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

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ABSTRACT:

Purpose: Direct compression is a mostly used and required process in the pharmaceutical industry. The coprocessing is the most widely explored method for the preparation of directly compressible excipients. The present research work was targeted to develop a 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. Coprocessed excipient was optimized by a central composite design where the concentration of binder (X1) and concentration of disintegrant (X2) was selected as independent variables from the preliminary studies. Carr's index, wetting time, disintegration time, and Friability were selected 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 by 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. An in-vitro dissolution study showed faster disintegration of the drug compared to the conventional tablets. Instrumental studies like FT-IR and DSC proved the compatibility of various materials with each other. **Conclusion:** The present investigation underlines the fact that co-processing may be adopted for the development of directly compressible adjuvant for the use in pharmaceuticals.

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

INTRODUCTION:

In present years scientists have established that single-component excipients do not always provide the necessary performance to tolerate certain active pharmaceutical ingredients to be formulated or manufactured acceptably. Hence, there is a requirement to have excipients with multiple characteristics build into them such as enhanced flow, low/no moisture sensitivity, superior compressibility and quick disintegration ability.

METHODOLOGY :

Analytical method

- Preparation of Standard Stock Solution of Carvedilol
- Calibration Curve of Carvedilol

Preformulation studies

- Identification of drug
- Determination of melting point of Carvedilol

EVALUATION PARAMETERS:

Co-processed Excipients

- Angle of repose
- Carr's Index
- Hausner's Ratio

Characterization of Optimized Co-processed Excipient

- Kawakita Analysis
- Kuno Analysis
- Heckel Plot Analysis
- Granular Friability Index
- Effect of Lubricant
- Dilution Potential Study

Fast disintegrating tablets

- Weight uniformity
- Hardness & Thickness
- Friability & Tensile strength
- In vitro disintegration time
- Wetting time
- In vitro dissolution study
- Drug content

PRELIMINARY STUDIES:

❖ **Selection of a method for preparation of co-processed excipient**

- Wet granulation, Melt agglomeration, Solvent evaporation

❖ **Selection of binder and optimization of binder in co-processed excipient**

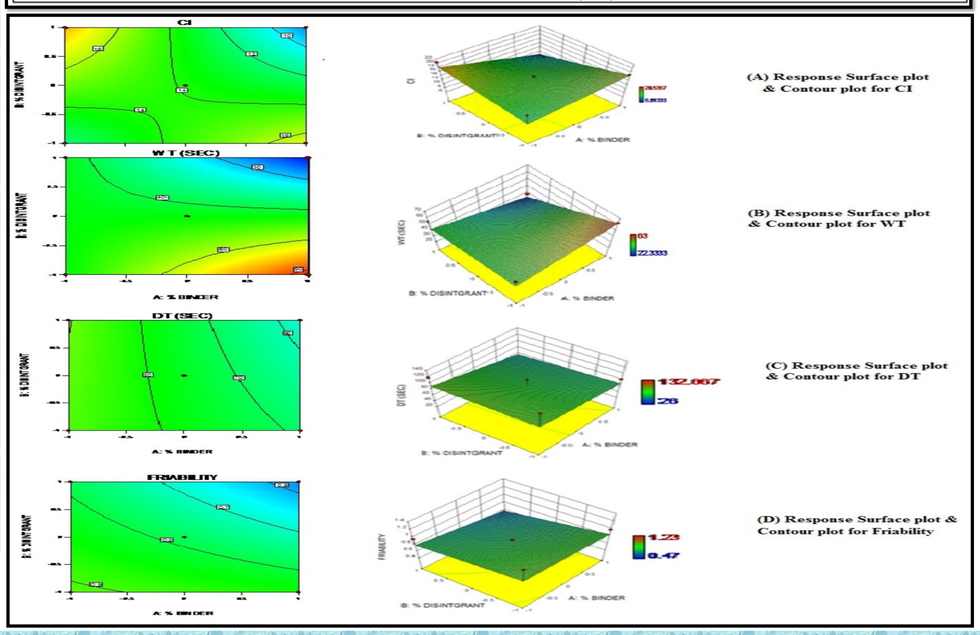
❖ **Optimization of disintegrant in co-processed excipient**

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

Excipients	Angle of Repose*	Carr's Index (%)*	Hausner's Ratio*	Bulk density (gm/mL)	Tapped density (gm/mL)	Melting point (°C)
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)



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

- Quality Target Product Profile of Co-processed excipients
- Risk analysis;Risk identification by Ishikawa diagram

❖Y is the dependent variables, $\mathbf{b_0}$ is arithmetic mean response of the nine runs, $\mathbf{b_1}$is the estimated coefficient for the factor X_1. The main effects ($X_1$and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. Experimental Design;The data were subjected to 3-D response surface plot in Design-Expert®9.0.2.0 (a software developed by Stat-Ease)

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

(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

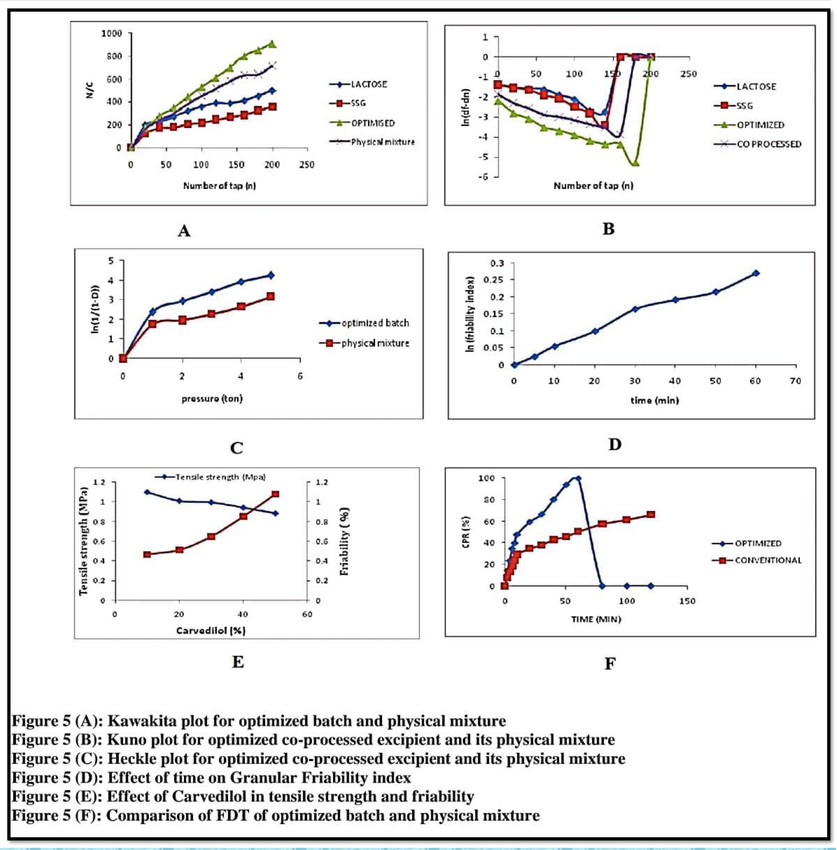


Figure 5 (A): Kawakita plot for optimized batch and physical mixture
Figure 5 (B): Kuno plot for optimized co-processed excipient and its physical mixture
Figure 5 (C): Heckle plot for optimized co-processed excipient and its physical mixture
Figure 5 (D): Effect of time on Granular Friability index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

CONCLUSION:

It was demonstrated that multivariate techniques such as Experimental design, PCA, response surface modeling and optimization can be successfully used to characterize the cause or source of variability. Briefly, it was inferred that co-processing is the potential alternative for the development of directly compressible adjuvants. Thus, melt agglomeration is a potential alternative to make directly compressible excipient that is effective to increase the flowability and compressibility of low compressible drugs like Carvedilol. The optimized co-processed excipient was characterized by 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. An in-vitro dissolution study showed faster disintegration of the drug compared to the conventional tablets.

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