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Evaluation of xanthan and highly substituted galactomannan from *M. scabrella* as a sustained release matrix

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Abstract

A highly substituted galactomannan (G) from *Mimosa scabrella* Bentham (Man:Gal 1.1:1), isolated from the seeds of a Brazilian leguminous tree and xanthan (X), an exopolysaccharide secreted by *Xanthomonas campestris* (Keltrol), were evaluated as a hydrophilic matrix system (XG) for controlled release (CR) of diclofenac sodium (DS) in tablets and capsules. The performance of XG (2:1) matrices containing 50 mg (A) or 100 mg (B) of DS was compared with a commercial CR product of DS. The drug release studies were carried out using a dissolution apparatus (paddle method) with gradual increase of pH values, from pH 1.4, to pH 4.0 (after1 h) and to pH 6.8 (after 2 h). The results suggested the potential of XG systems as release retarding materials, which released 78.6 and 35.1% of drug after 24 h for capsules (A) and tablets (A), respectively. Drug release decreased with the increase of amount of drug and it is dependent of dosage form. Analysis of release data indicate a rather zero-order drug release with the erosion mechanism playing a dominant role.

Keywords: Galactomannan; Xanthan; Drug release; Diclofenac sodium

1. Introduction

Polymeric hydrogels are being increasingly studied for controlled-release applications because of their biocompatibility (Kudela, 1987), producing close to zero-order drug release kinetics (Möckel and Lippold, 1993), with complex interaction between swelling, diffusion and erosion mechanisms (Colombo et al., 1995; Munday and Cox, 2000; Reynolds et al., 1998).

Mimosa scabrella Bentham, known as bracatinga, is a leguminous Brazilian tree of the Mimosaceae family. The extraction of its seeds provide 30% (w/w) of galactomannan (G) with a typical chemical structure, consisting of a (1 → 4) linked β-D-mannopyranosyl backbone substituted at O-6 with single unit α-D-galactopyranosyl residues, in a Mannose:Galactose (Man:Gal) ratio of 1.1:1 (Ganter et al., 1992). Galactomannans are used in their native state to thicken aqueous systems. Their properties depend mainly on their chemical structure, i.e. molecular weight, availability of *cis*-OH-groups, substituents, and steric hindrance between molecules. The molecular weight of the polysaccharide, influences viscosity and rheological properties of the aqueous solution. Solubility in water depends on the extent of intermolecular hydrogen bonding and whether steric hindrance keeps the chains at such distances from each other than water can penetrate and hydrate or dissolve the galactomannan. Thus, by an increase of

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substitution with galactose, nature establishes a steric hindrance between the molecules and thus enhances water solubility (Bayertein, 1993). The rheological properties of galactomannan solutions from *M. scabrella* were investigated by Ganter et al. (1992). They are characteristic of a random coil polymer with a low viscoelastic behaviour.

Galactomannan from the seeds of *Cyamopsis tetragonoloba*, known as guar, with Man:Gal of 2:1 and locust bean gum from the seeds of *Ceratonia siliqua* (Man:Gal of 3.5:1) are the main commercial sources of galactomannan (Dea and Morrison, 1975).

The best solubility is found with galactomannan with a Man:Gal ratio 1.1:1, as the one obtained from *M. scabrella*. The high substitution by galactose obviously establishes so much steric hindrance that it dissolves easily in water and prevents attack for some time from degrading enzymes (Ganter and Reicher, 1999).

The potential for guar galactomannan to be use for controlled release has been previously studied (Baveja et al., 1991; Khullar et al., 1998; Nürnberg and Retting, 1974). Nürnberg and Retting (1974) observed the influences of mechanical strength on the single-layered tablets (containing a retarding layer of galactomannan) and two-layered tablets (containing a retarding layer of galactomannan and another, without galactomannan). They concluded that the use of varying pressures during manufacture has an insignificant effect on the release of the 3-pyridylmethanol. Khullar et al. (1998) examined the manner by which guar gum exerts its effect on the swelling process of matrices and the correlation of swelling behaviour with the drug-release profile. The authors (Khullar et al., 1998) observed that like all swellable polymers, guar gum swells as it absorbs water and the thickness of the layer formed varies as a function of time, producing a linear plot between the square root of time and volume of the tablet. They suggest the drug release mechanism was essentially through a diffusion process (Khullar et al., 1998).

Xanthan (X) is a commercial hydrophilic polymer, secreted from *Xanthomonas campestris*. The xanthan structure consists of a β-(1 → 4)-D-glucopyranosyl backbone substituted at O-3 on every second unit with a charged trisaccharide side-chain composed of a glucuronic acid residue between two mannose units. The terminal mannosyl unit may be substituted at O-4 and O-6 by a pyruvate acetal. An *O*-acetyl group is frequently present at O-6 of the inner mannose (Nürnberg and Retting, 1974).

This polymer is studied for the fabrication of matrices with uniform drug release characteristics (Baird et al., 1983; Billa and Yuen, 2000; Cox et al., 1999; Lu et al., 1991; Munday and Cox, 2000; Sujja-areevath et al., 1998; Talukdar and Plaizier-Vercammen, 1993; Talukdar et al., 1998). Hydrophilic gels have been shown to produce near zero-order drug release kinetics (Colombo et al., 1985; Möckel and Lippold, 1993). Sujja-areevath et al. (1998) observed that Fickian diffusion is dominant during the fist half of the dissolution period of DS mini-matrices with xanthan gum of different ratios, while erosion predominates during the latter half facilitating an approach toward zero-order release.

Xanthan solutions have high intrinsic viscosity and a pronounced pseudoplastic flow at relatively low concentrations. Although xanthan solutions exhibit weak gel-like properties at low shear rates, which make it suitable as a suspending agent, it does not form true gels at any concentration or temperature (Millane and Wang, 1990).

Xanthan (X) and galactomannan (G) are just water soluble thickening agents, but when they are mixed, an original gelation occurs (Dea and Morrison, 1975; Rocks, 1971). The less substituted galactomannans show a greater synergic effect (Dea and Morrison, 1975). The mechanism of gelation of aqueous mixture of xanthan and galactomannan was studied by Bresolin et al. (1997, 1999) using rheological, calorimetric and chiroptical methods. They demonstrated that even with high galactose content of galactomannnan from *M. scabrella* the gel formation between XG was obtained.

A drug delivery tablet system of xanthan and locust bean gum (Man:Gal 3.5:1), commercially known as TIMERx®, was developed by Penwest Pharmaceuticals Company (Baichwall and Neville, 2002). The system is based on the synergistic interaction of heteropolysaccharides, which in the presence of dextrose form a strong binder gel in water. The in vitro and in vivo controlled release potential of this system has been demonstrated (McCall and Baichwall, 1994; Staniforth and Baichwall, 1993). Tobyn et al. (1996) investigated the interaction between TIMERx® and low molecular weights model compounds using electron spin resonance (ESR). They reported an ideal

distribution of all the model compounds throughout the matrix, with no interaction between spin labels at the molecular level. The authors also proposed that the xanthan/locust bean gum matrix (TIMERx®) provides a chemical as well as physical barrier to the release of model compounds.

Diclofenac sodium (DS) is a nonsteroidal anti-inflammatory drug, causing irritation on gastrointestinal tract. It is commercialised in CR formulations (Reynolds, 1989).

Considering the galactomannan (G) from the seeds of *M. scabrella*, a highly substituted galactose polymer (Man:Gal 1.1:1), with consequently high solubility in water, as well the synergy between xanthan: galactomannan system (XG), we propose to study the potentiality of DS controlled release, from capsules and tablets using a matrix of XG (*M. scabrella*).

2. Materials and methods

2.1. Materials

The *M. scabrella* Bentham seeds were obtained from Embrapa (Brazilian Agricultural Research Company, Curitiba-PR, Brazil). Xanthan (Keltrol) was purchased from Kelco Division Merck. Diclofenac sodium (DS) pharmaceutical grade (Galena) was analysed resulting in a positive IR spectrum, 100.3% potency (perchloric acid titration) and loss on drying of 0.04%, and was thus approved (British Pharmacopeia, 2000). All other chemicals were of reagent grade. The commercial product (DS CR) is a DS tablet of controlled release containing hydroxypropylmethylcellulose (HPMC), a polymer used to retard the release of drugs from a matrix and also used as film-coating (Kibbe, 2000).

2.2. Extraction and analysis of galactomannan

The milled seeds of *M. scabrella* Bentham were boiled in water for 10 min for enzymatic inactivation. The galactomannan was obtained by water extraction under mechanical stirring for 4 h at 25 °C. The dispersion was centrifuged at 2000 × *g* for 15 min at 25 °C. The supernatant was precipitated with one volume of ethanol, washed in a gradient of ethanol (70–100%) and dried under vacuum at 30 °C, resulting in an off-white coloured powder with a yield of 20% (w/w).

The Man:Gal ratio of 1.1:1 was confirmed by gas liquid chromatography (GLC) as previously described (Ganter et al., 1992) using a model 5890 SII HP Gas chromatograph at 220 °C (free induction decay and injector temperature, 250 °C) with a DB-225 capillary column (0.25 mm i.d. × 30 m) and nitrogen as a carrier gas. The intrinsic viscosity $[\eta]_{25}$ of 750 ml/g was calculated by viscometric analysis in a Rheometer (RS 75, Haake). The protein content (Bergmeier, 1983) was 4.4%. The total carbohydrate was determined by the phenol sulphuric method (Dubois et al., 1956). The loss on drying was 0.4% and the total ash was 2%.

2.3. Preparation of the tablets and capsules

Two formulations, A (0.2% G, 0.4% X, 0.05% DS, 70% water, 29.35% ethanol) and B (0.2% G, 0.4% X, 0.1% DS, 70% water, 29.3% ethanol), were prepared. The gums were dispersed in water by mechanical stirring until they became homogeneous gel system. The DS was dissolved in ethanol and slowly added to gel under continued agitation. It was then homogenized for six hours. Later, the gel was dried in a forced air-circulated oven for 12 h at 36 °C, resulting in the Formulations A and B, with 50 and 100 mg of DS/unity, respectively. After cooling, the moisture of powders was analysed by Moisture Analyser (LJ 16, Mettler Toledo).

The DS potency of both formulations (A and B) was determined by spectrometry. After powder solubilization in 0.1 M NaOH and filtration of samples (A and B) the measurements were performed in a Shimadzu UVPC 1601 Spectrophotometer at 275 nm, using 1 cm quartz cell. The standard curve was determined with DS previously desiccated, dissolved with the same solvent in the range of 10–100 μg/ml. Each concentration was made in triplicate, and the linear regression of curve resulted in a r^2 of 0.9999.

The dry powder formulations were fractionated by size using U.S. standard sieves from 0.250 to 0.125 mm. The powder of both formulations that passed through the 0.250 mm and were retained in the 0.125 mm, were encapsulated into hard gelatin capsules, number 00. The powder of both formulations that passed through the 0.125 mm was compressed using 11 mm round, flat faced punches on a single

station tabletting machine eccentric press (Lawes, Brazil).

2.4. Characterization of tablets and capsules

An average aliquot of 20 units of tablets and capsules (with A and B formulations) was dissolved in 0.1 M NaOH and assayed by as described above for the powder.

The weight variation of dosage units was measured as described in United States Pharmacopeia (2000).

Tablet hardness was measured on the Erweka (TBH 20) hardness tester, and an average of 10 tablets was calculated.

2.5. In vitro release

In vitro release was evaluated by spectrometry. Initially, a standard curve was constructed with DS previously desiccated, dissolved in buffer pH 6.8 in the range of 10–90 μg/ml, at 275 nm, using buffer pH 6.8 as control. Each concentration was made in triplicate, and the linear regression of curve resulted in a r^2 of 0.99991. As xanthan and galactomannan solutions absorbed at 275 nm (data not shown), one placebo measurement was carried out without DS. The absorbance determination at each time was taken into account to calculate the DS released.

The release of DS from A and B formulations was measured using the USP dissolution test (DT 80, Erweka), apparatus II, 100 rpm, in 900 ml dissolution medium with different pH environments, to reproduce digestive physiological phases, maintained at 37 ± 0.1 °C. The dissolution medium initially consisted of a mixture of 50 mM hydrochloric acid, 50 mM glacial acetic acid and 50 mM phosphoric acid, at pH 1.4. After 1 h, the pH was increased to 4.0, and finally to pH 6.8 after 2 h, by the addition of drops of 12 M sodium hydroxide. At suitable intervals, samples (2 ml) were withdrawn (without reposition of dissolution medium), filtered, neutralized at 6.8 pH and diluted when necessary with buffer pH 6.8. Samples were analysed spectrophotometrically (Shimadzu UVPC 1601) at 275 nm, using the standard curve described above. The resulting volumes in dissolution cubes, decreased to 891 ml at the end of the experiment, were taken into account in order to calculate the percentage of DS released. The test was performed with 6 units of each formulation, and the average was calculated.

3. Results and discussion

3.1. Analysis of granules

After the incorporation of DS in the XG (0.4:0.2%) gel, the system XG DS was dried and sieved. The resulting microparticles showed the following characteristics: bulk density of 0.343 and 0.400 g/ml; and DS potency of 97.1 and 95.2%, for A and B batches formulations, respectively. The resulting potency in formulations (A and B) was taken into account to perform the DS dosage forms.

3.2. Analysis of DS matrices

Tablets were obtained with 11 mm in diameter, 5 mm in height and off-white colour. The capsules weighed approximately 800 mg (Table 1).

The formulations were approved for dosage uniformity since the amount of the active ingredient in each of 10 units tested was within the range of 85.0–115.0% and the coefficient of variation (CV) were less than 6.0%, as shown in Table 1.

The results of the assay show that the formulations comply with a potency range of 90–110% as specified by United States Pharmacopeia (2000) and have a suitable hardness.

3.3. In vitro release

When hydrophilic polymers come into contact with a liquid hydrate, a gel layer is formed, essential for sustaining and controlling drug release from polymer solid dosage form. The thickness of this hydrate layer determines the diffusion of the drug molecules through the polymer mass into the liquid medium, but this is not the only mechanism controlling the drug release. The rate and extent of the drug release also depends on the swelling and erosion of the hydrate polymer preparation.

The DS is a phenylacetic acid derivative with a pK_a of 4.0, therefore its solubility is markedly dependent on the pH of the medium so that it does not exceed 2 mg/ml in acidic conditions but is freely soluble above

Table 1
Pharmaceutical characteristics of Formulations A and B

Formulations	Weight (mg)[a]	Potency variation (%)	CV (%)[b]	Assay (%)[c]	Hardness (*N*)[c]
Tablet A	752	104–107	0.78	106	74.8
Tablet B	813	108–111	0.80	109	101.5
Capsule A	756	101–105	1.62	103	–
Capsule B	808	99–109	2.45	104	–

[a] Average of 10 units.
[b] Coefficient of variation (CV), determined from 10 units.
[c] Average of 10 units, determined spectrophotometrically, average of 10 units, Formulation A and B, with 50 and 100 mg of DS/unity, respectively.

pH 6.5 (Prasad et al., 1998). The DS undergoes an intramolecular cyclization in an acidic medium (Racz, 1989), so that the presence of gastric juices may result in the inactivation of the compound.

Fig. 1 illustrates the release profiles of DS from A and B formulations, in different pH dissolution media. As expected, the dissolution rate of DS increases as the pH of the medium increases. Very low percentages of dissolved DS were observed in pH of 1.4 and 4.0 (pH values apply for 2 h) followed by a progressive increase of dissolved DS at pH 6.8 (after 2 h) (Fig. 1). The pH variation experiment used to study the in vitro release simulates the changes of pH observed on gastrointestinal tract, but other factors may influence the drug dissolution from matrices in vivo and more studies may be carried out to establish the in vivo/in vitro correlation.

All formulations containing XG showed (Fig. 1) more prolonged release profiles than the commercial product (DS CR). The differences of release profiles observed between XG DS system and DS CR can be attributed to the polysaccharide composition of both matrices as well as the coat effect of HPMC (matrix composition of DS CR). The release profile of the capsules are closer to that of the DS CR than the profiles obtained with the tablets, over a 24 h period after reach pH 6.8, as shown in Fig. 1.

The formulations were maintained in aqueous solution for 2 h (acid medium) without a significant drug release. In this period, the matrices slowed and the principal barrier to drug release was their solubility. At pH 6.8, between these systems, the XG DS capsules show a faster rate of drug release compared to those from the XG DS tablets.

This behaviour may be due to smaller particles (that passed through the 0.125 mm sieves) used in the manufacturing of the tablets, compared to the capsules which are manufactured with powder retained in 0.125 mm sieves. A strong consolidation can be expected with a smaller granule size range because of

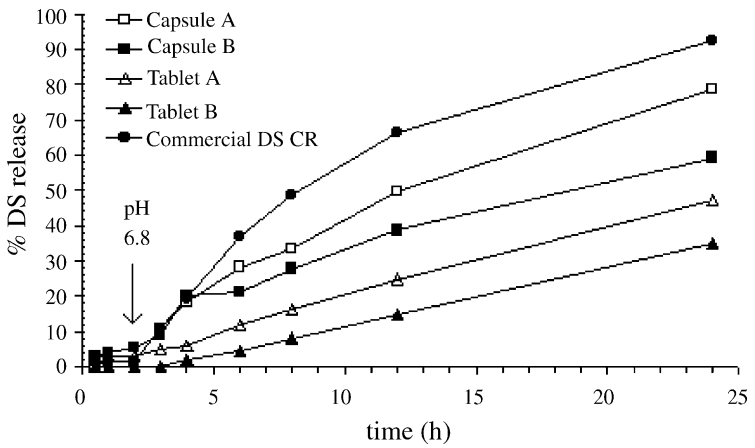

Fig. 1. In vitro drug release of DS CR, DS capsules and tablets (A and B).

closer and more intimate packing and an increase in area of contact (Leuenberger et al., 1989). The drug release from the compressed hydrophilic matrices usually is preceded by polymer erosion or hydration, or a combination of both processes (Lapidus and Lordi, 1968), and their higher superficial area may influence the hydration of the moving rubbery/glassy front within the tablet. Additionally, the hydrate outler layer may persist longer under these circumstances resulting in a slower disintegration and drug release. Similar results were found by Billa and Yuen (2000) with DS release from cellulose and xanthan tablets compressed from different granule size range.

Considering the final gum:drug ratio of 16:1 and 8:1 (Formulations A and B, respectively), it was observed that increasing the amount of the drug led to a decrease in the drug release, in both capsules and tablets (Fig. 1). Munday and Cox (2000), using directly compressed matrices containing xanthan gum and diclofenac sodium (ratios of gum:drug of 3:1 and 1:1), also observed the influence of the drug quantity on the drug release system. They demonstrated that the rate of drug release decreased with the increase in the amount of drug used. They argued that the matrices containing a lower proportion of gum would decrease the ability of the matrix to absorb water.

Apparently, relatively few of the polysaccharide strands become detached from tablets and capsules during the dissolution period. However, the XG DS capsules showed an evident higher swelling with a strong degree of water uptake in comparison to the tablet, probably due to the stronger binding in the latter. Prasad et al. (1998) observed the ability of guar gum to retain the integrity of indomethacin tablets obtained by direct compression with micro crystalline cellulose in the physiological environment of stomach and small intestine. The drug release studies were performed in 0.1 M HCl for 2 h and in pH 7.4 Sorensen's phosphate buffer for 3 h.

For the XG DS tablets, a straight line obtained from the drug release showed in Fig. 1 occurred in dissolution medium at pH 6.8, suggesting that this system can be induced by a different release mechanism.

In order to investigate the probable mechanism of drug release, the following kinetic models were used: a zero-order relation, first-order relation, matrix mechanism used in the Higuchi equation and the cube root relationship (Bamba et al., 1979).

Table 2
Kinetic release of DS in different formulations (A and B)

Formulation	r_0^2	r_1^2	r_H^2	$r_{\text{cube root}}^2$
Capsule A	0.9617	0.9958	0.9818	0.9958
Capsule B	0.9538	0.9897	0.9767	0.9811
Tablet A	0.9945	0.9903	0.9287	0.9933
Tablet B	0.9844	0.9739	0.8758	0.9780
DS CR	0.9206	0.9916	0.9666	0.9928

r^2 coefficient of correlation: 0 = zero-order kinetic; 1 = first-order kinetic; H = diffusion mechanism; cube root = cube root relationship; Formulations A and B, with 50 and 100 mg of DS/unity, respectively; DS CR is the commercial product.

The analysis of correlation coefficient of linear relationship (r^2) between drug release and time was established for the evaluation of the dissolution kinetic (Table 2).

Bamba et al. (1979) has proposed a method to determine the mechanism of release from the matrix-type delivery tablet systems (quinidine sulfate with carrageenan, alginate, guar or locust bean gum (carob) as controlled release polymer). The (a) permeation of water, (b) gelation rate, (c) dissolution rate of the drug in the penetrating water, (d) diffusion rate of the drug in the gel, and (e) Higuchi (1963) porous penetration were the proposed mechanisms for rate-determination in the release of drug from these systems. If the release pattern of the drug from the matrix-type is governed by dissolution of drug (case c), then a cube root relationship should be applied (Eq. (1)). If it is dictated by porous penetration (e) then the Higuchi square root law should be applied (Eq. (2)). In the other three processes (a, b or d), one might expect an equation of first-order release (Eq. (3)).

$$\sqrt[3]{100} - \sqrt[3]{m} = Kt \tag{1}$$

$$100 - m = Q\sqrt{t} \tag{2}$$

$$\ln m = -bt + a \tag{3}$$

where m is percentage of drug not dissolved, t is time (usually in hours), K is the cube root dissolution rate constant (mass/time$^{1/3}$), a (time^{-1}) and b are slopes and intercepts of log-linear plots of type in Eq. (3), and Q (percent per square root of time) is a Higuchi constant.

The mechanism of drug release from the XG DS capsules (A and B formulations) appeared to fit well with the first-order model (Table 2). As expected, the

Table 3
In vitro release parameters of formulations (A and B)

Formulation	Time (h)		
	t_{50}	t_{75}	t_{99}
Capsule A[a]	11.6	22.1	70.6
Capsule B[a]	18.0	36.4	121.8
Tablet A[b]	25.3	38.0	50.2
Tablet B[b]	34.4	50.6	66.1
DS CR[c]	8.9	15.4	31.6

[a] Calculated to first-order kinetic.
[b] Calculated to zero-order kinetic.
[c] Cube root kinetic; Formulations A and B, with 50 and 100 mg of DS/unity, respectively; DS CR is the commercial product.

release rate of hydrophilic matrix is governed by the permeation of water, gelation rate and diffusion rate of drug in the gel for this system (Bamba et al., 1979; Billa and Yuen, 2000; Khullar et al., 1998). The commercial product (DS CR) showed a better fit with the cube root relationship, although the correlation coefficient for the first-order model is very close to the Eq. (1) as observed in the XG DS capsules (Table 2).

Ford et al. (1987) suggested that the mechanism by which HPMC retards drug release is due to the ability to rapidly form a gel layer around the surface of a matrix exposed to aqueous fluids and the passage of drugs, via diffusion, through this gel layer. This process controls the dissolution of water-soluble drugs, giving release rates which are dependent on the square root of time and follow Eq. (2).

However, Ford et al. (1991) related that diffusion is not the only mechanism by which solutes are released from HPMC matrices and erosion will contribute to the overall release. They also observed that although equations such as those derived by Higuchi adequately describe the release from HPMC matrices, a better fit can be made on the assumption that release rates are not dependent on the square root of time and suggested an equation incorporating a lag period.

The XG DS tablets (A and B formulations) seem to fit well with the zero-order model, where erosion of the gel controls release rather than diffusion (Peppas and Sahlin, 1989).

Table 3 shows the in vitro parameters t_{50}, t_{75} and t_{99}, calculated by graphic interpolation, following first-order kinetics (capsule with A and B formulations), the cube root relationship (commercial product—DS CR) or zero-order kinetics (tablet with A and B formulations).

As shown in Table 3, the rate of DS released is greatest in commercial product DS CR, followed by capsule A and tablet A, as shown by t_{50} of 8.9, 11.6 and 25.3 h, respectively, in agreement with Fig. 1. The higher the proportion of drug, the lower the release rate of the system is, as shown by the time of 50, 75 and 99% drug release (Table 3). The results shown in Table 3 indicate that the release rate of DS decreases in the order commercial drug (DS CR) to capsules to tablets.

The kinetics of the release data were also analysed in terms of the well-known exponential equation (Korsmeyer et al., 1983):

$$M_t/M_a = K \times t^n \quad (4)$$

where M_t/M_a is the fractional (0.1–0.8) drug release at time t, K is a constant incorporating the properties of the macromolecular polymeric system and the drug, and n gives an indication of the release mechanism. For example, $n = 0.45$ for Case I or Fickian diffusion, $n = 0.89$ for Case II transport, $0.45 < n < 0.89$ for anomalous behaviour or non-Fickian transport, and $n > 1.0$ for Super Case II transport (Ritger and Peppas, 1987). The calculated n values of capsules were (2.0) and (2.2), of tablets (2.9) and (1.3), for A and B formulations, respectively. These values indicate a Super Case II transport for these matrices.

Further, the contribution of Fickian diffusion and Case II transport over the initial 60% drug release was determined (Peppas and Sahlin, 1989), as Eq. (5).

$$\frac{M_t}{M_\infty} = K_1 t^m + K_2 t^{2m} \quad (5)$$

where K_1 is the Fickian kinetic constant and K_2 is the relaxational/erosion rate constant, the coefficient m is the purely Fickian diffusion exponent for the device. The value of m for our formulations was 0.45 (cylinders). The calculated erosional contribution (K_2) was (9.2) and (4.0) for capsules and (8.8) and (8.0) for tablets in A and B formulations, respectively. The diffusional contribution (K_1) was (0.01) for capsules and (−6.3) and (−7.8) for A and B tablets. The K_2 values are considerably greater than K_1 values, implying that the relaxational contribution is the major factor contributing to drug release.

In conclusion, the XG matrices were capable to produce near zero-order drug release, with erosion playing the major role, making them potentially useful for delivering highly irritant drugs, such as nonsteroidal anti-inflammatory drugs. However, the excessive sustained release of drug may be due to the amount of biopolymers in the formulations. This point to the development of a matrix system with lower polymer concentration and/or the addition of a dissolution agent to speed up the drug release.

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