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Original Article

Comparison of hydrophilic natural gums and cellulosic polymers in formulation of sustained-release matrix tablets of terbutalin sulfate

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Abstract

The short half-life of terbutaline sulphate (TBS) requires frequent dosing for controlling chronic pulmanary disorders, such as night asthma. The purpose of the present study was to prepare sustained-release (SR) tablets of TBS to decrease the number of doses frequency and to promote the paitent compliances. It was also desirable to evaluate the capability of natural gums for preparation of SR oral dosage forms in comparison with the cellulosic polymers. SR tablets of TBS (7.5 mg) were prepared using either natural gums; Guar (G) or Xanthan (X) and cellulosic polymers; hydroxypropyl methylcellulose (H) or carboxymethyl cellulose (C) by direct compression method. Different ratios of 0:100, 20:80, 40:60, 60:40 of C : H, G : X, X : H or H : G were used. After evaluation of physical characteristics of tablets, release rate were compared with the standard tablets (Bricanyl® SR) in phosphate buffer solution (pH 7.4). All tablets met the official physical properties. Tablets with 80:20 ratio of polymers, H_8X_2 and G_8X_2 had smaller $DE_{8\%}$ (Dissolution Efficiency) and higher MDT (Mean Dissolution Time). In the ratio of 60:40 and 40:60 formulations H_4X_6 and H_6X_4 had the highest MDT, and the smallets $DE_{8\%}$. Formulation H_4X_6 released the drug with zero-order kinetics while H_6X_4 followed a Higuchi pattern such as standard tablet. It is concluded that formulation containing Guar and Xanthan (G_8X_2) released the drug with a zero-order kinetic and was the most similar formulation to the standard.

Key words: Guar, Terbutaline, Sustained-release, Xanthan

INTRODUCTION

Asthma is an inflammatory disease of the airways that is frequently characterized by marked circadian rhythm. Nocturnal and early morning symptoms are quite common among patients with asthma. Increased mortality and decreased quality of life are associated with nocturnal asthma. According to international guide-lines, patients with persistent asthma should receive long-term daily anti-inflammatory therapy. If preventive environmentally control of the disease and low to moderate doses of inhaled corticosteroids do not eliminate nocturnal symptoms, the addition of a long-acting bronchodilator is warranted (1). It is desirable that broncho-dilator therapy results in an overall 24-h improvement in bronchial patency or at least provides cover for the nocturnal decline. The sustained-release (SR) oral drug delivery may provide this cover and improve therapy, especially if administered at bedtime to cover the night 'no-dose' period. A SR preparation will provide available drug over an extended period, which may enhance control of disease

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states, e.g. asthma symptoms. In particular, short acting β_2-adreno ceptor stimulants have a short plasma half-life (4–6 h) and require frequent dosing, making these agents ideal candidates for SR formulations. The advantages for SR oral drug delivery to the respiratory tract include extended duration of action, reduction in drug use, improved management of therapy, improved compliance, reduction in side effects, together with potential cost savings that exist for SR therapy (2).

TBS, a β-adrenergic receptor agonist, is a cellulosic sympatomimetic amine used in the treatment of bronchial asthma, chronic bronchitis and emphysema (3). In the treatment of bronchial asthma it is given orally in a dose of 5 mg two or three times daily. Having a short biological half-life (3–4 h) (3), TBS needs to be administered frequently. However, such a dosing schedule may be inconvenient for the patients. Therefore, a sustained release TBS formulation is desirable to improve patient compliance. The SR preparation of TBS 7.5mg seems to be of clinical value in preventing or relieving nocturnal asthma and early morning dipping. The flexible dose technique, with a higher evening dose, results in further improvements in these patients (4, 5). A comparison of SR TBS with ordinary salbutamol in bronchial asthma had shown that the morning Peak-Flow was higher during the period on the depot tablets compared to that of the ordinary tablets. No differences were found in side effects (6).

There are several studies in the literature regarding the prolongation of TBS release. In these studies, cellulose acetate phatalate (7), ethylcellulose (8) and Eudragit RS (9) have been used for the encapsulation of TBS in a microparticulate system (10). SR coated pellets of TBS were also prepared by hydroxypropyl cellulose coated with ethylcellulose (11).

Hydrophilic polymers are becoming very popular in formulating of oral controlled release tablets. As the dissolution medium or biological fluid penetrates to the dosage form, the polymer material swells and drug molecules begin to move out of the system by diffusion at a rate determined by the nature and composition of the polymer as well as formulation technology. Developing of the oral controlled release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these systems, if not formulated properly, may readily release the drug at a faster rate and are likely to produce the toxic concentrations, when administered orally (12). Natural gums are among the most popular hydrophilic polymers because of their cost-effectiveness and regulatory acceptance. Guar gum (G) is a natural non-ionic polysaccharide derived from the seeds of *Cyamopsis tetragonolobus* (Family Leguminosae). In pharmaceuticals, it is used in solid dosage forms as a binder and disintegrant (13). Xanthan gum (X) is another natural, biocellulosic edible gum and an extracellular polysaccharide produced by the bacterium *Xanthomonas campestris*, and consists of glucose, mannose and glucuronic acid (14). It is used in different foods as thickening and stabilizing agent (15). As there is no report on the use of natural gums in production of matrix of SR tablets of TBS, the objective of this work was to use natural gums (X and G) as suitable hydrophilic matrix systems in production of SR tablets of TBS. Comparison to the extensively investigated hydrophilic matrices, i.e., HPMC/CMC in respect of *in vitro* drug release and hydration rate of the polymers are carried out in this study. The probable synergistic effect of triple mixture of natural gums and HPMC on retarding the drug release was also studied.

MATERIALS AND METHODS

Terbutaline sulphate (as gift from Iran Hormon Company, Iran), Guar gum

(Hercules, USA), Xanthan gum (Farabi Company, Iran), hydroxypropyl methylcellulose K4M (Fluka, Switzerland), carboxymethyl cellulose (Merck, Germany), magnesium stearate (Merck, Germany), Avicel PH 101 (FMC, USA), sulforic acid (Merck, Germany), sodium hydroxide (Merck, Germany), potassium phosphate monobasic (Merck, Germany), Bricanyl® SR 5 mg (Astrazeneca, France). All other chemicals and reagents were of analytical grade.

Preparation of TBS matrix tablets

Matrix tablets of TBS (7.5 mg) were prepared by direct compression. Magnesium stearate was used as lubricant and Avicel PH 101 as filler-binder for increasing the compressibility and flow of the ingredients. The total weight of tablets was set at 100 mg. Table 1 shows the constituents of various formulations and their polymer compositions prepared in this study. Each formulation was coded according to the name and ratio of polymers for example X_8G_2 is a formulation with Xanthan and Guar in the ratio of 8:2. All ingredients were sieved through an 18 mesh sieve, weighed and mixed for 10 min in a mixer (WAB TURBULA, T2C, Switzerland). Magnesium stearate was added and mixed for an additional 2 min and the tablets were compressed by a single punch tableting machine (Type K5, Kilian GmbH, Germany), fitted for of 2.4 mm height and 6.2 mm in diameter. The tablets were compressed in order to obtain a 40-50 N hardness (Tablet Hardness Tester, Type T.B.42, Erweka, Germany).

Determination of drug content

The TBS matrix tablets were tested for their drug content. Twenty tablets were finely powdered; a portion of the powder equal to 10 mg of TBS was accurately weighed and transferred to a 50 ml volumetric flask. Then, 10 ml 0.05N sulfuric acid and 20 ml water were added and allowed to shake for 15 min to ensure

Table 1. Formulations of 7.5 mg terbutalin sulfate tablets prepared by direct compression method. All tablets contain 26.8 mg Avicel as the filler-binder and 0.7 mg magnesium stearate as the lubricant. (HPMC=hydroxypropylmethyl cellulose, CMC=carboxy-methyl cellulose, G=Guar gum, X=Xanthan gum)

Formulation code	HPMC	CMC	Xanthan	Guar
	mg			
H_8C_2	52	13	-	-
H_6C_4	39	26	-	-
H_4C_6	26	39	-	-
H_2C_8	13	52	-	-
G_8H_2	13	-	-	52
G_6H_4	26	-	-	39
G_4H_6	39	-	-	26
G_2H_8	52	-	-	13
G_4X_6	-	-	39	26
G_6X_4	-	-	26	39
G_8X_2	-	-	13	52
H_4X_6	26	-	39	-
H_6X_4	39	-	26	-
H_8X_2	52	-	13	-
H	65	-	-	-
G	-	-	65	-
X	-	-	-	65
$X_6H_2G_2$	13	-	52	13
$X_2H_6G_2$	52	-	13	13
$X_2H_2G_6$	13	-	13	52

Table 2. Physical properties of tebutalin sulfate tablets (n=10)

Formulation code	Hardness (N) ± SD	Friability (%)	Drug content (mg) ± SD
H_8C_2	74.90±1.59	0.62	7.22±0.25
H_6C_4	75.71±2.79	0.57	7.23±0.24
H_4C_6	78.11±2.99	0.57	7.22±0.23
H_2C_8	69.32±5.88	0.58	7.29±0.19
G_8H_2	36.25±2.48	0.61	7.35±0.25
G_6H_4	37.41±2.11	0.62	7.41±0.21
G_4H_6	52.51±2.83	0.62	7.31±0.27
G_2H_8	59.81±0.78	0.27	7.22±0.24
G_4X_6	63.51±5.31	0.81	7.18±0.23
G_6X_4	41.61±3.59	0.98	7.27±0.39
G_8X_2	35.11±4.62	0.55	7.38±0.32
H_4X_6	63.42±4.62	0.47	7.28±0.28
H_6X_4	71.52±4.62	0.37	7.23±0.33
H_8X_2	76.61±4.08	0.47	7.23±0.30
H	72.72±2.81	0.51	7.22±0.25
G	38.00±2.92	0.94	7.23±0.21
X	55.71±6.49	0.37	7.30±0.27
$X_6H_2G_2$	54.32±3.43	0.45	7.20±0.45
$X_2H_6G_2$	53.11±2.13	0.41	7.25±0.25
$X_2H_2G_6$	35.52±3.80	0.65	7.32±0.29

complete solubility of the drug. The volume was made up with water and the mixture was centrifuged (Type: 2000, Clements, Australia). The absorbance of the supernatant was determined spectrophotometrically (UV-Visible 1240 CE, Shimadzu, Japan) at 277.8 nm (16).

In vitro drug release studies

The matrix tablets were subjected to the basket dissolution method using 900 ml of phosphate buffer solution pH 7.4 ± 0.2 as the dissolution medium. The dissolution test was performed at 100 rpm and the temperature was set at 37 ± 1°C. At predetermined time intervals over an 8 hr period, 4 ml samples were withdrawn, centrifuged and assayed spectrophotometrically at 279.9 nm (16). After each sampling, equal volume (4 ml) of fresh buffer solution with the same temperature was replaced. All experiments were run three times and the calibration curve specifications were y = 0.0068X ± 0.0162 (r^2 = 0.9983, n = 9).

Mass loss and water uptake studies

Erosion and water uptake of the tableted formulations were determined under conditions identical to those described above for dissolution testing. Three tablets were used per time point. At the predetermined times the tablets were lightly patted with tissue paper to remove excess surface water. The wet weight of tablets was determined and then they were dried at 70°C for 10 days, before reweighing. The remaining dry weight was determined. Placebo tablets consisting of pure polymer were treated in the same way (17). Water uptake and mass loss of the tablets were determined gravimetrically according to the following equations:

(1) $$water\ \ uptake\ (\%) = \frac{wet\ \ weight - remaining\ \ dry\ weight}{remaining\ \ dry\ weight} \times 100$$

(2) $$mass\ loss\ (\%) = \frac{remaining\ \ dry\ weight - original\ \ dry\ weight}{original\ \ dry\ weight} \times 100$$

(3) $$erosion\ at\ time\ t\ (\%) = mass\ loss\ (\%)\ at\ time\ t - drug\ released\ (\%)\ at\ time\ t$$

Data analysis

Zero-order $(Q_t = Q_0 + K_0 t)$, first-order $(\ln Q_t = \ln Q_0 + K_1 t)$, Higuchi $(Q_t = K_H t^{1/2})$, Hixson-Crowell $(Q_0^{1/3} - Q_t^{1/3} = K_S t)$ (18) and Korsmeyer-Peppas $(Q_t / Q_\infty = Kt^n)$ models (19, 20) were fitted to the dissolution data using linear regression analysis. Model independent approaches i.e., dissolution efficiency (DE) (21) and mean dissolution time (MDT) (22) were used to translate the profile differences into single values. $DE_8\%$ is defined as the dissolution efficiency percentage up to 8 hr of dissolution test:

$$DE_8\% = \frac{\int_0^t y\ dt}{y_{100}\ t} \times 100 \quad (4)$$

MDT is a measure of the dissolution rate: the higher the MDT, the slower the release rate.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \quad (5)$$

Where *i* is the dissolution sample number, *n* is the number of dissolution sample time, t_{mid} is the time at the midpoint between *i* and *i-1* and ΔM is the amount of drug dissolved between *i* and *i-1* (22).

The similarities between two dissolution profiles were assessed by a pair-wise model independent procedure such as similarity factor (f_2) (22):

$$f_2 = 50\ Log\ \{[1 + 1/n \sum_{n=1}^{n=i} (R_t - T_t)^2]^{-0.5} \times 100\} \quad (6)$$

Where *n* is the number of pull points, w_t is an optional weight factor, R_t is the reference profile at time point *t* and T_t is the test profile at the same time point, the value of f_2 should be between 50 and 100 (22).

Table 3. Diffusion exponent (n) of Peppas model and regression coefficient (r^2) of tebutalin sulfate release data from studied matrices according to different kinetic models (n=3).

Formulation	n	Zero-order	First-order	Higuchi	Hixson-crowell
H_8C_2	0.74	0.915 ± 0.019	0.805 ± 0.022	0.958 ± 0.010	0.767 ± 0.017
H_6C_4	0.17	0.570 ± 0.054	0.926 ± 0.015	0.783 ± 0.042	0.848 ± 0.034
H_4C_6	0.32	0.709 ± 0.011	0.956 ± 0.006	0.898 ± 0.008	0.937 ± 0.027
H_2C_8	0.18	0.450 ± 0.020	0.671 ± 0.006	0.696 ± 0.018	0.688 ± 0.045
G_8H_2	0.72	0.930 ± 0.007	0.832 ± 0.150	0.969 ± 0.021	0.894 ± 0.082
G_6H_4	0.64	0.885 ± 0.012	0.921 ± 0.050	0.969 ± 0.008	0.891 ± 0.097
G_4H_6	0.61	0.734 ± 0.021	0.953 ± 0.017	0.893 ± 0.013	0.927 ± 0.009
G_2H_8	0.97	0.925 ± 0.016	0.920 ± 0.021	0.971 ± 0.006	0.905 ± 0.026
G_4X_6	0.49	0.933 ± 0.023	0.894 ± 0.016	0.954 ± 0.065	0.831 ± 0.017
G_6X_4	0.70	0.853 ± 0.036	0.949 ± 0.009	0.929 ± 0.043	0.931 ± 0.017
G_8X_2	0.94	0.982 ± 0.004	0.843 ± 0.090	0.967 ± 0.004	0.896 ± 0.090
H_4X_6	0.91	0.943 ± 0.016	0.867 ± 0.023	0.961 ± 0.007	0.844 ± 0.032
H_6X_4	0.69	0.919 ± 0.042	0.902 ± 0.073	0.973 ± 0.004	0.931 ± 0.048
H_8X_2	1.01	0.989 ± 0.003	0.752 ± 0.060	0.934 ± 0.006	0.765 ± 0.012
H	0.73	0.965 ± 0.003	0.897 ± 0.087	0.963 ± 0.014	0.953 ± 0.024
G	0.75	0.976 ± 0.006	0.808 ± 0.029	0.971 ± 0.018	0.843 ± 0.071
X	0.69	0.967 ± 0.012	0.740 ± 0.041	0.966 ± 0.006	0.769 ± 0.133
$X_6H_2G_2$	0.93	0.930 ± 0.004	0.829 ± 0.033	0.969 ± 0.002	0.846 ± 0.087
$X_2H_6G_2$	1.07	0.947± 0.004	0.900 ± 0.017	0.972 ± 0.001	0.852 ± 0.025
$X_2H_2G_6$	0.90	0.941 ± 0.004	0.928 ± 0.012	0.982 ± 0.006	0.878 ± 0.039
Bricanyl	0.78	0.968 ± 0.008	0.848 ± 0.060	0.975 ± 0.003	0.844 ± 0.032

An f_2 value of 100 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between release profiles increases.

Comparison amongst multiple means were made by one-way analysis of variance followed by LSD's test at the 95% level of confidence (SPSS vs.11).

RESULTS

As table 2 shows the hardness of the tablets ranged from 35 to 78 N. Tablets with high percentages of Guar gum (G_8H_2, G_6H_4, G_8X_2, G and $X_2H_2G_6$) did not meet the requirements of tablet hardness. All formulations satisfied the content uniformity of TBS and friability between 0.3-0.98% (Table 2).

Release profiles of TBS from the matrices containing different percentages of HPMC, Guar, and Xanthan are shown in Figure 1. Figure 2 shows the effect of combination of natural gums with HPMC

Table 4. Release parameters of tebutalin sulfate from different matrices (n=3). (MDT: Mean Dissolution Time, DE_8%: Dissolution Efficiency up to 8 hr of release test, and f_2: similarity factor)

Formulation code	MDT (min) ± SD	DE_8 (%) ± SD	f_2
H_8C_2	192.39±4.64	61.12±0.40	54.26
H_6C_4	66.15±11.21	84.83±1.66	23.48
H_4C_6	82.29±8.58	84.45±1.82	27.36
H_2C_8	33.25±1.60	94.92±3.12	18.67
G_8H_2	189.73±29.77	59.19±5.64	61.57
G_6H_4	144.25±23.43	67.06±0.47	50.52
G_4H_6	90.78±2.46	82.75±2.34	31.42
G_2H_8	151.48±9.93	70.53±1.61	50.41
G_4X_6	158.23±14.29	71.03±1.62	45.83
G_6X_4	114.17±19.15	73.56±1.96	43.25
G_8X_2	212.04±12.46	54.99±2.56	62.80
H_4X_6	173.73±6.51	63.18±2.15	62.05
H_6X_4	161.02±23.10	65.76±5.29	57.97
H_8X_2	244.41±5.511	49.45±0.78	48.91
H	190.52±17.86	55.72±1.65	62.94
G	200.11±4.90	58.36±0.95	67.25
X	218.10±4.09	54.96±0.64	58.35
$X_6H_2G_2$	177.73±5.44	63.81±0.97	61.62
$X_2H_6G_2$	184.65±4.91	64.16±0.72	64.04
$X_2H_2G_6$	171.51±4.59	65.53±0.60	61.64
Bricanyl	191.30±8.67	60.70±1.82	-

on drug release profiles. The curve fitting of release data to zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models followed by linear regression analysis are seen in Table 3. Release parameters of TBS tablets of different formulations are compared to Bricanyl® SR in Table 4.

In an effort to obtain some evidence for the relationship between release mechanism and water uptake and matrix mass loss kinetics additional studies were conducted. The mass loss and water uptake percentage of some formulations as functioning of time are depicted in Figures 3 and 4, respectively.

DISCUSSION

Different combinations of natural gums (G or X) with HPMC and also a triple mixture of these polymers were used to provide matrix tablets for SR of water-soluble TBS. A total 65% of release retardant polymer(s) was used in the formulations.

Figure 1 indicates an initial burst release of the drug from Guar and HPMC matrices, however, this is absent in Xanthan matrices. Such a burst effect was also observed by other investigators who suggested the addition of other hydro-colloids like HPMC in relatively large amounts (23).

Table 3 shows data analysis of release profiles according to different kinetic models. When HPMC is the only retarding agent drug release profile better fits with a Higuchi model. According to Peppas equation a value of n = 0.5 in indicates case I (Fickian) diffusion or square root of time kinetics, 0.5 < n < 1 anomalous (non-Fickian) diffusion, n = 1 Case-II transport and n > 1 Super Case-II transport (20). Examining data by Peppas equation also indicated the non-Fickian diffusion (Table 3). This polymer showed less mass loss (Figure 3) and water uptake (Figure 4) compared to natural gums. The hydration

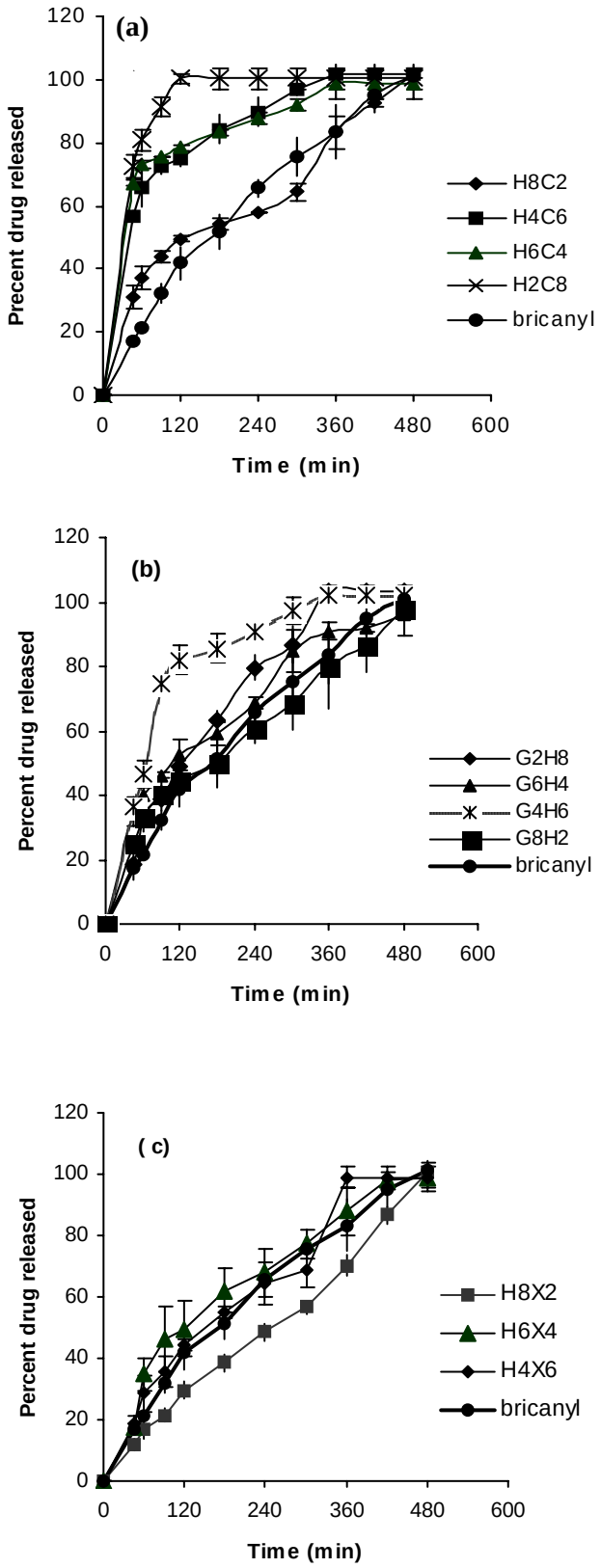

Figure 1. Release profiles of terbutalin sulfate from the matrices containing different percentages of (a) HPMC:CMC, (b) Guar gum and (c) Xanthan in phosphate buffer solution (n=3).

rate of this cellulosic polymer relates to its hydroxypropyl substitutes percentage. HPMC-K4M contains the greatest 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 like it to be used in SR formulations (24). Combination of HPMC with CMC in H_8C_2 showed the most similar release profile to Bricanyl® (Figure. 1a). This formulation and H_2C_8 also release the drug by a Higuchi model ($p < 0.05$) (Table 3), whereas changing the percentage of these polymers to H_6C_4 and H_4C_6 caused a first-order release kinetics with a diffusion mechanism (Table 3).

When Guar gum was used as the only retarding polymer a Higuchi model with a non-Fickian release mechanism (Table 3) is observed. In an effort to obtain some evidence for the relationship between release mechanism and water uptake and matrix mass loss kinetics additional studies were conducted. The Figure 3 indicates that Guar matrices have negligible mass loss (~7%) but a high water uptake (~60%) after 8 hr (Figure 4). Three processes of water penetration, gelatinization and diffusion rate have also been reported by Ughini et al. (25) as the rate-limiting steps for the release of water-soluble drugs with first-order release kinetics form Guar matrices. Al-Saidian et al. (26) reported a first-order kinetics via Fickian-diffusion for diltiazem HCl release from Guar gum matrix tablets. In most formulations of HPMC and Guar combination, drug release kinetic is predominantly a Higuchi model kinetic ($P < 0.05$) via non- Fickian diffusion (Table 3). As HPMC and Guar are both hydrophilic colloids and water-soluble, dissolve and form pores filled with liquid in which drug can thereafter diffuse (27). However, in G_4H_6 the Hixon-Crowell kinetic and in G_2H_8 the relaxation or super-case II mechanism seems better fit with

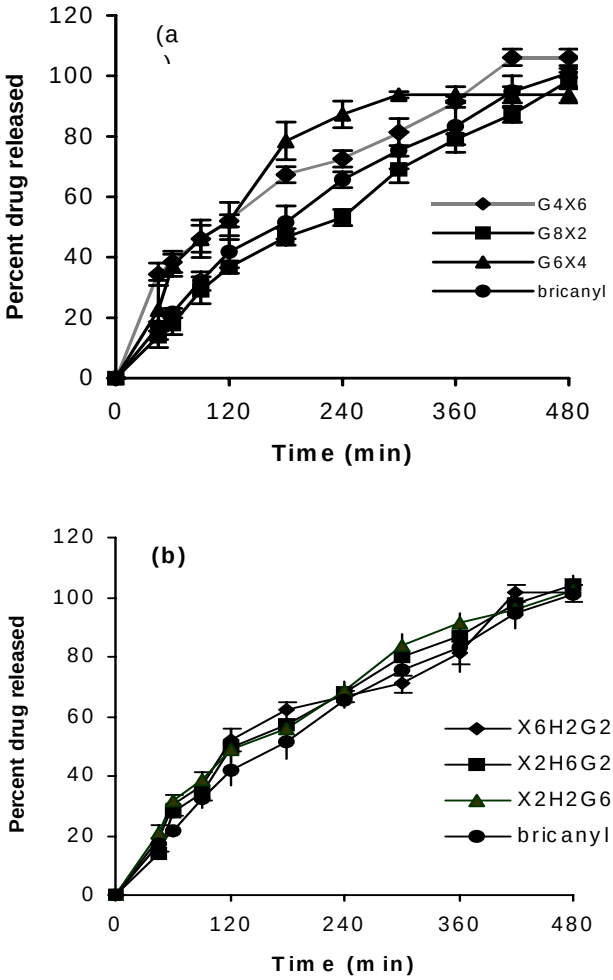

Figure 2. Release profiles of terbutalin sulfate from the matrices containing combination of (a) natural gums or (b) triple mixture of natural gums with HPMC in phosphate buffer solution (n=3).

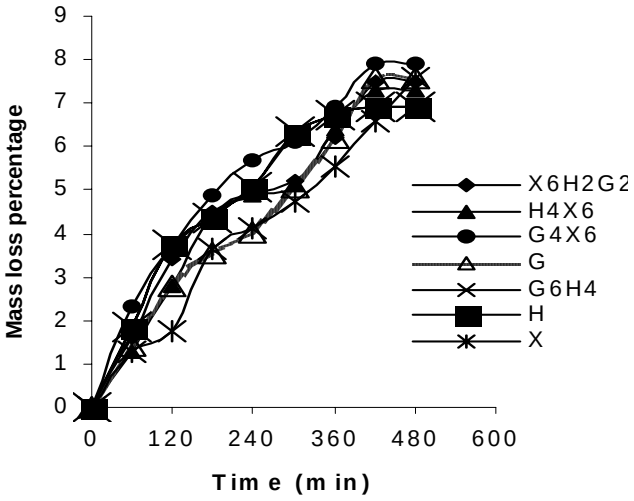

Figure 3. Mass loss percentage with time of some formulations of matrix tablets of terbutalin sulfate (n=3).

release data (Table 3).

Table 3 also shows that when Xanthan is used as the only retarding hydrophilic polymer, drug release follows a Higuchi model with a non-Fickian diffusion mechanism (Table 3). However, our previous studies (28) with Xanthan gum, showed that the drug release from this microbial exocellular polysaccharide follows zero-order or almost time–independent release kinetics, which is in accordance with findings of others (29-31). In high concentrations of Xanthan combined with HPMC (H_4X_6), the most similar release profile with the standard tablet was seen (Fig. 1c). This formulation along with lower concentration of Xanthan in H_8X_2 showed a zero-order release kinetic with a super-case II mechanism (Table 3). However, H_6X_4 showed a non-Fickian mechanism (Table 3).

In combination of Xanthan with Guar the most similar profile to Bricanyl ® was seen in G_4X_6 (Figure 2a). With the exception of X_8G_2, which showed a zero-order release kinetic and a non-Fickian diffusion, other combinations of these polymers showed the Higuchi release model. Triple mixtures of Xanthan, Guar and HPMC also showed a zero-order release kinetics. Bricanyl that was used as a reference formulation followed the Higuchi release model with a non-Fickian diffusion of the drug (Table 3).

Comparing the MDT and DE_8% of tablets consisting double combination of polymers (natural and / or cellulosic) with a two–way ANOVA test showed that the type of the combination of two polymers, the ratio of the two polymers and also their interaction, had main effects on MDT and DE_8% ($p < 0.05$). This test showed that the combination of a Xanthan gum with HPMC leaded to a greater MDT compared to two natural gums (Table 4) in the order of: HX > GX > GH = HC. The two–way ANOVA test also showed that in all types of the polymers the higher ratios caused the greater MDT of TBS: 80:20 > 40:60 > 60:40 (Table 4). A reverse order of the effect of double combination of polymers was seen on the DE_8%, i.e., HC > GX > HX = GH and 60:40 > 40:60 > 80:20 (Table 4). As Table 4 indicates the greatest and the least MDT relates to Xanthan and cellulosic polymers, respectively ($p < 0.05$) (Table 4).

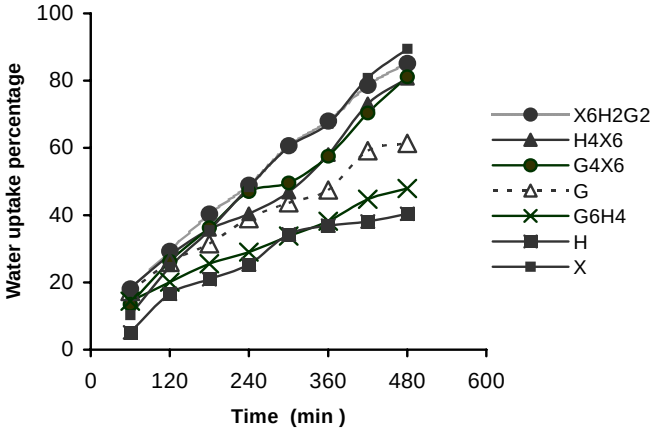

Figure 4. Water uptake percentage (x 0.1) with time of some formulations of matrix tablets of terbutalin sulfate (n=3).

The overall rate of release of TBS from HPMC:CMC matrices was significantly higher than that from Xanthan and Guar matrices ($p < 0.05$), which also indicated the smallest MDT for H_2C_8 (33.25 ± 1.60 min) and the highest MDT for H_8X_2 and G_8X_2 matrices (244.41 ± 5.11 and 212.04 ± 12.46 min respectively) (Table 4). These results clearly indicated that Xanthan and Guar had higher drug retarding ability than HPMC:CMC. However, because of the low compressibility of Guar tablets (Table 2) it seems that Xanthan is a better retarding agent for TBS. Bhalla et al. (23) also reported that Guar gum is not able to retard salbutamol release when used alone. However, Altaf et al. (32) showed Guar gum-based matrix tablets represent sustained-release properties for diltiazem. HPMC alone showed the most similar MDT to Bricanyl® (Table 4). Formulations of the mixture of three polymers are capable to retard drug release considering their MDT and all of them show f_2 (similarity factor) of greater than 50.

Formulations with f_2 factor between 50-100 indicated the most similar formulations to TBS. $X_2H_6G_2$ showed greater MDT compared to the other triple mixtures of polymers ($p < 0.05$) (Table 4). However, it doesn't seem to be any synergistic effect between them as there are other formulations with two polymers or even one that showed greater MDT and f_2 values (Table 4). H_8X_2 also showed the least DE_8% while H2C8 had the greatest DE_8% ($p < 0.05$) (Table 4).

Xanthan has higher drug retarding ability than Guar gum. The combination of each natural gum with HPMC leads to a greater retarding effect compared to a mixture of two cellulosic polymers. No synergistic effect was seen for triple mixtures of polymers. H_8X_2, G_8X_2, H_4X_6 and H_6X_4 can retard TBS release. However, according to the similarity factor (f_2), G_8X_2, H_4X_6 and H_6X_4 were the most similar formulations to Bricanyl® SR. Although G_8X_2 and H_4X_6 released the drug with a zero-order model, H_6X_4 like Bricanyl® followed the Higuchi model.

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