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Rapidly disintegrating tablets of metoclopramide hydrochloride using novel chemically modified cellulose

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ABSTRACT

The purpose of the study was to modify cellulose using hydrochloride salt of 2-aminoethanoyl chloride with optimum hydrophilic and hydrophobic properties to impart it a superdisintegrant activity and also to formulate and evaluate rapidly disintegrating tablets of metoclopramide hydrochloride using this novel chemically modified cellulose. A novel polymer, chemically modified cellulose was synthesized by chemically modifying microcrystalline cellulose with hydrochloride salt of 2-aminoethanoyl chloride. The formation of novel polymer was confirmed by Fourier Transform Infrared (FTIR) and Nuclear Magnetic Resonance (NMR) spectroscopy and by differential scanning calorimetric (DSC) and elemental analysis. The toxicity study proved the novel modified cellulose to be non toxic. Rapidly disintegrating tablets of metoclopramide hydrochloride were prepared using novel modified cellulose and compared for the release of drug with control formulation, prepared using non modified microcrystalline cellulose. The tests like wetting time, water absorption ratio and in vitro disintegration time were carried out to elucidate the relationship between them. The study revealed that novel modified cellulose in a concentration of 2% released the drug faster than at a concentration higher than that. Hence it could be concluded that microcrystalline cellulose, a polymer which is devoid of superdisintegrant activity, can suitably be modified by controlled chemical modification of it with hydrochloride salt of 2-aminoethanoyl chloride or similar groups with optimum hydrophilicity and hydrophobicity to convert it into a superdisintegrant material. It can also be concluded that rapidly disintegrating tablets of metoclopramide hydrochloride can suitably be developed for the efficient management of emesis.

KEY WORDS: Chemically modified cellulose, Microcrystalline cellulose, Metoclopramide hydrochloride, Rapidly disintegrating tablets, Superdisintegrant.

RESUMEN

The purpose of the study was to modify cellulose using hydrochloride salt of 2-aminoethanoyl chloride with optimum hydrophilic and hydrophobic properties to impart it a superdisintegrant activity and also to formulate and evaluate rapidly disintegrating tablets of metoclopramide hydrochloride using this novel chemically modified cellulose. A novel polymer, chemically modified cellulose was synthesized by chemically modifying microcrystalline cellulose with hydrochloride salt of 2-aminoethanoyl chloride. The formation of novel polymer was confirmed by Fourier Transform Infrared (FTIR) and Nuclear Magnetic Resonance (NMR) spectroscopy and by differential scanning calorimetric (DSC) and elemental analysis. The toxicity study proved the novel modified cellulose to be non toxic. Rapidly disintegrating tablets of metoclopramide hydrochloride were prepared using novel modified cellulose and compared for the release of drug with control formulation, prepared using non modified microcrystalline cellulose. The tests like wetting time, water absorption ratio and in vitro disintegration time were carried out to elucidate the relationship between them. The study revealed that novel modified cellulose in a concentration of 2% released the drug faster than at a concentration higher than that. Hence it could be concluded that microcrystalline cellulose, a polymer which is devoid of superdisintegrant activity, can suitably be modified by controlled chemical modification of it with hydrochloride salt of 2-aminoethanoyl chloride or similar groups with optimum hydrophilicity and hydrophobicity to convert it into a superdisintegrant material. It can also be concluded that rapidly disintegrating tablets of metoclopramide hydrochloride can suitably be developed for the efficient management of emesis.

PALABRAS CLAVE: Chemically modified cellulose, Microcrystalline cellulose, Metoclopramide hydrochloride, Rapidly disintegrating tablets, Superdisintegrant.

INTRODUCTION

In the past one decade, there has been an enhanced demand for more patient friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost effective dosage forms[1].

Many patients find it difficult to swallow tablets and hard gelatin capsules; consequently they do not take medication as prescribed. It is estimated that 50% of the population is affected by this problem which results in a high incidence of incompliance and ineffective therapy[2,3]. Hence the development of an orally disintegrating tablet or rapidly disintegrating tablet (RDT) has attracted not only the pharmaceutical industry, but also the academia[4].

RDTs are preferred by an increasing number of patients especially children and elderly, but also adult consumers who like to have their medication readily available at any time5. This dosage form is also suitable for those who are suffering from dysphagia and thus lead to improved patient compliance[6].

RDTs are useful in bedridden or developmentally disabled patients who may face problems in swallowing conventional tablets or capsules and liquid orals or syrups leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attacks or coughing for those who have an active life style. RDTs are also useful when local action in oral cavity is desirable such as local anesthetic for toothaches, oral ulcers, cold sores or teething[7-13]. Recent developments in rapidly disintegrating tablets provide a convenient solution for patients who have difficulties in swallowing tablets and other solid dosage forms. The solid RDT dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free of suffocation risk[14].

RDTs are becoming increasingly popular around the world. Based on the request from patients to increase their treatment and quality of life, new types of RDTs have been developed[15]. RDTs have been in ever increasing demand since the last decade and the field has emerged as a rapidly developing area in the pharmaceutical field[16-19].

Metoclopramide hydrochloride is chemically 4-amino-5-chloro-N[2-(dimethylamino)-ethyl]-2-methoxybenzamide monohydrochloride monohydrate. It is a potent dopamine receptor antagonist. It is a potent antiemetic and is effective in the treatment of nausea and vomiting associated with cancer chemotherapy, pregnancy, migraine etc. It is highly water soluble and is rapidly absorbed after oral administration. It has a short biological half life (3-5 h) and is usually administered in a dose of 10-15 mg four times a day. A conventional oral administration has good absorption (>90%) but is extensively metabolized by the liver (0-68%)[20-22]. Hence, this drug was selected as a candidate drug to formulate a rapidly disintegrating dosage form using the novel superdisintegrant, cellulose chemically modified with hydrochloride salt of 2-aminoethanoyl chloride (1% substitution).

The present study was aimed to formulate and evaluate rapidly disintegrating tablets of metoclopramide hydrochloride and also to evaluate chemically modified cellulose for its possible superdisintegrant activity.

MATERIALS AND METHODS

Materials

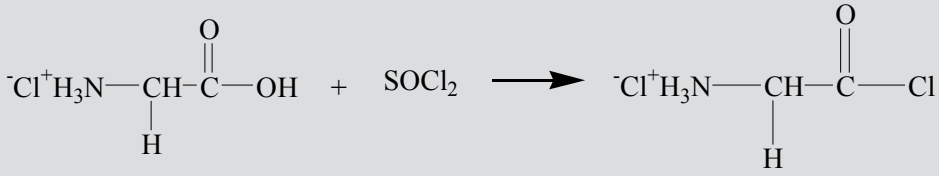
Microcrystalline cellulose, hydrochloride salt of 2-aminoethanoic acid and vanilla flavor were procured from Rajesh Chemicals (Mumbai, India). Metoclopramide hydrochloride was supplied as the gift sample by Mediorals Pvt. Ltd. (Satara, India). Spray dried lactose was supplied by Medule Pharma (Goa, India). All the other chemicals used were of analytical grade and were used as procured.

Experimental Design

Modification of microcrystalline cellulose with hydrochloride salt of 2- aminoethanoyl chloride (1% substitution): A molar ratio of microcrystalline cellulose to hydrochloride salt of 2-aminoethanoyl chloride was computed on the basis of molecular weight, number of monomers, and free hydroxyl groups present in each monomer of microcrystalline cellulose and a molar ratio of 1% substitution of microcrystalline cellulose with hydrochloride salt of 2-aminoethanoyl chloride was calculated. Initially hydrochloride salt of 2-aminoethanoic acid was converted to hydrochloride salt of 2-aminoethanoyl chloride by reacting with thionyl chloride and distilling off the excessive thionyl chloride used in the reaction. Microcrystalline cellulose (10g) was added to 200 ml of 10% sodium hydroxide solution in water to produce swollen alkali cellulose that is chemically more reactive than untreated cellulose[23]. To this swollen alkali cellulose, hydrochloride salt of 2- aminoethanoyl chloride (0.54 g) was added, and the reaction mixture was heated at 40 0C for 36 h. After the completion of reaction, the product was filtered and was provided with several washings of water to remove excess of alkali and any unreacted hydrochloride salt of 2-aminoethanoyl chloride, and traces of thionyl chloride if present in product, dried in vacuum desiccator, and passed through a #30 mesh screen. The scheme of synthesis is given in figure 1.

Figure 1: Scheme of synthesis of chemically modified cellulose using hydrochloride salt of 2- aminoethanoyl chloride.

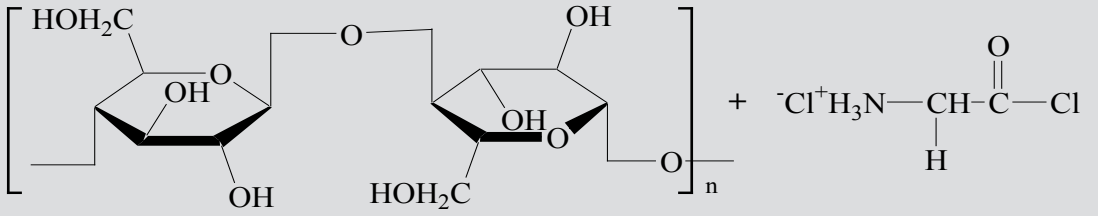
Step I: Reaction of hydrochloride salt of 2- aminoethanoic acid with thionyl chloride to produce hydrochloride salt of 2-aminoethanoyl chloride



Hydrochloride salt of 2-aminoethanoic acid

Hydrochloride salt of 2-aminoethanoyl chloride

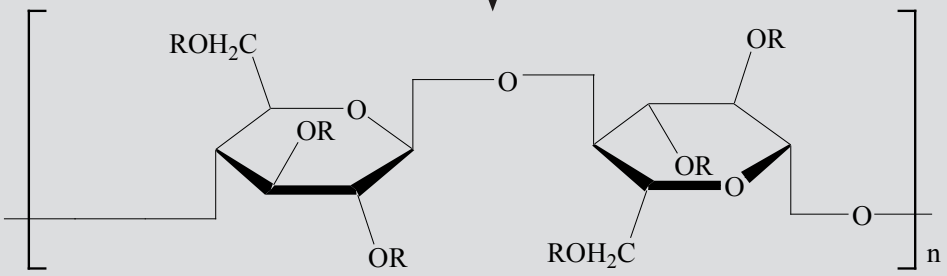
Step II: Reaction of cellulose with hydrochloride salt of 2- aminoethanoyl chloride



Cellulose

Hydrochloride salt of 2-aminoethanoyl chloride

10% NaOH



Where, R may be H, or $-COCH_2NH_2$

Characterization of novel chemically modified cellulose

FTIR spectroscopy: FTIR spectra of microcrystalline cellulose and cellulose modified with hydrochloride salt of 2-aminoethanoyl chloride were recorded using FTIR spectrophotometer (Jasco 4100, Japan) between wavelengths of 400-4000cm^{-1}.

NMR spectroscopy: Nuclear magnetic resonance (NMR) analysis was done to characterize the modified cellulose using a 300 MHz NMR and 1H NMR spectrum was recorded on a Varian Mercury 300 MHz spectrometer using deutorated chloroform as the solvent.

Thermal analysis: Thermal analysis of cellulose and chemically modified cellulose was carried out using Mettler Toledo 821^{e} DSC (Switzerland) thermal analyzer. The samples (1-2 mg) were hermetically sealed in an aluminum pan and heated at a constant rate of 100C per minute, over a temperature range of 50 0C- 500 0C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 20 ml/ min.

Elemental analysis: Elemental (C, H, N) analysis of cellulose and chemically modified cellulose was done using Thermo Finnigan (Thermo Fischer Scientific, U.S.A.) elemental analyzer (EA 1112).

Toxicity studies

The acute oral toxicity studies were carried out on chemically modified cellulose with hydrochloride salt of 2-aminoethanoyl chloride on Swiss Albino Mice according to OECD guidelines {OECD guideline No. 425

Table 1. Composition of rapidly disintegrating tablets of metoclopramide hydrochloride.

Ingredients	Formulation					
	F1	F2	F3	F4	F5	CF
Metoclopramide hydrochloride	10	10	10	10	10	10
Modified Cellulose	5	10	15	20	25	---
Microcrystalline cellulose	---	---	---	---	---	25
Spray dried lactose	225	220	215	210	205	205
Vanilla flavor	2.5	2.5	2.5	2.5	2.5	2.5
Sodium Saccharine	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight	250	250	250	250	250	250

(Up and Down Method)} for toxicity studies. The powder of test material was suspended in 0.5% CMC in water. The suspension was freshly prepared before dosing. The concentration of the test material suspensions was adjusted to allow administration of all test doses in a constant volume. All doses were administered orally to the test animals in a constant dosing volume of 0.4 ml /10 g bodyweight of the animal. One group of animals acted as a control group, which received the vehicle alone in a similar manner. The animals were observed for signs of intoxication and mortality, if any, up to the end of 14 days after administration of the dose. The animals were observed during the course of treatment for clinical signs of toxicity and mortality, body weight, ill health, together with any behavioral changes or reaction to treatment. At the end of 14 days after dosing, all surviving mice were sacrificed under pentothal / ether anesthesia. Complete necropsies were carried out on all the animals.

Preparation of tablets:

Rapidly disintegrating tablets were prepared by direct compression according to the formulae given in table 1. All the ingredients were passed through # 60 mesh separately, weighed accurately and added in a blender in ascending order of their weight and blended for 30 min. The blend was then used further to compress the tablets using 10 mm normal concave punches to get tablets of 250 mg weight on a single punch tablet machine (Cadmach, Ahmedabad, India). Control formulation (CF), which contained microcrystalline cellulose instead of modified cellulose was also formulated to investigate the type of drug release from the formulation. A batch of 100 tablets was prepared for all the designed formulations.

Characterization of the tablets:

Compatibility Studies: The compatibility of the drug with the excipient was carried out using FTIR spectrophotometer (Jasco, 4100, Japan). FTIR spectra were recorded using potassium bromide (KBR) dispersion method. The base line correction was done using dried potassium bromide. Later on the spectrum of dried mixture of drug and potassium bromide was run followed by drug with excipients.

Physical parameters: Tablets from all the formulations were evaluated for various parameters such as diameter (Vernier caliper), thickness (Micrometer screw guage), hardness (Pfizer hardness tester), weight variation test and friability (Roche friabilator).

Wetting time and water absorption ratio: A piece of tissue paper folded twice was kept in a petri dish (internal diameter of 5.5 cm) containing ≈ 6 ml of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time. The same procedure without amaranth powder was followed for determining the water absorption ratio. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the equation 1[13].

$$R = \{(Wa - Wb) / Wb\} \times 100 \quad (1)$$

Where, Wb and Wa are the weights of the tablet before and after study.

In vitro disintegration test: As many reports indicated the unsuitability of USP disintegration test apparatus for rapidly disintegrating tablets, a more suitable apparatus, described by khan et al was developed to study the disintegration time of the rapidly disintegrating tablets. The apparatus consisted of a glass beaker of 1000 ml capacity with the wire basket positioned in the beaker with the help of a support in such a way that when the beaker contained 900 ml of PBS pH 6.8, the basket had only 6 ml of it. A magnetic bead was placed at the bottom of the beaker and the temperature of the medium was maintained at 37 ± 2°C. Disintegration test was performed at 50 rpm and

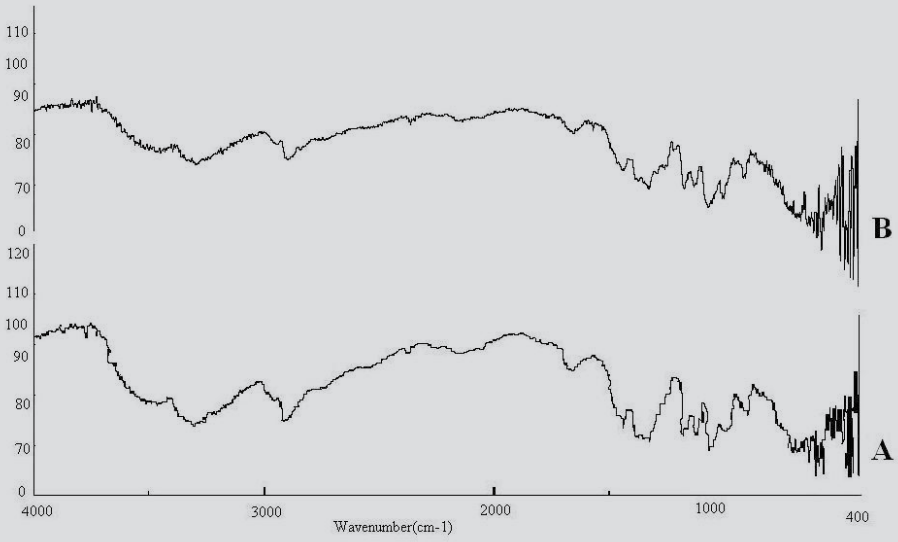


Figure 2: Overlain FTIR spectra of microcrystalline cellulose (A) and cellulose chemically modified with hydrochloride salt of 2-aminoethanoyl chloride (B).

the time required for complete disintegration of the tablets was determined. The results of the two methods were compared[13,24-26].

In Vitro dissolution study: In vitro dissolution study of rapidly disintegrating tablets of metoclopramide hydrochloride was carried out using USP XXIII type II dissolution apparatus (TDT 08L, Electrolab, Mumbai, India) employing a paddle stirrer at 50 rpm using 900 ml of phosphate buffer solution pH 6.8 at 37 ± 0.5 ^{o}C as dissolution medium 27. Aliquots of dissolution medium were withdrawn at specified time intervals and were analyzed for drug content by measuring the absorbance at 309 nm. Sink conditions were maintained throughout the experiment. Cumulative percent of metoclopramide hydrochloride released was calculated using the software PCP Disso V3 and plotted against time. The study was carried out in triplicate.

Statistical analyses:

The in vitro release data was analyzed statistically using the software Graph Pad prism version 4 to analyze whether significant difference lies in the in vitro drug release profile of formulations containing modified cellulose and the control formulation One way ANOVA was performed on all the data sets and Dunnett's multiple comparison test was applied to compare between all columns of formulations containing modified cellulose with the column of control formulation at 95% confidence interval.

RESULTS AND DISCUSSION

Characterization of modified cellulose:

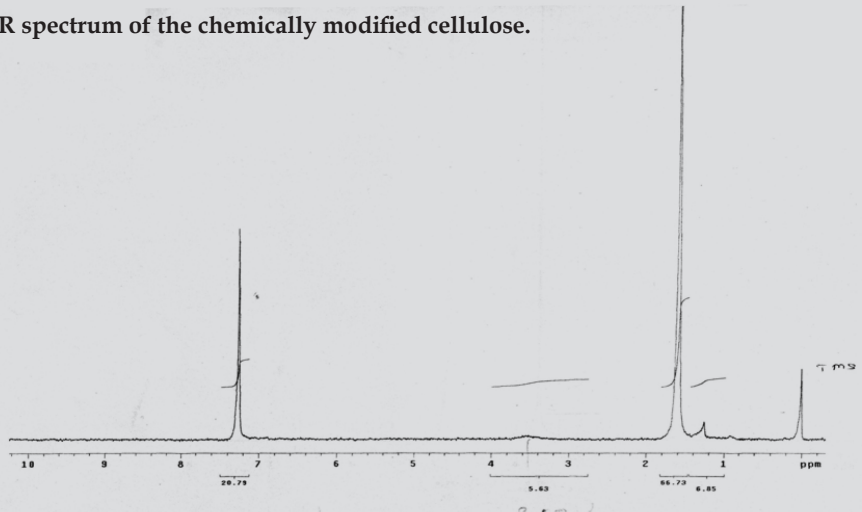
FTIR spectroscopy: From the FTIR spectra of modified cellulose and that of cellulose, it was clearly evident that the slight change at about 3400 cm^{-1} can be attributed to acylation of a fraction of the free hydroxyl groups in cellulose by hydrochloride salt of 2-aminoethanoyl chloride. Similarly a slight increase in intensity of the band at about 3300 cm^{-1} was due to the addition of amino group to the polymeric structure as shown in figure 2.

NMR spectroscopy: The ^{1}H NMR spectrum of the modified polymer, as shown in figure 3, indicates the presence of amino group proton at 3.5 ppm which confirms chemical modification of cellulose by acylation of a fraction of free hydroxyl groups with 2-aminoethanoyl chloride. Confirmation of introduction of primary amino group along with the presence of carbonyl ester that was indicated in the FTIR spectrum is a satisfactory evidence for the proposed chemical modification.

Thermal analysis: As both microcrystalline cellulose and modified cellulose do not have exact melting points and char when heated, no sharp endothermic peaks were observed for both of them indicting no exact melting points as shown in figure 4. A broad endothermic bend in thermogram 3A from 37-105^{o}C for cellulose and from 37-118 ^{o}C in thermogram 3B for chemically modified cellulose can plausibly be attributable to the glass transition of the polymer and the vaporization of the moisture present in the samples.

Elemental analysis: The elemental analysis of cellulose and novel chemically modified cellulose is summarized in table 2. It is to be noted that the empirical formula of both polymers can be approximated due to their high polydispersity. The theoretical values for C and H are 42.10%, and 6.43% which correlates well with the observed values of 41.90%, and 6.22% respectively. The theoretical value for nitrogen was 0.14%, whereas in case of modified cellulose, it was 0.12%, exhibiting close resemblance with

Figure 3. ^{1}H NMR spectrum of the chemically modified cellulose.



the values for nitrogen.

Toxicity studies

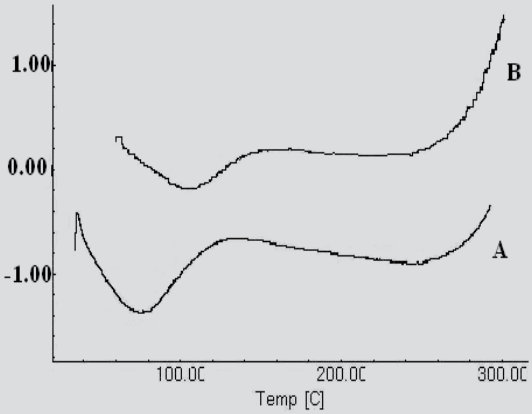
Toxicity Signs like changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions and autonomic activity such as lacrimation, piloerection, pupil size, unusual respiratory pattern, circulatory, autonomic and central nervous systems, and somatomotor activity were not observed in any of the animal treated with the test substances. Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, sterotypy or bizarre behavior were not observed in any of the animals. Other signs like tremors, convulsions, salivation, diarrhea, lethargy, sleep and coma were not seen in animal during Study.

The animal that died during study was dissected and observed for changes in the alimentary tract. It was observed that the animal that died in the study was due to severe bloating of alimentary tract and accumulation of air in the alimentary tract. These observations suggest that the dose administered obstructed the gastrointestinal tract and caused severe pressure on vital organs that might had resulted into death. In necropsy, no significant changes were observed in these animals. The data for the survival of the animals during acute oral toxicity study is given in table 3.

Compatibility studies

It was found that the important peaks that were present in FTIR spectrum of drug, metoclopramide hydrochloride, were found to be present in the FTIR spectra of drug with polymers, namely novel modified cellulose, and cellulose as shown in Figure 5. Hence it could be concluded that the drug and polymers were compatible with each other.

Figure 4. Overlain differential scanning calorimetric thermograms of microcrystalline cellulose (A) and cellulose chemically modified with hydrochloride salt of 2-aminoethanoyl chloride (B).



Physical parameters of tablets

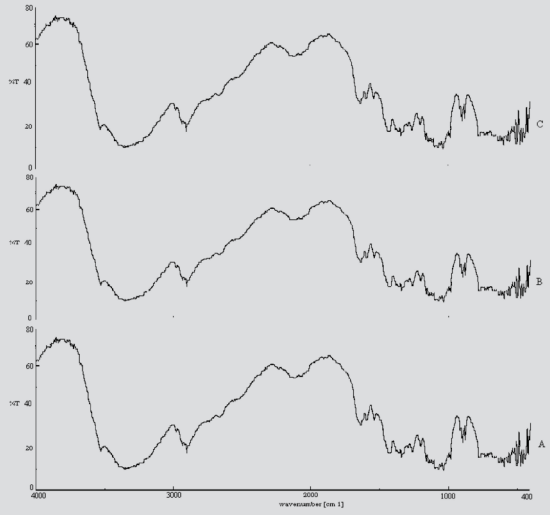
Tablets prepared by direct compression method were evaluated for various official and non official parameters. As the material was free flowing, tablets were obtained of uniform weight, due to uniform die fill with acceptable variation as per I.P. specification (<5%). Thickness of

Table 3. Survival data of animals in toxicity studies.

Test Material	Survival
Chemically modified cellulose with hydrochloride salt of 2-aminoethanoyl chloride	OXOOO

X- Death, O- Survival of animal

Figure 5.Overlain FTIR spectra of metoclopramide hydrochloride (A), metoclopramide hydrochloride with modified cellulose (B), metoclopramide hydrochloride with cellulose (C).



the tablets was found to be in the range of 3.33-3.53 mm whereas diameter was observed in the range of 10.06-10.13 mm. Hardness of the tablets was found to be in the range of 3.3 – 3.83 kg/cm^2. Friability was found to be below 1% which was an indication of good mechanical strength of the tablets that can withstand the shocks during shipping or transportation. The values obtained for physical parameters of the tablets are given in table 4.

Wetting time and water absorption ratio:

Wetting time was found to be increased from formulation F1-F5, which contained novel modified cellulose as the superdisintegrant. It was 86.67 Sec for formulation F1 while it was found to be 180.33 Sec for formulation F5. For control formulation (CF), it was found to be 14.55 min. The values for wetting time and water absorption ratio are given in the table 5.

The water absorption ratio was found to be decreased from F1-F5. It was found to be in the range of 80.99% - 50.49% for formulations F1-F5. For control formulation, it was found to be 45.77%.

The increase in the wetting time and the decrease in the water absorption ratio for formulations F1-F5 may be due to reduction in the capillary action, which may be due to the blockade of the pores of the formulation. Higher value of wetting time and least value of water absorption ratio was observed for control formulation. This may be due to absence of water soluble groups in the structure of microcrystalline cellulose and may be due to poor capillary action.

Disintegration time:

The disintegration times obtained are as given table 5. The least disintegration time of 41.33 sec was observed in formulation F1, which contained 2% of 1% modified cellulose while it was found to be 18.32 min for control formulation (CF), which contained non modified microcrystalline cellulose. Disintegrating time was found to be increasing from F1-F5.

The superdisintegrant property may be imparted to cellulose due to addition of highly hydrophilic and water soluble moiety by the way of chemical modification. But paradoxically it was found that novel modified cellulose in a concentration of 2% is having good superdisintegrant activity as compared to its higher concentration in other formulations. This may be due to increased number of terminal –NH2 groups, which may be responsible for the reduction in the capillary action of the compound and may possibly resulted into the increased disintegration time of the formulation as the same was evident from the wetting time and water absorption ratio.

Due to addition of –CO-CH_2-NH_2 group, the water assessable polarity of modified cellulose might have been improved due to the presence of an electron withdrawing carbonyl group bridged to an electron releasing group through a methylene bridge. Therefore the ability of modified cellulose to take up water by capillary action might have been enhanced and superdisintegrant activity might be imparted to it.

Thus, it can be concluded that this chemical modification could account for the reduction in the disintegration time

Table 4. Evaluation of Tablets.

Formulation	Thickness (mm)	Diameter(mm)	Hardness (Kg/cm^2)	Friability(%)	Weight Variation Test †
F1	3.4±0.07	10.1± 0.1	3.33±0.28	0.47±0.12	Passes
F2	3.37±0.14	10.13±0.12	3.67±0.29	0.47±0.09	Passes
F3	3.3 ± 0.14	10.06±0.12	3.33±0.21	0.47±0.13	Passes
F4	3.43± 0.07	10.06±0.06	3.67±0.23	0.35±0.18	Passes
F5	3.53± 0.14	10.1±0.1	3.83±0.18	0.31±0.17	Passes
CF	3.47± 0.14	10.13±0.12	3.83±0.18	0.36±0.12	Passes

* indicates the mean of 3 determinations ± SD. † indicates n = 20

Table 5. Evaluation of Tablets.

Formulation	Wetting Time (Sec)	Water absorption ratio	Disintegration Time (Sec)	
			USP Apparatus	Modified Apparatus (50 rpm)
F1	86.67 ±1.53	80.99±0.73	41.33± 1.15	53.67 ± 1.53
F2	102.67 ±1.15	76.50±0.46	91 ± 1.32	111.66 ± 0.57
F3	105 ± 1.19	60.33±0.62	131.67±1.52	145.67 ± 0.59
F4	69.33 ± 1.15	56.38±1.07	141.67±1.53	157.66 ± 2.09
F5	80.33 ± 0.58	50.49±0.50	166.33±0.58	182.33 ± 2.51
CF	14.55±0.02 †	45.77± 0.49	18.39±0.07†	21.86 ± 0.29 †

* indicates the mean of 3 determinations ± SD. † indicates time in min.

to the modified cellulose.

In Vitro Dissolution Study:

For all the designed formulations prepared with modified cellulose and unmodified cellulose, the time required for complete drug release was found to be different. Formulation F1 required 6 min time for complete drug release, whereas formulation F5 took 20 min for complete drug release. This may be due to an increase in the wetting time and a decrease in the water absorption ratio from F1-F5, which in turn may be due to blockade of the openings or a reduction in the capillary action of the formulation which contained higher amounts of modified cellulose. The complete drug release from formulation F1 was obtained in 6 min. whereas the control formulation, CF, was found to release the drug completely at the end of 40 min.

This improved efficiency of the chemically modified cellulose can be attributed to relative decrease in non bonded polar interactions between the polymer and relatively polar drug as the chemically modified cellulose is relatively less polar than that of microcrystalline cellulose. The in vitro drug release profile for all the formulations is as given in table 6 and figure 6.

Statistical Analyses:

After analyzing statistically it was found that there was a significant difference ($P<0.05$) in the drug release profile of formulations containing novel modified cellulose and the control formulation. From the statistical analyses it was clear that modified cellulose could be a promising superdisintegrant.

From the above discussion, it could be concluded that formulation F1, which contained 2% novel modified cellulose could be the optimized formulation as it took least time for disintegration, its water absorption ratio was good and wetting time was less, and moreover it released the drug in less time (6 min) as compared to formulations F2-F5, which contained the same modified cellulose but in higher concentrations.

Figure 6. In-vitro dissolution profile of all formulations.

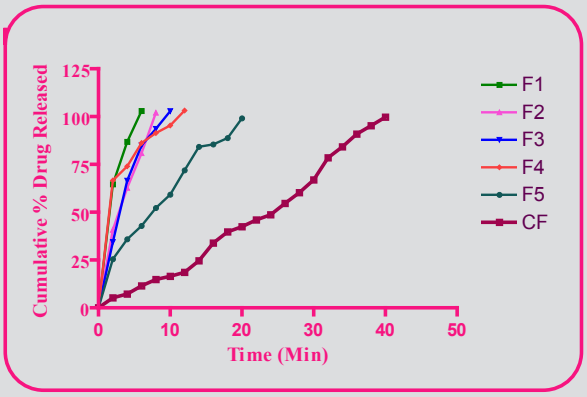


Table 6. Time taken for complete drug release in PBS pH 6.8.

Formulation	Cumulative % drug released*	Time required, Min
F1	102.97 ± 0.15	6
F2	101.99 ± 0.32	8
F3	102.83 ± 0.16	10
F4	103.21 ± 0.25	12
F5	99.10 ± 0.21	20
CF	99.78 ± 0.31	40

* indicates the mean of 3 determinations ± SD.

CONCLUSION:

Modification of microcrystalline cellulose by controlled chemical modification with hydrochloride salt of 2-aminoethanoyl chloride produced a compound with a superdisintegrant activity. The formation of chemically modified cellulose was confirmed with FTIR and NMR spectroscopy and by elemental and DSC analysis. The acute oral toxicity studies proved the novel modified cellulose to be non toxic. The drug release studies indicated that the modified polymer was able to release the drug faster

than unmodified cellulose. Hence it could be concluded that microcrystalline cellulose, a polymer which is devoid of superdisintegrant activity, can suitably be modified by controlled chemical modification of it with hydrochloride salt of 2-aminoethanoyl chloride or similar groups with optimum hydrophilicity and hydrophobicity to convert it into a superdisintegrant material. It can also be concluded that an efficient rapidly disintegrating formulation can suitably be developed incorporating chemically modified cellulose as the superdisintegrant.

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