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Superior disintegrating properties of calcium cross-linked *Cassia fistula* gum derivatives for fast dissolving tablets

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ABSTRACT

The present investigation was aimed at evaluating the feasibility of using calcium salts of carboxymethylated (CaCOG) or carbamoylethylated (CaCEG) derivatives of *Cassia fistula* gum as superdisintegrant while formulating fast disintegrating tablets (FDTs) exhibiting lowest disintegration time (DT) at highest mechanical strength. FDTs prepared with CaCOG (5%, w/w) or CaCEG (5%, w/w) were directly compressible and showed superior disintegrating property due to decreased water sorption time, increased particle packaging index, without any significant change in swelling index and effective pore radius. The mechanisms of superdisintegration suggested that probably the presence of Ca^{2+} resulted in intra and/or inter cross-linked bridges in the CaCOG or CaCEG that supported water transporting system even when the aqueous channels in the FDTs were blocked. Thus, the findings indicated great potential for using CaCOG or CaCEG as superdisintegrants in FDTs with high mechanical strength and low DT.

1. Introduction

Ideally, superdisintegrants should not only produce stronger tablets but also, disintegrate the tablet in the oral cavity in less than 30 s. In addition, directly compressible superdisintegrant(s) are preferred probably due to the reason that direct compression method is inexpensive, most convenient and produces tablets of sufficient mechanical integrity without the use of complicated unit operations (Terashita & Imamura, 2002). However, the disintegration of fast dissolving tablets (FDTs) prepared by direct compression method is often compromised while improving the tensile strength of tablets. Superdisintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate can disintegrate the tablets faster. However, they are of limited use when tablets are prepared with crushing strength of more than 4 kg (Fukami, Ozawa, Yonemochi, Yoshihashi, & Terada, 2005). Also, microcrystalline cellulose (Avicel-PH101 & PH102) or dicalcium phosphate added in FDTs for enhancing their disintegration often causes unpleasant feeling of grittiness in mouth.

Faster wetting of the superdisintegrating system accompanied with rapid swelling was considered to be the most vital requirement for exhibiting effective superdisintegration. The findings also suggested that increase in mechanical strength (i.e. increase in compression) led to increase in wetting time that resulted in increase in disintegration time and hence, loss of superdisintegration potential (Goel, Kaur, Tiwary, & Rana, 2010). On this basis attempts made at developing a combination of wetting agent (like amino acids) and swelling agents (like carmellose, alginates, etc.) for preparing FDTs with sufficient mechanical strength by direct compression have not been found suitable for water soluble drugs like ondansetron HCl (Goel, Vora, & Rana, 2008; Vora & Rana, 2008). Hence, there is a need to develop an alternative sweet tasting disintegrating system for preparing FDTs for water soluble drugs having sufficient mechanical strength and quick disintegration that is independent of tablet crushing strength (TCS).

Gum obtained from the seeds of *Cassia fistula* comprises β-(1 → 4) linked D-mannopyranose units with random distribution of α-(1 → 6) linked D-galactopyranose units as side chain having mannose:galactose ratio of 3.0 (Shrivastava & Kapoor, 2005). Carboxymethylation as well as carbamoylethylation of *Cassia* gum is reported to improve cold water solubility, improve viscosity and increase microbial resistance as compared to native gum (Sharma, Kumar, & Soni, 2003; Soni & Sharma, 2000). Therefore, an attempt was made to incorporate calcium or sodium salts of carboxymethylated or carbamoylethylated *C. fistula* gum as superdisintegrant in the formulation development of FDTs.

Metoclopramide hydrochloride (MET) is an antiemetic agent. It is used for the prophylaxis of vomiting associated with cisplatin or other chemotherapeutic agents. The drug is highly soluble in water and is rapidly absorbed after oral administration (Ganza-Gonzalez, Anguiano-Igea, Otero-Espinar, & Blanco Mendez, 1999; Reynolds, 1993). It has a short biological half life and is usually administered in a dose of 10–15 mg four times a day to maintain effective concentration throughout the day. Rapid action of MET is not achievable

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by administering it in conventional tablet form. This is because the persistent vomiting resulted in loss of hydrochloric acid, alkalosis and dehydration, which in turn may precipitate further vomiting. Hence, when this condition appears the patient cannot swallow even a small quantity of fluid. Thus, swallowing conventional tablet of MET with water is not possible. Hence, FDTs of MET seem to offer distinct advantage over its conventional tablet form in terms of ease of administration and enhance pre-gastric absorption, thereby ensuring immediate effect.

In the light of the above, the present investigation was aimed at evaluation of *C. fistula* gum derivatives as superdisintegrants in the FDTs formulations having sufficient mechanical strength as well as fast disintegration time. The study involves screening of calcium or sodium salts of carboxymethylated or carbamoylethylated *C. fistula* gum as superdisintegrant for developing FDTs containing a water soluble drug (1.5 g/ml), metoclopramide HCl. Further, the superdisintegration effect of gum derivatives with respect to increase in tablet crushing strength was also evaluated and compared with known superdisintegrants. Further, the superdisintegration potential of gum derivatives was explored through evaluation of powder properties.

2. Materials and methods

2.1. Materials

C. fistula seeds were collected from *C. fistula tree* situated in the hills at Nangal, District Ropnagar, Punjab, India. Metoclopramide HCl (99.9% Nayan Pharmaceuticals Ltd., Patiala, Punjab, India) crospovidone and croscarmellose sodium (Panacea Biotech Ltd. Lalru, India) were received as gift samples. Spray dried lactose (CDH, Mumbai, India) were used as supplied. All other reagents were of analytical grade.

2.2. Methods

2.2.1. Extraction and purification of C. fistula gum

C. fistula seeds were size reduced to fine powder. 100 g of this fine powder was soaked in 500 ml of 2% v/v acetic acid and stored at 45 °C in shaking incubator overnight. The jelly mass was diluted with lukewarm water to 1000 ml and filtered using muslin cloth to obtain gum mucilage. This mucilage was added drop wise to 500 ml of acetone. The gum precipitates were filtered. These precipitates were again dissolved in water, filtered to remove any debris and re crystallized using acetone. The precipitates obtained after filtration were dried in oven at 45 °C for 12 h and size reduced to get powdered gum of #80 sieve fraction.

2.2.2. Carboxymethylation of C. fistula gum

Carboxymethylated *C. fistula* gum (CCG) was prepared by modifying the method reported by Goyal, Kumar, and Sharma (2007). In brief, *Cassia* gum (5 g) was dispersed in 16 ml of 45% (w/v) ice cold sodium hydroxide solution. After stirring, 7 ml of 75% (w/v) monochloroacetic acid was added with constant stirring for 1 h. The temperature of the mixture was then raised to 75 °C and stirring was continued for further 30 min. Separately, 80%, v/v methanol solution in water was prepared and neutralized to pH 7.0 by adding glacial acetic acid. The reaction mixture in the gelled condition was cooled to room temperature, subdivided and suspended in this methanolic solution. The suspended precipitates were filtered thorough muslin cloth and washed three times with 80%, v/v methanol (pH 7.0). The washed product was redissolved in water and dialysed for 24 h. The dialysed CCG was freeze dried. The dried powder was passed through #80 sieve and stored in vacuum desiccators after sealing in double lined polyethylene bag till further use.

The degree of substitution of CCG was determined by a method reported earlier (Whistler, 1963). The degree of substitution was found to be 0.46.

2.2.3. Carbamoylethylation of C. fistula gum

Carbamoylethylation of *C. fistula* gum (CEG) was prepared by modifying the method reported by Sharma et al. (2003). *C. fistula* gum (5 g) was dispersed in 20 ml of ice cooled 45% (w/v) NaOH solution. The mixture was stirred at 1000 rpm for 1 h at 5–7 °C. Acrylamide solution (10 ml, 75%, w/v) was added gradually and then constantly stirred for 1 h at 25 °C. This reaction mixture was further heated on water bath (70 °C) with constant stirring for another 1 h. The reaction mixture was cooled at room temperature and neutralized with glacial acetic acid. The CEG was precipitated by adding methanol: water (80:20) mixture. The precipitates were separated by filtration and precipitates were washed thrice with methanol:water (80:20) mixture. The washed product was redissolved in water and dialysed for 24 h. The dialysed CCG was than freeze dried. The dried powder was passed through #80 sieve and stored in vacuum desiccators after sealing in double lined polyethylene bag till further use.

The degree of substitution of CEG was determined by a method reported earlier (Whistler, 1963). The degree of substitution was found to be 0.42.

2.2.4. Preparation of calcium cross linked carboxymethyl or carbamoylethylated C. fistula gum

The calcium cross linked gum derivatives were prepared by reacting the respective derivative with calcium chloride. 2.5 g of carboxymethyl or carbamoylethylated *C. fistula* gum was dissolved in 50 ml of water. Calcium chloride (5%, w/v, 50 ml) solution in water was added drop wise to the gum solution (5%, w/v, 50 ml) with constant stirring. IPA (50 ml) was added drop wise to the gum–calcium chloride solution mixture with stirring to obtain thick, uniform and gelatinous precipitates. These precipitates were repeatedly washed with distilled water to remove unreacted calcium and/or gum. The washing was stopped when the filtrate did not yield red color from blue color after adding it to standard magnesium–EDTA complex solution containing Eriochrome black T indicator solution. These washed precipitates were freeze dried and then passed through #80 sieve.

2.2.5. Preparation of metoclopramide FDTs by direct compression

Calcium carboxymethyl *C. fistula* gum (CaCOG, 1–15%, as superdisintegrant) or calcium carbamoylethylated *C. fistula* gum (CaCEG, 1–15%, as superdisintegrant) or conventional superdisintegrant (croscarmellose (5%, w/w) or crospovidone (5%, w/w)) was mixed with colloidal silica (0.5%, w/w, as lubricant) in dry state. To this mixture, spray dried lactose (q.s) and metoclopramide HCl (10%, w/w) were added and blended by tumbling for 30 min. The resulting blend was compressed into tablets with a multipunch six station rotary tableting machine (A.K. Industries, Nakodar, Punjab, India). The average weight and diameter of round shaped FDT was 100 ± 5 mg and 6 ± 0.5 mm, respectively.

2.2.6. Evaluation of powder blends

Pure excipients alone or their combinations in dry state were subjected to estimation of water sorption time, effective pore radius and swelling index.

2.2.6.1. Water sorption time (WST) and swelling index (SI). The water sorption time and swelling index were estimated as per the method reported by Vora and Rana (2008). In brief, the sample (250 mg) was filled into micropipette tips (transparent, 2 ml) for estimating WST and SI. The tip outlet was first blocked with a tiny swab of Nylon fiber to avoid leakage of the powder. After placing the solid sample

into the tip, it was tapped 10 times by dropping on a hard surface from 10 cm height to obtain approximately the same packing. The plastic tip was weighed (W_a) then dipped into a 2–3 mm layer of phosphate buffer pH 6.8. The time taken by the liquid to reach to the top of the powder bed was estimated as WST. The filled tip was again weighed (W_b) at the end of the experiment. The SI was estimated as

$$\mathrm{SI} = \frac{W_b - W_a}{W_a} \times 100 \quad (1)$$

The experiments were repeated six times and average values were taken for calculation.

2.2.6.2. Effective pore radius ($R_{eff.p}$). $R_{\mathrm{eff.p}}$ of the powder blend was estimated according to the method reported by Goel et al. (2010). In brief, the micropipette tip (2 ml, transparent) was filled with the powder and weighed (W_A). Then n-hexane [surface tension (γ) 18.4 mN/m] was poured dropwise on the bedtop till the solvent filtered out at the bottom of the tip. The tip was weighed again (W_B). The experiments were repeated six times.

$$R_{\mathrm{eff.p}} = \frac{W_B - W_A}{2\pi\gamma} \quad (2)$$

2.2.7. Evaluation of FDTs

2.2.7.1. Tablet crushing strength. Texture analyzer (TA XT plus, Stable Microsystems, UK) was used to measure the hardness of tablets. The tablet tensile strength is the force required to break a tablet by compressing it in the radial direction. For measuring the hardness of the tablets, the texture analyzer was adjusted to compression mode. The other parameters included: 0.5 mm/s pretest speed, force target mode with 50 g force at a holding time of 60 s. Tablet crushing strength (TCS) was calculated using the formula:

$$\mathrm{TCS} = \frac{2F}{\pi dt} \quad (3)$$

where '*F*' is the crushing load and '*d*' and '*t*' denote the diameter and thickness of the tablet, respectively.

The data reported is the mean of six individual determinations.

2.2.7.2. Particle packaging index (PPI). Particle packaging index was calculated on FDTs compressed to its maximum extend by modifying the method reported by Michael and Okor (2005). It is a indicator of compactness of powder. The particle packaging index is a ratio of density of tablet to density of particles. Density of tablets (ρ_{tablet}) was determined using the following formula:

$$\rho_{\mathrm{tablet}} = \frac{W_{\mathrm{tablet}}}{\Pi r^2 t} \quad (4)$$

where W_{tablet} is the weight of tablet, r is the radius of tablet and t is the thickness of tablet. Density of particles was determined by n-hexane displacement method.

2.2.7.3. Weight variation. The weight variation test was performed on randomly collected 20 tablets from a batch of 100 tablets according to the method specified in USP30NF25.

2.2.7.4. Content uniformity. Thirty tablets were randomly selected from each batch and 10 tablets were analyzed individually. The amount of metoclopramide HCl was analyzed at 320 nm in 0.1 N HCl (Beckman DU-640B UV/VIS).

2.2.7.5. In vivo disintegration time (DT). The *in vivo* DT was assessed in six healthy male volunteers for each batch of tablets (Abdelbary et al., 2005). The volunteers were informed of the protocol and purpose of the study. All the volunteers were asked to rinse their oral cavity with distilled water prior to the test. Each volunteer was asked to place one tablet on the tongue and a stopwatch was started immediately. The volunteers were given strict instructions not to chew or swallow the tablets, although licking was allowed. The end point of disintegration in the oral cavity was measured as the time when the tablet placed on the tongue disintegrated without leaving any lumps. All the volunteers were instructed to rinse their mouth after completion of test.

2.2.7.6. In vitro release studies. Metoclopramide HCl release from FDTs was evaluated by using the US pharmacopoeia dissolution apparatus II – paddle (Tab-Machines, Mumbai, India) at 37 ± 0.5 °C using 300 ml of simulated saliva pH 6.8 as a dissolution medium with stirring speed of 50 rpm. Aliquots (5 ml) withdrawn at various time intervals were immediately filtered through Watmann filter paper, diluted suitably and analyzed for metoclopramide HCl spectrophotometrically (Beckman DU-640 B UV/VIS spectrophotometer) at 320 nm. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally (r^2 = 0.9922). The *in vitro* dissolution test was performed in triplicate for each batch.

2.2.7.7. Similarity and dissimilarity factors. A model independent approach was used to estimate dissimilarity factor (f_1) and a similarity factor (f_2) to compare dissolution profile of optimized calculated FDTs with FDTs containing superdisintegrants.

The FDA and SUPAC-IR guidelines defines difference factor (f_1) as the calculated percent (%) difference between the reference and test curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \left\{ \left[\frac{\sum_{t=1}^{n} (R_t - T_t)}{\sum_{t=1}^{n} R_t} \right] \right\} \times 100 \quad (5)$$

The similarity factor (f_2) is given by the following equation:

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n \sum_{t=1}^{n} (R_t - T_t)^2} \right]^{-0.5} \times 100 \right\} \quad (6)$$

where n is the number of pull points, R_t is the reference batch profile at time point t and T_t is the test batch profile at the same time point t. For an *in vitro* dissolution curves to be considered similar f_1 values should be in the range of 0–15 while values of f_2 should lie within 50–100.

3. Results and discussion

Most of the researchers are looking for a superdisintegrant that meets the criteria of an ideal superdisintegrant. However, most of the available superdisintegrants are either mixture of two compounds (like glycine with alginates or chitosan, etc.) or if used alone they are unable to behave as superdisintegrants at high tablet crushing strength (like croscarmellose, crospovidone, etc.) (Fukami, Yonemochi, Yoshihashi, & Terada, 2006; Goel, Rai, Tiwary, & Rana, 2008; Goel, Vora, Tiwary, & Rana, 2009). Therefore, an attempt was made to evaluate a single compound that bears resemblance to an ideal superdisintegrant or close to an ideal superdisintegrant for preparing FDTs that would exhibit fast disintegration even when prepared at high compression force so as to withstand handling stress while packaging.

3.1. Preparation and evaluation of FDTs

Sodium or calcium salt of COG or CEG was examined for its superdisintegration potential. Various concentrations of *C. fistula* gum derivatives were employed for preparing different batches of FDTs containing MET (10 mg). The evaluation of different FDT

Table 1
Evaluation of FDTs prepared using various concentrations of modified or unmodified *Cassia fistula* gum.

Superdisintegrant	Concentration (%, w/w)	MET (mg/tablet)	Evaluation of FDTs					
			Weight variation (%)	Friability (%)	Content uniformity (%)	Tablet crushing strength (TCS) at Maximum compression (kg/cm^2)	DT (at maximum TCS)	Remarks
Pure *Cassia fistula* gum	5	10	7.52 ± 0.23	5.2 ± 1.2	85.32 ± 2.5	2.10 ± 0.12	310 ± 10	No superdisintegration potential
	10	10	10.25 ± 0.12	7.3 ± 1.3	80.12 ± 2.1	2.30 ± 0.11	295 ± 12	
	15	10	12.31 ± 0.21	10.1 ± 1.5	79.92 ± 2.1	2.50 ± 0.21	290 ± 13	
COG	5	10	2.10 ± 0.11	4.12 ± 0.9	85.1 ± 2.1	3.12 ± 0.11	250 ± 12	No superdisintegration potential
	10	10	1.92 ± 0.11	3.92 ± 0.8	89.20 ± 2.1	4.32 ± 0.10	243 ± 14	
	15	10	1.89 ± 0.23	3.12 ± 0.7	89.32 ± 2.3	4.53 ± 0.12	241 ± 12	
CEG	5	10	1.93 ± 0.21	3.33 ± 0.8	92.12 ± 1.2	4.32 ± 0.21	150 ± 14	No superdisintegration potential
	10	10	1.87 ± 0.32	3.20 ± 0.7	92.32 ± 1.3	4.10 ± 0.10	130 ± 10	
	15	10	1.81 ± 0.32	3.30 ± 0.7	93.13 ± 1.2	8.10 ± 0.11	110 ± 10	
CaCOG	5	10	1.12 ± 0.11	0.33 ± 0.01	99.9 ± 1.1	8.20 ± 0.10	16 ± 1	Superdisintegration potential
	10	10	1.32 ± 0.21	0.47 ± 0.01	98.9 ± 1.1	8.10 ± 0.10	17 ± 1	
	15	10	1.43 ± 0.33	0.13 ± 0.01	99.9 ± 1.2	8.30 ± 0.10	15 ± 1	
CaCEG	5	10	0.93 ± 0.02	0.17 ± 0.01	99.30 ± 1.1	7.90 ± 0.10	16 ± 1	Superdisintegration potential
	10	10	0.94 ± 0.01	0.18 ± 0.01	98.92 ± 1.2	7.90 ± 0.10	14 ± 1	
	15	10	0.99 ± 0.02	0.16 ± 0.01	99.20 ± 1.1	8.10 ± 0.10	14 ± 1	
CC	5	10	0.13 ± 0.01	0.27 ± 0.01	99.3 ± 1.2	7.20 ± 0.10	79 ± 2	Loss of superdisintegration potential
	10	10	1.17 ± 0.01	0.23 ± 0.01	98.22 ± 1.1	7.10 ± 0.11	72 ± 3	
	15	10	1.23 ± 0.01	0.21 ± 0.01	98.32 ± 1.2	7.20 ± 0.11	63 ± 5	
CP	5	10	1.37 ± 0.01	0.32 ± 0.01	99.17 ± 1.2	6.80 ± 0.12	65 ± 5	Loss of superdisintegration potential
	10	10	1.11 ± 0.01	0.37 ± 0.01	99.54 ± 1.2	6.90 ± 0.10	60 ± 4	
	15	10	1.33 ± 0.01	0.35 ± 0.01	99.43 ± 1.1	7.10 ± 0.10	52 ± 4	

CC, croscarmellose; CP, crosspovidone; CaCOG, calcium crosslinked carboxymethyl *Cassia fistula* gum; CaCEG, calcium crosslinked carbamoyl ethylated *Cassia fistula* gum.

batches is summarized in Table 1. The results suggested that the pure *C. fistula* gum was not directly compressible and it did not provide sufficient mechanical strength to tablets. All the batches containing *C. fistula* gum derivative showed no significant influence on weight variation. However, the FDT batches containing COG, CEG did not pass the content uniformity evaluation test as well as friability performance evaluation test. The failure of content uniformity test indicated non-uniform distribution of MET. The incorporation of COG or CEG probably produced more friable tablets because the tablets could not be compressed at high pressure due to their poor binding property. Thus, *C. fistula* gum alone, COG or CEG was unable to provide strength to FDTs. Further, evaluation of DT (at maximum TCS) did not suggest superdisintegration potential of pure gum, COG or CEG. Thus, these could not be considered for preparing directly compressible FDTs. However, FDTs prepared using CaCEG or CaCOG showed paradoxical influence on DT, weight variation, friability, content uniformity in addition to high TCS of 8 kg/cm^2. Further, all FDTs containing CaCOG (5–15%, w/w), CaCEG (5-–15%, w/w) or conventional superdisintegrants (CC (5–15%, w/w) or CP (5–15%, w/w)) were found to be directly compressible and passed the evaluation tests for FDTs as specified in the USP 30NF25. Interestingly, increasing the concentration of CaCOG or CaCEG from 5% (w/w) to 15% (w/w) did not produce depression or enhancement in DT, thus suggesting disintegration to be independent of their concentration. However, FDTs containing pure gum, COG (1–5%, w/w), CEG (1–5%, w/w), CaCOG (1–5%, w/w) or CaCEG (1–5%, w/w) showed high DT even at lower tablet crushing strength of 3 kg/cm^2 while retaining directly compressible property.

The % drug release of MET (10%, w/w) from FDTs prepared using CaCOG (5%, w/w) or CaCEG (5%, w/w) was conducted in simulated saliva (PH 6.8). The dissolution profiles of all the FDT batches revealed that 95% of metoclopramide HCl was released within 60 s. Further, the comparison of dissolution data with FDTs containing CC (5%, w/w) or CP (5%, w/w) was conducted using f_1 and f_2 statistics. An f_1 of 0.953 for CaCOG vs. CC; 0.253 for CaCEG vs. CC; 0.974 for CaCOG vs. CP or 0.327 for CaCEG vs. CP and f_2 of 52.11 for CaCOG vs. CC; 52.75 for CaCOG vs. CC; 52.87 for CaCOG vs. CP or 52.54 for CaCOG vs. CP indicates that the release profile of MET FDTs containing CaCOG or CaCEG in simulated saliva were comparable and in good agreement with each other.

Overall, these findings suggested overwhelming effect of CaCOG (5%, w/w) or CaCEG (5%, w/w) on DT of FDT prepared at 8 kg/cm^2 of TCS. Hence, these novel superdisintegrants could be used for preparing MET FDTs for the treatment of nausea and vomiting.

3.2. Influence of TCS on DT of MET FDTs containing CaCOG or CaCEG

The results obtained from Table 1 suggested high TCS (8 kg/cm^2) of FDTs containing CaCOG or CaCEG without significantly influencing DT. However, CP (5–15%, w/w) or CC (5–15%, w/w) loose its superdisintegration potential when compressed at TCS of 7 kg/cm^2. Therefore, additional batches of FDTs were prepared at different TCS in order to explore the influence of TCS on DT. The results are shown in Fig. 1. The DT of FDTs was found to increase with increase in TCS of FDTs when prepared with CC (5–15%, w/w) or CP (5–15%, w/w) as superdisintegrants. However, the appearance of plateau in the correlation between TCS and DT indicated insignificant ($p < 0.05$) influence of TCS on DT of FDTs when prepared with CaCOG or CaCEG. This suggested transportation of water inside the tablet (that is necessary for swelling of CaCOG or CaCEG which disintegrate tablet quickly) not to be effected at high compression.

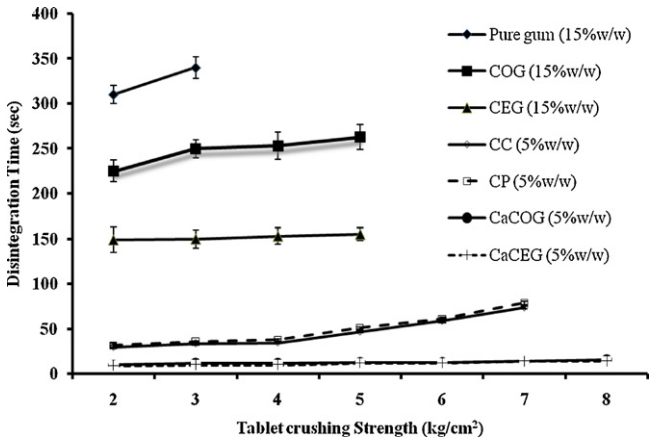

Fig. 1. Correlation of tablet crushing strength of FDTs prepared using various gum derivatives on disintegration time.

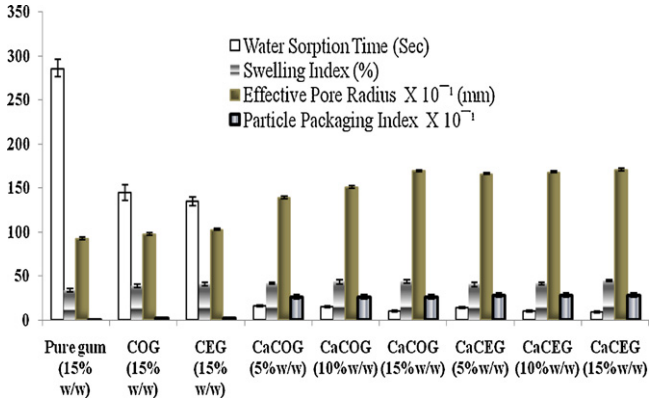

Fig. 2. Powder characteristics of pure *Cassia fistula* gum and its derivatives.

3.3. Exploring the mechanism of superdisintegration potential of CaCOG or CaCOG

The superdisintegration potential of CaCOG or CaCEG was evaluated using powder blend characterization. Buffer pH 6.8 was found to wet the pure *C. fistula* gum, COG and CEG in 286 ± 5 s, 145 ± 6 s and 135 ± 2 s, respectively suggesting poor wicking property of the pure gum and its derivatives (Fig. 2). However, the COG and CEG

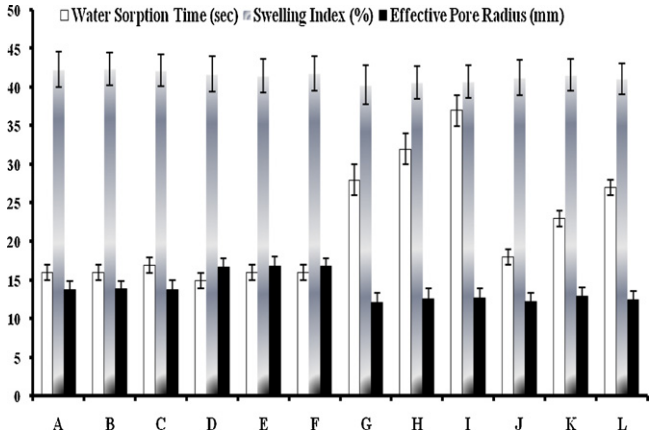

Fig. 3. Influence on powder characteristics when aqueous channels were blocked by adding increasing concentration of MET in to powder blend [A–C = CaCOG 5%, w/w; D–F = CaCEG 5%, w/w; G–I = CP 5%, w/w; J–L = CC 5%, w/w; A, D, G = MET 5%, w/w; B, E, H = MET 10%, w/w; C, F, I = MET 15%, w/w].

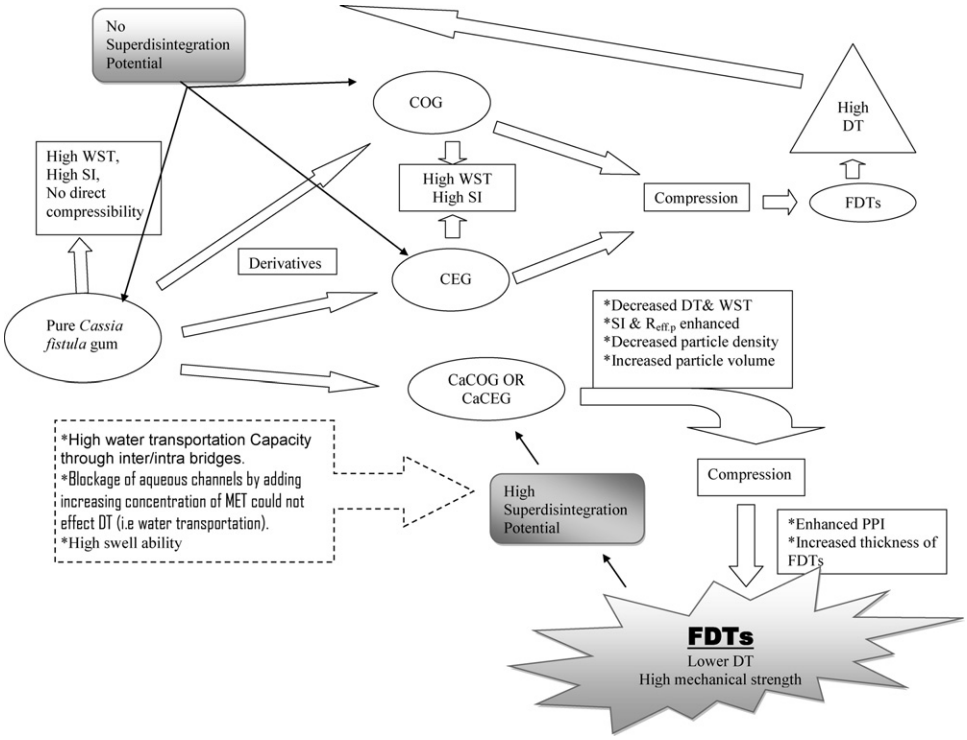

Fig. 4. Possible mechanism of superdisintegration potential of CaCOG and CaCEG.

derivatives of *C. fistula* gum were found to significantly ($p < 0.05$) enhance the swelling potential of gum. Thus, it seems logical to assume that the poor wicking property of gum and its derivatives would have resulted in loss of superdisintegration despite the high swelling property. However, the cross-linking of COG or CEG with calcium to form respectively, CaCOG or CaCEG enhanced the wicking potential without influencing the swelling behavior of COG or CEG (Fig. 2). Further, the SI as well as $R_{eff.p}$ of CaCOG was found to significantly increased along with reduction in WST. This suggested that the incorporation of $-CH_2$ moieties in CaCOG enhanced its superdisintegration potential. It is interesting to note here that $R_{eff.p}$ is an indicator of porosity of powder. The increase in $R_{eff.p}$ of CaCEG as compared to CaCOG resulted in highly porous nature of CaCOG and hence, high compressibility. This highly porous nature of CaCEG and CaCOG as compared to other derivatives of *C. fistula* gum seems to be responsible for enhancement in the superdisintegration potential. The lower $R_{eff.p}$ reflected lower porosity of tablet blends containing either CEG or COG. This probably created non-uniformity in the distribution of MET in the lattice of powder blend that resulted in failure of content uniformity test of tablet batches containing COG or CEG. Furthermore, introduction of Ca^{2+} could have resulted in building of intra and/or inter cross-linked bridges in the CaCOG or CaCEG. This would resulted in enhanced transportation of water leading to enhanced WST.

PPI is an indicator of compactness of a powder. The PPI of CaCOG and CaCEG was found to be more than that of pure gum, COG or CEG (Fig. 2). The increase in PPI is a indicator of decrease in particle density (i.e. increase in particle volume and decrease in mass of particles) along with increase in thickness of FDTs. Therefore, the enhanced volume of CaCOG or CaCEG particles suggested an increase in $R_{eff.p}$ (i.e. increase in porosity) that resulted in enhanced WST, inter/intra particle binding and DT. Thus, this further suggested the reason for increased mechanical strength without interfering with DT of FDTs.

Vora and Rana (2008), Goel, Rai, et al. (2008), and Goel, Vora, et al. (2008) reported that water soluble drugs form saturated solution in the pores of tablets that were usually the aqueous channels in the tablets, thus blocked the transportation of water. This led to increase in DT when water soluble drug was used for preparation of FDTs. On this basis the concentration of MET was increased from 5% (w/w) to 15% (w/w) in the powder blend containing CaCOG (5%, w/w), CaCEG (5%, w/w), CC (5%, w/w) or CP (5%, w/w). The results shown in Fig. 3 suggested blockage of aqueous channels by increasing concentration of MET did not influence the DT as compared to conventional superdisintegrants (CC or CP). Thus, these findings suggested transportation of water not to influenced by CaCOG or CaCEG. The summary of superdisintegration potential of CaCOG and CaCEG is shown in Fig. 4.

4. Conclusion

The present investigation revealed high superdisintegration potential of CaCOG and CaCEG. The FDTs containing pure *C. fistula* gum, COG or CEG were neither directly compressible nor did they pass the evaluation test for FDTs as per USP30NF25. However, FDTs prepared using CaCOG (5%, w/w) or CaCEG (5%, w/w) were directly compressible and passed the tests as specified in the USP30NF25. FDTs prepared with CaCOG (5%, w/w) exhibited DT comparable to those prepared with CaCEG (5%, w/w). However, the FDTs containing CaCOG could be prepared at high mechanical strength of 8.2 kg/cm^2. Therefore, CaCOG can be suggested to yield better performance of FDTs as compared to CaCEG. The mechanism of superdisintegration suggested decreased WST without effecting SI and $R_{eff.p}$ to be the cause of superdisintegration potential. In addition, presence of Ca^{2+} that builds intra and/or inters cross-linked bridges in the CaCOG or CaCEG supported water transporting system even when the aqueous channels in the FDTs were blocked. Overall, the findings pointed CaCOG and CaCEG could be the superdisintegrants that provides FDTs with sufficient mechanical strength with lowest DT. Thus, these superdisintegrants could be considered useful in near future for the formulation development of FDTs.

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References

Abdelbary, G., Eouani, C., Prinderre, P., Joachim, J., Reynier, J., & Piccerelle, P. (2005). Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. *International Journal of Pharmaceutics*, *292*, 29–41.

Fukami, J., Ozawa, A., Yonemochi, B., Yoshihashi, Y., & Terada, K. (2005). Development of fast disintegrating compressed tablets using amino acid as disintegration accelerator: Evaluation of wetting and disintegration of tablet on the basis of surface free energy. *Chemical and Pharmaceutical Bulletin*, *53*, 1536–1539.

Fukami, J., Yonemochi, B., Yoshihashi, Y., & Terada, K. S. (2006). Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose. *International Journal of Pharmaceutics*, *310*, 101–109.

Ganza-Gonzalez, A., Anguiano-Igea, S., Otero-Espinar, F. J., & Blanco Mendez, I. (1999). Chitosan and chondroitin microspheres for oral administration controlled release of metoclopramide. *European Journal of Pharmacy and Biopharmaceutics*, *48*, 149–155.

Goel, H., Kaur, G., Tiwary, A. K., & Rana, V. (2010). Formulation development of stronger and quick disintegrating tablets: A crucial effect of chitin. *Yakugaku Zasshi*, *130*, 729–735.

Goel, H., Rai, P., Tiwary, A. K., & Rana, V. (2008). Orally disintegrating systems: Innovations in formulation and technology. *Recent Patents on Drug Delivery and Formulation*, *2*(3), 258–274.

Goel, H., Vora, N., & Rana, V. (2008). A novel approach to optimize and formulate fast disintegrating tablets for nausea and vomiting. *AAPS PharmSciTech*, S1530–S9932.

Goel, H., Vora, N., Tiwary, A. K., & Rana, V. (2009). Formulation of orodispersible tablets of Ondansetron HCl: Investigations using glycine–chitosan mixture as superdisintegrant. *Yakugaku Zasshi*, *129*, 513–521.

Goyal, P., Kumar, V., & Sharma, P. (2007). Carboxymethylation of tamarind kernel powder. *Carbohydrate polymer*, *69*, 251–255.

Michael, U., & Okor, R. S. (2005). Effect of humidity on the disintegrant property of α-cellulose. Part II: A technical note. *AAPS PharmSciTech*, *6*(1), E31–E34.

Reynolds, J. R. (1993). *Martindale's extra pharmacopoeia* (30th ed.). London: Pharmaceutical Press., pp. 892–894.

Sharma, B. R., Kumar, V., & Soni, P. L. (2003). Carbamoylethylation of Cassia tora gum. *Carbohydrate Polymers*, *54*, 143–147.

Shrivastava, M., & Kapoor, V. P. (2005). Seed galactomannana: An overview. *Chemistry and biodiversity*, *2*, 295–317.

Soni, P. L., Sharma, P. (2000). Cassia tora gum as viscosifier and fluid loss control agent, *Indian Patent* Application No. 680, DEL.

Terashita, K., & Imamura, K. (2002). Preparation of antipyretic analgesic by direct compression and its evaluation. *Chemical and Pharmaceutical Bulletin*, *50*, 1542–1549.

Vora, N., & Rana, V. (2008). Preparation and optimization of mouth/orally dissolving tablets using a combination of glycine, carboxymethyl cellulose and sodium alginate: A comparison with superdisintegrants. *Pharmaceutical Development and Technology*, *13*, 1–11.

Whistler, R. L. (1963). *Method in carbohydrate chemistry*. New York: Academic Press., pp. 23.