

Preparation and In Vitro Evaluation of Sustained-Release Matrix Tablets of Flutamide Using Synthetic and Naturally Occurring Polymers

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Abstract

Frequent dosing of the potent anti-androgen, flutamide, is necessary to reach a therapeutic level for the treatment of prostatic carcinoma. Sustained delivery of the drug could reduce the adverse effects such as gastrointestinal disorders and improve patient compliance. In the present study sustained-release matrix tablets of flutamide were prepared by direct compression method using different polymers. Cellulose ethers (HPMC and NaCMC), natural gums (guar and xanthan gums) and compressible Eudragits (RSPO and RLPO) and their combinations were used in different ratios to examine their influence on tablet properties and drug release profile. Tablets were evaluated by measurement of hardness, friability, content uniformity, weight variation and drug release pattern. All the tablets met the pharmacopoeial requirements for physical tests, based on USP 29. Almost in all formulations, with increasing the percentage of polymer, release rate decreased, though drug release pattern was mainly dependent on the type of polymer. Formulations H₂F₄ (contained 25% HPMC) and S₃F₄ (contained around 40% RSPO) met the desired requirements for a sustained-release dosage form. These two formulations released their drug content with a first order kinetic.

Keywords: Flutamide; Matrix tablets; Sustained-release; Hydrophilic polymers; drug release; Kienetic studies.

Introduction

Flutamide (2-methyl-N-[4-nitro-3-(trifluoromethyl) phenyl] propanamide), Figure 1, is a potent non-steroidal anti-androgen which is used in the palliative treatment of prostatic carcinoma. It blocks the androgen receptors on the cancer cells and inhibits the androgen-dependent cell growth. The usual oral dose of flutamide is 250 mg three times daily. Its oral absorption is rapid and complete, with peak plasma concentrations

occurring 1 h after a single dose. Flutamide is rapidly and extensively metabolized to its major metabolite, 2-hydroxy-flutamide, which possesses anti-androgenic properties (1, 2). Treatment with flutamide may cause a variety of side-effects including diarrhea, tiredness, impotence, breast fullness and liver malfunction (3). In order to decrease the frequency of drug administration and therefore the incidence of adverse effects, a sustained-release formulation of flutamide is desirable. Sustained delivery of flutamide could reduce the incidence and severity of adverse effects, especially gastrointestinal disorders and hepatic impairment. A flutamide treatment

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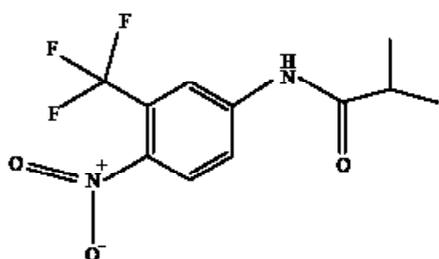


Figure 1. Chemical structure of flutamide.

regimen consisting of 400-mg sustained-release tablets twice daily was investigated in a study to enhance patient compliance and reduce local side effects (4). Hydrogel microspheres prepared by multiple emulsions have been used for controlled delivery of flutamide and showed sustained-release profiles (5, 6). Preparation of microspheres is a multistep time-consuming process. It is essential to develop cost-effective and less tedious procedures for preparation of sustained release formulations in the industrial scale.

The most commonly used method for fabricating drugs in a controlled-release formulation is by incorporating them into a matrix containing a hydrophilic rate controlling polymer (7). Matrix systems are widely used in oral controlled drug delivery because of their flexibility (which results in obtaining desirable drug release profile), cost effectiveness and broad regulatory acceptance (8). Cellulose ethers such as hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC), copolymers of acrylic-methacrylic acid (Eudragits) such as Eudragit RL and RS and some natural gums like guar gum and xanthan gum are widely used hydrophilic polymers as release retardants (8, 9).

To the best of our knowledge, this is the first report regarding preparation of sustained release flutamide matrix tablets. The goal of the present study was to develop a matrix type sustained-release formulation of flutamide. Different matrix tablets containing 400 mg flutamide were prepared using various amounts of HPMC, NaCMC or their mixture, guar gum, xanthan gum, Eudragit RL and RS or their mixture by direct compression method. The effect of type and amount of polymer on drug release profile,

swellability and erosion of the matrices were examined to compare between synthetic and natural polymers and determine the effect of swellability and erosion of the matrices on drug release rate.

Experimental

Materials

Flutamide was purchased from Aldrich (Canada). HPMC K4M and NaCMC were obtained from Fluka (Switzerland). Xanthan and guar gums were from Arthur Branwell (UK) and Hercules (USA), respectively. Sodium lauryl sulfate, monobasic potassium phosphate, Avicel and lactose were purchased from Merck (Germany). All other chemicals and solvents were of analytical grade.

Methods

Preparation of tablets

Tablet ingredients for different formulations were weighed, milled and mixed thoroughly. After mixing with 1% magnesium stearate, tablets containing 400 mg flutamide were prepared by direct compression method using a single-punch (11 mm diameter) tablet compression machine (Killian Co, GmbH Koln-Niehl, Germany). Table 1 shows the constituents and polymer compositions of different formulations.

Physical evaluation of tablets

Weight variation

20 tablets from each formulation were weighed using an electronic balance (Sartorius, 2434, Germany) and mean and relative standard deviation of the weight were determined based on an official method (10).

Hardness and friability

The diametrical crushing strength test was performed on 10 tablets from each formulation. 10 tablets were tested using an Erweka TB24 (Germany) hardness tester.

For each formulation, the friability of 20 tablets was determined using a Roche type friabilitor (Erweka, Germany). 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min. After removing of dusts, tablets were re-weighed and friability

Table 1. Different formulations of flutamide matrix tablets along with their codes.

Formulation code	Tablet ingredients (mg per tablet)									
	Flutamide	HPMC	HCCAC	Xanthan Gum	Gum Gera	Emulgipit ELPO	Emulgipit ESPO	Avicel	Avicel	Magnesium stearate
E ₁ F ₀	400	300	-	-	-	-	-	100	10	5
E ₂ F ₀	400	200	-	-	-	-	-	200	10	5
E ₃ F ₀	400	150	-	-	-	-	-	250	10	5
E ₄ F ₀	400	100	-	-	-	-	-	300	10	5
E ₅ F ₀	400	50	-	-	-	-	-	350	10	5
G ₁ F ₄	400	-	300	-	-	-	-	100	10	5
G ₂ F ₄	400	-	200	-	-	-	-	200	10	5
G ₃ F ₄	400	-	100	-	-	-	-	300	10	5
G ₄ F ₄	400	-	50	-	-	-	-	350	10	5
X ₁ F ₀	400	-	-	200	-	-	-	200	10	5
X ₂ F ₀	400	-	-	50	-	-	-	350	10	5
G ₁ F ₀	400	-	-	-	200	-	-	200	10	5
G ₂ F ₀	400	-	-	-	100	-	-	300	10	5
G ₃ F ₀	400	-	-	-	50	-	-	350	10	5
L ₁ F ₄	400	-	-	-	-	200	-	200	10	5
S ₁ F ₄	400	-	-	-	-	-	300	100	10	5
S ₂ F ₄	400	-	-	-	-	-	200	200	10	5
S ₃ F ₄	400	-	-	-	-	-	50	350	10	5
E ₁ C ₁ F ₄	400	100	100	-	-	-	-	200	10	5
L ₁ S ₁ F ₄	400	-	-	-	-	25	275	100	10	5
L ₁ S ₂ F ₄	400	-	-	-	-	50	250	100	10	5
L ₁ S ₃ F ₄	400	-	-	-	-	100	200	100	10	5

percentage was calculated using the following equation (10):

$$\%F = \frac{W_1 - W_2}{W_1} \times 100 \quad (1)$$

Drug content determination

20 tablets from each formulation were finely powdered and a portion equal to 400 mg flutamide was transferred to a 100 ml volumetric flask, dissolved in methanol-water (95:5) and brought to volume. After centrifugation of the sample, the supernatant was diluted (1:100) and the absorbance determined photometrically using a UV spectrometer (UV-Visible 1420, Perkin-Elmer, USA) at 307 nm (11).

Content uniformity

Content uniformity test was performed on 10

tablets individually. Each tablet was transferred to a 100 ml volumetric flask and 50 ml methanol-water (95:5) mixture added and sonicated for 20 min. Then made up to volume and mixed. After centrifugation at 2000 rpm for 5 min, 1 ml of the supernatant was diluted (1:100) and its absorbance was determined by a UV-visible spectrophotometer at 307 nm. The amount of drug in each tablet was measured according to a validated calibration curve (11).

Drug release studies

Dissolution test was carried out on 6 tablets from each formulation, using the USP apparatus II (paddle method, Pharma test, PTWS3, Germany) at 75 rpm. Dissolution medium for all formulations was 900 ml phosphate buffer pH 6.8 containing 2% sodium lauryl sulfate maintained at 37±0.5 °C. The drug release studies continued for 8 h and at certain time intervals, 5 ml samples

of the dissolution medium were withdrawn, centrifuged and assayed at 307 nm. After each sampling, an equal volume of fresh buffer solution, at the same temperature, was replaced (12).

Analysis of dissolution data

Two parameters i.e., dissolution efficiency (DE) (13, 14) and mean dissolution time (MDT) (14, 15) were used to compare the release profiles of different formulations. DE% is defined as the ratio of area under the dissolution profile at a given time to the total area at the same time once the entire content is released which is calculated by the following equation:

$$DE \% = \frac{\int_0^t y dt}{y_{100} \cdot t} \times 100 \quad (2)$$

DE% could be defined for every sampling time. In this study because of versatile release profiles of different formulations, DE% was calculated at 90 and 420 min.

MDT is a measure of the dissolution rate which is calculated based on the following equation:

$$MDT = \frac{\sum_{i=1}^n t_{mid} \times \Delta M_i}{\sum_{i=1}^n \Delta M_i} \quad (3)$$

Where, i is the sampling number, n is the number of dissolution sample time, t_{mid} is the time at midpoint between t_i and t_{i-1} (easily calculated with the expression $(t_i + t_{i-1})/2$) and ΔM_i is the additional amount of drug dissolved between t_i and t_{i-1} .

Kinetic models

Dissolution data were fitted to Zero-order, $W = W_0 - k_0 t$, First-order, $\ln W = \ln W_0 - k_1 t$, Hixson-Crowell's cube root of time, $W^{1/3} = W_0^{1/3} - k_2 t$ and Higuchi square-root of time, $W = W_0 - k_H t^{1/2}$ kinetic models, where W is the amount of drug released at time t and W_0 is the initial amount of drug. Fitting was performed employing SPSS 11 by linear regression method to determine the

most probable release kinetic by using standard error of estimates (16, 17).

To estimate the drug release mechanism, dissolution data were also analyzed by Korsmeyer-Peppas model, $M_t/M_\infty = kt^n$, where M_t/M_∞ is the amount of drug released at time t , k is a constant incorporating structural characteristics of the dosage form and n is the release exponent. When $n < 0.5$, the drug diffuses through the polymeric matrix by a Fickian (case I) diffusion mechanism. For $0.5 < n < 1$, an anomalous (non-Fickian) mechanism occurs. $n = 1$ indicates a zero-order (case II) and $n > 1$ indicates non-Fickian super case II release mechanism (17).

Statistical analysis

Comparison between two means was performed using Student's t-test. ANOVA followed by LSD test was used for comparison between more than two means for example drug release profiles, MDT and regression coefficients at 95% level of confidence (SPSS 11). P-value less than 0.05 were considered significant.

Results and Discussion

Physical evaluation of tablets

Matrix tablets of flutamide were prepared by the direct compression method and subjected to different evaluation tests. Based on USP (12), drug content of each tablet should be in the range of 85-115% and the CV% for drug content of 10 tablets, shown less than 6%. According to the results of physical evaluation of tablets in Table 2, drug content distribution of each formulation was uniform and CV% of the drug amount for all formulations was less than 0.15%. All the formulations showed good uniformity in drug content and the percentage of drug content was 97.5 ± 0.67 to 99.75 ± 0.24 . Results of tablet hardness test (Table 2) show that the hardness and friability percentage of all formulations were ranged from 55 ± 1.23 N to 76.61 ± 4.08 N and 0.39-0.8%, respectively, which met the pharmacopoeial requirements (12). Tablets hardness for all formulations were in the required limits of higher than 50 N (10). A small difference between formulations is related to the

Table 2. Results of the physical evaluations conducted on flutamide matrix tablets prepared.

Formulation code	Drug content ^a (%)	Hardness ^b (N)	Friability ^c (%)	Weight variation ^d (%)	Content uniformity ^e (mg)
E ₁ F ₄	98.75±0.25	51.78±2.83	0.45	0.33	399.29±0.15 (0.037)
E ₂ F ₄	99.75±0.24	51.93±2.63	0.41	0.24	399.53±0.21 (0.037)
E ₃ F ₄	97.50±0.67	51.00±1.23	0.45	0.13	399.83±0.28 (0.070)
E ₄ F ₄	98.80±0.19	37.33±3.49	0.51	0.14	399.80±0.21 (0.037)
E ₅ F ₄	99.80±0.25	38.78±2.81	0.47	0.17	399.79±0.22 (0.037)
C ₁ F ₄	99.25±0.24	51.32±4.82	0.47	0.14	399.84±0.18 (0.043)
C ₂ F ₄	99.25±0.21	56.61±4.08	0.80	0.16	399.87±0.13 (0.037)
C ₃ F ₄	98.50±0.33	51.73±2.79	0.51	0.14	399.89±0.15 (0.037)
C ₄ F ₄	98.25±0.39	30.32±5.88	0.53	0.18	399.84±0.16 (0.040)
X ₁ F ₄	99.80±0.27	51.71±3.49	0.37	0.19	399.93±0.11 (0.037)
X ₂ F ₄	98.25±0.33	38.72±2.11	0.35	0.13	399.85±0.15 (0.038)
G ₁ F ₄	98.50±0.25	37.16±1.83	0.41	0.19	399.94±0.12 (0.030)
G ₂ F ₄	99.50±0.21	39.33±3.13	0.43	0.17	399.92±0.11 (0.038)
G ₃ F ₄	98.75±0.25	38.17±2.23	0.39	0.14	399.82±0.12 (0.030)
L ₁ F ₄	99.25±0.31	51.00±1.23	0.54	0.13	399.92±0.18 (0.037)
S ₁ F ₀	98.23±0.25	63.00±2.81	0.41	0.12	399.85±0.18 (0.037)
S ₂ F ₀	98.73±0.25	63.78±3.43	0.45	0.13	399.94±0.12 (0.030)
S ₃ F ₀	99.30±0.28	68.98±4.62	0.47	0.10	399.85±0.18 (0.037)
L ₁ S ₁ F ₀	98.73±0.24	65.23±3.59	0.37	0.16	399.79±0.21 (0.037)
L ₁ S ₂ F ₀	98.23±0.45	63.65±2.83	0.39	0.16	399.84±0.15 (0.037)
L ₁ S ₃ F ₀	99.00±0.27	63.51±2.48	0.45	0.24	399.53±0.51 (0.137)
E ₁ C ₁ F ₄	98.30±0.18	61.11±2.56	0.35	0.11	399.83±0.29 (0.073)

^aAll values are reported as mean±SD, n=10.

^bAll values are reported as mean, n=20.

^cAll values are reported as mean±SD, n=18 (values in parentheses are CV%).

type and percentage of the retarding polymer. Since tablet hardness is not a perfect index to evaluate the strength of the tablets, friability percentage was also used to test the hardness of tablets. For all the prepared formulations, friability percentage was less than 1%, being in the acceptable range recommended by official references (10). According to the pharmacopoeial recommendation (10, 12), for tablets weighing more than 324 mg, ±5% deviation from the mean weight is acceptable. As the results show, the average weight deviation percentage of 20 tablets taken from each formulation was less than ±0.5%, and all the formulations met the requirement.

Drug release studies

When matrices containing swellable

polymers are exposed to dissolution medium, tablet surface becomes wet and hydrated to form a gel layer. The initial release of drug from these matrices occurs by the drug dissolution in the water penetrated into the matrix. The overall drug release from these matrices is governed by hydration, gel layer formation and drug diffusion into the gel layer and to the dissolution media (18, 19). Polymer erosion also plays a major role in releasing drug from these matrices (20). These considerations indicate that hydrophilic polymers have the potential to sustain the release of drug from matrix tablets. In this study, various retarding hydrophilic synthetic and natural polymers were used to control the release of flutamide from matrix tablets. In order to investigate the effect of polymer type and percentage on

Table 3. Values of regression coefficients (R^2) and release exponents (n, obtained from the Peppas model) for the release of flutamide from different formulations, based on various kinetic models.

Formulation	Zero order		First order		Higuchi		Korsmair-Corradi		Peppas	
	R^2	Standard error	R^2	Standard error	R^2	Standard error	R^2	Standard error	R^2	n
H ₁ F ₁	0.972648733	2.2844	0.972648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	1.232448697
H ₂ F ₁	0.997048733	1.9947	0.972648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	1.232448697
H ₃ F ₂	0.972648733	0.8984	0.999648733	0.1139	0.972648733	0.7922	0.999648733	0.9999	0.999648733	0.999648733
H ₃ F ₁	0.972648733	22.8984	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	1.232448697
H ₃ F ₃	0.972648733	26.0474	0.972648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
O ₂	0.999648733	22.1762	0.972648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	1.232448697
O ₃	0.999648733	24.2284	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	1.232448697
O ₃	0.972648733	27.0974	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
O ₃ F ₁	0.999648733	24.2284	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
X ₁ F ₁	0.999648733	0.2489	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	1.232448697
X ₃ F ₂	0.999648733	2.0498	0.972648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
H ₁ F ₁	0.999648733	2.1779	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	1.232448697
H ₁ F ₁	0.972648733	0.2489	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	1.232448697
H ₃ F ₂	0.999648733	26.0474	0.972648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
H ₃ F ₁	0.999648733	24.2284	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	1.232448697
H ₃ F ₁	0.972648733	2.0498	0.972648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
H ₃ F ₁	0.999648733	27.0974	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
H ₃ F ₂	0.999648733	26.0474	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
H ₃ F ₂	0.999648733	24.2284	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
H ₃ F ₂	0.999648733	26.0474	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
H ₃ F ₂	0.999648733	24.2284	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
H ₃ F ₂	0.999648733	26.0474	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
H ₃ F ₂	0.999648733	24.2284	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
H ₃ F ₂	0.999648733	26.0474	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733
H ₃ F ₂	0.999648733	24.2284	0.999648733	0.2489	0.999648733	0.2820	0.999648733	0.9999	0.999648733	0.999648733

* All values are expressed as mean±SD (n=6).

drug release profile, different formulations containing various percentages of HPMC, NaCMC, guar and xanthan gum, Eudragit RSPO and RLPO and their combinations were prepared. HPMC is a hydrophilic cellulose ether, which is used as a retarding polymer in swellable matrices (21). Figure 2a shows the release profiles of formulations containing different amounts of HPMC. In formulation H_{0.5}F₄, which contained less than 10% of HPMC, about 80% of the drug released in the first 2 h and a sustained-released profile was not observed (MDT=55 min, Table 4). By increasing the amount of HPMC in the formulation, release rate was decreased, as in formulation H₃F₄. In fact, drug released too slow to be not suitable for a sustained release system (MDT=283 min, DE₄₂₀%=19, Table

4). A suitable sustained release dosage form should release its content within 8-10 h. In this series, formulation H₂F₄ which contained 25% of HPMC, released about 70% of flutamide in 8 h, that could be considered as a sustained release formulation. This formulation could release more than 90% of its content within 10 h. This indicates that the formulation releases the drug in a desirable sustained manner. Different studies have shown that the rate and amount of drug release is inversely proportional to the HPMC percentage in formulations (22). By increasing the polymer percentage, a viscous gel layer is formed, resisting to erosion and the diffusion of the drug is controlled primarily by the gel viscosity (23). Regression coefficients of different kinetic models presented in Table 3 showed

Table 4. Results of DE% and MDT calculated for different formulations of flutamide matrix.

Formulation code	MDT (min)	DE ₉₀ %	DE ₉₅ %
H ₁ F ₄	283.26±1.91	2.87±0.13	19.00±0.41
H ₂ F ₄	234.91±3.93	6.43±0.26	32.20±0.47
H ₃ F ₄	149.11±0.37	20.75±0.09	62.13±0.03
H ₄ F ₄	110.30±4.33	29.67±0.15	74.92±0.32
H ₅ F ₄	33.37±0.01	50.03±0.26	-
C ₁ F ₄	39.49±2.02	66.92±0.46	-
C ₂ F ₄	24.93±1.71	76.24±0.29	-
C ₃ F ₄	17.23±1.21	82.17±0.21	-
C ₄ F ₄	16.38±1.26	83.53±0.21	-
X ₁ F ₄	239.83±13.14	0.40±0.06	1.30±0.03
X ₂ F ₄	179.86±4.02	7.59±0.17	19.79±0.41
G ₁ F ₄	222.12±10.36	11.50±0.96	17.97±0.14
G ₂ F ₄	141.10±0.36	29.53±0.47	38.79±0.18
G ₃ F ₄	30.13±2.22	62.16±0.46	-
L ₁ F ₄	37.93±0.06	59.97±0.26	-
S ₁ F ₄	238.79±4.30	4.14±0.90	46.30±0.25
S ₂ F ₄	74.93±4.18	48.44±0.04	-
S ₃ F ₄	43.43±0.96	63.02±0.23	-
H ₁ C ₁ F ₄	181.07±3.32	12.00±0.08	-
L ₁ S ₁ F ₄	80.91±1.02	39.99±0.36	-
L ₁ S ₂ F ₄	37.73±1.07	53.20±0.43	-
L ₁ S ₃ F ₄	43.08±0.08	54.44±0.14	-

All values are reported as mean±SD (n=6).

that first order and Hixson-Crowell models are more probable, which are resulted from diffusion and to some extent matrix erosion. This finding is similar to the study on matrix tablets of aspirin (21) which gave a better fit with first order kinetics. Based on the value of n ($n > 1$) obtained using the Peppas equation, release mechanism from matrices containing higher amounts of HPMC was found to be super case II. In super case II, in addition to diffusion, other release mechanism including matrix erosion and polymer relaxation might be involved. While, release mechanism from formulations containing lower percentages of HPMC was considered to be non-Fickian (anomalous), which results from diffusion and erosion release mechanisms.

Formulations containing NaCMC (Figure 2b), released their entire content completely in the first 2-3 h as indicated by smaller values of MDT ranging from 16-39 min.

By increasing the polymer content, MDT value increased, however, none of the formulations showed a desirable sustained-release profile. This fast release profile is because of the presence of the ionized carboxylic acid groups in NaCMC, which causes rapid dissolution and disintegration (23). In these series of formulations, first order release and Fickian mechanism (diffusion, $n < 0.5$) was prominent. In the combinatory formulation of HPMC and NaCMC (formulation H₁C₁), release profile (Figure 2c) was more desirable than formulations containing NaCMC alone (Figure 2b). By mixing the two polymers, a better MDT (181 min) and DE₉₀% (12%) was achieved. The addition of NaCMC to non-ionic cellulose like HPMC increases the viscosity. This was attributed to the strong hydrogen bonding between the carboxyl groups on NaCMC and the hydroxyl groups on HPMC, leading to a strong cross-linking between the two polymers (23). In this formulation, similar to sustained-release

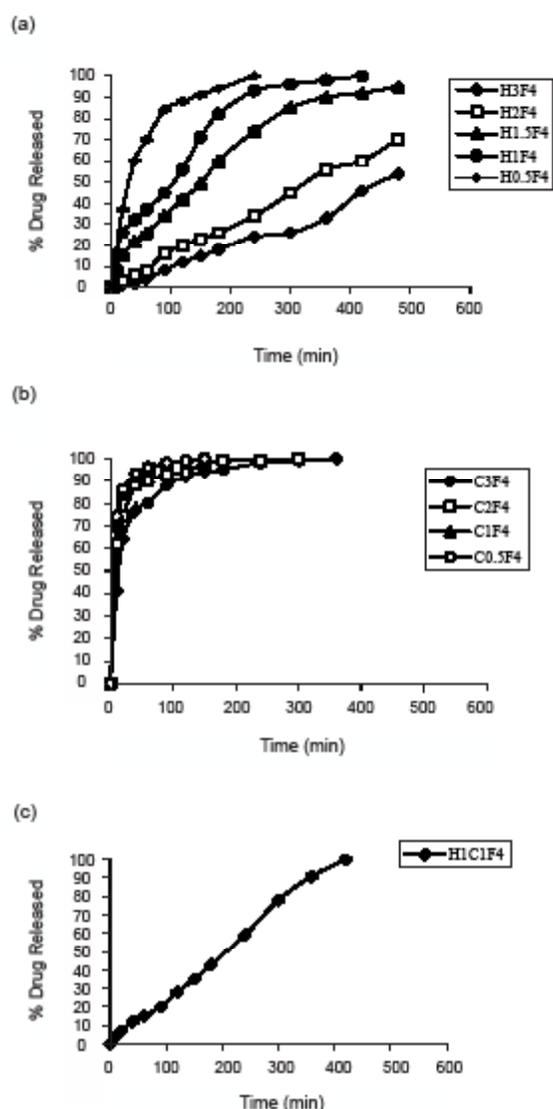


Figure 2. Release profiles of flutamide from matrices containing different percentages of (a) HPMC, (b) NaCMC and (c) combination of HPMC and NaCMC in phosphate buffer solution containing 2% sodium lauryl sulfate (n=6).
 H₃F₄: 300 mg HPMC, H₂F₄: 200 mg HPMC, H_{1.5}F₄: 150 mg HPMC, H₁F₄: 100 mg HPMC, H_{0.5}F₄: 50 mg HPMC, C₃F₄: 300 mg NaCMC, C₂F₄: 200 mg NaCMC, C₁F₄: 100 mg NaCMC, C_{0.5}F₄: 50 mg NaCMC, H₁C₁F₄: 100 mg HPMC, 100 mg NaCMC. All formulations contained 400 mg flutamide.

formulations of HPMC, super case II release mechanism was observed.

A similar study on matrices containing different ratios of NaCMC and HPMC has shown that in water, the values of n for most formulations are close to unity, indicating super case II release mechanism (24).

Since natural gums are more cost effective

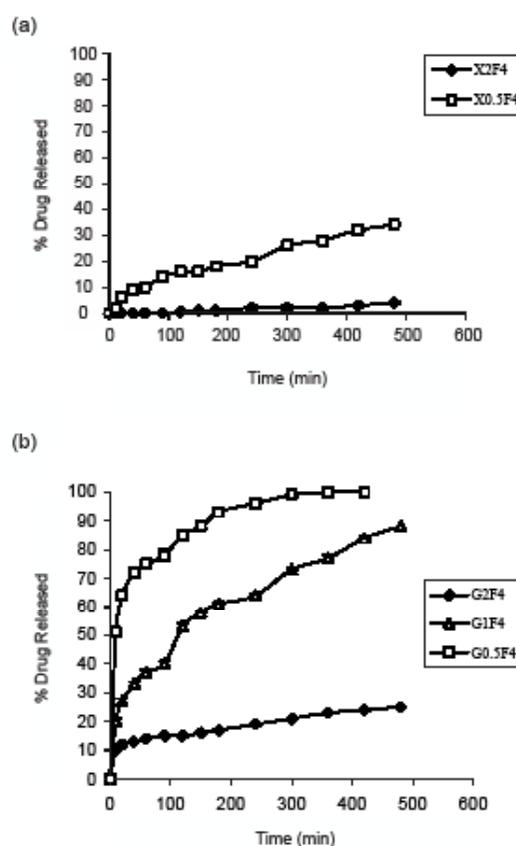


Figure 3. Release profiles of flutamide from matrices containing different percentages of (a) xanthan and (b) guar gum in phosphate buffer solution containing 2% sodium lauryl sulfate (n=6).
 X₂F₄: 200 mg xanthan gum, X_{0.5}F₄: 50 mg xanthan gum, G₂F₄: 200 mg guar gum, G₁F₄: 100 mg guar gum, G_{0.5}F₄: 50 mg guar gum. All formulations contained 400 mg flutamide.

and safer, two natural gums were also used to prepare matrix tablets (25). Different studies have been reported on the use of these two gums for the preparation of matrix tablets by the direct compression method (26-28). Their compaction and flowability properties have found to be suitable for direct compression. A study has shown that the overall compaction characteristics of xanthan gum is quite similar to HPMC and xanthan gum is more readily flowable than HPMC (27).

Profiles of the drug release from tablets containing natural gums are depicted in Figure 3. Xanthan gum is a polymer with high retarding effect: in formulation X₂F₄, containing 25% of xanthan, negligible amounts of drug was released within 8 h (Table 4, very low value for DE%). By decreasing the polymer content to 5%

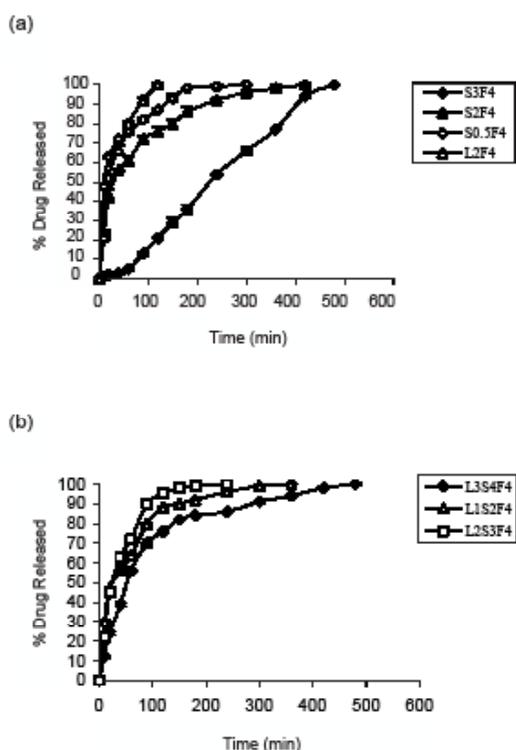


Figure 4. Release profiles of flutamide from matrices containing different percentages of (a) Eudragits (RLPO and RSPO) and (b) their combination in phosphate buffer solution containing 2% sodium lauryl sulfate ($n=6$).

S_3F_4 : 300 mg Eudragit RSPO, S_2F_4 : 200 mg Eudragit RLPO, $S_{0.5}F_4$: 50 mg Eudragit RSPO, L_2F_4 : 200 mg Eudragit RLPO, $L_3S_4F_4$: 25 mg Eudragit RLPO, 275 mg Eudragit RSPO, $L_2S_3F_4$: 100 mg Eudragit RLPO, 200 mg Eudragit RSPO, $L_1S_2F_4$: 50 mg Eudragit RLPO, 250 mg Eudragit RSPO. All formulations contained 400mg flutamide.

(formulation $X_{0.5}F_4$), drug release was improved and a faster release was observed, however, this did not fulfill the characteristics of an optimized sustained-release formulation, as the release rate was still low. In comparison with sustained release formulations of HPMC, the drug release rate of xanthan gum matrices is very low, which is due to the lower drug diffusivity out of the xanthan gum gel than the HPMC gel. Furthermore, xanthan gum can produce much more viscous gels than the HPMC (28). Release data of tablets prepared with xanthan gum showed best fitting with first order and Higuchi kinetics models, which means that diffusion is the most probable mechanism of release. These findings are in accordance to the results of the study on directly compressed glipizide sustained-release matrices. This study showed that xanthan gum is the major

excipient responsible for the diffusional release profile (26).

Formulations containing guar gum as the swellable matrix, exhibited a slow release of drug. After a short time period, a linear release behavior was observed. This behavior was more remarkable, as the amount of polymer increased in tablets, as seen in formulation G_2F_4 (Figure 3). The process of drug release from guar matrix involves water penetration into the matrix, hydration and swelling of the polymer and drug dissolution and diffusion out of the matrix. The two consecutive steps of the drug release from the matrix is the result of high hydrophilicity of guar gum. When water penetrates into the matrix, the polymer swells to a constant level (25). Drug release from guar matrices depends on the rate of water penetration and drug diffusion out of the matrix (29). When matrix swells, a portion of dissolved drug is released and after reaching a constant state of gelling, greater amounts of drug could be released by diffusion (25). In formulation G_2F_4 , that showed the most sustained profile in these series, first order and Higuchi release kinetic models are more probable. In a study on guar gum for the preparation of sustained release tablets (29), release data were found to be best fitted with the Higuchi release kinetics (The release kinetics have not been studied in that article, but the release data are available). Another study on guar gum matrix tablets containing metoprolol has shown that metoprolol tartrate release from guar gum matrices followed Fickian diffusion. When the hydrophilic guar gum tablets come into contact with the dissolution medium, they take up water and swell, forming a viscous gel barrier. In case of guar gum matrix tablets, the initial swelling of the gum may aid dissolution of the drug, and the dissolved drug diffuses out of the swollen gel barrier into the dissolution medium. Unless the swollen gel barrier erodes, further seeping-in of the dissolution medium does not occur. Thus, the release rate of the drug depends on the strength of the gel barrier (i.e. the proportion of the hydrophilic guar gum in the matrix tablet), its rate of hydration and viscosity (30).

pH independent compressible Eudragits (RLPO and RSPO) were used for preparation of matrix tablets. Eudragits RLPO and RSPO are freely flowable powders which can be used

for direct incorporation within the matrix or as a coating for sustaining the drug release profile. They could be used as retarding polymers for preparing matrix systems, granulating agent for controlled-release tablets or pH-independent rate control coatings. A previous study has proven the efficacy of Eudragit RSPO for development of sustained release didanosine matrix tablets (31). Another study has also shown the efficacy of a 0.7:0.3 w/w mixture of Eudragit L100 and Eudragit RLPO, for controlling the release of theophylline from directly compressed matrix tablets (32). When RLPO was used as the only retarding polymer for flutamide tablets (Figure 4, formulation L₂F₄), the entire drug content was released within 2 h and a sustained drug release pattern was not observed (MDT=37 min). This might be due to the higher number of quaternary ammonium groups and greater permeability of RLPO. Formulations containing RSPO released their drug content in a more sustainable fashion than formulation L₂F₄ (Figure 4). Amongst the formulations containing RSPO as the retarding polymer, formulation S₃F₄ which contained 40% RSPO provided the slowest release profile and 90% of the drug content was released after 8 h. A lag time was observed in the release profile of formulation S₃F₄, which can be interpreted by the higher amount of Eudragit RSPO. This in turn resulted in a delayed water penetration and gelling of the polymer. MDT (238 min) and DE₄₂₀% (50%) of this formulation in comparison with the other two formulations, denote it as the most appropriate formulation in this series. By implying a small change in polymer content, a desirable release profile could be obtained. In all the formulations prepared in this series, the diffusion mechanism was predominant and the Higuchi and first order drug release kinetic models are more probable. Similar studies on didanosine matrix tablets containing Eudragit RSPO, and sustained-release zidovudine matrix tablets containing Eudragits RSPO and RLPO have also shown that the best fitting release kinetics is the Higuchi models (31, 33). In order to omit the lag time of the drug release from formulation S₃F₄, different combinations of RSPO and RLPO were used to prepare matrix tablets. However, as can be seen in Figure 4, none of these combinatory formulations provided a suitable sustained-

release profile. This could be attributed to the high permeability of Eudragit RLPO, since the DE₉₀% values obtained for all the formulations prepared in this series were less than 55%.

As the results show, the best fitting release kinetic models for all formulations are first order and Higuchi models. As a general rule, release of the drug from a matrix tablet containing hydrophilic polymers involves factors related to diffusion. Diffusion is related to transport of drug from the dosage matrix into the surrounding in-vitro medium, and depends on the drug concentration. As gradient varies, the drug is released and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases. This is referred to as the square-root kinetics or the Higuchi's kinetics model (8).

In conclusion, formulations contained HPMC, guar gum and Eudragit RSPO seem to produce a more appropriate sustained-release profiles than other polymers. Formulations H₂F₄ and S₃F₄, which respectively released 70% and 90% of their drug content within 8 h, were considered more desirable and met the requirements. Drug release from these formulations followed first order kinetics. For both these formulations, a super case II release mechanism was observed.

Acknowledgment

This work has been supported by the Research Council of Isfahan University of Medical Sciences.

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