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Research Article

USING CHITOSAN AND NATURAL POLYMER MIXTURES AS RELEASE RETARDING POLYMERS IN SUSTAINED RELEASE MATRIX TABLETS OF VENLAFAXINE HCL

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ABSTRACT

Sustained release matrix tablets were produced using single natural polymer xanthan gum (XG), guar gum (GG) and different binary mixtures of Chitosan (CH) /XG and GG ratios. These hydrophilic polymers were used to control the release of the drug Venlafaxine HCl. Drug (D), XG/GG and CH/XG, GG were investigated at different ratios of 1:2.8, 1:1, 1:4 and 4:1 respectively. The tablets were prepared by the wet granulation method. The tablets were evaluated for hardness, weight variation, thickness, friability and drug content and found to be within the limits. *In-vitro* drug release was carried out using distilled water. The drug release mechanism was studied. Compared with single polymers, Chitosan –xanthan gum based system caused a further slowdown of the drug release rate. Among them, CH –XG matrix system at 1:4 ratios exhibited the best-sustained release behavior. Fourier transform infrared spectroscopy (FTIR) studies demonstrated that polyelectrolyte complexes (PECs) were formed on the tablet surface, which played an important role in retarding erosion and swelling of the matrix. In conclusion, this study demonstrated that formulation CH/XG (1:4) showed a better-sustained release of Venlafaxine HCl with the desired rate. Thus Chitosan – xanthan gum at 1:4 ratio seems to be a potential release retardant material for sustained drug delivery of Venlafaxine HCl.

INTRODUCTION:

Polymer-based monolithic matrix tablets are most commonly used to fabricate oral extended-release dosage forms because of the economic benefits, the relative simplicity of process development and scale-up procedures. For decades, hydrophilic matrices have been widely utilized to prepare matrix tablets [1]. The use of hydrophilic polymers for sustained drug delivery has attracted the attention of investigators in recent years. Among the hydrophilic polymers, natural polysaccharides are preferred due to their nontoxicity, biocompatibility, biodegradability and acceptance by

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the regulating agencies [2]. Polysaccharide hydrogels that swell in an aqueous medium have been widely used to formulate extended- release tablets. The release of drugs from swellable systems usually depends on one (or) more of the following processes: wetting of the polymer matrix by the solvent, swelling of the polymer, diffusion of drug through the hydrated polymer, dissolution of the drug in the solvent and erosion of the polymer [3]. Blending different hydrophilic polymers improve the physicochemical and release modifying properties of the resultant property of the resultant polymer, leading to the design and formation of an optimized controlled-release product and the proper selection of polymers can help to control the release profile of drugs [4].

Chitosan refers to a series of polymers that are deacetylated derivatives of the natural polysaccharide, chitin, with different degrees of deacetylation and molecular weights. Although Chitosan is a very promising polymer for use as carrier material in drug delivery systems, it has a limited capacity for controlling drug release from oral dosage forms due to its fast dissolution in the stomach [5]. To overcome these disadvantages, many researchers have investigated the Interpolymer complexes IPC of Chitosan with other anionic polymers like sodium alginate, carrageenan, hyaluronate sodium, pectin and polyacrylic acid for controlled release formulations. Drug release from tablets containing physical mixtures of polymers will form in-situ polyion complexes that afford more sustained effect. Bhise et al founded that, minimum drug release was observed for Naproxen from matrices containing a physical mixture of Chitosan and k-carrageenan at acidic and alkaline pH and this may be due to the formation of in-situ polyelectrolyte complexes that could be suitable for sustained drug delivery [6]. Controlled release matrix tablets of Diltiazem and ibuprofen have been prepared by a three-dimensional network inter polyelectrolyte complex between Chitosan and polycarbophil [7]. It was reported that when Chitosan (CS) - sodium alginate (SA) physical mixture was used as the matrix to prepare tablets, in situ polyelectrolyte complexes (PEC's) could be formed on the surface of the tablets in the simulated gastrointestinal fluid due to self-assembly or spontaneous association. However, drug release from CS-SA based system obvious drug solubility dependence and is not suitable to control the release of highly water soluble drugs [8].

We expected to achieve this objective by choosing natural polymers alone and also used in combination of Chitosan to control the release of a highly water-soluble drug. Xanthan gum and Guar gum were chosen for the present study since these polymers have proven to be effective in sustaining the drug release from a matrix system. Xanthan gum is an anionic high molecular weight polysaccharide produced by fermentation by the microorganism *Xanthomonas campestris*. It has a β-(1→4)) D-glucose backbone where second glucose unit is attached to a trisaccharide consisting of mannose, glucuronic acid, and mannose. The negatively charged carbohydrates from glucuronic acid allow it to form highly viscous fluids at appropriate pH. Guar gum is a natural polysaccharide obtained from the endosperms of *Cyamopsis tetragonolobus (L.)*. It is composed of linear chains of D-galactose and D-mannose, with a ratio of between 1:1.4 and 1:2, which may be described chemically as a galactomannan. When guar gum is used in contact with water, it swells almost immediately and forms a highly viscous, thixotropic sol [9, 10].

Venlafaxine hydrochloride, a novel third-generation antidepressant mainly acting by selectively inhibiting the uptake of serotonin and noradrenaline was selected as a challenging model in the current study. Due to high water solubility, first pass metabolism, low bioavailability, and short half-life, extended release formulation of Venlafaxine hydrochloride become a prime requirement to eliminate multiple daily dosages and minimize side effect [11]. Therefore, the aim of the current study was to design extended release oral matrix tablets of venlafaxine hydrochloride using varying physical mixtures of Chitosan, Xanthan gum, and Guar gum. The objective was to enhance the release retarding property of the polymers leading to the formation of an optimized formulation of the highly water soluble drug.

1. MATERIALS AND METHODS

2.1 Materials

Venlafaxine hydrochloride was purchased from Hermes chemical company Pvt, Ltd,

Hyderabad. Xanthan gum and Guar gum from Vasundhara Industries, Rajasthan. Di basic Calcium chloride, Chitosan, Isopropyl alcohol and PVP K-90 from Sisco Research Laboratories Pvt. Ltd. (SRL), Hyderabad, India was used. All other materials were of analytical or reagent grade.

2.2 Preparation of matrix tablets

Three groups of tablets were prepared as shown in Table 1. In the first group, the drug was compressed with xanthan gum (XG) or guar gum (GG) in a drug to polymer ratio (D: P) of 1:2.8 and labeled F1 and F2, respectively. In the second group, the drug was compressed using different binary mixtures of Chitosan (CH) and (XG) (1:1, 1:4 and 4:1 and labeled F3, F4, and F5, respectively). In the third group, the drug was compressed using different binary mixtures of Chitosan (CH) and (GG) (1:1, 1:4 and 4:1 and labeled F6, F7, and F8, respectively).Wet granulation technique was used to prepare matrix tablets. The above ratios of F1, F2, F3, F4, F5, F6, F7 and F8 were mixed well in a mortar using a spatula and the mixture is passed through sieve #44. The granules were prepared by utilizing PVP K-90 (5% w/v in Isopropyl alcohol). Then the wet mass was passed through sieve #16. The wet granules were air dried for 2 h. The granules were then sized by sieve #22. Tablets were compressed using a multistation rotary punching machine using 9-mm diameter punch. The hardness of the tablet and was adjusted to 5-6 kg/cm^2.

2.3 Evaluation of Tablets

2.3.1 Physical evaluation

The flow properties of the prepared granules were determined by the angle of repose (θ), by using fixed funnel method. The bulk and tapped densities for the prepared granules were determined by tapping method and the compressibility index was calculated by using the data. The tablets were evaluated for thickness, diameter, weight variation, hardness, friability using the reported procedure. The thickness and diameter of the tablets were carried out using vernier calipers. Weight variation was performed according to the U.S.P procedure. Hardness was determined by using a Monsanto hardness tester. Friability was determined using Roche friability testing apparatus [12].

2.3.2.**Drug content estimation:**Ten tablets containing Venlafaxine hydrochloride were crushed to a fine powder with the help of mortar and pestle. Weigh accurately a quantity of powder equivalent to 75 mg of venlafaxine hydrochloride, transfer to a 100ml volumetric flask and add about 10 ml of purified water, mix and sonicated for 2 h. Water was added slowly until the clear solution was obtained. The final volume was made up to 100 ml with purified water. This was filtered through what man filter paper No.41 and suitably diluted. Drug content was determined by using double beam UV-spectrophotometer (Shimadzu) at 225nm. The drug content was calculated using the standard plot concentration versus absorbance [13].

2.3.2 *In-vitro* dissolution studies

In-vitro drug release study (n=3) was carried out in a USP dissolution apparatus I (Electrolab) in 900ml of distilled water at 37°C±0.5°C. Five ml samples were pulled at predetermined times. The drug solution was replaced with an equal volume of distilled water. The samples were diluted with water and analyzed at 225nm using UV-visible spectrophotometer (Shimadzu) [14].

2.3.3 Kinetics of drug release

In order to investigate the kinetics of drug release from matrix tablets, the data of *in-vitro* drug release were fitted to zero order, first order, Higuchi equation and Korsmeyer - Peppas model.

$Q = Q_0 + k_0 t$ (Zero Order)

$lnQ = lnQ_0 + k_1 t$ (First Order)

$Q = k_H t^{1/2}$(Higuchi model)

$Q/Q_T = k_{kp} t^n$ (Korsmeyer-Peppas model)

Where Q amount of drug release at time t, Q_0 Is the initial amount of drug, Q_T Is the total amount of drug release. k_0, k_1, k_H And k_{kp} Are the constants of Zero order, first order, Higuchi, Korsmeyer- Peppas models, respectively, and n is the release exponent[4].

2.4 Fourier transform infrared (FTIR) spectroscopy

FTIR studies were performed by using the following method; an approximately minimum quantity (less than 4 mg) of the sample was thoroughly blended with an adequate quantity of IR grade KBr (less than 100 mg) in the mortar. The mixture was then made into KBr pellets by hydraulic compression lever. The

samples were analyzed in an FTIR spectrophotometer using KBr pellet [15].

2.5 Erosion and swelling behavior of the optimized formulation

The erosion and swelling behaviors of the developed matrix system were evaluated simultaneously by measuring the amount of water uptake and weight loss in a dissolution tester. Three tablets were used per time point. At the predetermined time, the tablets were lightly patted with tissue paper to remove excess surface water. The swollen weight of the tablets was determined (Ts) and then the same tablets were dried in a vacuum oven at 40 °C for 48 h, the remaining dry weight of the tablet (Tf) was determined. The study was carried out in triplicate. Swelling (%) and erosion (%) was calculated using Eq 1 and 2, respectively [16].

Swelling (%) = (Ts – T) /T x 100…... (1)

Where this is the weight of the swollen tablet and T is the initial of the tablet, i.e., prior to the test.

Erosion (%) = (T – Tf) /Tf x 100…... (2)

Where T is the initial weight of the tablet and Tf is the weight of the tablet after the erosion test.

3 RESULTS AND DISCUSSION

3.1 Physical properties of powdered blends

The granules of eight formulations (F1 to F8) were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio showed in Table 2. It was found that formulations F1, F2, F3and F6, the granules has excellent flow property as they showed the angle of repose value less than 30, whereas formulations F4,F5,F7and F9 represents good flow property. Carr's index value was found to be less than 15 showing good flow property except formulation F4, F5, F7and F9 which showed 16.94, 18.87, 16.00 and 20.11 respectively. Hausner's ratio was found to be less than 1.12 -1.18 showing good flow property except formulation F4, F5, F7and F9 which showed 1.20, 1.23, 119 and 1.25 respectively.

3.2 Physical properties of matrix tablets

Formulated matrix tablets were evaluated for physical parameters such as hardness, thickness, weight variation, friability, drug content, the results were shown in Table 3. The total weight of each formulation was maintained constant; the weight variation of the tablets was within the permissible limits. According to IP specification, for tablets weighing more than 250 mg, ±5% deviation from the mean weight is acceptable. The weight of the tablet was fixed at 300 mg and was maintained for all the formulations in order to minimize the effect of weight on the drug release because the effect of retardant/polymer concentration is the only area of interest. Tablet hardness varies from 4.9 to 5.93 Kg/cm^2. Tablet thickness was also used to assess the quality of the tablets. The thickness of matrix tablets ranged from 4.22 to 4.33 mm. Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion less than 1%. The drug content in all formulations was calculated and the presence of active ingredient ranged from 98.4 to 101.6%.

3.3 *In-vitro* dissolution studies

In-vitro dissolution studies were performed in distilled water and the results depicted in Table 4. The release profiles of formulations F1, F2 made with xanthan gum or guar gum as a single release retardant material could sustain the release of the drug up to 24 h and 16 h and released 89.3 and 90 % respectively as shown in Fig. 1. These formulations F1, F2 containing single release retardant material matrix tablets resulted in a rapid release of the drug after 2 h, may be due to the high solubility of the drug, differences in the hydration behavior and molecular interactions of the hydrophilic polymers in the matrices. In case of formulations F3, F4 and F5 containing different binary mixtures of Chitosan and xanthan gum as release retardant material sustain the release the drug up to 24 h and 20 h and released 82.1 (24 h), 71.25 (24 h) and 93.68 % (20 h) respectively as shown in Fig. 2. Among these formulations F5 showed rapid release of the drug after 2 hours and could not able to sustain the release up to 24 h, the drug release from this formulation F5 matrix tablets, containing Chitosan and xanthan gum in the ratio of 4:1 could be attributed due to the high solubility and poor swelling property of Chitosan when compared with formulation F3. The strong synergistic interactions between Chitosan and xanthan gum in formulations F3 and F4 containing Chitosan and xanthan gum in the ratio of 1:1 and 1:4 resulted in the formation of a network with decreased porosity able to retard the dissolution of the drug (Adnan Badwan et al., 2014) up to 24 h.

Table 1: Composition of different formulations of Matrix tablets using D: P and CH: XG/GG ratios

Formulation code	Quantity of ingredients (mg)						Total (mg)
	Drug (D)	Chitosan (CH)	Xanthan Gum (XG)		Guar Gum (GG)	PVP K-90	
F1 (1:2.8) /(D: XG)	75	-	210		-	15	300
F2 (1:2.8) /(D: GG)	75	-	-		210	15	300
F3 (1:1) / (CH: XG)	75	105	105		-	15	300
F4 (1:4) / (CH: XG)	75	42	168		-	15	300
F5 (4:1) / (CH: XG)	75	168	42		-	15	300
F6 (1:1) / (CH: GG)	75	105	-		105	15	300
F7 (1:4) / (CH: GG)	75	42	-		168	15	300
F8 (4:1) / (CH: GG)	75	168	-		42	15	300

Table 2: Results of physical properties of powdered blends

Formulation code	Angle of repose (°) [a]	Bulk density (gm/ml) [a]	Tapped density (gm/ml) [a]	Carr's Index (%)[a]	Hausner's ratio
F1	23.73±1.62	0.3135±0.001	0.3625±0.001	13.51±0.18	1.15±0.002
F2	24.53±1.30	0.3184±0.001	0.3679±0.001	13.44±0.28	1.15±0.003
F3	25.49±0.71	0.3187 ± 0.003	0.3664 ±0.001	13.01 ±0.78	1.16 ±0.01
F4	31.15±2.18	0.3145 ±0.001	0.3786 ±0.001	16.94 ±0.25	1.20 ±0.003
F5	32.02±1.43	0.3158 ±0.002	0.3893 ±0.001	18.87 ±0.48	1.23 ±0.007
F6	25.02±0.75	0.3033±0.002	0.3551±0.002	14.57±0.86	1.17±0.011
F7	31.53±0.59	0.3165±0.001	0.3768±0.002	16.00±0.40	1.19±0.005
F8	32.86±0.78	0.3175±0.001	0.3975±0.003	20.11±0.70	1.25±0.011

[a] (Mean ± SD), n=3

Table 3: Results of physical properties of matrix tablets

Formulation code	Weight Variation (mg)[a]	Hardness (Kg)[b]	Thickness (mm)[b]	Friability (%)[c]	Drug Content (%)[c]
F1	0.303±0.007	5.26±0.50	4.25±0.04	0.66±0.05	98.4±1.11
F2	0.299±0.001	5.03±0.20	4.33±0.07	0.46±0.05	101.6±2.80
F3	0.297±0.004	5.13±0.07	4.22±0.02	0.45±0.02	99.3±1.52
F4	0.295±0.013	4.97±0.06	4.25±0.01	0.51±0.02	100.3±1.15
F5	0.29±0.006	5.93±1.28	4.24±0.05	0.49±0.01	101.7±1.15
F6	0.3±0.001	4.9±0.1	4.22±0.04	0.66±0.04	99.6±1.52
F7	0.299±0.009	4.9±0.35	4.23±0.01	0.59±0.01	100.7±0.57
F8	0.302±0.006	5.06±0.25	4.24±0.02	0.36±0.02	100.2±0.76

[a] (Mean ± SD), n=20; [b] (Mean ± SD), n=6; [c] (Mean ± SD), n=3

Table 4 Results of *In-vitro* dissolution studies of matrix tablets

Time (hrs)	Mean % drug release[a]							
	F1	F2	F3	F4	F5	F6	F7	F8
1	30.7±1.42	37.9±0.92	28.3±3.18	24.9±1.8	31.17±4.9	36±1.97	31.2±2.1	33.6±1.2
2	36.8±1.21	39.5±0.62	31.2±2.56	28.2±2.7	44.15±7.5	38.45±1.93	39.15±1.95	46.5±0.3
4	50.0±2.83	58.8±1.58	37.9±0.91	41.85±0.45	58.3±9.8	49.6±1.42	52.65±4.35	68.25±1.65
6	57.0±6.53	71.3±2.04	46.0±1.13	45.15±1.05	66.25±11.2	61.1±1.51	63.00±2.1	78.6±0
8	70.9±7.78	79.7±2.11	55.8±1.37	52.05±0.15	74.62±13	70.4±0.92	71.7±1.8	82.9±1.95
12	80.3±2.25	89.1±0.79	69.1±2.69	58.8±2.1	83.37±14.8	86.6±1.71	82.3±0.15	98.1±13.5
16	85.5±1.31	90.0±0.9	74.6±1.21	61.5±0.9	89.17±16	92.2±1.21	87.45±1.05	
20	87.1±0.91		78.1±1.51	67.95±2.25	93.68±18.1	94.5±1.59		
24	89.3±0.34		82.1±0.75	71.25±1.95				

[a] (Mean ± SD), n=3

Table 5: Release kinetics of matrix tablets

Formulation	Zero Order	First Order	Higuchi	Peppas- Korsemeyer	
Code	R	r	r	r	n
F1	0.854	0.957	0.950	0.979	0.363
F2	0.860	0.956	0.945	0.954	0.361
F3	0.931	0.982	0.978	0.969	0.373
F4	0.902	0.965	0.976	0.984	0.344
F5	0.872	0.996	0.965	0.984	0.363
F6	0.926	0.988	0.975	0.968	0.364
F7	0.845	0.965	0.948	0.981	0.355
F8	0.908	0.928	0.976	0.986	0.434

r= Correlation coefficient, n=Diffusional exponent

Fig.1-Influence of single release retardant material on the release of drug Venlafaxine HCl from matrix tablets

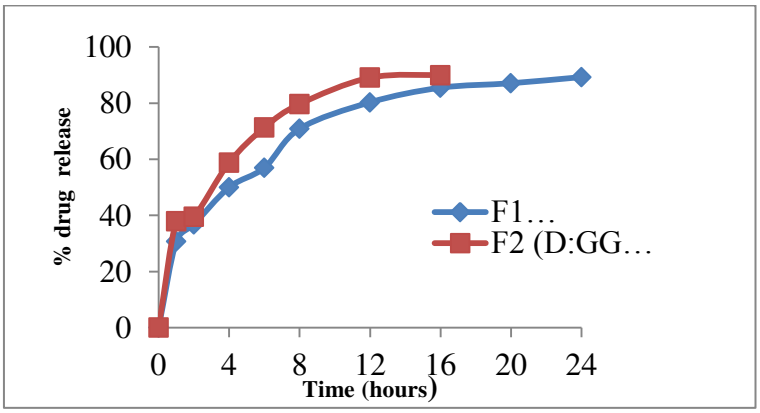

Fig.2 -Influence of Chitosan and xanthan gum ratio on the release of drug Venlafaxine HCl from matrix tablets

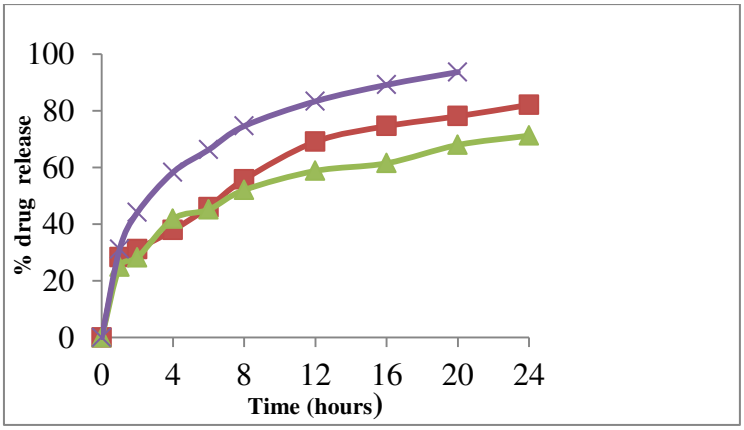

Fig.3 -Influence of Chitosan and guar gum ratio on the release of drug Venlafaxine HCl from matrix tablets

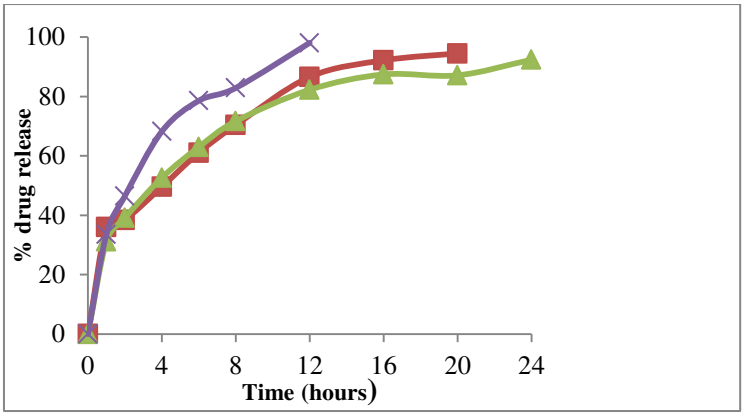

Fig.4 –FTIR spectra of physical mixture of CH: XG 1:4

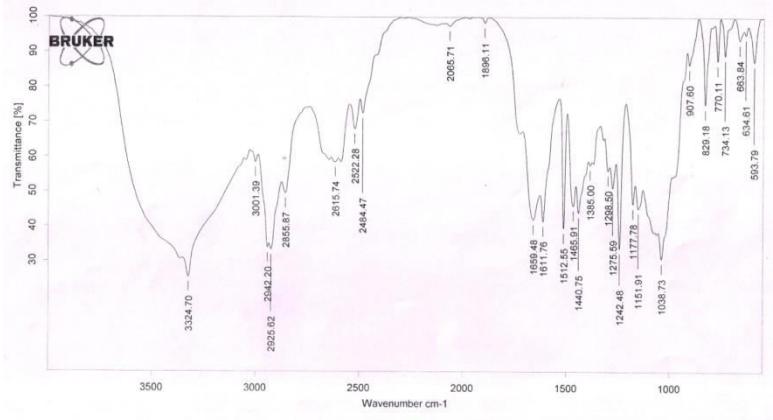

Fig.5 –FTIR spectra of the outer film of swollen tablets at 24 hours with CH:XG 1:4

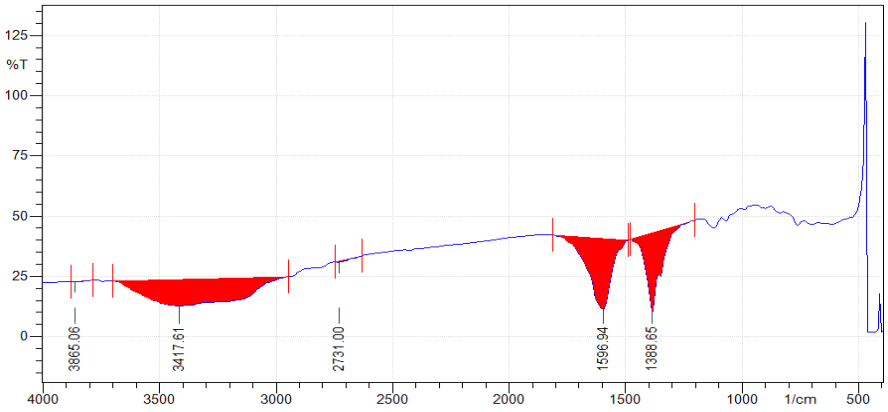

Fig.6 – Erosion and swelling behavior of CH: XG 1:4 based matrix tablets, a: Swelling ratio; b: Remaining ratio.

Formulations F6, F7, and F8 containing different binary mixtures of Chitosan and guar gum as release retardant material sustain the release of the drug up to 20 h, 16 h, and 12 h released 94.5, 87.45 and 98.1% respectively as shown in Fig. 3. Among these formulations, F8 showed a rapid release of the drug after 2 hours and able to sustain the release up to 12 h. In the case of formulation F7 matrix tablets, containing Chitosan and guar gum in the ratio of 1:4, the release was sustained up to 16 h. This is due to the hydrophilic nature of guar gum polymer, and its rate of hydration has increased by the rise of its concentration, resulting in a decreased dissolution rate. But when Chitosan and guar gum was used in the ratio of 1:1, showed sustained release of drug up to 20 h only when compared with F3 and F4, this due to nonavailability of ionic interactions of nonionic guar gum with Chitosan.

3.4 Kinetics of drug release

Release kinetics is an essential aspect of drug formulation development and kinetic data are employed in setting *In vivo- In vitro* correlation (IVIVC) of dosage forms. The kinetic model with the highest correlation coefficient value (r) was selected as the model that best described the dissolution data[4]. Table 5 present the kinetics of drug release of all matrix tablets respectively. The drug release from all matrix tablets using single release retardant material and different binary mixtures of Chitosan, xanthan gum, and guar gum followed first order kinetics indicated by "r" values (0.928-0.996), which were slightly higher when compared to those of zero order release model (0.845-0.931). When percent drug remaining was plotted against time on a semi-logarithmic graph, straight lines were obtained for all matrix tablets indicated that the release pattern followed first order kinetics. The plots of log mean percent of drug released versus log time of all matrix tablets were found to be linear. The "r" values of these matrix tablets are very nearer to one further indicating peppas- korsemeyer equation was more suitable for explaining the release kinetics and the diffusional exponent (n) values were ranging from 0.344 to 0.434 indicating the release mechanism followed Fickian diffusion. It was found that all matrix tablets, followed the Higuchi model (r=0. 948-0.978) to describe the drug dissolution. The results of the study indicated that the release of drug from the entire matrix tablets, followed first order kinetics via Fickian diffusion.

3.5 FTIR Studies

Based on the literature, it was found that the polyelectrolyte complex (PECs) was formed on the tablet surface of Chitosan – sodium alginate based and Chitosan- xanthan gum based matrix tablets during the dissolution process. (Shirui Mao et al., 2015). In our study, FTIR was applied to characterize the physicochemical properties of the film collected from the dried tablet surface. In the spectrum of the physical mixture of CH: XG 1:4, the characteristic peak at 1659 $cm^{-1}$and 1611 cm^{-1} corresponds to symmetric NH_3^+ (N-H bend) and the carbonyl group respectively was shown in Fig 4. Meanwhile, a broad peak around 1590 cm^{-1} has appeared in the spectrum of outer film of swollen tablet at 24 hours with CH/XG 1:4 in Fig 5, which may be assumed to be the overlapped peak of carbonyl and NH_3^+ peak, indicating that the CH/XG ionic polyelectrolyte complex was formed[17].

3.6 Erosion and Swelling behavior

It is well known that swelling and erosion are two mechanisms influencing drug release from hydrophilic matrices. Therefore, first of all, swelling and erosion properties of these matrix tablets were characterized before any drug release studies [3]. The release of Venlafaxine HCl from CH/XG 1:4 matrix tablets occurred largely because of swelling mechanism rather than by an erosion mechanism. Initially, the matrix tablets of formulation F4 exhibited fast swelling behavior in the first 6 hours at a swelling rate 48.2% per hour (swelling ratio 411.9%). Thereafter, the swelling rate slows down gradually during 6-24 hours. As shown in the Fig 6, erosion was fast at the early stage with the erosion rate approximately 3.3% per hour in the first 6 hours. Thereafter, erosion rate was extremely slow down and had no significant decrease was observed in the following time period.

Shirui Mao et al., 2015 demonstrated that polyion complex formation in Chitosan and xanthan gum layer prevented over swelling, strengthened the wet matrices and sustained the drug release. Hence, in our study results indicated that erosion mechanism had no significant effect on drug release, whereas significantly increased and decreased swelling ratio due to formation of polyion complex gum layer on the surface of Chitosan- xanthan gum tablet surface exhibited the retardation of drug release from the matrix tablets of formulation F4.

4. CONCLUSION

In conclusion, the present work showed that a binary mixture of naturally hydrophilic polymers, i.e., Chitosan and xanthan gum could be used to produce sustained release formulations. Among them, CH-XG at 1:4 ratio based matrix system exhibited the best-sustained release behavior. Fourier transform infrared spectroscopy studies demonstrated that polyelectrolyte complexes (PECs) were formed on the tablet surface. The PECs played an important role in retarding erosion and swelling of the matrix, and therefore drug release. Thus, the Chitosan- xanthan gum based matrix tablets seems to be a potential candidate for sustained drug delivery

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