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Original Article

OPTIMIZATION OF FAST-DISSOLVING TABLETS OF CARVEDILOL USING 2^3 FACTORIAL DESIGN

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ABSTRACT

Objective: Optimization of carvedilol fast-dissolving tablets through a 2^3 factorial design employing starch hyaluronate as a new superdisintegrating agent.

Methods: The esterification method was used for producing starch hyaluronate. A direct compression process was used to develop carvedilol tablets utilizing a mix of starch hyaluronate (SH) as a novel superdisintegrant, crospovidone, and sodium starch glycolate. The prepared tablets are analyzed for physical characteristics, drug dissolution, *in vivo* pharmacokinetic, and stability studies.

Results: New superdisintegrant synthesized was a fine, free-flowing crystalline powder. In the DSC study, starch hyaluronate had no interaction with the drug. NMR and FTIR investigations supported the ester connection between starch and hyaluronic acid. CF2, the optimized formulation, had the shortest disintegration time of 26±2 seconds. The percentage of drugs dissolved in ten minutes from the optimized composition was 93.4±1.32%. The optimized composition achieved peak plasma concentration in a short time and demonstrated higher relative bioavailability for the drug.

Conclusion: A formula containing a 5% concentration of starch hyaluronate was optimized and has a proper potential for application in the formulation of rapidly disintegrating tablets, in addition to improving clinical obedience throughout the efficacious treatment of hypertension.

Keywords: Carvedilol, Factorial design, Superdisintegrant, Antihypertensive, *In vivo* study

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INTRODUCTION

Despite huge advances in drug delivery, because of precise dosage, affordable therapy, self-medication, and ease of administration, the oral route is still the favored method for administering therapeutic agents, which results in a high rate of patient consent [1, 2]. The most widely used dose forms are traditional pills [3]. However, one significant disadvantage of such tablets or capsules is 'Dysphagia', which implies trouble in gulping [4-6]. Due to this dysphagia condition, they don't follow prescriptions, which brings about non-compliance to prescriptions [7]. Using fast-dissolving tablets (FDTs) is advantageous for patients facing trouble in swallowing tablets. Superdisintegrants are substances integrated into tablets that dissolve quickly to speed up the disintegration process. Starch hyaluronate is a modified starch having high hydrophilicity and cross-linking, which inhibits gel formation and increases solubility, especially in contact with water. A multiple-action cardiovascular medication is called carvedilol and is used to treat a variety of conditions, including angina pectoris, extensive hypertensive crisis, and cardiac arrhythmia. In these conditions, a rapid onset of action is required. Hence, carvedilol can be formulated as fast-dissolving tablets using a safe, newly developed modified starch superdisintegrant known as starch hyaluronate [8]. Quality by design (QBD), has gained popularity recently, attracting researchers to create and improve various drug delivery systems. QBD is a crucial helpful component to realize the variables and their interaction effects on dependent responses by an intended set of studies [9]. Factorial Design is a statistical optimization technique and the best method for examining factors with two-level variability.

Carvedilol is a biopharmaceutical classification system II drug having low solubility. To enhance the solubility, dissolution rate, absorption, and therapeutic action FDTs were developed with starch hyaluronate as a new superdisintegrant. The present research focuses on an attempt to optimize carvedilol fast-dissolving tablets by 2^3 factorial design that makes use of SSG, CP and starch hyaluronate (new super disintegrating agent) as an independent response, disintegration time (DT), percent drug dissolved in 10 min (PD_{10}) as well as dissolution efficiency in ten mins (DE_{10}%) as a dependent variable.

MATERIALS AND METHODS

Materials

Hyaluronic acid, carvedilol, starch(potato), crospovidone, and sodium starch glycolate, have been acquired through S. D fine (Hyderabad, India). The starch hyaluronate employed is laboratory-processed. microcrystalline cellulose, aspartame, magnesium stearate and talc were purchased from Finer Chemicals Ltd., Mumbai, India.

Methodology

Synthesis of starch hyaluronate (a new superdisintegrating agent)

Potato starch 10 gms was placed in a container having 15 ml of distilled. Hyaluronic acid (10 gm) was distributed in purified water, and subsequently incorporated into the starch slurry, 10 ml NaOH was used to adjust the pH of the slurry to 3.5 and left idle to allow the esterification process to take place. Following that, the entire mixture was rinsed with distilled water to eliminate all undissolved HA and dried at 60 °C to produce a dried mass. The dry starch hyaluronate has been passed through a # 120 to obtain homogeneous particles and then kept in a desiccator [10].

Starch hyaluronate characterization

Organic solvents like alcohol, acetone, dichloromethane, $CHCl_3$, DMSO, and ether of petroleum were used to assess the new superdisintegrants solubility. The pH was determined with a pH meter. The melting point device can be utilized to measure the melting point. The starch hyaluronate was placed in a desiccator and its hygroscopic nature was assessed while maintaining a relative humidity of 84% at room temperature. Viscosity was determined using an Ostwald viscometer. By making 7 % w/v dispersion of an SH as well as starch in DW, and then warming the dispersion for about 30 min at around 100 °C, the gelling capacity of starch hyaluronate and starch was assessed. The sieve analysis method has

been used to measure the particle size of starch hyaluronate. The density (g/cc) of a starch hyaluronate dispersion in distilled water was calculated using the liquid displacement method. The below equation assess the bulk and tapped density.

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Volume of the packing}}$$

$$\text{Tapped bulk density} = \frac{\text{Mass of the powder}}{\text{Tapped volume of the powder}}$$

Fixed funnel procedure can be utilized to determine the flowability, and the below equation can be applied to determine the angle of repose

$$\tan\theta = \frac{h}{r}$$

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

Where Θ =angle of repose, h = height of the pile, r = radius of the pile.

The compressibility index was calculated with the equation given below.

$$\text{Compressibility index} = \frac{\text{Final} - \text{Inital}}{\text{Final}} \text{X } 100$$

Where Final=Tapped bulk density, initial =Loose bulk density.

Swelling index (SI)

Accurately weighed 200 mg of starch hyaluronate was transferred in two graduated measuring (MC) cylinders with 10 ml of distilled water and light liquid paraffin one of them in each MC. These MCs had been safeguarded while keeping them aside for 12 h. The value of starch hyaluronate in each MC was noted. The SI of starch hyaluronate has been determined by the following formula [11].

Ester test

1 mg of SH has been combined with two milliliters of ethanol and one milliliter of 0.1 ml of NaOH. When a phenolphthalein indicator was added to this, a color shift was noted [12].

The FTIR spectra of potato starch and the novel superdisintegrant were discovered with KBR in a Bruker FTIR (Tokyo, Japan) 5-10 min within the spectral range of 500-4000 cm^{-1} under an 800MPa stress [13]. The structure of a newly synthesized starch hyaluronate has been analyzed using ^1H NMR spectra (CD_3OD) and a Bruker 400MHz NMR spectrometer [14]. With the use of a Ni filter, an X-ray diffractometer has been employed to evaluate the nature of a starch hyaluronate and pure drug 45 kV, 40 mA, and a full range i.e. 2000. DSC measurements of carvedilol, carvedilol with starch hyaluronate (1:1) have been measured on a Perkin Elmer thermal analyzer with 50-300 °C heating temperature with a 10 °C/min heating rate [15]. The morphology of starch hyaluronate was seen under a scanning electron microscope.

Preparation of carvedilol fast-dissolving tablets

Table 1: Formulae of carvedilol FDTs

Composition (100 mg/tablet)	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8
Carvedilol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Starch hyaluronate (A)	-	5	-	5	-	5	-	5
SSG (B)	-	-	5	5	-	-	5	5
CP (C)	-	-	-	-	5	5	5	5
MCC	50	50	50	50	50	50	50	50
Mannitol	31.5	26.5	26.5	21.5	26.5	21.5	21.5	16.5
Aspartame	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2

The carvedilol FDTs are made with the direct compression methodology by three disintegrants such as SH, SSG, and CP. The contents based on different compositions of carvedilol FDTs are listed in table No. 1. Where amounts of superdisintegrants were chosen in two levels, i.e., bottom and elevated levels of concentration. The bottom level was zero, and the elevated level was 5 percent. Before combining, every constituent was run across the screen with a mesh size of 120 to ensure uniformity in particle size. All of the excipients, including the SH, SSG, CP, and mannitol, along with aspartame and MCC, were weighted, combined, and triturated; carvedilol has been added. Lastly, talc and magnesium stearate have been added to the powder blend. Finally, the blended mixture was compressed into a tablet [16].

Experimental design

23 factorial design (Three Factors, Two Levels) was used to investigate the interactions and primary influence of the factor, which is independent of dependent responses, as well as to statistically optimize the design parameters. Design Expert software (Version 7.00, Stat-Ease Inc., USA) was used to build a polynomial equation. DT (Y1), PD10 (Y2), and %DE10 (Y3) were measured at two distinct levels of SH (A), SSG (B), and CP (C). [17]. The factors that were chosen and their each correspond to every levels have been displayed in table 2.

Post-compression evaluation tests

Hardness

The ability of a dosage form to endure mechanical shocks while handling and transportation was calculated with a Monsanto tester. It was expressed in kg/cm^2. Three tablets were randomly selected from each batch, and the hardness of the tablets was determined.

Friability test

The Roche friabilator was used to assess the tablets' friability. For this test, samples of tablets were dropped over a certain time. Tablets were weighed before and after the test. Finally, % friability had been calculated by using the formula [18].

$$F\ \% = (1 - W_0/W) \times 100$$

Weight variation test

The mean mass of the 20 tablets has been calculated. According to the USP monograph, the average tablet weight does not differ from any individual tablet weight by more than two, and none by more than twice the proportion of tablet weight.

Table 2: Factors and their levels employed in a factorial design

Factor code	Factors considered	Low (-1)	Elevated (+1)
A	Starch hyaluronate (mg)	0	5
B	Crospovidone (mg)	0	5
C	Sodium starch glycolate (mg)	0	5

Wetting time

The time taken for a tablet to be wet was recorded after it was placed on a folded piece of tissue paper and kept in a petri dish with six ml of a 6.8-pH phosphate buffer containing 1 ml of a water-soluble dye [19].

WAR (Water absorption ratio)

A folded tissue has been inserted on a tiny petri plate with 6 ml of distilled water. The tablet had been positioned over the paper and left to become fully moistened. After that, the moisturize tablet had been re-weighed. Below equation (R) used to calculate the WAR

$$R = W_a - W_b / W_b \times 100$$

Where W_a = mass of tablet later absorption, W_b = mass of tablet previous absorption

Drug content uniformity

10 tablets had been weighed at random and ground into a fine powder. Weighted powder equal to ten had been diluted with 100 milliliters of phosphate buffer with a pH of approximately 6.8, filtered, and measured spectrophotometrically at 242 nm. To determine the drug's dosage, the standard calibration curve was used [20].

***In vitro* disintegration time**

Disintegration time has been tested using a USP device. The dosage forms were kept inside a 1 liter of 6.8 pH phosphate buffer at about 37±0.2 °C. Six tablets were chosen at random, one placed into all individual basket rack assembly tubes containing the disintegration medium, while the duration that the tablet had taken to disintegrate entirely (no residue is left behind) was measured in seconds [21].

***In vitro* dissolution**

The dissolution rate of carvedilol FDTs has been studied in a pH 6.8 phosphate buffer around 37±0.5 °C temp as well as 50 rpm agitation speed. The sample was collected at periodic times and analyzed spectrophotometrically at 242 nm [22].

Stability studies

According to ICH and WHO recommendations, an optimized composition of carvedilol rapidly dissolving tablets needs to undergo accelerated testing simply storing them in containers made of HDPE over 6 mo around a temp of 40 °C and 75 °RH. These samples have been tested since alterations in a physical change and drug release characteristics both during as well as after being stored for 6 mo [23].

***In vivo* pharmacokinetic studies**

The Institutional Animal Ethical Committee has approved the study's protocol. Balaji Institute of Pharmaceutical Sciences, Narsampet (Approval No: 01/BIPS/IAEC/2022). Three male Wister rats were kept in a wire cage with free access to food, and water and were exposed to a 12-hour cycle of light and a 12-hour interval of dark each day within an atmosphere of cleanliness along with an ambient temp (20-25 °C). Wister male rats (200–250g) were chosen at random and put in three batches, each with 6 rats. All groups received different treatments: one group received pure medication (52.08 µg/kg body weight), the second group received CF2 formulation (52.08µg/Kg body weight), and the third group was treated with a marketed formulation (carloc). Rats were restricted for 12 h before the study started and they only had intermittent availability of water and food while it was being conducted. Wister rats received their dose by catheter. Following the medication's administration, the rats were given mild ether anesthesia. Blood was drawn from a lateral tail vein at predetermined frequencies about zero (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h. The blood plasma samples had been stored at-20 °C following centrifugation (5000 rpm for 25 min). The samples have been evaluated employing with known HPLC technique for investigating the pharmacokinetic data [24].

RESULTS AND DISCUSSION

Starch hyaluronate is a fine, free-flowing, slightly crystalline powder. Physical along with micrometric properties of potato starch and starch hyaluronate as a new superdisintegrant was summarised in table 3. Fig. 1 and 2 show the FTIR spectrum of PS and SH. The FTIR characteristic band of the ester (starch hyaluronate) had been found near 1697.41 cm^{-1}

In the FTIR spectra of carvedilol and carvedilol with starch hyaluronate, the distinctive peaks of NH,-OH, CH, C-O, C=C, C-N, and $C=CH_2$ were observed. The spectra of carvedilol with starch hyaluronate (fig. 4) reveal a prominent absorbance band at 3331 cm^{-1} due to N-H stretching. The spectra at 2923 cm^{-1} could be caused by O-H connection stretching. 2309 cm^{-1} is due to C-H stretching, 1251 cm^{-1} was due to C-O stretching, 1595 $cm^{-1}$was due to C=C aromatic,1336 cm^{-1}due to C-N stretching, 1537 cm^{-1}because of N-H stretching in the chain, and 852 cm^{-1} caused by $C=CH_2$ bending. The same peaks were also observed in the FTIR spectrum of a pure drug (fig. 3) (-NH) 3337.16, (-OH) 2922.6, (-CH)2833.19, (-CO) 1249.6, (-C=C)1589.88, (-C-N) 1215.7, ($C=CH_2$) 620.96. Carvedilol with starch hyaluronate does not show any appearance/disappearance of characteristic peaks so, it was concluded that the drug maintains its identity without undergoing any chemical interactions with starch hyaluronate.

Table 3: Starch hyaluronate physical and micrometric properties

Content	Starch hyaluronate
Solubility in aqueous and organic solvents	Insoluble
pH (1% w/v aqueous dispersion)	5.41±0.06
Bulk density (gm/cm^3)	0.52±0.007
Tapped density (gm/cm^3)	0.63±0.01
The angle of repose (θ)	23.47±1.56
Carr's index (%)	11±1
Hauser's ratio	1.15±0.03
Melting point (°C)	253±2
Gelling property	No gel was formed
Swelling index %	97±0.02
Ester test	Color change
Moisture absorption	4.3±0.2
Viscosity1% (cps)	1.042±0.004
Average particle size	24 µm

n=3, mean±SD

Carvedilol pure drug and drug with starch hyaluronate (1:1) thermograms generated by DSC revealed a significant melting endothermic peak at 117.59 °C and 119.23 °C, indicating that the drug was pure. The DSC spectra didnot show any interaction with the and starch hyaluronate (Fig. 5 and fig. 6) The broad sign between 3.5 and 3.65 ppm in a 1H-NMR spectrum from starch-hyaluronic acid (HA) refers to the tetrahydropyran nucleus that comprises the sugar molecule present in both Starch and HA. At 1.15 to 1.19 ppm, the methyl ($-CH_3$) protons located in the N-acetyl ring in HA, as well as the 6th position of the glucose molecules at starch, seemed as an intense signal. The signal's characteristic appearance at 4.57 and 4.85 ppm corresponds to 2 anomeric charged moieties coupled because the carbons were exactly adjacent to an oxygen component that is composed of sugars found in Starch as well as HA. Due to the interaction with the neighboring ring carbon proton, an amine proton (-NH) displayed as a doublet at 5.2 ppm. The removal of the HA's carboxylic hydroxyl proton [-C(=O) OH] in the 1H-NMR spectrum when it had been transformed into the ester connection between HA with starch was verified. ester linkage between the HA as well as starch was verified. As a result, it confirmed that the potato starch, as well as HA, were bound through an ester bond depicted in fig. 7. The X-ray diffraction of the new superdisintegrant exhibited typical spectra near 2 theta angles about 5.673°, 9.950°, 11.28°, 14.175°, 15.061°, 17.187°, 19.730°, 22.263°, 24. 060° and 26.260° fig. 8 demonstrates the slightly crystalline form of starch hyaluronate.

The SEM of the starch hyaluronate has confirms slightly crystalline in shape, as shown in fig. 9.

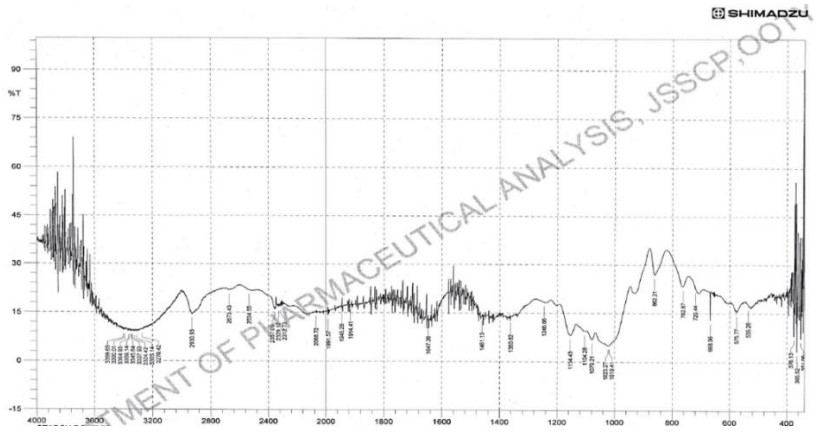

Fig. 1: FTIR spectra of potato starch

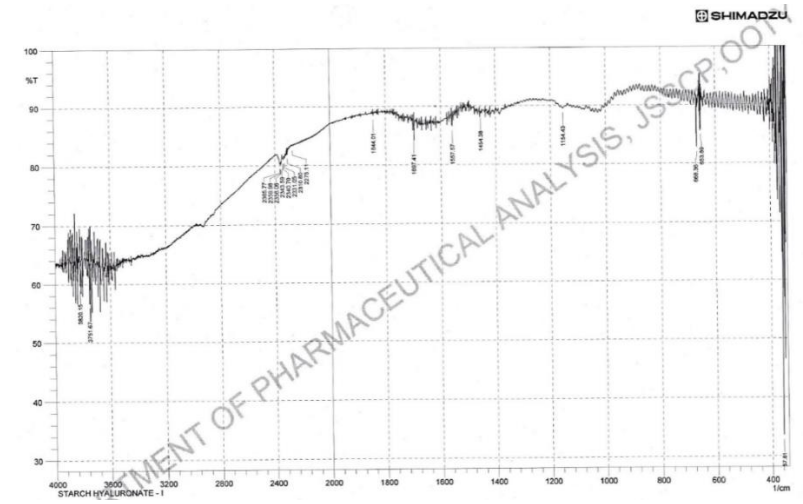

Fig. 2: FTIR spectrum of starch hyaluronate

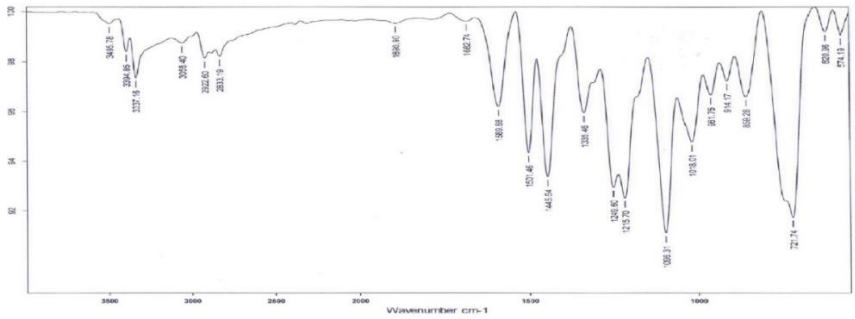

Fig. 3: FTIR spectrum of carvedilol

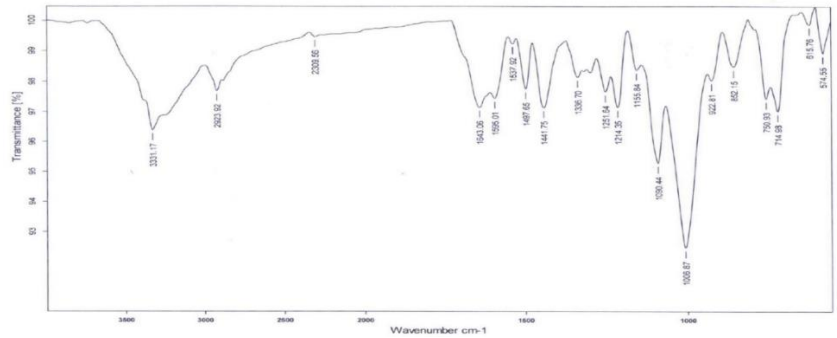

Fig. 4: FTIR spectrum of carvedilol–starch hyaluronate

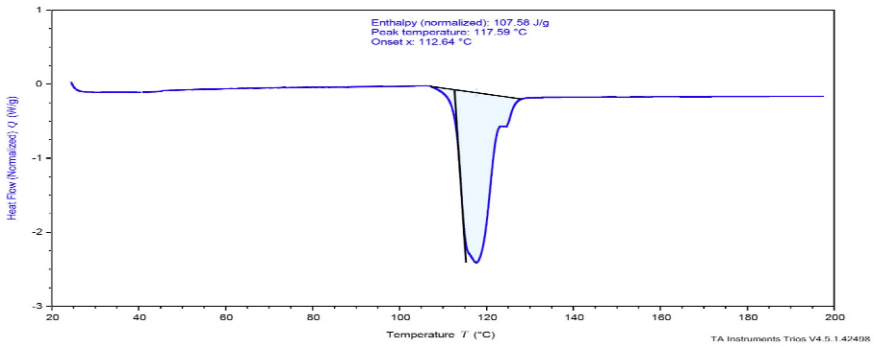

Fig. 5: DSC thermogram of carvedilol

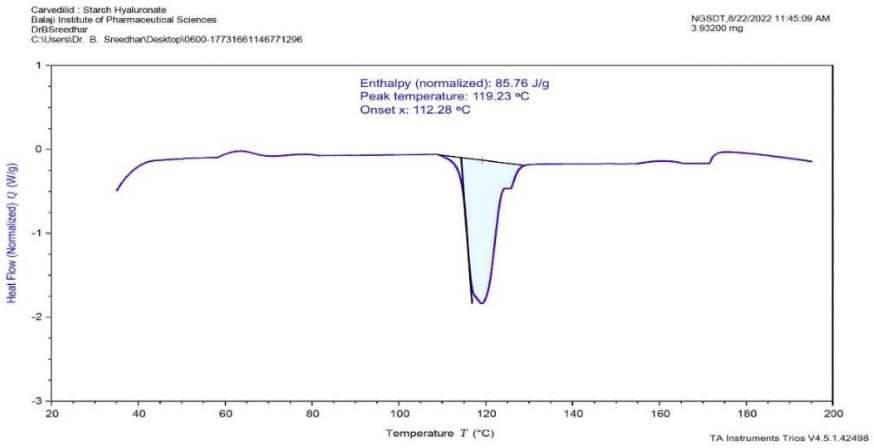

Fig. 6: DSC thermogram of carvedilol with starch hyaluronate

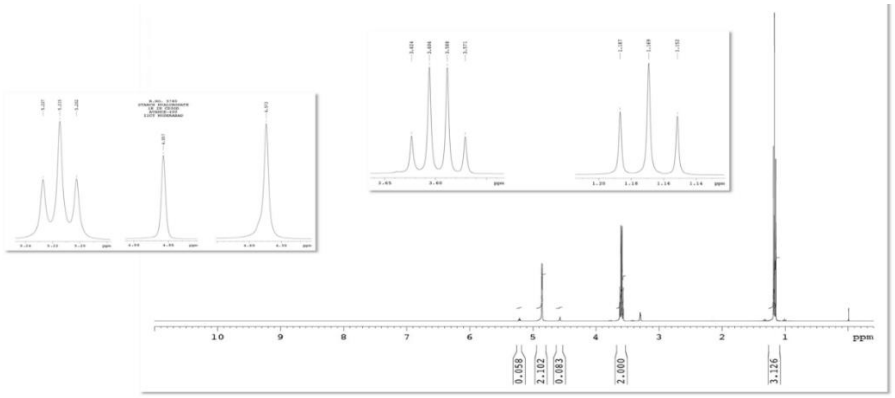

Fig. 7: Starch hyaluronate proton nuclear magnetic resonance (1H NMR)

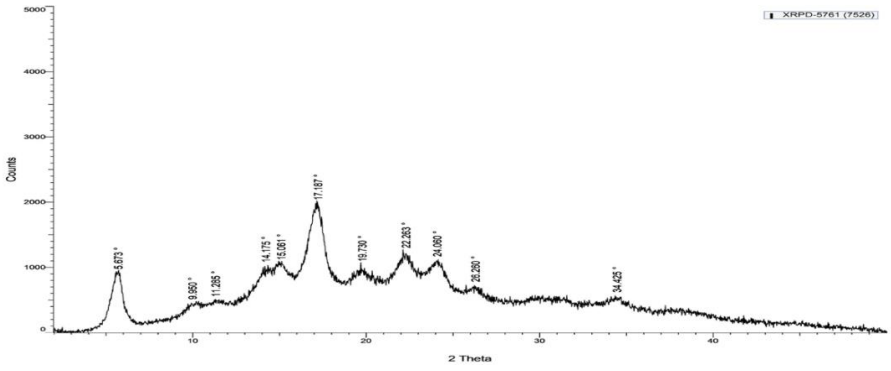

Fig. 8: Starch hyaluronate with an X-ray diffraction pattern

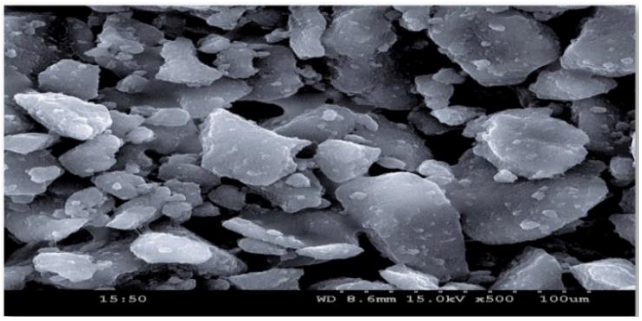

Fig. 9: Starch hyaluronate SEM (x500) illustration

The evaluation of all post-compressional parameters revealed that they had been all inside the specified range. (Table 4) The formulations' mechanical strength, which varied from 3.7±0.26 to 4.0±0.91 kg/cm^2, showed excellent mechanical strength. The hardness of the tablets was higher when compared to the tablets i. e 3.5 kg/cm^2 prepared according to S. Jaya, *et al.* [25]. Tablet mechanical resistance remained good, as evidenced by tablet friability being less than 1% of the evaluated tablets' weights. All compositions meet pharmacopoeial standards of drug content and weight variation. Wetting time and moisture absorption ratio have been identified to be between 363±0.53 to 5±0.67 sec and 22±1.75 to 75±1.32 respectively. The wetting time was shorter than that of the tablets made by Kumari A *et al.*, which had a wetting time of 76.4 sec [26].

In vitro disintegration time

The DT of all developed tablets ranged from 768±2 to 8±2 seconds as represented in table No. 4, optimized composition CF2 having a disintegration time of 26±2 seconds this was comparatively less than the tablets made by Malode Lochna L *et al.*, which had a disintegration time of 47.44±2.49 sec [27].

Table 4: Physico-chemical evaluation tests of carvedilol fast dissolving tablets

S. No.	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Content uniformity (%)	WAR	WT (sec)	DT (Sec)
CF1	98±0.75	3.7±0.56	0.67±0.25	98.26±1.37	22±1.75	363±0.53	768±2
CF2	101±0.64	3.9±0.24	0.59±0.68	97.56±1.43	66±1.42	23±0.36	26±2
CF3	102±0.39	3.8±0.43	0.65±0.52	98.62±1.75	62±1.24	20±0.75	28±2
CF4	101±0.27	4.0±0.91	0.54±0.91	97.66±1.12	70±1.46	9±0.61	15±2
CF5	102±0.33	3.7±0.26	0.65±0.73	97.18±1.36	68±1.64	17±0.38	21±2
CF6	101±0.98	4.0±0.23	0.61±0.42	98.78±1.94	69±1.72	8±0.56	10±2
CF7	98±0.27	4.0±0.89	0.58±0.83	97.83±1.26	70±1.54	8±0.54	11±2
CF8	101±0.19	3.8±0.64	0.65±0.97	98.14±1.81	75±1.32	5±0.67	8±2
MF(Carloc)	101±0.29	5.0±0.23	0.57±0.63	97.89±1.21	36±1.32	157±0.41	394±2

n=6, mean±SD, MF-Marketed formulation

In vitro dissolution studies

Fig. 10, and table 5 display the results of an *in vitro* dissolution. CF6 contains 5% CP, as well as 5% starch hyaluronate, and has demonstrated high PD_{10} i.e., 99.8±1.59% (% dissolving in 10 min) this was rather higher than the tablets that were manufactured per Parfati N *et al.* and had a 92.46% release after one hour [28]. and dissolution efficiency (DE_{10}%) i.e.,59.7. Formulation CF2 contains a 5% concentration of starch hyaluronate was comparable to formulation CF6. Therefore, just one unique superdisintegrant i.e., starch hyaluronate, CF2 was confirmed to be less expensive than CF6. The number of folds increase in dissolution efficiency (DE_{10}%) has been specified in table 5.

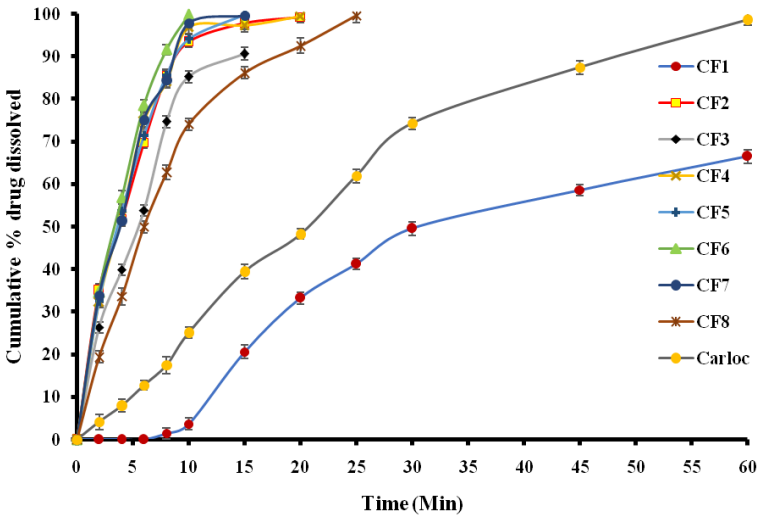

Fig. 10: Cumulative percent drug dissolved profile of formulations (CF1–CF8). Error bars indicate SD value of three determinations

Table 5: Dissolution parameters of carvedilol FDTs

Time (min)	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	Carloc
PD_{10}	3.7	93.4	85.28	96.8	94.12	99.8	97.8	74.1	25.16
	±0.25	±1.32	±0.46	±0.63	±1.35	±1.59	±1.68	±1.35	±1.16
DE_{10}	0.007	0.578	0.47	0.58	0.58	0.62	0.59	0.41	0.1102
$\%DE_{10}$	0.668	57.81	47.5	58.4	58.1	62.3	58.8	40.6	11.02
No. of Folds increase in DE	-	86.54	71.1	87.5	87	93.3	88	60.8	16.497

Every value is stated by mean±SD, where n=6. PD_{10} Percent dissolved in 10 min, DE_{10}%-Dissolution efficiency in 10 min

Statistical analysis was conducted using a factorial design

SH (A), SSG (B), and CP (C) constitute independent variables, while DT, PD_{10}, and DE_{10}% were response variables that were interrelated using regression analysis. Considering DT, PD_{10}, and DE_{10}%, below formulas 1, 2, and 3 were provided as polynomial equations.

Y1 (DT) =+110.88-96.63A-97.63B-96.88C+93.88AB+90.88AC+92.38BC-89.63ABC

Y2 (PD_{10}) =+80.63+10.40A+7.87B+10.83C-13.45AB-14.90AC-13.37BC+7.04ABC

Y3 (DE_{10}%) =+47.21+6.00A+4.05B+7.01C-7.87AB-10.12AC-8.59BC+2.90ABC

Disintegration time

As shown in table 4, the disintegration time of FDTs was between 34±2 and 73±2 seconds. The mathematical model produced for Disintegration Time (Y1) has been discovered to be considerable. Making use of contour and 3D response graphs, the impact of the main as well as variable interactions over DT was then explained. The linear relationship was projected by the contour plot. Response and contour plots showed that increased superdisintegrant amounts may shorten the disintegration time. This concept may well be attributed to a greater proportion of superdisintegrants, which may result in faster tablet disintegration. The effects of response 3D contour plots and surface plots showing the influence between SH and SSG, at a fixed level of CP on disintegration time are depicted in fig. 11. According to the plots, the percentage of superdisintegrant varies between 3.75 to 5%, resulting in a lower DT of the tablet.

Dissolution efficiency and percent drug dissolved in ten minutes

The contour plots showed a nonlinear association between PD_{10} and DE_{10}%. While a super disintegrant level differs by 3.75 to 5%, a tablet accomplishes a greater PD_{10} and DE_{10}% according to response surface and contour plots. The effects of contour plots and surface plots showing the influence between SH and SSG, at a fixed level of CP on PD_{10} and DE_{10}% are depicted in fig. 12 and 13.

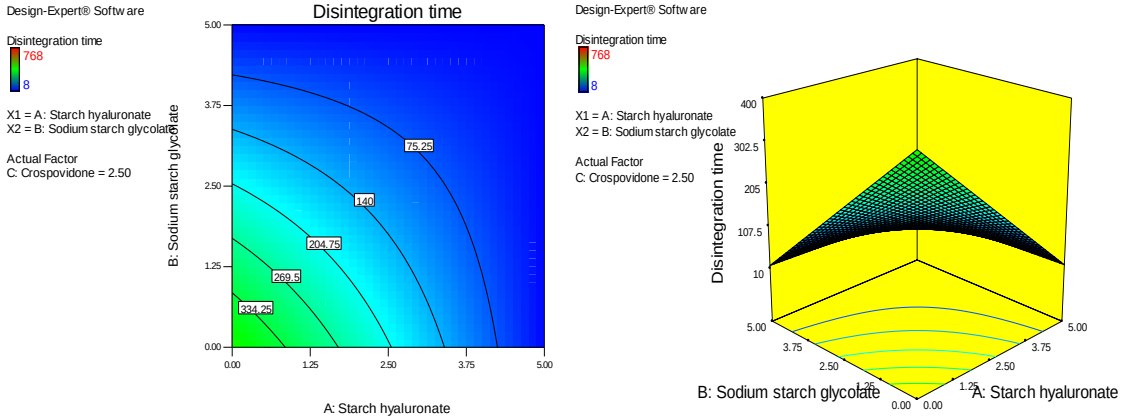

Fig. 11: The contour and response (3D surface graph) demonstrate the effect of sodium starch glycolate and starch hyaluronate at a fixed level of CP on DT

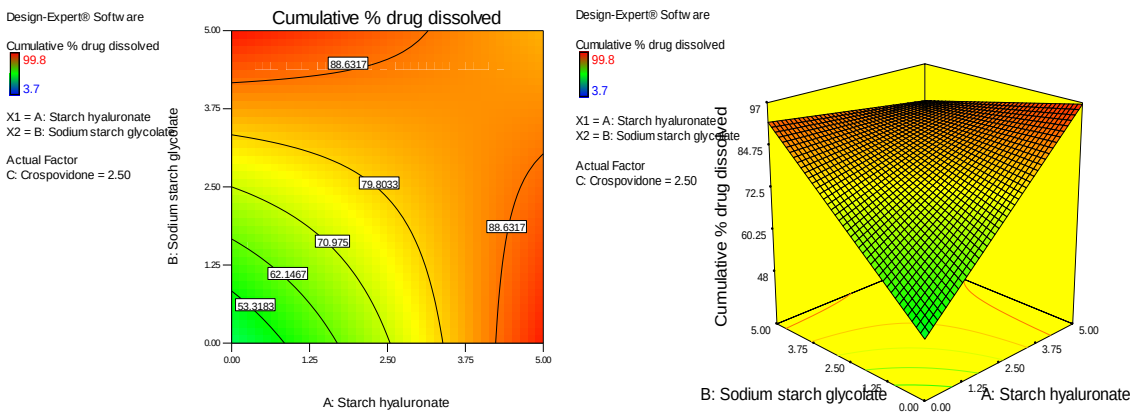

Fig. 12: The contour and response (3D surface graph) demonstrate the effect of SH and SSG at a fixed level of CP on PD_{10}

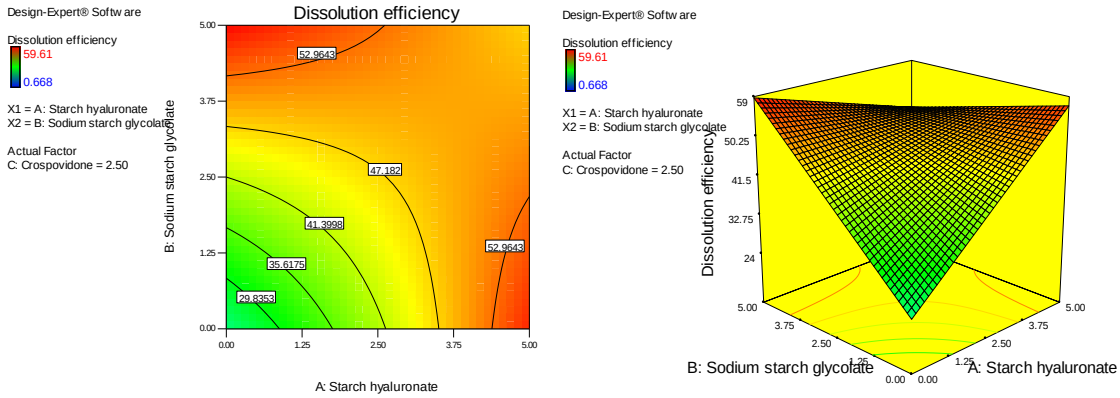

Fig. 13: The contour and response (3D surface graph) demonstrate the effect of SH and SSG at a fixed level of CP on DE_{10}%

Optimum composition

According to the findings of the experiment, the formulation CF2 uses a newly synthesized superdisintegrant. In ten minutes, starch hyaluronate at 5% concentration demonstrated maximum dissolution and dissolution efficiency. As a result, the CF2 formulation can be regarded as an optimized formulation that is economical.

Pharmacokinetics studies

The AUCs of pure drug, marketed formulation (carloc), and CF2 after oral doses were 976.2±10.2, 1725.59±17.3, and 2748.48±15.4 ug. h/ml. The C_{max}) for the optimized formulation CF2 was discovered to be higher than those of pure drug and marketed drug plasma concentrations, i.e. The optimized rapid dissolving tablet formulation had a C_{max} of 5207.18±4.02 ug/ml. According to the findings, SH aids in the rise of carvedilol plasma concentration. These results agreed with the results obtained by Aboud HM *et al.* [29]. Table 6 and fig. 14 show the other pharmacokinetic parameters in this study.

Stability studies

Stability tests show that the optimized (CF2) composition of carvedilol FDTs employing starch hyaluronate was stable in accelerated conditions and found comparable with the carvedilol tablets prepared by Aboud HM *et al.* [29]. The dissolving profile of the optimized composition CF2 was shown in fig. 15 both before and after six months.

Table 6: Summary of pharmacokinetic parameters

Parameter	Pure drug	Carloc	CF2
K_{el} (h^{-1})	0.407±0.02	0.540±0.01	0.711±0.02
K_a (h^{-1})	0.643±0.50	0.81±0.20	0.937±0.30
$AUC_{0-\infty}$ (µg. h/ml)	976.2±10.2	1725.59±17.3	2748.48±15.4
C_{max} (µg/ml)	755.76±3.12	1503.43±3.19	5207.18±4.02
T_{max} (h)	0.86±0.14	1.37±0.04	1.57±0.19
RBA (%)	-	176.7±1.69	281.5±0.54

*n=3, mean±SD

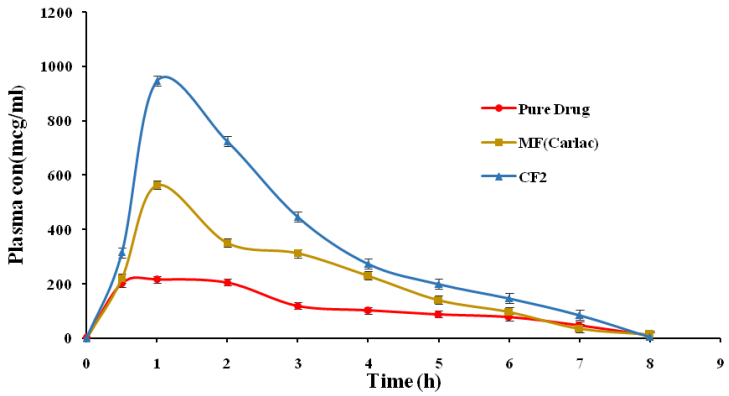

Fig. 14: Plasma concentration-time profile of a pure drug, optimized carvedilol (CF2), and marketed formulation

Table 7: Stability studies of optimized formulation

Time to retest the optimized formula (CF2)	WT (sec)	DT (Sec)	The profile of *in vitro* drug dissolution (%)	The drug content (%)
Initial day	23±0.36	26±2	93.4±1.32	98.22±1.80
30 d	23±1.46	26±2	94.19±1.12	98.17±1.65
60 d	24±10.36	26±1	93.93±1.64	98.11±1.54
120 d	22±0.86	25±2	93.81±1.31	98.03±1.49
180 d	22±1.12	24±1	94.47±1.86	97.89±1.21

*n=6, mean±SD

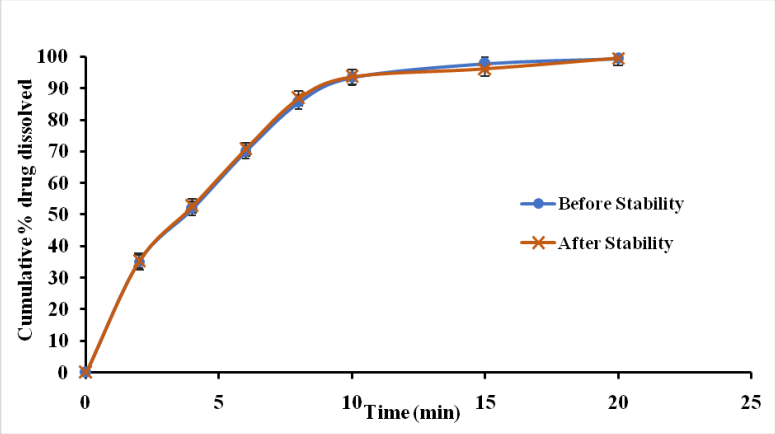

Fig. 15: Carvedilol FDTs CF2 dissolution profiles during the stability study, both before and following 6 mo of storage

CONCLUSION

Synthesized starch hyaluronate was found to be a fine, crystalline, and free-flowing powder with superdisintegrant properties. SH as novel superdisintegrants was employed for the development of carvedilol FDTs by direct compression technique employing a 2^3 factorial design. Compared to marketed and other formulations, the optimized formulation of carvedilol (CF2) FDTs containing SH of 5% had a reasonable DT, maximal dissolution, and DE_{10}%. The optimized formula was stable, acquired peak plasma concentrations quickly, and demonstrated enhanced drug absorption and relative bioavailability. From the study outcomes, it was discovered that starch hyaluronate had a quicker rate of dissolution and disintegration. Thus, SH can be suggested as a superdisintegrant in the formulation of fast dissolving tablets of poorly soluble drugs.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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