed as mean $\pm$ SD (n = 3), compared using a one-way analysis of variance (ANOVA), and two-tailed student's t-test assessed differences between means. $P < 0.05$ was considered statistically significant.

RESULTS

Entrapment efficiency, loading capacity, and yield

The highest encapsulation efficiencies were observed in EL5 and HP4 prepared with Eudragit® L 100 (3:1), and hydroxypropyl methylcellulose acetate succinate (1:3), respectively. The AC-HSDs had % yields ranging from 70 – 91 % and 66 – 79 % for EL and HP, respectively (Table 1). Formulations (EL5) with higher percentage yields were observed to give higher encapsulation efficiency and loading capacity. Both EL and HP solid dispersions exhibited good flow characteristics.

Morphological characteristics

The AC.SDs morphology determined by SEM is presented in Figure 1. The photomicrographs revealed a mixture of various discrete, irregular particle sizes and shapes. Aggregated particles were also observed (Figure 1).

DSC thermograms

The DSC thermograms of pure AC and solid dispersions of Eudragit L 100 (EL.SDs) and hydroxypropyl methylcellulose acetate succinate (HP.SDs) revealed melting point at 154.56, 72.72, and 69.23 °C, respectively. Aceclofenac solid dispersions (AC.HSDs) showed a broad melting peak with a low enthalpy (Figure 2).

Table 1: Yield, encapsulation efficiency, and flow properties

Batch	EE (% $\pm$ SD)	LC (% $\pm$ SD)	Y (%)	AOR (° $\pm$ SD)	BD (g/mL $\pm$ SD)	TD (g/mL $\pm$ SD)	HQ	CI (%)
EL1	92 $\pm$ 0.11	23 $\pm$ 0.13	69.85	19 $\pm$ 0.11	0.4 $\pm$ 0.02	0.7 $\pm$ 0.01	1.84	46
EL2	80 $\pm$ 0.39	19 $\pm$ 0.03	70.40	19 $\pm$ 0.01	0.4 $\pm$ 0.04	0.7 $\pm$ 0.11	1.72	23
EL3	75 $\pm$ 1.03	20 $\pm$ 0.22	78.66	14 $\pm$ 0.03	0.6 $\pm$ 0.01	0.6 $\pm$ 0.02	1.12	11
EL4	51 $\pm$ 0.03	15 $\pm$ 0.05	81.70	15 $\pm$ 0.02	0.6 $\pm$ 0.11	0.7 $\pm$ 0.21	1.21	17
EL5	96 $\pm$ 0.01	18 $\pm$ 0.11	91.67	25 $\pm$ 0.12	0.4 $\pm$ 0.20	0.6 $\pm$ 0.11	1.53	35
HP1	85 $\pm$ 0.04	29 $\pm$ 0.03	65.60	13 $\pm$ 0.01	0.5 $\pm$ 0.10	0.6 $\pm$ 0.13	1.35	26
HP2	67 $\pm$ 0.04	21 $\pm$ 0.02	71.72	17 $\pm$ 0.03	0.6 $\pm$ 0.22	0.7 $\pm$ 0.12	1.14	13
HP3	71 $\pm$ 0.11	23 $\pm$ 0.22	67.60	14 $\pm$ 0.21	0.3 $\pm$ 0.02	0.5 $\pm$ 0.11	1.41	29
HP4	90 $\pm$ 0.01	30 $\pm$ 0.01	79.38	13 $\pm$ 0.11	0.4 $\pm$ 0.11	0.5 $\pm$ 0.03	1.38	28
HP5	60 $\pm$ 0.01	19 $\pm$ 0.23	68.08	17 $\pm$ 0.01	0.4 $\pm$ 0.01	0.6 $\pm$ 0.01	1.62	38

EL1 – EL5 and HP1 – HP5 (solid dispersions formulated with Eudragit L 100 and hydroxypropyl methylcellulose acetate succinate (containing drug: ratio 1:1, 1:2, 2:1, 1:3, and 3:1), respectively; EE (encapsulation efficiency); LC (loading capacity); FR (flow rate); AOR (angle of repose); BD (bulk density), TD (tapped density); HQ (Hausner's index); CI (compressibility index); SD (standard deviation)

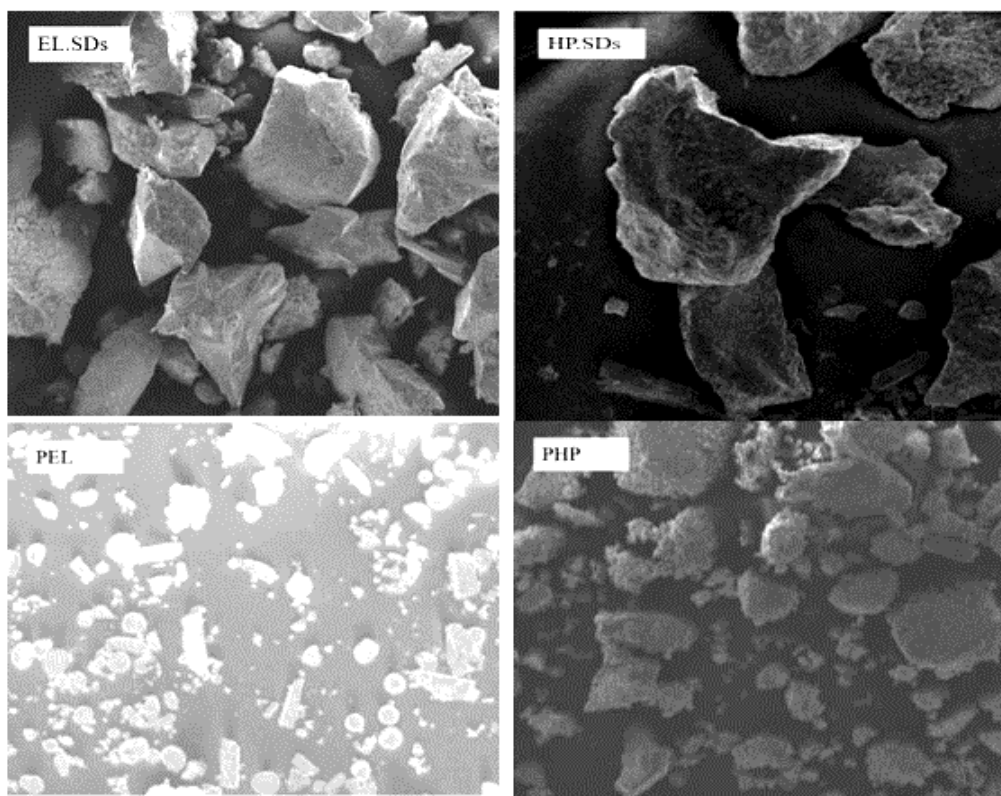


Figure 1: Scanning electron microscopy (SEM) of solid dispersion of Eudragit L 100 (EL.SDs) and hydroxypropyl methylcellulose acetate succinate (HP.SDs), pure sample Eudragit L 100 (PEL), and pure sample hydroxypropyl methylcellulose acetate succinate (PHP)

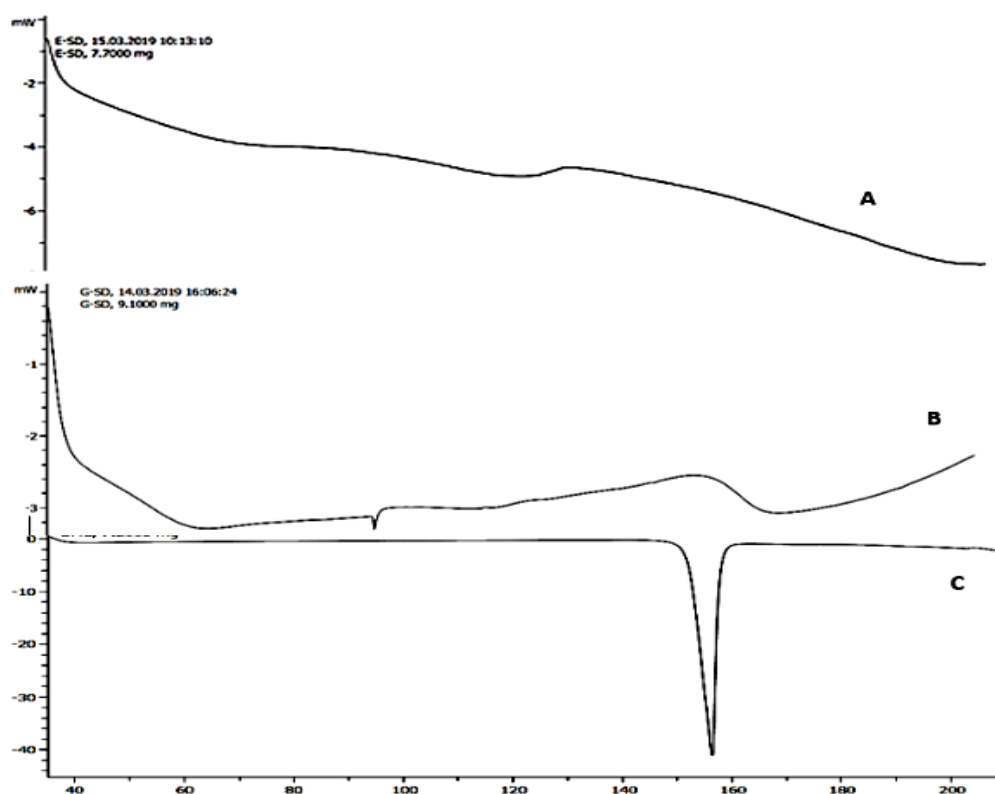


Figure 2: DSC of solid dispersion of Eudragit L 100 (A), hydroxypropyl methylcellulose acetate succinate (B), and pure aceclofenac (C)

***In vitro* release of aceclofenac hydrogel solid dispersions sustained release**

In vitro AC release from the solid dispersion (AC.HSDs) modified with gelatins capsules (MGCs) is shown in Figure 3. Based on the results for the two developed MGCs, AC release was insignificant in SGF (pH, 1.2). The MGCs commenced drug release by swelling and expanding with gradual AC release in SIF (pH,

6.8). Batches EL.SDs and HP.SDs showed $T_{50\%}$ (time for 50 % release) at 10 and 12 h and $T_{80\%}$ at 12 and 14 h using MGX1, whereas MGX2 showed $T_{50\%}$ at 6 and 8 h and $T_{80\%}$ at 8 and 11 h, respectively. A significant sustained and prolonged drug release ($p < 0.05$) was observed in the release profile using MGX1 compared to MGX2. In both medium, there was no premature drug release (Figure 3).

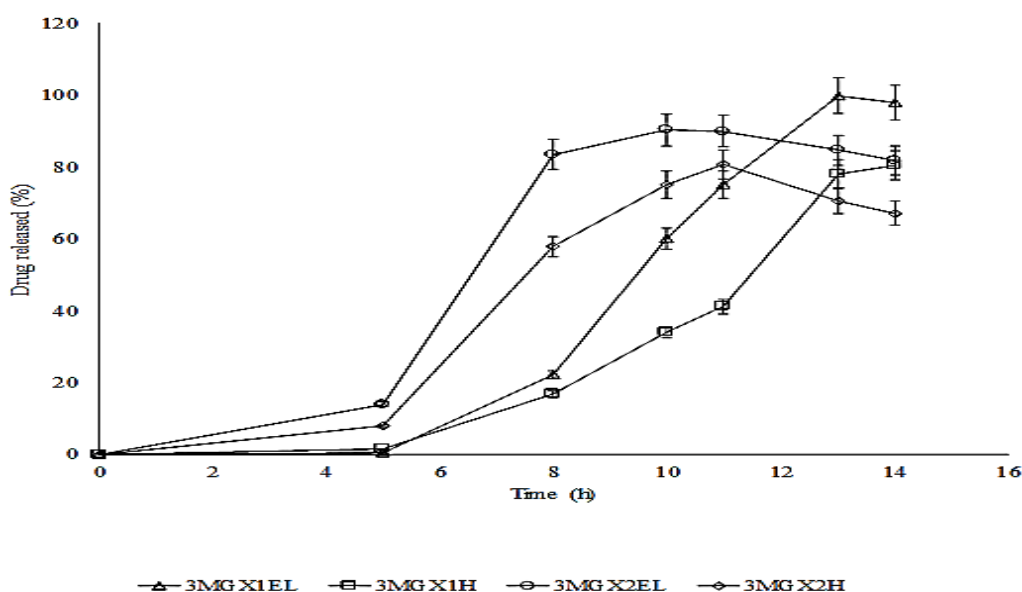


Figure 3: Release of aceclofenac solid dispersion (AC.SDs) using the 3-h developed MGX1 and MGX2. MGX1 (developed capsules containing a chemically modified cap and body with needle puncture at both ends and a seal with a coating solution; MGX2 (containing chemically modified body and an unmodified cap sealed from the joint); 3MGX1EL and 3MGX1H (drug release using developed 3-h capsule MGX1 for formulations EL.SDs and HP.SDs, respectively); and 3MGX2EL and 3MGX2H (drug release using developed 3-h capsule MGX2 for formulations EL.SDs and HP.SDs, respectively)

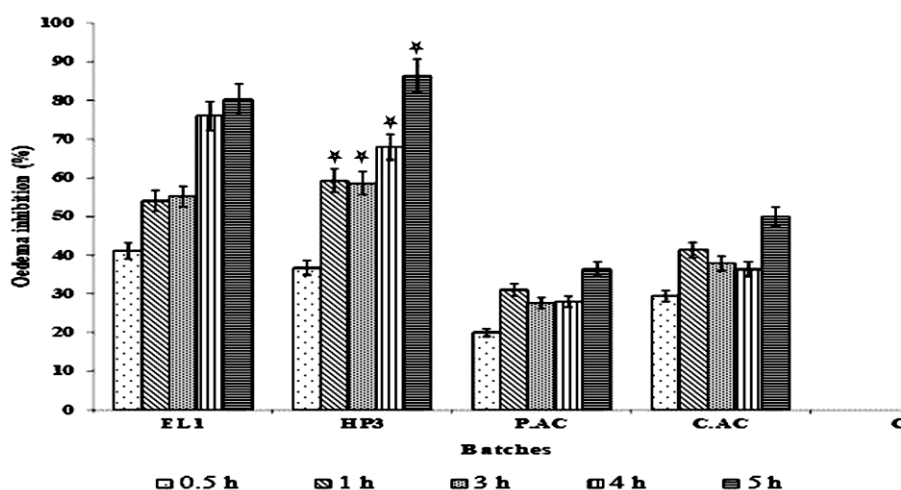


Figure 4: Anti-inflammatory activity of aceclofenac hydrogel-based solid dispersions (AC.HSD). Key: EL1 and *HP3 ($p < 0.05$; aceclofenac solid dispersions formulated with Eudragit® L 100 ratio 1:1 and Hydroxypropyl methylcellulose acetate succinate ratio 1:3 respectively, P.AC and C.AC (pure aceclofenac and commercial aceclofenac, respectively), C (control)

DISCUSSION

The ability of a formulation to encapsulate a drug is a fundamental quality that expresses percentage entrapment efficiency (% EE), while the loading capacity (LC) conveys the proportion between the entrapped drug molecules and the entire weight of the carrier. Previous reports have shown that poor aqueous nature of the drug, type of constituents, combination power of the components, and formulation technique may affect the loading capacity of drug formulation [14]. The AC.HSDs formulated with HP showed higher % EE and LC at higher carrier concentrations, in contrast to EL formulations consistent with an earlier report [15]. Thus, formulations with equal or more carrier concentrations had good drug encapsulation. However, complexes with higher drug contents exhibited higher loading capacity.

Density of a material is one of the important parameters that determine flow characteristics. Bulk and tapped densities provide insights into the packing, arrangement of particles, and compaction profile. A material with high bulk density will have low porosity resulting in low deformation potential. This reduces the space required for restructuring during compression causing less intimate contact between the particles [16]. Bulk and tapped densities are used to predict the flow behaviour and compressibility of a powder. The AC.HSD batches showed good bulk and tapped densities indicating that the samples would have good packing properties required for drug delivery consistent with previous reports [17].

Packing volume of a powder depends on some factors such as particle shape, particle size distribution, true density, and cohesiveness due to surface properties such as moisture and so on. Earlier reports have shown that an angle of repose $\leq 30^\circ$ indicated free flow, while an angle of repose $\geq 40^\circ$ indicated poor flow [17,18]. Focusing on the AOR, all the AC.HSDs showed good flow with angle of repose $< 40^\circ$ [11,19]. This indicated that the formulations have low inter-particulate cohesion and therefore exhibited good flow properties and may be easily encapsulated in a uniform dose per time. Compressibility index and Hausner's ratio measure the flowability and consolidation qualities of materials. A powder with an adequate CI and HR flows at minimum bulk density and consolidates to maximum density if compressed [16]. Hausner's ratio (HR) ≤ 1.25 indicates good flow, while Hausner's ratio ≥ 1.25 indicates poor flow [19]. Carr's index of 5 to 16 % indicates good flow, while 18 to 23 % shows fair flow [19].

Thus, dose variability will be limited. In SEM, the presence of aggregated particles observed may be due to dehydration of the formulation during SEM sample preparation prior to imaging under a high vacuum area. The DSC melting peak showed a sharp endothermic peak which described the crystalline nature and purity of the AC similar to previous finding [12]. A broad endothermic peak was observed in AC.HSDs with a low enthalpy show that the drug particles were modulated to achieve amorphous dispersions. This low enthalpy is an indication of the generation of an incomplete crystal lattice which enhances drug solubilization.

The AC drug release from the encapsulated AC.HSDs were characterized by swelling and expansion of the MGCs which made provision for fluid penetration into the SDs. Some earlier reports have investigated that fluid imbibition perhaps caused gel formation with the potential to delay drug release [20-21,12]. Thus, the 3-h developed capsules (MGX1 and MGX2) controlled any irrational drug release since they allowed the highest drug release to occur at the lower GIT such that up to 80 % AC was released within 12 - 14 h. The highest AC release observed in MGX1 was basically due to the designed nature of the MGX1 which contains both a chemically modified cap and body. The high *in vivo* anti-inflammatory effect of the AC.HSDs obtained showed that the solid dispersion presented the AC at a molecular level and enhanced drug absorption more than the commercial brand and pure drug, which may have existed in a crystalline form in the aqueous medium.

CONCLUSION

This study has demonstrated that poor aqueous solubility, short residence time, and low bioavailability of conventional AC delivery are enhanced using aceclofenac hydrogel-based solid dispersions (AC.HSDs) encapsulated in modified gelatin capsules for effective sustained drug release of AC. Hence, AC.HSDs encapsulated in MGCs are a promising technology to achieve sustained drug delivery of aceclofenac.

DECLARATIONS

Acknowledgement/Funding

The authors acknowledged the technical assistance received from Ahmadu Bello University (ABU) Zaria for DSC and SEM analyses, the Department of Pharmacology and Toxicology, UNN for the animal study and the

Department of Veterinary Medicine, UNN for the histopathology study and all the technical staff of Pharmaceutical Technology and Industrial Pharmacy, UNN.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Dr. Calister E. Ugwu carried out the experimental work, while Kingsley C. Eze and Dr. Calister E. Ugwu read and approved the manuscript.

Availability of data and materials

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

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