Original Article

Development and Optimization of Dispersible Tablet of *Bacopa monnieri* with Improved Functionality for Memory Enhancement

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**Introduction:** The *Bacopa monnieri* is traditional Ayurvedic medicine, and reported for memory-enhancing effects. The Bacoside is poorly soluble, bitter in taste and responsible for the memory enhancement action. Memory enhancer is commonly prescribed for children or elder people. **Objective:** Poor solubility, patient compliance and bitterness were a major driving force to develop taste masked β-cyclodextrin complex and dispersible tablets. **Materials and Methods:** The inclusion complex of *Bacopa monnieri* and β-cyclodextrin was prepared in different molar ratios of *Bacopa monnieri* by Co-precipitation method. Phase solubility study was conducted to evaluate the effect of β-cyclodextrin on aqueous solubility of Bacoside A. The characterization was determined by Fourier transformation infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) and X-ray diffraction study (XRD). Crospovidone and croscarmellose sodium were used as super disintegrant. The 3² full factorial design was adopted to investigate the influence of two superdisintegrants on the wetting time and disintegration time of the tablets. **Conclusion:** The result reveals that molar ratio (1:4) of inclusion complex enhance 3-fold solubility. Full factorial design was successfully employed for the optimization of dispersible tablet of *B. monnieri*. The short-term accelerated stability study confirmed that high stability of *B. monnieri* in inclusion complex.

**Keywords:** *Bacopa monnieri*, dispersible tablet, memory enhancer, β-cyclodextrin

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How to cite this article: Thakkar VT, Deshmukh A, Hingorani L, Juneja P, Baldaniya L, Patel A, et al. Development and optimization of dispersible tablet of *Bacopa monnieri* with improved functionality for memory enhancement. *J Pharm Bioall Sci* 2017;9:208-15.
bioavailability due to poor aqueous solubility; hence, solubility enhancement is quite necessary to enhance the oral bioavailability of *B. monnieri*, and meanwhile, it also helps to decrease the dose and dose-related side effect of drug.\(^8\) Solubility enhancement can be achieved by a variety of means. Supersaturated solid formulations such as cyclodextrin (CD) inclusion complex, solid dispersion, and self-emulsifying drug delivery system are widely examined by researchers.\(^9\) As taste masking was also to be achieved in the formulation of *B. monnieri*, CD inclusion complexation technique\(^10\) was chosen in the present work to achieve the dual goals of solubility enhancement and taste masking. The method can be easily adopted at industry since scale up can be done. Super disintegrant can be used to facilitate the preparation of dispersion just before use by the patients. The regulators currently demand the use of a scientific approach in the formulation development work.\(^11\) Full factorial design was adopted in the present work to examine the influence of two super disintegrates. To examine the reason of solubility enhancement of *B. monnieri* extract, analytical tools such as infra-red (IR) and X-ray diffraction (XRD) were used. Finally, the optimized formulation was evaluated for routine tableting properties such as crushing strength and friability.

**Materials and Methods**

*B. Monnieri* extract Bacognize™ was obtained as gift from Pharmanza Herbal Pvt. Ltd. (Dharmaj, Gujarat, India). It contained 16% of bacosides, analyzed by USP method high-performance liquid chromatography method, as per data obtained from supplier. β-CD was procured from SD fine Chem Pvt. Ltd., (Vadodara, Gujarat, India). Crospovidone, croscarmellose sodium, Avicel PH 101, and mannitol were purchased from Astron Chemicals Pvt. Ltd., (Ahmedabad, Gujarat, India). Aerosil, Mg-stearate, talle, mannitol, and PVP-K30 were procured from Astron Chemicals Pvt. Ltd., (Ahmedabad, Gujarat, India).

**Phase solubility study**

Phase solubility study was conducted according to the method described by Higuchi and Connor.\(^12\) An excess amount of bacopa extract was placed into 25-ml glass flasks containing different concentrations of beta CD (1%, 2%, 3%, and 4% w/v) in 20 ml water. All the flasks were stoppered to avoid solvent loss. The content was shaken for 24 h in orbital shaking incubator at 100 rpm at 37°C. After 72 h, supernatant was withdrawn and filtered through Whatmann filter paper and analyzed using a ultraviolet (UV) – visible spectrophotometer at 260 nm.\(^13\) The solubility measurements were performed in triplicate.

**Preparation of inclusion complex and solid dispersion of bacosides by coprecipitation method**

Inclusion complex were prepared with bacosides: β-CD in 1:1, 1:2, 1:3, 1:4, and 1:5 molar ratios by coprecipitation method.\(^14\) Accurately weighed quantity of β-CD was dissolved in ethanol using magnetic stirrer (REMI, 1MLH, Ahmedabad, India). Subsequently, weighed quantity of bacoside was mixed. Distilled water was added to the ethanolic mixture and stirred for 30 min. The complex was collected by filtration, dried in an oven at 55°C for 6 h, and then passed through sieve #100. The samples were stored in a screw-capped glass vial until use.

**Characterization of inclusion complex of Bacoside A**

Solid-state study and characterization were performed for bacosides, β-CD in inclusion complex of selected batch.

**Infra-red spectrometry**

IR spectrometry was conducted using an Fourier transformation IR (FTIR) spectroscopy spectrophotometer (Spectrum GX-FT-IR, Perkin Elmer, USA). The spectrum was recorded in the range of 4000-400 cm\(^{-1}\). The procedure consisted of dispersing the samples in potassium bromide and gently ground, thus avoiding solid transition possibly inducing by extended grinding. The spectrum was scanned at a resolution of 0.15 cm\(^{-1}\) and scan speed 20 scan/s.\(^15\) The IR spectra of Bacopa and the excipients (β-CD) and its inclusion complex were recorded on FTIR spectrophotometer to detect the existence of interaction between the drug and excipients.

**Differential scanning calorimetry**

Differential scanning calorimeter (DSC-PYRIS-1, Phillips, Netherlands) was performed to assess the thermal behavior of the samples. The experiments were performed in dry nitrogen atmosphere. The samples were heated at a rate of 10°C min\(^{-1}\) from ambient temperature to the melting point. The calorimeter measuring range was 1 μW–750 mW with 11% accuracy. Empty aluminum pan was used as a reference.

**X-ray diffraction**

Vacuum grease was applied onto a glass slide to stick the sample. The samples, namely, pure untreated *B. monnieri* and inclusion complex of *B. monnieri* and β-CD were spread on the glass slide in approximately 0.5 mm thickness. The slide was then placed vertically at 0° in the X-ray diffractometer. The results were recorded over a range of 0–900 limits using the Cu-target X-ray tube and Xe filled detector. The operating conditions...
were voltage 40 kV; current 20 mA; scanning unit per min temperature of acquisition: room temperature; detector: scintillation counter detector; sample holder: nonrotating holder.

**Preparation of dispersible tablet of β-cyclodextrin complex of Bacoside A by direct compression method**

Trial formulations were prepared using different ratios of the croscarmellose sodium, crospovidone and PVP K30 with the fixed quantity of Aerosil, magnesium stearate, and talc. Avicel PH 101 was added to adjust the total weight of tablet to 250 mg. The ingredients were sieved through 80# and weighed accurately. Table 1 shows composition of tablets. *B. monnieri* was mixed with required quantity of superdisintegrants, mannitol, and binder for 5 min. The blend was lubricated with 1% magnesium stearate and 2% talc. The blends were compressed on 16 station rotary tablet press (Cadmach, Ahmedabad, Gujarat, India) using 9 mm flat-face round punches. The batch size was 500 tablets.

**Optimization of formulation parameters**

**Experimental design**

A 3^2 full factorial design was selected for optimization of the concentration of crospovidone and concentration of croscarmellose sodium to achieve low wetting time (Y_1) and disintegration time (Y_2). Eleven trials including two center point batches were conducted for this design [Tables 1 and 2].

**Optimization data analysis and validation of optimization model**

The responses wetting time (Y1) and disintegration time (Y_2) of all formulations were analyzed by Design-Expert® software (Version 9, Stat-Ease, Inc., Minneapolis, MN). Models were evolved (equations 1 and 2). The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the coefficient of variation, the multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2), and the predicted residual sum of square (PRESS). PRESS indicates how well the model fits the data, and for the chosen model, it should be small relative to the other models under consideration.[16]

Linear model:

\[ Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 \quad \text{(Equation 1)} \]

Quadratic model:

\[ Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_3 X_1^2 + \beta_4 X_2^2 \quad \text{(Equation 2)} \]

Where, \( \beta_0 \) is the intercept representing the arithmetic average of all quantitative outcomes of the 11 runs;

\( \beta_i \) are the coefficients computed from the observed experimental values of \( Y \) and \( X_1 \) and \( X_2 \) are the coded levels of the independent variable(s) (IVs). The terms \( X_1 X_2 \) and \( X_i^2 \) represent the interaction and quadratic terms, respectively. Statistical validity of the polynomials was established on the basis of analysis of variance (ANOVA). Subsequently, the feasibility and grid searches were performed to locate the composition of optimum formulations. In addition, two-dimensional contour plots were constructed using Design Expert software shown in Figure 5.

**Evaluation of dispersible tablets**

All formulations were evaluated for precompression parameters such as angle of response, bulk density, tapped density, percentage compressibility, and Hausner’s ratio.

**Postcompression evaluation parameter of dispersible tablet**

**Weight variation**

The test was performed as per Indian pharmacopoeia. Twenty tablets were selected from each formulation, weighed individually and the average tablet weight and % variation of weight was calculated.
**Friability**

Six tablets were weighed and placed in the Roche friabilator test apparatus (Electrolab Pvt. Ltd., Mumbai, Maharashtra, India), the tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 evolutions, the tablets were dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets. The friability (F) was given by the formula:

\[ F = \left(1 - \frac{W}{W_0}\right) \times 100 \]

Where, \( W_0 \) was the weight of the tablets before the test and \( W \) was the weight of the tablet after the test.

**Hardness**

Hardness was measured using the Monsanto hardness tester (Electrolab Pvt. Ltd., Mumbai, Maharashtra, India). The observations were recorded in triplicate.

**In vitro disintegration study**

Along with the conventional test for tablets described in Indian pharmacopoeia, a modified method was also used to check the disintegration time. About 6–8 ml of phosphate buffer with pH 6.8 was taken in 10 ml of measuring cylinder. Tablet was placed in the cylinder and the time needed for complete dispersion of tablet was recorded.

**Wetting time**

The tablets were placed at the center of two layers of absorbent paper fitted into a dish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water diffuse from the wetted absorbent paper throughout the entire tablet was then recorded as wetting time using a stopwatch.[17]

**In vitro drug dissolution**

The dissolution study was conducted in USP paddle apparatus, using phosphate buffer with pH 6.8, as the dissolution medium (300 ml) at 50 rpm and at 37°C ± 0.5°C. Samples were withdrawn at predetermined time and analyzed for the drug content by UV spectrophotometry method.

**Accelerated stability studies of optimized batch**

The optimized formulation of dispersible tablet of B. monnieri was selected for conducting the stability study. The accelerated stability study was carried out according to ICH guidelines by storing the samples at 40°C ± 2°C and 75% ± 5% RH for 3 months. The tablets were evaluated for hardness, drug content, and dissolution test.

**RESULTS AND DISCUSSION**

**Phase solubility study**

According to the Higuchi and Connors classification, the diagram [Figure 1a] shows the AN type curve where the solubility of Bacopa constituents increases linearly with β-CD concentration and further deviates negatively at higher β-CD concentrations. The product obtained in coprecipitation method exhibited highest solubility constant, i.e., 505.43 M⁻¹. Phase solubility diagram of B. monnieri with β-CD illustrate the solubility enhancement capability of CD. The phase solubility study show that the molar ratio 1:4 exhibits the highest solubility, and after that, a decline in the solubility was noticed [Figure 1b].

**Characterization of inclusion complex bacoside**

IR spectrum obtained for bacosides presented typical molecule bands and peaks: 3379–3087 cm⁻¹ (O–H), 1639 cm⁻¹ (C=O), 1571 cm⁻¹ (C=C), 1371 cm⁻¹ (C–OH), and 1274 cm⁻¹ (C–O–C) [Figure 2a]. IR spectrum of

![Figure 1: Phase solubility of inclusion complex a) Phase solubility diagrams of B. monnieri in inclusion complex. b) The phase solubility diagram corresponds to AL-type profiles.](image-url)
β-CD presented a large band and a peak in the region of 2900–3900 cm\(^{-1}\), a short band between 1600 and 1700 cm\(^{-1}\) and a large band containing distinct peaks in the region of 900–1200 cm\(^{-1}\) [Figure 2b]. IR spectrum obtained for bacosides-β-CD solid was exhibited the overlapped peak [Figure 2c], except for those in the 3000 cm\(^{-1}\) region and between 850 and 1000 cm\(^{-1}\). The reduction of intensity of bands and peaks, the presence of a new peak in the between 1000 and 1150 cm\(^{-1}\) when compared with bacosides extract suggest an interaction bacosides and β-CD.

**Differential scanning calorimetry study**

The DSC patterns are represented in Figure 3. Negligible change in the melting endotherms of the *B. monnieri* extract and β-CD (1:4) in prepared inclusion complex of *B. monnieri* extract was noticed. Melting point of inclusion complex was found to be almost same but with a slight reduction, which is not significant. Sharp peaks of *B. monnieri* extract were observed at temperature 106.6°C, and 225.05°C. There was a noticeable reduction in endothermic peak height and of heat of fusion. This suggest that the physical state of changed from crystalline to amorphous.

**X-ray diffraction**

The XRD study spectra of *B. monnieri* and inclusion complex of *B. monnieri* and β-CD are shown in [Figure 4a and b]. The XRD scan of untreated Bacopa extract showed intense peaks of crystallinity whereas the XRD pattern of inclusion complex exhibited a reduction in both number and intensity of peaks compared to the untreated extract. This may be due to decrease in crystallinity or partial amorphization of the drug.

**Optimization of formulation parameters**

**Experimental design**

Full factorial design (\(3^2\)) was explored to systematically investigate the influence of super disintegrants on disintegration and wetting time. Design Expert software (version 9) was batches for optimization of formulation. The design was chosen since it is suitable for investigating the quadratic response surfaces. Best-fitted polynomial equation involving the main effects and interaction terms were selected based on correlation coefficient (\(R^2\)) and the PRESS. As presented in Table 3, the quadratic model was selected as a suitable statistical model, it had the smallest value of PRESS. PRESS is a measure of the fit of the models to the points in the design. The smaller PRESS value is the indication of best model fits to the given data points.

For estimation of significance of model, ANOVA was determined as per the provision of design expert using 5% significance level. A model is considered statistically significant if \(P < 0.05\). The significant coefficients \((P < 0.05)\) are represented in boldface letters in Table 3.

**Contour plots and response surface analysis**

2-D contour plots and 3-D response surface plots are presented in Figure 5. For both the response, when the IVs X1 and X2 where increased from low to high (i.e., from 2.5 to 5 mg), the response Y1 and Y2 decreased. This behavior may be due to superior performance of the disintegrants. The contour plots also indicate non-linear relationship between IV and DV.

**Validation of model**

To verify the evolved models, two formulations were prepared. Table 5 shows the results for both the responses. The predicted and observed values of
responses were quite close to each other. This proves the predictive ability of the equations within the design space.

**Evaluation of dispersible tablet**

The hardness of all formulations was measured in kg/cm². Hardness of all the formulation batches were found in the range of 2.2 to 3.4 kg/cm². The value of friability were found to be less than 1%. The results of friability indicate that the tablets were mechanically stable and could handle the rigors of transportation and handling. Further tablets were subjected for the evaluation of disintegration time for all eleven formulations varied from 25 to 60 sec. The disintegration time is 25 sec which is from F2 due to it contains the 5% of crocarmellose sodium and crospovidone.

**In vitro drug release study**

*In vitro* drug release (pH 6.8) study showed that the drug release within the standard limit (more than 60% within 50 min) as shown in Figure 6. Batch F1 containing the crospovidone (2.5%) showed the less drug release than the other batches. As the concentration of croscarmellose sodium increases the drug release increases. However, after 15 min batch F3, F4, F5, and F6 showed lesser drug release compared to Batch F7, F8, F9, F10, F11.

**Table 3: Analysis of variance analysis of Y1 (wetting time) and Y2 (disintegration time) of the tablets**

| Source                          | Sum of squares | Degrees of freedom | Mean squares | F       | P       |
|--------------------------------|----------------|--------------------|--------------|---------|---------|
| Response Y1: Wetting time (s)   |                |                    |              |         |         |
| Model                          | 996.24         | 5                  | 199.25       | 53.37   | 0.0002  |
| X₁ - concentration of cross povidone | 352.67         | 1                  | 352.67       | 94.46   | 0.0002  |
| X₂ - concentration of croscarmellose sodium | 400.17         | 1                  | 400.17       | 107.19  | 0.0001  |
| β₁₂  | 144.00         | 1                  | 144.00       | 38.57   | 0.0016  |
| β₁ ² | 22.80          | 1                  | 22.80        | 6.11    | 0.0564  |
| β₂ ² | 51.30          | 1                  | 51.30        | 13.74   | 0.0139  |
| Response Y2: Disintegration time (s) |              |                    |              |         |         |
| Model                          | 1928.76        | 5                  | 385.75       | 34.46   | 0.0007  |
| X₁ - concentration of cross povidone | 912.67         | 1                  | 912.67       | 81.54   | 0.0003  |
| X₂ - concentration of croscarmellose sodium | 661.50         | 1                  | 661.50       | 59.10   | 0.0006  |
| β₁₂  | 36.00          | 1                  | 36.00        | 3.22    | 0.1329  |
| β₁ ² | 75.90          | 1                  | 75.90        | 6.78    | 0.0480  |
| β₂ ² | 161.07         | 1                  | 161.07       | 14.39   | 0.0127  |

**Table 4: Comparative levels of predicted and observed responses for optimized formulations**

| Formulation composition (X1:X2) | Response variable | Experimental value | Predicted value | Percentage of error |
|---------------------------------|-------------------|--------------------|-----------------|---------------------|
| 4.90%:5%                        | Y1                | 16.96              | 18              | 5.23                |
|                                 | Y2                | 25.00              | 27              | 5.4                 |
| 2.5%:2.5%                       | Y1                | 25                 | 26              | 3.7                 |
|                                 | Y2                | 36                 | 38              | 5.2                 |

*aPredicted error (%)=(observed value−predicted value)/predicted value×100%

**Table 5: Stability studies of optimized batch**

| Parameters                      | F10 (initial) | 7 days | 14 days | 21 days | After 3 months |
|---------------------------------|---------------|--------|---------|---------|----------------|
| Disintegration time (s)         | 20.15±1.30    | 21.32±1.37 | 21.55±0.98 | 23.77±0.94 | 24.33±1.43 |
| Wetting time (s)                | 13.33±1.52    | 14.33±1.68 | 14.45±1.67 | 15.11±1.52 | 15.52±1.72 |
| Drug content (%)                | 98.23±0.23    | 97.33±0.32 | 96.33±0.57 | 95.02±0.11 | 95.22±0.28 |
and F12. Batch F7, F8, F9, F10, and F11 contain mixture of crospovidone and croscarmellose sodium. The batch F10 showed that mixture of 5% crospovidone and 5% croscarmellose sodium respectively, showed higher dissolution rate. So batch F2 was considered optimized batch as it showed 20 s disintegration time and higher drug release rate 97% within 30 min.

**Accelerated stability studies of optimized batch**

The results of short-term stability studies carried out according to ICH guidelines indicate that optimized batch showed no change in disintegration time as well as wetting time as shown in Table 5. In addition, drug content showed negligible effect after 3 months.

**Conclusion**

From the present investigation, it can be concluded that dispersible tablets of *B. monnieri* can be successfully prepared by direct compression method. The inclusion complex using β-CD with 1:4 molar ratio of *B. monnieri*: β-CD exhibits 3-fold solubility enhancement. FTIR spectra and DSC studies revealed that there was no interaction between drug and polymer. 32 full factorial design was used to optimize concentration of super disintegrant. The dispersible tablet formulated with 5% crospovidone and 5% croscarmellose sodium showed less disintegration rate and wetting time. Batch F2 showed least disintegration and wetting time. Drug content, disintegration time, and wetting time did not change in stability study.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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