FORMULATION AND EVALUATION OF PARACETAMOL TABLETS TO ASSESS BINDING PROPERTY OF ORANGE PEEL PECTIN

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ABSTRACT

The aim of present work was to extract pectin from dried orange fruit peels to assess its binding property in tablets using paracetamol as model drug. Initially orange fruit peel powder was subjected to simple water based soxhlet extraction and pectin was isolated using ethyl alcohol as precipitating agent. 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. Precompression and post compression studies were performed for each formulation. *In-vitro* release data was subjected to application of various kinetic models. The results obtained for all pre-compression and post compression parameters were found within acceptable range of pharmacopoeias. On the basis of drug release behavior it can be summarized that release of all four batches under study was less than that of reference batch. Orange peel pectin can act as excellent binder in dosage forms. Since it is of natural origin and orange peels available at low cost it may prove to be better binder over commercially used synthetic binders.

Keywords: binding property, orange peel pectin, release kinetics, water based extraction.

INTRODUCTION

Many strategies are available for the design and development of modified-release drug delivery formulations. 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[1]. Pectin consists mainly of the partial methyl esters of polygalacturonic acid and their sodium, potassium, calcium and ammonium salts. These are obtained by extraction in an aqueous medium of appropriate plant material. Pectin occurs as a white to light brown powder or granular, and is odorless or has slightly characteristic odor[2]. Generally, high methylated pectin is of commercial importance as the one obtained from citrus fruits. Until recent era pectins have been used in food industry in jams and jellies but, recently they are being explored for their other pharmaceutical applications. 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 orange peel pectin as binding agent, against the commercially used one's like starch. For this purpose, paracetamol which is analgesic and antipyretic was selected as a model drug.

MATERIALS AND METHODS

Materials: Paracetamol was purchased from ALCHEM LABORATORIES, Baddi, Himanchal Pradesh. Starch, lactose and talc were obtained from Central Drug House, New Delhi. All the chemicals and reagents were of analytical grade.

Extraction of pectin: Dried Orange fruit peel powder (200g) was used for extraction using soxhlet apparatus. The water to be used for extraction was acidified using 0.5N citric acid and pH was maintained about 2. The content of the round bottom flask was heated continuously at 75º C for around 7 to 8 h after the start of first siphon cycle. The proportion of powder to solvent was taken in ratio 1:6. After the heating period was over, the mixture was passed through two fold muslin cloth and was cooled to room temperature[3-5].

Isolation of pectin: Isolation of pectin was carried out using ethyl alcohol as precipitating agent. Ethyl alcohol was used as a precipitating agent for pectin. For this purpose, twice amount of ethyl alcohol was added to the cooled solution and continuous stirring was done for 15 min. Then the mixture was kept aside for 2h 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 18.36%. It was then stored in desiccators until further use.

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 1. 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 six hours. The dried granules were stored in desiccators until compression of tablets. Prior to compression the dried granules were subjected to micromeritic study and evaluated for their flow characteristics. The required amounts of granules were weighed and compressed using Cadmach 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[6-7].

For the comparative reason, controlled tablets were prepared using starch as binding agent instead of isolated pectin.

Table 1: Formula used to prepare tablet.

Ingredients	Formulations				
	Batch F1	Batch F2	Batch F3	Batch F4	Reference
Drug (mg)	250	250	250	250	250
Binder (mg)	10	20	30	40	-
Disintegrant (mg)	30	30	30	30	30
Lactose (mg)*	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Talc (%)	1	1	1	1	1

*Weight of each tablet equals 400mg

Evaluation of granules: Granules were evaluated for all pre-compression parameters like angle of repose, bulk density, tapped density, bulkiness, hausner's ratio and compressibility index. The evaluation was done using all the methods as per specified in pharmacopoeias[3-9.]

Evaluation of Tablets

Weight variation: All prepared tablets were evaluated for weight variation as per USP XXIV monograph. Twenty tablets of each batch were used to evaluate weight variation among tablets and mean and standard deviation was calculated[10].

Friability: Tablets of all batches were used to evaluate friability as per USP XXIV monograph. Friability testing was done by Roche Friabilator with readings in triplicate[10,11].

Hardness: Hardness of all batches was determined using Digital Force Gauge (Model:EL=500N, Electrolab). The test was carried out in triplicate for all batches as per USP XXIV monograph for uncoated tablets[10,11].

Thickness*:* The thickness of the matrix tablets was determined using vernier caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of 10 determinations, with standard deviations[12-14].

Drug content: The tablets were powdered, and 250 mg equivalent weight of Paracetamol in tablet powder was accurately weighted 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-2450, Japan). The drug content of the each sample was estimated from their previously prepared standard curve[8,9].

***In-vitro* drug release study:** *Invitro* drug release was studied using LabIndia Dissolution Apparatus (LABINDIA DS 8000, India), in 900 ml phosphate buffer pH 7.4, maintained at 37±1°C for 4 h, at 100 rpm. 5ml of sample was withdrawn after specified time interval, and was replaced by an equal volume of fresh dissolution medium. Collected samples were analyzed spectrophotometrically at measured wavelength of 247nm, and cumulative percent drug release was calculated[10,11]. The test was performed in triplicate to assure significance of results. Drug release profile was studied using percentage drug release Vs time (h) plot.

Kinetics of drug release: Various models such as Zero order kinetics (cumulative percentage amount of drug release versus time), First order kinetics (log cumulative percentage of drug remaining to release versus time), Higuchi (fraction of drug release, Mt/Mi, versus square root of time) and Korsermeyer-Peppas (log fraction of drug released, log Mt/Mi, versus log time) were applied to assess the kinetics of drug release from prepared tablets. Most suited model for drug release was predicted on the basis of regression coefficient i.e. nearer the value of regression coefficient towards 1, greater the suitability of best fitted release mechanism.

RESULTS

As per the data obtained by the experiment, pectin derived from orange peels showed good binding property as compared to starch. The various micromeritic characteristics and flow properties of the granules obtained by wet granulation for each batch and reference batch did not show any significant variation in their values. The values of physical properties of all batches are shown in table 2 having average of triplicate readings, with standard deviation (table 2).

The prepared tablets were evaluated for post compression parameters such as weight variation, hardness, thickness, drug content uniformity, and *in vitro* release characteristics. The readings were obtained in triplicate and values were presented as mean with standard deviation. Weight variation among all tablets ranged between 0.065 (±0.224) mg to 0.090 (±0.31) mg. Hardness values, which were obtained within limits ranged from 21.0 (±0.01) N to 22.5 (±0.02) N. Similarly, the maximum drug release in four hours was found to be 18.85% in batch F3, which is far less than the release of drug in reference batch (approximately 21.98%). All these values have been tabulated below in table 3.

In-vitro release profile of the drug from the tablets was major governing criteria to decide whether the natural polymer (orange peel pectin) or the commercially used binder (starch as in reference batch) is good binding agent. The release profile for the drug was taken for a period of four hours which can best be depicted by graph between percentage drug release and time. Batch F4 containing orange peel pectin as binder showed minimum release of 12.26 % as compared to other batches of same polymer and against the tablets of reference batch (Figure 1).

Table 2: Pre-compression properties of granules[#].

Properties	Formulations				
	Batch F1	Batch F2	Batch F3	Batch F4	Reference
Bulk density (g/cm^3)	0.376(0.017)	0.404(0.021)	0.436(0.025)	0.424 (0.032)	0.426(0.030)
Tapped density (g/cm^3)	0.427(0.022)	0.434(0.019)	0.456(0.025)	0.430 (0.033)	0.445(0.020)
Bulkiness (cm^3/g)	2.66(0.031)	2.48(0.024)	2.29(0.029)	2.36(0.025)	2.35(0.026)
Carr's index	11.857(0.31)	8.415(0.37)	4.40(0.33)	14.0(0.36)	4.38(0.30)
Hausner's ratio	1.130(0.30)	1.074(0.32)	1.046(0.26)	1.014(0.24)	1.045(0.31)
Angle of repose (degrees)	28.37(0.028)	27.73(0.022)	21.49(0.021)	22.57(0.025)	22.06(0.020)

[#]value in parenthesis show standard deviation of triplicate readings

Table 3: Evaluation parameters of tablets[#].

Parameters	Batch F1	Batch F2	Batch F3	Batch F4	Reference
Weight variation (mg)	0.071(±0.025)	0.090(±0.031)	0.065(±0.224)	0.073(±0.09)	0.082(±0.035)
Hardness (N)	20.8(±0.022)	21.0(±0.01)	22.5(±0.02)	22.0(±0.01)	21.3(±0.024)
Thickness (mm)	2.78(±0.012)	2.77(±0.031)	2.81(±0.017)	2.76(±0.023)	2.80(±0.022)
Drug content (mg)	247.0(±0.19)	249.31(±0.21)	248.5(±0.13)	249.0(±0.09)	249.30(±0.16)

[#]value in parenthesis show standard deviation of triplicate readings

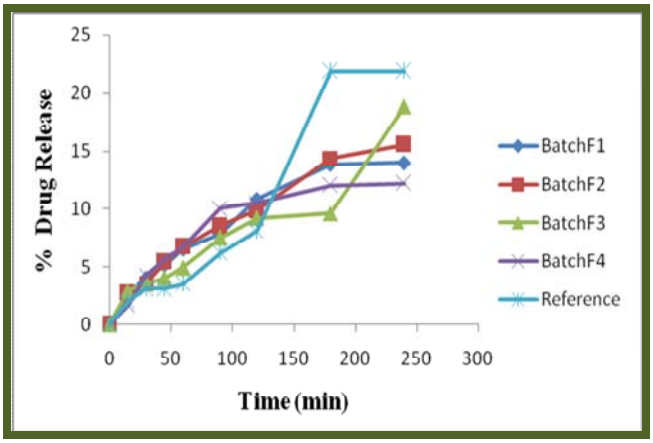
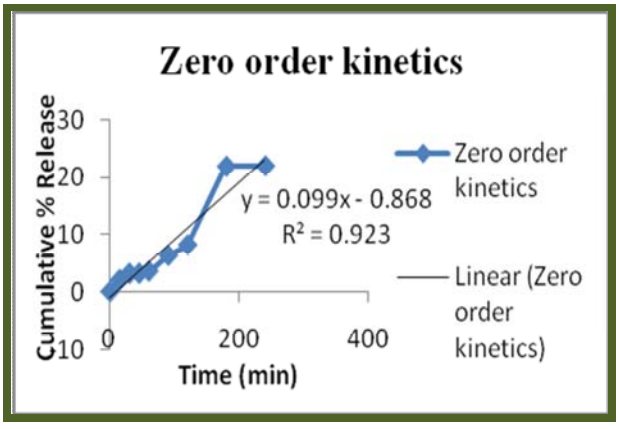
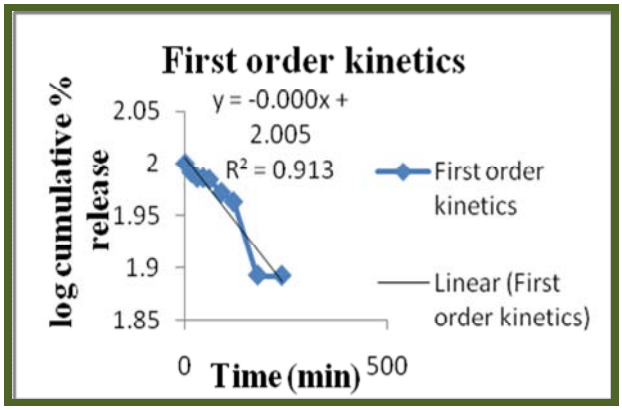


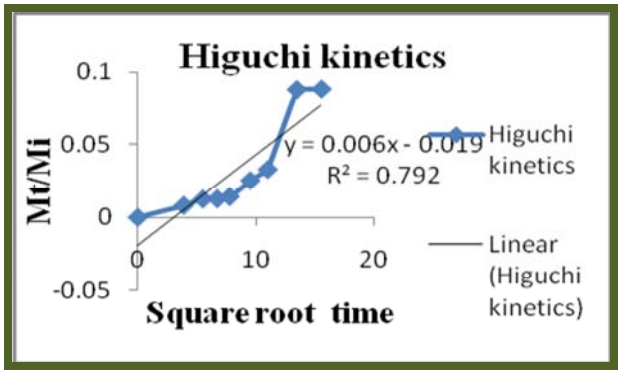
Figure 1: Comparitive *in vitro* release profile of drug from different batches.

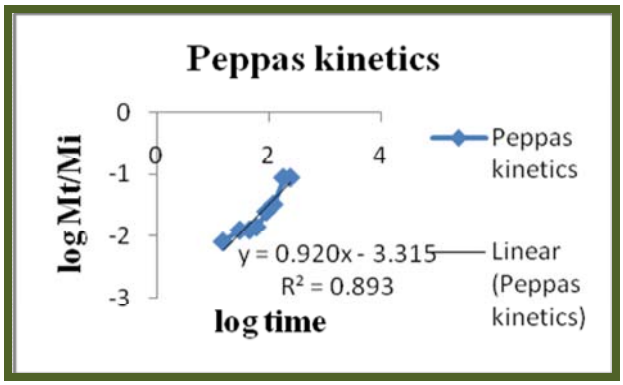
On the basis of *in vitro* release profile, it is easy to decide suitable batch for formulating drug using pectin as binder on commercial scale. Batches F1, F2, F3 and reference batch exhibited significantly lower drug release-retarding efficiency than the pectin based tablets of batch F4.

Figure 2: Best fit kinetic release data of formulation (F4).









On the basis of applied kinetics in the present experiment, it can be easily seen that varying concentration of the drug and polymer leads to approach of different kinetic theory. Wherein most accepted values of correlation coefficient differed from batch to batch and even from the reference batch taken as standard. Batches F1 & F2 followed Korsermeyer-Peppas model with correlation values of 0.989 in both cases. Other batches showed best fit correlation values of 0.929 (first order release), 0.944 (higuchi kinetics), 0.923 (first order) respectively for batch F3, F4 and reference batch. The values for each batch are given in table 4.

Table4: Values of correlation coefficient for all formulations.

Formulations/ Models	Zero-order Kinetics		First order kinetics		Higuchi Kinetics		Kosermeyer-Peppas model	
	R^2	K_0	R^2	K_1	R^2	K'	R^2	n
F1	0.935	0.053	0.94	0.000	0.975	1.016	0.989	0.637
F2	0.954	0.063	0.963	0.000	0.976	1.012	0.989	0.666
F3	0.929	0.066	0.921	0.000	0.861	1.016	0.919	0.64
F4	0.814	0.050	0.814	0.050	0.944	1.002	0.912	0.695
Reference	0.923	0.099	0.913	0.000	0.792	1.045	0.893	0.920

DISCUSSION

Drug-Excipient interaction: There was no interaction between drug and orange peel derived pectin and also no interaction was found between drug and starch including other excipients. This can be predicted on the basis of no change in peak in the characteristic fourier transformation infrared spectroscopy.

Physical properties of granules: Parameters studied were angle of repose, carr's index, hausner's ratio, bulk density, tapped density and bulkiness. Lesser bulkiness showed ease of compaction into tablet dosage form over conventional dosage forms containing binders such as starch. As per the results of physical characterization batch from F1 to F4 and especially the reference batch, do not show much difference in micromeritic studies and granule flow property. The values ranged within that of the pharmacopoeial limits. Friability results were also less than 1%, which showed efficiency of dosage form formulation and development. These physical parameters lead to the fact that such type of dosage form can be easily formulated, using the method involved, with no loss of material during packaging and transportation. Moreover, all batches, containing orange peel pectin showed better results than the reference batch, considering one or the other parameter.

Post compression parameters: Among these parameters, all were within specified official limits. This indicated that there shall not be any problem while formulating tablet dosage form using orange peel derived pectin as binder. However, the fact can be illustrated that, orange peel derived pectin shall not put any formulation difficulties if it replaces any conventionally used binder.

***In-vitro* release profile:** The release profile of the tablets containing pectin as binder showed that the formulated tablets showed lesser release than starch based tablets. Batch F3 controlled the release to the maximum extent, which released only 18.85% of total drug incorporated during the time duration of drug release. These values of release were considerably less than those of reference batch, which released 21.98% of drug during study period in phosphate buffer (pH 7.4). Thus, orange peel pectin stands as a good binder and has excellent binding capacity, which can be exploited on commercial scale.

Kinetic profile of 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 F4 was found to be optimized among all four batches containing pectin as binder and followed Zero order kinetics. Reference batch containing starch as binder also followed zero order kinetics.

CONCLUSION

Simple water based soxhlet extraction is an efficient method for extracting pectin from orange peel powder. Also, a major conclusion can be derived on the basis of above experiment that orange peel pectin which is a polymer of natural origin, has immense potential to replace the commercially existing polymers used as binders in tablet dosage forms.

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