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Investigation of Different Lipid Based Materials as Matrices Designed to Control the Release of a Hydrophobic Drug

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ABSTRACT
The present study was designed to evaluate the effect of different hydrophobic materials and their loading level on the release profile of etoricoxib, a model lipophilic drug, from matrix systems. Matrix tablets of the drug were prepared using compritol, precirol, glyceryl monostearate, cetostearyl alcohol and eudragit as release retarding agents by direct compression process. The resulting monolithic tablets were found to have optimum hardness, uniform thickness, high content uniformity and low friability. All tablet formulations yielded quality matrix preparations with satisfactory tableting properties. Increasing the concentration of hydrophobic materials significantly decreased the friability (from 2.73 to 0.46 in case of eudragit) and subsequently increased the tensile strength (0.237 to 0.908 in case of eudragit) of the formulated tablets. At higher hydrophobic level (50% of the matrix), the rate and extent of drug release was significantly reduced due to increased tortuosity and reduced porosity of the matrix. Compritol imparted the strongest retardation of drug release amongst the selected lipid based materials. *In vitro* drug dissolution and mathematical modeling were used to characterize drug release rate and extent. The release kinetics was found to be governed by the type and content of hydrophobic materials in the matrix. Numerical fits indicate that the Higuchi square root of time model (TEUD I, TEUD II, TCSA I and TCSA II), Hixson-Crowell cube root model (TGMS I, TCOM I and TPRE I) and Korsemeyer Peppas model (TGMS II, TCOM II and TPRE II) were the most appropriate one for describing the release profile of etoricoxib from hydrophobic matrices. Mathematical modeling indicated that the drug release followed a combination of diffusion and erosion mechanism.

Keywords: Eudragit, Compritol, Hixson-Crowell cube root model, etoricoxib.

INTRODUCTION

Tablet matrix system containing hydrophobic lipid based materials have been widely used in formulations for controlled drug delivery applications because of their chemical inertness [1], cost effectiveness, regulatory acceptance and above all flexibility to achieve the desired drug release profile. [2] These are widely used as release retardants in the design of sustained release tablets, suspensions, beads, implants, and microcapsules.

Compritol 888 ATO, chemically known as glyceryl behenate [3], and Precirol, chemically known as glyceryl palmito-stearate, are hydrophobic polymer which can be used as glyceride bases for potential applications as lipidic binders to develop dosage forms with sustained-release properties. [4] Glyceryl monostearate, a waxlike solid in the form of beads, flakes, or powder, is used as a lubricant for tablet manufacturing and may be used to form sustained-release matrices for solid dosage forms. [5-6] Eudragits are copolymers of methacrylic acid and methyl methacrylate which have been used successfully to obtain appropriate sustained-release matrix formulations of different active materials. [7] Cetostearyl alcohol, a mixture of fatty alcohols consisting predominantly of cetyl and stearyl alcohols, is commonly utilized as matrix forming components and is extensively used for sustaining the release of drugs. [8]

Etoricoxib (5-chloro-2-[6-methyl pyridin-3-yl]-3-[4-methylsulfonylphenyl] pyridine) is a novel, selective second generation cyclo-oxygenase-2 inhibitor administered orally as an analgesic and anti-inflammatory drug that is used for the treatment of osteoarthritis, rheumatoid arthritis and gouty arthritis. [9-10] It is an off-white crystalline powder, relatively insoluble in water, and freely soluble in alkaline aqueous

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solutions. [11] Etoricoxib is available in tablet dosage forms (60, 90, 120 mg). [12]

Wide varieties of different lipid based hydrophobic materials are available for sustaining drug action. The present study is designed to evaluate the comparative efficiency of different lipid matrices in controlling the release of active ingredient from the tablet formulation. Comproitol, Precirol, Glyceryl Monostearate (GMS), Cetostearyl Alcohol were used as the hydrophobic matrices and their drug release-retardant ability were studied in terms of *in vitro* dissolution testing and compared with formulation batch prepared with Eudragit RSPO (standard release retardant). The matrices being used possess different physico-chemical property and imparted a diversified impact on the rate and extent of drug release. Etoricoxib was chosen as the model drug. The kinetics and mechanism of drug release from the prepared matrix systems has been explored and explained with the help of various exponential models.

MATERIAL AND METHODS

Materials

Etoricoxib was received as a gift sample from Helios Pharmaceuticals Ltd., Baddi, India. Vivapur-102 (Microcystalline cellulose NF) and Vivapress- CA 800 (Calcium Carbonate USP, DC-Grade) were gift samples from S. Zhaveri, Mumbai, India. Compritol and precirol were kindly gifted by Indswift Ltd., Chandigarh, India. Glyceryl monostearate and cetostearyl alcohol were purchased from CDH, Mumbai, India. Talc and Magnesium stearate were procured from S D Fine Chemicals Ltd. Mumbai, India. All other chemical/reagents were of analytical grade and used as such.

Preparation of Tablets

Vivapur-102 and Vivapress CA-800 were mixed in 2:1 ratio to form a diluent mixture. The powdered release retardant material (compritol, precirol, GMS, cetostearyl alcohol and Eudragit RSPO) was mixed thoroughly with the diluent mixture. Talc (1 % w/w) and magnesium stearate (1 % w/w) were incorporated as glidant/lubricant. All the batches were formulated as per formula detailed in Table 1 and Table 2. The tablet weight was kept 250 mg for all the batches and was compressed using single stroke mutipunch tableting machine (AK Industries, Nakodar, India).

Table 1: Formulation of matrix tablets at 25% release retardant polymer level

Ingredient	TCOM -I	TPRE-I	TGMS -I	TCSA-I	TEUD-II
Etoricoxib	50	50	50	50	50
Compritol	62.5	-	-	-	-
Precirol	-	62.5	-	-	-
Glyceryl Monostearate (GMS)	-	-	62.5	-	-
Cetostearyl Alcohol	-	-	-	62.5	-
Eudragit RSPO	-	-	-	-	62.5
Diluent (Vivapur 102: Vivapress CA 800)	132.5	132.5	132.5	132.5	132.5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5
Total Weight	250	250	250	250	250

Determination of Content Uniformity

The formulated matrix tablets were tested for their drug content. Twenty tablets were finely powdered; 400 mg of the powder was accurately weighed and transferred to a 50-mL volumetric flask. Then the volume was made up with 0.1N HCl and shaken for 10 min to ensure complete solubility of drug. The mixture was centrifuged (Remi, India) and 10 mL of the supernatant liquid was diluted 20 times with 0.1N HCl, and after centrifugation the absorbance was determined spectrophotometrically (Systronics 2202 model, India) at 233 nm.

Table 2: Formulation of matrix tablets at 50% release retardant polymer level

Ingredient	TCOM -II	TPRE-II	TGMS -II	TCSA-II	TEUD -II
Etoricoxib	50	50	50	50	50
Compritol	125	-	-	-	-
Precirol	-	125	-	-	-
Glyceryl Monostearate (GMS)	-	-	125	-	-
Cetostearyl Alcohol	-	-	-	125	-
Eudragit RSPO	-	-	-	-	125
Diluent (Vivapur 102: Vivapress CA 800)	70	70	70	70	70
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5
Total Weight	250	250	250	250	250

Physical Properties of Tablets

All the fabricated hydrophobic matrix tablets were evaluated for diameter, thickness, hardness and friability.

Diameter and thickness: A calibrated vernier caliper was used for diameter and thickness evaluation of the tablets.

Hardness: Ten tablets from each batch were examined using Monsanto hardness tester.

Friability: For friability tests, ten tablets were weighed (W_1) and rotated at one hundred revolutions for 4 min in a Roche friabilator. The tablets were then reweighed (W_2) and the percentage of friability (% F) was calculated:

$$\%F = \left(\frac{W_1 - W_2}{W_2} \right) \times 100$$

Friability below 0.8 % is usually considered satisfactory.

Determination of Tensile Strength

The tensile strength (T) of tablet which is a measure of the stress necessary to cause diametral fracture of the compact was determined from the mean data obtained from the hardness test carried out on the tablets (n = 10) using the Mosanto hardness tester according to Brook and Marshal. [13] The T values were computed from equation below [14] :

$$T = \frac{2P}{\pi Dt}$$

Where P is the load applied on the tablet that causes tensile fracture of the tablet of diameter, D, and t is the tablet thickness.

In Vitro Drug Release Studies

The matrix tablets were subjected to the paddle dissolution method using 900 mL of 0.1 N HCl solution as the dissolution medium. The dissolution test was performed at 50 rpm and the temperature was set at 37°C ± 1°C. At predetermined time intervals over 24 h period, 5 mL samples were withdrawn, and assayed spectrophotometrically at 233 nm. After each sampling, equal volume (5 mL) of fresh media solution with the same temperature was replaced. All experiments were carried out in triplicate.

Table 3: Physical parameters of the formulated tablets

S. No	Diameter (mm) n=10	Thickness (mm) n=10	Friability (%) n=10	Hardness (kg/cm^2) n=10	Tensile Strength (MN/m^2) n=10	Assay
TGMS I	8.40 ± 0.02	4.75 ± 0.04	1.3 ± 0.05	1.5 ± 0.42	0.239 ± 0.020	99.1 ± 0.01
TCOM I	8.42 ± 0.01	4.78 ± 0.02	0.48 ± 0.06	3.25 ± 0.25	0.514 ± 0.035	98.6 ± 0.05
TCSA I	8.42 ± 0.02	4.76 ± 0.03	0.74 ± 0.04	2.0 ± 0.80	0.317 ± 0.025	98.9 ± 0.04
TPRE I	8.43 ± 0.03	4.75 ± 0.01	0.59 ± 0.04	3.5 ± 0.40	0.556 ± 0.060	98.2 ± 0.02
TEUD I	8.40 ± 0.05	4.78 ± 0.01	2.73 ± 0.08	1.5 ± 0.20	0.237 ± 0.084	99.0 ± 0.03
TGMS II	8.42 ± 0.02	4.80 ± 0.04	0.67 ± 0.02	2.0 ± 0.60	0.315 ± 0.042	97.5 ± 0.01
TCOM II	8.45 ± 0.05	4.75 ± 0.02	0.49 ± 0.02	3.5 ± 0.15	0.555 ± 0.030	98.2 ± 0.05
TCSA II	8.43 ± 0.02	4.78 ± 0.01	0.53 ± 0.01	5.5 ± 0.50	0.869 ± 0.070	98.6 ± 0.08
TPRE II	8.41 ± 0.01	4.77 ± 0.04	0.56 ± 0.02	3.75 ± 0.85	0.595 ± 0.055	97.9 ± 0.01
TEUD II	8.42 ± 0.04	4.79 ± 0.03	0.46 ± 0.04	5.75 ± 0.70	0.908 ± 0.040	98.5± 0.02

Table 4: Kinetic studies on hydrophobic matrix tablets

Batch No.	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
	r^2	k_0 (h^{-1})	r^2	k_1 (h^{-1})	r^2	k_H ($h^{-/2}$)	r^2	n value	k_{KP} (h^{-n})	r^2	k_{HC} ($h^{-1/3}$)
TGMS I	0.9783	0.1253	0.8691	-0.0043	0.6889	0.8691	0.8792	0.1087	1.7475	0.9801	0.0021
TCOM I	0.9620	0.2695	0.8613	-0.0026	0.8864	4.9675	0.8887	0.7220	0.0840	0.9801	0.0065
TCSA I	0.7942	0.1491	0.8349	-0.0028	0.9848	2.4402	0.8987	0.3481	1.1483	0.8814	0.0098
TPRE I	0.6629	0.1462	0.8876	-0.0030	0.7384	3.2674	0.8348	0.5182	0.7034	0.9691	0.0179
TEUD I	0.9416	0.2155	0.9340	-0.0022	0.9867	4.0515	0.9245	0.5136	0.6279	0.8652	0.0061
TGMS II	0.9504	0.0704	0.9915	-0.0009	0.9901	2.3619	0.9931	0.5086	0.3571	0.8684	0.0022
TCOM II	0.8025	0.0376	0.9423	-0.0004	0.9139	1.3174	0.9433	0.5391	0.1635	0.7209	0.0015
TCSA II	0.9501	0.2616	0.9230	-0.0045	0.9675	6.1327	0.9472	0.5273	0.6978	0.9130	0.0055
TPRE II	0.6398	0.1437	0.8561	-0.0029	0.7697	4.354	0.8664	1.0229	0.2602	0.5081	0.0033
TEUD II	0.9532	0.1962	0.9667	-0.0024	0.9814	5.4968	0.9498	0.6802	0.2003	0.9046	0.0047

Kinetic Studies

The *in vitro* drug release data of the formulated batches of the matrix tablets was fitted into the following models and respective plots were made: zero order kinetic model (cumulative % drug release vs time); first order kinetic model (log cumulative of % drug remaining vs time); higuchi model (cumulative % drug release vs square root of time); power law (log cumulative % drug release vs log time) and hixson-crowell model (cube root of drug % remaining in matrix vs time.

The zero order model (equation 1) describes concentration independent drug release rate from the formulation whereas first order model (equation 2) describes concentration dependent drug release from the system. Higuchi [15], (equation 3) described the release of drugs based on Fickian diffusion as a square root of time dependent process from swellable insoluble matrix whereas the Hixson-Crowell cube root law (equation 4) correlated the release from systems with polymer erosion/dissolution resulting in a change in surface area and diameter of particles or tablets. [16] The power law [17] (equation 5) describes the influence of polymeric hydration and swelling on drug release rate.

$$C = k_0 t \quad (1)$$

Where, K_0 is zero-order rate constant expressed as concentration/time and t is the time.

$$LogC = LogC_0 - \frac{k_1}{2.303} \quad (2)$$

Where, C_0 is the initial concentration of drug and k is first order constant.

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

Where, k is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t \quad (4)$$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and k_{HC} is the rate constant for Hixson-Crowell rate equation.

$$\frac{M_t}{M_\infty} = k_{KP} t^n \quad (5)$$

where, M_t / M_∞ is the fraction of drug release, k_{KP} is the release rate constant, n is the diffusional release exponent indicative of the drug release mechanism (Table 1), and t is the dissolution time.

RESULTS AND DISCUSSION

All the batches of hydrophobic matrix tablets were formulated under similar conditions to avoid processing variables. The prepared tablets were evaluated for various physical parametric tests. Table III gives the physical parameters (diameter, thickness, hardness and friability) and content uniformity of all the formulated tablet batches. The diameter and thickness of the prepared tablets was found to be 8.43 ± 0.02 mm and 4.75 ± 0.05 mm, respectively. The tablet formulations in all the batches prepared contained etoricoxib within 100 ± 2.5 % of the drug content.

Friability is an important factor in tablet formulation to ensure that the tablet can stay intact and withhold its form from any outside force of pressure. The amount of hydrophobic material was found to have a significant affect on friability, hardness and tensile strength of the prepared tablets. The % friability was found to be ranging from 0.48 to 2.73 in case of 25 % release retardant loading and 0.46 to 0.67 in case of 50 % retardant loading, clearly indicating the dependence of friability on percentage of hydrophobic material in the matrix tablets. Values of the friability index shows that the tablets became less friable with increase in hydrophobic material concentration in the tablets. The tablets generally displayed a low friability index; the maximum recorded friability was 2.73 % of TEUD I batch. The results obtained are in line with previous research investigations carried out by Basak et al. [6]

The hardness and tensile strength values are also presented in Table 3. The hardness and tensile strength of the fabricated tablets was found to increase with the increase lipid content. These observations are in accordance with previous studies where a waxy material promoted a greater plastic

deformation of the particles during compaction. This plastic deformation leads to an increase in the area of particle–particle contact and cohesion further leading to the formation of hard tablets. [18] A highly significant variation was observed in case of matrices formulated with eudragit where hardness increased from 1.5 kg/cm^2 to 5.75 kg/cm^2 as the polymer content is increased from 25 % (TEUD I) to 50 % (TEUD II) material load, respectively. There is a proportionate increase in tensile strength values as is evident from the TCSA I (0.317 MN/m^2) and TCSA II (0.869 MN/m^2) and TEUD I (0.237 MN/m^2) and TEUD II (0.908 MN/m^2) formulated batches.

The physico-chemical composition of different hydrophobic materials imparted a significant impact on the rate and extent of drug release as depicted in Fig. 1 and 2. Also the overall release rate of etoricoxib from different hydrophobic materials was found to be significantly different ($P<0.0001$). In case of matrices containing 25 % of the release retarding material, compritol and eudragit imparted strongest retarding effect (87.30 % and 83.82 % drug released in 300 min, respectively) on the release of etoricoxib, whereas GMS could not impart a significant sustaining effect on the drug release (80 % drug released in 30 min). The higher extent of release in case of GMS could be attributed to its surface-active property (HLB value 3.8). [19] Compritol decreases the hydration of matrix and retards the release by erosion mechanism owing to its hydrophobic property. Release profiles of etoricoxib from TCSA I and TPRE I were almost superimposable on each other. The cumulative release after 4 hours was 86.93 % and 89.98 % respectively for these two matrices. The aliphatic portion present in the cetostearyl alcohol matrix provides sufficient hydrophobicity and impedes wetting of the matrix surface by dissolution fluid. There is an initial burst release in all the formulation in the following order GMS (82.84%) > > CSA (40.66%) > EUD (29.6%) > PRE (21.86%) > COM (18.8%) during the first 30 min. The initial burst release of the drug from the hydrophobic system is often therapeutically undesirable because the total amount of drug released is remarkably influenced by this initial control of release from the dosage form. [20] The presence of burst release for all the polymers being studied clearly indicates that hydrophobic materials at 25 % level were not sufficient to produce a desirable pharmacokinetic profile.

In case of formulations containing 50 % of the hydrophobic material again COM represents the best-sustained release action on the release of the drug amongst the selected hydrophobic release retardants. Further, except for CSA matrix (40.66 % in case of 25 % and 33.45 % in case of 50 %), increasing the hydrophobic materials' level greatly reduced the initial release. The fact can be reasoned in the way that, an increase in the polymer content results in a decrease in the drug release rate due to a decrease in the total porosity of the matrices (initial porosity plus porosity due to the dissolution of the drug). [21] Increment in polymer content also increases the tortuosity of the matrix and drug diffusion path-length, which in turn slows down diffusion and erosion from/of the matrix. [22] The release profile in case of GMS demonstrated a significantly different trend as is depicted in the Fig. 1 and 2. Here the drug release was 66.11 % in 6 h and the initial burst decreased from 82.84 % to 12.35 % as the amount of GMS is increased from 25 % to 50 % in the formulation. The drug release profile represented somewhat linear pattern but could not show significant effect of change of polymer concentration on drug release although the initial brust decreased from 29.6 % to 17.86 %. Release profiles of drug from TCSA I and TPRE I were again found to be almost superimposable on each other but are showing more sustaining affect on the drug release than the previous case.

Different semi-imperical kinetic equations (zero-order, first-order, Higuchi's equation, Korsmeyer peppas and Hixson Crowell) were applied to interpret the release rate from matrix system. The model that best fitted the release data was evaluated by correlation coefficient (R^2). R^2 values for all formulations in various models are given in Table 4.

In case of the matrix tablets containing 25 % release retardant, TCSA I and TEUD I could be best explained by Higuchi model, as the plots showed high linearity (Fig. 3), with correlation coefficient (R^2) values 0.9848 and 0.9867 respectively. Whereas, the best fit with higher correlation was found with the Hixson Crowell model in case of TGMS I, TCOM I and TPRE I with R^2 values of 0.9801, 0.9801 and 0.9691 respectively (Fig. 4). The diffusion mechanism of drug release was further confirmed by Korsmeyer-Peppas plots that showed fair linearity with R^2 values between 0.8348 and 0.9245 and slope values ranging from 0.1087 to 0.7220, demonstrating the tendency of drug release by Fickian or Case I mechanism for all the batches except TCOM I. Compritol matrix system, on the other hand, showed a greater deviation from case I or Fickian kinetics ($n = 0.7220$) and showed much adherence to anomalous or non-fickian release. This suggests that, at this polymeric load, some level of swelling and dissolution of matrix must be operating within the compritol matrix system which causes it to deviate from the Fickian release and remain in moving boundary condition. [23] Presence of higher proportion of diluent (Vivapur-102 and Vivapress CA-800) in the system also enhances the penetration of water into the matrix and facilitates the contact of compritol with eluting media. Increasing the hydrophobic material load, however, brought about changes in the kinetics of drug release and consequently in the value of release exponent. At 50 % level, TCSA II and TEUD II were found to be following Higuchi kinetic equation with R^2 values of 0.9675 and 0.9814 respectively (Fig. 3). Whereas Korsmeyer-Peppas equation demonstrated best fit with R^2 value of 0.9931, 0.9433 and 0.8664 in case of TGMS II, TCOM II and TPRE II formulated batches, respectively (Figure 5). The n values for the batches containing 50 % hydrophobic load varied from 0.5086 to 1.0229 indicating a significant variation from case I or Fickian transport thereby showing combined effect of diffusion and erosion mechanisms for controlled drug release. An increase in the release retardant content decreases the hydration of matrix and retards the release by erosion mechanism owing to their hydrophobic property. Hence it can be inferred that the release of drug from a hydrophobic matrix tablet generally involves both pore diffusion and matrix erosion.

The approach of the present study was to make a comparative evaluation among the hydrophobic materials as release retarding agents. The finding suggests that the hydrophobic material imparted binding property along with sustaining effect on drug release from the matrix of the tablet formulations. Further it was ascertained that the variations in polymeric type and content have significant effect on the release profile of etoricoxib. The study also reveals that, it is

possible to formulate matrix tablet by appropriate combination of these hydrophobic matrices with rate controlling agents to get an acceptable pharmacokinetic profile in the fluctuating *in vivo* environment.

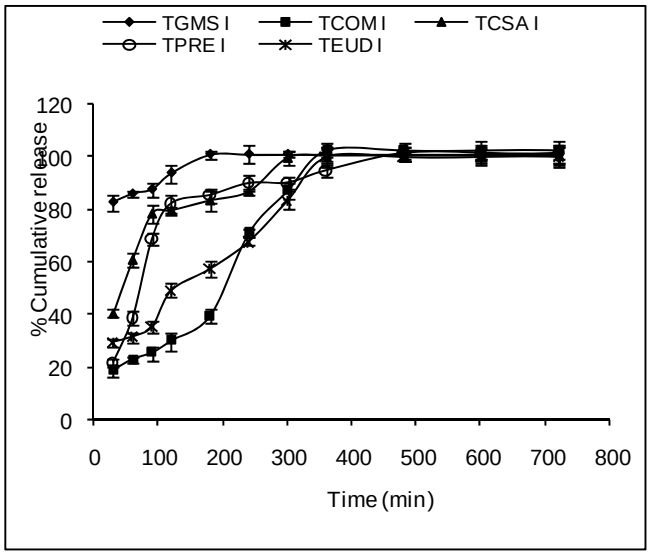

Fig. 1: Release profile of etoricoxib from lipid based matrix tablets at 25% hydrophobic material load.

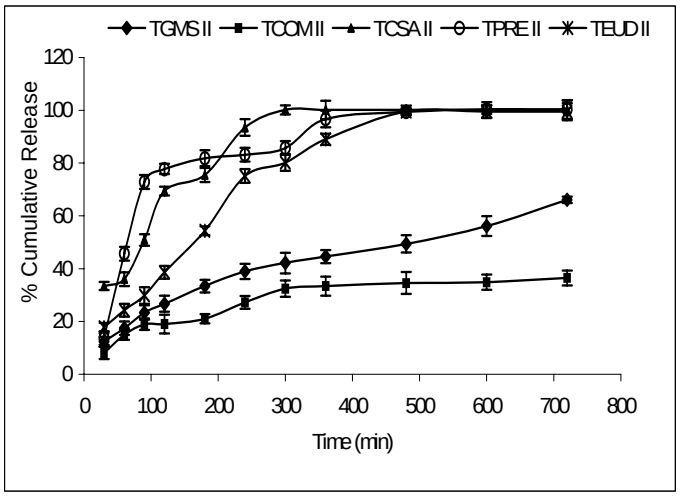

Fig. 2: Release profile of etoricoxib from lipid based matrix tablets at 50 % hydrophobic material load.

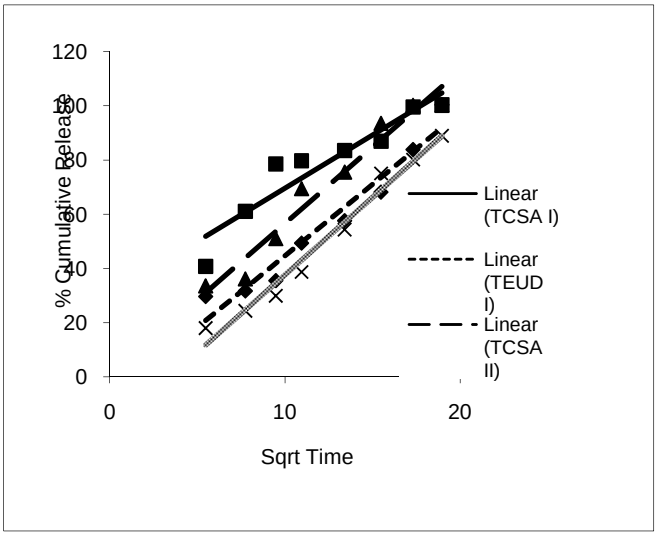

Fig. 3: Higuchi release model of etoricoxib hydrophobic matrix tablet formulations

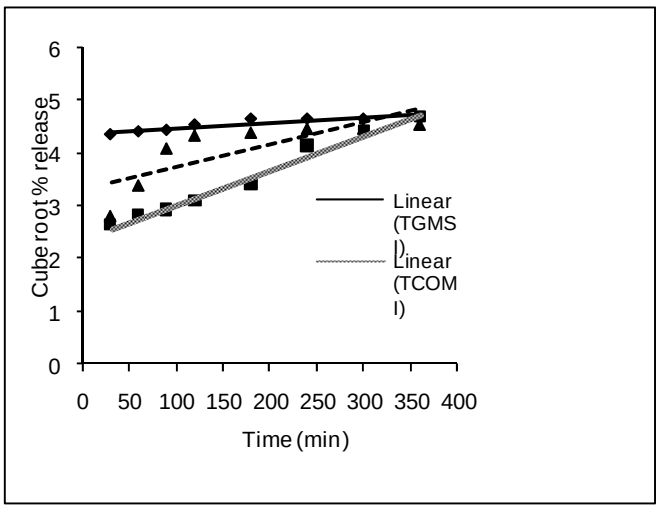

Fig.4: Hixson-Crowell cube root plots of etoricoxib from the formulated tablets

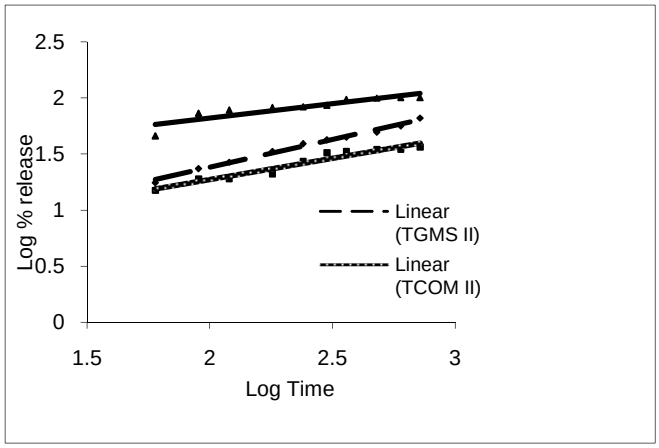

Fig. 5: Korsmeyer – Peppas Model for mechanism of drug release (first 60% drug release)

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