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Preparation and In-Vitro Evaluation of Sustained Release Matrix Diclofenac Sodium Tablets Using HPMC KM 100 and Gums

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Abstract

Objectives: The impact of hydroxypropylmethyl cellulose (HPMC K 100M) alone and in combination with the guar gum, xanthan gum and gum tragacanth on the release of the diclofenac sodium matrix tablets were evaluated.

Materials and Methods: The granules were prepared using wet granulation method and compressed into tablets using different ratio of drug and gum ratio. The physical properties of the tablets were within acceptable pharmacopeial limits. The release profiles of the matrix tablets were evaluated in-vitro, using USP dissolution apparatus II (paddle method).

Results: The formulations containing HPMC K 100M drug ratio 1:1.3 and 1:1.6 and formulations containing HPMC, gum and drug with different ratio also sustained the release of diclofenac sodium for 12 hours. The mechanism of drug release from the matrix tablets was studied using Zero order, First order, Higuchi and Korsmeyer's models using regression coefficient method. The stability of the selected formulations was evaluated at 40˚C and 70% RH for 6 months.

Conclusions: HPMC K100M alone and in combination with natural gums as the retarding material retarded the release up to 12 hours and showed little deviation from the theoretical release pattern.

Keywords:

HPMC, Guar Gum, Xanthan gum, Gum Tragacanth, Sustained Release, Diclofenac Sodium

Introduction

Frequently used approaches to achieve adequate control of drug release include hydrophilic and lipophilic matrix systems, where the drug release mechanism is based on a combination of diffusion and erosion processes. Hydroxypropylmethylcellulose (HPMC, hypromellose) is one the most frequently hydrophilic semi synthetic materials studied, since early 1960s [1,2,3,4,5,6]. On contact with water, HPMC hydrates rapidly and forms a gelatinous barrier layer around the tablet [7]. This swelling and hydration property of HPMC eliminates the burst release. The higher percentage of drug release at the end of the dissolution period can be attributed to the erosion of the matrix, which takes place after complete hydration of outer layer. Therefore, mechanisms of drug release from these systems are complex, involving up to three moving boundaries, usually termed the swelling, diffusion, and erosion fronts [8]. HPMC displays good compression properties, can accommodate high drug loading, and is considered non-toxic [9].

Natural polymers like cellulose, xanthan gum, locust bean gum, gaur gum and chemically modified gums have been studied in hydrophilic matrix tablets for controlled drug delivery [10, 11, 12, 13, 14]. These natural polymers are usually cost effective, nontoxic and easily available. Guar gum in pharmaceuticals is used as disintegrant, binder [15, 16, 17] and as a hydrophilic matrix for sustaining drug release [18,19,20,21]. Xanthan gum is an another industrially important exocellular heteropolysaccharide natural gum, used as thickening agent [22] and also has been used as hydrophilic sustained release matix material for different drugs [23,24]. Tragacanth is a naturally occurring dried gum comprised of bassorin (60-70%), the water insoluble portion and tragacanthin, water soluble portion (30-40%). When water permeates, the tragacanthin dissolve forming colloidal hydrosol and bassorin swell up to form a gel like material and by this mechanism the release of the drug from the matrix system is controlled.

The successful sustained release (SR) formulations of salbutamol and ketoprofen using HPMC have been reported [25]. On the other hand, lipophilic materials have been also employed as matrix carriers for SR solid dosage forms.

Materials and Methods:

Materials

Diclofenac sodium, (Ningbo Smart Pharmaceutical Co.Ltd, China), Hydroxypropylmethylcellulose (methocel HPMC K100M, nominal viscosity 100,000 cps), (Dow chemical company Ltd. UK). Guar gum,Xanthan gum, Gum Tragacanth (Medicraft pharma. Pvt. Ltd. Peshawar, Pakitan), Lactose (The Lactose Newzeland Company, Newzeland), Starch (Rafhan Maize Products Co. Ltd, Faisalabad, Pakistan), Potassium chloride, Boric Acid, Talc, Sodium acetate, Sodium chloride, Sodium hydroxide, Cetyl alcohol, Magnesium Stearate, Sodium bicarbonate (BDH,

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England), Sodium citrate, Di-Sodium hydrogen phosphate (Merck, Germany), Concentrated hydrochloric acid (Riedel de Haen,Munich Germany), Methanol(Merck Germany).

Instrumentation / Equipments

Oscillating granulator (F.D & C Karachi, Pakistan), Top loading balance (T200, China), Oven / Dryer, ZP19 Rotary compression machine, Coating pan, Tablet Hardness Tester (model THB 28, Erweka, Germany), U.S.P. Dissolution Apparatus II (Erweka DT6R Dissolution Tester, Germany), Fribilator (Erweka, Germany), UV / Visible spectrophotometer (Hitachi, Japan), High Performance Liquid Chromatograph with UV – Visible detector (HPLC, Perkin Elmer Series 200).

Methods Of Preparation Of Sustained Release Diclofenac Sodium Tablets Using Polymers And Natural Gums

Various formulations (each batch of 600 gram) with different concentrations of HPMC both alone and in combination with the natural gums as shown in Table-1 were prepared. Briefly, the diclofenac sodium, sustaining material(s), diluents and buffer were weighed, mixed thoroughly for 10 minutes. Then ethanol (360 ml) was added in installments and mixed enough to obtain cohesive mass. The wet mass was then sieved through mesh No 16; granules were dried at 40°C for 12 hours and passed through mesh No.22. Talc and magnesium stearate were then added. The practical weight of tablets was calculated based on the drug content of the granules. Finally, granules were compressed at a compression force of 6500-7500 Newton (11.8 mm diameter, beveled edge punches) using a ZP 19 Rotary tablet compression machine.

Evaluation of Granules

Various physical properties of the granules like angle of repose, loose and tapped bulk densities [26] and compressibility index [27] were determined. Drug contents in granules and tablets were determined according B.P [28].

Physical Characterization Of Matrix Tablets

The weight variation and friability of the tablets was determined according to B.P [28], the thickness and the hardness of tablets (n =20) was measured using Pharma test hardness tester.

Dissolution Profile

Drug release from the tablets (n = 6) from each batch of formulations were evaluated using USP dissolution apparatus II, adjusted at 50 rpm. Water (900 ml) adjusted at 37°C ± 1.0 was used as medium. Samples were collected periodically and analyzed for the drug contents.

The Difference Factor (*f*1) and Similarity Factor (*f* 2)

The dissolution data for various formulations was evaluated for the difference factor (f1) [29] and similarity factor (f2) [30] using equation I and II, respectively.

$$f1 = \left(\frac{\lfloor \sum_{t=1}^{n} (Rt - Tt) \rfloor}{\sum_{t=1}^{n} (Rt)} \right) x\ 100$$

Where, n is the number of time points, Rt is the dissolution value of the reference Product (voltral) at time t, and Tt is the dissolution value of the test batch at time t. generally f1 values varies from 0 to 15 [29].

$$f2 = 50 \times \log \left[\left\{ \left(1 + \frac{1}{n} \right) \sum_{t=1}^{n} (Rt - Tt)^2 \right\} \right]^{-0.5} \times 100$$

If the value of f1 is less than 15 and value of f2 is between 50 and 100, then formulations under studies are considered as similar to the reference drug. FDA and EMEA suggested that two dissolution profiles are declared similar if *f*2 is between 50 and 100. It should be noted that in the *f*2 SUPAC-IR and EMEA Guidance *Rj* and *Tj* are defined as the percent dissolved in each sampling time point *j* [31].

Determination of the release rate of Diclofenac sodium

The cumulative drug release (%) as a function of time (Zero Order), log of the cumulative drug release (%) as a function of Time (First Order), cumulative drug release (%) as a function of square root of time (Higuchi Model) and cube root of remaining drug vs time (Hixon-Crowell) plots were constructed to understand the drug release mechanism.

To understand the mechanism from the polymeric system Korsmeyer's-Peppas model was applied, the value of "n" less than 0.45 shows the Fickian Diffusion, between 0.45 and 0.89 indicates the non-Fickian or anomalous diffusion, 0.89 indicates the case-II transport and above 0.89 shows super case II diffusion. .

HPLC Analysis of Drug Samples

The diclofenac sodium in serum samples was analyzed using Perkin Elmer HPLC (series 200) equipped with UV-Visible detector (Perkin Elmer Series 200). The analytes were separated on Kromasil KR100 – 10 C_{18} (ODS; 5 C-18 µm; 250 x 4.6 mm) column and measured at 245 nm. The analytical column was protected with the guard column (Guard-Pak filled with a µ Bondapak C-18 cartridge, Merk, Germany).

Results

Evaluation of Physical properties of Granules

Different batches of granules were prepared using hydroxypropyl methylcellulose (HPMC K100M) alone and in combination with natural gums (Table-1) to study the sustaining effect of the polymers. The granules were subjected to physical characterization by evaluating the angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index, total porosity, and drug content (Table-2), before compressing into tablets. The results of angle of repose and compressibility index (%) ranged from 20.34 ± 0.02 to 21.76 ± 0.03, and 9.32 ± 0.02 to 10.45 ± 0.04, respectively.

The (Mean ± SD) angles of repose of the formulations were from 22.06 ± 0.03 to 25.82 ± 0.03. The (Mean ± SD) compressibility index of the granules of the formulations of HPMC / admixed polymers was ranged from 10.12 ± 0.04 to 12.82 ± 0.04. The (Mean ± SD) drug content in a weighed amount of granules of all formulations ranged from 97.84 ± 0.04 to 100.44 ± 0.02%.

Generally, all formulations have good flow properties as evident from the data obtained for angle of repose and compressibility index. The results of LBD and TBD ranged from 0.292 ± 0.02 to 0.301 ± 0.03 and 0.322 ±

0.02 to 0.336 ± 0.05, respectively. The drug content in the granules of all the formulations was uniform and ranged from 98.66 ± 0.03 to 100.44 ± 0.03 %. All these results indicate that the granules possessed satisfactory flow properties, compressibility, and uniform drug content.

Evaluation of Physical properties of Tablets

The granules were compressed using rotary tableting machine ZP 19. Samples were collected randomly from each batch of the compressed matrix tablets and evaluated for physical and chemical properties, the results are shown in the (Table-3). The thickness of the tablets ranged from 4.09 ± 0.02 to 4.32 ± 0.02 mm. The average percentage deviation of 20 tablets of each formula was less than ± 5 %. The hardness and percentage friability of the tablets of all batches ranged from 75 ± 2.2 to 1107 ± 2.2 N and 0.17 ± 0.04 to 0.68 ± 0.05%, respectively.

Tablets of all the formulations showed uniform thickness. The average percentage weight deviation of all tablet formulations was found within the limits. The percentage of drug content was more than 96% indicating good uniformity. A linear relationship between the concentration of HPMC and the hardness of the tablets was observed in the formulations, the tablets of formulation DFH4 showed a comparatively high hardness value of 107 ± 2.6 N. The percentage friability for all the formulations was below 1%, indicating that the friability was within the prescribed limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the pharmacopial specifications for weight variation, hardness, friability and drug content.

Drug Release Studies

The in vitro drug release characteristics were studied in the dissolution media (900 ml), consisted of simulated gastric fluid (without pepsin) of pH 1.2 for the first 2 hours and simulated intestinal fluid (without pancreatin) of pH 6.8 for the remaining time, maintained at 37°C ± 0.5°C using USP XXIII dissolution apparatus II. The results of dissolution studies of formulations DFH1, DFH2, DFH3 and DFH4 are shown in Figure-1. Tablets from the formulations DFH1, DFH2, and DFH3 and DFH4 released 8.40%, 7.98%, 6.82% and 6.66 % of diclofenac sodium at the end of 2 hours; only the formulation DFH4 extended the release upto 12 hours i.e. 96.28%, the rest of formulation were unable to sustained the drug release upto 12 hours. The rate of release of diclofenac sodium decreased as the amount of the polymer increased from formulation DFH1 to DFH4. It has been reported that the increase of HPMC K100M content with the same drug concentration resulted in a decreased release rate of drugs [32]. The drug release is controlled by the hydration of HPMC, which form gelatinous barrier layer at the surface of the matrix. In addition, the resistance of such a gel layer to the erosion is controlled by the viscosity grade of HPMC. At low concentrations, the viscosity of the matrix was very low therefore; the release of the drug from formulations DFH1, DFH2 and DFH3 was fast as compared to DFH4. An increase in the polymer amount caused an increase in the viscosity of the gel and the formation of the gel layer with a longer diffusion path. This could cause the effective diffusion coefficient of the drug and results in slow drug release rate.

The dissolution profile of HPMC K100M extended release matrix tablets showed that at the level of 130 mg of HPMC K100M per tablet (DFH4), the release of diclofenac sodium was extended up to 12 hours and the profile was close to the theoretical drug release as shown in the Figure-1. Hence, the formulation DFH4 was selected for further formulation development. Different buffers were incorporated in the formulations (DFH5, DFH6 and DFH7) as shown in the Table-1. The results of dissolution studies of these formulations (Figure-2) indicate that the formulations DFH5, DFH6 and DFH7 released 28.54%, 24.64%, and 20.14% of diclofenac sodium at the end of 2 hours and 98.1%, 95.58%, and 88.72% at the end of 10 hours, respectively as compared to DFH4 which released only 75.4% of drug and sustained the drug for 12 hours. The dissolution results indicate that the inclusion of buffers (sodium bicarbonate, calcium carbonate, and sodium citrate) in the HPMC K100M matrix tablets increased the release of the diclofenac sodium (Figure-2). It shows that buffers might have enhanced the permeability of the HPMC K100M surface gel layer, which at higher concentrations result in the pseudogel which finally fails the diffusion barrier and its ability to control release. Buffers can compete for the water of hydration and reduce the hydrophilic matrix integrity [33]. It might also be due to the higher solubility of diclofenac sodium in alkaline media. The inclusion of sodium bicarbonate and calcium carbonate in the HPMC K100M matrix improved the diclofenac sodium dissolution; however, the effect of sodium citrate on the dissolution of diclofenac sodium was comparatively low.

The dissolution profile of formulations H_4, H_2G_2, H_2X_2, and H_2T_2, composed of HPMC K100M alone and in combination with guar gum (1:1); HPMC K100M and xanthan gum (1:1); HPMC K100M and gum tragacanth (1:1), are shown in Figure-3. Matrix tablets of these formulations released 21.82%, 25.46%, 26.72% and 28.38% of diclofenac sodium at the end of 2 hours respectively; 94.64%, 97.16%, 89.76% and 91.84% of drug at the end of 12 hours, respectively.

The triple formulation as given in the Table-4, H_2GX was prepared by incorporating guar gum and xanthan gum into HPMC K100M in the ratio of 2:1:1. H_2GT was prepared by mixing HPMC K100M with guar gum and gum tragacanth in the ratio of 2:1:1. Similarly, H_2XT was obtained by mixing HPMC K100M with xanthan gum and gum tragacanth in the ratio of 2:1:1. The results of dissolution studies of these triple mixture matrix tablets are shown in the Figure 3, indicate that H_2GX, H_2GT, and H_2XT released 24.18%, 29.84% and 22.48% of diclofenac sodium at the end of 2 hours and 91.86%, 94.36% and 82.45% at the end of 12 hours, respectively.

Kinetics Of The Drug Release

The cumulative amount of diclofenac sodium released from HPMC K100M and HPMC K100M admixed with different proportions of natural gums matrix tablets at different time intervals was fitted to zero-order kinetics, first-order, Higuchi equation and the model developed by Korsmeyer, et al., 1983, in order to find out the drug

release mechanism from the formulations [34]. The percent of drug released from the formulations was plotted against time on a log-log scale, and analyzed for linearity using least squares method. The correlation coefficients were calculated and used to find the fitness of the data.

The in-vitro kinetic data for the formulation with HPMC alone is shown in the Table-4, the data demonstrate that matrix tablets best follow Higuchi kinetics $R^2 = 0.997$, where as Korsmeyer equation also showed linearity with $R^2 = 0.9950$ and n = 0.927. The release data of the diclofenac sodium from matrix tablets containing admixed polymers fitted to zero order showed linearity (R^2 from 0.980 to 0.9950), which is lower to the R^2 obtained with Higuchi model, the values for R^2 ranged from 0.9970 to 0.9990.

In the formulations of the combination of HPMC K100M and guar gum, drug release kinetics is predominantly Higuchi model kinetics via Non- Fickian diffusion. As HPMC and guar gum are both hydrophilic colloids and water-soluble, they dissolve and form pores filled with liquid in which drug can thereafter diffuse but because of the poor solubility of diclofenac sodium the process of diffusion was slow, therefore, the diffusion was accompanied by erosion of the matrix. On the other hand, xanthan gum had shown the highest erosion and water uptake among the studied formulations. In high concentrations of xanthan gum (H_2X_2), Higuchi model release kinetic was concluded with $R^2 = 0.999$. When plotted with Korsmeyer model, H_2X_2 matrix formulation showed high linearity ($R^2 = 1.00$) with a slope value n = 0.679. This n-value indicates a coupling of diffusion and erosion mechanism – so called anomalous diffusion. It may be concluded that drug was released both by diffusion and erosion within the matrix. When release data from the formulations H_2GX and H_2XT was fitted to zero order equations the R^2 values were 0.995 and 0.991 respectively. The data showed higher linearity when fitted to the Korsmeyer equation with R^2 values = 0.9990 both and the n value of 0.751 and 0.734 respectively showing Non-Fickian anomalous release profile.

When the percent of diclofenac sodium released from formulations was fitted to the model developed by Korsmeyer, the mean diffusional exponent values (n) for the formulations DFH1, DFH2, DFH3 and DFH4 ranged from 1.2 to 1.17 showing Super case II release which indicates the erosion of the matrix. The n values for DFH5, DFH6 and DFH7 ranged from 0.527 to 0.654 indicate Non-Fickian release.

Presence of swelling polymers within the matrix structure might be responsible for the drug release controlled by more than one process. The formulations DFH1, DFH2, DFH3 and DFH4 contain 70mg, 90 mg 110 mg and 130 mg of HPMC K 100M per matrix tablet (Table-1), which is maximally 32.3 % per tablet. Since the hydration and the swelling rate of these matrix tablets relates to the hydroxypropyl substitutes percentage on the polymer and the concentration of this polymer per tablet. HPMC K100M contains the highest amount of these groups and produces strongly viscose gel that plays an important role in drug release especially at the beginning of the release profile. Therefore, the quick hydration and subsequent gel formation is a foremost and important property of an excipient to be used in sustained-release formulations [35]. The release of the drug from the formulation DFH5, DFH6 and DFH7 which, contain about 32.3% HPMC K 100M and also carbonates / buffers per matrix tablet followed Non-Fickian diffusion. The carbonate and buffers help in the solubility of the diclofenac sodium there by releasing the drug by diffusion mechanism.

Stability Studies

All the matrix tablets were stored at the temperature of 40°C and 75% relative humidity for 6 months. At the end of the storage period, the matrix tablets were observed for changes in physical appearance, analyzed for drug content, and subjected to in vitro drug release studies Figure-4. No significant changes in the appearance of the matrix tablets were observed at the end of the storage period. The drug content was found to be 98.4% ± 2.3%. At the end of 12 hours of dissolution testing, the amount of the drug released from all matrix tablets was significantly indifferent from the release of the drug from the formulations at zero time, indicating that the formulation could provide a satisfactory shelf life.

In present study initially, matrix tablets H_4 were prepared with polymer HPMC K100M alone as the retarding material retarded the release up to 12 hours. In the next phase buffers were incorporated to study their effect on the release kinetics and in third phase HPMC K100M was partially replaced with the natural gums in different proportions.

Conclusions

The results of our study show that the natural gums used in combination with HPMC K100M to prepare matrix tablets. All of these formulations effectively extended the release up to 12 hours and showed little deviation from the theoretical release pattern. From a commercial point of view, locally available gums are more economical than the synthetic or semi-synthetic polymers. Hence, admixed polymers are the most successful and cost-effective formulation among the matrix tablets developed in the present study.

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Conflict of interest:

All the authors have no conflict of interest

Table-1: Composition of Diclofenac sodium tablets (100 mg)

S. N.	Formula	HPMC K100M	Guar gum	Xanthan gum	Gum Tragacanth	Lactose	Buffer
1	DFH1	70mg	-	-	-	220	-
2	DFH2	90 mg	-	-	-	200	-
3	DFH3	110 mg	-	-	-	180	-
4	DFH4	130 mg	-	-	-	160	-
5	DFH5	130 mg	-	-	-	150	10mg Sod. bicarbonate
6	DFH6	130 mg	-	-	-	150	10mg Cal. carbonate
7	DFH7	130 mg	-	-	-	150	10mg Sod. citrate
8	H_4	160	-	-	-	130	-
9	H_2G_2	80	80	-	-	130	-
10	H_2X_2	80	-	80	-	130	-
11	H_2T_2	80	-	-	80	130	-
12	H_2GX	80	40	40	-	130	-
13	H_2GT	80	40	-	40	130	-
14	H_2XT	80	-	40	40	130	-

H = Hydroxypropylmethylcellulose(HPMC K 100M), HG =HPMC + Guar gum,
HX = HPMC + Xanthan gum, HT = HPMC + Gum Tragacanth,
HGX = HPMC+ Guar gum + Xanthan gum,
HGT = HPMC+ Guar gum + gum Tragacanth, HXT= HPMC+ xanthan gum + gum Tragacanth.

Table-2: Physical properties of granules prepared from HPMC K100M and HPMC in combination with Natural Gums as sustaining material

Formulation	Angle of repose	Loose bulk density (g/ml)	Taped bulk density (g/ml)	Compressibility Index (%)	Drug content (%)
DFH1	20.34 ± 0.02	0.292 ± 0.02	0.322 ± 0.02	9.32 ± 0.02	99.61±0.05
DFH2	20.56 ± 0.02	0.297 ± 0.03	0.328 ± 0.03	9.45 ± 0.04	98.94±0.03
DFH3	21.31 ± 0.03	0.299 ± 0.04	0.330 ± 0.02	9.39 ± 0.03	99.22±0.02
DFH4	21.76 ± 0.03	0.301 ± 0.02	0.332 ± 0.04	9.34± 0.02	99.84±0.03
DFH5	20.93 ± 0.04	0.301 ± 0.03	0.333 ± 0.04	9.61 ± 0.04	99.12±0.04
DFH6	20.78 ± 0.03	0.300 ± 0.02	0.335 ± 0.05	10.45 ± 0.04	98.66±0.03
DFH7	20.72 ± 0.03	0.301 ± 0.02	0.336 ± 0.05	10.42 ± 0.04	98.84±0.02
H_4	22.06 ± 0.03	0.308 ± 0.02	0.344 ± 0.04	10.46± 0.02	99.42 ± 0.04
H_2G_2	25.82 ± 0.03	0.408 ± 0.02	0.468 ± 0.04	12.82 ± 0.04	100.44±0.02
H_2X_2	22.96 ± 0.02	0.426 ± 0.02	0.474 ± 0.05	10.12 ± 0.04	99.64 ± 0.04
H_2T_2	25.38 ± 0.02	0.424 ± 0.02	0.478 ± 0.04	11.29 ± 0.03	97.84 ± 0.04
H_2GX	24.46 ± 0.03	0.431 ± 0.02	0.482 ± 0.03	10.58 ± 0.02	98.44 ± 0.04
H_2GT	24.32 ± 0.04	0.416 ± 0.04	0.468 ± 0.03	11.11 ± 0.04	98.92 ± 0.04
H_2XT	24.52 ± 0.03	0.428 ± 0.04	0.484 ± 0.03	11.57 ± 0.02	99.08 ± 0.02

All values represent mean ± SD (n = 3).

Table-3: Physical and chemical properties of Diclofenac sodium matrix tablets prepared from HPMC K100M as sustaining material

Formulation	Thickness (mm)	Weight (mg)	Friability (%)	Hardness (N)	Drug content (%)
DFH1	4.27 ± 0.02	401.6 ± 2.8	0.62 ± 0.03	75 ± 2.2	99.12 ± 0.05
DFH2	4.19 ± 0.01	402.6 ± 3.1	0.68 ± 0.05	86 ± 2.4	98.78 ± 0.02
DFH3	4.28 ± 0.03	402.7 ± 2.0	0.34 ± 0.04	97 ± 2.3	97.82 ± 0.05
DFH4	4.09 ± 0.02	401.3 ± 3.0	0.17 ± 0.04	107± 2.6	98.75 ± 0,04
DFH5	4.18 ± 0.03	401.9 ± 1.9	0.22 ± 0.03	102 ± 2.4	98.35 ± 0.05
DFH6	4.32 ± 0.02	403.0 ± 2.1	0.19 ± 0.04	104 ± 2.4	99.08 ± 0.04
DFH7	4.24 ± 0.03	402.1 ± 2.5	0.20 ± 0.03	105 ± 2.2	98.22 ± 0.04
H_4	4.21 ± 0.02	404.6 ± 2.8	0.22 ± 0.03	104 ± 2.2	99.24 ± 0.05
H_2G_2	4.29 ± 0.03	403.2 ± 3.4	0.18 ± 0.05	86 ± 2.4	98.80 ± 0.02
H_2X_2	4.26 ± 0.02	401.5 ± 2.4	0.25 ± 0.04	97 ± 2.3	99.24 ± 0.05
H_2T_2	4.18 ± 0.03	403.4 ± 2.2	0.19 ± 0.04	88± 1.9	99.54 ± 0,04
H_2GX	4.20 ± 0.04	401.6 ± 1.8	0.21 ± 0.03	86 ± 2.4	98.50 ± 0.05
H_2GT	4.32 ± 0.02	403.0 ± 2.1	0.19 ± 0.04	81 ± 1.9	99.84 ± 0.04
H_2XT	4.24 ± 0.03	402.1 ± 2.5	0.22 ± 0.03	87 ± 2.1	99.82 ± 0.04

All values represent mean ± SD (n = 20).

Table 4. Data showing In-Vitro release kinetics (Analyzed by regression coefficient method) of diclofenac sodium from different batches of HPMC K 100M matrix

Formulation	Zero order	First order	Higuchi	Korsmeyer			
	R^2	R^2	R^2	R^2	n	k	
DFH1	0.9878	0.9506	0.9640	0.9334	1.2	0.858	Super case II
DFH2	0.9894	0.9569	0.9598	0.9266	1.16	0.860	Super case II
DFH3	0.9936	0.9375	0.9707	0.9385	1.17	0.788	Super case II
DFH4	0.9923	0.9131	0.9810	0.9484	1.16	0.753	Super case II
DFH5	0.9901	0.9671	0.9785	0.9288	0.527	1.43	Non-Fickian
DFH6	0.9935	0.9683	0.9791	0.9395	0.586	1.36	Non-Fickian
DFH7	0.9919	0.9599	0.9804	0.9451	0.654	1.36	Non-Fickian
H_4	0.9860	0.906	0.9970	0.9950	0.927	1.10	Super caseII
H_2G_2	0.980	0.8870	0.9980	0.9900	0.732	1.21	Non-Fickian
H_2X_2	0.9910	0.9310	0.9990	1.00	0.679	1.22	Non-Fickian
H_2T_2	0.9920	0.9350	0.9970	1.00	0.656	1.826	Non-Fickian
H_2GX	0.9950	0.9370	0.9960	0.9990	0.751	1.15	Non-Fickian
H_2GT	0.9840	0.9260	0.9970	0.9970	0.655	1.28	Non-Fickian
H_2XT	0.9910	0.9290	0.9980	0.9990	0.734	1.13	Non-Fickian

Figure 1 Cumulative percentage (mean ± SD) of Diclofenac sodium released from SR matrix tablets using different amount of HPMC K100M (n = 3)

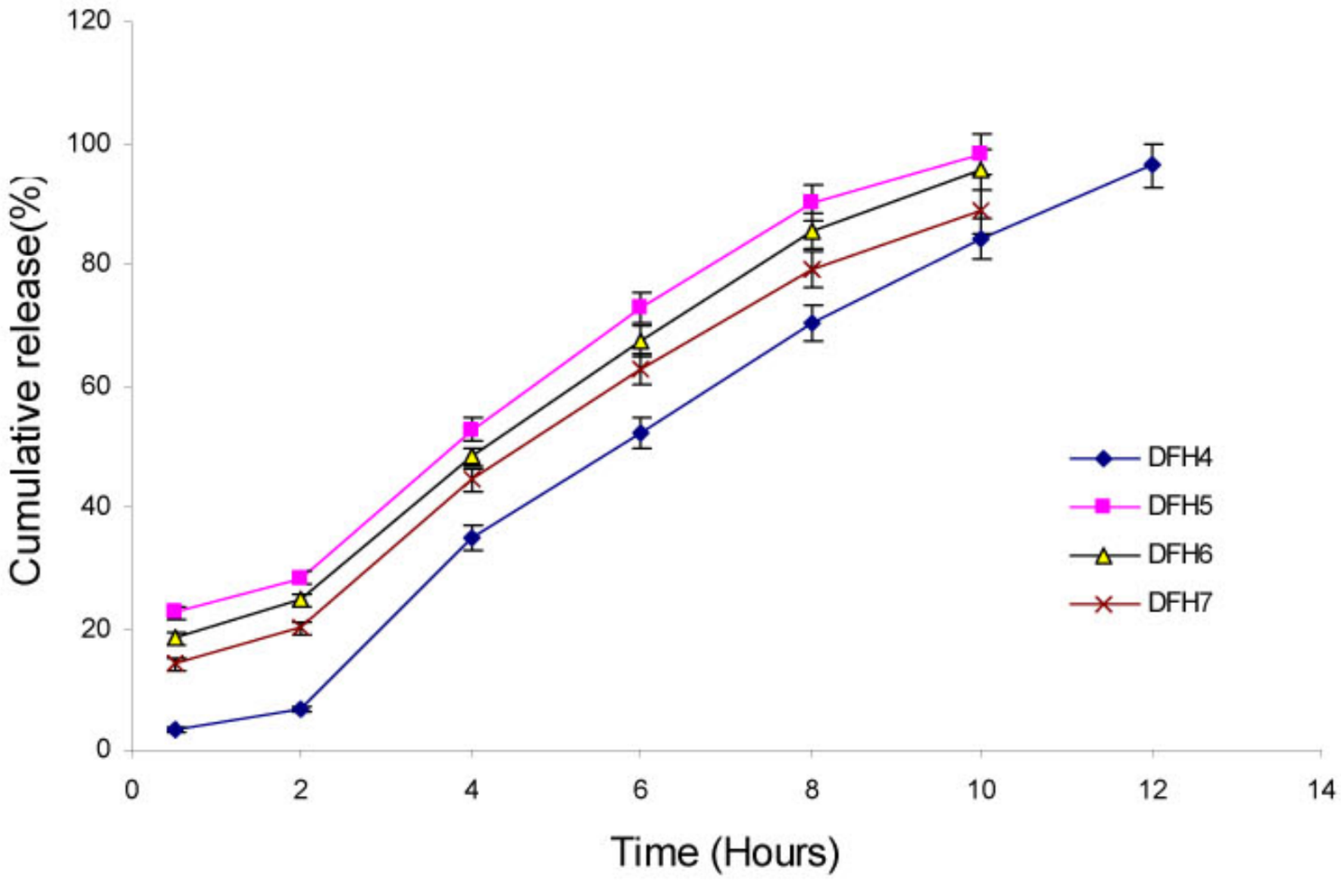

Figure 2. Effect (mean ± SD) of different buffers on the release of diclofenac sodium from HPMC K100M matrix tablets (n=3)

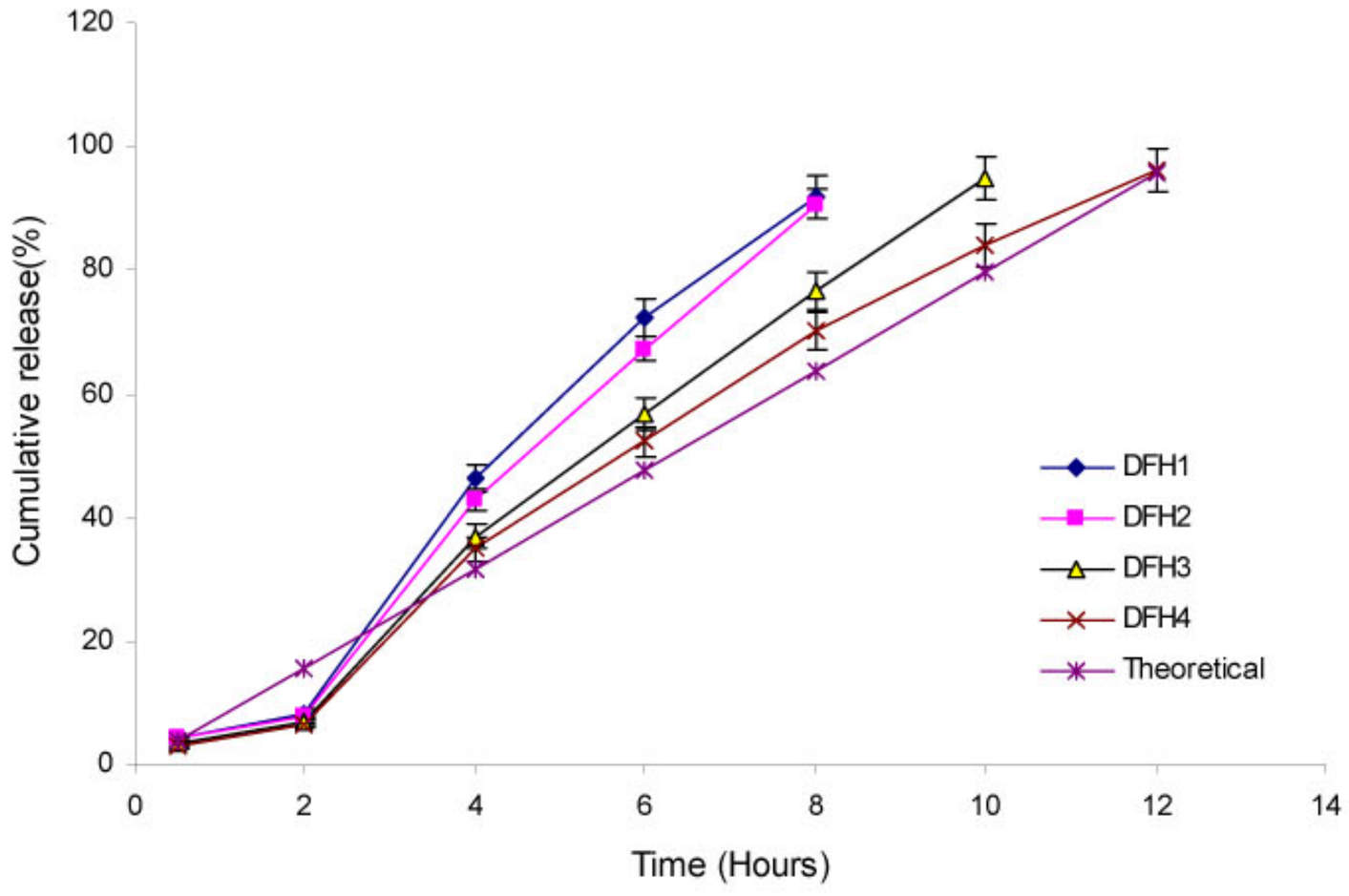

Figure 3 Percent (mean ± SD) of diclofenac sodium released from the matrix tablets containing HPMC alone and combination of HPMC with natural gums in phosphate buffer solution (n = 3)

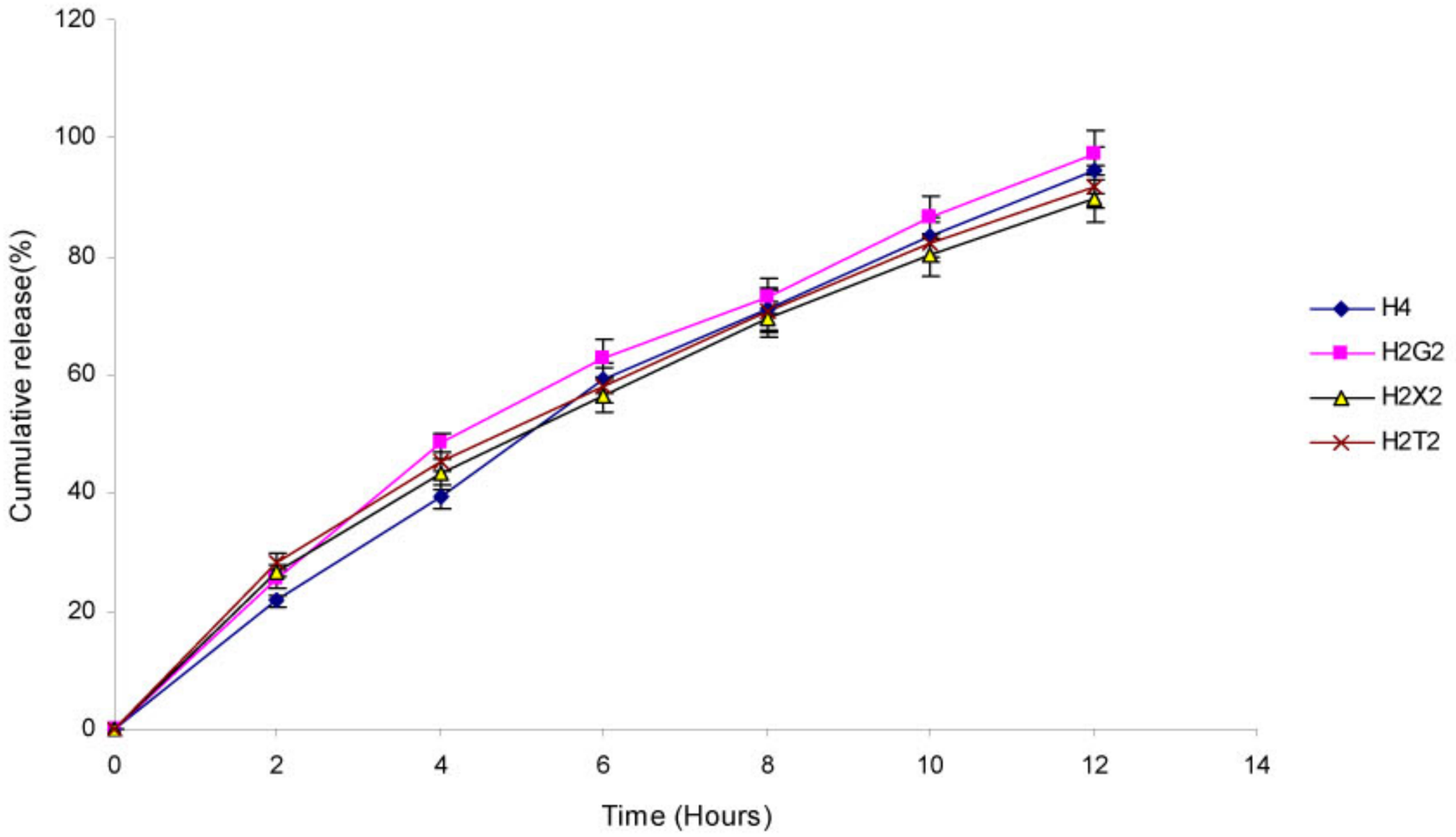

Figure 4 Effect (mean ± SD) of storage temperatures on the release of diclofenac sodium from HPMC K100M (DFH4) matrix tablets (n=3)