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Research Article

Formulation and *In-vitro* Characterization of Multiple Unit Sustained Release Matrix Pellets of Lornoxicam Using Natural Gums

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ABSTRACT

The present study involves preparation and characterization of extended release matrix pellets by using Lornoxicam as a model drug for prolong release of drug for extended period of time after predetermined lag time for the chronotherapy of rheumatoid arthritis. The pellets were prepared by the Extrusion and Spheronization method using as release retarding polymers like xanthan gum, xyloglucan and is combination with PVP K-30 and MCC PH-101 as pelletization aid. Matrix Pellets had characterized by flow properties, differential scanning calorimetry, scanning electron microscopy, particle size, circularity, roundness, aspect ratio, crushing strength, percent drug content, percent production yield, percent friability and in vitro drug release. The effects of various formulation variables on the size and drug release were also investigated. In this study, the feasibility and influence of incorporation of natural gums by itself and in combination with other gums on the ability to form spherical pellets by extrusion spheronization techniques. Matrix pellets containing 30% xanthan gum, 30% of xyloglucan and 30% combination of XG: Xg which showed sustained release of lornoxicam for15 h.

INTRODUCTION

Pellets are a dominating player in the world of multiparticulate oral drug delivery and their use is on rise these days. Pelletization is an agglomeration process that converts fine powder or granules of bulk and excipients into small, free flowing spherical or semi-spherical units, typically from about 0.5mm to 1.5mm, referred to as pellets [1]. Multiparticulates have several therapeutic and technological advantages over single-unit dosage forms. Being small (<2 mm), pellets or multiparticulates can distribute evenly in the gastrointestinal tract, resulting in fewer adverse effects. Pellets also reduce the risk of dose dumping compared to single unit dosage forms and result in a reproducible bioavailability. Pellets can be either filled into capsules or compressed into tablets called multiple unit pellet systems (MUPS), which rapidly disintegrate into smaller units [2 -4].

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Multiunit pellet systems (MUPS) are an approach to develop capsule formulation for controlled release. Capsule containing MUPS, when administered rapidly disperses in the GIT, each pellet act as a sub unit, consequently as a separate drug delivery system. Controlled release pellets which delivers the drug at a predetermined rate, at a predetermined region, reduces peak plasma fluctuations, consequently potential side effects can be minimized. MUPS have good desirable transit time and reduced chance of gastric irritation owing to the localization of drug delivery [5].

Lornoxicam is a non-steroidal anti-inflammatory drug with analgesic properties and belongs to the class oxicams. The mode of action of Lornoxicam is based on the inhibition of prostaglandin synthesis (inhibition of the cyclo-oxygenase enzyme). Lornoxicam is absorbed rapidly and almost completely from the gastro-intestinal tract. Lornoxicam is used in the treatment of rheumatoid arthritis, post-traumatic pain, masculo-skeletal and joint

disorders [6]. As the drug has short elimination half life (3-4 hours), the drug is administered 3-4 times a day. For rheumatoid arthritis sufferers, the optimal time for anti-inflammatory drug such as lornoxicam would be more effective when taken after the evening meal [7].

Added to that, lornoxicam shows a distinct pH-dependent solubility characterized by very poor solubility in acidic conditions present in the stomach. Thus, it remains in contact with the stomach wall for a long period which might lead to local irritation and ulceration so Sustained release formulation is needed to minimize the G.I. disturbances such as peptic ulceration with or without bleeding if present in larger concentration in G.I. tract [8].

Natural polymers like cellulose, xanthan gum, locust bean gum, tamarind gum and chemically modified gums have been studied in hydrophilic matrix tablets for controlled drug delivery. Natural gums and polysaccharides and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms. Polysaccharides are the choice of materials among the hydrophilic polymers used, because they are nontoxic and acceptable by the regulatory authorities [9].

The present study was aimed at developing matrix pellets of lornoxicam using Xanthan gum and xyloglucan as polymer for colon targeting in order to provide an effective and safe therapy for rheumatoid arthritis. In the present work, Matrix pellets prepared by using natural gums like xanthan gum and xyloglucan with PVP K 30 using lornoxicam as a model drug. The formulated pellets were further coated with Eudragit RS 100 and Eudragit RL 100 in the ratio of 1:2% w/w to achieve the desired lag time of 4-5 hrs before release of lornoxicam from matrix pellets. The main aim is focus on the study of effect of natural gums used in pellets formulation on particle size, sphericity, roundness, circularity, friability, crushing strength and in vitro drug release study. In this study, the feasibility and influence of incorporation of naturals gums by itself and in combination with other gums on the ability to form spherical pellets by extrusion spheronization techniques. Pellets properties such as Pellet size, size distribution and their flow properties, aspect ratio, sphericity, crushing strength and in vitro drug release profile were evaluated.

MATERIALS AND METHOD

Materials

Lornoxicam was obtained as a gift sample from Glenmark Pharmaceuticals Ltd (Nashik, India), Xanthan gum (LOBA Chemie, Mumbai, India), Xyloglucan was procured from Encore natural polymer, private limited, Ahmadabad , Eudragit RS 100 and Eudragit RL 100 are procured from Evonik Degussa, Mumbai, India. Microcrystalline Cellulose pH 101 (Avicel PH 101) PVP K30, PEG 4000 (S.D. Fine Chem Ltd., Mumbai) All the other solvents, reagents and chemicals used were of either Pharmacopoeial or analytical grade.

Method

Drug-loaded matrix pellet cores were prepared by extrusion–spheronization. As per the following formula Lornoxicam (LRN) (20%), Xanthan gum, Xyloglucan and PVP K30 (5%) microcrystalline cellulose and were mixed in a blender for 20 min. The granulating liquid, a 10% PEG 4000 aqueous solution as a pore forming agent in the formulation, was added slowly to this powder blend, which was then mixed until a homogeneous, cohesive, plastic mass was obtained. The resulting wet mass was extruded at a speed of 18 rpm (Umang Pharmatech, India), through perforations of 0.8mm in diameter. Spheronization was performed in a spheronizer (Umang Pharmatech, India) with a rotating plate of regular cross-hatch plate, at a speed of 800-1500 rpm, for 15 min. The wet pellets were dried at room temperature for 24 h and sieved to obtain the desired size distribution. The fraction with a pellet size of 400µm to 800µm was used for the further experiments.

Formulations shown in Table 1 were suitable for the extrusion– spheronization process, as long as the amount of granulation water was enough to provide adequate plasticity. That amount of water was determined by trial and error. The pellet size was mainly determined by the spheronizer speed, increasing the spheronizer speed decreases the pellet size.

Characterization and evaluation of matrix pellets

Micromeritic properties

The pellets were characterized by their micromeritic properties, such as bulk density, tapped density, compressibility index and flow properties. The bulk (b) and tapped density (t) of pellets and granules were determined using a tapping machine (n = 3). A 10 ml measuring cylinder was filled with the sample up to the mark.

Table 1: Formulation batches of pellets containing Lornoxicam

Composition	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lornoxicam	20	20	20	20	20	20	20	20	20
Xanthan gum	10	20	30	10	15	20	-	-	-
Xyloglucan	-	-	-	20	15	10	10	20	30
PVP K-15	5	5	5	5	5	5	5	5	5
MCC	60	55	45	45	45	45	60	55	45

The volumes at the beginning (bulk volume, V0) and after 100 taps (tapped volume, V100) were recorded. The bulk density was calculated as the ratio of mass and initial volume V0, while the tapped density was calculated as the ratio of mass and tapped volume V100. The compressibility index (C %) and Hausner ratio (HR) were calculated according to the following equations Eqs. (1), (2) and (3), [10] .

$$\text{Carr}'\text{s Index } (\%) = \frac{\rho t - \rho b}{\rho t} \times 100 - - - (1)$$

$$\text{Hausner ratio } = \frac{\rho t}{\rho b} - - - - (2)$$

Where, ρt -tapped density and ρb-bulk density of pellets.

$$\tan\theta = \frac{h}{r} - - - - - - (3)$$

Where, h and r are the height and radius of the powder cone

Size analysis of Matrix pellets

Size analysis was carried out for all above mentioned formulations with or without drug loading using SEM and Motic microscopy. In motic microscopy randomly selected 20 pellets of these formulations were observed under Motic DMWB2-223 digital microscope fitted with 1/3 CCD camera imaging accessory and using Motic Images 2000 (1.3 Version) image analysis software (Motic, China). The images of pellets were analyzed for their average diameter and different shape factors such as roundness and circularity factor. The software reported roundness values, generated using the following expression [11].

$$\text{Roundness} = \frac{0.9399P^2}{4\pi A} - - - - - - (4)$$

$$\text{Circularity} = 4\pi A/P^2 - - - - - (5)$$

Where, P is the perimeter of the pellet image and A is the area determined by the total number of pixels within the feature. The factor 0.9399 corrects the perimeter for the effect of the corners produced by digitization of the image. A roundness value of 1 corresponds to the image of a perfect sphere, and higher values correspond to less spherical images.

Particle size analysis

Particle size analysis of pellets was done by Sieve analysis method. The particle size distribution of the pellets was determined using a set of test sieves having ASTM no of 16, 18, 20, 22, 44 and having sieve size of 1000µm, 900µm, 850µm, 710µm, 550µm attached to a sieve shaker (Mechanical sieve shaker) operated for 10 min at a frequency of 50 Hz and an amplitude of 2mm. The percentage of weight retained was plotted against the mean size of pellets in each fraction [11].

Determination of % yield

The yield of formulated pellets were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of pellets and percent yields were calculated as per the formula mentioned in Eq (6) [10].

$$\%\text{Yield} = \frac{Pm}{Tm} \times 100 - - - - (6)$$

Where, Pm - Practical yield

Tm - Theoretical yield of formulated pellets respectively

Determination of drug entrapment efficiency

Drug entrapment efficiency represents the proportion of the initial amount of drug, which has been incorporated into the pellets. To assess the entrapment efficiency, specific amount of crushed pellets (10 mg) were suspended in 100 ml of pH 6.8 phosphate buffer with constant agitation at room temperature for 24 h. Finally,

the solution was filtered through Whatman filter paper, drug content was determined spectrophotometrically (Shimadzu 1800), at the wavelength of 376 nm using 6.8 pH phosphate buffer as blank. The entrapment efficiency of pellets was calculated by using the Eq. (7) [10]

$$\text{Entrapment Efficiency (\%)} = \frac{\text{AQ}}{\text{TQ}} \times 100 - -(7)$$

Where AQ is the actual quantity of drug present in the pellets and TQ is the theoretical quantity of drug present in the pellets.

Crushing strength of pellets

The crushing strength of pellets of different formulations (Table) was assessed using a universal testing instrument with a 5 kg load cell (CT-5, Engineering Systems, Nottingham, UK). The pellets were strained until failure occurred. The load was recorded and the tensile strength was calculated applying Eq. (2) [12, 13].

$$\text{CF(s)} = 0.4\text{F}/\text{pR}^2 - - - (8)$$

Where, CF(s) is the crushing strength,
F is the failure load, and R is the radius of the pellet.
Fifty pellets of each batch were analysed.

Friability

The friability of the pellets was determined by using a friability tester described by Schultz et al. For the test the particle fraction, 710 mm of each batch was removed by sieving. Per batch, 8.000 g (m1) was whirled in a stream of air with 450 l/min for 16 min. Abrasion was removed with the air. The pellets were weighed after the test (m^2) and the abrasion (F) calculated from Eq. (9)

$$\text{Friability} = [1-(W_t/W)] \times 100 \text{ --------- (9)}$$

Where, F = Friability in percentage, W = Initial weight of pellets and W_t = Weight of pellets after friabiation.

Scanning Electron Microscopy

SEM pictures Additionally, beads were examined by scanning electron microscopy (SEM) (S-4800 5.0kV 6.9 mm40 SEM) to determine their size, shape and surface characteristics. Scanning electron microscopy (SEM) was used to visualize the surface morphology of the coated pellets. For the assay, dry samples were placed on a double face tape adhered to a metal support and coated with colloidal gold under vacuum. Photomicrographs were taken with a scanning electron microscope Fig. 3-5.

Determination of Drug Content:

For determination of drug content weighed the amount of pellets that are equivalent to the dose of lornoxicam drug and were placed into the 100 ml of 0.1 N NaOH solution of each formulation and kept for few hrs for sonication on ultrasonicator. Then filter the solution and analysed the filtrate spectrophotometrically at 377 nm in UV spectrophotometer [14].

***In vitro* drug release studies:**

Two sets of In vitro drug release studies were performed in a USP I dissolution apparatus (Dissolution test TDT-08L plus, Electrolab, India) with basket speed at 50 rpm. Drug loaded pellets equivalent to 8 mg pure drug, filled in '0' size hard gelatine capsule were used for all dissolution studies. In-vitro drug release studies were conducted in 900mL of simulated gastric fluid 0.1N HCl (pH 1.2) as dissolution media for 2h and then remaining studies in simulated intestinal fluid phosphate buffer (pH 7.4) until 15h. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper, concentration of Lornoxicam was determined in samples spectrophotometrically (UV-1800, Shimadzu, Japan) at 376 nm. Volume of dissolution medium (900 ml), stirring speed 50 rpm) and temperature of medium (37 ± 0.5^0C) were kept same for all dissolution studies. Percentage cumulative drug release was calculated [15].

RESULT AND DISCUSSION

Micromeritic properties

The pellets were characterized by their micromeritic properties, such as bulk density, tapped density, compressibility index and flow properties. The physical characterization of the matrix pellets comprising the lornoxicam as a model drug are the various physical parameters like bulk density, tapped density, Hausner ratio, Carr's index and angle of repose. The various densities and all of these parameters of the formulations are shown in Table 2.

Pellets containing natural gums with Avicel PH 101 showed higher bulk densities, which may be due to the particle size and higher density of Avicel PH 101. Pellets containing xanthan gum and xyloglucan showed high bulk and tapped densities, which may be due to size of pellets and highest circularity.

Table 2: Flow Properties of matrix pellets of various batches

Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Angle of Repose (θ^0)	Hausner ratio
F 1	0.5405±0.84	0.64516±0.99	16.21±1.93	25.45±0.4	1.193±0.08
F 2	0.5128±0.97	0.6257±1.04	17.949±1.35	21.19±0.65	1.218±0.34
F 3	0.5405±0.70	0.6667±0.92	18.919±1.45	27.10±0.39	1.233±0.24
F 4	0.5263±0.91	0.64103±0.88	17.895±1.90	24.49±1.72	1.217±0.02
F 5	0.5000±0.75	0.6060±0.90	17.501±1.84	24.44±1.61	1.21±0.03
F 6	0.5556±0.79	0.6896±1.09	19.444±1.67	24.34±1.09	1.24±0.17
F 7	0.5369±0.95	0.6451±0.76	16.770 ±1.49	29.92±1.51	1.20±0.43
F 8	0.5714±0.89	0.7142±0.93	20.01±1.623	21.74±1.49	1.25±0.23
F 9	0.5263±0.54	0.6451±1.05	18.42±1.83	20.10±1.53	1.22±0.19

(n=3, mean ± S.D.)

Table 3: Particle size, ferret diameter, crushing strength, Roundness, circularity aspect ratio and perimeter of different formulation batches of pellets

Batch code	Particle size in (µm)	Diameter (µm)	Crushing Strength (MPa)	Circularity	Roundness	Aspect Ratio
F 1	570.34±0.94	3446.49±127.09	9.546±0.22	0.99±0.03	0.94±0.08	1.07±0.03
F 2	510.21±1.04	3035.57±179.04	9.307±0.93	0.99±0.03	0.94±0.05	1.06±0.01
F 3	307.75±1.34	2535.25±194.23	8.29±0.68	0.99±0.09	0.94±0.09	1.08±0.08
F 4	390.51±1.09	3319.42±145.37	9.15±0.86	0.99±0.05	0.94±0.03	1.09±0.06
F 5	305.41±1.19	2791.13±167.04	8.13±0.78	0.99±0.04	0.94±0.01	1.10±0.009
F 6	493.14±1.20	2988.20±185.96	9.009±0.95	0.99±0.10	0.94±0.02	1.12±0.08
F 7	416.55 ±1.39	2733.71 ±210.9	9.148±0.73	0.99±0.04	0.94±0.01	1.05±0.03
F 8	389.23 ±1.43	2734.86±178.93	7.205±0.64	0.99±0.01	0.94±0.04	1.08±0.01
F 9	319.46±1.32	2512.89±222.54	9.335±0.72	1.01±0.09	0.92±0.01	1.03±0.012

Table 4: Friability, entrapment efficiency and % yield for matrix pellets

Formulation code	Friability (%)	Entrapment Efficiency (%)	% Yield
F 1	0.59±0.03	74.13793±0.80	60.9±1.49
F 2	0.423±0.04	85.86207±0.50	49.7±1.96
F 3	0.683±0.02	87.4138±0.77	52.8±1.78
F 4	0.516±0.08	78.0216±0.58	69.28±2.10
F 5	0.639±0.07	93.7144±0.92	53.8±2.11
F 6	0.661±0.19	95.34483±0.52	57.71±1.93
F 7	0.534±0.04	82.845 %±0.38	55.93±1.58
F 8	0.614±0.03	87.012 %±0.59	49.52±2.17
F 9	0.593±0.05	87.34 %±0.90	45.89±2.00

(n=3, mean ± S.D.)

High density of mixed pellets can also be attributed to the setting of natural gums within the void spaces of MCC micro fibrils, thereby making the pellets denser. Hausner ratio may be a result of their higher size distribution and angle of repose shows proper flow rates of the different formulations. Pellets containing xanthan gum (F1 - F3) , xyloglucan (F7- F9) and

the combination of both of gums (F4 - F6) had both near about circular as well as high density and as a result they showed very low angle of repose as well as a MCC had the least satisfactory flow properties which may be attributed to their surface and shape irregularities. Angle of repose (θ^0) values for the pellets was in the range 20.00 to 25.45 indicating good flow properties of the pellets.

Sieve analysis of Matrix pellets

The results of pellet size and distribution are shown in Table 3. MCC shows good extrusion behavior at an optimal concentration and influences on the mean diameter of the pellets. Due to good binding properties of MCC, it provide cohesiveness to a wetted mass, able to retain a large quantity of binding agent helps to provide large surface area and high internal porosity. MCC also improves the plasticity of wetted mass and enhancing spheronization. It can be observed that the presence of natural gums influence the morphological characteristics i.e. size and shape of the pellets. For this parameter, a value close to 0.8 mm would be expected since, because of a screen with this gap was used during the extrusion process. The overall result reflected that the size and size distribution of pellets were influenced by the presence of xanthan gum and xyloglucan in the formulation. The smaller size and uniform size distribution in particularly within the selected size range of (450 to 800) could be when natural gums were incorporated in to formulation.

Due to the gums incorporated in to formulation of pellets the size of pellets lesser that's depend on the concentration of gums used in formulation and size get reduces due to higher quantity of gums which required higher spheronization speed for the roundness or sphericity of the pellets and ultimately that formulation and process parameter affects on the size of pellets.

Pellets size and shape analysis

The individual size of the pellets is an important parameter when a drug release system is being designed because the smaller the particles are, the faster the drug release rate will be and vice versa. Similarly, pellets with a narrower size distribution will assure a more homogeneous drug release. It can be observed that the presence of natural gums influence the morphological characteristics of the pellets. The images of pellets were analyzed for their average diameter, aspect, morphological quality and circularity degree. All of these parameters can be seen from Table 3.

The particle sizes of matrix pellets of all batches were found in the range of 0.5 to 0.8 mm which matches to standard limits. The roundness and circularity values were also found in the range of within limits. The result of image analysis indicates that almost all matrix pellets had an acceptable aspect ratio (AR 1.2). Likewise the mixture containing lower concentration of gums either 10% of xanthan gum and xyloglucan had different pellet diameter than the higher concentration of xanthan gum and xyloglucan.

At lower concentration of gums (up to 10%) and 60% of MCC have higher mean diameter than higher concentration of gum in pellets. This may be attributed to the fact that Avicel PH 101 acts as molecular sponge and causes changes in the pellet size due to presence of Avicel PH 101 and the concentration of gums. According to the sponge model, the extrusion and subsequently the spheronization properties of MCC (Avicel PH 101) depend on the microfibers of MCC and voids spaces between them. Apart from the water present inside the pore of the fibres, water present in these void spaces provides adequate rheological properties to the wet mass which furthers help in extrusion - spheronization. When small amount of gums (i.e. up to 20%) are added to this mass in small concentration (up to 70%) they could well reside and fibers in these void spaces and fibers will be able to retain their own properties and also have its own binding property and also acts as release retardant with little effect of the presence of other fillers. The pellets of (F1-F2) containing xanthan gum with 60% of MCC have better pellet sphericity with uniform size distribution.

Circularity is an important pellets characterization parameter as the shape of the pellets can affect properties such as flowability and coating performance. Concerning the degree of circularity of the pellets, it was observed that the xanthan gum xyloglucan and combination of both of this gum pellets shows circularity in the range of (0.9100 - 1.100) respectively.This value obtained (0.9100 - 1.100) indicates that the pellets are near about circular because the value are close to 1, a value that characterizes a perfect circle. The circularity of pellets depends on presence of the xanthan gum and xyloglucan in which proportional affect the circularity. Pellets subjected to attrition and rounding force during extrusion- spheronization process, these gums

are more resistant to deformation and spheronization. The Avicel PH 101 with lower density allows pellets to deform more quickly and easily in to more spherical pellets. Incorporation of xanthan gum and xyloglucan also affected the circularity parameters. Quantity of xanthan gum and xyloglucan increases, that ultimately affect the circularity of pellets leads to increase in number of dambelled shape pellets. Whereas the pellets containing 10 - 20% of gums (F1- F2 and F7 - F8) have proper circularity and pellets containing 10% xanthan gum, xyloglucan and combination of these two polymers (F5) were somewhat spherical and had a smooth surface.

Determination of % yield and Entrapment efficiency

The encapsulation efficiency and % yield of the matrix pellets are given in Table 4. For a successful extrusion-spheronisation process and the formulation, a high percentage of pellets should be produced within a desired size range.

The percentage of weight retained was plotted against the mean size of pellets in each fraction. The matrix pellets of xanthan gum (F3), xyloglucan (F9) and combination of both of xanthan gum and xyloglucan, where the pellets formulation containing higher concentration of gums i.e. the formulation batches (F3, F4, F5, F6, F9) have very low yield due to higher spheronization speed and higher spheronization time required for sphericity of pellets which causes decrease in sphericity and sizes of pellets and irregularity in shape and sizes causes decrease in production yield of the pellets and having higher entrapment efficiency. Most of the pellets are retained on 22/44 sieve of 710 µm of size. Due to higher concentration of these polymers in pellets formulation that causes the swelling when come in contact with water and form matrix gel and drug get incorporated in to this matrix gel and therefore these formulation batches have higher entrapment efficiency as compared to other formulation batches.

Crushing strength of matrix pellets

Mechanical crushing force gives indication of its mechanical robustness of pellets. Crushing strength was in general higher for pellets prepared from xanthan gum and xyloglucan and the result shown in Table 3**.** It appears that's lornoxicam matrix pellets, had higher mechanical strength due to the natural polymers used in pellets formulation because of pellets from natural polymers are harder than other polymers. The result revealed that by increase in the proportion of xanthan gum: xyloglucan, the crushing strength of pellets increased which mean formulation containing only xanthan gum as a binder produce harder pellets and mechanical strength increased.

Friability of pellets

The percent friabilities of all the formulations containing natural gums (F1 - F9) were below 1% and shown in Table 4. Pellets prepared from the natural gums are harder due to gums used in the pellets formation so the 10% solution of PEG 4000 used as plasticizer for maintaining the plasticity of pellets during spheronization. Obtained values of pellet friability and their hardness indicated pellet quality sufficient to withstand further processing parameters like attrition forces inside the spheronizer. Friability of pellets contains natural gums was found to less hardness of this matrix pellets.

Fourier Transform Infra Red (FTIR) Spectroscopy

Fourier Transform Infrared spectra of drug, physical mixture of lornoxicam, xanthan gum, lornoxicam, xyloglucan and physical mixture of lornoxicam, xanthan gum, Xyloglucan with PVP K 30 are shown in Fig. 1. From interpretation can conclude that there is no drug–polymer interaction. Pure Lornoxicam spectra showed sharp characteristic peaks which doesn't shows any interaction with natural gums.

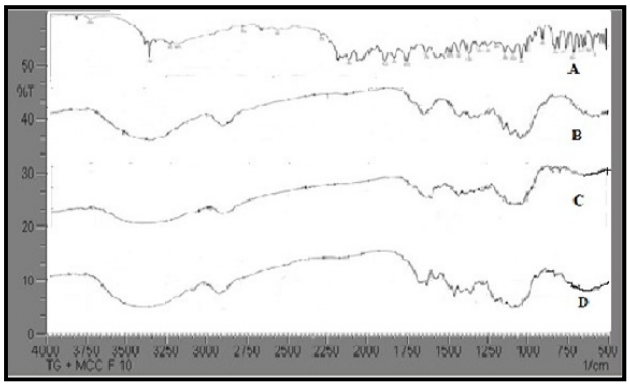

Figure 1: FTIR spectra of physical mixture of A - Pure lornoxicam, B - Lornoxicam and xanthan gum, C - Lornoxicam , xanthan gum and xyloglucan, D - Lornoxicam, xyloglucan.

Differential Scanning Calorimetry (DSC)

DSC thermogram of pure lornoxicam drug, physical mixture of xanthan gum and xyloglucan are shown in Fig. 2 respectively. DSC

thermograph of lornoxicam showed sharp exothermic peak at 231.08^{0}C due to its melting sows in Fig 2. Drug melting peak is present even in its physical mixtures with xanthan gum and xyloglucan shows in Fig 2. But small lowering of peak temperature and broadening of sharp exothermic peak occurs due to related enthalpy variation was observed due to the mixture of components. Comparative Fig 2, elucidate that there was not any major difference in onset temperature and peak temperature, when compared with Lornoxicam thermogram Fig. 2.

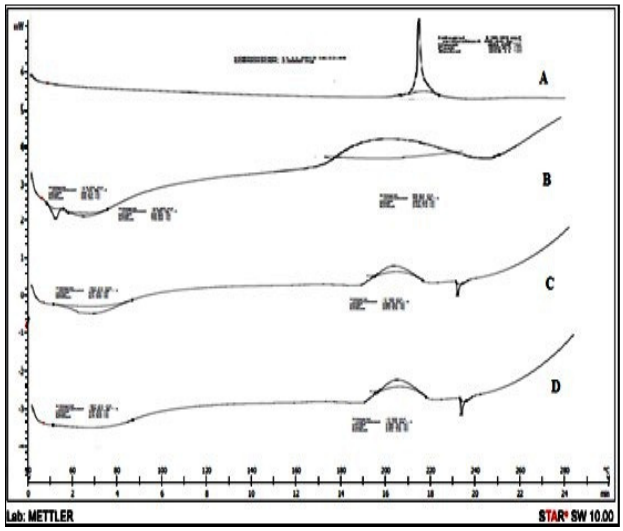

Figure 2: DSC thermograph of A-Lornoxicam and physical mixture of B- Lornoxicam and xanthan gum, C- Lornoxicam , xanthan gum and xyloglucan, D- Lornoxicam, xyloglucan.

Scanning Electron Microscopy

The morphology of the pellets analyzed by scanning electron microscopy is shown in Fig 3, 4 and 5 which shows the sizes and surface properties of pellets. Some fractures on the surface of the pellets containing xanthan gum and xyloglucan can be observed. Analyses were performed under magnifications of 75 and 3500-fold. It was possible to observe the general aspect of sets of pellets as well as details of their surface, such as pores.

Fig 3, 4 and 5 shows the SEM images obtained from the uncoated pellets. Under the smaller magnification, the surface seems to be very rough. Under the greatest magnification, some pores can be seen on the pellets surface and its roughness becomes more evident. The change in the shape of the pellets resulting from a change in the formulation parameters can be clearly seen here. The pellet shape changed fairly spherical (Fig 3) from dumbbell shape. Further it is clearly visible that when MCC is added to the formulation (F1, F2, F7, and F8), the sphericity and smoothness of the pellets increased (Fig 3, 4 and 5), whereas by dumbbell shape pellets due to incorporation of high quantity of natural gums. The size of matrix pellets according to SEM images were found to be a 829 µm, 930 µm for F2 batch, 724 µm ,702 µm for F5 batch and 843 µm, 924 µm for F8 batch respectively.

***In vitro* drug release studies**

After pellets characterization, in vitro release profile of uncoated and coated pellets were determined in different pH buffers i.e. 1.2 pH buffer and then 6.8 phosphate buffer respectively. The dissolution study of were carried out with or without addition of rat caecal contents to pH 6.8 phosphate buffer solution. In vitro drug release profile of Lornoxicam presented in Fig 6 A and 6 B respectively. The influence of concentration of xanthan gum, xyloglucan and combination of both of this polymers with 5 % PVP K30 in each formulation on in vitro release of drug and is directly proportional to the liquid uptake, swelling and erosion properties of polymers. The formulation containing 10 % and 20 % of xanthan gum, 10% and 20% of xyloglucan did not swell to great extend than the swelling capacity of the 30% XG and 30% of xyloglucan formulation. The formulation batches F1 to F3 contains 10%, 20% and 30% of xanthan gum which releases drug depends on the concentration of polymer used in matrix pellets. As the concentration of xanthan gum increases in the matrix pellets there is an increase in swelling property which gives more sustaining effect.

The release from this matrix pellets is retarded by the swelling and erosion nature of xanthan gum when exposed to dissolution medium. The drug release from the XG / Xg/ XG: Xg with 5% PVP K30 matrix was too slow released of lornoxicam up to 15 h. The hydrophilic polymers i.e. xanthan gum, xyloglucan with hydrophobic polymer PVP K30 had to be added to enhance the drug release rate. This extended-release effect was attributed to the integrity of the matrix structure which was maintained during the dissolution study. Changing the XG concentration allowed to modify the drug release as increasing concentration of XG enhanced drug release. 102.13% of lornoxicam was released from formulation containing 10% XG, whereas the total drug load was released within this time from matrix pellets containing 20% and 30% XG.

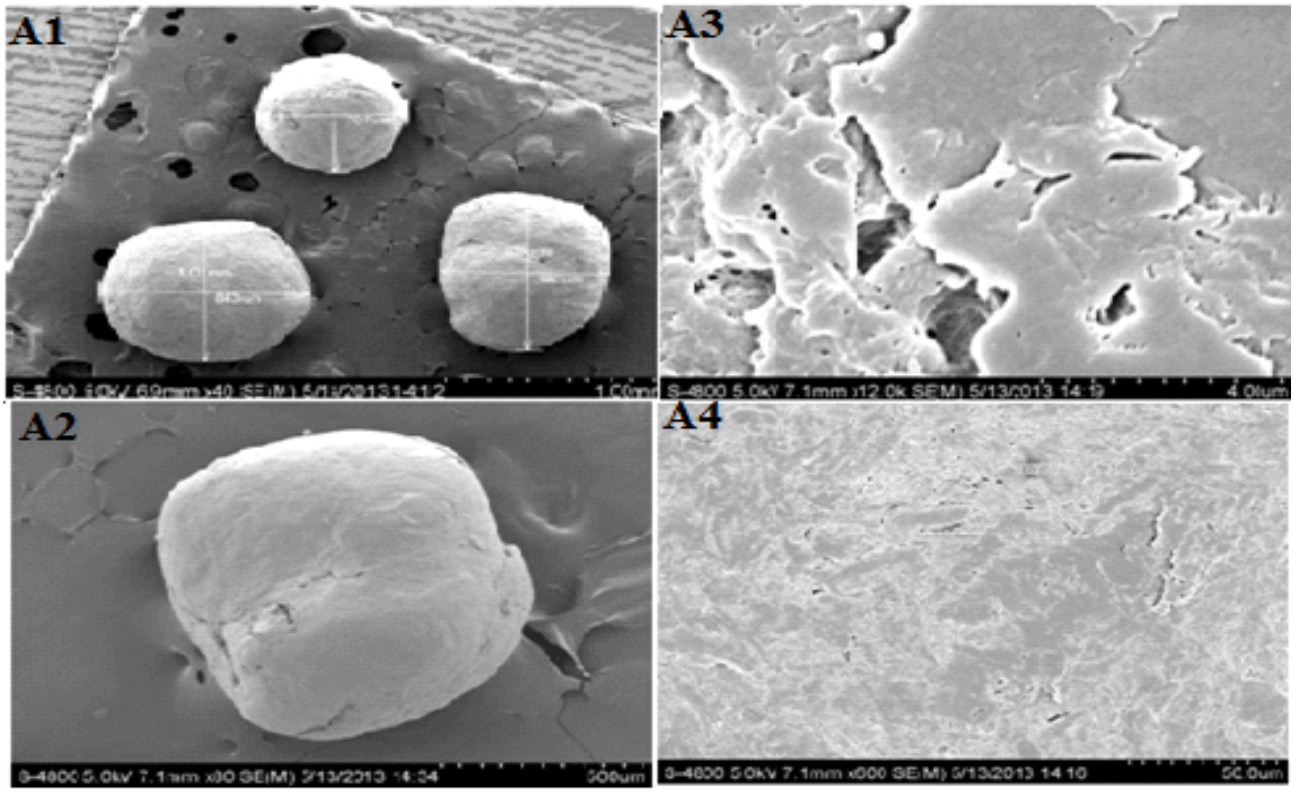

Figure 3: SEM images of F2 Formulation batch xanthan gum matrix pellets shows surface morphology of matrix pellets under different magnification (A1-100µm, A2-500µm, A3-4µm and A4-50µm).

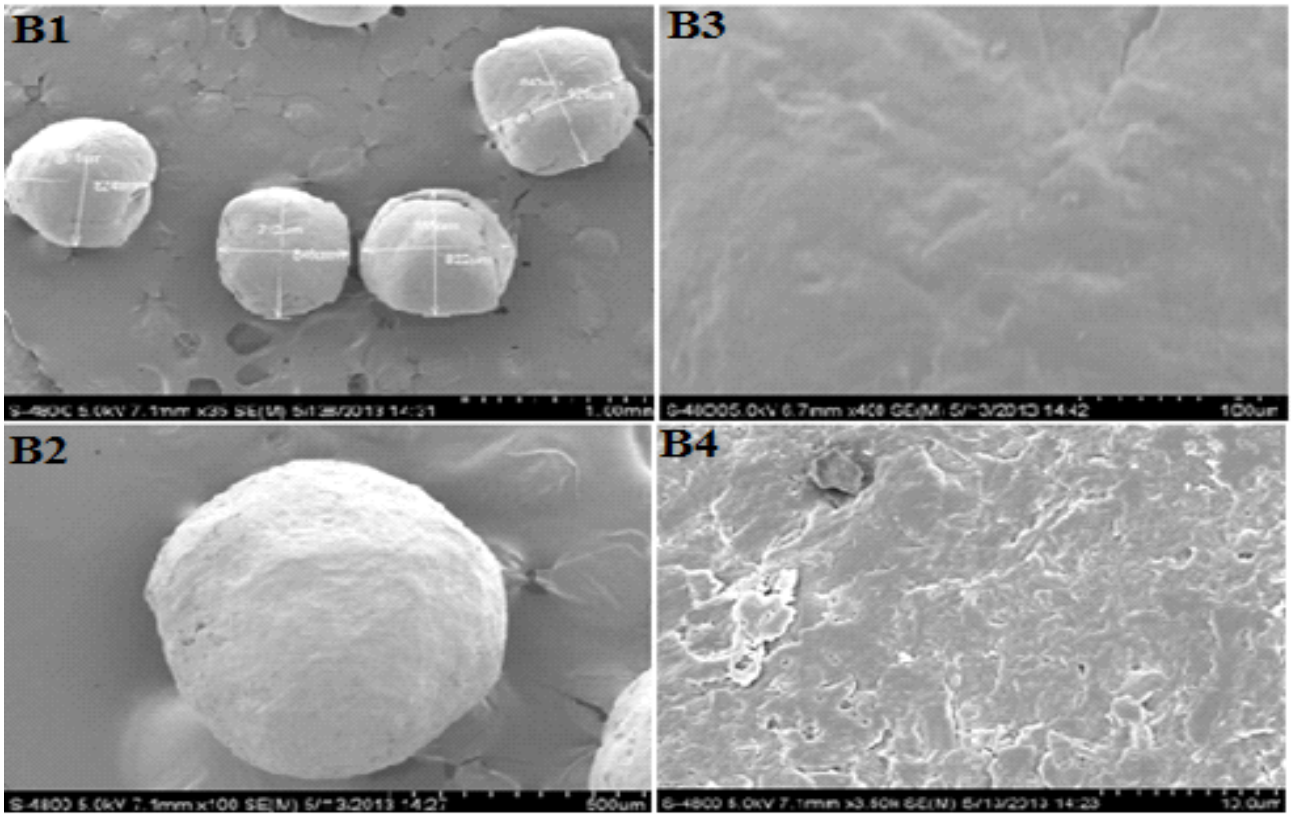

Figure 4: SEM graphs of F5 Formulation batch containing combination of xanthan gum and xyloglucan at different magnification (B1-100µm, B2-500µm, B3-4µm and B4-50µm).

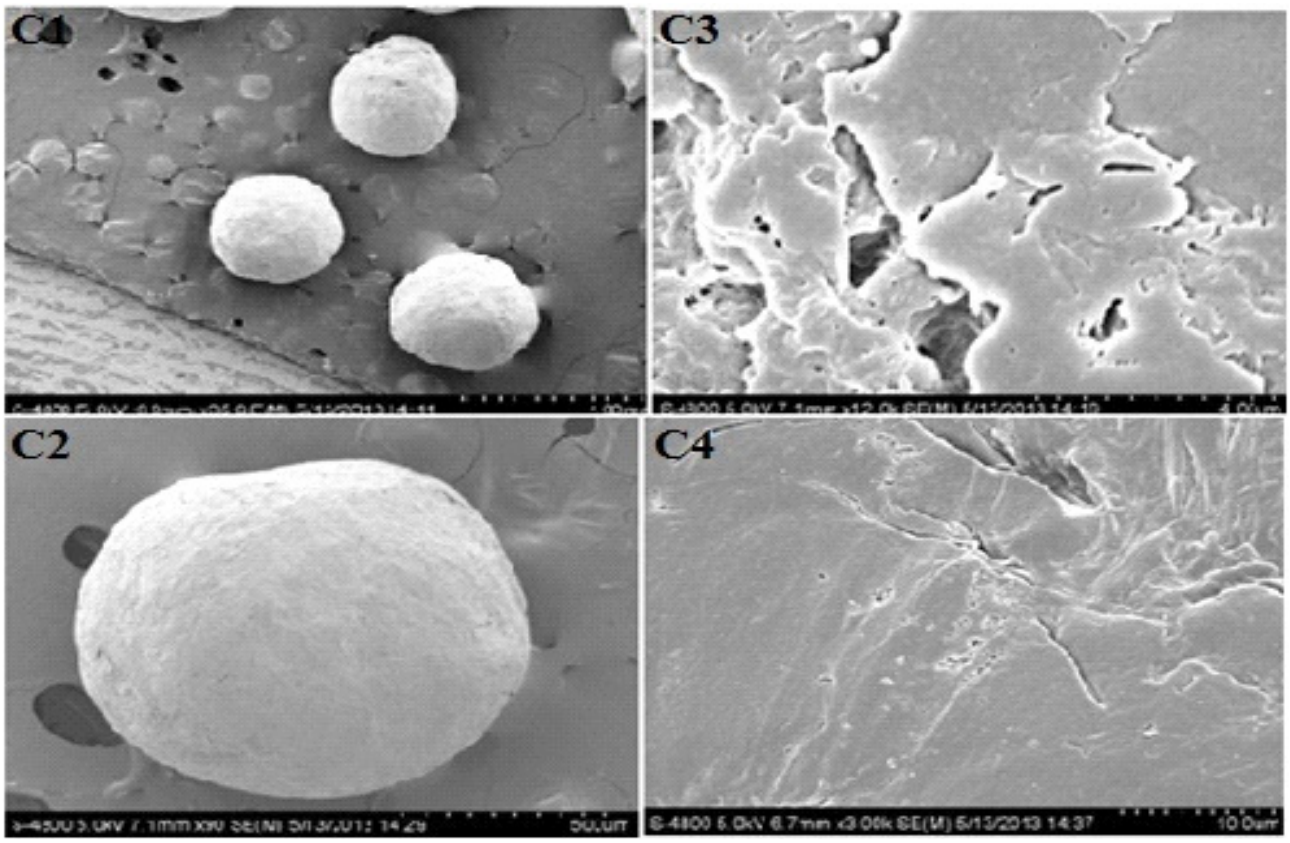

Figure 5: SEM graphs of F8 Formulation batch containing xyloglucan at different magnification (C1-100µm, C2-500µm, C3-4µm and C4-50µm).

As in case of natural polymers i.e. xanthan gum and xyloglucan as a hydrophilic matrix, the drug release rate from matrices decreased at higher concentration of xanthan gum and xyloglucan, due to an increase in viscosity and thickness of the hydrated gel layer, instantly formed around that matrix pellets upon contact with dissolution medium. This gel barrier restricted water penetration into and drug diffusion from matrix pellets, delaying drug release for prolong time. However as the system under investigation there is not pure hydrophilic matrix used in matrix pellets but a combination of hydrophilic matrix with hydrophobic polymer and hydrophilic additives like MCC the higher degree of swelling did not impede drug release as the swelling of natural gums opened the structure of matrix pellets, creating pores due to PVP K30 and PEG 4000 used in matrix pellets through which the lornoxicam was released. From the *in vitro* dissolution data in Fig 6A, it was found that formulations F1 to F3 containing 10%, 20% and 30% of xanthan gum as release retardant with PVP K30 that released drug 102.13%, 98.2285%, 94.27847% in 15 h respectively. As the percentage of polymer increased, the kinetics of release decreased.

The F3 formulation containing 30 % of xanthan gum along with 5 % PVP K30 which shows slow release of drug than F1 and F2 formulation batches. A significant difference is observed in the behavior of the 20% and 30% XG in the F2 and F3 formulation batches, there is release properties were altered when larger sample size of pellets in the capsules. The release rate for 20% and 30% of formulation was reduced by increasing the concentration of XG and sample size of matrix pellets in dissolution baskets.

Due to the rapid swelling of XG at 20% and 30% after hydration by dissolution medium, the matrix pellets sticks together with increasing the sample size, and increased diffusion path length which ultimately reduced the drug release rate.
Similar drug release mechanism also observed for the xyloglucan. The formulation batch F2 has a pronounced as most effective batch in sphericity and other properties of matrix pellets along with in vitro drug release. The natural gum in alone does not give as much sustaining effect but the combination of two natural polymers give better release effect as compared to the single polymer in matrix formulation. The results of release studies of formulations F4 to F6 are shown in Fig 6A.

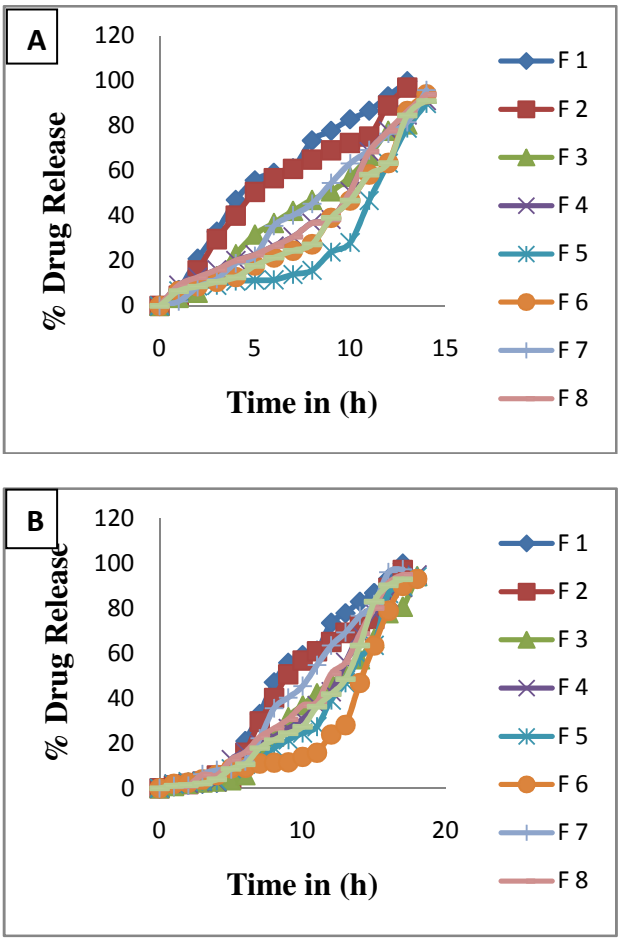

Figure 6: *In vitro* dissolution profile of lornaxicam A) Uncoated pellets B) Coating pellets

The formulation F4 to F6 contains the combination of xanthan gum and xyloglucan in different ratio that batches shows better release than the gum shows alone. The F4, F5 and F6 batches contains XG: Xyloglucan ratio 1:2, 1:1 and 2:1 which shows drug release 94.830 %, 89.9129 %, 93.6392 % in 15 h respectively. All of these 3 batches of combination show slow release of drug than other one. This may be due to the greater degree of swelling of Xanthan gum and xyloglucan and both of this hydrophilic polymers shows synergistic effect which retard the release and control the onset of action. The release of drug depends not only on the nature of matrix but also upon the amount polymers.

Here, we tried to find the bacterial effect on the formulation F3, F5 and F9 and we found that the drug release from the system was increased by upto 15% to 30% in presence of rat caecal content. This clearly indicates the effect of colonic bacteria on the drug release rate that degrades the natural polysaccharide (XG, Xyloglucan), increased erosion and decreased lag time in presence of rat caecal content which shows the onset of drug action.

Fig 7 shows that the presence of rat caecal content in the dissolution medium resulted in a significant increase in drug release, when compared with in vitro drug release from matrix pellets without caecal content. Fig 8 shows in vitro drug release of optimized formulation batches F3, F5 and F9 after lag time with or without rat caecal content. The mean % of drug release at the end of 17 h of dissolution study from formulation batches F3, F5 and F9 was found to be 103.27%, 99.95% and 99.849% with rat caecal content % respectively. The matrix pellets prepared from the natural gums are more susceptible to the attacks colonic microbial enzymes. This enzymes causes the erosion of polysaccharides present in the pellets, were completely degraded in the presence of rat caecal contents there by releasing the drug from the pellets in to rat caecal content dissolution medium than the dissolution study without rat caecal contents.

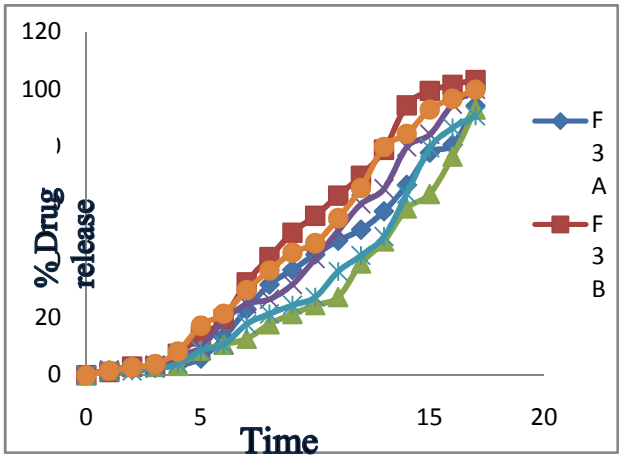

Figure 7: *In vitro* drug release of matrix pellets with or without rat caecal content after lag time.

Stability study

Stability studies were performed as per ICH guidelines. Drug content and drug release was determined at the interval of 15, 30, 60 and 90 days are shown in Table 5. It was found that the pellets of optimized batch (F3), (F5) and (F9) were stable even at exaggerated condition of temperature and humidity.

CONCLUSION

In order to the lornoxicam extended release matrix pellets were prepared using the natural gums i.e. xanthan gum and xyloglucan by extrusion spheronization method.

Table 5: Stability studies with respect to formulation batch (F3) (F5) (F9)

Batch	F3		F5		F9	
Days	Drug Content (%)	Drug Release (%)	Drug Content (%)	Drug Release (%)	Drug Content (%)	Drug Release (%)
0	87.41	98.43	93.71	93.97	87.34	92.93
15	86.23	98.90	90.34	95.94	85.89	95.49
30	85.46	99.89	89.53	99.78	80.34	98.35
60	82.89	100.45	88.20	103.41	80.21	101.56
90	79.96	102.67	85.20	198.89	79.971.9	106.9

The pellets formed with xanthan gum and xyloglucan, as the concentration of xanthan gum and xyloglucan increases in the pellets formulation, the irregular shaped pellets are formed and crushing strength is high and ultimately slowly release of drug. Pellets matrix integrity was destroyed in the first hour of dissolution test due to the disruption of the matrix structure probably due to the excessive swelling of the gums whether alone or in combination with other gum. The pellets prepared by xanthan gum and xyloglucan may hard due to gums so to maintain the plasticity of pellets 10 % solution of PEG 4000 is used. In pellets, destruction of the matrix integrity was also due to 10% solution of PEG 4000 as a pore former and plasticizer in pellets. As concerns these extended release matrix pellets system becomes more of prolong release type and release get increases due to colonic content and prevent the morning stiffness and pain occurs due to rheumatoid arthritis. It can be concluded that concentration of these natural gums affect the size, shape, circularity, crushing strength parameters and in vitro drug release of the pellets.

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