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Comparative Evaluation of Hydroxy Propyl Methyl Cellulose from Different Manufacturing Sources

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ABSTRACT

The aim of this study was to investigate the performance and release behavior of drug from hydroxypropyl methylcellulose (HPMC) matrix tablets prepared using HPMC from three different manufacturers. Three various brands of HPMC used were Methocel, Novocoat, and Zhongbao. A protocol was followed to evaluate these three HPMC samples their physico-mechanical properties such as appearance, particle size distribution, bulk density, tapped density, angle of repose, compressibility index (CI), Hausner's ratio, swelling and morphology. Formulations were prepared using Carbamazepine (CAR) as a drug molecule, by varying drug loading and polymer concentration to evaluate the physical and comparative performance characteristics. Various drug release kinetic models were evaluated for the best fit of the formulations in order to understand the underlying release mechanisms from the formulations. The best performance with respect to release kinetics was exhibited by Methocel,while Novocoat and Zhongbao were found to have similar performance.

Keywords: HPMC, Methocel, Novocoat, Zhongbao, Carbamazepine.

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INTRODUCTION

For preparation of hydrophilic modified release matrix tablets,hypromellose or hydroxypropyl methylcellulose (HPMC) is the polymer of choice. HPMC is a nonionic cellulose ether derivative which consists of a backbone of cellulose with methoxylic and hydroxypropoxylic moieties substituted on to the glucose units [1,2] Release of the drug from the matrix dosage form is mainly controlled by the physicochemical properties of polymer and the drug chosen for the study [3]. Physico-chemical properties of powder excipients such as particle size distribution, flow, density, compressibility, viscosity etc play a critical and essential role in the formulation development, processing, in vitro and in vivo performance of the finished dosage forms [4-9] Identification and the determination of critical properties of drug formulation become necessary to obtain the product with desired and reproducible attributes.

Variations in the one or more physico-mechanical properties of the powder excipients have been reported form vendor to vendor and in a inter lot batches. Due to broad range specifications, powder excipients may show similarity in the physical characterization but while processing them during various unit operations and various formulations they show remarkable difference in the end products [10]

Solution properties of HPMC can be altered by changing the molar mass and / or degree of substitution and thus there are different substituent and viscosity grades commercially available for pharmaceutically approved HPMC [11, 12]. However control of the drug release rate by a proper selection of polymer grades has not always been achieved, and batch to batch variations within grades have been reported [13, 14]. This to some extent is explained by the broad specifications for commercial grades allowing rather large variability in parameters such as viscosity and substitution [12].

It is expected to have a similar functionality and behavior for the same HPMC grades which comply with pharmacopoeial specifications, manufactured by the two different sources. But the specifications provided are of broad range and depicts only average values of the polymer properties. Variations observed between the polymers are sufficient to demonstrate the relevant effects of drug release[10]. The effect of chemical heterogeneity of HPMC on drug release from matrix tablets was also studied by[14].

Quality control tests must be performed on excipients or powders to ensure certain attributes of the excipients or powder to fall within a predefined range. These attributes include chemical composition, particle size, color, moisture and flow properties. This study would help the

formulation scientist to screen the excipients before actual development of the products. Formulation scientist should not be biased for the selection of excipients. Mere similar grades of same excipients manufactured by two different companies will not be always same and they do have impact on the variations in the final product or dosage form.

There are two major goals in present study. First is to investigate the physico-mechanical properties and second is to verify the performance in terms of release retarding property of the hydroxypropyl methylcellulose from the different manufacturing sources. Physico-mechanical properties were characterized by flow properties, density, viscosity, particle size distribution etc. Release retarding properties were evaluated by performing dissolution study on matrix tablets. For performance evaluation study two different set of experiments were performed, in first case drug concentration was varied form 10-70% and in second case polymer concentration was varied from 10-40%.

MATERIALS AND METHODS:

Carbamazepine (Batch No. CAR/1001B/0010) was obtained from Amoli Organics Pvt Ltd. India. Hydroxypropyl methylcellulose (HPMC) were purchased from three widely used sources, namely Methocel K100M (Batch number WJ05012N03 Dow Chemical co.), Novocoat K100M (Batch No. 20110420, Novo Excipients), Zhongbao K100M (Batch No. 200906011, Zhongbao Chemicals.).Microcrystalline cellulose (Avicel PH 102) was procured from FMC Biopolymers U.S.A. (Lot. No – P106817006), Magnesium stearate and talc were procured of pharmaceutical grade.

Evaluation of physico-mechanical properties

All the three HPMC samples were evaluated for their various physico-mechanical properties as per USP specifications. Following properties were evaluated, angle of repose, density (bulk and tapped), compressibility index (CI), Hausner's ratio, moisture content, friability of powders, swelling index, particle size distribution and morphology by Scanning Electron Microscopy.

Measurement of apparent viscosity

HPMC was dispersed in deionized water with gentle stirring at room temperature. 2% aqueous solutions of all HPMC were prepared. The apparent viscosity of all the samples was measured using a Brookfield digital viscometer (model RVD, Brookfield Engineering Laboratories, Inc., USA) with ultra low adaptor at 25 ^{o}C and a speed of 20 rpm. The measurements were made in triplicate.

Particle size distribution

All the three HPMC samples were subjected to particle size distribution using sieve analysis. For this study a stack of sieves was arranged in reverse order (top sieve has the largest screen opening). A weighed mass was poured on to the top sieve. Each lower sieve in the stack has smaller openings than the one above. This stack of sieves was shaken for 15 minutes.After the shaking the material retained on each sieve was weighed. The weight of the sample of each sieve is then expressed as percentage retained on that particular sieve.

Scanning electron microscopy (SEM)

The morphology and surface characteristics of HPMC samples were studied by scanning electron microscopy (SEM). Double sided carbon tape was affixed on aluminum subs. The HPMC samples were sprinkled onto the tape. The aluminum subs were placed in the vacuum chamber of a scanning electron microscope. Gaseous secondary electron detector (working pressure 0.8 Torr, acceleration voltage: 10.00kV) was used for analysis. Gold ion coating was done for 5 to 6 minutes and the particles were observed for surface characteristics. Morphology of the samples was observed using a scanning electron microscope (SEM; JSM-6380LA, Jeol, Japan).

Infrared spectroscopy

To determine the uniformity of content within a batch, three samples were taken from one particular batch of polymer & subjected to Infrared spectroscopy. 20 mg of each HPMC K100M sample was weighed and mixed with KBr to prepare pellets. These pellets were used to record IR spectra. IR spectra were recorded on Perkin Elmer spectrum RX FTIR instrument (Part Number – L1185247).

***In Vitro* drug release study**

An *in vitro* drug release of Carbamazepine from matrix tablets was studied using dissolution apparatus II (Electrolab Model TDT 08, India) as per USP 30-NF 25(15). 900 mL of purified water as the dissolution medium was placed in the dissolution vessels, the apparatus assembled, and the dissolution medium equilibrated to 37 ± 0.5 ^{o}C. The rotation speed of paddle was 100 rpm. At predetermined time intervals (3, 6, 9, 12 and 24 hour), the dissolution medium was removed for determining a drug concentration and fresh medium was replaced. The amount of carbamazepine released in the dissolution medium was measured using a UV spectrophotometer (model Shimadzu UV 1650PC) at the wavelength of 284 nm. The dissolution study was performed using 6 tablets. The cumulative percentage of drug release was calculated and plotted against time.

In vitro drug release was performed for two different set of experiments.

Performance evaluation study by varying drug loading:

Matrix tablets weighing 300 mg were prepared containing drug loading from 10, 30, 50 and 70 %. The polymer concentration was kept constant at 25%. The blends were prepared by mixing drug, HPMC and Avicel PH 102. These blends were further lubricated with talc and magnesium stearate. The resulting blend was directly compressed using a single punch Cadmach compression Machine (Cadmach Ahmedabad) with 10 mm diameter standard concave punch. Model drug used in this study was Carbamazepine. The tablet hardness was fixed at 6-7 kg/cm$^{2.}$ The tablets were prepared using the formulae given in table 1.

Table 1: Formulae for Performance evaluation study by varying drug loading

Ingredients	10% Drug Loading	30% Drug Loading	50% Drug Loading	70% Drug Loading
	All quantities in %			
Carbamazepine	10	30	50	70
HPMC K100M	25	25	25	25
Avicel PH 102	63	43	23	3
Talc	1	1	1	1
Mag.Stearate	1	1	1	1
Total	100	100	100	100

Performance evaluation study by varying polymer concentration:

Matrix tablets weighing 300 mg were prepared varying the polymer concentration from 10, 20, 30 and 38%. The drug concentration was kept constant at 60%. The blend was prepared by mixing drug, HPMC andAvicel PH 102. The blend was further lubricated with talc and magnessium stearate. The resulting blend was directly compressed using a single punch compression machine (Cadmach Ahmedabad) with 10mm diameter standard concave punch. Model drug used in this study was Carbamazepine. The tablet hardness was fixed at 6-7 kg/cm^2.The tablets were prepared using the formula given in table 2.

Table 2:Formula for Performance evaluation study by varying polymer loading

Ingredients	10% Polymer Loading	20% Polymer Loading	30% Polymer Loading	38% Polymer Loading
		All quantities are in %		
Carbamazepine	60	60	60	60
HPMC K100M	10	20	30	38
Avicel PH 102	28	18	8	-
Talc	1	1	1	1
Mag.Stearate	1	1	1	1
Total	100	100	100	100

Mathematical modeling of release kinetics [16, 17]

The dissolution kinetics data were fitted into various release kinetics model reported in literature. These models employ various mathematical equations as shown below:

First order model:

$$\ln(M_0/M_t) = k_1 t \quad (1)$$

Zero order kinetic model:

$$M_0 - M_t = k_0 t \quad (2)$$

Higuchi model:

$$M_t = K (t)^{1/2} \quad (3)$$

Hixswon-crowell cube root model:

$$(W_o)^{1/3} - (W_t)^{1/3} = k_{1/3} t \quad (4)$$

KoresemeyerPeppas model:.

$$M_t / M_\infty = kt^n \quad (5)$$

Where, M_0, M_t and M_∞ correspond to the initial amount of drug, amount of drug dissolved at a particular time, t, and at infinite time, respectively. The terms W_0 and W_t refer to the weight of the drug taken initially and weight of drug dissolved at time t, respectively. Various other terms like k, k_o, k_1, $k_{1/3}$ and K refer to the release kinetic constants obtained from the linear curves of Korsemeyer–Peppas, zero-order, first-order, Hixson-Crowell cube root law and Higuchi model, respectively.

RESULTS AND DISCUSSION

Physico- mechanical properties of HPMC

Table 3 shows the various physical properties for the HPMC from various sources. Among all the physical properties of powders, flowability is a major factor for several processes in the pharmaceutical industry, such as mixing, compaction process, content uniformity etc. The characterization of three HPMC sources revealed some differences in their flow properties, material density and compressibility. Novocoat showed a higher angle of repose as compared to Methocel and Zhongbao. Novocoat and Zhongbao exhibited higher bulk and tapped densities than Methocel. In contrast Methocel yielded the highest CI and Hausner's ratio whereas Zhongbao yielded the lowest CI and Hausners ratio. This indicates that Methocel had a high degree of consolidation.

Apparent viscosity

Apparent viscosity of 2 % w/v solution of HPMC was determined at 25^o C with rotational viscometer as shown in table 3. The values of apparent viscosity of individual HPMC are not significantly different and have passed the specifications for viscosity as per specifications. Specifications for viscosity for the said polymers as per their certificate of analysis was as

follows: Novocoat (75000 – 140000 cps), Methocel (80000 – 120000 cps), Zhongbao (75000 – 140000 cps).

Table 3: Physical properties of HPMC from various sources

Properties	Sources of HPMC		
	Methocel	Novocoat	Zhongbao
Angle of repose (^{o})	22.55	30.00	21.80
Bulk density (g/mL)	0.294	0.303	0.385
Tapped density (g/mL)	0.455	0.455	0.526
Hausner's ratio	1.54	1.50	1.36
Compressibility index (%)	35.29	33.33	26.92
Friability (%)	0.176	0.155	0.234
Moisture content (%)	0.453	0.511	0.478
Viscosity (2% w/v solution) cps	96000	90000	94000
Swelling index (%) (Tablet, 24 Hours)	692.28	728.34	683.73

Particle size distribution using sieve analysis

Particle size distribution pattern was as shown in table 4 and figure 1. Methocel and Novocoat HPMC revealed a similar particle size distribution pattern, whereas Zhongbao HPMC particle size was much finer.

Table 4: Particle size distribution of the various grade excipients

Particle Size (µ)	Methocel K100M	Novocoat K100M	Zhongbao K100M
	% Retained		
Greater than 425	0	0	0
425-250	1.01	0.671	0
250-180	4.835	3.715	0
180-150	7.439	6.398	0.539
150-125	69.66	62.229	9.321
125-106	2.55	11.146	14.601
106-75	1.382	5.728	26.239
Less than 75	13.124	10.114	49.3

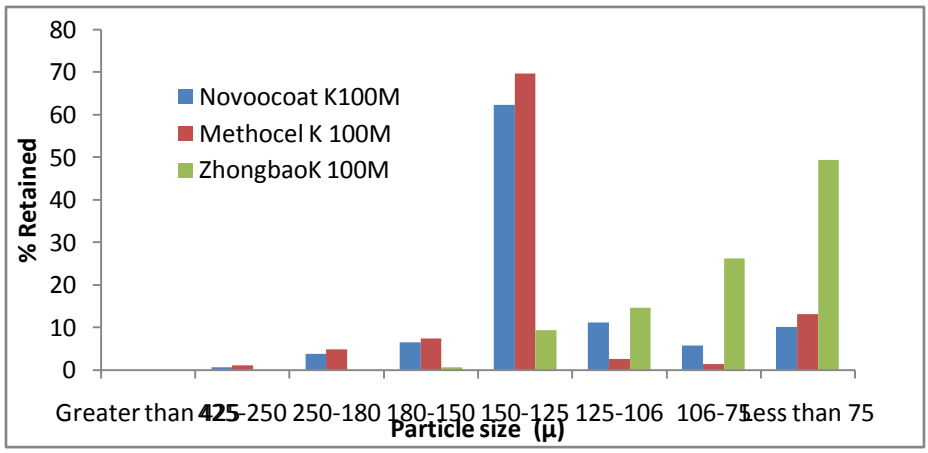
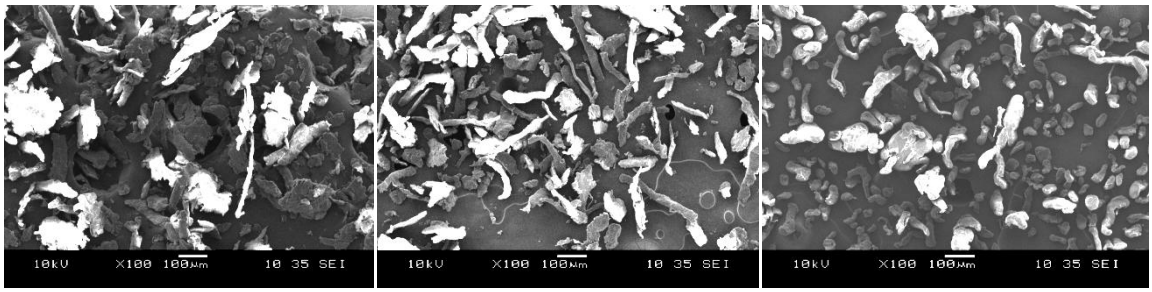


Figure 1: Particle size distribution pattern of three HPMC samples

Scanning electron microscopy

No significant variation was observed in the morphology of the HPMC samples. Novocoat sample (figure 2b) showed needle like particles while Methocel (figure 2a) tends towards a flake like appearance. Zhongbao HPMC (figure 2c) was found to contain a blend of rod like structure and fines.



(a) (b) (c)

Figure 2: SEM images of HPMC a) Methocel K100M, b) Novocoat K100M, and c) Zhongbao K100M

Infrared spectroscopy

All the three samples of HPMC grade showed the presence of functional groups as desired in the product. Methocel HPMC sample (figure.3) showed all the peaks which were super imposable as the product was more uniform compared to Novocoat (figure.4) and Zhongbao (figure.5). Zhongbao showed a much distorted structure as IR spectra's were not overlapping.

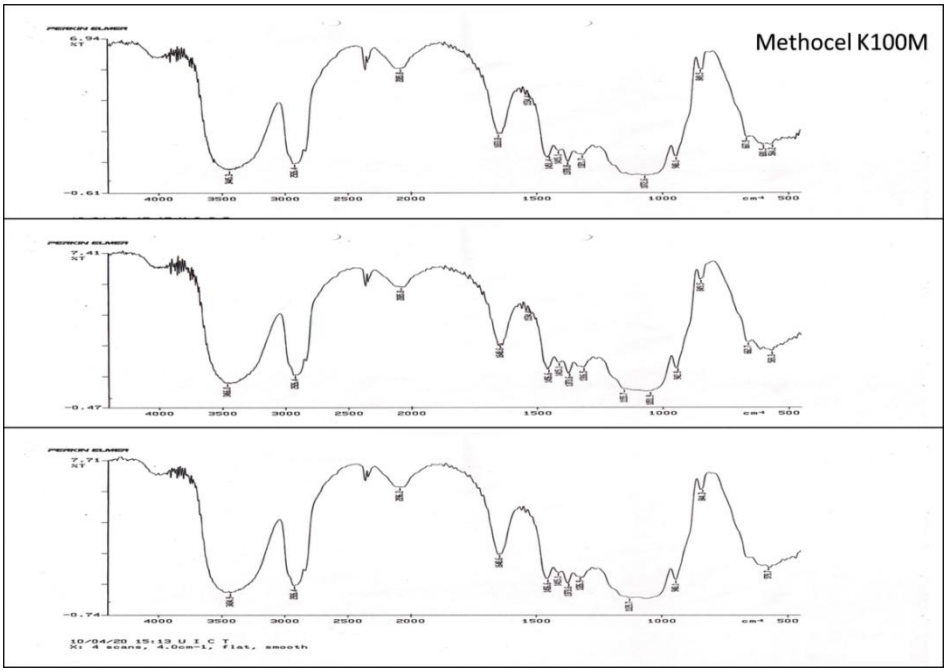


Figure 3: IR spectra of Methocel K100M (n=3): Methocel HPMC showing overlapping peaks, explaining polymer homogeneity.

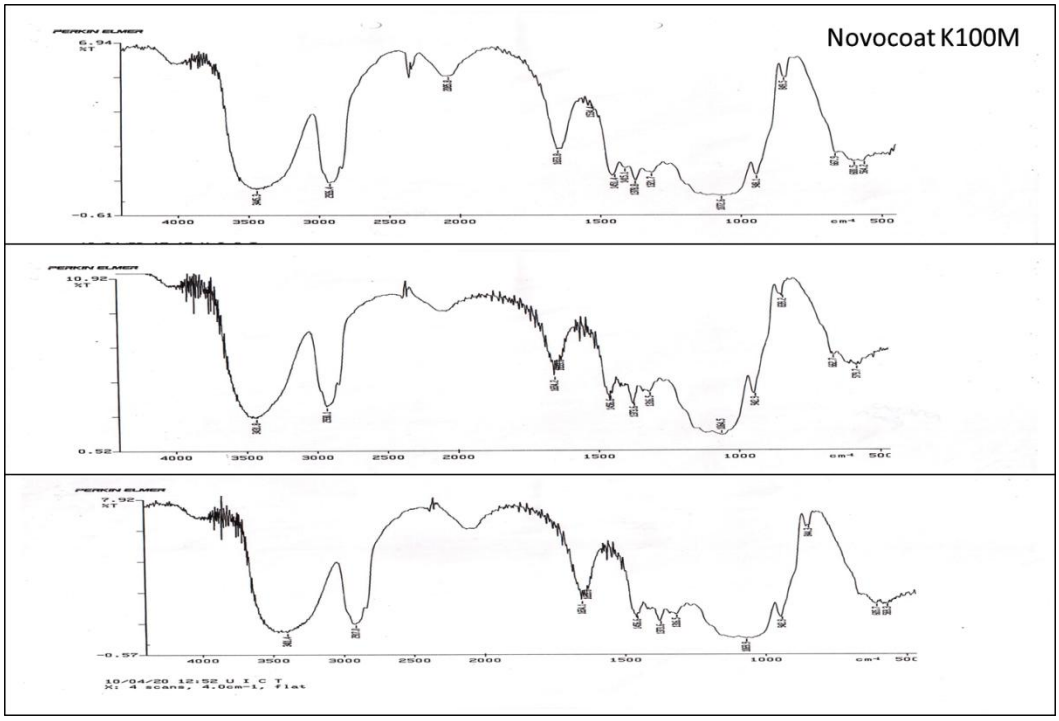


Figure 4: IR spectra of Novocoat K100M (n=3)

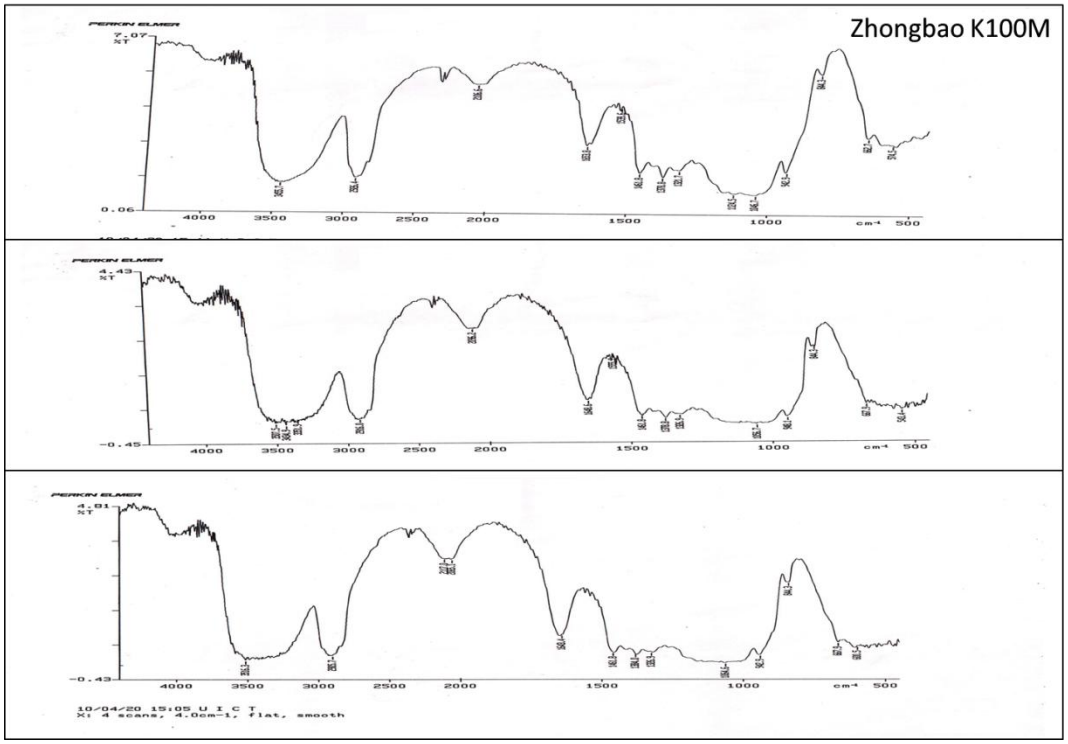


Figure 5: IR spectra of Zhongbao K100M (n=3)

***In vitro* drug release studies**

In vitro drug release from HPMC matrix tablet formulations of three different HPMC brands was as depicted in Figure. 6 and Figure. 7. Each data point represents the mean of six measurements of each formulation.

Varying drug concentration: -

Release of carbamazepine from tablets prepared using Zhongbao was faster than prepared using Methocel and Novocoat. Methocel and Novocoat HPMC showed similar release profiles when drug concentration varied from 10 % to 70%. As the particle size of Zhongbao was very fine the release rate initially was very quick i.e. burst effect was observed. At all the four drug levels Methocel was superior in retarding the drug release effectively than the other two brands.

Varying polymer concentration: -

It was observed that Methocel and Novocoat HPMC gave comparable release profiles (figure. 7). There was initial burst release in the formulations containing Zhongbao HPMC. As the polymer loading increased, the drug release was in excellent agreement. Higher amount of polymer was necessary for tablet formulations containing Zhongbao HPMC in order to obtain equivalent drug release profiles to those of formulations containing Methocel and Novocoat HPMC. An optimum concentration of 20-30% is required of Methocel and Novocoat to retard release of CAR.

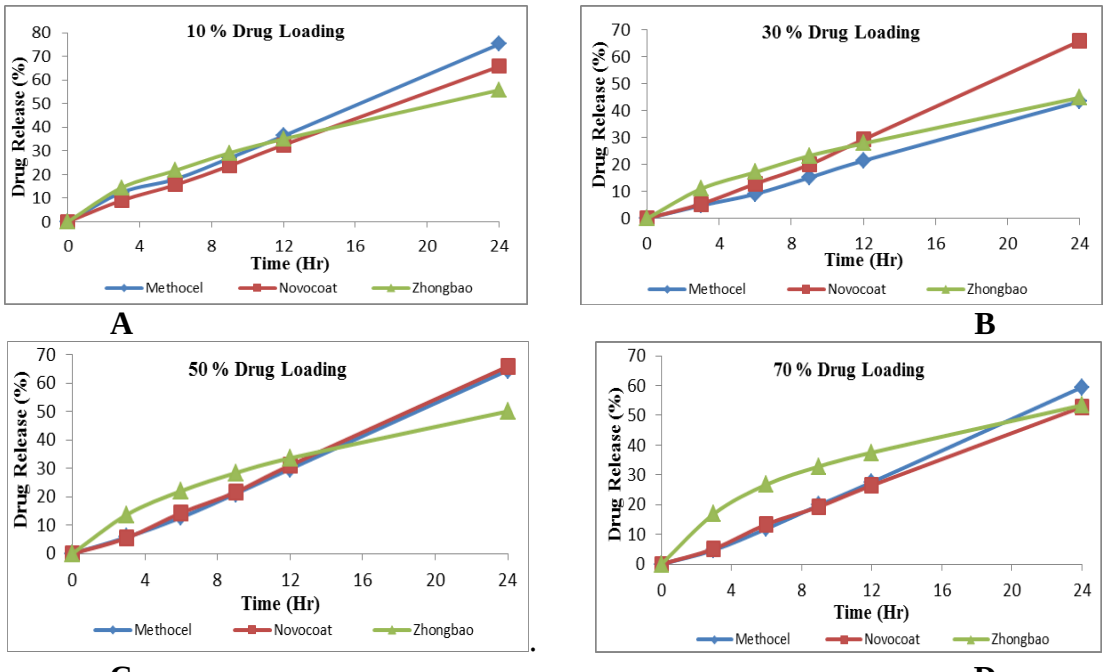


Figure 6: Drug release profile for varying drug loading a. 10% drug loading, b. 30% drug loading, c. 50% drug loading, d. 70% drug loading.

Mathematical model fitting

The release kinetics data was analyzed and fitted in various mathematical models. The fitness of data was as shown in the table 5 and 6 for varying percent drug loading and percent polymer loading batches respectively . The table enlists the regression parameters acquired subsequent to fitting various release kinetic models to the *in vitro* dissolution data.

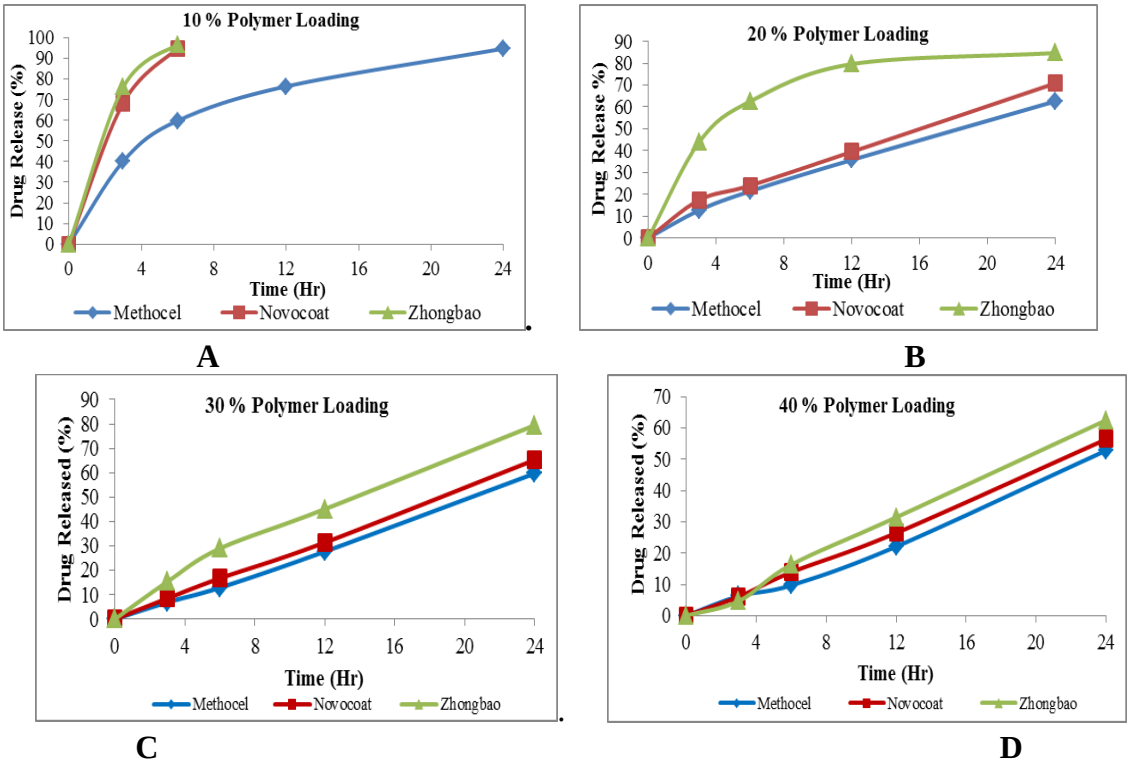


Figure 7.Drug release profile for varying polymer loading a. 10% polymer loading, b. 20% polymer loading, c. 30% polymer loading, d. 40% polymer loading.

Table 5: Statistical parameters for batches containing varying percent drug loading.

Formulation	Model	R^2			Slope		
10 % drug loading		Methocel	Novocoat	Zhongbao	Methocel	Novocoat	Zhongbao
	First	0.9583	0.9261	0.9083	-11.522	-10.422	-15.232
	Zero	0.9955	0.999	0.9918	-1.0844	-1.2172	-1.17072
	Higuchi	0.8783	0.8783	0.9791	0.0593	0.067	0.0862
	Hixoncrowell	0.7264	0.7434	0.6023	-7.5873	-7.9758	-7.3369
	KoresmayerPeppas	0.9781	0.9955	0.9989	1.1136	1.0336	1.528
30 % drug loading		Methocel	Novocoat	Zhongbao	Methocel	Novocoat	Zhongbao
	First	0.9005	0.9005	0.9005	-9.1843	-9.1843	-14.62
	Zero	0.9988	0.9975	0.9913	-0.5949	-0.3812	-0.6972
	Higuchi	0.8624	0.8294	0.9754	0.099	0.0636	0.1068
	Hixoncrowell	0.7724	0.8082	0.6114	-6.4468	-5.7665	-5.5204
	KoresmayerPeppas	0.9972	0.9995	0.9995	0.9246	0.8314	1.4735
50 % drug loading		Methocel	Novocoat	Zhongbao	Methocel	Novocoat	Zhongbao
	First	0.8895	0.8657	0.868	-8.4302	-8.1891	-15.633
	Zero	0.9991	0.9995	0.9757	-0.2357	-0.2319	-0.3911
	Higuchi	0.8429	0.8501	0.9913	0.0655	0.0645	0.0962
	Hixoncrowell	0.7965	0.7913	0.5761	-4.8461	-4.7758	-4.2944
	KoresmayerPeppas	0.9996	0.9965	0.9978	0.8549	0.8405	1.6035
70 % drug loading		Methocel	Novocoat	Zhongbao	Methocel	Novocoat	Zhongbao
	First	0.8668	0.8509	0.8526	-8.006	-8.7195	-17.604
	Zero	0.9997	0.9991	0.9615	-0.182	-0.2122	-0.2798
	Higuchi	0.8446	0.8788	0.9981	0.0709	0.0823	0.0907
	Hixoncrowell	0.7993	0.7594	0.5374	-4.4369	-4.4765	-3.5848
	KoresmayerPeppas	0.9978	0.9929	0.9939	0.8218	0.9011	1.8182

Table 6: Statistical parameters for batches containing varying percent polymer loading.

Formulation	Model	R^2			Slope		
10 % polymer loading		Methocel	Novocoat	Zhongbao	Methocel	Novocoat	Zhongbao
	First	0.8281	0.6634	0.6593	-22.941	-18.599	-25.337
	Zero	0.9125	0.999	0.999	-0.2115	-0.063	-0.0807
	Higuchi	0.9766	0.9211	0.9928	0.0499	0.0307	0.0246
	Hixoncrowell	0.4827	0.8266	0.8073	-2.9249	-0.8941	-0.8675
	KoresmayerPeppas	0.9776	0.999	0.999	2.4017	1.2476	1.3302
20 % polymer loading		Methocel	Novocoat	Zhongbao	Methocel	Novocoat	Zhongbao
	First	0.9294	0.9711	0.7044	-13.085	-14.921	-26.152
	Zero	0.9983	0.9995	0.7613	-0.2359	-0.2163	-0.2436
	Higuchi	0.9546	0.9563	0.9131	0.0747	0.0673	0.0513
	Hixoncrowell	0.6744	0.6519	0.4278	-4.2347	-4.0108	-2.7698
	KoresmayerPeppas	0.9996	0.9844	0.9192	1.3076	1.4475	2.8785
30 % polymer loading		Methocel	Novocoat	Zhongbao	Methocel	Novocoat	Zhongbao
	First	0.9401	0.9305	0.9681	-9.6091	-10.265	-26.544
	Zero	0.9984	0.9991	0.9929	-0.2181	-0.2057	-0.5767
	Higuchi	0.8739	0.8955	0.9864	0.0725	0.0679	0.1335
	Hixoncrowell	0.7892	0.7603	0.4921	-4.7399	-4.5034	-4.1093
	KoresmayerPeppas	0.9977	0.9992	0.9783	0.9538	1.0249	2.571
40 % polymer loading		Methocel	Novocoat	Zhongbao	Methocel	Novocoat	Zhongbao
	First	0.97	0.9101	0.8875	-9.7189	-9.3481	-13.654
	Zero	0.9903	0.9989	0.9871	-0.2423	-0.233	-0.7247
	Higuchi	0.8461	0.884	0.8461	0.0806	0.0774	0.0806
	Hixoncrowell	0.8045	0.7809	0.6391	-5.0395	-4.7831	-5.8429
	KoresmayerPeppas	0.9802	0.998	0.9937	0.9413	0.9432	1.3922

Overall the Zero order release and Korsmeyer – Peppas model described drug release kinetics in the most befitting manner. After fitting the drug release data including these time points, these correlations were also found to be statistically significant with Zero order and Korsmeyer – Peppas model. In the formulations containing Methocel and Novocoat HPMC and varying drug concentration (polymer concentration 25%), the goodness of fit for various models examined for systems classified in the order of; Zero order >Korsmeyer – Peppas> First order > Higuchi > Hixson – Crowell cube root law. While Zhongbao HPMC systems by and large showed Korsmeyer – Peppas release kinetics. For the batches containing varying polymer concentration (10-40%), at lower concentration Methocel HPMC follows the order of Korsmeyer – Peppas> Zero order >Higuchi > First order > Hixson – Crowell cube root law. But as polymer concentration increased to 30-40% release kinetics tends to shift towards zero order following the order of; Zero order >Korsmeyer – Peppas> First order > Higuchi > Hixson – Crowell cube root law. No significant effect of polymer concentration was found in case of Novocoat based formulations with respect to release kinetics as R^2 value trend remained unchanged and found in the order of; Zero order>Korsmeyer – Peppas> First order > Higuchi > Hixson - Crowell cube

root law. Zhongbao HPMC again showed by and large Korsmeyer – Peppas release kinetics. Overall, the values of diffusional exponent 'n', obtained from the slopes of the fitted Korsmeyer–Peppas model, ranged between 0.8218 and 2.4017. The corresponding values of n lower than the standard value of 0.45 are indicative of Fickian release behavior. Similarly non-Fickian behavior can be declared for the formulation showing n value greater than 0.45. Statistical parameters of various formulations obtained after fitting the drug release data to various release kinetic models was shown as below:

CONCLUSION:

Comparative study shows that there are several differences in the physicochemical characteristics of the three HPMC sources. These differences include density, flow, particle-size distribution, particle morphology, and particle shape and most important release retarding properties. Although all the HPMC batches investigated were supplied as equivalent with regard to chemical and physical properties (as per label claim), both manufacturers and users must be aware of the polymer characteristics, which could generate great variation in the behavior of end-product formulations made from HPMC of the same commercial grade.

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