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Formulation and Evaluation of Aceclofenac Controlled Release tablets Employing Olibanum Resin

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ABSTRACT

The objective of the study is to evaluate Olibanum resin, a natural resin polymer as matrix polymer for controlled release tablets and to design matrix tablets of aceclofenac for controlled release. Matrix tablets of aceclofenac were formulated employing Olibanum resin in different proportions of drug and polymer, the tablets were evaluated for drug release kinetics and mechanism .Two diluents namely lactose (water soluble) and DCP (water insoluble) were included in the formulations to assess their influence on drug release characteristics of olibanum resin matrix tablets .Matrix tablets were found to be non- disintegrating in water, acidic (pH 1.2) and alkaline (pH 7.4) fluids and were considered suitable for oral controlled release. Aceclofenac release from the matrix tablets formulated was slow and spread over 24 h and depended on the concentration (%) of olibanum resin in the matrix tablets and nature/type of diluent. As the concentration of olibanum resin in the matrix tablets was increased, drug release was decreased. Release was relatively faster with water soluble diluent lactose when compared to water insoluble diluent DCP at all concentrations of olibanum resin. Drug release from the tablets followed first order kinetics and followed non - Fickian (anomalous) diffusion release mechanism. Good linear relationships were observed between percent polymer and release rate in each case. The results of the study thus indicated olibanum resin could be used as rate controlling matrix in design of controlled release tablets. Both water soluble and water insoluble diluents can be included in the olibanum resin matrix tablets without affecting its rate controlling efficiency. Matrix tablets formulated employing olibanum resin (AF2) are considered suitable for controlled release of Aceclofenac over 24 h (i.e. once-a-day administration).

Keywords: Olibanum resin, Aceclofenac, Matrix tablets, Controlled release.

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INTRODUCTION

Controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to tissue. Drug release from these systems should be at a desired rate predictable and reproducible. Among the various approaches, preparation of drug-embedded matrix tablets is one of the least complicated approaches for obtaining controlled release and is widely used in industry.

The polymer used in matrix tablets plays a vital role in either controlling the drug delivery or enhancing bioavailability of the contained drug. Though a wide range of polymers are reported for preparing matrix tablet, there is a continued need to develop new, safe and effective polymers for controlled released matrix tablets.

The objective of the present study is to evaluate olbinum resin as a matrix former for controlled release of aceclofenac.

Olibanum is a gum resin obtained from *Boswellia serrata*, Roxburgh and other species of *Boswellia*. Olibanum consists [1] of chiefly of an acid resin (50 - 60%), gum (30-36%) and volatile oil (2-8%). The resin consists [2] mainly a resin acid (boswellicacid) and a resin (olibanoresine) in equal proportions.

Either soluble resin extracted from olibanum exhibited excellent release retarding and rate controlling properties in matrix tablets and microcapsules for controlled release [3-5]. Preliminary studies indicated that the resin also has good mucoadhesive property. In the present study, Olibanum resin was evaluated as rate controlling matrix material for controlled release. Matrix tablets of aceclofenac were formulated employing Olibanum resin in different proportions of drug and polymer and the tablets were evaluated for drug release kinetics and mechanism.

Aceclofenac has short biological half life of 2-4 h and is required to be administered repeatedly 3 or 4 times a day. It causes gastric disturbances such as nausea, ulceration with bleeding, vomiting, abdominal pain and constipation if present in large concentration in the gastrointestinal tract. Hence controlled release or sustained release formulations are needed for aceclofenac to prolongs its duration of action; reduce frequency of administration with better patient compliance and to reduce undesired gastric disturbances.

EXPERIMENTAL

Materials

1. Aceclofenac (gift sample from M/s. Micro labs Ltd., Pondicherry)
2. Olibanum resin (prepared in laboratory); (Olibanum gum was procured M/S Girijan Co-operative Corporation Ltd., Visakhapatnam)

3. Talc I.P. (Loba Chemie)
4. Magnesium stearate I.P. (Loba Chemie)

All other materials used were of Pharmacopoeial grade.

Methods

Preparation of Olibanum Resin

Olibanum resin used as coat material was extracted from olibanum gum in the laboratory as follows: powder olibanum (10g) was extracted repeatedly with 4×50 mL quantities of solvent ether. The ether extract was collected in a porcelain dish and concentrated to dryness at 40°C. The dried mass obtained was powdered and passed through mesh No. 120.

Preparation of Matrix Tablets

Matrix tablets of Aceclofenac are prepared as per the formulae given in Table.1. The required quantities of medicament, diluent (lactose/DCP) and matrix materials were mixed thoroughly in a mortar by following geometric dilution technique. The granulating fluid (solvent blend of water and alcohol in 1:1 ratio) was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60^0C for 4 h. The dried granules were passed through mesh No. 16 to break aggregates. The glidant talc and lubricants magnesium stearate were passed through mesh No. 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary tablet punching machine (M/s Cadmach machinery Co. Pvt. Ltd., Mumbai) to a hardness of 5-6 kg/sq.cm. using 9 mm round and flat punches.

Evaluation of Tablets:

Hardness of the matrix tablets prepared was tested using a Monsanto Hardness Tester. Friability of the matrix tablets prepared was determined in a Roche friabilator. Disintegration time were determined in Thermonic tablet disintegration test machine using water, 0.1 N HCl, and phosphate buffer of pH 6.8 as test fluids.

Estimation of Drug Content in Tablets

Five tablets were accurately weighed and powdered. Tablets powder equivalent to 20 mg of the drug was taken for assay into 25 ml volumetric flask and 20 ml of methanol were added. The mixture was shaken thoroughly for about 30 min. to extract Aceclofenac. The solution was then made up to volume with methanol. The methanolic solution was subsequently diluted suitably with phosphate buffer of pH 6.8 and assayed for Aceclofenac at 275 nm. Aceclofenac content of the tablets was calculated using the standard calibration curve.

Drug Release Study

Release of Aceclofenac from the matrix tablets prepared was studied in phosphate buffer of pH 6.8 (900 ml) using an eight station dissolution rate test apparatus with a paddle stirrer at 50 rpm and 37 $\pm$ 0.5^0C. One matrix tablet containing 100 mg of aceclofenac was used in each test. Samples of dissolution fluid (5 ml) each were withdrawn through a filter (0.45µ) at different time intervals and were analyzed at 275 nm for aceclofenac using double beam spectrophotometer. The sample (5 ml) taken at each sampling time was replaced with fresh dissolution medium (5 ml). The drug release experiments were conducted in triplicate.

Data Analysis

Release data were analyzed as per zero order, first order, Higuchi's [6] and Peppa's [7] equation models to assess the drug release kinetics and mechanism from the matrix tablets prepared.

RESULTS AND DISCUSSION

Matrix tablets of aceclofenac could be prepared employing different proportions of olibanum resin, a new natural resin by conventional wet granulation method. Two diluents namely lactose (water soluble) and DCP (water insoluble) were included in the formulations to assess their influence on drug release characteristics of olibanum resin matrix tablets. Olibanum resin was added at 2, 5, 10 % strength in the matrix. Physical properties of these matrix tablets are given in Table 2. Hardness of the tablets was in the range of 5-6 kg/cm^2. Weight loss in the friability test was less than 0.32% in all the cases. All the matrix tablets formulated contained 100 ± 5.0 % of the labeled claim. All the matrix tablets were found to be non- disintegrating in water, acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such, the formulated matrix tablets were of good quality with regard to drug content, hardness and friability. As the tablets formulated employing olibanum resin were non-disintegrating in acidic and alkaline fluids, they are considered suitable for oral controlled release.

Drug Release Characteristics

Aceclofenac release profiles of various matrix tablets formulated are shown in Figs 1 & 2. Aceclofenac release from the matrix tablets formulated was slow and spread over 24 h and depended on the concentration (%) of olibanum resin in the matrix tablets and nature/type of diluent. As the concentration of olibanum resin in the matrix tablets was increased, drug release was decreased. Release was relatively faster with water soluble diluent lactose when compared to water insoluble diluent DCP at all concentrations of olibanum resin.

Analysis of release data as per zero order and first order kinetic models indicated that the drug release from the tablets followed first order kinetics. The correlation coefficient (R^2) values were higher in the first order model (Tables 3&4) than in the zero order model. When the release data were analyzed as per Peppa's equation, the release exponent 'n' was in the

range 0.5323 – 0.7111 with all the matrix tablets indicating non - Fickian (anomalous) diffusion as the release mechanism from all the matrix tablets formulated with olibanum resin. Plots of percent released versus square root of time were found to be linear with ($R^2 > 0.9229$) with all the matrix tablets formulated indicating that the drug release from these tablets was diffusion controlled. Release parameters are summarized in Tables 5&6. As the olibanum resin proportion (%) in the matrix tablets was increased, release rate was decreased in both the series formulated using lactose or DCP as diluent. Good linear relationships were observed between percent polymer and release rate in each case (Figs 3&4). The relationships could be expressed by the following linear equations

Y= 4.1951 - 0.108x (in the series made with olibanum resin with lactose as diluent)
Y= 3.2014 - 0.0714x (in the series made with olibanum resin with DCP as diluent)

Where Y is the release rate (K_o) and x is the polymer concentration (%) and

Y= 0.1197 - 0.0058x (in the series made with olibanum resin with lactose as diluent)
Y= 0.0625 – 0.0024x (in the series made with olibanum resin with DCP as diluent)

Where Y is the release rate (K_1) and x is the polymer concentration (%).

Thus, drug release from the matrix tablets could be controlled by varying the proportion of drug: polymer in the matrix. The results of the study thus indicated olibanum resin could be used as rate controlling matrix in design of controlled release tablets. Both water soluble and water insoluble diluents can be included in the olibanum resin matrix tablets without affecting its rate controlling efficiency. Matrix tablets formulated employing olibanum resin (AF2) are considered suitable for controlled release of Aceclofenac over 24 h (i.e. once-a-day administration).

Table 1: Composition of Aceclofenac (100mg) Matrix Tablets Formulated

Composition (mg/tablet)	Lactose			Dicalcium Phosphate (DCP)		
	AF1	AF2	AF3	AF4	AF5	AF6
Aceclofenac	100	100	100	100	100	100
Polymer (Olibanum Resin)*	4.4	11.0	22.0	4.4	11.0	22.0
Lactose	106.8	100.2	89.2	-----	-----	-----
DCP	-----	-----	-----	106.8	100.2	89.2
Talc	4.4	4.4	4.4	4.4	4.4	4.4
Magnesium stearate	4.4	4.4	4.4	4.4	4.4	4.4

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Table 2: Weight Variation, Hardness, Friability, Disintegration Time and Drug Content of Aceclofenac Matrix Tablets Formulated

Formulation code	Weight variation (%)	Friability (%)	Hardness (Kg/cm^2)	DT (min.)	Aceclofenac content (%) ($\bar{x}$ ± s.d)
AF1	219.0 ± 1.42	0.32 ± 0.02	5.50 ± 0.14	Non-disintegrating	97.85 ± 0.09
AF2	216.0 ± 1.68	0.45 ± 0.01	6.00 ± 0.30	Non-disintegrating	96.53 ± 0.07
AF3	221.2 ± 1.35	0.37 ± 0.04	5.00 ± 0.19	Non-disintegrating	96.12 ± 0.15
AF4	218.6 ± 1.89	0.54 ± 0.06	6.00 ± 0.33	Non-disintegrating	97.02 ± 0.06
AF5	217.9 ± 1.74	0.62 ± 0.05	5.50 ± 0.21	Non-disintegrating	97.53 ± 0.12
AF6	216.8 ± 2.62	0.51 ± 0.07	6.00 ± 0.15	Non-disintegrating	96.98 ± 0.11

Table 3: Correlation Coefficient (R^2) Values in the Analysis of Release Data of Aceclofenac Matrix Tablets Prepared Employing Olibanum resin Using Lactose as Diluent as per Various Kinetic Models

Formulation	Correlation Coefficient (R^2) Values			
	Zero order	First order	Higuchi's	Peppa's
AF1	0.8893	0.9892	0.9733	0.9637
AF2	0.9850	0.9043	0.9557	0.9834
AF3	0.9737	0.9347	0.9332	0.9290

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Table 4: Correlation Coefficient (R^2) Values in the Analysis of Release Data of Aceclofenac Matrix Tablets Prepared Employing Olibanum resin Using DCP as Diluent as per Various Kinetic Models

Formulation	Correlation Coefficient (R^2) Values			
	Zero order	First order	Higuchi's	Peppa's
AF4	0.9770	0.9585	0.9464	0.9570
AF5	0.8876	0.9546	0.9818	0.9652
AF6	0.9039	0.9584	0.9900	0.9910

Table 5: Release Characteristics of Aceclofenac Matrix Tablets Prepared Employing Olibanum resin Using Lactose as Diluent

Formulation	Polymer Concentration (%)	T_{50} (h)	K_o (mg/h)	K_1 (h^{-1})	'n' in Peppa's Equation
AF1	2	6	4.07	0.114	0.7111
AF2	5	14	3.51	0.081	0.6322
AF3	10	14	3.17	0.065	0.5377

Table 6: Release Characteristics of Aceclofenac Matrix Tablets Prepared Employing Olibanum resin Using DCP as Diluent

Formulation	Polymer Concentration (%)	T_{50} (h)	K_o (mg/h)	K_1 (h^{-1})	'n' in Peppa's Equation
AF4	2	14	3.13	0.060	0.5822
AF5	5	12	2.73	0.047	0.564
AF6	10	14	2.53	0.040	0.5323

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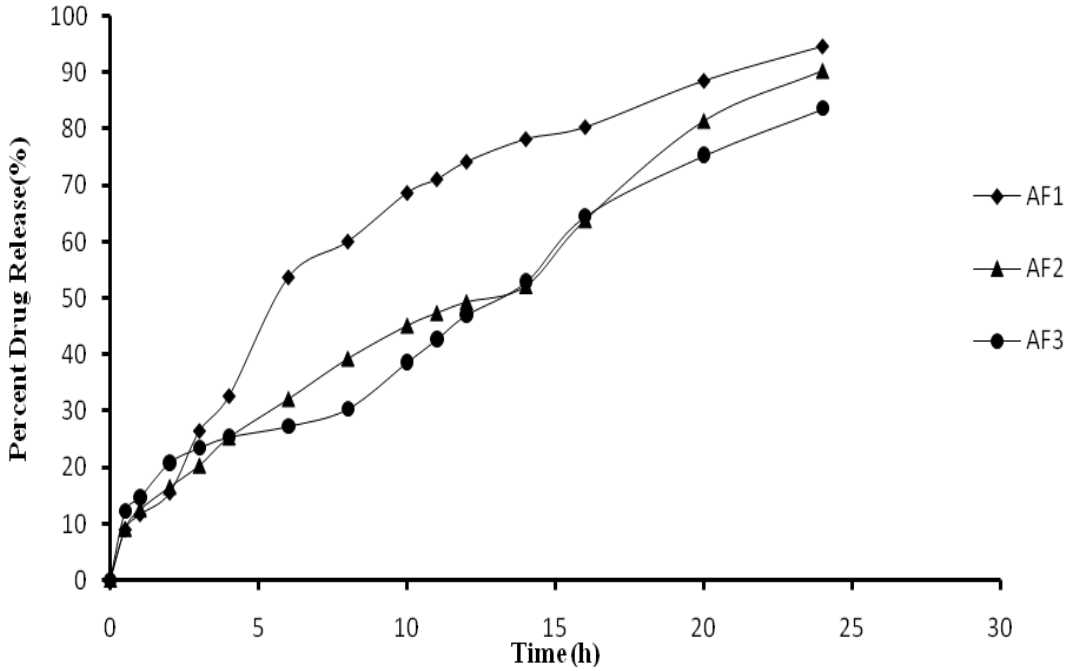

Fig 1 Release Profiles of Aceclofenac Matrix Tablets Prepared Employing Olibanum resin Using Lactose as Diluent

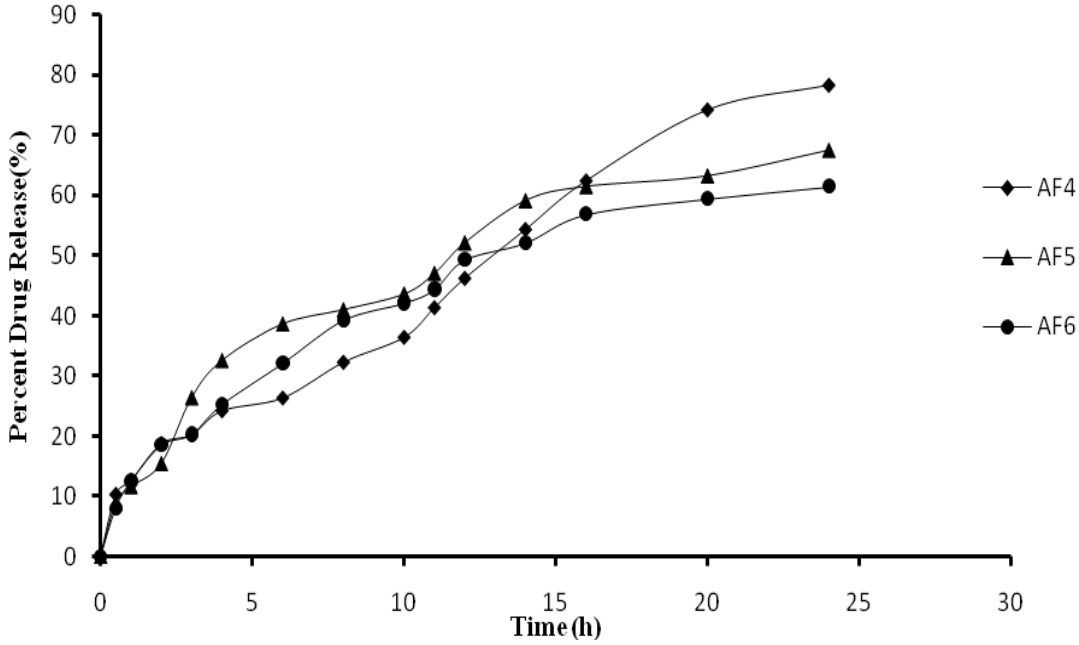

Fig 2: Release Profiles of Aceclofenac Matrix Tablets Prepared Employing Olibanum resin Using DCP as Diluent

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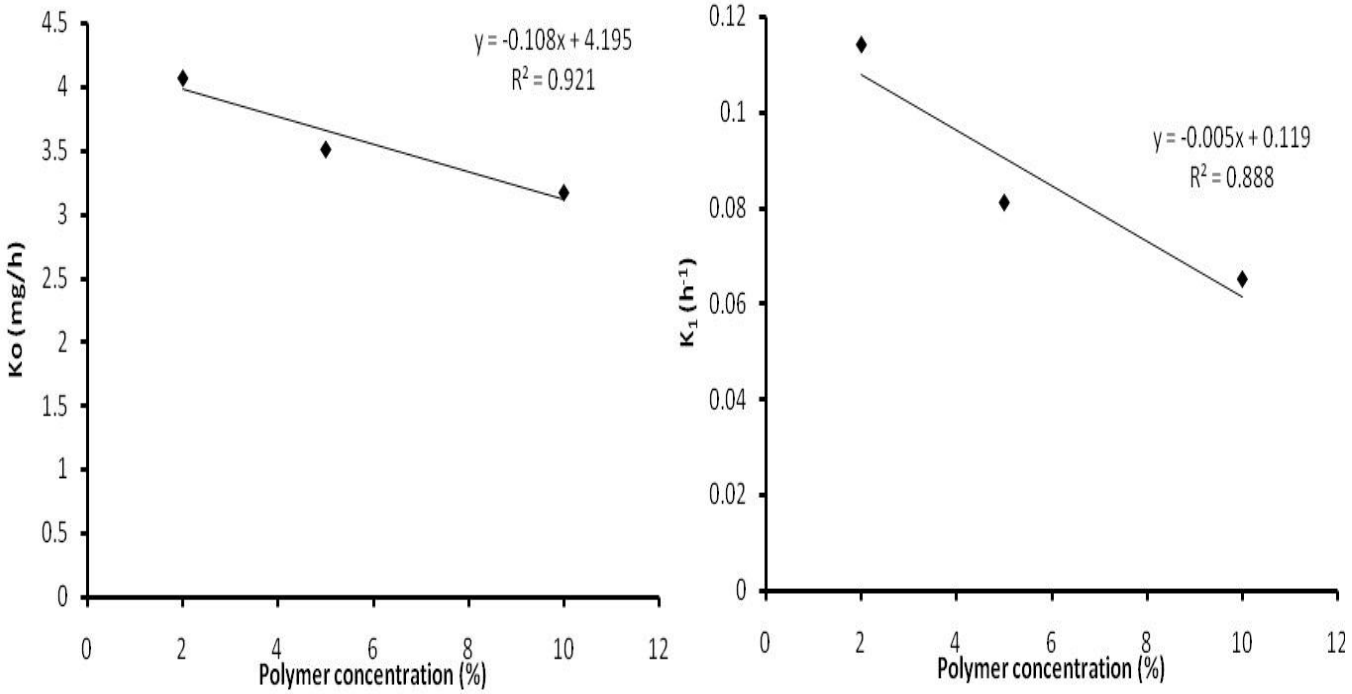

Fig 3: Relationship between Percent Polymer and Release Rate, K_0 & K_1 of Aceclofenac Matrix Tablets Prepared Employing Olibanum resin Using Lactose as Diluent

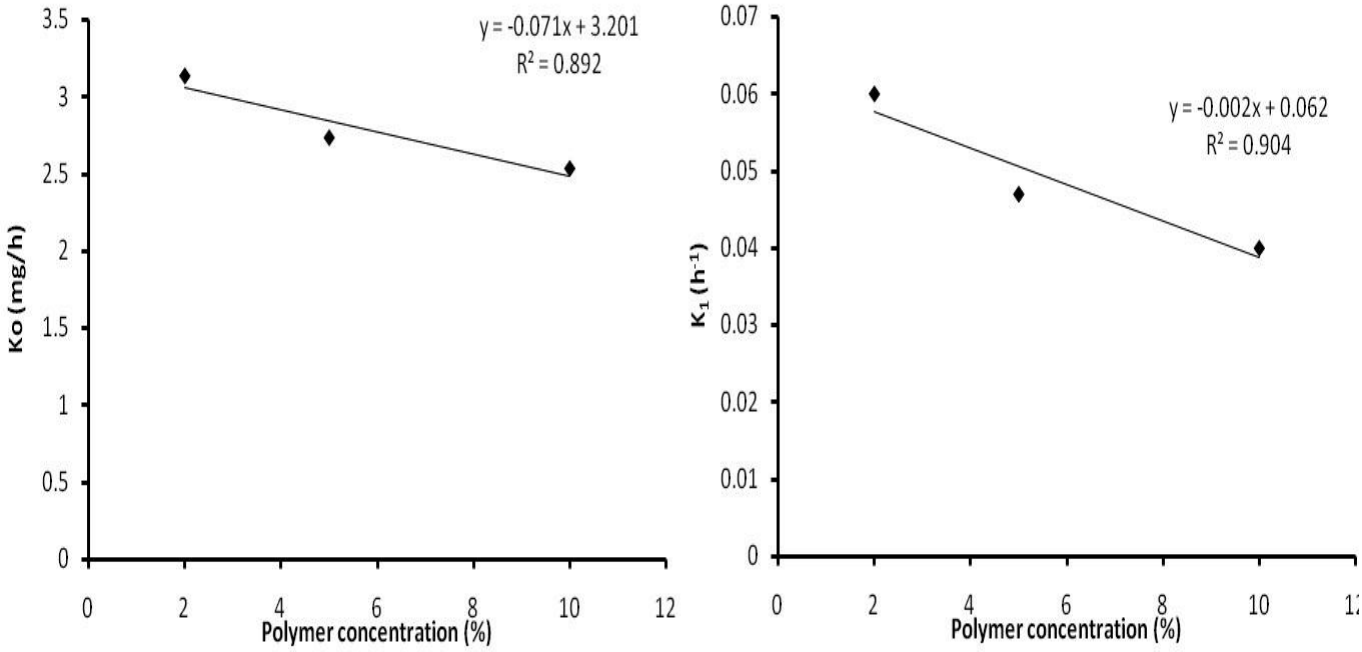

Fig 4: Relationship between Percent Polymer and Release Rate, K_0 & K_1 of Aceclofenac Matrix Tablets Prepared Employing Olibanum resin Using DCP as Diluent

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