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Development of oral Sustained release dosage form for low melting chiral compound Dexibuprofen and it's in virto-in vivo evaluation

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Abstract

Newly developed single-unit of oral sustained release dosage form for low melting chiral compound, S (+)-ibuprofen have been prepared by the wet granulation method. The hydrophilic matrix was prepared with xanthan gum with additives Avicel PH101. In vitro drug release was carried out; these studies indicated that the drug release can be modulated by varying the concentration of the polymer and fillers. The data was evaluated according to zero-order, first-order, Higuchi and Peppas equations. A open, randomized, two-treatment, two period, single dose crossover, bioavailability study in 12 fasting, healthy, male, volunteers was conducted. After dosing, serial blood samples were collected for the period of 24.0 h. Various pharmacokinetic parameters including AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $T_{1/2}$, and elimination rate constant (K_{el}) were determined from plasma concentration of both formulations of test (Dexibuprofen 300 mg tablets) and reference (Dexibuprofen 300 mg tablets). The extent of absorption of drug from the sustained release tablets was significantly higher than that for the marketed dexibuprofen tablet because of lower elimination and longer half-life.

Keywords: Dexibuprofen; Sustained release formulation; Xanthan Gum; Release Kinetic studies; Pharmacokinetic parameters.

Introduction

Ibuprofen (2-(4-isobutylphenyl) propionic acid) is a non-steroidal anti-inflammatory drug (NSAID) used widely in rheumatoid arthritis, osteoarthritis and a number of other painful conditions. It has a chiral carbon atom on the propionic side-chain and therefore exists in two enantiomeric forms. S(+)-ibuprofen is the pharmacologically active form and 160 times more potent than R(+)-ibuprofen. R (+)-ibuprofen is inverted to S(+)- ibuprofen in vivo[1] to the extent of 57–69%[2,3]. The production of mini-matrices uses a tabletting technique that is widely understood, diverse and offers less constraints than, for example extrusion or spheronisation. In addition, the mini-matrices have dosing flexibility [4, 5]. The aim of this work was to prepare mini-matrix tablets containing S (+)-ibuprofen, used as a model drug, and xanthan gum or karaya gum as the hydrophilic matrix to retard drug release. Hydroxypropyl methylcellulose (HPMC) was also used as a hydrophilic matrix for comparative purposes. The in vitro dissolution studies were performed on the formulation for drug release from hydrophilic matrices is known to be a complex interaction between dissolution, diffusion and erosion mechanisms. This work was an attempt to

determine the relative contribution of the various drug release mechanisms from these matrix formulations. The LOQ of the present method is 0.6 µg/mL and linearity was in the range of 0.6-18.0 µg/mL. No method reported previsouly estimation of dexibuprofen in plasma by using the solid phase extraction in the literature. The present work was aimed at developing a sensitive High Performance Liquid Chromatographic (HPLC) for determination of dexibuprofen in human plasma. The advantages of present method include single step optimized extraction procedure using SPE and short run time. The optimization of extraction procedure was carried out by comparing protein precipitation, and liquid-liquid extraction for recovery and interference. SPE was selected because it had obvious advantages such as shorter processing time; lesser organic solvent consumption, fewer steps, and good plasma sample clean up. Only limited analytical methods have been developed for the determination of dexibuprofen in biological methods. Along them HPLC and LC-MS and detection have been reported previously (Menon. S 2008**;** Eller, N, 1998; Seo-Ryung Kim 2011; Sadaba, B et al., 2006). There were no simple, rapid and reproducible methods so far reported for the estimation of by using high performance liquid chromatography of dexibuprofen in plasma. The outcome of a study depends upon the reliability, reproducibility and sensitivity of the analytical methodology employed. Therefore, the bioanalytical method was validated in accordance with USFDA guidelines prior to the initiation of the study.

Materials and methods

Materials

S (+)-ibuprofen was procured from Novan life sciences (Hyderabad, India). HPMC gums (Colourcon, Goa); xanthan gum were purchased from Lucid Colloidal Company (St. Louis, MO).

Preparation of DXI Tablets

DXI matrix tablets were prepared by the wet granulation method. All the composition (Table 1) with the exception of magnesium stearate and aerosol were thoroughly mixed in a tumbling mixer wet mass was sived (16 mesh) and granules were dried at 40 C for 16 hr. The dried granules were sieved (22 mesh) and these granules were lubricated with a mixture of magnesium stearate and aerosol (2:1). The DXI tablets were prepared using an electrically operated punching machine. Compression was performed after granulation process with a single punch press applying a compression force of a 9 KN (preliminary work) or 12 KN (experimental design), equipped with an 12 mm concave punch. For the preliminary work, batches of 100 tablets. Batches were prepared for each formulation and the compositions of different batches of DXI SR tablets are given in Table.

Table 1 : Granule properties of the different formulations of dexibuprofen.

Formulation F[a]	Angle of repose (θ°**)**	LBD[b] (g/ml)	TBD[c] (g/ml)	Carr's Index (%)
F1	28.52	00.319	0.391	18.414
F2	29.64	28.96	29.36	31.75
F3	30.18	32.95	33.82	32.26
F4	00.302	00.318	28.13	00.325
F5	00.315	00.325	00.32	00.314
F6	00.319	00.324	00.389	00.4
F7	00.398	00.39	0.397	00.394
F8	00.395	00.396	00.4	22.365
F9	20.500	18.342	19.231	18.136
F10	18.782	20.506	19.444	19.000

[a]Code of formulations, [b]Loose Bulk Density, [c]Tapped Bulk Density.

Granule properties

The granulation properties were evaluated the following: loss on drying, particle size distribution (after drying and final blend), geometric mean diameter, bulk and tap densities and percent compres suability (Carr's index).

Standard physical test of tablets

The physical testing of tablets was performed after the period of at least 24 h stored at the same RH conditions than powders. The tablet average weight and the standard deviation (SD) were obtained from 20 individually weighed (Sartorius analytical balance, Mumbai) tablets according to USP. The thickness of ten tablets was measured individually using an electronic micrometer (Mitutoyo MDC-M293, Tokyo, Japan)**.** The resistance to crushing of ten tablets was determined by diametral loading with a Monsanto hardness tester. Tablet friability was calculated as the percentage weight loss on using 20 tablets, 4 min at 25 r.p.m. in an (Electrolab Mumbai) friability tester.

Drug Content

Five tablets were weighed individually and crushed in mortar. An accurately weighed quantity of powered tablets (300 mg) was extracted with phosphate buffer and the solution was filtered through 0.45µ membrane. The drug content was estimated by HPLC under suitable optimized condition.

In vitro drug release studies

The in vitro dissolution studies of the marketed immediate (IR) tablets and the developed sustained release (SR) tablets were carried out using USP type II apparatus (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of distilled water maintained at 37 ± 0.5°C. The drug release at different time intervals was measured using an HPLC instrument. It was made clear that none of the ingredients used in the matrix formulations interfered with the absorbance of the drug. The release studies were conducted for three tablets in a batch and the mean values were plotted against time.

Kinetics of drug release

The cumulative amount of dexibuprofen released from matrix tablets at different time intervals were fitted to zero order kinetics using Least-Squares Method of analysis to find out whether the drug release from the formulations is providing a constant drug release. The correlation coefficient between the time and the cumulative amount of drug released was also calculated to find the fitness of the data to zero order kinetics. The fitness of the data to first order kinetics was assessed by determining the correlation coefficient between the time and the amount of drug to be released from the formulations. The data were also fitted to the model developed by Korsmeyer (1983) in order to find out the drug release mechanism from the formulations. The cumulative percent of drug released from the formulations was plotted against time on log–log scale, and analyzed for linearity using Least-Squares Method. Calculating correlation coefficients between time and the cumulative percent of drug released on log–log scale tested the fitness of the data.

HPLC analysis of dexibuprofen in dissolution fluids and matrix tablets

The quantitative determination of dexibuprofen was performed by HPLC. A gradient HPLC (Shimadzu HPLC Class VP series) with two LC-2010A HT VP pumps, dual wave length programmable UV/VIS Detector SPD-10A VP, CTO-10AS VP Column oven (Shimadzu), SCL-10A VP system controller (Shimadzu), a disposable guard column LC-18 (Pelliguarde, LC-18, 2 cm, Supelco, Inc., Bellefonte, PA.) and RP C-18 (250 × 4.6 mm, particle size 5µ) was used. The HPLC system was equipped with the software 'Class-VP series version 6.04 (Shimadzu)'.The mobile phase used was a mixture of 50mM Sodium acetate, and acetonitrile in the ratio of 60:40. The filtered mobile phase components were pumped at a flow rate of 1.0 ml/min. The eluent was detected by

UV detector at 222 nm, and the data were acquired, stored and analyzed with the software 'Class-VP series version 6.04 (Shimadzu).

Stability Studies

No significant change was observed for the formulated sustained release tablets of dexibuprofen with respect to its physicochemical parameters and in vitro drug release as evident by Table 3. The developed formulations for is stable at various temperature and humidity conditions for a period of 3 months.

In vivo studies in healthy human volunteers

The study protocol was approved by J.S.S.College of Pharmacy, Ooty, India. Twelve healthy male volunteers (60–70 kg, age between 20 and 30 years) participated in the study, and all were nonsmokers and non-alcoholics. The biochemical examination of the volunteers revealed normal function of the kidney and liver. The nature and purpose of the study were fully explained to them. An informed written consent was obtained from every volunteer. None of the volunteers were on drug treatment one week prior to the participation of the study. The volunteers were free to withdraw from the study under their discretion. The volunteers were divided into two equal groups (groups-I and -II), and a cross over study was followed. An immediate release tablet dosage form containing 300 mg of dexibuprofen was chosen as a reference formulation, and administered orally to six volunteers (group I). The group II six volunteers were administrated with 300 mg of dexibuprofen. After a washout period of 7 days, group-I volunteers received sustained release tablet and group-II volunteers received the immediate release tablet. Both the tablet formulations were administered with 240 ml of water after a 12h overnight fast. Food and drinks were withheld for at least 2 h after dosing. Blood samples were collected from the volunteer's antecubital vein via a hypodermic syringe (rinsed with dilute heparin solution) over a period of 24 h (0, 0.5, 1, 1.5, 2, 2.5, 3, 4.0, 6, 8, 12, 18 and 24 h). The blood samples were immediately centrifuged at 4000 rpm, plasma was separated and analyses were done by using HPLC.

HPLC analysis of dexibuprofenin human plasma

The quantitative determination of dexibuprofenin human plasma was performed by a reverse phase HPLC at the time of analysis, the samples were removed from the deep freezer and kept in the room temperature and allowed to thaw. Phenomenex Strata C_{18} solid phase extraction cartridge was conditioned with methanol, water frequently. To this 0.5 mL of plasma sample and 0.4 mL (500 ng/mL) of internal standard (Aceclofenac) was added. The cartridge was washed with sufficient quantity of water. The drug and internal standard was eluted from the cartridge using 0.5 mL of mobile phase. The eluted sample was injected. There was a high recovery (89.9–93.5%) of dexibuprofen indicating that the HPLC method was highly accurate. The typical chromatogram of sample is presented in Fig. 1.

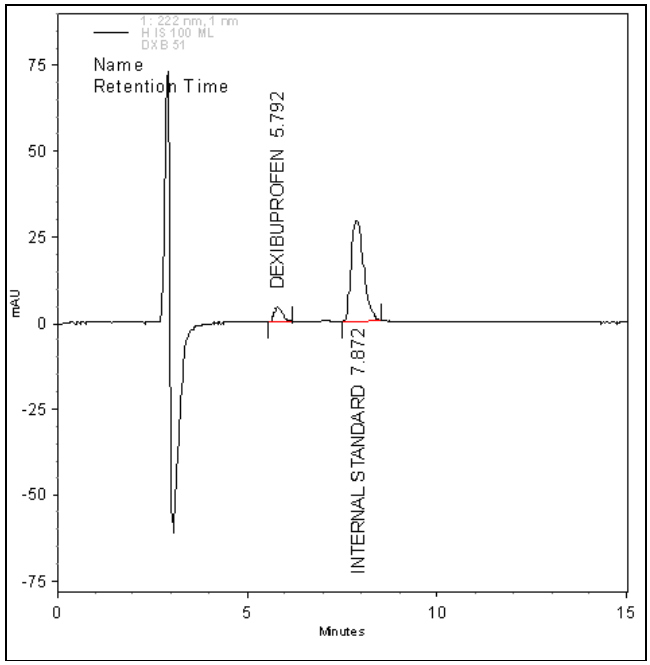


Fig. 1. Volunteer chromatogram at 1.5 hrs Dexibuprofen and Internal Standard.

Pharmacokinetic analysis

The plasma concentration of dexibuprofen at different time intervals after oral administration of the tablet formulations to human volunteers was subjected to pharmacokinetic analysis to calculate various parameters such as maximum plasma concentration C_{max} time to reach maximum concentration T_{max} and area under the curve (AUC_{0-t}). The values of C_{max} and T_{max} were directly read from the arithmetic plot of time versus plasma concentration of Dexibuprofen. The overall elimination rate constant Keli was calculated from the slope of the terminal elimination phase of a semi-logarithmic plot of concentration versus time, after subjecting it to linear regression analysis (El-Sayed, 1995; El-Said, et al, 1991). The relative bioavailability of dexibuprofen from matrix tablets in comparison to reference formulation (immediate release dosage form) was calculated by dividing its AUC_{0-t} with that of immediate release tablet dosage form after applying dosage correction.

Results and Discussion

Granulation is the key process in the production of many dosage forms. The sustained release tablets were prepared by wet granulation technique. Physical properties of granules such as specific surface area, shape, hardness, surface characteristics and size can significantly affect the rate of dissolution of drugs contained in a heterogenous formulation. The granules of different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density and Carr's index as shown in Table 1. The results of angle of repose indicate good flow properties of the granules. However, the granules had fair to poor Carr's index values. Aerosil therefore was added to dried granules prior to compression to improve the flow.

The physical properties of different batches of developed tablets are given in Table 2. All the batches showed uniform thickness. The average percentage deviation of 20 tablets of each formula was less than ±5% and hence all formulations passed the test for uniformity of weight as per official requirements (Pharmacopoeia of India 1996). Good uniformity content was found among three different batches of tablets.

Another measure of tablets with less than 1 % w/w of their weight is generally considered acceptable. In the present study, the percentage friability for all the formulations was below 1%w/w, indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmaceutical properties and complied with the specifications for variation, drug content, hardness and friability.

Table 2 : Comparison of the physical properties of the matrix tablets containing dexibuprofen.

Formulation F_a	Hardness (Kg/cm_2)[b]	Thickness (mm)[b]	Weight (g)[b]	Friability (%)[b]
F1	5.000±0.79	3.53±0.03	0.5080±0.0029	0.329±0.08
F2	4.700±0.84	3.38±0.45	0.5092±0.0030	0.355±0.07
F3	4.900±0.82	3.568±0.04	0.5106±0.0027	0.294±0.05
F4	5.000±0.79	3.564±0.04	0.5100±0.0026	0.333±0.07
F5	4.900±0.65	3.56±0.05	0.5096±0.0024	0.307±0.07
F6	5.000±0.79	3.566±0.03	0.5104±0.0030	0.320±0.08
F7	4.900±0.74	3.618±0.06	0.5098±0.0033	0.318±0.08
F8	4.800±0.76	3.58±0.03	0.5088±0.0032	0.331±0.08
F9	5.000±0.79	3.554±0.04	0.5088±0.0025	0.326±0.07
F10	4.800±0.91	3.576±0.05	0.5090±0.0027	0.348±0.06

[a] Code of formulations,[b] Results represents the mean of replicate determination with the standard deviation given in parenthesis.

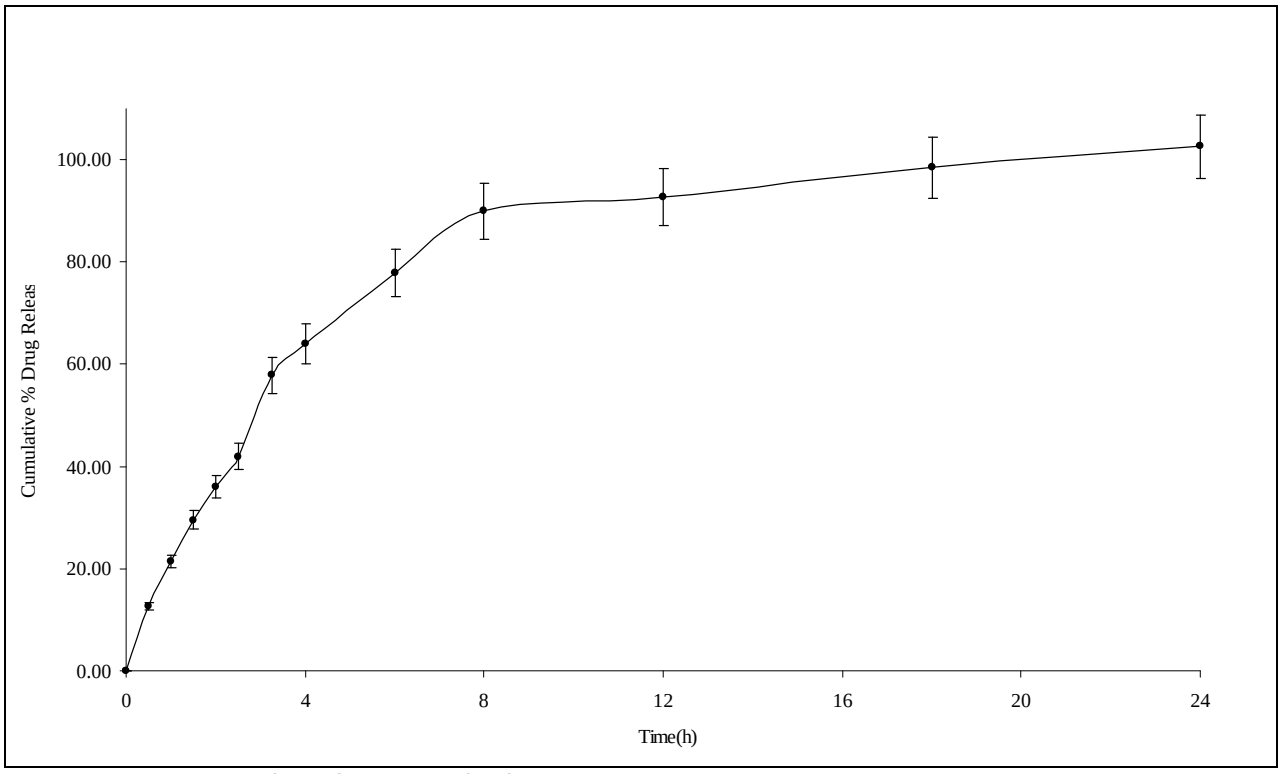


Fig. 2. Release profiles of dexibuprofen from Xanthene (polymer) containing Formulations.

Friability values of all the batches were less than 1%. There was no accordance between hardness values and friability observations. Small values in friability imply much less friability during transportation. The release profile of Dexibuprofen is presented in Fig. 2.

A suitable in vitro dissolution method serves as a valuable quality control tool to assess batch to batch release performance and to assure the physiological availability of the drug. The in vitro dissolution test is also used to guide formulation development and to monitor manufacturing process. As a regulatory test, it is used to approve minor changes in formulation, changes in the site of manufacturing and also to assess the scale-up of the bio-batch to the production batch. All the batches have shown that as the polymer concentration increases, the drug release rate decreases for dexibuprofen. The in vitro drug release characteristics of the developed sustained release (SR) and the marketed immediate release (IR) tablets were studied. Dissolution data for all the experiments were highly reproducible and hence only the average values were plotted. The dissolution of the marketed IR tablets indicated that more than 80% of the drug is released within 1 h, which complies with the pharmacopoeial specifications. In all the batches, we observed that as the polymer concentration increases, the drug release rate decreases.

To know the mechanism of drug release from these formulations, the data were treated according to Zero-order, first order, Higuchi and Peppas equvations that are clearly revealed in Figures.

The release profile the DXI, when plotted according to Higuchi's equvation and Peppas equvation (Higuchi, 1963; Hosny, 1997; Peppas, et al, 1997) confirm that drug release was diffusion control as evident by the values of correlation (r^2) Fig. 3-6.

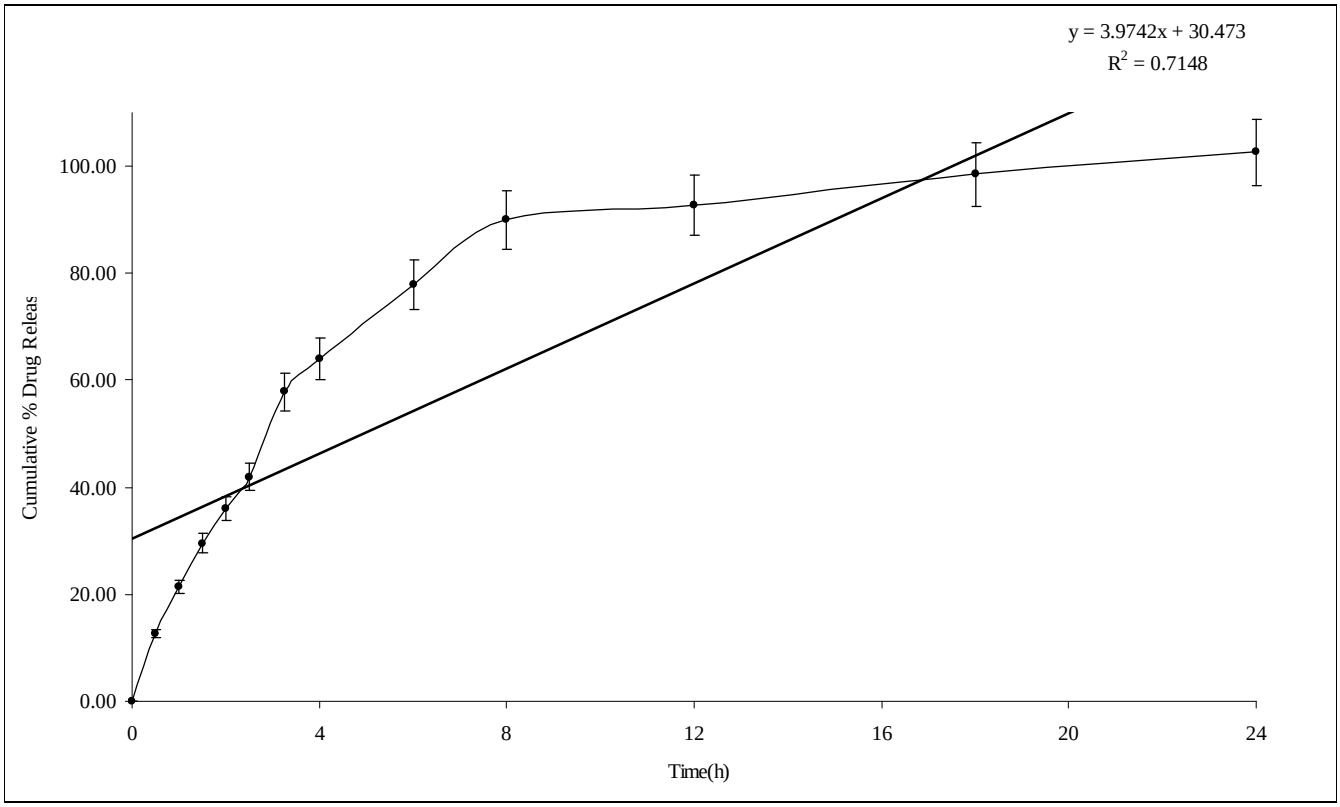
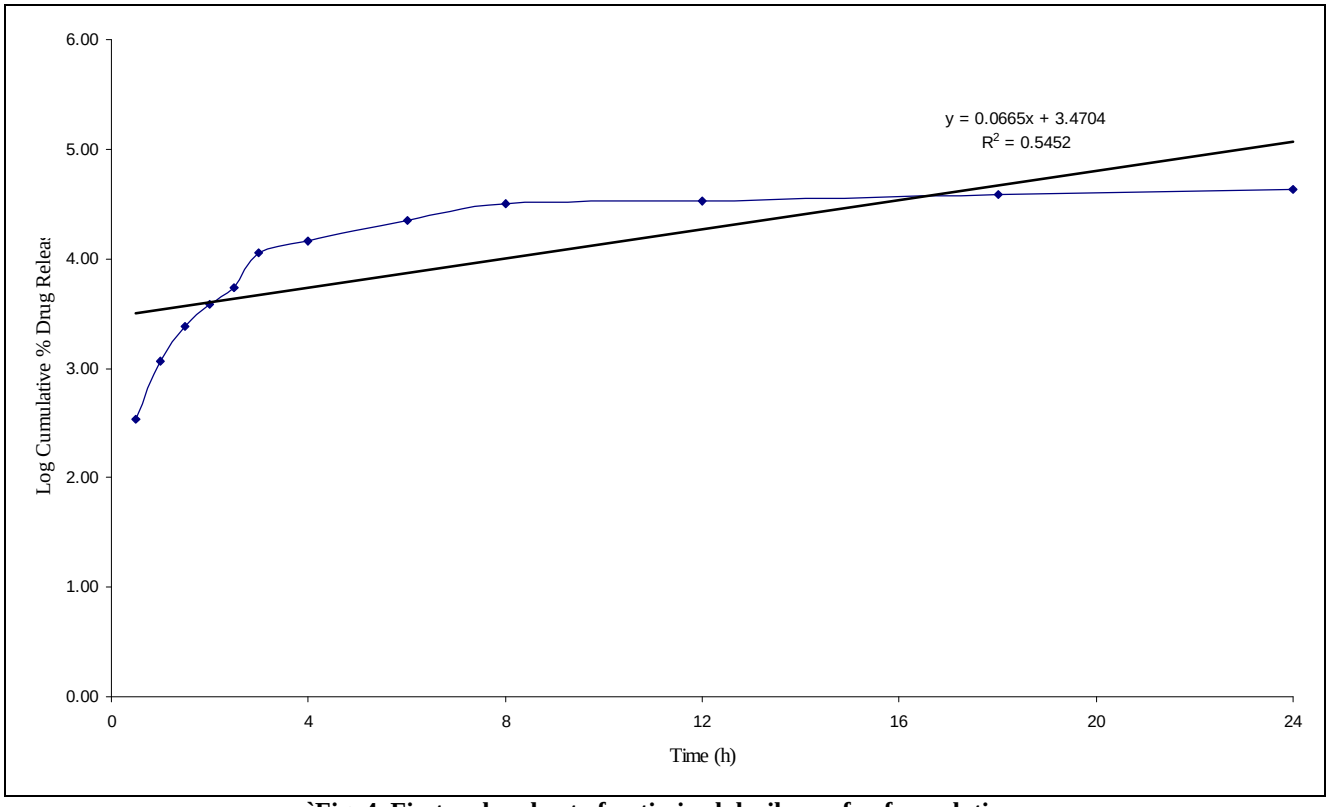


Fig. 3. Zero order chart of optimized dexibuprofen formulation.



`Fig. 4. First order chart of optimized dexibuprofen formulation.

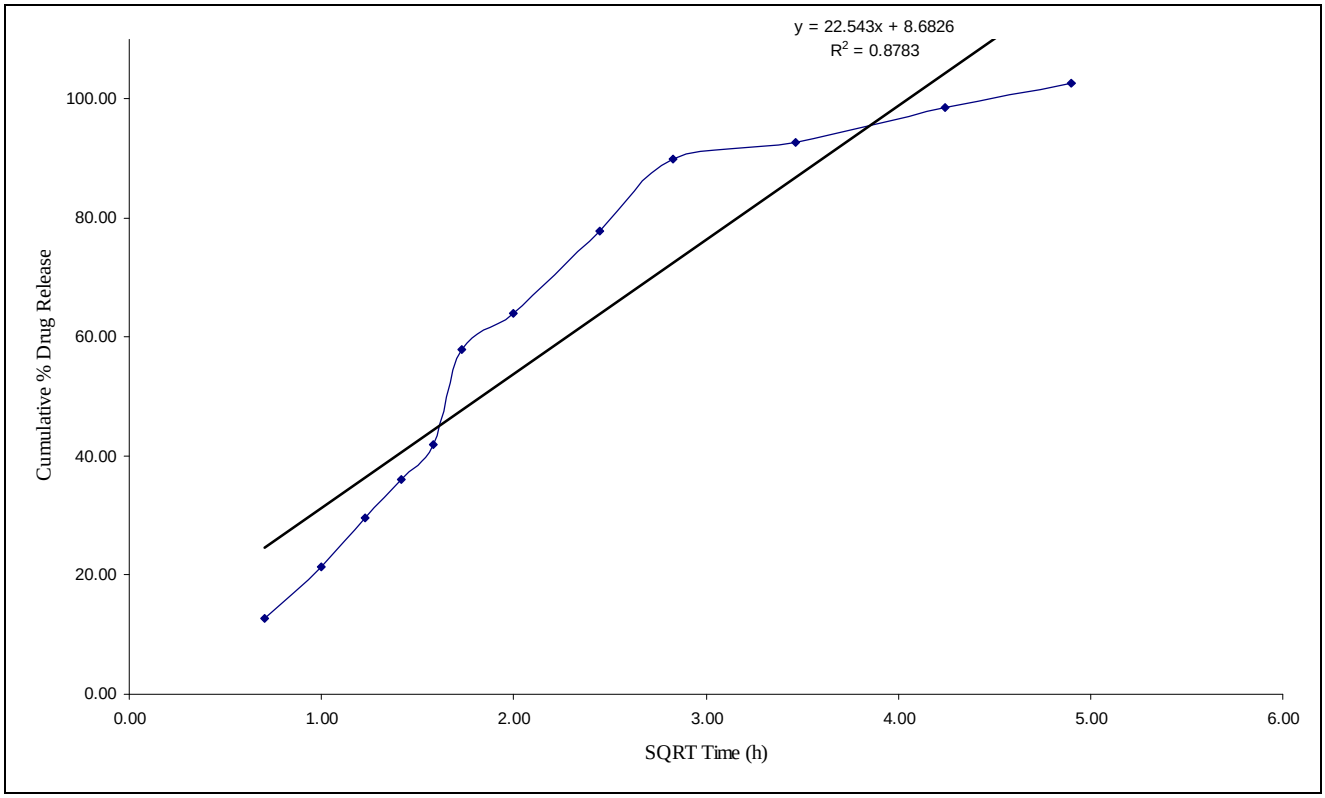


Fig. 5. Higuchi chart of optimized dexibuprofen formulation.

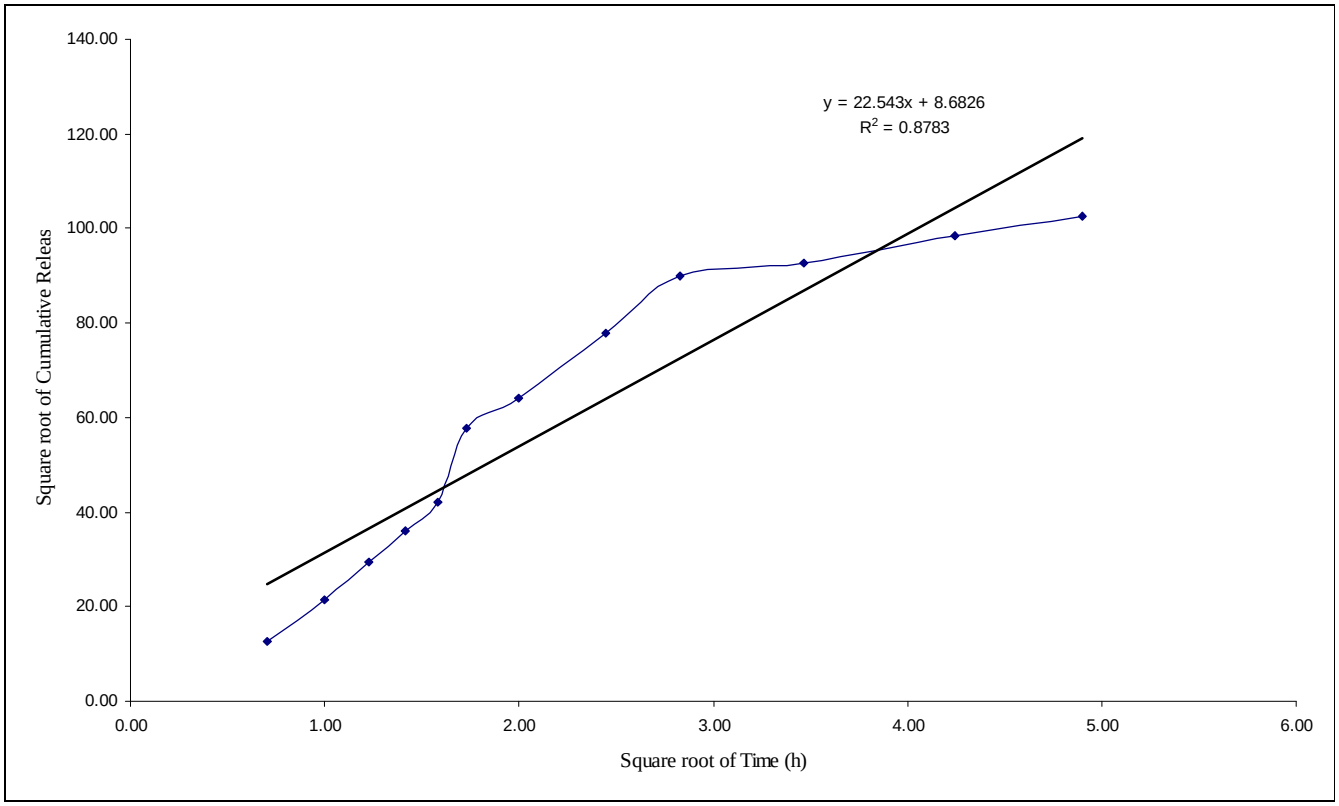


Fig. 6. Peppas chart of optimized dexibuprofen formulation.

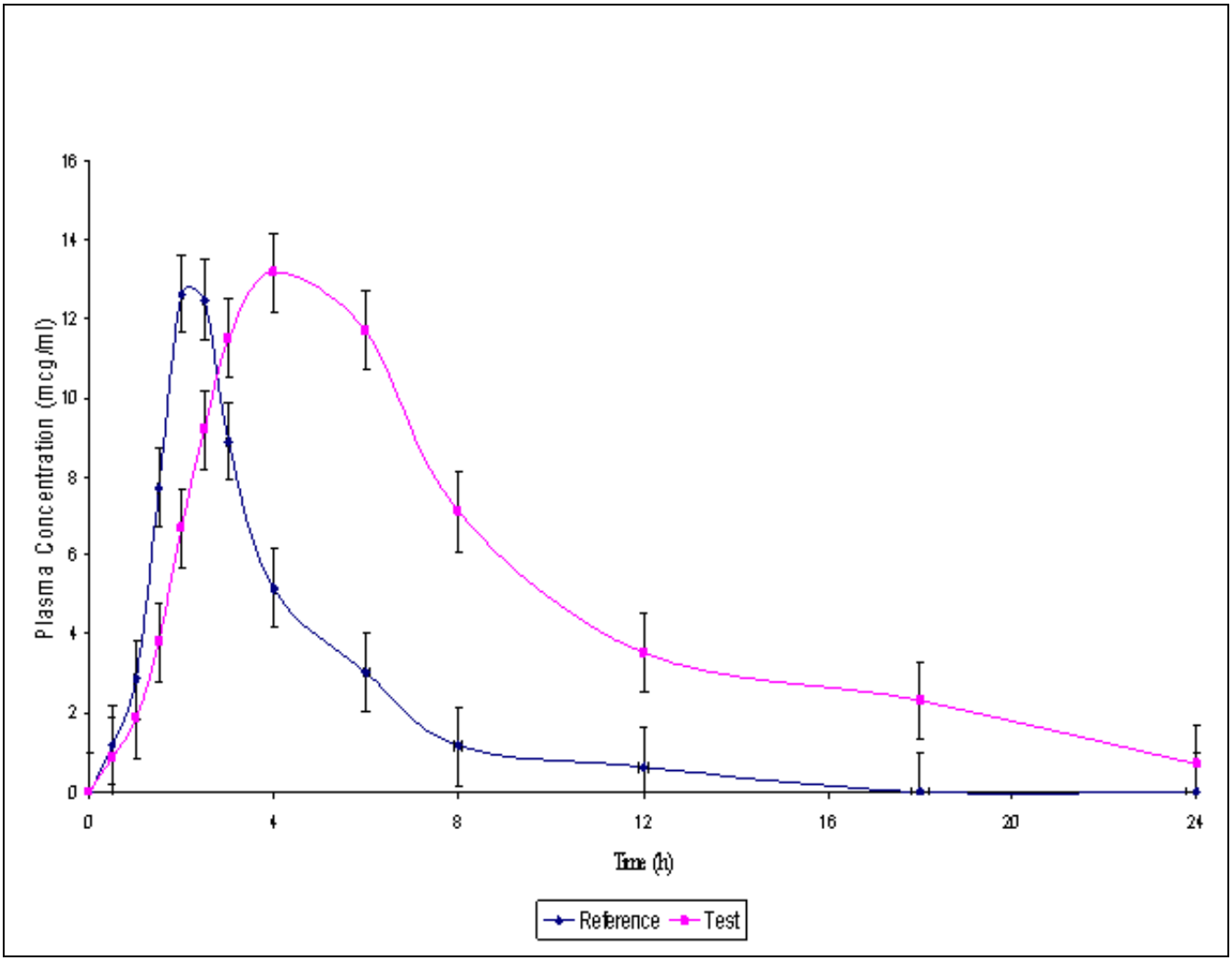


Fig. 7. Mean concentration-Time curve for 12 Volunteers. (REFERENCE AND TEST PRODUCT)

The relative bioavailability of the SR 300 mg tablets given daily was compared with one dose of the marketed 300 mg DXI tablet. The developed SR tablet produced a plasma concentration-time profile typical of the prolonged dissolution characteristic of a SR formulation, as evident from Fig. 7 and Table 4. The developed SR tablets demonstrated a longer time to reach a peak concentration than the marketed tablets and appeared to have more consistent over all performance.

Table 3 : Stability data at the end of three months for Dexibuprofen.

Parameter	Initial[a]	Real time[a]	Accelerated[a]
Thickness mm	3.576±0.05	3.569±0.04	3.572±0.04
Hardness (kg/cm^2)	4.800±0.91	4.799±0.93	4.905±0.86
Friability (%)	0.348±0.06	0.347±0.07	0.349±0.06
Drug content (%)	99.10	99.14	99.09

Table 4 : Pharmacokinetic parameters.

Pharmacokinetic parameters	Reference	Test
C_{max}	13.8127±1.072	14.1786±0.701
T_{max}	2.25±0.273	5.00±1.095
AUC_{0-t}	45.5910±6.331	117.8437±14.537
K_{eli}	0.3184±0.024	0.1457±0.008
Half life	2.1884±0.175	4.7722±0.303
$AUC_{0-\infty}$	47.6214±6.242	122.6206±14.552

This was no significant difference in extent of absorption as assessed by measurement AUC_{0-t}. However $AUC_{0-\infty}$ values for the SR tablets were higher than the marketed IR tablets indicating more efficient and controlled drug delivery, which would maintain plasma DXI levels better. This was also evident by the lower elimination rate and higher $t_{½}$ Values.

Conclusions

The sustained release tablets of dexibuprofen were well absorbed and the extent of absorption was higher than that of the marketed tablet. The sustained and efficient drug delivery system developed in the present study will maintain plasma dexibuprofen levels better, which will overcome the drawbacks associated with the conventional therapy.

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