IJPSR (2012), Vol. 3, Issue 04 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 December, 2011; received in revised form 01 February, 2012; accepted 27 March, 2012

FORMULATION AND EVALUATION OF DICLOFENAC CONTROLLED RELEASE TABLETS EMPLOYING OLIBANUM RESIN

K.P.R. Chowdary [1] and G. Rami Reddy*[2]

A.U. College of Pharmaceutical Sciences, Andhra University [1], Visakhapatnam, Andhra Pradesh, India
Greenland Organics [2], Surampalli, Vijayawada, Andhra Pradesh, India

Keywords:
Olibanum resin,
Diclofenac,
Matrix tablets,
Controlled release

Correspondence to Author:

G. Rami Reddy

Greenland Organics, Surampalli,
Vijayawada, Andhra Pradesh, India

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 diclofenac for controlled release. Matrix tablets of diclofenac were formulated employing Olibanum resin in different proportions of drug and polymer and 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. Diclofenac 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(DF2) are considered suitable for controlled release of diclofenac over 24 h (i.e. once-a-day administration).

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 tablets, 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 Diclofenac.

Olibanum is a gum resin obtained from *Boswellia serrata*, Roxburgh and other species of *Boswellia*. Olibanum consists of chiefly of an acid resin (50 - 60%), gum (30-36%) and volatile oil (2-8%). The resin consists 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 [1-3]. 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 Diclofenac was formulated employing Olibanum resin in different proportions of drug and polymer and the tablets were evaluated for drug release kinetics and mechanism

Diclofenac sodium is a widely used non-steroidal anti-inflammatory analgesic and anti-pyretic drug. Controlled release formulation is needed for diclofenac because of its short biological half life[4] of 2.0 h. The drug also causes [5] gastro intestinal disturbances, peptic ulceration with bleeding if present in large concentration in gastrointestinal tract.

Hence, diclofenac is a suitable drug for oral sustained and controlled release and it would be advantageous to slow down its release in gastrointestinal tract not only to prolong its therapeutic action but also to minimize possible side effects of diclofenac.

EXPERIMENTAL:

Materials:

1. Diclofenac (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 Diclofenac 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°C 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/cm^2 using 9 mm round and flat punches.

TABLE 1: COMPOSITION OF DICLOFENAC (100MG) MATRIX TABLETS FORMULATED

Composition (mg/tablet)	Lactose			Dicalcium Phosphate (DCP)		
	DF1	DF2	DF3	DF4	DF5	DF6
Diclofenac	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

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, 0.1N HCl and phosphate buffer of pH 7.4 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 Diclofenac. The solution was then made up to volume with methanol. The methanolic solution was subsequently diluted suitably with phosphate buffer of pH 7.4 and assayed for Diclofenac at 275 nm. Diclofenac content of the tablets was calculated using the standard calibration curve.

Drug Release Study: Release of Diclofenac from the matrix tablets prepared was studied in phosphate buffer of pH 7.4 (900 ml) using an eight station dissolution rate test apparatus with a paddle stirrer at 50 rpm and 37±0.5°C. A sample matrix tablets equivalent to 100 mg of Diclofenac were 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 Diclofenac 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 Diclofenac 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 0.25% 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 in both the cases were non-disintegrating in acidic and alkaline fluids, they are considered suitable for oral controlled release.

Drug Release Characteristics: Diclofenac release profiles of various matrix tablets formulated are shown in **Figs. 3 & 4.** Diclofenac 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 0.5622 – 0.7043 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.

TABLE 2: WEIGHT VARIATION, HARDNESS, FRIABILITY, DISINTEGRATION TIME AND DRUG CONTENT OF DICLOFENAC MATRIX TABLETS FORMULATED

Formulation code	Weight variation (%)	Friability (%)	Hardness (Kg/cm^2)	DT (min.)	Diclofenac content (%) ($\bar{x}$ ± s.d)
DF1	214.8 ± 0.86	0.46 ± 0.05	5.00 ± 0.34	Non-disintegrating	99.34 ± 0.45
DF2	217.0 ± 0.35	0.52 ± 0.09	5.00 ± 0.27	Non-disintegrating	97.45 ± 0.57
DF3	215.4 ± 1.23	0.54 ± 0.03	5.50 ± 0.18	Non-disintegrating	98.78 ± 0.28
DF4	218.0 ± 0.75	0.65 ± 0.04	6.00 ± 0.43	Non-disintegrating	95.36 ± 0.27
DF5	219.2 ± 0.82	0.47 ± 0.07	5.50 ± 0.47	Non-disintegrating	96.28 ± 0.16
DF6	218.4 ± 1.21	0.36 ± 0.03	5.50 ± 0.34	Non-disintegrating	96.57 ± 0.19

TABLE 3: CORRELATION COEFFICIENT (R^2) VALUES IN THE ANALYSIS OF RELEASE DATA OF DICLOFENAC 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
DF1	0.9796	0.9414	0.9471	0.9703
DF2	0.9612	0.9442	0.9654	0.9719
DF3	0.9541	0.8838	0.9633	0.9827

TABLE 4: CORRELATION COEFFICIENT (R^2) VALUES IN THE ANALYSIS OF RELEASE DATA OF DICLOFENAC 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
DF4	0.9778	0.8854	0.9229	0.9339
DF5	0.9574	0.9381	0.9771	0.9718
DF6	0.9550	0.9267	0.9748	0.9885

TABLE 5: RELEASE CHARACTERISTICS OF DICLOFENAC 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
DF1	2	11	3.94	0.098	0.7043
DF2	5	12	3.53	0.080	0.6283
DF3	10	14	2.99	0.060	0.5622

TABLE 6: RELEASE CHARACTERISTICS OF DICLOFENAC 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
DF4	2	14	3.37	0.077	0.5656
DF5	5	12	3.32	0.072	0.6232
DF6	10	14	2.94	0.056	0.5763

Y= 4.153 - 0.117x (in the series made with olibanum resin with lactose as diluent). Y= 3.527 - 0.056x (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= 0.105 - 0.004x (in the series made with olibanum resin with lactose as diluent). Y= 0.083 – 0.002x (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 (%).

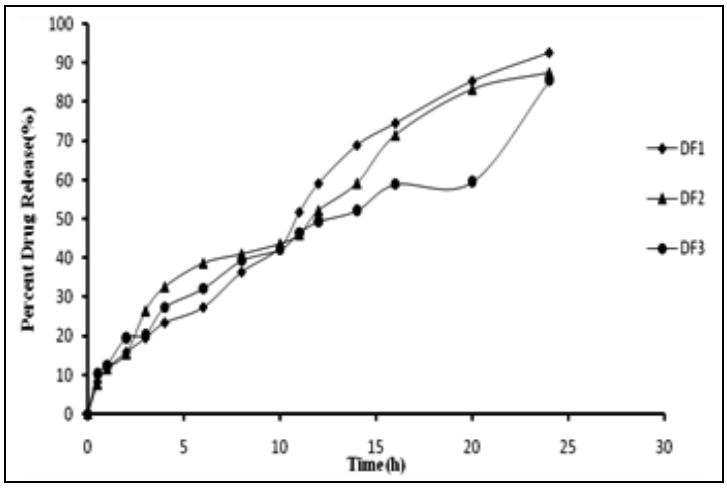

FIG. 1: RELEASE PROFILES OF DICLOFENAC MATRIX TABLETS PREPARED EMPLOYING OLIBANUM RESIN USING LACTOSE AS DILUENT

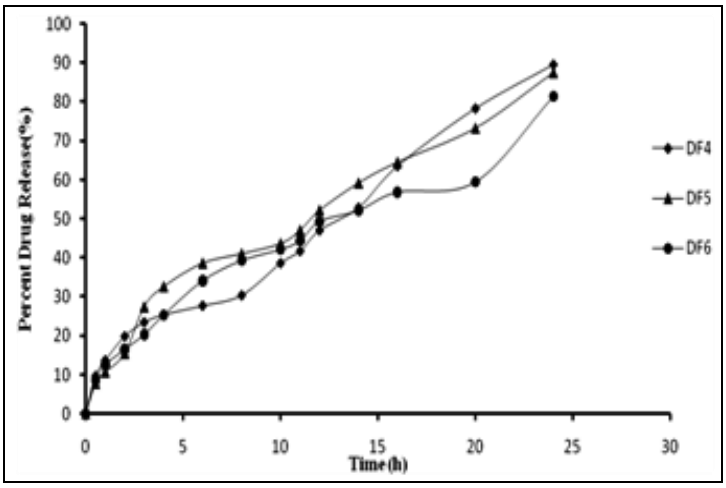

FIG. 2: RELEASE PROFILES OF DICLOFENAC MATRIX TABLETS PREPARED EMPLOYING OLIBANUM RESIN USING DCP AS DILUENT

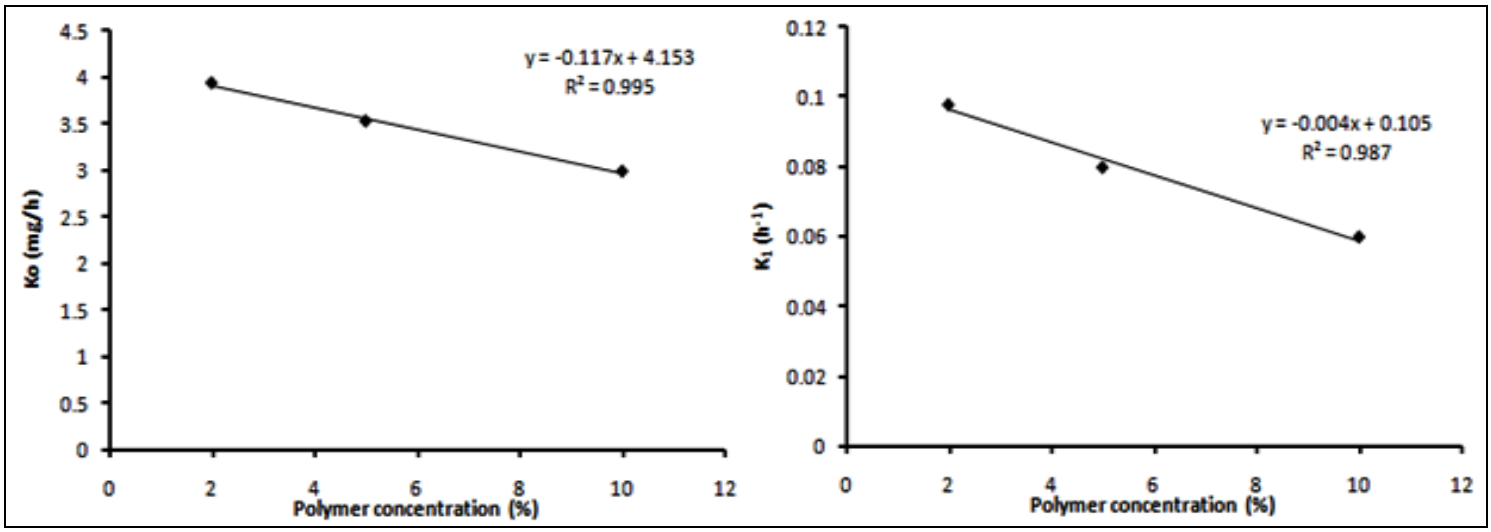

FIG. 3: RELATIONSHIP BETWEEN PERCENT POLYMER AND RELEASE RATE, K_0 & K_1 OF DICLOFENAC MATRIX TABLETS PREPARED EMPLOYING OLIBANUM RESIN USING LACTOSE AS DILUENT

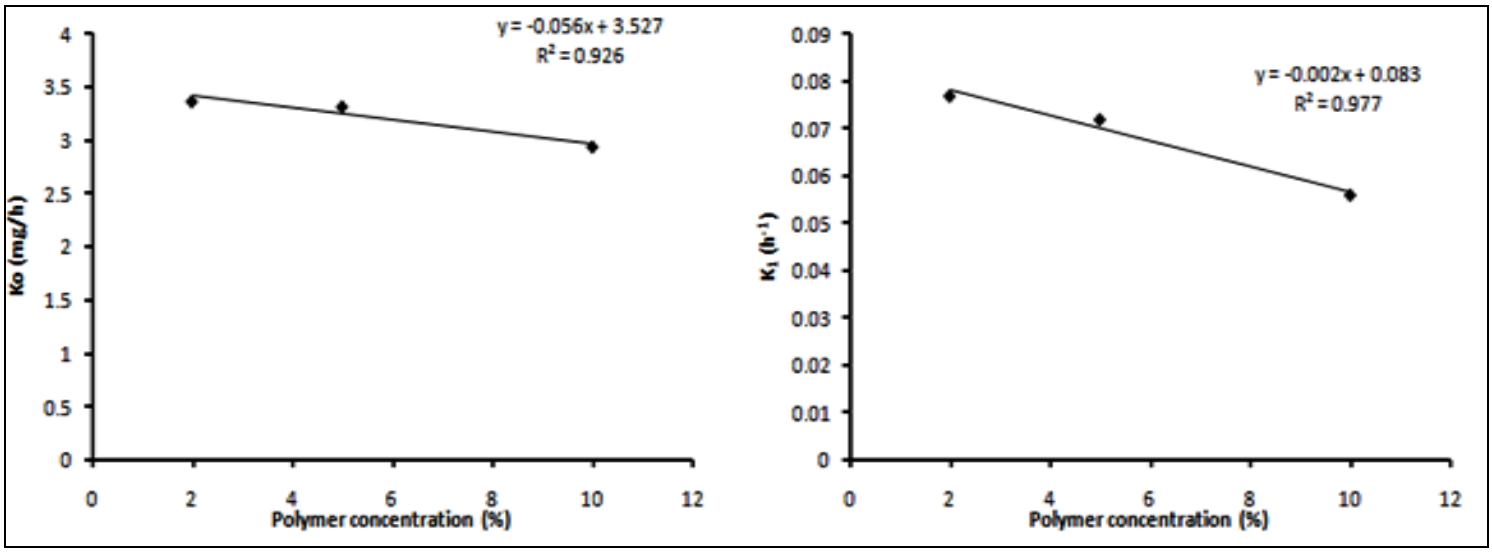

FIG. 4: RELATIONSHIP BETWEEN PERCENT POLYMER AND RELEASE RATE, K_0 & K_1 OF DICLOFENAC MATRIX TABLETS PREPARED EMPLOYING OLIBANUM RESIN USING DCP AS DILUENT

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 (DF2) are considered suitable for controlled release of Diclofenac over 24 h (i.e., once-a-day administration).

CONCLUSION: Matrix tablets of diclofenac were formulated employing Olibanum resin in different proportions of drug and polymer and 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.

Diclofenac 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 (DF2) are considered suitable for controlled release of diclofenac over 24 h (i.e. once-a-day administration).

REFERENCES:

1. Chowdary KPR, Mohapatra P and Murali Krishna MN, Evaluation of olibanum and its resin as rate controlling matrix for controlled release of diclofenac. Indian J Pharm Sci 2006; 68: 497-500.
2. Chowdary KPR and Srinivas P. Evaluation of Olibanum Resin as Microencapsulating Agent for Controlled Release of Glimepiride. Asian J. Chem. 2008; 20: 5391-5398.
3. Chowdary KPR, Mohapatra P and Murali Krishna MN, Evaluation of olibanum resin as microencapsulating agent for controlled drug delivery. Indian J. Pharm. Sci., 2006; 68: 461-464.
4. Kobayashi KA, Bauer LA, Horn JR, Opheim K, Wood F Jr and Kradjan WA., Glipizide pharmacokinetics in young and elderly volunteers. Clin. Pharm. 1988; 7(3): 224-228.
5. Rang HP, Dale MM and Ritter JM, In; pharmacology, 4th Edn., Churchill Living Stone, London. 1999; 230.
6. Higuchi T. Mechanism of Sustained-action Medication. Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices, J Pharm Sci. 1963; 52:1145-1149.
7. Ritger PL and N. A. Peppas. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J. Control. Release. 1987; 5(1): 37-42.

****