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# Formulation and Evaluation of Aluminium Ion ($Al^{+3}$) Cross-Linked Carboxymethyl Guar Gum Matrix Tablets For Colon Delivery

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## Abstract

Targeting of drugs to the colon by the oral route could be achieved by different approaches including matrix and coated systems, for which the drug release is controlled by the gastrointestinal pH, transit times and intestinal flora. The method by which the drug release will be triggered by the colonic flora appears to be more interesting with regard to the selectivity. Metronidazole is only used antibiotics which can be used in colonic diseases. Matrix tablets were prepared by mixtures of Pectin and Guar gum, in which Metronidazole was selected as model drug. Six Matrix (F-I to VI) and coated (F VII to XII) tablet formulations of Metronidazole were prepared by different mixtures of pectin and guar gum then coated with Eudragit RS 100, for coated tablets. The results of drug release studies, performed according to the USP paddle method by using 0.1N hydrochloric acid for 2 hrs, pH 7.4 phosphate buffer for 3 hrs and pH 6.8 phosphate buffer for 24 hrs. And In vitro dissolution study for metronidazole tablets in Rat cecal content were performed. Matrix tablets of guar gum with metronidazole in the ratio of 1:1, 1:2 and 1:3 shows percent drug release after 24 hrs as 83%, 63% and 55% respectively. Pectin in the ratio of 1:1, 1:2 and 1:3 shows percent drug release after 24 hrs as 100%, 95% and 82% respectively. Coated tablets of guar gum with metronidazole in the ratio the ratio of 1:1, 1:2 and 1:3 shows percent drug release after 24 hrs as 96%, 60% and 52% respectively. Pectin in the ratio of 1:1, 1:2 and 1:3 shows percent drug release after 24 hrs as 97%, 99% and 95% respectively. All these batches in first two hours i.e. pH 1.2 hydrochloric acid shows very neglible release, then it showed slight increase in pH 7.4 Phosphate Buffer. Drug release up to 5 hours but it showed high and fast increase in drug release from 6th hour in pH 6.8 Phosphate buffer, as it enters in colonic pH. So natural polymers are most cheap and suitable for colonic drug delivery.

## Introduction

Natural polymers are naturally occurring components in plants, animal and microbial. They are polysaccharides. Polysaccharides are a class of biopolymers constituted by simple sugar monomers.The monomers (monosaccharides) is linked together by O-glycosidic bonds that can be made to any of the hydroxyl groups of a monosaccharide, conferring polysaccharides the ability to form both linear and branched polymers. They are heterogeneous in composition upon hydrolysis they yield simple sugar units such as arabinose, galactose, glucose, mannose, xylose or uronic acids, etc. Differences in the monosaccharide composition, chain shapes and molecular weight dictate their physical properties including solubility, gelation and surface properties. (Patricia. B 2007). In recent years, considerable attention has been focused on natural polymers in the design of various dosage form drug delivery system. Polymers have been successfully employed in the formulation of solid, liquid and semi-solid dosage forms and are specifically useful in the design of modified release drug delivery systems. Both synthetic and natural polymers have been investigated extensively for this purpose (Guo et al. 1998, Varshosaz et al. 2006). The selection of polymer or mixture of polymers depends on where and how the drugs are intended to be released. Delivery systems involving synthetic polymers make use of costlier raw materials, complex process conditions, make use of noxious organic solvents that makes the product costlier and often makes the product unsuitable because of the presence of residual organic solvent (Michael 1989). The use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic, and capable of chemical modifications, potentially biodegradable and with few exceptions, also biocompatible (Satturwar et al. 2003,

Chaurasia et al. 2006, Malafaya et al. 2007, Chivate et al. 2008). Of increasing importance is the fact that plant resources are renewable and if cultivated or harvested in a sustainable manner, they can provide a constant supply of raw material (Perepelkin, 2005). However, substances from plant origin also pose several potential challenges such as being synthesised in small quantities and in mixtures that are structurally complex, which may differ according to the location of the plants as well as other variables such as the season. This may result in a slow and expensive isolation and purification process. Another issue that has become increasingly important is that of intellectual property rights (Lam, 2007, Mc Chesney et al. 2007).

Traditionally, excipients were included in drug formulations as inert vehicles that provided the necessary weight, consistency and volume for the correct administration of the active ingredient, but in modern pharmaceutical dosage forms, they often fulfil multi-functional roles such as improvement of the stability, release and bioavailability of the active ingredient, enhancement of patient acceptability and performance of technological functions that ensure ease of manufacture (Hamman and Tarirai 2004).The specific application of plant-derived polymers in pharmaceutical formulations include their use in the manufacture of solid monolithic matrix systems, implants, films, beads, micro-particles, nanoparticles, inhalable and injectable systems as well as viscous liquid formulations (Panday and Khuller 2004, Chamarthy and Pinal 2008, Alonoso-Sanda et al. 2008).

Within these dosage forms, polymeric materials have fulfilled different roles such as binders, matrix formers or drug release modifiers, film coating formers, thickeners or viscosity enhancers, stabilisers, disintegrant, solubilisers, emulsifiers, suspending agents, gelling agents and bioadhesives (Guo et al. 1998). Polymers are often utilized in the design of novel drug delivery systems such as those that target delivery of the drug to a specific region in the gastrointestinal tract or in response to external stimuli to release the drug. This can be done via different mechanisms including coating of tablets with polymers having pH dependent solubilities or incorporating non-digestible polymers that are degraded by bacterial enzymes in the colon. Non-starch, linear polysaccharides are resistant to the digestive action of the gastrointestinal enzymes and retain their integrity in the upper gastrointestinal tract. Matrices manufactured from these polysaccharides therefore remain intact in the stomach and the small intestine, but once they reach the colon they are degraded by the bacterial polysaccharidases. This property makes these polysaccharides exceptionally suitable for the formulation of colon-targeted drug delivery systems (Chaurasia et al. 2006, Shirwaikar et al. 2008). It has, however, certain disadvantages like, poor stability, poor mechanical strength, low elasticity, low antigenic response, tissue irritation etc. Natural polymers have been modified to overcome some of its drawbacks, like uncontrolled rate of hydration, thickening, drop in viscosity during storage, microbial contaminations etc (Durso, 1980). Various natural polymers like cellulose, pectin, inulin, alginate, carrageenan, rosin, guar gum, locust bean gum, gum arabic, psyllium, starch, aloe gel, xanthan and chitosan have been used for the development of controlled or sustained release dosage forms.

## Materials and Method

**Materials**

Metronidazole was supplied as sample gift by the CAPLET India. Pvt. Ltd, Kolkata India. Guar gum was supplied by the Merk Specialities Pvt. Ltd. Aluminium chloride (AlCl3) was supplied by S.D. fine-chem. Ltd. Boisar-401506. Sodium hydroxide (NaOH) was supplied by Finar, chemicals Ltd. Hydrochloric Acid (HCl) was supplied by Merk Specialities Pvt. Ltd. Potassium di-hydrogen phosphate ($KH_2PO_4$) was supplied by Merk Specialities Pvt. Ltd. Methanol was supplied by Merk Specialities Pvt. Ltd. Magnesium stearate was suppliedby SD fine chem. Ltd, Boisar-401506. Glacial acetic acid was supplied by Thermo Fisher Scientific India Pvt,Ltd.

**Methods**

**Weight variation test of the tablets:**

20 tablets, collected at random, were weighted individually and average weight was determined. The variation of the weight of each tablet from the average weight was determined.

**Hardness test of tablet:**

Hardness of each tablet was measured using Monsanto type hardness tester. Average hardness of 5 tablets was reported.

**Friability test of tablet:**

6 tablets were weighted and taken in a Roche friabilator (Friabilator, Veego, and Mumbai, India). The tablets were rotated at 25 rpm for 4 minutes. The tablets were then de-dusted and reweighed. Average friability of 6 tablets was calculated.

**Thickness test of tablet:**

Thickness of each tablet was measured using a side calliper (Digimatic Calliper, model CD-6”CS, Mitutoyo Corporation, Japan). Average thickness of 5 tablets was reported.

**Content uniformity test of tablets:**
2 tablets were collected at random. Each tablet was powdered in a glass mortar. The powder was quantitatively transferred in a 250 ml conical flask and 250 ml acid buffer solution (pH 1.2) was added. The stoppered flask was shaken for 2h in a mechanical shaker. The mixture was filtered and an aliquot following suitable dilution was analyzed spectrophotometrically at 278 nm for metronidazole content and finally potency of the tablet was determined using the calibration curve constructed using acid buffer.

**Fourier transforms infra- red (FT- IR) analysis**
The infrared spectra of metronidazole and powered tablet containing the drug were recorded in a FTIR spectrophotometer (Perkin Elmer, model RX-1, UK). The samples were mixed with KBr and converted into pellets at 5.5 ton pressure using a hydraulic press. The spectra were taken in the wave number region of 4000-400cm-1.

**Differential scanning Calorimetry (DSC) study:**
DSC thermograms of metronidazole and powered tablet containing the drug were obtained in the following way: weighed amount (6.8 to 8.2 mg) of samples was kept in hermetically sealed aluminium pan and heated at a scan speed of $10^0$C/min over a temperature range of 30-500ºC in a differential scanning calorimeter (DSC Q2000 V24.2 Build 107 model Universal V4 TA Instruments U.K).

**X-ray diffraction analysis (XRD)**
The qualitative X-ray diffraction studies of metronidazole and powered drug were performed using an X-ray diffractometer (Paanalytical XPERT; PRO. Holland). The powdered samples were scanned from 0-100°diffraction angle (2θ) range under the following measurement conditions: source, Ni filtered Cu-Kα radiation; voltage 45kv; current 30 mA; scan speed 1° /min.

**In Vitro Drug Release Study:**
In vitro drug release studies were carried out in USP II tablet dissolution rate test apparatus (model TDP-06P, Electro Lab, Mumbai, India) at 37±0.5$^0$C and 75 rpm speed. The tablets of each formulation were immersed in simulated gastric fluid (900ml, acid buffer, pH1.2) and dissolution was carried out for the first 2h.Thereafter the pH of dissolution media was change by phosphate buffer of pH 6.8 and the dissolution study was carried out for 12 hr. in 900 ml buffer medium. During the dissolution study 5ml aliquot was withdrawn from the dissolution medium at predetermine time & replaced with 5 ml of fresh respective fluid. The absorbance was measured at 278nm for acid buffer & 319 nm for buffer solution of pH 6.8.The absorbance were measured using spectrophotometrically UV-VIS spectrophotometer (Model Cary-50 Bio, VARIAN, Australia). The amount of drug release from the tablet was calculated using the respective calibration curve.

## Result and Discussion

**Determination of degree of substitution of O-carboxymethyl group in guar gum:** The determination of degree of substitution of carboxymethyl guar gum was conducted by method.

**Table: 1**

| No of observations | Weight of sodium carboxymethyl guar gum (mg) | Volume of 80 % v/v methanol(ml) | Volume of Water (ml) | Volume of sodium hydroxide (ml) |
|---|---|---|---|---|
| 1 | 200 | 1.50 | 20 | 5.0 |
| 2 | 200 | 1.50 | 20 | 5.0 |
| 3 | 200 | 1.50 | 20 | 5.0 |

**Table: 2**

| Strength of sodium hydroxide (N) | Total volume of mixture (ml) | Volume of 0.4 (N) Hydrochloric acid used (ml) | A | Degree of Substitution | Mean D.S. ± S.D. |
|---|---|---|---|---|---|
| 0.4901 | 26.50 | 4.5 | 3.212 | 0.639 | |
| 0.4901 | 26.50 | 4.6 | 3.011 | 0.591 | 0.643 ± 0.076 |
| 0.4464 | 26.50 | 4.6 | 3.454 | 0.699 | |

**FTIR study of guar gum & carboxymethyl guar gum:**
The characterization of modified guar gum was done by FTIR & X-RD analysis. FTIR spectra of native Guar gum (GG) and Carboxymethyl guar gum (CMGG) are represented in figure **6.2**. The broad band around 3399.03 cm−1 is attributed to -OH stretching vibration. We can also observe the -$CH_2$ symmetrical stretching vibrations at 2924.34 cm−1. In native guar gum, the band at 1651 cm−1 is assigned to scissoring of two -OH bonds of absorbed water molecules and the bands at 871.75 and 814.92 cm−1 are due to skeletal stretching vibrations of guar gum. The

carboxymethyl guar gum shows new bands at 1620, 1416 and 1325 cm−1. The characteristic peaks at 1620 cm−1 correspond to the -COO− asymmetric stretching vibration. 1416 and 1325 cm−1 are the -COO− symmetric stretching vibration.The new bands are assigned to carboxymethyl moieties and this indicates that the hydroxyl groups of guar gum molecules were carboxymethylated.

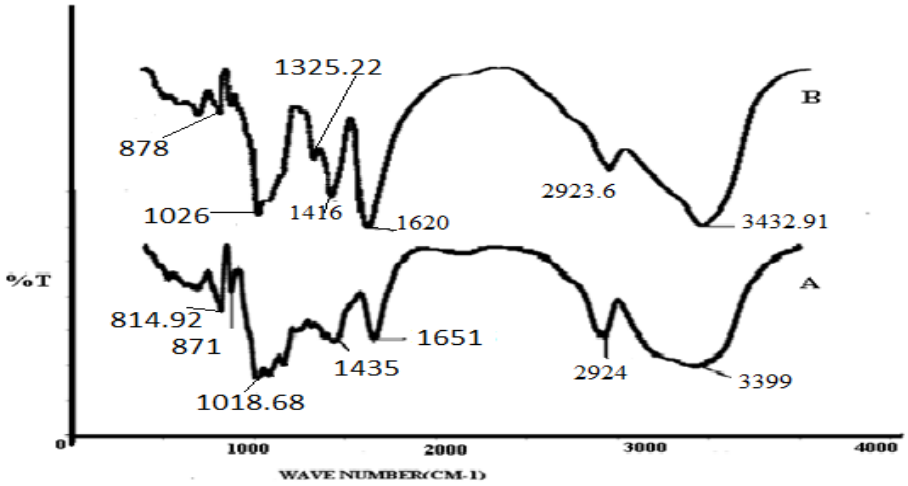


**Figure:** FT-IR spectra of (A) guar gum (B) sodium carboxymethyl guar gum

**X-RD study of guar gum & carboxymethyl guar gum:**

The wide angle X-ray diffractrograms of native guar gum and a representative carboxymethyl guar gum is presented in Fig. **6.3**. From Fig. 6.3a, it is obvious that native guar gum is typical of amorphous substance while that of carboxymethyl guar gum is typical of crystalline substances with the characteristic peak appearing at $31^0$, $43^0$, $58^0$, $76^0$, and $82^0$.Incorporation of carboxymethyl group probably imparted some degree of crystalinity.

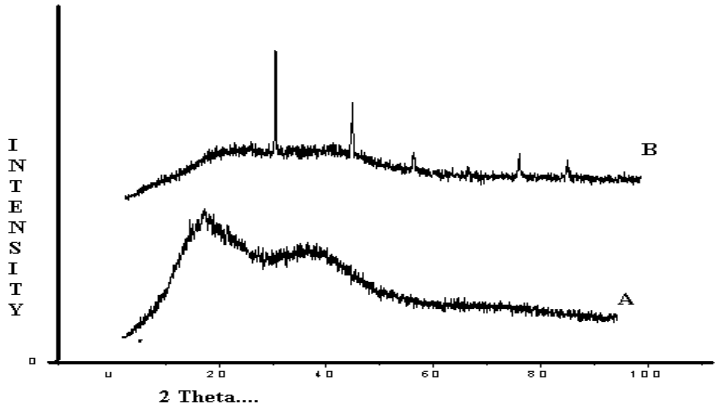


**Fig .**X-RD of Guar gum (A) and Carboxymethyl Guar gum (B)

**Stability of the drug in matrix tablet:**

The compatibility of the drug in matrix tablets was assessed through FTIR, DSC, and XRD analysis. In the FTIR, the absorption bands at 3223, 3100, 1535, 1370 and 1076 $cm^{-1}$were assigned as the finger prints of metronidazole. (Ramukuty. **2012**).

FTIR spectra of MTNZ showed the characteristics bands of –OH stretching, C-H &C=CH stretching, N-O stretching, -NO2 symmetrical stretching, and –C-O stretching respectively at 3219.6, 3100.6,1535.37,1368.75 and 1074.74 cm-$^{1}$. The spectra obtained from the powdered tablet showed the presence of the all above characteristic bands of the drug almost at the same wave numbers.

## Conclusion

Polymers are macromolecules having very large chains, contain a variety of functional groups, can be blended with other low- and high–molecular-weight materials, and can be tailored for any applications. Polymers have been successfully employed in the formulation of solid, liquid and semi-solid dosage forms and are specifically useful in the design of modified release drug delivery systems. Both synthetic and natural polymers have been investigated

extensively for this purpose. The delivery systems involving synthetic polymers make use of costlier raw materials, complex process conditions, make use of noxious organic solvents that makes the product costlier and often makes the product unsuitable because of the presence of residual organic solvent. Therefore, the use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic, and capable of chemical modifications, potentially biodegradable. Various natural polymers like cellulose, pectin, inulin, alginate, carrageenan, rosin, guar gum, locust bean gum, gum arabic, psyllium, starch, aloe gel, xanthan and chitosan have been used for the development of controlled or sustained release dosage forms. It has, however, certain disadvantages like, poor stability, poor mechanical strength, low elasticity, low antigenic response, tissue irritation etc. Natural polymers have been modified to overcome some of its drawbacks, like uncontrolled rate of hydration, thickening, drop in viscosity during storage, microbial contaminations etc. Among the natural polysaccharide, guar gum has been extensively studied for colon targeted drug delivery system.

Guar gum is a naturally occurring galctomannan polysaccharide consisting of a linear chain of β-D-mannopyranose joined by β-(1–4) linkage with α-D-galactopyranosyl units attached by 1, 6-links in the ratio of 1:2. It is susceptible to microbial degradation in the large intestine. However, guar gum alone is unable to control premature release of drug in the upper gastrointestinal tract because of its swelling and erosion in aqueous medium. Research reports are available on modification of guar gum to carboxymethyl guar gum followed by cross-linking either ionically with $Ca^{+2}$, $Ba^{+2}$ ions or covalently with glutaraldehyde to form multi unit dosage form such as beads, micro particles, microsphere etc. To the best of our knowledge, there is no report on matrix tablets prepared using ionically cross linked carboxymethyl guar gum for colon delivery. Since, Amoebiasis is an infection of the lower GIT caused by Entamoeba histolytica, a single celled protozoan parasite. The trophozoites of Entamoeba histolytica can invade the colonic epithelium, causing amoebic colitis. Metronidazole is the preferred drugs used in treatment of the lower GIT diseases like amoebiasis, giradiasis, trichomonasis and anaerobic infections. But pharmacokinetics profile of metronidazole shows that drug is completely absorbed in approximately 1 h after a single dose of 500 mg. The administration of this drug in conventional tablet dosage form provides a minimal amount of metronidazole for local action in the colon, still resulting in the relief of amoebiasis, but with more unwanted systemic toxicity. The objective of the present investigation was to develop $Ca^{+2}$ ion cross-linked carboxymethyl guar gum matrix tablets by wet granulation method and to examine its suitability as colon specific drug delivery system. Metronidazole has been selected as a model drug in this study .It is an antiprotozoal drug and extensive used to eradicate protozoal infections which usually are prevalent in lower part of gastro intestinal tract. The study also includes synthesis and characterization of carboxymethyl guar gum. Matrix tablets containing various proportions of carboxymethyl guar gum and calcium gluconate were prepared by wet granulation technique.

The tablets were evaluated for weight variation, content uniformity, thickness, hardness and friability. All the formulation was found to comply with the Pharmacopoeial requirement. The release of the drug from the tablets was studied initially in acid solution (pH-1.2) for 2hr.After which the pH of the dissolution medium was increased to pH 7.4. After 3hr of dissolution study in pH 7.4, the pH was shifted to pH 6.8, and the dissolution was carried out upto 12hr. The effect of CMGG/CG ratio on the drug release was studied with the tablets (F1 to F8) which were prepared using CMGG/CG ratio of 10:0 to 1:5 at a fixed hardness of $3kg/cm^2$. Drug release was found to follow the order: F1>F2>F3> F4<F5<F<6<F7<F8. The results indicate that the tablets prepared using CMGG release the drug faster. Incorporation of CG decreased the drug released due to cross-linking between the –COOH group of CMGG and $Ca^{+2}$ ion of CG. The high the amount of CG the slower was the drug release. However, after a certain concentration of CG, the drug release increased probably due to channeling effect of excess CG. The effect of hardness of tablets on drug release was evaluated with matrix tablets (F9 – F14) having 100 mg of drug and containing CMGG/CG in a ratio of 1:3 or 1:5.

The tablets were prepared at various compression force to impart hardness of 3, 6 or 9 kg/cm2 to the tablets. The release profiles of the drug from the tablets having various hardness were found to be superimposible. The ANOVA test of the AUCs calculated from release profiles revealed no significant difference ($p>0.05$).This indicates that hardness of the tablets did not influence the drug release appreciably. The effect of drug load (50mg,75mg,100 mg to 125mg) on drug release was studied with tablets (F15- F18) prepared using CMGG/CG ratio of 1:1 w/w and same compression force (tablet hardness 3 kg/cm2) to eliminate the effect of gel strength of matrix and hardness of the tablets on drug diffusion. The result indicated that the tablet having higher potency tended to release the drug faster. ANOVA test on AUCs also showed significant difference ($p<0.05$). The release study indicates that the formulation F4 released only about 26% drug in 5hr and 58% drug in 12hr. The release data of the drug from various tablets were fitted in Korsmeyer-Peppas equation. It was found that the value of n varied from 0.538 to 0.83. This indicates that the mechanism of drug release followed anomalous or Non-Fickian modal and the drug released occurred by both diffusion and erosion. Compatibility of the drug in polymer matrix was analysed with FTIR and DSC studies.

FTIR spectra of MTNZ showed the characteristics bands of –OH stretching, C-H &C=CH stretching, N-O stretching, -NO2 symmetrical stretching, and –C-O stretching respectively at 3219.6, 3100.6,1535.37,1368.75 and 1074.74 cm-$^{1}$. The spectra obtained from the powdered tablet showed the presence of the all above characteristic bands of the drug almost at the same wave numbers. The DSC curves of MTNZ exhibited a sharp endothermic peak corresponding to the melting point of the drug at 160° C. The endothermic peak of the drug in tablet was found almost at the same temperature. XRD pattern of MTNZ clearly indicated its crystalline nature. The crystalline nature of the drug was also maintained in the tablet although the intensity of the peaks obtained from the tablet was reduced. The results of FTIR and DSC studies confirmed the absence of any interaction between drug and excipients and that of XRD study indicated that no polymorphic transformation of the drug took place during tabletting by wet granulation process. FTIR study also confirmed the modification of guar gum to carboxymethyl guar gum. The stability of matrix tablet was assessed with formulation F4 by keeping under stress condition of 40°C/ 75%RH for 1 and 3months. The tablets after 1 and 3 month did not show any change in appearance and drug content. Comparison of release profile of tablet (F4) after 1and 3 months showed almost similar release profile with that of the freshly prepared tablet with a similarity factor (f2) value of 57 to 60. However, the tablet which was kept in open container released the drug faster with f2 value of 44. The above results indicated Ca+2 ion cross-linked CMGG could be a potential matrix for developing a dosage form that could be used to deliver metronidazole in the colon to cure various colonic diseases like amoebiasis, giradiasis, trichomonasis and anaerobic infections with minimal systemic side effects by preventing the release of drug in the upper part of GIT. However, future work involve to further decrease the release of drug in gastric and small intestinal fluid and to provide complete release in colon.

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