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Development of a simple and rapid Formulation and evaluation of Metformin HCl extended-release tablets in comparison with Glucophage® XR

Fariba Kakaei*, Arash Khodam

Department of research and development, Mahban pharmaceutical Co., Saveh, Iran

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Abstract

Metformin HCl is the first-line therapy for type 2 diabetes. It is available in both immediate-release and extended-release tablet forms, with the extended-release tablet being more beneficial. In this study, 34 formulations using five sustained-release agents, alone or in combination, were evaluated. The granular flowability, angle of repose, bulk Density, tapped Density, compressibility index, and Hausner ratio were assessed. Furthermore, the compressed tablets were tested for appearance, hardness, friability, and in-vitro drug release. Eleven formulations were evaluated for dissolution profiles according to the standards specified in the United States Pharmacopeia. After calculating the similarity factor (f1) and difference factor (f2), eight formulations were identified for further investigation. The combination of xanthan gum and hypromellose (HPMC K100) demonstrated superior results regarding the sustained-release agent amount and tablet appearance. This noteworthy finding led to continuing the study to explore further formulations with different amounts of xanthan gum and Hypromellose K100. As a result, formulation F34 was identified as the optimal choice because of its higher drug-to-polymer ratio. In conclusion, the final formulation is a rapid, cost-effective, and straightforward method due to the less time required for drying, the amount of sustained-release agents, and the number of components.

∗Corresponding Author
Name: Fariba Kakaei
Phone: +989104963917
Email: dr.faribakakaei@gmail.com

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INTRODUCTION

Metformin hydrochloride is a biguanide hypoglycemic agent widely used as first-line therapy for treating type 2 diabetes [1]. Furthermore, it is also used off-label for treating antipsychotic-induced weight gain, preventing type 2 diabetes mellitus, treating gestational diabetes mellitus, and preventing and treating polycystic ovary syndrome (PCOS). It is available in both immediate-release and extended-release tablets [2]. Metformin HCl extended-release tablet versus immediate-release tablet is associated with improved patient compliance due to the

Table 1 Formulation of Metformin HCl extended-release tablet

Formulation code	Metformin HCl	Cetyl alcohol	Cetostearyl alcohol	HPMC K100	Polymethacrylate	Xanthan gum	PVP K30	Total weight	Drug-to-retardant agent ratio
F1	500	300	-	-	-	-	30	830	1.67
F2	500	400	-	-	-	-	30	930	1.25
F3	500	500	-	-	-	-	30	1030	1.00
F4	500	-	300	-	-	-	30	830	1.67
F5	500	-	400	-	-	-	30	930	1.25
F6	500	-	500	-	-	-	30	1030	1.00
F7	500	400	100	-	-	-	30	1030	1.00
F8	500	300	100	-	-	-	30	930	1.25
F9	500	300	200	-	-	-	30	1030	1.00
F10	500	100	300	-	-	-	30	930	1.25
F11	500	200	300	-	-	-	30	1030	1.00
F12	500	150	150	-	-	-	30	830	1.67
F13	500	200	200	-	-	-	30	930	1.25
F14	500	250	250	-	-	-	30	1030	1.00
F15	500	-	-	200	-	-	30	730	2.50
F16	500	-	-	300	-	-	30	830	1.67
F17	500	-	-	400	-	-	30	930	1.25
F18	500	-	-	-	200	-	30	730	2.50
F19	500	-	-	-	300	-	30	830	1.67
F20	500	-	-	-	400	-	30	930	1.25
F21	500	-	-	-	-	300	30	830	1.67
F22	500	-	-	-	-	400	30	930	1.25
F23	500	-	-	-	-	500	30	1030	1.00
F24	500	-	-	200	-	180	-	880	1.32
F25	500	-	-	200	-	180	30	910	1.32
F26	500	-	-	200	-	180	15	895	1.32
F27	500	-	-	200	-	180	20	900	1.32
F28	500	-	-	120	-	100	20	740	2.27
F29	500	-	-	120	-	150	20	790	1.85
F30	500	-	-	180	-	150	20	850	1.52
F31	500	-	-	180	-	100	20	800	1.79
F32	500	-	-	180	-	130	20	830	1.61
F33	500	-	-	120	-	130	20	770	2.00
F34	500	-	-	150	-	130	20	800	1.79

preference for once-daily administration [3]. Furthermore, extended-release formulations may enhance tolerability and reduce adverse effects such as dyspepsia [4]. In the formulation of extended-release tablets, polymers significantly control the drug release rate over time.

Moreover, polymers act as a barrier to protect drugs from degradation in the stomach and reduce side effects that can irritate the upper gastrointestinal tract. A wide variety of natural and synthetic polymers with different physicochemical properties can be used in tablet formulations [5]. The current study aims to develop extended-release tablets of Metformin HCl using various sustained-release agents, including fatty alcohols like Cetyl alcohol and cetostearyl alcohol, and polymers such as

Table 2 Relationship between powder flowability, compressibility index (Carr's index), Hausner ratio, and angle of repose

Type of flow	Angle of repose (°)	Carr's index (%)	Hausner Ratio
Excellent	25-30	1-10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very Poor	56-65	32-37	1.46-1.59
Very Very Poor	>65	>37	>1.59

Table 3 USP 46, dissolution test 1 and 2

Time (hour)	Dissolution range
1	20-40%
2	35-55 %
3	45-65 %
6	65-85 %
10	NLT 85%

hypromellose (HPMC K100), Polymethacrylate (Eudragit® RS 100), and Xanthan gum, either individually or in combination, and evaluation of them to achieve the optimal formulation [6].

MATERIALS AND METHODS

MATERIALS

Metformin hydrochloride was procured from Mahban Chemi, Saveh, Iran. Polyvinylpyrrolidone (PVP K30) was purchased from Rahavard Tamin, Saveh, Iran. Hypromellose (HPMC K100) was obtained from Kerry, Norwich, England. Xanthan gum was obtained from Deosen Biochemical Ltd., Inner Mongolia, China. Cetyl alcohol was received from Emery Oleochemicals, Dusseldorf, Germany. Cetostearyl alcohol was obtained from Croda Pharma, Yorkshire, UK, and Polymethacrylate (Eudragit® RS 100) was received from Evonik, Darmstadt, Germany. All other materials used throughout the study were of analytical grade.

METHODS:

Preparation of Metformin HCl extended-release tablets

The compatibility of Metformin HCl with excipients was verified theoretically [7]. Metformin HCl extended-release tablets were prepared using the wet granulation method. In this study, five excipients, including Cetyl alcohol, cetostearyl alcohol, HPMC K100, Polymethacrylate, and Xanthan gum, were considered retardant agents. These agents were used alone and in combination with others in different amounts, resulting in the preparation of 34 formulations. The ingredients of the formulations and the drug-to-retardant agent ratios are listed in Table 1. The ingredients were weighted accurately. A mixture of PVP K30 in ethanol and water (3:1) was prepared as the binding solution and slowly added to the blend of Metformin HCl and retardant agent, then mixed. The final blend was dried to reach a moisture content of 2 %, passed through a 25-mesh sieve, and compressed into 17*7 mm oblong tablets using a rotary tablet compression machine.

Pre-compressional evaluation:

The flowability of the granules was measured by several indirect methods as follows [8]:

The angle of repose was tested using the fixed height cone method.

Bulk Density and tapped Density were determined by densitometer.

Compressibility index or Carr's index: $\frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$

Hausner ratio: $\frac{\text{Tapped Density}}{\text{Bulk Density}} \times 100$

The flowability classification, based on test results, is shown in Table 2.

Post-compressional evaluation:

Table 4 Physical properties of granules

Formulation code	Bulk Density (g/cm^3)	Tapped Density (g/cm3)	Carr's index (%)	Hausner ratio (%)	Angle of repose (º)	Flowability
F1	0.56	0.65	13.85	1.16	24	Excellent
F2	0.56	0.65	13.85	1.16	24	Excellent
F3	0.56	0.64	12.50	1.14	24	Excellent
F4	0.55	0.65	15.38	1.18	25	Excellent
F5	0.55	0.66	16.67	1.20	25	Excellent
F6	0.55	0.66	16.67	1.20	25	Excellent
F7	0.56	0.65	13.85	1.16	24	Excellent
F8	0.56	0.65	13.85	1.16	24	Excellent
F9	0.56	0.65	13.85	1.16	24	Excellent
F10	0.55	0.66	16.67	1.20	25	Excellent
F11	0.55	0.66	16.67	1.20	25	Excellent
F12	0.57	0.66	13.64	1.16	24	Excellent
F13	0.56	0.66	15.15	1.18	24	Excellent
F14	0.56	0.65	13.85	1.16	24	Excellent
F15	0.52	0.60	13.33	1.15	32	Good
F16	0.52	0.59	11.86	1.13	32	Good
F17	0.51	0.58	12.07	1.14	34	Good
F18	0.50	0.57	12.28	1.14	35	Good
F19	0.51	0.57	10.53	1.12	35	Good
F20	0.51	0.57	10.53	1.12	36	Fair
F21	0.57	0.69	17.39	1.21	22	Excellent
F22	0.58	0.70	17.14	1.21	22	Excellent
F23	0.58	0.71	18.31	1.22	21	Excellent
F24	0.55	0.63	12.70	1.15	28	Excellent
F25	0.56	0.68	17.65	1.21	24	Excellent
F26	0.55	0.65	15.38	1.18	26	Excellent
F27	0.56	0.67	16.42	1.20	24	Excellent
F28	0.55	0.65	15.38	1.18	26	Excellent
F29	0.57	0.69	17.39	1.21	25	Excellent
F30	0.57	0.68	16.18	1.19	26	Excellent
F31	0.56	0.66	15.15	1.18	28	Excellent
F32	0.56	0.67	16.42	1.20	27	Excellent
F33	0.57	0.69	17.39	1.21	25	Excellent
F34	0.56	0.67	16.42	1.20	26	Excellent

The tablet hardness test was performed using the tablet hardness tester. The tablet friability tester determined the friability of the tablets.

In-vitro drug release study:

Dissolution test of Metformin HCl extended-release tablets was performed using USP type II apparatus (Noavaran, Tehran, Iran) in pH 6.8 phosphate buffer solution (1000 mL) at 37°C, at a speed of 100 rpm, according to USP 46, test 1 and 2. At specified time points (1, 2, 3, 6, and 10 hours), 10 ml samples were collected and replaced with an equal fresh medium. The samples were filtered, suitably diluted, and analyzed at 232 nm by UV-spectrophotometer. Acceptable amounts of dissolution at each time point are shown in Table 3 [9].

In-vitro bioequivalence studies:

The formulations with acceptable drug release were chosen to participate in in-vitro bioequivalence studies. The in-vitro release

Table 5 Physical Characteristics of Metformin HCl extended-release tablet

Formulation code	Hardness (KPa)	Friability (%)
F1	18	0.52
F2	18	0.51
F3	19	0.49
F4	18	0.50
F5	18	0.50
F6	18	0.51
F7	18	0.50
F8	18	0.50
F9	18	0.52
F10	18	0.51
F11	18	0.50
F12	19	0.53
F13	18	0.51
F14	18	0.50
F15	11	0.74
F16	10	0.79
F17	10	0.77
F18	8	0.83
F19	8	0.81
F20	8	0.80
F21	18	0.66
F22	19	0.62
F23	20	0.54
F24	10	0.84
F25	16	0.68
F26	12	0.79
F27	15	0.69
F28	14	0.74
F29	16	0.66
F30	15	0.66
F31	13	0.70
F32	14	0.69
F33	16	0.62
F34	15	0.63

profile of Glucophage® XR was performed under conditions similar to those used in the dissolution test. The difference factor (f_1) and similarity factor (f_2) between each formulation and reference tablet were determined using the data obtained from the drug-release studies. The difference factor should be under 15, and the similarity factor should be 50-100. These factors were determined as following equations:

$$f_1=\{ [\sum_{t=1}^{n} |R_t - T_t|] / [\sum_{t=1}^{n} R_t] \} *100$$

$$f_2 = 50 * \log \{[1+ (1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} *100\}$$

RESULTS AND DISCUSSION

Evaluation of granules

Bulk Density, tapped Density, compressibility index, Hausner ratio, and angle of repose of granules were assessed. Based on the results, all formulations exhibited fair to excellent flowability. (Table 4)

Evaluation of tablets

The hardness of all the formulations is acceptable. However, formulations based on Polymethacrylate and hypromellose K100 alone

Table 6 In-vitro drug release of Metformin HCl extended-release tablet

Formulation code	% Drug release				
	1 hour	2 hours	3 hours	6 hours	10 hours
Reference	33.2	51.0	57.7	72.7	93.1
F1	34.6	56.4	73.4	86.2	98.9
F2	29.6	52.9	69.6	84.1	94.8
F3	23.8	46.4	59.8	75.3	95.7
F4	38.2	58.5	78.4	90.4	96.1
F5	34.8	56.0	72.6	85.3	97.1
F6	31.2	54.3	68.7	82.4	94.7
F7	28.1	52.5	68.3	80.2	95.3
F8	32.7	55.0	69.5	74.2	96.0
F9	16.8	28.4	41.6	67.9	96.2
F10	35.0	54.6	71.8	80.6	96.4
F11	15.2	30.8	43.7	66.8	97.8
F12	19.1	32.6	47.0	73.1	94.8
F13	17.0	30.5	45.6	69.8	95.3
F14	14.2	26.5	39.8	65.3	98.2
F15	33.7	48.4	63.0	84.8	99.2
F16	26.3	40.8	56.1	77.2	94.0
F17	20.4	34.0	49.1	68.2	90.4
F18	49.9	70.8	84.6	95.3	98.6
F19	43.0	62.5	77.3	90.6	97.8
F20	38.8	56.5	69.2	82.7	97.3
F21	42.9	58.7	73.9	84.8	97.3
F22	37.1	53.5	67.8	79.8	94.6
F23	32.6	48.1	62.4	73.5	96.3
F24	27.5	40.6	57.8	77.3	95.5
F25	12.3	29.5	42.3	62.9	93.4
F26	23.7	36.4	49.0	69.5	91.8
F27	18.8	32.5	46.8	64.0	86.6
F28	49.7	65.2	80.4	93.7	96.9
F29	37.2	52.8	64.0	80.6	94.3
F30	24.0	39.5	50.9	66.3	89.3
F31	34.5	54.8	60.7	78.2	95.0
F32	30.1	48.6	53.8	68.6	90.8
F33	39.6	55.3	68.4	84.7	94.8
F34	33.2	51.0	57.7	72.7	93.1

have the lowest hardness. According to the Pharmacopoeia, tablet friability should be less than 1.0%, and all the formulations meet this requirement and are therefore acceptable. (Table 5)

Evaluation of in-vitro drug release

The most critical parameter in the formulation of extended-release tablets is the dissolution rate, presented in Table 6. According to the United States Pharmacopeia (Table 3), the dissolution rates of 11 formulations (F3, 15, 16, 23, 24, 26, 29, 30, 31, 32, 34) were acceptable. These Eleven formulations were included in in-vitro bioequivalence studies, and their similarity and difference factors were evaluated (Table 7). Additionally, the drug release rate of Eight formulations, which met the acceptance criteria for similarity and difference factor comparison with a reference sample, is illustrated in Figure 1.

Table 7 Difference and similarity factors

Formulation code	f1 (Difference factor)	f2 (Similarity factor)
F3	7.9	62.1
F15	17.8	47.5
F16	9.5	61.3
F23	12.0	55.2
F24	11.2	58.8
F26	5.3	65.9
F29	17.7	47.7
F30	5.1	71.7
F31	15.7	51.3
F32	5.5	69.2
F34	10.1	58.8

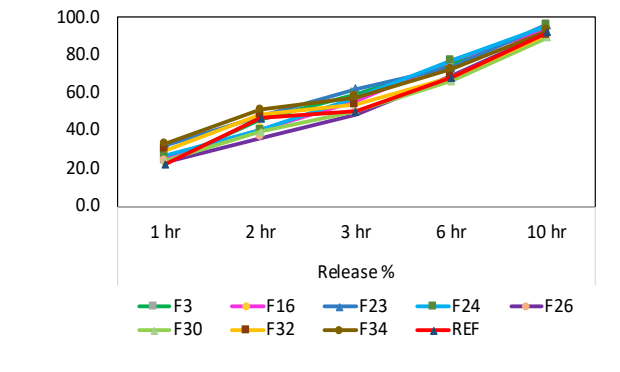

Figure 1 Drug release rate of Metformin HCl extended-release tablet

CONCLUSION

Based on various studies, including flowability, hardness, friability, in-vitro drug release studies, and In-vitro bioequivalence studies, it was found that eight formulations (F3, 16, 23, 24, 26, 30, 32, 34) achieved acceptable results. F34 was determined to be the best formulation among these formulations due to its higher drug-to-polymer ratio, allowing for a lower weight of final formulations and higher doses of extended-release tablets. It was observed that cetyl alcohol and cetostearyl alcohol are unsuitable as sustained-release agents for Metformin HCl since they require a high amount to retard drug release. Additionally, they resulted in the inappropriate appearance of tablets. Similarly, xanthan gum alone was unsuitable as it needed a large amount of polymer, equivalent to the metformin HCl weight.

Furthermore, it was found that HPMC K100 and Eudragit® RS 100 alone were not recommended as sustained-release agents due to their low compressibility. Therefore, the combination of xanthan gum and HPMC K100 in different amounts was investigated, leading to the choice of F34 as the optimum formulation. In conclusion, the final formulation is a rapid, cost-effective, and straightforward method due to the less time required for drying, the amount of sustained-release agents, and the number of components.

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