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Original Article

Optimized Formulation of Carvedilol Fast-Dissolving Tablets Using Modified Super disintegrants: Breaking Solubility Barriers of BCS Class II Drugs

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ABSTRACT

Background: The BCS Class-II faces major challenge, low solubility and poor bioavailability issues. Carvedilol, an anti-hypertensive drugs, has a bioavailability 20-25%. **Objectives:** This research focuses on the development of fast dissolving tablets for Carvedilol (CARV), utilizing sorghum starch modified with humic acid as a novel superdisintegrant through factorial design to achieve rapid drug dissolution, bioavailability and patient compliance. **Materials and Methods:** Sorghum starch was isolated through a modified alkaline treating method from sorghum flour then it was modified with humic acid to form starch humate. Various tests such as gelatinization, viscosity, pH and flowability were performed. Quality by design was applied to identify the most important characteristics (response variables) such as disintegration time, dissolution efficiency and cumulative percent drug dissolved at the end of 10 min. The independent variables are starch humate, sodium starch glycolate and crospovidone. The direct compression approach was used to develop carvedilol fast dissolving tablets with a 2^3-factorial design. The formulations were assessed for flow characteristics, drug compatibility using FTIR, DSC and XRD, morphology using a scanning electron microscope, amount of drug, *in vitro* and *in vivo* drug release profiles and stability. **Results:** The modified starch-starch humate has a higher viscosity, pH value, and better flowability than sorghum starch. FTIR and DSC investigations revealed no interaction with the drug and the superdisintegrants. Optimized CARV-FDTs with 5% starch humate demonstrated adequate friability (0.59±0.68%), disintegration time (28±0.02 sec), % PD10 (98.40±0.64%), wetting time (22±0.36 sec), water absorption ratio (68±1.41) and DE (70.9±0.34). They also demonstrated satisfactory stability under accelerated conditions along with improved relative bioavailability, reaching the highest plasma concentration in a short time. **Conclusion:** This study discovered that modified starch humate can potentially be extracted and developed into fast dissolving tablets by QbD in the management of hypertension exhibiting enhanced relative bioavailability and patient acceptance.

Keywords: Bioavailability, Fast Dissolving Tablets, Sorghum starch, Starch humate, Superdisintegrant.

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INTRODUCTION

The oral route of administration is the most widely preferred method for both systemic and local drug delivery and it remains a standard approach in the area of pharmaceutics. This method is recognized for its safety, convenience, patient acceptance and cost-effectiveness, making it the optimal choice for ensuring patient compliance. However, oral drug delivery systems (ODDS) encounter significant challenges due to the harsh physiological and physicochemical conditions present in the Gastrointestinal (GI) tract. These challenges can limit drug bioavailability and complicate targeted delivery.[1-3]

For oral administration, tablets and capsules are commonly prepared to achieve systemic effects, as most patients find them easy to handle. In emergency situations, however, injectable forms are preferred for their rapid onset of action. Other dosage forms, such as patches, gels and suppositories, can be utilized based on the patient's specific condition.[4] Despite their widespread use, tablets and capsules share a significant drawback: many patients experience difficulty swallowing them, which can lead to poor acceptance, particularly among children. To enhance patient compliance and simplify the administration process, there is a growing emphasis on the development of novel dosage forms.

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Fast-Dissolving Tablets (FDTs) are initiated as a swap in oral DDS; the World Health Organization (WHO) has appraised flexible solid oral dosage forms, including fast-dissolving tablets, as the most reasonable and appropriate pediatric-specific dosage form, one developed to disintegrate in the mouth without any water, disintegrant or disperse when it contacts with saliva[5] with good agreeable mouth feeling, the active moiety release quickly within 5-30 sec, gives maximum bioavailability when compared with conventional Oral drug delivery systems are particularly useful in situations where water is unavailable or prohibited, such as before surgery.[6,7]

Hypertension is a major concern not only in the elderly but also in younger patients.[8] According to the Biopharmaceutical Classification System (BCS), Class II drugs do not face issues with membrane permeation. The main challenge for these drugs is their low aqueous solubility, which limits their entry into the circulatory system due to a slow dissolution rate.

Carvedilol is a one of the antihypertensive drugs under cardiovascular classification. Carvedilol is a non-selective blocker of both α- and β-adrenergic receptors, used clinically to treat cardiovascular conditions such as hypertension, ischemic heart disease and congestive heart failure. It works by reducing peripheral vascular resistance through vasodilation, which helps prevent tachycardia.[9] CARV faces challenges in oral bioavailability, with only 25% due to its slow rate of absorption.

The therapeutic action and quick onset of action are essential to increase the drug release and bioavailability of CARV. Presently, 3.125 mg, 6.25 mg, 12.5 mg and 25 mg standard doses are available.

The primary objective of this research is to design, optimize and evaluate fast dissolving tablets of Carvedilol (CARV) utilizing a newly modified starch humate, along with crospovidone and sodium starch glycolate. This study employs a 2^3 factorial design to systematically assess the effects of these components. The modified starch humate, derived from sorghum starch treated with weak acid humic acid, is specifically examined for its effective application as a superdisintegrant. The research aims to quantify how these ingredients influence the dissolution rate of carvedilol, ultimately enhancing its bioavailability and addressing challenges related to ineffective therapeutic and pharmacological responses.

MATERIALS AND METHODS

Materials

Carvedilol was obtained from Yarrow Chem Products, Mumbai. Starch Humate and sorghum starch were synthesized in the GIET School of Pharmacy Research Lab. Crospovidone and Microcrystalline cellulose, Sodium starch glycolate and Mannitol were acquired from Yarrow Chem Products, Mumbai and Loba Chemie Pvt. Ltd., respectively. Talc and Magnesium stearate were sourced from Loba Chemie Pvt. Ltd., and Burgoyne Urbidges and Co., respectively.

Methods

Extraction of sorghum starch

Initially, sorghum millet is collected from local market Rajahmundry and unwanted materials and debris are removed; the isolation of starch from millets is performed using the wet milling method, steeped in water because removing kernel requires 2-4 days. In millet, starch granules are tightly bound to the matrix; therefore, chemical solutions are used during the steeping method to increase starch yield and purity. Alkaline and acid solutions increase steeping efficiency, but the alkali method leads to the easy removal of the protein layer from the tight matrix of millet; hence, it is considered the best method for starch extraction. 0.25% W/V sodium hydroxide used softened grains allowed 18-24 hr, removed supernatant layer, followed by several filtration using conventional methods like muslin cloth and continuous centrifugation (REMI P24, Mumbai) at 5000-7000 rpm at 10 min to remove protein. The above procedure is repeated several times to increase starch yield. The final residue of starch is subjected to drying in a hot air oven, at 40°C for 24 hr. The yield percentage, chemical composition and other properties of isolated starch highly depend on the method adopted for isolation.[10,11]

Preparation of Starch Humate (SH)

Ten parts of starch dissolved in 25 parts of distilled water, in another beaker ten parts of humic acid dissolved in 10 mL of distilled water. Transfer the humic acid content to a beaker containing starch and give a mix, using magnetic stirrer stir the mixture for 1 hr. The starch-humic acid dispersion was adjusted to a pH of 5-6 by using 0.1N Sodium hydroxide, allowed by conditioning for 16 hr at room temperature. Separate the supernatant liquid from the collected suspension to eliminate unreacted humic acid. The prepared solid mass was washed with distilled water and transferred as a suspension to a stainless-steel tray at 60°C. The resulting solid mass was dried and sieved via a #120 sieve and the dried product was further passed and stored in desiccators and evaluated for the following.

Iodine Test

The starch solution was treated with iodine solution, resulting in a blue-violet color, which indicated the presence of starch.

pH

5 g of SH were combined with 25 mL of CO_2-free distilled water and mixed for 1 min, then allowed to stand for few minutes. The pH value was then measured using a pH meter.

Moisture content

3 g of SH powder were placed in the analyzer to test moisture content (Wensar PGB-1MB) and allowed to stabilize for a short period. The measurement commenced and was concluded once the moisture content reading was obtained.

Measurement of loss on drying

1 g of starch was measured and placed into a pre-heated tared weighing bottle (heated at 105°C for 30 min) with its lid. The bottle was then transferred to an oven set at 105°C and dried until it reached a constant weight.

Measurement of ash content

The sample was heated to a temp. High enough to decompose and evaporate the organic compounds and their derivatives, leaving only mineral elements and inorganic residues. The resulting ash content should be less than 1%.

$$\% \text{ ASH} = ((\text{ashed wt.}) - (\text{crucible wt.})) \times 100 / ((\text{crucible and sample wt.}) - (\text{crucible wt.}))$$

Swelling index

A pre-weighed centrifuge tube was used to mix 1 g of SH with 20 mL of water and the mixture was heated in a shaking water bath at 50, 60, 70, 80 and 90°C for 30 min. After allowing it to cool to room temperature, the mixture was centrifuged at 3500 rpm for 15 min. Swelling power (SP, g/g) was determined by calculating the weight increase of the hydrated sample relative to the initial dry starch weight. The supernatant was then dried in a pre-weighed petri dish and the Solubility Index (SI) was calculated by dividing the mass of the dried supernatant by the initial weight of the dry starch.[12]

Formulation of FDTs of carvedilol by direct compression method

In the preparation, carvedilol 12.5 mg, superdisintegrants, diluents and excipients were taken in a glass mortar and smoothly mixed; at the end lubricant and glidant were added and blended. A Mini Press tablet compression (Shakti Pvt. Ltd.,) machine was used to compress the tablets by direct compression method with hardness around 3.5-5 kg/cm^2.

Fourier Transform Infrared Spectroscopy (FT-IR)

FTIR is an analytical spectral technique for identifying functional groups. Samples of CARV and SH in KBr pellets were analyzed spectra using a BRUKER FT-IR instrument under approximately 850 Pascals of hydrostatic pressure, scanning in the spectral limits 4000-500 cm^{-1}.[13]

Differential Scanning Calorimetry (DSC)

DSC (STA 7300 Hitachi, Japan) was used for thermal analysis of CARV alone and FDTs superdisintegrant SH (1 mg samples) using in DSC aluminum crucibles and seal the pan with a lid to prevent the loss of sample in a dynamic nitrogen atmosphere with a 10°C/min scanning rate and temperature range of 30-350°C.[14]

X-ray Diffraction (XRD)

X-ray diffractometry was utilized to analyze both the pure drug and its combination with starch humate at room temperature. The diffraction patterns were recorded for the samples within a 2θ range of 10° to 90°, with specific experimental parameters established for the analysis.[15]

Scanning Electron Microscopy (SEM)

SEM is the best technique for focusing the surface morphology with high resolution and magnification. 1-2 mg of starch humate was placed on the sample stub using double-sided carbon tape with an approximately 200 mm thickness to avoid agglomeration and achieve even distribution. The vacuum level in the SEM chamber was set and the acceleration voltage was adjusted. Scanning photos are recorded at different magnifications and resolutions to determine the surface morphology of starch humate.[16]

Characterization of CARV tablets

The prepared CARV tablets were tested for various post-compression parameters to evaluate their quality, quantity, efficacy and performance of tablets. The major evaluation conducted were.

Hardness

Hardness is a key characteristic that assesses a tablet's ability to resist mechanical stress and avoid breakage during handling and transportation. The firmness of the tablet was measure using a Monsanto hardness tester.[17]

Friability

Friability test was demonstrated using a friabilator tester and the amount of weight was evaluated. It is determining the tablets resistance power to abrasion and producing fines or fragments during handling, packaging and travelling.[18]

Wetting time and water absorption ratio

Wetting and water absorption ratio executed tablet hydrophilicity and helps to understand the internal structure, porosity nature leads to quicker absorbing moisture and starts disintegration when contact with liquid. It determines by tablets placing on a folded tissue paper in a small petri dish which containing amaranth red dye. Calculated time for wetting and water absorption ratio.

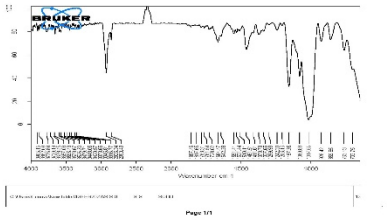

Figure 1a. FTIR of Sorghum starch

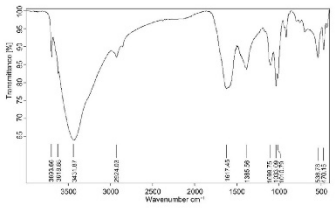

Figure 1b. FTIR of Humic acid

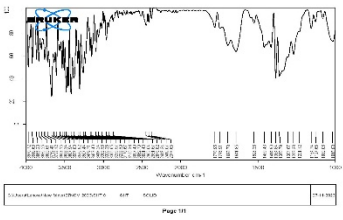

Figure 1c. FTIR of Strach humate

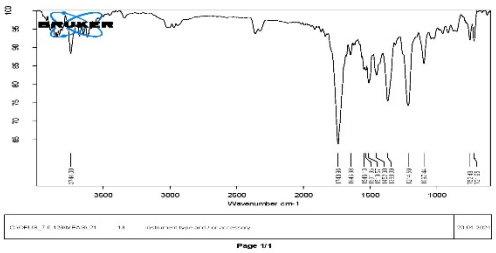

Figure 1d. FTIR of Carvedilol

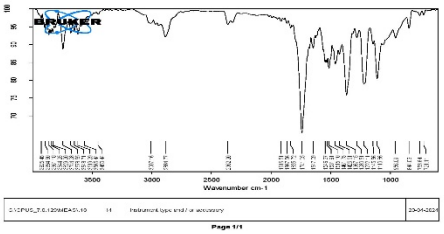

Figure 1e. FTIR of Carvedilol with SH

Figure 1: FTIR Spectrums of drug with excipients.

In vitro disintegration time

In vitro disintegration time was evaluated using a disintegration test apparatus, *in vitro* disintegration time is the facility to break up the tablet into fine particles when exposed to an appropriate environment, such as simulated buffer solutions.[19]

Drug content uniformity

The tablets were tested to assess the uniformity of their drug content each tablet contains equal amount of the drug. UV spectroscopy was used to quantify the CARV concentration.

In vitro dissolution studies

In vitro dissolution studies were carried using dissolution apparatus, to find out the rate of drug released from tablets the dissolution medium used was the 900 mL pH 6.8 buffer. At prearranged intervals, 5 mL of the sample was obtained, purified, analyzed with a T360 UV/Visible double-beam spectrophotometer at 242 nm.[20]

RESULTS

This research is focused on designing, optimizing and evaluating CARV fast-dissolving tablets with starch humate, crospovidone and sodium starch glycolate by the 2^3 factorial design approach. In this study, the newly modified superdisintegrant starch humate was extracted from sorghum millet and humic acid and was assessed for its potential as a superdisintegrant.

Physicochemical parameters like pH of SH was found to be 6.82±0.35, moisture content was found to be 10.72±2.34%, loss on drying and ash content were found to be 10.36±1.17% and 1.63±0.86% respectively, swelling index was found to be 86%.

The post-compression parameters relevant to the fast dissolving tablets of CARV are tabulated in Table 1. The concentration of CARV was determined with the help of a UV-visible spectrophotometer at 242 nm in pH 6.8 phosphate buffer.

The drug, CARV, with the remaining excipients, Starch humate, was compared using FTIR studies. The presence of aliphatic chains, commonly found in the polysaccharide backbone of starch, is indicated by the CH_2 stretch at 2925.34 cm^{-1}, 1461.51 cm^{-1}, C-O stretch vibrations at 1080.88 cm^{-1} and the C-O-C band at 1157.35 cm^{-1}, 1648.38 cm^{-1} these functional groups indicates the polysaccharide nature of starch. The presence of carbohydrate chains characteristic of starch molecules in sorghum millet starch was further confirmed by the CH_2 and C-O stretches shown in Figure 1a.

Humic acid exhibited broad signal at 3431 cm^{-1}, 1725 cm^{-1}, 1099 cm^{-1}, which can be attributed to hydrogen bonded OH group, C-O stretching of COOH, C-C double bond. A band was observed at 2924 cm^{-1} due to aliphatic C-H group, 1385 cm^{-1} because of O-H bending shown in Figure 1b. 1725 cm^{-1} band in humic acid and 1648.38 cm^{-1} band in sorghum starch were disappeared and a new peak at 1617.45 cm^{-1} was indicate the formation of ester (starch humate) depicts in Figure 1c.

The FTIR spectra obtained from both samples exhibited identical peak patterns, suggesting a lack of significant interactions between Carvedilol (CARV) and the accompanying excipients utilized in this study. The absence of notable alterations in the infrared peaks indicates that CARV maintained its molecular structure and integrity throughout the formulation process. Furthermore, the combination of CARV with the remaining superdisintegrants and excipients play a crucial role in ensuring the desired therapeutic

effects, thereby enhancing the formulation's suitability for potential pharmaceutical use, as illustrated in Figures 1d, e.

The DSC thermogram of CARV displayed a sharp endothermic peak at 118.12°C, while the DSC thermogram of CARV-SH showed a sharp endothermic peak at 118.51°C, corresponding to its melting point. This suggests that CARV-SH has similar in nature to the native crystalline form of CARV, depicts in Figures 2.

X-ray diffraction have helped to know the physical characteristics of SS and SH. XRD of SH indicated its typical amorphous SS has a fine-diffused and slightly crystalline nature SEM of the SS confirms fine and slightly crystalline in shape. SEM of the SH confirms the amorphous nature shown in Figure 3.

Design, Optimization and Assessment of CARV Tablets Using 2^3 Factorial Design with SH, SSG, CP

This study aimed to develop, optimize and evaluate CARV tablets utilizing novel modified superdisintegrants: Starch humate, Sodium starch glycolate and Crospovidone through a 2^3-factorial design. Total of 8 formulations were prepared, each containing 12.5mg of CARV and produced via direct compression as outlined in Table 1.

Before compression, the ingredient blend of each formulation was analyzed for its flow characters. The angle of repose, bulk and tapped density and Carr's index were calculated to assess these properties. The angle of repose (θ) is in the range from 22° to 24°. Carr's index (%) ranges 11% to 13%. For all the formulations, bulk and tapped density are also acceptable.

The study proceeded with in-process quality control evaluations of the prepared tablets, including hardness, friability and disintegration time. Finished quality control tests encompassed dissolution release rate and drug content analysis.

Tablet hardness was found to be 3.6±0.16 to 4.0±0.89 kg/cm^2, ensuring adequate mechanical strength for handling and transportation without breakage. Friability tests demonstrated good resistance to abrasion, with weight loss remaining below 1% for all selected formulations, indicating minimal production of excessive fines during handling.

The drug content analysis verified that the tablets contained the correct amount of the Active Pharmaceutical Ingredient (API), with the CARV content ranges from 97.04±1.51 to 99.36±.1.41.

The time of tablet disintegration ranged from 7±0.12 to 850±0.22 sec. This means all the tablets ensured a fast disintegration. Wetting time and water absorption ratio were found to be 487±0.12 to 32±0.14 and 72±1.22 to 32±1.32 respectively. All the post compression evaluation test results are given in Table 2.

The dissolution of the formulations was assessed using 6.8 pH phosphate buffer, evaluated through kinetic orders, dissolution efficiency and number of folds for each tablet.

In other words, it shows that the dissolution rate is always constantly proportional to the amount of the API remaining in the tablet. Figure 4 provides a comprehensive drug dissolution profile for various CARV tablet formulations and this can be portrayed visually in drug release behavior in function of time. This information identifies the need to understand the kinetic behavior of CARV tablets in the optimization of their therapeutical efficacy.

Dissolution efficiency, DE indicates a rate of drug dissolved, which is very important in achieving immediate action. It is assured of the drug availability that is related to bioavailability and therapeutic effect. Higher DE means faster drugs release from tablets ranged from 0.9% to 70.9%.

The fold increase in DE determines the number of folds of used superdisintegrants in the tablet formulation. The higher fold increase determines that the SH as superdisintegrants will effectively improve the dissolution rate of 21% to 53%. The no of folds increase in the DE of all formulations were given in Table 3.

A 2^3 factorial design was employed in formulating the CARV fast dissolving tablets to determine systematically the effects of three independent variables-Starch humate, Sodium Starch Glycolate and Crospovidone. In a 2^3 factorial design each factor was tested at two different levels. Subsequently, the effects of these variables

Table 1: Formulation of CARV fast dissolving tablets through 2^3 factorial designs.

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Carvedilol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
SH	-	5	-	5	-	5	-	5
SSG	-	-	5	5	-	-	5	5
CP	-	-	-	-	5	5	5	5
Microcrystalline cellulose	50	50	50	50	50	50	50	50
Mannitol	33.5	28.5	28.5	23.5	28.5	23.5	23.5	18.5
Magnesium stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2
Total	100	100	100	100	100	100	100	100

Table 2: Post compression Evaluation parameters of CARV fast dissolving tablets.

Formulation	Weight variation (mg)	Hardness Kg/cm	Friability (%)±S.D	Drug content uniformity (mg/tab)±S.D	Disintegration Time(s)±S.D	Wetting time (sec)±S.D	Water Absorption (%)±S.D
F1	99±0.23	3.8±0.21	0.67±0.25	99.36±0.1.41	850±0.22	487±0.12	32±1.32
F2	102±0.34	3.8±0.32	0.59±0.68	98.76±1.32	28±0.02	45±0.11	68±1.41
F3	101±0.21	3.7±0.41	0.65±0.52	97.42±1.65	21±0.41	471±0.11	59±1.51
F4	101±0.38	4.0±0.89	0.54±0.91	98.56±1.13	10±0.32	51±0.12	74±1.33
F5	101±0.33	3.6±0.16	0.65±0.73	97.28±1.41	15±0.32	53±0.21	69±1.51
F6	102±0.82	4.0±0.23	0.61±0.42	97.48±1.61	9±0.32	49±0.20	70±1.31
F7	99±0.31	4.0±0.69	0.58±0.83	98.63±1.16	9±0.52	48±0.12	71±1.81
F8	98±0.12	3.9±0.14	0.65±0.97	97.04±1.51	7±0.12	32±0.14	72±1.22

Table 3: No of folds increase in the DE of CARV fast dissolving tablets.

Formulation	DE	No. of folds increase in DE
F1	0.9	-
F2	70.9	78.77
F3	59.1	65.66
F4	66.7	74.11
F5	68.9	75.44
F6	69.9	77.66
F7	61.3	68.11
F8	65.4	72.66

on the dependent outcomes-Disintegration Time, Percentage of Drug Dissolution in 10 min and Dissolution Efficiency in 10 min-were very closely examined.

The final equations for the dependent variables were then determined, selecting based on parameter significance with the correct $p<0.05$ confidence interval. Polynomial equations then arose to represent the relationships between the independent variables-percent SH, SSG and CP-and the dependent variables: DT; PD10 and DE10.

In this research study, utilizing an ANOVA 2^3 factorial design and testing the generated data, mathematical models are being built that describe the impact of SH, SSG and CP contents percentages on significant CARV- FDT parameters-these are DT, PD10 and DE10. The main effects and interactions of the selected factors were being measured by ANOVA. We evaluated how each factor had statistical significance to determine how their variables were affected. A 2^3factorial design (three factors, two levels) was employed to investigate the interactions and primary influence of the factors, which are independent of dependent responses, as well as to statistically optimize the design parameters. DT (Y1), PD10 (Y2) and % DE10 (Y3) were measured at two distinct levels of SH (X1), SSG (X2) and CP (X3). The factors were selected and their corresponding levels were determined. Analysis of the experimental results was conducted using ANOVA, fitting the response variables within the framework of the factorial design. Design Expert software 12.0.3.0 (State-Ease Inc., Version 12.0.3.0, Minneapolis, USA) was utilized to construct polynomial equations.

For SH, SSG and CP, a coding system was adopted where -1 stood for 0% and +1 represented 5%. It helps to analyze and combine concentration effects for easier formulation.

$$Y=\beta0+\beta1\ X1+\beta2\ X2+\beta3\ X3+\beta1\ \beta2\ X1X2+\beta1\ \beta3\ X1X3+\beta2\ \beta3\ X2X3+\beta1\ \beta2\ \beta3\ X1X2X3$$

In this study, Y represents the dependent variables, while β0 denotes the arithmetic mean response across the formulations (F1-F8). The coefficient β1 corresponds to the predicted value associated with the interaction of the factors X1, X2 and X3. The primary effects of the factor combinations X1X2, X1X3 and X2X3 are reported, illustrating the changes observed when each factor is incrementally increased from a low to a high value. The response dynamics shift when all three factors are varied simultaneously, as indicated by the inclusion of the interaction term X1X2X3 in the equation. The dependent variables of interest-Disintegration Time (DT), Percentage of Drug Dissolution in 10 min (PD10) and Dissolution Efficiency in 10 min (DE10) are defined as follows:

$$Y1\ (DT)=+123.38-105.38\ X1-105.63\ X2-108.63X3+101.63X1X2+103.13\ X1X3+101.38\ X2X3-100.88\ X1X2X3$$

$$Y2\ (PD10)=+86.19+10.14\ X1+8.28\ X2+10.19\ X3-10.23\ X1X2-11.37\ X1X3-10.11\ X2X3+9.06\ X1X2X3$$

$$Y3\ (DE10\%)=+58.59+9.64\ X1+5.94\ X2+9.21X3-8.11\ X1X2-9.79\ X1X3-7.54\ X2X3+7.\ 46X1X2X3$$

Y1- Response of Disintegration Time (DT)

Y2-Response of Percentage Drug dissolved in 10 min (PD10)

Y3-Response of Dissolution Efficiency 10 min (DE10)

The positive coefficient for factor X1(Starch Humate) in the equation for Y1 (Disintegration Time, DT) indicates a direct relationship between the concentration of Starch Humate and the disintegration time of the tablets. Specifically, this suggests that an increase in the concentration of superdisintegrants decreases the disintegration time, thereby facilitating a more rapid disintegration of the tablets.

Furthermore, the experimental data indicate that all factors, including X1 (SH), X2 (SSG) and X3 (CP), significantly decrease the disintegration time of the tablets. The concentration of each of these superdisintegrants plays a crucial role in determining the duration required for drug release. Notably, higher concentrations of all superdisintegrants lead to a reduction in disintegration times. The study compared the *in vitro* drug release parameters obtained through experimental data with those calculated using polynomial equations. Response Surface Plots (RSP) were used to depict the effects of X1, X2 and X3 on percentage of drug dissolution in 10 min (PD10) and dissolution efficiency in 10 min (DE10). These plots explored the relationship between the all factors and the selected response variables, enabling the identification of the best formulations to achieve the better outcomes in drug release and dissolution efficiency.

According to the response surface and contour plots, an increased superdisintegrant amount may enhance PD_{10} and DE_{10}%.

The optimized formulations, thus, validated the derived equations of the dependent variables, namely, *In vitro* disintegration time, PD10 and DE10. This validation further confirms that the polynomial equations are reliable in expecting the disintegration time, drug release and dissolution efficiency of CARV tablets.

Optimized formulation tablets F2: The disintegration time of the optimized formulation tablets F2 was observed to be 22±2 s and the drug dissolution was recorded to be 99.73±1.7% within 10 min and 78.77% dissolution efficiency in the same period.

The data suggests a significant relationship between the quantity of superdisintegrants and the disintegration time of the dosage form. Specifically, an increase in the amount of superdisintegrant correlates with a reduction in disintegration time. This finding suggests that increasing the concentration of superdisintegrants promotes faster tablet disintegration, which is essential for

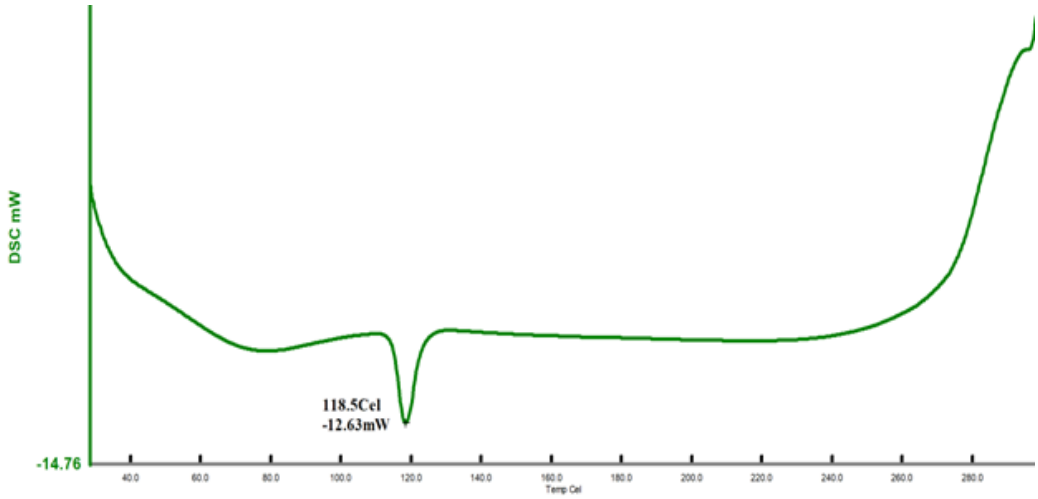

Figure 2: DSC of Carvedilol with starch humate.

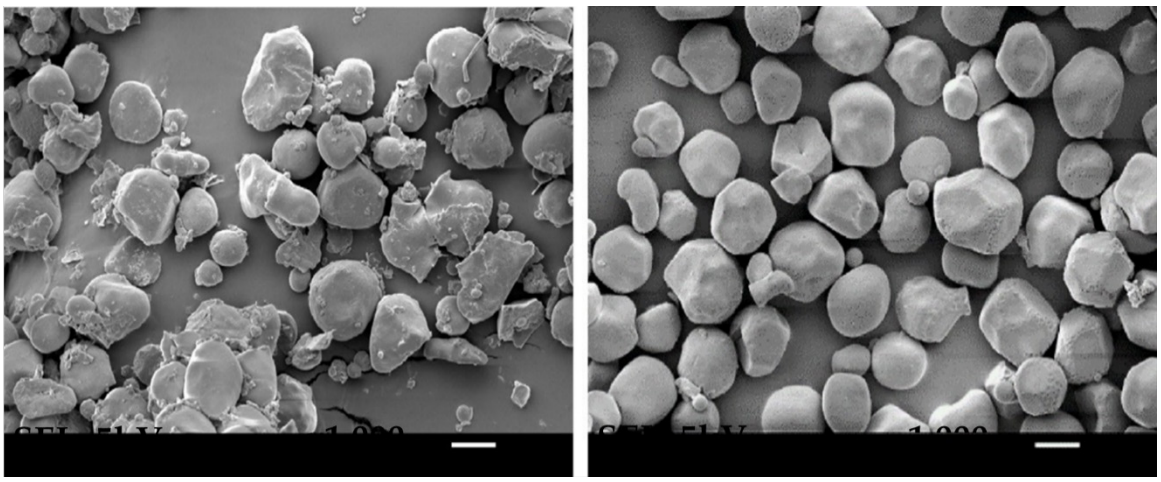

Figure 3: SEM of Sorghum starch.

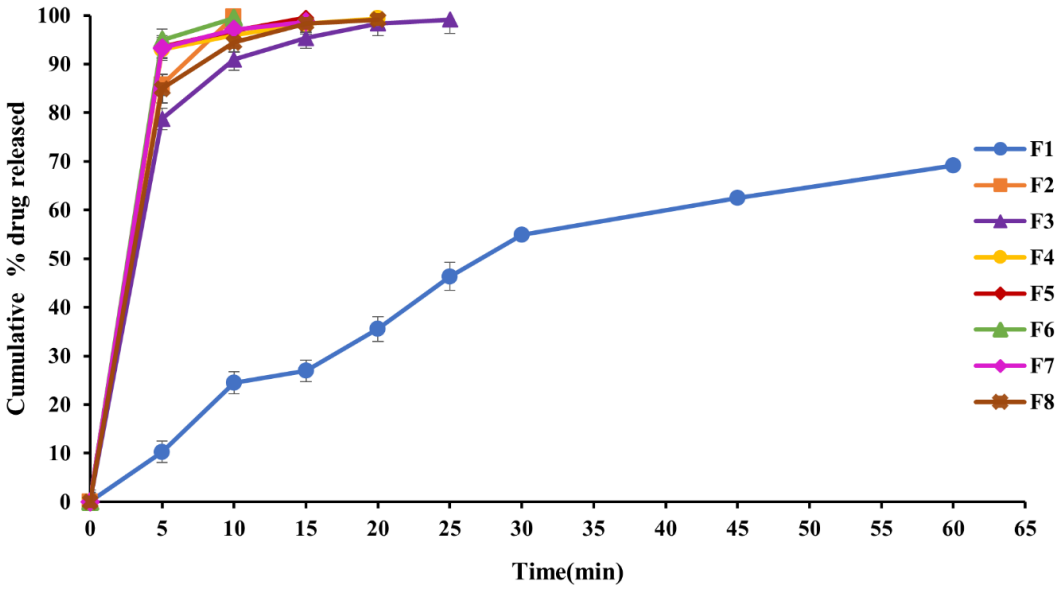

Figure 4: *In vitro* drug dissolution profile of carvedilol FDTs (F1-F8) (n=6, Mean±SD).

ensuring quick drug release. The effects of response 3D contour plots and surface plots, illustrating the interaction between SH and CP, SH and SSG and CP and SSG on DT, PD_{10} and DE_{10}%.

Moreover, the drug release profile can be effectively manipulated by adjusting the levels of variables X1, X2 and X3. This flexibility allows for tailored drug release profiles, enhancing the potential for customized therapeutic applications.

Comparative Analysis of Formulations

Formulation F6 exhibited a remarkable disintegration time of 12±2 sec, with 99.46±5.6% dissolution within 10 min and a dissolution efficiency of 69.4%. It utilized a combination of superdisintegrants, which contributed to its enhanced performance.

Formula F6, employing 5% concentration of SH and 5% of CP had a greater percentage of drug dissolved at the end of 10 min. Based upon this, formulation F6 was regarded as the ideal FDTs of carvedilol. The formulation F2 which contains 5% starch humate showed maximum drug dissolved and more dissolution efficiency at the end of 10 min. Therefore, the F2 formula was regarded as an optimized formulation. This reinforces the notion that starch humate is a promising superdisintegrant, effectively enhancing dissolution rates and reducing disintegration times of CARV tablets. Such improvements could lead to better drug delivery systems and enhanced therapeutic outcomes.

DISCUSSION

This work was dedicated to the formulation, optimization and assessment of 12.5 mg Carvedilol (CARV) tablets using a new superdisintegrant, Starch Humate (SH), in combination with Sodium Starch Glycolate (SSG) and Crospovidone (CP). Direct compression has been considered to be efficient and cost-effective in the production of drugs. The powder blend of the tablet had excellent flow properties and this is essential for the uniform weight and content in the tablets, which leads to consistent therapeutic effects, drug content results were within the limit. All the tablets have good wetting time and water absorption ratio. All the tablets met the official disintegration time standards for uncoated tablets; thus, they disintegrate within the required time frame after ingestion, thus facilitating rapid drug release and absorption. Increased concentrations of SH resulted in lowered disintegration time of tablets, implying that the increased level of SH promotes faster tablet disintegration, hence increasing the drug release rate. This can be attributed to the absorption of water, followed by swelling of tablet, leading to a further breakdown of the tablet matrix.

CONCLUSION

Based on the findings of this research, it can be concluded that Starch Humate (SH) is a promising new superdisintegrant that can be effectively utilized in the formulation and optimization of fast dissolving tablets. The study demonstrated that SH, when used alongside established superdisintegrants like SSG and CP, significantly enhances the disintegration and dissolution properties of CARV tablets. The implications of these results are noteworthy for pharmaceutical development. The ability of SH to reduce disintegration time while maintaining enhanced release profile suggests that it can improve the bioavailability of CARV, leading to enhanced therapeutic outcomes. This is particularly important for drugs that require rapid onset of action, as faster disintegration and dissolution can lead to quicker absorption and effectiveness. In summary, the incorporation of Starch Humate as a superdisintegrant not only meets the necessary pharmacological standards but also holds potential for broader applications in the formulation of various fast dissolving drug delivery systems.

Future studies could explore the scalability of this formulation and its performance with other Active Pharmaceutical Ingredients (APIs), further establishing the versatility and efficacy of Starch Humate in pharmaceutical applications.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ABBREVIATIONS

CAR: Carvedilol; **BCS:** Biopharmaceutics Classification System; **FTIR:** Fourier-transform infrared**; DSC:** Differential Scanning Calorimeter**; XRD:** X-ray diffractometer**; FDT:** Fast dissolving tablets; **SH:** Starch humate; **DT:** Disintegration time; **PD10:** Percentage dissolving in 10 min; **WT:** Wetting time; **WAR:** Water absorption ratio; **CARV-FDTs:** Carvedilol fast dissolving tablets; **DE:** Dissolution efficiency; **QbD:** Quality by design**; SS:** Sorghum starch**; DDS:** Drug delivery system; **WHO:** World Health Organization; **UV:** Ultraviolet; **cm:** Centimeter**; mm:** Millimeter; **kg:** Kilogram; **NaOH:** Sodium hydroxide; **KBr:** Potassium Bromide; **mm:** Millimeter; **RSD:** Relative Standard Deviation; **SSG:** Sodium starch glycolate; **CP:** Crospovidone; **API:** Active Pharmaceutical Ingredient.

ETHICAL STATEMENT

This study did not involve experiments on humans or animals. The research adhered to internationally accepted guidelines for pharmaceutical studies and good laboratory practices to ensure scientific rigor and integrity.

SUMMARY

The study aimed to develop fast-dissolving tablets of Carvedilol to enhance drug release and shorten disintegration time, improving patient compliance. The solubility of the drug was increased using a newly modified superdisintegrant, starch humate. FTIR studies confirmed excellent compatibility between the drug and excipients. The tablets were prepared using the direct compression method, incorporating established superdisintegrants such as sodium starch glycolate and crospovidone. The findings revealed improved solubility, faster disintegration and better drug release. This research highlights the potential of novel modified superdisintegrants in improving the performance and cost-effectiveness of fast-dissolving tablets.

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