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Formulation of sumatriptan succinate orodispersible tablets using chitosan and sodium starch glycolate for immediate migraine relief

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Abstract: Migraine is one of the common neurological disease affecting around 23% of the Pakistani population. Prompt treatment is required to regain the functional ability of patients. The present study was designed to develop sumatriptan succinate orodispersible tablets that would quickly overcome acute migraine episodes using 2^2 full-factorial design. The chitosan and sodium starch glycolate were taken as independent variables; friability, disintegration, dispersion time and water absorption ratio as response variables. Eight trial formulations were generated by Design Expert® software. The main effect plots were used to check the interaction of formulations with response variables. All trial formulations showed good micromeritic properties in terms of angle of repose (19.59°-24.57°), Carr's index (17.08-24.90%) and Hausner's ratio (1.20-1.33). The tablets wetted quickly (17.1- 39 sec) in dispersion medium, showed higher water absorption ratio (188-341 sec) and disintegrated quickly (13-20 sec) with an excellent dissolution rate (94-99%). The main effect plots show interactions between the independent variables against most of the study responses. A 2^2 full-factorial model was found to be effective in studying the influence of formulation variables on response parameters. Both chitosan and sodium starch glycolate can be used in combination to fabricate an effective orodispersible formulation of sumatriptan succinate.

Keywords: Orodispersible, optimization, 2x2 full-factorial design, sumatriptan succinate, chitosan, sodium starch glycolate, superdisintegrant.

INTRODUCTION

Swallowing of conventional tablets is problematic not only in patients having difficulty in swallowing but also in psychiatrics, geriatrics and pediatrics patients (Darwesh *et al.*, 2021; Sharma & Singh, 2020; Vlad *et al.*, 2023). Orosdispersible tablets (ODT) may be best suited for such patients. According to European Pharmacopeia, ODTs disperse in fewer than three minutes after administration (usually within the mouth before swallowing) (Council of Europe, 2013), whereas the Food and Drug Administration (FDA) defines the ODTs as the formulations which disintegrate within 30 seconds duration (Food and Drug Administration, 2008). It offers numerous advantages over conventional immediate release tablets (Vanbillemont *et al.*, 2020) such as rapid disintegration in saliva, fast onset of action, improved patient adherence (Velmurugan & Vinushitha, 2010), no requirements of chewing or water, (Kumari *et al.*, 2023; Roy, 2016) better stability, portability, ease of packaging (Alam *et al.*, 2014; Kumar & Ghosh, 2019; Thapliyal *et al.*, 2018) and increased bioavailability (bypasses hepatic metabolism) (Alam *et al.*, 2014; Kumari *et al.*, 2023; Velmurugan & Vinushitha, 2010) etc.

An ODT is best suited for acute treatment of migraine (Spandana *et al.*, 2020). Globally, migraine is regarded as the sixth most prevalent disease, affecting greater than 1 billion people (Choudry *et al.*, 2022). In 2019, the prevalence rate of migraine in Pakistan was 22.5%, which was higher globally (15%) (Herekar *et al.*, 2017).

Sumatriptan succinate has been approved by FDA for the treatment of headaches associated with migraines (fig. 1). The half-life of the drug is around 2 hours and its effect last to 4-6 hours after oral drug administration (Abo Zaid *et al.*, 2021).

Many formulations of sumatriptan succinate ODT have been prepared for migraine headaches that were manufactured by the direct compression method, contained synthetic superdisintegrants (mainly croscarmellose sodium, sodium starch glycolate and crospovidone) (Baghel *et al.*, 2019; Mishra & Jain, 2019; Munija & Srikanth, 2018; Yadav *et al.*, 2021). Some formulations were manufactured using expensive methods such as spray drying, solid dispersion, solvent casting method and freeze-drying technology (Gugulothu *et al.*, 2015; Kumar *et al.*, 2013; Sheshala *et al.*, 2011).

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The disintegrators are primarily important in an ODT formulation. It helps in rapid liberation and quick absorption of drugs (Al-Khattawi & Mohammed, 2013). Sodium starch glycolate is widely used in tablet formulations as a superdisintegrant (Putra *et al.*, 2024). Chitosan is a relatively new superdisintegrant approved by the FDA in fast dissolving tablets (Alam *et al.*, 2014). However, the potential of chitosan as a superdisintegrant in ODT alone or in combination with sodium starch glycolate has not been explored well in the current literature. Therefore, an attempt has been made in the present study to develop ODT of sumatriptan succinate using chitosan and sodium starch glycolate.

MATERIALS AND METHODS

API &Chemicals

Sumatriptan succinate (API) was courteously provided by Platinum Pharmaceuticals (Pvt.) Limited, Port Qasim, Bin Qasim Town, Karachi, Pakistan. Chitosan from Marine Hydrocolloids (Kerela, India). Sodium starch glycolate, mannitol, magnesium stearate, Avicel pH 102, orange flavor, Monobasic potassium phosphate, sodium hydroxide and hydrochloric acid were purchased from Merck, Germany.

Methods

Experimental design of sumatriptan succinate orodispersible tablets

Sumatriptan succinate ODT trials were generated using 2 x 2 full factorial method by Design Expert® (version 10.0.1, Stat-EaseInc., Minnesota, USA). Eight formulations were generated by Design Expert (four at low and high levels of independent variables; four at center points). Chitosan and sodium starch glycolate selected as independent variables whereas friability, disintegration, dispersion time and water absorption ratio as dependent variables. API and other formulation excipients were kept constant but the quantity of Avicel pH 102 was varied to adjust the compression weight (table 1). The trials were coded and stored for pre-formulation analysis.

Compression of ODTs

Sumatriptan succinate, Avicel pH 102, orange flavor and mannitol were passed through sieve #40 to get uniform particle size. The API and Avicel mixed together by geometric dilution followed by the addition of other ingredients except magnesium stearate. The pre-blend was mixed thoroughly in a mortar and pestle for about 10 minutes. It was transferred into a polybag along with the magnesium stearate, (already passed through sieve #80). The final blend was further mixed for 4 minutes by tumbling. The tablets were compressed on a single punch machine (KORSCH Erweka, Germany) with plain concave punches of 8 mm diameter at a target weight of 200 mg/tablet.

Pre-compressional Characterization of powder blends

Bulk density and Tapped density: These densities were determined using aerated and tapped volume of powder mixture respectively. Around 5 g powder mixture was poured into a 50 mL graduated cylinder and the volume noted followed by tapping against a hard surface approximately at the height of one inch (100 times) and calculations performed by (United States Pharmacopeial Convention, 2017; Zubedi & Mohammed, 2018);

$$\text{Bulk density} = \text{Total Weight (g)} / \text{Bulk volume (ml)} \quad \text{Eq. 1}$$

$$\text{Tapped density} = \text{Total Weight (g)} / \text{Tapped volume (ml)} \quad \text{Eq. 2}$$

Compressibility index and Hausner's ratio

Both of these were determined using the data generated by bulk and tap densities. The calculations performed by Carr's index (Taylor & Aulton, 2022):

$$\text{Compressibility Index} = [(\text{Trapped density} - \text{Bulk density}) / \text{Trapped density}] \times 100 \quad \text{Eq. 3}$$

$$\text{Hausner's Ratio} = \text{Trapped density} / \text{Bulk density} \quad \text{Eq. 4}$$

Angle of repose

Fixed funnel method was used to determine angle of repose by pouring powder blend through funnel and measuring height and diameter of the resulting cone. The static angle computed by (United States Pharmacopeial Convention, 2017):

$$\text{Tan}(a) = \text{Height} / (0.5)\text{Base} \quad \text{Eq. 5}$$

Post-compressional analysis of sumatriptan succinate orodispersible trials

Weight variation of tablets

Twenty tablets of each trial were taken randomly, weighed on a digital balance (Mettler Toledo). Individual weight of 20 tablets was determined and compared with the official USP criteria set for weight variation which in present case is ±10% of the target weight (United States Pharmacopeial Convention, 2017).

Thickness &diameter

Ten tablets were selected randomly from each trial batch. The dimensions (thickness and diameter) were measured using a Vernier caliper (Seiko, China).

Hardness test

Ten tablets selected at random for hardness testing using Erweka hardness Tester (Fujiwara Seisukusho Corporation, Japan). A tablet placed diametrically on a lower anvil and pressure was applied manually to check tablet crushing strength. Official compendia recommend a hardness of 3-4 kg/cm^2 suitable for ODT.

Friability

Ten tablets were selected randomly, weighed (W_o) and then placed in the Roche friabilator (GmbH TA 2000,

Germany). The friabilator rotated at speed of 25 rpm for four minutes to complete 100 revolutions. After the test, tablets were de-dusted, reweighed (W_f) and friability computed (Kumar *et al.*, 2013; Singh *et al.*, 2012):

$$\% \text{ Friability} = \frac{W_o - W_f}{W_o} \times 100 \quad \text{Eq. 6}$$

Wetting time & water absorption ratio

Circular tissue papers in five layers were placed in a petri dish. Around 10 mL of eosin-dye was poured into the petri-dish. A tablet initially weighed (W_b) was placed onto the surface of tissue paper. Time taken by the dye to wet and spread on the tablet surface was noted as wetting time.

For water absorption ratio, final tablet weight (W_a) was noted this ratio calculated by (Samineni *et al.*, 2013):

$$\text{Water Absorption Ratio} = \frac{W_a - W_b}{W_b} \times 100 \quad \text{Eq. 7}$$

In-vitro dispersion time

Either 5mL of simulated saliva of phosphate buffer (pH 6.8) or distilled water was taken in a graduated cylinder. A tablet was dropped in respective medium and time taken to disperse the unit completely was noted (Vishal *et al.*, 2011).

In-vitro disintegration time

The test conducted in basket rack assembly without disks using distilled water maintained at 37±0.5°C (Erweka ZT-2, Germany). The ODT should disintegrate in < 30 seconds (US, FDA) or < 180 seconds (Eur Pharm) (Food and Drug Administration, 2008).

Drug content

Ten tablets were crushed in a mortar and pestle. Amount equivalent to 25 mg of sumatriptan succinate (one tablet) was taken in a 50 mL volumetric flask, around 20 mL 0.01N HCl added, shaken vigorously to dissolve API. The volume made upto 50mL using same solvent (0.5mg/mL). The stock solution was diluted serially and analyzed at 227nm spectrophotometrically (Sheshala *et al.*, 2011).

In-vitro dissolution studies

Dissolution test conducted in USP (Apparatus II) using 900 mL 0.01N HCl as dissolution medium (37±0.5°C). The paddle was rotated at 30 rpm. Around 5 mL test sample was drawn at 5, 10, 15, 30 and 45 minute's time intervals. Same volume of fresh medium added immediately after each withdrawal to maintain a constant volume of dissolution medium. Samples were filtered through Whatman filter paper No. 41, analyzed by UV spectroscopy after dilutions using the wavelength of 227 nm. Cumulative drug dissolved was calculated by (Sheshala *et al.*, 2011; United States Pharmacopeial Convention, 2017).

$$\% \text{ Drug Dissolved} = \frac{\text{Absorbance of Sample}}{\text{Absorbance of Standard}} \times 100 \quad \text{Eq. 8}$$

STATISTICAL ANALYSIS

MS Excel® and Design Expert® (version 10.0.1, Stat-Ease Inc., Minnesota, USA) softwares were used for data analysis.

RESULTS

A 2^2 full factorial design was selected for the present study. The flow of powder blends were evaluated by indirect methods, followed by determination of quality attributes of trial formulations. Micromeritic parameters predicted excellent or fair to passable flow of powder blends based on Angle of repose (19.59 to 24.57°), Carr's index (17.1-25.1%) and Hausner's ratio (1.20-1.33) respectively. Post-compression parameters such as weight variation (200-201mg), hardness (4-4.1) and friability (0.87-0.93%) were also found within the acceptable limits. Compressed tablets wetted quickly (17.1- 39 sec) in dispersion medium that resulted a lower value of water absorption ratio (188-341 sec). Earlier disintegration (13-20 sec) and higher dissolution (94-99%) indicated manufacturability of a successful ODT formulation of sumatriptan succinate (table 2). The interaction of independent variables on selected responses were interpreted by line fit plots (fig. 2-5). Disintegration, dispersion time (phosphate buffer) and water absorption ratio showed interaction as detected by line fit plots. However, no interaction was found in case of friability.

DISCUSSION

The objective of present work was to explore role of chitosan and sodium starch glycolate in the ODT formulation of Sumatriptan succinate. A two level full factorial mathematical model was selected for present study using chitosan and SSG as independent while friability, disintegration, dispersion time and water absorption ratio as dependent variables. Eight formulations blends were evaluated for its suitability in DC followed by post-compression characterization.

Pre and Post Compressional Evaluation of sumatriptan succinate ODT

Comparable powder densities, better flowability and compressibility are prerequisite characteristics in the formulation of oral solid dosages forms. Carr's index and Hausner ratio predicted fair to passable flow properties contrary to the angle of repose that showed excellent propensity of powder blends. The formulations were easily compressed by direct compression without any tableting defects and subjected to post-compression evaluation.

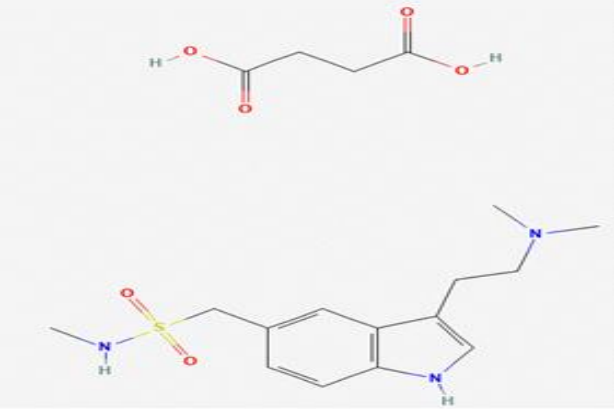
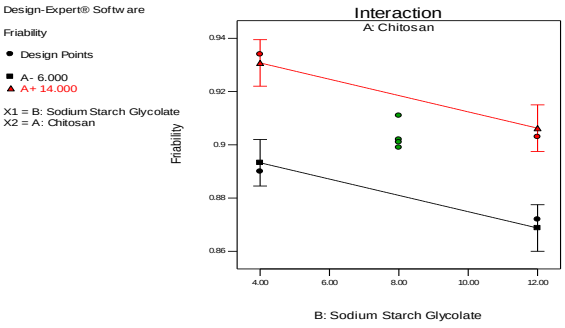
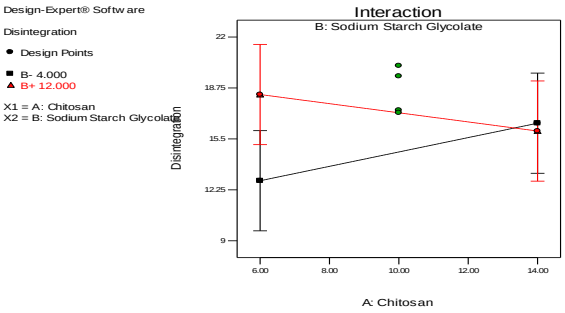


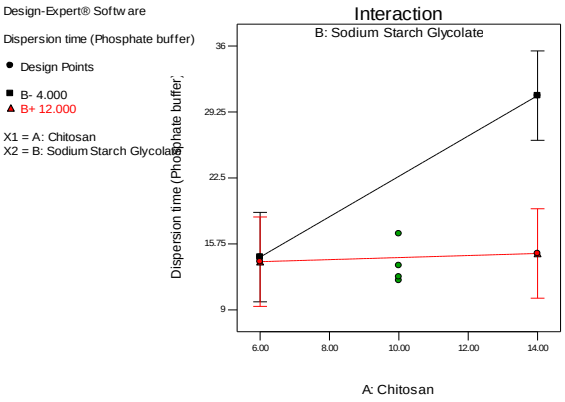
Fig. 1: Molecular structure of sumatriptan succinate (Information, 2020)



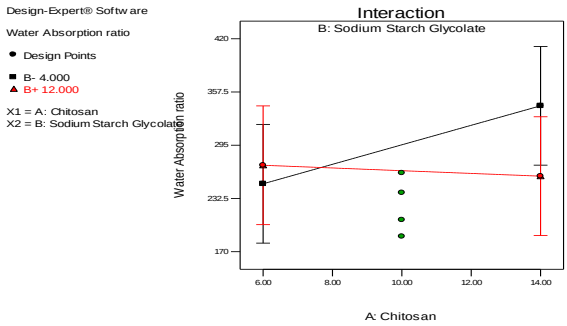
(a)



(b)



(c)



(d)

Fig. 2: Main effect plots showing the effect of superdisintegrants on the selected responses (a) Friability, (b) Disintegration, (c) Dispersion time (phosphate buffer) and (d) Water absorption ratio.

The compressed tablets showed lower deviation from the target weights (200 mg/tablet) that ranged from 199.65±2.11mg to 200.30±1.94 mg. In a study, Gowthami *et al.* (2013) prepared sumatriptan succinate ODTs using superdisintegrants alone or with crosspovidone, cross carmellose sodium and sodium starch glycolate. They reported an average weight of 196 mg to 202 mg thus the ODT complied official limits set for compressing tablets.

The hardness of ODTs tablets is always less in comparison to immediate release and sustained/extended-release products. In the present study, the trials were compressed at the lower compressional force that resulted in lower hardness (3.90±0.11 to 4.10±0.10 kg/cm^2) but fulfilled USP criteria set for hardness testing (i.e., up to 4kg) (Gugulothu *et al.*, 2015). Beside hardness, friability of ODTs is also very critical in terms of lower tensile strength. Friability of trials were found to be > 0.8%. Although friability is at a higher side, yet passed USP guidelines of friability. Nyamweya *et al.* (Nyamweya & Ngugi, 2019) had formulated paracetamol ODTs by direct compression method and reported >1% friability. In another study, Ali *et al.* (Ali *et al.*, 2017), studied tensile strength of ODT using high shear granulation technology and reported an increment in the crushing strength with a lower disintegration time. From these researches, it is apparent that the tensile strength depends on the manufacturing technology which is evident from the friability data reported here.

Wetting time is also one of the significant parameters that establish the credibility of an ODT formulation. Lower wetting time facilitates the immediate drug dispersion and dissolution. The wetting time of formulations ranged from 17.06±0.60 to 38.73±0.70 seconds. Previously, Singh *et al.* (Singh & Bajpai, 2011) developed an ODT formulation using either SSG or chitosan. Both found to be effective in terms of lowering wetting time (29-35 Vs 20 to 32 seconds for SSG and chitosan). Our results are comparatively better with Sigh *et al.* study.

Table 1: Formulation composition of sumatriptan succinate (25 mg) ODT

S. No.	Ingredients (mg)	Functionality	B1	B2	B3	B4	B5	B6	B7	B8
1.	Sumatriptan succinate	Active Pharmaceutical Ingredient	25	25	25	25	25	25	25	25
2.	Chitosan	Superdisintegrant	6	14	10	10	14	10	6	10
3.	Sodium Starch Glycolate	Superdisintegrant	12	12	8	8	4	8	4	8
4.	Orange Flavor	Flavoring agent	2	2	2	2	2	2	2	2
5.	Magnesium Stearate	Lubricant	2	2	2	2	2	2	2	2
6.	Mannitol	Sweetener	20	20	20	20	20	20	20	20
7.	Avicel PH 102	Diluent	133	125	133	133	133	133	141	133
Total Compression Weight (mg/Tab)			200	200	200	200	200	200	200	200

Table 2: Post-compression evaluation parameters

Formulation	Average Weight (mg) Mean ± SD n=20	Thickness (mm) Mean ± SD n=10	Diameter (mm) Mean ± SD n=10	Hardness (kg) n Mean ± SD =10	Friability (%) Mean ± SD n=10	Wetting Time (second) Mean ± SD N=03	Water absorption Ratio Mean ± SD N=03	Dispersion Time (sec) (DW) Mean ± SD n=03	Dispersion Time (sec) (pH 6.8) Mean ± SD n=03	Disintegration Time (sec) Mean ± SD N=06	Drug Content (%) Mean ± SD n=20	Drug Dissolution (%) Mean ± SD
B1	201.00±2.248	3.97±0.04	8.70±0.05	4.09±0.103	0.89±0.047	28.34±5.28	249.69±10.58	14.90±0.40	14.40±0.38	12.83±1.94	98.28±1.72	96.55±1.09
B2	200.00±1.214	3.95±0.05	8.77±0.08	4.02±0.074	0.93±0.013	20.56±1.84	341.25±15.73	16.12±0.41	30.92±1.06	16.50±2.59	96.55±1.72	91.95±2.09
B3	199.85±1.226	3.96±0.05	8.85±0.25	3.93±0.133	0.87±0.049	33.31±0.69	271.46±1.16	16.17±0.31	13.93±0.05	18.33±1.21	97.70±1.00	99.14±2.11
B4	200.10±0.970	3.97±0.05	8.78±0.10	4.00±0.145	0.90±0.049	38.72±0.70	258.67±15.49	12.05±0.84	14.77±0.38	16.00±1.55	99.43±1.00	99.14±0.14
B5	200.20±1.240	3.97±0.07	8.74±0.03	3.95±0.120	0.90±0.053	20.62±3.72	262.45±16.73	22.15±1.57	16.79±0.91	20.17±0.98	94.83±1.72	98.28±1.54
B6	200.30±1.949	3.98±0.04	8.75±0.05	3.98±0.129	0.90±0.055	20.91±7.19	239.22±11.98	16.63±0.88	13.54±1.28	17.33±1.03	97.70±1.00	95.40±1.41
B7	199.65±2.110	3.97±0.05	8.74±0.05	4.04±0.118	0.91±0.051	17.06±0.60	187.90±9.10	15.99±0.44	12.01±0.98	19.50±1.05	96.55±1.72	75.29±2.56
B8	199.85±1.843	3.97±0.05	8.73±0.04	3.91±0.112	0.90±0.046	28.05±8.06	207.35±6.6.	15.61±2.14	12.38±0.32	17.17±1.17	95.98±1.00	99.14±1.81

Likewise wetting time, water absorption ratio also showed variation that ranged from 187.90 ± 9.10 to 341.25 ± 15.73. This behavior reflects the absorption capacity of the tablets that dependents on the tablets' porosity. However, no exact correlation has been established between water absorption ratio and wetting or disintegration time (Pabari & Ramtoola, 2012).

Dispersion time of ODTs were studied in two medias (distilled water and phosphate buffer (pH 6.8). The media selection was based on the literature (distilled water) or to study ODT performance in saliva (phosphate buffer pH 6.8). A slight variation in dispersion time was found in the studied medias. The tablets dispersed quickly in distilled water (12.05±0.84 to 22.15±1.57 seconds) comparatively to phosphate buffer (12.01±0.98 seconds to 30.92±1.06 seconds). A lower dispersion time is desirable in ODT formulations that may facilitate quicker drug absorption.

Ideally, ODTs are designed to disintegrate rapidly within seconds to make the drug content available in short time and eventually lead to quick onset of drug action (Alam *et al.*, 2014). Disintegration time of ODT in the present study ranged from 12.83±1.94 to 20.17±0.98 seconds which is in agreement with US FDA (less than 30 seconds). The possible reason of earlier disintegration may be inclusion of two disintegtrants. However, this behavior is concentration dependent. Chitosan is known to extend when comes in contact with water, it bursts due to capillary action and imparts disintegration (Pahwa & Gupta, 2011) but it also possess a good ability to form hydrogels (Draksiene *et al.*, 2021). It might be the possible reason of higher disintegration time in the formulation containing high amount of chitosan and vice versa.

Previously, ODTs of sumatriptan succinate (25mg) using different combinations of synthetic superdisintegrants including SSG, crosscarmellose sodium and crospovidone were reported. The disintegration time reported was 11 to 58 seconds and 24 to 31 seconds, respectively (Kumar *et al.*, 2013; Samineni *et al.*, 2013). In the present work, tablets disintegrated quickly and combination of both disintegrants appears to be effective in lowing disintegration time.

API content in the composite sample ranged from 94.83 to 99.43%. According to USP, sumatriptan tablets, contents should be 90% to 110%, thus, all formulations complied USP standard as set for tablet assay.

In-vitro cumulative profiles of most of the trials showed greater than 80% drug release in initial 5 minutes. However, one formulation (B7) showed below 80% drug release that may be due to lower concentration of both superdisintegrants. The drug release greater than 90% in 10 minutes (B1 to B6 and B8) indicates fulfillment of pharmacopeial dissolution requirements. The cumulative drug release at 10 minutes interval may be ordered as B4 > B3 > B5. Overall, B4 showed highest and faster drug release while B7 exhibited lowest and slower drug release. It may be due to the enhanced de-aggregation of drug particles by chitosan and SSG. Previously, Munija *et al.* (Munija & Srikanth, 2018) used sodium starch glycolate in the formulation of an IR formulation of sumatriptan succinate tablets. Only 70% drug dissolution

occurred in 15 minutes. Similar findings was also witnessed by Benita *et al.* (Benita *et al.*, 1984). However, Darwis *et al.* (Sheshala *et al.*, 2011) formulated an orodispersible formulation of sumatriptan succinate tablet and reported optimal formulation that contained 5% Kollidon CL-SF. This formulation showed >90% drug release within 15 minutes. From these researches, it is evident that chitosan and SSG are the key factors that has controlled the drug release.

Interaction study of independent variables with selected responses

The main effect plots were used to study the effect of chitosan and SSG on the selected responses (fig. 2). In case of disintegration time, dispersion time and water absorption ratio interactions was detected but in friability, no interaction was detected between chitosan and SSG. The two lines were found parallel in friability which indicates that an increment in one independent variable with other may have a negative effect on friability. Contrary to friability, an interaction between two variables detected in disintegration. A lower concentration of SSG and a higher concentration of chitosan showed positive response to the system. Likewise disintegration, chitosan and SSG showed interaction in dispersion time conducted in phosphate buffer. A higher concentration of SSG showed no effect on the system because the line is almost flat with an increment in chitosan concentration. However, positive effect was detected at the lower concentration of SSG with increment in chitosan concentration. Finally, water absorption ratio also show interaction as the two lines are not parallel rather crossing each other near to the origin of line fit plot. The results are similar, although less pronounced as described earlier in dispersion time. From these inferences, it appears that a lower concentration of chitosan and a higher concentration of SSG may be best suited in achieving desirable characteristics of sumatriptan succinate ODT tablets. The Formulation B1 meets these criteria and may be declared as the best formulation of the present study. However, evaluation of *in-vivo* performance is mandatory to assure actual potential of this new formulation in biological system

CONCLUSION

Sumatriptan succinate ODTs were successfully formulated by 2^2 full-factorial design using a direct compression method. The main effect plots helped in the designing of a robust ODT formulation. Both chitosan and SSG can be used in combination to fabricate a robust ODT formulation of sumatriptan succinate. *In-vivo* studies are recommended for future studies that ensure the actual performance of this new formulation in the biological system. Further, the role of chitosan with other disintegrants should also be explored in the future studies that will help in exploring the actual behavior of this excipent in the drug delivery system.

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