DEVELOPMENT OF CO-PROCESSED EXCIPIENTS FOR FAST-DISSOLVING TABLETS OF CARVEDILOL BY MULTIVARIATE ANALYSIS AND QBD

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Conflict of interest

All authors declare that they have no conflict of interest.

Abstract

Purpose: Direct compression is a mostly used and required process in the pharmaceutical industry. The most extensively studied approach for preparing directly compressible excipients is co-processing. This research work was targeted to develop novel directly compressible co-processed excipient to prepare fast disintegrating tablets of Carvedilol.

Methods: From the preliminary trials, Lactose was selected as a directly compressible excipient and sodium starch glycolate was used as a super disintegrant. PEG 4000 was used as the binder from the preliminary batches. A melt agglomeration technique was selected to prepare the suitable co-processed excipient. Co-processed excipient was optimized by a Central composite design where the concentration of binder (X1) & concentration of disintegrant (X2) was chosen as independent variables from the preliminary studies. Carr's index, wetting time, disintegration time & Friability were chosen as dependent variables as they were having the highest effect on co-processed excipient and tablet properties.

Results: The optimized co-processed excipient was characterized for Kawakita's and Kuno's analysis, Heckel plot analysis, granular friability index, and lubricant sensitivity ratio. Results of dilution potential revealed that poorly compressible drug; Carvedilol was sufficiently incorporated into co-processed excipient for the preparation of fast disintegrating tablets. *In-vitro* dissolution study showed faster disintegration of drug compares to the conventional tablets. Instrumental studies like FT-IR and DSC proved the compatibility of various materials with each other.

Conclusion: The current study highlights the possibility of using co-processing to produce a directly compressible excipient for pharmaceutical applications.

Keywords: Co-processed excipients, Fast disintegrating tablet, Carvedilol, Quality by design (QBD), Multivariate Analysis.

INTRODUCTION

Single-component excipients do not always have the output needed for certain active pharmaceutical ingredients to be accepted, manufactured, or processed successfully, according to scientists. As a result, excipients with multiple properties, like enhanced flow, minimum/no moisture sensitivity, superior compressibility, & fast disintegration efficiency, are required. An innovative combination of present materials, excipients, & a new grade of present materials will all be used to create excipients with enhanced functionality. The primary goal of co-processing is to produce a value-added product based on its functionality/cost ratio. The formulation of a co-processed excipient begins with the joint selection of excipients, desired number, the choice of a preparation technique to obtain an optimal product with ideal physicochemical parameters, & it concludes with batch-to-batch variance minimization.(S. S. Patel et al., 2013)

The term "Quality by Design" (QbD) refers to a pharmaceutical production approach that emphasizes formulation development and manufacturing processes in order to maintain product quality.(Nadpara et al., 2012) Multivariate analysis (MVA) is based on the multivariate statistics mathematical theorem, which entails an evaluation as well as the study of several statistical outcome variables at the same time. The aim of this research work was to develop novel co-processed excipient with improved functionality for the preparation of fast dissolving tablets of Carvedilol. Because of rod-shaped crystalline form of Carvedilol, it seems particularly unsuitable for directly compressible tablet manufacturing. It is an antihypertensive with poor solubility and poor compressibility. Hence, the present study is targeted to overcome the above-mentioned hurdles by improving the compressibility. Fast dissolving tablets will also provide a rapid onset of action in seizures. So, the major objectives of the study are to develop co-processed excipients with improved processability by combining suitable directly compressible excipients and superdisintegrants and to finalize the preliminary batches by quality by design and multivariate analysis techniques.

METHODOLOGY

Analytical method

Preparation of Standard Stock Solution of Carvedilol

A standard stock solution of Carvedilol (100 µg/mL) was prepared by dissolving 10 mg of Carvedilol in a little quantity of 0.1 N HCl containing 20% w/v PEG 400 & the volume was made up to 100 mL by 0.1 N HCl (Dhingani et al., 2013).

Calibration Curve of Carvedilol

From the standard stock solution, different aliquots of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, and 7 were pipette out and volume was made up to 10 mL with 0.1 N HCl. These prepared solutions were analyzed using UV-spectrophotometer at λ_{max} value. A graph of concentration vs. absorbance was plotted.

Preformulation studies

Identification of drug

For Fourier transform infrared (FTIR) study, pure API was mixed with potassium bromide to get pellets at 1 ton/cm^2. A spectrum was noted over the range 4000-400 cm^{-1}.

Determination of melting point of Carvedilol

The capillary process was used to calculate the melting point. The API was mounted in a capillary tube (10-15 cm long with an internal diameter 1 mm) and closed at one end for melting point measurement. The sample capillary and thermometer are then suspended in a beaker filled with liquid paraffin so that they can be heated steadily and uniformly. The melting point was determined by the temperature range in which the sample was observed and the melt drug sample was observed.

Micromeritics

Carvedilol's micromeritic properties, like bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio, were assessed. High angle of repose indicates slow drug movement, which may be caused by particle-particle frictional forces. The relative movement of pharmaceutical content is inextricably linked to compressibility. The relative movement of the medicinal substance is inextricably linked to compressibility.(Hooda et al., 2012)

Preliminary studies

(A) Selection of a method for preparation of co-processed excipient

Three methods were used to prepare co-processed excipient, wet granulation, melt agglomeration, and solvent evaporation. One directly compressible excipient and one disintegrant were used for co-processing. Wet granulation, melt agglomeration and solvent evaporation each consist of twelve formulations. The evaluation of all batches was done on the basis of the micromeritics properties. The batch with best results was used for further studies.

Method for preparation of co-processed Excipients

Wet granulation

By adding the required amount of all excipients and an appropriate amount of binder solution, the powder mixture was transformed into a moist mass. To promote granulation, the mass was dried for 15–30 minutes at 60 ^{o}C in a hot air oven. The wet coherent mass was then run through a 44 no sieve. The wet granules were dried for 90 minutes at 60 ^{o}C in a tray drier. For future usage, the 44 mesh fraction granules were stored in a tightly sealed bag. Formulations were mention in table 1.(Gohel et al., 2007)

Melt agglomeration

The first binder was applied to a pre-heated porcelain dish on a water bath held at 90^{0} C, followed by the excipients, which were eventually added with continuous starring. To split the mass into agglomeration, the mixture was heated for 10-15 minutes at 90^{0} C with continuous starring. After that, the agglomerate was left to cool to room temperature. Thus, the agglomerates passed through the sieve no 44, then it was consolidated by sieving and set aside in a strongly closed glass jar awaiting further use. Formulations were mention in table 1.(Gohel & Jogani, 2002; Jacob et al., 2007)

Solvent evaporation

To an appropriate organic solvent, a mixture of excipients was added. A magnetic stirrer was used to stir the contents of the beaker. The temperature was held between 65 and 70 degrees Celsius, and stirring was done until much of the solvent had evaporated. A 60-mesh sieve was used to granulate the wet coherent mass. The wet granules were dried for 20 minutes in a tray

dryer at 60°C. The dried granules were passed through sieve no 60 before being placed in an airtight bag. Formulations were mention in table 1.(Gohel et al., 2007)

(B) Selection of binder and optimization of binder in co-processed excipient

After selecting the melt agglomeration technique various binders were used and different batches were prepared. PEG 4000 and PEG 6000 were used and all the co-processed excipients were evaluated for different micromeritics properties. After selecting PEG 4000 as a binder, various concentrations of binder ranging from 2.5% to 15% w/w were taken and co-processed agglomerates were evaluated for different micromeritics properties.

(C) Optimization of disintegrant in co-processed excipient

After selecting SSG as a disintegrant, the various concentration of SSG ranging from 2% to 10% w/w was taken and all the agglomerates containing various amounts of SSG Were prepared. Then tablets were prepared on a 9 mm flat round bottom punch adding Magnesium stearate 1% and talc 2% for lubrication and evaluated for disintegration time and wetting time.

Quality by design approach for preparation of Co-processed excipients:

Quality Target Product Profile of Co-processed excipients:

The QTPP definition is the first step in the QbD paradigm. The QTPP is used to design prescription drug product development. The quality properties that a drug product must have in order to achieve the goals set out in the target product profile as quantitative characteristics are enumerated in the target product quality profile. The International Conference on Harmonization (ICH) Q8 (R2) guidance defines the QTPP as "A prospective summary of the quality characteristics of a drug product that ideally will be accomplished to certify the desired product quality, taking into account safety and efficacy considering the administration route, dosage form, strength, bioavailability & stability of the pharmaceutical product". Hence it sought to form the foundation for ascertaining the Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs) and control strategy.

Risk identification by Ishikawa diagram:

For the analysis of significant risks of the formulation & process variables on the CQAs of Co-processed excipients, an Ishikawa diagram (also known as the fish-bone diagram, herringbone diagrams, or cause-and-effect diagram) was developed. Several possible risk factors were identified based on previous expertise and preliminary experiments. After the analysis, these key variables were identified for screening in subsequent studies.

Risk analysis:

The ICH Q9 guidance manual developed the idea of quality risk management as a means of assessing, communicating, monitoring, and updating risks to drug quality over the course of a product's shelf life. The drug product was linked to substance attributes and process parameters for risk evaluation. CQAs for CCA and Tablets have been discovered. The CQAs are primarily determined by the formulation type, type of dosage form, processing methodology, & other factors that were chosen from a wide range of options. As a result, we established the formulation and manufacturing process based on feasibility studies. An overall risk assessment of the Co-processed excipients components was performed by classifying risk in Low, Medium and High-risk CQAs in achieving QTPP.

Experimental Design

To decrease the number of trials essential to achieve the greatest number of information on invention properties, the screening was performed applying a circumscribed central composite design. The concentration of binder and concentration of super disintegrants were demarcated as factors, while micromeritics properties of agglomerates, wetting time, disintegration time (for tablet) to be used responses. This method levels and variables through investigational values were given in table 2 (a). Needy variables were shown in table 2 (b). This design has 2 factors among 5 levels were probed to investigate the main and interaction effect of the two factors on five response. This plan considered of 4 factorial points, 4-star points, & a center point including 9 experiments in total. Result of this design allowable the response to be model by appropriates a second order polynomial, they can be stated an equation to the following.(Dhingani et al., 2013; Hao et al., 2012; Pabari & Ramtoola, 2012)

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Evaluation parameters

Co-processed Excipients

Angle of repose(Kumare et al., 2013; NF-24, n.d.; Tomar et al., 2017)

Angle of repose was used to determine flow property of co-processed excipients. This was determined by measuring the height & radius of the pile of co-processed excipients. A funnel was set to a stand and the base of the funnel was fixed at a height of 1 cm from the plane. Calculate the height & radius of the pile.

$$\theta = \tan^{-1} \frac{h}{r} (1)$$

Where, h = height of pile, r = radius of pile

Carr's Index(Gandhi, 2016; Kumare et al., 2013; NF-24, n.d.)**.**

Carr's compressibility index was used to calculate the compressibility index of the powder blends. It was a simple test to determine a powder's BD and TD as well as the rate at which it filled down. Carr's Index was calculated by using the formula as below:

$$\text{Carr's Index} = \frac{\text{Tepped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100 \quad (2)$$

Hausner's Ratio(Kumare et al., 2013; NF-24, n.d.)

The interparticle friction is attributed to Hausner's ratio, which is correlated to the flowability of powder materials. Using the following formula, it was measured from tapped mass to bulk density:

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}} (3)$$

Characterization of Optimized Co-processed Excipient

Kawakita Analysis

The samples' packing capability was determined by tapping them into a measuring cylinder with a tapped density apparatus. 10 g Optimized agglomerates were first weighed, then transferred in a measuring cylinder and placed in a tapped density apparatus. Then, the tapped volume was registered after 10, 20, 30, 50, 60, 80, 100, and 200 tapping, the volume remained slightly unchanged after a rise of 200 taps. The following equation was used to measure packability.(S. S. Patel et al., 2009; Prakash et al., 2011; Zhang et al., 2004)

$$\frac{n}{c}=\frac{1}{ab}+\frac{n}{a} \qquad (4)$$

Where, a and b are the constant, n= no of tapping

$$c = \frac{V0-Vn}{Vn} \qquad (5)$$

Where Vo and Vn are bed volumes of the agglomerate at the first as well as n^{th} tapped states, correspondingly. Since tapping of powder or agglomerates a and b is inversely proportional to yield intensity of the agglomerates, the value of implies a decrease in whole volume. The flow & compression efficiency of the agglomerates were studied using the values of a and b. Thus, the combination of Kawakita parameters a and b-1 can be used to investigate the frequency of particle reorganization during compression and, as a result, the relative importance of the preliminary stage for overall compression efficiency.

Kuno Analysis

In 1979, scientist Kuno described the relation between alter in apparent density & the number of tapping. Equation is:

$$\text{In } (\rho t\text{-}\rho n) = \text{-}Kn + \ln(\rho t\text{-}\rho o) \qquad (6)$$

Where ρt is the apparent density at equilibrium, ρn the apparent density at the n^{th} number of tapping, ρo is the apparent density at the first cascade state, & the constant K represents the rate of packing method under tapping.(S. S. Patel et al., 2009; Prakash et al., 2011; Zhang et al., 2004)

Heckel Plot Analysis

The hydraulic press (Technosearch Instruments, Mumbai, India) was used to compress the accurately weighted volume of samples at a steady compression at varying pressures for one minute of dwell time. Dies & punches were lubricated with 1 percent w/v magnesium stearate in acetone solution. The compacts were able to settle in a vacuum at an optimal temperature for 24 hours, & the data collected was measured using the equation below.(S. S. Patel et al., 2009; Prakash et al., 2011; Zhang et al., 2004)

$$ln\frac{1}{1-D} = kp + A \quad (7)$$

Where,

D = relative density (ratio of compact density to true density of powder) of the compacts,

P = functional compression pressure

k & A = constants.

As a result, the observed mean yield strain (Py), was determined using linear regression as the reciprocal of the slope k. In case of strain, each material's sequence was calculated separately. Densification at low pressure is represented by the constant A. K is equal to 1/3 σ_0 wherever σ_0 is yield strength & 3 σ_0 is mean yield pressure (Py). Here, from the volume and mass of compacts, the density of the compacts for the Heckel parameter was determined.

Granular Friability Index

Granular friability index was performed to estimate the mechanical strength of the co-processed excipient. In a Roche friabilator, an optimized batch of Agglomerates (10 g) was rotated at 25 rpm/min for 5, 10, 20, 30, 40, 50, and 60 minutes. The mean particle size was determined after the samples were analyzed in terms of their particle size distribution. Friability Index (FI) was determined by considering the relationship between the mean particle size of untreated agglomerates & average particle size of friabilator-treated agglomerates.(Gohel & Jogani, 2002)

Effect of Lubricant

The co-processed excipient with magnesium stearate packed into tablets in a 99:1 ratio. The lubricant sensitivity ratio was calculated by dividing the difference in tensile strength between

an unlubricated & a lubricated tablet by unlubricated tablet's tensile strength.(Almaya & Aburub, 2008; S. S. Patel et al., 2013)

Dilution Potential Study

The quantity of poorly compressible medicament that could be compressed into a tablet with a directly compressible excipient was referred to as the dilution potential. The dilution efficiency of an optimized batch was evaluated using carvedilol (model drug). The tensile strength and friability of tablets were checked.(Ambore et al., 2014)

Fast disintegrating tablets

Weight uniformity

20 tablets were taken and weighed separately. The average weight was then computed, and the percent variation of each tablet from the average weight was compared to the standard limit.(Dhanasekaran & Sacher, 2013; Soni et al., 2015)

Hardness test

Tablet hardness was calculated using Monsanto hardness tester. Average of 3 reading was taken and tabulated.(Rane et al., 2012; Soni et al., 2015)

Thickness

Tablet thickness was calculated by using a screw micrometer. Three tablets from every formulation batch were tested & the average reading was noted.(Soni et al., 2015)

Friability test

The tablets' friability was calculated using the Roche Friabilator. 6 tablets were accurately weighed and placed in the tumbling chamber, where they were rotated at 25 rpm for 4 minutes. The tablets were removed and weighed once more. The following formula was used to calculate the percentage of weight loss. The experiment was repeated three times, with the average was noted.(Reddy et al., 2013)

$$\%\text{friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100 \qquad (8)$$

Tensile strength

The dimension was calculated by using a micrometer. Hardness was calculated by using a Monsanto hardness tester after 24 hrs. (time for stress relaxation) of compression. Obtained values from thickness (L, cm), diameter (D, cm), & hardness (P, Kg), the tensile strength (T) (MPa) was determined by using the following equation.

$$T = \frac{0.0624 \times \mathrm{P}}{\mathrm{D} \times \mathrm{L}} \quad (9)$$

***In vitro* disintegration time**

It was determined by disintegration test apparatus. The time necessary to the tablet for totally disintegrate into fine particles was illustrious. This process was continuous in replicates of three tablets (n = 3) and mean SD values were noted.(H. A. Patel et al., 2010)

Wetting time

A double-folded piece of tissue paper was placed in a petri dish containing 10 mL of water and soluble dye (methylene blue). A tablet was put on the page, and the time it took for the tablet to fully wet was measured.(Dave et al., 2017; Gholve et al., 2015)

***In vitro* dissolution study**

In vitro dissolution study was completed according to USP Type II dissolution test apparatus at 50 rpm using 900 ml of 0.1N HCl at 37$\pm$0.5ºC as a dissolution medium. At regular time interval, sample was withdrawn & appropriate dilutions were made to predict the amount of drug release by measuring the absorbance of the sample in a UV spectrophotometer.(Basu et al., 2014)

Drug content

Three tablets, each containing 150 mg of Carvedilol, were crushed into fine particles and dissolved in ethanol. After proper dilution, absorbance was estimated at max 242 nm in a UV visible spectrophotometer.(Raj et al., 2016)

Instrumental studies

Fourier Transform Infrared (FTIR) Spectral study

To assess the chemical stability of the excipients, FTIR spectral data was collected. FTIR spectra of pure drug, co-processed agglomerates of the optimized batch in the same ratio were obtained and compared with each other.(Eraga et al., 2015) Drug at 3342.64 cm-1(N-H stretching vibration band), 2922.16 cm^{-1} (C-H), 1097.50 cm^{-1} (C-O bending vibration band), 1502.55 cm^{-1} (C=C stretching vibration band) and 1211.30 cm^{-1} (C-N stretching vibration band) present in the physical mixture & were also found in co-processed excipient that confirms that the co-processed excipients are chemically compatible.

Differential Scanning Calorimetry (DSC) study

The pure drug, co-processed agglomerate, and physical combination were all subjected to DSC analysis. Samples weighing 2-5 mg were put in aluminium and heated at a slope rate of 10°C/min below a stream of nitrogen from 30-300°C.(Eraga et al., 2015)

Stability Study

A stability analysis was conducted (as per ICH guidelines) on an optimized batch of quick dissolving tablets. For one month, these compositions were enclosed in aluminium foil and subjected to a temperature of 40°C + 2°C and a relative humidity of 75% ± 5%. At pre-determined intervals, an *in vitro* drug release test was performed.

RESULTS & DISCUSSION

Preformulation study

Melting point

Capillary tube technique was used to determine Carvedilol's melting point and it was found to be 115º C. This value is similar to that of the literature citation 114º C.

Identification of Drug

(a) FT-IR Spectroscopy

FTIR study was done for identification of the molecule & to assess the purity of the drug. Carvedilol FT-IR Spectrum was shown in figure 1. Results recommended that the most off peaks indicating the characteristic functional groups were available in the spectra. Thus, drug sample was originated to be Carvedilol.

Micromeritic Properties

The result of Micromeritic properties for Carvedilol were shown in table 3. The maximum Angle of Repose value indicates poor flow of the drug, which may be due to particle-particle frictional force. Carr's Index and Hausner's Ratio for the medication were found to be 34.90% and 1.44% respectively, indicating that the drug has a deprived flow property. Carvedilol's poor flow may be due to rod-formed crystals of the compound.

Micromeritic Properties of excipients

The result of Micromeritic properties for excipients were shown in table 3. The maximum value of Angle of Repose suggests that bad flow of excipients and this may be due to intraparticle frictional force.

Preliminary studies

Formulation and development of Co-processed excipient

In this study, one directly compressible excipient and one disintegrate was used in proper proportions to make suitable and required co-processed excipient. Two methods were selected primarily to make the co-processed excipient, melt agglomeration, solvent evaporation, and wet granulation.

Selection of a method for preparation of Co-processed excipient

Wet granulation technique

12 combinations of directly compressible excipients and disintegrants were processed by using starch paste in the wet granulation technique. All the batches were evaluated for AOR, CI and HR and the data are shown in Table 4.

The combination of MCC and CP Demonstrate that AOR, CI, and HR were Decreases Respectively, while other combination show increase in result of AOR, CI, and HR. So, we consider Mannitol and CP as best combination by using wet granulation technique.

Melt agglomeration technique

12 combinations of directly compressible excipients and disintegrants were co-processed by using PEG 4000 in the melt agglomeration technique. The amount of PEG 4000 was kept the

same for all the batches. All batches were evaluated for AOR, CI and HR and the data are shown in Table 4.

The combination of LM and SSG demonstrate that AOR, CI, and HR were decreases Respectively, while other combinations show an increase in the result of AOR, CI, and HR. So, we consider LM and SSG as the best combination by using the melt agglomeration technique.

Solvent evaporation method

12 combinations of directly compressible excipients and disintegrants were co-processed by using ethanol in the solvent evaporation technique. The amount of ethanol was kept the same for all the batches. All the batches were evaluated for AOR, CI and HR and the data are shown in Table 4. As shown in Figure 4 the combination of Mannitol and CP Demonstrate that AOR, CI, and HR Were Decreases Respectively, while other combinations show an increase in the result of AOR, CI, and HR. So, we consider Mannitol and CP as the best combination by using Solvent evaporation. On the basis of evaluation parameters such as AOR, CI, and HR we have selected a melt agglomeration technique using excipients Diluents as a LM and disintegrant as a SSG.

Choice and optimization of binder

The co-processed excipient containing LM and SSG was prepared by using two different binders like Polyethylene Glycol (PEG) 6000 and 4000 and results were obtained and evaluated for CI, HR, and AOR. In this study, 2 different binders were taken and agglomerates were prepared. Here PEG 4000 was compared with PEG 6000 and agglomerates were prepared and evaluated for micromeritic properties. PEG 4000 was selected for further study as it was showing better results compared with other binders.

Optimization of binder

Six batches were prepared using a different concentration of PEG 4000 from 2.5 to 15.0 % and results were compared by CI, HR and AOR. 6 batches were prepared by taking different concentrations of PEG 4000 and the batches were evaluated and optimization of binder

concentration was done. All six batches were containing the same amount of disintegrant SSG. LM was used as directly compressible excipients in all the batches.

Optimization of disintegrants in co-processed excipients

Agglomerates were prepared by using various concentrations of disintegrant. The disintegration time and wetting time were both reduced as the concentration of disintegrant rises. The above 8% disintegration time increases may be due to gelling and its subsequent viscosity producing effects.

QTPP of Co-processed excipients:

The QTPP is essential for defining the CQAs - the desired outputs of the manufacturing process. It is similarly important for mapping the design space, which understands the relative influence of input variables on CQAs. As previously mentioned, the type of formulation and method chosen affects how QTPP is defined. The parameter that was centred in our analysis was chosen and enlisted as QTPP for Co-processed excipients based on the preliminary studies performed. As a result, the steps to describe the QTPP are not addressed, apart from defining our QTPP. The CQA of Co-processed excipients was determined using the represented QTPP as a foundation.

RISK IDENTIFICATION BY ISHIKAWA DIAGRAM:

The aim of risk analysis was to compile a list of all potential variables that could influence product quality. An Ishikawa diagram was used to group these variables hierarchically in order to identify the formulation and process parameters for a given manufacturing system, as well as to assess their ability to affect the CQAs of Co-processed excipients. The failure modes were identified using the parameters described in the Ishikawa diagram. Several variables were identified as essential factors of Co-processed excipients based on previous scientific knowledge & preliminary investigation, as these features are likely to influence product and process characteristics.

RISK ANALYSIS

Experimental design

Lactose and SSG were selected as a directly compressible excipient and disintegrant correspondingly to make Co-processed excipient. PEG 4000 was used as a binder to inform enough reliability to the granule in the melt agglomeration process. Beginning trials were conducted to check the effect binder and binder concentration. Six batches for binder concentration were prepared from 2.5% to 15%. As the concentration of PEG 4000 was increased from 2.5-15%, the % fines decreased, representing that a high amount of PEG 4000 is enviable to provide better strength to the granules. Thus, it was decided to optimize PEG 4000 between 2.5-15%. Using a similar concentration of PEG 4000 (5%) but a different concentration of disintegrant SSG prepared five batches. From the evaluation results of both excipients and tablets are mention in Table 5. It was observed that the wetting time decreased with the increased concentration of disintegrant. So, it was decided to take 2% to 10% concentration of disintegrant. Based on the results of beginning investigations of the process parameters, it has been seen that factor such as the concentration of binder (X1) & concentration of disintegrant (X2) exhibited significant influence on response variables; hence, they were utilized for further systematic studies. As part of a two-factor central composite design, excipients were co-processed while the binder and disintegrant concentrations were varied as separate operational variables. Various physicochemical properties of granules & tablets like properties of powder, % fines, AOR, CI, and HR were studied.

PRINCIPAL COMPONENT ANALYSIS (PCA)

The main variables that influence the properties of co-processed excipients were investigated using PCA. PCA is said to be a valuable tool for examining the relationship between a vast number of variables. Thus, PCA was performed on all batch sets of data using Unscrambler® 10.4, with the objective of scrutinizing the critical responses. The effects of PCA can be reduced to latent variables that explain the key variance. Score and loading plots of the first two principal components (PC1 and PC2) are shown in figure 2a and figure 2b, The first principal component (PC1) accounted for 11% of the overall variation in the data collection, while the second (PC2) accounted for 88 percent, for a total output of 99 percent. The correlation loading

plot was also used to figure out which variable was the most important to optimize further. Figure 2c shows the similarity loading map, while figure 2d shows the 3D loading plot. The four most critical variables (CI, WT, DT, and Friability) are depicted as they are encircled by two eclipses. The data obtained were also classified by agglomerative Hierarchy Cluster analysis (AHCA) using the Euclidean Distance (nearest neighbor method). The resulting PC score was analyzed by a clustering approach. The correlation loading plot was shown in figure 2e obtained of co-processed excipients properties. The clustering method is frequently treated as the most efficient way to do classifications. Each sample began as a single cluster with hierarchical average connectivity, a phenomenon known as agglomeration. Before all samples were merged into a single cluster, the mean distance of all items in the clusters (weighted by the number of members) was used to determine cluster similarity. AHCA classified the 9 experimental design experiments into separate classes. It was used to compare and contrast both of the trials. All of the formulations were divided into four categories: category 1 (R3 and R7), group 2 (R4, R5, and R6), group 3 (R8 AND R9), and group 4 (R8 AND R10) (R1 AND R2), A scree plot shows the rate of change in the magnitude of the eigen values for PC when the eigen values are plotted against the corresponding PC. XLSTAT® software version 2017.15.1.01 was used to quantify eigenvalues for all PCs (addinsoft, Italy). This scree plot shows that between components 1 and 2, there is a big gap/break in the results, and then the eigen values begin to flatten out with component 3. Just these two components should be held and interpreted in this case. Finally, it was hypothesised that CI, WT, DT, & Friability were the most relevant variables in the formulation of co-processed excipients, so they were chosen for further optimization.

Summary of regression analysis

Because P values were more than 0.05, the Carr's Index b_2, b_{11}, b_{12}, and b_{22} were deemed to be inconsequential and were therefore omitted from the entire model. Values of b_2, b_{12}, and b_{11} were inconsequential for wetting time and were thus excluded from the entire model. Similarly, for disintegration time, values of b_{12}, b_{11}, and b_{22} and for friability values of b_{12} & b_{22} were

insignificant and hence removed from the full model. Table 6 shows the results of the analysis of variance (ANOVA) perform to defend the removal of insignificant factors. The maximum values of correlation coefficients that CI, WT, DT, and friability suggest a good fit. The critical values of F for CI, WT, DT & friability were found to be 9.28 (df = 3, 3), 9.12 (df 4, 4), 9.12 (df 3, 3) & 9.12 (df 2, 2) respectively, at p = 0.05. Furthermore, the measured F value was discovered to be less than a critical value, indicating that the full & reduced models have no discernible differences.

Influence of Formulation Composition Factor on CI

The value of Carr's index between 5-15 and 15-20 indicates excellent & good flow respectively. Although value greater than 20 indicates poor flow. All the batches except F1, F2, and F3 were found to be greater than 15, indicating poor compression properties. The positive sign of the coefficient of the X1 factor indicates that the factor decreases the Carr's index value and thus yields a product with good flow. The lowest value of 10.58 was obtained with batch F5 containing a moderate proportion of PEG 4000 and a higher concentration of disintegrant. Response Surface plot and Contour plot for CI are shown in figure 3(a).

$$Y = 14.34 + 0.66X_1 + 3.06X_2 + 2.13X_1X_2 + 0.24X_1^2 + 0.24X_2^2$$

Influence of Formulation Composition Factor on Wetting Time (WT)

The disintegration time of the tablets increased as the binder concentration increased, as predicted. The response surface plot for WT (Figure 3b) illustrated the strong influence of the X1 factor (binder concentration). The highest WT (63 sec) was observed with batch F4 containing a high level of X1 factor (binder concentration). This might be as a result of the creation of harder compacts with increasing in the binder concentration. To increase the multifunctionality of the agglomerates, the disintegration data suggested the addition of a higher % of superdisintegrant in the formulation to reduce the disintegration time.

$$Y = 32.82 + 14.86X_1 - 0.53X_2 + 5.41X_1X_2 + 2.78X_1^2 + 9.09X_2^2$$

Influence of Formulation Composition Factor on Disintegration Time (DT)

As predictable, with an increase in the binder content, the tablet disintegration time increased. The response surface plot for DT (Figure 3c) illustrated the strong influence of the X1 factor (binder concentration). A Lowest DT (26 sec) was observed with batch F5 containing a low level of X1 factor (binder concentration). Thus, increase binder concentration to increase DT time that might be due to the formation of harder compacts with increasing in the binder concentration. The positive value for the b2 coefficient for DT suggests the same. To increase the multifunctionality of the agglomerates, the disintegration data suggested the addition of a higher % of superdisintegrant in the formulation to reduce the disintegration time.

$$Y = 90.02 + 28.35X_1 – 14.52X_2 – 20.97X_1X_2 - 24.30X_1^2 + 3.15X_2^2$$

Influence of Formulation Composition Friability:

As predictable, both (concentration of binder and conc. superdisintegrants) independent effects were shown (Figure 3d) a significant effect on friability. The Friability is <1 indicating good friability. Although other batch compares to F1 and F3 batches showed a little bit high value indicating poor friability. These may be due to low conc. of the binder. The positive sign of the coefficient of X1 factor indicates that the increase in the concentration of binder thus decreases the friability.

$$Y = 0.76 + 0.225X_1 – 0.10X_2 – 0.10X_1X_2 – 0.03X_1^2 + 0.03X_2$$

Optimized Batch Analysis

The Optimized batch was chosen based on the following criteria: lowest CI, lowest WT, lowest DT, and lowest Friability values. Figure 4 shows an overlay plot created with Design Expert 10.0.7.1 (Stat-Ease, USA) to obtain an optimal batch. A related approach was used to equip an optimised batch of co-processed excipient seen in Table 7 (a). As a result, the calculated values from the regression equations were applied to the results of CI, wt, DT, and Friability. As all (experimentally derived and technically computed) values were compared, the percent error for both answers was found to be less than 8% (Table 7). (b). For both answers, this supported the use of existing contour plots & a reduced polynomial equation.

Characterization of Optimized Co-processed Excipient

(1) Kawakita & Kuno Analysis

By comparing the constants a, b, and k in Kawakita's & Kuno's equations similarly, the packability was determined. The proportion of consolidation as similar to packing as possible is represented by constant a. The packing velocity is represented by the reciprocal of b & k. The outcome for optimized batch (0.22) was lower than for the physical mixture, as seen in Table 8 (a) (0.299). This finding means that even without tapping, the co-processed excipient has strong packaging. The tailored batch's higher 1/b value (0.968) demonstrated that the co-processed excipient's packing velocity was faster than that of its physical mixture (Figure 5). The larger value of k in Kuno's equation (Table 8 (a)) follows the above results. The proportion of the powder bed consolidation per tap correlates to the sluggish packing velocity. As compared to the physical mixture, an optimized batch of a co-processed excipient shows (Figure 5) increased compression as a result of improved packability.

(2) Heckel Plot Analysis

The Heckel equation was used to calculate the data obtained over a range of compression pressures ranging from 1 to 5 tonnes. The yield pressure (Py) was calculated using the reciprocal of the regression line's slope k. (Figure 5). The Py value represents the material's compression properties. The larger the plastic deformation, the lower the Py value. The slope k of the co-processed excipient & the physical mixture was found to be 0.471 and 0.351, respectively, while the Py value was found to be 1.9 and 1.3. As a result, owing to the inclusion of lactose, the co-processed excipient demonstrated plastic deformation.

(3) Granular Friability index

Excipient mechanical strength, granule strength, and granular friability are important considerations to consider since they represent tablet quality. During processing (e.g., mixing, transportation), the directly compressible excipient is exposed to stress, and friable excipients can fail to produce appropriate tablets. As a quality management instrument, the granular friability index may be used. Figure 5 illustrates the impact of time on the Granular Friability index. The granular friability index was found to be close to one, and the friability rate constant

was found to be close to zero, implying that agglomerates are mechanically solid. For an optimised batch of co-processed excipient after 60 minutes, the granular friability index and friability rate constant were found to be 0.764 & 0.0049 min-1, respectively. As a result, the prepared co-processed excipient was determined to have a low friability.

(4) Effect of Lubricant

The lubricant is thoroughly mixed, forming a coating around the granules that stops them from sticking together. This resulted in a reduction in tablet tensile strength. This effect is more evident in plastic deforming materials than in brittle fractured materials. Table 8 (b) shows that combining magnesium stearate for a longer period decreases the tensile strength of the capsules, but only to a minor degree. A material's ability to mix with lubricant is expressed numerically by the lubricant sensitivity ratio. The stronger the material's capacity to mix with lubricant, the higher the lubricant sensitivity ratio. As a result, the improved co-processed excipient exhibits extremely low lubricant sensitivity.

(5) Dilution Potential Study

Carvedilol was chosen as the model drug for the analysis of dilution capacity. Carvedilol was used in the formulation of the tablets, which were tested for TS and percent friability. Table 8 displays the results (c). The batch with a TS of more than 0.85 MPa and a percent friability of less than 1 % was chosen. According to the findings, all of the batches generated suitable tablets, & up to 30% of Carvedilol was efficiently absorbed into the co-processed excipient. The TS decreased as the % of Carvedilol was raised, as seen in Figure 5. This indicates that Carvedilol has a low compressibility and elastic regeneration, which influences the percentage friability. Even with 10% Carvedilol, a simple physical mixture of excipients was unable to produce satisfactory tablets (Table 8 (c)). The effect of Carvedilol on tensile strength and percent friability is seen in Figure 5.

Evaluation of Fast Disintegrating Tablets

They can be done by the prepared co-processed excipient showed acceptable tableting characteristics with the chosen drug (Carvedilol). Fast disintegrating tablets were mention in Figure 5.

In vitro Dissolution Study

The dissolution study was performed for prepared fast disintegrating tablet and the tablet of the physical mixture. Thus, shown in Figure 5, a fast-disintegrating tablet showed 99.48% of drug release at the end of 60 min and conventional show 50.43% release. This suggests the versatility of co-processed excipient that it can be used to give the quick release of the drug.

Instrument study

(1) Fourier Transform Infrared (FTIR)

FTIR spectra of both optimized batch & its co-processed excipients were recorded and shown in Figure 1(b) and 1(c). The essential peaks observed in the Optimized batch were also found in the Co-processed excipient, suggesting that the excipients did not interfere. Excipients with distinctive peaks at 2939.52 cm-1 (C-H stretching vibration band), 1514.12 cm-1 (C=C), and 1080.14 cm-1 (C-O) detected in the physical mixture were also found in co-processed excipients, indicating chemical consistency. In the absence of chemical modifications, a company's regulatory issues during the production process are reduced.

(2) Differential Scanning Calorimetry (DSC)

DSC of Carvedilol (figure 6(a)) showed an endothermic peak at 114.72ºC equivalent to its melting point. Physical mixture and Optimized batch showed in figure 6(b) and figure 6(c). That showed an endothermic peak at 111.99 ºC and 113.62 ºC corresponding to the melting point of SSG and Carvedilol. Further DSC thermogram of co-processed excipient no significant difference in the endothermic peaks of both the excipient. So, it can be concluded that both the excipients and drug compatible with each other.

Stability Study

The stability test was conducted at a temperature of 40°C ± 2°C & a relative humidity of 75%±5%. A month was spent on an *in vitro* drug release trial. During the experiential period,

there was no significant difference in the dissolution profile of fast dissolving tablets. It depicts the fast-dissolving table's dissolution profile prior to and after the stability test. Other test parameters such as DT, WT, TS, and friability outcome were conducted after the stability analysis was completed.

Conclusion

It was shown that the QbD approach can be successfully employed in the advancement of directly compressible excipient of Carvedilol. Multivariate approaches such as experimental design, PCA, reaction surface simulation, and optimization have been shown to be effective in identifying the cause or source of variability. Co-processing was suggested as a possible solution for the production of directly compressible adjuvants. The proposed melt agglomeration method can be accepted in pharmaceutical industries because it is cost effective compared to the other newer techniques like spray drying which includes high capital investments with low percentage yield. Thus, melt agglomeration is a potential alternative to make directly compressible excipient that is effective to increase flowability and compressibility of low compressible drugs like Carvedilol.

Conflict of interest

All authors declare that they have no conflict of interest.

Statement of Human and Animal Rights

This article does not contain any studies with human and animal subjects performed by any of the authors.

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Table 1: Formulation table of wet granulation technique

Batch			Methods			Directly compressible excipient	Directly compressible excipient (gm)	Disintegrant	Disintegrant (gm)
B_1	B_{13}	B_{25}	WG	MA	SE	MCC	4.35	CCS	0.15
B_2	B_{14}	B_{26}	WG	MA	SE			CP	0.15
B_3	B_{15}	B_{27}	WG	MA	SE			SSG	0.20
B_4	B_{16}	B_{28}	WG	MA	SE	LM	4.35	CCS	0.15
B_5	B_{17}	B_{29}	WG	MA	SE			CP	0.15
B_6	**B_{18}**	B_{30}	WG	MA	SE			SSG	0.20
B_7	B_{19}	B_{31}	WG	MA	SE	DCP	4.35	CCS	0.15
B_8	B_{20}	B_{32}	WG	MA	SE			CP	0.15
B_9	B_{21}	B_{33}	WG	MA	SE			SSG	0.20
B_{10}	B_{22}	B_{34}	WG	MA	SE	MANNITOL	4.35	CCS	0.15
B_{11}	B_{23}	**B_{35}**	WG	MA	SE			CP	0.15
B_{12}	B_{24}	B_{36}	WG	MA	SE			SSG	0.20
WG: Wet granulation; MA: Melt agglomeration; SE: Solvent evaporation									

Table 2: (a) Factor and level of the Circumscribed Central Composite Design & (b) Experimental plan in central composite design

(a) Factor and level of the Circumscribed Central Composite Design

Variable	**Actual level**				
	-α	-1	0	1	A
X_1= concentration of binder	2	3.91	8.5	13.09	15
X_2 = concentration of disintegrate	2	3.18	6	8.82	10

(b) Experimental plan in central composite design

Batch Code	**Variable levels in Coded form**		**Actual value of variable**	
	X_1	X_2	X_1	X_2
F1	-1	-1	3.91	3.18
F2	1	-1	3.91	8.82
F3	-1	1	13.09	3.18
F4	1	1	13.09	8.82
F5	-α (-1.414)	0	2	6
F6	α (1.414)	0	15	6
F7	0	-α(-1.414)	8.5	2
F8	0	α(1.414)	8.5	10
F9	0	0	8.5	6

Table 3: Micromeritic properties of Carvedilol and excipients

Excipients	Angle of Repose*	Carr's Index (%)*	Hausner's Ratio*	Bulk density (gm/mL)	Tapped density (gm/mL)	Melting point (ºC)
Carvedilol	47.84±0.63	34.90±1.78	1.44±0.06	0.36±0.005	0.55±0.015	115
MCC	40.46±1.014	17.14±1.07	1.2±0.01	NOT APPLICABLE TO EXCIPIENTS		
LM	43.52±0.60	17.81±3.64	1.19±0.02			
DCP	39.68±0.68	35.88±2.33	1.55±0.06			
MANNITOL	44.89±0.72	27.76±1.13	1.38±0.02			
SSG	41.34±1.48	28.53±2.04	1.4±0.04			
CCS	38.98±1.23	29.45±2.31	1.41±0.04			
CP	41.77±0.66	31.01±2.20	1.44±0.050			
MCC-Microcrystalline Cellulose, LM-Lactose Monohydrate, DCP-DiCalcium Phosphate, CCS-CrosCarmellose Sodium, CP – Cross Povidone, SSG- Sodium Starch Glycolate.						
*All data are shown in mean (n=3)						

Table 4: Result of preliminary study for agglomerates prepared by different techniques

Batch			Co-processed excipients	Angle of repose (°)*			Carr's index (%)*			Hausner's ratio*		
WG	**MA**	**SE**		**WG**	**MA**	**SE**	**WG**	**MA**	**SE**	**WG**	**MA**	**SE**
B_1	B_{13}	B_{25}	MCC + CCS	27.32 ±0.25	26.55± 0.91	25.94± 0.26	24.66± 1.67	16.77± 1.07	22.36± 0.94	1.32± 0.02	1.17±0 .11	1.28±0 .01
B_2	B_{14}	B_{26}	**MCC + CP**	**23.9±0 .27**	24.22± 0.48	27.91± 0.89	**20.69± 2.70**	15.26± 0.92	22.50± 0.87	**1.26± 0.04**	1.10±0 .07	1.28±0 .01
B_3	B_{15}	B_{27}	MCC + SSG	26.25± 0.53	28.063 ±0.51	26.56± 0.46	25.80± 1.51	15.74± 1.00	22.06± 1.09	1.34± 0.02	1.18±0 .01	1.27±0 .01
B_4	B_{16}	B_{28}	LM + CCS	25.17± 0.47	28.94± 0.50	27.61± 0.68	29.81± 1.78	14.01± 0.79	24.68± 0.63	1.42± 0.03	1.15±0 .01	1.32±0 .01
B_5	B_{17}	B_{29}	LM + CP	30.39± 0.65	22.29± 0.49	29.24± 0.43	21.46± 1.91	13.14± 3.56	29.83± 1.38	1.27± 0.02	1.14±0 .05	1.42±0 .02
B_6	**B_{18}**	B_{30}	LM + SSG	27.78± 0.68	**22.12± 0.28**	27.47± 0.45	20.87± 1.70	**9.66±0 .67**	24.77± 0.99	1.26± 0.03	**1.06±0 .011**	1.37±0 .06
B_7	B_{19}	B_{31}	DCP + CCS	29.67± 0.43	34.85± 0.59	30.11± 0.43	26.02± 2.20	30.48± 3.04	30.77± 1.26	1.31± 0.03	1.48±0 .01	1.44±0 .02
B_8	B_{20}	B_{32}	DCP + CP	32.60± 0.81	29.82± 0.24	32.20± 0.41	31.64± 2.58	37.71± 1.02	31.31± 1.65	1.46± 0.05	1.6±0. 03	1.45±0 .03
B_9	B_{21}	B_{33}	DCP + SSG	34.59± 0.66	28.92± 2.09	31.09± 0.63	31.38± 2.65	32.63± 0.94	27.55± 1.16	1.45± 0.05	1.43±0 .06	1.37±. 0.02
B_{10}	B_{22}	B_{34}	MANNITOL + CCS	26.25± 0.70	25.49± 0.71	25.94± 0.53	29.44± 1.52	15.51± 0.70	28.64± 0.84	1.41± 0.03	1.12±0 .005	1.39±0 .01
B_{11}	B_{23}	**B_{35}**	MANNITOL + CP	29.53± 0.66	26.1±0. 79	**24.85± 0.27**	32.36± 4.13	16.13± 1.42	**21.48± 1.33**	1.41± 0.08	1.16±0 .02	**1.27±0 .02**
B_{12}	B_{24}	B_{36}	MANNITOL + SSG	24.7±0 .00	23.58± 0.27	25.79± 0.70	21.7±2 .26	18.09± 1.65	28.22± 0.61	1.27± 0.03	1.17±0 .02	1.38±0 .01

WG: Wet granulation; MA: Melt agglomeration; SE: Solvent evaporation; MCC-Microcrystalline Cellulose, LM-Lactose Monohydrate, DCP-Di Calcium Phosphate, CCS-CrosCarmellose Sodium, CP – Cross Povidone, SSG-Sodium Starch Glycolate.

*All result are shown in mean (n=3)

Table 5: Evaluation of Parameters for Co-processed Excipient

Batch code	X1	X2	% fines	AOR*	CI*	HR*
F1	3.91	3.18	24.86	23.26±0.48	16.56±0.30	1.19±0.00
F2	3.91	8.82	17.96	20.46±0.76	20.53±4.08	1.25±0.06
F3	13.09	3.18	9.63	19.11±0.78	16.92±2.66	1.16±0.02
F4	13.09	8.82	9.584	18.94±0.30	6.81±0.13	1.07±0.00
F5	2	6	10.05	20.96±1.14	16.58±0.29	1.19±0.00
F6	15	6	10.78	20.46±1.26	13.14±0.42	1.14±0.00
F7	8.5	2	10.73	21.46±0.28	12.12±2.26	1.13±0.02
F8	8.5	10	13.49	19.96±0.29	13.5±1.77	1.15±0.02
F9	8.5	6	18.26	20.12±1.54	15.01±1.64	1.17±0.01

*All result are shown in mean (n=3)

Table 6: Calculation of testing the model in portions

	DF	SS	MS	R2	F
CI					
Regression					
FM	5	114.9705	22.9941	0.9079	DF = (4,4)
RM	1	102.4414	102.4414	-	
Error					F_{CAL}= 5.9176740
FM	3	11.657	3.8856	0.8089	
RM	7	24.1861	3.4551	-	F_{TAB} = 6.388
WT					
Regression					
FM	5	1922.4733	384.4946	0.97114	DF = (3,3)
RM	2	1757.2231	878.6115	-	
Error					F_{CAL}= 20.196012
FM	3	57.1144	19.03814	0.88767	
RM	6	222.3647	37.06078	-	F_{TAB} = 9.276
DT					
Regression					
FM	5	10322.7733	2064.5546	0.98307	DF = (3,3)
RM	2	6846.3762	3423.1881	-	
Error					F_{CAL}=5.620885
FM	3	177.6764	59.2254885	0.65200	
RM	6	3654.0735	609.01226	-	F_{TAB} = 9.276
Friability					
Regression					
FM	5	0.47316	0.09463	0.9774	DF = (2,2)
RM	3	0.46698	0.15566	-	
Error					F_{CAL}= 45.5527
FM	3	0.01090	0.003635	0.96470	
RM	5	0.01708	0.003417	-	F_{TAB} = 19.00

DF-Degree of Freedom, SS-Sum of Squares, MS-Means of Squares, R-Regression Coefficients, FM-Full Model, RM-Reduced Model, CI-Carr's index, WT- Wetting Time, DT-Disintegration Time.

Table 7: (a) Composition & (b) results of optimized batch

(a) Composition of optimized batch				
Batch code	Variables levels in Coded form		Actual value of the variable	
	PEG 4000 (%W/W) (X1)	SSG (X2)	PEG 4000 (%W/W) (X1)	SSG (X2)
Optimized batch	0.50	0.78	10.79	7.52

(b) Result of optimized batch			
Responses	Predicted value	Experimental Value*	Relative error (%)
CI	11.47	11.22±0.06	2.17
WT	30.63	32.54±1.03	6.23
DT	65.94	64.29±0.54	2.50
Friability	0.64	0.63±0.26	1.56

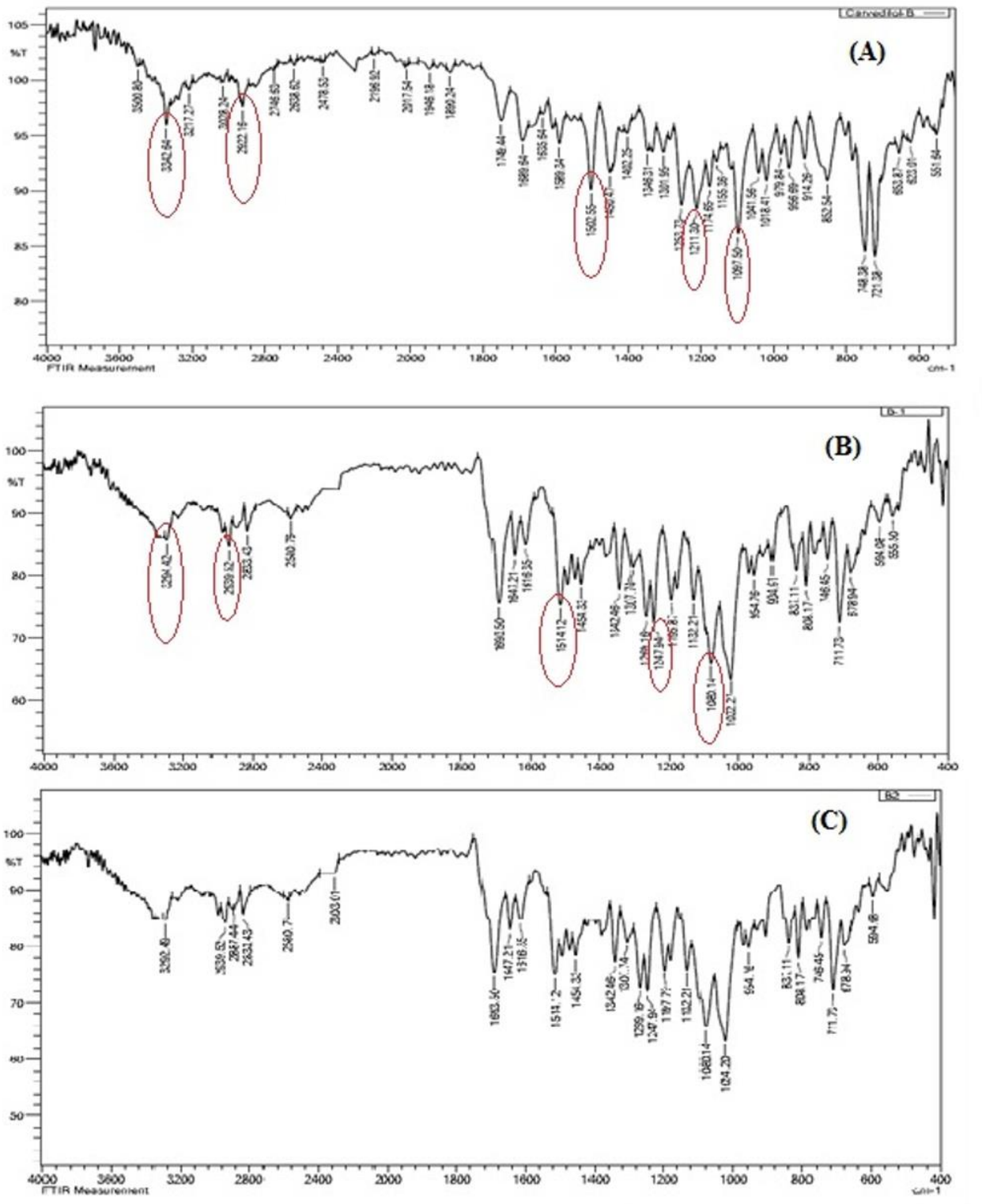
*All result are shown in mean (n=3)

Table 8: (a) Packability parameter of co-processed excipients and physical mixture, **(b)** Effect of magnesium stearate on co-process excipients & **(c)** Result of dilution potential

(a) Packability parameter of co-processed excipients and physical mixture			
Batch	**Kawakita's Constant**		**Kuno's Constant**
	A	B	K
LMH	0.507	0.998	0.01
SSG	0.704225	1	0.013
Physical mixture	0.299	0.99866	0.011
Optimizes batch	0.22	0.968	0.014

(b) Effect of magnesium stearate on co-process excipients			
Parameters	**B1**	**B2**	**B3**
Co-processed excipients of agglomerates (%)	100	99	99
Magnesium stearate	-	1	1
Mixing time		1	30
Tensile strength	1.16±0.05	1.13±0.5	1.06±0.42
Lubricant sensitivity ratio	-	0.025	0.086

(c) Result of dilution potential			
Parameters	**B1**	**B2**	**B3**
Co-processed excipients of agglomerates (%)	100	99	99
Magnesium stearate	-	1	1
Mixing time		1	30
Tensile strength	1.16±0.05	1.13±0.5	1.06±0.42
Lubricant sensitivity ratio	-	0.025	0.086



FTIR spectra of (A): Carvedilol (B) Co-processed excipients (C) Optimized batch

Figure 1(a): FTIR spectra of Drug

Figure 1(b): FTIR spectra of co-processed excipients

Figure 1(c): FTIR spectra of Optimized batch

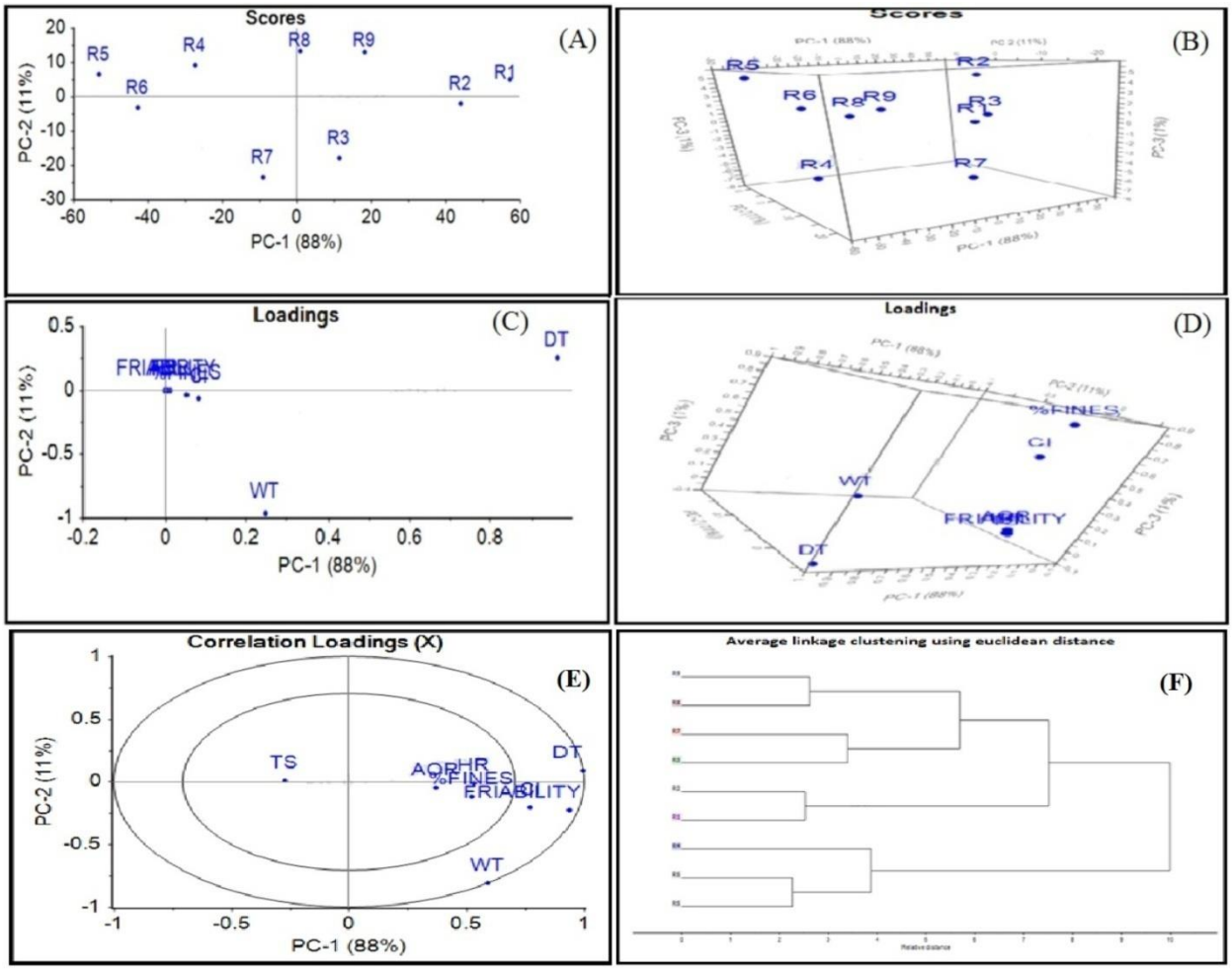
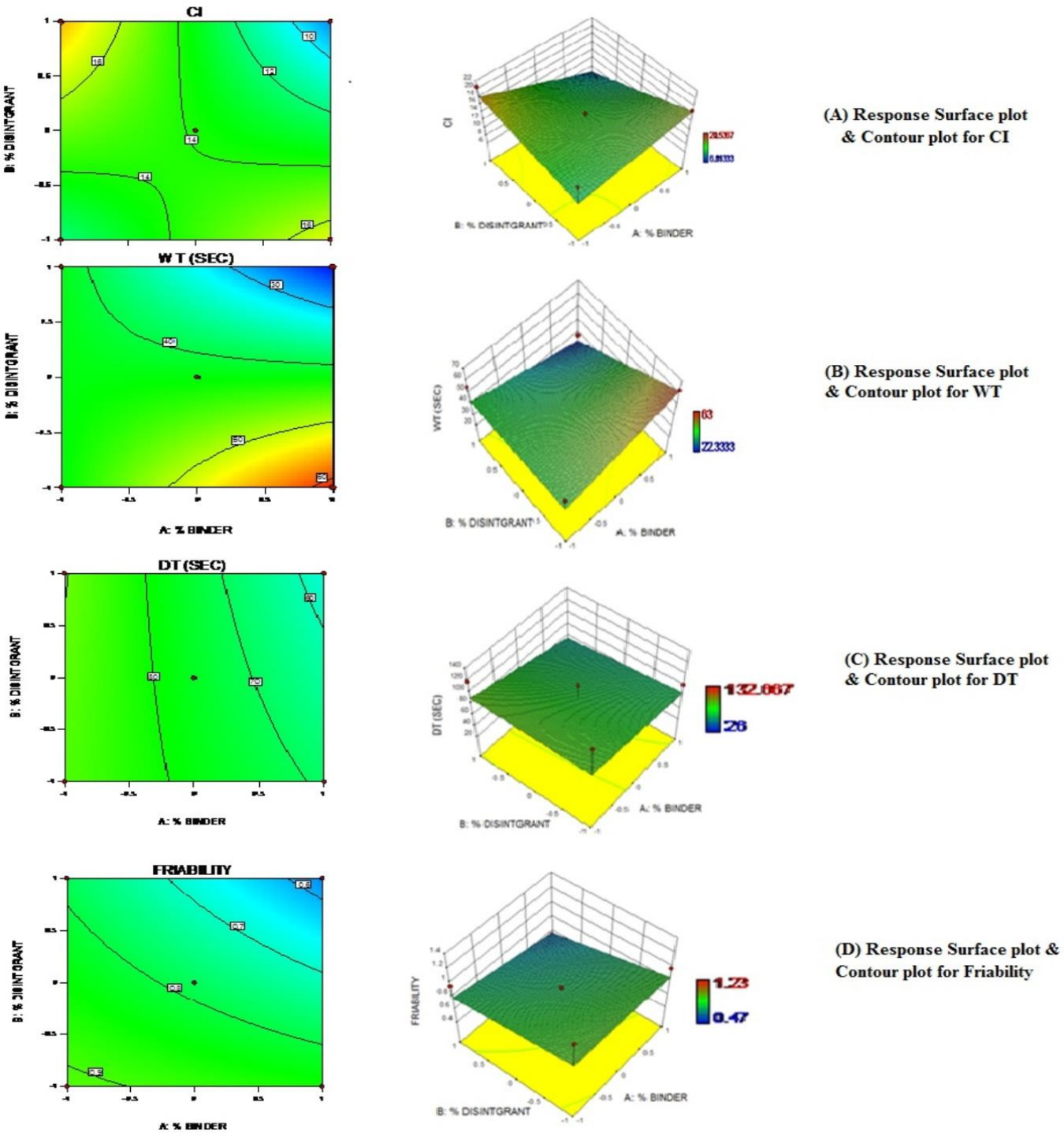


Figure 2a: Score plot from PCA of Co-processed excipients batches
Figure 2b: 3D score plot
Figure 2c: Loading plot from PCA of Co-processed excipients batches
Figure 2d: 3D loading plot
Figure 2e: Correlation loading plot obtained by PCA of Co-processed excipients properties
Figure 2f: Dendrogram from AHCA of Co-processed excipients batches



(A) Response Surface plot & Contour plot for CI

(B) Response Surface plot & Contour plot for WT

(C) Response Surface plot & Contour plot for DT

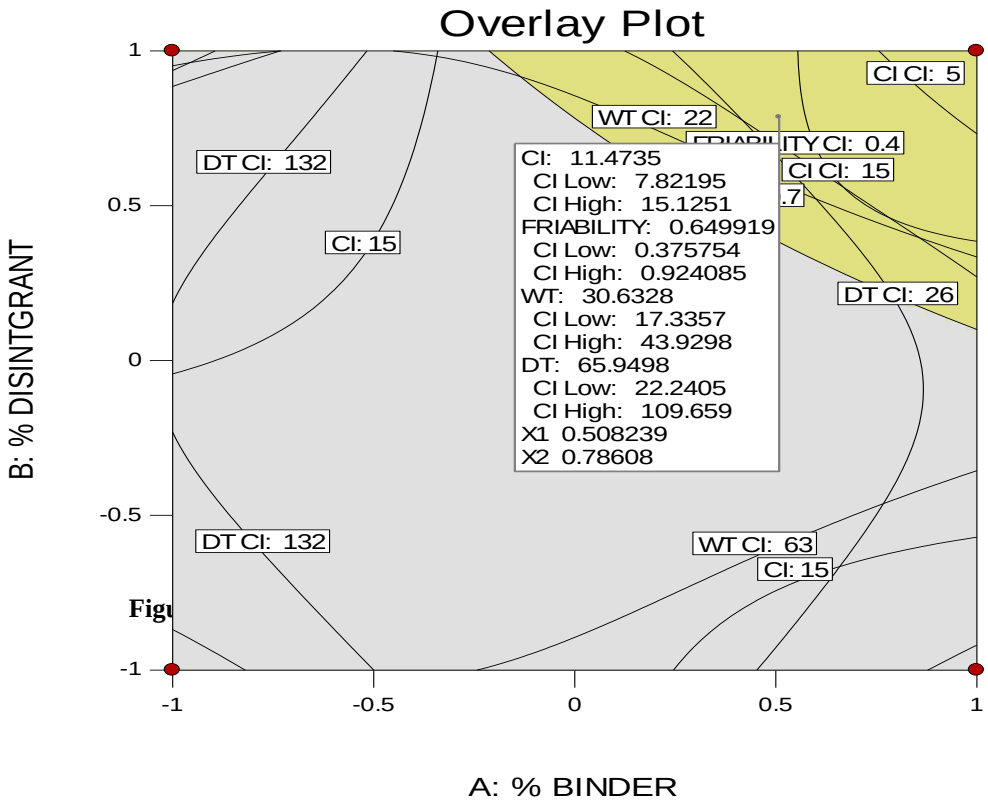
(D) Response Surface plot & Contour plot for Friability

Figure 3 (a): Response surface plot & contour plot of CI,

3 (b): Response surface plot & contour plot of WT

3 (c): Response surface plot & contour plot of DT

3 (d): Response surface plot & contour plot of friability


Overlay Plot
CI Cl: 5
WT Cl: 22
ITY Cl: 0.4
CI Cl: 15
.7
DT Cl: 132
CI: 15
DT Cl: 26
DT Cl: 132
WT Cl: 63
CI: 15
CI: 11.4735
CI Low: 7.82195
CI High: 15.1251
FRIABILITY: 0.649919
CI Low: 0.375754
CI High: 0.924085
WT: 30.6328
CI Low: 17.3357
CI High: 43.9298
DT: 65.9498
CI Low: 22.2405
CI High: 109.659
X1 0.508239
X2 0.78608
B: % DISINTGRANT
A: % BINDER
1
0.5
0
-0.5
-1
-1
-0.5
0
0.5
1

Figu

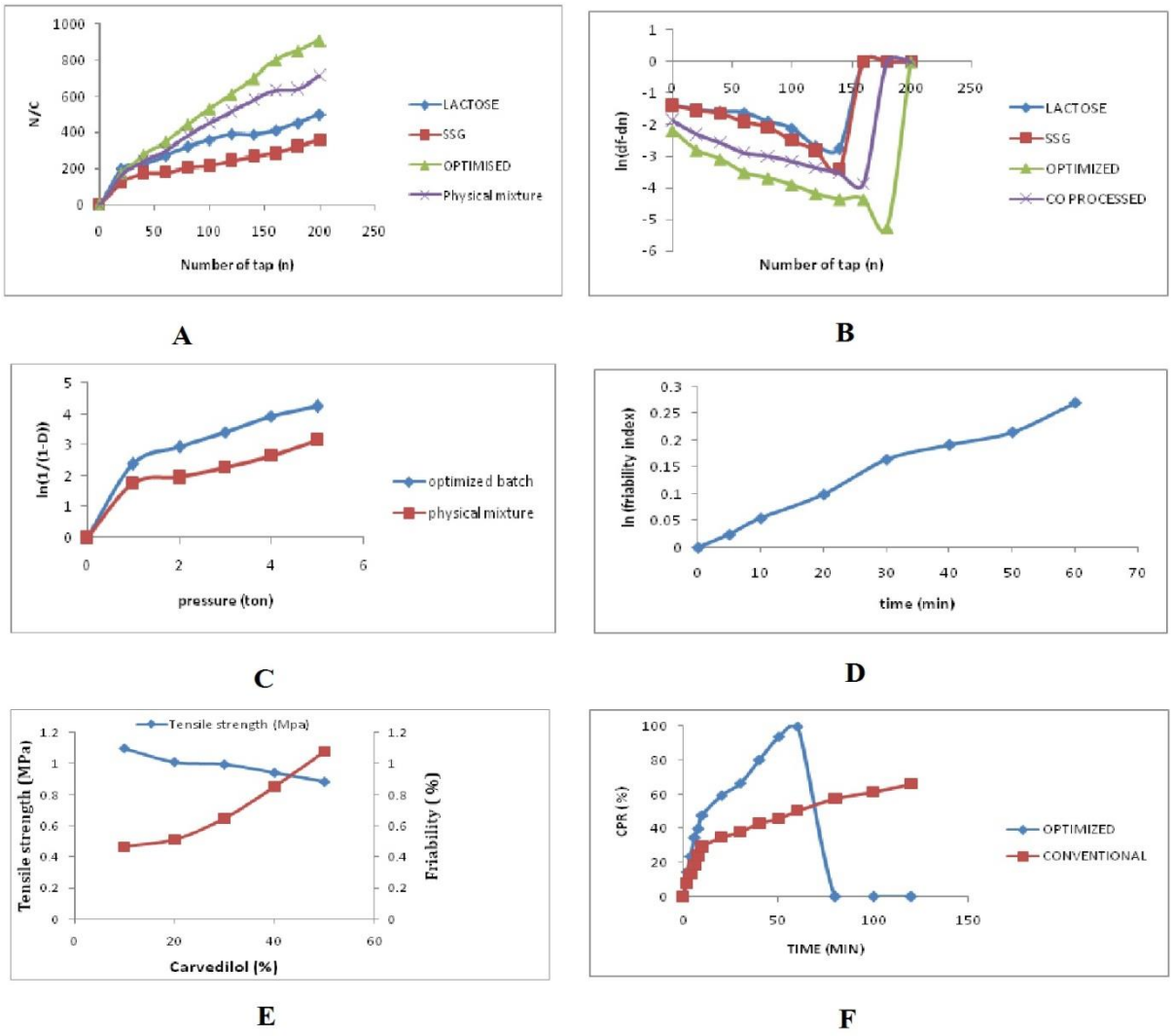
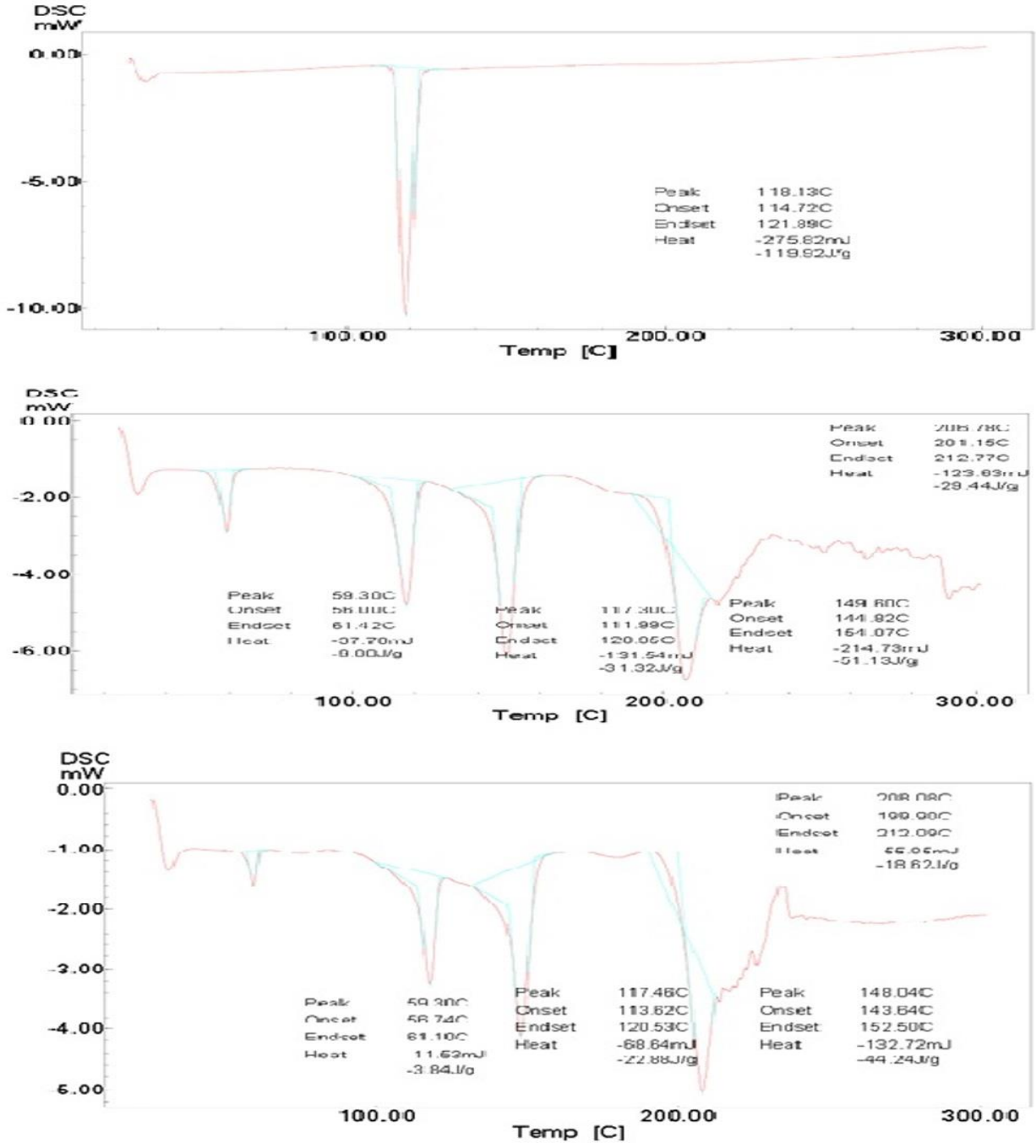


Figure 5 (A): Kawakita plot for optimized batch and physical mixture
Figure 5 (B): Kuno plot for optimized co-processed excipient and its physical mixture
Figure 5 (C): Heckle plot for optimized co-processed excipient and its physical mixture
Figure 5 (D): Effect of time on Granular Friability index
Figure 5 (E): Effect of Carvedilol in tensile strength and friability
Figure 5 (F): Comparison of FDT of optimized batch and physical mixture



DSC Thermogram of (A) Pure drug (B) Physical mixture of excipients (C) Coprocessed excipient

Figure 6 (a): DSC Thermogram of pure drug

Figure 6 (b): DSC Thermogram ofPhysical mixture of excipients

Figure 6 (c): DSC Thermogramof co-processed excipient