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Extraction of pectin from citrus fruit peel and use as natural binder in paracetamol tablet

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ABSTRACT

The aim of present study was to extract pectin from dried citrus fruit peels. In order to increase profits for citrus fruit growers and processors, citrus fruit peels, a by-product of citrus fruit processing, were investigated as a source of pectin. Pectin extraction was optimized from this by-product. Pectin was extracted under pH 2; Ethanol ratios(ER) 1:1 and extraction periods 120 min, at this condition highest yield was obtained 18.21%. Pectin assess its binding property in tablets using paracetamol as a model drug. Thereafter, four batches were formulated using pectin in different proportions. A reference batch of starch was also prepared to carry out the comparative study and to assess the binding property of pectin. Pre-compression and post-compression studies were performed for each formulation and compared to range as per pharmacopoeias. In vitro dissolution studies revealed that batch M3 showed 81.88% drug released. In-vitro release kinetic of all four batches followed korsmeyer-peppas models. Citrus peel pectin can act as excellent binder in dosage forms. Since it is of natural origin and citrus peels available at low cost it may prove to be better binder over commercially used synthetic binders.

Key Words: Binding property, ER, pH, release kinetic.

INTRODUCTION

Pectin is a polysaccharide consisting mostly of two moieties. These are homogalacturonan, (1-4) linked, a-D-galacturonic acid and its methyl ester; and rhamnogalacturonan I, (1-2) repeating linked, a-L-rhamnose-(1-4) a-D-galacturonic acid disaccharide. Rhamnogalacturonan II contains arabinan, galactan and arabinogalactan side chains. These monosaccharide units comprise most of sugar units found in pectin [1].Pectin occurs as a white to light brown powder or granular, and odorless or has slightly characteristic odor. Natural polymer like pectin is easy to isolate and purify, it is non-toxic and biocompatible [2, 3]. Pectins have been used in food industry but recently they are being explored for their other pharmaceutical applications such as binding, thickening, suspending properties [4]. Generally, high methylated pectin is of commercial importance as the one obtained from citrus and orange fruits. In an attempt to verify the use of pectin as polymer in dosage forms, this research work was initiated. The scope of present work is to establish citrus peel pectin as binding agent, against the commercially used one's like starch [5]. Many strategies are available for the design and development of modified-release drug delivery formulations [6, 13]. Conventional oral dosage forms often produce fluctuations of drug plasma level that either exceed safe therapeutic level or quickly fall below the minimum effective level; this effect is usually totally dependent on the particular

agent's biologic half-life, frequency of administration, and especially the release rate. For this purpose, paracetamol which is analgesic and antipyretic was selected as a model drug [16].

MATERIALS AND METHODS

Materials: All the chemicals and reagents used were of analytical grade.
Raw material: Fresh citrus fruit was purchased from local market. The peels were cut into small pieces and dried at 55^0C in oven for 48 hrs [9].

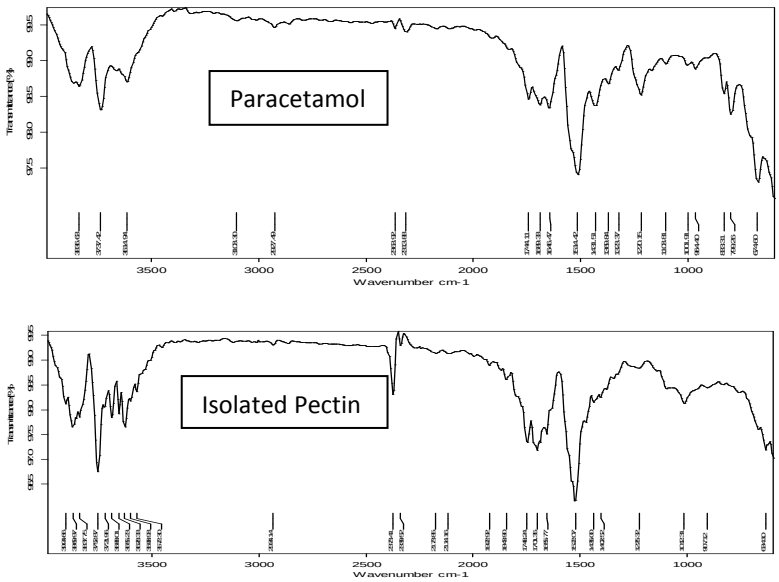
Other materials: Paracetamol was a generous gift sample from Medopharm Ltd., Bangalore. Ethanol, Citric acid, MCC, starch and talc were purchased from S.D Fine Chemicals Ltd, Mumbai. All the chemicals and reagents were of analytical grade.

Isolation of Pectin:
Dried Citrus fruit peel powder (50g) was blended with 300ml distilled water. The water to be used for extraction was acidified using 40% citric acid and pH was maintained at1.2, 2 (Table-1). The acidified mixture of blended peel powder was then heated at 60º C for around 120min. After the heating period was over, the mixture was passed through two fold muslin cloth and was cooled to room temperature. Isolation of pectin was carried out using ethyl alcohol as precipitating agent. Ethyl alcohol was used as a precipitating agent for pectin. Following that, concentrated pectin extracts were precipitated in 95% ethanol. One volume of extracts added in various volume of ethanol. The orange fruit extracts and ethanol ratios (ER) 1:0.5, 1:1, 1:1.5 and continuous stirring was done for 15 min. Then the mixture was kept aside for 2hrs without stirring. Pectin was filtered through four layered muslin cloth. The precipitate was washed 2 to 3 times by ethyl alcohol, to further remove any remaining impurity. Finally, precipitate was kept for drying at 35ºC to 40ºC in hot air oven and percentage yield was found to be around 18.21%. It was then stored in desiccators until further use. [4, 6, 9]

Table1: Composition of Pectin Formulation

Formulation Code	pH	ER	Practical Yield	% Yield
A	1.2	1:0.5	2.645	5.29
B	1.2	1:1	4.93	9.86
C	1.2	1:1.5	4.535	9.07
D	2	1:0.5	3.67	7.34
E	2	1:1	9.105	18.21
F	2	1:1.5	8.815	17.63

Drug excipient interaction:
FTIR spectra of pure drug, polymer (pectin), physical mixture of drug and pectin were obtained in ZnSe disc at moderate scanning speed between 4000-600 cm^{-1} using a Brucker Alpha E FTIR spectrophotometer [4].



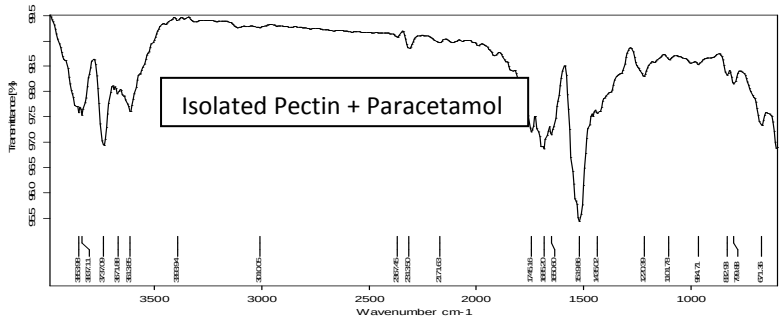


Fig.1: IR Spectra of Drug and Pectin.

Preparation of tablets:
Four different batches of tablet were prepared using wet granulation technique. The composition of single tablet per batch is given in table 2. Calculated amount which was required to prepare 400 mg paracetamol tablets, containing 250 mg drug, binder and filler was mixed uniformly. A sufficient amount of granulating agent (water) was added slowly to prepare wet mass. Granules were prepared by sieving method using 20# sieve. Further, granules were dried at 35-45ºC for one hour. The dried granules were stored in desiccators until compression of tablets. Prior to compression the dried granules were subjected to their flow characteristics. The required amounts of granules were weighed and compressed using Jaguar 8station punching machine having 12mm flat faced punch diameter. The compressed tablets of each batch were stored in air tight container at room temperature for further study. Such method of tablet production has previously been described by several authors who provided reproducible experimental results in terms of in vitro release. For the comparative reason, controlled tablets were prepared using starch as binding agent instead of isolated pectin.

Table2: Composition of Paracetamol Tablet

Ingredient	Formulation Code			
	M_1	M_2	M_3	Reference
Paracetamol	250	250	250	250
Pectin	10	20	30	-
Starch	-	-	-	30
PVP K-30	25	25	25	25
MCC	110	100	90	90
Mg Stearate	2	2	2	2
Talc	3	3	3	3

**Weight of each tablet = 400mg*

Evaluation of granules:
Granules were evaluated for all pre-compression parameters like bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose as shown in table 3. The evaluation was carried out using the methods specified in pharmacopoeias. All the determinations were carried in triplicate and averages reported. [16, 18].

Evaluation of Compressed Tablets:
Weight variation:
All prepared tablets were evaluated for weight variation as per IP 1996 (the weight variation limit is ± 5 %) monograph. Twenty tablets of each batch were used to evaluate weight variation among tablets and mean and standard deviation was calculated [16].

Friability:
Friability testing was determined using Roche Friabilator with readings in triplicate. Preweighed 20 tablets were allowed for 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets [16]. The percentage friability was then calculated by:

$$\%F = \frac{Wo - Wt}{Wo} \times 100$$

Where,
%F= percent friability, Wo= initial weight of 20 tablets, Wt = final weight of 20 tablets

Hardness:
The Pfizer tablet hardness tester was used to determine the tablet hardness. The hardness of the tablet was expressed in kg/cm^2 [16].

Thickness:
The thickness of formulated tablets was determined using Digital Vernier Caliper and the results were expressed as mean values of 10 determinations with SD.

Drug Content:
The 20 tablets were powdered, and powder equivalent to 250 mg of Paracetamol was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of phosphate buffer (pH 7.4) was added and shaken for 10 min. Thereafter, the volume was made up to 100 ml with buffer. Subsequently, the solution in volumetric flask was filtered, and 1 ml of the filtrate was diluted and analyzed at 247nm using UV-visible spectrophotometer (Shimadzu UV-1800, Japan). The drug content of each sample was estimated from standard curve of Paracetamol using phosphate buffer pH 7.4 [16].

Disintegration test:
The USP device to test disintegration was six glass tubes that are 3 long, open at the top and held against 10 screen at the bottom end of the basket rack assembly. Single tablet was placed in each tube and basket rack was positioned in 1 liter beaker of distilled water at 37± 2ºC, such that the tablets remained below the surface of the liquid on their upward movement and descended not closer than 2.5 cm from the bottom of the beaker. Suspend the assembly in the beaker containing water and operate the apparatus for 15 min. The assembly was removed from the liquid. The tablets pass the test if all of them have disintegrated.

In Vitro Drug Release Studies:
In vitro drug release was studied using USP Dissolution Apparatus Electro Lab TDT 08L taking 900ml phosphate buffer pH 7.4 as a dissolution medium maintained at 37 ± 2ºC for 5 hrs at 50 rpm. 5ml of sample was withdrawn at specified time intervals and was replaced by an equal volume of fresh dissolution medium. Samples were analyzed UV spectrophotometrically at 247 nm and the percentage drug release was calculated. The test was performed in triplicate to assure significance of results. Drug release profile was studied using percentage drug release Vs time (hrs) plot.

RESULTS AND DISCUSSION

Yield of Pectin: The pectin yield (%) with various parameters like pH and ER. According highest pectin yield were obtained at pH 2, the yield was peaked at the ER of 1:1. The yield ranged from 5.29 to18.21% (Table 1). Pectin was extracted by water based extraction technique and 9.105gm of pectin was obtained from 50gm of dried citrus fruit peel.

The drug-excipient interaction study was carried out by FTIR spectroscopy revealed that there was no interaction between the drug and citrus peel derived pectin as there was no significant shift in the principle peaks of Paracetamol.

Flow Properties of granule: Bulk density, Tapped density, Hausner's ratio, Carr's index and Angle of repose were studied for all the formulations. The results obtained from these studies of different batches showed in table 3. The values of micromeritic studies ranged within the acceptable limits [17, 18].

Table3:Pre-compression flow properties of granules

Properties	Formulation Code			
	M_1	M_2	M_3	Reference
Bulk density (gm/cm3)	0.228	0.277	0.223	0.228
Tapped density (gm/cm3)	0.292	0.333	0.263	0.3007
Hausner's ratio	1.280	1.202	1.1801	1.31
Carr's index	23.23	16.81	15.20	24.17
Angle of repose (degrees)				
Without glidant	35.74	33.29	32.14	35.87
With glidant	33.41	32.04	31.22	34.67

The prepared tablets were evaluated for post compression parameters such as weight variation, hardness, friability, thickness, drug content determination, disintegration and *in vitro* drug release studies as shown in Table 4. Weight variation, Hardness, friability and disintegration time of all the batches showed least variation and found to be within the Pharmacopoeial limits [17, 18].

Table 4: Physical Parameters of Tablet Formulation

Sr. No.	Parameters	Formulation Code			
		M_1	M_2	M_3	Reference
1	Weight variation(gm)	0.4031±0.0042	0.4055±0.0083	0.4019±0.0036	0.4036±0.0045
2	Friability (%)	0.4315	0.3995	0.2273	0.3866
3	Hardness (kg/cm^2)	5.50	5.60	5.80	5.60
4	Thickness (mm)	2.81±0.014	2.78±0.01	2.76±0.021	2.80±0.026
5	Drug content (mg)	248.7±2	249.1±3.5	249.6±2.8	249.1±3.2
6	Disintegration time (min: sec)	12:48	14:12	15:00	14:22
7	In vitro % drug release	94.87	90.16	81.59	84.32

The *in vitro* drug release studies (Fig.2) was performed for a period of 5 hr using pH 7.4 phosphate buffer and it was observed that M_3 showed 81.88 % drug release. The drug release data for the various formulated tablets did not fit into the classical power law expression. Moreover, on basis of drug release kinetics batch M3 was found to be optimized among all four batches containing pectin as binder and followed Korsmeyer-Peppas model. Reference batch containing starch as binder also followed Korsmeyer-Peppas model. Various kinetic models such as Zero order kinetics, First order kinetics, Higuchi, Hixon-Crowell and Korsmeyer-peppas were applied to determine the kinetics of drug release from the prepared formulations. As per the data obtained from the applied kinetics it can be easily seen that all the formulations showing same release kinetics even in varying the concentration of polymer (pectin). The values of correlation co-efficient for all the formulations were shown in Table 5. From the data it can be inferred that pectin has a better binding property than as that of starch. Thus citrus peel pectin having an excellent binding capacity, which could be exploited on commercial scale, as possessed all the requisite qualities of a binding agent.

Table 5: Values of Regression-coefficients and Rate constants for release of all formulations

Form Code	Zero order kinetics		First order kinetics		Higuchi matrix model		Hixon Crowell model		Korsmeyer Peppas model	
	R^2	K_1	R^2	K_2	R^2	K_3	R^2	K_4	R^2	K_5
M1	0.9541	15.514	0.9041	-0.2416	0.9422	46.21	0.9188	-0.6431	0.9801	0.9957
M2	0.9689	16.053	0.9236	-0.3024	0.9581	50.03	0.9511	-0.5792	0.9813	1.1634
M3	0.9673	16.897	0.9804	-0.182	0.9719	62.99	0.9839	-0.4906	0.9895	1.4126
Ref.	0.9753	17.381	0.9751	-0.4213	0.9665	55.86	0.9802	-0.4556	0.9861	1.3749

Fig.2: *In vitro* dissolution profiles of different formulations

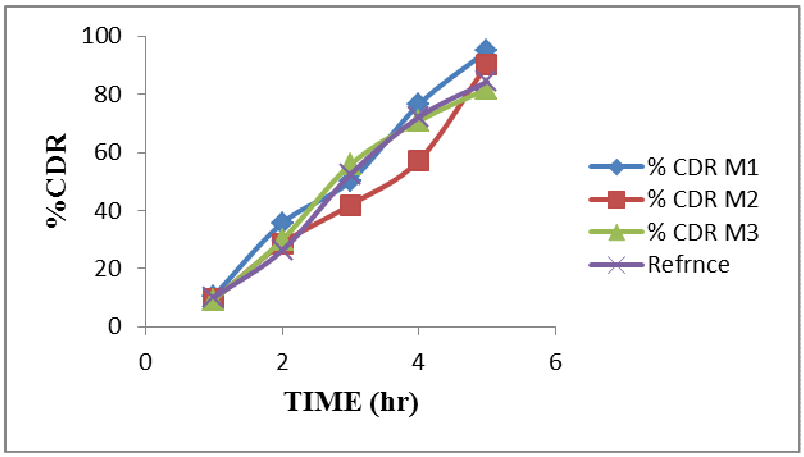
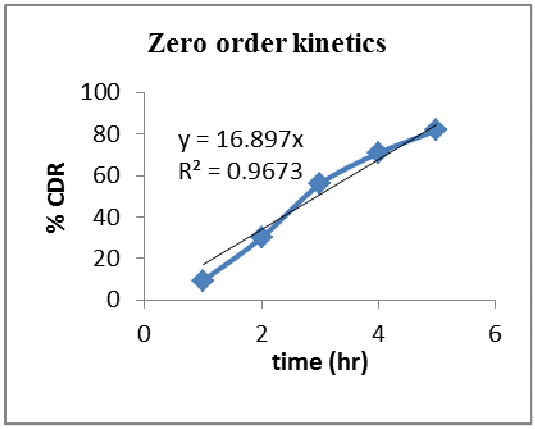
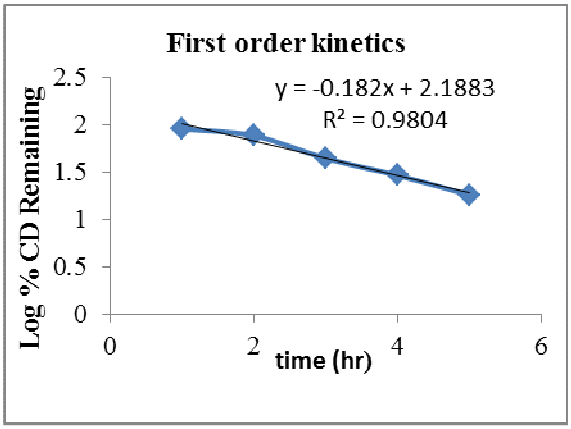
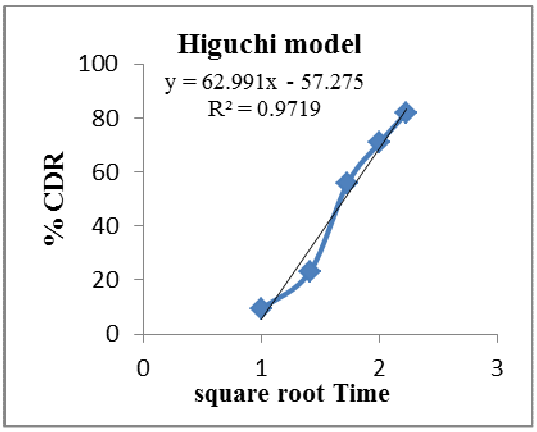
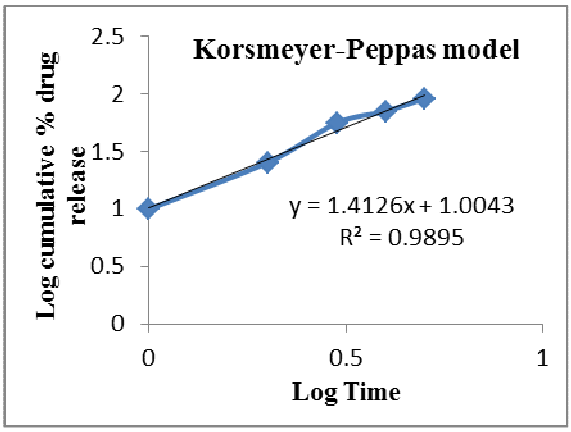


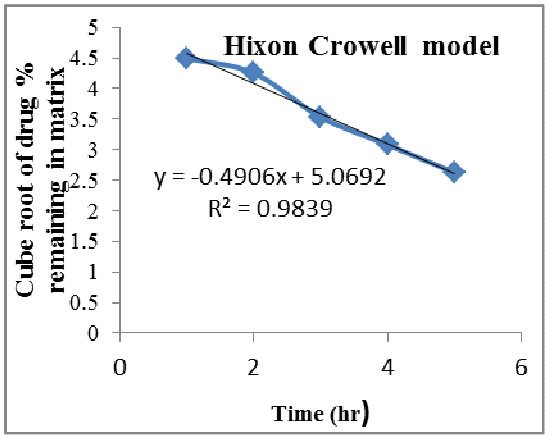
Fig.3: Best fit Release kinetics data of M_3formulation (30mg of pectin)











CONCLUSION

Simple water based extraction was an efficient method for extracting pectin from citrus peel powder. Also, a major conclusion can be derived on the basis of above experiment that citrus peel pectin, a natural polymer having an excellent binding property in tablet dosage form.

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