Application of polyacrylamide grafted barley as promising drug formulating agents

Kartick Prasad Dey*, Sumit Mishra*

Department of Chemistry, Birla Institute of Technology-Mesra, Ranchi 835215, Jharkhand, India

*Corresponding author: Tel: (+91)-9546532064; (+ 91)-9431337645;
E-mail: chem.kartick@gmail.com; sumitmishra1@gmail.com

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Abstract

In this article, we have reported the synthesis of Polyacrylamide grafted Barley (Ba-g-PAM) by free radical copolymerization technique. Ceric ammonium nitrate (CAN) was used as a free radical initiator for this synthesis process. Various grades of Ba-g-PAM were synthesized by varying the CAN and AM concentration. The swelling properties of these different grades of Ba-g-PAM were performed in different pH media like 1.2, 6.8& 7.4 at 25^0C and 37^0C. All grades showed better swelling properties at 37^0C than 25^0C. The matrix tablets of different grades of grafted materials were prepared by following the standard protocol using 5-flurouracil as a model drug. The swelling and erosion property of each matrix tablet was performed at 37^0C in different pH media like 1.2, 6.8& 7.4. The percentage of drug released from different matrix tablets was determined in different pH media like 1.2, 6.8& 7.4 (similar to GI tract). The drug release kinetics was also determined with the help of percentage drug release results. The matrix tablet of best grade i.e. Ba-g-PAM5 follows non-fickian kinetics, so, the diffusion rate of drug from matrix tablet and the relaxation rate of the polymer chains in the matrix tablets are comparable. The acute oral toxicity test was performed on the basis of Organization of Economic Co-operation and Development (OECD) guidelines, showing non-toxic behavior. The above results support that the controlled release of 5-flurouracil in the colonic region has been successfully carried out. This developed material may be of help in the colon cancer treatment.

Keywords: Barley, graft copolymer, radical polymerization, controlled drug delivery, 5-flurouracil.

Introduction

The mechanism of Controlled drug release methodology has been evolving since last three decades. The drug delivery research has been going on since 1952 [**1**] and has been classified into three generations i.e. 1st generation (1950-1980), second generation (1981-2010) and third generation (2011 till date)[**2**]. While the 1st generation drug delivery research mainly focused on developing oral and transdermal sustained release systems and established the release mechanism [**3**], the second generation drug delivery reported zero order drug release, smart polymer and hydrogel for environmental sensitive self-relegated release, peptide and protein delivery, nanoparticles for tumour targeted delivery [**4-6**]. Now the third generation drug delivery research is being carried on the targeted drug delivery for anticancer drug, long term drug delivery system, in vitro-in vivo correlation for prediction of pK profile from in vitro drug release study [**7-10**]. So the targeted drug delivery research continues to be evaluated and is researched further for better results. The major advantages of this system are its biocompatibility, nontoxic nature and reproducibility in results. The drug delivery system controls the therapeutic level of drug within the desired range, thus decreasing the toxicity of drug and delivering it to the targeted place in a controlled way [**11-13**]. Till now, various types of formulation routes of drug have been reported using graft copolymer, hydrogel based on polysaccharide, nano gel using polysaccharide etc [**14-17**]. The graft copolymers using polysaccharide play an important role in formulation in the pharmaceutical industries. As the polysaccharides are easily available, cost effective, non toxic and biodegradable, this technique is increasingly becoming popular and surpassing the conventional means and materials for drug delivery.

Among polysaccharides, Barley (*Hordeum vulgare L.)* is an important natural resource worldwide, being the fourth most abundant cultivated product in the world [**18**]. The main component of barley is polysaccharide i.e 90 to 95% and rest is protein and fats [**19-20**]. The carbohydrate and dietary fibres are the main component in barley. Starch is the carbohydrate component which consists of about 25 to 30% of amylase and rest amylopectin. Amylase is a linear carbohydrate made up by D-Glucose unit and amylopectin is a branched carbohydrate of glucose made up by $\alpha(1\rightarrow4)$ glycosidic bonds [**21**]. In dietary fibres, β- glucan is a well-known

component. It is made by the D-Glucose monomer linked by β-glycoside bond [**22**].

Grafting is one of the recently preferred methods for the modification of polysaccharide. Due to grafting the properties of polysaccharide change considerably which makes it suitable for diverse applications [**23, 24**]. It is a type of branched copolymer. The graft copolymer is defined classically as "when monomers molecules attach on the polymeric backbone as formed polymer through covalent linkage" [**25**].

Among all the methods, free radical copolymerization methods using radical initiator are being used for synthesis of graft copolymers [**26, 27**]. These types of modified polysaccharides are very popular in pharmaceutical industries for the formulation of cancer treatment drugs [**28-30**]. 5-Flurouracil is an "antimetabolite" drug for the treatment of cancer. It is the mostly used for treatment of colon and rectal cancer, breast cancer, gastrointestinal cancer and ovarian cancer etc [**31**]. The biological half life time is 10-20 minutes owing to rapid metabolism and incomplete or negligible oral absorption in the gastrointestinal tract (GIT) [**32**]. So, the therapeutic level of the drug is very high. Thus, the main aim of novel drug delivery system is to decrease the therapeutic level of the drug and reducing the side effects as well as toxicity of the drug.

Although, several modified food polysaccharides have been used for the drug formulation [**33, 34**], but barley has not been explored upon any such applications before. In this article, we have explored the research in the drug formulation field by modification of barley using acrylamide monomer followed by radical polymerization technique. The matrix tablet was prepared by the synthesized materials for the formulating of 5-flurouracil drug. The controlled drug release behavior of matrix tablet has been studied using it as a model drug in different pH regions simulating the GIT environment. Acute oral toxicity according to OECD guidelines have also been carried out to confirm its nontoxic nature.

Experimental

Materials

Barley was procured from Reckitt Benckiser, Ltd. New Delhi, India and Mfd. By Modern Flour Mills (P) Ltd. and Acrylamide was supplied by CDH, New Delhi, India. Ceric ammonium nitrate was supplied by Thermo Fisher Scientific India Pvt. Ltd, Mumbai, India and Assay (after drying) is 98-102%. Acetone was purchased from RANKER, RFCL Limited, New Delhi, India and Assay (GC) is NLT 99.5%. Hydrochloric acid was supplied by Thermo Fisher Scientific India Pvt. Ltd, Mumbai, India and Assay is 35.8-38%. Potassium chloride was supplied by RANKER, RFCL Limited, New Delhi, India and Assay is NLT 99.5%. Disodium hydrogen phosphate anhydrous was supplied by RANKER, RFCL Limited, New Delhi, India and Assay is NLT 99%. Sodium dihydrogen orthophosphate dihydrate were supplied by Thermo Fisher Scientific India Pvt. Ltd, Mumbai, India and minimum Assay (acidimetric) is 98%. 5-Fluorouracil (AR grade) was supplied by Spectrochem, Mumbai, India and minimum purity is 99%. All the chemicals were used as received; without further purification.

Synthesis and purification of Polyacrylamide grafted barley

The grafting reaction was carried out following the free radical copolymerization method using ceric ammonium nitrate as an initiator. In this procedure, we chose 250 ml conical flask for placing the reaction mixture under nitrogen atmosphere. Measured amount of barley was taken in 40 ml distilled water in this conical flask with constant stirring. Nitrogen gas was purged to achieve inert atmospheric condition in the reaction mixture. Separately, desired amount of acrylamide was dissolved in 10ml distilled water and added slowly into the conical flask and mixed well. Afterwards, the calculated amount of ceric ammonium nitrate was added drop wise and stirred; the reaction vessel was left undisturbed for 24h under inert atmosphere. Normal room temperature was maintained throughout the reaction. A gel like mass was obtained in the reaction vessel which was precipitated in excess acetone to collect the grafted materials. Then, the materials were kept in hot air oven at 45^0C for 72h till a constant weight was obtained. Different grades were obtained by varying the acrylamide and ceric ammonium nitrate concentration.

In this reaction, the probability of formation of Polyacrylamide (homopolymer) is negligible. To ensure this, grafted materials were kept in excess amount of acetone for 72h to extract the homopolymer from the grafted materials. The percentage grafting and grafting efficiency are calculated by the following equation:

$$\%G = \frac{\text{wt. of graft copolymer - wt. of polysaccharide}}{\text{wt. of polysaccharide}} \times 100$$

$$\%GE = \frac{\text{wt. of graft copolymer - wt. of polysaccharide}}{\text{wt. of monomer}} \times 100$$

All synthesis details have been reported in our earlier publications.

Preparation of matrix tablet

The matrix tablets using these synthesized graft copolymers were prepared following the direct compression method. In this procedure, finely ground graft copolymer was taken with the model drug (5-Flurouracil) and poly vinyl pyrrolidone (binder) in 10:1:1 ratio and mixed well. Further, this mixture was moisturized with ethanol and mixed further [**9, 29**]. Then it was kept in hot air oven at 45^0C to remove ethanol and get a constant weight. Later, a mixture of silicon-di-oxide and magnesium stearate (2:1 ratio) as a lubricant was mixed with it and used to lubricate sieve (20 mesh). Tablets of 250 mg each were prepared using tablet making machine. The weight of drug loaded in each matrix was 250 ± 2 mg.

Swelling and erosion study of each matrix tablet

The swelling studies of different matrix tablets were performed in different pH media (i.e. 1.2, 6.8 & 7.4) at 37^0C & 25^0C following the standard procedure. In this procedure, different matrix tablets (250 ± 2 mg) are taken in different pH dissolution medium (50ml) in 80ml beakers and kept at specified temperature for 12h. Later, the swollen tablet was blotted with filter paper and weighed again. The percentage swelling was determined using this equation [**35**].

$$P_s = \frac{\text{Weight of swollen tablet - Weight of dry tablet}}{\text{Weight of dry tablet}} \times 100$$

The tablets disintegrate during drug release; depicting the erosion behavior of the matrix tablet. The percentage erosion of each matrix tablet was evaluated in different pH dissolution medium at 37^0C by standard procedure. In this procedure, each matrix tablet is immersed in 50 ml dissolution medium at 37^0C for 12h. Later, the tablet was blotted with filter paper and weighed again. The percentage erosion was determined using this equation [**35**].

$$D(t) = \frac{W_i - W_{d(t)} - W_d(1 - (M_t / M_\alpha))}{W_i} \times 100$$

where, W_i is the initial dry weight of the tablet, $W_{d(t)}$ is the weight of tablet at a time t, W_d is the initial weight of drug , M_t is the percentage of drug release at a time t and M_α is the percentage of drug release at infinite time. The % swelling and % erosion value has been tabulated in **Table 1**(supporting information).

Acute oral toxicity study

The acute oral toxicity study of the developed materials has been evaluated on the basis of the Organization of Economic Co-operation and Development (OECD) guidelines for the test of chemicals 425, adopted Dec 17, 2001. This protocol was approved by the animal ethics committee of Birla Institute of Technology, Mesra, Ranchi, India. (Approval No. BIT/PH/IAEC/04/2014 dated 30/4/2014). In this protocol, five week old Albino mice were taken to perform this study. At first, Mice were housed in a polycarbonate cage with sufficient food and deionized reverse osmosis water was available to them ad libitum at 20 − 25 ° C and 40 −70% relative humidity in a 12 h light on / light off cycle [**18, 30**]. A single dose of 2000 mg/kg body weight of Ba-g-PAM 5 was administered by garvages using a stomach tube to the first animal. The same dose was administered to the remaining four animals after survival of the first animal. The animals were kept under continuous observation upto 4 h after dosing. The observation was continued up to 14 days. The mortality rate was evaluated by visible observation and reported accordingly.

Results and discussion

Synthesis of Ba-g-PAM and its characterization

The Polyacrylamide grafted barley was synthesized following the free radical copolymerization method using acrylamide as monomer and ceric ammonium nitrate as an initiator. Free radicals are generated on the barley backbone via redox process after the acrylamide monomer is grafted on the barley backbone in form of a polymer i.e. Polyacrylamide. The reaction is optimized by varying the concentration of monomer and initiator. The detailed discussion of the formation of Polyacrylamide grafted barley and its characterization is already reported in our earlier study [**25**].

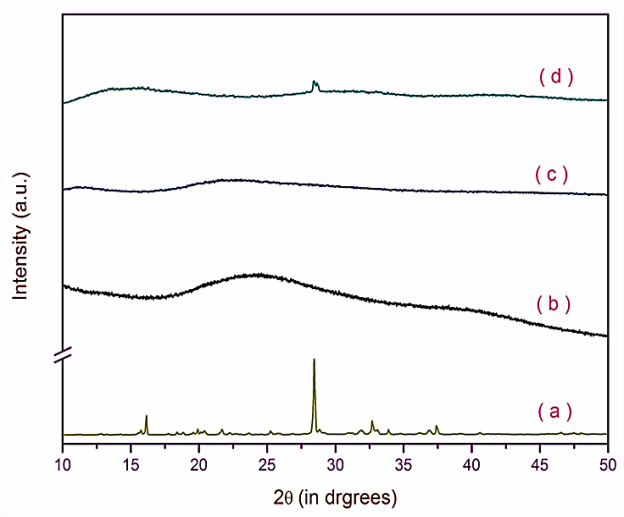


Fig 1: XRD patterns of (a) 5-FU (b) Ba-g-PAM5 (C) PVP (d) Matrix tablet.

Interaction of 5-FU drug in matrix tablet

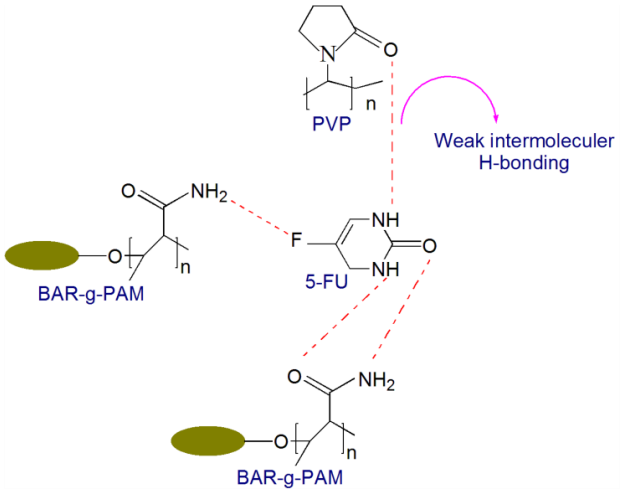
The interaction of 5-FU drug into the matrix tablet has been confirmed by the X-ray diffraction (XRD) pattern. The Ba-g-PAM5, drug (5-FU), PVP and matrix tablet were scanned 10 to 80^0 2θ using Powder X-ray diffraction (XRD) pattern in a Bruker axis diffractometer (D8-Advance) using CuKα radiation. The recorded spectrum is reported in **Fig. 1(a)**, **(b), (c)** & **(d)**. From the diffractogram **Fig 1(a)** of 5-FU it is observed that 5-FU is highly crystalline in nature. 5-FU shows characteristic peak values at 2θ of 16.19^0, 28.43^0, 32.66^0 and 37.39^0. The 2θ value at 28.43^0 is very intense showing the crystalline nature of 5-FU.

In **Fig. 1(b)** no such characteristic peaks for Ba-g-PAM 7 and PVP is observed, showing its amorphous nature. The characteristic peaks disappear in the matrix tablet **Fig. 1(d)**, confirming the drug dispersion in the matrix tablet due to some intermolecular attraction of the polar and non-polar atoms present in Ba-g-PAM5, 5-FU & PVP. This is shown in **Scheme 1**. A low intensity peak with 2θ value at 28.50^0 is observed, confirming the presence of 5-FU in the matrix tablet.

Swelling and erosion study of the matrix tablet

Swelling and erosion of the matrix tablets prove that % swelling and % erosion increase with the percentage grafting **Table 1**(supporting information).

As the number of polymeric chains attached on the barley backbone increases due to the grafting reaction; the void space for absorbing water molecules also increases. So, the void space of the graft copolymer depends upon percentage grafting. % swelling increases with increasing percentage grafting due to which water uptake capacity increases. Erosion results show that the barley based matrix tablet disintegrates very fast in all pH media compared to all other grades. On the basis of these results, it is confirmed that 5-FU drug release from the matrix tablets of Ba-g-PAM based will be in controlled manner.



Scheme 1: Schematic representation of binding mode in the matrix tablet.

On the other hand, % swelling is faster in pH=7.4 medium compared to 1.2 & 6.8 medium. This is because in acid medium (pH=1.2) polyacrylamide chains do not ionize compared to 6.8 & 7.4. In basic medium, the ionization rate of Polyacrylamide chains increases, so the relaxation rate of the Polyacrylamide chains also increases. As a result, the % swelling increases, consequently the drug release rate of 5-FU from the polymeric matrix tablets also increases. The correlation between % swelling and % erosion with percentage grafting for matrix tablets have been shown in **Fig 2(a)**, **2(b) & 2(c)**.

In vitro drug release study

In vitro drug release phenomena of 5-FU from developed matrix tablets was evaluated on the basis of United States Pharmacopeia (USP) rotating paddle method. In this method, each matrix tablet was immersed in 900ml dissolution media (pH = 1.2, 6.8 & 7.4) at 37^{0}C with a constant rotation of 65rpm for 12h. Aliquot was withdrawn by pipette at 1h interval periodically and equal volume of same fresh dissolution solution was added in the isothermal bath to maintain the constant volume each time [**36**]. The absorbance of the collected samples was measured at λ_{max}= 520nm by UV-Vis spectrophotometer. The amount of drug release was determined with the help of standard calibration curve of 5-FU in different dissolution media.

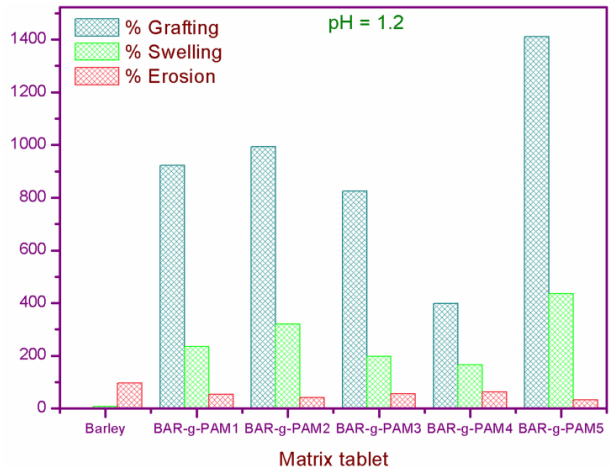


Fig. 2. (a) Correlation between % Swelling , % Erosion and % Grafting of matrix tablet of barley and various grades of Ba-g-PAM in pH= 1.2 at 37^{0}C.

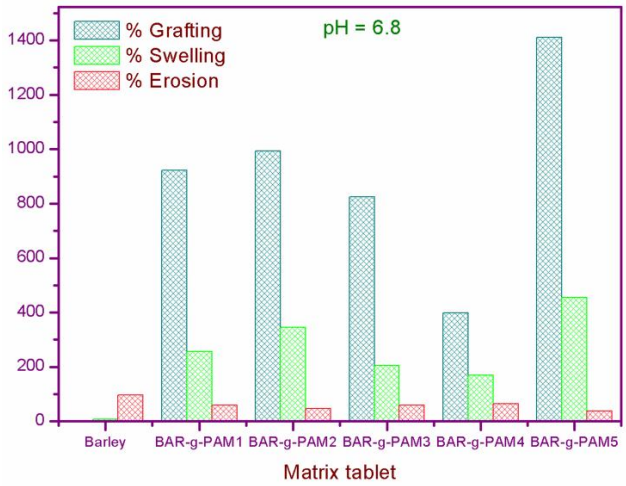


Fig 2. (b) Correlation between % Swelling , % Erosion and % Grafting of matrix tablet of barley and various grades of Ba-g-PAM in pH= 6.8 at 37^{0}C.

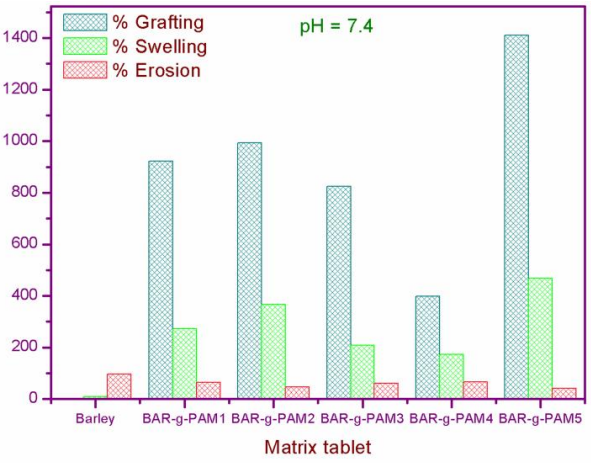


Fig 2. (c) Correlation between % Swelling , % Erosion and % Grafting of matrix tablet of barley and various grades of Ba-g-PAM in pH= 7.4 at 37^{0}C.

The drug release profile i.e. cumulative drug release vs. time has been depicted in **Fig 3(a)**, **Fig 3(b)** and **Fig 3(c)**. The drug release kinetics of 5-FU from different matrix tablets is evaluated on the basis of amount of drug released. The percentage swelling of matrix tablet at 37^0C is greater than 25^0C in different pH conditions like pH=1.2, 6.8 &7. This is a good evidence for in vitro drug release study performed at 37^0C. The correlation between % Swelling of barley and different grades of Ba-g-PAM with corresponding % grafting at pH=1.2 , 6.8 & 7.4 at 25^0c and 37^0c temperature respectively has been shown in **Fig 3(a)** , **Fig 3(b)**&**Fig 3(c)** .

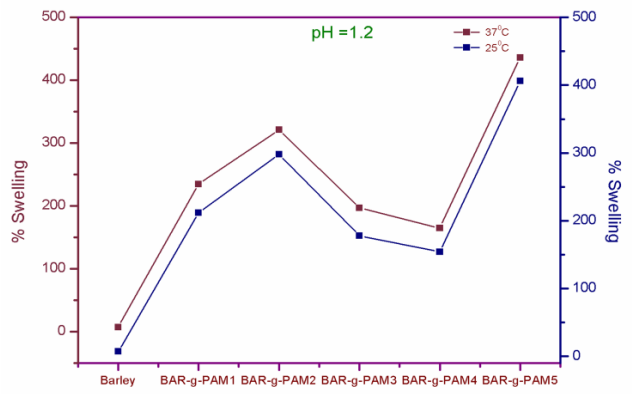


Fig 3. (a) Correlation between % Swelling of matrix tablet of barley and different grades of Ba-g-PAM with corresponding % Grafting at in pH= 1.2 at 25^0c and 37^0c temperature.

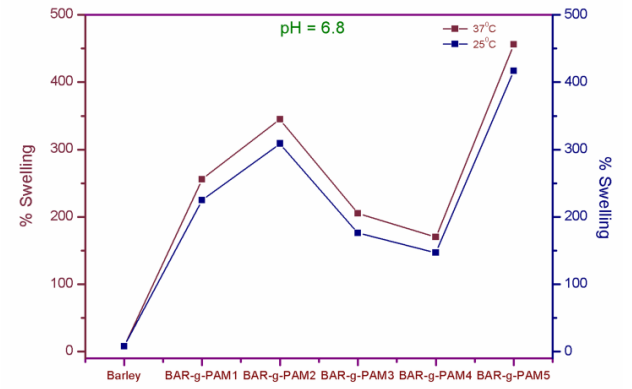


Fig 3. (b) Correlation between % Swelling of matrix tablet of barley and different grades of Ba-g-PAM with corresponding % Grafting at in pH= 6.8 at 25^0c and 37^0c temperature.

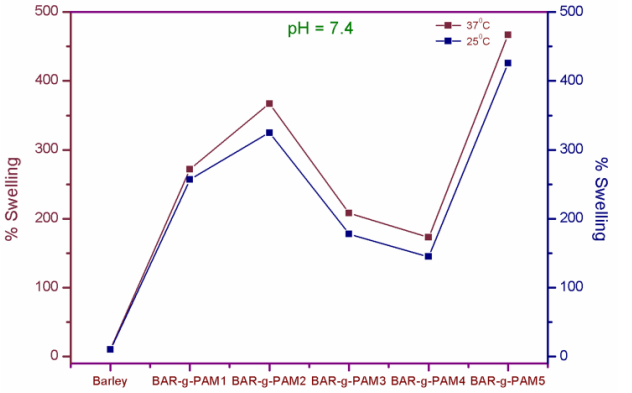


Fig 3. (c) Correlation between % Swelling of matrix tablet of barley and different grades of Ba-g-PAM with corresponding % Grafting at in pH = 7.4 at 25^0c and 37^0c temperature.

In vitro drug release

The percentage of drug release vs. time (in minutes) has been shown in the **Fig 4(a), Fig 4(b) & Fig 4(c)** on the basis on 'In vitro' drug release performance. The 't_{50}' values (time taken for release of 50% of the enclosed drug from matrix tablet) have been evaluated on the basis of controlled drug release results and tabulated **Table 1** (supporting information). The 't_{50}' values from matrix tablet prepared from barley is too low in all pH conditions and all matrix tablets prepared using different grades of Ba-g-PAM remain intact even after 12h drug release study. So, these results indicate that barley based matrix tablet is not suitable for controlled drug release study. The 't_{50}' values in acidic medium (i.e. pH=1.2) of all matrix tablet is higher than pH = 6.8 & 7.4 medium. In acidic medium, the–$CONH_2$ group of Polyacrylamide chains contain unipositive charge but in the case of pH = 6.8 medium the –$CONH_2$ group will be free and at pH = 7.4 medium –$CONH_2$ group may be partially hydrolyzed and –$CONH_2$ group will be free. On the other hand, at pH= 6.8 & 7.4 medium, 5-FU gains extra stability. As a result, the drug release rate is faster in pH =7.4 medium rather than pH= 6.8 & 1.2. This is shown in **Scheme 2.**

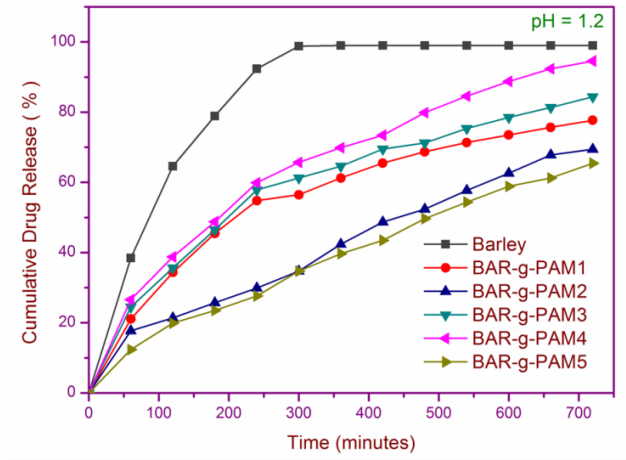


Fig 4(a). Drug release profile in pH= 1.2 dissolution medium.

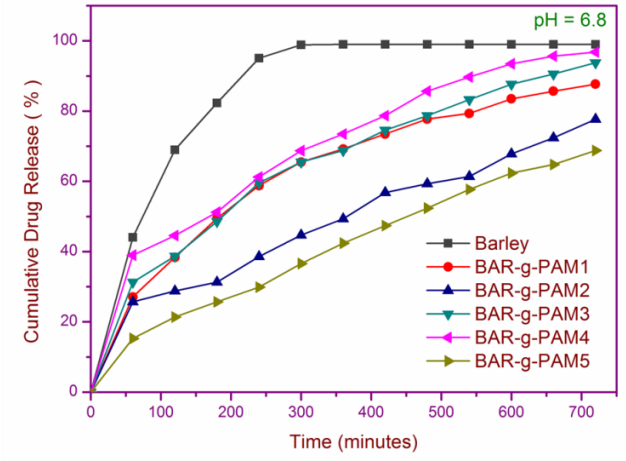


Fig 4(b) : Drug release profile in pH= 6.8 dissolution medium.

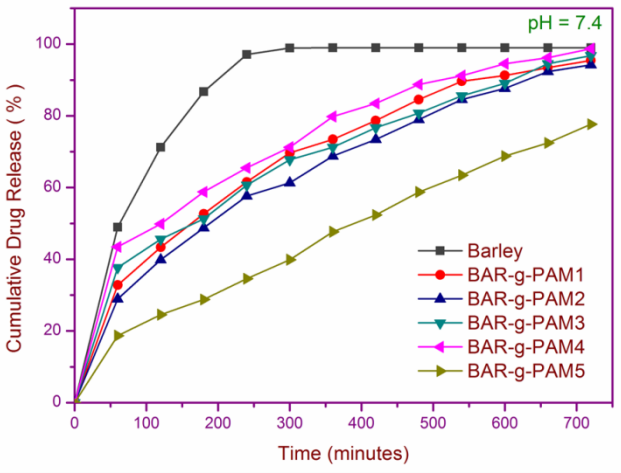
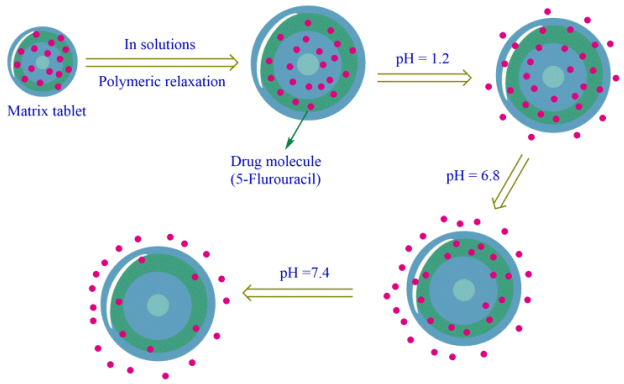


Fig 4. (c). Drug release profile in pH= 7.4 dissolution medium.



Scheme 2: Schematic representation of 5-FU release from matrix tablet in different pH media.

The 't_{50}' values of different matrix tablets increase with increase in the percentage grafting because the hydrodynamic volume and number average molecular weight increases with the percentage grafting. As a result, weak intermolecular attraction between 5-FU, PVP & Ba-g-PAM persists. So, drug release from the matrix tablet will be slower.

Mechanism of drug release

The drug release phenomena of 5-FU from different matrix tablets follows three steps. As the dissolution solution enters inside the matrix tablets i.e hydration of the matrix tablet occurs. Then, the branching chains of the graft copolymers relax in presence of dissolution medium or erosion of the matrix tablet takes place. Finally, the drug molecules come out in the dissolution medium i.e transport of drug in the dissolution medium takes place. So, we see that the drug release from the matrix tablet is a diffusion phenomenon. Till now, three types of diffusion mechanisms have been developed for drug transport phenomena i.e. Fickian diffusion, non-fickian diffusion and case II diffusion [**35**]. Korsemeyar–Peppas model is the best relationship for understanding the drug release mechanism from matrix tablet [**37, 38**].

$$M_t/M_\infty = k\, t^n$$

where $M_t$and M_∞ represent the amount of drug released from the matrix tablet at time t and at infinite time (equilibrium state), respectively ,'k' is a constant representing the apparent release rate (%/min) that takes into account the structural and geometric characteristics of the release device. 'n' is the diffusion exponent. The value of 'n' is useful for the determination of drug release mechanism. This equation holds only for the first60% of the fractional drug release from the tablets ($M_t/M_\infty \leq 0.6$; $\log(M_t/M_\infty) \leq -0.22$), for which the one-dimensional diffusion under a perfect sink condition holds true [**39**]. When 'n' value is $n \leq 0.45$, it indicates Fickian diffusion, so the rate of diffusion is less than rate of relaxation. When the 'n' value ranges $0.45 < n < 0.89$, it indicates non-fickian diffusion, here diffusion and relaxation rates are comparable. When 'n' value is $n > 0.89$, it indicates that the case II diffusion i.e. relaxation controlled transport where diffusion rate is very fast compared to the relaxation rate of the polymer. When 'n' value is equal to 1, it indicates that it follows the 1st order kinetics. The value of 'n' was calculated from the slopes of the $\log(M_t/M_\infty)$ vs. $\log t$ plot in acidic and neutral pHs.

$$\log\left(\frac{M_t}{M_\infty}\right) = \log k + n \log t$$

Plots of log(Mt/M∞) against log(t) for the barley and synthesized grades of Ba-g-PAM in acidic medium (pH = 1.2) and pH = 6.8 & 7.4 medium, are shown in **Fig 5(a) , Fig 5(b) & Fig 5(c).**

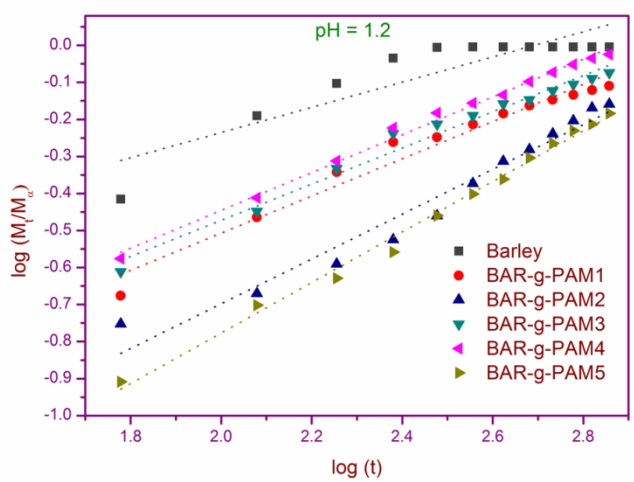


Fig. 5(a).Plots of log (M_t/M_α) vs log(t) for the barley and various grads of Ba-g-PAM at pH= 1.2.

From this plot we calculated the n, k and R^2 values, tabulated in **Table 2** (supporting information). From **Table 2** (supporting information) it is clear that the matrix tablet of barley shows that 'n' value is lessthan 0.45 in all pH media, so it shows Fickian diffusion. Other matrix tablets i.e Ba-g-PAM1, Ba-g-PAM2, Ba-g-PAM3, Ba-g-PAM4 & Ba-g-PAM5 shows the 'n' value between 0.45 and 0.89 in pH= 1.2 medium, itsmatrix tablets follow the non-fickian diffusion in pH =1.2 medium. At pH=6.8,

the 'n' value of matrix tablet (Ba-g-PAM4) is less than 0.45, it shows Fickian diffusion. Also, at pH= 7.4, 'n' value of the matrix tablets i.e. Ba-g-PAM1, Ba-g-PAM3 & Ba-g-PAM4 is less than 0.45, which shows Fickian diffusion. As the 'n' value of the matrix tablet (Ba-g-PAM5) is between 0.45 and 0.89 in all pH media, it shows non-fickian. So, the diffusion rate of drug from matrix tablet and the relaxation rate of the polymer chains in the matrix tablets are comparable.

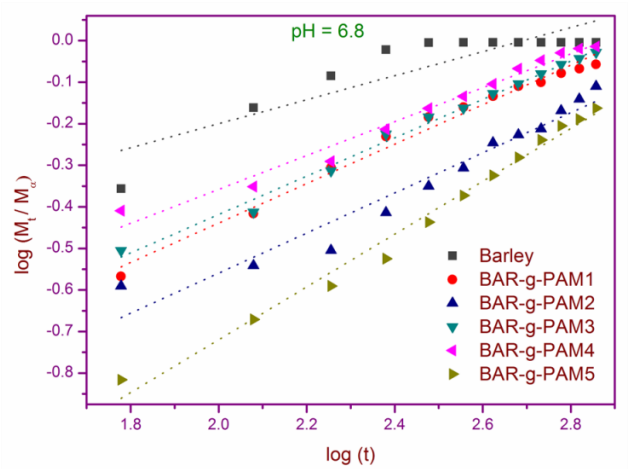


Fig. 5(b) : Plots of log (M_t/M_α) vs log(t) for the barley and various grads of Ba-g-PAM at pH= 6.8.

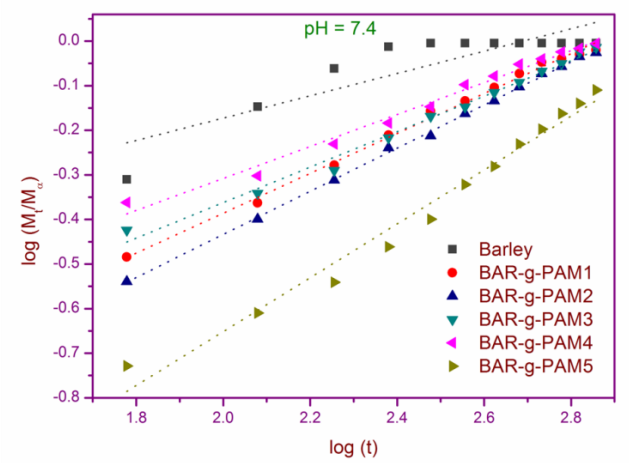


Fig. 5(c) : Plots of log (M_t/M_α) vs log(t) for the barley and various grads of Ba-g-PAM at pH= 7.4.

Acute oral toxicity study

From the oral toxicity study of Ba-g-PAM5 it was found that there was no abnormal behavior of Albino mice after 7 days observation period. According to Organization of Economic Co-operation and Development (OECD) guidelines for the test of chemicals 425, adopted Dec 17, 2001, Annexure-4, the LD_{50} value is greater than the 2000mg/kg dose of Ba-g-PAM5, so for animal welfare, testing in animals is discouraged. According to globally harmonized system (GHS), if the LD_{50} value is greater than the 2000mg/kg dose, then the tested materials fall under "category 5" and the toxicity rate will be "zero''. So the grafted materials (Ba-g-PAM5) fall under the "category 5", so its toxicity rating is "zero" [**18, 30**].

Conclusion

The Polyacrylamide grafted barley demonstrated the controlled drug release of 5-FU from matrix tablets in low erosion rate. The drug release rate directly depends upon the percentage grafting. Higher the percentage grafting, lower will be the drug release rate. The drug release also depends upon the pH medium. According to the experimental results, the drug release rate in pH = 7.4 medium is higher than pH = 6.8 & 1.2. So, it indicates the release rate of 5-FU in colonic region is in higher rate. The diffusion constant of matrix tablet prepared from Ba-g-PAM5 (best grade) lies between 0.45–0.89 range. This simply indicates that it follows non-fickian diffusion. The grafted material is nontoxic in nature on the basis of acuteoral toxicity study. According to the above results, the grafted material is suitable to be used as a drug formulating agent for treatment of colon cancer.

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Author's contributions

Conceived the plan: Dr. Sumit Mishra ; Performed the experiments: Mr. Kartick Prasad Dey; Data analysis: Mr. Kartick Prasad Dey & Dr. Sumit Mishra; Wrote the paper: Mr. Kartick Prasad Dey. Authors have no competing financial interests.

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