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Investigation of using pectin and chitosan as natural excipients in pellet formulation

Ladan Nejati [a], Foroogh Kalantari [a], Neda Bavarsad [a,b], Farinaz Saremnejad [c], Pooria Taghavi Moghaddam [a], Abbas Akhgari [d,*]

[a] Department of Pharmaceutics, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[b] Nanotechnology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[c] Department of Food Science and Technology, Ferdowsi University of Mashhad, Mashhad, Iran
[d] Targeted Drug Delivery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

This study aimed to evaluate the potential of applying pectin and chitosan polysaccharides in pellet formulation. These biopolymers have advantages such as biocompatibility, low toxicity, low price and easy processing which make them interesting candidates for drug delivery purposes. Careful control of pellet porosity is essential to achieve an appropriate drug release profile. Replacing microcrystalline cellulose (MCC) with polysaccharides, especially pectin, leads to increased pellet porosity. Theophylline, dimenhydrinate and ibuprofen were chosen as model drugs. Investigation of possible ionic interactions between drugs and excipients is crucial to optimize the formulation of pellets with acceptable drug release. Differential scanning calorimetry of chitosan showed an endothermic peak; however, this peak was not observed in thermograms of the pectin, implying the lack of interaction between polysaccharides. Fourier transform infrared analysis did not indicate any interaction between drugs and polymers. Incorporation of MCC into the pellet formulation significantly increased the mean dissolution time while substitution of MCC with polysaccharides led to a faster release for each of the three drugs – that were different in their net charges – in both acidic and buffer media. These results highlight the potential value of polysaccharides in improving drug delivery characteristics of pharmaceutical pellets.

1. Introduction

Oral delivery is still the most popular route for drug administration owing to its ease of use and patients5 preference and compliance. Therefore, a major trend in pharmaceutics is to design and develop efficient and safe drug delivery systems with optimum solubility, release and biocompatibility characteristics. Recently, there has been an increased interest in the use of natural polymers such as polysaccharides for drug delivery. This class of polymers includes alginates, amylose, carrageenans, cellulose, chitin, chitosan, dextran, glycogen, inulin, pectin, pullulan and starch. These biopolymers are endowed with numerous advantages which make them effective excipients in pellet formulation [1,2]. Polysaccharides have many reactive functional groups (OH, NH_2, COOH) which can be involved in polymer-analogous reactions with various reagents. The binding of a drug to a polymer can result in the improvement of its physicochemical (*e.g.* solubility and stability to metabolic degradation) and biological (*e.g.* bioavailability and toxicity) properties [3,4]. Several lines of evidence have suggested the versatile roles of polysaccharides for targeted delivery of drugs [5–9].

Pectin is an anionic polysaccharide (Fig. 1A) that is found abundantly in plants' cell wall. As a ubiquitous component of fruits and vegetables, pectin has been used as a gelling agent and stabilizer in food products for a long time. Pectin is also a dietary fiber that is associated with gastrointestinal health, reduced risk of some cancers, glucose tolerance, lipid digestion and weight management [10,11]. However, owing to the thickening, stabilizing and gelatinizing characteristics of pectin gels, there has been a recent interest in the use of these gels for controlled drug delivery purposes [12]. Pectin is a soluble fiber that is resistant to gastrointestinal (GI) conditions. In the distal part of the gastrointestinal tract, pectin is degraded by the colon natural flora; hence, it could be considered as a suitable vehicle for delivering drugs to the gastrointestinal tract [13,14]. Commercial pectin with a low degree of esterification is effective as a delivery vehicle for oral drugs [10].

Chitosan is one of the most abundant natural cationic polysaccharides (Fig. 1B) that is mainly obtained by deacetylation of chitin in alkaline media [15]. Chitosan and its derivatives have been applied in many fields such as biomedicine, food industry, cosmetics, agriculture, environmental protection and waste management due to their

* Corresponding author.
E-mail address: akhgaria@mums.ac.ir (A. Akhgari).

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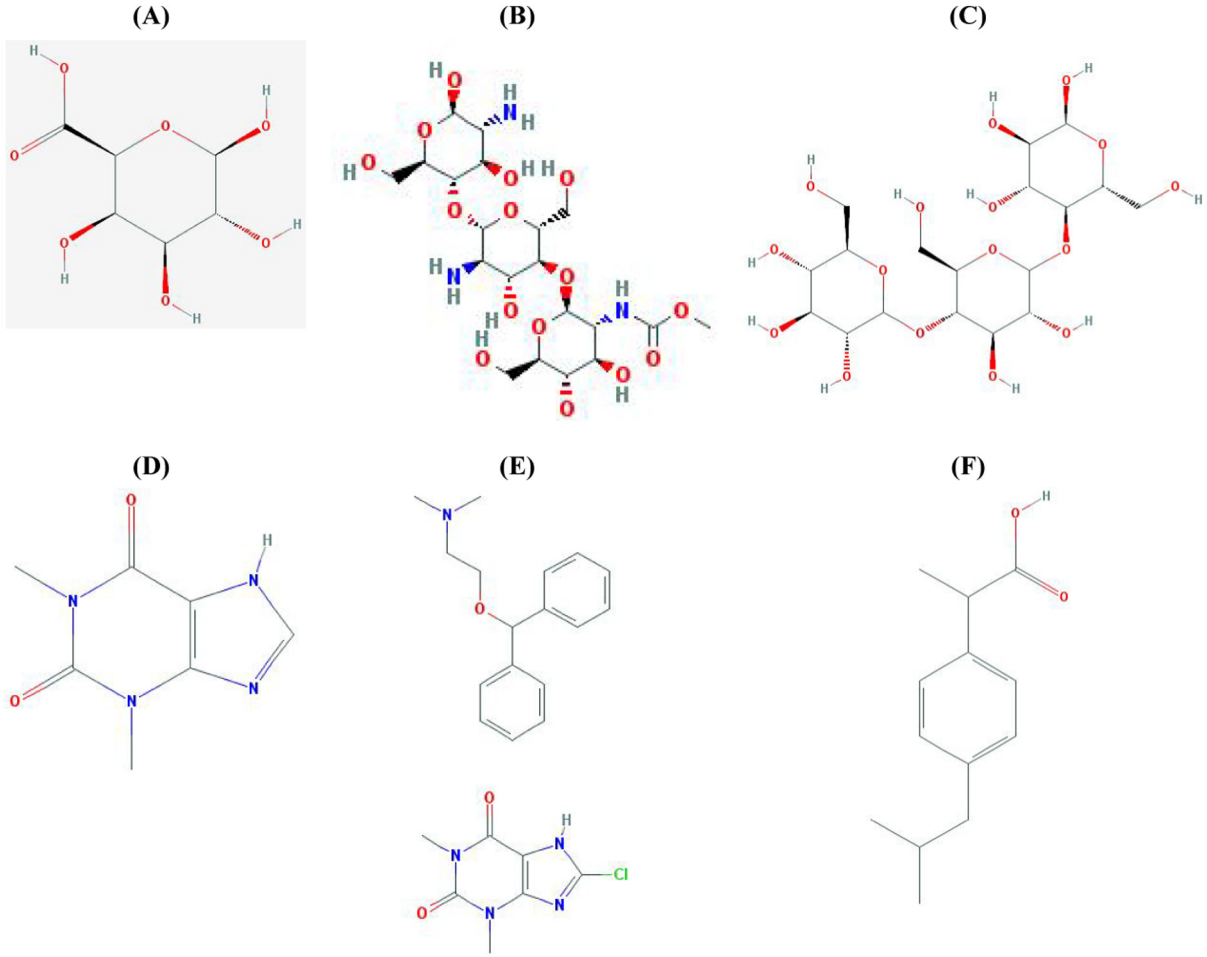

Fig. 1. Chemical structure of (A) pectin, (B) chitosan, (C) MCC, (D) theophylline, (E) dimenhydrinate, and (F) ibuprofen. (Source: PubChem, URL: https://pubchem.ncbi.nlm.nih.gov).

biocompatible, biodegradable, non-toxic and non-allergenic properties [16]. In particular, chitosan and its derivatives have attracted considerable attention as biomedical materials owing to their unique biological effects such as antioxidant, anti-allergic, anti-inflammatory, anticoagulant, anti-cancer, anti-bacterial, anti-human immune deficiency virus (HIV), anti-hypertensive, anti-Alzheimer, anti-diabetic, anti-obesity and matrix metalloproteinases inhibitory activities [17–20]. Chitosan could enhance drug penetration due to its ability to separate the strong junctions between the epithelial cells. Also, the positive charge of chitosan in the physiological pH of gastrointestinal tract imparts mucoadhesive properties which can increase the residence time of drug at the site of administration. Currently, chitosan is widely applied as an aid beside other polymers for the preparation of sustained-release pellets [21].

Pellets are defined as spherical or nearly spherical, and free-flowing particles with a narrow size distribution varying between 500 and 1500 μm that are used for pharmaceutical applications [22]. Because of their multi-unit structure, pellets have several important technical and pharmacological advantages compared with conventional single-unit dosage forms. Some of these advantages include fast stomach depletion, high absorption and bioavailability, less fluctuation in plasma concentration profile of drug, lack of dose dumping, appropriate flowability, easy coating and the possibility of incorporating two or more agents with different release profiles in a single dosage form [23–26].

Extrusion-spheronization is the most commonly used multistep method for preparing small spherical granules with similar sizes and characteristics. One important advantage of this method is the ability to combine large amounts of effective agents without the need to produce extremely big particles. Using this method also allows easy combination of two or more effective agents. There are many variables that affect the quality of produced spheres such as combining method, time, type and amount of granulation liquid, spheronization time, and type of extruder and spheronizer devices [26].

Microcrystalline cellulose (MCC) (Fig. 1C) is the most common commonly used polymer in pellet formation using the extrusion-spheronization method [27]. MCC contributes to the formation of spheres but pellets produced by this process are not always perfectly spherical. One of the factors that could affect the sphericity of pellets is the amount of MCC used as the spheronizing agent [28]. To overcome the above-mentioned challenge, several excipients have been tested to improve pellet disintegration and/or drug release, either in combination with MCC or as alternatives to MCC. Some of these excipients, include starch-dextrin blend [29], K-carrageenan [30,31], powdered cellulose [32] and isomalt [33]. Recently, other suitable polymers have also been reported as excipients that could provide desirable pellets when used in combination with MCC [21,34].

The aim of this study was to evaluate the characteristics of two polysaccharides, pectin and chitosan, in pellet formulation. An important prerequisite for any excipient used in extrusion-spheronization is lack of effect on drug release. In the current study, we tested the probable interactions of the mentioned anionic and cationic polysaccharides with each other and with different drugs, and the eventual effects on drug release and morphology of the pellets. Theophylline (Fig. 1D), dimenhydrinate (Fig. 1E) and ibuprofen (Fig. 1F) were chosen as model neutral, cationic and anionic drugs, respectively.

2. Materials and methods

High-methoxy apple pectin with a methoxylation degree of >6.7% (P8471) was purchased from Sigma Aldrich Co. (Germany). According to the manufacturer, the degree of esterification was 72–76% and the galacturonic acid composition of the studied pectin was >74%. High molecular weight chitosan (310–375 kDa) with a deacetylation degree of >75% and viscosity of 800–2000 cps (419419) was purchased from Sigma Aldrich Co. (Germany). Theophylline (Abidi Pharmaceuticals, Iran), dimenhydrinate (Abidi Pharmaceuticals, Iran), ibuprofen (Tehran Darou, Iran), NaOH, HCl, monobasic potassium phosphate, ethanol (Merck, Germany) and MCC (FMC BioPolymer, Irland) were purchased from indicated sources.

2.1. Preparation of pellets

Formulations containing specific ratios of drug, MCC, pectin and chitosan were prepared using extrusion-spheronization method. Table 1 depicts the constituents of all formulations. Water and ethanol were used as granulating liquids. A paste was prepared by adding the granulating liquid to the mixture of drug and excipients and extruded using a screw extruder (Type HC 732, Dorsa, Iran) with a 1 mm screen at 100 rpm. Pellets were prepared *via* spheronizing the extrudates using a spheronizer (Type HC 732, Dorsa, Iran) with crosshatched plate at 1000 rpm. The pellets were dried in an oven (Type WV 30 UL, Memmert, GmbH, Germany) at 40 °C.

2.2. Determination of porosity

The porosity of the pellets was measured using a Penta pycnometer (PPY-15, Quanta chrome Instruments, USA). The porosity of the formulations was determined using the following equation:

$$\text{Porosity} = \left[1-\left(V_{true}/V_{tap}\right)\right] \times 100 \quad (1)$$

where, V_{true} and V_{tap} refers to the volume of pellets before and after compressing, respectively.

2.3. Scanning electron microscopy (SEM)

SEM was carried out using scanning electron microscope (1455VP, LEO, Germany). The samples were primarily silver sputter-coated under argon to render them electrically conductive. The pictures were then taken at an excitation voltage of 15 kV.

Table 1
Composition of experimental formulations.

Formulation	Pectin (%)	Chitosan (%)	Microcrystalline cellulose (%)	Drug (%)
F1t	0	0	70	30
F2t	22.5	7.5	40	30
F3t	20	20	30	30
F4t	10	30	30	30
F5t	0	40	30	30
F1i	0	0	70	30
F2i	22.5	7.5	40	30
F3i	20	20	30	30
F4i	10	30	30	30
F5i	0	40	30	30
F1d	0	0	70	30
F2d	22.5	7.5	40	30
F3d	20	20	30	30
F4d	10	30	30	30
F5d	0	40	30	30

2.4. Differential scanning calorimetry (DSC)

DSC thermogram assessment of all formulations and pure powders was carried out using DSC (Mettler, Toledo, Switzerland) at the rate of 10 °C/min and the temperature range between 25 and 350 °C.

2.5. Fourier transform infrared (FTIR)

FTIR spectroscopy was carried out using IR spectrometer equipment (vortex 70, Bruker, Germany) over a range of 4000–500 cm^{-1}. The samples were prepared using the KBr disk method (2 mg sample in 200 mg KBr).

2.6. Dissolution studies

Dissolution studies were carried out in a USP dissolution apparatus I (DT800, Erweka, Germany) in 900 mL medium at 37 °C at a rotation speed of 50 rpm. The release test in HCl (0.1 N), as the simulation gastric fluid (SGF), was performed within 2 h for 42 mg of theophylline and 90 mg of dimenhydrinate. To simulate the intestinal fluid (SIF), the release test was performed in 900 mL of phosphate buffer (pH = 6.8) for 42 mg of theophylline pellets, 90 mg of dimenhydrinate pellets and 60 mg of ibuprofen pellets within 8 h, separately. At predetermined intervals, the samples were taken from the vessel and were analyzed using UV spectrophotometry method with a UV/visible spectrophotometer (Biowave II, WPA, England) at the wavelengths of 274 and 277 nm in acidic and buffer media for theophylline, 277 nm for dimenhydrinate, and 224 nm for ibuprofen ($n = 3$).

3. Results & discussion

3.1. Porosity

Porosity is an important characteristic which determines the properties such as friability, flowability and wettability. Also, porosity affects the structure of pellet, which in turn influences their drug release behavior [35]. Therefore, careful management of pellet porosity is essential to achieve appropriate drug release from pellets [36]. Porosity essentially depends on variables such as pellet formulation, the volume of the granulation liquid, spheronization speed and time, and drying conditions [37,38].

In this study, the range of porosity for all formulations was 43–66% (Table 2). Accordingly, the highest porosity belonged to F2t, F2d and F2i formulations which had the highest level of pectin. Also, F5 formulations of the drugs that contained the highest amount of chitosan had significant porosity. Similarly reported that the porosity of pellets increases with an increase of chitosan amount [39]. On the other hand, the porosity of F1t, F1d, and F1i with the highest amounts of MCC that there were no any polysaccharides in their formulation was relatively low. In aqueous solutions MCC loses its particulate appearance after extrusion, resulting in a low porosity because of the shrinkage during drying [40]. So the results show that the substitution of MCC by polysaccharides - especially pectin - leads to increased pellet porosity.

Table 2
Porosity of formulations.

Theophylline		Dimenhydrinate		Ibuprofen	
Formulation	Porosity (%)	Formulation	Porosity (%)	Formulation	Porosity (%)
F1t	43.98946	F1d	48.99096	F1i	52.50654
F2t	66.3781	F2d	62.34049	F2i	54.17087
F3t	44.98824	F3d	50.92344	F3i	45.50101
F4t	46.65113	F4d	58.39444	F4i	46.60696
F5t	55.99191	F5d	49.70057	F5i	44.98746

Drug release was found to be directly related to the pellet porosity. As can be seen from Figs. 5 to 6 drug release rate from F2t, F2d and F2i formulations are high. With an increase in porosity, water penetration into the pellet matrix becomes easier, drug dissolution might become faster, and hence drug release is increased [41]. These findings are in good agreement with data reported in the literature. For instance, carrageenan pellets were much more porous than MCC pellets. Hence, the increased drug release rate observed with carrageenan-based pellets [42].

The results of porosity were confirmed by SEM. As evolved from SEM images, incorporation of pectin and chitosan (Fig. 2B and D) into pellet formulation enhances the interior porosity, while pellets produced by MCC (Fig. 2A and C) as the only pelletizing agent were less porous and had a more uniform surface. Similarly, in another investigation, SEM-pictures show a flake-like appearance of the chitosan particles forming the pellet [39]. Thus it can be assumed that by substitution of MCC by polysaccharides, larger pore spaces remain.

3.2. DSC

One important feature which must be regarded for selection of excipients used in extrusion-spheronization is the lack of any adverse effect on drug release. Possible ionic interaction between excipient and drug may be a parameter affecting drug release from pellets. This interaction was not unexpected and has already been shown in the previous study by Thommes and Kleinebudde [43]. Substitution of MCC by κ-carrageenan was investigated and it was shown that drug release from dimenhydrinate pellets was affected by the possible ionic interaction between cationic drug and κ-carrageenan. Therefore, investigation of this parameter will be crucial to optimize the formulation of pellets with acceptable drug release.

The thermograms of pure theophylline (positive control) and its formulations are presented in Fig. 3A. Theophylline (Fig. 3A) showed an endothermic peak at about 270 °C which is related to drug melting. This finding is the same with studies that investigated thermograms of theophylline [44–46]. DSC thermograms of pure dimenhydrinate as positive control as well as its formulations were shown in Fig. 3B. An endothermic peak between 105 and 115 °C was observed which is related to the melting point [47]. Fig. 3C showed the thermograms of pure ibuprofen (positive control) and its formulations. Ibuprofen has a sharp endothermic melting peak at about 75 °C due to its highly crystalline structure [48].

In terms of DSC diagrams of the formulations, F2t and F5t formulations showed an endothermic peak between 255 and 265 °C. The endothermic peaks of F2d, F3d, and F5d formulations occurred between 80 and 90 °C. Their second endothermic peak was observed between 150 and 160 °C for these formulations. The second endothermic peak was observed between 145 and 155 °C for the formulations of F2i and F3i. The endothermic peak of F3 formulations indicated the carboxylate linkage between pectin COO^- and NH_3^+ groups of chitosan. These results confirm the lack of significant interaction between excipients and drug. Also, formulations exhibited no endothermic peak corresponding to the melting of drug indicating that the drug is dispersed in the pellet matrix.

The thermograms of pectin showed no peaks (Fig. 3A-b, B-b, and C-b). But chitosan showed two peaks: one at about 140 °C and the second was observed at about 295 °C (Fig. 3A-c, B-c, and C-c). The appearance of endothermic peak might be due to the evaporation of bound water and melting of chitosan. The second peak of chitosan was due to degradation of the polymer [46]. Generally, improvement in the dissolution and drug release from pellets for different blends of polysaccharides owing to lack of possible ionic interaction between excipient and drug confirmed from DSC studies.

3.3. FTIR

Since the drug and excipients were present in the pellet, FTIR studies were performed to evaluate any possible chemical interactions. If the drug and the excipient would interact, then the functional groups in the FTIR spectra would show band shifts and broadening compared to the spectra for the pure drug and excipient [49]. The spectrum for the pure drugs (positive control) and excipients are presented in Fig. 4.

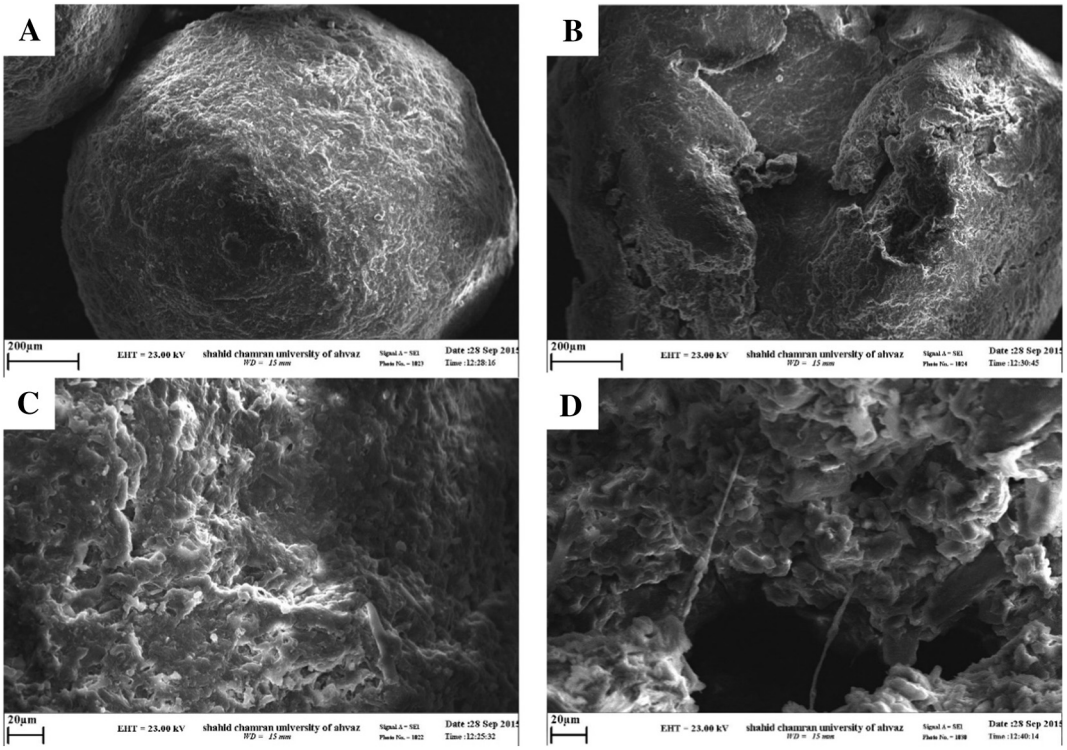

Fig. 2. Scanning electron micrographs of pellets based on (A) F1d and (B) F3d (magnification 80×), (C) F1d and (D) F3d (magnification 400×) formulations.

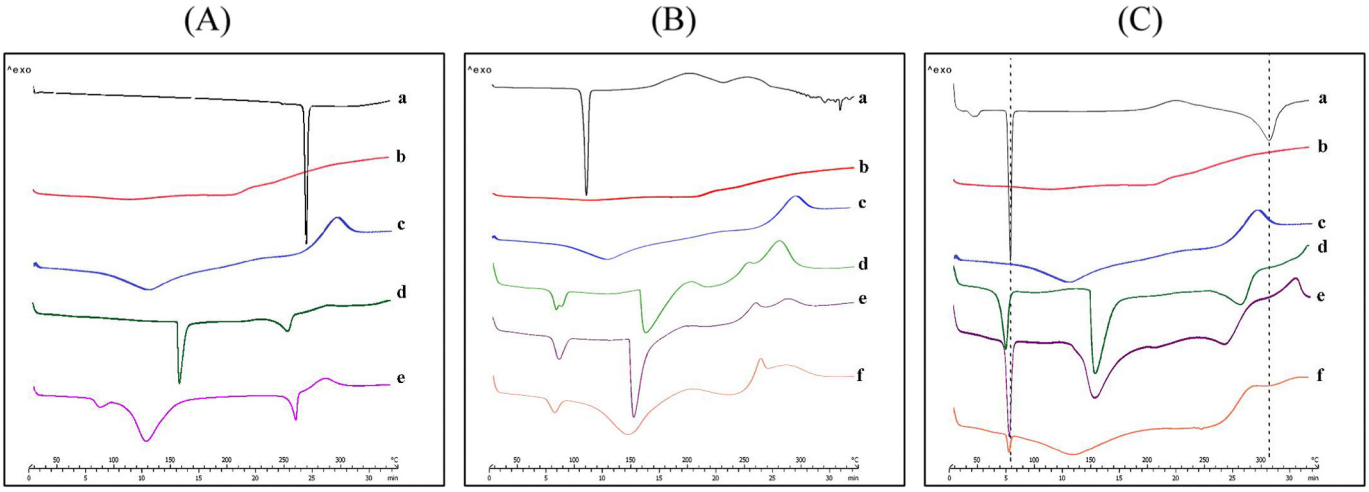

Fig. 3. DSC curves of (A) a: theophylline, b: pectin, c: chitosan, d: F2t, e: F5t; (B) a: dimenhydrinate, b: pectin, c: chitosan, d: F2d, e: F3d, f: F5d; (C) a: ibuprofen, b: pectin, c: chitosan, d: F2i, e: F3i, f: F5i.

The major characteristic IR absorption bands and their assignments for theophylline are displayed as follows: 3119 cm^{-1} (N—H stretching), 3063, 2989 and 2828 cm^{-1} (C—H stretching), 1718 and 1667 cm^{-1} (C═O stretching bands), 1568 and 1445 cm^{-1} (ring stretching) [44]. Fig. 4B represents the FTIR spectrum for dimenhydrinate where the characteristic peak is observed at 1100 cm^{-1}, belonging

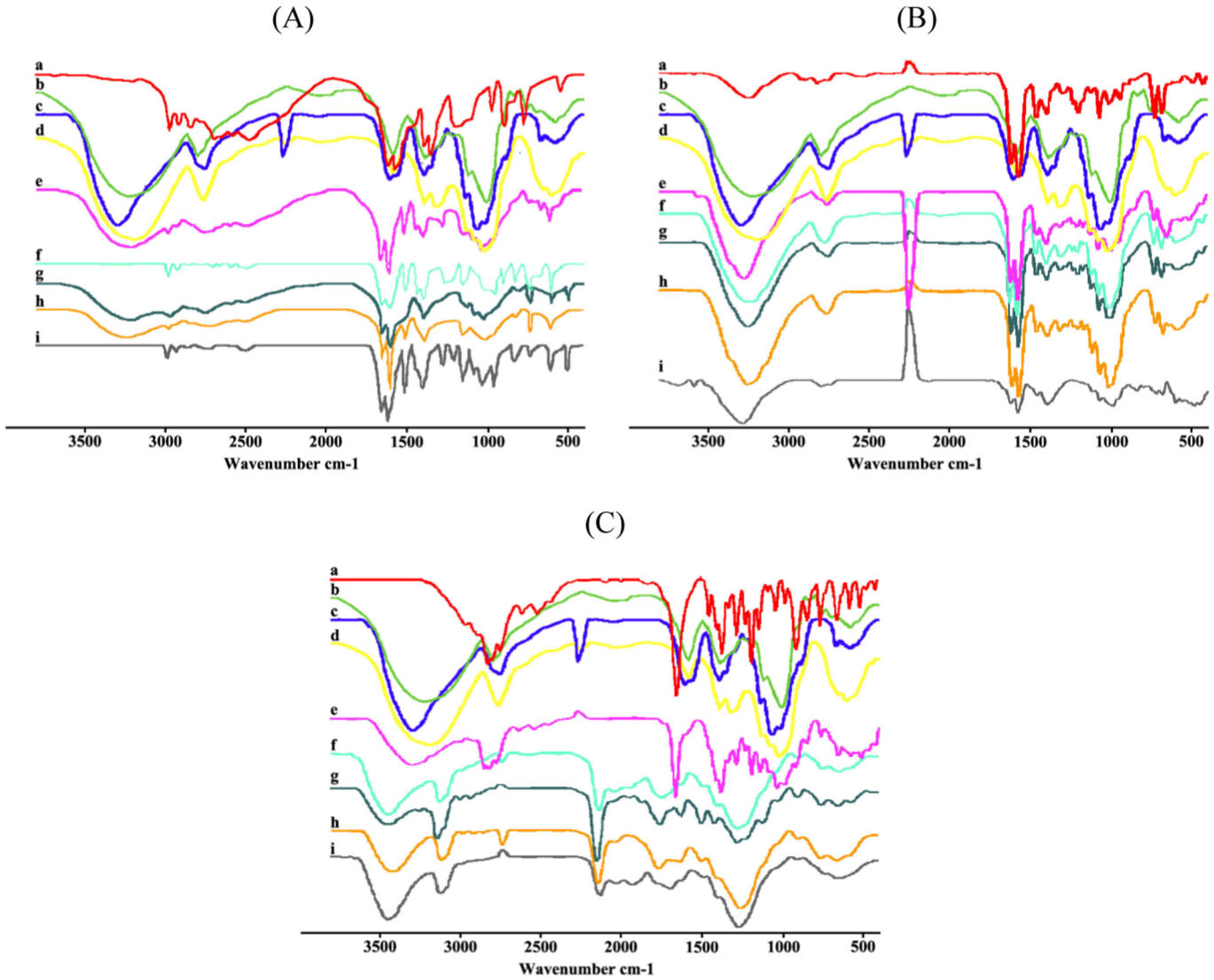

Fig. 4. FTIR spectra of (A) theophylline, (B) dimenhydrinate, (C) ibuprofen, (a) drug powder, (b) pectin, (c) chitosan, (d) MCC, (e) F1, (f) F2, (g) F3, (h) F4 and (i) F5 formulations.

to C—Cl stretching. The peaks around 1650 cm^{-1} may be due to C═O and C═C bonds [50]. The characteristic peak of ibuprofen FTIR spectra was observed at 1718.69 cm^{-1} (Fig. 4C) which indicated carbonyl stretching of the carboxylic acid group [51].

All the bands that were observed in drugs have also appeared in the FTIR spectra pellet formulations, indicating the chemical stability of drugs after use in the pellet matrix. This proved no chemical interaction of drugs with excipients. But in case of ibuprofen, the carbonyl peak at 1047.85 cm^{-1} in F4i spectrum compared to F5i (1059.95) and ibuprofen (1718.69) spectra, occurred at stronger fields that there probably are some minor interactions between acidic ibuprofen and basic chitosan, which probably is because of hydrogenic linkage and gravity forces between the carboxylic groups of ibuprofen with NH_3^+ moiety in chitosan. Results was in agreement with the other investigations [44,47,52].

The FTIR spectra of pectin (Fig. 4-b) showed sharp peaks at 1028.78 cm^{-1} that suggested the presence of C═O stretching of the carboxyl group. In case of chitosan (Fig. 4-c), a sharp peak with a strong intensity was observed at 1082.42 cm^{-1} which is the characteristic peak of the amino group [53]. The FTIR spectra of pectin–chitosan inter-polymer complex indicated a strong peak in the range of 1650–1750 cm^{-1} as shown in Fig. 4A–e (F2d; pectin–chitosan; 22.5:7.5), in Fig. 4A–f (F3d; pectin–chitosan; 20:20), in Fig. 4A–g (F4d; pectin–chitosan; 10:30). This suggests the presence of COO^- and NH_3^+ groups and inter-polymer complexes between pectin and chitosan in pellets [54]. Similar results were obtained in the fabrication of pellets by mixtures of chitosan/alginates [55]. Structural determination by means of FTIR and DSC indicated the formation of a polyelectrolyte complex between sodium alginate and chitosan. According to the authors, this may explain the successful pelletization by extrusion-spheronization. Fig. 4-d demonstrates the FTIR spectra for MCC. The intensity of the characteristic peak at 1050.74 cm^{-1} could be mainly due to the presence of free hydroxyl group of MCC [56]. Presence of free hydroxyl group of MCC may be due to increased interactions between a carboxylic acid group of ibuprofen and the hydroxyl group of MCC [56].

In general, it seems that characteristic peaks of all three drugs preserved in pellet formulations which proved no chemical interaction of drugs with MCC and polysaccharides.

3.4. Dissolution test

In vitro studies were carried out in dissolution media with pH 1.2 and 6.8 to mimic the GI environment. Drug release rate from all the formulations in the acid medium was higher than the release in the buffer medium. This may be partly due to the better solubility of drugs at pH 1.2. But ibuprofen was the exception in this case and hence its release from pellets was investigated only in the buffer medium (Fig. 7).

According to the results of release tests of theophylline in acidic media (Fig. 5A), the lowest drug release belonged to F1t. MCC as a pelletizing excipient can lead to slower pellet disintegration in the acidic media. Penetration of dissolution media into the pellets is a time-consuming process but pellets containing pectin and chitosan are more hydrophilic due to the charged nature of these two polysaccharides, thereby causing a faster pellet dissolution [27]. In phosphate buffer (Fig. 5B), F1t showed lower drug release compared with other pellets while F2t had the highest drug release. The carboxylic acid groups of pectin become ionized in phosphate buffer that leads to a less integrated network in which phosphate buffer could easily penetrate and dissolve pectin. This results in a faster drug release in a formulation containing higher amounts of pectin compared with other pellets [57]. Similar results were observed for the release profile of dimenhydrinate in both media (Fig. 6). The slowest release belonged to F1d while F2d and F5d had faster drug release compared with other formulations. Pellets containing only MCC as a pelletizing aid showed a slower release profile compared with the formulations containing pectin and chitosan along with MCC. It was observed that as the amount of MCC decreased, the drug release rate increased correspondingly. MCC loses its swelling

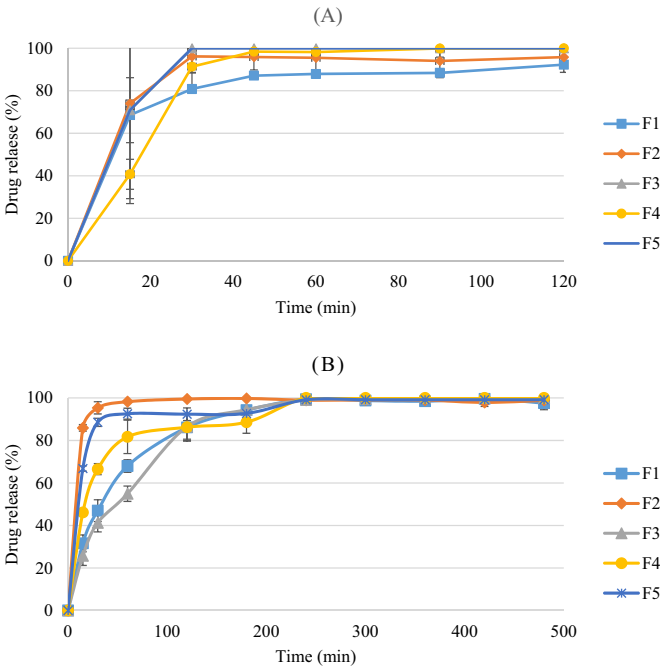

Fig. 5. Dissolution profile of theophylline formulations in (A) HCl 0.1 N and (B) phosphate buffer (pH = 6.8).

properties through the pellet preparation process which prevents disintegration of the pellets and complicates drug contact with the dissolution fluid [61,62]. The most noticeable feature of the results is that the dissolution rate was greatly increased by increasing the amount of pectin and chitosan in formulations. The ionization of pectin carboxylic acid groups is more than that of chitosan amine groups in phosphate buffer, thereby causing a better dissolution of the former polymer due to the loosening of the surface network of pellets and easier drug release [11]. The effect of using pectin and chitosan on the release of drugs from pellets was comparable to MCC formulations. This approach

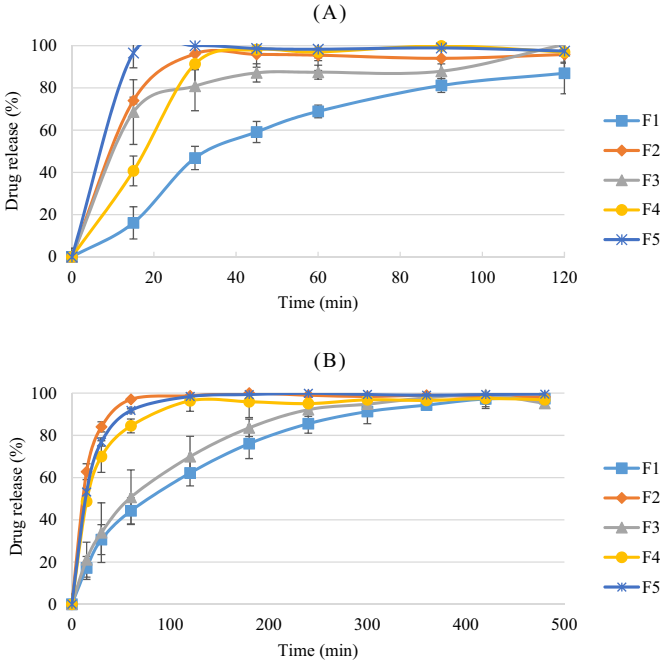

Fig. 6. Dissolution profile of dimenhydrinate formulations in (A) HCl 0.1 N and in (B) phosphate buffer (pH = 6.8).

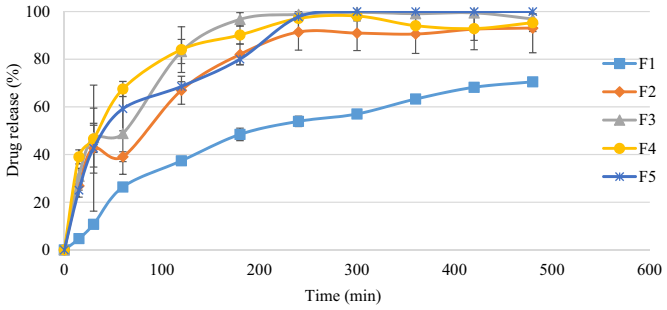

Fig. 7. Dissolution profile of ibuprofen formulations in phosphate buffer (pH = 6.8).

mitigated several drawbacks of MCC. This finding was in agreement with the other investigations [43] in which κ-carrageenan introduced as an alternative pelletization aid for MCC.

The dissolution rate of the ibuprofen was very low. Several studies have already proved the poor dissolution of ibuprofen [51,58,59]. It is probably due to the less water solubility of ibuprofen compared to theophylline and dimenhydrinate. Considering Fig. 7, F2 showed slower release profile in comparison with other formulations. Furthermore, the acidic property of ibuprofen facilitating interactions of its carboxylic acid group with amine and hydroxyl groups of basic chitosan producing NH_3^+ and COO^- that make ionic interactions, thereupon decelerate drug release.

4. Conclusion

Overall, incorporation of MCC into the pellet formulation significantly increased the mean dissolution time while substitution of MCC with pectin and chitosan led to a faster release for each of the three drugs that were different in their net charges, in both acidic and buffer media. This effect of MCC becomes more noticeable with poorly soluble drugs like ibuprofen. Pectin and chitosan as pelletizing polysaccharides can be appropriate substitutions or even better options than MCC in producing pellets of these kinds of drugs. As discussed above, in specific ratios of pectin-chitosan (F3), the velocity of ibuprofen dissolution in phosphate buffer becomes much better while it is still less than the other two drugs (theophylline and dimenhydrinate) which have better solubility. Using pectin and chitosan could be a promising way to overcome the problems caused by the application of MCC in pellet formulation. Finally, pectin and chitosan are two natural polysaccharides, existing abundantly in the environment, which do not require industrial processing like MCC and thus have less production costs.

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