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Influence of Different Hydroxypropyl Methylcellulose Polymers in Defining the Micromeretic Properties, Erosion, Drug Entrapment and Release from Tramadol Hydrochloride Microspheres

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ABSTRACT

Purpose: To comparatively evaluate the effect of three hydroxylpropyl methylcellulose (HPMC) molecular weight grades (K4M, K15M and K100 M) on drug release from Tramadol Hydrochloride Microspheres. **Methods:** Microspheres containing Tramadol Hydrochloride was prepared by emulsion solvent evaporation technique at various Drug/HPMC ratios and evaluated for their water uptake, erosion and dissolution characteristics over a period of 16 h. Their release data were analyzed according to various release kinetic models. **Results:** The release rate of tramadol hydrochloride decreased with increase in polymer content and was dependent on the HPMC type used, with the lower release rate observed in formulations containing the higher molecular weight grade HPMC K15M and HPMC K100M. Formulations containing the higher molecular weight HPMC (F4, F5 and F6) showed higher water uptake than those containing the lower molecular weight polymer (F1,F2 and F3) ($p < 0.05$). The formulations incorporating the lower molecular weight HPMC K4M (F1, F2 and F3) showed higher erosion than those that contained HPMC K15M (F4, F5 and F6) ($p < 0.05$). Kinetic data based on the release exponent, [n] in Peppas model, showed that n values were between 0.14 and 0.55, indicating that drug release from HPMC matrices was predominantly by diffusion. **Conclusion:** This study demonstrates that the molecular weight (MW) of HPMC does affect the water uptake and erosion as well as the rate of drug release from of HPMC matrices.

INTRODUCTION

Controlled release formulations have gained a lot of popularity in recent period because of its improved applications, protective functions and increase in the patient compliance. Use of devices such as polymer based disks, rods, pellets, or microparticles that encapsulate drug and release it at controlled rates for relatively long periods of time is common for controlled release system. Such systems offer several potential advantages over traditional methods of administration. First, drug release rates can be tailored to the needs of a specific application; for example providing a constant rate of delivery or pulsatile release. Second, controlled release systems provide protection of drugs, especially proteins that are otherwise rapidly destroyed by the body. Finally, controlled release systems can increase patient comfort and compliance by replacing frequent (e.g., daily) doses with infrequent (once per month or less) injection[(i)].

There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor. Microencapsulation is used to modify and delayed drug release form pharmaceutical dosage forms. Microspheres is efficiently utilized in controlled delivery of many drugs but wastage of drug due to low drug entrapment efficiency is the major drawback of such micro particulate system[(ii)]. Well designed microspheres can overcome such problems by enhancing the loading efficiency of a particular drug and minimizing the wastage of drug. It is the reliable means to increase the loading efficiency, if formulation as well as process variables are optimized. This is only possible by understanding the effect of various variables which affect the drug entrapment efficiency of these microspheres.

Tramadol, a synthetic codeine analog that is a central analgesic and a weak μ-opioid receptor agonist. The absence of clinical relevant cardiovascular or respiratory side effects explains its use for post operative pain than other opioids [(iii)]. Immediate release formulations of Tramadol show the incidence of headache and nausea in 29% and 21%, respectively, whereas sustained release formulations shows only 18% and 11% respectively [(iv)]. The half life of the drug is 5 hrs and dose is 50 -100 mg every 4 to 6 hrs. The major adverse effect of Tramadol is headache and nausea. A sustained release formulation of Tramadol is desirable for pain management with

lesser side effects. Microspheres have been selected as dosage form due to the ease of its formulation, taste and odor masking behavior and to prolong and control GI transit of the drug.

Hydroxypropyl methylcellulose (HPMC) is probably the most important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems. One of its most important characteristics is high swellability, which has a significant effect on the release kinetics of an incorporated drug [(v)]. The overall drug release mechanism of HPMC-based pharmaceutical devices strongly depends on the design (composition and geometry) of the particular delivery system. On imbibing water, HPMC swells, resulting in dramatic changes in polymer and drug concentrations, and increased dimensions of the dosage system. Upon contact with water, the incorporated drug dissolves and diffuses out of the device. Depending on the chain length and degree of substitution of the HPMC type used, the polymer itself dissolves more or less rapidly. Diffusion, water uptake and erosion are the most important rate controlling mechanisms of commercially available controlled release products which applies in the HPMC based matrix systems too

The objective of the present investigations was to comparatively evaluate three HPMC molecular grades ; HPMC K4M, HPMC K15M and HPMC K100M for their water uptake and erosion properties in tramadol hydrochloride microspheres system as well as drug release characteristics, and thus elucidate the kinetics and mechanism of drug release from the matrices of microspheres.

MATERIALS AND METHODS

Materials

Tramadol Hydrochloride, Methylene chloride, n- Hexane and light liquid paraffin was received as a gift from QMed Formulations Pvt. Ltd., Bhaktapur, Nepal. HPMC K4M, K15M and K100 M were received from Deurali Janata Pharmaceuticals, Nepal.

Drug-Excipient Compatibility Studies:

The samples of Tramadol Hydrochloride and their selected pharmaceutical excipients in 1:1 ratio (100 mg each) were accurately weighed into 5 ml borosilicate glass vial (n=3) with screw cap followed by mixing in a vortex mixer for 4 minutes and to this mixture 20µl of purified water was added using a micropipette to achieve water concentration of 10% w/w. This mixture was

further mixed for 4 minutes in a vortex mixer in order to achieve homogenous mixing. These vials after proper sealing were stored for 1 month at 50 ± 2°C in an oven. Drug–excipient mixture without added water served as control and stored in a refrigerator. The drug–excipient mixture was periodically examined visually for any unusual color change.

The compatibility of drugs with the respective excipients was studied by FTIR spectroscopy. For FTIR studies, 25 mg of potassium bromide dried on a moisture balance and 1-2 mg of drug-excipient blend test sample was taken in an Agate mortar. Proper mixing was carried out and this blend was placed on the sample plate directly in the FTIR. Thus obtained powder blend was analyzed by diffuse reflection method in FTIR in the IR range of 4000 to 400 cm^{-1} taking average of 20 consecutive scans. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction. The purity of the sample was also determined by the help of HPLC analysis.

Formulation of the microspheres

Microencapsulation based on emulsion solvent evaporation method was employed to formulate the micro-particles of Tramadol hydrochloride. Different concentration of different grades of HPMC polymers were dissolved in 50 mL of Dichloromethane. Then, 1 g of Tramadol hydrochloride was dispersed in the polymer solution. About 50 ml of Paraffin oil was taken in burette and added to drug-polymer dispersion solution drop by drop with continuous stirring at 500 rpm for about four hours. The supernatant was decanted and n-hexane was added to wash paraffin oil. The microparticles were filtered and again washed with n-hexane and distilled water to remove paraffin oil and free drug particles from the surface of micro-particles. Finally the micro-particles were dried at 40ºC in an oven and stored in an air-tight glass container at room temperature for the characterization step.

Table 1. Composition of the Tramadol Hydrochloride microspheres

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	50%	33.33%	25%	20%	50%	33.33%	25%	20%	50%	33.33%	25%	20%
HPMC k-100M	50%	66.67%	75%	80%	-	-	-	-	-	-	-	-
HPMC k 15 M	-	-	-	-	50%	66.67%	75%	80%	-	-	-	-
HPMC k 4 M	-	-	-	-	-	-	-	-	50%	66.67%	75%	80%

Analysis of entrapment efficiency:

The entrapment efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation:

The percentage of drug entrapment can be calculated by the following equation:

$$\% \text{ drug entrapment} = \frac{\text{calculated drug concentration} \times 100}{\text{Theoretical drug content}} \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Analysis of Release profile:

The assay and the dissolution profile was done according to the pharmacopeal specification as described in USP' 2015.

In order to investigate the mode of drug release from the tablets, the release data were subjected to the following mathematical models: zero order (Eq 2), first order (Eq 3), Higuchi (Eq 4) and Korsemeyer-Peppas (Eq 5).

$Q = kot$ ..... *(2)*

$ln\ (100 - Q) = ln\ Q0 - k1t$ ..... *(3)*

$Q = kHt1/2$ …….. *(4)*

$Q = kptn$ …….. *(5)*

where Q is the percent of drug released at time t, and k0, k1 and kH are the coefficients of the respective equations; kp is a constant incorporating the structure and geometric characteristics of the release device and *n* is the release exponent indicative of the mechanism of release. In case of the spherical bodies like microspheres, when *n* approximates to 0.43, a Fickian/diffusion-controlled release is implied; where $0.43<n<0.85$, Anomalous transport is indicated while n = 0.85 suggests zero order (case II transport).

Analysis of the microsphere size:

The mean particle sizes of the beads were determined by sieving method.

Microspheres were separated into different size fractions by sieving for 10 minutes using mechanical sieve shaker (Cuprit Electrical Co. India) containing standard sieves having apertures of 1000, 710, 500, 355, 250 & 180 µm (Indian Pharmacopoeia, 1996). The particle size

distribution of the microspheres for all the formulations was determined and mean particle size of microspheres was calculated by using the following formula:

$$\text{Mean Particle size} = \frac{\Sigma\ (\text{Mean particle size of the fraction X weight fraction})}{\Sigma\ \text{Weight fraction}} \quad \text{……..(6)}$$

The size of the microsphere was evaluated with the help of Radial Trinocular Stereo Zoom Microscope. A suitable quantity of powder to be examined are weight and suspended in 10ml of suitable medium in which the powder doesn't dissolve. A portion of the homogeneous suspension into a suitable counting cell was introduced and it was scanned under a microscope to an area corresponding to not less than 10 micro g of the powder to be examined.

Water Uptake Studies:

Equilibrium weight method [vi] was used to perform the water uptake studies using USP XXVII basket dissolution test apparatus. The microspheres were accurately weighed and placed in a

dissolution basket. It was then immersed in a dissolution vessel containing 900 ml of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°C; speed of rotation was 100 rpm. At regular intervals, the basket-matrix system was removed from the dissolution vessel, blotted with tissue paper to remove excess water, and reweighed.

The percentage water uptake (i.e., the degree of swelling due to absorbed medium) was calculated using the following equation:

$$\%\text{Water uptake} = \frac{Wt}{W_o} \times 100 \text{.....(7)}$$

Where W_o and *Wt* are weights of dry and swelled tablet at time *t*, respectively.

Matrix Erosion Studies

A matrix erosion method similar to Ebube et al.[vii] was done to evaluate the polymer erosion from the matrix of microspheres. USP XXVII type I dissolution test apparatus was used for this purpose. The dry matrices were weighed, placed in dissolution basket containing 900 ml of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°C, and the basket was rotated at 100 rpm. At regular intervals, the whole basket-matrix assembly was removed from the dissolution vessels and dried to a constant weight in a hot air oven at 50°C.The matrix erosion (*E*) at time, *t*, was estimated from the following equation:

$$\text{Matrix erosion } (\%) = \frac{Wdt}{W_o} \times 100 \text{.....(8)}$$

Wdt and W_o are weights of dried tablet and initial weight of dry tablet at time *t*, respectively

Statistical analysis

One-way ANOVA analyze the dissolution data obtained for each batch of formulation in order to compare the rate of drug release from the microsphere. The software used was SPSS, version 12 and minitab 16.1 and the confidence limit was set at 95 %.

RESULTS AND DISCUSSION

Drug: Excipient Compatibility Studies:

As depicted by the structure, Tramadol HCl shows prominent peaks due to O-H stretching ,C-H stretching ,C=C asymmetric stretching ,C=C aromatic stretching , CH_3 bending vibration, O-H bending vibration ,C-N stretching ,C-O stretching , CH_2 and CH bending and O-H bending vibrations.

There were very minor changes in wavenumber shift between the pure drug and the combination of drug and polymers HPMC K4M, HPMC K15M, HPMC K100M in control sample, Ist sample (which is applied with 10% moisture and kept at oven in 50^0C for 1 month) and stability sample (which is sealed in bottle and kept in an environment of 40^0C and 75% RH). The data of wavenumber of pure drug and combination with polymers at different condition is given in table. This confirms that there is no significant interaction between Tramadol Hydrochloride and the polymers which were considered in this particular study.

Also the purity index is more than 0.95 for the peak of tramadol hydrochloride and excipients Ist and control sample which also shows the absence of marked changes in the IR peaks.

Studies with HPLC:

The interaction between tramadol hydrochloride and the excipients (Polymers) could be explained on the basis of the purity of the sample of tramadol hydrochloride obtained after the application of heat and humidity to the sample of the drug-excipient after 1 month (Ist sample). Purity was determined between 99 to 101% explains lack of interaction on the drug-excipient mixture.

Table 2. HPLC studies for drug-excipient compatibility studies

Sample	Excipient	weight of Spl	Area of STD	Conc. Of spl	Area	Assay
CONTROL (Freeze)	T+HPMC K 4M	101.9	411797.8	0.20380	419010	100.74076
	T+HPMC K 15M	101.9	411797.8	0.20380	413015	99.2994077
	T+HPMC K 100M	101.9	411797.8	0.20380	415171	99.8177654
	Tramadol	50.5	411797.8	0.10100	412595	100.082375
SAMPLE (Oven)	T+HPMC K 4M	100.9	411797.8	0.20180	409593	99.4526539
	T+HPMC K 15M	101.8	411797.8	0.20360	409535	98.5594481
	T+HPMC K 100M	99.4	411797.8	0.19880	401989	99.0792709
	Tramadol	50.7	411797.8	0.10140	413959	100.017131

Table 3. Microenvironment pH change studies:

Sample	pH at 0 Time	pH of Control Sample	pH of IST Sample	pH of Stability Sample
T+HPMC K 4M	5.57	4.78	3.65	3.61
T+HPMC K 15 M	5.28	4.18	3.92	3.85
T+HPMC K 100M	5.34	4.22	3.94	3.92

Table 4. Color change studies

Sample	0 Time	Control Sample	IST Sample
T+HPMC K 4M	-	-	-
T+HPMC K 15 M	-	-	-
T+HPMC K 100M	-	-	-

Micromeretic Studies:

Physical characterization of all twenty batches of sustained release microspheres were analyzed for Angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The results are shown in Table. Results of physical testing for microspheres indicated passable to

excellent flow properties with angle of repose ranging between 18.6 to 34.63. Formulations F1, F3, F8 and F12 showed excellent flow properties.

Table 5. For microspheres with HPMC K100M

Formulation	% YIELD	Bulk Density	Tapped Density	Hausners ratio	Compressibility Index	Angle of repose	Flow property
F1	80 %	0.42	0.50	1.19	15.8	25.05	excellent
F2	90 %	0.43	0.53	1.23	18.6	31.57	Good
F3	84.4 %	0.44	0.50	1.12	10.5	18.60	excellent
F4	72 %	0.45	0.55	1.23	18.8	32.78	Good

Table 6. For microspheres with HPMC K15M

Formulation	% YIELD	Bulk Density	Tapped Density	Hausners ratio	Compressibility Index	Angle of repose	Flow property
F5	92.4	0.49	0.59	1.21	17.5	33.00	Good
F6	98	0.91	1.14	1.26	20.4	34.63	Good
F7	84	0.38	0.50	1.33	24.8	34.22	Good
F8	94.8	0.41	0.50	1.21	17.4	29.57	excellent

Table 7. For microspheres with HPMC K4M

Formulation	% YIELD	Bulk Density	Tapped Density	Hausners ratio	Compressibility Index	Angle of repose	Flow property
F9	78	0.45	0.53	1.16	14.0	32.78	Good
F10	94	0.44	0.55	1.24	19.2	32.72	Good
F11	84.2	0.46	0.54	1.16	13.8	33.00	Good
F12	96	0.91	1.10	1.21	17.2	29.31	excellent

Size Analysis:

The size analysis done with the help of sieving method and optical microscopy showed that there was a close relation between microsphere size, polymer concentration and kind of polymer (viscocity). The size of the microspheres ranged from 855 µm to 336 µm with increasing in size with its concentration. It is widely observed phenomenon that the particle size of the microspheres increases as the ratio of polymer increases inside the microspherical system because of increase in viscosity of the polymer which results in formation of larger emulsion droplets and thus consecutively larger size of the microsphere. The explanations were well observed in an experiment by Patel et.al where the particle size of aspirin loaded microsphere was analyzed by optical microscopy. The average particle size of microspheres was found to be in the range of 328 to 990 µm.

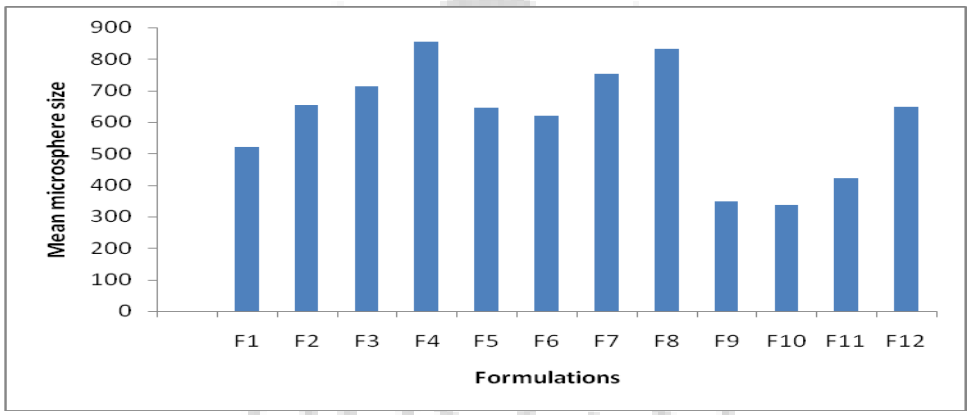

Figure 1. Size analysis of microspheres by sieving

Water uptake studies

Water uptake data is shown in Fig 1. Water uptake increased with time. The water uptake data may correlate with the molecular weight grade of HPMC, as the formulations containing the higher molecular weight HPMC K100M (F1 TO F4) showed higher water uptake than those containing the lower molecular weight polymer comprising of HPMC K15 M and HPMC K100 M (F5 TO F12). Also, increase in the content of polymer in the microsphere resulted in water uptake increase ($p < 0.05$).

Table 8. Water Uptake Studies for different formulations

Formulation	1 hr	2 hr	4 hr	6 hr	8 hr
F1	375	405	485	512	535
F2	408	415	517	545	578
F3	451	475	536	597	613
F4	489	499	578	654	666
F5	275	350	450	450	470
F6	300	310	415	475	491
F7	314	345	474	505	517
F8	347	384	498	542	557
F9	190	240	350	415	420
F10	200	275	400	465	482
F11	247	305	421	498	512
F12	286	311	429	516	532

Young and Nelson equation can be used to explain the sorption and desorption profile of different viscocity grades of HPMC polymers. These equations describe three locations of the sorbed moisture: monolayer adsorption, externally adsorbed moisture, and internally absorbed moisture. Increase in the polymer size results in reduction in amount of internal water absoption and increase in external adsoption. In an experiment on elucidating the moisture sorption and desorption profile of different viscosity grades of HPMC (K4M, K15M and K100M), it was observed that the lowest value of internally absorbed moisture was obtained for HPMC K100M [(viii)].

Polymer erosion studies

All the formulations investigated eroded over time. The formulations incorporating the lower molecular weight HPMC K4M (F1 to F4) showed higher erosion than those that contained HPMC K15M and K100 M (F5 to F12) ($p < 0.05$). Drug release from the polymer matrices are usually due to diffusion and erosion. In one study of release from matrices of hydroxypropyl methylcellulose (HPMC), it was observed that drug release due to polymer erosion was found to be the function of average molecular weight of the polymer and diffusional rates were

independent of the number of average molecular weight of the polymers studied. For those drugs with good water solubility, the permeation rate of the medium into the matrix and for those drugs with lower water solubility, the erosion rate of the matrix system has ample importance in the drug release. The permeation rate of the medium into the matrices can be controlled by changing the interspace volume by use of materials like lactose which quickly rinse out of the matrix system and thus increases the release of the drug from the system. The erosion study indicated that polymer diffusion of the HPMC polymer chains through the aqueous diffusion layer was the rate-limiting step for polymer erosion. In general, polymer erosion was found to be inversely related to the polymer number average molecular weight [(ix)]. Since viscosity of the HPMC polymers are related to the molecular weight and has a large influence on the erosion rate of the matrix tablet, the erosion rate can be adjusted by the choice of HPMC polymer viscosity or by mixing polymers of different viscosity grades [(x)]. A higher molecular weight HPMC polymer thus has a higher water holding capacity and the matrices of such polymeric system are less prone to erosion [(xi)].

Table 9. Polymer Erosion studies of different formulations

Formulation	1 hr	2 hr	4 hr	6 hr	8 hr
F1	3.8	6.4	9.1	12.1	12.3
F2	3.2	6.1	8.5	10.3	11.2
F3	2.9	5.4	8.0	8.9	9.3
F4	1.8	4.7	7.7	8.2	8.6
F5	5.2	9.4	12.4	16.7	21.1
F6	3.1	5.2	7.2	12.1	15.3
F7	2.5	4.6	5.2	10.1	11.3
F8	2.1	3.4	4.8	9.8	10.9
F9	10.3	12.2	15.4	20.5	24.6
F10	8.9	10.6	12.4	15.4	17.6
F11	7.2	8.2	9.9	11.9	12.8
F12	6.5	7.3	8.3	10.7	11.2

Drug Release

Different drug release profiles were obtained for microspheres formed with different polymers. The drug release profiles obtained indicated two distinct phases of drug release - an initial burst phase followed by a controlled release phase which is associated with hydration/water uptake of the polymer [(xii)]. Microspheres containing HPMC K100 M and HPMC K15 M displayed the lower release rate; those polymers are also of higher viscosity grade in view of its greater molecular weight. Thus, the greater degree of entanglement at high molecular weight would reduce the effective molecular diffusion area and hence drug permeation across the matrix gel. This supports the observation of Jafar Akbari et. al during their study of drug release from the matrix tablets of Diclofenac Sodium with HPMC K4 M and HPMC K15 M as polymers which shows matrix tablets of HPMC K15M showed lower release rates [(xiii)] . Another study done by Nellore *et al shows* that the higher viscosity gel layers of Methocel K100M matrix provided a more tortuous and resistant barrier to diffusion than Methocel K100LV matrix, resulting in slower release of metoprolol tartrate from the matrix of the former[(xiv)]. Drug release from HPMC systems has been reported to be influenced by polymer concentration, drug: polymer ratio, polymer particle size, and the polymer's degree of substitution [(xv)]. The decrease observed in drug release in our study as HPMC content increased, is likely due to increase in the viscosity of the polymer gel leading also to a longer diffusional path. The result would be a decrease in the effective diffusion coefficient of the drug and hence reduction in the drug release rate. In the present study, it seems that when the microsphere was placed in the dissolution medium, initial drug release occurred from the outer surface/layers of the microspheres, which constituted 'burst' release. Subsequently, water molecules travelled through long, tortuous channels of the matrix to reach the drug in the deeper layers of the microsphere. As erosion gradually reduces the diameter of the microsphere, the diffusion path length also decreased. When the penetration of water in the gel matrix exceeds a critical concentration (i.e., the concentration at which the interaction between water and polymer increased, with a consequent reduction of polymer-polymer interactions), the polymer chains begin to separate, thus further exposing the drug. At this stage, the erosion rate increases [(xvi)].

In order to achieve the desired release, therefore, the relative rate of hydration of the polymer plays a critical role since the polymer selected must hydrate quickly enough to form a gel layer

before the contents of the matrix microsphere dissolves. The higher the viscosity of the gel, the more resistant the gel is to dilution or erosion; thus, the viscosity of a gel also is a rate-controlling factor in drug dissolution. If the matrix gel has good durability, soluble drugs may diffuse out of the gel before matrix erosion occurs. Thus, both diffusion and erosion contribute to controlling drug release from a hydrophilic matrix, although one process often plays a predominant role over the other, depending on polymer characteristics.

Table 10. Release order studies of different formulations

TYPE OF MICROSPHERE	RATIO	ZERO ORDER	FIRST ORDER (R2)	HIGUICHI	KROSMEYER PEPPAS	
		R2			n	R2
	1:1	0.85	0.7	0.94	0.48	0.94
Tramadol:HPMCK100M	1:2	0.93	0.74	0.99	0.85	0.96
	1:3	0.98	0.84	0.98	0.93	0.99
	1:4	0.93	0.72	0.98	1.08	0.96
Tramadol:HPMC K15M	1:1	0.82	0.78	0.92	0.29	0.95
	1:2	0.79	0.75	0.88	0.36	0.91
	1:3	0.97	0.92	0.95	0.73	0.94
	1:4	0.97	0.89	0.96	0.78	0.95
Tramadol:HPMC K4M	1:1	0.81	0.76	0.92	0.32	0.95
	1:2	0.78	0.66	0.89	0.55	0.92
	1:3	0.8	0.67	0.9	0.63	0.94
	1:4	0.88	0.67	0.88	0.67	0.94

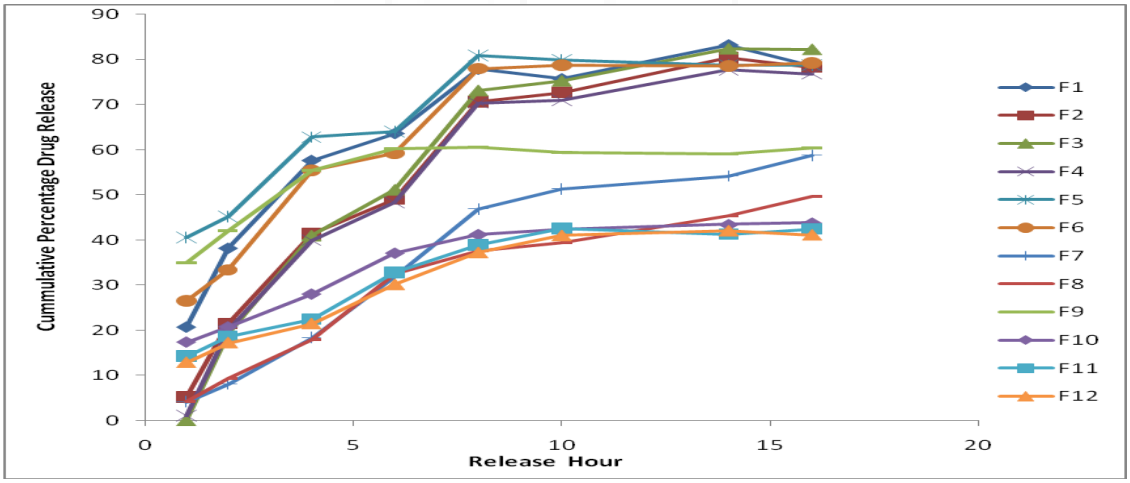

Figure 2. Cumulative drug release over a period of 16 hours

Analysis of the entrapment efficiency:

It has been observed that a higher molecular weight polymer has a greater degree of entanglement and thus will reduce the molecular diffusion area and permeation of the drug across the matrix gel. As seen from the experiment, the highest entrapment was seen in the case of formulations which comprised of 75 and 80 percentage of polymer concentration with highest entrapment observed in HPMC k-100M microspheres followed by HPMC k-15M and HPMC k-4M respectively. When the polymer concentration increases, there would be increase in the viscosity of the polymer gel and thus leading to longer diffusional path [(xvii)]. This causes a decrease in the diffusion coefficient of the drug and reduction in the release rate of the drug. In order to achieve a constant zero order or sustained type release, the polymer should hydrate fast to form a gel layer before the contents of the matrix tablet gets dissolved. For the higher viscosity gels, they become more resistant to dilution and erosion [(xviii)]. On the other hand, the polymer forming the loose network in the matrix is seen to decrease the release rate and encapsulation efficiency as the network allows the drug particles to leach out during the microsphere production [(xix)]. It has been observed and widely accepted that an increase in the polymer concentration increases the entrapment of the drug inside the microspherical systems. The main reasons for this phenomenon can be explained with the help of following points.

i. **Effect due to increase in viscosity:**

As explained earlier, high concentration of the polymer used to devise the microspherical systems causes the increase the viscosity of the solution and delays the drug diffusion within the polymer droplets.

ii. **Effect of increase in velocity of precipitation:**

When, the concentration of the polymers increases or the ratio of drug: polymer decreases, the polymers tend to precipitate faster on the surface of the dispersed phase and it can prevent drug diffusion across the phase boundary.

iii. **Effect of increase in size:**

With the increase in polymer concentration, the size of the microsphere increases. This causes a decrease in the surface area of the microspheres and decreased exposure to water. Thus the drug loss due to diffusion from the gel layer also decreases. Decreasing the polymer concentration also leads to reduction in loading efficiency due to maximum drug: polymer ratio and small size

of microspheres which result in more loss of drug from surface during washing of microspheres. In an experiment by Saravanan et. al. where they formulated the floating microspheres of ranitidine hydrochloride with ethyl-cellulose as polymer, they observed that increase in the polymer concentration increased the drug entrapment with maximum entrapment seen at a drug: polymer ratio 1:3 [(xx)].

Table 11. Study of Entrapment Efficiency of different formulations

Formulation No.	weight	area1	area2	average	assay	Entrapment Efficiency
F1	51.2	225023	227135	226079	25.32	72.34
F2	50.6	238599	238393	238496	27.03	77.21
F3	50.8	259494	258799	259146.5	29.25	83.57
F4	50.2	151578	151028	151303	17.28	86.41
F5	50.1	117667	117914	117790.5	13.48	67.40
F6	51	129366	129852	129609	14.57	72.86
F7	51.1	348947	348081	348514	39.11	78.21
F8	49.8	258846	257782	258314	29.74	84.97
F9	51.9	281296	280880	281088	31.05	62.11
F10	50.1	204213	204152	204182.5	23.37	66.76
F11	50.6	231976	235675	233825.5	26.50	75.70
F12	51.8	68116	68171	68143.5	7.54	77.20

CONCLUSION

The results of the kinetic analysis of the drug release data indicate that except for formulation F3 in the drug: polymer HPMC K100M ratio of 1:3 which shows zero order release, the various formulations did not follow a particular model. Thus formulation F3 can be taken as suitable formulation for controlled release of drugs. According to the Noyes-Whitney and Nernst-Brunner drug dissolution models, several factors may influence drug dissolution kinetics. These include the effective surface area of the solid drug, diffusion coefficient of the drug, thickness of the diffusion layer, saturation solubility of the drug, volume of the dissolution medium, and the

amount of drug in the solution. It is evident from the present work that swellable matrix microspheres are activated by water, and drug release is controlled by the interaction between water, polymer and drug. Thus delivery kinetics depends on the drug gradient in the gel layer and hence, the drug concentration and thickness of the gel layer governed drug flux.

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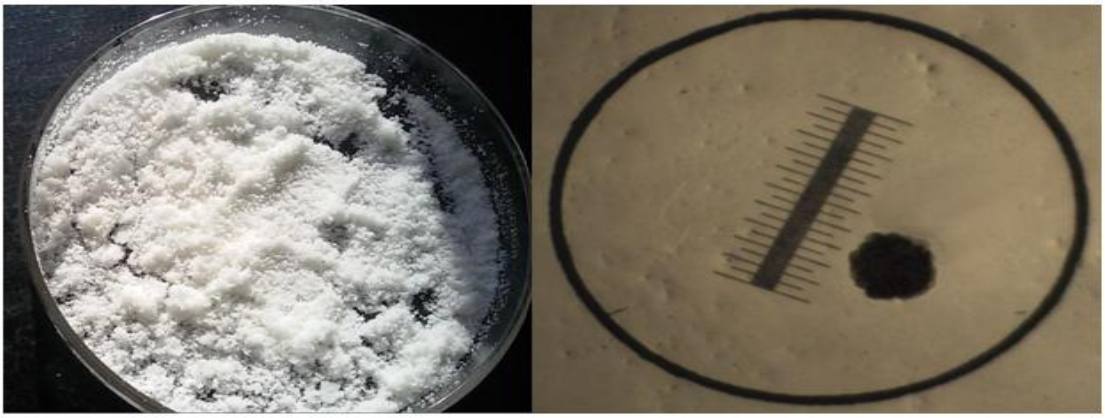
Conflict of Interest:

The authors declare no conflict of interest on the manuscript



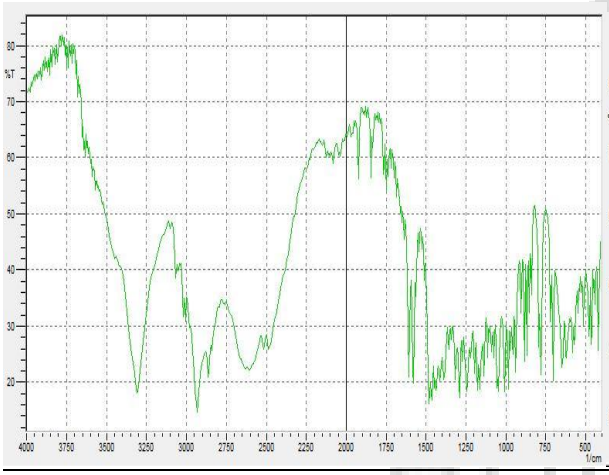
Microsphere of HPMC k4 formulation (F11) Microsphere observed with microscope (1 division=10 micron)

Microsphere of HPMC k15 formulation (F7) Microsphere observed with microscope (1 division=10 micron)

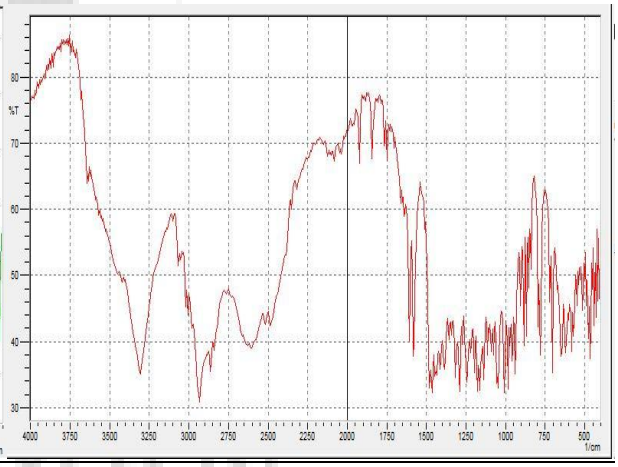
Microsphere of HPMC k100 formulation (F3) Microsphere observed with Trinocular Stereo Zoom microscope (1 division=10 micron)

FTIR Studies

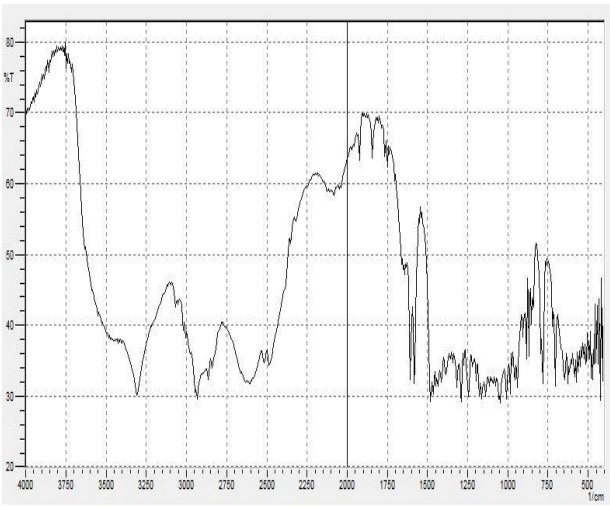
TRAMADOL+HPMC K100M 0 MONTHS



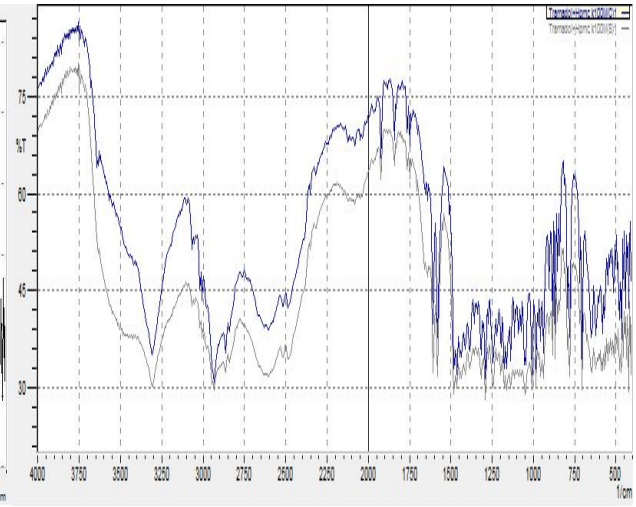
TRAMADOL+HPMC K100M CONTROL



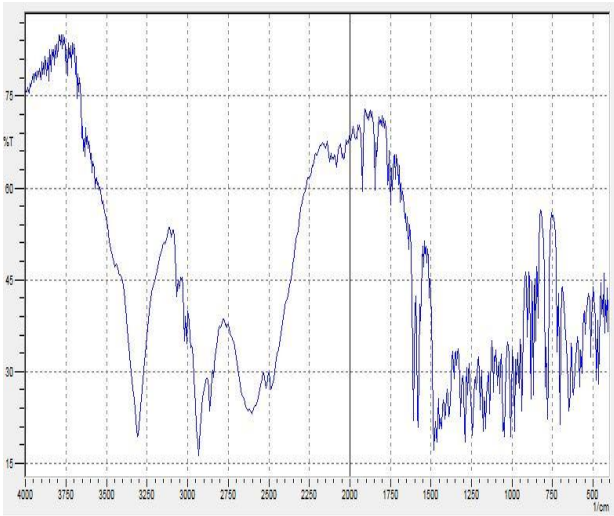
TRAMADOL+HPMC K100M IST SAMPLE



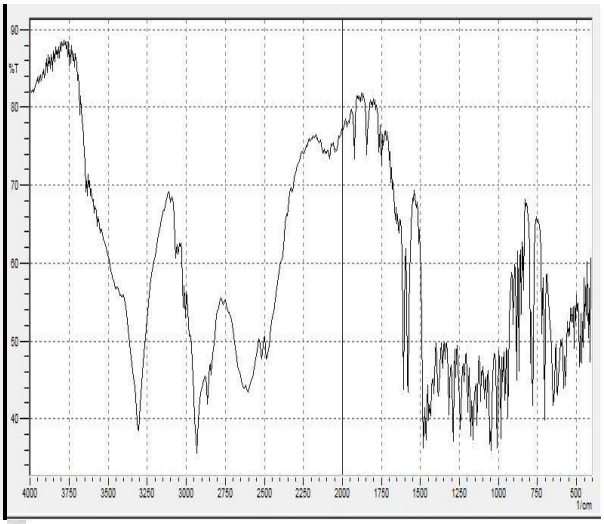
TRAMADOL + HPMC K100M (SAMPLE AND CONTROL)



TRAMADOL+HPMC K15M 0 MONTHS



TRAMADOL+HPMC K15M CONTROL



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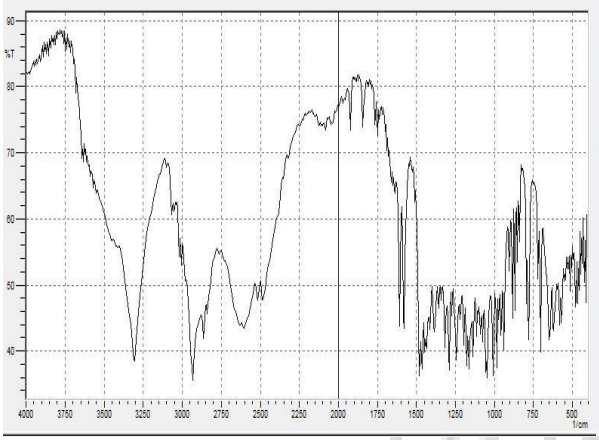
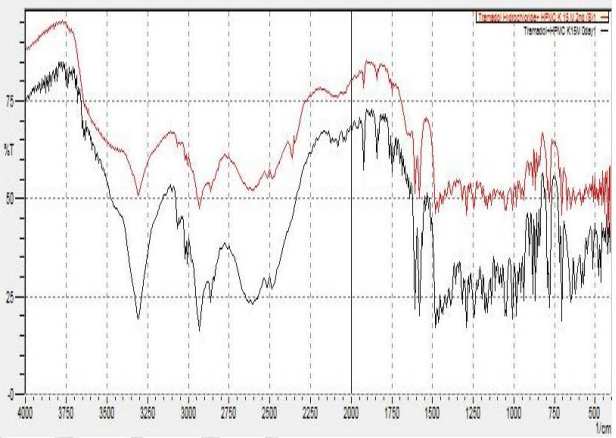
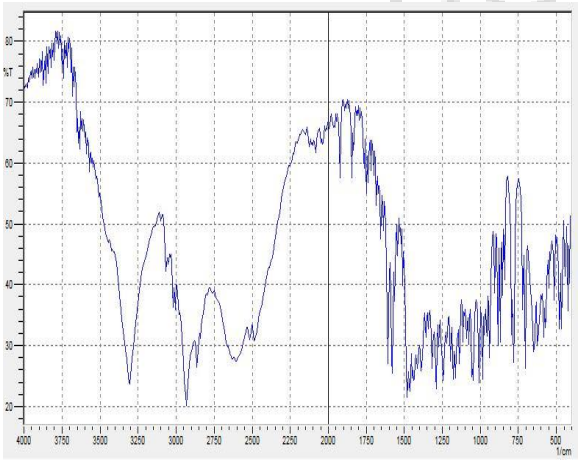


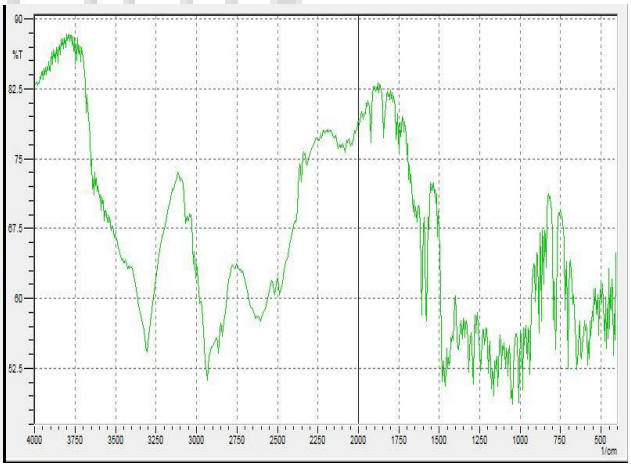
TRAMADOL + HPMC K15 M (SAMPLE AND CONTROL)



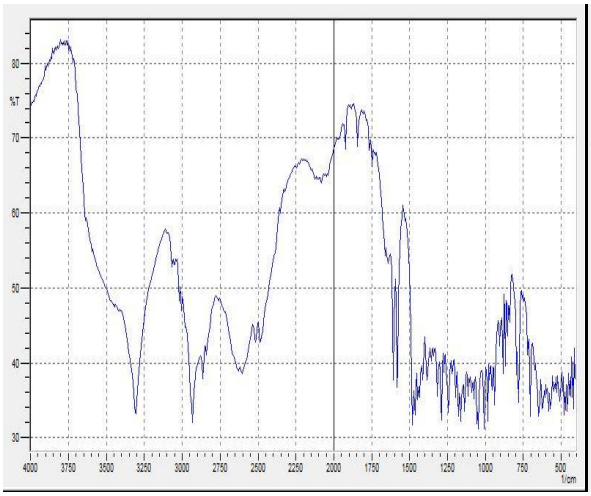
TRAMADOL+HPMC K4M 0 MONTHS



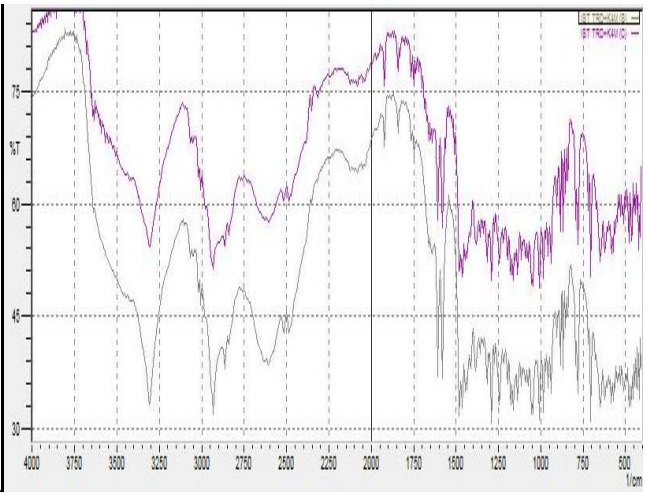
TRAMADOL+HPMC K4M CONTROL



TRAMADOL+HPMC K4M IST SAMPLE



TRAMADOL + HPMC K4 M (SAMPLE AND CONTROL)



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