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Original Article

INFLUENCE OF PARTIALLY AND FULLY PREGELATINIZED STARCH ON THE PHYSICAL AND SUSTAINED-RELEASE PROPERTIES OF HPMC-BASED KETOPROFEN ORAL MATRICES

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ABSTRACT

Objective: This study aims to investigate the effect of two types of pregelatinized starch on the physical performance of HPMC matrices containing Ketoprofen as a model drug.

Methods: The design of the experiment was inspired by the monothetic analysis, in which testing factors or causes is done one factor or cause at a time, to achieve system improvements. Tablets were prepared by direct compression. The impact of the type of modified starch on the tablet's physicochemical properties was studied by testing for weight variation, friability, hardness, and drug release properties. PCP dissolution software was used to investigate the kinetics of drug release from matrix tablet formulation.

Results: The impact of the type of modified starch on tablet physicochemical attributes revealed that the weight variation of tablets was affected by the amount of modified starch used and that the combination of 64.7% partially pregelatinized starch (Starch® 1500) with 9.5% HPMC (F8) was found to be the better in terms of weight variation (%RSD= 1.73%) when compared with those containing fully pregelatinized starch (LYCATAB®). All formulation runs have friability that complies with pharmacopeial limits of less than 1% loss upon test conduction except for (F1). Formulations containing LYCATAB® showed better friability than those containing Starch® 1500, and similar results were observed in tablet hardness as well, in which the formulation containing the highest LYCATAB®concentration showed a significant increase in mechanical strength (P = 0.0004) than those containing the highest concentration of Starch® 1500. Finally, all formulations containing LYCATAB®exhibited sustained-release behavior, less than 60% of the drug was released from matrices over 14 h, and it is believed that the drug is transported via Fickian diffusion and followed either Higuchi or Peppas model (n>0.5), while all formulations containing Starch® 1500 released ~90% of the drug around 2 h, this might probably be due to the high disintegration effect of the partially pregelatinized starch, which is lost upon full pregelatinization.

Conclusion: Tablet weight variation, hardness, friability, and $T_{50\%}$ were found to be influenced by both the type and concentration of modified starch used. While drug release characteristics were greatly affected by the type of modified starch used. For sustain-release formulations, only fully pregelatinized starch is thought to be suitable.

Keywords: Fully pregelatinized starch, Partially pregelatinized starch, Drug release, HPMC matrices, Sustain release

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INTRODUCTION

The development of controlled-released delivery systems is still an area of great interest in the pharmaceutical industry and the success accompanying controlled-release delivery systems can be attributed to their ease of manufacturing and the reproducibility of the desired biopharmaceutical qualities [1]. Controlled-release delivery systems are engineered to deliver medications to the intended local or systemic site of action at a predetermined rate over a specified duration of time [2, 3]. They offer several advantages over conventional delivery systems such as minimizing drug plasma level fluctuations by maintaining a sustained-steady state and providing better compliance due to the decrease in dosing frequency [4].

Matrices systems or diffusion-controlled delivery systems, especially those containing Hydroxypropyl methylcellulose (HPMC), are among the most common techniques used to control drug release [5].

Numerous formulation factors were found to impact drug release from HPMC matrices; among those is the type and nature of excipients used [6]. For instance, fillers/diluents were found to greatly affect the drug release from HPMC matrices. They can be classified according to their water solubility into highly water-soluble fillers, water-insoluble swellable fillers, and partially water-soluble and swellable fillers [7].

Starch is a natural polymeric carbohydrate that is extensively used in the pharmaceutical industry, and because of its physical and chemical properties, it has been employed to serve many different functions in tablet formulation (filler, binder, disintegrant, and lubricant) [8]. Pharmaceutical excipient manufacturers heated native starch in a process known as pregelatinization to obtain particles that form a gel in contact with cold water [9]. This modification resulted in improved flowability, hardness, and processing time [8].

In a previous study, filler type was found to impact weight variation, friability, and drug release attributes of oral HPMC matrices containing Ketoprofen [10]. Ketoprofen was selected as the model drug in this study because of its short half-life (1.5-4 h), which results in the need for frequent administrations to maintain fixed levels in the blood, it also has side effects on the gastrointestinal tract, which can be alleviated when it is taken as modified drug delivery systems, these reasons also led to various attempts to deliver ketoprofen in various novel dosage forms such as micro-particles [11], micro-spheres [12, 13], nano-emulsions [14, 15] and transdermal films [16, 17].

The current study is a subsequent effort to better understand the possible interaction between fillers and HPMC polymer. This research aims to study the effect of the type of pregelatinized starch on the physicochemical properties of ketoprofen oral matrices and to understand the difference between fully and partially pregelatinized starch when incorporated in an oral controlled release HPMC matrix.

MATERIALS AND METHODS

Materials

Working standard Ketoprofen (Zhejiang East Asia, China), fully pregelatinized starch (LYCATAB® PGS, Roquette, France), partially pregelatinized starch (Starch 1500®, Colorcon, France), purified talc (Imerys, Italy), magnesium stearate (Greven, Netherland), colloidal silicon dioxide (Aerosil®, Anatwerpen, Germany) were kindly donated by Azal Pharmaceutical Company, Sudan. Hydroxypropyl methylcellulose (K4M HPMC, 4000cps, Feicheng Ruitai Fine Chemicals, China) was generously donated by Blue Nile Pharmaceutical Industry, Sudan. These materials and other reagents were pharmaceutical or analytical grades and obtained from different commercial sources.

Preparation of matrix tablet formulations

All experimental runs were prepared by direct compression. Ketoprofen, HPMC, and either LYCATAB® PGS or Starch 1500® were mixed using mortar and pestle for 10 min. The blend was then passed through #0.71 mm with purified talc and colloidal silicon dioxide, then mixed for 5 min. Magnesium stearate was added and powder was mixed gently for 3 min. Finally, the powder blend was compressed by a rotary press tableting machine (ZP7 rotary press, Shanghai Yali, China) equipped with a size 9 mm flat round punch to produce the required matrix tablets.

Qualification of matrix tablets

Random samples were taken from all formulation runs and underwent different pharmacopeial tests to evaluate their pharmaceutical properties.

Weight variation

20 randomly selected matrix tablets were selected from each run and weighed. Mean value and relative standard deviations (%RSD) from mean value were calculated and evaluated for the pharmacopeial limits compliance [18].

Friability

From each run, 20 matrix tablets were weighed together and placed in a friabilator (Electronic 902, India), which, which is then rotated at 25 rounds per minute (rpm) speed for 4 min. Matrices were de-dusted and weighed again, then friability was calculated by taking the percentage of the ratio of the weight loss to the original weight before running the friabilator [19].

Matrix hardness

10 randomly selected matrix tablets from each run were evaluated for the force (in kg/cm^2) required to break matrix tablets using a Pharmatest® hardness tester (Hainbursg, Germany) [20].

In vitro drug release test

USP paddle apparatus settings were used for the dissolution testing of the matrix tablets. The dissolution instrument (Pharmatest®, D-63512, Hainbursg, Germany) was operated at 100 rpm during the test. 900 ml of the dissolution media (phosphate buffer pH 6.8) was maintained at 37±0.5 °C throughout the test duration. For each formulation run, three matrix tablets were subjected to the test, which lasted for 14 h or until>85% of the drug content was released, 10 ml samples were withdrawn at predetermined time intervals, filtered, and assayed by UV-spectrophotometry at λ_{max} 255 nm (UV-vis spectrophotometer, Shimadzu®, Japan), phosphate buffer was used as blank [21]. The drug release profile was then generated by plotting the mean cumulative percentage of drug release against time. Time for 50% drug release ($T_{50\%}$) and dissolution efficiency (DE) was used to compare different formulation runs.

PCP dissolution software was used to investigate the kinetics of drug release from matrix tablet formulation, in which release data obtained from *in vitro* release study were entered into the software and fitted into various kinetic equations like zero order, first order, and Higuchi matrix. Also, the Peppas model was used to determine the mechanism of drug release. Values of n indicate the primary mechanism of drug release.

Validation and calibration of UV method for assay of standard Ketoprofen in dissolution samples

A UV spectrophotometric reported method was selected and validated for the determination of Ketoprofen in dissolution samples [21]. 30 mg Ketoprofen was accurately weighed and dissolved in 100 ml pH 6.8 phosphate buffer to form a stock solution. Drug solutions of different concentrations (0.9-10.5 µg/ml) were then prepared by serial dilutions of the stock solution. UV spectrophotometric absorbance of different drug concentrations were determined at 255 nm and graphed against respective drug concentration to generate a calibration curve with a nominated determination coefficient (r^2) and probability significance (p).

The validation of the selected UV spectrophotometric method for the Ketoprofen assay was assured by preparing standard solutions of the drug (in pH 6.8 phosphate buffer) over a known concentration range (0.9-10.5 µg/ml). Linearity between absorbance and concentrations was established using the statistical determination coefficient (r^2) and probability significance (p) criteria. In addition, solutions with the known concentration of Ketoprofen were then subjected to analysis in triplicate, each by the UV method. The concentration for each solution was then determined using the data generated from the calibration curve. Solutions were analyzed within and between days. Precision, repeatability, and reproducibility of the spectrophotometric method were established by calculating the recovery % and the relative standard deviations associated with repeatability (RSD_r) and reproducibility (RSD_R) [22].

Statistical analysis

All values were represented as mean±SD. T-test was used to compare individual groups and p values<0.05 were considered statistically significant. One-way analysis of variance (ANOVA) was used for statistical analysis. GraphPad Prism Version 6 (Graph Pad Software Inc., San Diego, CA) and Microsoft Excel were used.

RESULTS AND DISCUSSION

The following experimental run layout was used in this study (table 1). Monothetic analysis (one factor at a time) was used in the designing of the experiments, by involving the testing of factors, or causes, one at a time. We used this method because the primary goal of this study was to attain improvements in the system, and experimental error is not large compared to factor effects, which must be additive and independent of each other.

Calibration and validation of the UV method for Ketoprofen analysis

Fig. 1 and table 2 show the UV calibration curve of standard Ketoprofen and the validation parameters of the selected method, respectively.

Table 1: Experimental runs layout

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ketoprofen	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
LYCATAB® PGS	53.85%	60%	64.70%	47.95%	43.21%	0%	0%	0%	0%	0%
Starch 1500®	0%	0%	0%	0%	0%	53.85%	60%	64.70%	47.95%	43.21%
HPMC K4M	12.31%	10.67%	9.41%	21.92%	29.63%	12.31%	10.67%	9.41%	21.92%	29.63%

For each formulation run, N (number of tablets) was 200 tablets.

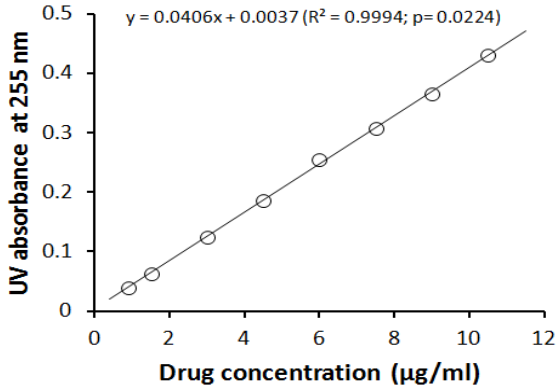

Fig. 1: UV calibration curve of standard Ketoprofen in pH 6.8 phosphate buffer measured at λ_{max} 255 nm. Each data point is the average of three determinations

Table 2: Validation parameters of the UV method for determination of Ketoprofen in dissolution samples

Drug concentration level	N	% Recovery[a]	RSD_r	RSD_R
Intraday				
0.90 µg/ml	6	99.78%	0.330%	0.265%
3.00 µg/ml	6	101.11%	0.262%	0.356%
10.00 µg/ml	6	99.22%	0.221%	0.399%
Between days				
0.90 µg/ml	6	102.18%	0.443%	0.324%
3.00 µg/ml	6	99.87%	0.164%	0.215%
10.00 µg/ml	6	100.65%	0.377%	0.283%

N is the number of analysis replicates, [a]Accuracy in the calculation of the concentration (obtained/actual *100%), RSD_R and RSD_r stand for relative standard deviation under repeatability and reproducibility conditions, respectively, where RSD is (standard deviation/mean value *100%)

Influences of starch type and amount on matrices weight variation properties

The percentage of relative standard deviation to tablet weight (%RSD) is displayed in table 3. All formulation runs were found to be within the accepted limit for weight variation according to the category of<500 mg solid oral dosage form in which the maximum accepted %RSD is 5% [18].

The amount of modified starch used, regardless of its type, influenced matrix weight variation (t-test, p= 0.00018). The same was observed with the amount of HPMC used (p=0.0003).

These results also showed that a lower %RSD was observed with Starch 1500® when compared with those containing LYCATAB® PGS. The lowest %RSD was observed in the formulation with the highest Starch 1500®, lowest HPMC, and no LYCATAB® PGS, and the highest %RSD was observed with a 60% LYCATAB® PGS, 10.6% HPMC, and no Starch 1500®.

The combination of 64.7% Starch 1500® with 9.5% HPMC (F8) was found to be the better in terms of weight variation (%RSD= 1.73%) when those two excipients were used together, while the combination of 60% Starch 1500® and 10.6% HPMC (F7) was the worst (%RSD= 2.71).

For LYCATAB® PGS, F1 and F5 (53.8% LYCATAB® PGS, 12.3% HPMC and 43.21% LYCATAB® PGS, 29.63% HPMC, respectively) have almost the same %RSD of 2.35%, which happens to be the lowest. On the other hand, F2 (60% LYCATAB® PGS+10.6% HPMC) has the highest %RSD of 2.80%.

Generally, tablet weight variation is related to the powder blend flow ability and is affected by both filler type and concentration used. The lower RSD% observed with Starch 1500® might be because partially pregelatinized starch retains some of its anti-adherent and lubricant effects when used dry along with the informal particle size distribution, thus acting similarly to native starch, which in another study showed the lowest RSD% when used in higher concentrations, which comply with our observation in this study [23, 24].

However, we believed that there is great interaction of various factors with the weight variation property like API percentage, processing method, and applied compression force, so further investigation using multi-factorial design will aid in revealing more information about weight variation in starch-containing matrices.

Table 3: %RSD, friability, and hardness of different matrix tablet formulation

Run	Weight variation (%RSD)	Friability (%)	Hardness (kg/cm²) mean±SD
F1	2.35	1.50	3.00±0.53
F2	2.80	0.21	7.23±1.27
F3	2.49	0.55	6.42±1.74
F4	2.69	0.42	5.76±0.99
F5	2.36	0.33	7.25±1.15
F6	2.12	0.37	3.54±0.38
F7	2.71	0.26	4.13±0.34
F8	1.73	0.82	3.99±0.30
F9	1.96	0.50	4.10±0.77
F10	1.80	0.22	5.99±0.40

N (sample size) for weight variation, friability, and hardness was 20, 20, and 10 tablets, respectively. Each test was performed in triplicate.

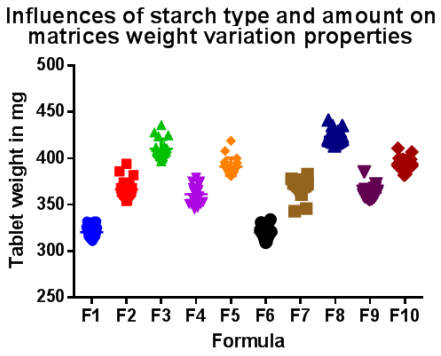

Fig. 2: Weight variation %RSD of different matrix formulations (N is 20 tablets per formulation run)

Influence of starch type and amount on tablet friability

Except for F1, all formulation runs have friability that complies with pharmacopeial limits of less than 1% loss upon test conduction (fig. 3) [19]. The reason behind F1 failure to meet the pharmacopeial limits is believed to be due to the relatively high percentage of Ketoprofen (30%), which is present in form of coalescence powder rather than granules, resulting in poor flowability and compressibility. The same can be said for F4 and F9; both have a high percentage of Ketoprofen (~27%) and exhibited friability just below 0.5% (0.42% and 0.50%, respectively). F3 and F8 both contain the highest percentage of modified starch, and that did affect their friability negatively (0.55% and 0.82%, respectively). Generally, it is believed native starch (non-pregelatinized) doesn't compress well and is associated with increased tablet friability when used in high concentrations [24]. On the other hand, the higher concentration of pregelatinized starch yields good friability, but tablet hardness must be considered too, because there is a strong direct relationship between tablet friability and hardness.

Influence of starch type and amount on matrix tablet hardness

The hardness of all experimental runs is displayed in fig. 4, in which it was obvious that formulations containing LYCATAB® PGS showed better hardness than those containing Starch 1500®. Both the percentage of starch and HPMC used were found to have a significant impact on matrices' hardness ($p<0.05$). However, given the higher percentage of the API in all the formulation runs in comparison with starch and HPMC percentage and its poor flowability and compressibility, we believe that it has the greatest effect on matrix hardness.

In comparison between the two types of starch, at the highest percentage (F3 and F8), LYCATAB® PGS showed a significant increase in mechanical strength ($P = 0.0004$) as shown in fig. 4.

These results are in line with other literature and technical reports that confirm the superiority of Starch 1500® over other types of fillers in improving formulations through binding capability, also improved disintegrant/dissolution properties, enhanced flow and lubricity, as well as moisture protection [25].

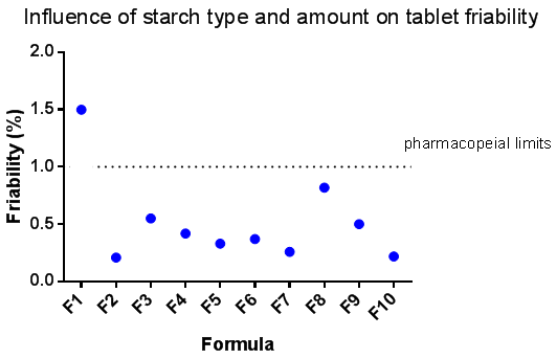

Fig. 3: Friability of different matrix formulations (N is 20 tablets for each formulation run)

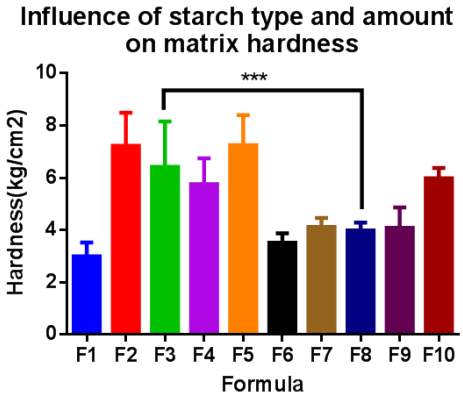

Fig. 4: Hardness of different matrix formulations (N is 10 tablets for each formulation run. Data are shown as mean ± SD)

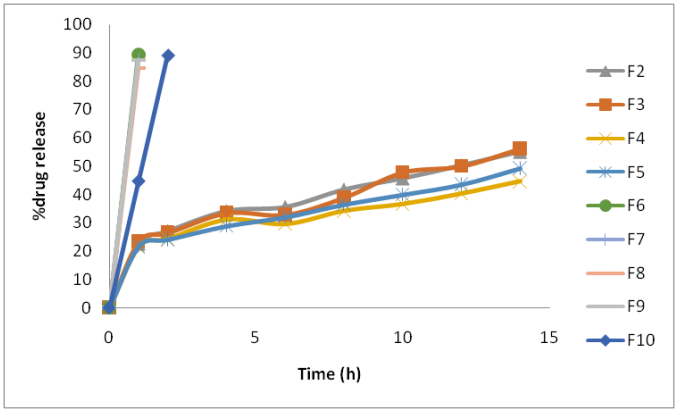

Fig. 5: Ketoprofen release profile from matrix formulations (phosphate buffer pH 6.8 at 37±0.5 °C, N is 3 tablets for each formulation run)

Influence of starch type and amount on drug release properties of matrix tablet formulation

The release profile of Ketoprofen from the different formulation runs is shown in fig. 5. As it can be seen from fig. 5, there is a significant difference between the formulations containing LYCATAB® PGS and those containing Starch 1500®. With LYCATAB® PGS, all the formulations, regardless of the percentage of LYCATAB® PGS or HPMC, sustained the release for over 14 h, with less than 60% of the drug released. On the other hand, formulations

containing Starch 1500® released almost 90% of the loaded drug in around 2 h (F6, F7, F8, and F9) and 4 h (F10). This is probably due to the higher disintegration effect of partially pregelatinized starch as we mentioned previously, compared to the fully pregelatinized one.

Tables 4 and 5 show that $T_{50\%}$ values vary with different formulations and range from 36 to 1008 min, and DE_{0-1} values ranged from 10.79 to 44.65%. However, only $T_{50\%}$ were significantly affected by the type and percentage of modified starch used ($p<0.05$), while DE_{0-1} was only affected by the type of the modified starch used and not the percentage used.

All the formulations containing LYCATAB® PGS exhibited sustained release of the drug, and it is believed that the drug is transported via Fickian diffusion and following either Higuchi or Peppas model ($n>0.5$).

Table 4: Drug release attributes for formulation runs containing LYCATAB® PGS (F1-F5

Run	$T_{50\%}$ (min)	DE_{0-1}	Release kinetics (n)[a]	(R^2)[b]			
				Zero-order	First order	Higuchi	Peppas
F1	-	-	-	-	-	-	-
F2	768	11.29	0.3271	0.7138	0.8658	0.9697	0.9698
F3	672	11.7	0.3225	0.7393	0.8793	0.9649	0.9546
F4	1008	10.79	0.2572	0.5134	0.7059	0.9277	0.9649
F5	972	10.84	0.2997	0.6662	0.8166	0.9592	0.9755

N (sample size) for *in vitro* drug dissolution was 3 (from each formulation) and the test was done for each formulation in triplicate. [a]n stands for diffusion exponent that characterizes the drug release, [b]determination coefficient for power-law fitting.

Table 5: Drug release attributes for formulations containing Starch 1500® (F6, F7, F8, F9, and F10)

Run	$T_{50\%}$ (min)	DE_{0-1}
F6	36	44.65
F7	36	43.80
F8	36	42.25
F9	36	43.68
F10	66	22.39

N (sample size) for *in vitro* drug dissolution was 3 (from each formulation) and the test was done for each formulation in triplicate.

The reason for this significant difference in the release profile between the formulation containing fully pregelatinized starch and those containing partially pregelatinized starch is mainly due to the level of pregelatinization of the starch. Generally, partially pregelatinized starch can be used as disintegrant, it has very limited obstructive gel formation capability, and when it comes into contact with water, it swells, resulting in weakened intra-particles bonds, which eventually broke, leading to tablet disintegration and release of the drug [26, 27]. Also, full pregelatinization of starch results in starch losing its disintegrant abilities, while partially pregelatinized starch has a mixture of native and pregelatinized starch, so it still retains its disintegrant activity, making it less effective in sustaining drug release [28]. Herman and Remon suggested that only fully pregelatinized starch with amylose content equal to or less than 25% is capable of producing a strong gel layer that can ensure a sustained drug release [29]; however, some studies suggested the possibility of partially pregelatinized starch retarding the drug release [26, 27], especially when used in high concentration.

CONCLUSION

The type and concentration of pregelatinized starch affected weight variation, friability, hardness, and $T_{50\%}$. Drug release attributes were found to be greatly impacted by the type of pregelatinized starch used, level of pregelatinization is the main reason behind this effect, where the ability of the pregelatinized starch to form an obstructive gel is dependent on amylose content. The use of Starch 1500® as a filler in the HPMC matrix formulation was responsible for rapid tablet disintegration and drug dissolution.

Hence, it's not suitable for developing sustain release matrixes. Although this study did provide a clear insight into the effect of the type of pregelatinized starch on the pharmaceutical properties of Ketoprofen matrices, further studies are needed utilizing different starch and polymer types and better experimental design.

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AUTHORS CONTRIBUTIONS

Both authors discussed the outcomes and contributed to the final manuscript. Waleed Elballa performed all the experimental work and prepared the manuscript. Dr. Mohammed Salih carried out the statistical analysis and revised the manuscript.

CONFLICT OF INTERESTS

Declared none

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