ORIGINAL ARTICLE

Formulation optimization and evaluation of aceclofenac sustained release dosage form based on Kollidon sustained release

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Sustained release aceclofenac matrix tablets constituting Kollidon sustained release (KSR) (polyvinyl acetate and povidone-based matrix retarding polymer) were developed in this study in an attempt to design a dosage form that manifests desirable release profile and thorough adherence to official monographs. Nine matrix tablet formulations were prepared by dry blending and direct compression method by varying the proportion of KSR and compression load with fixed percentage of aceclofenac. Among this, by comparing response variables of the prepared formulations with that of the marketed product, two formulations (KSR5 and KSR7) were chosen as the optimized formulations. The formulation showed close resemblance to commercial products and compliance with United States Pharmacopoeia USP specification. The exponential model was applied to characterize the drug release behavior from polymeric systems. It was found that non-Fickian release is predominant in tablets containing KSR with a trend toward zero-order kinetics. The study also involves *in vivo* evaluation of the optimized formulations to find out relevant pharmacokinetic parameters. Correlation of *in vitro* drug release with that of amount of drug absorbed *in vivo* has also been performed.

Key words: *Aceclofenac, dosage form, Kollidon, sustained release*

INTRODUCTION

The most conventional and important method of administering drugs for systemic effect is the oral route. Solid dosage forms are the most commonly used and preferred class for orally administered drugs. Among the solid dosage forms, tablets are the first choice. Provided the dose size and frequency of administration are correct, therapeutic steady state plasma concentrations of a drug can be achieved promptly and correctly by the repetitive administration of conventional per oral dosage forms.[1] Controlled release technology evolved with matrix technology. Several articles in the 1960s reported simple matrix tablets or monolithic granules. In 1952, a timed release formulation was developed by Smith Kline and French that launched a wide spread search for other applications in the design of dosage forms.[2] Matrix tablets are the sensible choice for sustained release tablets. There has been a quest in the research community to develop a cost-effective, cheap excipient for controlling the release of drugs from such type of sustained release tablets. In this context, Kollidon (polyvinyl acetate (PVAc)/polyvinyl pyrrolidone (PVP) co-polymer) seems to be a good candidate for controlling drug release.

Kollidon sustained release (KSR) is one of the recently developed matrix-forming agents with plastic behavior. Chemically, KSR is PVAc and PVP-based matrix retarding agent particularly suitable for the manufacture of pH-independent sustained release matrix tablets.[3-5] PVAc is a plastic material that can form a coherent mass even under low compression

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force. When the tablets prepared with KSR are introduced into gastric or intestinal fluid, the water-soluble PVP is leached out to form pores through which the active ingredients slowly diffuse outward in a controlled and pre-determined fashion.[6] KSR is normally inert to the drug molecule since it does not contain an ionic group. KSR has got high flow ability, low reposition angle, and excellent compressibility characteristics. These characteristics help to develop tablets with the desired hardness and low friability, at the same time reducing the process variables and processing cost.[7] This experiment was aimed to develop sustained release aceclofenac tablets with a suitable release profile using KSR as matrix former that also complies with pharmacopeial specifications. Fixed amount of aceclofenac was used in all the experimental batches while the amount of KSR was decreased gradually and the reduced amount of KSR was replaced by microcrystalline cellulose to modulate the drug release pattern. Along with the experimental batches, dissolution profile of marketed product HifenacSR (Intas Pharmaceutical Ltd, Ahmedabad, India) was also investigated for comparison and modulation purpose of the proposed formulations. The objective of the present study was to investigate the possible use of KSR in directly compressed matrix tablets. Drug release kinetics has also been examined in this study to investigate the release characteristics of aceclofenac from KSR matrix tablets with the help of an exponential model.

MATERIALS AND METHODS

Materials

Aceclofenac was a kind gift from Aarti Drugs Ltd., Mumbai, India. KSR was used as received from BASF Mumbai Ltd. Microcrystalline cellulose was obtained from JRS Pharma India. Aerosol (Silicon dioxide) and magnesium stearate was from Degussa, Germany. Potassium dihydrogen orthophosphate, sodium hydroxide, trichloro acetic acid, and hydrochloric acid were purchased from Merck AG, UK.

Preparation of aceclofenac matrix tablets using Kollidon SR

A 3^2 full-factorial design[8-10] was employed for the optimization of sustained release tablets of aceclofenac using KSR. The total weight was fixed as 700 mg. Each tablet contained 200 mg of aceclofenac. The independent variable factors selected were the compression load and the quantity of KSR in the formulation. The dependent variables selected were the cumulative % drug release after 6 h (R6), 12 h (R12), 24 h (R24), similarity factor (f_2), and time taken to release 50% of the drug (t_{50}). Pre-optimization studies were carried out before choosing the level of each independent factor. The design of matrix for the optimization of the tablet formulation was as shown in Table 1.

Microcrystalline cellulose MCC was added to the formulations in required quantity to adjust the tablet weight to 700 mg. Ingredients were passed through a No. 44 sieve, mixed by geometric dilution and mixed in a mortar for 15 min. Then, the powdered mixture was compressed using a Cadmach 16 station rotary tablet press with 13 mm diameter round-shaped flat punches. 1% Magnesium stearate and 0.5% aerosil were used in the formulation as lubricant. The drug release profiles from the prepared tablets were determined by *in vitro* dissolution study. The formulation with the highest similarity factor was chosen as the optimized formulation. The tablet formulations were coded as KSR1-KSR9.

Dissolution studies

In vitro drug release studies from the prepared matrix tablets were conducted for a period of 24 h using a six-station USP XXII type I apparatus at 37 ± 0.5°C and 50 rpm speed. The dissolution studies were carried out in triplicate for 24 h (initial 2 h in simulated gastric fluid and rest 22 h in phosphate buffer of pH 7.4). At every 1-h interval, samples of 10 ml were withdrawn from the dissolution medium and replaced with fresh dissolution medium to maintain the a constant volume. After filtration and appropriate dilution, the sample solution was analyzed for aceclofenac by a UV spectrophotometer at 276 nm (Jasco, Japan). The amount of drug present in the samples was calculated with the help of appropriate calibration curves constructed from aceclofenac reference standards. Drug dissolved at specified time periods was plotted as percentage release versus time (hour) curve.

Kinetics of drug release

To study the release kinetics, data obtained from the *in vitro* drug release studies is plotted in various kinetic models: Zero-order[11-13] (Eq. 1) as cumulative amount of drug released versus time, first-order[11-13] (Eq. 2) as log cumulative percentage drug remaining versus time, and Higuchi's model[14-16] (Eq. 3) as cumulative percentage of drug released versus square root of time.

$$C = K_0 t \quad (1)$$

where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of

Table 1: Design of matrix for the optimization of the tablet formulation

Code	Polymer content per tablet (%)	Compression load (ton)
KSR1	35	3
KSR2	35	4
KSR3	35	5
KSR4	40	3
KSR5	40	4
KSR6	40	5
KSR7	45	3
KSR8	45	4
KSR9	45	5

KSR: Kollidon sustained release

concentration versus time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$$\log C = \log C_0 - kt/2.303 \quad (2)$$

where C_0 is the initial concentration of drug, k is the first-order constant, and t is the time.

$$Q = Kt^{1/2} \quad (3)$$

where K is the constant reflecting the design variables of the system and t is the time in hours. Q is the drug release.

To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets, the data are also plotted using Hixson–Crowell cube root law.[12,17,18]

$$3\sqrt{Q_0} - 3\sqrt{Q_t} = K_{HC} \times t \quad (4)$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in the tablet and K_{HC} is the rate constant for the Hixson–Crowell rate equation, as the cube root of the percentage of drug remaining in the matrix versus time.

Mechanism of drug release

To evaluate the mechanism of drug release from the optimized tablet formulations, data for first 60% of drug release is plotted in Korsmeyer *et al*.'s equation as the log cumulative percentage of drug released versus log time, and the exponent n is calculated through the slope of the straight line portion of the curve.[11,13,17,18]

$$M_t/M_\infty = Kt^n \quad (5)$$

Where M_t/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of drug release.

A value of $n \leq 0.45$ indicates case-I (Fickian) diffusion or square root of time kinetics, $0.45 < n < 1$ anomalous (non-Fickian) diffusion, $n = 1$ case-II transport and $n > 1$super case-II transport.

Pharmacokinetic evaluation (*in vivo* drug release study)

Preparation of calibration curve

A primary stock solution of 1 mg/ml aceclofenac in methanol was prepared and diluted with methanol to produce 100, 200, 300, and 400 µg/ml concentration.[12]

Extraction of aceclofenac from serum

The procedure is modified from the High performance liquid chromatography HPLC and pharmacokinetics of aceclofenac in rats as described by Musmade *et al*,[19] 0.9 ml of serum was spiked with 0.1 ml of the 100 µg/ml standard aceclofenac solution. 1.5 ml of 10% trichloro acetic acid solution was added as the protein-precipitating agent and centrifuged for 15 min. The supernatant was transferred to another test tube to which 1 ml of 1 N hydrochloric acid was added. The drug was extracted using diethyl ether[20] (5 ml × 2) and the organic layer containing the drug was separated and evaporated to dryness. The residue was reconstituted in 5 ml of methanol and analyzed using Jasco V-530 UV Spectrophotometer. First, the sample was scanned for testing the presence of aceclofenac in the extract, and then the absorbance was taken at 276 nm. The procedure was repeated by spiking other standard solutions and a blank was performed as well.

Calibration data were used for interpolating the absorbencies obtained from extracts of rabbit blood collected at different time intervals after oral administration of the tablets.

Determination of rabbit blood drug levels after single dose oral administration

Adult albino rabbits (weighing 1.5-2 kg) obtained from Central Animal House, Government Medical College, Trivandrum, Kerala, India were used. Eighteen rabbits of either sex were randomly selected and used for the study. The animals were fasted overnight prior to the study with water *adlibitum*. The Institutional Animal Ethical Committee Medical College, Trivandrum (IAEC), India approved the experimental protocol (IAEC No.:01/76/2008/MCT). All protocols and experiments were conducted in strict compliance with the ethical principles and guidelines provided by the committee for the purpose of control and supervision of experiments on animals. Six rabbits were maintained as control, and the other 12 rabbits were divided in two groups each containing six rabbits. One group was given the formulation KSR5 and other was given the marketed tablet (Hifenac SR) equivalent to 5.714 mg of aceclofenac. Blood samples of 2 ml were collected from the marginal ear vein and transferred to a test tube containing 1 ml of 3.8% sodium citrate solution as anticoagulant at time intervals 0, 30 min, 2, 4, 6, 8 12, and 24 h. Test tube was centrifuged and plasma was collected. The drug was extracted using the same procedure described under the preparation of calibration curve analyzed at 276 nm using UV spectroscopy. The calibration was used to find out the amount of drug/ml in the blood and a graph of concentration versus time was plotted. The test was repeated in all animals of each group and the average was taken.

Analysis of pharmacokinetic parameters

A graph of concentration versus time and log concentration versus time of the blood drug levels following oral administration of tablet from both group was plotted and used to determine the maximum concentration (C_{max}), Peak time (t_{max}), Area under curve AUC, Area under first moment curve (AUMC), Mean residence time (MRT), etc.

In vitro–in vivo correlation[13,21]

The data generated in the bioavailability study were used to develop the IVIVC. The percent of drug dissolved was determined using the dissolution testing method and the fraction of drug absorbed was determined using the method of Wagner–Nelson from the aceclofenac plasma concentration versus time data following the oral administration of the formulations. Correlation models were developed by plotting a graph showing mean fraction of drug dissolved *in vitro* versus the mean fraction of drug absorbed *in vivo*.

Linear regression analysis was used to examine the relationship between percent of drug dissolved and percent of drug absorbed. Correlation coefficient was found out by using Graph PadIn Stat 3 software.

RESULTS AND DISCUSSION

Table 2 shows the independent and dependent variables of the formulations.

By comparing the response variables of the prepared formulations with that of the marketed product, the formulations KSR5 and KSR7 were chosen as the optimized formulations. The result indicates that the quantity of KSR and compression load are directly proportional to the retarding nature of the matrix tablets. These formulations were prepared in bulk for further *in vitro* and *in vivo* studies. Table 3 shows the optimized formula for KSR5 and KSR7. Figure 1 shows release pattern of the optimized formulations.

Kinetics of drug release

Table 4 shows release rate constant and regression coefficient from various kinetic models such as zero-order, first-order, Higuchi's model, and Hixson–Crowell plot for the optimized formulations.

From the values of coefficient of determination (r^2) determined from the above mathematical models, it is clear that KSR5 and KSR7 follow zero-order kinetics.

Mechanism of drug release

Table 5 shows the Korsmeyer–Peppas release exponent and regression coefficient for the optimized tablet formulations.

From the values of release exponent (n) determined from the above mathematicalmodel, it is clear that, KSR5 and KSR7 showed non-Fickian (anomalous) release.

Pharmacokinetic evaluation

Calibration curve

Table 6 shows data of the prepared calibration curve in plasma. Figure 2 shows linearity in the concentration range investigated with an r^2 value of at least 0.9980.

Plasma drug concentration

Table 7 shows plasma drug concentration of KSR5 and marketed product after single-dose oral administration of the formulation.

Statistical analysis showed that plasma drug level after the oral administration from the prepared formulation is almost comparable to the marketed product ($P > 0.05$).

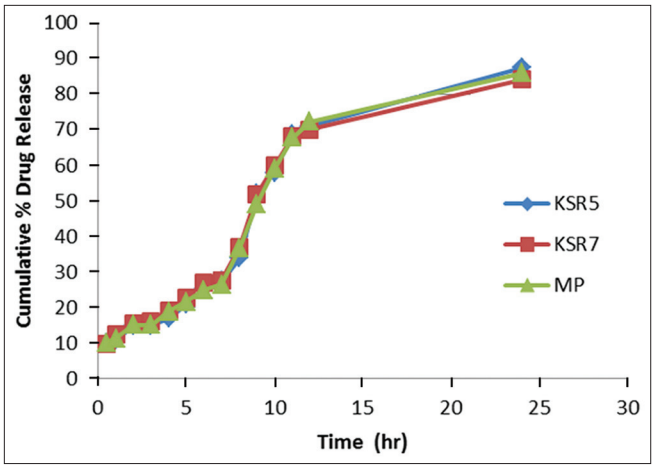

Figure 1: Drug release pattern of optimized formulations and marketed products

Table 2: Independent and dependent variables of the formulations

Formulation	Independent variables		Response variables				
	Level of polymer (%)	Compression load (ton)	R_6	R_{12}	R_{24}	t_{50} (h)	f_2
KSR1	35	3	37.50±0.62	85.04±1.32	102.00±0.29	7	27
KSR2	35	4	32.12±1.43	81.47±1.19	97.82±0.92	8	35
KSR3	35	5	30.12±0.89	80.88±1.98	104.87±0.14	9	30
KSR4	40	3	28.32±0.56	82.47±0.69	95.32±1.89	8	39
KSR5	40	4	25.23±3.14	70.89±1.92	87.44±2.34	9	80
KSR6	40	5	22.87±1.13	72.85±0.87	73.13±2.09	10	32
KSR7	45	3	26.83±1.83	69.98±2.03	84.01±0.98	9	69
KSR8	45	4	19.42±0.73	58.72±0.89	70.82±1.24	10	30
KSR9	45	5	18.32±1.53	61.83±0.63	69.85±1.86	11	31
MP	-	-	24.93±0.53	72.23±0.58	85.87±1.62	9	-

KSR: Kollidon sustained release, MP: Marketed product

Figure 3 illustrates plasma drug levels of the administered formulations at different time intervals.

Analysis of pharmacokinetic parameters

Table 8 shows Pharmacokinetic parameters evaluated in the study for KSR5 and marketed product. Data were subjected to statistical analysis. The difference in pharmacokinetic parameters of KSR5 and marketed product was not significant ($P > 0.05$).

In vitro-in vivo correlation

An attempt to correlate the amount of drug released *in vitro* with the amount of drug absorbed *in vivo* was performed. Table 9 shows the *in vitro* and *in vivo* data used for the IVIVC correlation.

Figure 4 shows the relation between amount of drug absorbed *in vivo* and amount of drug released *in vitro*. A very good linearity could not be achieved for the curve ($r^2 = 0.914$).

SUMMARY AND CONCLUSIONS

The approach of the present study was to develop a sustained release aceclofenac matrix tablet with KSR. Sustained release tablets of aceclofenac using KSR have been successfully optimized to the drug release pattern similar to the marketed product. The tablet formulations KSR5 and KSR7 were found to be most comparable to the marketed product in terms of similarity factor. Factorial design has been used to study the effects of various formulation factors affecting the release pattern of sustained release tablet. It was noted that both compression load and polymer level had significant effect on the drug release pattern. Commercial availability of KSR and its direct compression characteristics will reduce the unit cost of product by decreasing process steps; the presence of PVP in the KSR matrix will modulate the drug release to an acceptable pharmacokinetic profile. Pharmacokinetic analysis of the optimized tablet formulation using KSR to find out the relevant pharmacokinetic parameters has been

Table 3: Optimized formula for KSR5 and KSR7

Ingredients	Quantity per tablet (mg)	
	KSR5	KSR7
Aceclofenac	200	200
Kollidon SR	280	315
MCC	209.5	174.5
Magnesiumstearate	7	7
Aerosil	3.5	3.5

KSR: Kollidon sustained release, MCC: Microcrystalline cellulose

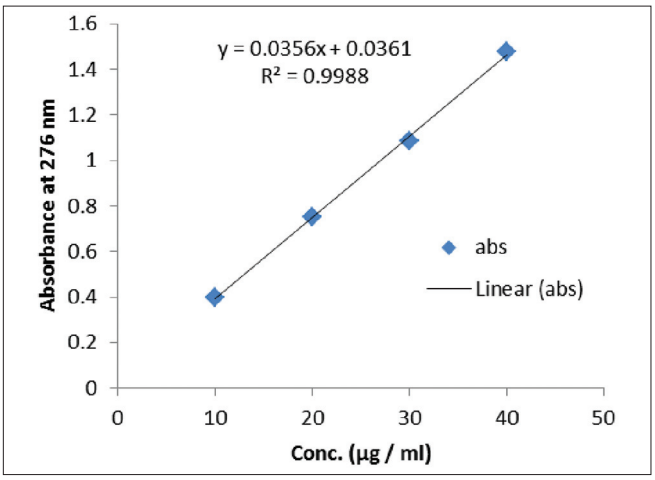

Figure 2: Calibration curve of Aceclofenac in Serum

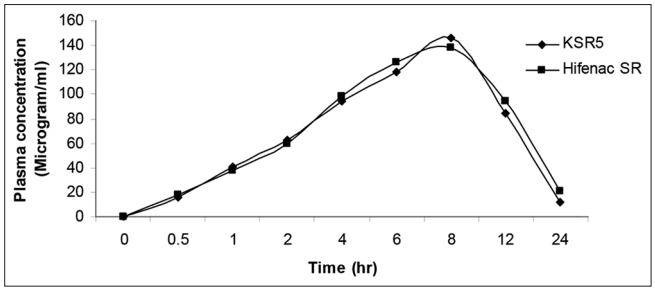

Figure 3: Plasma concentration profile of optimized and marketed products

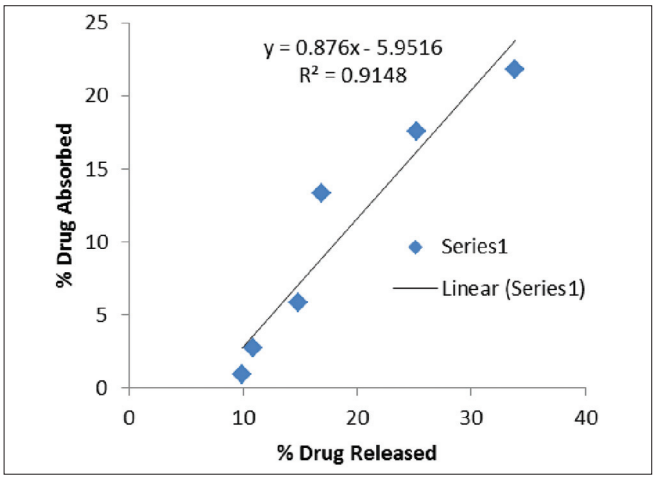

Figure 4: *In vitro-in vivo* correlation

Table 4: Release rate constants for various kinetic models

Formulation	Zero-order		First-order		Higuchi		Hixson-crowel	
	K_0	r^2	K	r^2	K_H	r^2	K_{HC}	r^2
KSR5	4.058	0.870	0.031	0.026	21.82	0.858	0.116	0.818
KSR7	3.898	0.867	0.022	0.904	21.02	0.861	0.110	0.813

KSR: Kollidon sustained release

Table 5: Korsmeyer-Peppas release constants for optimized formulations

Formulations	*n*	r^2
KSR5	0.671	0.803
KSR7	0.650	0.829

KSR: Kollidon sustained release

Table 6: Datas of calibration curve of aceclofenac in plasma

Concentration (µg/ml)	Absorbance at 276 nm	r^2
10	0.3996	0.9980
20	0.7486	
30	1.0828	
40	1.4756	

KSR: Kollidon sustained release

Table 7: Plasma drug concentrations of optimized and marketed products

Time (h)	Plasma concentration (µg/ml) ± SD	
	KSR5	Hifenac SR
0	0	0
0.5	16±0.88	18±2.18
1	41±1.73	38±0.63
2	63±2.93	60±1.73
4	94±1.39	98±2.19
6	118±0.93	126±0.73
8	146±1.83	138±0.08
12	84±0.66	94±2.16
24	12±2.07	21±1.73

KSR: Kollidon sustained release

Table 8: Pharmacokinetic parameters of the optimized and marketed products

Pharmacokinetic parameters	KSR5	Hifenac SR
AUC_{0-24}(µg/ml h)	1739.00	1867.50
$AUC_{0-\infty}$(µg/ml h)	1748.60	1899.31
AUMC (µg/ml)	23476.20	26330.25
MRT (h)	13.42	14.099
K_e (h/1)	1.241	0.6602
V_d (ml)	200.00	252
C_l (ml/h)	248.20	165.05
C_{max} (µg/ml)	146	138
t_{max} (h)	8	8

KSR: Kollidon sustained release, AUC: Area under curve, AUMC: Area under first moment curve, MRT: Mean residence time

Table 9: Datas for *in vitro-in vivo* correlation

Time (h)	Drug released *in vitro* (%)	Drug absorbed *in vivo* (%)	r^2
0.5	09.89	0.90	0.914
1	10.87	2.70	
2	14.83	5.80	
4	16.93	13.30	
6	25.23	17.56	
8	33.88	21.82	

tried. The results showed that C_{max}, t_{max}, AUC, AUMC, MRT, etc., were comparable to the marketed aceclofenac sustained release preparation. An attempt to correlate the amount of drug released *in vitro* to the amount of drug absorbed *in vivo* has been done. But, a very good correlation could not be observed. Accelerated stability studies of the tablets according to various guidelines and in blister packing and IVIVC correlation of the product have to be studied in detail.

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