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Controlled Release Binary and Ternary HPMC-HPC-Gelucire® 50/13 Hybrids Based Solid Dispersions of Indomethacin: *In vitro* Evaluation and *In vivo* Anti-inflammatory Studies

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Authors' contributions

This work was carried out between all the authors. Author KCO designed the study. Authors CGN and AMN carried out the analyses and experimental studies. Author JNRO wrote the manuscript. Author FCK proof read the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The aim of this study is to formulate and evaluate solid dispersions of indomethacin based on Gelucire 50/13, Hydroxylpropyl methylcellulose and/or Hydroxylpropyl cellulose hybrid binary or ternary system, with a view of enhancing oral bioavailability, sustaining drug release with optimum anti-inflammatory activity and minimal side effects.
Methodology: Solid dispersions were prepared by solvent-evaporation method at varying polymer ratios (with HPMC and Gelucire 50/13 at 1:1, 2:1, 3:1, 4:1, 1:2, 1:3, 1:4 and HPMC, HPC and Gelucire 50/13 at 1:1:1) with a constant concentration of indomethacin (100 mg). The formulations were characterized in terms of morphology, stability and drug content. The release profiles of indomethacin from the solid dispersions were examined *in vitro* using two different media i.e. SGF and SIF, without enzymes. The anti-inflammatory properties were evaluated.

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Results: The formulated solid dispersions were stable and almost spherical to irregularly-shaped. The drug content of the formulations was accepted according to the Pharmacopoeial limit. *In vitro* dissolution studies showed an increased dissolution rate at pH 7.4 compared to pH 1.2 for the various batches with solid dispersions showing a faster and sustained dissolution rate than the pure crystalline drug. The percentage inhibitions of edema produced by the formulations in the *in vivo* studies were significantly higher and sustained than the pure drug.
Conclusion: Solid dispersions prepared with these biodegradable polymer hybrids, HPMC/HPC/Gelucire® 50/13, showed promising potential in clinical practice for enhancing the delivery of indomethacin.

Keywords: Binary and ternary hybrids; solid dispersion; controlled systems; indomethacin; anti-inflammatory studies; in vitro dissolution studies.

1. INTRODUCTION

One of the major problems faced by drug discovery and development scientists is the issue of poor aqueous solubility and dissolution rate of a range of active pharmaceutical ingredients (API), which is now a common occurrence among newer drug candidates over the past years [1,2]. The biopharmaceutics classification system (BCS) class II and IV drugs fall into this category. After oral administration, the absorption of these agents into the systemic circulation is limited by solubility or dissolution rate stage [3]. Numerous approaches to circumvent the problem of poor aqueous solubility of these classes of drugs have been investigated and reported in literature namely micronisation [4], use of cyclodextrin in complexation [5], formation of prodrugs [6], formation of salts of these agents, nanotechnology approaches [7] etc. But, these approaches have some limitations ranging from particle agglomeration, inability to convert into active forms in the body system, toxicity to expensive laborious techniques.

Solid dispersion has been considered as one of the most successful approach to enhance the delivery of these poorly soluble drugs partly because it overcomes the foregoing limitations [8]. It can be referred to as a group of solid products consisting of at least two different components, generally a hydrophilic matrix (crystalline or amorphous in nature) and a hydrophobic drug dispersed molecularly as amorphous or crystalline particles in the former. It has been adopted to improve the solubility of several drugs namely Carbamazepine [9], Felodipine [2], etc. However, judicious choice of the polymers could possibly delay or slow down the release pattern of a drug formulated as a solid dispersion [6,10]. There is availability of a wide variety of polymers that are themselves poorly soluble or which swell under aqueous conditions which when utilized to form solid dispersions not only improve the dissolution rate but can also achieve a controlled delivery of the poorly aqueous soluble drugs, including Indomethacin [11].

Indomethacin is a non-steroidal anti-inflammatory drug (NSAIDs) used to relieve pain and inflammation in osteoarthritis, rheumatoid arthritis, bursitis, tendonitis, gout, ankylosing spondylitis etc [12]. It produces this pharmacological effect by inhibiting the cyclooxygenase (COX) enzyme non-selectively that participates in production of prostaglandins (PGE_2, PGF_2, prostacyclin (PGI_2) and TXA_2) from arachidonic acid [13]. It is a methylated indole derivative (structure is as shown in Fig. 1) with a prominent anti-inflammatory and analgesic-pyretic activity relative to the salicylates.

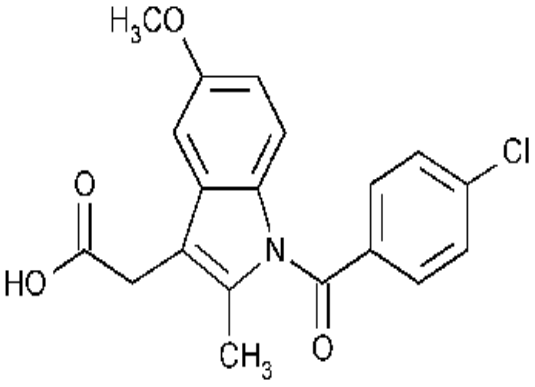

Fig. 1. Structrure of indomethacin

In BCS, it belongs to the class II drugs and is practically insoluble in water [14]. It is associated with gross bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. This has limited the clinical

use of this drug as a first line NSAIDs in the treatment of arthritis [15]. Also, the short half-life of this drug which is about 4.5 h necessitates its frequent administration leading to poor patient compliance.

The enhancement of drug dissolution and release rate by amorphous solid dispersions may cause drug precipitation/recrystallization from their supersaturation states. Those would invariably decrease drug bioavailability, defeating the original goal of the formulation. However, this problem has been overcomed with the development of third generation solid dispersions which involves the use of surface active agents or self emulsifiers as carriers or adjuncts. These agents are known to improve not only the wettability of the drug through the formation of micelles or adsorption on drug particle surfaces but also ensure its physical and chemical stability [2,16]. Gelucire 50/13 is such a surfactant (also known as stearoyl macrogol-32 glycerides, EP) which is made up of approximately 8% (w/w) free PEG 1500, 20% (w/w) mono-, di, and tri-glycerides of hydrogenated palm oil (mainly stearic and palmitic acid), and 72% (w/w) monoacyl- (MPEG) and diacyl- (DPEG) derivatives of PEG 1500 [17]. It has been conventionally utilised as a sustained release matrix device in pharmaceutical formulations and also for formulating fast release systems. It is readily compatible with many drugs, has low melting point and virtually non-toxic [18].

Furthermore, HMPC and HPC are swellable hydrophilic polyethylene oxide cellulose derivatives which serve as emulsifiers [19]. The former is a viscoelastic, non-ionic, surface active polymer which is utilized for the preparation of controlled-release formulations. It readily dissolves in water and other solvents to form a pseudoplastic solution [20]. The use of combinations of Gelucire 50/13, HPMC and/or HPC to form biodegradable and biocompatible polymer hybrids of optimum characteristics might be promising and viable means of alleviating the solubility and dissolution problems of indomethacin, extending its release as well as offer some gastroprotection from the adverse effects of the drug.

Therefore, the purpose of this research is to formulate and evaluate solid dispersions of indomethacin using Gelucire 50/13, HPMC and/or HPC hybrid binary or ternary system, with a view of enhancing oral bioavailability, sustaining drug release with optimum anti-inflammatory activity and minimal side effects.

2. MATERIALS AND METHODS

2.1 Materials

Indomethacin (Afrab Chem Limited, Lagos, Nigeria), Indocid® (Yangzhou Pharmaceutical Co. ltd, China), was used as the commercially available product, Gelucire 50/13 (Stearoyl Macrogol-32 Glycerides) was supplied by Gattefosse, cedex, France, Hydroxylpropyl methylcellulose (HPMC K4M), Hydroxylpropyl cellulose (HPC), methylene chloride, absolute ethanol were purchased from Sigma-Aldrich (Steinheim, USA), Sodium hydroxide (BDH, England), and dialysis membrane tubing (cut off 5000 – 8000, Germany). Bidistilled water was used throughout the study. Simulated intestinal fluid (SIF) and simulated gastric fluid (SGF), without enzymes, were prepared and titrated to pH 7.4 and 1.2, respectively.

2.2 Screening of Starting Materials

2.2.1 Polymer and drug solubility assessment

In order to ascertain the appropriate volume and type of solvent suitable for the study, increasing amounts of indomethacin (5 – 50 mg) as well as the polymers (HPMC, HPC and Gelucire 50/13) were dissolved in 10 ml of different solvents (ethanol, methylene chloride, methanol, and acetone) under magnetic stirring (Thermomixer, Eppendorf, Germany) at 100 rpm for 1 h at 37 ± 1°C. The solubility of each system was evaluated for visual homogeneity upon cooling at room temperature.

2.2.2 Preparation of binary hybrid mixtures

Binary hybrid mixtures of HPMC and Gelucire 50/13 (HPMC-Gel 50/13) were formed in the ratio of 1:1, 1:2, 1:3, 1:4, 2:1, 3:1 and 4:1 using solvent evaporation method. Briefly, HPMC and Gelucire 50/13 each was individually weighed and dissolved in 2 ml of absolute ethanol and methylene chloride respectively under magnetic stirring at 100 rpm for 20 min. The resulting solutions formed were mixed together, transferred into a rotary evaporator (Ika, Stanfen, Germany) and heated at 37 ± 1°C to evaporate the solvent. The thin film polymer hybrid formed was removed and stored for further investigations.

2.2.3 Preparation of ternary hybrid mixtures

Ternary hybrid mixtures of HPMC, HPC and Gelucire 50/13 (HPMC-HPC-Gel 50/13) were prepared by the same method stated above in the ratio of 1:1:1. In this case, the weighed samples of HPMC and HPC were dissolved in 2 ml of absolute ethanol while the Gelucire 50/13 was dissolved in 2 ml of methylene chloride.

2.3 Preparation of the Ind-HPMC-Gel 50/13 and Ind-HPMC-HPC-Gel 50/13 Solid Dispersions

Solid dispersions were prepared by solvent evaporation method as previously described [21] with some modifications. Different batches of solid dispersions were formulated with different ratios of HPMC-Gel 50/13 binary hybrid and HPMC-HPC-Gel 50/13 ternary hybrid systems. The variations in polymer ratio were represented with different formulation codes as shown in Table 1. The drug and hybrid polymers were accurately weighed and dissolved with (2 ml) dichloromethane and methanol (1:1) in a volumetric flask. The resultant solutions were transferred to a rotary evaporator where the solvents were evaporated by heating at a constant temperature of 37 ± 1°C. The residues were transferred to an aluminum pan and allowed to dry at 25°C. The dried samples were pulverized and screened through a 52-mesh (Ika, Germany). The resultant solid dispersions were packed in screw capped containers and stored in desiccators with silica gel as a desiccant until further use. The different batches formulated are as shown in Table 1.

2.4 Determination of Practical Yield

The practical yields of the solid dispersions formulated were determined to evaluate the efficiency of the method of preparation by measuring their weights. The percentage yields were calculated using the equation [22]:

$$Percentage\ yield = \frac{Weight\ of\ prepared\ solid\ dispersions}{Theoritical\ yield} \times 100 \quad (1)$$

2.5 Particle Size and Morphology of Solid Dispersions

The particle size, morphology and surface characteristics of the solid dispersions were analyzed by mounting each sample on a glass slide followed by viewing with the help of a Motic Cam 2.0 fitted microscope. The images of the solid dispersions were captured at a magnification of x100 and examined.

2.6 Drug Content Determination

The drug content of the formulated solid dispersions was determined as follows. Briefly, 200 mg (amount equivalent to 25 mg indomethacin) of each batch of the formulated solid dispersions was accurately weighed and dissolved into 10 ml of absolute ethanol, sonicated for 20 min and filtered. Then, the filtrate was transferred to a volumetric flask and made up to 100 ml with phosphate buffer, pH 7.4. The resultant solution was diluted by 20 folds and analyzed against blank consisting of ethanolic phosphate buffer using UV/Visible spectrophotometer (Jenway 6405, Germany) at 320 nm. The percentage of drug present in the solid dispersions was calculated with respect to standard plot.

2.7 *In vitro* Drug Dissolution Studies

Briefly, an amount of each batch of formulation equivalent to 25 mg of indomethacin was enclosed in a dialysis membrane tubing (MWCO 5000 – 8000, Germany) and hermetically sealed at both ends. The diffusion surface area was maintained by using membranes with same length (4 cm) and width (3 cm) for all the tests. The enclosed samples were suspended in 900 ml of SGF, pH 1.2 and subsequently in same volume of SIF, pH 7.4 in a beaker mounted on a magnetic stirrer assembly and each medium was maintained at 37 ± 1°C and stirred at 50 rpm. Series of 5 ml volumes of the test solutions were withdrawn at interval for 24 h (2 h in SGF and 22 h in SIF), diluted to 25 ml with distilled water and assayed using the UV–Vis spectrophotometer at 320 nm.

2.8 Release Kinetics

The kinetics and mechanism of drug release were determined using different models. The percentage amount of drug released from the formulated dispersions at different time intervals were fitted to the following plots: zero order kinetic model using percentage drug release versus time or 'Q vs t' [23]; first order kinetic model using log % drug remaining versus time or 'log (100 - Q) vs t' [24]; Higuchi model using cumulative % drug release versus square root of time or 'Q vs $t^{1/2}$ [25,26]. The linearity of these plots was determined by their R^2 values and the plot (model) with the highest linearity was taken

as that which described the kinetics and mechanism of drug release.

2.9 *In vivo* Anti-inflammatory Studies

2.9.1 Animal protocols

Albino Wistar rats of both sex and weighing 200 - 250 g (obtained from the Department of Pharmacology and Toxicology's animal utility house, University of Nigeria Nsukka) were used for the study. The animals were housed in propylene cages maintained under standard conditions. They were fed with standard rat pellet diet and provided free access to water. They were allowed to equilibrate in these conditions for a period of one week. All animal experimental procedures were reviewed and approved by the Committee for Animal Research of the Department of Pharmaceutics, University of Nigeria, Nsukka, Nigeria, and were in compliance with the Federation of European Laboratory Animal Science Association and the European Community Council Directive of November 24, 1986 (86/609/EEC).

2.9.2 Experimental design

Anti-inflammatory activity was assessed by carrageenan-induced rat paw oedema models as previously described by M. Momoh et al (2015) with some modifications [27]. The γ - carrageenan was first weighed individually for each animal according to their body weight and then solubilized with 0.2 ml saline just prior to injection. The test formulations were prepared as a solution. The commercially available product (Indocid®) was prepared as a homogenous suspension with normal saline (0.9%w/v NaCl). A total of fifty (50) Wistar albino rats, selected randomly and divided into ten groups (n = 5), were used for the study.

2.9.3 Evaluation of anti-inflammatory activity

a) Groups I- VIII (In-SD1, In-SD2, In-SD3, In-SD4, In-SD5, In-SD6, In-SD7 and In-SD8, respectively) received the test formulations administered orally at a dose of 3.2 mg/kg.
b) Group IX (positive control group) received the Indocid (0.4 mg/kg) dispersed in normal saline.
c) Group X (negative control group) received normal saline.

One hour after oral administration of the formulations, drug sample and normal saline, each rat received an injection of 0.1 ml of 0.2 %w/w γ - carrageenan solution in the right hind paw. The paw volumes of the rats were measured at time intervals (1, 2, 4, 6 and 8 h). The percentage oedema inhibition was calculated using the following formula [27].

$$\%\ Edema\ Inhibition = \frac{I_c - I_t}{I_c} \times 100 \qquad (2)$$

Where I_c is the oedema rate of negative control group; I_t is the oedema rate of treated groups.

2.10 Stability Studies

The stability studies of different batches of indomethacin solid dispersions were analyzed according to International Conference of Harmonization (ICH) guidelines (40 ± 2°C and 75 ± 5% RH) for a period of one month and three months in a humidity chamber. The formulations were packed in amber colored bottles. After one and three months, samples were withdrawn and re-evaluated for the drug content.

Table 1. Formulation compositions of the solid dispersions and some physicochemical properties of indomethacin solid dispersion systems

Batch code	Formulation type	Ratio of polymer used (HPMC /Gelu/HPC)	Percentage (%) yield	Mean particle size ± SD (μm)
In-SD1	D : HPMC:Gelu	1 : 1	98.39	0.138 ± 0.14
In-SD2	D: HPMC:Gelu	2 : 1	97.82	0.287 ± 0.02
In-SD3	D: HPMC:Gelu	3 : 1	97.38	0.228 ± 0.09
In-SD4	D: HPMC:Gelu	4 : 1	97.11	0.322 ± 0.05
In-SD5	D: HPMC:Gelu	1 : 2	96.43	0.506 ± 0.01
In-SD6	D: HPMC:Gelu	1 : 3	93.14	0.505 ± 0.03
In-SD7	D : HPMC:Gelu	1 : 4	92.80	0.474 ± 0.12
In-SD8	D:HPMC:Gelu:HPC	1:1:1	98.78	0.233 ± 0.04

SD means standard deviation, Gelu means Gelucire, HPMC means hydroxylpropyl methylcellulose, HPC means hydroxylpropyl cellulose

2.11 Statistical Analysis

All experiments were performed in replicates for validity of statistical analysis. Results were expressed as mean ± standard deviation (SD). Student's t-test was performed on the data sets generated using Statistical Package for Social Sciences (SPSS) software, version 12 (Chicago, IL). Differences were considered significant at p-values < 0.05.

3. RESULTS AND DISCUSSION

3.1 Practical Yield

Different batches of Indomethacin SDs (Ind-SDs) were successfully and suitably prepared by solvent evaporation method. From the results shown in Table 1, the practical yield of the solid dispersions prepared was excellent and ranged from 92.80 – 98.78%. This indicates the efficiency of the method adapted for the formulation of the SDs as well as giving an indication of complete removal of any organic solvent used. The highest and least practical yield was shown by In-SD8 and In-SD7 formulations, respectively. This may be attributed to their varying concentration of HPMC and Gelucire 50/13. The small losses might have occurred during the process of preparation through weighing, mixing, transference, etc.

3.2 Particle Size and Morphological Characteristics

Indomethacin HPMC/HPC-Gelu 50/13 hybrid based solid dispersions were powdery and had a tint of yellow colour. Representative photomicrographs showing the morphology of the different indomethacin solid dispersion systems are presented in Figs. 2a–b, respectively. This depicts a discrete, spherical to irregularly shaped solid particles. The irregular shape was observed mostly with Ind-SD5, Ind-SD6 and In-SD7 formulations with increasing concentrations of Gelucire 50/13. The particle sizes of the formulated solid dispersions ranged from 0.138 ± 0.14 µm to 0.506 ± 0.01 µm as shown in Table 1. Generally, the small particle size observed depicts an increased surface area and thus improved dissolution of solid dispersions and drug dispersed within. However, the particle size of the different batch of formulated SDs was observed to increase in those formulations (In-SD5, In-SD6 and In-SD7) containing increased concentrations of Gelucire 50/13, but no significant ($p > 0.05$) increase in particles size was observed with In-SD2, In-SD3 and In-SD4 binary systems containing increasing concentrations of HPMC. This may be attributed to the hydrophobic component of Gelucire 50/13.

3.3 Drug Content

Drug content of the various solid dispersions prepared was estimated spectrophotometrically by measuring the absorbance at predetermined wavelength of 320 nm. All the formulated batches were found to have an excellent entrapment of the drug. Indomethacin drug content in all the solid dispersions were found to be in the range of 81.98 – 97.95% as shown in Fig. 3. This is an indication of the high drug loading capacity of the polymer hybrids. However, In-SD8 formulation (containing HPMC-HPC-Gelu 50/13 polymer hybrids at a ratio of 1:1:1) showed the highest drug content of 97.95%, while In-SD7 formulation (containing HPMC-Gelu 50/13 polymer hybrids at a ratio of 1:4) had the least drug content of 81.98%. This may be attributed to varying composition of the different polymers used for formulation. Therefore, it suffices to say that drug content of the Ind-SDs might have increased with increased concentration of HPMC in combination with Gelucire. The increased concentrations of Gelucire in combination with HPMC as seen in In-SD5, Ind-SD6 and In-SD7 did not improve the loading capacity of the polymer hybrids.

3.4 *In vitro* Dissolution Studies

Dissolution profiles of pure indomethacin sample, its solid dispersions in comparison with that of the commercially available product in SGF, pH 1.2 and SIF, pH 7.4 without enzymes are shown in Fig. 4. Generally, the Ind-SDs recorded faster and almost complete dissolution of indomethacin when compared to the pure drug. They showed a significant ($p<0.05$) faster release rate of the drug in SIF when compared with the drug release in SGF. In SGF, less than 7.0% of indomethacin was released from the SDs as well as the pure drug sample at the end of 2 h. This was not the case for the commercially available product which recorded approximately 23.0% drug release at the end of 2 h in SGF. However, the dissolution rate of the drug from the formulations significantly ($p<0.05$) increased in SIF, as shown in Fig. 4. Dissolution profiles of SDs in this medium depicted a faster but sustained dissolution of drug from the SDs when compared

to the commercially available product and pure indomethacin sample. This indicates not just the ability of the polymer hybrids to enhance the dissolution of the drug, but also their potential in controlling the release of indomethacin. This is crucial in achieving effective steady concentrations of the drug in the biological systems as well as avoiding dose dumping of indomethacin in a particular compartment in the GIT. Also, the encapsulation of the drug in these matrices protects the stomach from undesirable GIT disturbances including severe bleeding which the drug is often associated with. The different batches of the formulations showed a higher release rate in the trend: In-SD7>In-SD6>In-SD5>In-SD1>In-SD2>In-SD8>In-SD4> In-SD3. This may be attributed to the variations in the composition of the hybrid polymer matrices used for formulating the SDs. Dissolution rate of the drug as well as its sustained release was higher for In-SD3, In-SD4 and In-SD8 formulations in which a higher concentration of HPMC and/or HPC in combination with Gelucire 50/13 polymer was used in formulating the SDs. Thus, the presence of these two or three polymers could have formed a hybrid with improved properties which contributed to the enhanced dissolution together with sustained release of the drug observed with the formulations.

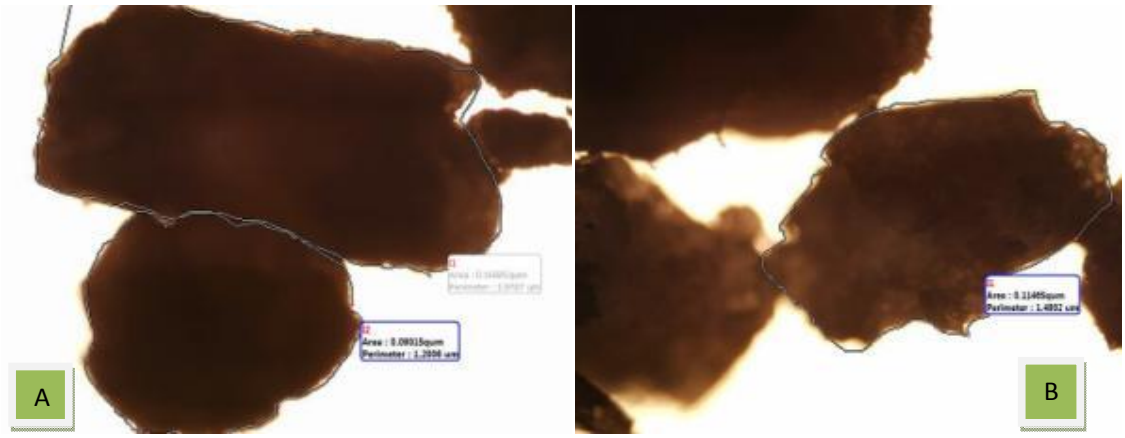

Fig. 2 a - b. Representative photomicrographs of indomethacin solid dispersions (magnification x 100)

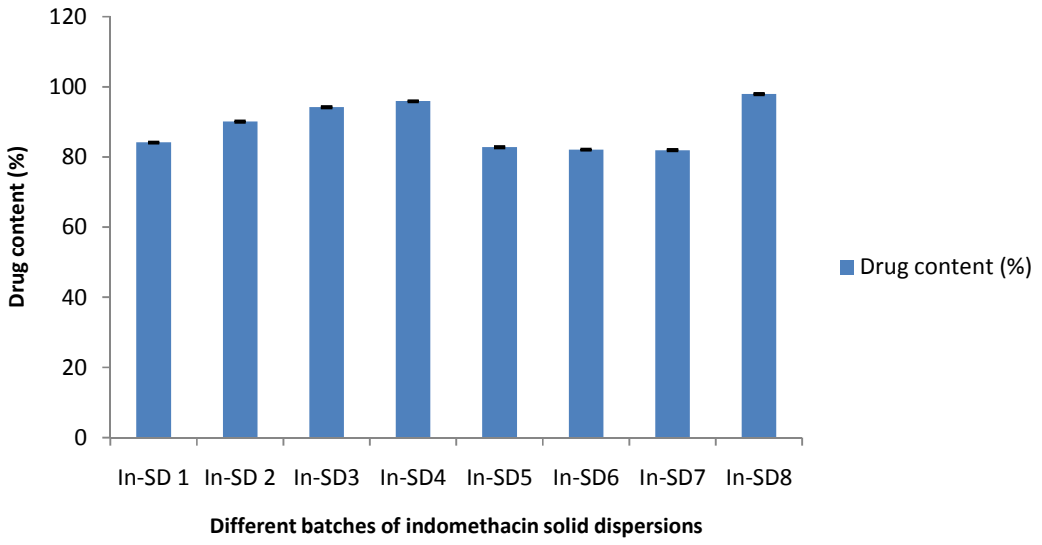

Fig. 3. Percentage drug content of different batches of indomethacin solid dispersions

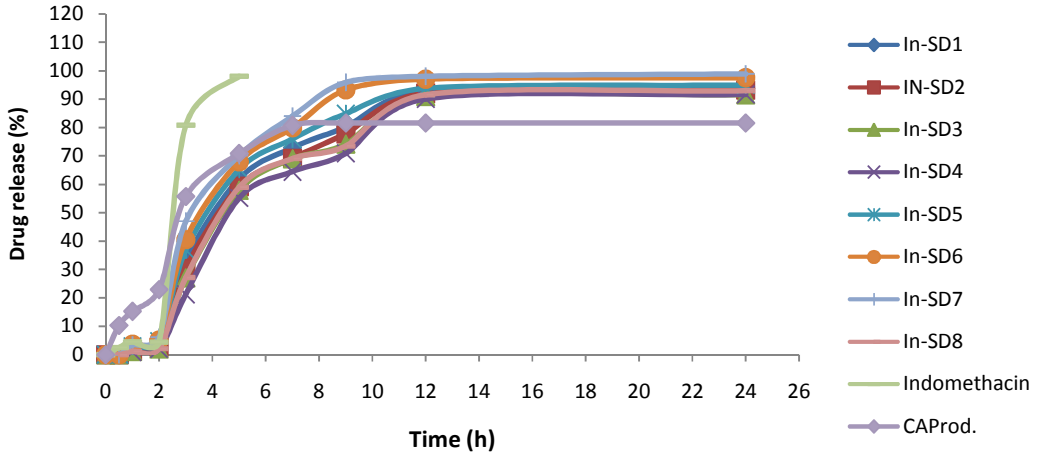

Fig. 4. Dissolution profiles of different batches of indomethacin solid dispersions in comparison with pure drug and commercially available product in SGF, pH 1.2 and SIF, pH 7.4

The possible mechanisms which explain the observed increased dissolution rate could be attributed to the reduction of crystalline size, solubilisation effect of the polymer hybrids, absence of aggregation of the drug, improved wettability and dispersibility of the drug from the dispersion, dissolution of the drug in the polymer matrix and the conversion of the drug to an amorphous state. As the polymer dissolved, the insoluble drug got exposed to dissolution medium in the form of fine particles for quicker and faster dissolution [28].

3.5 Release Kinetics

Drug release from all the solid dispersions formulated followed the First order kinetics as evidenced by their correlation coefficients values (r^2 as shown in Table 2) which were slightly higher compared to that of Zero order release model and almost closer to one. The comparative contribution of drug diffusion and erosion to drug release was confirmed with the subjection of the dissolution data to Higuchi model. The correlation coefficients obtained from different batches indicate that diffusion of the drug as well as erosion of the matrices could be the possible mechanism governing the drug release from these formulations as evidenced by the high correlation coefficient values from the Higuchi model.

3.6 *In vivo* Anti-inflammatory Studies

All the test formulations exhibited some anti-inflammatory activity as evidenced by their high percentage inhibition of oedema as shown in Table 3 and Fig. 5. It can be depicted from this result that all the test formulations significantly ($p< 0.05$) produced greater inhibition of edema compared to the pure drug sample. This confirms the improved dissolution and consequently greater bioavailability of the drug by virtue of its formulation as solid dispersions. In addition, the inhibition of edema produced by all the formulation was sustained for up to 8 h following oral administration. The most sustained edema inhibition of 90.55±1.66% was observed in the group treated with Ind-SD3 formulation which could be in correlation with the high concentrations of HPMC in its matrix. Also, a greater potential for sustained release of indomethacin from the SDs can be depicted from the value of percentage inhibition of edema produced by groups treated with Ind-SD4, Ind-SD2 and Ind-SD8 formulations containing increased concentrations of HPMC and/or HPC in combination with Gelucire 50/13. This corresponds with earlier works reported in the literature of the ability of these polymers not only to improve the dissolution of poorly water soluble drugs but also to retard their release from their matrix [1].

3.7 Stability Studies

The results of stability studies carried out on different batches of Ind-SDs are shown in Fig. 6. It is evident from these figures that there was an insignificant difference ($p>0.05$) in the content of indomethacin after three months of storage. This indicates stability of the drug in the SDs formulated with these polymer hybrids even after some period of storage.

Table 2. Some data from dissolution studies and release kinetics of the indomethacin solid dispersion systems

Formulations	Correlation coefficient (r^2)			Q_{12} (%)
	Higuchi	First order	Zero order	
In-SD1	0.8517	0.8502	0.6875	93.00
In-SD2	0.8608	0.8599	0.7258	92.02
In-SD3	0.8640	0.8457	0.7092	90.89
In-SD4	0.8695	0.8684	0.7366	90.04
In-SD5	0.8447	0.8520	0.6688	93.79
In-SD6	0.8322	0.8344	0.6484	97.00
In-SD7	0.8215	0.8616	0.6291	98.01
In-SD8	0.8626	0.8662	0.7150	91.50

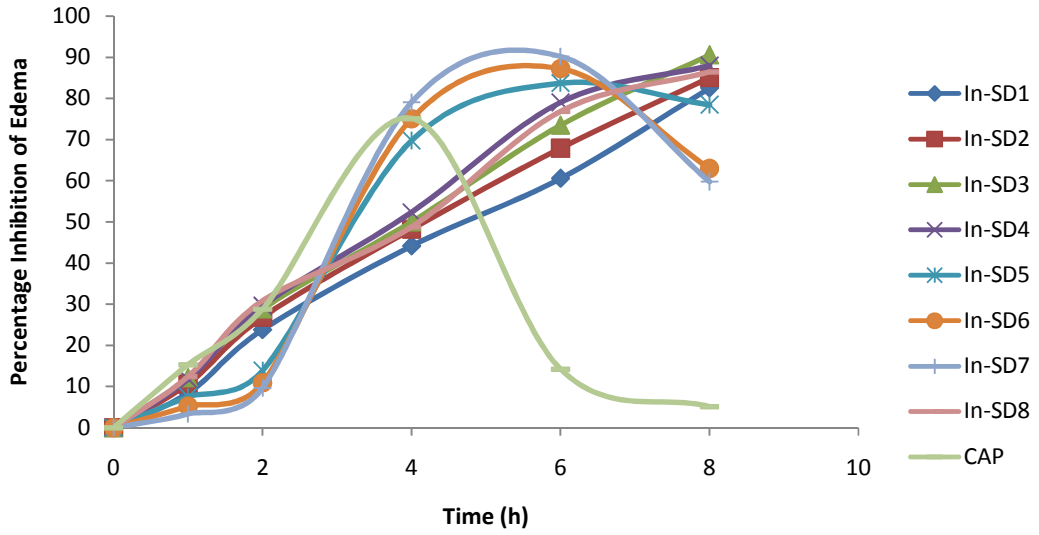

Fig. 5. Percentage inhibition of edema from different groups of rats treated with the indomethacin solid dispersions versus the commercially available product (CAP)

Table 3. *In vivo* anti-inflammatory activity of the indomethacin solid dispersions systems versus commercially available product

Batch /	Percentage inhibition of edema (%)				
Time (hours)	1	2	4	6	8
In-SD1	08.42±1.02	23.81 ± 1.11	44.15 ± 0.18	60.56 ± 2.97	82.50 ± 3.43
In-SD2	10.67±2.10	26.85 ± 2.18	48.19 ± 3.92	67.87± 2.85	85.01 ± 3.21
In-SD3	12.18 ± 0.98	28.85 ± 0.83	50.01± 4.21	73.48 ± 1.93	90.55 ± 0.92
In-SD4	11.77 ± 1.39	29.63 ± 0.35	52.33 ± 0.99	78.99± 0.90	87.95 ± 1.47
In-SD5	07.51 ± 0.99	13.86 ± 0.77	69.72 ± 1.67	83.67 ± 1.53	78.41 ± 1.49
In-SD6	05.23 ± 3.18	10.90 ± 2.13	75.03 ± 3.32	87.19 ± 2.41	62.94 ± 2.33
In-SD7	03.36 ± 0.38	09.67 ± 0.87	79.05 ± 1.86	90.18 ± 0.44	59.78 ± 3.56
In-SD8	12.44 ± 0.78	30.86 ± 2.31	48.79 ± 2.22	76.83 ±1.01	86.45 ± 1.66
IND (positive control)	15.33 ± 0.94	28.81 ± 2.15	75.11 ± 3.17	14.23 ± 3.25	05.13 ± 1.07

In-SD1 to In-SD8 represent different batches of the formulated solid dispersions containing different ratios of HPMC/HPC and Gelucire 50/13 as shown in Table 1 , IND = Indomethacin capsule commercially available, values are mean ± SD (n = 5), Significant $p < 0.05$ as compared to the control

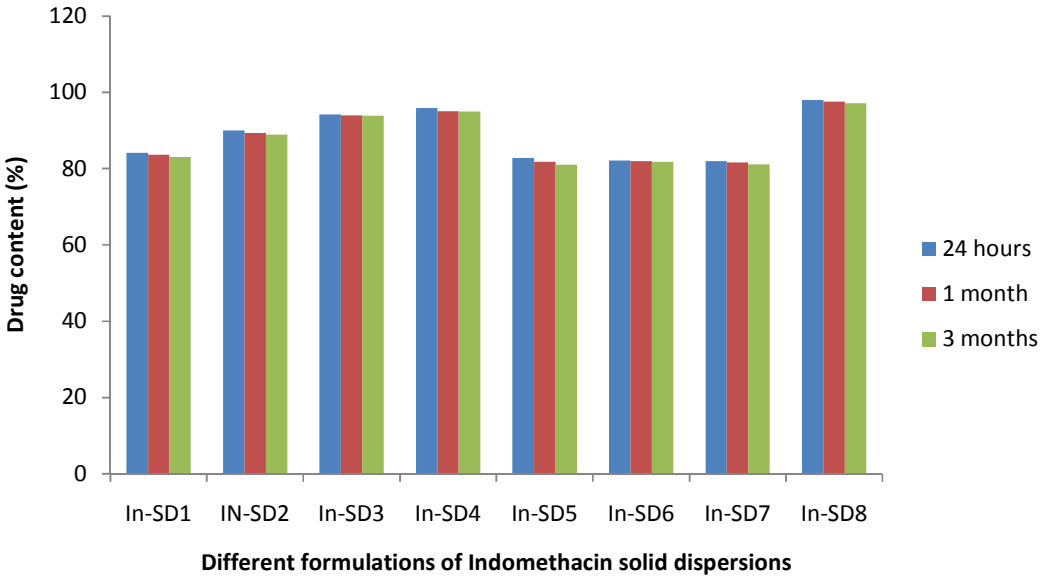

Fig. 6. Stability profile of different formulations of indomethacin solid dispersions for a period of three months

4. CONCLUSION

Controlled release binary and ternary HPMC-HPC-Gelucire® 50/13 hybrid based solid dispersions of indomethacin were successfully formulated using solvent evaporation technique. The formulations had excellent yield and morphology, and were free flowing. All the formulations showed not only an improved dissolution rate of indomethacin but also its sustained release from the hybrid matrices of the formulations, with batch In-SD3 showing the best controlled release potential. Drug release from the matrices of the entire formulations followed First order model and was governed by a combination of diffusion/erosion mechanism. The sustained release potential and anti-inflammatory property of the formulations in relation to the pure drug sample was proved by the increased percentage of edema inhibition produced. The formulations were stable even after subjecting them to different stability conditions for a storage period of three months. Thus, solid dispersions prepared with these biodegradable polymer hybrids, Gelucire 50/13® in combination with cellulose derivatives, HPMC and HPC with optimized physicochemical properties showed promising potential in clinical practice for enhancing the delivery of indomethacin as well as ensuring patient's compliance and tolerance of the drug as this delivery system has not only improved dissolution of indomethacin but has also extended its release.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approval was obtained.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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