Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 2, 2015

Original Article

COMPARATIVE EVALUATION OF XANTHAN, GUAR AND TREATED GUAR GUMS AS DRUG RELEASE BARRIERS IN ORAL MATRICES

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Received: 26 Nov 2014 Revised and Accepted: 20 Dec 2014

ABSTRACT

Objective: This study addresses comparative efficiency of three natural gums, namely, xanthan gum, guar gum and thermally treated guar gum, as drug release barriers for sparingly and free water soluble model drugs.

Methods: guar gum, xanthan gum or thermally primed treated guar gum (as matrix forming gum) were each used with microcrystalline cellulose (as supportive polymer) and either Propranolol-HCl, as a water soluble drug or Diclofenac-Na, as a water insoluble drug, to produce a series of matrix formulations using direct compression. Matrices were then qualified for friability, hardness, and drug release attributes.

Results: With an exception to guar gum based matrices which measures very low hardness, all matrices were found within the acceptable limit or criteria for friability and hardness. Guar gum demonstrated more ability to sustain the release of loaded drugs as compared to other gums. Although both drug solubility and gum type were shown to influence drug release profiles of investigated matrices, only drug solubility demonstrated to affect the kinetics of drug release, especially with xanthan gum matrices.

Conclusion: Compared to treated guar and xanthan gums, guar gum can be effectively used to fabricate sustained release matrices for both water soluble and insoluble drugs.

Keywords: Guar gum, Treated guar gum, Xanthan gum, Matrices, Propranolol-HCl, Diclofenac-Na.

INTRODUCTION

In pharmaceutical applications, natural gums have many advantages over synthetic ones because of their biodegradability, biocompatibility, low cost, local availability and better patient tolerance properties [1]. Both guar and xanthan gums are natural polysaccharide that are used as excipients in many pharmaceutical formulations and food products. Treatment of guar gum is reported to produce a treated gum with enhanced properties for pharmaceutical application [2,3]

Pharmaceutical applications of xanthan and guar gums cover a wide range of utility in conventional drug products [1,4] and many attempts concerning application of the two gums, as individual or in combination, for novel drug delivery have been reported [5-7].

Although numerous researches dealing with individual evaluation of xanthan or guar gum for pharmaceutical applications have been cited [8-11], studies concerning comparative evaluation of xanthan and guar gums as drug release barriers are little [12,13].

Based on the nature of their molecular structure, xanthan (anionic), guar gum (nonionic), thermally treated guar gum (nonionic with low molecular weight) are expected to reveal different effects on physical performance of fabricated oral controlled drug delivery matrices as a consequence of their disparate hydration, swelling, gel strength and erosion characteristics.

The objective of this study is to evaluate, in a comparative manner, xanthan gum, guar gum and thermally treated guar gum as drug release barriers in matrix tablets using Diclofenac-Na and Propranolol-HCl as sparingly and free water soluble model drugs, respectively. It should be emphasized that, the objective of the present study aims at adding knowledge on interchangeability between guar and xanthan gums as matrix forming agents, moreover, it provides a chance to study the comparative performance of native and thermally treated guar gum as drug release barriers, a topic which have received a little interest among formulation scientists in the past.

MATERIALS AND METHODS

Materials

Diclofenac-Na and Xanthan gum were pharmaceutical grade products of Shin Poong Pharmaceutical Co. (South Korea) and were generously donated by General Medicine Company (Sudan). Propranolol-HCl HCl was a pharmaceutical grade product of United Pharma Industries Co. (China) and was made available by Abdel Moniem Medical Industries (Sudan). Guar gum was a pharmaceutical grade product of Nanjing Co, (China).

Treated guar gum, was obtained by thermal processing of guar gum. Microcrystalline cellulose (Avicel® 101) was a Pharmaceutical grade product of JRS Pharma (Germany) and was kindly received as a gift sample from Amipharma Laboratories (Sudan). Mg stearate was a product of Huzhou Zhanwang Pharmaceutical (China). Other materials and reagents were either analytical or pharmaceutical grade obtained from different commercial sources.

Preparation of thermally treated guar gum [2, 14]

Known weight of guar gum was wetted with a small amount of absolute ethanol (0.5 ml ethanol per 100mg guar) and then dispersed in pH 6.0 phosphate buffer (KH_2PO_4 and Na_2HPO_4) containing 0.2M NaCI using a magnetic stirrer. Obtained solution was then heated at 70 ^oC for 10 minutes and the resultant content was dried in hot air oven to obtain thermally treated guar gum.

Preparation of matrices

A total of six matrix batches were made-up (Table 1). For each batch, ingredients equivalent to 400 matrix tablets were sequentially passed through sieve number 80, weighed (Electronic balance (ABS 120-4, Germany), thoroughly mixed for 10 minutes using mortar and pestle, lubricated with 1% Mg stearate and then directly compressed into tablets using single punch tablet machine equipped with size 9 mm flat faced punches (Cadmach machinery Co. India). In all formulation runs, drug: natural gum and MCC: natural gum ratios were fixed as 1:0.5 and 1:1, respectively. Produced matrix tablets

contained 100mg of loaded model drug and weighed in average 202mg.

Matrix tablets' characterization

Produced tablets within all batches were subjected to hardness, friability and drug release characterizations.

Friability and hardness attributes

Matrix tablets within all runs were subjected to the official friability and hardness testing of Ph. Eur [15]. A total of 20 tablets from each produced tablets batch were weighed and placed in the drum of tablet friability tester (Erweka GmbH, Germany) that operates at 25 round/min for 4 minutes. After dedusting, tablets were weighed and the friability was calculated using the average % loss from the two drums. For the diametrical crushing strength (hardness) test, 10 tablets from each formulation runs were tested in hardness tester (Erweka GmbH, Hensenstamm, Germany). The device measures the force required to break the tablet in Newton (N). The measured values and their relative statistics were calculated and recorded automatically by computer program connected to the device.

Table 1: Composition of different matrix formulations

Batch runs	Prop	Diclo	GG	TGG	XG	MCC	Mg st
GG-Prop	100mg	-	50mg	-	-	50mg	2mg
GG-Diclo	-	100mg	50mg	-	-	50mg	2mg
TGG-Prop	100mg	-	-	50mg	-	50mg	2mg
TGG-Diclo	-	100mg	-	50mg	-	50mg	2mg
XG-Prop	100mg	-	-	-	50mg	50mg	2mg
XG-Diclo	-	100mg	-	-	50mg	50mg	2mg

Prop, Diclo, GG, TGG, XG and MCC stand for Propranolol-HCl, Diclofenac-Na, guar gum, treated guar gum, xanthan gum and microcrystalline cellulose, correspondingly.

***In vitro* drug release**

Drug release studies from the prepared matrix tablets for both drugs were carried out in USP XXII type 1 apparatus (Erweka GmbH, Germany) at 37 ± 0.5° C and 50 rpm. Dissolution medium was simulated gastric fluid for the initial 2 hours and phosphate buffer of pH 6.8 for the next 6 hours. At predetermined time intervals, 5 ml were withdrawn from the dissolution medium and replaced with fresh medium. Withdrawn samples were filtered and analyzed for the drugs spectrophotometrically either at 277 nm for diclofenac sodium [16] or at 290 nm for Propranolol-HCl [17] using UV spectrophotometer (Shimadzu, Japan). Amount of drug released was calculated by making use of pre-conducted calibration curves for both drugs and the cumulative percentage of drug released was subsequently calculated.

Drug release kinetics

Dissolution data related to both drugs were subjected to model fitting and statistical analysis in order to explore the kinetics of drug release from different gums. The model selected was power law [18] where dissolution data equivalent to < 60% drug release was fitted to the model in a search for the value of the diffusion exponent, *n,* which characterizes drug release mechanism.

Statistical data analysis

Values of investigated matrix friability and hardness properties were presented as mean ± SD (standard deviation). Inferential statistics relying on either analysis of variance (ANOVA) or student t'test were used to qualify the variation in friability, hardness, drug release and release kinetics within different gum matrices. Determination coefficient (r^2) was used to evaluate the fitting strength of dissolution data to the power law model during the determination of the diffusion exponent of the drug release. Analysis was aided by the software package STATISTICA® (version 8, Statsoft Inc., 2007) and in all cases, probability ≤ 0.05 was considered as a cutoff point for statistical significance.

RESULTS AND DISCUSSION

Effects of gums on matrix friability

Displayed values of matrix friability among different formulations were ranged 0.2-1.0% (Fig. 1a) and despite the discrepancy observed in friability values, all matrix formulations were found to be within the Pharmacopeial acceptable limit for friability [15].

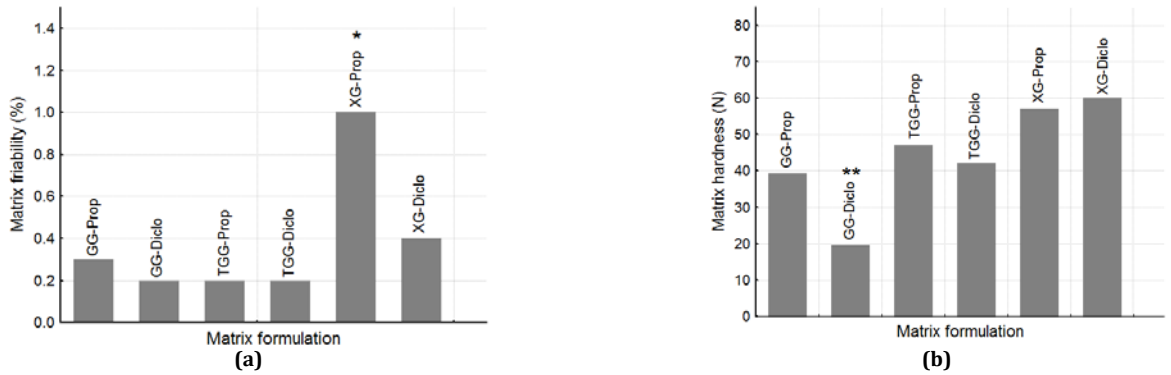

Fig. 1: Average values of (a) matrix friability and (b) hardness of Propranolol-HCl (Prop) and Diclofenac-Na (Diclo) loaded in guar gum (GG), treated guar gum (TGG) and xanthan gum (XG) based matrices with * and ** indicating significant variation at p < 0.05 and p < 0.01, respectively

Among different matrices, TGG based matrices reveal the lowest friability (0.2 ± 0.03%) irrespective to the type of loaded drug in comparison to GG and XG based ones. Both guar gum and xanthan gum have been evaluated as binders in formulation technology [1,19] and, moreover, treated guar gum is expected to have improved mechanical properties, as compared to native guar gum [2,20]. In the light of such scenario, displayed low values of friability associated with TGG based matrices might be attributed to the

improved compressibility and/or deformation properties of the gum. Based on displayed friability values of XG and GG based matrices, it might be assumed that guar gum is more efficient as binder than xanthan gum. These findings correlate well with a relative reported work [19] and could possibly be explained in terms of the different chemical structure, binding capacity and mechanical properties characterizing the two gums.

Although only differences in friability values of XG-Prop matrices proved to be considerable (ANOVA, p = 0.032), the three gums could be ranked as TGG > GG > XG depending on the desired low matrix friability.

In another occasion, whilst drug solubility shows no effect on friability of GG and/or TGG based matrices, friability of XG based matrices appears more sensitive to solubility of loaded drug where higher friability value was realized with those containing water soluble drug, XG-Prop (Fig. 1a).

Effects of gums on matrix hardness

Demonstrated values of matrix hardness among different formulations are varied in the range 19.6 ± 3.8 - 60.0 ± 7.1 N (Fig. 1b). Compared to GG based matrices, XG and TGG ones have achieved high hardness level that is less sensitive to variation in drug solubility.

The compression process results in decrease powder volume owing to elastic and/or plastic deformation and the degree of particle attrition behaviors of the particle-particle bonds in the powder mass [21]. Thus, observed variation in hardness among different matrix formulations might be attributed to the dissimilar deformation properties that the three gums might possess upon stressing. However, the considerable low hardness level revealed by GG based matrices (ANOVA, p = 0.0013), especially with Diclofenac-Na, could be due to the documented inferior compaction character of the gum [22].

Based on the achieved matrix hardness level, the gums can be ranked as XG > TGG > GG which is not in accordance with a previous work that reported a satisfactory high hardness with guar gum based matrix rather than xanthan gum one [19]. However, the disagreement in findings observed between the two studies might be due to the difference in the supply sources of the gums. In a more recent published work [23], authors were able to show that the supply source of excipients could have an influential impact on physical performance of matrix formulations.

Effects of gum type on drug release

Drug release profile from any delivery system is the most important criteria in the evaluation of the efficiency of that delivery system. Release profiles of Propranolol-HCl and Diclofenac-Na from the three gums are shown in fig. 2. It appears that the release profiles of loaded drugs from matrix formulations vary according to the type of utilizing gum.

From fig. 2, it is obvious that fraction ≥ 95% of the loaded drugs has been released in 8 hrs from TGG based matrices whereas at 8 hrs interval, GG based matrices demonstrate release of less than 50% of the loaded Diclofenac-Na and 85% of contained Propranolol-HCl. Moreover, release of both drugs from XG based matrices measure an intermediate profile between those related to TGG and GG matrices.

For better comparisons, drug release data of matrix formulations were transformed to dissolution efficiency term (DE), which is widely used for evaluation and comparison of drug release profiles from solid dosage forms [3].

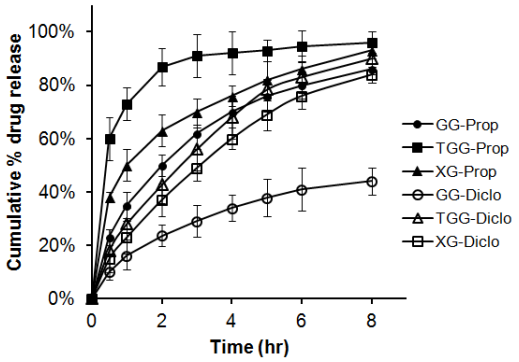

Fig. 2: Release of Propranolol-HCl (Prop) and Diclofenac-Na (Diclo) from guar gum (GG), treated guar gum (TGG) and xanthan gum (XG) based matrices

Average values of dissolution efficiency at 8hr (DE_{8hr}) for different matrices are presented in table 2. The results substantiate that among the three gums investigated in this study, TGG based matrices have exhibited the most enhanced release for both drugs (DE_{8hr} = 0.86 and 0.62 for Propranolol-HCl and Diclofenac-Na, respectively), followed by XG based matrices. Moreover, values of DE_{8hr} associated with matrices incorporating Propranolol-HCl (DE_{8hr} ranged 0.63-0.86) are obviously higher than that associated with matrices containing Diclofenac-Na (DE_{8hr} ranged 0.31-0.62), irrespective to the gum that constituting the matrix.

Table 2: Drug dissolution efficiency (DE) and release kinetics of matrix formulations

Formulations	$DE_{8\,hrs}$	Diffusion exponent (*n*)	r^2
GG-Prop	0.63 ± 0.07	0.520 ± 0.013	0.999
GG-Diclo	0.31 ± 0.01 **	0.591 ± 0.028	0.990
TGG-Prop	0.86 ± 0.08	0.662 ± 0.038	0.998
TGG-Diclo	0.62 ± 0.05 *	0.632 ± 0.005	0.999
XG-Prop	0.71 ± 0.07	0.459 ± 0.018	0.998
XG-Diclo	0.55 ± 0.05 *	0.612 ± 0.022 **	0.999

r^2 stands for model determination coefficient whereas * and ** indicate significant variation between compared formulations at $p < 0.05$ and $p < 0.01$, respectively.

For both drugs, the observed discrepancy in achieved values of DE_{8hr} as a consequence of variation in the type of gum constituting the matrix was demonstrated to be significant (ANOVA, p= 0.0002-0.0228). In addition, for each type of gum, the average attained value of DE_{8hr} measured by the two drugs that contained in that type of gum based matrices was computed as statistically varied (t'test, p ranged 0.00143-0.03223 for the three gums). In other words, statistical analysis supports that both drug solubility and gum type could have a role on the drug release process in this study.

From the results, it might be apparent that GG based matrices have demonstrated more ability to sustain the release of both loaded drugs as compared to the performance of TGG and XG based matrices and, consequently, the three gums can be ranked as GG > TGG > XG, based on the sustainability duration of loaded drugs.

In these matrices, drug release is known to be controlled by a combination of polymer hydration, front movement, drug dissolution, hydrated gel formation, drug diffusion through the hydrated gel and matrix erosion. Accordingly, variation in drug

release profiles among matrices of the three gums could be attributed to the disparity in any of these controlling factors.

In a recent work, the three gums have been ranked as GG > XG > TGG according to their swelling capability [2]. Therefore, difference in drug release profiles of matrices fabricated with these gums, in the present study, might be because of their dissimilar hydration and swelling attributes that determine the rate at which the surface viscous barrier (controlling gel) is being formed.

With TGG based matrices, the reported low hydration and swelling capabilities of the gum permit the enhancement of drug release as a result of the delay in formation of the gel layer that controls the drug release. On the contrary, the known high hydration and swelling capacities of GG allow the rapid hydration and formation of surface gel layer around the matrix that hinders the drug release and, moreover, renders drug diffusion and matrix erosion outweigh the other determining factors for the drug release. Owing to such situation, it might be not surprising that XG based matrices, which was reported to have an intermediate level of swelling capacity between those related to GG and TGG [2], have achieved release profiles of both drugs that are located in between those related to the two gums (Fig. 2).

These results are not in accordance with relevant published work on comparative evaluation of guar gum, xanthan gum, and hydroxypropyl methylcellulose as matrixing agents [24]. However, present findings are agreed well with published reports addressing ranking order of these gums as a consequence of either their swelling capacity or drug release profiles [2,19] and, moreover, support the assumed inverse relation that reported between drug release and the swelling index of natural gums [25].

Effect of drug solubility on drug release profile

It is known that pK_a and solubility of a drug are important determining factors for drug release from solid dosage forms. On another hand, upon contact with the surrounding fluid, matrices fabricated with hydrophilic gums start to hydrate and swell to form a viscous surface which controls the liquid penetration into and the drug release from the matrix as described before. Therefore, the initial swelling of the gum would support dissolution of the freely soluble drugs and diffusion of dissolved drug through the formed gel into the dissolution medium and, moreover, only with erosion of gel barrier, further permeation of dissolution medium into the matrix would be anticipated [11].

During the first 2 hrs of the drug release profiles, Diclofenac-Na containing matrices showed very low drug release in 0.1N HCl in comparison to those loaded with Propranolol-HCl (Fig.2). This is probably due to the limited solubility and, subsequently, dissolution of Diclofenac-Na at pH 1.2 [26]. On the other hand, reported burst release phenomena of Propranolol-HCl as a result of its high dissolution in matrices [24] might also contribute to the observed differences in the initial drug release between matrices loaded with the two drugs.

Propranolol-HCl is a weak basic drug (pK_a 9.5) which is soluble in acidic media [27] and, therefore, considerable amount of the drug would dissolve from the surface of the matrix and release directly into the dissolution medium before the effective gel barrier being formed.

These findings support the assumption made before that drug solubility probably plays a role in drug release profile of these matrices, at least at the initial phase of the release profile, which is in agree with relevant published works concerning release of the two model drugs used in this study from different matrices [11,24,26].

It should be, however, noted that from 2-8hr interval, solubility of Diclofenac-Na is enhanced due to change of dissolution medium to the phosphate buffer pH 6.8 and, moreover, effective gel barrier of different matrices would be in effect. Therefore, the influence of drug solubility on release profile would be vanished between the two drugs at this interval, permitting only drug diffusion and/or swollen gel erosion to characterize the drug release profile.

Effects of drug solubility and gum type on the drug release kinetics

Model-estimated values of *n* are ranged 0.459-0.662 and 0.591-0.632 for matrices including Propranolol-HCl and those containing Diclofenac-Na, respectively (Table 2).

Differences in displayed values of *n* for the two drugs as a consequence of variation in the type of gum constituting the matrix were demonstrated to be trivial (ANOVA, p varied between 0.12976 and 0.05279 for both drugs). Similarly, values of *n* observed with drug release of GG or TGG based matrices were found, in each, to be comparable irrespective to the loaded drug (t' test, $p > 0.05$). However, *n* values related to drug release of XG based matrices confirmed to be considerably varied with the type of loaded drugs (t' test, $p = 0.004$).

These findings, in turn, authenticate that loading drugs of different solubility in XG based matrices would result in considerable changes in drug release kinetics, as the result implies.

In swellable matrix tablets, drug release kinetics is associated with the dynamics of gel layer thickness. Relative contributions of drug diffusion, polymer relaxation and matrix erosion to drug release produce values of diffusion exponent (*n*) that range from 0.5 to 1.0.

With Propranolol-HCl, values of *n* associated with GG and XG based matrices were 0.520 and 0.459 for both matrices (Table 2), denoting the Fickian kinetics, in which drug diffusion is expected to determine the drug release from the two matrices. Findings are agreed with a relevant reports addressing release kinetics of Propranolol-HCl and Ambroxol-HCl from guar and xanthan gums [13,24].

For the three matrices that incorporate Diclofenac-Na and, in addition, TGG based matrices containing Propranolol-HCl, the displayed values of *n* for the four matrices are ranged 0.591-0.682 (Table 2), encouraging the consideration of the non-Fickian anomalous kinetics where drug diffusion and gum erosion appear to determine the drug release from these matrices. The non-Fickian kinetics have been concluded in relevant works to describe the release of Diclofenac-Na and other poorly water soluble drugs from xanthan and guar gum matrices [9,12,28].

As appear in table 2, values of determination coefficient (r^2) associated with fitting of drug release data to the power low were arrayed as 0.990-0.999 ($p < 0.05$) for all matrices, designating the suitability and efficiency of the selected model for estimation of diffusion exponent values of different matrix formulations.

CONCLUSION

All matrices fabricated with guar, treated guar or xanthan gum are demonstrated to be within the acceptance limit for friability. Attained hardness with guar gum based matrices could be categorized as very low whilst that accomplished by xanthan and treated guar gum based matrices could be ranked as high hardness. Guar gum based matrices appears to have more ability to sustain the release of loaded drugs as compared to other gum matrices.

Drug solubility and gum type are proved to influence the drug release process in this study and despite that gum type could have a negligible influence on drug release kinetics of different matrices. Drug solubility demonstrated to affect the kinetics of drug release from xanthan gum based matrices.

ACKNOWLEDGMENT

Authors would like to admit General Medicine Company (GMC) and Amipharma Laboratories for the generous materials donation

CONFLICT OF INTERESTS

Declared None

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