Mechanical and release behaviour of theophylline from matrix tablets containing psyllium powder in combination with grewia polysaccharides

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Abstract

This study was aimed at investigating the effect of grewia polysaccharides on the mechanical and release properties of tablet matrices containing binary mixtures of the polysaccharide with psyllium. Two grades of grewia polysaccharides (GG and GDS) were extracted and binary mixtures of the polysaccharides with psyllium were formulated into tablet matrices containing theophylline as the model drug. The true, bulk and tapped densities, Carr's compressibility index of the powders and binary composites were determined before tablet compression. Tablet properties (hardness, porosity, and drug release from the matrices) were investigated. The dissolution test was carried out in 0.1M HCl (pH 1.2) and phosphate buffer (pH 6.8). The results show that GG and GDS produced tablets with good mechanical strength (108.33 N and 95.70 N, respectively) while psyllium produced softer tablets (7.13 N). The combination of psyllium and grewia polysaccharides in the matrices resulted in a significant increase in the mechanical strength of the matrices when compared to matrices containing psyllium alone as the matrix former. The results also showed that GG and GDS reduced the dissolution rate and effectively eliminated the burst release of theophylline from the psyllium matrices at both pHs. The matrices of GG or GDS and the binary mixtures conform to non-Fickian anomalous diffusion with $n > 0.45$. When overcoming the burst release of drug from matrices such as psyllium, grewia polysaccharides may provide an effective reduction and a more sustained drug release from such matrices.

Key words: *psyllium gum, grewia polysaccharides, matrices, theophylline, release behaviour.*

Introduction

Natural polysaccharides are increasingly becoming the focus of research efforts due to their ability to hydrate and swell once in contact with water to form highly viscous solutions or dispersions [1]. The swelling allows the formation of the hydrated gel layer which controls drug release from tablet matrices [2]. Transport across this layer is by diffusion, but erosion can also occur when the polymer chains begin to untangle, as this happens the drug begins to be released [3]. The natural polymers have been used as matrices for sustained release [4–12] stabilizers or suspending agents in liquid dosage forms [13] and in bioadhesive drug delivery systems [14,15]. Apart from the fact that the natural materials are biocompatible, they have the additional advantages of being low cost and relatively abundant [16–18] compared to their synthetic counterparts.

Psyllium (PSY), also known as ispaghula is obtained from the husks of the seeds of Plantago ovata. This natural polymer is used in the food industry as a food thickener. Psyllium forms a viscous gel almost immediately when in contact with water ensuring faster control of drug release rate [19]. However, psyllium matrices have been reported to exhibit burst effects at low to intermediate polymer concentrations [20]. Another study [17], evaluated the release behaviour of propranolol HCl from psyllium matrices in the presence of HPMC K4M, sodium alginate, sodium carboxy methylcellulose (NaCMC) in different concentrations on the drug release from psyllium matrices. They found that binary mixtures of psyllium and HPMC, psyllium and sodium alginate and NaCMC and psyllium in various ratios caused a significant decrease in the release rate of propranolol HCl compared with when psyllium is used alone.

Grewia gum (GG) is obtained from the inner stem of the bark of *Grewia mollis* (Fam Malvaxeae) [16,21]. It is an inert natural polymer which can be used alone or in combination with other excipients in the formulation of pharmaceutical dosage forms [16]. The enzymatic digestion of the starch associated with the native grewia gum (GG) has been reported [22]. The starch-free grewia gum (GDS) was reported to exhibit physicochemical properties different from the GG. GG and GDS are highly compactible exhibiting high mechanical strengths in tablet matrices [7]. Consequently, it has also been suggested that GG or GDS could be combined with other polymers in certain compacts with low mechanical strength in order to increase its strength [7].

This study was aimed at investigating the effect of grewia polysaccharides on the release of theophylline from tablet matrices consisting of binary mixtures of psyllium and native grewia (GG) or starch-free grewia (GDS). PSY was chosen as a reference matrix due to

the burst release experienced from its matrices and the mechanically softer compacts it produces. The objectives were thus to assess the capability of GG and GDS polysaccharides in bringing about a controlled release with significant improvements in a drugs burst release as well as improving the mechanical strength of produced compacts with PSY.

Materials and Methods

Materials

The materials used for this study were used as procured from their manufacturers and they include: Lactose (Flowlac) monohydrate (Meggle, Germany), magnesium stearate (Merck, Germany), theophylline (TCI chemicals, Europe). Psyllium was supplied by Shiv Psyllium Industry, Sidhpur, Gujarat, India. The dissolution media which was prepared according to the USP 2003 method, consisted of potassium chloride (Acros organics, UK), hydrochloric acid and sodium hydroxide (Fisher scientific, UK), potassium monobasic (Fisher BioReagents, UK), absolute ethanol (Sigma, UK), Termamyl 120L (Megazyme, UK). Native grewia polysaccharide and starch-free grewia polysachharide were extracted in our laboratory.

Extraction of native grewia gum (GG)

The protocol for extraction of GG was reported previously [7,22]. Briefly, the fresh inner bark from the stems of G. mollis was air-dried, then shredded before maceration under ambient conditions in 0.1% w/v sodium metabisulphite for 24 h. A muslin bag was used to separate the swollen gum dispersion from the extraneous matter. The filtrate was precipitated using absolute ethanol. Thereupon, the precipitate was further purified by redispersion in water and final precipitation in 2 volumes of absolute ethanol for another 4 h to give GG which was then oven-dried at 50 °C for 24 h.

Extraction of starch-free grewia gum (GDS)

The starch content of GG was digested according to previous methods [22]. Termamyl 120L pretreated by heating at 70 °C for 30 min (to deactivate pectinases and arbinoxylanases) was added (1%w/v) to exactly 3L of 1% w/v GG while stirring continously at 70 °C for 4 h. Complete starch digestion was tested for every 1 hour by removing an aliquot of the dispersion for test of the presence of starch. After 3 h, the sample did not test positive for starch and subsequently, protein from the sample was precipitated by adjusting the pH to 4.5 with 2 M HCl and centrifuging at 4400 rpm for 20 min. The resultant supernatant was dialysed against deionised water for 72 h using cellulose membrane (molecular weight cut-off - 12,500 Da). Following dialysis, the material was precipitated using two volumes of 95% ethanol followed

by solvent exchange using one volume of isopropanol. The precipitate was oven dried for 24 h at 50 °C. This sample was named GDS.

Preparation and mixing of powders

The powders of psyllium (PSY), GG and GDS were pulverised using the Retsch mill MM400 (Retsch, UK) under the same conditions to produce free flowing powders that were compactible. Three balls were placed in the 25 mL sample holder containing the powder and mounted unto the sample stand. The mill was set to vibrate at a frequency of 20rev/sec for 4 min. The mixing of the formulation blends (Table 1) (except the magnesium stearate) was conducted using a Turbula™ mixer (Willy. A Bachofen, Switzerland) for 10 minutes to ensure a homogenous mix. Upon addition of the magnesium stearate, the formulation was mixed for a further 2 min.

True densities, Bulk & tapped densities, and Carr's compressibility

True density of the pure powders and formulation blends were determined on a pycnometer Accupyc II 1340 (Micromeritics, USA). The bulk and tapped densities of the powders were determined by pouring pre-weighed amounts of the powders gently into a measuring cylinder and the respective volumes recorded. Thereafter, the cylinder was tapped until there was no further change in weight and the tapped volume was recorded. The bulk and tapped densities were calculated using equation 1 and 2. Carr's compressibility index was calculated using equation 3.

$$Bulk\ density = \frac{weight\ of\ powder}{untapped\ volume\ of\ powder} \quad \text{(Equation 1)}$$

$$Tapped\ density = \frac{weight\ of\ powder}{tapped\ volume\ of\ powder} \quad \text{(Equation 2)}$$

$$Carr's\ compressibility\ index\ (\%) = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} X\ 100 \quad \text{(Equation 3)}$$

Tablet formulation and compression

All the powder mixes were compressed into tablets using a manual single punch tableting machine Model MTCM-1 (Globe Pharma, US). The pressure was fixed at 150 MPa. Round convex tablets were produced, with an average diameter of 10 mm. The powders were weighed and blended according to Table 1 before compression.

Table 1: Per tablet formula of tablets containing different ratios of polysaccharide powders

Sample Ratio	Theophylline (%)	GG (%)	GDS (%)	PSY (%)	Magnesium stearate (%)	Lactose (%)	sample weight (mg)
PSY:GG (1:2)	41.50	33.33		16.67	1	7.5	300
PSY:GG (1:1)	41.50	25.00		25.00	1	7.5	300
PSY:GG (2:1)	41.50	16.67		33.33	1	7.5	300
PSY:GDS (1:2)	41.50		33.33	16.67	1	7.5	300
PSY:GDS (1:1)	41.50		25.00	25.00	1	7.5	300
PSY:GDS (2:1)	41.50		16.67	33.33	1	7.5	300
PSY	41.50			50.00	1	7.5	300
GG	41.50	50.00			1	7.5	300
GDS	41.50		50.00		1	7.5	300

Tablet dimensions and hardness

The tablet compacts were left to recover for 48 h. Thereafter, the tablet dimensions and hardness were determined. The width and diameters were also measured using a digital calliper. The tablet hardness was tested in triplicates using a hardness tester (PharmaTest, Germany).

***In-vitro* release studies**

In vitro release studies were performed on an automated USP Type II (paddle method) dissolution apparatus, Pharma Test DT 70 (PharmaTest, Germany). The dissolution medium was 900 mL 0.1 N HCl (pH 1.2) or phosphate buffer (pH 6.8) equilibrated to 37 ± 0.5 °C with a paddle stirring speed of 100 rpm. Samples were automatically withdrawn at selected time intervals from 5 min up to 720 min using a peristaltic pump and the concentrations of theophylline in the samples determined by UV spectrophotometry at 272 nm. The tablets were placed in a sinker to prevent floating of the tablets before placing tablets in the dissolution medium.

Dissolution parameters (dissolution efficiency (DE) and mean dissolution time (MDT))

The time for the drug to dissolve under the prevailing *in vitro* dissolution conditions also known as the mean dissolution time (MDT) is suitable for dosage forms having different mechanisms of drug release [23,24] and was calculated according to equation 4. Also the dissolution efficiency (DE), which is the area under the dissolution curve up to a certain time t, expressed as a percentage of the area of a rectangle described by 100% dissolution in the same time t [25], was calculated according to equation 5.

$$MDT = \frac{\sum_{j=1}^{n} t_j \, \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \qquad \text{(Equation 4)}$$

Where j is the sample number, n is the number of dissolution sample times, t_j is the time at midpoint between t_j and t_{j-1} and ΔM_j is the additional amount of drug dissolved between t_j and t_{j-1}.

$$DE = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100 \quad \text{(Equation 5)}$$

Where y is the drug percent dissolved at time t

Similarity Factor

Similarity between the drug release profiles was determined according equation 6, using similarity factor *f2* [26–28] using the release profile of PSY matrices as reference. The *f2* values ranging from 50 to 100 indicate similarity between the two profiles. The closer the *f2* value is to 100, the more similar or identical the release profiles. Values of *f2* less than 50 indicate dissimilarity between two dissolution profiles [29].

$$f2 = 50\ log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n} w_t(R_t - T_t)^2\right]^{-0.5} X\ 100\right\} \quad \text{(Equation 6)}$$

Where, n is the number of pull points for tested samples; w_t is the optional weight factor; R_t is the reference assay at time point t; T_t is the test assay at time point t.

Kinetics of drug release

The cylindrical tablets produced from this study were subjected to kinetic modelling to determine the kinetics of theophylline release from the matrices using the Korsmeyer-Peppas equation [30]. For cylinders, which were the shape of the tablet matrices made in this study, n values of up to 0.45 suggest Fickian diffusion, and values of above 0.89 suggest Case-II transport. A value between these two suggests anomalous transport as reported in numerous studies [17,31–34].

Results and Discussion

Physical properties of pure powders and formulation blends

Both GG and GDS polymers exhibited lower bulk (0.46 and 0.36 g/cm^3 respectively) and tapped densities (0.67 and 0.55 g/cm^3 respectively) than PSY (0.54 for bulk and 0.79 g/cm^3 for tapped density), suggesting that they were packed tightly and in theory should produce harder tablets. Particle rearrangement to occupy a different spatial volume occurs during tapping and movement from particles from loosely packed to a more tightly packed arrangement occurs. PSY is known to exhibit large particle size, in addition to being irregularly elongated in shape [20]. This would have affected the PSY powder's ability to undergo tight

packing. It would hence be expected that the powder would have poor compressibility and produce tablets of low mechanical strength.

Effects of GG or GDS on properties of PSY matrices

The addition of the excipients in making the formulations followed the same trend with regards to the bulk and tapped densities for the pure polymers (GG, GDs and PSY). It was difficult to establish a real trend in the bulk and tapped densities with the increasing amount in either GG or GDS content in the PSY matrices (Table 2). This was also the case for the true density values (Table 2). Carr's index is an indirect method which allows the measuring of powder flow. As can be seen from the results, all the powders exhibited relatively poor flow (Table 2).

The hardness and porosity of the tablet matrices are presented in Figure 1a and b. The results show that GG matrices exhibited the highest hardness of 108.33 N, followed by GDS-containing matrices (95.7 N). PSY-containing matrices alone exhibited the lowest tablet hardness (7.13N). The effect of GG or GDS on the hardness and porosity of the tablets is obvious from Figure 1. It can be seen that the addition of GG or GDS in various proportions resulted in appreciable increase in the hardness of the tablets that is concentration dependent. The present result shows that at the same level of concentration (or ratio) in the tablets, GG imparts more hardness to the tablets than GDS. The present results contradicts previous report [7] that GDS forms harder compacts than GG. In this report however, the grewia polysaccharides were being evaluated differently and as such the differences could be ascribed the influence of the excipients used in this study.

The results also show that PSY-containing matrices exhibited the lowest porosity (41 %) when compared to GG (55 %) and GDS-containing matrices (47 %) (Figure 1a and b). When GG and PSY were mixed in the tablet matrices (Figure 1a), the results showed that the porosity of the matrices increased with an increase in the concentration of GG. Conversely, it was observed that, increasing the concentration of GDS in the conjugate polysaccharide matrices resulted in increased tablet porosity to a maximum, and thereafter the porosity of the matrices start to decrease. Nep et al., 2016 [22] reported no appreciable difference in the porosity of GG and GDS in tablet matrices. When a tablet is porous, in theory more medium would be able to get into the tablet and hence dissolve it. The more porous a tablet, the quicker the drug release from the tablet matrices. However, higher porosity can result in faster swelling of the gel layer resulting in an increased diffusional path length, which could delay the release of drug.

251 **Table 2: Properties of formulation blends after mixing**

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	PSY	GG	GDS	PSY:GG (1:1)	PSY:GG (2:1)	PSY:GG (1:2)	PSY:GDS (1:1)	PSY:GDS (2:1)	PSY:GDS (1:2)
True density (g/cm^3)	1.50	1.86	1.65	1.53	1.52	1.68	1.56	1.53	1.55
Bulk density (g/cm^3)	0.62	0.30	0.49	0.37	0.47	0.38	0.54	0.54	0.52
Tapped density(g/cm^3)	0.83	0.48	0.64	0.64	0.70	0.58	0.72	1.08	1.00
Carr's index (%)	31.37	31.42	39.61	38.46	29.21	28.57	25.00	29.99	35.99

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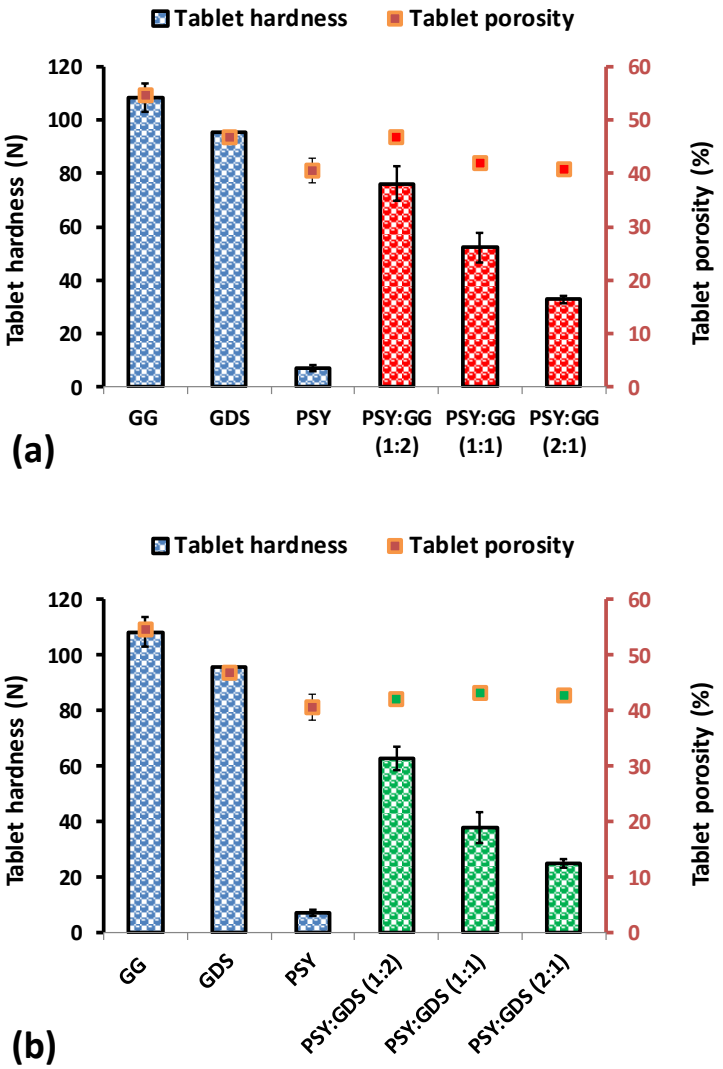

Figure 1. Tablet matrix properties of porosity and hardness for pure polymer formulations and formulated blends of combination with the grewia polysaccharides with psyllium (a) Grewia gum, (b) destarched Grewia gum.

Note: GG is Grewia gum, GDS is destarched Grewia gum, PSY is Psyllium.

Drug release from matrices

The in vitro release profiles of theophylline from the pure polysaccharide matrices in acidic and phosphate buffer media are presented in Figure 2a and b. The result shows that matrices of PSY exhibited fast dissolution. The psyllium husk was not able to produce extended release profiles of theophylline, instead, dose dumping of theophylline in both 0.1N HCl (pH 1.2) and phosphate buffer (pH 6.8) occurred. Over 70 % of the theophylline drug was released within

the first 10 min of dissolution. Similar observation was reported elsewhere [17]. Conversely, matrices of pure GG and GDS exhibited slower release of theophylline from the matrices in both media. Higher release of theophylline was observed from GG matrices in phosphate buffer (pH 6.8) relative to the GDS matrices (Figure 2b). The initial burst release displayed by PSY matrices has been attributed to rapid dissolution of the drug from the tablets surface due to both diffusion and erosion as theophylline is medium soluble drug [20].

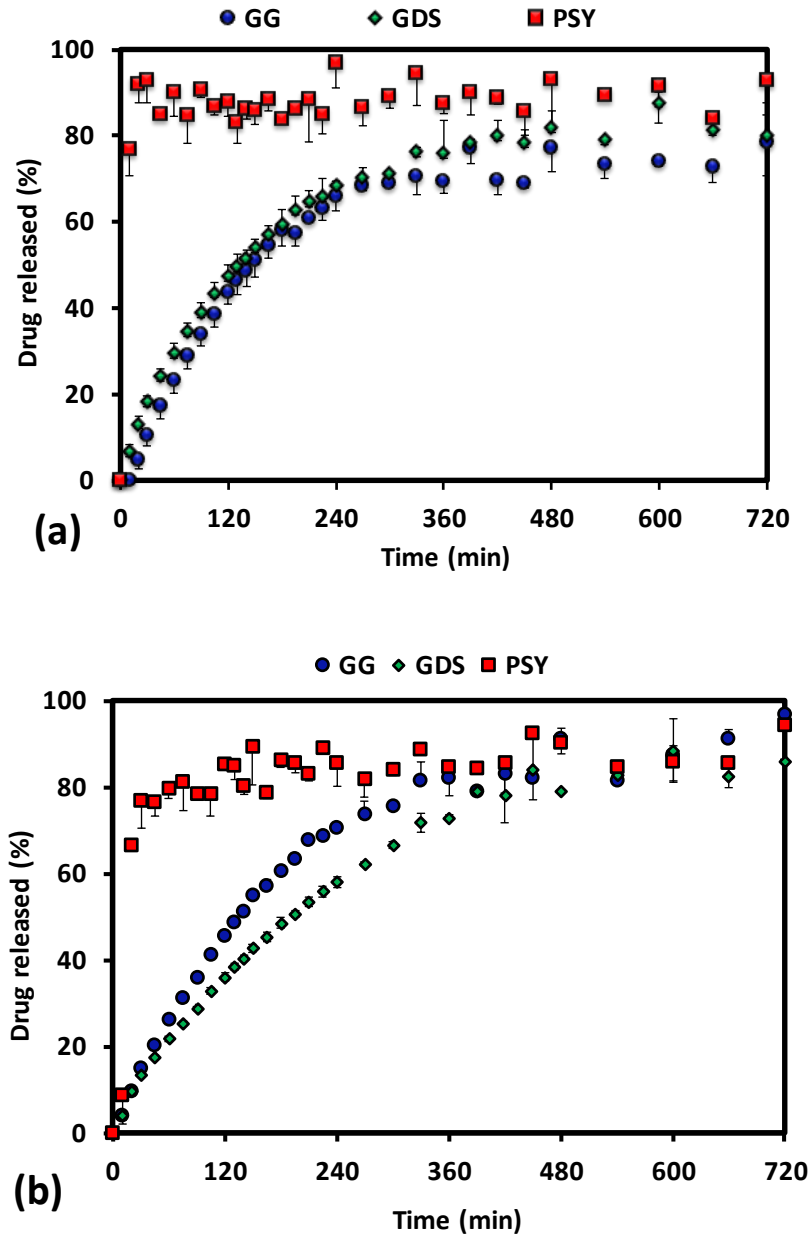

Figure 2. Release profiles of theophylline from pure gum matrices in: (a) 0.1N HCl (pH 1.2) and (b) phosphate buffer (pH 6.8) equilibrated to 37 °C and agitation speed of 100 rpm. Note: GG is Grewia gum, GDS is destarched Grewia gum, PSY is Psyllium.

The release profiles of theophylline from matrices containing binary mixtures of polysaccharides are presented in Figure 3 and 4, for PSY:GG and PSY:GDS matrices respectively. The result shows the effect of GG or GDS on the matrices containing binary mixtures of the polysaccharides. It can be observed that both GG and GDS effectively slowed down the dissolution of theophylline from the matrices of the binary mixtures of polysaccharides in both 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8). The burst effect witnessed with matrices containing psyllium only was completely eliminated.

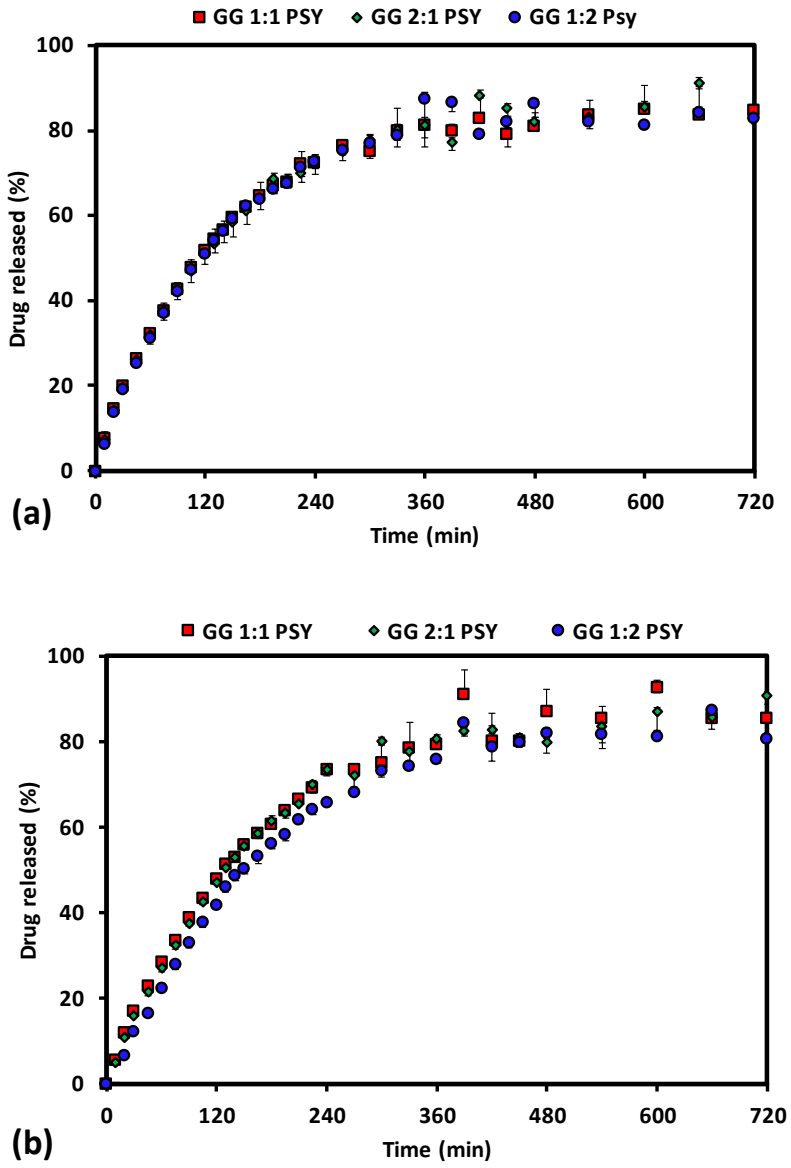

Figure 3. Release profiles of theophylline from composite gum matrices of GG and PSY in: (a) 0.1N HCl (pH 1.2) and (b) phosphate buffer (pH 6.8) equilibrated to 37 °C and agitation speed of 100 rpm.

Note: GG is Grewia gum, GDS is destarched Grewia gum, PSY is Psyllium.

The release of theophylline from the polysaccharide matrices was further compared using dissolution efficiency (DE), mean dissolution time (MDT) and similarity factor (f_2). The results are presented in Table 3. The results show that the MDT of all the matrices was higher in phosphate buffer (pH 6.8) than in 0.1N HCl (pH 1.2). The values of MDT, DE, f_2 could not be calculated for pure PSY matrices due to the fast release of theophylline from the matrices. In acidic media, pure GDS matrices exhibited the highest MDT while in alkaline media, the highest MDT was exhibited by PSY 1:2 GDS.

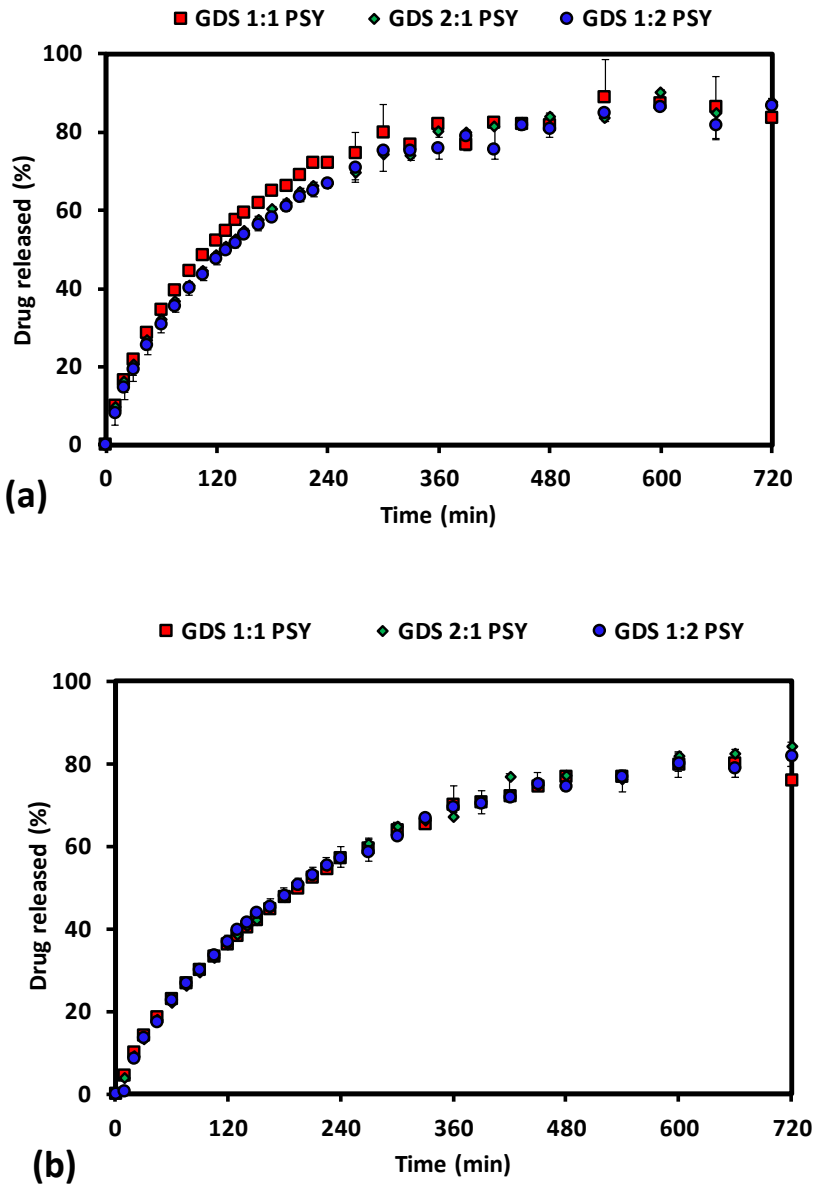

Figure 4. Release profiles of theophylline from composite gum matrices of GDS and PSY in: (a) 0.1N HCl (pH 1.2) and (b) phosphate buffer (pH 6.8) equilibrated to 37 °C and agitation speed of 100 rpm.
Note: GG is Grewia gum, GDS is destarched Grewia gum, PSY is Psyllium.

Pure GG matrices exhibited higher DE in media pH 6.8 than in media pH 1.2. All matrices with combinations of PSY with GG, and PSY with GDS exhibited higher DE in acidic media (pH 1.2) as compared with phosphate buffer (pH 6.8). The highest DE for the binary composites (71.06%) was displayed by matrices containing PSY:GG (2:1) in phosphate media (pH 6.8).

Table 3. Dissolution parameters from release profiles of Pure and Composite matrices of PSY with GG or GDS (n=3)

	0.1N HCl (pH 1.2)				Phosphate buffer (pH 6.8)			
	MDT (min)	**DE (%)**	**Diffusional exponent (*n*)**	**Similarity factor (*f2*)**	**MDT (min)**	**DE (%)**	**Diffusional exponent (*n*)**	**Similarity factor (*f2*)**
Pure PSY matrices	*	*	*	-	*	*	*	-
Pure GG matrices	153.4	61.7	1.08	19.4	179.3	70.2	0.91	26.7
Pure GDS matrices	170.5	66.9	0.74	21.8	185.8	63.8	0.79	22.7
PSY:GG (1:2) matrices	110.3	70.2	0.79	23.1	132.3	65.8	1.11	24.6
PSY:GG (1:1) matrices	125.8	70.6	0.74	23.4	126.9	70.33	0.82	27.5
PSY:GG (2:1) matrices	104.7	71.1	0.74	23.2	169.5	69.3	0.85	27.1
PSY:GDS (1:2) matrices	157.6	67.8	0.67	22.0	190.9	60.2	1.08	22.5
PSY:GDS (1:1) matrices	107.5	71.0	0.66	22.9	149.4	60.2	0.74	22.4
PSY:GDS (2:1) matrices	151.2	69.8	0.63	22.5	197.6	61.1	0.79	22.4

***Values could not be determined due to the quick release of theophylline from the matrices

The release profiles of the matrices were also compared using similarity factor (*f2*) with pure PSY matrices as reference (Table 3). It can be seen that the values of similarity factor for all the matrices were less than 50. This indicates that none of the release profiles of theophylline from the matrices containing binary polysaccharide mixtures was similar to that of pure PSY matrices. This implies that GG or GDS when combined with PSY in matrices result in formulations that exhibit release profiles which are different from the release profile of drug from matrices of PSY.

Kinetics of theophylline release from GG, GDS and PSY matrices

The release kinetics for the polysaccharide matrices are presented in Table 3. The release of theophylline from GDS matrices in acidic (pH 1.2) and alkaline media (pH 6.8) has been reported [22] to be typically non-Fickian with a best fit to Korsmeyer– Peppas model

indicating that drug release was by a combination of diffusion and erosion.. Similarly, the release was reported to be anomalous (non-Fickian) and diffusion controlled release for theophylline in GG matrices. The present result corroborates previous report and shows that none of the values of the diffusional exponent (n) was below 0.45, suggesting that Fickian diffusion is not taking place. Values between 0.45 and 0.89 represent anomalous transport. Values above 0.89 display case II transport. Case II transport is occurring for the sample ratios PSY:GDS (1:2) and for PSY:GG (1:2). In both cases it is occurring when PSY is in one part and GDS and GG are in 2 parts in the tablet matrix. In acidic solution only matrices containing Pure GG exhibited case II transport, whereas all the other samples are displaying anomalous transport.

Conclusion

This study has shown that GG and GDS have very good potential as matrix formers that can modify drug release. These polysaccharides work particularly well or synergistically with psyllium in controlling its drug release, eliminating burst effect, and in producing tablets of better quality and mechanical strength. This was evidenced by the increase in tablet hardness experienced by the PSY matrices with increases in either GG or GDS content. Also as MDT was not measurable for the PSY matrices and the general decrease in MDT experienced by the binary mixtures of PSY and GG or GDS matrices suggests the polymers working in a synergistic way. These polymers are natural alternatives and hence more cost effective than the synthetic alternatives available and the manipulation of drug release and kinetics in either acidic or basic media can be achieved through an exploitation of various polymer ratios or combinations thus giving a formulator options.

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