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Effect of Guar Gum on Dissolution and Sustained Release of Metronidazole Effervescent Tablets

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ABSTRACT

PURPOSE: The present investigation or proposal study being carried out to maximize the therapeutic effect of metronidazole tablet with respect to time, thereby, pre formulating the API, enhancing effervescent phenomena approach, incorporating the excipient guar gum, assuring its stability and compatibility parameters with the API and therefore resulting in sustained release profile of metronidazole, further masking taste of API and possessing binding property, eventually controlling programmed drug delivery rates.

METHOD: The methodology involved the pre formulation or prototype formulation development thesis, evaluating the physicochemical and flow properties of ingredients and formulation stability under different circumstances. Initially excipients/ingredients were identified with the incorporation of guar gum in formulation, testing their flow properties. Secondly compatibility and stability studies were carried out via FTIR and DSC including physical appearance test, mixing proportions of excipients with API, mixture examined initially after mixing and further examined under stress conditions of temperature 40-45 degree Celsius and relative humidity of 75%. Third parameter was the evaluation of particle size by distribution via method of different mesh size (20, 25, 30, 35, 40, 70 and 100) and size calculated. Further important parameters involved bulk and tap density, compressibility index, angle of repose and hygroscopicity of excipients/powders evaluation.

For effervescent phenomena approach method of mixing and granulation should be so considered to assure stability of dosage form. The purpose served by evaluating or examine the appropriate method of granulation , selecting either of the compatible methods from the two wet granulation or thermoplastic method of granulation, keeping in consideration the ingredients particularly guar gum.

Furthermore, post compression evaluation conducted to assure weight variation, friability values, pH of solution, measurement of CO2 content, hardness of tablets, effervescent cessation time, thickness, assay profiles, content uniformity, water content, equilibrium moisture content of metronidazole effervescent tablets. Post formulation parameters being examined include in vitro studies evaluating calibration graph of metronidazole, dissolution time, disintegration time of effervescent formulation of metronidazole tablets incorporating guar gum as excipient for sustained release and in addition for its binding ability and taste masking ability.

RESULT: Results indicating that guar gum tested to be compatible with other effervescent formulation ingredients with API metronidazole as guar gum has good flow properties and is non-hygroscopic, so is compatible with moisture conditions fulfilling stability criteria, having good solubility index in water and can be formulated via wet granulation. Guar gum also having good pH range 1-10, maintaining its pH-stability with any material hence less reactive.

CONCLUSION: Our formulation research proposal studies expecting to be a successful approach in future, ultimately fulfilling the demand for patient satisfaction and compliance.

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OBJECTIVE

The purpose of the present study is to formulate an effervescent metronidazole tablets by using guar gum as an excipient which served as a binder and taste masking agent as well as responsible for sustained release of the drug.

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CHAPTER ONE
LITERATURE REVIEW

The most popular way of taking medication is the oral route despite having some disadvantages like slow absorption and thus onset of action is prolong however, it can be overcome by administering the drug in liquid form but, many medicinal agents have limited stability in liquid form. So, effervescent tablets acts as an alternative dosage form[1]. As per proposed definition of US Food and Drug Administration "effervescent tablets are tablet intended to be dissolved or dispersible in water before administration". Effervescent tablets have some advantages over liquids, mixtures and suspensions;

The drug absorption is faster and complete because it is already in solution form at the time of consumption.

Faster onset of action due to faster absorption of effervescent tablets.
Liberation of carbondioxide gas helps in taste masking of bitter tasting drugs.
More gentle effect on patient's stomach.
Better patient compliance and marketing aspects[2].

Mechanism of effervescence

The tablet is broken into pieces by the internal liberation of Carbondioxide in water which is obtained by the chemical reaction of Citric acid and Tartaric acid with metal carbonates or bicarbonates. They generally consist of acids (COOH) and bicarbonates (HCO3) or carbonates (CO3). Occasionally, an active ingredient itself could act as the acid or alkali metal component for effervescent reaction[3].

$C_6H_8O_7.H_2O + 3NaHCO_3\ (aq) \rightarrow Na_3C_6H_5O_7 + 4H_2O + 3CO_2\ (g) \uparrow$
Citric acid + Sodium bicarbonate → Sodium citrate + Water + Carbon dioxide

$C_4H_6O_6 + 2\ NaHCO_3 \rightarrow Na_2C_4H_4O_6 + 2H_2O + 2CO_2\ (g) \uparrow$
Tartaric acid + Sodium bicarbonate → Sodium tartrate + Water + Carbon dioxide [3]

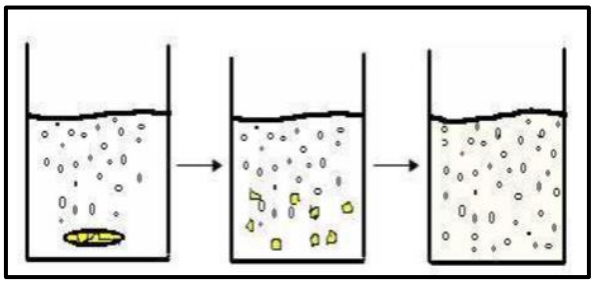

Figure 1 : Mechanism of effervescence [3]

The Guar or cluster bean (Cyamopsis tetragonoloba) is an annual legume and the source of guar gum which is also known as Gavar, Guwar or Guvar bean. Guargum, also called guaran, is a galactomannan and principally grown in India and Pakistan, with smaller crops grown in the U.S, Australia, China and Africa. It is primarily the ground endosperm of guar beans. The guar seeds are dehusked, milled and screened to obtain the guargum. Chemically, guargum is a polysaccharide composed of the sugars galactose and mannose, the back bone is the linear chain of β 1,4-linked mannose residues to which galactose residues are 1, 6-linked at every second mannose, forming short side-branches.

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Guargum is economical because it has almost eight times the water-thickening potency of cornstarch only a very small quantity is needed in effervescent for producing sufficient binding effect, viscosity and masks solid particles in solution and furthermore works as stabilizer because it helps to prevent solid particles from settling and thus enhance solubility by effervescent base. Increasing the viscosity with rheological modifier such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds[4].

Recent similar studies of new formulations of effervescent tablets of other pharmaceutical products were quoted in references 5.

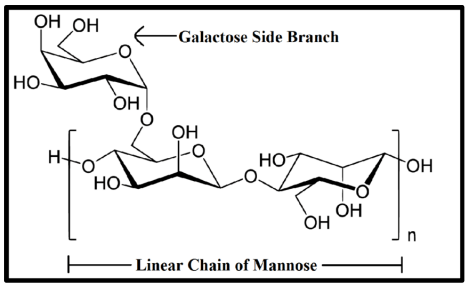

Figure 2: chemical structure of guar gum

Metronidazole (2-methyl-5-nitro-1H-imidazole-1-ethanol) is a synthetic nitroimidazole derivative with antiprotozoal and antibacterial activities that can be administered orally, IV, and topically[6].

Metronidazole is an effective treatment for some anaerobic bacterial infections including *Clostridium, Eubacterium, Peptococcus, Bacteroides fragilis* group, *Fusobacterium* and antiprotozoal activity against *Entamoeba histolytica, Trichomonas vaginalis* [7]. The nitro group reduction of metronidazole by anaerobic organisms is likely responsible for the drug's antimicrobial cytotoxic effects, causing DNA strand damage to microbes. Common infections treated by metronidazole are Bacteroides species infections, Clostridium infections, and Fusobacterium infections, as well as Peptococcus and Peptostreptococcus infections. It is also used off-label in the treatment of Crohn's disease and rosacea, as a prophylactic agent after surgery, and in the treatment of Helicobacter pylori infection. It has also been studied in the prevention of preterm births and to treat periodontal disease[6].

Commonly available commercial dosage forms include 250- and 500-mg oral tablets. Metronidazole is a very bitter medication. Although compounding pharmacists can grind up the tablets and make a pediatric suspension, but the taste cannot be masked and children will refuse the medication[8].

In addition, patients may avoid carrying the medication with them when away from home, resulting in poor compliance and the failure of therapy[2].

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CHAPTER TWO
METHODOLOGY

2.1 PRE FORMULATION AND PROTOTYPE FORMULATION DEVELOPMENT

The whole purpose for this pre-formulation study is to make an effervescent tablet of metronidazole so the objectives regarding the formulation is to evaluate the appropriate form of excipients, their physiochemical properties, flow properties of ingredients and formulation stability under different circumstances. [9]

2.1.1 Identification of excipients :

It is all clear that tartaric acid and citric acid play a vital role as acidic agent to cause effervescence and are the basic excipients for the formulation of effervescent dosage form. In addition sodium bicarbonate also act as a basic excipients in effervescent tablets. [10]

However our main focus is to add guar gum in our formulation as stabilizers and can also act as binder. [4]

Whereas for other necessary excipients including binder, antioxidants, acidulant, buffering and flavoring agents are available in many variety for effervescent dosage form which will evaluate as per compatibility and stability parameters as well as according to the flow properties as it influence on granulation, **Table 1**. [1], [10]

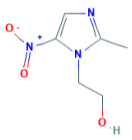
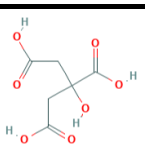
Table 1: Recommended excipients for effervescent tablets

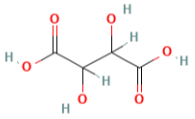
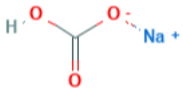
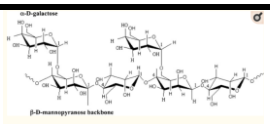
S. No	Excipients	Application
1	**PED 6000** **PEG 4000**	Binder
2	**Sodium lauryl sulphate** **Sodium benzoate** **Magnesium stearate**	Lubricants
4	**Sodium citrate**	Buffering agent
5	**Fumaric acid & ascorbic acid**	Antioxidants

2.1.2Compatibility and Stability Studies :

For the evaluation of compatibility of above excipients we have to perform FTIR, DSC and physical appearance test by mixing the same proportions of excipients with API, as shown in **Table 2**. The mixture should evaluate at initial day and then kept in stressing condition of recommended temperature 40-45℃ and relative humidity of 75%. [11]

Table 2: Proportion of ingredients. [6],[12],[13],[14],[15]

S. No.	Ingredients	Structure	Specification	Quantity	
1	**Metronidazole**		USP	200	
2	**Citric acid**		BP	200	

3	**Tartaric acid**		BP	200	
4	**Sodium bicarbonate**		BP	200	
5	**Guar gum**		BP/USP	200	

FTIR spectrophotometer is perform to determine either there will any functional group changes occur between drug and excipients or not by placing sample on spectrum holder with a frequency range of 4000-400cm.

DSC will perform for scanning calorimetry in which heat flow will measure as function of heat. Sample will heat on aluminum pans under nitrogen flow at a scanning rate of 10°C/min from 0 to 300°C. [16]

Table 3: Drug-Excipient Compatibility Standards [11]

Tests	Appearance criteria
Appearance	White, odorless, crystalline powder, having a slightly bitter taste
FTIR	Functional group should remain intact
DSC	change in melting point NMT ±2%

2.1.3 Particle Size :

Particle size distribution in granulation can be evaluate by sieve method of different mesh size (20, 25, 30, 35, 40, 70 and 100), placed on top of each other through which 100g of powder will pass. Shake for 10 mins and average size calculated by the following equation

$$d=\frac{\sum x d_i}{100}$$

x = Average size of both the upper and lower sieve
d_i = Percent of the value i in that range of bulk.

2.1.4 Bulk Density :

For the assessment of flowability of sample powders in comaparision with standard values, as shown in **Table 4**, samples will be pour in measuring cylinder and note the volume without displacing the cylinder.

$$\rho\ bulk = \frac{m}{Vbulk}$$

2.1.5 Tapped Density :

After measuring bulk density tap the cylinder containing sample from the height of 2.5 cm for 2secs and note the volume. It can be calculated as follow:

$$\rho\ tapped = \frac{m}{Vtapped}$$

2.1.6 Compressibility Index :

With help of sample densities we can evaluate the flow properties by calculating Carr's index with the formula given below:

$$\%C = 100 * [\frac{\rho\ tapped - \rho\ bulk}{\rho\ tapped}]$$

2.1.7 Angle Of Repose :

It will be measure by fixed funnel method. The funnel is fixed at certain height (h) above the surface on which paper is placed. Gradually pour the samples from the funnel until the pile just hit the tip of the funnel. Draw the circle around the granules and calculate the angle of repose by following:

$$\text{Tan } \theta = \frac{h}{r}$$

Where, θ = Angle of repose, h = Height of the cone, r = Radius of the cone. [2], [10]

Table 4: Standard chart

Angle of Repose	Carr's Index	Type Of Flow
<25°	5-15%	Excellent
25-30°	12-16%	Good
30-40°	18-21%	Fair to passable
-	23-35%	Poor
-	33-38%	Very poor
>40°	>40%	Extremely poor

2.1.8 Solubility by Shake Flask Method :

Solubility testing will help to predict the dissolution medium of suitable pH for the formulation as well as the stability of formulation in different medium.

The procedure will require a 200ml flask in which 100ml of solvent (buffers/purified water) will be added. Maintain the temperature of 37℃ and shake the flask on magnetic stirrer. Add the samples until it remain undissolved. After that shake the flask for continuous 12 hours. Now filter the solution and analyses filtrate by UV-Vis to evaluate the pH-dependent solubility of API.

2.1.9 Hygroscopicity :

Hygroscopicity is the measurement of a material's ability to absorb or release water as a function of humidity (i.e. water activity). The ideal way of measuring Hygroscopicity would be to create a Moisture sorption isotherm by looking at the change in water content vs. relative humidity at a constant temperature. [11]

2.2 FORMULATION TECHNIQUE

2.2.1 Wet granulation :

Widely used technique as granulation makes the compresses the tablet very well rather than direct compression because granulation make the ease of physical portability of the formulation. General steps that will involve in the formulation of effervescent tables by this technique are as follow:

- Blend A will prepared as powder mixture of drug and excipients.
- Blend B will prepare as a binder solution.
- Mix both blend and pass through sieve to form granules.
- Dry the granules and again pass through the sieve.
- Mix it with lubricant to provide lubrication during compression of granules via compression machine. [17]

Monograph	Average weight	Deviation (%)
IP/BP	<80 mg	10
	Between 80 and 250 mg	7.5
	>250 mg	5
USP	<130 mg	10
	Between 130 and 325 mg	7.5
	>325 mg	5

Figure Weight variation specification.

2.2.2 Thermoplastic granulation :

This is the advance technique in which there is no need to wet the granules so ultimately the reduction drying phase, because meltable binders are use which can melt up to 50-80℃. The steps include:

- Mix the drug and excipients.
- Add meltable binder in it and heat up to 50-80℃.
- Pass the mixture through a sieve to form granules.
- Lubricate the granules before compression.

2.3 POST COMPRESSION EVALUATION

2.3.1 Weight variation :

The procedure described in United States Pharmacopeia (USP 2006) will be employed to determine the weight variation of the tablets. Twenty tablets will be randomly selected from the batch and weigh on the electronic balance and the average weight will be calculated. The tablets will be weighed individually and then compare with average weight. The tablets will pass the test if not more than two tablets fall outside the % limit and none of tablet differs by more than double % limit. [2], [18]

2.3.2 Friability :

Twenty weighed tablets are placed in the friabilator which is then operated at 25 rpm for 4 min. The tablets will be weighed again and difference in the two weights will be used to calculate friability as:
Friability percent = (Weight of tablets before test − Weight after test)/ (Weight of tablets before test) ×100. [2], [19], [20]

USP limit is 0.5 to 1%.

2.3.3 pH of solution :

To determine the pH of solution, one tablet will be dissolved in purified water. After complete dissolution, the solution pH will be measured by using pH meter. Repeat experiment three times for each tablet. [17], [18]

2.3.4 Measurement of CO2 content :

One effervescent tablet will be dissolved in 100ml sulfuric acid 1N and weight changes will be determined after dissolution end. The obtained difference will show the amount (mg) of CO2 per tablet. This experiment will be conducted on three tablets for each formulation. [2], [17], [19]

2.3.5 Hardness :

The ability of tablets to resist chipping or breakage under conditions of storage, transportation, and handling before usage depends on its hardness. It is measured by Monsento Hardness Tester in terms of kg/cm². The hardness of 3-5 kg/cm² is considered to be satisfactory for uncoated tablets. [2], [17]

2.3.6 Effervescent cessation time :

A tablet will be placed in a glass containing purified water at 20°+- 1˚C and effervescent time will be measured by a stopwatch. The mean of three measurements of each formulation will be reported. [2], [17], [19]

2.3.7 Thickness :

Ten tablets of each formulation will be evaluated by using a calibrated dial caliper. [17]

2.3.8 Assay :

A tablet will be placed in a 100 ml volumetric flask and dissolved in phosphate buffer pH 5. After dilution, the amount of the drug was determined by UV spectrophotometer at 229.8 nm against blank. 10 tablets of each formulation would be evaluated. [2]

2.3.9 Content uniformity :

After selecting 10 tablets randomly, each of it will be transferred into a 50ml volumetric flask, dissolved and diluted to 50 mL with phosphate buffer pH6.8. 1 mL of this solution will be diluted to 100 mL with phosphate buffer pH 6.8. The amount of drug present in each tablet will determined by UV spectroscopy at 246 nm. Standard limit is
USP:- active less than 25mg or 25%.
10 tabs limit NMT 1 tab deviate 85 – 115% & none outside 75 – 125% of the average value
If 2 0r 3 individual values are outside the limits 85 – 115% of the average value, & none outside 75 – 125% repeat for 20 tablets. [2], [17]

2.3.10 Water content :

In a desiccator containing activated silica gel, 10 tablets of each formulation weighed before and after will be placed for 4 h.

The percentage of water content will be calculated by using formula: [2], [19], [20]

$$\frac{\text{Weight before drying} - \text{weight after drying}}{\text{Weight before drying}} * 100$$

2.3.11 Equilibrium moisture content :

Three dessicators will be prepared containing saturated salt solutions of potassium nitrate (RH 90%), sodium chloride (RH 71%), and sodium nitrate (RH 60%) at 18˚C. three tablets will be placed in dessictaor and the equilibrium moisture content will determined by Karl Fischer method and the autotitrator device in the first day and after seven days. [2], [17]

2.4 IN VITRO STUDIES

2.4.1 Calibration Graph Of Metronidazole :

20, 40, 60, 80 and 100 µg/mL concentrations of drug solutions will scan against 0.1N HCl as reference solution at 277 nm under UV spectrophotometer. These working dilutions will scan at 277 nm for their absorbencies by using UV spectrophotometer. A graph will be plot by taking absorbencies on Y-axis and concentration (µg/mL) on X-axis. This graph yields standard calibration graph of drug solutions. [10]

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2.4.2 Dissolution time :

The sample effervescent tablet will place inside the dissolution vessel. The dissolution apparatus use for this study should be USP TYPE II apparatus 9 of which paddle will set at a speed of 75 rpm. Samples of 1ml were withdrawn at time intervals 10, 20, 30, 40, 50 and 60 min. to maintain the sink condition 1ml of dissolution medium will replace with aliquot. In this study the dissolution medium of 900 ml of 0.1N HCl will be use and temperature of 37 ± 0.5 0C will maintain throughout the dissolution studies according to BP. Each sample will dilute to 10 ml and analyze at 277 nm using double beam UV and visible Spectrophotometer against reagent blank.

2.4.3 Disintegration time :

Place sample effervescent tablet in a 250 ml beaker containing 200 ml of water R at 15–25° C. numerous bubbles of gas are evolved. When the evolution of gas around the tablet or its fragments ceases, the tablet should have disintegrated, being either dissolved or dispersed in the water so that no agglomerates remain. Repeat the operation on five additional tablets. The tablets comply with the test if each of the six tablets used in the test disintegrates within 5 minutes, unless otherwise specified in the individual monograph. [17]

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CHAPTER THREE
SUGGESTED OUTCOMES

Formulation of effervescent tablets of metronidazole with guar gum aims to provide sustained effect and can render the taste can be successful as it has been previously shown that an antibiotic ciprofloxacin has been successfully formulated with guar gum. There are more than half of the chances that metronidazole will be compatible with guar gum and also with other excipients as metronidazole effervescent tables has already made using the ingredients including citric acid, tartaric acid, PEG-4000, Fumaric acid and sodium carbonate. Also the guar gum have shown significant results with these excipients so it can be highly suspected that the compatibility test of our formulation will be passed.

Also the studies has shown that guar gum has good flow properties and are non-hygroscopic so it can maintain its stability in higher moisture conditions. It has good solubility index in water so can be formulated via wet granulation. But we are aiming to formulate sustained effect effervescent tablets and guar gum are also stable at room temperature and are consider as meltable binder as it melts within 50-80℃ in this way it reduce the cost of binder too so its better to formulate via wet granulation technique.

Guar gum has also good pH range, scaling from 1-10 due to its non-ionic and uncharged behavior so it is suspected that guar gum can maintain its pH-stability with any material and can be less reactive.

So overall guar gum have good physiochemical profile and as per profile and literature review we are expecting that our formulation can be successful in future and is a present need for patient's satisfaction.

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