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CHEMICAL MODIFICATION AND CHARACTERIZATION OF PECTIN AS A POTENTIAL DRUG RELEASE RETARDANT

Harika Puppala Satya Krishna, Bharath Srinivasan*, Basavaraj Basappa Veerabhadraiah, Deveswaran Rajamanickam, Madhavan Varadharajan

M.S. Ramaiah College of Pharmacy, M.S.R. Nagar, M.S.R.I.T Post, Bangalore, Karnataka, India

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ABSTRACT

The present study deals with the chemical modification of pectin by acetylation of their free hydroxyl groups to yield high ester pectin and to evaluate its solubility and swelling behaviour along with the effect on the release pattern of the drug. Modified pectins were prepared by acetylation process using various strengths of 20%, 40% and 60% v/v acetyl chloride in ethanol. The prepared modified pectins were subjected to various physico-chemical characteristics like solubility, gelling studies, acid value, saponification value and ester value. FTIR studies were carried out to confirm the chemical modification of pectin. Matrix tablets of tramadol were formulated using various strengths of modified pectins in different concentrations and its impact on drug release was studied. All the formulated batches were subjected to weight variation, hardness, friability, drug content and the values obtained were within the acceptable range. The *in-vitro* drug release characteristics from the formulated tablets were compared with commercial sustained release tablet of tramadol. The optimized tablet formulation F4 sustained the drug release over a period of 8hours as comparable to the marketed product. Thus the synthesized modified pectin proved to be an ideal drug release retarding polymer.

KEYWORDS: Modified pectin, Chemical modification, Tramadol, Sustained release.

***Author for correspondence**

Bharath Srinivasan, M.S. Ramaiah College of Pharmacy, M.S.R. Nagar, M.S.R.I.T Post, Bangalore, Karnataka, India
Email: bharath1970in@yahoo.com

INTRODUCTION

Pectin is a structural heteropolysaccharide contained in the primary cell walls of terrestrial plants. Apple, quince, plume, gooseberry, oranges, cherries and grapes contain pectin. It is an essential component in the initial growth and in the ripening process and has been found to be useful in area of drug delivery[1]. It is produced commercially as a white to light brown powder, mainly extracted from citrus fruits and is used in food industry as a gelling agent particularly in jams and jellies. Pectins are a family of complex polysaccharides that contain 1,4-linked α-D-galacturonic acid residues. The acid groups along the chain are largely esterified with methoxy groups in the natural product. Pectin is highly hydrophilic in nature. Hydrophilic matrices are widely used in oral controlled drug delivery and for the preparation of modified release formulation because of their flexibility to obtain a desirable drug release profile[2]. The release from the hydrophilic matrix is controlled by the viscous layer barrier around the tablet that opposes the penetration of solvent into the tablet[3]. Nowadays, pectin is gaining importance as a polymer for modified release drug delivery formulation because of its cost-effectiveness[4]. However, the major challenge of using pectin for the development of modified drug formulation is to overcome its solubility in aqueous medium which may contribute to the undesirable, premature and local release of the active medicament from the polysaccharide matrix. One of the options to reduce the high solubility of polysaccharides could be to chemically modify them without affecting their biodegradability[5-7]. Pectins can be modified by saponification catalysed by mineral acids, bases, salts of weak acids, enzymes, concentrated ammonium systems and primary aliphatic amines[8].

Tramadol is a centrally-acting analgesic, used in treating moderate to moderately severe pain. The drug has a wide range of applications, including treatment for restless leg syndrome, acid reflux and fibromyalgia.

In this work, we propose the chemical modification of pectin by the reaction with acetyl chloride in ethanol. The objective of this modification was to reduce the polarity of pectin by reducing the number of free hydroxyl groups and to study the release of the tramadol from tablets prepared using this modified pectins[9].

MATERIALS AND METHODS

Tramadol was gifted by Surien Pharmaceuticals Pvt. Ltd., Chennai. Pectin was purchased from S.D.Fine Chemicals, Mumbai, India, Acetyl Chloride from Merck Specialities Pvt. Ltd. Mumbai. All other chemicals and reagents used were of analytical grade.

Synthesis of modified pectin

A weighed quantity of 10 g pectin was gradually added into the flasks containing 20 ml of freshly prepared 20% v/v, 40 % v/v, 60% v/v acetyl chloride in ethanol and stirred for a period of 60 min. in a closed condition over a magnetic stirrer. The product was filtered and dried in a hot air oven at 50ºC. The dried product was triturated and passed through sieve no# 24.

Physicochemical characterization of modified pectins

a) Solubility studies

The solubility studies of the modified pectins in various solvents like distilled water, chloroform, methanol were studied. Accurately weighed quantity of 100 mg modified pectin was added to 10 ml of particular solvent in a 50 ml beaker and was shaken for 24 hrs on a water bath shaker. Then the solution was filtered through pre weighed Whatman filter paper No. 41 and the paper was re-weighed after complete drying. The solubility of the modified pectin in a particular solvent was determined by the difference between the final weight and initial weight of paper. Solubility data of the modified pectins was shown in **Table 1**.

b) Gelling or Swelling Factor

A watch glass was taken containing a weighed quantity of 100 mg of modified pectin and to that distilled water was added gradually till no further absorption could be visibly observed[10]. The gelling capacity of the modified pectin was determined by the difference in the weight of watch glass before and after addition and absorption of water. Data for this gelling or swelling factor was shown in **Table 2**.

c) Determination of acid value

The acid value is the number which expresses in milligrams the amount of potassium hydroxide necessary to neutralize the free acid present in 1 gram of the substance[11].

10 g of modified pectin was dissolved in 50 ml of a mixture of equal volumes of ethanol (95%) and ether, previously neutralized with 0.1 M potassium hydroxide to phenolphthalein solution. If the sample does not dissolve in cold solvent, then the flask was connected with reflux condenser and warmed slowly with frequent shaking. 1 ml of phenolphthalein solution was added and titrated with 0.1 M potassium hydroxide until the solution remained faintly pink after shaking for 30 sec. The acid value was calculated from the expression:

Acid value = 5.61 n/w

where **n** is the number of ml of 0.1 M potassium hydroxide required and **w** is the weight, in g, of the substance. Acid value data of modified pectins was shown in **Table 3**.

d) Saponification value

The Saponification value is the number of milligrams of potassium hydroxide required to neutralize the free acid and to saponify the esters present in 1 g of the sample.

In this, 2 g polymer was taken into a 200 ml flask of borosilicate glass fitted with a reflux condenser. 25 ml 0.5 M ethanolic potassium hydroxide solution and a little pumice powder was added and refluxed on a water-bath for 30 minutes.1 ml of phenolphthalein solution was added and titrated immediately with 0.5 M hydrochloric acid (**a** ml). For the blank, the experiment was repeated in absence of polymer (**b** ml). The saponification value was calculated from the expression:

Saponification value = 28.05(b-a)/w

where **w** is the weight of the polymer (g).

Saponification value data of modified pectins was shown in **Table 3.**

e) Ester value

Ester value is the amount of potassium hydroxide (mg) required to saponify the esters present in 1 g of the sample. Ester value data was shown in Table 3.

The ester value was calculated from the expression:

Ester value = Saponification value – Acid value

f) FTIR studies of the modified pectins

Samples of modified pectins (MP-20, MP-40, MP-60) and pure pectin were mixed with KBr powder and then pressed by a hydrostatic press at a pressure of 5 ton/cm^2 for 5 minutes. The scanning range of infrared spectra was 500 – 4000cm^{-1} using computer-mediated Fourier transformed infrared spectroscopy (FTIR) (model-8400S, shimadzu).

Formulation of pectin based tablets of tramadol

Tablets of tramadol were prepared by using modified pectins MP-20, MP-40 and MP-60 at varying ratios using lactose as the diluent, starch paste as a binder with magnesium stearate and purified talc as the glidant and lubricant respectively (**Table 4**). Weighed quantities of

tramadol and modified pectin were triturated and mixed thoroughly. Lactose was added and mixed homogeneously. Then sufficient quantity of starch paste (5 % w/v) was added and mixed to form dough mass. The wet mass was passed through a 16-mesh sieve and the obtained granules were dried at 40ºC for 8hrs. The dried granules were again passed through18-mesh sieve and blended with purified talc and magnesium stearate. The compression of tablets was performed with a flat round 8mm punches using a single rotary tablet press (Rimek, Ahmedabad).

Evaluation of matrix tablets

All the prepared matrix tablets were evaluated for its uniformity in weight, hardness, friability and drug content according to official methods. The values were shown in **Table 5**.

a) Weight Variation Test

Randomly selected 20 tablets of each formulation batch were weighed using an electronic digital balance and the test was performed according to the Indian Pharmacopoeia.

b) Hardness Test

The tablet crushing strength was tested by using Monsanto tablet hardness tester. A tablet was placed between the anvils and the crushing strength which causes the tablet to break was recorded. Three tablets from each formulation batch were tested randomly and the average readings were expressed as mean values of triplicates.

c) Drug content

Twenty tablets from each batch were weighed and crushed to powder with mortar and pestle. Triturated powder equivalent to 100 mg of the drug was accurately weighed, suitably diluted with purified water and analyzed for drug content at 271nm using UV-Visible spectrophotometer (UV-1601, Shimadzu).

d) *Invitro* Drug Release Studies

The *in-vitro* drug release studies of all the formulations were carried out using USP dissolution test apparatus type II using phosphate buffer pH 7.4 as the dissolution media of volume 900ml, with rotational speed of 50rpm and temperature maintained at 37±0.5^{0}C. The samples were withdrawn at different intervals, diluted suitably with purified water and analyzed spectrophotometrically for the tramadol release at 271 nm.

e) Drug release kinetics

The drug release data of all the formulations were analyzed as per zero order, first order, higuchi and peppas model using the software PCP-Disso-v3 and the release mechanism with the best fit model were predicted. The drug release kinetics data was shown in **Table 6**.

RESULTS AND DISCUSSION

The hydrophilicity of the pectin polymer was reduced by acetylation process with the partial chemical treatment in various concentrations of 20%, 40% and 60% v/v of acetyl chloride in ethanol solution. The obtained modified pectins of different fractions were studied for various physicochemical properties. The solubility and swelling property of modified pectin in water decreased with the increased degree of acetylation process as compared to pure pectins (**Table 1 & 2**).

The decreased results of acid value and increased saponification and ester values of modified pectins (MP-20,MP-40 and MP-60) as compared to pure pectin showed that acetylation has occurred with the free hydroxyl groups of the pectin (**Table 3**). Further, the IR spectra of all the modified pectin samples remained almost similar but when compared with the pure pectin, it was found that the pure pectin having the –OH Stretch of alcohol (3500-3200 cm^{-1}) shown by strong broad band were found to be absent in all the IR spectra of modified pectins, confirming the chemical modification of pectin during the acetylation process (**Figures 1-4**).

The tablet formulations of tramadol using various fractions of modified pectins were prepared by wet granulation method. The formulations obtained were subjected to un-official and official tests for tablets and the values obtained were within the acceptable range (**Table 5**). The results of *invitro* drug release studies showed a sustained release of tramadol with all the formulations. It was found that the drug retarding efficiency of modified pectin increased in the order of MP-60 > MP-40 >MP-20. The dissolution data obtained were processed with the software PCP-Dissov2.08 to predict the best fit model. The values of (n) and (k) authenticated that the formulations F1 and F2 followed Peppas model, whereas the formulations F3 to F6 including marketed product showed matrix type of drug release (**Table 6**).

Further the drug release profile of formulation F4 was found to be similar to marketed Tramadol –SR tablet showing a sustained release of 68.61% drug release over a period of 8h. (**Figure 5**).

In conclusion the modified pectin synthesized by acetylation process showed promising results as a drug retarding agent. The results from this study enable us to state that matrix tablets containing modified pectin are an interesting way of formulating oral sustained release solid dosage form. Since pectin is also a natural polymer,

further extensive work could be carried out as it would be a cost effective process also.

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Table 1: Solubility parameters

Quantity of polymer (mg)	Solvent	Quantity of modified polymer dissolved (mg)		
		Modified Pectin		
		MP-20	MP-40	MP-60
100	Distilled water	49	40	31
100	Chloroform	51	59	62
100	Methanol	59	64	69

MP-20 (Pectin treated with 20% v/v of acetyl chloride in ethanol).
MP-40 (Pectin treated with 40% v/v of acetyl chloride in ethanol).
MP-60 (Pectin treated with 60% v/v of acetyl chloride in ethanol).

Table 2: Gelling or swelling factor of modified Pectins

Quantity of polymer	Solvent	Quantity of Water uptake (swelling factor %)[a]			
		Modified Pectin			Pure Pectin (mg)
		MP-20	MP-40	MP-60	
100 mg	Distilled water	0.230 g	0.169 g	0.159 g	0.510 g

[a] % w/w of g of water absorbed per 100 mg of chemically modified polymer.

Table 3: Acid value, Saponification value, Ester value of modified pectins in comparison to pure pectin

Polymer	Acid value	Saponification value	Ester value
Pure Pectin	19.54	140.25	120.71
Modified Pectin (MP-20)	5.61	230.01	224.40
Modified Pectin (MP-40)	5.41	235.62	230.21
Modified Pectin (MP-60)	4.91	238.43	233.52

Table 4: Composition of tablet formulations

Formulation Code	Ingredients (mg)							
	Tramadol	Acetylated Modified Pectin			Starch Paste (5%w/v)	Purified Talc	Magnesium stearate	Lactose (q.s)
		MP-20	MP-40	MP- 60				
F1	100	75	-	-	q.s	10	5	300
F2	100	125	-	-	q.s	10	5	300
F3	100	-	75	-	q.s	10	5	300
F4	100	-	125	-	q.s	10	5	300
F5	100	-	-	75	q.s	10	5	300
F6	100	-	-	125	q.s	10	5	300

Table 5: Evaluation of Tramadol tablets

Formulation Code	Weight variation (mg±S.D.)	Hardness* (Kg/cm^2±S.D.)	Friability test (%)	Drug content* (%)
F1	305±4.7	2.8±0.1	0.28	98.34±3.2
F2	300±3.6	3.0±0.2	0.34	99.61±2.4
F3	302±4.6	3.6±0.2	0.31	99.92±1.7
F4	304±4.9	4.5±0.3	0.37	98.94±1.9
F5	303±3.8	4.2±0.2	0.29	99.17±2.1
F6	299±2.9	4.5±0.3	0.32	98.73±1.2

* Average of three determinations.

Table 6: Drug release kinetics analysis

Formulation	n	k	Best fit model
F1	0.3954	37.0516	Peppas
F2	0.3995	41.7363	Peppas
F3	0.4717	28.1768	Matrix
F4	0.4852	23.7115	Matrix
F5	0.5353	28.5418	Matrix
F6	0.5044	24.6996	Matrix
Marketed Product	0.5277	21.6645	Matrix

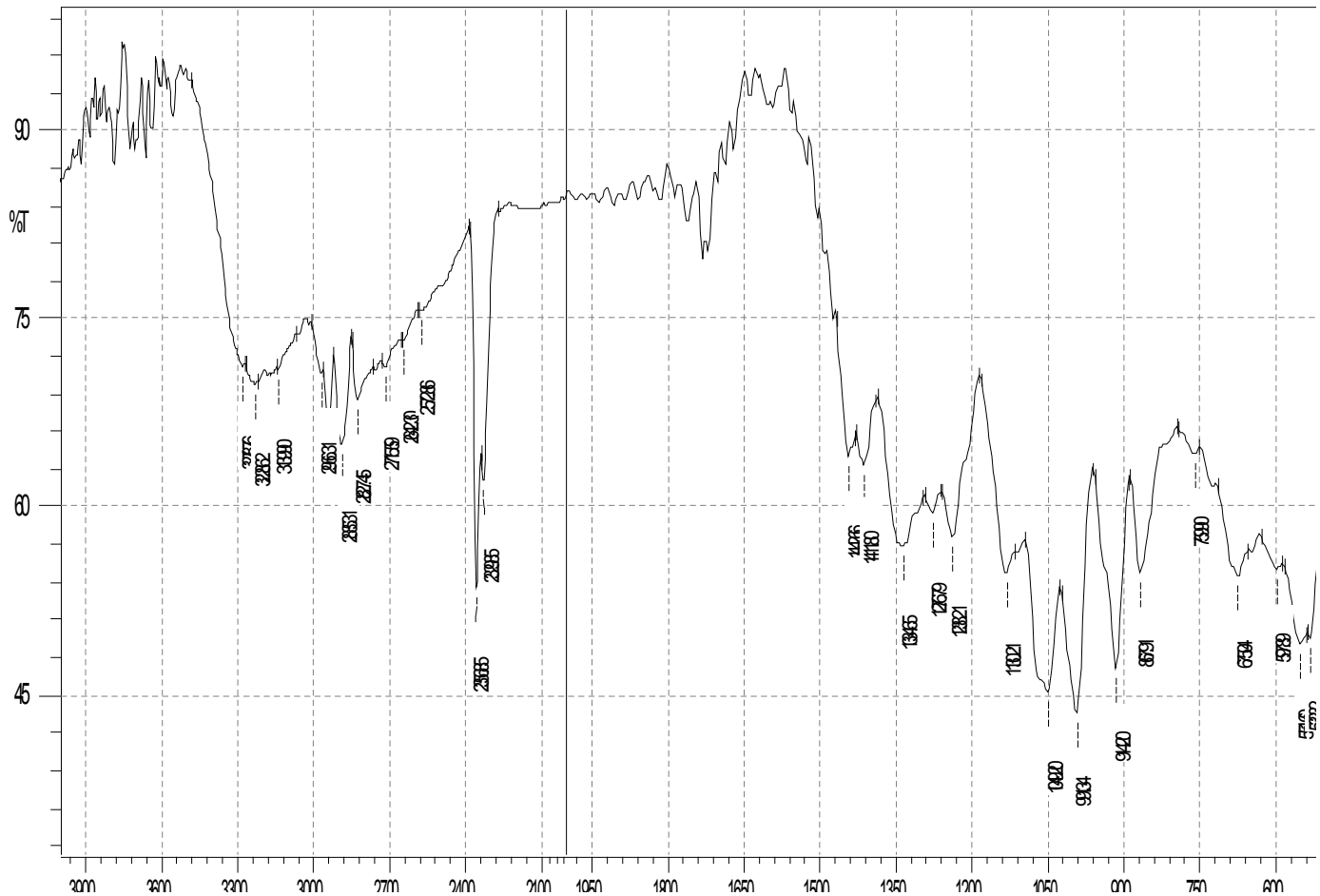

Fig.1 IR Spectra of pure pectin

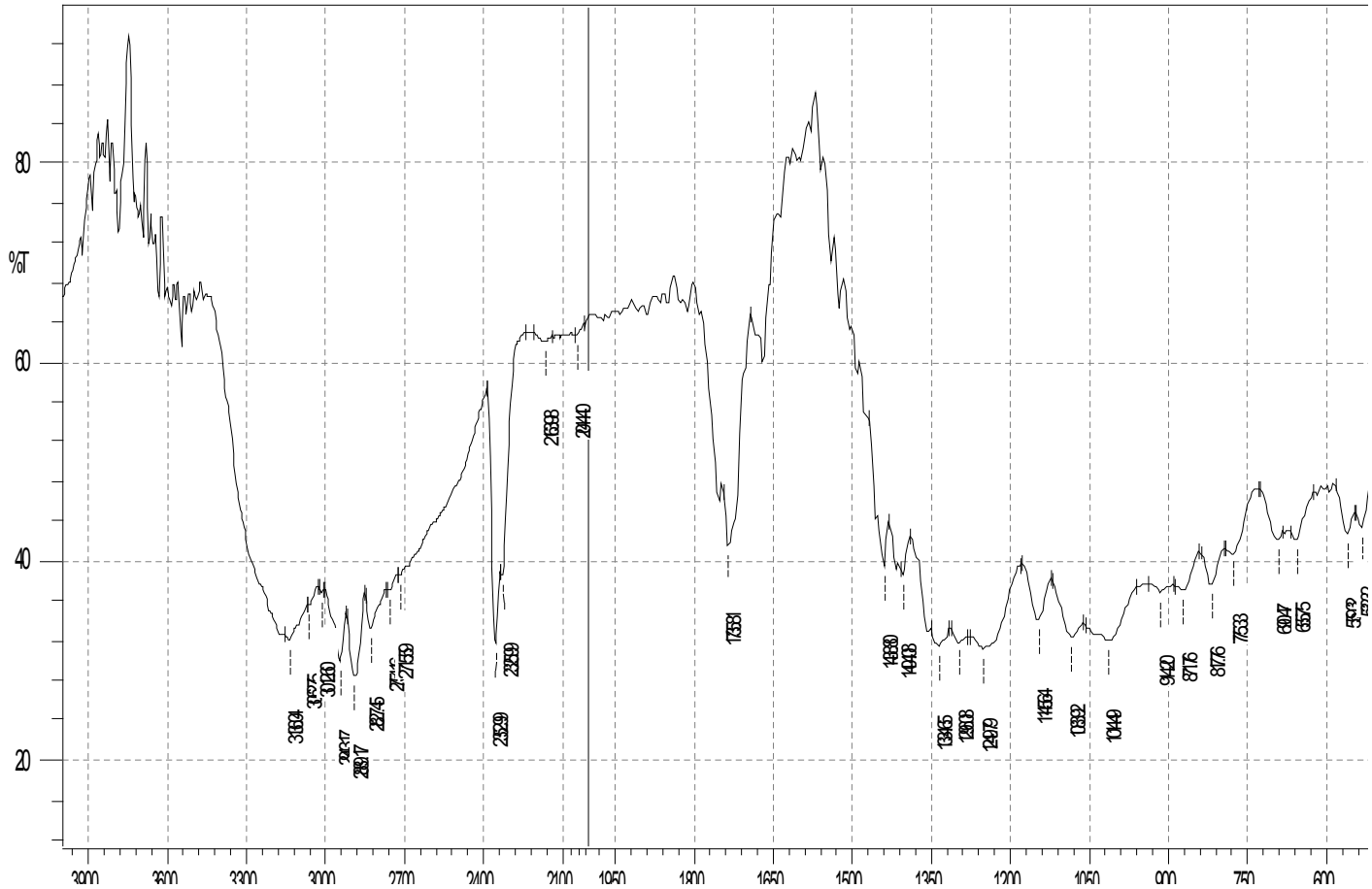

Fig.2 IR Spectra of MP-20 modified pectin

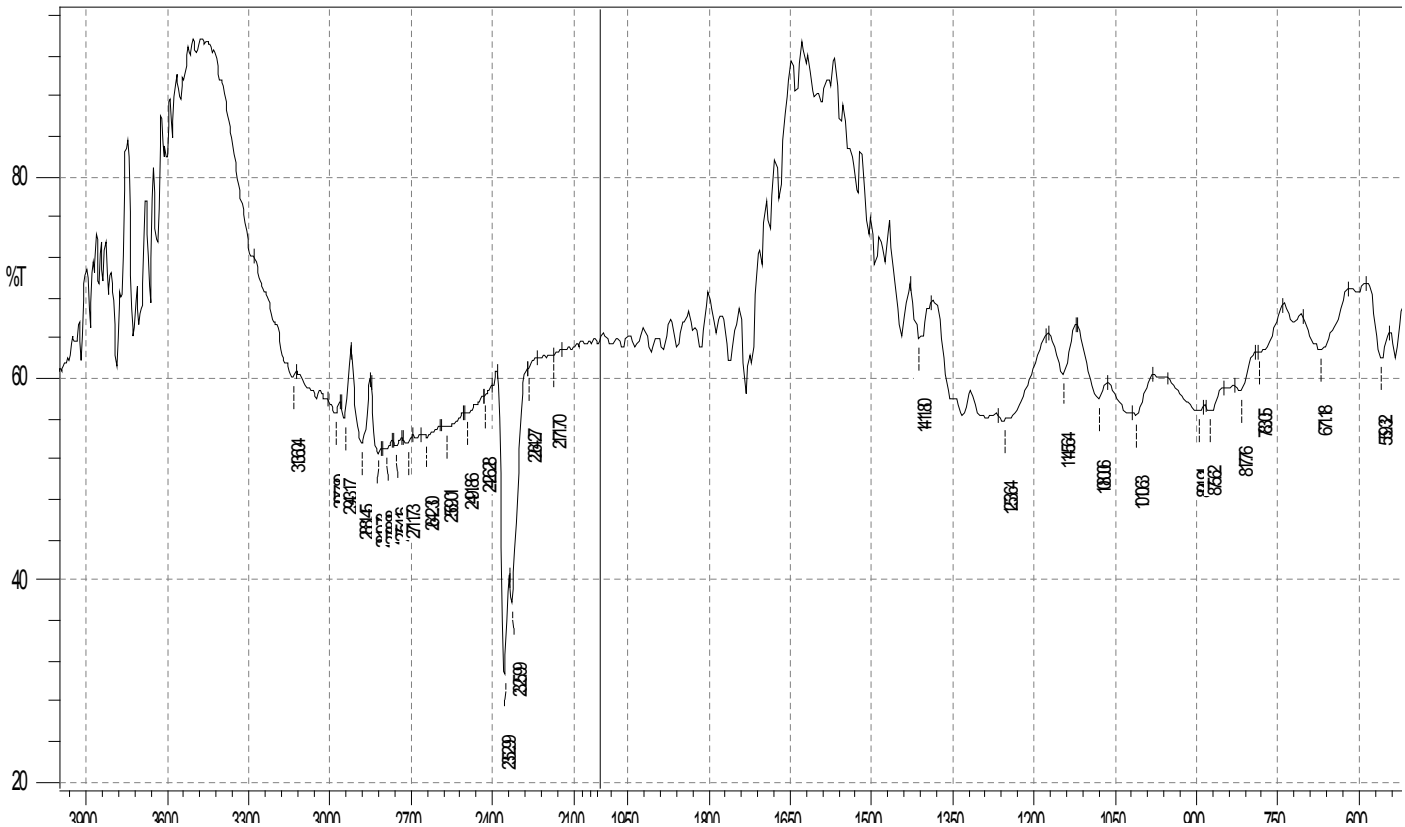

Fig.3 IR Spectra of MP-40 modified pectin

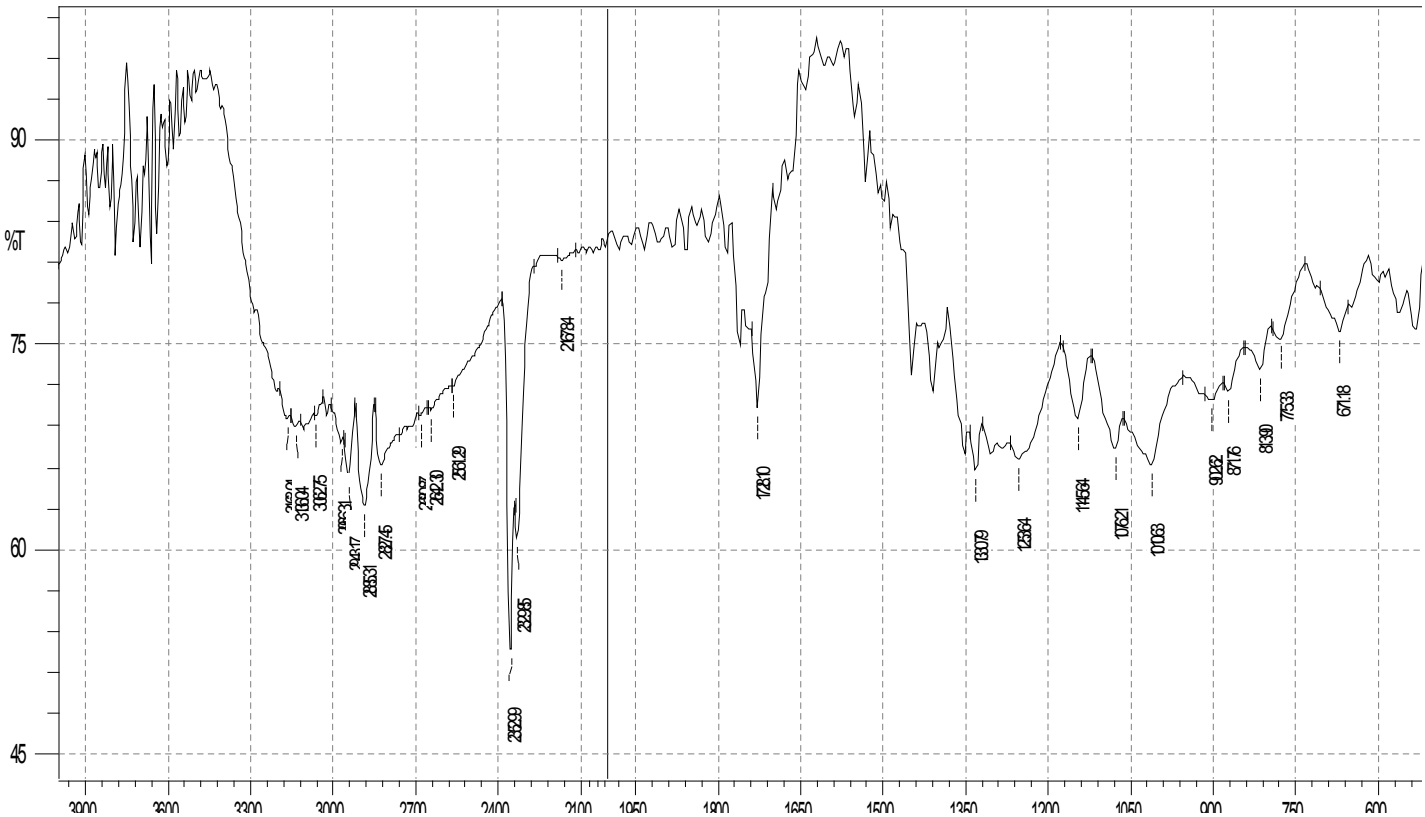

Fig.4 IR Spectra of MP-60 modified pectin

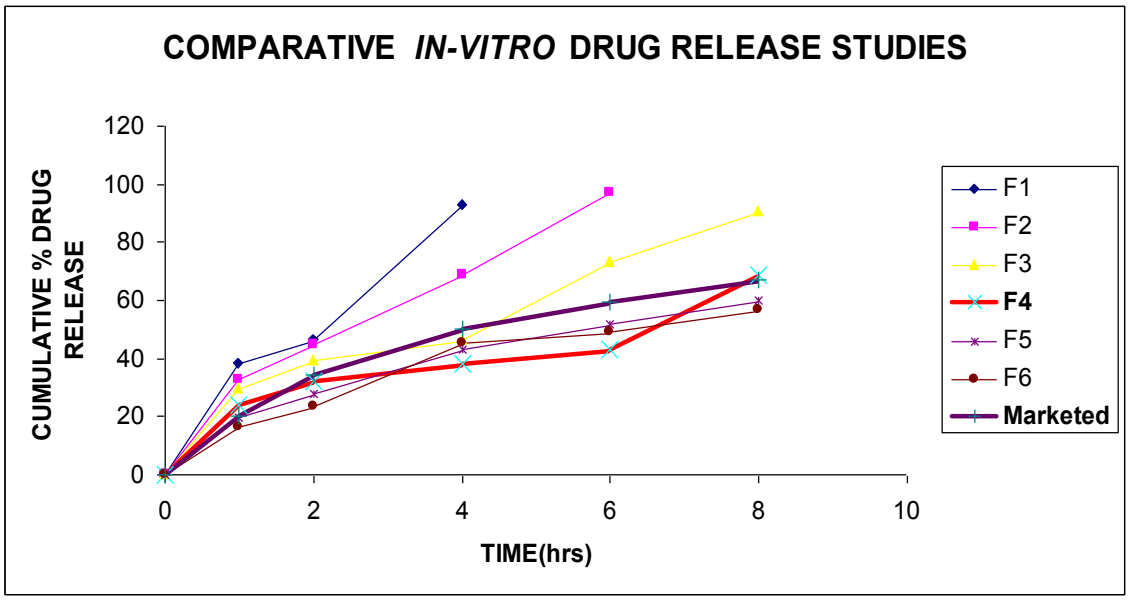

Fig.5 Comparative *in-vitro* drug release profile of formulations and marketed product

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