IJPSR (2013), Vol. 4, Issue 3 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 November, 2012; received in revised form, 16 January, 2013; accepted, 25 February, 2013

IN-VITRO RELEASE CHARACTERIZATION OF KETOROLAC TROMETHAMINE LOADED MATRIX TABLETS

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Keywords:
Ketorolac Tromethamine, Kollidon SR, Formulation, Matrix Tablets, Hydroxy Propyl Methyl Cellulose

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ABSTRACT: The present investigation highlighted the formulation and release characterization of Ketorolac Tromethamine loaded matrix tablet. Various formulations of tablets were prepared by direct compression method along with Kollidon SR and Hydroxy Propyl Methyl Cellulose (HPMC) as release retardant polymers. Each of the formulated tablets contains 50mg Ketorolac Tromethamine. The evaluation involved physical properties studies (weight variation, thickness, length, width, hardness, friability, and drug content) of tablets and *in vitro* release kinetics assessment. The USP paddle method was operated at 50 rpm selected to perform the dissolution test and 900 ml phosphate buffer of pH 7.4 was used as dissolution medium. The drug release from each formulation was analyzed by using release kinetics theories. All formulations followed Higuchi release kinetics. When the release data was plotted into Korsemeyer-Peppas equation, then it was confirmed that F-1 to F-5 exhibited fickian type drug release whereas F-6 exhibited non-Fickian type drug release. The *in-vitro* release studies revealed that the formulation F-4 can be taken as an ideal or optimized formulation of sustained release tablets. Furthermore, the dissolution of the formulation-4 was performed in SLS (1%, 1.5%, and 2%) medium, which was observed gradually decreasing release rate as concentration of SLS medium increased.

INTRODUCTION: Ketorolac Tromethamine is a novel Non-steroidal anti-inflammatory drug (NSAID) with potent analgesic & modest anti-inflammatory activity. In postoperative pain it has equaled the efficacy of morphine, but does not interact with opioid receptors & is free of respiratory depressant, dependence producing, hypertensive & constipating side effects. In short lasting pain, it has compared favorably with aspirin.

Ketorolac Tromethamine is dihydrolizine carboxylic acid derivatives structure related to indomethacine [1]. Ketorolac have a chiral center and is used as a racemate marketed under the name Toradol the (-)-s isomer has many times greater analgesic potency than the (+)- R-isomer [2].

Ketorolac Tromethamine is off-white crystalline powder and has a pK value of 3.49. Ketorolac is quite lipophilic with a log PC (partition coefficient) value of 2.72 [3]. Ketorolac Tromethamine is extremely soluble in aqueous solution at pH 4-8, with a very long self-life at 25°C. However it is light sensitive with decarboxylation, especially in the presence of oxygen [4-5].

Matrix tablets offer a great potential as oral controlled drug delivery systems due to easy and low cost of production like conventional rapid release tablets. Various controlled release agents including natural and synthetic polymers (HPMC, Kollidon SR etc) have used in production of matrix tablets for soluble and insoluble drugs for years [6-9].

The aim of this study was to design matrix tablets of Ketorolac Tromethamine in order to maintain drug in the systematic circulation for a long period of time. Matrix tablets of Ketorolac Tromethamine were prepared by using various polymers as HPMC and Collidon SR. Drug release from tablets in various dissolution mediums were tested and drug release mechanisms were discussed considering kinetic release models

MATERIALS AND METHODS:

Materials: Ketorolac Tromethamine (KT) was received as a gift sample from Glove Pharmaceuticals Ltd, Polymer Kollidon SR (BSAF Germany) and Hydroxypropyl Methyl Cellulose (HPMC) were obtained as a gift sample from BASF Bangladesh Ltd, Kollidon SR is insoluble in water but very soluble in N-methyl pyrrolidon, Magnesium stearate and Lactose were obtained from Novo Pharmaceuticals Ltd Bangladesh. All other chemicals used were of analytical reagent grade and distilled water was used throughout the experiments. Standard Ketorolac Tromethamine was used in calculation as label claimed from the source.

Preparation of Matrix Tablets: Matrix tablets, Ketorolac Tromethamine (KT) each containing 555mg were prepared by direct compression. The active ingredient and other excipients were accurately weighted for twenty five tablets according to the formulations. Properly weighed ingredients were blended in a laboratory designed small drum blender. Particular attention has been given to ensure through mixing and phase homogenization. Finally the resultant blend was compressed using a pilot plant tablet machine having (5 punch and die, India) fitted with cylindrical shape punch and die.

TABLE 1: SUSTAINED RELEASE KETOROLAC TROMETHAMINE MATRIX FORMULATIONS

Ingredent	Amount (mg)					
	F_1	F_2	F_3	F_4	F_5	F_6
Ketorolac Tromethamine	50	50	50	50	50	50
Kollido SR	300	350	100	100	350	0
HPMC	100	100	300	350	0	350
Lactose	100	50	100	50	150	150
Mg-stearate	5	5	5	5	5	5
Total	555	555	555	555	555	555

Evaluation of Tablets:

1. **Length, Width, Size and Shape:** The length and width of tablets depends on the die and punches selected for making the tablets. The tablets of various sizes and shapes are prepared but generally they are circular with either flat or biconvex faces. Here, we prepared round cylindrical shape tablets.

2. **Thickness:** The thickness of a tablet can vary without any change in its weight. This is generally due to the difference of density of granules, pressure applied for compression and the speed of compression. The thickness of the tablets was determined by using a Digital Caliper (range 0-150 mm).

3. **Uniformity of Weight:** It is desirable that every individual tablet in a batch should be in uniform weight and weight variation within permissible limits. If any weight variation is there, that should fall within the prescribed limits (generally ±10% for tablets weighing 130 mg or less, ±7.5% for tablets weighing 130 to 324 mg and ±5% for tablets weighing more than 324 mg) [10].

4. The weights of 10 tablets of each batch were taken at individually and calculate the average weight of 10 tablets. The weights were determined by using an electronic balance (Adventurer TM electronic balance, Model AR2140, Capacity (Max) - 210 gm, Readability 0.0001 gm). Then determine the percentage of weight variation of each tablet by using following formula;

Percentage of weight variation= (Average weight – Individual weight)/ Average wt. ×100

5. **Friability:** Friability test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The

instrument used for this test is known as 'Friability Test Apparatus' or 'Friabilator'. It consists of a plastic chamber which is divided into two parts and revolves at a speed of 25 rpm. A number of tablets were weighed (W_1) and placed in the tumbling chamber which was rotated for four minutes or for 100 revolutions. During each revolution the tablets fall from a distance of six inches to undergo shock. After 100 revolutions the tablets were again weighed (W_2) and the loss in weight indicates the friability. The acceptable limits of weights loss should not be more than 1 percent [11].

$$\text{Friability} = \{(W_1 - W_2)/W_1\} \times 100$$

6. **Hardness:** The hardness of tablet depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression. The hardness also depends on the nature and quantity of excipients used during compression. The hardness of the tablets was determined by using a hand operated hardness tester apparatus (Electrolab EH-01P). A tablet hardness of about 6-8 kgf was considered for mechanical stability [10]. If the finished tablet is too hard, it may not disintegrate in the required period of time and if the tablet is too soft it may not withstand the handling during packing and transporting. Therefore it is very necessary to check the hardness of tablets when they are being compressed and pressure adjusted accordingly on the tablet machine.

Assay of Ketorolac Tromethamine:

Preparation Sample Solution: 555 mg of crushed tablet powder (equivalent to 50 mg) was dissolved in phosphate buffer solution and made the volume up to 100 mL. The solution was diluted 100 times and absorbance was taken. Then the percentage of potency was calculated by the following equation:

% of Potency=

$$\frac{A_{spl} \times W_{std} \times P_{std} \times \text{Average Weight}}{A_{std} \times W_{spl} \times \text{Label claimed value}}$$

Where,

A_{spl} =Absorbance of Sample

W_{std} =Weight of Standard

P_{std} =Potency of standard

A_{std} = Absorbance of standard

W_{spl} =Weight of sample

***In-vitro* Release Studies:**

Dissolution Study Procedure: The *in vitro* dissolution studies were performed using USP type-II dissolution apparatus (Rotating Peddle method) at 50 rpm. The dissolution medium consisted of potassium di-hydrogen phosphate buffer of pH 7.4 up to 900 mL, maintained at 37°C ± 0.5°C. An aliquot (5 mL) was withdrawn at specific time intervals which replaced by equivalent amount of buffer solution. The drug content was determined by UV-visible spectrophotometer (SHIMADZU UV-1800 spectrophotometer) at 322 nm. The release studies were conducted in triplicate.

Analysis of Release Data: The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of drug release versus square root of time), Korsemeyer-Peppas (log cumulative percentage of drug release versus log time) and Hixson-Crowell (cubic root of percentage drug release versus time) equation models.

Dissolution data were also fitted according to the well-known exponential equation, which is often used to describe the drug release behavior from polymeric systems introduced by Korsmeyer-Peppas *et al* [12].

$$M_t / M_\infty = k\, t^n$$

Where, M_t is the amount of drug release at time t, M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusion exponent indicative of the mechanism of drug release. A value of n = 0.45 indicates Fickian (case I) release, > 0.45 but < 0.89 for non-Fickian (anomalous) release and > 0.89 indicates super case II type of release.

Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release [13].

RESULTS AND DISCUSSIONS:

Drug Content and Physical Evaluation of Ketorolac Tromethamine Matrix Tablets: The prepared tablets were subjected to preliminary characterization such as physical parameters (thickness, diameter, hardness and friability) and weight uniformity of all the fabricated tablets. The values are indicated in **Table 2**. Table 2 also shows the drug content of these tablets.

TABLE 2: PHYSICAL PARAMETERS AND DRUG CONTENT OF KETOROLAC TROMETHAMINE FROM PROPOSED FORMULATION

Code	Weight variation* (%) ±SEM	Thickness (mm)** ±SEM	Length (mm)** ±SEM	Width (mm) ±SEM	Hardness (Kf)** ±SEM	Friability (%) **	Drug content** (%) ±SEM
F-1	555.13±1.19	8.3±0.1	17.5±0.3	5.05±0.15	6.21±0.19	0.41	99.2±1.4
F-2	555.51±0.79	8.29±0.1	17.6±0.25	5.03±0.13	6.77±0.35	0.37	99.36±1.1
F-3	555.81±0.95	8.31±0.15	17.5±0.23	5.01±0.15	6.51±0.23	0.65	99.52±0.7
F-4	555.67±0.49	8.3±0.17	17.47±0.23	5.01±0.13	6.32±0.17	0.57	101.75±0.8
F-5	555.83±0.66	8.33±0.15	17.51±0.29	5.07±0.1	6.56±0.37	0.47	98.72±1.2
F-6	555.97±0.88	8.28±0.15	17.49±0.31	5.06±0.13	6.29±0.33	0.53	101.49±1.7

*n=10, ** n=3

All the batches showed uniform thickness, length and widths. The average percentage deviation of 10 tablets of each formulation was less than (5%) and hence all formulations passed the test for uniformity of weight as per official requirements. The hardness of all the formulations is within the range of limit. The use of Kollidon SR & HPMC has facilitated the compression of the tablets and made it possible to impart proper hardness settings.

It is possible to have better control in a larger production control. Tablets hardness is, however, not an absolute indicator of strength. The percentage of friability of the tablets of all the formulations also within the range. In the present study, the percentage friability for all for formulations was below 1% w/w, indicating that the friability is within the prescribed limits.

So, all the tablet formulations showed acceptable pharmacopoeial properties and complied with pharmacopoeial specifications for weight variation and friability. All the formulations showed good uniformity in drug content and the percentage of drug content was 99.2±1.4, 99.36±1.1, 99.52±0.7, 101.75± 0.8, 98.72±1.2 and 101.49±1.7 respectively to formulation 1, 2, 3, 4, 5 and 6.

***In-vitro* Drug Release Studies:** The dissolution data (from the values of 0 to 8 hours to know which drug release) of all formulations were fitted into various mathematical models (zero-order, first-order, Higuchi, Korysmeyer-Pappas model, Hixon-Crowell plot) to know which mathematical model will best fit for the drug release profile. **Table 3** represents the obtained dissolution data of all the formulations and **fig. 1** represents the plotted figure respectively.

TABLE 3: RELEASE KINETICS PARAMETERS OF DESIGNED SUSTAINED RELEASE MATRIX TABLETS OF KETOROLAC TROMETHAMINE

Code	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Korsmeyer's-Peppas (r^2)	Hixon-Crowell (r^2)
F-1	0.872	0.917	0.979	0.991	0.539
F-2	0.769	0.821	0.913	0.958	0.460
F-3	0.908	0.940	0.984	0.971	0.561
F-4	0.899	0.932	0.980	0.952	0.515
F-5	0.829	0.900	0.956	0.978	0.443
F-6	0.962	0.980	0.983	0.990	0.611

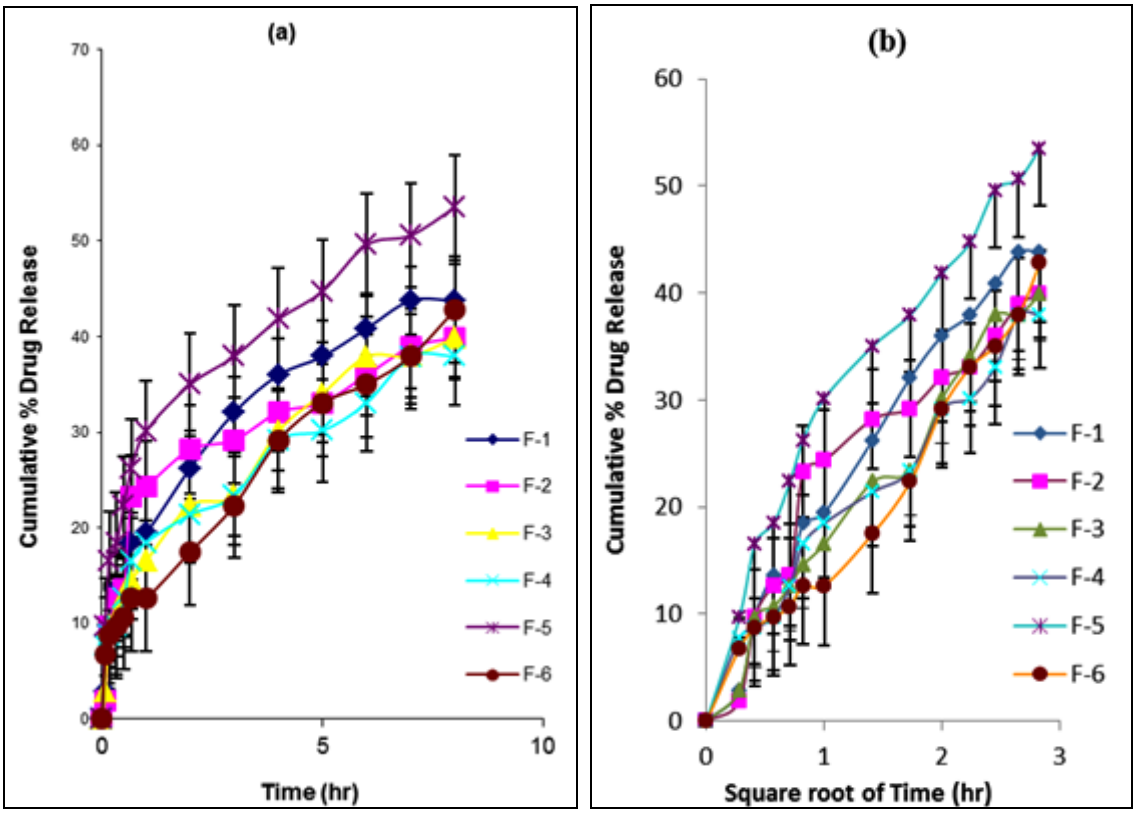

FIG. 1: RELEASE MODEL OF KETOROLAC TROMETHAMINE SUSTAINED RELEASE FORMULATIONS (a) ZERO-ORDER RELEASE MODEL AND (b) HIGUCHI RELEASE MODEL

From release kinetics parameters we can say that the highest regression coefficient value (r^2) the best-fit model for all formulations was Higuchi model. It is clearly indicated that, the formulations did not follow a zero-order release pattern because the regression value for all formulations did not show high linearity. When the data were plotted according to the first-order equation, the tablets showed a first order release, with regression value of (F1 to F6) 0.917, 0.821, 0.940, 0.932, 0.900, 0.980. The formulations showed to be best expressed by Higuchi's equation, as the plots showed high linearity with regression value of (F1 to F6) 0.979, 0.913, 0.984, 0.980 ,0.956, 0.983 indicating that the release of drug follows the Higuchi release kinetics and diffusion is the dominating mechanism for drug release.

The dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation), which is often used to describe the drug release behavior from polymeric systems. In **table 4,** the n values are 0.399, 0.235, 0.443, 0.369, 0.280 and 0.595 for F-1 to F-6 formulation respectively. From the table, we can say that, F-1 to F-5 exhibited fickian type drug release whereas F-6 exhibited Non-fickian type drug release from the tablet matrix. After 8 hours various percent of drug release were found from various formulations. The releases were 43.79032, 39.89247, 39.8871, 37.95161, 53.505 and 42.79032 indicating F-1 to F-6 formulation respectively. Among the formulations F-4 formulation is the best formulation as sustain release drug, which contain 1:3.5 ratio polymer (Kollidon SR: HPMC). **Fig. 2,** a bar diagram showing effect of the polymer on drug release rate of various ratio.F-1 to F-6 formulation contain polymer (Kollidon SR: HPMC) of different ratio as 3:1, 3.5:1, 1:3 , 1:3.5, 3.5:0, 0:3.5, F-4 formulation show lowest release rate. From this study, its helps to predict that HPMC when incorporated with Collidon SR it slower the dissulition rate as described in Banik S *et al***.**[14]

TABLE 4: IN VITRO DRUG RELEASE MECHANISM FOR PROPOSED FORMULATIONS OF KETOROLAC TROMETHAMINE SUSTAINED RELEASE MATRIX TABLET USING KORSMEYER-PEPPAS MODEL

	Release rate constant (k)	Diffusion exponent (n)	Release type
F-1	1.300	0.399	Fickian
F-2	1.373	0.235	Fickian
F-3	1.207	0.443	Fickian
F-4	1.235	0.369	Fickian
F-5	1.463	0.280	Fickian
F-6	1.086	0.595	Non-Fickian

Time for 25%, 50%, and 75% Drug Release according to Higuchi equation: Based on highest regression coefficient value (r^2) the best-fit model for all formulations was Higuchi model. Time required for 25%, 50% and 75% of drug release was corrected using linear equation of Higuchi plot. From this study, it was observed that formulated tablets of formulation-4 required for 75% released more than 32.86 hours

TABLE 5: TIME REQUIRED FOR 25%, 50% AND 75% DRUG RELEASE

Code	$Time_{25\%}$ (hr)	$Time_{50\%}$ (hr)	$Time_{75\%}$ (hr)
F-1	2.01	9.03	21.09
F-2	2.277	11.39	27.462
F-3	3.002	12.98	29.95
F-4	3.00	13.904	32.86
F-5	0.99	6.147	15.69
F-6	2.983	12.35	28.10

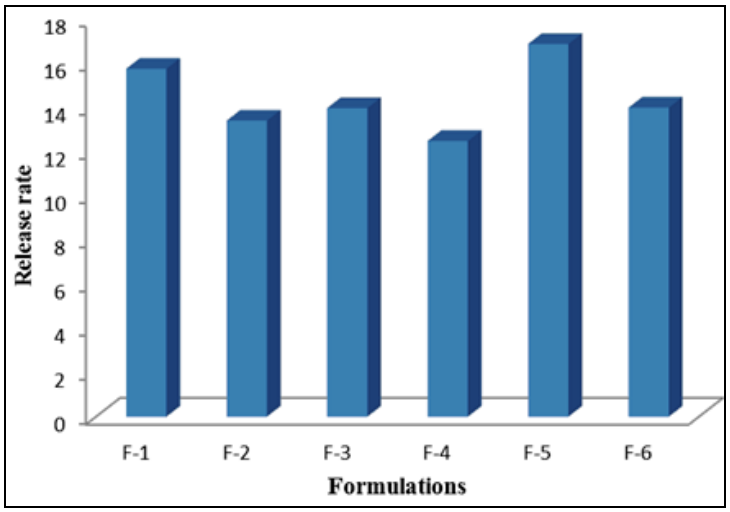

FIG. 2: EFFECT OF POLYMER CONTENT ON RELEASE RATE (HIGUCHIAN RELEASE)

Effect of Surfactants in Dissolution Medium in Drug Release Mechanism: Surfactants are usually organic compounds that are amphiphilic, meaning they contain both hydrophobic groups (their *tails*) and hydrophilic groups (their *heads*). Therefore, a surfactant molecule contains both a water insoluble (and oil soluble) component and a water soluble component. Surfactant molecules will diffuse in water and adsorb at interfaces between air and water or at the interface between oil and water, in the case where water is mixed with oil. The insoluble hydrophobic group may extend out of the bulk water phase, into the air or into the oil phase, while the water soluble head group remains in the water phase.

This alignment of surfactant molecules at the surface modifies the surface properties of water at the water/air or water/oil interface [15]. Sodium lauryl sulfate (SLS) is a commonly used surfactant in dissolution media. However, it has occasionally been observed that SLS negatively impacts the dissolution of drug products [16].

This study investigated the effect of SLS in sustain drug release. Different viscous dissolution medium were prepared by dissolving 1%, 1.5%, and 2%, SLS in distilled water [17]. Then dissolution of the formulation-4 which show lowest release rate was performed in SLS (1%, 1.5%, and 2%) medium.

In-vitro release data presented in **Fig. 4 and 5** shows that drug release was faster in medium without SLS, but it continuously decreased when the percentage of SLS incorporation in medium increased. Medium with 2% SLS contributes around 32.10% drug release after 8 hr while 1% SLS containing medium showed 35.99% drug release.

From this, it was assessed for determining the drug release mechanism by treating the data in different fashion, we found that drug release from the matrix tablets predominantly followed the Higuchi release rather than zero-order kinetics which was showed in medium without SLS as well as in phosphate buffer pH 7.4.

Dissolution media containing SLS can significantly hinder the disintegration of tablets containing cellulose-based disintegrants resulting in a very slow dissolution rate but other surfactants, ionic and nonionic, did not exhibit this effect [16].

In our formulation, we used HPMC, which is cellulose derivatives, so we also predicted the similar phenomena as described by Shlyankevich A. *et al* [17]**.**

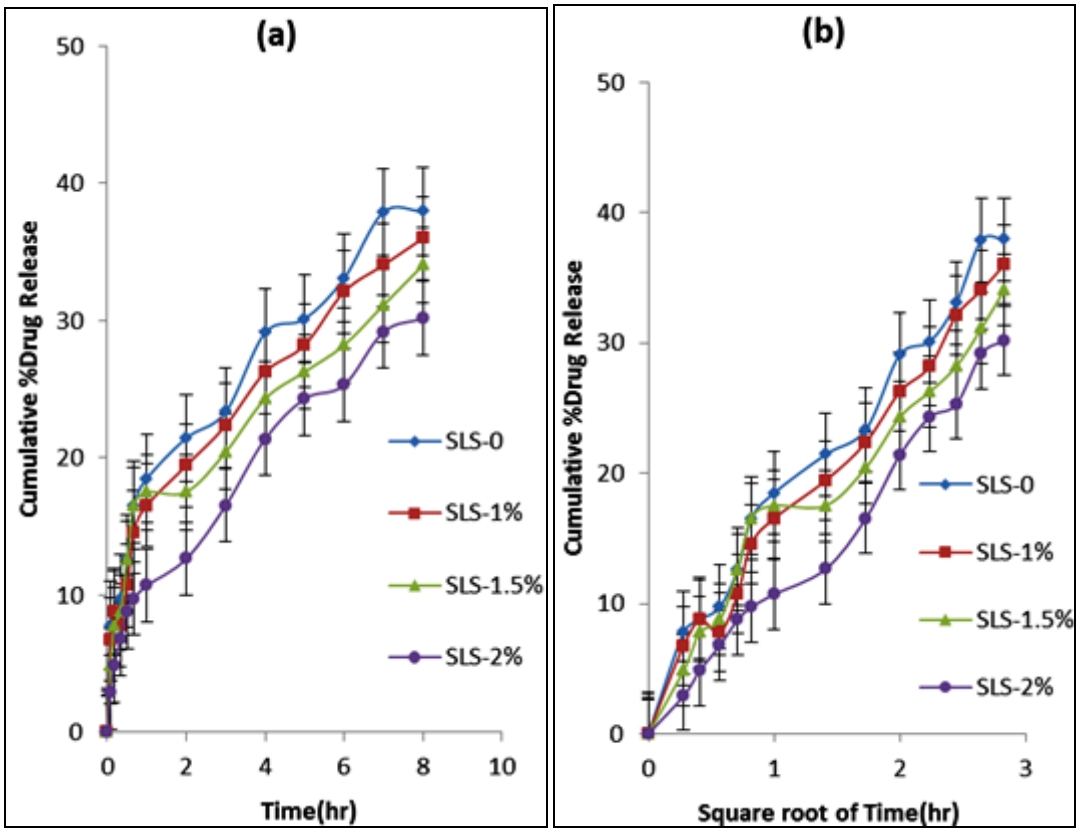

FIG. 3: RELEASE PROFILE OF KETOROLAC TROMETHAMINE SUSTAINED RELEASE FORMULATIONS IN DIFFERENT CONCENTRATION (1%, 1.5% AND 2%) OF SLS (a) ZERO-ORDER RELEASE MODEL AND (b) HIGUCHI RELEASE MODEL

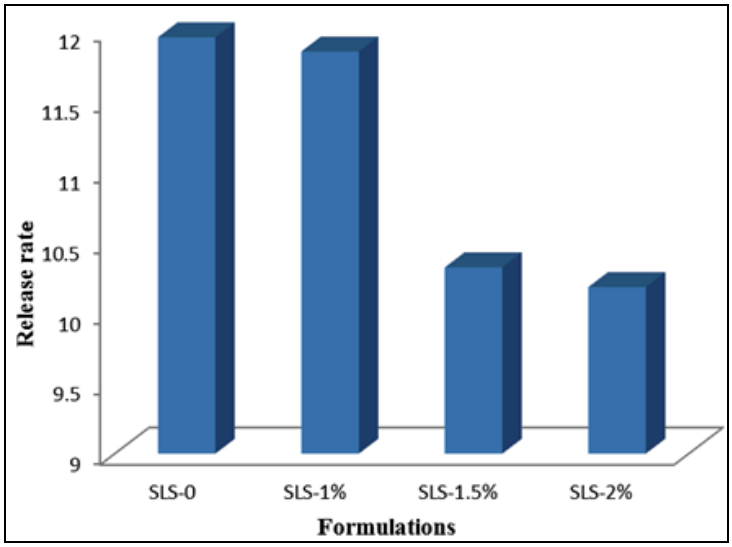

FIG. 4: RELEASE RATE OF WITHOUT SURFACTANTS & WITH VARIOUS CONCENTRATION (1%, 1.5%, AND 2%) OF SURFACTANTS AS DISSOLUTION MEDIUM

CONCLUSION: From the study, it is possible to conclude that the proposed tablet formulations were suitable for direct compression method. The incorporation of Kollidon SR and Hydroxy Methyl Cellulose as a polymer entails the stronger rate-retarding agents. According to the release studies, it was observed that the rate of drug release increases with decrease in total polymeric content of the matrix.

According to Higuchi release rate, the formulated tablets of formulation- 4 sustained the release effects more than 24 hours. Furthermore dissolution was performed in different concentration (1%, 1.5% and 2%) of SLS medium, for the formulation- 4 it was observed that, the gradual increased of the concentration of SLS medium resulting gradually decreases of the release rate of the drug. In future research, we are planning to get the bio-availability data by administrating these formulated tablets in animal model.

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How to cite this article:
Ahamed SA, Banik S and Hossain MS: *In-vitro* Release Characterization of Ketorolac Tromethamine Loaded Matrix Tablets. *Int J Pharm Sci Res* 2013; 4(3); 1140-1147.