International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 17, Issue 1, 2025

Original Article

FORMULATION AND EVALUATION OF AN ORAL TIMED PULSATILE DRUG DELIVERY FOR ALLEVIATING PAIN IN RHEUMATOID ARTHRITIS

PASAM JYOTHIRMAYI[1], ARIGELA BHARATHI[2*], D. RAMA SEKHARA REDDY[3*]

[1]Krishna University, Krishna District, Andhra Pradesh, India. [2]K. V. S. R. Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh, India. [3]Department of Chemistry, Krishna University, Krishna District, Andhra Pradesh, India
[*]Corresponding author: Arigela Bharathi; [*]Email: dachuru@gmail.com

Received: 15 May 2024, Revised and Accepted: 10 Oct 2024

ABSTRACT

Objective: The present study was aimed to formulate and evaluate an oral timed-release pulsatile drug delivery of AceclofFenac (AF) for rheumatoid arthritis pain by the Chronopharmaceutical approach with early morning breakthrough of AF as analgesic and anti-inflammatory agent for the treatment of rheumatoid arthritis.

Methods: A solubility was enhanced by formulating it as a self-emulsified system with a suitable oil and surfactant mixture. The interaction between the drug and the excipient was examined using Fourier Transform Infra-Red (FTIR) spectroscopy. The prepared formulation consists of 2 different parts: The basic design consists of burst-release core tablets with solid self-emulsified AF by using different super disintegrants, and the press-coating of optimised tablets by using different compositions of Ethylcellulose (hydrophobic) and Hydroxy Propyl Methyl Cellulose (HPMC K100) (hydrophilic) polymers.

Results: FTIR studies revealed no interaction between drug and excipients. From the solubility data, suitable oil and surfactants were selected. Pseudo-ternary plots help in finding of suitable surfactant mixtures for solid self-emulsified AF. Core tablets were evaluated for pre-compression characteristics, disintegration time, drug content**,** weight variation, hardness, friability, thickness, and % drug release. Among all solid self-emulsified formulations, S1C6 is successful, with 98.88% drug release in 20 min. The compression coat formulations were also evaluated for Hardness, weight variation, thickness, lag time, and *in vitro* drug release profile. Among them, F4 was optimised by its suitable lag time and drug release of 97.23% at the end of 6 h.

Conclusion: The system released the drug after a predetermined lag time of 4 h and thus, the dosage form can be taken at bedtime so that the drug will be released when the symptoms are prominent. Nine formulations were prepared, of which F4 formulation showed the highest drug release of 97.23 % at the end of 6 h and showed compliance with the chronotherapeutic objective of rheumatoid arthritis.

Keywords: Pulsatile drug delivery system, Chronotherapeutic, Aceclofenac, Rheumatoid arthritis

DOI: https://dx.doi.org/10.22159/ijap.2025v17i1.51458 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Oral drug delivery is the largest segment of the entire drug delivery market. It is the foremost preferred route for drug administration. The controlled release system for oral administration exhibits a typical drug release pattern in which the drug concentration is maintained within the therapeutic window for a long time, thereby providing a long-term, sustained therapeutic effect. There are certain conditions for which such a delivery design isn't appropriate that request arrival of medication after a lag time. In other words, they require a pulsatile drug delivery system (PDDS) [1, 2].

Pulsatile drug delivery systems are designed by the biological rhythm of the body. Modified-release dosage forms have acquired importance in the current pharmaceutical R and D business. These systems can control drug release patterns and better control drug therapy [3]. Traditionally, drugs are released in an instantaneous or extended fashion. A pulsatile drug release, where the drug is released rapidly after a well-defined lag time, could be advantageous for many drugs or therapies.

This phenomenon drastically decreases the time available for drug absorption and limits the success of the delivery system. These considerations have prompted the improvement of oral controlled-release drug delivery having gastric maintenance abilities. A normal time needed for a dosage unit to transverse through Gastro-Intestinal Tract (GIT) is 3-4 h, although slight change exists among different dosage forms, such as tablets for 5.8 h, pellets for 4.6 h, capsules for 4 h and solutions for 4 h. [4, 5] Incomplete absorption of the medication and more limited residence time of the dosage form in the upper GIT prompt the lower bioavailability.

AceclofFenac (AF) is known as an oral Non-Steroidal Anti-Inflammatory Drug (NSAID), which helps reduce inflammation and relieve pain. AF primarily works by reducing the production of prostaglandins through selective inhibition of Cyclo Oxisanase-2 (COX-2), with a COX-2/COX-1 ratio of 0.26 for its half maximal inhibitory concentration (IC50). During clinical studies, AF demonstrated the ability to suppress prostaglandin synthesis both in the synovial fluid of patients with acute knee osteoarthritis (OA) and in the peripheral blood leukocytes of OA patients [6]. In four 12-to 24-week randomised clinical trials involving patients with confirmed active rheumatoid arthritis (RA), the efficacy of AF at a dosage of 100 mg twice daily was comparable to that of diclofenac, indomethacin, ketoprofen, and tenoxicam. It effectively reduced pain intensity and joint inflammation while also improving morning stiffness and hand grip strength. AF taken orally is quickly and fully absorbed by the body, reaching its highest concentration in the bloodstream around 1.25 to 3.0 h after being taken. AF mean elimination half-life is approximately 4 h [7, 8].

The aim of the present study is to develop a PDDS approach as an oral timed-release pulsatile drug delivery of AF for early morning symptoms of rheumatoid arthritis pain. The poor solubility and low bioavailability of AF were addressed through the development of solid self-emulsifying systems and by the time-lagged press-coated formulations.

MATERIALS AND METHODS

Materials

AF was obtained from Pure Chem. Pvt. Ltd., Gujarat. Cross Carmellose Sodium (CCS) was obtained from Spectrum Chemicals., Cross povidone was obtained from Shreeji chemicals., Sodium Starch Glycolate (SSG) was obtained from Lobachemie Pvt Ltd, HPMCK100 was obtained from Yarrow chem. Products, Lactose was obtained from Thomas Baker chemicals Pvt. Ltd., Ethylcellulose was obtained

from Rolex chemicals industries, Microcrystalline cellulose (MCC), Magnesium stearate, and Talc were obtained from SD fine chem. Limited.

Drug-polymer compatibility by fourier-transform infrared spectroscopy (FTIR)

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the pre-formulation stage during the development of a dosage form. The FTIR used here was Bruker Alpha II FTIR spectrometer with a Zinc Selenide Crystal ATR (Attenuated Total Internal Reflectance) accessory. Samples were placed directly on the Zinc selenide crystal plate. Here transmission of the IR radiation through the sample was not measured; how much the Infra Red (IR) radiation is attenuated by the sample was measured. The sample was placed on a crystal with a high refractive index [9, 10]. When the light rays strike the interface between the zinc selenide crystal and the sample, they undergo total internal reflectance. An evanescent wave travels beyond the surface of the crystal into the sample, approximately 0.5 to 5 µm before being refracted back into the crystal. Because of this, the sample must be in tight contact with the crystal. The evanescent wave will be attenuated in regions where the sample absorbs IR radiation [11]. The IR beam exits at the opposite end of the crystal and passes to the detector, which measures the attenuation. The spectral image is recorded in mid-infrared region (4000–400 cm^{-1})

Calibration curve of AF

A stock solution 1 (1 mg/ml) of AF was prepared in pH 6.8 phosphate buffer. From the stock solution 1, a stock solution 2 (100µg/ml) was prepared. Solutions of different concentrations from 2 to 40 µg/ml were prepared from stock solution 2. Absorbance of the resulting solutions were measured by Ultra Violet, UV-visible spectrophotometer (UV-1900I SHIMADZU) at λmax 273 nm [12].

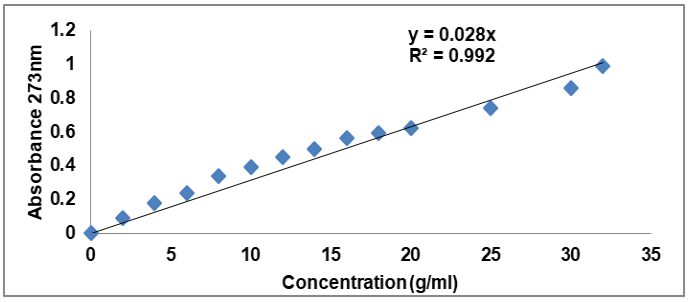

Fig. 1: Calibration curve of aceclofenac in pH6.8 buffer

Determination of solubility of API

A quantity of 5 mg of AF was weighed and transferred into different conical flasks containing distilled water, phosphate buffer pH 6.8, methanol, 0.1N HCl, Di Methyl Sulf Oxide (DMSO), oleic acid, almond oil, castor oil, sunflower oil, and coconut oil. The flask was closed appropriately and placed in a sonicator. The sonicator was allowed to operate at 50 rpm for 24 h, maintaining at 37±1 °C. Then the conical flask was removed from the sonicator, and the samples were filtered using Whatman filter paper [13, 14]. The clear solution obtained by filtration was notes in UV Spectrophotometer at 273 nm by using corresponding solvent as the blank solution.

Selection of surfactant mixture

Similarly to solubility in different media, different surfactants were studied for the preparation of a self emulsified system. Among those, Span80 and tween 80 were selected in combination with propylene glycol and Polypolyethylene glycol (PEG 400) as co-surfactants [15]. From the solubility study of surfactant and consistency of surfactant mixture ratios as shown in fig. 2, the following surfactant mixture combination of $S_{mix}1$ and S_{mix} 2 were prepared by the combination of Span80-PG and Tween80-PEG400 respectively, in a ratio of 1:4.

Construction ternary phase diagram

A pseudo-ternary phase diagram was created by employing the water titration method. This involved combining oleic acid with a surfactant mixture in weight ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9 in glass vials for a duration of 5 min [16]. Each oil-to-smix ratio was titrated with distilled water in increments of 0.5% w/w, followed by vigorous mixing for at least 2 min. The mixture was then allowed to equilibrate at 25 °C for 10 min before the next addition of water. The procedure was reiterated until either the sample became turbid or reached a water addition of 90.9% w/w. The phase behavior of each ternary phase system was monitored throughout the titration process. Samples exhibiting a clear, slightly bluish appearance were identified as being within the micro-emulsion region [17, 18]. The percentage composition of each component in the ternary system was established, and the results were plotted on triangular coordinates to construct the phase diagram. The concentrations of oil, surfactant, and co-surfactant that resulted in a clear emulsion were chosen as the self-micro-emulsion for formulating the AF Self-Emulsified Drug Delivery Systems (SEDDS).

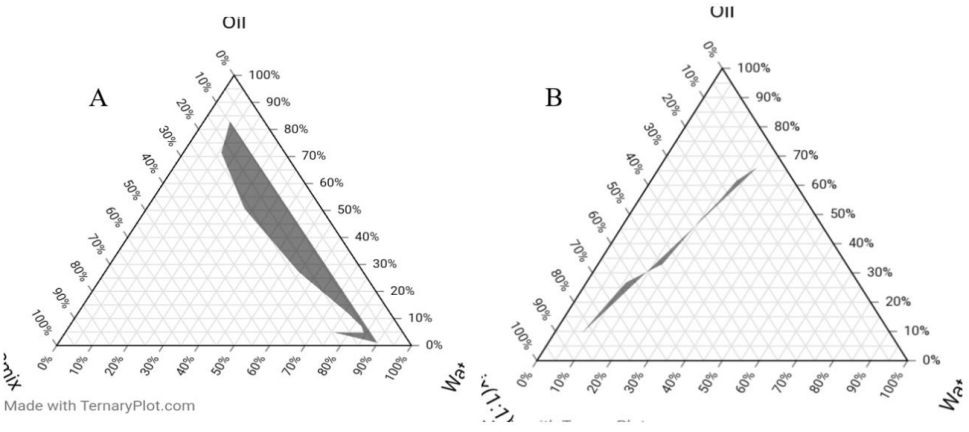

Fig. 2: Pseudo-ternary phase diagrams of aceclofenac in S_{mix1}, and S_{mix2}

Solubility enhancement of AF by SEDDS

From the obtained ternary plots in fig. 2 at their dark portion, the composition of oil and surfactant mixtures were selected to prepare SEDDS. By the suitable adsorbent, the liquid SEDDS is converted to solid SEDDS, which is then further used to develop burst-release tablets [19].

Formulation of pulsatile drug delivery system of AF

Formulation of burst release solid self-emulsified core tablet

By the use of a ternary phase diagram, selected $S_{mix}1$ and $S_{mix}2$ compositions, and by the use of solid carrier lactose, twelve formulations SF1 to SF8 were formulated. Among these, S1C1 to S1C6 were formulated with $S_{mix}1$, and S2C1 to S2C6 were formulated with $S_{mix}2$. With the prepared solid mass granules were formulated [20, 21]. All the ingredients were passed through mesh no. 60. The required amount of each ingredient was taken from the specified formulation; all the ingredients were dry blended for 30 min. The powder blend was evaluated for flow properties such as angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The mixtures were then further blended for 10 min. 200 mg of the resultant powder blend was subjected to compression using a 12-station rotary tablet press to obtain the core tablet.

Formulation of mixed blend for barrier layer

The various formulation compositions containing Ethyl cellulose and Hydroxy Propyl Methyl Cellulose (HPMC k100) were weighed and blended for about 10 min. This was used as press-coating material to prepare press-coated pulsatile tablets [22].

Table 1: Different compositions of burst release core tablet

Ingredients (mg)	S1C1	S1C2	S2C3	S1C4	S1C5	S1C6
Aceclofenac SEDDS	10	10	10	10	10	10
CCS	5	10	-	-	-	-
Crosspovidone	-	-	5	10	-	-
SSG	-	-	-	-	5	10
Magnesiumsterate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Lactose	31	31	31	31	31	31
MCC	150	147	150	147	150	147
Total (mg)	200	200	200	200	200	200

Table 2: Different compositions of burst release core tablet

Ingredients (mg)	S2C1	S2C2	S2C3	S2C4	S2C5	S2C6
Aceclofenac SEDDS	10	10	10	10	10	10
CCS	5	10	-	-	-	-
Crosspovidone	-	-	5	10	-	-
SSG	-	-	-	-	5	10
Magnesium sterate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Lactose	31	31	31	31	31	31
MCC	150	147	150	147	150	147
Total (mg)	200	200	200	200	200	200

Formulation of press-coated tablets

The core tablets were press-coated with 300 mg of mixed blend as given in table 4. 150 mg of barrier layer material was weighed and transferred into a 13 mm die, and then the core tablet was placed manually at the centre. The remaining 150 mg of the barrier layer material was added into the die and compressed using 12 station rotary tablet press to obtain the press-coated tablet [24].

Table 3: Different concentrations of pulsatile drug delivery system of press-coated tablet

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMCK100	200	210	220	230	240	250	260	270	280
Ethyl Cellulose	100	90	80	70	60	50	40	30	20
Total(mg)	300	300	300	300	300	300	300	300	300

Characterization of core and press-coated tablet

The pre-compression characteristics of core tablets, disintegration time, and drug content values were represented in table 6. The physical properties, such as weight variation, tensile strength, thickness, and friability of core tablets and press-coated tablets were given in table 7. For the drug content, Tablets were finely powdered, and quantity of the powder equivalent to 10 mg of AF was accurately weighed and transferred to a volumetric flask containing 100 ml of phosphate buffer (pH 6.8) and mixed thoroughly. 1 ml of filtrate with suitable dilution was estimated for Aceclofenac content at 273 nm using a double-beam spectrophotometer (Shimadzu Corporation, Japan, UV-1700).

Lag time and dissolution study of core and press-coated tablet

Lag time is the time at which the polymer coat ruptures and drug release starts. Dissolution of Aceclofenac tablets was performed in a United States of Pharmacopoeia (USP) dissolution tester, paddle method (Electrolab TDT-08L Plus, Dissolution tester USP Mumbai, India), under stirring at 100 rpm. The dissolution media consisted of 900 ml of phosphate buffer (pH 6.8) at 37 °C. Samples were withdrawn at regular time intervals, then filtered and analysed at 273 nm using a UV spectrophotometer. An equivalent volume of temperature-equilibrated fresh buffer was replaced following the removal of each sample. From these studies, both lagtime and % drug release were represented in fig. 5.

Drug release kinetics and stability studies

The formulated AFtablets were subjected to various kinetic studies like zero order (Cumulative percentage of drug released vs. time), first order (log cumulative percentage of drug unreleased vs. time), Higuchi equation (Cumulative percentage of drug unreleased vs. Square root of time), and Korsemeyer's (log cumulative percentage released vs. log time). Accelerated stability study was carried out for optimised batch (F4) at 40±2 °C/75±5% RH over a 3-month period according to International Conference of Hormonisation (ICH) guidelines in the stability chamber (Thermolab India). At the end of the 3 mo, the tablets were examined for physical characteristics and

drug content. In the fig. 6, stability studies data of *in vitro* drug release and lag time at the end of 3 mo (180 d) were represented [25, 26].

RESULTS

The drug AF was preliminarily identified by FT-IR spectroscopy, and organoleptic properties were evaluated. Pulsatile release tablet was prepared by direct compression method. The tablets were evaluated for weight variation, hardness, thickness, friability, drug content, and dissolution and stability studies. The results of pre-compression parameters were shown in table 6. Evaluations of prepared burst-release core tablets and press-coated pulsatile release tablets were shown in table 7. Muhammed R *et al*., have discussed about several approaches in colon targeting pulsatile therapies [27].

Table 4: Aceclofenac solubility of different solvents and oils (mean±SEM, n = 6)

S. No.	Solvent	Solubility	Oil	Solubility (mg/ml)
1.	Water	Insoluble	Oleic acid	8.12±0.25
2.	0.1N HCl	Freely soluble	Almond oil	8.86±0.24
3.	Methanol	Partially soluble	Castor oil	1.31±0.36
4.	pH6.8phosphate buffer	Partially soluble	Sunflower oil	1.33±0.28
5.	DMSO	Freely soluble	Coconut oil	0.42±0.22

Data are expressed as mean±SD, n=3

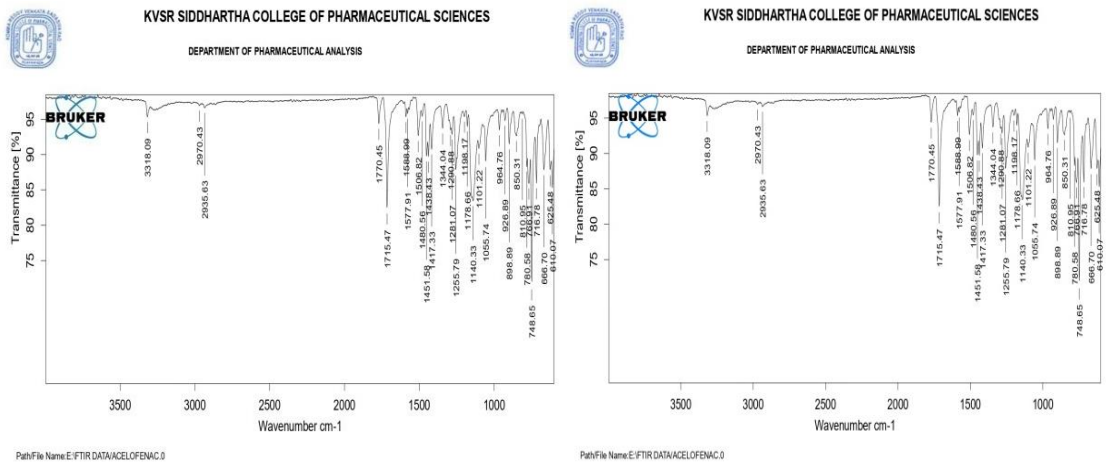

Fig. 3: FT-IR spectra of pure aceclofenac and its formulation

Table 5: Selection of surfactant mix

Surfactant	Concentration ratio	Appearance
Span80-PEG400	04:01	cloudy
	02:03	cloudy
	03:02	Clear
	01:04	Clear
Tween80-PEG400	04:01	Cloudy
	02:03	Cloudy
	03:02	Clear
	01:04	Clear

Table 6: Pre-compression studies and evaluation of core tablets (S1C1-S1C6 and S2C1 to S2C6)

Code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner' s ratio	Carr's index (%)	Angle of repose (°)	Disintegration time (sec)	Drug content
S1C1	0.53±0.02	0.61±0.02	1.15±0.11	13.48±0.11	23.97±0.24	95±2	100.2±1.2
S1C2	0.51±0.04	0.60±0.04	1.17±0.12	15.38±0.12	24.08±0.26	96±3	98.86 ±0.5
S1C3	0.50±0.02	0.59±0.04	1.17±0.01	14.68±0.16	25.29±0.28	98±2	100.8±0.8
S1C4	0.56±0.03	0.63±0.05	1.12±0.08	11.57±0.12	24.24±0.18	95±4	99.26± 0.6
S1C5	0.45±0.02	0.53±0.04	1.17±0.11	14.3±0.08	26.02±0.36	98±2	98.28±0.2
S1C6	0.46±0.01	0.54±0.01	1.16±0.12	14.09±0.12	27.12±0.35	95±4	97.78±0.3
S2C1	0.49±0.03	0.57±0.02	1.14±0.11	12.85±0.22	26.05±0.24	98±2	99.52±0.6
S2C2	0.50±0.02	0.58±0.03	1.15±0.12	13.21±0.24	25.45±0.20	95±4	99.26 ±0.5
S2C3	0.52±0.04	0.60±0.02	1.15±0.10	13.32±0.20	25.07±0.24	96±4	98.26 ±0.8
S2C4	0.52±0.04	0.59±0.02	1.12±0.12	11.66±0.22	25.12±0.25	94±3	97.62 ±0.24
S2C5	0.48±0.02	0.58±0.04	1.16±0.13	12.24±0.24	26.54±0.26	97±2	98.28±0.3
S2C6	0.52±0.01	0.56±0.02	1.14±0.14	13.22±0.20	25.28±0.24	98±2	97.98±0.4

Data are expressed as mean±SD, n=3

Table 7: Characterization of tablets

Code	Weight variation	Hardness (kg/cm³)	Friability%	Thickness (mm)
S1C1	200.97±0.22	3.83±0.08	0.71±0.03	3.56±0.22
S1C2	201.78±0.12	3.92±0.12	0.41±0.02	3.43±0.20
S1C3	201.77±0.32	3.96±0.06	0.53±0.03	3.2±0.16
S1C4	200.86±0.25	3.73±0.08	0.83±0.05	3.53±0.18
S1C5	201.09±0.32	3.86±0.10	0.71±0.01	3.46±0.12
S1C6	202.19±0.33	3.96±0.11	0.31±0.02	3.56±0.16
S2C1	198.02±0.24	3.90±0.12	0.42±0.03	3.36±0.15
S2C2	201.33±0.42	3.86±0.14	0.71±0.04	3.5±0.13
S2C3	203.12±0.21	3.96±0.08	0.39±0.02	3.53±0.22
S2C4	200.86±0.36	3.82±0.10	0.48±0.02	3.44±0.26
S2C5	199.28±0.25	3.86±0.12	0.26±0.06	3.48 ±0.18
S2C6	500.44±0.42	3.54±0.22	0.32±0.03	3.52±0.11
F1	501.27±0.33	3.83±0.06	0.71±0.01	5.56±0.12
F2	500.86±0.25	3.92±0.04	0.41±0.02	5.43±0.24
F3	501.09±0.36	3.96±0.06	0.53±0.04	5.2±0.23
F4	502.19±0.33	3.73±0.12	0.83±0.04	5.53±0.12
F5	498.02±0.22	3.86±0.14	0.71±0.02	5.46±0.11
F6	501.33±0.16	3.96±0.14	0.31±0.06	5.56±0.10
F7	503.12±0.18	3.90±0.11	0.42±0.02	5.36±0.14
F8	500.86±0.22	3.86±0.06	0.71±0.04	5.5±0.18
F9	499.28±0.26	3.96±0.08	0.39±0.06	5.53±0.10

Data are expressed as mean±SD, n=3

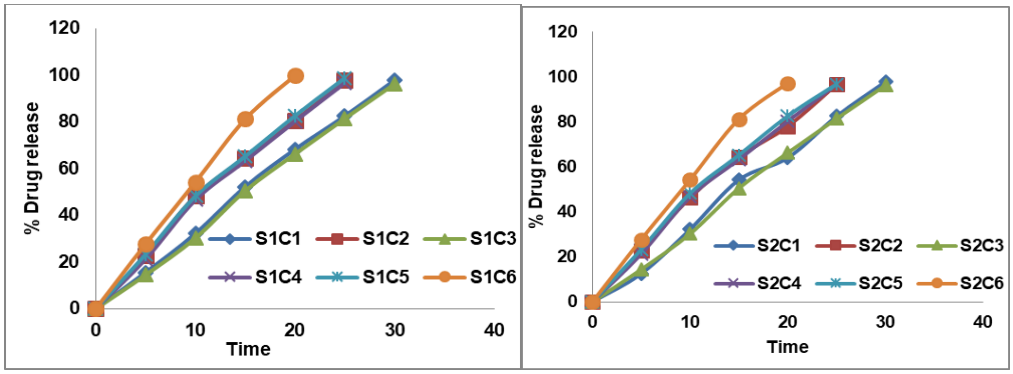

Fig. 4: *In vitro* drug release of formulations S1C1-S1C6 and S2C1 –S2C6

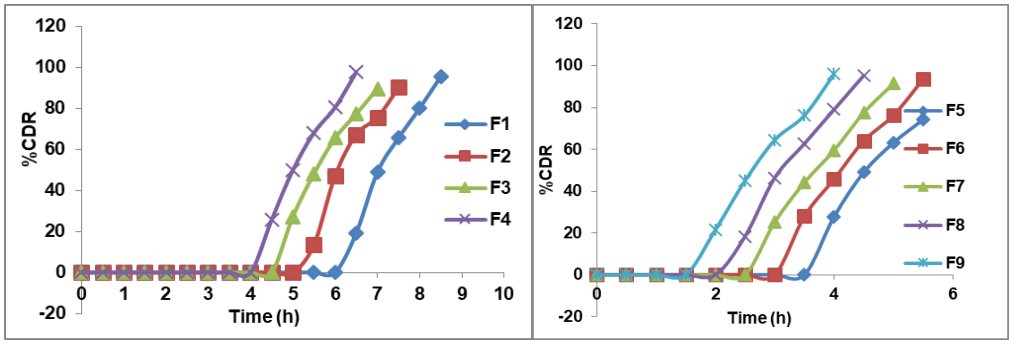

Fig. 5: *In vitro* drug release of formulations (F1-F9)

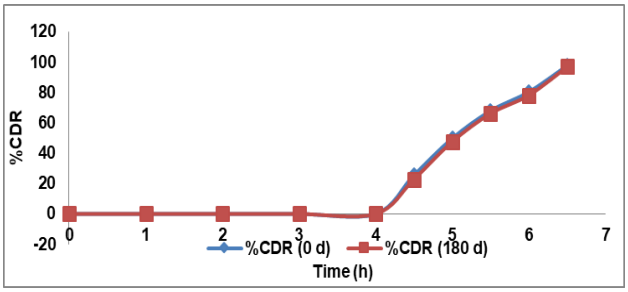

Fig. 6: Stability studies of optimized formulation

DISCUSSION

AF drug was primarily identified by FTIR, which shows that possible identified spectral peaks of AF both in its pure drug form and in its formulation. Melting point was found to be 150 °C. Solubility of AF was carried out using different solvents like Water, pH6.8 phosphate buffer, methanol, 0.1N HCl, acetic acid as shown in the table 4. Poor solubility of AF was observed by D. N. CP *et al.* [28]. The solubility studies in different oils helps in selection of oil. From the given table of values oleic acid was selected as oil phase. Calibration of AF was done in ph 6.8 buffer and was shown in fig. 1. From the data obtained from table 5, the surfactant mixtures $S_{mix}1$, and S_{mix} 2 were selected by the selection of oleic acid water titration method was used to construct ternary phase diagram which were shown in fig. 2. The suitability of Self emulsifying systems in colon-targeted pulsatile therapy is discussed by Zhang, L, and his co-workers [29]. Ternary phase diagrams have excellent role in enhancement of solubility, which was here developed to prepare burst-release core tablet. In both the diagram the dark portion revealed the composition of oil, surfactant and cosurfactant compositions for SEDDS. With the help of suitable adsorbents, this self-emulsified AF is converted into solid SEDDS. The obtained powdered blend was evaluated for bulk density; tapped density, angle of repose, Hausner's ratio, compressibility index, and the results are shown in table 6.

Bijapuri Srivastava *et al.* developed solid self-emulsified systems of AF with different combinations of oil, surfactant and co-surfactant mixtures. In the present study S1C1 to S1C6, and S2C1 TO S2C6 were formulated as solid SEDDS. [30] *In vitro* release profiles of prepared burst-release core tablets during 30 min studies were found to have very good drug release. In the formulated tablets, all the formulations show the drug release within 30 min. But in the formulation, S1C1 to S1C6 Containing $S_{mix}1$ composition, and among them, S1C6 releases the maximum amount of drug, 98.88% in 20 min. Results of *in vitro* by study revealed that AF solubility was enhanced, and superdisintegrants SSG also help in drug release within 20 min. From S2C1 to S2C6, the formulation S2C6 containing $S_{mix}2$ composition will release the maximum amount of drug, 96.45%, in 20 min. Both $S_{mix}1$ and $S_{mix}2$ were successful in developing the burst release core formulations of AF with the drug release within 20 min. by using the optimised S1C6 formulation as the core tablet, compression-coated formulations F1 to F9 were prepared. In the coat formulations both HPMCK100 and ethyl cellulose play an important role in the delay of drug release. Rashid R *et al.* were worked and succeeded in developing core and coat tablets with suitable lag time [31]. Matrix formed with the combination of these polymers helps to obtain suitable lag-time. These values can be represented in fig. 5. HPMCK100, with its swelling nature along with insoluble ethylcellulose will help in obtaining a suitable lag-time of 4 h. Among all the formulations, F4 shows maximum drug release of 97.23% at the end of 6^{th} h.

The release profile of the compression-coated tablet exhibited lag time followed by burst release, in which the outer shell broke into two halves. Release of drugs from the compression-coated tablet follows two consecutive steps: 1) penetration of dissolution media into the compressed-coated tablet 2) swelling or erosion by hydrophilic and hydrophobic polymers such as HPMCK100 and ethyl cellulose, respectively. The release kinetics profile of AF tablets was found to obey zero-order kinetics ($R^2$of 0.988) and with Higuchi kinetics (R^2 of 0.997). Stability testing findings indicate that formulation was stable for a period of 3 mo with 98% drug release with suitable lag-time and are represented in fig. 6.

CONCLUSION

The present study was aimed at formulating a dosage form to successfully deliver AF and to provide relief from early morning rheumatoid arthritis symptoms. This can be achieved by designing a pulsatile chronopharmaceutical formulation. The formulation has to be taken as after a meal timed pulsatile release tablet with delayed "burst" release will attenuate pain in the morning. This will provide an ideal therapeutic regimen with enhanced patient compliance. In the present work, pulsatile tablets of AF were prepared by direct compression of self-emulsified AF with different superdisintegrants and press-coated barrier polymers like HPMC K100 and Ethyl Cellulose. This technique can be successfully used in the development of time-lagged press-coated formulations based on rupturable (ethyl cellulose) and erodable, swellable (HPMC K100) polymers to achieve the desired pulsatile release profile after a programmed lag time. The formulations were subjected to different evaluation parameters. The formulation F4 was optimised out of all nine formulations due to its higher % of drug release and desired lagtime, the formulation F4 showed 97.23% at 6^{th} h. Hence, considering the drug release rate and according to the biological rhythm of the body. At this time, F4 formulation also starts releasing the drug and exhibits its therapeutic effect.

ACKNOWLEDGEMENT

The authors would like to acknowledge Pure Chem. Pvt Ltd, Gujarat for providing gift sample of Aceclofenac and KVSR Siddhardha College of Pharmaceutical Sciences, Vijayawada for carrying out spectral analysis studies. The authors would also like to acknowledge Krishna University, Machilipatnam, Jawaharlal Nehru Technological University, Kakinada, and Vikas College of Pharmacy, AP, India, for providing a facility for experimentations.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

This study was done in collaboration with all authors PJ, Research scholar of Krishna University, designed this study. PJ, AB, and DRR participated in the conduct of the study. PJ, AB, and DRR analyzed the data. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS

Declared none

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