

Exploring Cross-linked Tragacanth as Novel Excipient-proof-of-concept

Anroop B. Nair¹, Santosh Fattepur², N. Raghavendra Naveen³, Prakash Goudanavar³, Naga Prashant Koppuravuri⁴, Buduru Gowthami⁵, Mallikarjun Telsang⁶, Riyaz Ali Osmani⁷, Nagaraja Sreeharsha^{1,8}, Mohammed Habeebuddin⁹

¹Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University, Al-Ahsa, Saudi Arabia, ²School of Pharmacy, Management and Science University, Shah Alam, Selangor, Malaysia, Departments of ³Pharmaceutics and ⁴Pharmaceutical Chemistry, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B.G. Nagara, Karnataka, ⁵Department of Pharmaceutics, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India, ⁶Department of Medicine, College of Medicine, King Faisal University, Al-Ahsa, Saudi Arabia, ⁷Nanomedicine Lab, Department of Biosciences and Bioengineering, Indian Institute of Technology Bombay (IIT-B), Mumbai, ⁸Department of Pharmaceutics, Vidya Siri College of Pharmacy, Bengaluru, India, ⁹Department of Biomedical Sciences, College of Medicine, King Faisal University, Al-Ahsa, Saudi Arabia

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ABSTRACT

Background: Tragacanth, a natural gum, is frequently used as stabilizer for colloidal systems and as a binder in tablets. Materials from natural sources are in increasing demand to solve the current global environmental problems arising from synthesis involving petroleum-based substances.

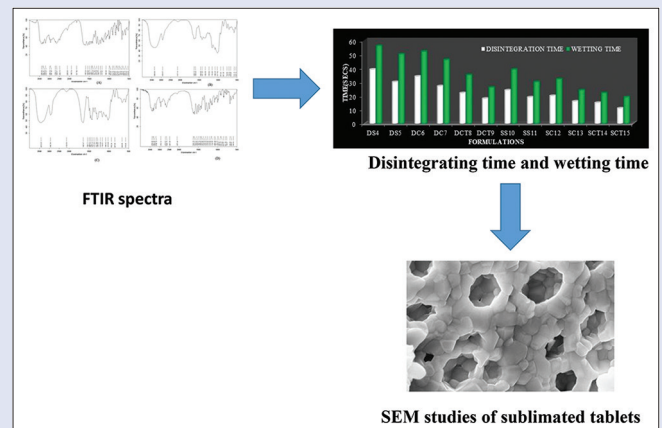
Objectives: In this context, we improved functionality of tragacanth through crosslinking and extended its application for directly compressed fast dissolving systems. Fast dissolving formulations upon settling on the tongue disintegrate promptly and release the medicament, thus making it especially suitable for paediatrics, geriatrics, bedbound, or incapacitated patients. **Materials and Methods:** Cross-linked tragacanth (CLT) was explored as a potent disintegrant and compared with sodium starch glycolate and Croscopovidone for its effect on compressibility and release of metoclopramide hydrochloride from tablets made by direct compression and sublimation method. Formulations made using CLT were optimized for swelling capacity, absorption efficiency, and moisture sorption capacity.

Results: The most appropriate controls for linkage of tragacanth were 1:0.4 proportion of tragacanth: Epichlorohydrin, at 105°C temperature for 45 min of reaction. Prepared formulations showed desired disintegration and wetting time. Formulations made using camphor showed porosity because of sublimation and favored rapid disintegration. Based on the drug release study, it is confirmed that formulation with 4% CLT and 20% camphor prepared by sublimation process exhibited highest drug release, i. e. 99.23% within 15 min. **Conclusion:** This study demonstrates the novel applicability of tragacanth as an effective natural superdisintegrant after cross-linking and provides a sustainable alternative to synthetic superdisintegrants while formulating the fast-disintegrating tablets.

Key words: Cross-linked tragacanth, metoclopramide hydrochloride, natural disintegrant, orodispersible tablets, tragacanth

SUMMARY

- Synthesized CLT was evaluated for swelling capacity, absorption efficiency, and moisture sorption capacity. Based on the drug release profiles using MTH as a model drug, it is concluded that preparation consisting of 4% optimized CLT and 20% camphor showed the highest drug release of 99.23% at the end of 15 mins.



Abbreviations used: CLT: Cross-linked tragacanth; ODT: Orally disintegrating tablets; MTH: Metoclopramide hydrochloride; SSG: Sodium starch glycolate; CP: Croscopovidone; SEM: Scanning electron microscopy; FTIR: Fourier transform infrared spectroscopy.

Correspondence:

Dr. Anroop B. Nair,
Department of Pharmaceutical Sciences,
College of Clinical Pharmacy, King Faisal
University, Al-Ahsa, 31982, Saudi Arabia.
E-mail: anair@kfu.edu.sa

Dr. N. Raghavendra Naveen,
Sri Adichunchanagiri College of Pharmacy,
Adichunchanagiri University, B.G. Nagar,
Mandya - 571 448, Karnataka, India.
E-mail: nrrn@accp.co.in

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INTRODUCTION

Nature derived materials are often more beneficial than the synthetic or artificial because of their attainability, biocompatible, inexpensive, and ecologically sound nature. Herbs are inexhaustible sources for low-cost supportable supplies to the pharmaceuticals.^[1] Plant polysaccharides such as tragacanth, comply with the several expectations of pharmaceutical excipients such as availability, non-toxicity, biocompatibility, and hence are extensively used in the formulation development. Furthermore, plant-based excipients are

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extracted at relatively low cost and can be easily modified chemically to suit-specific needs and impart novel characteristics.^[2,3]

Tragacanth is a natural heteropolysaccharide synthesized by injured plant bark as a result of the defense process to overcome infections and dehydration.^[4] Gum tragacanth is extensively used in conventional medicine and the food industry due to the ease of purification, accessibility, inexpensiveness, and their biocompatibility considering their long-term use.^[5] It is broadly utilized in line of food, cosmetics, and pharmaceuticals as a protective for colloidal systems, stabilizer, emulsifier, and thickening agent.^[6] Despite the use of tragacanth for drug delivery^[7] and wound healing, it is not yet explored for orodispersible tablets (ODTs). Solid dosage preparations such as tablets and capsules are majorly chosen formulations owing to their stability, ease in formulation, handling, dosing, and administration in contrast to other dosage forms. Regrettably, the conventional tablets possess some hindrances related to the onset of action and swallowing in geriatric, pediatric, and unconscious patients.^[8] To alleviate this drawback and to enhance patient adherence, mouth dissolving or ODT was formulated. ODTs do not require water to swallow as they quickly melt and absorbed in the oral cavity.^[2,9] According to British Pharmacopoeia, ODT is uncoated tablets that are desired to swiftly dissolve in the mouth before swallowing and must have a disintegration time of <3 min. Since the past 20 years, ODT achieved commercial recognition and has been renowned as a substitute for tablets.^[10] At present, ODTs are widespread and obtained over the counter for the treatment of various ailments such as fever, cold, and allergies.^[11] Quick dissolution of ODT is attributed to the occurrence of a great porous facet in the tablet matrix. Volatile compounds, namely, sublimating agents are employed in tablet manufacturing to enrich the porous nature.^[1,12] that can easily get sublimated out of the finished tablet. Further freeze-drying methods can also be employed to develop highly porous ODT.^[13,14]

Metoclopramide hydrochloride (MTH), a water-soluble potential antiemetic agent, was selected as a model drug for designing ODT. MTH stimulates contractions in the upper gastrointestinal tract, thus enhancing the rate of gastric emptying. It is often used as second-line therapy in the management of hyperemesis gravidarum in pregnant women.^[15] Moreover causatively by emergency health-care providers while shifting conscious and spinally immobilized patients. MTH has antagonist effects on D2 ligand at the chemoreceptor trigger zone present in CNS, thus impeding the stimulation of nausea and vomiting. At high doses, serotonin receptor (5-HT3) antagonist effects can provide antiemetic actions. MTH has a gastroprokinetic activity, controlled by cholinergic actions, dopamine antagonist (D2), and serotonin agonist (5-HT4) activities. The self-gastroprokinetic actions may render the antiemetic effects and ameliorate the lower oesophageal sphincter tone.^[16]

The present research work is focused on the development of novel excipient by synthesizing cross-linked tragacanth (CLT) and exploring its functionality as a superdisintegrant for making ODT formulations that would enhance the bioavailability of MTH.

MATERIALS AND METHODS

Materials

MTH was presented by Wallace Pharmaceuticals Pvt. Ltd., Goa. Sodium starch glycolate (SSG) was procured from Micro labs, Bangalore. Tragacanth and cross-povidone (CP) were purchased from Yarrow chemicals, Mumbai. Other ingredients and solvents used were of analytical grade.

Methods

Synthesis of cross-linked tragacanth and optimization of tragacanth cross-linkage

A chemical process was used to synthesize CLT. Dried tragacanth powder and epichlorohydrin were taken in various proportions as 1:0.2, 1:0.5, 1:0.8 [Table 1] and reacted at 60°C to 105°C for a varying period between 45 and 75 min.^[17] Since the boiling temperature of epichlorohydrin is 116°C, the reaction temperatures were between 60°C and 105°C. The temperature of the reaction showed a notable impact on the speed of reaction.^[18] Optimization was done by evaluating the CLT for swelling capacity, absorption efficacy, and moisture sorption capacity.



Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR) spectra of equivalent mixtures (1:1) of MTH and distinct excipients including CLT were conducted to identify the feasible interactivity of drug and excipients through the KBr pellet technique using Perkin-Elmer FTIR series (model-1615) spectrophotometer.^[19,20]

Preparation of metoclopramide hydrochloride oral dissolving tablets

Oral disintegrating tablets of MTH were prepared by direct compression and sublimation methods using CLT, SSG, and CP as per the formula mentioned in Table 2. MTH 200 mg tablets each consisting of 10 mg drug were formulated. For all the preparations, mannitol was taken as a diluent. The recommended amount of the drug and excipients were quantified thoroughly and passed through sieve #44 individually, before blending. The contents were then mixed geometrically for 15 min. The resultant mixture was compressed into tablets on single station press machine with 8 mm punches with flat surface.^[21,22] The compression pressure was modified to achieve the tablet hardness in a specified range of 2–4 kg/cm³. The tablets produced by the sublimation process using camphor were subjected to drying [Figure 1] at 60°C in an oven until weights remained unchanged. A total of 15 formulations were prepared using varying concentrations of the selected super disintegrants as tabulated in Table 2.

Table 1: Optimization parameters in preparing cross-linked tragacanth

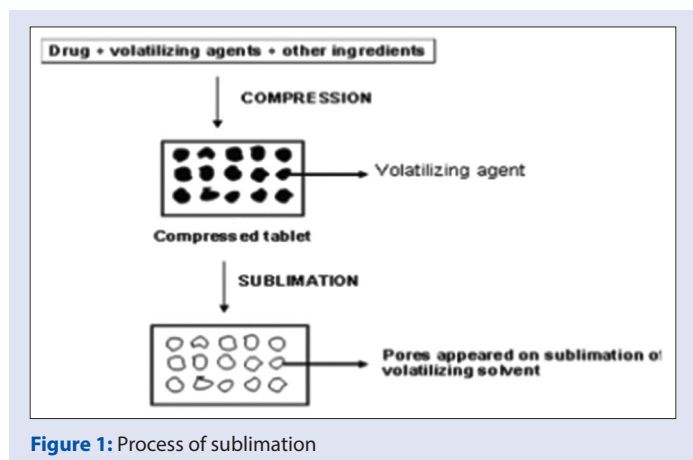
Code	Cross-linking temperature (°C)	Reaction time (min)	The ratio of tragacanth powder and epichlorohydrin
CLT-1	60	45	1:0.2
CLT 2			1:0.5
CLT 3			1:0.8
CLT 4	60	75	1:0.2
CLT 5			1:0.5
CLT 6			1:0.8
CLT 7	85	45	1:0.2
CLT 8			1:0.5
CLT 9			1:0.8
CLT 10	85	75	1:0.2
CLT 11			1:0.5
CLT 12			1:0.8
CLT 13	105	45	1:0.2
CLT 14			1:0.5
CLT 15			1:0.8
CLT 16	105	75	1:0.2
CLT 17			1:0.5
CLT 18			1:0.8

CLT: Cross-linked tragacanth

Table 2: Formulation of Metoclopramide hydrochloride oro-dispersible tablet for optimization of cross-linked tragacanth

	DS ₄	DS ₅	DC ₆	DC ₇	DCT ₈	DCT ₉	SS1 ₀	SS ₁₁	SC ₁₂	SC ₁₃	SCT ₁₄	SCT ₁₅
CLT	-	-	-	-	6	8	-	-	-	--	8	8
SSG	6	8	-	-	-	-	8	8	-	-	-	-
CP	-	-	6	10	-	-	-	-	10	10	-	-
Camphor	-	-	-	-	-	-	20	40	20	40	20	40
Mannitol	136	134	136	132	136	134	114	94	112	92	114	94
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

*Each preparation consists of 10 mg of MTH, 40 mg of MCC, 2 mg of aspartame, 4mg of aerosil, 2 mg of Mg. stearate. MTH: Metoclopramide hydrochloride; CLT: Cross-linked tragacanth; SSG: Sodium starch glycolate; CP: Cross-povidone

**Figure 1:** Process of sublimation

Estimation of powder blend (preloading variables)

The powder was evaluated for different flow characteristics such as angle of repose, density indices, Carr's index, and Hausner's ratio.^[23]

Post-compression examinations^[17]

Hardness

Tablet hardness is the pressure that is essential for breaking a tablet in a specific diametral compression. Erweka Hardness Tester (Erweka, Germany) was utilized in the study. The tester exerts absolute pressure on the tablet. Six tablets were examined and their mean was computed

Friability

The friability (F) was determined using Roche friabilator (ERWEKA, Germany). The weight of 20 tablets was noted individually and subjected for rotation at 25 rpm for 4 min. After dedust tablets were again reweighed. The loss % was quantified. The allowable range of friability is <1%.

Weight variation test

Weight variation test was performed by taking weight of 20 tablets separately, computing the mean weight and compare the independent tablet weight to the mean weight.

In vitro disintegration test

Tablet was kept in a beaker consisting of 20 ml distilled water at 37°C ± 0.5°C. The required time for entire tablet disintegration was determined in triplicate.

Thickness uniformity

The thickness of each tablet crown was estimated by digital vernier calipers. Thickness variation must be <5%.

Water absorption ratio (R)

A double folded tissue paper was kept in a petri plate of 5 cm inner diameter and consisting of 6 ml water. A compressed tablet with 100 mg

of CLT was positioned vigilantly on the tissue in the petri plate. The water absorption ratio (R) was calculated based on the formula below:

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

Where "W_b" and "W_a" were tablet weights before and after water absorption, correspondingly. The degree of swelling as measured by the water absorption ratio.

Determination of moisture uptake

Before conducting the test, compressed CLT tablets were held in a desiccator for 1 day to ensure complete film drying. Then, the weight of the CLT tablets was noted and were stored at 75% RH, at ambient temperature for 1 week. Tablets were reweighed, and the percent of weight increase due to moisture absorption was recorded.

Wetting time

The wetting time can be determined by an easy process. A filter paper of 10 cm diameter was positioned in a Petri dish and 1 ml of water-based color amaranth was added. A tablet was cautiously kept on top of the filter paper. The required time for water to get to the tablet superficial facet was recorded.^[24] Three estimations were conducted.

Scanning electron microscopy

It was performed to study the exterior facet and internal organization of the formulated tablets. SEM pictures were recorded by Philips XL30 SEM (Eindhoven, The Netherlands). Through surgical scalpel, samples were prepared from the tablet surface and internal sheets. A further sample was boarded on the aluminum stump and sputter deposit-varnished with gold. Photographs were captured at an increasing potential of 10 kV and a magnifying resolution of × 10.^[13]

In vitro dissolution studies

USP dissolution test apparatus type 2 paddle (Electrolab TDT-08 L Dissolution testers USP) was employed for the test. A volume of 900 ml phosphate buffer pH 6.8 was taken in a vessel and maintained at 37 ± 0.5°C. The paddle rotation was set to 50 rpm. Samples were drawn at interim of every 5 min, and drug content was estimated by UV Vis spectrophotometrically at a wavelength of 273 nm.^[25] Drug concentration was calculated from the calibration curve and denoted as aggregate percent drug dissolved.

Stability studies

This test was conducted by settling the sample instability cabin at 40°C ± 20°C/75% ± 5% RH for 3 months as specified in ICH guidelines. The standardized set was chosen for the stability test. Tablets were tested for disintegration time and *in vitro* drug release after an interim of 1 month.^[26,27]

RESULTS AND DISCUSSION

Nature has provided us a wide variety of ingredients which are biologically active as well as inactive and thus help improve and sustain the health directly or indirectly. With a continuous increasing interest

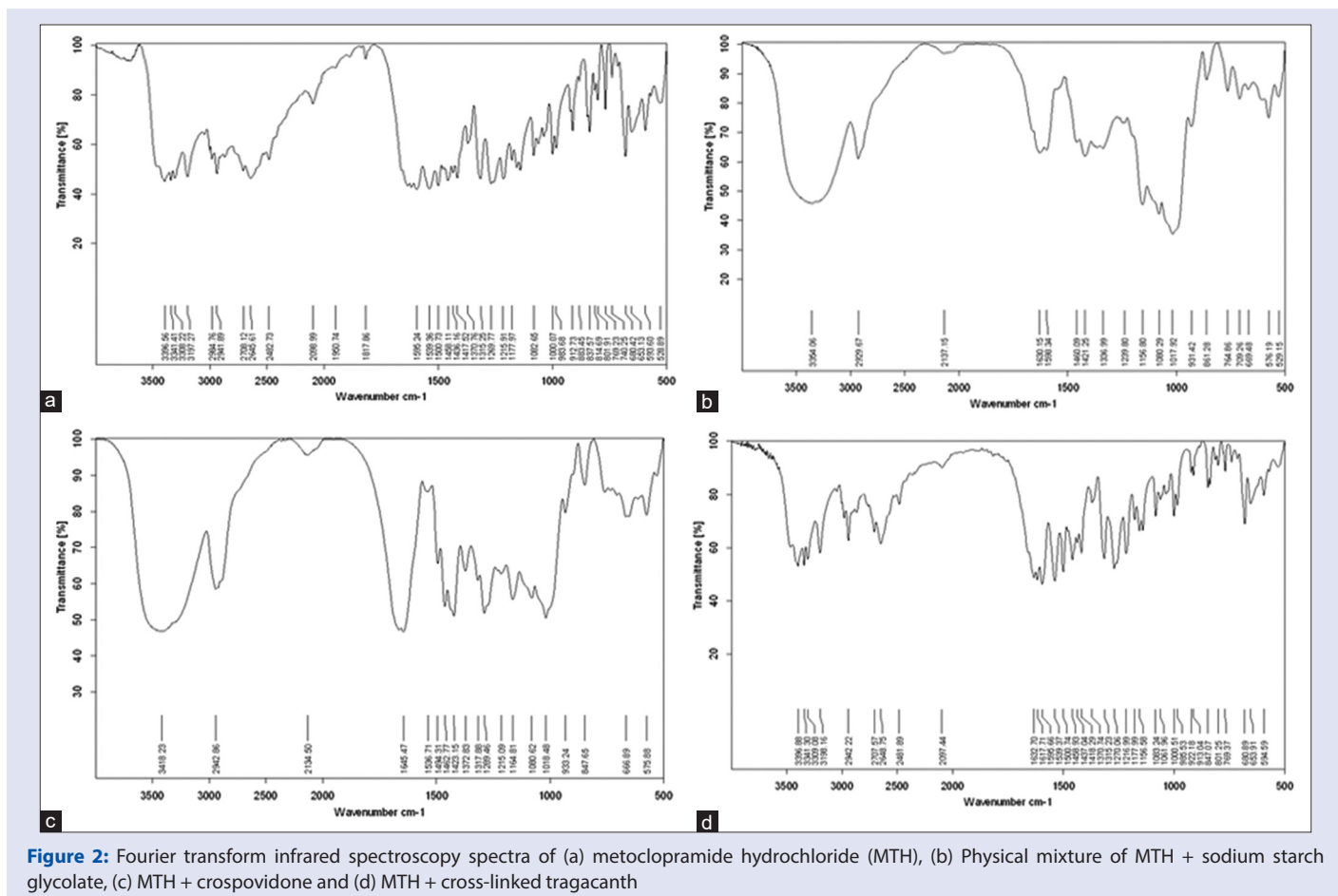


Figure 2: Fourier transform infrared spectroscopy spectra of (a) metoclopramide hydrochloride (MTH), (b) Physical mixture of MTH + sodium starch glycolate, (c) MTH + cospovidone and (d) MTH + cross-linked tragacanth

in polymers of herbal origin, the pharmaceutical world has compliance to use most of them in their formulations. Pharmaceutical preparations require a variety of nonactive ingredients in addition to the active drug molecule for variety of purposes such as diluent, binder, thickeners, stabilizer, emulsifier, gelling, coloring, and sweetening. In the recent years, there is a continuous demand for the use of green natural or semi-synthetic ingredients that can be used in place synthetic chemicals.

Drug-excipient interactions studies by Fourier transform infrared spectroscopy

The peak observed for every preparation corresponds with the peak of the drug spectrum. It denotes that the drug and formulation additives used are compatible. The spectra for all formulations are displayed in Figure 2. The IR spectrum of the pure MTH shows characteristic peaks at 3396 and 3308 per cm due to -NH and -OH groups correspondingly [Figure 2a and Table 3]. The physical mixture of MTH + SSG, MTH + CP, and MTH + CLT, also exhibited similar peaks for the groups mentioned above. This validates the uninterrupted structure of the drug in the formulations. Thus, no interactions were observed between drug and excipients.

Optimization of preparation of cross-linked tragacanth

CLT was prepared with different ratios of epichlorohydrin, reaction temperatures, and reaction time. Considering the inherent features of tragacanth [Table 4], the standardized conditions for cross-linking were observed as (CLT 14);

Table 3: Peaks observed in Fourier Transform Infrared Spectroscopy spectrum of pure metoclopramide hydrochloride and physical mixture with super disintegrants

Compound Frequency	Absorption peak (cm ⁻¹)			
	Pure MTH	MTH + SSG	MTH + CP	MTH + CLT
N-H str	3396	3396	3396	3396
O-H str	3308	3308	3308	3309
C-H str	2941	2942	2940	2942
N-H1	2645	2648	2748	2648
C=O	1595	1597	1593	1595
N-H2	1539	1537	1539	1539
C-O-C	1269	1261	1263	1270

MTH: Metoclopramide hydrochloride; CLT: Cross-linked tragacanth; SSG: Sodium starch glycolate; CP: Cross-povidone

- 1:0.4 ratio of tragacanth: Epichlorohydrin
- The temperature of 105°C for reaction
- The reaction time of 45 min.

Evaluation of the powder blend

The angle of repose (θ) is an attribute of inner abrasion or particle coherence. It is high for cohesive powders and low for noncohesive powders. All preparations exhibited good to allowable flow properties as stipulated by the values of angle of repose (23.18°–28.32°). The angle of repose <30° denotes free-flowing material and >40° with inferior flow characteristics. Carr's index exhibited a value of 20 indicating that the formulated powder mix possesses allowable to good flow

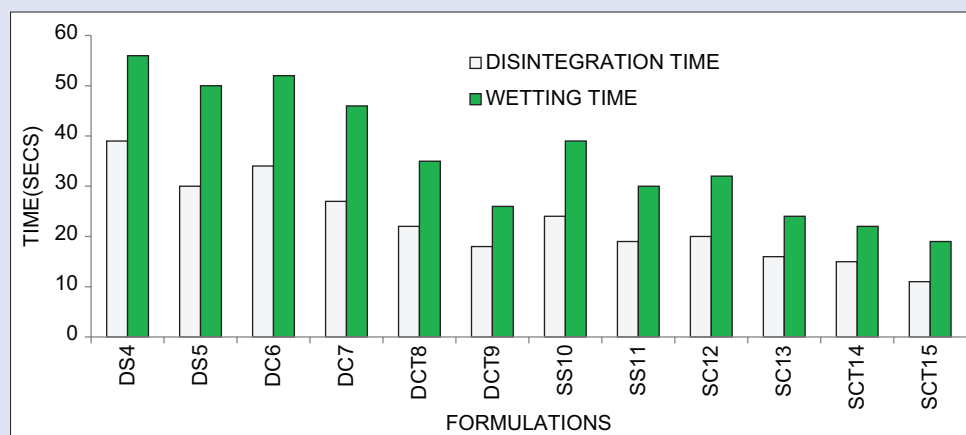


Figure 3: Graph representing a comparison of disintegrating time and wetting time for prepared formulations

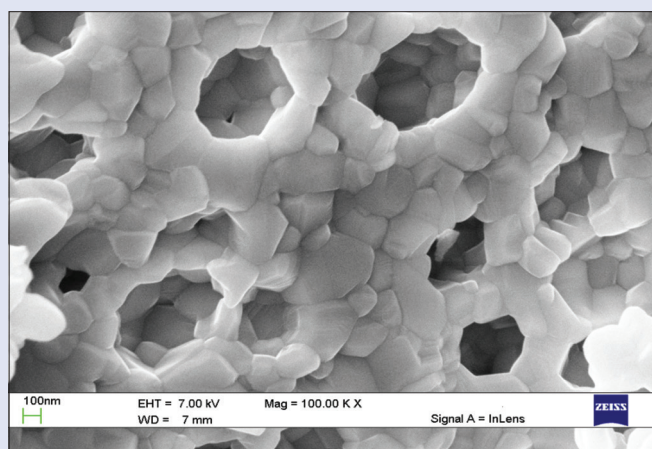


Figure 4: Scanning electron microscopy studies of sublimated tablets

Table 4: Evaluation of prepared cross-linked tragacanth

Code	Swelling capacity	Absorption efficiency	Moisture sorption capacity
CLT-1	65	16	22
CLT 2	95	28	39
CLT 3	74	22	35
CLT 4	74	18	29
CLT 5	108	34	42
CLT 6	86	25	36
CLT 7	114	21	28
CLT 8	120	35	44
CLT 9	98	28	36
CLT 10	85	26	32
CLT 11	90	36	48
CLT 12	110	32	39
CLT 13	120	34	42
CLT 14	142	41	49
CLT 15	130	38	47
CLT 16	125	36	45
CLT 17	127	43	44
CLT 18	134	40	46

CLT: Cross-linked tragacanth

behaviour. Powders with less interparticle resistance, exhibited Hausner's ratios around 1.09–1.25, denoting good flow characters. All the preparations were found to have a Hausner's ratio within the specified range [Table 5].

Evaluation of tablets

The tablets prepared were evaluated for the physical and chemical characteristics. The tablets were observed to be within the allowable pharmacopeial range for weight variation and qualified for uniformity of weight. The hardness of the tablets was from 2.8 to 3.5 kg/cm². For all the preparations, friability (%) was <1 denoting that the tablets were instinctively firm and can resist adversity during transit and operation [Table 6].

Wetting dispersion times decreased by increasing both the SSG and CP concentration. Formulation DCT8 and DCT9 prepared by sublimation approach containing CLT exhibited a reduction in wetting and dispersion times compared to the formulation prepared by direct compression method [Figure 3].^[28] The same results were obtained for tablets prepared by the sublimation method. It was also found that all sublimated preparations exhibited decreased values of wetting and dispersion times compared to direct compression formulations.

The reduction of wetting and dispersion times in all preparations is ascribed perhaps to the existence of super-disintegrant that draw

up water and distend resulting in tablets blowout.^[27,29] Further, the camphor present in the tablets formulated by the sublimation process allows the tablet to be porous and promotes the dissemination of the wetting medium, and results in tablet bust. Dispersal time is critical for oral disintegrating tablets which is ideally required to be <1 min. This swift breakdown aids in swallowing and also absorption in the oral cavity and consequently enhances bioavailability.^[30] Tablet formulations SCT14 and SCT15 were noted to be favorable as they showed minimum wetting and disintegration time, which make them suitable for use in the oral cavity.

Scanning electron microscopy

Sublimated tablets were evaluated for SEM for the evidence of pores formation [Figure 4]. In sublimated tablets, pores were developed on the evaporation of volatile agent (camphor) leaving tablet core which favors for rapid and fast disintegration.

In vitro dissolution studies

Based on the data of *in vitro* dissolution test, it was observed that there is a rise in the amount of drug release as the concentration of superdisintegrants increased up to a certain concentration

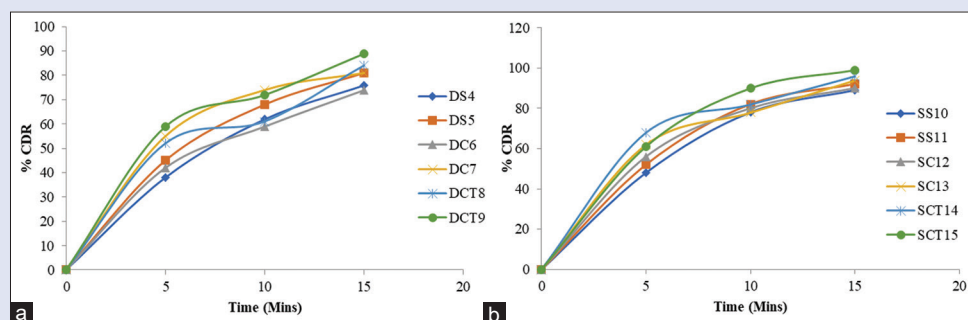


Figure 5: Comparison of dissolution profiles of formulations prepared by (a) direct compression and (b) sublimation process

Table 5: Precompression parameters for prepared batches (values are mean of six determinations±standard deviation)

	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio*
DS ₄	28.32±0.341	0.4033±0.014	0.4763±0.017	14.61±1.67	1.1810±0.026
DS ₅	27.46±0.173	0.4152±0.045	0.4792±0.026	12.32±1.53	1.1541±0.023
DC ₆	23.29±0.198	0.4072±0.009	0.4837±0.032	15.54±1.72	1.1878±0.033
DC ₇	25.45±0.241	0.3747±0.049	0.4681±0.022	14.87±1.27	1.2491±0.062
DCT ₈	27.72±0.372	0.4276±0.089	0.4664±0.037	13.12±1.37	1.0907±0.045
DCT ₉	23.18±0.127	0.4104±0.019	0.4532±0.042	12.83±1.83	1.1042±0.038
SS ₁₀	27.89±0.258	0.3909±0.064	0.4641±0.058	14.71±1.32	1.1872±0.026
SS ₁₁	26.28±0.174	0.4186±0.024	0.4696±0.084	12.37±1.65	1.1218±0.023
SC ₁₂	26.46±0.341	0.4075±0.021	0.4827±0.059	15.15±1.83	1.1845±0.033
SC ₁₃	25.62±0.218	0.3912±0.016	0.4602±0.036	13.48±1.32	1.1763±0.062
SCT ₁₄	28.27±0.284	0.4106±0.052	0.4894±0.028	14.32±1.71	1.1919±0.025
SCT ₁₅	25.82±0.215	0.3807±0.029	0.4549±0.039	13.63±1.39	1.2067±0.034

Table 6: Post-compression parameters for prepared batches

	Hardness (kg/cm ²)	Friability* (%)	Thickness (mm)*	Weight variation* (mg)
DS ₄	3.0	0.74±0.014	3.89±0.14	199.82±1.9
DS ₅	3.5	0.57±0.041	3.64±0.28	198.1±0.28
DC ₆	3.4	0.58±0.027	3.68±0.21	199.08±1.11
DC ₇	3.2	0.66±0.062	3.79±0.13	199.3±0.47
DCT ₈	3.0	0.74±0.021	3.87±0.16	200.44±0.5
DCT ₉	2.9	0.77±0.054	3.89±0.13	200.69±1.7
SS ₁₀	2.8	0.79±0.084	3.90±0.18	198.6±0.87
SS ₁₁	2.9	0.78±0.062	3.88±0.16	199.75±0.7
SC ₁₂	3.0	0.75±0.043	3.85±1.62	198.4±0.77
SC ₁₃	3.1	0.69±0.057	3.86±0.14	199.69±1.8
SCT ₁₄	3.3	0.61±0.029	3.71±0.18	198.33±1.1
SCT ₁₅	2.8	0.78±0.061	3.91±0.11	199.86±0.9

*Mean±SD, n=6. SD: Standard deviation

Table 7: Stability studies for selected optimized formulation

Test	Initial	25°C±2°C + 60%±5% RH		40°C±2°C + 75%±5% RH	
		3 M	6 M	3 M	6 M
Disintegration time (s)	11	12	12	13	12
f ₂	--	96.28	95.24	96.01	94.87

RH: Relative Humidity

(optimum concentration), regardless of the superdisintegrant used. The maximum drug release for the directly compressed tablets with CLT (4%) was found to be 89.36% at the end of 15 min. The maximum drug release for the sublimated tablets with CLT (4%) was found to be 99.23% at the end of 15 min [Figure 5a and b]. By changing the preparation method

of tablets to sublimation, the dissolution pattern of the tablets prepared by the camphor sublimation method at 20% concentration was observed to be rapid than those prepared by direct compression and sublimation with 10% camphor.^[21] This was because of their low hardness and the porous behavior which infiltrates dissolution medium into the tablet pores formed by sublimation of camphor which facilitates quick and complete disintegration. While tablets formulated with SSG showed lesser release than formulations with CP. The rapid disintegration and dissolution of formulations with CLT was due to high swelling power and wicking property compared to SSG and CP.

Stability studies

No alteration was seen in the physical aspects of SC15 in both the storage circumstances throughout the study period. The dissolution test samples were compared by calculating similarity and dissimilarity factors using the optimized formulation (initial) as a reference to ensure the same release pattern. As required, all the samples showed an excellent similarity profile (>90) concerning the reference formulation [Table 7].

CONCLUSION

Plant-based materials are renewable and can be obtained in a sustainable manner, thus meeting the requirements of constant availability supply of the raw material. CLT was synthesized, and the process was optimized for ratio of reactants and reaction time and temperature. Synthesized CLT was evaluated for swelling capacity, absorption efficiency, and moisture sorption capacity. Considering the inherent features of tragacanth, the standardized conditions for cross-linking were observed as, 1:0.4 proportion of tragacanth: Epichlorohydrin, reaction temperature 105°C for 45 min. Based on the drug release profiles using MTH as a model drug, it is concluded that preparation consisting of 4% optimized CLT and 20% camphor made into ODT by sublimation method showed the

highest drug release of 99.23% at the end of 15 min. This study provides a proof-of-concept for the use of natural polysaccharide as a super disintegrant after chemical modification. The easy to scale up platform technology used in the present study can be commercialized and applied to several other oral medications the require rapid onset of action

Plant-based materials are renewable and may be obtained in a sustainable manner therefore fulfill the criterion of consistent availability supply of the raw material. This study provides a proof-of-concept for the use of natural polysaccharide as a super disintegrant following chemical modification. The easy to scale up platform-technology employed in the present work can be commercialized and used to various other oral drugs the require quick onset of action.

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Conflicts of interest

There are no conflicts of interest.

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