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Full Length Research Paper

Improving the physicomechanical properties of psyllium husk and evaluation its ret+arding properties on a water-soluble model drug

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Psyllium is a natural polysaccharide which is administered as bulk laxative. This study was undertaken to investigate psyllium's physicomechanical properties and also evaluation of its retardant properties. Several formulations containing variable amounts of psyllium and excipients examined to achieve optimized formulations. Then flowability, friability and hardness of prepared formulations were studied. Ultimately to evaluate the effects of mentioned formulations on dissolution profile of sodium diclofenac and release retardant property of psyllium, dissolution test was done. The results showed that better flowability was obtained when using different fillers in combination with psyllium. Incorporation of fillers showed harder compacts and better results were obtained using microcrystallincolloluse as filler. Formulations including sodium diclofenac mentioned, caused retardation of drug in dissolution tests that is suitable for preparing sustained release formulations. By introducing novel formulations in this study not only did physicomechanical properties of psyllium improve but also made it possible to alternate this natural polysaccharide as retardant polymer instead of other expensive synthetic or semi-synthetic polymers.

Key words: Psyllium, physicomechanical properties, sodium diclofenac, retarding ability.

INTRODUCTION

The largest use of powders pharmaceutically is to produce tablets and capsules. So mixing and compression properties of powders such as flowability and compressibility are so much important to achieving an optimized formulation. Powder flowability should be evaluated because it has an important role in production of pharmaceutical dosage forms. Some of reasons for producing free flowing powders include uniform feed from bulk storage containers or hoppers into the feed mechanisms, weight uniformity, and decrease uneven powder flow due to air entrapment within powders, on the other hand uneven powder flow from excess fine particles increase particle-die-wall friction, causing lubrication problems and increase dust contamination risks during powder transfer.

Therefore to achieve mentioned goals, alternation of particle size, particle shape or texture, surface forces, process conditions and formulation additives by flow activators are proposed (Aulton, 2002).

Most of the time process alternation is cost and time consuming. Alternation of surface forces requires addition of active surface agents or some other materials that increase formulation incompatibility or degradation of active agents. So practically in this study we utilized flow activators to improve flowability of powders. Later by granulation, we changed particle size and shape to obtain better physicomechanical properties of powders.

The presence of molecular forces such as van der Waals and electrostatic forces produces a tendency for solid particles to stick themselves and to other surfaces.

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Table 1. Combination of administered formulations.

Formulation	Psyllium husk (mg)	Lactose (mg)	MCC (mg)	Method of preparation	Binder
F1	500	0	0	DC	-
F2	250	250	0	DC	-
F3	125	375	0	DC	-
F4	83	417	0	DC	-
F5	250	0	250	DC	-
F6	125	0	375	DC	-
F7	83	0	417	DC	-
F8	500	0	0	WG	Hydroalcohol (50:50)
F9	250	250	0	WG	Hydroalcohol (50:50)
F10	125	375	0	WG	Hydroalcohol (50:50)
F11	83	417	0	WG	Hydroalcohol (50:50)
F12	250	0	250	WG	Hydroalcohol (50:50)
F13	125	0	375	WG	Hydroalcohol (50:50)
F14	83	0	417	WG	Hydroalcohol (50:50)
F15	500	0	0	WG	Water
F16	250	250	0	WG	Water
F17	125	375	0	WG	Water
F18	83	417	0	WG	Water
F19	250	0	250	WG	water
F20	125	0	375	WG	water
F21	83	0	417	WG	water

Adhesion and cohesion can be considered as two parts of the same phenomenon.

Psyllium is used for nomination of plants from genus *Plantago* (Cui, 2001). Psyllium husk, coat of dried seeds of *Plantago ovata*, has some characteristics which makes it suitable for pharmaceutical applications. These characteristics are biocompatibility, being inert, environmental friendly, frequently availability and not expensive price. Psyllium seeds because of water absorption in aqueous solution form natural three dimensional structures due to gel forming properties (Marlett and Fischer, 2002). Psyllium is an effective natural fiber for mechanical function of the bowels, which is frequently used to dissolve constipation (Alabaster et al., 1996; Nakamura et al., 2004).

Due to strong gelling property of psyllium, polymeric networks swell quickly by sorption of water in external aqueous environment (Agarwal et al., 2002). Then medicine is entrapped inside and between gel structures (Couvreur and Puisieux, 1993; Madsen and Peppas, 1999). Therefore, designing novel oral delivery systems with constant level of medicine release and improvement of patient compliance are supposed to be achievable by means of psyllium as a natural polymer (Lowman and Peppas, 1999; Tan and Newton, 1990). In order to improve adhesive/cohesive properties of psyllium powders, we examined several formulations containing variable amounts of psyllium and excipients mixture, ultimately to investigate the effect of mentioned formulations on dissolution of sodium diclofenac, and release retardant property of psyllium in prepared sustained release dosage forms, dissolution test was done.

MATERIALS AND METHODS

Micro crystalline celloluse (MCC) (Mingtai, Taiwan), sodium diclofenac was provided by Zahravi Co. (Tabriz, Iran), potassium phosphate monobasic (Merck, Germany), sodium hydroxide (Merck, Germany), hydrochloridic acid (Merck, Germany), and psyllium (Herbi Daru, Tabriz, Iran) were used.

A flow-meter (Erweka, Germany), tablet machine (Riken, P-16B, Japan), a tablet hardness tester (Erweka-TBH 30 MD-Germany), a dissolution tester USP II (Erweka, DPT6R, Germany), and UV/visible spectrophotometer (Shimadzu-120, Japan) were used in this study.

Evaluation of physicomechanical characteristics of psyllium based powder mixtures

To prepare psyllium based powder mixtures, psyllium, lactose (water- soluble filler) or MCC (insoluble filler) with 1:1, 1:3 and 1:5 ratios and also Mg Stearate (as lubricant) were prepared via random mixing process (Table 1). Then all of the formulations represented in Table 1, were evaluated for bulk density, tangent of angle of repose, flowability and compatibility, before compression.

Evaluation of flow rate

To evaluate the flow properties of prepared formulations, hopper flow rate, angle of repose and also Carr's index examined. In hopper technique, 100 cm^3 of powder is placed in the funnel of the flow-meter; hopper is filled with powder; the shutter is then removed, meanwhile the time is recorded until completely pure of powder. By dividing powder volume by the time, a flow rate is obtained which was used for quantitative comparison of different powders.

Angle of repose was measured according to the fixed funnel and free standing cone method. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip 10 cm high, H, above a graph paper placed on a flat horizontal surface. Powder starts to flow and forms conical pile just reaches the tip of the funnel. The mean diameter, 2R, of H, base of the powder cone, was determined and the tangent of the angle of repose was given by:

$$\tan \alpha = H / R$$

where α is the angle of repose.

The compressibility index (CI) (Carr, 1965; Molerus and Nywlt, 1984) was calculated via bulk volumes and tap volumes of administered powder (V_{bulk} and V_{tap}), measured according to the test for apparent volume:

$$CI\% = \frac{V_{bulk} - V_{tap}}{V_{bulk}} \times 100$$

Carr's index of 5 to 15% indicate excellent flow, 12 to 16% good flow, and >23% indicate poor flow.

Preparation of sodium diclofenac sustained release tablets

Powder is compressed using lubricated punch by means of a manual tablet machine. Tablets form with maximum compression pressure (P_{max}) from 20 to 300 kg/cm^2 for 5 s to obtain optimum tabletting pressure. Compressed tablets were kept in special well closed chambers without air or steam transfer for about 24 h in 30°C (until dissolution test).

Evaluation of thickness and tensile strength of prepared sodium diclofenac tablets

Final thickness (T_t) and tablet tensile strength (T) of prepared tablets were measured by tablet hardness tester and calculated via bellow standard equation:

$$T = 2H / \pi D_t T_t$$

H, D_t and T_t represent hardness, diameter and thickness of the tablets, respectively.

***In-vitro* dissolution test**

Paddle method with stirring rate of 50 ± 1 rpm was used. 900 ml of 0.1 N HCl, pH = 1.2 dissolution medium was used for first two hours and within 15, 30, 45, 60 and 120 min, 4 ml of the sample was taken through a millipore filter. The dissolution media was then replaced by 4 ml of the same fresh media by the same temperature (37 ± 0.1°C).

For the next 6 h, medium changed into phosphate buffer pH = 6.8 (900 ml, 37 ± 0.1°C, n = 3). Then samples were withdrawn within 180, 240, 300, 420 and 480 min.

Release profiles of tablets were compared using similarity factor, f_2, as defined by the following equation:

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t) \right]^{-0.5} \times 100 \right\}$$

n, Number of time points, R_t, dissolution percent of one formulation at a given time point and T_t, percent of dissolved of other formulation.

Spectrophotometric analysis

Analysis of all specimens in aqueous solutions in two different mediums was done at 273.5 and 276.2 nm wave length. Standard line was achieved for different concentrations of stock solution of the drug (at pH = 1.2 or 6.8).

Statistical analysis

Analysis of variance (ANOVA) was used for statistical analysis. Mean ± SD was used for reporting the results. Results by the range of $p < 0.05$ are significant.

RESULTS

Molecular forces such as van der Waals and electrostatic forces produce a tendency for solid particles to stick themselves and other surfaces (Lewis and Simpkin, 1994). Adhesion and cohesion can be considered as two parts of the same phenomenon. In order to improve adhesive/cohesive properties of psyllium powders and achieve acceptable flowability, in this investigation, several formulations containing variable amounts of psyllium and excipients mixture examined. Therefore, various formulations were prepared as presented in Table 1.

By improving psyllium physicomechanical properties such as flowability and compressibility, there would be a good opportunity to produce other dosage forms of psyllium, like tablet or capsule instead of bulk preparations. Granules possessing best mechanical and physical characteristics will produce tablets with best pharmaceutical properties. It is apparent that the type and concentration of binder used in the granulation step would influence the corresponding tablet properties (Desai et al., 2007). All of the suggested formulations demonstrate (Table 2) better flowability in comparison with pure psyllium powder.

As seen in Table 2, simple powder mixture in formulations F2 to F7 in comparison with pure psyllium (F1) have better flow rates; however, wet granulations by

Table 2. Results showing flow properties of prepared formulations.

Formulation	Average of angle of repose (°) ± SD	CI (%)	Average of flow rate (cm^3/s) ± SD
F1	39.60 ± 1.31	24.0	9.75 ± 3.59
F2	34.03 ± 1.53	32.0	12.54± 2.02
F3	33.71 ± 2.36	42.0	13.17 ± 4.35
F4	30.37 ± 2.06	36.0	11.82 ± 1.77
F5	32.38 ± 0.92	22.0	15.82 ± 0.72
F6	33.44 ± 3.08	20.0	10.36 ± 2.48
F7	33.28 ± 2.98	18.0	10.75 ± 1.67
F8	36.04 ± 0.95	10.0	11.86 ± 0.56
F9	30.78 ± 0.76	20.0	20.11±0.43
F10	31.46 ± 0.58	22.0	19.71 ± 0.95
F11	31.52 ± 0.60	18.0	14.36 ± 0.36
F12	30.39 ± 0.67	18.0	15.78 ± 0.43
F13	31.52 ± 1.83	16.0	23.06 ± 0.39
F14	33.26 ± 1.41	10.0	21.09 ± 0.20
F15	36.46 ± 2.06	20.0	11.79 ± 1.73
F16	33.65 ± 0.43	12.0	12.38 ± 1.04
F17	35.09 ± 1.38	14.0	18.21 ± 3.50
F18	34.31 ± 1.31	8.40	12.95 ± 0.65
F19	36.30 ± 0.77	18.0	12.08 ± 0.67
F20	33.47 ± 0.62	18.0	12.38 ± 0.84
F21	34.82 ± 0.15	16.0	12.76 ± 0.25

means of hydro-alcoholic binder (F9 to F14) showed better flowability in comparison with their counterparts (F2 to F7 and F16 to F21). Results demonstrate that wet granulation of psyllium with excipients improved flowability in comparison with simple psyllium (F1 and F8). It is obvious that due to reduction of molecular forces in granulated dosage forms, particles can flow freely. To investigate flowability, in addition of mentioned test, average angle of repose is measured too. As results show (Table 2), all formulations in comparison with F1 have smaller angle of repose. As a general guide, powders with greater angle of repose have poor flowability. In F9 to F14, we observed smaller angle of repose than F15 to F21. It shows that hydro-alcoholic binder acts better than water in wet granulation. Finally, to determine another physicomechanical property, bulk and tapped density were measured to evaluate compressibility via compressibility index (CI) (Molerus and Nywlt, 1984). CI is applied not only to determine compressibility but also it is used as an indirect method for flowability estimating. CI results (Table 2) show that pure psyllium powder has poor compressibility (CI = 24%) but F8 to F21 decreased the compressibility acceptably between 10 and 20%. Regarding the applied formulations, better compressibility was obtained when wet granulation used, however there is not significant differences between hydro-alcoholic (50:50) binder and water. Because of lowered porosity and molecular forces during wet granulation, granules have significant lower compactibility. Small amounts of MCC bind other materials during compaction with the low bulk density of MCC, and the broad range of particle sizes. An excipient with a low bulk density will exhibit a high dilution on a weight basis, and a broad particle size range provides optimum packing density and overage of other excipient materials (Herbert et al., 1989).

To evaluate the drug release from various prepared formulations, dissolution studies were performed and their results are demonstrated in Figures 1A to D. Previous studies had evaluated sustained release of amoxicillin trihydrate from matrix tablets by the means of psyllium husk as a natural polymeric release retardant. Its release compared with synthetic polymers (Chavanpatil et al., 2005). In another study, a new gastroenretentive formulation for ofloxacin was developed with retarding polymers such as psyllium husk, HPMC and crosspovidone (Chourasia and Jain, 2004). Most previous studies had been undertaken to evaluate psyllium sustain releasing property; however, we not only examined its retardability but also examined various formulations to improve physicomechanical properties of psyllium and see the differences between sustain releasing of psyllium in combination with two common excipients such as lactose and MCC.

Figure 1A represents drug release profiles of psyllium in combination with two water-soluble lactose and

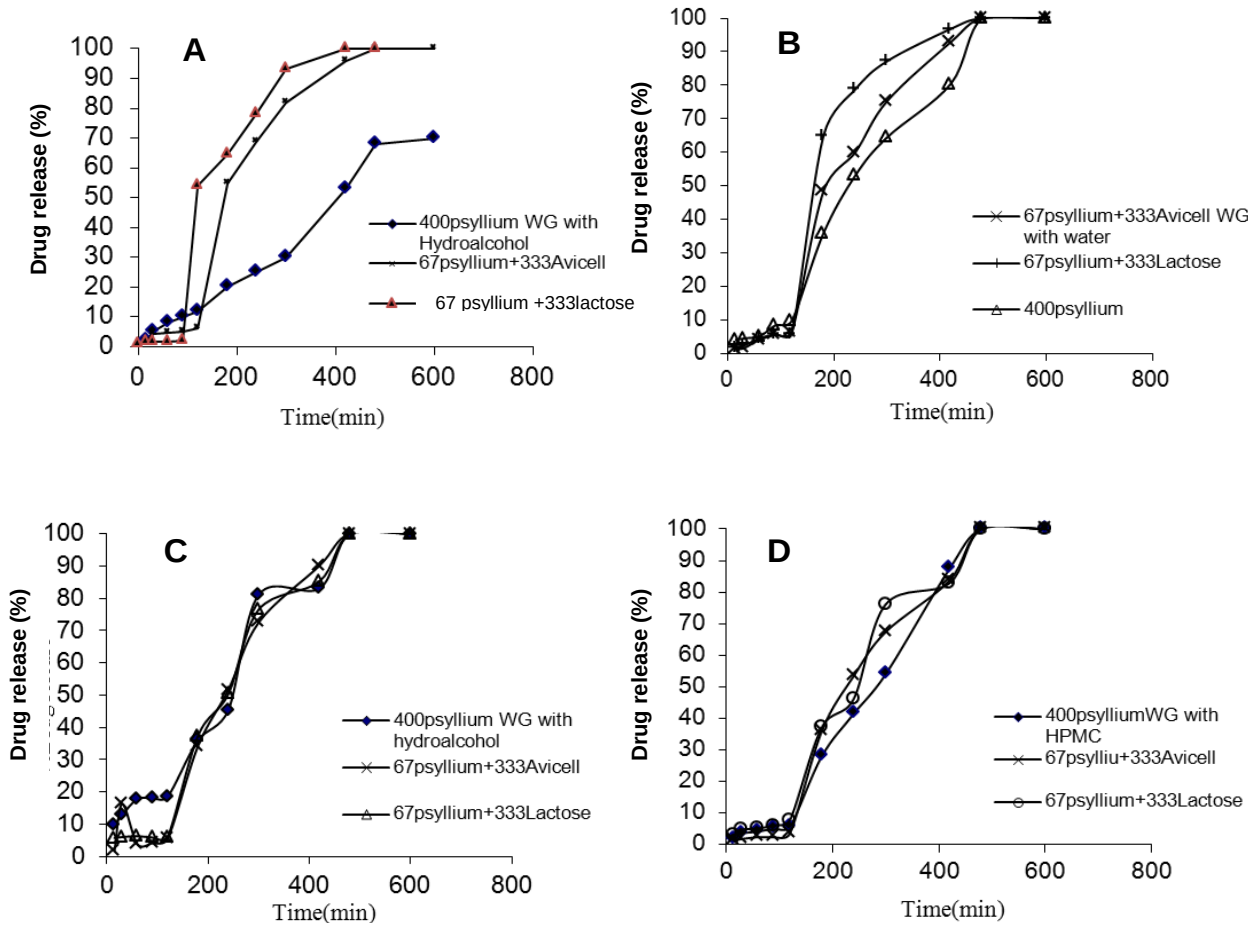

Figure 1. A to D represents dissolution profile of sodium diclofenac sustained release tablets containing 10%W/W drug in two different pH = 1.2, 6.8; during 8 h, (n = 3).

insoluble (MCC) common excipients (F22 to F49). As diagram F22 in Figure1A shows, because of pure psyllium powders have retarding ability and due to formation of tri-dimensional structures, sodium diclofenac entraps between tri-dimensional spaces, therefore this formulation has shown drug releasing profile in lower rate than the others.

As shown in Figure1A, psyllium granules containing MCC and lactose have acceptable drug release rate in comparison with pure psyllium. Type of lactose has an important effect on disintegration. Tablets from either α-lactose monohydrate or crystalline β- lactose disintegrated very quickly in water as a result of rapid liquid uptake (Deshpande et al., 1996). Disintegration mechanism changes gradually from real disintegration for tablets compressed at low compaction pressure to dissolution at pressures of 150 or 225 MPa. According to these findings, disintegration time depends on compaction load. Another study by Khan and Rhodes approved these findings. They examined this hypothesis on available spray-dried lactose. When the amorphous substance is moisturized, the outer layer of the powder bed dissolves forming a viscous gel, which includes the crystallization of lactose (Van Kamp et al., 1986; Khan and Rhodes, 1976).

Another study take place via Van Kamp et al. showed that crospovidone is an effective disintegrant. It is due to capillary action of crospovidone (Vromans, 1985; 1986).

Tablets composed of hard compaction of MCC disintegrate rapidly due to the rapid passage of water and breaking of hydrogen bonds. Figure 1A and B illustrate these facts clearly. It is shown that tablets containing lactose in comparison with MCC, release the medicine a little sooner.

Figure1C and D indicate similar results as previous formulation, but instead of hydro-alcoholic binder, water has been added to the powder mixture. Then to evaluate if there is a difference between incorporation of sodium diclofenac into the granules and without its insertion, another formulation is provided. It is demonstrated that by insertion of sodium diclofenac in granules obvious decrease in release profile is observed.

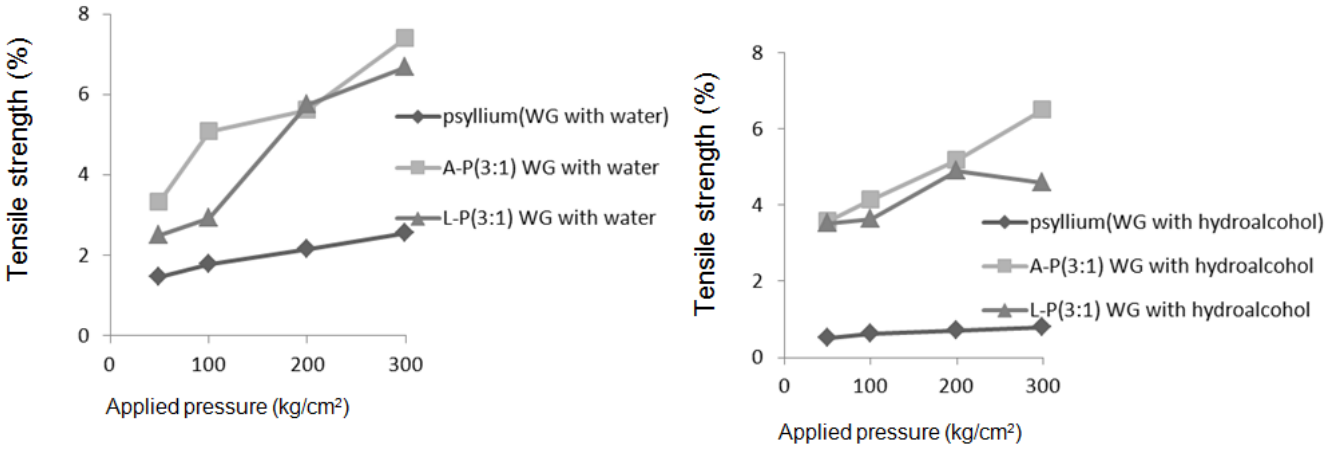

Figure 2. Relationship between tensile strength and applied compaction pressure (n = 5).

Ultimately, it shows slower drug release rate for hydroxy propyl methylcellulose (HPMC) containing formulations. HPMC is a semi-synthetic polymer with strong binding ability of formulation components.

Results related to tensile strength are shown in Figure 2. A linear relationship between tensile strength and compression pressure was determined.

As illustrated in Figure 2, with constant compression force, formulations containing lactose or MCC produced harder compacts compared with pure psyllium. Also, MCC containing tablets showed harder compacts comparing with their counterpart prepared by lactose.

DISCUSSION

Overall review of diagrams shows that in all formulations, psyllium amount has contradictory effect on drug release profile. Results represent that psyllium husk produces satisfactory release profile and referring to this polysaccharide properties such as biocompatibility, inexpensive price, being inert, environmental friendly and easily availability, it can be a suitable alternative instead of expensive synthetic retardants.

MCC is very compactable filler of all the direct-compression fillers. It is due to MCC's strong hydrogen bonds which are responsible for strength and cohesiveness compactions (Vromans, 1986).

The swellable hydrophilic polymers such as poly vinyl alcohol (PVA), MCC, hydroxyl propyl cellulose (HPC), and HPMC are used for designing of controlled release pharmaceutical dosage forms. However, due to relatively expensive price of these semi-synthetic polymers, in some researches, natural materials like guar gum, xanthan gum and psyllium has been carried out as release retardants (Chourasia and Jain, 2004; Deshpande et al., 1996). But nowadays, among all natural materials, psyllium usage due to its outstanding properties is going to be very common in sustained release systems. However, there is a main problem with psyllium physicomechanical properties, so it is packed in bulk dosage forms.

On the other hand, tablet and capsule have some advantages among other dosage forms. For example easy administration, acceptable physicochemical stability and exact dosage are advantages that caused popularity among consumers and producers. Therefore in the present study, we proposed to improve two main physicomechanical properties of psyllium powder to possible its formulation as tablets or capsules.

Conclusion

By this technique, not only do physicomechanical properties of psyllium improve, but also this natural polysaccharide could be used as a retardant polymer in preparation of sustained release formulation of water soluble drugs instead of other expensive synthetic or semi-synthetic polymers.

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