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Inulin and poly(acrylic acid) grafted inulin for dissolution enhancement and preliminary controlled release of poorly water-soluble Irbesartan drug

Mohammad M. Fares[a,*], Mu'taz Sheikh Salem[b], Mai Khanfar[b]

[a] Department of Applied Chemistry, Faculty of Science & Arts, Jordan University of Science and Technology, P.O. Box 3030, Irbid 22110, Jordan
[b] Department of Pharmaceutical Technology, Faculty of Pharmacy, Jordan University of Science and Technology, P.O. Box 3030, Irbid 22110, Jordan

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ABSTRACT

In this article, inulin and poly(acrylic acid) grafted inulin copolymer were used to enhance the dissolution of poorly water-soluble Irbesartan drug and to control its drug release rate, respectively. Topological structure of inulin showed sleazy separable flower-like platelets and granules accumulated above each other, which adapt it to physically bind Irbesartan drug and enhance its dissolution. Consequently, the increase of inulin content in the polymeric matrix was found to increase the drug dissolution gradually until it reaches its maximum (~90%) within the first 60 min. The release rate had followed zero-order transport mechanism. On the other hand, the poly(acrylic acid) grafted inulin copolymer, characterized using ^{1}H NMR, FTIR, TGA, and SEM techniques, was found to form highly consistent amorphous systems of two-dimensional surfaces with some voids topology. Such features adapted it to control Irbesartan drug dissolution (~33%) and show Fickian diffusion mechanism.

1. Introduction

Poorly water-soluble drugs are drugs that have lower solubility than 100 μg/ml in aqueous solution (Watanabe et al., 2004). The poor solubility could result with low bioavailability in oral administration due to slower rate of absorption than dissolution rate. The improvement of oral bioavailability of the poorly water-soluble drugs could be achieved through the improvement of the dissolution rate. Various methods and/or techniques have been used for this purpose such as meso-porous silica (Heikkilä et al., 2007; Mellaerts et al., 2008), self-emulsifying drug delivery systems (Gursoy and Benita, 2004), solid dispersion (Chiou and Riegelman, 1971; Serajuddin, 1999; Sumnu, 1986; Kawabata et al., 2010), nanocrystal formation (Shegokar and Müller, 2010), spray-dried powders (Uchiyama et al., 2010) and water-soluble polymer carriers such as polyethylene glycol (PEG), poly(vinylpyrrolidone), hydroxypropylmethylcellulose and chitosan (Yamashita et al., 2003).

Inulin is a natural polysaccharide composed of a mixture of oligo- and/or polysaccharides constituted of fructose unit chains linked by β (2→1) fructose bond, and terminated generally by a single glucose unit (French, 1993). Due to its degradable and biocompatible nature in human body, inulin was found to contribute in versatile applications such as food industry (Roberfroid, 1999), evaluation of the blood brain barrier permeability (Kakee et al., 1997), and control of drug release (Sinha and Kumira, 2001; de Souza et al., 2009; Fares et al., 2010; Itoh et al., 2007; Castelli et al., 2008). Different polysaccharides were reported to control the release rate due to its ability to remain intact in the upper GI tract and then show a specific degradation and digestion into the colon by colonic microflora (Sinha and Kumira, 2001), which makes them a potential oral drug delivery system. Among the most well known polysaccharides used were chitosan-based (de Souza et al., 2009), pectin-based (Fares et al., 2010; Itoh et al., 2007), and inulin-based (Castelli et al., 2008; Hinrichs et al., 2005; Poulain et al., 2003) polymers and others.

Irbesartan is potent long-acting non-peptide angiotensin II receptor blocker (ARB) that has been widely used to treat hypertension (Christen et al., 1991; Goldberg et al., 1995; Lu and Feng, 2011). It exhibits an antihypertensive efficacy that is similar to that of other antihypertensive drugs, with an improved safety profile when used as monotherapy (Reeves et al., 1998). It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at pH of 7.4, and low aqueous solubility. The estimated bioavailability is greater than 60%; however, the plasma levels do not increase proportionally with the increase in dose (Chawla and Bansal, 2007).

The insertion of hydrophilic moieties, via grafting, into the backbone structure of the natural polysaccharide to form grafted copolymers aims to increase the hydrophilicity of the formed copolymer, and hence increase dissolution rate of the poorly water-soluble, Irbesartan drug, and eventually, increase its bioavailability. Aim of this study was to evaluate inulin and grafted inulin,

* Corresponding author.
E-mail address: fares@just.edu.jo (M.M. Fares).

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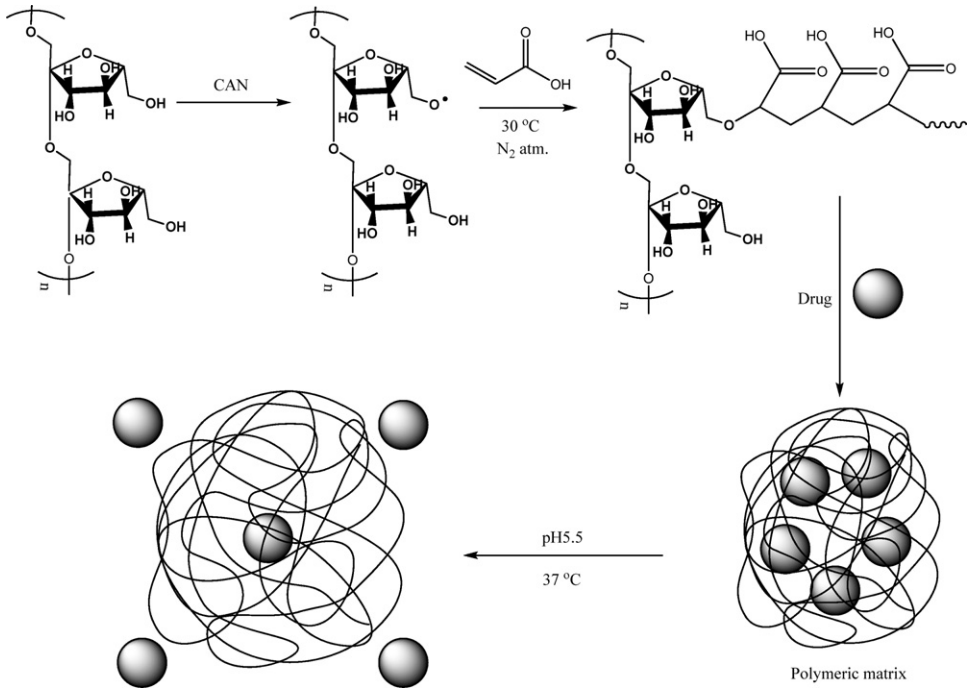

Scheme 1.

poly(acrylic acid) grafted inulin, as a successful candidate for the enhancement of the dissolution of Irbesartan drug, as poorly water-soluble drug. Furthermore, poly(acrylic acid) grafted inulin was used to control successfully drug release rate in the *in vitro* conditions.

2. Experimetal

2.1. Materials

Inulin was purchased from Acros Organics, Belgium, and acrylic acid (AA) monomer (98%) was obtained from Aldrich and used as received. Ceric ammonium nitrate (CAN) (Scharlau) was used as 0.1 M solution in molar nitric acid. Mono- and di-basic phosphate buffer was used for pH 5.5. Irbesartan drug was kindly supplied by *Dar El-Dawa* Pharmaceuticals, Jordan. Deionized and double distillated water was used in all experiments. All other reagents were of analytical grade and used as supplied without further purification.

2.2. Physicochemical characterization tools

^1H NMR: The ^{1}H NMR spectra for structural changes of the copolymers were recorded on a Bruker Biospin Spectrometer of 400 MHz in deuterated water and acetone. The samples were macerated in solvent for three days. Chemical shifts (δ) are given in ppm with tetramethylsilane (TMS) as an internal standard.

FTIR: Thermo Nicolet (avator-360, USA) FTIR spectrophotometer for functional groups were recorded in the range of 4000–400 cm^{-1} using KBr pellets.

Thermogravimetric analysis (*TGA*): Thermogravimetric analyzer (TGA) model: Shimadzu TA-50 (JAPAN), under nitrogen atmosphere was used for gravimetrical changes and decomposition temperatures. The heating rate used was 10 °C/min with temperature range from room temperature to 500 °C.

Scanning electron microscope (*SEM*): was used for morphological and topological changes of the copolymers. Micrographs was of Polaroid films, the samples in the form of films were mounted on the specimen stabs and coated with gold ion by sputtering method with (DSM 950 (ZEISS) model) (USA), Polaron (E6100) model.

2.3. Synthesis of poly(acrylic acid) grafted inulin

1.0 g of inulin was added into 200 ml of deionized double distilled water and stirred magnetically under nitrogen gas atmosphere at elevated temperature up to 40 °C until inulin was completely soluble, then treated with 10% (w/w) CAN with respect to acrylic acid monomer concentration for 10 min to facilitate free radical formation on inulin. CAN was used as 0.1 M solution in molar nitric acid. This treatment was followed by drop wise addition of 1.0 g acrylic acid monomer. The total volume was made up to 250 ml by deionized water and then polymerization was carried out at 30 °C for 4.0 h. After polymerization was over, the solution was allowed to cool and since the grafted copolymer was very soluble in water, freeze dried technique was used to precipitate the graft copolymer through freezing process followed by sublimation of water at reduced pressure as follows:

Steps	Cooling rate (°C/min)	Temperature (°C)	Time (h)
Pre-freezing		5	3
1	3.0	−40	5
2	2.5	−30	8
3	1.5	−15	8
4	3.0	−5	4
5	1.5	0	5

Finally, the formed grafted inulin copolymer was dried to constant weight and kept in zero humidity environments for further investigation (Scheme 1). The percent of grafting (%*G*) was evaluated using the below mentioned formula:

$$\%G = \frac{W_{\text{PolyAA}}}{W_{\text{Inulin}}} \times 100 \quad (1)$$

where W_{PolyAA} was the peak area of poly(acrylic acid) in the copolymer (*i.e.* fraction of poly(acrylic acid) in the copolymer) located

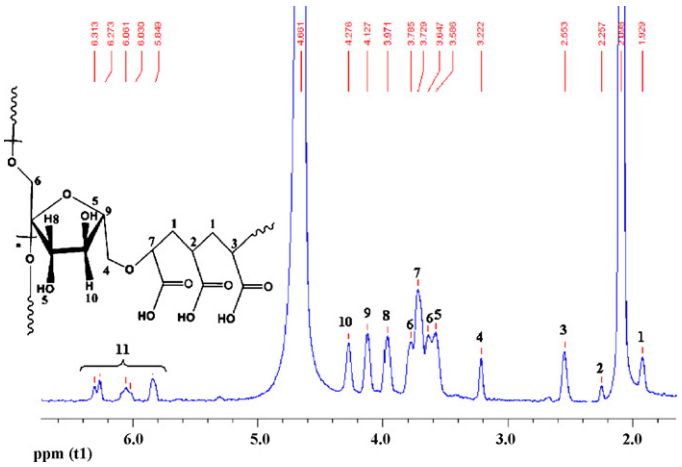

Fig. 1. ^{1}H NMR spectrum of poly(acrylic acid) grafted inulin.

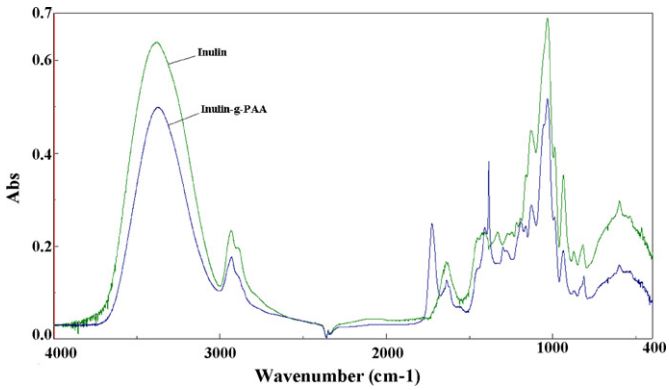

Fig. 2. FTIR spectra of pure Inulin and poly(acrylic acid) grafted inulin copolymer.

at 394 °C, whereas the W_{Inulin} was the peak area of inulin in the copolymer (Fares et al., 2003) (*i.e.* fraction of inulin in the copolymer) located at 260 °C. Peak areas were derived from the derivative of the TGA thermogram software.

The %Irbesartan release could be used to calculate proportionality constant (k) and diffusional exponent (n) from the following relation (Ritger and Peppas, 1987):

$$\frac{M_t}{M_\infty} = kt^n \quad (2)$$

where M_t and M_∞ are the concentrations of the drug released to the medium at time t and time ∞, respectively. M_∞ was used as 150 mg, where it would be the maximum amount of drug released at infinite time. The proportionality constant, k value, accounts for coherency, structural and geometrical properties of the polymeric matrix, and the diffusional exponent, n value, accounts for the release rate and diffusivity. If $\ln(M_t/M_\infty)$ was plotted versus $\ln(t)$ a linear curve would be obtained where the proportionality constant, k value, and the diffusional exponent, n value, would be determined from the intercept and slope, respectively. If $n \leq 0.5$ then the diffusion is said to diffusion controlled (Fickian diffusion), if $0.5 < n < 1.0$ then the diffusion is said to be anomalous diffusion (non-Fickian) and if $n = 1.0$ then the diffusion mechanism is said to be zero-order transport mechanism. Statistical coefficient, R^2, was larger than 0.98.

2.4. In vitro drug release of Irbesartan using inulin and grafted inulin

An amount of 150 mg of Irbesartan model drug was physically mixed with different amount of inulin or grafted inulin (50, 75, 100, 125, 150, 200, and 300 mg, respectively) in a closed glass tube using vortex. Tablets were made by 10 tons compression and transferred to Pharmasource dissolution tester (TDT-801, USA) equipped with paddle apparatus containing 900 ml of the same buffer solution maintained at physiological temperature 37.0 °C ± 0.1. The external solution was continuously stirred at 100 rpm for one hour. At predetermined time intervals 2.0 ml sample aliquots were withdrawn, filtered by a cellulose membrane filter (pore size 0.45 μm) and then replaced by fresh buffer solution. Results were expressed as mean values ± standard deviation (S.D.) UV-1800 Shimadzu UV-Vis Spectrophotometer was used for the analysis of Irbesartan drug. Full UV-Vis range was taken using 150 mg solution of Irbesartan in buffer solution to confirm λ_{max} of 230 nm of Irbesartan. Free base drugs like weak base Irbesartan drug, show higher solubility in the high acidity stomach medium (pH 1–2) than in the low acidity duodenum-small intestine (pH 5.5), due to acid–base interactions. Furthermore, for low solubility basic drug, the drug molecule once dissolved in the stomach can precipitate out in the small intestine (Sugano, 2010; Sugano, 2011). Furthermore, polysaccharide copolymers (inulin and grafted inulin) used for dissolution enhancement are known to be degradable in high acidity stomach medium (pH 1–2). Hence, enteric-coated dosage forms must be used to avoid variations and polymeric degradation due to stomach acidity (Karrout et al., 2009). Once the polymeric-drug matrix reached the small intestine (*i.e.* pH 5.5), it will show high %drug dissolution and hence much better absorption and bioavailability would occur. Continuous rise up of pH value to 6.8 and 7.4 would cause expected precipitation of the drug (Sugano, 2010), and hence much less absorption and bioavailability of the drug would occur. Therefore, pH used in this study was 5.5.

3. Results and discussion

3.1. Characterization of poly(acrylic acid) grafted inulin

^{1}H NMR: Fig. 1 illustrates the *^{1}H NMR* spectrum for the poly(acrylic acid) grafted inulin copolymer. It could be seen that poly(acrylic acid), PAA, and inulin moieties were available in the spectrum. For poly(acrylic acid) moiety; C***H***$_2$ peaks of the backbone located at $\delta = 1.929$ ppm (peak 1), C***H*** peaks of the backbone located at $\delta = 2.257$, 2.553 and 3.729 ppm (peaks 2, 3 and 7). On the other hand, different proton positions of different chemical shift demonstrated the presence of inulin; C***H***$_2$ peaks of the backbone located at $\delta = 3.222$ and 3.647 ppm (peaks 4 and 6), O***H*** peak at $\delta = 3.586$ ppm (peak 5), and C***H*** peaks of the 3.971, 4.127 and 4.276 ppm corresponding to 8, 9 and 10 positions were available. Due to freeze dried technique used in the precipitation of the grafted copolymer, trace amounts of left unreacted acrylic acid monomer were found in spectrum that correspond to un-removable traces of acrylic acid (Peak 11). Two sharp peaks corresponding to solvent were found at $\delta = 2.098$ and 4.661 ppm.

FTIR: Corresponding functional group stretchings and bendings of inulin and poly(acrylic acid) grafted inulin were shown in Fig. 2 and Table 1. For inulin moiety; *OH* str., aliphatic CH_2 str. and *COC* bending were located at 3380, 2931 and 1030 cm^{-1}, respectively. On the other hand, three characteristic peaks have emerged in poly(acrylic acid) moiety, namely symmetric and asymmetric COO^- stretchings, and carbonyl stretchings that were located at 1410, 1617 and 1725 cm^{-1}, respectively. Moreover, it was noticed that the intensity of *OH* stretching was reduced due to the grafting of poly(acrylic acid) via the *OH* bond of inulin. Furthermore, the absorbance of aliphatic CH_2 stretching band available in inulin and poly(acrylic acid) moieties were supposed to intensify as result of grafting process. However, its intensity was reduced. This reduc-

Table 1
FTIR characteristic peaks of inulin and poly(acrylic acid) grafted inulin copolymer.

Polymer	υ (cm^{-1})	Abs	Remarks
Inulin	3380	0.64	OH str.
	2931	0.23	Aliphatic CH_2 str.
	1030	0.69	COC bending
Poly(acrylic acid) grafted inulin	3380	0.50	OH str.
	2931	0.18	Aliphatic CH_2 str.
	1617	0.11	Asymmetric COO str.
	1410	0.24	Symmetric COO str.
	1725	0.25	C = O str. of carboxylic Acid
	1030	0.52	COC bending

tion could be explained on the basis of expected partial hydrolysis and decomposition of inulin during grafting processes (Ritger and Peppas, 1987), which were left in solution upon precipitation of grafted copolymer. The partial hydrolysis takes place through β (2→1) glycosidic bond breakage in presence of nitric acid. The reduction of β (2→1) glycosidic band intensity in poly(acrylic acid) grafted inulin at 1030 cm^{-1} gives a clear clue on that. As a result, the *%hydrolysis* of inulin could be estimated as 24.6% (*i.e. %hydrolysis* = ((0.69 − 0.52)/0.69) × 100 = 24.6).

Thermogravimetric analysis: Thermal stability and decomposition temperatures are the main characteristic features of thermogravimetric analysis, TGA, thermogram. In addition, using the derivative of TGA thermogram the area under the curve could show the change of degradable %mass loss in temperature interval, in mg min^{-1} K^{-1}. This change could present the fraction of certain moiety in the copolymer. Un-grafted inulin showed decomposition temperature at 271 °C (Fig. 3A), whereas, grafted inulin in the copolymer showed down-shift in its decomposition temperature with around 11 °C (*i.e.* 260 °C), and poly(acrylic acid) moiety

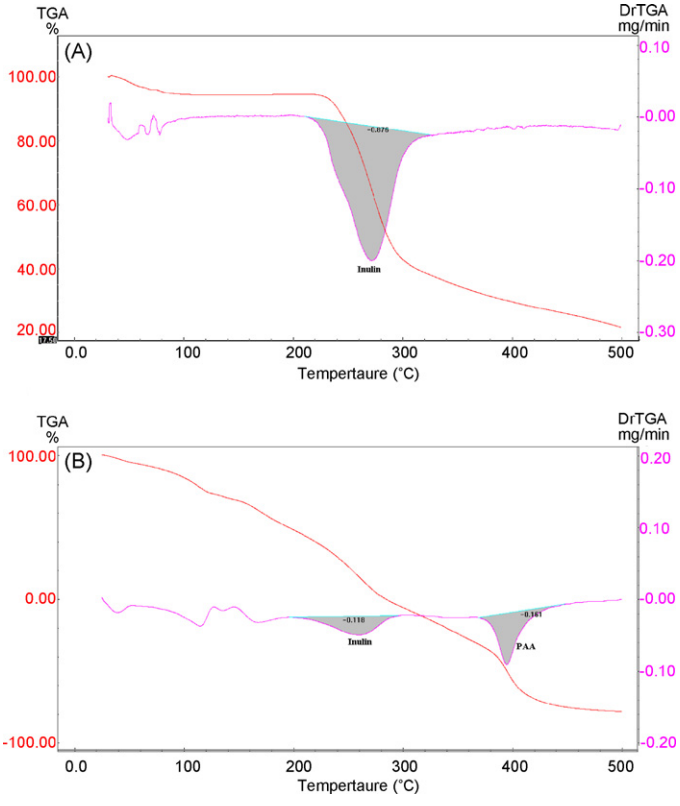

Fig. 3. TGA profile and its derivative, DrTGA, for (A) pure inulin and (B) grafted poly(acrylic acid) onto inulin copolymer.

showed a decomposition temperature of 394 °C. Lowering of thermal stability of inulin moiety in the copolymer could be attributed to destruction of crystalline regions in inulin as a result of grafting process (Zimeri and Kokini, 2002). Such destruction would lead to larger free volume between chains, less consistent structures, more amorphous regions, and hence lower decomposition temperature.

From the derivative of TGA thermogram for inulin and grafted poly(acrylic acid), Fig. 3B, the fraction of inulin and poly(acrylic acid) in the copolymer could be obtained and therefore percent grafting could be determined from Eq. (1) (*i.e.* %*G* = 136.4). The high percent grafting of the copolymer implies higher carboxylic acid content in the copolymer, that was assumed to respond effectively at different pH values along the gastrointestinal tract and hence capable to control the release of Irbesartan drug effectively.

Topology: Scanning electron microscopic micrographs could show the topological changes that takes place as a result of chemical modification at the micro or nano level. Fig. 4 illustrates the morphology of the pure inulin and the formed poly(acrylic acid) grafted inulin copolymer. It could be seen that pure inulin, Fig. 4A, manifests on the separable semi spherical flower-like flaky platelets that were accumulated above each other. On the other hand, poly(acrylic acid) grafted inulin copolymer showed highly amorphous and consistent systems, with two-dimensional surfaces than contains some voids, Fig. 4B. In addition, small crystalline regions were also existed especially in Fig. 4C and E. The presence of crystalline regions was either due to left over non-destroyed crystalline regions as a result of grafting process or due to inter- and intra-molecular interactions between inulin and bounded poly(acrylic acid) that might enhance chain alignment. However, the relative high amorphous system was definitely due to destruction of crystalline regions of inulin as a result of grafting process, which led to lower decomposition temperature as mentioned in TGA analysis.

Release of Irbesartan from inulin: One of the most chronic but significant obstacles in pharmaceutical industries was drug dissolution. Many drugs were found to be poorly water-soluble and hence their absorption and bioavailability by human tissues was also very poor, which required raising the concentration of the dose given to patients, regarding its side effects, to fulfill their needs for cure. Thus, the enhancement of dissolution of such poorly water-soluble drugs, via inulin, to make fairly or good water-soluble drugs could form a break-through from two sides; the drug dose required to cure in presence of inulin would decrease due to higher solubility and moreover lesser side effects of the drug would be expected.

Fig. 5 illustrates the dissolution profiles of physically mixed tablets of 150 mg Irbesartan drug with different masses of inulin (50, 75, 100, 150, 200 and 300 mg) at pH 5.5 for 60 min. Irbesartan drug dissolution profile was used as a control experiment. Obviously, the %drug dissolution of the Irbesartan, as a control experiment, was 8.11% within the first 60 min, which confirms its poorly water-soluble nature (Watanabe et al., 2004). However, it could be seen that the incorporation of inulin with Irbesartan drug matrix show gradual and drastic change in dissolution behavior. Within 60 min, gradual increase of the %drug dissolution from 48.2% for 50 mg inulin up to 89.5% for 300 mg inulin. This outstanding increase in drug dissolution was definitely due to the presence of inulin moiety. The role of inulin could be explained by the physical interaction of drug particles with inulin macromolecules, which could act as a dissolution agent and a vehicle at the same time that facilitate its transfer to aqueous solution and hence increase its dissolution capacity. Deeper inspection of physical parameters such as the proportionality constant, *k* value, and the diffusional exponent, *n* value, could show better comprehensive insight (Table 2).

It could be seen that increasing the content of inulin in the polymeric matrix result with larger consistency of polymeric matrix (*i.e.* larger *k* value) which was due to the relative increase of inter- and intra-molecular interactions and relative smaller free

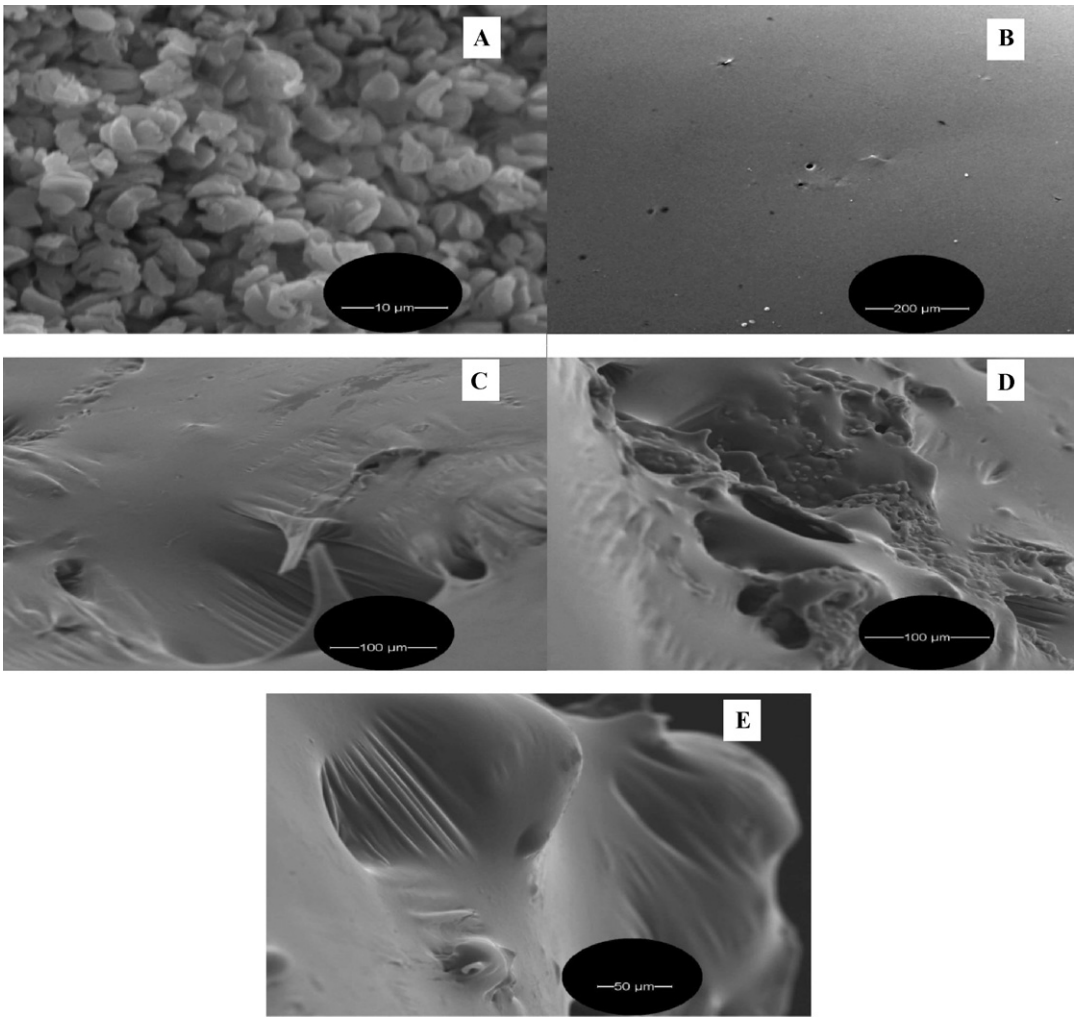

Fig. 4. SEM micrographs of (A) pure inulin and (B–E) different side views of grafted poly(acrylic acid) onto inulin.

Table 2
Physical parameters of inulin/Irbesartan drug[a] polymeric matrix at pH 5.5.

Inulin (mg)	*n*	*k*
Pure drug	0.24	–
50	1.37	0.17
75	1.22	0.34
100	1.19	0.49
150	1.11	1.02
200	1.15	0.70
300	1.08	1.19

[a] In all experiments mass of Irbesartan drug used was 150 mg.

volume between inulin macromolecules. This increase in consistency of polymeric matrix does not seem to affect the release rate of the drug. Quite high diffusional exponent value, very close to $n = 1$ value were obtained for all samples, which indicates zero-order diffusion mechanism. This high release rate of the drug could be explained by sleazy separable micro-structure of inulin, seen in Fig. 4A, that were highly porous and incapable to impede the flux of the drug into the aqueous solution. Therefore, inulin macromolecules have assisted to largely increase the dissolution of Irbesartan drug, and show zero-order diffusion mechanism. The very low *n* value for pure drug was due to its poor solubility.

Preliminary controlled release from grafted inulin: The purpose of grafting inulin with poly(acrylic acid) was meant to increase the inter- and intra-molecular forces between chains, increase the consistency of the copolymer, decrease the free volume between chains, and hence adapt the copolymer to substanially control the release of the drug. Fig. 6 shows the preliminary dissolution profiles, for one hour, of the physical mixture tablets of Irbesartan drug and the grafted inulin copolymer. At the first 10 min, 300 mg sample of un-grafted inulin show 8.11% drug release (Fig. 5), whereas 300 mg sample of grafted inulin show 23% drug release (Fig. 6).

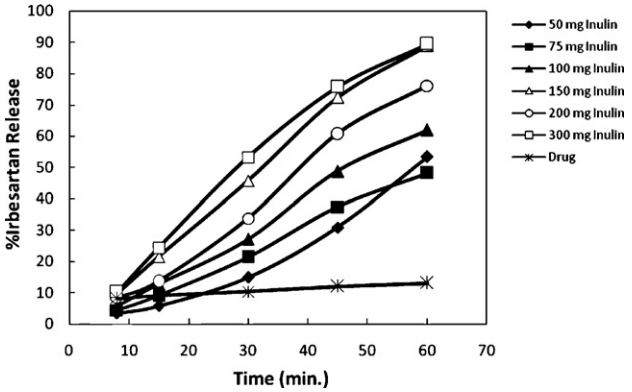

Fig. 5. The dissolution profiles of Irbesartan drug that were physically mixed with increasing masses of inulin. Each point was assumed to represent the mean ± S.D.

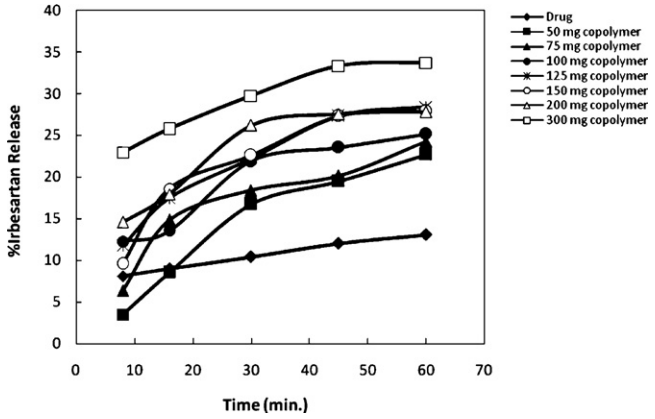

Fig. 6. The dissolution profiles of Irbesartan drug that were physically mixed with increasing masses of inulin-g-PAA copolymer. Each point was assumed to represent the mean ± S.D.

Table 3
Physical parameters of grafted inulin/Irbesartan drug[a] polymeric matrix at pH 5.5.

Grafted inulin (mg)	*n*	*k*
Pure drug	0.24	–
50	0.35	5.58
75	0.40	5.13
100	0.44	4.85
150	0.59	3.11
200	0.44	5.67
300	0.22	14.4

[a] In all experiments mass of Irbesartan drug used was 150 mg.

The better drug dissolution was owed to the electrostatic interaction between negatively charged carboxylic acid groups of the copolymer with positively charged groups, protonated nitrogen atoms, NH^+ and NH_2^+, of the drug, formed at pH 5.5, which pulls larger amount of insoluble drug molecules into aqueous solution and increase its dissolution capacity. Nevertheless, this behavior does not persist for inner core drug molecules. The preliminary %drug release of 300 mg grafted inulin sample shows 33.7% after 60 min. This much slower release rate of the drug that follows Fickian diffusion mechanism was owed to the uprising electrostatic interaction (*i.e.* uncoiling of polymeric chains) coming from higher content of poly(acrylic acid) moiety (%G = 136.4) in the copolymer. Table 3 illustrates the n and k values for grafted inulin polymeric matrix.

Since n value was almost less than 0.5 (*i.e.* $n \leq 0.5$) then the diffusion followed Fickian diffusion mechanism. This slow release mechanism could ensure sustained release of Irbesartan drug in prolonged time. Furthermore, it could be noticed that as the mass of grafted inulin in the matrix increased, the release rate first increased up to maximum threshold value of $n = 0.59$, where drug/copolymer ratio equal 1.0, then it declined exponentially. The increase in copolymer concentration led to better incorporation between copolymer and the drug, which simultaneously led to better dissolution and larger release rate. However, larger concentration of the copolymer (*i.e.* 200 mg and above) induces larger electrostatic interactions, larger consistency (*i.e.* larger k value), less porous material which automatically prevents simultaneous release of the drug.

Conclusively, the un-grafted inulin was successfully used to increase the dissolution of the drug by around eight folds, whereas the grafted inulin was used as a successful candidate for the control of the dissolution and the %release of Irbesartan model drug.

4. Conclusion

The use of inulin and poly(acrylic acid) grafted inulin for the enhancement of the drug solubility in aqueous solution and for substantial control of Irbesartan drug release and as drug carriers was performed. The granulistic flower-like platelets of inulin accumulated above each other adapted it to physically bind Irbesartan drug and enhance its dissolution. Where, the increase of inulin content in the polymeric matrix increased the drug dissolution gradually until it reaches its maximum (∼90%) after 60 min, and the %release had followed zero-order transport mechanism. In addition, the formed poly(acrylic acid) grafted inulin copolymer was characterized using ^{1}H NMR, FTIR, TGA, and SEM techniques. Its topology showed highly consistent amorphous system, of two-dimensional surfaces with some voids, where such characteristics adapted it to control Irbesartan dissolution rate (∼33%) and hence showed Fickian diffusion mechanism.

Acknowledgement

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