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Role of naturally isolated pear starch on the bioavailability of famotidine

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ABSTRACT

Purpose- The bioavailability of any drug in the formulation is affected by various excipients presents in it. In case of tablets the role of binders is very important for dissolution of dosage form as well as bioavailability of drug. Thus in following study an attempt is made to improve the dissolution of drug by using pear starch as binding agents. The starch was extracted from the Pear fruits and used as a binder in different concentrations, in famotidine tablets and then evaluate them.

Methods-The tablets were formulated by wet granulation method by using 2% w/v, 4% w/v, 6% w/v and 8% w/v of pear starch as binding agent. Then formulated famotidine tablets were further evaluated for various parameters i.e. weight variation, hardness, friability, disintegration time and *in-vitro* drug release and *in vivo* study.

Results-The hardness and disintegration time of the tablets was found to be increased with increase in starch concentration. Tablets with highest binder concentration showed maximum hardness 6.5 kg) and disintegration time (10 min) and minimum friability (0.48%). After one hour tablets with 4% w/v starch showed maximum drug release (80.69%). The optimized formulation then go for *in vivo* study, shows better bioavailability as compares to marketed one. Hence isolated starch shows increase in the dissolution and bioavailability, when used as binder in tablet formulations.

Conclusions- The results from various evaluations show that pear starch has significant binding characteristics. Hence it can be used as tablet binder in pharmaceutical formulations for future aspects.

Keywords: Starch, binder, tablets, in-vitro dissolution, famotidine

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Introduction

The physiochemical properties of any drug may affect the solubility and dissolution of drugs. The drugs with poor solubility show various problems in formulation developments and also affect the bioavailability of drug. Thus the bioavailability of drug is depends upon the solubility parameters. The excipient present in the formulation is also affect the solubility and dissolution behavior of drugs.

A binder[1] is a material that is added to a formulation in order to improve the mechanical strength of a tablet. The role of binders is very important in case of tablet formulated by wet granulation methods[2]. The choice of binding agents is depends upon various parameters like its availability, cost, compatibility, mechanical strength etc. that why rational choice of binder is very essential for any type of formulation. The role of the binders[3] in direct compression is especially important when a high dose of a poorly compressible drug is used in the formulation.

Different types of starch like corn starch, wheat starch, potato starch and maize starch are used as binder in different concentration in pharmaceutical formulation[4]. The main role of binding agent is to enhance the cohesive forces between the particles as well as to maintain them in intact form. It also helps to improve the flow property of granules. Depending upon the requirements binder can be used in both in dry as well as in liquid form in the formulations[5].

In the present study was done to improve the solubility and dissolution rate of a drug by using pear starch and studying the effect of excipients on it. The starch was isolated from the pear and the isolated starch was evaluated and then used as binder for the preparation of famotidine tablets. Wet granulation method was used for the preparation of tablets. The tablets were then evaluated for the various evaluation parameters.

Materials and methods

Materials:

The starch source was purchased from local market then starch is extracted in laboratory. Famotidine was obtained as gift sample from Sun Pharma, Jammu. Carboxy methyl cellulose, magnesium stearate, Talc (Central Drug House, New Delhi). All other chemicals were analytical grade.

Method:

Extraction of starch:

Take the fresh fruit of pear and after washing, peeled it and chopped in to grinder. Mixed 0.5% w/v NaOH solution into it in a ratio of 1:3 and kept for 2 hr. Filter the mixture and washed with saline water for several times to remove all the soluble impurities[6]. Then treated with petroleum ether to remove any fatty material and then filtered it. Left for 24 hr. and sedimented starch was collected and again washed with ethanol. Then scrapped off it and dried at room temperature. Then pulverized it into fine powder and stored in containers prior to use and analysis[7]

Characterization of starch:

Identification test.

1 g of starch was boiled with 50 ml of water separately. After cooling to 1 ml of the mucilage, 2 drops of iodine solutions were added and the colour change was noted[8].

Particle size determination.

It was determine under the microscope by using calibrated eyepiece. The small amount powder starch was mounted over the slide is observed under the microscope. Note the value and calculate the mean particle size[9].

Paste clarity.

The % paste clarity was measured at 650 nm .A 1% aqueous suspension of starch was heated in a boiling water bath for 30 min and after cooling it was observed under U.V. The measure the light transmittance at 650 nm against water blank[10].

Moisture content.

A 2 g weight (W_1) each of starch was dried for 24 hr. at 105°C in hot air oven and weight (W_2). Then moisture content calculated as –

$$\textbf{M.C. (\%)} = W1 - W_2 / W_1 \times 100$$

W_1 = Weight of wet sample (grams),

and W_2 = Weight of dry sample (grams)

Swelling capacity

Note the tapped volume of 1 gm of starch (*Vd)* in a 50 ml measuring cylinder was noted. This powder was then dispersed in 8.5 ml of distilled water and volume was made up to 10.0 ml with distilled water[11]. After 18 hrs of standing, the volume of the sediment, (Vw) was estimated and the swelling capacity was determined as-

$$\textbf{Swelling capacity} = Vw - Vd/Vd \ \%$$

Where, Vw= Volume of the sediment, Vd = Tapped volume

Ash value of starch.

Total 2 g quantity of starch[12] was weighed into a silica crucible and incinerated. Determination of ash value was done by measurement of the residue left after complete combustion in a muffle furnace at 350° C.

% Total ash value =

Wt. of total ash/ Wt. of crude drug taken X 100

Flow properties of starch

a. Angle of repose

It was determined by allowing powder to flow through a funnel and fall freely on to a surface. Further addition of powder was stopped as soon as the pile has touched the tip of the funnel. A circle was drawn around the pile without disturbing it[13]. The height and diameter of the resulting cone was measured. The same procedure was repeated three times and the average value was taken. Angle of repose was calculated by using the following equation:

$$\textbf{Tan } \theta = h/r$$

Where, h = height of the powder cone, r = radius of the powder.

b. Bulk density

Take about 100 gm of starch[14] in to to a dry 250 ml cylinder. The cylinder was filled carefully and level of powder was adjusted without compacting and the unsettled apparent volume (Vo) was noted. Bulk density was calculated, in g/ml. By using the formula:

$$\textbf{Bulk density} = M/Vo$$

Where, M = weight of the sample taken, Vo = bulk volume

c. Tapped density

Accurately weighed quantity of powder was introduced into a measuring cylinder[15]. The cylinder was tapped 500 times and the tapped volume (Va) was measured. Then the tapped density was calculated using the following formula:

$$\textbf{Tapped density} = M / Vf$$

Where, M = weight of the sample taken, Vf = final tapped volume

d. Carr's index

The compressibility index of granules was determined using Carr's compressibility index[16], as-

$$\textbf{Carr's index} = \frac{\textbf{(Tapped density – Bulk density) X 100}}{\textbf{Tapped density}}$$

e. Hausner's ratio

The Hausner's ratio was determined using the following formula:

Hausner's ratio = Tapped density / Bulk density

Table 1: Characterization of Starch

S. no.	Properties	Pear starch
	Identification test (Color with I_2)	Black
	Starch color	Yellow
	Particle size (μ)	22.70
	% Yield	57
	Paste clarity (%)	82.5
	Moisture content (%)	2.01
	Swelling capacity (%)	2.3
	Ash value (% w/w)	0.42
	Bulk density (g/ml)	0.119
	Tapped density (g/ml)	0.138
	Carr's index (%)	13.76
	Hausner's ratio	1.15
	Angle of repose	21.12
	Flow properties	Excellent

Identification of Starch

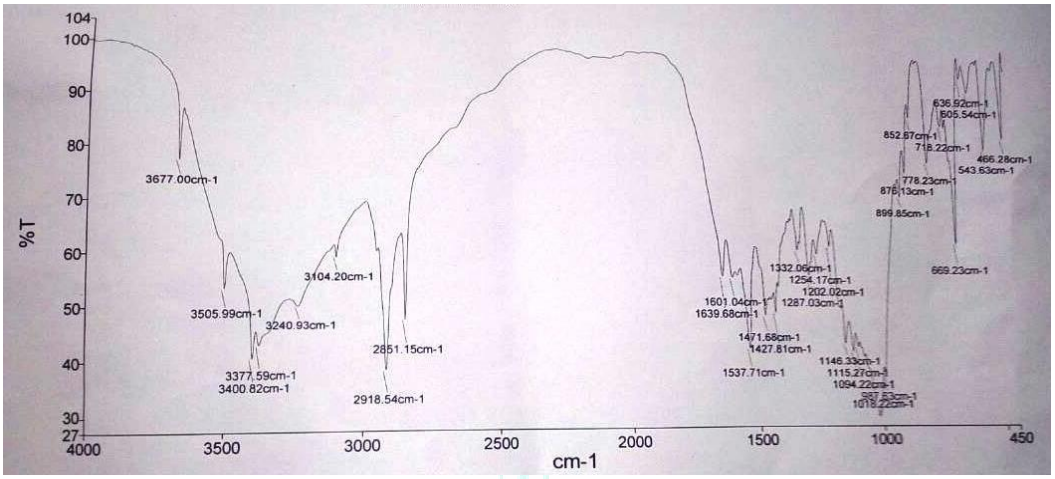

Figure –1 I.R. Spectrum of Pear Starch

Table 2: Interpretation of FTIR Spectra of Pear Starch

Peak (cm^{-1})	Interpretation	Pear starch
3200-3500	-OH	3400
2700-3000	-C-H stretching	2918
1640-1650	$-H_20$	1639.68
1300-1350	-C-O Stretching	1332
1100-1300	-C-O stretching	1287
700-750	-C-O-C Skeleton	718.22

Formulation and Evaluation of Famotidine Tablets

Formulation of Famotidine Tablets –

Four batches of the tablet[17] containing 20 mg famotidine were prepared. The batches contained pear starch as binders respectively in concentrations of 2, 4, 6, and 8% w/w. Carboxy methyl cellulose used as the disintegrant in 7.5 % with 0.5% magnesium stearate as lubricant[18].

Table 3: Formulation of Famotidine Tablet

S. No.	Ingredient	Category	Amount mg/tab
1	Famotidine	Active	20
2	Lactose	Diluents	Variable (153-140)
3	Sodium carboxy methyl cellulose (7.5%)	Disinterants	15
4	Pear Starch (2-8%)	Binder	Variable (4-16)
5	Talc (2.5%)	Glidant	5.0
6	Magnesium stearate (1.5%)	Lubricant	3.0
7	Total Wt.		200

Wet Granulation and Compression

Wet granulation method was used for the preparation of tablets[19]. The calculation was made for 30 tablets in each batch. Accurately weighed quantities of famotidine, lactose and sodium carboxymethyl cellulose were mixed in a mortar and passed them through sieve # 44. Then appropriate quantity of starch mucilage of various concentrations (2, 4, 6 and 8% w/w) was added as granulating agents and mixed for 20 min in a mortar until wet mass was formed. The damp mass was sieved with sieve no. # 22 and dried at 50^{0}C in an oven for 6 hrs. The dried granular mass was passed through sieve no. # 44 to obtain uniform sized granules. Then in different batches of the granules calculated amount of the disintegrant were mixed. Now added the magnesium stearate and talc in the granules and compressed the tablets by single punch machine.

Evaluation of Tablets

Hardness test

Hardness testing was carried out by using Monsanto hardness tester as per procedure given in I.P. Five tablets were selected at random from each batch to measure the hardness[20]. Then the mean hardness was calculated for each batch. The value of hardness was expressed in kg/cm^2.

Weight uniformity test

Twenty tablets from each batch were selected randomly and weight individually using a analytical balance. Then their mean weights were calculated[21].

Friability test

Friability testing was carried out by using Roche friabilator as per procedure given in I.P. 10 tablets were taken and the weight was determined. Then they were placed in the friabilator and allowed to make 100 revolutions at 25 rpm. The tablets were then dusted and reweighed. The percentage weight loss was calculated[22].

Disintegration Test:

It was performed as per official method prescribed in I.P. for uncoated tablets. 0.1 N HCl of 900 volumes was used as disintegrating medium used. The temperature of media was maintaining about 37ºC throughout the experiment. 5 tablets elected from each batch of formulation and put in the disintegration tube. The time taken to break up into small particles was recorded and calculates the mean disintegration time[22].

In-Vitro Dissolution studies:

Dissolution studies were performed as per procedure given in I.P. The test is performed by using USP-II dissolution apparatus. 900 ml of 0.1N HCl, pH 1.2 was used as dissolution medium. The temperature of medium was 37±2^{o}C throughout the experiments. The speed of rotation was 100 rpm. The samples were withdrawn at 10, 20, 30, 40, 50 and 60 min. by replacing equal amount of fresh dissolution medium. Then sample were analysed using U V Spectrophotometer and % cumulative drug release was calculated[22].

Table 4: Evaluation of Famotidine Tablets with Pear Starch

S. No.	Parameter	Binder concentration			
		2%	4%	6%	8%
1	Hardness (kg/cm^2)	4.4±0.5	5.6±0.12	6.0±0.6	6.5±0.11
2	Weight variation (g)	198±0.43	201 ±0.46	195±0.54	204±0.24
3	Friability (%)	1.02±0.21	0.72±0.23	0.63±0.42	0.48±0.15
4	Thickness (mm)	4.55±0.25	4.46±0.31	4.50±0.27	4.58±0.17
5	Disintegration time (min.)	4.5±0.10	5.8±0.00	7.0±0.20	10.0±0.28

Results have been expressed as mean ± S.D. (n = 3)

Table 5: *In Vitro* Dissolution Studies of Famotidine Tablets with Pear Starch

S.No.	Time (min.)	Percentage cumulative drug release			
		2%	4%	6%	8%
1	0.0	0.0	0.0	0.0	0.0
2	10	10.19±0.19	13.02±0.10	9.11±0.05	7.54±0.21
3	20	17.61±0.14	20.92±0.15	15.08±0.24	10.20±0.14
4	30	28.03±0.15	39.07±0.09	21.99±0.26	18.26±0.27
6	40	41.54±0.34	56.15±0.14	38.48±0.21	25.41±0.25
7	50	53.25±0.14	68.34±0.11	49.22±0.26	41.29±0.22
8	60	69.23±0.12	80.69±0.12	71.47±0.25	65.05±0.21

Results have been expressed as mean ± S.D. (n = 3)

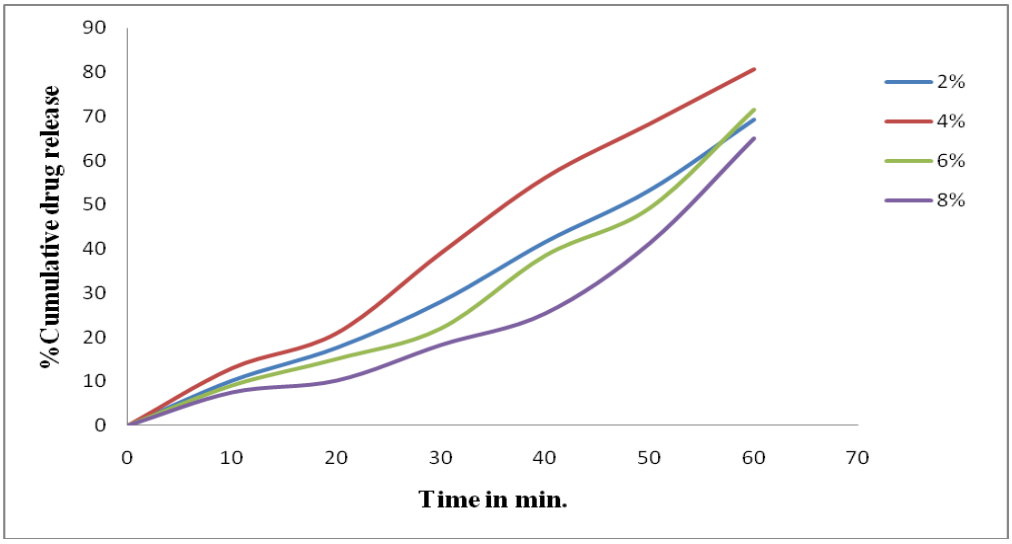

Figure 2*: In vitro* drug release of famotidine tablets

***In-Vivo* Study**

The *in-vivo* study was carried out for optimized formulation. Formulation having 2 % Pear starch shows maximum drug release used for further study. The experimental protocol for animal studies was carried by Deshpande Laboratories Pvt. Ltd., M.P. Bhopal, India, With Report Generation no. 031218 and CPCSEA / IAEC approval no. DL/IAEC/02/2018. Healthy Wistar rats of 3 to 4 months old, in the weight range of 150–250 g were used the study. Wistar Rats were housed in PP cages with free access to sterile food water and bedding material[23]. Animals were housed in light controlled 12-12h and noise controlled rooms with 25°C temp and controlled humidity. Animals were fasted overnight prior to drug administrations. The calculated dose was given through oral route. Then blood samples were withdrawn from animals at different time intervals and plasma samples were measured for OD on a UV. Spec. (Biotron) [24]. Data was analyzed and all the pharmacokinetic parameters were calculates and compare with marketed formulation as shown in Table 6 and 7.

Table 6- Release rate of drug in formulations

S. No.	Time (hr)	Marketed Formulation	Optimized Formulation
		Conc.	Conc.
1.	0.5	0.57 ±0.04	0.14±0.01
2.	5	1.08±0.11	0.66±0.03
3.	10	0.52±0.13	0.66±0.03

Table 7- Pharmacokinetic Parameters of *In vivo* release study

S. No.	Parameters calculated	Marketed Formulation	Optimized Formulation
1.	C max	1.10±0.06	0.65±0.11
2.	T max	5 ±0.12	5 ±0.21
3.	$T_{1/2}$	1.79±0.06	1.14±0.06
4.	$K_a(hr^{-1})$	0.3869±0.11	0.6045±0.10
5.	$K_E(hr^{-1})$	0.3707±0.03	0.2351±0.09
6.	V_d (L)	6.70±0.03	11.38±0.05
7.	C_L (L/hr)	1.79±0.09	0.65±0.11
8.	$T_{1/2}$	72±0.05	68±0.08
9.	AUC (µg / ml hr)	1.10±0.06	0.65±0.11

Results and Discussion

The famotidine tablet prepared by using pear starch as binding agent were evaluated for different factors such as hardness, weight variation, friability, disintegration time and *in- vitro* dissolution study. The starch was isolated from natural fruit was evaluated and the used in the formulation as binding agent. Table-1 shows all the characteristics properties of pear starch powder. The evaluation properties of tablets are shown in Table-4. The average weight variation of the tablets was found to be with the I.P. limits. The hardness values of the tablets were increased with the increase in the conc. of binding agents. The value of friability was decreased with increase in the conc. of binder. The tablet containing 2% starch friability was shows the friability more than 1%, but for others it was within limits. The disintegration time, were found to be increased with the increasing concentration of cucumber starch. The tablets

with 4 % binder conc. shows maximum drug release 80.69% after 1 hr as shown in table 5. The amount of drug in blood (bioavailability) was found to be better in optimized formulation than marketed formulation shown in table 6 and 7. All the significant result was found due to improved solubility and dissolution of drug which would lead to faster absorption and thus improved the bioavailability of famotidine. These results also confirm *in-vitro* and *in-vitro* correlation

Conclusion

From the fallowing study it was concluded the pear starch showed significant binding properties. The results from various evaluations show that pear starch had significant binding characteristics. Hence it can be used as tablet binder in pharmaceutical formulations and serve as best source for the production of industrial products.

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