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FORMULATION AND EVALUATION OF TIZANIDINE HYDROCHLORIDE MICROSPHERES BY USING 3^2 FULL FACTORIAL DESIGNS

Adimoolam Senthil*, Chavda Gajendrasnh Ambuji, Patel Jyotindra Natvarlal, Jimson Jose, Narayana Swamy VB
Department of pharmaceutics, Karavali College of Pharmacy, Mangalore-575028, Karnataka, India

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*A. Senthil. Email: senthilac12@gmail.com

ABSTRACT
Tizanidine hydrochloride is a centrally acting α-2 adrenergic agonist muscle relaxant. In the present study an attempt has been made to formulate and evaluate tizanidine hydrochloride microspheres by using hydroxypropylmethylcellulose K4M and carboxymethyl cellulose as polymers. Tizanidine hydrochloride microspheres were prepared by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Twenty preliminary trial batches, B1-B20 batches of microspheres were prepared by using different volume (2 to 10 ml) of glutaraldehyde as cross-linking agent, cross-linking time 1 to 4 hours and 3:1 ratio of polymer-to-drug with two different polymers. From these twenty batches of each polymer, the optimized formulation is selected based on the percentage of mucoadhesion, drug entrapment efficiency and sphericity of microspheres. A 3^2 full factorial design was employed to study the effect of independent variables, polymer-to-drug ratio (X1), and stirring speed (X2) on dependent variables percentage of mucoadhesion, drug entrapment efficiency, swelling index and in-vitro drug release study. The drug polymer compatibility studies were carried out using FTIR. Among the two polymers hydroxypropylmethyl cellulose K4M exhibited a high drug entrapment efficiency of 79% and a swelling index 1.260, percentage of mucoadhesive after 1hour was 80% and the drug release was also sustained for more than 10 hours.
KEYWORDS: Microspheres, Tizanidine hydrochloride, Hydroxypropylmethylcellulose K4M, Carboxymethylcellulose, Glutaraldehyde.

INTRODUCTION

A primary object of using mucoadhesive formulations orally would be to achieve a substantial increase in length of stay of the drug in the GI tract. Stability problem in the intestinal fluid can be overcome. Therapeutic effect of drugs insoluble in the intestinal fluids can be improved[5]. Microspheres carrier systems are made from the biodegradable polymers in sustained drug delivery. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems[1-3]. Microspheres form an important part of such novel drug delivery systems. They have carried applications and are prepared using assorted polymers[1]. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. It would therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes[6-9]. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres. Bioadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site[10-13].

Tizanidine hydrochloride is an imidazoline derivative, which acts as agonist on centrally located α2 receptors and this leads to myotonolytic effects on skeletal muscle. It is structurally and pharmacologically similar to clonidine and other α2-adrenergic agonists. The correct mechanism of tizanidine in decreasing muscle tone and frequency of spasm is not clearly understood. About 53% to 66% of the dose administered is being absorbed through the gastrointestinal tract after oral administration and the peak plasma concentration is reached within 1 to 2 h. Bioavailability of tizanidine is about 34% to 40% and half life is 2.5 h. The drug is widely distributed throughout the body and 30% of drug binds to plasma proteins. It undergoes rapid and extensive first pass metabolism in the liver (approximately 95% of a dose), leading to the oxidation of the imidazoline moiety, aromatic system, and the sulfur atom. Tizanidine is least absorbed from the lower part of the gastrointestinal tract and better absorbed from the stomach. The main limitations of the therapeutic effectiveness of tizanidine hydrochloride is its low bioavailability (30 to 40%), short biological half life (4.2 h) and the fact that it undergoes first pass metabolism. Thus the development of controlled release dosage forms would clearly be advantageous. Dosage forms that are retained in the stomach would increase the absorption, improve drug efficiency, and decrease dose requirements. Thus, an attempt was made by using synthetic mucoadhesive polymers HPMC K4M and CMC by using tizanidine hydrochloride as a drug. On the basis of the preliminary trials a 3^2 full factorial design were employed for all the polymers batches, to study the effect of independent variable X1 polymer-to-drug ratio and the stirring speed X2 on dependent variables percentage mucoadhesion, drug entrapment efficiency, and particle size. The drug polymer compatibility studies were carried out using FTIR.

MATERIALS AND METHOD

Materials

Tizanidine hydrochloride was obtained as gift sample from Sun Pharma Pvt. Ltd, India. Hydroxypropylmethylcellulose K4M was obtained from Danmed Pharmaceuticals, India. Carboxymethylcellulose was obtained from AET, Laboratories, Hyderabad. Span85 (0.5%w/v) was obtained from Loba Chemical Pvt. Ltd, Mumbai. Acetic acid, Petroleum ether 80:20, Light and heavy Liquid paraffin, Glutaraldehyde (25% v/v aqueous solution) of analytical grade are used.

Method

Microspheres were prepared by simple emulsification phase separation technique by using two different polymers HPMC K4M and CMC. The different volume of cross-linking agent glutaraldehyde was used as per method described in Thanoo *et al*[14]. Polymer (1.5gms) was dissolved in 150 ml of 1% v/v aqueous acetic acid solution and 500 mg of drug was dispersed in the polymer solution in B1 to B20 batches. The resultant mixture will be extruded through a syringe (No.20) in 1liter of liquid paraffin (heavy and light 1:1 ratio). Containing 0.5% Span 85 and stirring was performed using propeller stirrer at different stirring speed. After 15 min cross-linking agent glutaraldehyde was added and stirring was continued. The amount of cross-linking agents (2 to 10 ml) and cross-linking times were varied (1 to 4 hours), respectively, as showed in Table 1. In factorial design batches F1 to F9, the optimized amount of glutaraldehyde was used as a cross-linking

agent and cross-linking time. The Polymer-to-drug ratio (1:1, 3:1 and 4:1) and Stirring speed (500, 750 and 1000 rpm) were varied in batches F1to F9 was showed in Table 2. Microspheres thus obtained were filtered and washed with Petroleum ether (80:20) to remove traces of oil. They were finally washed with water to remove excess of glutaraldehyde. The microspheres were then dried at room temperature at 25^0 C & 60% RH for 24 hours.

EVALUATION OF MICROSPHERES

Drug Content

According to literature review the assay for tizanidine hydrochloride was estimated by UV spectrophotometric method. Aqueous solution of drug was prepared in 0.1N HCl and absorbance is measured on ultraviolet visible spectrophotometer at 319 nm[22].

Drug Entrapment Efficiency

50 mg of microspheres were crushed in a glass mortar and pestle, and the powdered microspheres was suspend in 10 ml of 0.1N HCl. After 24 hours, the solution filtered and the filtrate is analyzed for the drug content.

Particle Size

The particle size of the microspheres was determined by using optical microscopy method[23]. Approximately 50 microspheres are counted for particle size using a calibrated optical microscope.

Swelling Index of Microspheres

For estimating the swelling index, the 100 microspheres was suspended in 5 ml of simulated gastric fluid USP (pH 1.2)[24]. The particle size would be monitored by microscopy technique every 1 hour using an optical microscope. The increase in particle size of the microspheres will be noted for up to 8 hours and the swelling index is calculated as per method described by Ibrahim[25].

***In-Vitro* Wash-Off Test for Microspheres**

The mucoadhesive properties of the microspheres are evaluated by *in-vitro* wash-off test reported by Lehr *et al*[26]. A 1cm by 1cm piece of rat stomach mucosa was tied onto a glass slide (3inch by 1inch) using thread. Microspheres are spread onto the wet rinsed tissue specimen, and the prepared slide is hung onto one of the groves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus is operated such that the tissue specimen was given regular up and down movements in a beaker containing the simulated gastric fluid USP (pH 1.2). At the end of 30 minutes, 1 hour, and at hourly intervals up to 10 hours, the number of microspheres still adhering onto the tissue is counted.

Drug Release Study

The drug release study will perform using USP XXIV basket apparatus[22] at 37^0C±0.5^0C and 50 rpm using 900 ml of 0.1N HCl as dissolution medium. Microspheres equivalent to 10 mg of tizanidine hydrochloride were used for the test. The 5 ml of sample was withdrawn at predetermined time intervals and filtered through a 0.45 micron membrane filter, diluted suitably and analyzed spectrophotometrically by 319 nm.

Scanning Electron Microscopy

A scanning electron photomicrograph of drug loaded microspheres was taken. A small amount of microspheres was spread on glass stub. Afterwards, the stub containing the sample was placed in the scanning electron microscope chamber. The scanning electron photomicrograph is taken at the acceleration voltage of 20 kv chamber pressure or 0.6 mm Hg, Original magnification X 800[11].

Release Kinetics and Mechanism

To know the release mechanism and kinetics of tizanidine hydrochloride, optimized formulation was attempted to fit in to mathematical models and n, r^2 values for zero order, First order, Higuchi and Peppas models. The peppas model is widely used, when the release mechanism is not well known or more than one type of release could be involved.

$Mt/M\infty = ktn$

Where, $Mt/M\infty$ is fraction of drug released at time't', k represents a constant, and n is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-fickian release, the value of n falls between 0.5 and 1.0; while in case of fickian diffusion, n = 0.5; for zero-order release (case II transport), n = 1; and for supercase II transport, n > 1. Observation of all the r^2 values indicated that the highest r^2 (0.9756) value was found for Zero order release. According to 'n' value it is one, so it follows non-fickian diffusion with zero order release (case II transport).

Factorial Design

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y is the dependent variable, b0 is the arithmetic mean response of the nine runs, and bi is the estimated coefficient for the factor X1. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when two factors are simultaneously changed. The polynomial terms ($X1^2$ and $X2^2$) are included to investigate non-linearity. On the basis of the preliminary trials a 3^2 full factorial design was employed to study the effect of independent variables i.e. drug: polymer ratio (X1) and the stirring speed at rpm (X2) on dependent variables percentage of mucoadhesion, drug entrapment efficiency, and particle size.

RESULT AND DISCUSSION

The tizanidine hydrochloride microspheres were prepared by simple emulsification phase separation technique using HPMC K4M and CMC. Acetic acid from 1% to 4% v/v was used to prepare polymer solution. But there is no effect in concentration of acetic acid was observed on percentage mucoadhesion or drug entrapment efficiency, therefore 1% v/v of acetic acid was used. Polymer concentration is an important factor, mentioned in Lee *et al* based on viscosity of polymers solution. Three different concentrations 0.5, 1 and 2% v/v were selected for trial batches, from this 1% concentration showed a maximum sphericity was observed so we select 1% w/v of polymer in 1% v/v acetic acid was found to be the optimum concentration and 1:1 heavy and light paraffin was used as dispersion medium and 0.5% v/v of Span 85 is added as anionic surfactant to dispersion medium was found to be essential to minimize aggregation of microspheres. Preliminary trail batches B1 to B20 of microspheres were prepared by using HPMC K4M and CMC as polymers, the volume of cross-linking agent 2 to 10 ml and stirring speed were varied from 500, 750 and 1000 rpm shown in Table 1. From these forty batches, the B1-B4 batches of HPMC K4M and CMC were prepared by using 2 ml glutaraldehyde showed very irregular shaped microspheres and percentage of mucoadhesion also good but drug entrapment efficiency is not good. Batches B5-B8 prepared by using 4 ml of glutaraldehyde showed good mucoadhesion properties and drug entrapment efficiency. Batches B9-B12 of HPMC K4M and CMC was prepared by using 6 ml of glutaraldehyde showed spherical free flowing microspheres and also shows 63% to79% and 64% to 75% mucoadhesion, 54% to 60% and 56% to 61% of drug entrapment efficiency. Batches B13-B16 of HPMC K4M and CMC showed 60% to 80% and 67% to 84% of mucoadhesion, also showed 58% to 66% and 68% to 74% of drug entrapment efficiency. The batches B17-B20 was showed spherical free flowing microspheres and showed 70% to 73% and 74% to 67% of drug entrapment efficiency. The cross-linking agent increase means the mucoadhesivenes was decreases and cross-linking time did not show a significant effect on the percentage of drug

entrapment efficiency, shown in Table 1. From these twenty batches HPMC K4M and CMC the best optimized formula was B17 and B14 shown in Table 1. Thus, we conclude the cross-linking time did not have a significant effect on the percentage drug entrapment efficiency.

On the basis of the preliminary trials 3^2 full factorial design were employed, to study the effect of independent variable X1 (polymer-to- drug ratio 1:1, 3:1 and 4:1) and the stirring speed X2 (500, 750 and 1000rpm) on dependent variables percentage mucoadhesion, drug entrapment efficiency, and particle size. The results depicted in Table 2 clearly indicate that all the dependent variables are strongly dependent on the selected independent variable as they show a wide variation among the nine batches. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative).The dependent variables indicate a good fit. All the nine batches of two polymers HPMC K4M and CMC F1-F9 were prepare by using 10ml and 8ml of glutaraldehyde and 1 and 2 hours cross-linking time shown in Table 2. In-vitro wash of test for percentage mucoadhesion after 1 hour of HPMC K4M and CMC varied from 39% to 80% and 56% to 93% showed good correlation coefficient r^2 0.9805 and 0.9811. These, indicates that the effect of X_1(polymer-to-drug ratio) is more significant thanX_2 (stirring speed). Moreover, stirring speed had a negative effect on percentage mucoadhesion (the stirring speed increased means the percentage of mucoadhesion is decreased).This finding may be attributed to the change in particle size that affects mucoadhesion. Similar results were obtained for swelling index. Thus, the polymer concentration increased the swelling index also increased. The swelling index varied from 0.096 to 1.260 and 0.037 to 1.497 showed good correlation coefficient. Thus, we can conclude that the amount of polymer and stirring speed directly affect the percentage mucoadhesion and swelling index .The drug entrapment efficiency varied from 46% to 79% and 56% to 84% showed good correlation coefficient r^2 0.9811 and 0.9805. Indicates that the effect of X_1(polymer-to-drug ratio) is more significant thanX_2 (stirring speed). Moreover, stirring speed had a negative effect on drug entrapment efficiency (the stirring speed increased means the particle size and drug entrapment efficiency was decreased) and all the nine batches shows spherical and free flowing. They range in particle size from 42.5 to 68.4 and 46.2 to 85. The stirring speed has negative effect on drug release because as the particle size increased the drug release decreases. Batches F7 and F5 was the optimized formulation and they were spherical free flowing. The stirring speed and polymer ratio was increased; the % of mucoadhesion and the drug entrapment efficiency was decreased. From these nine formulations of HPMC K4M and CMC the best optimized formula was F7 and F5 batches were shown in Table 2. The In-vitro drug release studies were carried out the percentage drug dissolved at different time interval was calculated using the Lambert's-Beer's equation were shown in Table 3 & 4. The release mechanism and kinetics of tizanidine hydrochloride, optimized formulation was attempted to fit in to mathematical models and n, r^2 values for zero order, First order, Higuchi and Peppas models. The peppas model is widely used, when the release mechanism is not well known or more than one type of release could be involved and the report was given in Graphs 1 and 2, In-vitro Zero order dissolution studies and Hixon-Crowell models in Table 4, Graphs 3 & 4. The percentage of drug release for eight hours shows 84.52% for HPMC K4M and 81.61% for CMC which indicates the microspheres could sustain the release of the drug for more than 10 hours.

CONCLUSION

The results of a 3^2 full factorial design revealed that the polymer-to-drug ratio and stirring speed significantly affected the dependent variables percentage mucoadhesion, drug entrapment efficiency, particle size and swelling index. As the concentration of glutaraldehyde increases, the mucoadhesiveness decreases and there was no significant effect in time. Stirring speed has negative effect on drug release. Among these two polymers HPMC K4M microspheres exhibited a high percentage mucoadhesion of 80% after 1 hour and 79% drug entrapment efficiency. The microsphere of tizanidine hydrochloride could sustain the release of the drug for more than 10 hours. The percentage of drug release for eight hours shows 84.52% which indicates the mucoadhesive microspheres could sustain the release of the drug for more than 10 hours.

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Table 1: Preliminary trials of tizanidine hydrochloride microsphere by using HPMC, K4M and CMC

Batch Code	Vol. of Glutaraldehyde (ml)	Cross Linking Time(h)	% Mucoadhesion after 1 hr.		Drug Entrapment Efficiency (%)		Sphericity of microsphere
			CMC	HPMC K4M	CMC	HPMC K4M	
B1	2	1	87	92	37	36	Very irregular
B2	2	2	84	86	39	38	
B3	2	3	77	81	41	40	
B4	2	4	74	75	43	42	
B5	4	1	86	88	50	48	Slightly irregular
B6	4	2	80	82	54	52	
B7	4	3	76	75	56	55	
B8	4	4	70	68	59	58	
B9	6	1	75	79	56	54	Spherical from following
B10	6	2	72	73	58	56	
B11	6	3	66	66	60	59	
B12	6	4	64	65	61	60	
B13	8	1	84	80	68	58	
B14	8	2	80	73	72	60	
B15	8	3	74	64	73	64	
B16	8	4	67	60	74	66	
B17	10	1	63	68	67	70	
B18	10	2	60	59	69	72	
B19	10	3	56	48	72	73	
B20	10	4	48	44	74	73	

Note: All batches were prepared by polymer to drug ratio of 3:1 at 750 rpm speed

Table 2: Formulation of tizanidine hydrochloride microsphere by using HPMC K4M and CMC by using 3^2 full factorial design

Batch Code	Variable levels in coded from		% Mucoadhesion After1hr		Drug Entrapment Efficiency (%)		Swelling Index		Particle Size	
	X1	X2	HPMC K4M	CMC	HPMC K4M	CMC	HPMC K4M	CMC	HPMC K4M	CMC
F1	-1	-1	57	65	68.59	61.52	0.774	0.643	58.1	56.0
F2	-1	0	42	59	51.37	59.45	0.466	0.579	54.5	54.2
F3	-1	1	39	56	46.35	56.22	0.397	0.467	42.5	46.2
F4	0	-1	61	83	57.46	79.73	0.689	1.737	57.4	65.1
F5	**0**	**0**	55	**78**	53.75	**78.74**	0.538	**1.270**	53.7	**62.2**
F6	0	1	52	75	49.25	73.88	0.426	0.037	49.3	58.8
F7	**1**	**-1**	**80**	93	**79.33**	84.32	**1.260**	1.497	**68.4**	85.0
F8	1	0	76	85	64.15	80.76	0.107	1.453	63.5	76.8
F9	1	1	68	80	58.30	77.55	0.096	1.197	59.8	71.4

Variables level: Drug-to-polymer ratio (X_1) and Stirring speed (X_2)
Low (-1) = 1:1-500 rpm, Medium (0) = 3:1-750 rpm and Low (+1) = 4:1-1000 rpm.

Table 3: In-vitro release profile of tizanidine hydrochloride microspheres HPMC K4M-F7

Time	Root Time	Log time	Abs	CDR	% CDR	Log % CDR	% Drug Retained	Log % Drug Retained	(%Retained) $^{1/3}$
1	1	1	0	0.0286	4.89	24.45	1.388	75.55	1.878
2	2	1.414	0.301	0.0332	6.246	31.23	1.494	68.77	1.837
3	3	1.752	0.477	0.0374	7.544	37.72	1.576	62.28	1.794
4	4	2	0.602	0.0414	8.828	44.14	1.644	55.86	1.747
5	5	2.236	0.698	0.0466	10.446	52.23	1.717	47.77	1.679
6	6	2.441	0.778	0.0516	12.068	60.34	1.780	39.66	1.598
7	7	2.645	0.845	0.0603	14.682	73.41	1.865	26.59	1.424
8	8	2.828	0.903	0.0672	16.9	84.5	1.926	15.5	1.190

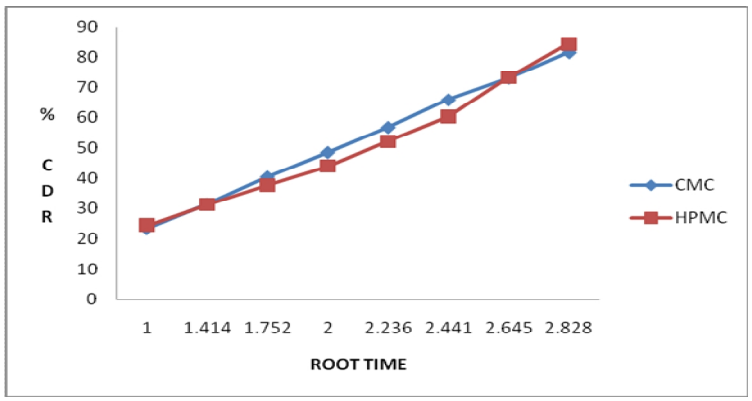
Table 4: In-vitro release profile of tizanidine hydrochloride microspheres CMC

Time	Root Time	Log time	Abs	CDR	% CDR	Log % CDR	% Drug Retained	Log % Drug Retained	(% Retained) $^{1/3}$
1	1	0	0.0278	4.698	23.49	1.370	76.51	1.883	4.245
2	1.414	0.3010	0.0335	6.306	31.53	1.498	68.47	1.835	4.091
3	1.752	0.4771	0.0398	8.128	40.64	1.608	59.36	1.773	3.900
4	2	0.6020	0.045	9.736	48.68	1.687	51.32	1.710	3.716
5	2.236	0.6989	0.0501	11.366	56.83	1.754	43.17	1.635	3.508
6	2.441	0.7781	0.0557	13.18	65.9	1.818	34.1	1.532	3.242
7	2.645	0.8450	0.0596	14.638	73.19	1.864	26.81	1.428	2.992
8	2.828	0.9030	0.0644	16.322	81.61	1.911	18.39	1.264	2.639

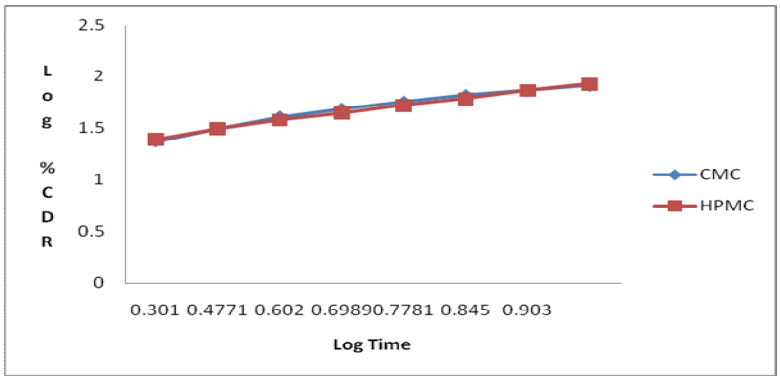
Table 5: Model fitting for the release profile of tizanidine hydrochloride microspheres HPMC K4M-F7 and CMC-F5

Formulation Code	Zero Order	First Order	Higuchi Matrix	Korsmeyer-Peppas		Hixon-Crowell	Best Fit Model
	R	R	R	R	N	R	
HPMC K4M	0.982	0.886	0.962	0.947	0.597	0.935	Zero
CMC	0.989	0.973	0.988	0.987	0.612	0.994	Zero

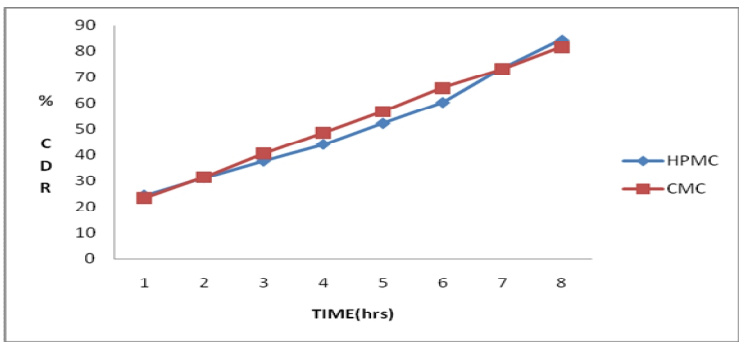
R= correlation coefficient; n= slope (≤0.5 – fickian diffusion; 0.5<n<1 – non fickian diffusion; 1 – Case – II transport; >1 – super case –IItransport)



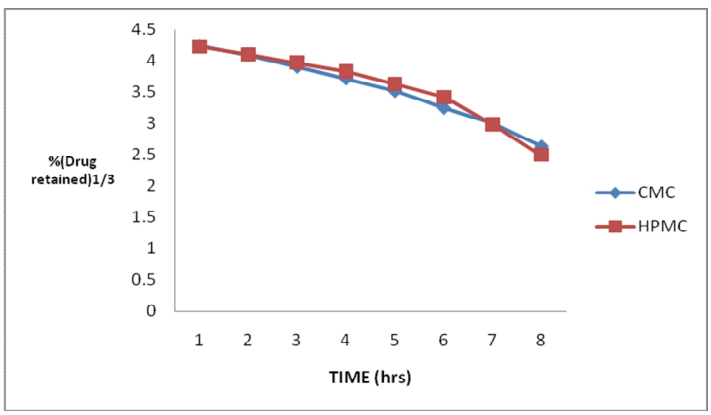
Graph 1: Tizanidine hydrochloride microspheres (HIGUCHI Model)



Graph 2: Tizanidine hydrochloride microspheres (KORSMEYER-PEPPAS Model)



Graph 3: In-vitro release profile of tizanidine hydrochloride microspheres (ZERO ORDER)



Graph 4: Tizanidine hydrochloride microspheres (Hixon-Crowell)

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