RESEARCH ARTICLE

Design and Evaluation of Fast Dissolving Tablets of Anti-Hypertensive Poorly Soluble Drug through 2^3 Factorial Designs

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ABSTRACT

The purpose of this study was to improve the anti-hypertensive effect of telmisartan fast-dissolving tablets by formulating them with a synthetic superdisintegrant. The effects of three factors—SH [A], SSG [B], and CCS [C] on dependent variables like the in vitro method, water absorption, and percent drug release at 10 minutes were investigated in this survey using three factors in a two-level (2^3) factorial design. The production of starch hyaluronate, a fine, freely-flowing crystalline powder, was accomplished by the esterification process. The ester bond between starch and hyaluronic acid was confirmed by FTIR analysis, and starch hyaluronate did not interact with the medication in the DSC testing. The formulation with the shortest disintegration time, TF2, took only 24±0.2 seconds to complete. In ten minutes, 93.68 ±1.32% of the medicines from the optimal composition had dissolved. Moreover, a mixture containing a 5% level of starch hyaluronate was refined and could be utilized in creating quickly dissolving tablets. This formula also improved clinical compliance during the effective treatment of hypertension. The optimized composition was able to achieve a low concentration of a novel synthetic super disintegrate in a short amount of time.

Key words: factorial design, Telmisartan, pH, Superdisintegrant, Antihypertensive

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INTRODUCTION

Despite significant advancements in drug delivery, the oral route remains the preferred technique for providing therapeutic agents, leading to a high incidence of patient consent. This is because it allows for accurate dosing, economical therapy, self-medication, and convenience of administration[1-2]. Conventional pill dosage types are most commonly employed[3]. Nevertheless, "Dysphagia," or difficulty swallowing, is a serious drawback of these tablets or capsules[4-6]. They don't follow prescriptions because of their dysphagia condition, which results in non-compliance with prescriptions[7]. It is beneficial for individuals who have difficulty swallowing tablets to use fast-dissolving tablets (FDTs). To hasten the disintegration process, superdisintegrants are materials incorporated into tablets that dissolve rapidly. Telmisartan is a multiple-action cardiovascular drug used to treat the following conditions: cardiac arrhythmia, severe hypertensive crisis, and angina pectoris. Under these circumstances, quick action is necessary. Thus, starch hyaluronate—a safe, recently produced modified starch superdisintegrant—can be used to create telmisartan into fast-dissolving tablets[8]. Recently, quality by design (QBD) has become more and more popular, drawing researchers to develop and enhance different medication delivery methods. To grasp the elements and how they influence each other on the outcomes through a specific collection of tests, QBD is a crucial and beneficial part [9]. When it comes to analyzing components with two-level variability, Factorial Design is the most effective statistical optimization strategy available. Low solubility is a characteristic of the biopharmaceutical classification system II medication telmisartan. A novel superdisintegrant called starch hyaluronate was used in the development of FDTs in order to improve their solubility, dissolving rate, absorption, and therapeutic action. This study focuses on a 23-factorial design Utilizing both SSG, CP, and starch hyaluronate as independent factors, this study observed the effects of disintegration time (DT) and percentage of medication dissolved within 10 minutes in the presence of a new super disintegrating agent in an effort to optimize telmisartan fast-dissolving tablets.

MATERIALS AND METHODS

Materials

Through S. D. Fine (Hyderabad, India), hyaluronic acid, Telmisartan, starch (potato), crospovidone, and sodium starch glycolate have been obtained. The starch hyaluronate used has been prepared in a lab. Finer Chemicals Ltd., Mumbai, India was the supplier of talc, magnesium stearate, aspartame, and microcrystalline cellulose that we bought.

Development of Starch Hyaluronate as a Novel Superdisintegrating Agent[10]:

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Table : 1 Formulae of Telmisartan fast dissolving tablets employing with starch hyaluronate

Ingredient(Mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Telmisartan	40	40	40	40	40	40	40	40
Starch hyaluronate (A)	---	20	---	20	---	20	---	20
SSG (B)	---	---	20	20	---	---	20	20
CCS (C)	---	---	---	---	20	20	20	20
Mannitol	30	20	20	10	20	10	10	---
MCC	112	112	112	102	112	102	102	92
Talc	4	4	4	4	4	4	4	4
Magnesium Stearate	4	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200	200

Ten grams of potato starch were added to a 15 milliliter bottle of distilled alcohol. After dispersing 10 grams of hyaluronic acid in filtered water and mixing it into the starch slurry, 10 milliliters of NaOH were added to bring the slurry's pH down to 3.5 and it was then let to stand for the esterification process to occur. After that, distilled water was used to rinse the entire mixture in order to remove any remaining HA, and it was dried at 60 °C to create a dry mass. After being homogenized by passing through # 120, the dried starch hyaluronate is stored in a desiccator[10].

Starch hyaluronate characterization

To find out if the new super disintegrant can dissolve, we used organic solvents like petroleum ether, acetone, dichloromethane, CHCl3, and DMSO. Using a pH meter, we checked the pH level. The melting point can be found by using a melting point apparatus. We put the starch hyaluronate in a desiccator at room temperature with 84% humidity to see how much moisture it absorbs. We measured the viscosity with an Ostwald viscometer. To see how well starch hyaluronate and starch gel, we dissolved them in water and heated them at around 100 °C for 30 minutes. The size of starch hyaluronate particles was determined using sieve analysis. We used the liquid displacement method to figure out the density (g/cc) of the starch hyaluronate dispersion in distilled water. The bulk and tapped density were calculated using an equation.

$$LED = \frac{Mass\ of\ powder}{volume\ of\ packing}$$

$$\text{TBD} = \frac{Mass\ of\ powder}{Tapped\ volume\ of\ packing}$$

The angle of repose can be calculated using the equation below, and the flowability can be determined using the fixed funnel method.

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

$$\theta = angle\ of\ repose : h = hight\ of\ pile : r = radius\ of\ pile$$

The compressibility index was calculated with the equation given below.

$$\%\ \text{Carr's Index} = \frac{TBD - LBD}{TBD} \times 100$$

Table 2: Factors and their levels used in a factorial experiment.

Factor code	Factors considered	Low (-1)	Elevated (+1)
A	SH (mg)	0	10
B	SSG (B)	0	10
C	CCS (C)	0	10

Swelling index (SI)

Two measuring cylinders were filled with 200 mg of precisely weighed starch hyaluronate, 10 ml of distilled water, and light liquid paraffin each. These cylinders were left for 12 hours and protected. The value of SH in each cylinder was recorded. An ester test was performed by mixing together 0.1 ml of NaOH, two milliliters of ethanol, and one milliliter of SH and observing a color change after adding a phenolphthalein indicator.[10]

Under an 800MPa stress, the FTIR spectra of potato starch and a new superdisintegrant were obtained using KBR in a Bruker FTIR (Tokyo, Japan) for 5–10 minutes from the spectral region of 500 to 4000 cm–1. Telmisartan and telmisartan with starch hyaluronate (1:1) were analyzed on a Perkin Elmer thermal analyzer using DSC at temperatures ranging from 50 to 300 °C with a heating rate of 10 °C/min. Finally, a scanning electron microscope was used for further examination. Three substances, SH, SSG, and CP, are used in the direct compression method to make telmisartan FDTs. The components for different formulations of telmisartan FDTs are listed in Table No. 1. The concentrations of superdisintegrants were selected at two levels: zero at the bottom and ten percent at the top. To ensure uniform particle size, each component was passed through a 120-mesh screen before being combined.

Table : 3 Starch hyaluronate physical and micrometric properties

Content	Starch hyaluronate
Solubility in aqueous and organic solvents	Insoluble
pH (1% w/v aqueous dispersion)	4.91±0.02
Bulk density (gm/cm3)	0.51±0.008
Tapped density (gm/cm3)	0.68±0.02
The angle of repose (θ)	22.25±1.42
Carr's index (%)	12±1
Hauser's ratio	1.19±0.01
Melting point (°C)	253±4
Gelling property	No gel was formed
Swelling index %	98±0.07
Moisture absorption	4.4±0.1
Viscosity1% (cps)	1.051±0.003
Average particle size	24 µm

Table : 4 Physico-chemical evaluation tests of Telmisartan FDTs

S. No.	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Content uniformity (%)	WAR	WT (sec)	DT (Sec)
TF1	198±1.35	3.6±0.84	0.62±0.278	99.12±1. 34	25±1. 92	360±0. 52	760±0.2
TF2	201±1.44	3.8±0.63	0.61±0.663	98.86±1.86	70±1. 28	25±0. 50	24±2.5
TF3	202±1.89	3.9±0.49	0.62±0.552	99.53±1.57	65±1. 38	21±0. 67	26±2 .6
TF4	201±1.47	4.1±0.27	0.59±0.96	98.49±1.36	75±1. 46	11±0. 63	11±1.6
TF5	202±1.93	3.8±0.95	0.61±0.56	98.86±1. 25	73±1. 24	20±0. 95	17±3.6
TF6	201±0.18	4.0±0.75	0.63±0.41	99.14±1. 14	72±1. 75	9±0. 15	8±2.95
TF7	198±0.77	4.0±0.37	0.60±0.96	98.37±1. 74	76±1. 68	9±0. 75	8±1.95
TF8	201±0.99	3.8±0.54	0.61±0.51	97.84±1. 85	79±1. 95	6±0. 58	5±8.0
MF	201±0.49	5.0±0.62	0.59±0.84	98.96±1.96	42±1.36	152±0.62	385±2.8

After mixing, weighing, and grinding all of the excipients - SH, SSG, CP, mannitol, aspartame, and MCC - telmisartan was added. Lastly, talc and magnesium stearate were added to the powder mixture before it was compressed into a tablet.

Experimental design

To improve the design and understand its main effects and interactions, a 23-factorial design with three factors at two levels was used. Design Expert software (Version 13.00, Stat-Ease Inc., USA) was utilized to create a polynomial equation. The impact of independent variables SH (A), SSG (B), and CP (C) on dependent variables DT (Y1), Percentage Dissolve at 10 min (Y2), and water absorption (Y3) was evaluated using two different levels for each. Table 2 displays the selected factors and their corresponding levels.[10]

Post-compression evaluation tests[10]

Hardness

Using a Monsanto tester, the dosage form's resistance to mechanical shocks during handling and transportation was computed. It was stated as kg/cm^2. From each batch, three tablets were chosen at random, and the tablets' hardness was assessed.

Friability test

The tablets' friability was evaluated using the Roche friabilator. Tablet samples were dropped over a predetermined period of time for this test. Both before and after the test, tablets were weighed. Ultimately, the formula was used to calculate the percentage of friability.

$$F=\frac{100\times W(initial)-W(final)}{W(initial)}$$

Weight variation test

It has been determined what the 20 pills' mean mass is. The USP monograph states that no tablet weight differs from the average by more than two, and none by more than twice the percentage of tablet weight.

Water absorption ratio

To measure how well a tissue paper absorbs water, we put a folded piece of it in a small dish with 6 ml of water. Then, we placed a tablet on the paper and let it soak up the water completely. After that, we weighed the soaked tablet to calculate the water absorption ratio (R) using this formula**.**

$$R=\frac{100(Wd-We)}{We}$$

Where,

Wd = Tablet weight after water absorption.

We = Tablet weight before water absorption.

Wetting time

To check how quickly tablets absorb water, we put five

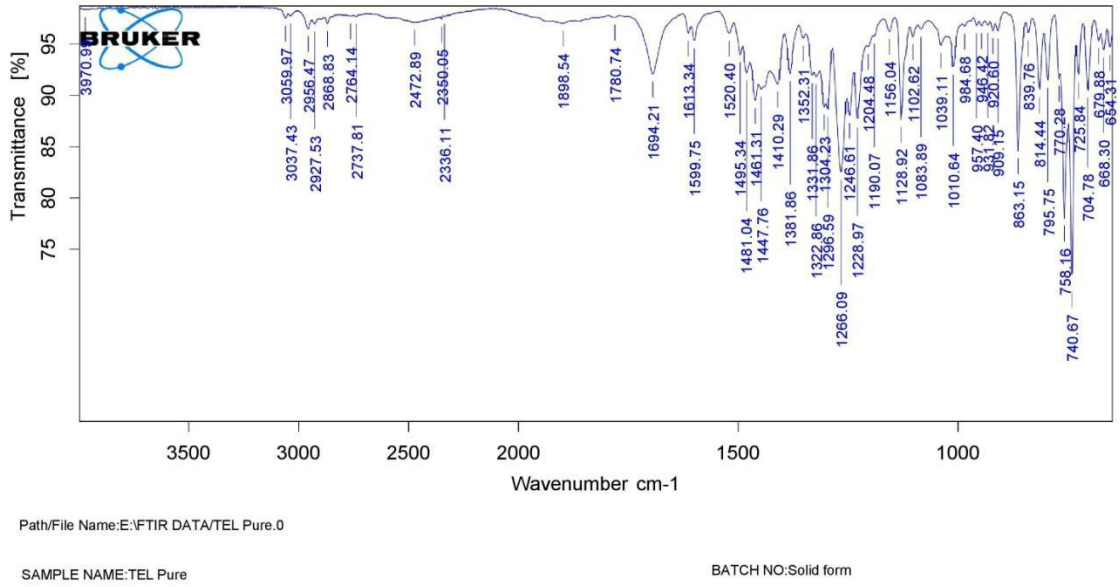


Figure 1: FTIR graph of Telmisartan pure drug

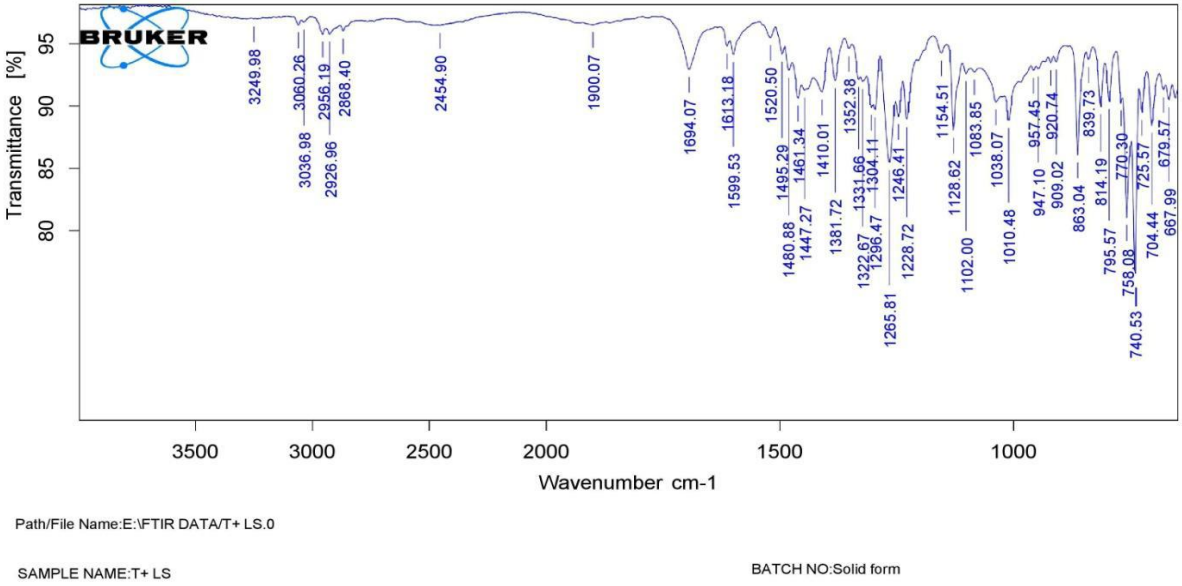


Figure 2: FTIR spectrum of starch hyaluronate

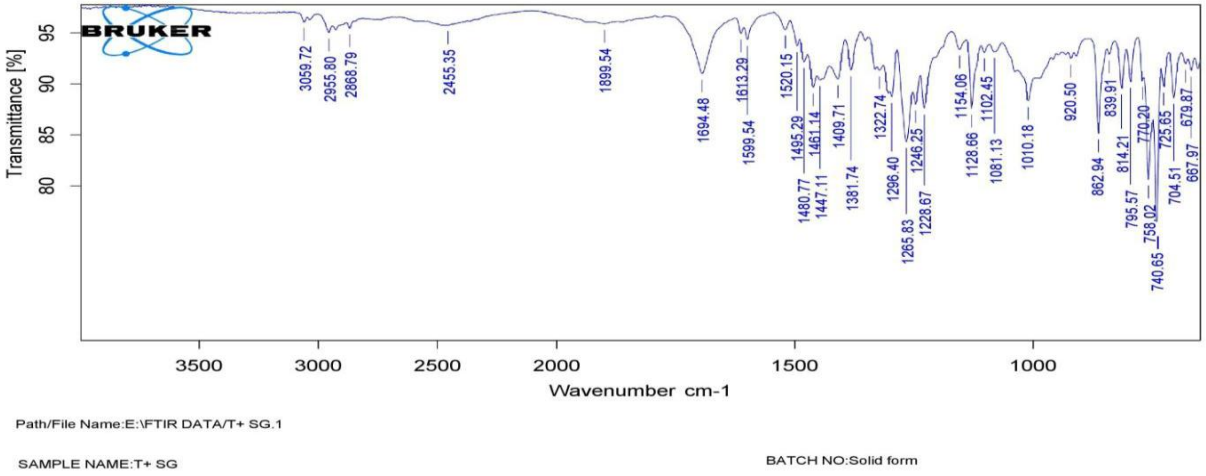


Figure 3: FTIR spectra of potato starch

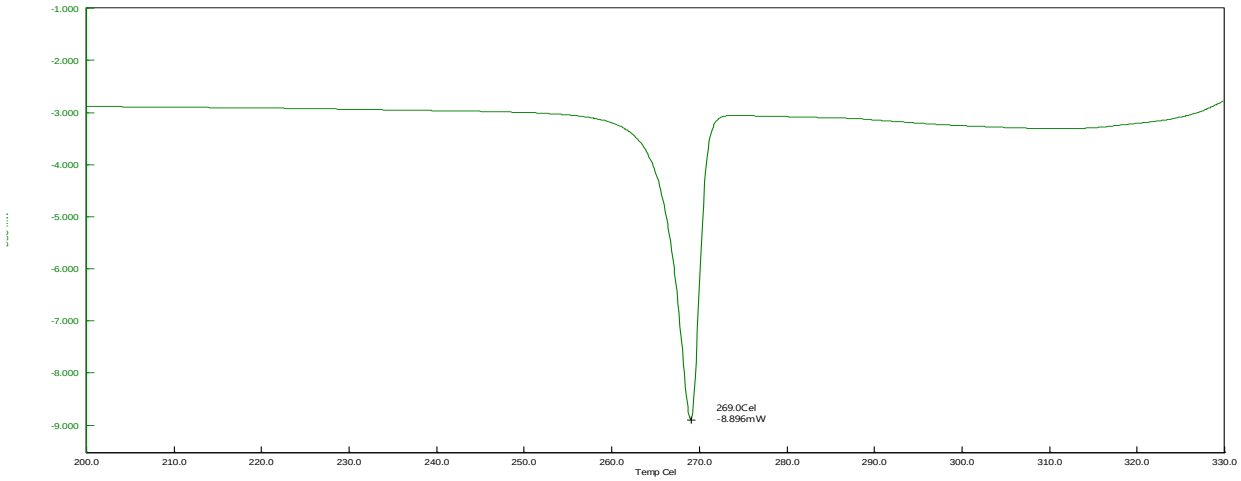


Figure 4: DSC thermogram of Telmisartan pure

tissue papers in a round dish that's about 0.10 meters wide. Then, we poured 10 milliliters of water with dye onto the dish. Next, we put a tablet on top of the tissue paper and timed how long it took for the water to soak through to the surface of the tablet.

Drug content uniformity

Ten tablets were randomly weighed and then finely

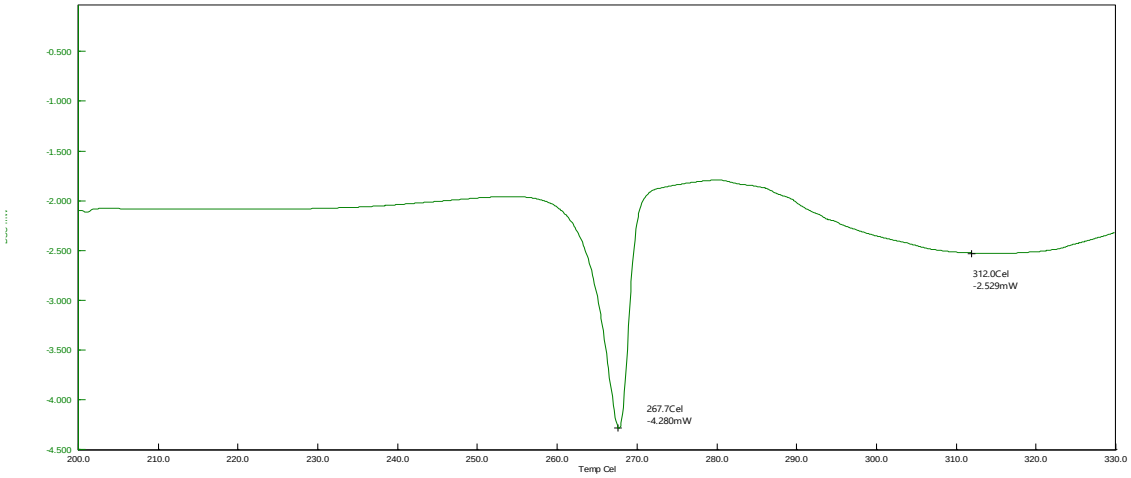


Figure 5: DSC thermogram of Telmisartan with starch hyaluronate

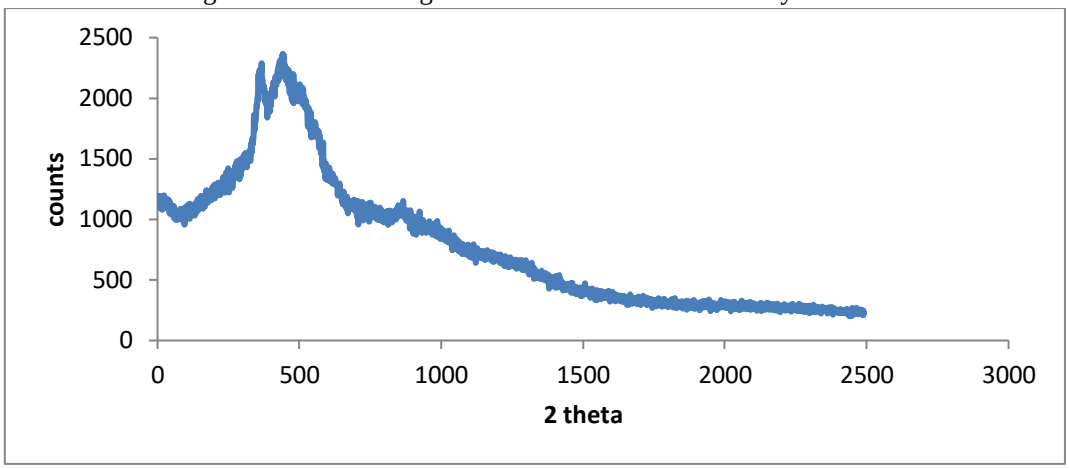


Figure 6: Starch hyaluronate with an X-ray diffraction pattern

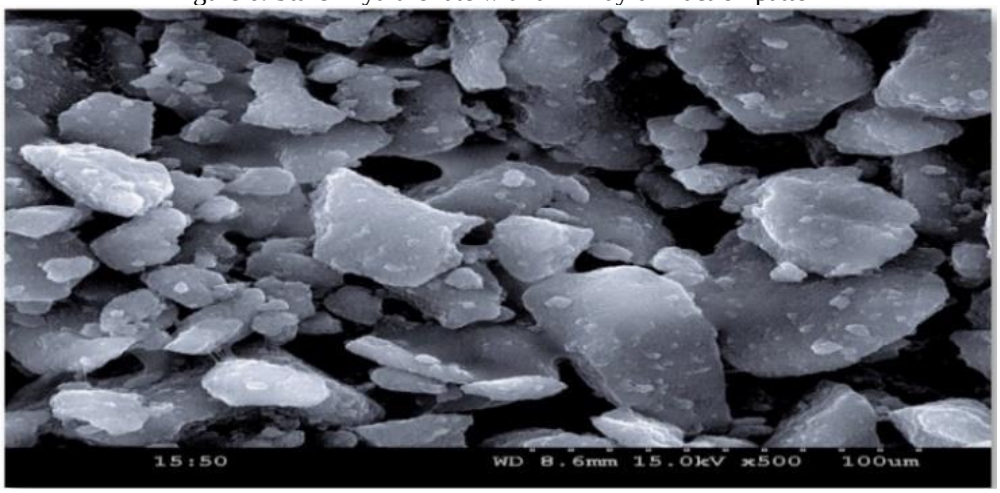


Figure 7: Starch hyaluronate SEM (x500) illustration

powdered. After being diluted with 100 milliliters of Hcl buffer, which has a pH of roughly 1.2, and filtered, a weighted powder equivalent to ten was measured spectrophotometrically at 296 nm. The standard calibration curve was utilized to calculate the drug's dosage.

***In vitro* disintegration time**

A USP device has been used to test disintegration time. The dosage forms were stored at 37±0.2 °C inside a 1 liter of pH Hcl buffer (1.2). Six tablets were selected at random, and one was put into each of the separate basket rack assembly tubes containing the disintegration medium. The number of seconds it took for each tablet to completely dissolve that is, to leave no residue behind was then recorded.

***In vitro* dissolution**

The research team studied how quickly telmisartan FDTs dissolve in a pH 1.2 Hcl buffer at a temperature of 37±0.5

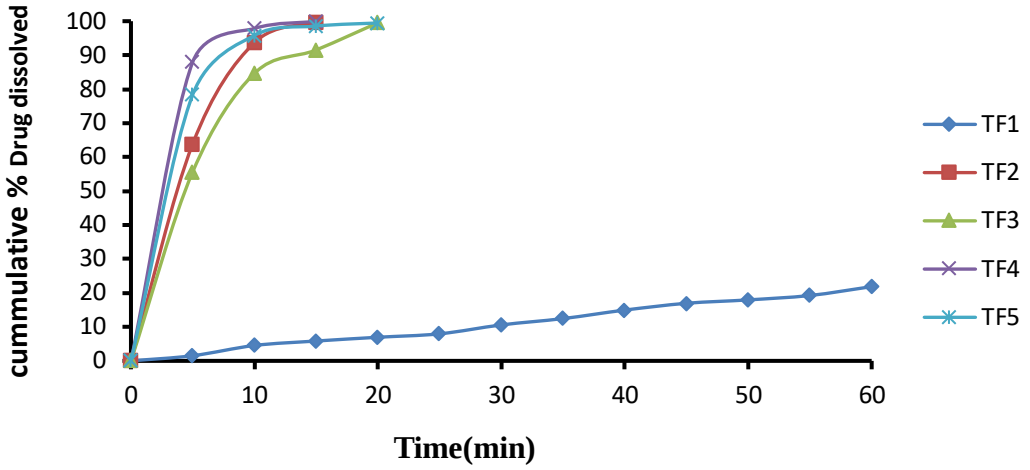


Figure 8: dissolution profiles of telmisartan FDTS employing Starch hyaluronate as new superdisintegrate (F1-F5)

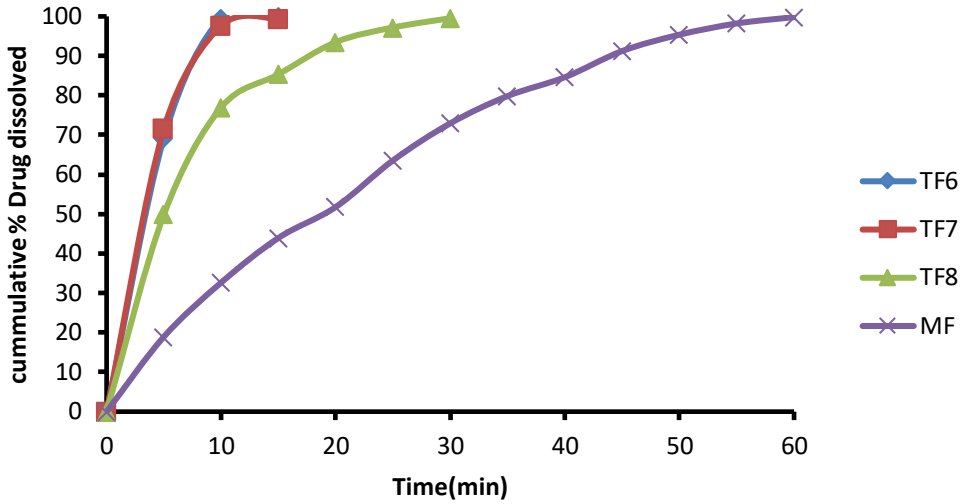
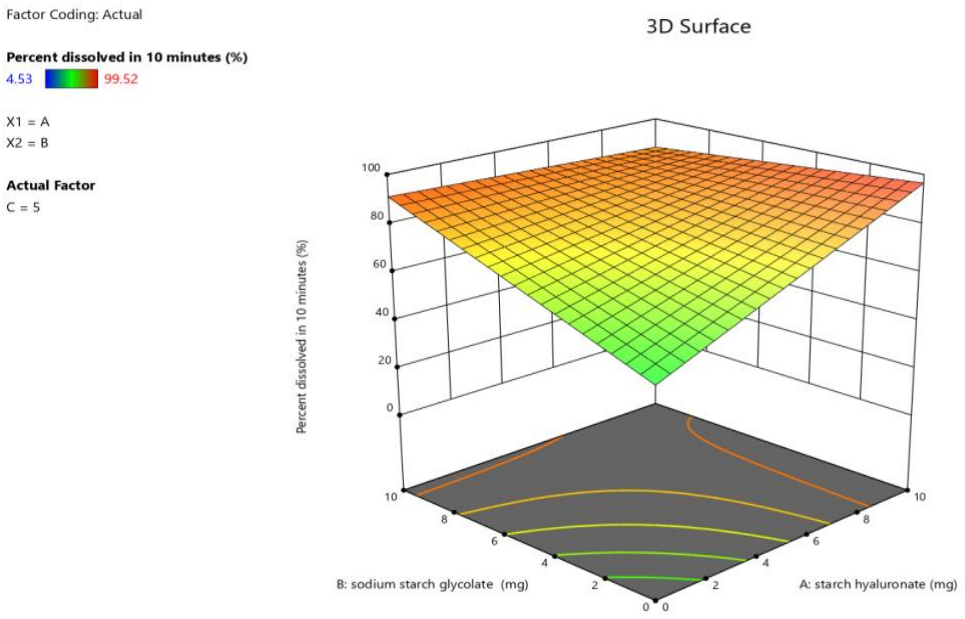


Figure 9: dissolution profiles of telmisartan FDTs employing Starch hyaluronate as new superdisintegrate (F6-F8 and Marketed formulation)

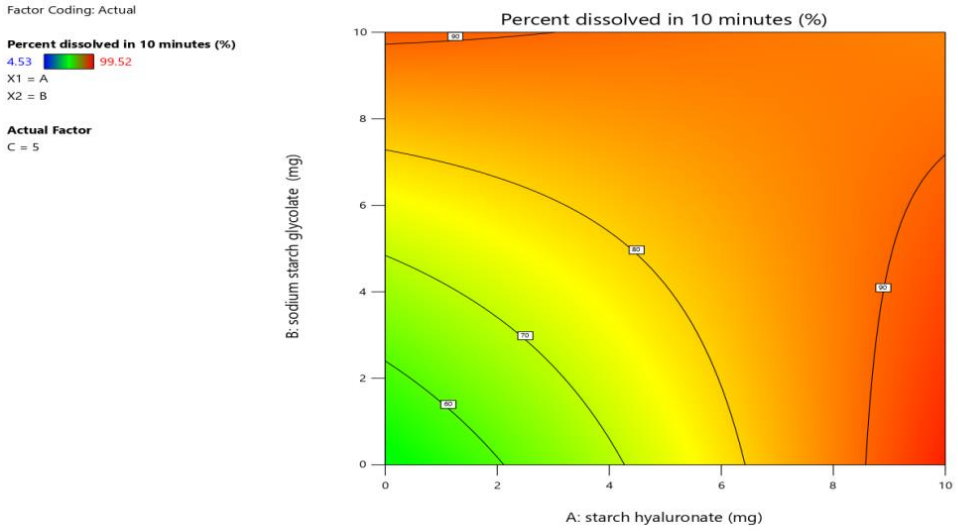
°C and agitation speed of 50 rpm. Samples were regularly taken and analyzed using spectrophotometry at a wavelength of 296 nm. Guidelines from ICH and WHO suggest that it is important to test the ideal composition of rapidly dissolving telmisartan tablets within six months, rather than simply storing them in HDPE containers at 40 °C and 75 °RH for that same period of time. The stored samples were monitored for changes in drug release properties and physical appearance throughout the six-month storage period.

RESULTS AND DISCUSSION

The powder called starch hyaluronate is fine, slightly crystal-like, and can flow easily. Table 3 outlines the physical and small-scale properties of both potato starch and starch hyaluronate, which is a new type of superdisintegrant. Figs. 1 and 2 show the FTIR spectra for PS and SH respectively. One specific band at 1694.70 cm-1 was found in the FTIR for the ester form of starch hyaluronate. The FTIR graphs of telmisartan and telmisartan with starch hyaluronate have specific peaks for NH,-OH, CH, C-O, C=C, C-N, and C=CH2. The spectra of telmisartan with starch hyaluronate (shown in fig. 3) have a distinct absorption band at 2995 cm-1 due to N-H stretching. The spectra at 2913 cm-1 may be caused by stretching of the O-H bond. Other peaks include C-H stretching at 2455 cm-1, C-O stretching at 1228 cm-1, and aromatic C=C bonding at 1520 cm-1. These same peaks were also present in the pure medication FTIR graph (fig. 3): (-NH) 2913, (-OH) 2455, (-CH)1228, (-CO) 1520, (-C=C)1322, and (-C-N) 1480. The drug was proven to be pure through DSC testing, which showed a clear melting peak at 269 °C for both telmisartan and starch hyaluronate (1:1) mixtures. No interaction was observed between the two components in the DSC spectra (shown in Figures 4 and 5). Figure 6 displays the crystalline nature of starch hyaluronate, while the X-ray diffraction analysis revealed characteristic patterns at angles around 500.12° to 2458.9°.



(a) Response Surface Plot



(b) Contour Plot

Figure 10: (a) Response Surface Plot (b) Contour Plot of telmisartan FDTs. (Effect of Starch hyaluronate superdisintegrate and Sodium starch glycolate on percent dissolved in 10 minutes)

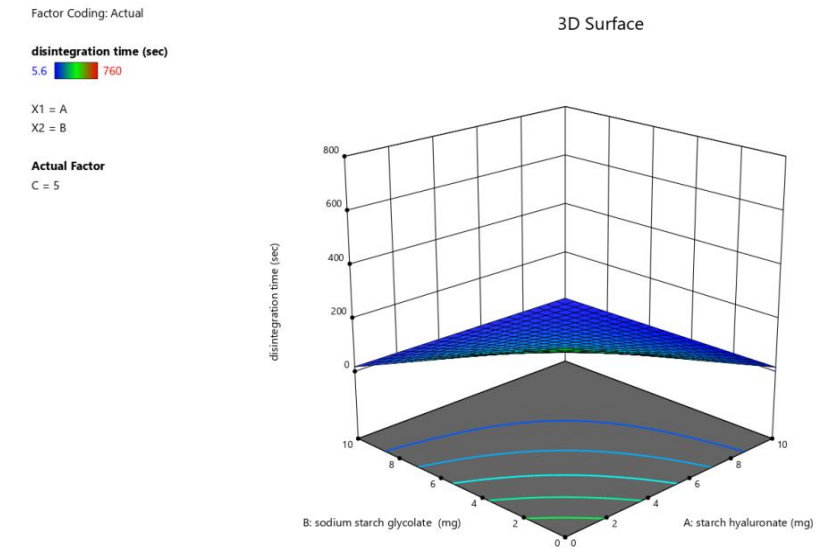
Additionally, SEM analysis (Figure 7) confirmed that starch hyaluronate has a somewhat crystalline structure. All post-compressional metrics were found to have been within the authorized range upon evaluation. Table 4 displays the outstanding mechanical strength of the formulations, ranging from 3.9±0.63 to 4.0±0.75 kg/cm2. In contrast to the tablets made in accordance with S. Jaya et al. [25], which had a hardness of 3.5 kg/cm2, the tablets had a harder texture. Tablet friability, which is less than 1% of the weight of the tablets under evaluation, shows that the mechanical resistance of the tablets has not changed. Every composition satisfies the drug content and weight variation pharmacopoeial criteria. The results show that the wetting time and moisture absorption ratio are, respectively, 360±0.52. to 52 to 6 ±0. 58 seconds and 79 ±1. 9 to 25±1. 92.

***In vitro* disintegration time**

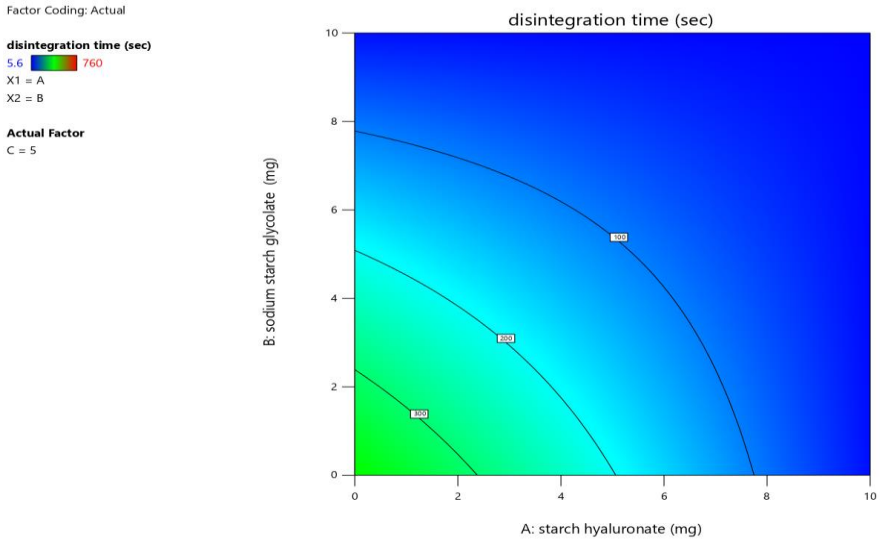
Table 4 shows that the disintegration time (DT) of all generated tablets ranged from 760±2 to 5±2 seconds. The optimized composition TF2 had a DT of 24±2 seconds, which was much less than that of the tablets manufactured by Malode Lochna L et al.

***In vitro* dissolution studies**

Fig. 8 and 9 shows the outcomes of an in vitro dissolution. 10% CCS and 10% starch hyaluronate are both present in TF6, which has shown a high percentage of medication dissolved in 10 minutes (99.52 ±1.59%) and a disintegration time of 8±2 seconds. Formulation TF2, which has a 10% starch hyaluronate content, is similar to formulation TF6. As a result, it was determined that just one distinct superdisintegrant—starch hyaluronate, or TF2—was less costly than TF6.



(a) Response Surface Plot



(b) Contour Plot

Figure 11: (a) Response Surface Plot (b) Contour Plot of FDTs. (Effect of Starch hyaluronate superdisintegrate and Sodium starch glycolate on disintegration time)

The drug was proven to be uncontaminated, as confirmed by the thermograms of telmisartan alone and combined with starch hyaluronate (in equal parts). To determine any relationship between the independent and response variables, a polynomial regression algorithm was utilized. This equation is a second order model and for the 2n experimental design, it was written as Equation.

$Y= \beta0 + \beta1A + \beta2B + \beta3C + \beta1\beta2\ AB + \beta1\ \beta3\ AC + \beta2\beta3\ BC + \beta1\beta2\ \beta3\ ABC$

Where, Y is the measured response
β0 is the arithmetic mean response

The coefficients for factors A, B, C, AB, AC, BC, and ABC are β1, β2, β3, β1β2, β1β3, β2β3, and β1β2β3 respectively. These correspond to the percentages of starch hyaluronate, sodium starch glycolate and croscarmellose sodium and their interactions. The following equation was used to determine these coefficients:.

$\beta = \Sigma\ XY/2n$

Where β : Coefficient
X : Corresponding variable (A,B,C)
Y : Response value (Percent dissolved in 10 minutes and disintegration time
n : Level

It has been found that the mathematical model generated for Disintegration Time is quite large. The effects of the main and changing interactions on DT were clarified using contour and 3D response graphs in simple. The contour plot projected the linear relationship. Increased superdisintegrant levels may reduce the disintegration period, according to response and contour plots. This idea could be explained by a higher percentage of superdisintegrants, which could cause tablets to dissolve

more quickly. Figures 10 and 11 show how response 3D contour plots and surface plots affect the time it takes for a tablet to break down, indicating the connection between SH and SSG when CCS is held constant. The graphs reveal that using a superdisintegrant percentage of 1.75 to 7.75 results in a shorter disintegration time for the tablet.

Final Equation in Terms of Coded Factors

Percent dissolved in 10 minutes=+81.32+10.68A+7.94B+11.15C-12.54AB-14.92AC-13.13BC+6.44ABC.

Disintegration time=+107.70-95.47A-94.63B-97.80C+90.70AB+92.43AC+91.97BC-89.30ABC

When looking at the effect of SSG (B) and starch hyaluronate (A) on the amount dissolved in 10 minutes, we can see that a higher concentration of starch hyaluronate leads to an increase in percentage dissolved. Additionally, the presence of the other superdisintegrants CCS (C) and SSG (B) also have a positive impact on the amount dissolved in 10 minutes. By examining Figure 10 b, it is evident that there is a linear relationship between the concentrations of A and B and the percentage dissolved within this range. This means that when A and B are between 2-8%, there is a higher percentage of FDTs that fully dissolve within 10 minutes.

Optimum Formula

The study examined the effects of independent variables and their interactions on the responses to determine the optimal concentration level of superdisintegrants (starch hyaluronate, SSG, and CCS) for fast dissolving tablets. The results showed that --- levels of starch hyaluronate and +++ levels of SSG and CCS favor fast dissolving tablets that dissolve in 10 minutes and DT. High levels of superdisintegrants are required in the formulation of Telmisartan FDTs to achieve higher percent dissolved in 10 minutes and greater drug dissolved. Formulation TF6, which used 10% concentrations of starch hyaluronate and 10% concentration of SSG, showed greater % dissolved in 10 min and DT. This formulation is considered the best for telmisartan fast-dissolving tablets, comparable to Formulation TF6, which contains three superdisintegrants and uses starch hyaluronate, a novel natural superdisintegrant. TF2 was found to be more economical when using mucilage from starch hyaluronate, a single novel superdisintegrant.

CONCLUSION

It was discovered that the created starch hyaluronate was a small, clear, smooth powder that could disintegrate quickly. In order to create telmisartan FDTs using a direct compression technique and a 23 factorial design, SH was used as unique superdisintegrants. The improved formulation of telmisartan (TF2) FDTs with 10% SH had a reasonable DT, maximal dissolution, and DT in comparison to other formulations and commercially available formulations. The modified formula showed improved drug absorption and relative bioavailability, was stable, and rapidly reached peak plasma concentrations. The results of the investigation showed that starch hyaluronate dissolved and disintegrated more quickly. Consequently, SH may be recommended as a superdisintegrant in the production of FDTs containing low soluble medications.

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