Development of Paracetamol Tablets by Using Novel Coprocessed Granulation Binder-Disintegrant

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ABSTRACT

Established disintegrating agents possess the disintegrating ability only and they rarely assist in the compactibility of powder blend except for starch. Many of the reported binders are proven to retard the release rate of the active drug from the dosage forms. Therefore the present work was aimed at developing a co-processed binder-disintegrant to overcome these functional drawbacks of the binders and disintegrating agents. The novel binder-disintegrant was prepared by co-processing crospovidone and the gel obtained from the husk of *Plantago Ovata* seeds. To confirm the functionality of the novel co-processed binder-disintegrant under investigation; paracetamol was selected as a model drug. The absence of chemical interaction between the co-processed materials and the formation of hydrogen bonding between them was confirmed by the analytical technique of ATR-FTIR. The functionality of the co-processed material as a granulation binder was confirmed by the Heckel treatment. The linear relationship between ln (1/1-D) and compression pressure applied on the paracetamol tablets, confirmed the functionality of co-processed material as a granulation binder. These tablets were prepared by adding the novel co-processed granulation binder-disintegrant intra-granularly at 5%. The functionality of novel co-processed material as a disintegrating agent was confirmed by analyzing the results of disintegration and dissolution studies of the paracetamol tablets. Paracetamol tablets exhibited faster disintegration when crospovidone was added extra granularly; than when a novel co-processed binder disintegrant was added. Thus, the functionality of the novel binder disintegrant was investigated by assessing the performance of the formulation of immediate-release tablets of paracetamol.

Key Words: *Heckel plot, Paracetamol, Binder-disintegrant, Plantago ovata, Crospovidone*

eIJPPR 2022; 12(4):1-7

HOW TO CITE THIS ARTICLE: Hardikar SR, Patil TR. Development of Paracetamol Tablets by Using Novel Coprocessed Granulation Binder-Disintegrant. Int J Pharm Phytopharmacol Res. 2022;12(4):1-7. https://doi.org/10.51847/33LE0rgRDk

INTRODUCTION

Wet granulation is a complex process involving several formulations and process variables having a quality impact on granulation and tablets. Solution binder is one of such variables that improve the compactibility and manufacturability of materials ready for tableting and assist in overcoming the risk of tableting failures [1]. The therapeutic success of the tablet dosage form depends on the release pattern of the drug incorporated in it. The release of the drug depends on the disintegration of the tablet which has to be followed by granular dissolution [2]. Many of the reported binders are proven to retard the release rate of the active drug; particularly from the immediate-release dosage forms. Established disintegrants/ super-disintegrants possess only the disintegrating ability and they rarely assist in the compactibility of powder blend except for starch. Starch is used as a binder and /or disintegrating agent in tablet formulations but has to be added in high proportion to get its dual functionality [3].

Co-processing is a novel concept of altering excipients' functionality by retaining the favorable attributes and supplementing with newer ones, by processing the parent excipients with other excipients [4]. Hydrogel isolated from the seed husks of *Plantago ovata* had been explored for its functionality as a binder [5]. Crospovidone is an established disintegrating agent and exhibits its functionality by 'high capillary activity (wicking) as a principal mechanism [6]. The physical properties of the

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Received: 04 June 2022; **Revised:** 10 August 2022; **Accepted:** 12 August 2022

established excipient can be modified by co-processing it with another material. The present work was aimed at developing co-processed binder disintegrants using crospovidone and the gel obtained from the husk of Plantago Ovata seeds.

The major mechanism of compaction of paracetamol is fragmentation; which results in weak and unacceptable tablets with a high capping tendency. Paracetamol is thus reported to possess a low compactibility and a low plastic deformation [7]. These material attributes of paracetamol might cause issues during the material's compaction process. The addition of solution binders offers flexibility and plasticity to granulation and absorbs the effects of elastic recovery of materials like paracetamol. Therefore paracetamol was selected as a model drug to investigate the functionality of a novel binder-disintegrant.

Functionality testing of any excipient is nothing but testing of the concerned function directly in a formulation and/or manufacturing process [8]. The compaction properties of the paracetamol granules prepared by using a novel binder-disintegrant were analyzed by using the Heckel equation [9]. The linear relationship was observed between 'ln (1/1-D)' and the compression pressure applied on the paracetamol tablets; prepared by adding the novel co-processed granulation binder-disintegrant at 5%. The linear relationship denoted plastic deformation of the granules and thus the functionality of novel co-processed excipient as a granulation binder was confirmed. The results of the disintegration time and dissolution studies revealed the disintegrating ability of the novel co-processed excipient.

MATERIALS AND METHODS

Materials

Paracetamol was gifted by Cipla, Mumbai. The seed husk of *Plantago ovata* was purchased from an authorized medical shop in Pune. Other chemicals used in the formulation were of pharmaceutical grade and the chemicals used in the analysis were of analytical grade and were used as received.

Experimental design

The present work was aimed at developing a co-processed binder-disintegrant using crospovidone and the gel obtained from the husk of *Plantago Ovata* seeds. The absence of chemical interaction between the co-processed materials and the formation of hydrogen bonding between them was confirmed by ATR-FTIR. The functionality of the co-processed material as a novel binder was confirmed by the Heckel treatment. Paracetamol is a poorly compressible drug and always needs a suitable binder for its tablet as a dosage form during manufacturing. Therefore, paracetamol was selected as a model drug in this work to investigate the functionality of the novel binder-disintegrant. The linear relationship was observed between ln (1/1-D) and applied compression pressure on the paracetamol tablets prepared by adding the novel co-processed excipient at 5% w/w. The linear relationship denoted plastic deformation of the granules of the paracetamol prepared by using the novel granulation binder-disintegrant. Thus the functionality of the novel co-processed material as a granulation binder was confirmed. The disintegrant property of the novel co-processed material was assessed considering the results obtained after performing disintegration and dissolution studies of immediate-release tablets of paracetamol.

Isolation and characterization of hydrogel from the seed husk of Plantago ovata

The hydrogel was isolated from the husk of *Plantago ovata* by soaking 2 gm in 150 ml of distilled water for 2 hrs. The entire bulk was homogenized till the viscous gel was obtained. The isolated hydrogel was characterized by appearance, specific gravity, and ATR-FTIR.

Co-processing of crospovidone and hydrogel obtained from the seed husk of Plantago ovata

The calculated quantities of crospovidone were soaked in a sufficient amount of hydrogel to obtain the physical mixtures (by weight) in 1:0.5, 1:1, and 1:1.5 proportions. These mixtures were kept overnight and then dried in a hot air oven at 40 - 50°C. The co-processed material was thus obtained. ATR- FTIR spectra of dried hydrogel, crospovidone, and co-processed material in proportion 1:1.5 were recorded and interpreted.

Preparation of granules for Heckel treatment

The paracetamol granules were prepared by using co-processed material as a novel granulation binder in the appropriate quantity (5% w/w) and isopropyl alcohol. These granules were wet screened using an 8 mesh screen. The granules formed were spread evenly on trays and dried in a hot air oven at 50°C. Then the dried granules were passed through the 10-mesh sieve. These granules were compressed at predetermined and gradually increasing compression pressures. The tablets (of Paracetamol 500 mg) were prepared by applying gradually increasing compression pressures from 1, 2, 3, 4, and 5 tons. The tablets were evaluated for physic-mechanical properties and the results are reported in **Table 1**. This data was used for verification of the Heckel equation.

Table 1. Physical properties of the tablets prepared for Heckel treatment

Compression pressure (Ton) P	Average Height of the tablets* (cm) h_1	Average Weight of tablets* (gm) w_1	Relative density $D=w_1.h_2/w_2.h_1$	1/1-D	ln(1/1-D)
1	0.491	0.5198	0.7667	4.286	1.455
2	0.4608	0.5168	0.8119	5.319	1.671
3	0.447	0.5218	0.8451	6.4599	1.866
4	0.4308	0.5202	0.8742	7.9554	2.0738
5	0.4118	0.519	0.9125	11.4286	2.4361

*n=5

Investigation of the functionality of the co-processed material as a disintegrating agent

The granules were prepared as per the process mentioned in the earlier section and were then lubricated by running powder (the mixture of talc: starch in proportion 1:4). Then, 5% crospovidone or 5% co-processed material (co-processed crospovidone) was added as an extra granular disintegrant in the granular bulk. The compositions of the two batches of paracetamol tablets are reported in **Table 2**. The tablets of both batches were thoroughly evaluated and the results are reported in **Table 3**.

Table 2. Composition of IR tablets of paracetamol

Ingredients in mg/ Tablet / Formulation code	Granules equivalent to 500 mg of Paracetamol	Running powder (2%)	Crospovidone	Co-processed crospovidone
CP	525	10.5	27	--
CPP	525	10.5	--	27

RESULTS AND DISCUSSION

Isolation and characterization of hydrogel from the seed husk of Plantago ovata

The hydrogel was gray and translucent in appearance with a specific gravity of 1.09 signifying its excellent water uptake property. The chemical composition of the hydrogel isolated from the seed husk of *Plantago ovata* is reported in the literature. The broad and prominent peak at 1034 cm^{-1} in ATR-FTIR of the dried hydrogel isolated from the husk of *Plantago ovata* seeds represented C-O-C glycoside linkages and C=O; the peak around 895 cm^{-1} denoted β-glycoside linkage; peaks at 1638 cm^{-1} and 1427 cm^{-1} presented asymmetric and symmetric stretching of the carboxylate groups **(Figure 1)** [10].

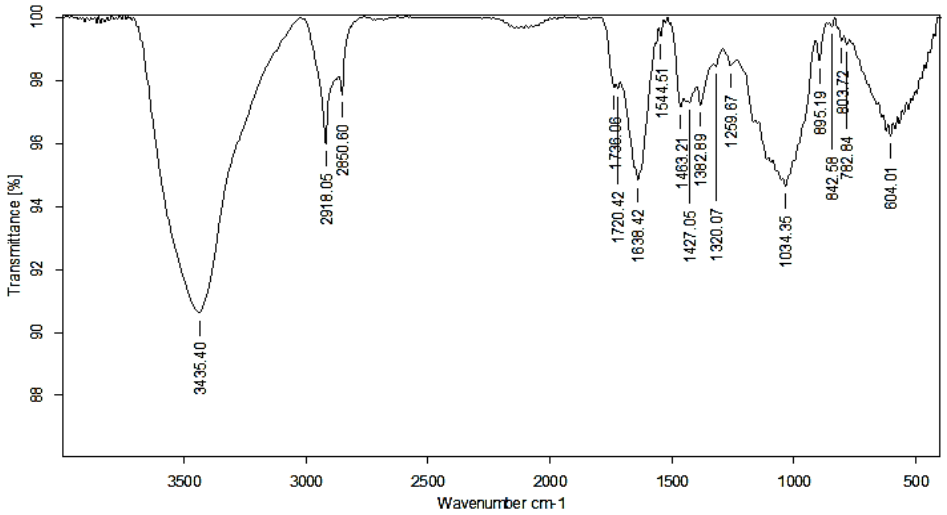

Figure 1. ATR-FTIR of Dried Hydrogel

Co-processing of crospovidone and hydrogel obtained from the seed husk of Plantago ovata

The choice of a novel excipient in the design of a drug product is based on many criteria. Since the present work was aimed at developing a novel binder-disintegrant; its physicochemical/material attributes are of prime concern. A thorough understanding of how the material attributes of any excipient (a novel excipient in particular) might affect

its functionality is an important part of the entire process of a new excipient development [11]. Particle size distribution is one of the important material attributes for a novel binder-disintegrant that can affect its desired functional performance. The scope of the present work was limited to the preparation and development of the formulations on a laboratory scale. Hence, particle size distribution is selected as the measurable material attribute of the novel binder-excipient being developed. Generally, lower particle size distribution enables a rapid rate of dissolution/ dispersion (when the binder is a granulation binder) due to its uniform or homogeneous distribution in the powder bulk during the granulation step [12]. The co-processed material of composition as 1:1.5 (the dried hydrogel isolated from the seed husks of *Plantago ovata:* crospovidone); was found to be most suitable in terms of processability. This material exhibited the lowest particle size distribution with acceptable flowability. Hence this composition of co-processed material was further explored to confirm its functionality as a granulation binder-disintegrant.

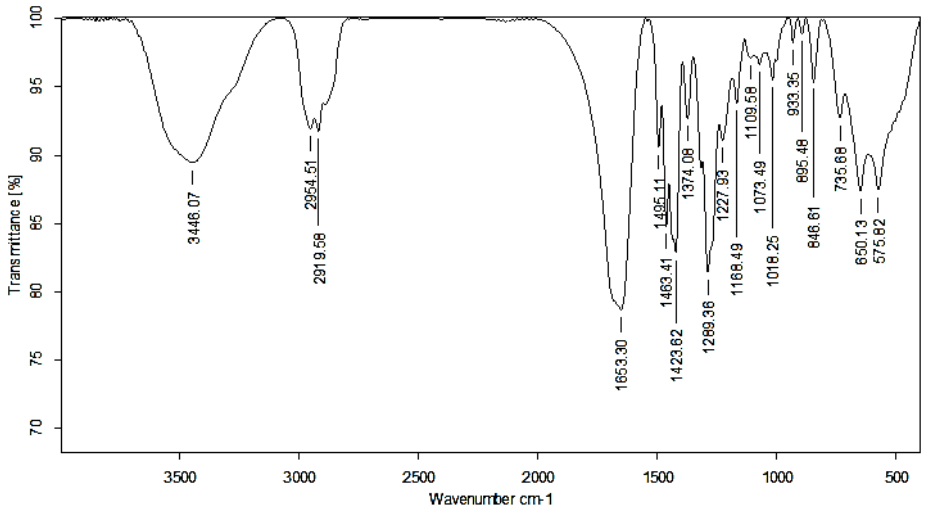

Figure 2. ATR-FTIR of Crospovidone

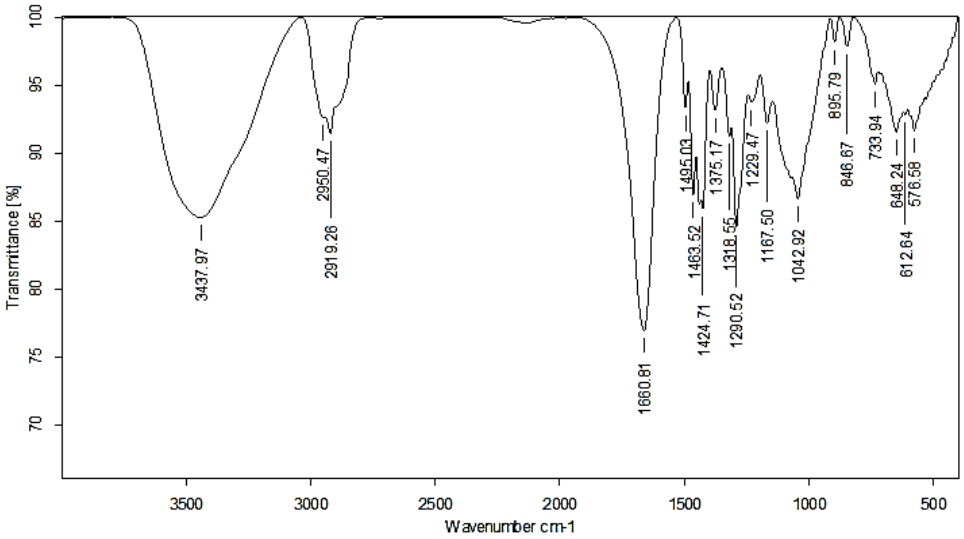

Figure 3. ATR-FTIR of Co-processed material

The absence of chemical interaction between the materials being co-processed is the prerequisite of successful co-processing. To confirm this, the ATR-FTIR of crospovidone alone as well as of dried hydrogel isolated from the husk of *Plantago ovata* seeds was carefully studied and reported here. The triplet at 1495 cm^{-1}, 1463 cm^{-1}, and 1420 cm^{-1} are the spectral peaks of the polymer that contains pyrrolidone moiety. This triplet at 1495 cm^{-1}, 1463 cm^{-1}, and 1423 cm^{-1} in ATR –FTIR of crospovidone **(Figure 2)** and also in ATR-FTIR of co-processed crospovidone **(Figure 3)**; is read. The peak due to carbonyl stretching vibration is at around 1650 cm^{-1}. This peak is also present in both spectra [13, 14]. Absorption peaks between 3000 -2840 are due to C-H stretching and are

observed in the ATR-FTIR of crospovidone (at 2954 cm^{-1} and 2919 cm^{-1}) and of dried hydrogel isolated from the husk of *Plantago ovata* seeds (at 2818 cm^{-1} and 2850 cm^{-1}) were intact in the ATR-FRIR of the co-processed excipient (at 2950 cm^{-1} and 2919 cm^{-1}). All these observations indicated the absence of any chemical changes.

Absorbance bands of hydrophilic groups of polymeric materials are shifted due to hydrogen bonds. The shift of infra-red frequency bands is more pronounced for stretching modes in hydrogen bonding. The stretching vibrations are usually decreased (3000 cm^{-1}-3500 cm^{-1}) but bending vibrations are increased due to hydrogen bond formation. The stretching frequency between 3570 cm^{-1}-3300 cm^{-1} arises because of polymeric intermolecular hydrogen bonds. ATR-FTIR has been preferred to investigate hydrogen bonding, and to substantiate inter-polymer interaction in particular by hydrogen bonding. This band is prominent in the ATR-FTIR spectrum of the dried hydrogel isolated from the husk of *Plantago ovata* seeds as well as of crospovidone **(Figures 1 and 3)**. Frequency shift from 3446 cm^{-1} (in ATR-FTIR belonging to crospovidone) to lower frequency at 3437 cm^{-1} in ATR-FTIR belonging to co-processed crospovidone indicated hydrogen bonding between them [15-18].

Data Treatment for the purpose of verification of the Heckel equation

The 'granulation binder' property of the novel co-processed material was investigated by verifying the Heckel equation –

$$\ln(1/1-D) = KP + A \qquad (1)$$

Where, D = Relative density of granules, P = Applied pressure, A = Constant suggested reflecting particle rearrangement and fragmentation, and K = Slope of the linear part of the relationship which reflects the deformation of the particle during compression (9). The average height of the paracetamol tablets (h_2) prepared by applying the highest compression pressure was 0.38 cm and the average weight (w_2) was 0.525 gm. Heckel treatment was given to the data generated as reported in **Table 1**.

Granulation binder is one of the variables that improve the compactibility and manufacturability of poorly compressible materials and assist in overcoming the risk of tableting failures. Binders tend to be plastic materials and under applied compression pressure these materials undergo plastic deformation. The linear relationship was observed between ln (1/1-D) and applied compression pressure **(Figure 4)**. The linear relationship denoted plastic deformation of the granules of the paracetamol prepared by using the novel co-processed material. Thus the functionality of this material as a granulation binder was confirmed [19].

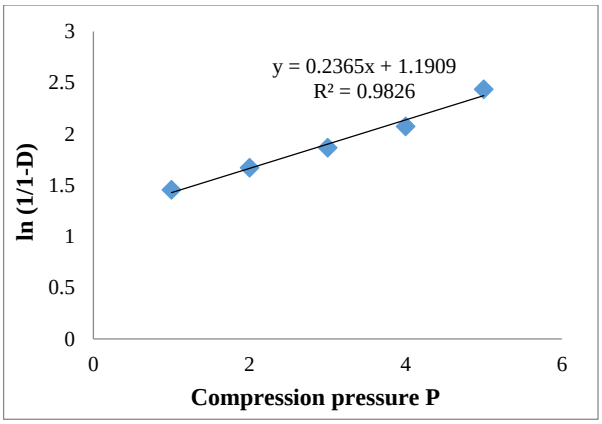

Figure 4. Heckel Plot

Investigation of the functionality of the co-processed material as a disintegrating agent

The mode of addition of the disintegrating agent in the wet granulation technology is one of the critical process attributes. Generally, 50% amount of the disintegrating agent is added intra- granularly and the remaining 50% is added extra granularly [20]. Immediate-release tablets of paracetamol of two different compositions **(Table 2)** were prepared and evaluated for their disintegration and dissolution performances along with their physic-mechanical properties **(Table 3)**.

The hardness of the tablets of the composition prepared by adding co-processed crospovidone (5%) extra granularly was more (but lesser friability) than the tablets of the composition prepared by using crospovidone alone. The disintegration time was also found to be prolonged and dissolution was delayed for the tablets of the composition with extra-granular co-processed crospovidone. The complete disintegration of the tablet never implies the complete dissolution of the drug from the tablet formulation [21, 22]. The dissolution rate of the paracetamol in this study not only depended on the mode of addition of the co-processed material but also on the nature of the binder used in the formulation [23-27]. Thus the results obtained in the study, if co-related scientifically; suggested better disintegration and dissolution performances of the tablets when co-processed crospovidone was added intra-granularly and crospovidone extra-granularly. Incorporation of the co-processed crospovidone (5%w/w) extra-granularly yielded tablets with more hardness impeding the disintegration of the tablets. Therefore it was concluded that the intra-granular (5%w/w) incorporation of the co-processed crospovidone proved to be an efficient granular binder-disintegrant in the present study.

Table 3. Data for the evaluation of immediate-release tablets

Formulation Code	Weight Variation* (mg) n=20	Friability* (%) n=20	Hardness* (Kg/cm^2) n=5	Disintegration Time* (min) n=6	% Dissolution at 30 min n=6
CP	560.63 ± 3.33	0.98%	4±1	9±2	85±2.36
CCP	562.45 ±4.05	0.09%	5±1	15±5	79±4.44

*All values indicate mean ± SD.

CONCLUSION

The physical mixtures of the dried hydrogel isolated from the seed husks of *Plantago ovata:* crospovidone; were co-processed in 1:0.5, 1:1, and 1:1.5 (w/w) proportions. The co-processed material of composition as 1:1.5 exhibited the lowest particle size distribution with acceptable flowability and therefore was selected to investigate its functionality as a binder-disintegrant. The functionality of co-processed material was investigated for its binding properties in paracetamol tablets. Paracetamol was used as a model drug in the present work as it is a poorly compressible drug. The paracetamol granules were prepared by wet granulation technique and compressed into tablets by applying gradually increasing compression pressures. The tablets were evaluated for physic-mechanical properties. The analysis of the experimental data after the Heckel treatment proved that the intra-granular incorporation of the co-processed material (5%w/w) conferred plasticity to the paracetamol granules with a 'yield pressure' of 4.22 tons. Two batches of immediate-release tablets of paracetamol were prepared by using a novel co-processed material as a granulation binder and either 5% crospovidone or 5% co-processed crospovidone as an extra granular disintegrant. The tablets exhibited fast disintegration prepared with crospovidone (5%w/w) as an extra granular disintegrant than when co-processed crospovidone was added. The results of disintegration, as well as dissolution studies of the tablets of these two batches, indicated that the co-processed crospovidone was an efficient granular binder-disintegrant in the present study.

Acknowledgments: The authors are thankful to the IIT, Powai, India for performing and providing results of ATR-FTIR analysis of co-processed material.

Conflict of interest: None

Financial support: None

Ethics statement: None

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