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Design, development and evaluation of diacerein sustained release matrix tablets

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This work aims at investigating the use of hydroxy propyl methyl cellulose (HPMC) polymer to formulate sustained release matrix tablets containing diacerein. The sustained release tablets of diacerein were prepared by wet granulation method using HPMC as a release retarding polymer. Various kinetic models were applied to interpret the release of drug from the matrix system. A complete cross over bioavailability study of the developed sustained and immediate release tablets was carried out in rabbits to prove the safety and efficacy of the formulation. The release of the drug from tablets showed non-fickian diffusion obeying first order kinetics. The pharmacokinetic parameters such as $AUC_{o-\infty}$ value were 20.449±8.83 and 13.479 6.31 µg/h/ml, C_{max} values were 2.22±1.15 and 3.30±0.02 µg/ml, t_{max} values were 4±0.69 and 2±0.24 h and mean plasma elimination half life ($t_{½}$) were 0.145±0.03 and 0.294±0.07 h, respectively, for the developed sustained and immediate release tablets of diacerein. The extent of absorption of drug from the developed diacerein sustained release tablets was significantly higher than that for developed diacerein tablets due to lower elimination rate and longer half-life.

Key words: Diacerein, hydroxy propyl methyl cellulose (HPMC), hydrophilic matrix, bioavailability.

INTRODUCTION

Increased complications and expenses incurred in marketing of new drug entities, has focused greater attention on the development of sustained release (SR) or controlled release drug delivery systems (Salsa et al., 1997). Among these delivery systems, matrix system is the most widely employed in the development of sustained release formulation. In fact, a matrix is defined as a composite of one or more drugs with a gelling agent such as hydrophilic polymer (Reza et al., 2003). They can be used for the development of controlled release of both water soluble and water insoluble drugs. The release behavior of the drugs varies with the nature of the matrix and it is the complex interaction of swelling, diffusion and erosion process (Colombo et al., 1995). Release of drugs from such matrices is governed by their physical properties, choice of gelling agent and setting up the conditions for fabrication (Vazquez et al., 1992).

Among hydrophilic polymers, hydroxy propyl methyl cellulose (HPMC) is a semi synthetic hydrophilic polymer widely used in SR dosage forms, due to its non toxicity, capacity to accommodate high levels of drug loading and non-pH dependence (Siepmann et al., 2000). HPMC was

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found to be a versatile material for the formulation of soluble matrix tablets. It is widely accepted as a pharmaceutical excipient and included in all major compendia. Owing to its wide range of molecular weight, effective control of gel viscosity is easily provided.

Diacerein is used in the treatment of osteoarthritis (Spencer et al., 1997) and it is characterized by rapid clearance due to shorter half-life, and thus warrants the use of sustained release formulation for prolonged action to improve the patient compliance. At present, there are no sustained release systems are available for diacerein, hence the purpose of our present study was to investigate the *in vitro* and *in vivo* performance of compressed matrix tablets prepared by granulating hydrophilic polymeric substance such as HPMC-K-100-CR, using poly vinyl pyrrolidine in isopropyl alcohol as granulating medium to produce a sustained release dosage form containing diacerein.

MATERIALS AND METHODS

Diacerein was obtained as a gift sample from Arihanthanam Organics Ltd., Vapi, Gujarat, India. HPMC (Methocel-K100-CR, apparent viscosity, 2% in water at 20°C is 80, 000 – 1,20,000 cP) was obtained as gift sample from Hetero Drugs Ltd., Andhra Pradesh, India. Microcrystalline cellulose (Avicel PH 101) was a gift from Signet Chemicals, Mumbai. Poly vinyl pyrrolidine (PVP-K-30) was a gift from Anshul Agencies (Mumbai, India). Magnesium stearate and talc were procured from S.D. Fine Chemicals, Mumbai. All other chemicals used in the study were of analytical or HPLC grade.

Drug-Excipients interactions

The physicochemical compatibilities of the drug and excipients were tested by Fourier transform-infrared (FT-IR) spectrometry and differential scanning calorimetry (DSC). FT-IR spectra and DSC thermograms of the drug alone and drug-excipient physical mixtures (1:1 w/w) were derived from a Shimadzu FT-IR 8400 and TA Instruments Differential Scanning Calorimeter Q200, respectively.

Development of diacerein immediate release (IR) tablets

Diacerein IR tablets were prepared by the wet granulation method. All the ingredients, with the exception of magnesium stearate and talc were mixed in a tumbling mixer for 5 min and wetted in a mortar separately using poly vinyl pyrrolidine (PVP K-30) in isopropyl alcohol as granulating fluid. The wet mass was passed manually through British standard sieve (BSS) with a 1.7 mm (sieve no 10) opening and granules were dried at 60°C for 3 to 4 h until the loss on drying not more than 2% w/w was obtained. The dried granules were passed through BSS 1.0 mm (sieve no. 16). The granules were blended with magnesium stearate and talc (2:1). The blends were compressed using 5 mm concave punches on a 10 station rotary tablet press (Rimek, Ahmedabad, India) and the compression force of a 9 KN (preliminary work) or 12 KN (experimental design), was kept for all the formulations. For the preliminary work, a batch of 50 tablets were prepared (drug content in the tablet was 7 mg). The composition of diacerein immediate release tablets are given in Table 1.

Development of diacerein sustained release (SR) tablets

Sustained release matrix tablets of diacerein were prepared by the wet granulation method. All the composition, with the exception of magnesium stearate and talc were mixed in a tumbling mixer for 5 min using poly vinyl pyrrolidine (PVP K-30) in isopropyl alcohol as granulating fluid. The wet mass was sieved (16 mesh) and granules were dried at 60°C for 3 to 4 h until the loss on drying not more than 2% w/w was obtained. The dried granules were sieved (22 mesh) and these granules were lubricated with a mixture of magnesium stearate and talc (2:1). The dried granules were passed through BSS 1.0 mm. The granules were blended with magnesium stearate and talc (2:1). The blends were compressed using 5 mm concave punches on a 10 station rotary tablet press (Rimek, Ahmedabad, India) and the compression force of a 9 KN (preliminary work) or 12 KN (experimental design) was kept for all the formulations. For the preliminary work, batches of 50 tablets were prepared (drug content in the tablet was 7 mg). The composition of different batches of diacerein sustained release tablets are shown in Table 1.

Evaluation of granules

The granules were evaluated for angle of repose (Cooper et al., 1986), bulk density (Shah et al., 1997), compressibility index (Aulton et al., 1988), and Hausner's factor (Lachman et al., 1987) using USP tapped density tester.

Evaluation of tablets

The thickness (Digital slide calipers, Mitutoyo, Japan), weight variation (Sartorius AG, Goettingen, Germany), hardness (Cadmach machineres, Ahmedabad, India), friability (Friability testing apparatus, Electrolab, Mumbai, India), drug content and *in vitro* drug release of the formulated tablets were evaluated.

Drug content

Five tablets from each formulation were weighed individually and powder equivalent to 3.5 mg of diacerein for immediate release tablets and 7 mg of diacerein for sustained release tablets was extracted with 100 ml of phosphate buffer (pH 6.8) and sonicated for 15 min. The solution was filtered through a filter paper (Whatmann, 0.22 µm pore size), diluted with the same buffer and the drug content was measured at 254 nm using HPLC (Waters Ltd, Mumbai). The HPLC equipment consisted of waters liquid chromatographic system and column C_{18} (250 × 4.6 mm, i.d 5 µ) was used at the flow rate of 0.8 ml/min with detection wavelength set at 325 nm for satisfactory separation. The mobile phase consisting of phosphate buffer pH 3: acetonitrile (55:45 v/v). The internal standard used was aspirin. The retention times of diacerein and aspirin were 3.3 and 5.6 min, respectively. The linearity for diacerein is 0.3 to 6.0 µg/ml. The validation was carried out as per ICH guidelines.

In vitro release studies

Dissolution studies for the developed immediate release tablets and sustained release tablets were performed in a dissolution media consisting of 900 ml of phosphate buffer pH of 6.8, 900 ml of phosphate buffer pH of 6.8 containing 0.03% (w/v) sodium lauryl sulfate maintained at 37±0.5°C and stirred at 50 rpm, using USP dissolution apparatus under perfect sink conditions (Electrolab, Mumbai, India). 5 ml of sample was withdrawn through a 0.45 µm filter and replaced with another 5 ml of a suitable fresh dissolution

Table 1. Composition of diacerein immediate and sustained release tablets.

Fa	Diacerein (mg)	Lactose (mg)	Croscarmellose sodium (mg)	HPMC (mg)	MCC (mg)	PVP-K-30 (mg)	Magnesium stearate (mg)	Talc (mg)	Total weight (mg)
IR	3.5	58.8	2.1	-	-	3.5	1.4	0.7	70
F_1	7.0	-	-	3.5	53.9	3.5	1.4	0.7	70
F_2	7.0	-	-	3.5	50.4	3.5	1.4	0.7	70
F_3	7.0	-	-	10.5	46.9	3.5	1.4	0.7	70
F_4	7.0	-	-	14.0	43.4	3.5	1.4	0.7	70
F_5	7.0	-	-	39.9	39.9	3.5	1.4	0.7	

Fa: Code of formulations; IR: Developed immediate release tablets; F_1: 5% of HPMC; F_2: 10% of HPMC; F_3: 15% of HPMC; F_4: 20% of HPMC; F_5: 25% of HPMC - Developed sustained release tablets with varying concentrations of polymer.

medium maintained under the same conditions at preselected intervals up to 24 h. The amount of the drug was determined by optimized HPLC conditions. Each test was conducted in triplicate (6 tablets in set) and the mean values were plotted against time with standard deviation of less than 3, indicating the reproducibility of the results.

Release kinetics

The *in vitro* drug release profiles were plotted according to zero order, first order, mean dissolution time (MDT), Higuchi and Peppas equations to understand the mechanism of drug release and compared the differences in the release profile of different batches of matrix tablets.

Bioavailability studies

A randomized, two treatment, two period, two sequence, single dose cross over bioavailability study was carried out for the developed immediate release tablets (reference product) containing 3.5 mg of diacerein and developed sustained release tablets (test product) containing 7 mg of diacerein was carried out in 6 healthy albino rabbits weighing 2.0 to 2.5 kg to prove the safety and efficacy of the formulations.

The protocol of the study was approved by the institutional animal ethics committee. Healthy albino male rabbits were obtained in individual cages for 30 days prior to the study in the departmental animal house for the purpose of acclimatization. A zero hour fasting blood samples were withdrawn early in the morning. The animals were divided into three groups. The doses of the drug for the rabbit were calculated on the basis of body surface area ratio of rabbit with respect to human. Group 1 (3 animals) received sustained release tablets (7 mg), group 2 (3 animals) received in house developed immediate release tablets (3.5 mg), and group 3 (3 animals as control). The tablets were administered to animals with 5 ml of water through oesophagal tube.

Blood samples (0.5 ml) was withdrawn from the marginal ear vein at predetermined time intervals of 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18 and 24 h using a disposable syringe. The blood samples were collected in the RIA vial containing an anticoagulant (100 µl of 11% sodium citrate) and centrifuged at 4000 rpm for 4 min to separate the plasma. The plasma samples were deprotinised by mixing equal volume of 10% perchloric acid and the contents were vortexed for 2 min. It was centrifuged at 4000 rpm for 4 min to separate the supernatent liquid. Estimation of drug in the plasma was carried out by optimized HPLC conditions. A reproducible analytical technique was developed for the estimation of drug in the plasma samples. Various pharmacokinetic parameters such as C_{max}, T_{max}, $t_{½}$, K_{el}, AUC_{o-t} and $AUC_{o-\alpha}$ were estimated using Winnonlin software.

Statistical analysis

Statistical analysis was performed using SPSS version 13.0. The pharmacokinetic parameters like C_{max}, T_{max}, $t_{½}$, K_{el}, AUC_{o-t} and $AUC_{o-\alpha}$ of the developed formulations are presented in mean ± standard deviation (SD). One way analysis of variance (ANOVA) was employed in the statistical analysis of the determined parameters in this study. Statistical significance was defined at $p<0.05$.

RESULTS AND DISCUSSION

The characteristic IR peaks for diacerein at 1770 cm^{-1} (C=O), 2916 cm^{-1} (C-H) and 2500 to 3000 cm^{-1} (COOH) were found to appear in the drug with polymer. It was found that the characteristic peaks of physical mixture of drug with HPMC polymer or other excipients reflected the characteristic features of diacerein alone indicating there was no evidence of interaction between diacerein and the used excipients.

The DSC analysis of drug alone elicited an endothermic peak at 224°C, which is very close to its reported melting point 218°C, where as pure HPMC exhibited endothermic peak at 77.91°C. No significant melting point changes were noted with the drug polymer mixture. Thus, it was thought to indicate the absence of chemical interaction between the selected drug and polymer.

The prepared powders were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), Carr's compressibility index and Hausner's Factor (HF). The angle of repose values of prepared powders ranged from 26.05°± 0.50 to 36.57°± 1.32. HF values of the prepared powders ranged from 1.23 to 1.38. The percentage compressibility, an indirect method of measuring powder flowability from bulk densities indicated that powders exhibited good flow ability and compressibility. The thickness of the prepared tablets ranged from 2.95 ± 0.03 mm to 3.15 ± 0.005 mm.

It was observed that increasing the polymer concentrations

Table 2. Regression coefficient (r^2) of according to different kinetic models and diffusion exponent (n) of Peppas model.

Fa	Zero Order	First Order (r^2)	Higuchi (r^2)	Peppas	
	r^2	r^2	r^2	n	r^2
F_3	0.7328	0.9808	0.9382	0.519	0.9649

Fa: Code of formulations.

Table 3. Mean pharmacokinetic profile of developed immediate and sustained release diacerein tablets.

Pharmacokinetic parameter	Type of formulation	
	Developed diacerein immediate release tablets	Developed diacerein sustained release tablets
C_{max}	3.30±0.02	2.22±1.15†
T_{max}	2.00±0.24	4.00±0.69‡
AUC_{o-t}	13.072±28.37	19.485±22.72‡
$T_{1/2}$	2.35±0.09	19.485±22.72‡
K_{el}	0.294±0.07	0.145±0.03†
$AUC_{0-\alpha}$	13.479±6.31	0.145±0.03†

‡Significantly higher than IR tablets ($p<0.05$). †Significantly lower than IR tablets ($p<0.05$). Values are Mean ± SD, n=6.

concentrations resulted in no alteration in the thickness of the tablets. The friability of the developed immediate and sustained release tablets fell into the range of 0.428 ± 0.16 to 0.587 ± 0.05%, respectively. Hardness of the prepared tablets fell into the range of 4.00 ± 0.03 to 4.00 ± 0.04 kg/cm^2 for the developed immediate release and sustained release tablets, respectively. These results also revealed that the increasing polymer concentration does not alter the hardness of the tablet significantly.

The *in vitro* release profile of diacerein from the developed immediate and sustained release tablets were carried out. Generally, the drug release rates from the developed sustained release tablets were significantly retarded when compared with the developed IR tablets. It is noted that a drug release rate from HPMC based matrix tablets decreased with an increase in the polymer level. This effect might be ascribed to an increase in the extent of gel formation in the diffusion layer and better mechanical properties of HPMC polymer. Among the prepared batches of formulations (IR and SR), the batch (F_3 of 15% of HPMC) has showed desirable *in vitro* release profile over 24 h (Figure 1).

The values of release exponent (n), kinetic constant (k), and mean dissolution time (MDT) are shown in Table 2. Irrespective of polymer level, the prepared hydrophilic tablet formulations exhibited non-fickian release, $0.5<n<0.89$. Thus, it was proposed that the formulations delivered their active compound by coupled diffusion and erosion (Figures 2 and 3).

The relative bioavailability of the developed diacerein sustained release tablets 7 mg (F_3) was compared with developed diacerein immediate release tablets 3.5 mg. The developed sustained release tablets produced a plasma concentration time profile typical of the prolonged dissolution characteristic of a sustained release formulation as evident from Figure 4 and Table 3. The developed sustained release tablets demonstrated a longer time to reach a peak concentration than the developed immediate release tablets and appeared to be more consistent in overall performance. There was a significant difference in the extent of absorption as assessed by measurements of AUC_{o-t}. However, $AUC_{o-\alpha}$ value for the developed sustained release tablets was 1.82 times higher than the developed IR tablets indicating more efficient and sustained drug delivery, which would maintain plasma diacerein levels better. This was also evident by the lower elimination rate (1.29 times lesser than the developed immediate release tablets) and higher $t_{½}$ values (1.32 times more than the developed immediate release tablets). The pharmacokinetic parameters of the two different developed formulations of diacerein were compared statistically by one way ANOVA using SPSS version 13.0. The pharmacokinetic parameters such as C_{max}, T_{max}, $t_{½}$, K_{el}, AUC_{o-t} and $AUC_{o-\alpha}$ of the developed immediate release and sustained release formulations of diacerein were found to be significantly different ($p<0.05$) by one way ANOVA.

Conclusion

The developed sustained release tablets of diacerein

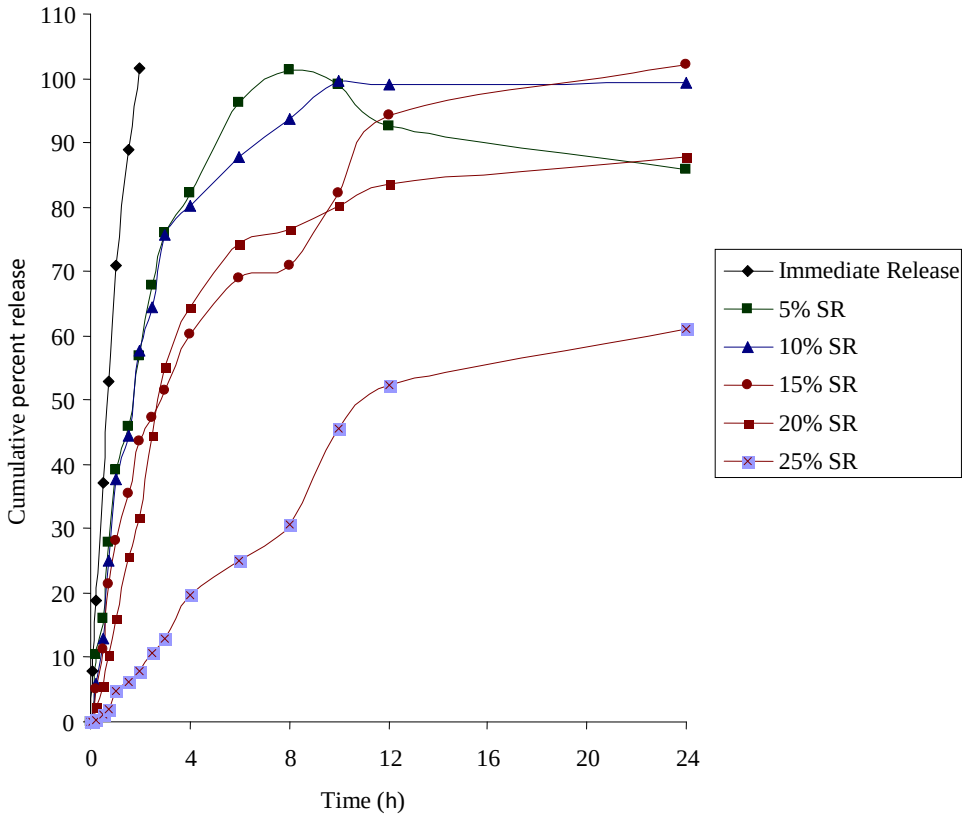

Figure 1. *In vitro* release profile of developed immediate release and developed sustained release (SR) diacerein tablets; F-1: 5% of HPMC, F-2: 10% of HPMC, F-3: 15% of HPMC, F-4: 20% of HPMC, F-5: 25% of HPMC.

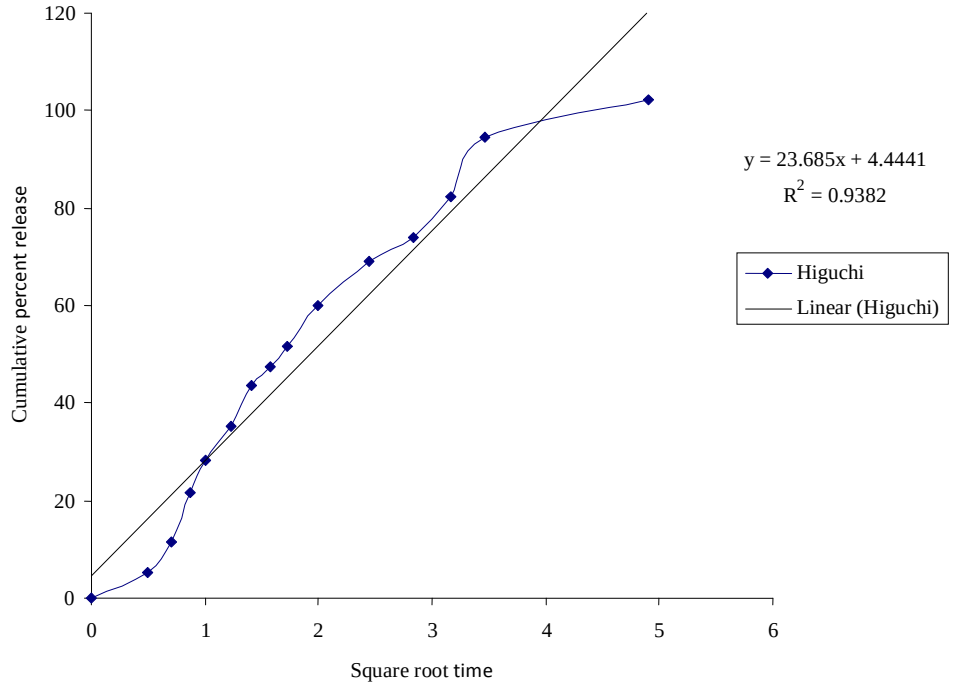

Figure 2. Higuchi's plot for developed sustained release diacerein tablets (F_3).

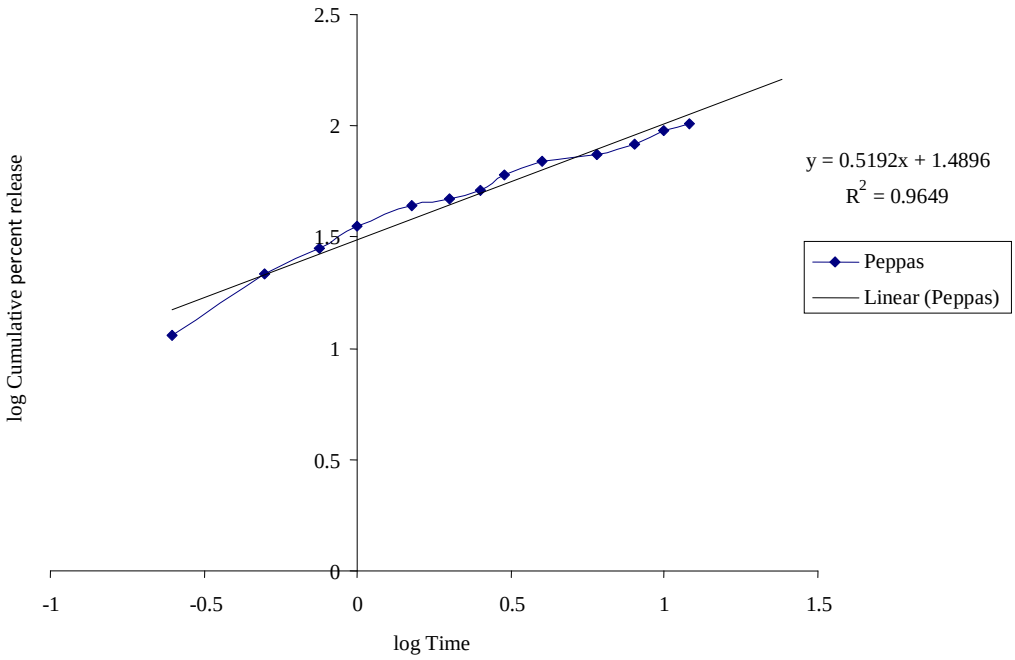

Figure 3. Peppas plot for developed sustained release diacerein tablets (F_3).

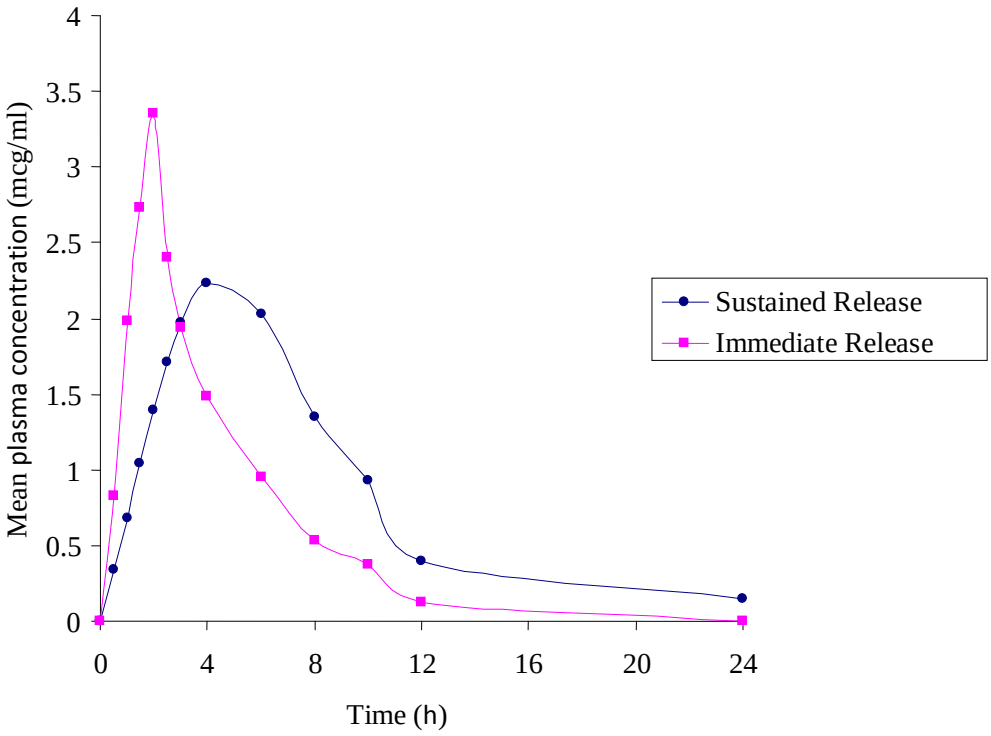

Figure 4. Mean plasma concentrations (ng/ml) for developed diacerein immediate release (♦) and sustained release tablets (F_3-■).

were well absorbed and the extent of absorption was higher than that of the developed immediate release tablets. The sustained release and efficient drug delivery system developed in the present study will maintain

plasma levels better, which will overcome the draw backs associated with the conventional therapy. However, bioavailability studies employing human volunteers needed to be carried out to establish its potential effect.

Conflict of interest

The author(s) declare(s) that they have no conflicts of interest to disclose.

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