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Original Article

STUDY OF THE FUNCTIONALITY OF A NOVEL SOLUTION BINDER OBTAINED FROM *OCIMUM BASILICUM* SEEDS: A MECHANISTIC APPROACH

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ABSTRACT

Objective: The aim of the present study was to investigate the functionality of the hydrogel isolated from the seeds of *Ocimum basilicum* (Gel) as a novel solution binder.

Methods: Paracetamol is known to possess poor manufacturability. Therefore it was selected as a model drug to study the efficiency of Gel as a solution binder. Paracetamol tablets were prepared at gradually increasing compression pressure from the granules prepared by using Gel of various viscosities as a solution binder. Compactibility parameter was calculated to assess the utility of Gel as a novel tablet binder. Optimization of the formulation was done by adopting factorial design as an appropriate DOE. Tablets of factorial batches were evaluated for disintegration time and crushing strength. The effect of viscosity of binder solution used to prepare granulation and compression pressure applied on granulation on the performance of the tablets was confirmed by analyzing the data using ANOVA.

Results: The addition of binder solution to prepare granulation with the viscosity ≥ 19.33 centipoises was found to be suitable to attain desired degree of agglomeration. The crushing strength of the tablets was found to be increased with an increase in compression pressure and an increase in viscosity of binder solution.

Conclusion: The compatibility parameter was observed to be increased as the viscosity of the binder solution added in the formulation was gradually increased. The Gel as a binder material was found to deform plastically at compression pressures 34.48 to 75.85 MPa. This confirmed its functionality as a solution binder in Paracetamol tablet preparation.

Keywords: Solution binder, Paracetamol, Compactibility

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INTRODUCTION

Poor compatibility and manufacturability of drugs drive researchers to investigate novel materials as binders. "Compactability" is an ability of powder/granules to form coherent compact under applied pressure. "Manufacturability" concerns tabletting failure such as capping and it is poor in such cases [1]. Binders are added to tablet formulations to add cohesiveness to powders; thereby conferring bonding properties to them. Agglomeration of powder material is promoted by binder addition leading to the formation of granules. These granules after application of optimum compression pressure are compacted to form a tablet. The compactibility of granular material depends on the efficiency of the binder added to it. The location of the binder within the granulation affects its functionality and hence the quality of granules [2]. Although binders in solid-state could be added to the powder mix and then wetted with water; the use of solutions of binders is preferred during granulation in practice. In wet granulation, the binder was found to be the prominent determining factor among the number of formulation variables that are considered to influence granule quality. For a binder to be effective, it shall form a film on the particle surface and thus binder efficiency depends on the method of its incorporation in the powder to be agglomerated. The effectiveness of binders was enhanced when it was used in the solution state [3-5]. Binder film formation around the agglomerated particles and deformation behavior of the binder film under applied compression pressure are the key determinants of granule and tablet strength [6]. Binders tend to deform plastically when compression pressure is applied during compression. As a consequence, after the compression pressure is removed, binders improve the plasticity of granules resulting in reduced elastic recovery leading to least capping chances during decompression. Thus the addition of binders mitigates the capping tendency of materials having poor manufacturability [2, 7].

The hydrogel obtained from the seeds of *Ocimum basilicum* (Gel) was investigated as a binder using paracetamol as a model drug in the present study. The method of isolation of hydrogel was reported earlier [8]. The advantages of developing Gel as a tablet binder are; ease of preparation, eliminating solution preparation manipulations and the possibility to acquire GRAS status from regulatory authorities [9]. Formation of poor quality or fragile tablets of paracetamol with a high tendency to cap is reported; since fragmentation is the main mechanism of its compaction [10, 11]. Therefore it is selected as a model drug to investigate the functionality of the novel binder. Binders' increases the strength of compacts under pressure by forming a cohesive network resulting in the formation of intergranular bonds. The level of binder to be added in the formulation necessitates a balance between the amount required to produce a robust, compressible granulate and to attain optimum biopharmaceutical properties. There is impedance in disintegration and hence in dissolution time of tablets as the granule strength increases with higher proportions of binders used.

The suitability of novel binder and its optimum level as a solution binder in Paracetamol tablet formulation was assessed empirically in the present work; by formulating and evaluating paracetamol tablets. Preliminary formulations were prepared by using the binder solution of various known viscosities and by changing certain process variables viz. speed of the rotary press and compression pressure. Optimization of viscosity (concentration) of a binder solution as a formulation variable and compression pressure as a process variable was done with the help of factorial design as the design of experiments [12, 13]. Compactibility conferred by the binder solution under investigation was quantified by measuring the specific crushing strength of compacts prepared at various compression pressures within the range confirmed by factorial design [14, 15].

MATERIALS AND METHODS

Materials

Paracetamol was gifted by Shrikrishna Pharmaceuticals Ltd. Mumbai. The hydrogel was obtained from the seeds of *Ocimum basilicum* collected from regional sources and the necessary processing was done in the laboratory. The plant was deposited in National Repository and then authenticated by CSIR-National Botanical Institute, Lucknow, India with authentication number-LWG-46. The ingredients used to prepare tablet formulation were of pharmaceutical grade.

Methods

Isolation of hydrogel as a binder

The seeds of *Ocimum basilicum* were soaked for 20 min in demineralized water in 1:20 proportion. The hydrogel-forming component present in seed pericarp swelled when seeds were put in demineralized water. The entire bulk was homogenized to isolate the hydrogel from the pericarp of the seeds and centrifuged to separate the seeds from the hydrogel. The hydrogel was isolated and its viscosity was measured. Procedure for isolation of Hydrogel and the viscosity measurement was repeated to confirm reproducibility in results. This hydrogel (Gel) was used as a binder solution (H) in the first set of preliminary tablet formulations of paracetamol.

Measurement of viscosities of binder solutions

The viscosity of the Gel was measured by using spindle number 61 on Brookfield (Model-DV II+) viscometer. About 800 ml Gel was taken in a 1 L glass beaker. Then the spindle was immersed in it up to the middle of the shaft indentation of the spindle. The spindle speed was selected as 100 rpm turned the viscometer on and allowed it to run until the constant reading was obtained and it was recorded in centipoises. The Gel was diluted with demineralized water in 1:0.25, 1:0.5, 1:0.75 and 1:1 and eventually used as binder solutions in further study. Viscosities of all the binder solutions with their codes are reported in table 1.

Preparation of granules for preliminary batches

Hydrogel i.e. novel binder under investigation was filled in an atomizer and delivered into 0.5 Kg of paracetamol in a mixing pan using a spray nozzle. For each granulation 50 gm of the liquid binder of specific viscosity was used. Wet granules were prepared by using sieve no. 16 and dried in tray dryer at 80 °C. The compositions of preliminary batches are reported in table 2.

Preparation of paracetamol tablets to elucidate the effect of processing parameters

The subsequent set of preliminary batches was prepared as per the compositions reported in table 2 for the formulation batches C, D, and E and evaluated for bulk properties. The granules of these batches were compressed at three compression speeds. For each composition of granules of batch C, D, E and at each rotational speed of the tablet machine, the compression pressure applied on the granulation was varied as reported in table 3. Tablets of this set of preliminary batches were carefully observed for capping and lamination during the post-compression phase. These observations are reported in table 3.

Preparation of paracetamol tablets by factorial design and quantification of compactibility

Granulation for preparation of paracetamol tablets was prepared of composition A, B and C (by adjusting the desired viscosities of respective binder solutions) reported in table 2. Formulations were prepared by adopting 2^2 factorial designs. Two independent variables viz. viscosity of binder solution (X_1) and compression pressure (X_2) were kept at 2 levels,+1 and-1. Dependent factors (responses) included disintegration time and crushing strength. The formulations were designed by adopting factorial design as the design of the experiment; to confirm the effect of selected factors at specified levels on the responses. As per the model total, four formulations were prepared as reported in Tables 4 and 5. All the factorial formulations were compressed at high machine speed i.e. 1177 mm/s to observe its implication on crushing strength of compacts by varying two factors were viscosity of binder solution and compression pressure. These factors were selected as they found to have an impact on the mechanical property of the compact/s. The viscosity of binder solution was kept 18 and 15 as realized from the preliminary study that higher viscosities (>H2) posed the problem of lamination.

Regression analysis

The responses were evaluated by applying ANOVA at $p \leq 0.05$ by quadratic model, which bears the form of the equation-

$$Y = b0 + b1X1 + b2X2 + b3\,X1X2 \ldots\ldots\ldots\ldots Eq^{n}.\ 1$$

Where the response variable is Y, b_0 is an arithmetic mean of all responses, b_1, b_2 are the regression coefficients, $b_3$is the interaction coefficient show how response changes when two factors are simultaneously changed. X_1 and X_2 stand for the main effect, X_1X_2 are the interaction terms. Design-Expert software (trial version 11) was used to describe the response surface curvature.

Quantification of compactibility

Data on the measurement of specific crushing strength was treated as suggested by JM Sonnergaard to quantify the compactibility. For the generation of the data few more batches were prepared as per the composition given below. The levels of variability in the viscosity of binder solution and compression pressure applied were tailored empirically by adopting factorial design as above. To quantify the compactibility i.e. functionality of novel binder was confirmed by the linearity between mechanical strength (specific crushing strength) and compression pressure applied for a specific viscosity of binder solution added in the formulation [15, 17].

RESULTS AND DISCUSSION

Isolation of hydrogel as a binder and measurement of its viscosity

The hydrogel was obtained from *Ocimum basilicum* seeds by using demineralized water. The use of an organic solvent in the isolation process was circumvented to sustain product performance [18]. The viscosity of the isolated hydrogel decreased proportionally when diluted with demineralized water. It was also observed in the rheological study that the hydrogel was a shear-thinning system.

Table 1: The binder solution viscosities

Binder solution code	Gel: D. M. Water	Viscosity in cP*
H	1:0 (Isolated hydrogel as such)	26.32±1.33
H1	1:0.25	22.41±0.65
H2	1:0.50	19.33±1.22
H3	1:0.75	15.29±0.98
H4	1:1	12.80±0.83

*Average±SD (n=5), Viscosity was measured by using spindle no. 61 at 100rpm and at torque>10%

Preparation of granules for preliminary batches

The extent of agglomeration of powder material depends on the cohesiveness of binder solution (granulation fluid) i.e. on the viscosity of binder solution in this study. The increase in bulk density of powder (with a proportional decrease in the Carr index) is related to the cohesiveness of the powder. In the present work, granules of composition A and B exhibited poor compressibility and

the compressibility was improved in granules of composition C, D, and E, respectively as evident from the Carr index (table 2). Since agglomeration of powder i.e. granulation results in densification and volume reduction of starting material; improvement in compressibility of granules prepared by using binder solutions with increasing viscosities was justifiable. This study indicated that binder solution with viscosity ≥ 19.33 centipoise was suitable to attain desired agglomeration [3].

Table 2: The compositions of the preliminary batches

Formulation code ingredients (mg/tablet)	A	B	C	D	E
Paracetamol	500	500	500	500	500
Seed mucilage (Gel)	50	50	50	50	50
Magnesium stearate	5.5	5.5	5.5	5.5	5.5
Talc	5.5	5.5	5.5	5.5	5.5
Binder solution code	H4	H3	H2	H1	H
Carr index of granules (%)	26.08	23.80	20.00	15.78	11.11

The basic factors that affect the binder distribution pattern in the powder bed are the method of delivery and delivery conditions of the binder solution. It is reported that when the binder solution was delivered at slow speed; its distribution efficiency was less dependent on the binder delivery method. Therefore the binder solution was delivered in a way to ensure uniform distribution of binder solution allowing its greatest coverage instead of localized over wetting of powder bed. The same granulation procedure was adopted for all the study batches prepared in this study. Five distinct mechanisms are identified at the level of particle-particle interaction after the addition of binders. One of them is the addition of a solution binder that adheres to the particles and softens solids and then hardens during drying. The physical movement of the particles during mixing generates enough contact area upon removal of the solvent to produce bonding contributing to compatibility during the compression phase [19, 20].

There is limited control over excipient quality through specifications when the excipient is isolated from a natural source. Greater control over physical characteristics of the novel excipient is obligatory in such cases [21]. Binder solution viscosity is a function of the concentration of hydrophilic adhesive solid material in water being employed as a binder. Thus viscosity of the binder solution is one of the formulation variables that affect the extent of bridging between primary particles in the dry granules contributing to tablet crushing strength. Therefore the addition of liquid binder of specific viscosity was selected as a highly influencing parameter on the crushing strength of the tablet [19, 22].

Preparation of preliminary batches paracetamol tablets to elucidate the effect of processing parameters

Many pharmaceutical materials exhibit time-dependent deformation and in such cases, it arises from the viscoelastic or viscoplastic characteristics of the material. As per previous reports, fragmentation is the predominant mechanism of compaction of paracetamol. Compaction characteristics of such materials that deform by fragmentation are unaffected by the speed of the machine. Consequently, the observations reported in table 3 are ascribed to the inclusion of a binder solution during granulation. Speed sensitivity of granulation for the integrity of tablets was found to be due to the viscoplastic deformation of a binder. In the present study capping of tablets was observed at high speed of tablet machine regardless of the viscosity of binder solution used in the preparation of granules. Whereas slower machine speeds or longer dwell times improved the mechanical properties of the tablets. It was clear from the observations reported in table 3 that the deformation characteristic of granulation of paracetamol prepared by using a novel binder was sensitive to tablet machine speed. These observations were in agreement with the findings reported earlier [6, 10]. When the tabletting process is scaled up to high-speed machines the effect of punch velocity is revealed. The next set of formulations was designed by adopting factorial design and results of evaluation parameters were analyzed by applying ANOVA.

Table 3: Effect of processing parameters on the integrity of the tablets

Formulation code	Compression pressure (MPa)	Machine speed (mms^{-1})	Integrity of the tablet
C	75.85	706.5	Intact
C	75.85	942	Intact
C	75.85	1177	Lamination
C	55.16	706.5	Intact
C	55.16	942	Intact
C	55.16	1177	Lamination
C	34.48	706.5	Intact
C	34.48	942	Intact
C	34.48	1177	Lamination
D	75.85	706.5	Intact
D	75.85	942	Intact
D	75.85	1177	Lamination
D	55.16	706.5	Intact
D	55.16	942	Intact
D	55.16	1177	Lamination
D	34.48	706.5	Intact
D	34.48	942	Intact
D	34.48	1177	Lamination
E	75.85	706.5	Lamination
E	75.85	942	Lamination
E	75.85	1177	Lamination
E	55.16	706.5	Lamination
E	55.16	942	Lamination
E	55.16	1177	Lamination
E	34.48	706.5	Intact
E	34.48	942	Intact
E	34.48	1177	Lamination

Preparation of paracetamol tablets by factorial design and quantification of compactibility

Table 4: Translation of coded value in actual unit

Variable levels	Low (-1)	High (+1)
X_1 = Viscosity of binder solution (Cp)	12	18
X_2 = Compression pressure (MPa)	75.85	34.48

Table 5: Factorial design for preparation of batches

Batch code	Variable levels in coded form	
	X_1	X_2
F1	+1	+1
F2	+1	−1
F3	−1	+1
F4	−1	−1

ANOVA for selected factorial model

The quadratic model was found to be significant with an F value of 66.84 (P<0.0001) for the effect of variables on disintegration time and with F value of 121.38 (P<0.0001) for the effect of variables on crushing strength. These levels of variables are useful to navigate the design space. The polynomial equations produced by evaluating the design are-

$$Y1 = 11.17 + 1.35X1 + 1.67X2 - 0.15X1X2 \quad \text{..... Eq}^{n}. 2$$

$$Y2 = 4.79 + 0.2208X1 + 0.2875X2 + 0.0875X1X2. \quad \text{..... ..... Eq}^{n}. 3$$

Where Y1 is Disintegration Time and Y2 is crushing strength. Positive coefficients of X_1 andX_2 suggested that; disintegration time was increased as the viscosity of binder solution in the formulation and the compression pressure applied increased. The interaction between factor X_1 and X_2 was could be neglected owing Very small coefficient of interaction signified negligible interaction between the factors X_1 and X_2. An increase in the viscosity of binder solution used in the formulation as well as compression pressure applied did not show a considerable effect on the crushing strength of the tablets as evident from the small coefficients of X_1 andX_2. A small coefficient of X_1X_2 exhibited insignificant interaction between the factor X_1 and X_2 [23].

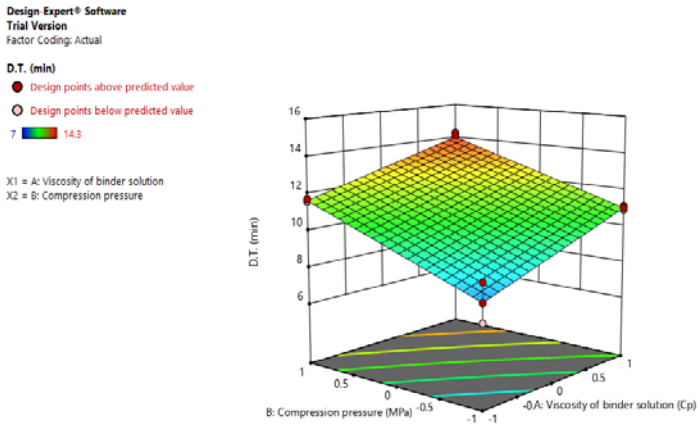

Fig. 1: The response surface plot showing the effect of formulation variables on disintegration time

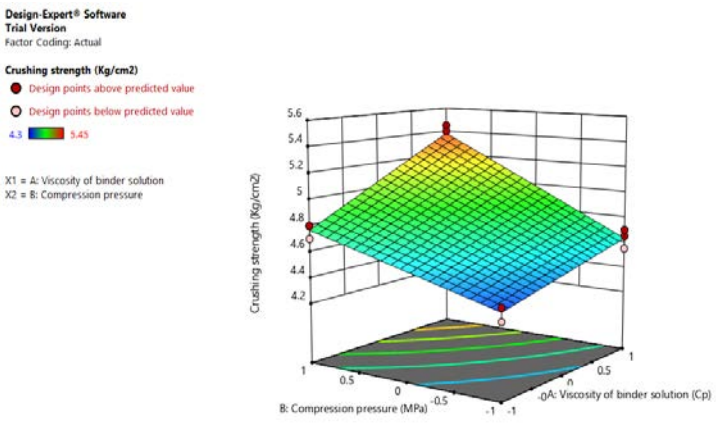

Fig. 2: The response surface plot showing the effect of formulation variables on crushing strength

Quantification of compactibility

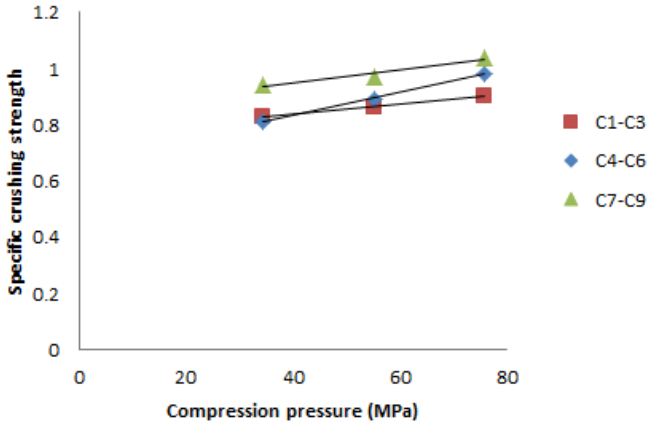

Fig. 3: Quantification of compactibility at various viscosities of binder solution added

The crushing strength of a compact is affected by the contact area between deforming particles, which in turn depends on the deforming behavior of binder and compaction variables. The most deformable binder increases tablet strength with an increase in compaction pressure. In this study, the crushing strength of the tablets was found to be increased with an increase in compression pressure and an increase in viscosity of binder solution as well. The compactibility parameter (represented by the slope of the line) increased as the viscosity of binder solution added in the formulation increased. The linear relationship between compression pressure (in the range selected) and the specific crushing strength confirmed that the maximum level of compression pressure selected for each composition is below threshold pressure (fig. 3). Compression pressure is to be kept below threshold value as the mechanical strength of compact decreases beyond this, resulting in capping and lamination. Thus the Gel as a binder material was found to deform plastically at compression pressures 34.48 to 75.85 MPa. This confirmed its functionality as a solution binder in Paracetamol tablet preparation [24].

CONCLUSION

The hydrogel isolated from the seeds of *Ocimum basilicum* (Gel) was a shear-thinning system. The compressibility of granulation was observed to be increased; when the viscosity of the Gel as a solution binder used in the preparation of granules was increased. Since the compressibility of granulation depends on the cohesiveness (viscosity) of binder solution; the functionality of Gel as a solution binder is justified. The data of crushing strength of tablets of factorial batches was analyzed for quantification of compactibility. The analysis revealed that the Gel as a binder material was found to deform plastically at compression pressures 34.48 to 75.85 MPa. As binders are tending to deform plastically; the results of the present study evidenced the functionality of Gel as a novel solution binder.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

There is no conflict of interest between authors.

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