Original Article

Noval Source Of Disintegrate

Dobariya Vithal Dhirubhai[1*], Dr. Nizant Oza[2],Radadia Ashwinbhai Arjanbhai[3], Chodvadiya Chandrika Upendra[4], Darji Yogeshkumar Govindbhai[5], Vijay K Patel[6]

[1*]Research Scholar, Development and Innovation Centre C. U. Shah University Wadhwan city – 363 030
[2]Profesor, Research Development and Innovation Centre C. U. Shah University Wadhwan city – 363 030
[3]Research Scholar, Development and Innovation Centre C. U. Shah University Wadhwan city – 363 030
[4]Research Scholar, Development and Innovation Centre C. U. Shah University Wadhwan city – 363 030
[5]Research Scholar, Development and Innovation Centre C. U. Shah University Wadhwan city – 363 030
[6]Associate professor, Sharda school of Pharmacy, Pethapur, Gandhinagar

***Corresponding Author:** Dobariya Vithal Dhirubhai

*Research Scholar Research Development and Innovation Centre C. U. Shah University, Wadhwancity – 363 030 Ph. 9327770619 Email: drharaj@yahoo.com
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Abstract

Microwave is a type of electromagnetic energy which lies at lower level of electromagnetic spectrum and has frequency in range of 300 – 300,000 megahertz which is equal to wavelength of range 1cm-1 mm. The microwave region of the electromagnetic spectrum lies between infrared and radio frequencies. The difference between microwave energy and other forms of radiation, such as X- and γ-rays, is that microwave energy is non-ionizing and therefore does not alter the molecular structure of the compounds being heated – it provides only thermal activation.

Keyword : Microwave **,** Disintegrant

INTRODUCTION

MICROWAVE

Microwave is a type of electromagnetic energy which lies at lower level of electromagnetic spectrum and has frequency in range of 300 – 300,000 megahertz which is equal to wavelength of range 1cm-1 mm. The microwave region of the electromagnetic spectrum lies between infrared and radio frequencies. The difference between microwave energy and other forms of radiation, such as X- and γ-rays, is that microwave energy is non-ionizing and therefore does not alter the molecular structure of the compounds being heated – it provides only thermal activation.

The heating effect used in microwave assisted organic transformations is mainly because of dielectric polarization. When a molecule is irradiated with microwaves, it aligns itself with the applied field. Changing in electric field (2.45 x 109 Hz) affects the molecule and as a result the molecule repeatedly attempts to align itself with the altering field and energy is absorbed.

The capability of a material to change electromagnetic energy into thermal energy is reliant on the dielectric constant. The superior the dielectric constant the greater is the coupling with microwaves. Thus, solvents like water, DMF, methanol,

METHOD USED IN PRESENT WORK:

OVERVIEW OF EXPERIMENTAL WORK DONE

Analysis of drug candidate

(A) Drug Identification
1. FT-IR characterization (Fourier Transform infrared spectroscopy)
2. UV spectrum of drug (Ultra violet spectroscopy)
3. Calibration curve of Ondansetron HCl in 0.1 N HCl

(B) Drug excipients compatibility study
1. FT-IR
2. DSC (Differential scanning calorimetery)

Characterization of Modified Polymer:

1. FT-IR study
2. Determination of Neutralization Equivalent (N.E):
3. Swelling index

4. Viscosity
5. Scanning Electron Microscopy
6. X-ray diffraction study

Formulation of Tablets by Direct compression technique

Evaluation of Tablets

- **Pre compressional parameters**

a. Angle of repose b. Bulk density
c. Tapped density d. Carr's index
e. Hausner ratio

- **Post compressional parameters**

a. Diameter b. Thickness c. Hardness d. Friability
e. Weight variation
f. Disintegration time
g. *In vitro* dissolution study

- **Accelerated Stability study of Fast disintegrating tablet**

ANALYSIS OF DRUG CANDIDATE

Drug identification.

Drug identification was carried out by UV spectroscopy and IR Spectroscopy.

FTIR of pure drug

Identification of Ondansetron Hydrochloride was carried out using FTIR study. For this the FTIR spectra of pure drug was recorded using FTIR **8400 S Shimadzu spectrophotometer**. The pellet of dried sample of drug was prepared with potassium bromide. The scans were performed at a resolution of **4000-400cm^{-1}.**

UV Spectroscopy

Determination of maximum wavelength

The solution of accurately weighed quantity of drug was prepared in 0.1 N HCl. The solution was scanned in the range of 200 to 400 nm to fix the maximum wavelength and UV spectrum was obtained. Here, 0.1 N HCl was used as a blank to determine maximum wave length.

Calibration curve of Ondansetron hydrochloride in 0.1 N HCl.

Accurately weighed 100 mg of Ondansetron HCl was transferred to 100 ml volumetric flask and dissolved in 0.1 N HCl. And volume make up to 100 ml with 0.1

N HCl. (solution A). Then 5 ml of solution A was transferred in 100 ml volumetric flask and make up to 100 ml with 0.1 N HCl. (solution B). From solution (B) 1, 2, 3, 4, 5 ml of aliquot was pipetted out and diluted to 10 ml with 0.1 N HCl to produce a solution of 5, 10, 15, 20, 25 µg/ ml respectively. Then absorbance of solution of different concentration was measured using **UV- Visible spectrophotometer** at **248.40 nm.**

Drug excipients compatibility study

FTIR spectroscopy

Compatibility of Ondansetron Hydrochloride with the used polymers such as Modified guar gum, MCC-101 individual excipients was studied by FTIR. For this the FTIR spectra of drug polymer mixture were recorded using FTIR 8400 S

Shimadzu spectrophotometer. The pellet of dried sample of drug was prepared with potassium bromide. The scans were performed at a resolution of 4000-400cm^{-1}.

DSC (Differential scanning calorimetriy)

The DSC thermo grams were recorded using a differential scanning calorimeter (**DSC 60, Shimadzu**). Approximately 2-5 mg of each sample was heated in a piecred aluminum pan from 50°C to 300°C at a heating rate of 10°C/min under a stream of nitrogen at rate 10ml/min.

MODIFICATION OF POLYMER

CARBOXYMETHYLATION OF GUAR GUM

Mechanism of carboxymethylation of guar gum

Parameters used for microwave assisted synthesis for carboxymethylation of guar gum:

Table 1 Various parameters used for carboxymethylation of guar gum

Batch	Polymer	Polymer concentration (% w/v)	Microwave Time (min)	Microwave Power	Microwave Temperature o (C)
A1			2		60
A2			4		80
A3			6		85
A4	Guar gum	2 %	8	80 %	90
A5			10		102

Procedure for Carboxymethylation of guar gum [8]

For carboxymethylation, 2 g of purified guar gum were dispersed in 100 ml distilled water, After the gum was well dispersed, an 45 %w/v (4.5 gm in 10 ml distilled water) sodium hydroxide solution was added, at a rate of 1 ml within 15 min, with continuous stirring at 5-8 ^{o} C temperature. And 75% W/V (10 gm of CAA in 4.5 ml Distilled water) chloro-acetic acid was then added to the reaction mixture, over a period of 10 min. The reaction mixture was then kept in the microwave oven at 80 % power at different time interval and it's temperature was recorded. After cooling, the mixture was neutralized with HCl (1:1). Then solution was Precipited with methanol.

Precipited than wash with methanol: water (80:20) and kept overnight. The final product dried at oven at 40^{o}C.

CROSSLINKING OF CMGG

Cross-linking of carboxymethyl guar gum was done with phosphorus oxychloride ($POCl_3$) in aqueous alkali containing sodium sulphate (Na_2SO_4 , 2% based on dry weight of gum) as described by Wu and Seib (1990).The concentration of gum in the slurry was 25%.Than after reaction mixture was adjusted the pH at 11.0 with 1 N NaOH. The concentration of $POCl_3$ was 0.25 %, 0.5 %, based on the dry weight of gum. Reaction temperature was maintained at 35 ^{o}C. Sample was taken after reaction period of 60 min. The sample was then neutralized using 1 N HCl to terminate the reaction and washed with distilled water before drying at 40 ^{o}C in an oven.

CHARACTERIZATION OF MODIFIED POLYMER

Determination Of Neutralization Equivalent (N.E.):[35]

When the standardized HCl is add to the modified polymer. It replaces the – COONa with H^+ to give –COOH. Then this system is titrated with the standardized NaOH using phenolphthalein as an indicator.
Than the calculation for NE is done by below equation,

1 equivalent acid= $\frac{x \times 1000}{y \times z}$

- x = Modified Polymer (gm)
- z = Normality of NaOH
- y = Volume of difference (Yb – Ys) (ml)

FT-IR Study

Identification of Modified guar gum was carried out using FTIR Study. For this, the FTIR spectrum of drug was recorded in FTIR 8400 S Shimadzu spectrophotometer. The Modified guar gum was mixed thoroughly with potassium bromide (KBr) and the scan was obtained at a resolution of 4000-400 cm^{-1}

Swelling Index[15,19]

To measure the sample swelling degree, pre-weighed dry samples were immersed in distilled water until maximum swelling was reached. After excessive surface water had been removed with filter paper, the weights of swollen samples were measured. The swelling degree (Q) was determined by

Q = (Ws – Wd) / Wd

Where Ws and Wd represent the weight of swollen and dry samples. Experiments were run in triplicate.

Viscosity [9, 53]

Viscosity of all the samples was carried out using **Brookfield Viscometer (LVDV – II + PRQ)** at 25°C, using spindle no 62 at 100 RPM. The concentrations of all the samples were kept at 1%w/v.

Scanning Electron Microscopy [6,53]

The morphology of the Modified polymer was examined under a **JSM-6400 (Joel, Japan).** The samples were previously fixed on a brass stub using double sided adhesive tape. The pictures were taken at an excitation voltage of 15 kV and magnification in the range of 100 to 500 X.

X-Ray diffraction Study [6]

Powder X-ray diffraction patterns were obtained on a **PANanalytical x'pert PRO** using Cu-*K*a radiation at a voltage of 45 kV, a current of 40 mA and a temperature of 40 ºC. The samples, which include Guar gum, Carboxymethyl guar gum were scanned in increments of 0.0080° from 5.0042° to 79.9882° at a rate of 5.7150s per step using a zero background sample holder.

EVALUATION OF TABLET

Pre compressional parameters a. Angle of repose

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom was closed and 10 gm of sample powder was filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, was found by measuring in different direction. The height of the heap was measured by using scale. The values of angle of repose are calculated by using the following formula

$\theta = \tan^{-1} h/r$ Where, h: height of the heap r: radius of the heap

Bulk density

A known quantity of powder was poured into the measuring cylinder carefully leve the powder without compacting, if necessary and read the unsettled apparent volume, to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula

Bulk density = Bulk Mass/ Bulk Volume c. Tapped density

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder was mechanically tapped and volume readings are taken until little further volume changes were observed.

Carr's Index

The compressibility index of all ingredients was determined by following equation.

Hausner Ratio

Hausner predict the flow properties of powder by using inter particle friction.

Hausner ratio = tapped density /poured density

Table 2 Standard value of Hausner ratio

Flow property	Hausner ratio
Good	≤1.25
Poor	≥1.25

Post compressional parameter a. Thickness and Diameter

Tablet thickness and Diameter was measured by Vernier caliper.

Hardness

The hardness is expressed as Kg/cm^2. The tablet crushing load, which is the force required to break a tablet into halves by compression .It was measured using a tablet hardness tester (Pfizer Hardness Tester).

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Pre-weighed sample of tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

Weight variation

USP weight variation test is done by weighing 20 tablets individually; calculating the average weight and comparing

the individual tablet weight to the average weight variation tolerance (Table 5.9)

Disintegration time

The disintegration time was measured using a modified disintegration method. According to this method, a Petri dish of 10 cm diameter was filled with 10 ml of distilled water, the tablet was carefully places at the center of the Petri dish, and the time necessary for the complete disintegration of the tablet in to fine particles was noted as disintegration time.

In vitro dissolution study

In vitro drug release studies of prepared matrix tablets were performed according to the USP Paddle method (Apparatus II) using 900ml of 0.1N HCl for 20 min thermo stated at $37 \pm 0.1\ ^{O}C$ and stirred at 50 rpm.
At time intervals of 2 min samples were withdrawn and replaced with an equal volume of fresh medium. The drug content was spectrometrically determined at 248.40 nm.

Accelerated Stability study of FDT as per ICH guideline

Best batch was placed for stability study at 40±0.5˚C/75±5 % RH for 1 month. Sample was collected after that and evaluated for physical parameters and *in vitro* dissolution study.

RESULT AND DISCUSSION

Analysis of drug candidate

Drug Identification

FTIR characterization:

From the data shown in table 6.1 and figure 6.1, it was observed that the FTIR peaks of sample Ondansetron HCl drug is nearly equal to the peaks reported for the standard Ondansetron HCl drug. Therefore it can be concluded that the given sample is pure Ondansetron HCl drug.

Table 3 FTIR Peaks of Ondansetron HCl

Sr. no	Functional group	Peak of standard Ondansetron HCl (cm^{-1})	Peak of sample Ondansetron HCl (cm^{-1})
1	N-CH_3	1080 – 1360	1085.96
2	- C = O	1670 – 1820	1639.55

Drug-excipient compatibility study:

The compatibility between the drug and excipient is important from the formulation perspective because it resolves the major issues like shelf life of final formulation as well as clinical safety of therapeutics. Both the physical and chemical compatibility was studied using the techniques discussed below:

FTIR analysis

The figure 6.4 shows the FTIR spectrum of physical mixture. From the results of FTIR spectroscopy it was observed that, all characteristic peaks of drug was present at their reported values (table 6.3) and there was no change in the peak values. Hence it can be concluded that no chemical interaction is present between the drug and polymer and they are compatible.

Table 4 FTIR peaks of physical mixture.

Sr. no	Functional group	Obtained Peak of Ondansetron HCl (cm^{-1})	Obtained Peak Of Physical mixture (cm^{-1})
1	N-CH_3	1085.96	1085.96
2	- C = O	1639.55	1639.55

NEUTRALIZATION EQUIVALENT (N.E.) [35]

The greater number of carboxyl groups (basicity) lower will be the N.E. value. Similar conclusion can also be drawn from the result as shown in Table 6.7, the % of NE decreased on moving from A1 to A4. A5 batch was failed as it showed charring on increasing microwave time duration of 10 min. Thus A4 batch was selected as the best batch.
There for A 4 batch was selected for further crosslinking at various concentration of phosphorous oxychloride.

VISCOSITY[9]

The results showed that on carboxymethylation of guar gum, its viscosity falls considerably. Carboxymethylation of guar

gum imparts anionic character to its backbone chains, which due to columbic repulsion prevent the entanglement of backbone chains resulting in fall of their viscosity.

Scanning Electron Microscopy [6, 53]

The native guar gum has discrete, elongated, irregular granular structure separated from each other. The morphology of carboxymethyl guar gum is shown in (Fig. 6.12.2), wherein the topology of the crosslinked carboxymethyl guar gum is changed and some of the granules get attached by adhering themselves. The granules of native guar gum have an irregular but smooth surface and are basically with no defects (Fig.6.12.3). The surface of crosslinked carboxymethyl guar gum shows rough, which looked like surface corrosion (Fig.6.12.4). The alkaline environment during the carboxymethylation process accounts for the structural changes and due to the crosslinking of carboxymethyl guar gum.

X-ray diffraction [6,7] :-

The wide angle X-ray diffractogram of native guar gum and a representative crosslinked carboxymethyl guar gum is presented in Figure. From Fig.6.13, it is obvious that native guar gum exhibits a small crytallinity. Similar appearance has been reported for native guar gum in the literature. After carboxymethylation.

Evaluation of fast disintegrating tablet

Pre compressional parameters

Flow property of powder for all formulated batches is shown in table no. 6.10. The bulk density varies between 0.40 to 0.50 gm/ml, the tapped density varied between 0.48 to 0.58 gm/ml; the Carr's index varies between 12.24 to 15.51 % and Hausner's ratio 1.13 to 1.18. Further, angle of repose 20.10 to 23.56 was found. So that prepared powder shows a good flow property.

Table 5 Precompressional parameters

Formulation	Parameter				
	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index	Hausner ratio
T1	22.69±0.14	0.47±0.01	0.54±0.02	12.96±0.04	1.14±0.01
T2	21.32±0.27	0.49±0.03	0.58±0.04	15.51±0.04	1.18±0.03
T3	23.10±0.15	0.41±0.03	0.48±0.05	14.58±0.03	1.17±0.04
T4	20.25±0.20	0.50±0.02	0.58±0.03	13.79±0.02	1.16±0.01
T5	23.30±0.19	0.48±0.04	0.55±0.04	12.72±0.07	1.14±0.02
T6	21.56±0.11	0.46±0.01	0.53±0.01	13.20±0.05	1.15±0.03
T7	23.56±0.11	0.42±0.02	0.49±0.02	14.28±0.03	1.16±0.04
T8	20.10±0.11	0.48±0.04	0.55±0.06	12.72±0.06	1.14±0.02
T9	22.54±0.15	0.43±0.01	0.49±0.02	12.24±0.07	1.13±0.03
T10	23.45±0.18	0.46±0.03	0.53±0.03	13.20±0.04	1.15±0.01
T11	21.60±0.15	0.43±0.02	0.49±0.03	12.24±0.05	1.13±0.02
T12	20.15±0.15	0.45±0.01	0.52±0.01	13.46±0.07	1.15±0.01

Post compressional parameters

From table no. 6.11 it was seen that all tablets passes the weight variation test as per IP. Further the parameters like hardness and thickness meet the criteria. The low value of % friability indicated the mechanical stability of the formulation.

Disintegration time [26]

The less concentration of CCMGG possesses insufficient swelling power to break the tablets. The tablets containing higher conc. (6% w/w) CCMGG showed nearly comparable disintegration time as shown by SSG based tablets. At higher conc. (8% w/w) the disintegration time of both the tablets, SSG based was decreased that may be due to formation of viscous gel mass which impede the penetration of water in to the tablets and retarded the disintegration power. The use of CCMGG as a tablet disintegrant in this study seemed to have the optimum concentration at 8 %w/w. but more disintegration time was required when compared to crospovidone. Because of crospovidone uses combination of swelling and wicking mechanisms of action to provide rapid disintegration.

In vitro Drug Release study of Fast disintegrating tablet

The results of the dissolution studies of SSG, Crospovidone, and Crosslinked carboxymethyl guar gum are shown in Table 6.13, 6.14, 6.15 respectively. The percentage of drug release from CCMGG (6%) containing FDT within 20 min was 94% compared with 93% for the SSG (6%) containing FDT. And 96% drug release from Crospovidone (8%) containing FDT reaches within 16 min as compared with CCMGG. Here, The percentage drug release from CCMGG (8%) containing FDT was decrease because may be due to formation of viscous gel mass which retard the dissolution of drug

same as SSG (8%).

Table 6 *In vitro* Drug Release study of SSG Containing FDT

Time (min)	% Drug Release (n=3), Mean ± SD			
	T1	T2	T3	T4
0	0	0	0	0
2	28.32±1.18	34.65±1.73	46.76 ±2.04	31.78±0.98
4	33.43±1.67	45.87±1.15	49.87±1.32	41.87±1.65
6	48.21±2.08	52.54±1.87	57.65±1.54	49.72±2.87
8	59.32±0.95	63.23±2.04	64.27±2.16	59.82±1.75
10	63.65±1.30	66.54±0.87	69.84±0.76	65.31±0.64
12	69.76±1.63	71.38±1.97	74.34±1.36	71.52±0.54
14	72.43±2.05	78.54±1.54	80.54±2.05	76.43±1.98
16	76.65±1.02	81.76±1.31	83.65±1.78	81.19±2.02
18	82.43±2.09	84.65±2.17	86.67±1.23	84.72±1.87
20	87.32±1.54	89.72±0.34	**93.17±0.67**	89.32±1.45

Stability Study

The stability study of suitable formulations was carried out at 40ºC±0.5% and 75% RH using stability chamber for one month. The different parameters that were studied are shape, colour, hardness, thickness, Disintegration and dissolution rate. The suitable formulations were found to be stable in terms of physical appearance, hardness, Disintegration time and *in vitro drug* release.

CONCLUSION

From the result and discussion following conclusions were drawn:
Time required for the carboxymethylation of natural polysaccharide was effectively decreased using microwave irradiated environment for heating.

Carboxymethylation of guar gum was characterized by various methods in which one of the techniques is FT-IR spectra determination which predicted the carboxymethyl group present in the native guar gum structure.

Carboxymethyl guar gum was synthesized with neutralization equivalent value of 344.40 for A4 batch (8 min) under microwave irradiation environment. And Crosslinking of Carboxymethyl guar gum achieved best swelling index 955.2 at 0.5 % concentration of $POCl_3$. Viscosity of Carboxymethyl guar gum was decreased as compared to the native guar gum due to columbic repulsion which prevents the entanglement of backbone chains.

Morphological features of modified polymer were studied by SEM. The SEM photographic data of modified polymer were found to be rough and rigid. And From XRD data it was concluded that crystallinity of native guar gum reduces due to attribution of carboxymethyl group and as well as by crosslinking. DSC and FTIR study shows that no interaction occurred between drug and modified polymer.

As the concentration of disintegrant was increased in range of 2 to 6 % w/w. It was found that there was decrease in disintegration time. On further increasing the concentration beyond 6 % w/w there was increase in disintegration time.
In – vitro dissolution study of FDT containing CCMGG (6%w/w) shows better drug release compared to SSG (6 %w/w) and less drug release compared to crospovidone.

Disintegration time of CCMGG was compared with SSG and crospovidone. From the result and discussion it can be concluded that CCMGG having better disintegration property as compared with the SSG. Cross-linked carboxymethylated guar gum could be used as a potential disintegrant in tablet dosage form at higher concentration (6%w/w).

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