OPTIMIZATION OF STARCH HYALURONATE AS A NEW SUPER DISINTEGRANT IN THE FORMULATION OF FAST-DISSOLVING TABLETS OF NISOLDIPINE

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Article History: Received: 03.12.2022 **Revised:**15.01.2023 **Accepted:** 20.02.2023

Abstract

Objective: Design and optimization of starch hyaluronate as a new superdisintegrant by employing a 2^3factorial design in the formulation of nisoldipine fast-dissolving tablets to increase the bioavailability and patient compliance. **Methods:** The esterification process was used to prepare starch hyaluronate. The micromeritics and physical characteristics of starch hyaluronate were assessed, and nisoldipine fast-dissolving tablets have been formulated by a direct compression method using starch hyaluronate as a new superdisintegrating agent. *In vitro* dissolution, *in vivo* pharmacokinetics, and post-compression parameters were assessed. According to ICH requirements, optimized formulation stability tests were carried out under accelerated conditions for six months. **Results:** The synthesized starch hyaluronate was crystalline and tested to be insoluble in both organic and aqueous solvents. Nisoldipine fast-dissolving tablets with excellent tablet properties and enhanced drug dissolution efficiency were produced by using starch hyaluronate as a super disintegrant. NMR study confirmed that the starch and hyaluronic acid were bonded with the ester linkage. The formulation NF6, which contained crospovidone, and starch hyaluronate in a 5 percent concentration as super disintegrants, demonstrated the lowest disintegration time (11±2se) and 99.6 percent drug dissolution within 10 minutes of all the formulations (NF1 to NF8). The drug dissolution characteristics of formulation NF6 were comparable to those of formulation NF2 (92.8%), which included a 5 percent concentration of starch hyaluronate. Optimized formulation NF2 demonstrated enhanced relative bioavailability of the drug and quickly reached peak plasma levels. **Conclusion:** Physical properties, disintegration time, pharmacokinetic studies, and *in vitro* dissolution studies led researchers to the conclusion that optimized formulation was stable, achieved peak plasma concentration quickly, and had greater relative bioavailability. Hence starch hyaluronate is also recommended as a new super disintegrant in the development of fast-acting tablets of poorly soluble drugs.

Keywords: Nisoldipine, Factorial design, Superdisintegrant, Antihypertensive, Bioavailability

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DOI: 10.31838/ecb/2023.12.3.120

INTRODUCTION

The oral route of drug delivery is far safest and most convenient drug delivery route. However, this route becomes undesirable for drugs that suffer from poor aqueous solubility, enzymatic degradation in GIT, and pH instability [1]. All these factors result in improper absorption and thus decreased bioavailability. In addition, this route is also not preferred for pediatric and elderly subjects who have difficulty swallowing [2]. Hence there is a massive requirement to advance development in oral formulations to overcome the challenges faced in an aspect of low bioavailability with rapid action onset [3]. Orally fast-dissolving tablets were among the recently developed oral drug delivery system, releasing the drug directly into systemic circulation via the mucosa of the buccal cavity [4]. Superdisintegrants have been utilized in fast dissolving dosage forms to help them dissolve quickly. According to a review of the literature, both synthetic and natural superdisintegrants are already on the market. Starch is a polymer that is easily useable, biodegradable, and biocompatible. It has been modified by multiple researchers [5,6,7]. Starch hyaluronate was prepared by the esterification process by reacting the hyaluronic acid with potato starch. Calcium channel blocker a 1,4-dihydropyridine derivative known as "nisoldipine" (ND) is a BCS class II, used to treat angina pectoris it has a very low oral bioavailability (5%) [8]. As a result, adding nisoldipine fast-dissolving tablets is an additional strategy for increasing ND's bioavailability [9]. In the current work, a 2^3 factorial design was attempted for the optimization of nisoldipine tablets, using starch hyaluronate (SH) as a new superdisintegrant in addition to sodium starch glycolate (SSG) and crospovidone (CP) as other superdisintegrants. Starch hyaluronate (A), sodium starch glycolate (B), and crospovidone (C) were taken as independent variables, and disintegration time (DT), dissolution efficiency in 10min (DE_{10}%), and percent dissolved in 10min (PD_{10}) were dependent variables in each case [10]. The main and interaction impacts of the formulation factors were examined using Stat-Ease Design Expert® V7.0.0[11].

MATERIALS & METHODS

Materials

S.D Fine (Hyderabad, India) gifted the Hyaluronic acid, potato starch, nisoldipine, crospovidone, and sodium starch glycolate, A laboratory-processed starch hyaluronate was utilized. Stearate of magnesium, microcrystalline cellulose, talc, and aspartame have been bought from finer chemicals Ltd., Mumbai, India.

Preparation of Starch Hyaluronate

Potato starch of 10 grams was suspended in a beaker containing distilled water to a volume of 15 mL. 10 grams of hyaluronic acid was weighed and then added to the starch slurry, the pH of a slurry was then adjusted to 3.5 with 10 mL sodium hydroxide and kept idle for esterification reaction. The mixture was then treated using distilled water to remove any remaining amounts of hyaluronic acid before being dried at 60^0C to form a dry mass. The dried starch hyaluronate was screened with a #120 sieve to get uniform-sized particles and preserved in the desiccator [12].

Characterization of Starch Hyaluronate

The following parameters were developed and assessed for starch hyaluronate:

Solubility

The produced starch hyaluronate's solubility in water, an aqueous buffer with a pH range of 1, 2, 3, 4, 5, and 7, as well as in organic solvents including acetone, alcohol, dichloromethane, petroleum ether, and chloroform, were evaluated.

pH

The pH of the starch hyaluronate dispersion in an aqueous solution was measured using a pH m^2 at 1% weight-to-volume.

Melting Point

Using the melting point equipment, the starch hyaluronate melting point was measured. To determine the melting point, starch hyaluronate had been put into a capillary vessel, which was then inserted into a slot in the melting point equipment [13].

Viscosity

The viscosity of a starch hyaluronate aqueous dispersion at 1% w/v was determined using an Ostwald viscometer.

Swelling Index

In two graduated measuring cylinders that had lastly contained 10ml of light liquid paraffin in one measuring cylinder and distilled water in the other, 200mg of the starch hyaluronate had been precisely weighed and added. For a whole 12h, these cylinders were put aside. The starch hyaluronate residue volume was measured in the two measuring cylinders after 12h. The formula below was used to compute the swelling index of starch hyaluronate.

$$S.I\ (\%) = \frac{\text{Volume of the residue in water-Volume of the residue in light liquid paraffin}}{\text{Volume of residue in light liquid paraffin}}$$

Gelling Property

By forming a 7 percent w/v dispersion of starch hyaluronate and starch in distilled water, and after heating this dispersion at 100°C for 30 minutes, the gelling property of the obtained starch hyaluronate as well as starch had been assessed.

Moisture Absorption

By putting the starch hyaluronate in the desiccator and keeping the relative humidity at 84 percent while it was at room temperature, the hygroscopic nature of the substance was assessed.

Particle Size Determination

The produced starch hyaluronate's particle size distribution was assessed using the sieve analysis technique, which included setting the standard sieves progressively in decreasing pattern and allowing the starch hyaluronate to pass through each sieve in turn. Once the quantity of starch hyaluronate collected on each sieve had been weighed, the particle size could then be calculated.

Density

In distilled water, starch hyaluronate was dispersed, and the density (g/cc) of the dispersion has been calculated with the liquid displacement technique [14].

Tapped Density & Bulk Density

A 50ml graduated measuring container was filled with the necessary amount of starch hyaluronate after being weighed. The initial volume of the starch hyaluronate was measured and recorded before the test. The final amount of starch hyaluronate was then calculated after 50 taps on the measuring cylinder. The initial and final volumes of the material in the measuring cylinders were used to calculate the tapped and bulk densities of the starch hyaluronate [15].

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

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

Angle of Repose

A new super disintegrant ideal attribute is that it must have excellent flow characteristics. The fixed funnel technique may be used to assess the prepared starch hyaluronate flow property. The fixed funnel technique gives the angle between the horizontal plane and the surface of the powder pile, commonly called the angle of repose [16]. This angle may be determined with the given equation:

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

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

Where h = *pile height,* θ = *angle of repose, and* r = *pile radius.*

Compressibility Index

The tapped as well as bulk density were used to compute the starch hyaluronate's compressibility index [18]. The starch hyaluronate inter-particulate interactions may be determined using the compressibility index. It may be calculated using the formula below:

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

Where Initial =*Loose bulk density*, Final=*Tapped bulk density*

FTIR (Fourier Transform Infrared Spectroscopy)

The functional group that was present in an unidentified molecule may be found using Fourier transform infrared spectroscopy. By using the FTIR spectrum, starch hyaluronate and potato starch were identified. The FTIR spectra of potato starch and starch hyaluronate were compared using potassium bromide at a spectrum of 4000-500cm^{-1} at 800MPa pressure for 5 to 10min to detect the ester functional group in the starch hyaluronate [17].

X-ray Diffraction

Using an X-ray diffractometer and a Ni filter, the typical nature (amorphous or crystalline) of starch hyaluronate was evaluated at 40mA, 45kV, and at full scale, or 2000 [18].

DSC (Differential scanning calorimetry)

Using a PerkinElmer 4000 model, Waltham, MA, DSC thermal analysis of starch hyaluronate was carried out in a 1:1 ratio of drug and super disintegrant. Indium was used to calibrate the instrument. Using dry nitrogen as the effluent gas, the samples were heated in aluminum pans. The thermograms were recorded at a 20°C/min of rate and in the temperature range of 20-200°C [19].

Scanning Electron Microscopy
It was utilized to determine the surface morphology of starch and starch hyaluronate.

Ester test
1 mg of starch hyaluronate was mixed with two millilitres of ethanol as well as one millilitre of 0.1 ml of sodium hydroxide. The shift of color had been observed upon adding a phenolphthalein indicator to this [20].

Nuclear magnetic resonance spectroscopy (NMR)
The chemical composition of a synthesized new super disintegrant was determined by the 1H NMR spectra Deuterated methanol (CD_3OD) and measured by Bruker 400MHz NMR spectrometer (Bruker, Billerica, MA) [19].

Preparation of nisoldipine fast-dissolving tablets

Table No. 1 contains the ingredients of a variant formulation of nisoldipine fast-dissolving tablets Accurately weighed the ingredients, and sieved # 120 to get a uniform size. Weighed and sieved ingredients were triturated in a clean and dry mortar and pestle as per composition. After all the ingredients were triturated, the drug was added and triturated. At two levels, superdisintegrant were added i.e. lower level (0) and higher level (5). The direct compression method was used to punch the tablets with a 10-station rotary compression machine ("Karnawathi Machineries Pvt, Ltd., Ahmedabad, India") [21].

Table 1: Formula of Nisoldipine FDTs employing starch hyaluronate

Ingredients (mg/tablet)	NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8
Nisoldipine	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
Starch hyaluronate (A)	-	5	-	5	-	5		5
Sodium starch glycolate (B)	-	-	5	5	-	-	5	5
Crospovidone (C)	-	-	-	-	5	5	5	5
Microcrystalline cellulose	50	50	50	50	50	50	50	50
Mannitol	35.5	30.5	30.5	25.5	30.5	25.5	25.5	20.5
Magnesium stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2
Aspartime	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100

Post-compression evaluation tests for nisoldipine fast-dissolving tablets

Thickness
Vernier calipers scale was utilized to find the thickness of the tablet. from each batch, six tablets were picked randomly and average thickness and standard deviation were measured [22].

Hardness
The tablet crushing load was the amount of force needed to compressively crush a tablet into pieces. It was evaluated with a Monsanto hardness tester [23]. From every batch of the formulation, ten tablets were randomly chosen, and the average reading was documented.

Friability
The tablet's friability was evaluated with the Roche Friabilator (Electrolab, India). With each turn of the plastic container, which spins at a speed of 25 rpm for 4 minutes, the tablets are dispensed six inches away. The friabilator was spun 100 times after receiving 20 pre-weighed tablets [24]. The tablets were dusted with a delicate muslin cloth and reweighed. The below formula provides the friability (F percent)

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

Where tablet weight before the test was denoted by W_0, tablet weight after test by W

Weight variation
The average weight of the twenty randomly selected tablets was determined. After every individually weighed tablet, the percentage deviation from the average was then calculated.

Wetting time (WT)
In a petri dish with a 10cm diameter, five circular tissue sheets were arranged. The petri dish received 10ml of water at 37^0 C ± 0.5^0 C that contained the water-soluble dye amaranth. The tablet was put softly on the surface of the tissue paper. The time taken by colored water to reach the tablets' top surface was recorded as the wetting time. Six tablets were chosen randomly from every batch of the formulation and tested; the average observation was recorded.

Water absorption ratio (WAR)
A double-folded tissue was placed in a small Petri dish consisting of 6ml of water. A tablet was kept on the tissue paper and allowed to be completely wet. The wetted tablet was then weighed [25].

The ratio of water absorption, R, was calculated with the following formula.

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

Where, W_a =, tablet weight after absorption, W_b = tablet weight before absorption

Content uniformity

Twenty tablets were chosen randomly, and the mean weight was determined. Tablets have been ground into a powder in a glass mortar. Drug content was measured spectrophotometrically at 237nm. Powder corresponding to 10 mg was weighed, diluted with 6.8 pH phosphate buffer, filtered, then measured [26].

***In-vitro* disintegration time**

At the base of the basket rack assembly, six glass tubes that are three long, open at the top, and pressed up against a ten-inch screen were the USP device to test disintegration. One tablet was put in each tube, and the basket rack was poisoned at a temperature of 37±2°C in a 1L beaker of buffer, and the duration required for the tablet to totally disintegrate without leaving any residue was recorded in seconds [27].

***In-vitro* drug dissolution studies**

Employing an 8-station dissolution test device (Electro TDL-08L) with a paddle, *in vitro* dissolution investigations were carried out. Fast-dissolving tablets were added to 900ml of 6.8 pH phosphate buffer at 37±0.5°C temperature and 50rpm as the dissolution medium [28]. At the pre-set intervals of 0, 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, and 60 minutes, the samples (5ml each time) were taken out and filtered using a 0.45 membrane filter. The samples were examined with a UV-Vis spectrophotometer at 237nm (Shimadzu).

Factorial design

To assess the interaction, and main effects of the independent variable on dependent outcomes as well as to statistically optimize the formulation components [29], a 2^3factorial design (two levels, three factors) was used. Data were processed with Design Expert® V7.0.0 software to produce polynomial equations and regression coefficients. Eight compositions (NF1-NF8) had been composed with 3 processing parameters i.e., disintegration time (DT) (Y1), cumulative percent dissolved of a drug in ten minutes (PD_{10}) (Y2), and dissolution efficiency ($DE_{10\%}$) (Y3**),** at two different levels of starch hyaluronate (A), sodium starch glycolate (B) and crospovidone (C) as independent variables [30].

Stability studies

An optimized formulation of nisoldipine tablets was put through accelerated testing under ICH and WHO standards by being stored in HDPE bottles for six months at 75°RH and 40°C temperatures. The physical features and drug release characteristics of these samples have been examined before and after being kept for six months. [31]

***In vivo* pharmacokinetic studies**

Both the pure drug and the optimized formulation were tested on male Wister rats. Male Wister rats were used as the animal model. The Institutional Animal Ethical Committee of the Balaji Institute of Pharmaceutical Sciences, narsampet, Warangal, accepted the pre-clinical study protocol (ApprovalNo.01/BIPS/IAEC/2022). In a wire cage with unrestricted access to water and food, three male Wister rats were housed. and their body weights ranged from 200 to 250g. Each day, the animals housed in these cages were subjected to a 12-hour cycle of light and darkness in a clean environment with a constant temperature of 20 to 25°C. Wister male rats, weighing 200-250g, were randomly selected and categorized into 2 groups of six each. One group got the pure medication (1.312mg/kg body weight), whereas the other group received an optimized formulation (1.312mg/Kg body weight). For 12h, rats were fastened before the study's initiation, and they had restricted access to water and food during the experiment. The oral feeding pipe delivered the dosage to the Wister rats. Blood was taken from a lateral tail vein after administering a moderate ether anesthetic to the rats at specified intervals of zero (pre-dosage), 0.5, 1, 2, 3, 4, 5, 6, 7, and 8h [32]. To avoid coagulation, these samples were placed into tubes containing 6 mg of the anticoagulant EDTA. After centrifuging (for 25min at 5000rpm), the samples of plasma were kept at -20°C for future analysis. Using a validated HPLC method, the plasma samples were examined to assess the pharmacokinetic characteristics [33].

RESULTS AND DISCUSSION

Synthesized starch hyaluronate as a new super disintegrant was a fine, free-flowing crystalline powder. Table 3 provides a summary of the new super disintegrants' physical and micrometric characteristics. Figures 1 and 2 depict the FTIR spectra of potato starch and starch hyaluronate respectively. A peak at 1697cm^{-1}, corresponding to the ester group, was seen in the starch hyaluronate FTIR spectra. Since there was no peak in the FTIR spectra of potato starch, it was deduced that hyaluronic acid treatment of potato starch resulted in the formation of an ester (starch hyaluronate).

The nisoldipine pure drug's spectrum (Figure 3) shows a strong absorbance band at 3319cm^{-1} because of N-H group stretching. The bands among both 2800 and 3250 cm^{-1} could be caused by benzene and aliphatic C-H connection stretching. Carbonyl groups of DHP's two side chains are responsible for two different absorption spectra at 1647 and 1703cm^{-1}. Two bands were produced by the NO2 stretching, one at 1487 cm-1 and another at 1309 cm-1. The benzene ring C-C attachment was represented by the band at 1493 cm-1. The C-O stretch causes the two bands at 1211 and 1105cm^{-1}. Whereas FTIR spectra of nisoldipine-starch hyaluronate (Fig.4) demonstrated similar characteristic bands at 3318.59(-NH), 2960.30 and 3246.62(-CH) 1647.58 and 1701.63(-COO), 1487.65 and 1308.58(NOO), 1211.34 and 1105.04. It was determined from the spectrum that starch hyaluronate did not interact with the chosen drug.

same signals of charged particles within tetrahydropyran nucleus of the sugar moieties present in both Starch as well as HA. The methyl (-CH_3) protons of the N-acetyl group of HA and the 6^{th} position of sugar moiety in starch appeared as an intense signal at 1.15 to 1.19 ppm. The characteristic appearance of the signal at around 4.57 and 4.85 ppm conforms towards the two anomeric charged particles connected to such carbons just next to an oxygen molecule of sugar present in Starch and HA. The amine proton (-NH) appeared at 5.2 ppm as a doublet due to the coupling with

the neighbouring ring carbon proton. It was confirmed that the disappearance of the carboxylic hydroxyl proton [-C(=O) OH] of the HA in the ^{1}H-NMR spectrum as it was converted to ester linkage between the HA and starch. Hence it confirmed that both the starch and hyaluronic acid were bonded together with the ester linkage shown in (fig.7)

XRD of starch hyaluronate indicated characteristic spectra at 2 theta angles at 5.673^{o},9.950^{o,} 11.28^{o}, 14.175^{o}, 15.061^{o}, 17.187^{o}, 19.730^{o}, 22.263^{o}, 24.060^{o}and 26.260° It indicated the crystalline nature of starch hyaluronate and depicts in (fig 8). The SH and potato starch SEM were shown in (figs 9 and 10 respectively). Starch hyaluronate has been discovered to be crystalline, whereas potato starch was found to be amorphous.

Table 2: The starch hyaluronate physical as well as micromeritics characteristics

Specifications	Indication
Solubility	Both organic and aqueous solvents examined were insoluble.
pH (1% w/v aqueous dispersion)	5.21±0.06
MP (ºC)	253±0.001
Viscosity (1% w/v aqueous dispersion) (cps)	1.042±0.004
SI (%)	44.66 ±0.02
Gelling property	It does not have the same gelling characteristics as potato starch.
Moisture absorption (%)	4.3±0.2
Density (g/cc)	0.63±0.01
Particle size (μm)	24±0.06
Angle of repose	23.47 ±1.56
Bulk density (g/cc)	0.52 ±0.007
CI (%)	11±1
Hauser's Ratio	1.15±0.03
Ester test	colorless

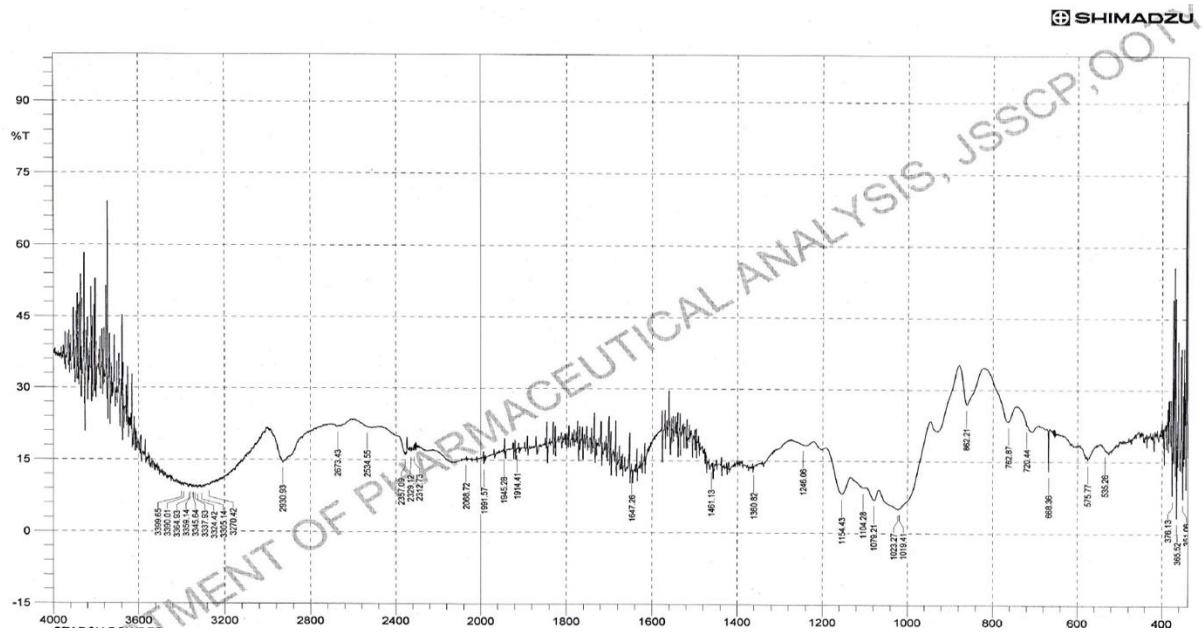

Fig. 1: FTIR spectra of potato starch

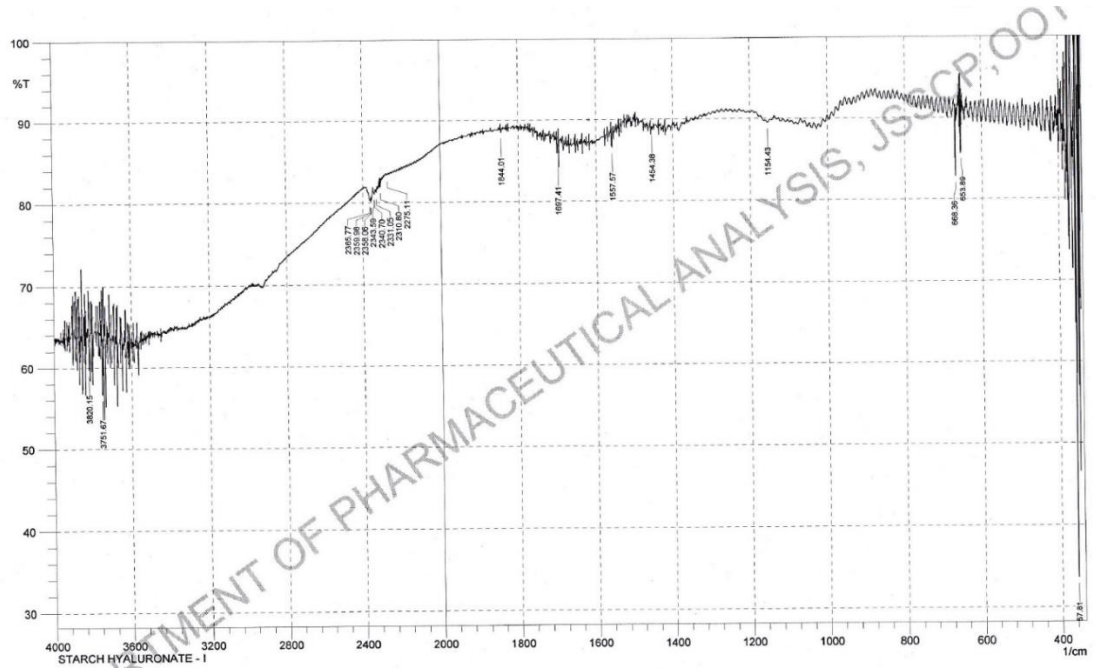

Fig. 2: FTIR spectra of starch hyaluronate

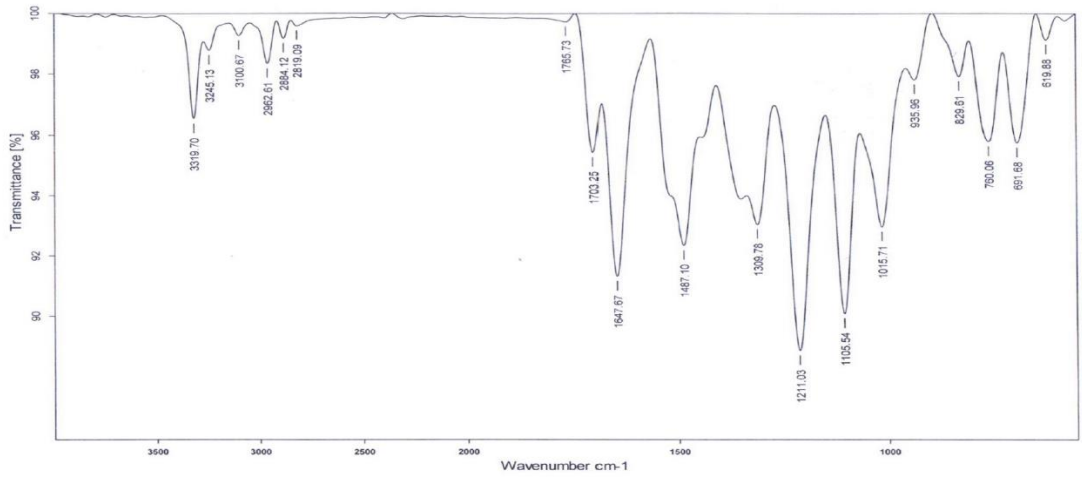

Fig. 3: FTIR spectra of nisoldipine

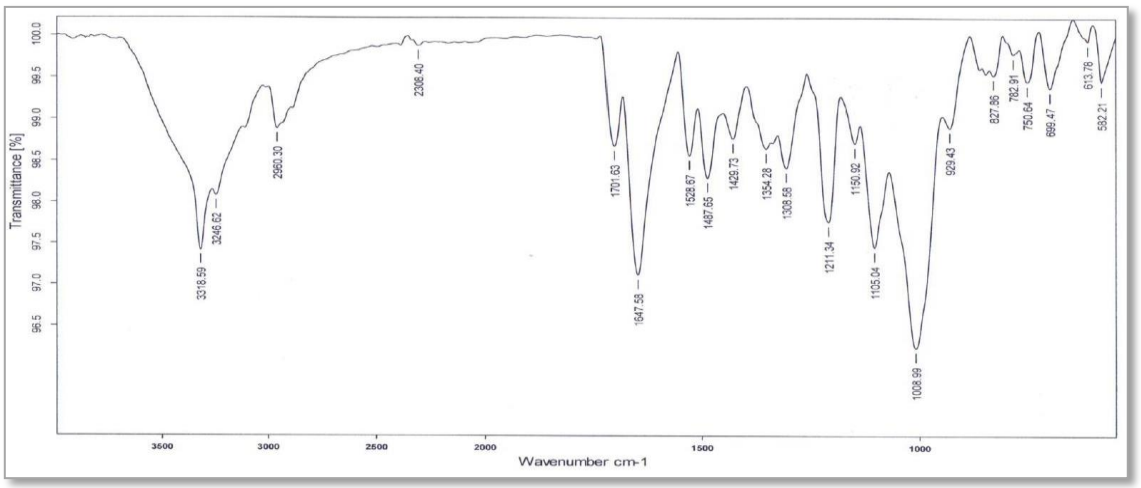

Fig. 4: FTIR Spectra of Nisoldipine and Starch hyaluronate

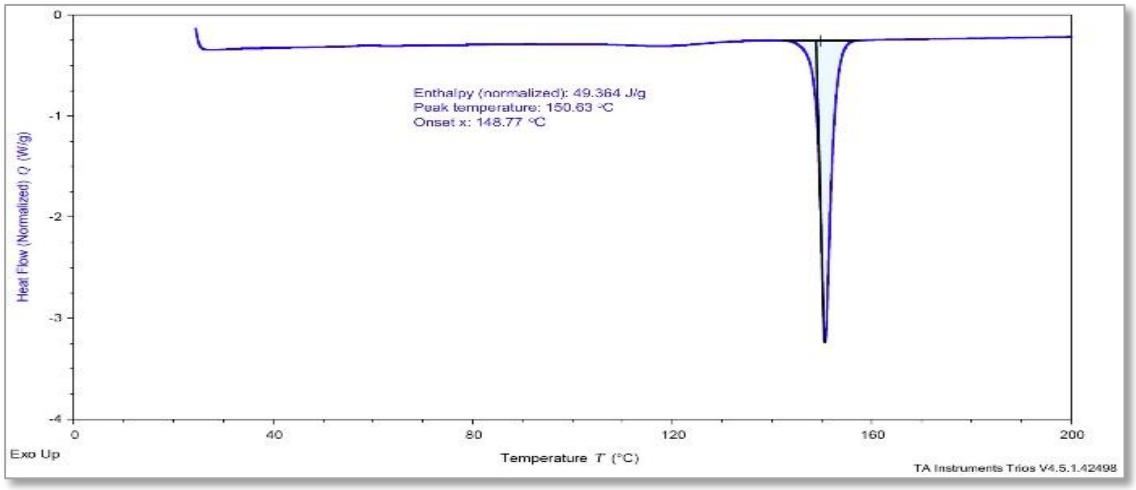

Fig. 5: DSC thermogram of nisoldipine

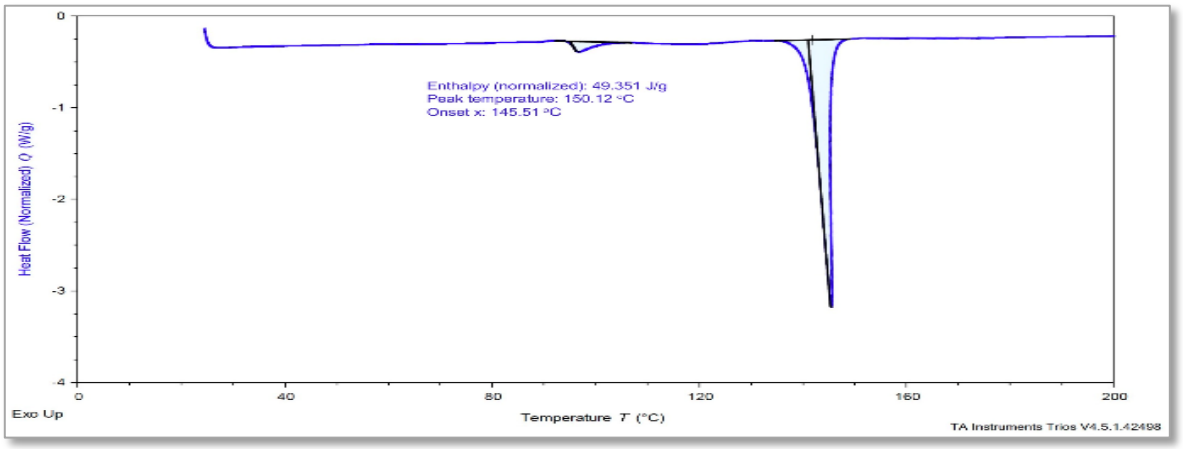

Fig. 6: DSC thermogram of nisoldipine with starch hyaluronate

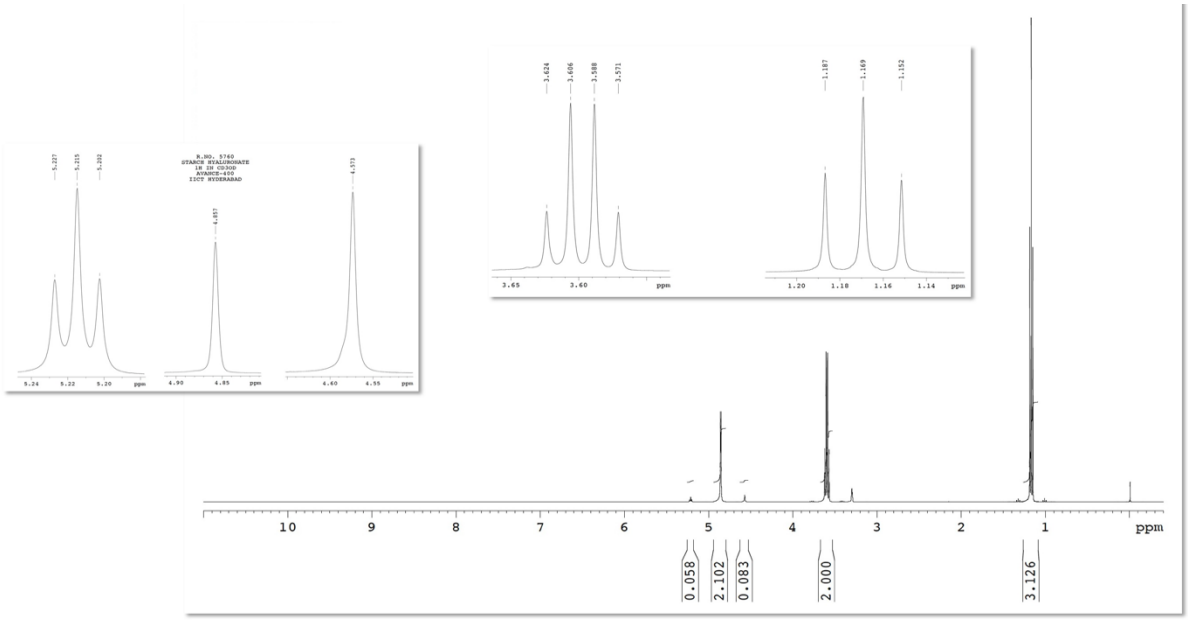

Fig. 7: Proton nuclear magnetic (1H NMR) of starch hyaluronate

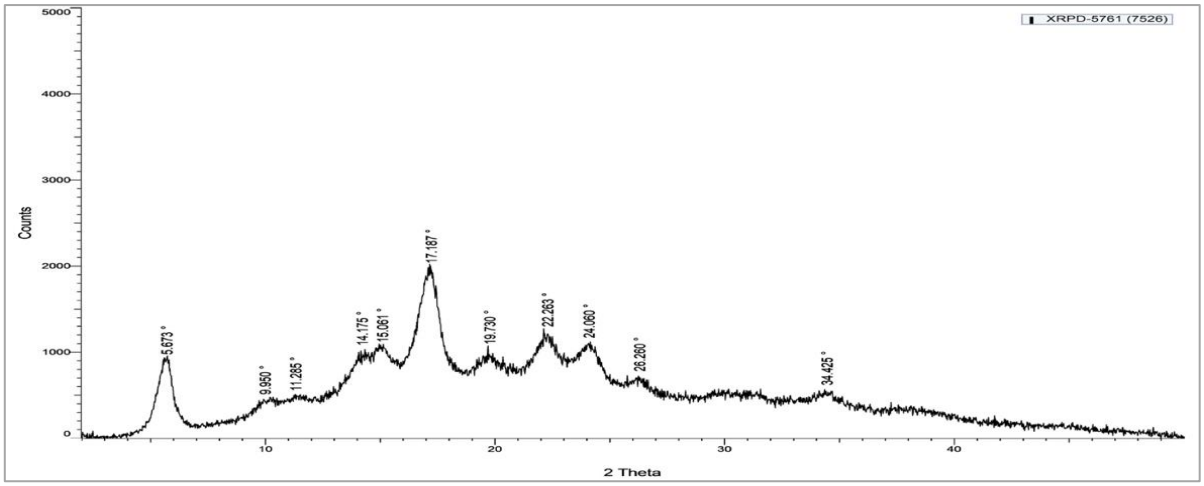

Fig. 8: X-Ray diffraction pattern of starch hyaluronate

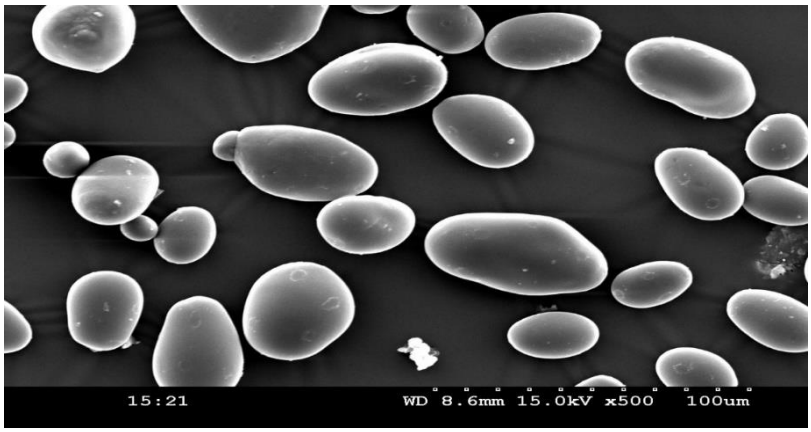

Fig. 9: SEM image of potato starch

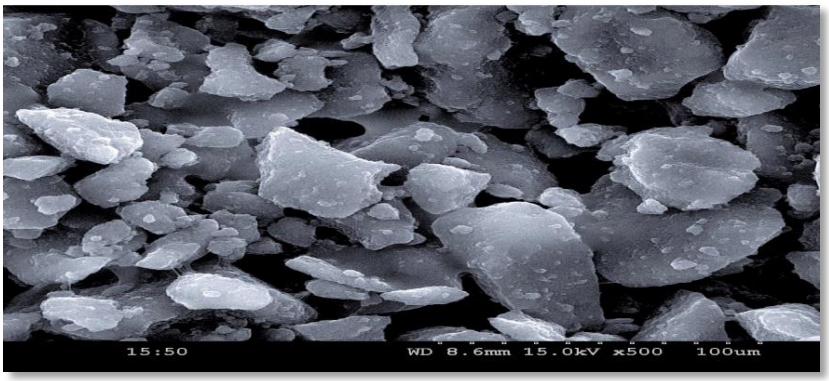

Fig. 10: SEM image of starch hyaluronate

Evaluation tests for nisoldipine fast-dissolving tablets

Hardness

Nisoldipine tablets passed the official IP hardness test with a hardness rating of 3.8 ±0.11 to 4.0±0.77kg/cm^2. Table 3 contains the data for hardness. All of the formulas had enough strength to resist handling, packaging, storing, and transportation without breaking.

Friability

Nisoldipine fast-dissolving tablets were determined to have a friability of less than 1 percent, passing the official IP friability test. Table 3 contains the findings of the friability analysis. All tablets meet IP requirements for strong mechanical strength and can endure mechanical shocks while being handled or transported.

Drug content uniformity

A range of 97.16±1.01 to 99.77±1.58 mg/tab of nisoldipine tablets was determined to be the drug content uniformity. Table 3 represents the outcomes of this uniformity. The official IP test for drug content uniformity was passed by all of the tablets (i.e., 85 to 115 percent of the average content).

Wetting time and water absorption ratio

The super disintegrant utilized in the formulation affects the nisoldipine tablets' WT and WAR. Table 3 displays the findings of these ratios. WT and WAR (Fig 8) have been identified to be between 352±0.26 to 20±1.37 sec and 6±0.42 to 76±1.46 respectively.

Table 3: Physical properties of nisoldipine FDTs

F.NO	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	#Content uniformity (%)	Water absorption ratio	Wetting time (sec)	DT (Sec)
NF1	101±0.67	1.4±0.05	3.8 ±0.45	0.63±0.12	99.11±1.63	20±1.37	352±0.26	820±2
NF2	101±0.98	1.2±0.14	3.9 ±0.12	0.61±0.07	98.45±1.24	61±1.21	21±0.24	24±2
NF3	100±0.28	1.3±0.36	4.0 ±0.34	0.64±0.15	98.16±1.17	52±1.92	26±0.45	29±1
NF4	99±0.82	1.2±0.90	3.9 ±0.89	0.59±0.22	97.16±1.01	71±1.68	10±0.65	12±3
NF5	100±0.45	1.3±0.23	3.8 ±0.11	0.62±0.08	99.21±1.22	65±1.33	22±0.83	23±2
NF6	100±0.73	1.2±0.14	3.9 ±0.43	0.58±0.14	99.27±1.39	72±1.83	9±0.38	11±2
NF7	101±086	1.4±0.64	4.0 ±0.12	0.61±0.28	98.18±1.89	73±1.73	7±0.86	10±2
NF8	101±0.71	1.4±0.28	4.0 ±0.77	0.58±0.19	99.77±1.58	76±1.46	6±0.42	7±3

*All the values are expressed as mean ±SD, where n=3, SD: Standard Deviation.

***In vitro* disintegration time**

Table No. 3 represents the DT of all prepared tablets ranging from 820±2 to 7±3seconds, according to the findings, disintegration time was influenced by the amount of super disintegrants applied to a composition. Among all formulations, the formulation (NF8) with starch hyaluronate, sodium starch glycolate, and crospovidone each of 5%, resulted in a shorter disintegration time, i.e 7±3 sec. The optimized formulation NF2 had a disintegration time of 24±2seconds, which was considerably less than the tablets with a DT of 47.44±2.49 sec that were formulated by Nani Parfati, *et al*. [34] NF2 and NF8 formulations both have shorter disintegration time as specified by USFDA. The order of disintegration time of nisoldipine fast dissolving tablets was found to be NF8<NF7<NF6<NF4<NF5<NF2<NF3<NF1.

***In vitro* dissolution study**

The formulation NF6, which used 5% starch hyaluronate and 5% crospovidone, demonstrated 99.6±0.32% dissolved in 10 minutes. As a result, formulation NF6 was regarded as the ideal fastest-dissolving tablet formulation of nisoldipine. Formulation NF2, which uses a new synthetic superdisintegrant, starch hyaluronate, at a concentration of 5%, was similarly equivalent (92.8±0.96%) to Formulation NF6, which uses two superdisintegrants, starch hyaluronate (5%) and crospovidone (5%). As a result, when compared to NF6, the NF2 formulation with single starch hyaluronate as a new superdisintegrant was found to be more cost-effective. Figure 11 and Table 4 showed the results of an *in vitro* dissolution

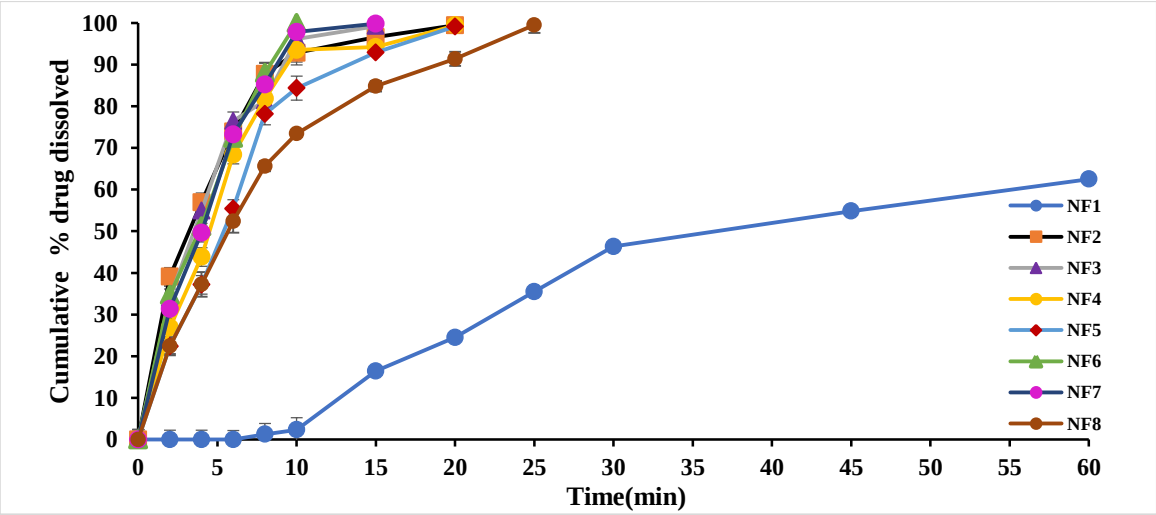

Fig 11: *In vitro* dissolution profile of nisoldipine FDTs (NF1–NF8) (n=6, mean ± SD)

Table 4: Nisoldipine FDTs dissolution parameters

Time (min)	NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8
PD_{10}	2.3±0.25	92.8±0.96	83.32±0.68	97.5±0.26	96.16±0.83	99.6±0.32	98.3±0.28	73.4±0.68
DE_{10}%	0.00486	0.60804	0.47034	0.5351	0.58936	0.59222	0.57664	0.4287
DE %	0.486	60.804	47.034	53.51	58.936	59.222	57.664	42.87
No of Folds increase in DE	-	125	96.7	110	121.26	91.9	78.74	88.2

*Every value is stated by mean ± SD, where n=3. PD_{10} Percent dissolved in 10min, DE_{10} %-Dissolution efficiency in 10min.

A 2^3 factorial design was used in the experiment's design.

Superdisintegrants like starch hyaluronate (A), crospovidone (B), and sodium starch glycolate (c) are independent variables, whereas disintegration time, PD in 10min (PD10), and DE in 10min (DE_{10}%) are response variables (dependent variables) that were co-related utilizing polynomial regression analysis [37]. Equations 1, 2, and 3 were given as polynomial equations for disintegration time, PD_{10}, and DE_{10}%, correspondingly.

Y1 (DT) = +117.00+103.50A+102.50B+104.25C-98.50AB-99.75AC-98.25BC+96.25ABC-Eq1(R2 = 1.000
Y2 (PD_{10}) = +80.08+10.74A+8.04B+11.11C-13.41AB-15.44AC-13.38BC+5.66ABC -Eq2(R2 = 1.000)
Y3 (DE_{10}%) = +47.57+6.54A+2.70B+7.11C-8.62AB-10.16AC-07.11BC+4.85ABC---Eq3(R2 = 1.000)

Disintegration Time

Response and Contour plot shows that DT of FDTs decreases, as the concentration of SH (A), SSG(B), and CP (C) increases. Using contour and 3D response surface plots, the main and interactive effects of the independent variables (A, B, C, AB, AC, BC, and ABC) on the disintegration time were further clarified. Figure 12.1 shows the effects of SH and SSG on DT. Figure 12.2 shows the effects of SH and CP on DT. Figure 12.3 shows the effects of SSG and CP on DT. The contour plots were seen as linear. From the plot (contour and response surface), conclude that when the concentration of super disintegrant ranges from 3.75 to 5%, less DT of the tablet was achieved.

Cumulative percent drug dissolved and dissolution efficiency

The cumulative % drug release from the fast-dissolving tablets in 10 minutes was discovered to be between 2.3±0.25 to 99.6±0.32 percent, as indicated in Table 4. The contour plots were nonlinearly indicating a non-linear relationship between the percent dissolved in 10 minutes and dissolution efficiency in 10 minutes. Based on the plot (response surface and contour), we can deduce that when the super disintegrant concentration ranges from 3.75 to 5%, the tablet achieves a greater Percent dissolved in 10 minutes and dissolution efficiency in 10 minutes. The effects of SH (A), SSG (B), and CP (C) and their interaction on disintegration time, percent drug dissolved in ten minutes, and dissolution efficiency in 10 minutes are tabulated in table 5. Figures 13.1, 13.2, and 13.3 depict, the effects of SH & SSG, SH & CP, and SSG & CP on $PD_{10.}$ Figures 14.1, 14.2, and 14.3 depict, the effects of SH & SSG, SH & CP, and SSG & CP on DE_{10}%

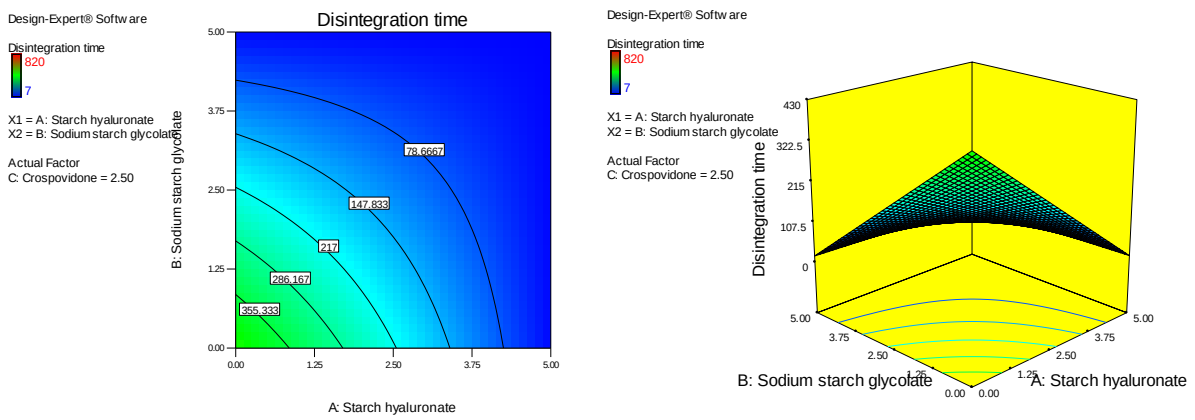

Fig. 12.1: Contour plot (A) and Response 3D surface plot (B) illustrating the impact between starch hyaluronate as well as sodium starch glycolate on disintegration time

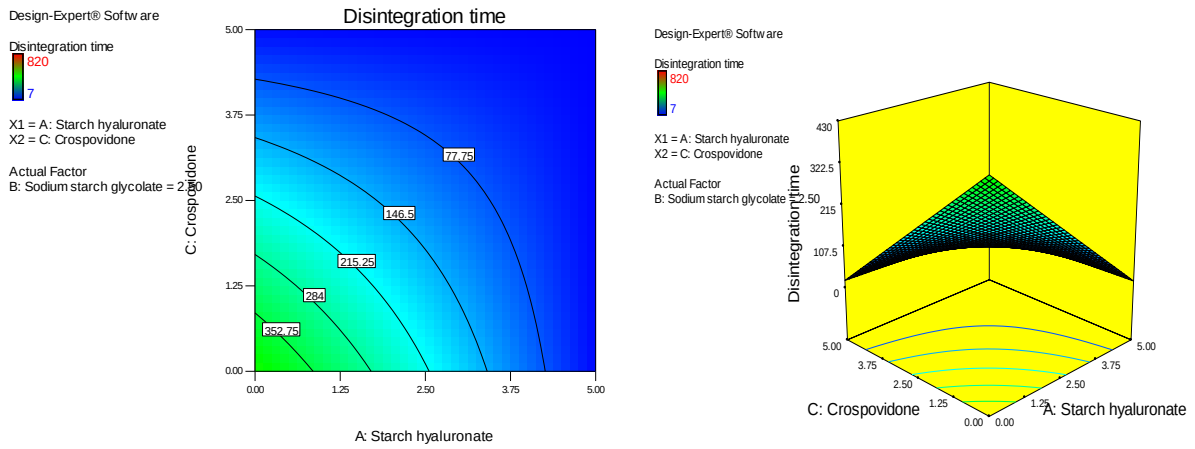

Fig. 12.2: Contour plot (A) and Response 3D surface plot (B) illustrating the impact between starch hyaluronate as well as crospovidone on disintegration time

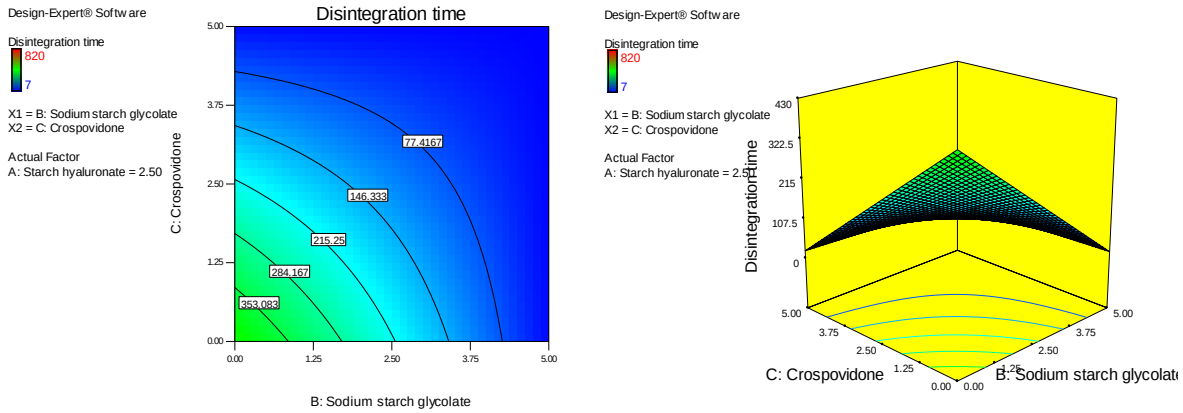

Fig. 12.3: Contour plot (A) and Response 3D surface plot (B) illustrating the impact between sodium starch glycolate as well as crospovidone on disintegration time

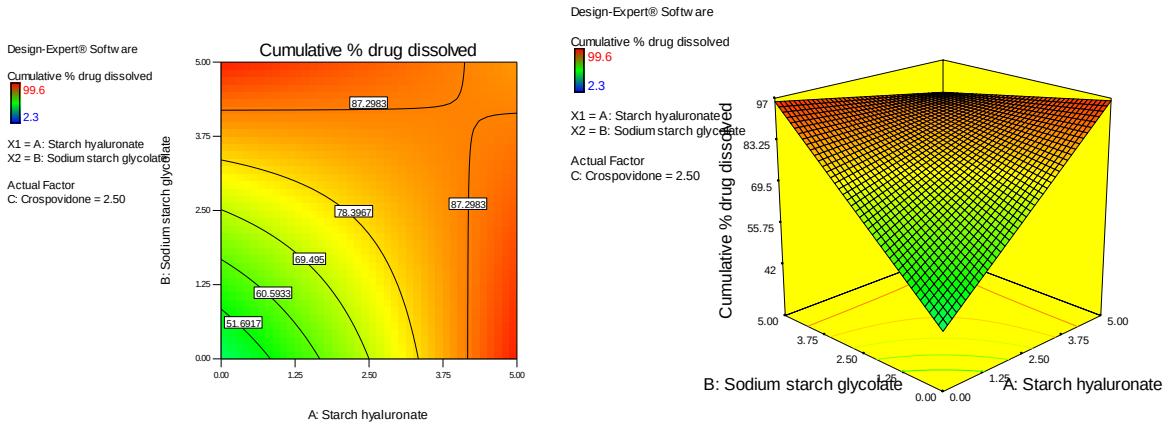

Fig. 13.1: Contour plot (A) and Response 3D surface plot (B) illustrating the impact between starch hyaluronate as well as sodium starch glycolate on cumulative percent drug dissolved

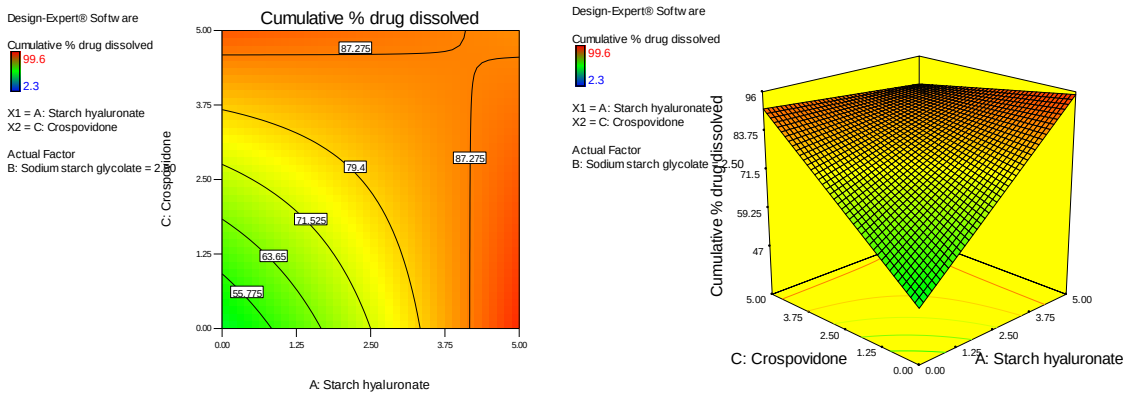

Fig. 13.2: Contour plot (A) and Response 3D surface plot (B) illustrating the impact between starch hyaluronate as well as crospovidone on cumulative percent drug dissolved

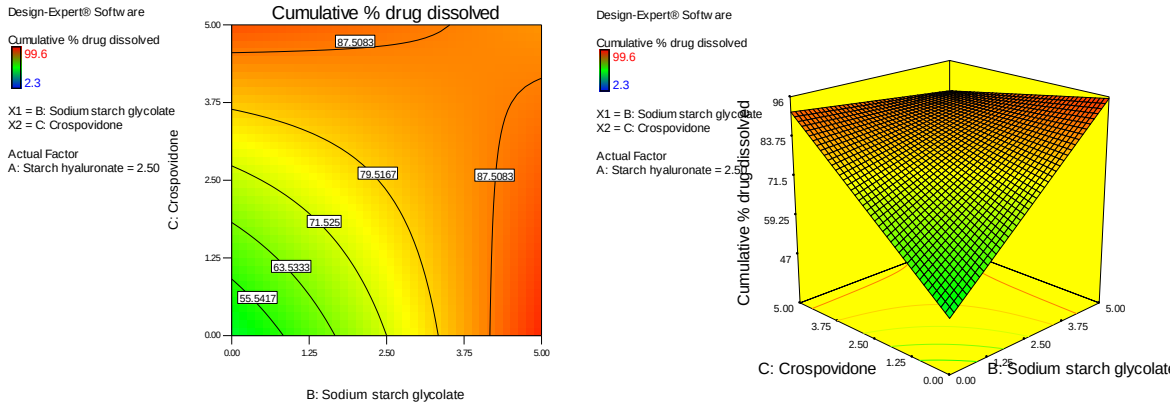

Fig. 13.3: Contour plot (A) and Response 3D surface plot (B) illustrating the impact between sodium starch glycolate as well as crospovidone on cumulative percent drug dissolved

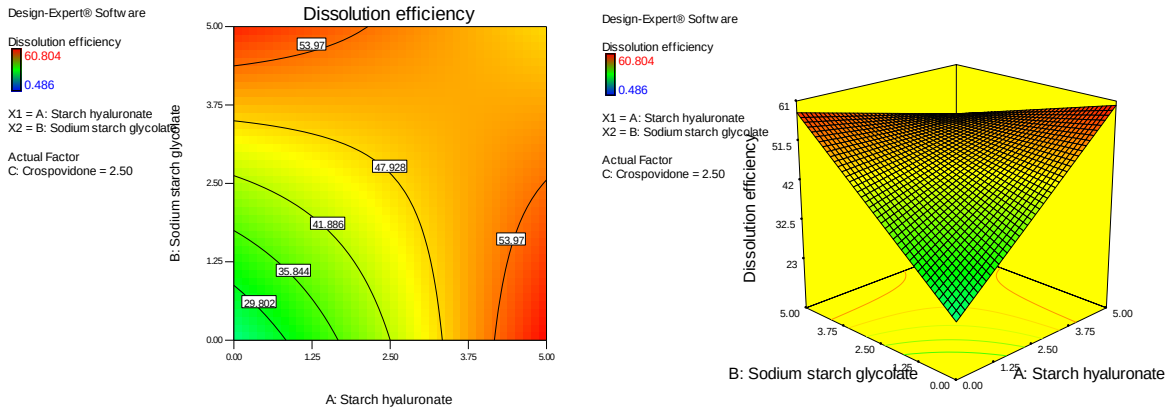

Fig. 14.1: Contour plot (A) and Response 3D surface plot (B) illustrating the impact between starch hyaluronate as well as sodium starch glycolate on dissolution efficiency

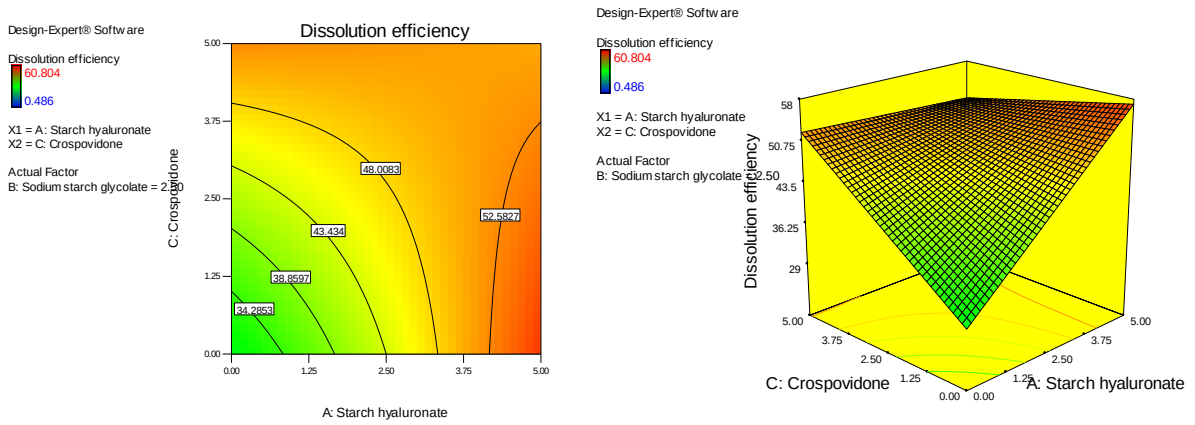

Fig. 14.2: Contour plot (A) and Response 3D surface plot (B) illustrating the impact between starch hyaluronate as well as crospovidone on dissolution efficiency

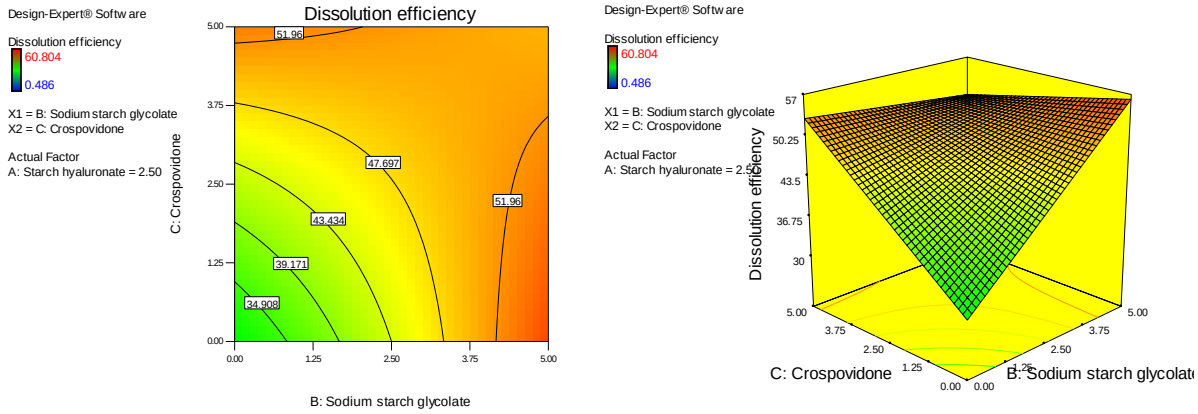

Fig. 14.3: Contour plot (A) and Response 3D surface plot (B) illustrating the impact between sodium starch glycolate as well as crospovidone on dissolution efficiency

Table 5: Interactions among super disintegrants as their impact on different responses

Interactions between super disintegrants	Effect on Disintegration time	Effect on Cumulative Percent dissolved in 10 min	Effect on dissolution efficiency
A-Starch hyaluronate	+	+	+
B- Sodium starch glycolate	+	+	+
C- Crospovidone	+	+	+
AB	-	-	-
AC	-	-	-
BC	-	-	-
ABC	+	+	+

Optimized formula

From the above investigation outcome, it was revealed that formulation NF2 employing newly synthesized superdisintegrant i.e. starch hyaluronate in the concentration range of 5% showed maximum drug dissolution and dissolution efficiency in ten minutes. Therefore, NF2 formulation can be considered as an optimized formulation that has been proven to be more cost effective.

Stability studies

The best formulation (NF2) of nisoldipine tablets using starch hyaluronate was shown to be stable under accelerated conditions, according to stability experiments. Table 6 lists several physical characteristics of the improved formulation, and figure 15 displays the dissolution profile of the formulation before and after storage for six months.

Table 6: Physical characteristics of optimized nisoldipine FDTs before and after storage

Retest time for Optimized formulation (NF2)	Wetting time (sec)	DT (Sec)	*In-vitro* drug release profile *(%)*	Drug content (%)
0-days	21±0.24	21±2	92.08±0.966	99.46±1.23
30 days	22±1.02	18±3	92.38±1.14	101.1±1.28
60 days	21±0.69	21±1	93.93±1.67	99.91±1.47
120 days	23±0.28	20±2	93.12±1.56	99.08±1.05
180 days	21±0.84	21±1	92.04±1.31	99.98±1.12

These values are written in mean ± SD, where n=3.

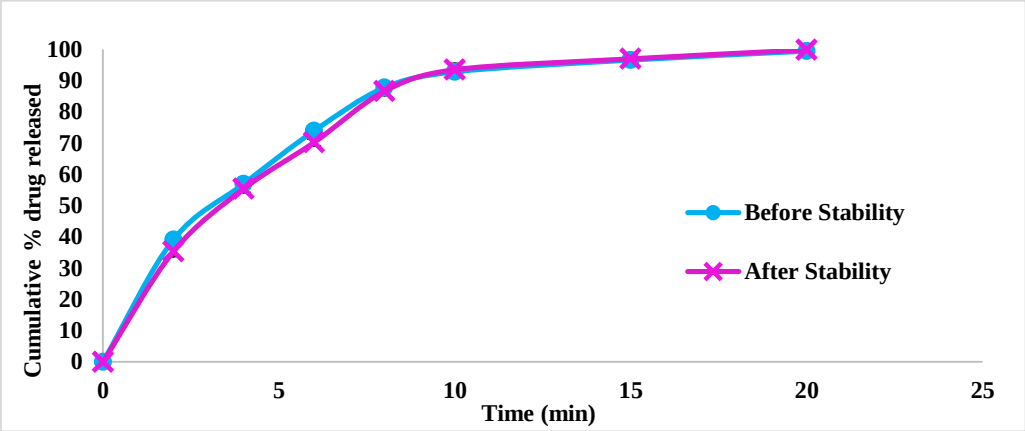

Fig. 15: Dissolution profiles of nisoldipine FTDs NF2 before and after six months of storage during the stability study

***In vivo* pharmacokinetic studies**

The area under the plasma concentration (AUCs) of nisoldipine fast-dissolving tablet and pure drug after oral administrations were 43.48 and 19.65µg/ml/h, respectively, with corresponding mean Tmax values was 1.2 and 1.17 hr. The Cmax and absorption rate constant (K_a) for optimized formulation NF2 was found to be greater than that of plasma concentration of nisoldipine pure drug i.e., Cmax value was 11.79 µg/ml and Ka was 1.202 h^{-1} for optimized fast dissolving tablet formulation whereas Cmax is 3.34µg/ml & Ka is 2.632(h^{-1}) for a pure drug. The results indicated starch hyaluronate (new super disintegrant) helps in the increase in plasma concentration and absorption rate constant of nisoldipine. The MRT of the pure drug was found to be 3.653 (hr) whereas the optimized formulation employing starch hyaluronate was found to be 2.89 (hr) which means optimized formulation NF2 showed a decrease in mean residence time. Optimized formulation resulted in an increase in relative bioavailability (221.2%) than the nisoldipine pure drug, other pharmacokinetic parameters in the current work are shown in Table 7.

Table 7: Summary of pharmacokinetic parameters

Parameters	Pure drug	NF2
C_{max}(µg/ml)	3.34	11.79
T_{max}(hr)	1.17	1.2
$AUC_{0-\infty}$ (µg.h/ml)	19.65	43.48
BA (%)	-	221.2
K_a(h^{-1})	2.632	1.202
K_{el}(h^{-1})	0.1437	0.468
$AUMC_{0-\infty}$ (µg.h/ml)	136.33	134.66
MRT(h)	3.653	2.89

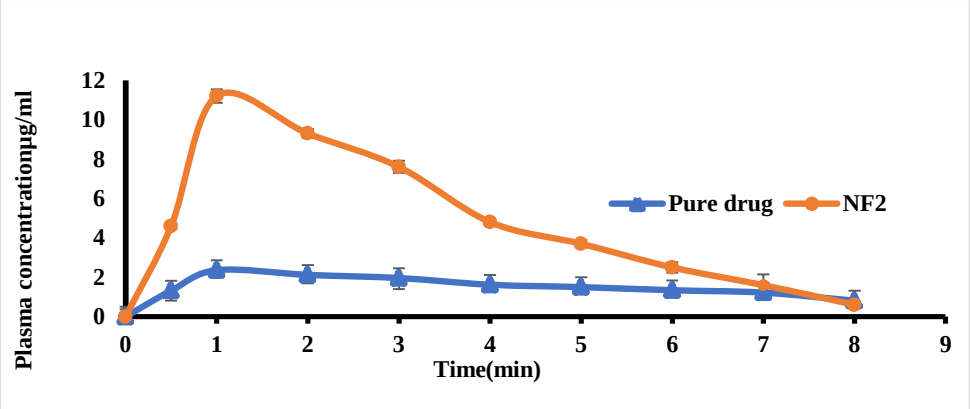

Figure 16. Optimized nisoldipine (NF2) and pure drug formulation plasma concentration-time profile

CONCLUSION

Employing crospovidone, sodium starch glycolate, and starch hyaluronate as a new super disintegrant, the nisoldipine FDTs were successfully made by direct compression technique. The study's findings showed that the starch hyaluronate synthesized by esterifying potato starch and hyaluronic acid showed good flow characteristics. The optimized formula (NF2), which contained 5% starch hyaluronate, was stable under accelerated stability conditions and demonstrated the maximum drug dissolution, and increased relative bioavailability. Overall, it was determined that starch hyaluronate was a super disintegrant that can also be used to make tablets that dissolve quickly, allowing the medicament to be released immediately Hence starch hyaluronate can also be recommended as a new superdisintegrant in the development of fast-dissolving tablets.

CONFLICT OF INTEREST

The authors of this work disclose no conflicts of interest.

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