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# Synthesis and evaluation of psyllium-g-poly (N-vinyl-2-pyrrolidone) as mucoadhesive gel

**Meenakshi Bhatia* and Munish Ahuja**

*Drug Delivery Research Laboratory, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, India*

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**ABSTRACT**

*The purpose of present study was to synthesize psyllium-g-poly (N-vinyl-2-pyrollidone) using microwave assisted synthesis. Microwave assisted graft co-polymerisation of N-vinyl-2-pyrollidone on psyllium husk was optimised using two factor, three level central composite experimental design. The observation obtained from optimization study displayed that higher concentration of ammonium per sulphate and lower concentration of N-vinyl pyrollidone increases the grafting efficiency. The graft coplymerised psyllium gel was also evaluated for its mucoadhesive properties. Mucoadhesion was determined by using modified physical balance method and it is found that there is two fold increase in mucoadhesion in case of psyllium-g-poly(N-vinyl-2-pyrollidone) and in vitro release study showed the sustained release of drug metronidazole over a period of 20 hrs in case of psyllium-g-poly(N-vinyl-2-pyrollidone).*

**Keywords:** Psyllium; graft co-polymerisation;d N-vinyl-2-pyrollidone; Metronidazole

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## INTRODUCTION

Natural polysaccharides including psyllium husk and their derivatives have been vastly used in pharmaceutical industry as biodegradable and biocompatible polymers for a large number of applications such as binding, thickening, emulsifying, gelling and as controlled release agent. Psyllium husk also known as ispaghula husk comprises of seed husks of *Plantago ovata Forsk (family plantaginaceae).*

In recent years, various chemical modification of Psyllium has been done to explore it as safe and effective drug carrier in pharmaceutical industry. Polyacrylamide based hydrogels of psyllium were prepared to study the release dynamics of of drug [1]. Radiation cross linked psyllium and polyacrylic acid based hydrogels were exploited for delivery of anticancer drugs to colon [2]. The carboxymethylation and ethylation of psyllium arabinoxylan was carried out heterogeneously with sodium mono chlorate and with ethyl iodide respectively in the presence of sodium hydroxide [3]. More recently, synthesis and characterization of the psy-*cl*-poly(AAm-*co*-AAc) hydrogels was done by chemical crosslinking methods [4].

Natural polysaccharides like chitosan, guar gum, xanthan gum, tamarind seed polysachharides, sodium alginate and gum kondagogu have been modified by grafting with a variety of vinyl monomers. N–vinyl-2-pyrrolidone (NVP), a hydrophilic and non toxic bioadhesive monomer has been extensively used in the field of pharmaceuticals [5-7]. Poly vinyl pyrollidone may be used in crystallising processes [8].

In the present study grafting of psyllium husk with NVP is described. The microwave assisted graft co-polymerisation of N–vinyl-2-pyrrolidone on psyllium husk was optimised using central composite experimental

design. The graft co polymer was further evaluated for its mucoadhesive application and in vitro release by formulating the gel using metronidazole as model drug.

## MATERIALS AND METHODS

### 2.1 Materials

Psyllium seed husk (Sidpur Sat Isabgol factory, Gujarat, India) was purchased from local market. Metronidazole was obtained as gift sample from Ranbaxy Laboratories, (Gurgaon. India). Ammoniumpersulphate and N-vinyl-2-pyrrollidone were obtained from Loba Chemie Pvt. Ltd (Mumbai, India) and used as received. Freshly excised chick ileum was obtained from the local butcher shop (Hisar, India). All other chemicals used were of analytical grade and used as obtained.

### *2.2 Preparation of graft co-polymer of NVP and psyllium seed husk*

Grafting of NVP on psyllium husk was done by microwave using the method as reported earlier [9]. Briefly psyllium seed husk (5%) was dispersed in N–vinyl-2-pyrrolidone (1-4%) followed by addition of ammonium persulphate (0-10 m mol/l), a redox initiator. The dispersion was then exposed to microwave at a power of 60% for a period of 60 seconds. The grafted gum so obtained was precipitated with acetone and washed with aqueous methanol thrice to remove the unreacted monomer and reagents if any, followed by drying in oven at $40^0$C till constant weight. The grafting efficiency was calculated according to the equation described below:

$$\textit{Grafting Efficiency}\ (\%) = \frac{W1-Wo}{W2} X\ 100$$

Where, $W_o$ is weight of gum, $W_1$ is weight of grafted co-polymer and $W_2$ is weight of N–vinyl-2-pyrrolidone.

### *2.3 Experimental design*

For nonlinear response central composite designs (CCD) are frequently employed second order models. The design effectively combines the advantageous features of both factorial design and star design [10]. In the present study two factor central composite design was employed for optimization of grafting of NVP on psyllium husk. The concentration of psyllium husk, NVP and ammonium per sulphate were selected as the independent variable and grafting efficiency (%GE) was selected as the dependent variable (Table 1). Each independent variable was investigated at three levels (i.e.-1,0,+1).

### *2.4 Characterisation by FT-IR spectroscopy*

The graft co-polymer of NVP and psyllium and psyllium -g –poly (N–vinyl-2-pyrrolidone) samples were subjected to FT-IR spectroscopy in a Fourier–transform infrared spectrophotometer (Perkin - Elmer spectrum) in range of 4000 $cm^{-1}$ to 500 $cm^{-1}$ using KBr pellet method.

### *3.0 Evaluation of grafted psyllium as mucoadhesive polymer*

### *3.1 Formulation of gels*

The gels were prepared by dispersing psyllium husk and grafted psyllium husk (2% w/v each) in aqueous solution containing the drug metronidazole (1% w/v) separately. Then both the formulations were left overnight to hydrate to form gels.

### *3.2 Ex – vivo mucoadhesion study*

Mucoadhesion study of Psyllium and psyllium -g –poly (N–vinyl-2-pyrrolidone gels was carried out using modified physical balance method reported earlier [11]. Briefly, the apparatus comprised of a physical balance, containing glass plates and the beaker on each pan. One glass plates was attached to the base of the stage, and second was attached to the pan of the balance. Fresh chick ileum membrane was used for mucoadhesive testing. Fresh chick ileum was glued to the upper side of the lower plate and another was glued to the lower side of the upper plate by using adhesive (Quick fix®). The weighed gel (1 g) was placed on the chick ileum glued to the upper side of the lower plate. Then, the upper plate was placed over the lower plate and 50 g preload force (or contact pressure) was applied for 5 min (preload time). After removal of the preload force, the water was dropped in to the beaker drop wise till the plates were detached from each other. The weight of the water (g) required for the detachment of the glass plates was considered as the mucoadhesion force of the applied gel.

### 3.3 In vitro release studies

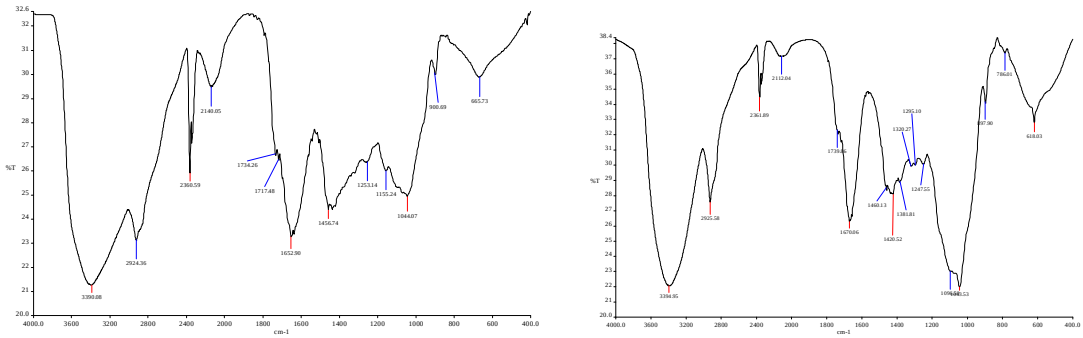
In vitro release studies of the drug metronidazole have been carried out by placing accurately weighed gel equivalent to 10 mg of the drug in the center of a hollow cylindrical dialysis membrane. This membrane was then folded and hermetically sealed from both ends which were then tied to the paddle of dissolution apparatus [12]. Dissolution was carried out in USP type II dissolution apparatus (TDL – 08L, Electrolab, India) and dissolution medium (250ml) was

Mcllvaine buffer pH 6.6. The entire system was kept at 37.0 ± 0.5°C with continuous stirring at 50 rpm. Sampling of 5 ml was done at time intervals of 0min, 15min, 30min, 60min, 2hr, 4hr, 6hr, and 10hr, 20hr, 24hr. The media volume was maintained by adding equal volumes of fresh media, and the concentration of MTZ was measured spectrophotometrically (Cary 5000, varian Australia) at 320 nm.

## RESULTS AND DISCUSSION

### 4.1 FT-IR spectroscopy

Fig.1 a & b exhibits the FT-IR spectrum of Psyllium and of psyllium -g –poly (N–vinyl-2-pyrrolidone) in the frequency region from 4000 to 500 cm-1.



**(a)** **(b)**

**Figure 1(a) FTIR spectra of psyllium (b) psyllium -g –poly (N–vinyl-2-pyrrolidone)**

The spectra of Psyllium shows a broad absorption band at 3401cm-1 which can be attributed to –OH stretching of alcohols. A peak appearing at 2926 cm-1 is due to - CH stretching of alkanes, while the peak at 1050 cm-1 ascribed to C-O-C stretch of ether. The peaks appearing at 896, 714 and 613 cm-1 may be due to polymer backbone bendings. The IR spectra of psyllium -g –poly (N–vinyl-2-pyrrolidone) shows a characteristic peak for C=O stretching vibration at 1652 $cm^{-1}$ of cyclic amide (lactam), a peak appearing at 1381 $cm^{-1}$ shows the stretching of tertiary amine that confirms the grafting of N–vinyl-2-pyrrolidone.

### *4.2 Effect of grafting conditions on grafting parameters*

The concentration of NVP and APS were selected as independent variables for the optimization study, while percent grafting efficiency was selected as dependent variable in this study pyrollidone on psyllium husk was carried out using two factor, three level central composite experimental design.

**Table 1: Central composite design using process variables with grafting efficiency**

| Run | Conc. Of APS (m mol/L) $X_1$ | Conc. Of NVP (% w/v) $X_2$ | % GE Y |
|---|---|---|---|
| 1 | 10 | 4 | 25 |
| 2 | 0 | 4 | 8.25 |
| 3 | 5 | 1 | 60 |
| 4 | 10 | 1 | 60 |
| 5 | 0 | 1 | 20 |
| 6 | 0 | 2.5 | 10 |
| 7 | 5 | 2.5 | 34 |
| 8 | 5 | 2.5 | 38 |
| 9 | 5 | 2.5 | 34 |
| 10 | 5 | 4 | 20 |
| 11 | 5 | 2.5 | 40 |
| 12 | 5 | 2.5 | 38 |
| 13 | 10 | 2.5 | 40 |

Fig 2 shows combined effect of NVP & APS on percent grafting efficiency of NVP on psyllium. It can be observed from the plot that concentration of APS has pronounced effect than NVP at lower levels of NVPO concentration. Increasing the concentration of APS at lower level of NVP results in greater degree of grafting which can be attributed to the formation of more amount of NVP free readicals. Thereby yielding greater grafting efficiency. However, on increasing the amount of NVP there is decrease in grafting efficiency which appears to be due to the formation of less number of NVP free radicals.

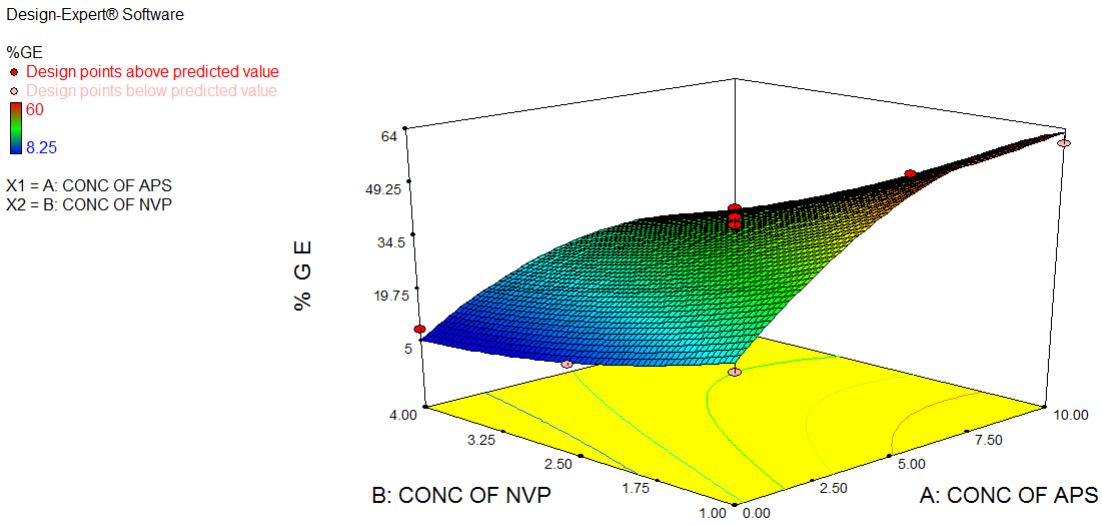



**Figure 2: 3 D response surface plot showing combined effect of conc. of APS and NVP on grafting efficiency**

Thus lower level of NVP and higher level of APS favour the formation of graft co polymer with greater grafting efficiency. Polynomial equation expressing the relationship between the concentration of APS, NVP and grafting efficiency can be described as:

$$Y(\%) = 34.029 + 90527X_1 - 12.995\ X_2 - 0.775X_1X_2 - 0.469X_1^2 + 1.446X_2^2$$

The ANOVA test was applied to the model to estimate its significance. The ANOVA analysis of the model showed the model to be significant ($P<0.05$) and value of $R^2$ being 0.9631 with non-significant 'lack of fit'. The adequate precision 20.406 (greater than 4.0) indicate adequate signal.

### *4.3 Mucoadhesion Study*

It was observed from the mucoadhesive study carried out by using modified physical balance method that the force required for the detachment of chicken intestinal membranes from psyllium -g –poly (N–vinyl-2-pyrrolidone) (0.284N) was more than double than psyllium gel (0.117N).

### *4.4 In vitro release*

Fig. 3 displays the *in vitro* release profile of metronidazole from various gel formulations. The release of metronidazole was found to be retarded for a period of 20 hrs.

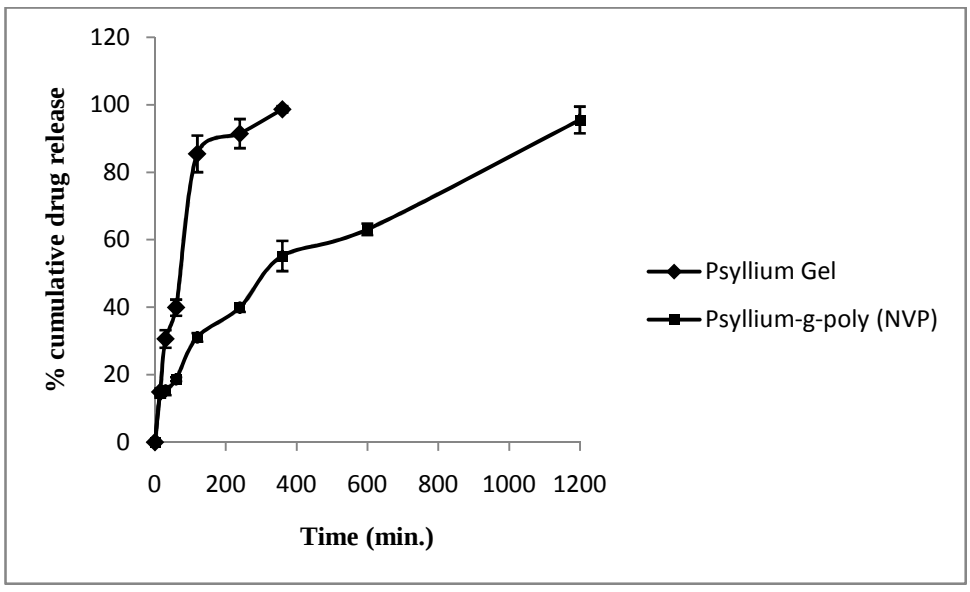



**Figure 3: in vitro release of metronidazole from psyllium and psyllium -g –poly (N–vinyl-2-pyrrolidone)**

The release of metronidazole loaded gels were fitted into various kinetic models to estimate their release kinetics and mechanism of release (Table 2).

**TABLE 2. Modeling and release kinetics of metronidazole gel formulations**

| Formulation | Zero order R2 | First order R2 | Higuchi R2 | Korsemeyer-Peppas R2 | n |
|---|---|---|---|---|---|
| **Psyllium gel** | **0.628** | **0.880** | **0.927** | **0.897** | **0.145** |
| **psy-g–poly (NVP) gel** | **0.722** | **-1.92** | **0.992** | **0.930** | **0..688** |

The results of release rate data for all the gel formulation fitted best into higuchi release kinetics. Further, the value of *'n'*, the release exponent of Korsemeyer and Peppas equation indicates that the release of MTZ from psyllium -g –poly (N–vinyl-2-pyrrolidone) (n>0.5) occurs by combination of polymer relaxation and diffusion through the polymeric matrix [12].

## CONCLUSION

Modification of psyllium was carried out by microwave assisted grafting with (N–vinyl-2-pyrrolidone) and is evaluated for bioadhesive delivery of metronidazole. Synthesis of psyllium – g - (N–vinyl-2-pyrrolidone) was carried out using microwave assisted and optimized using 2 factor, three level central composite experimental design. The results of optimisatio study revealed that increasing concentration of APS increases the graftng efficiency. The optimized calculated parameters were concentration of NVP (1.04%) and APS (9.25m mol/l). the optimized batch has grafting efficiency of 60%. On comparative evaluation of metronidazole loaded psyllium – g - (N–vinyl-2-pyrrolidone) with the psyllium gel, the gels of graft co polymer showed greater bioadhesion and prolonged release of drug in 24 hr. in conclusion, psyllium – g - (N–vinyl-2-pyrrolidone) can be posed as bioadhesive material for drug delivery.

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