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"DEVELOPMENT AND EVALUATION OF ORAL DISPERSIBLE TABLET OF PROMETHAZINE USING PLANTAGO OVATA SEED MUCILAGE AS A NATURAL SUPERDISINTEGRANT"

***Jaswal Ritu, Ghosh Niladry, Dr. Angshu Banerjee and Thakur Nisha**

School of Pharmaceutical Sciences, Bahra University, Shimla (H.P.).

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***Corresponding Author**
Jaswal Ritu
School of Pharmaceutical Sciences, Bahra University, Shimla (H.P.).

ABSTRACT

The need for delivering drugs to patients efficiently with minimum side effects has prompted industries to be engaged in development of new drug delivery systems. Recent advances in technology prompted researchers and scientists to develop oral disintegrating tablets (ODTs) with improved patient convenience and compliance. Mouth dissolving tablet that dissolve or disintegrate rapidly in oral cavity result in solution, is an ultimate remedy for this problem. In addition they give pleasing mouth feeling. An orally dispersible tablet or orally dissolving tablet is a drug dosage form available for a limited range of over-the-counter (OTC) and prescription medications. In the present work, fast disintegrating tablets of promethazine Hcl are designed with a view to enhance patient compliance by direct compression method. In this method mucilage of Plantago ovata is used as superdisintegrant to enhance the after effects and further improve the overall characteristics of the drug used and thus enhancing the overall tablets formulated. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio and in vitro dispersion time. Based on in vitro dispersion time, the various formulations were tested for the in vitro drug release pattern, short-term stability and drug-excipient interaction (IR spectroscopy). Among the promising formulations, the formulation prepared by using Plantago ovata mucilage emerged as the overall best formulation based on the in vitro drug release characteristics compared to conventional tablets formulation without disintegrant. The studies on the formulations indicate that there are various different methodologies that depict the various aspects of ODT formulation, superdisintegrants and technologies that are developed, along with various drugs explored, evaluation tests and marketed formulations in this field.

KEYWORDS: Promethazine, *Plantago ovata* mucilage, fast-disintegrating tablets.

Oral drug delivery has been known for decade as most widely utilized route of administration among all the route that have been explored for the systemic delivery of drug via various pharmaceutical product of different dosage form. The reason that the oral route achieved such popularity may be in part attribute to ease of administration as well as traditional belief that by oral administration the drug is well absorbed as the foodstuff that are ingested daily.

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Currently only 8% of new drug candidates have both high solubility and permeability. The absorption of the drug into the systemic circulation is a prerequisite to reach the site of action for all drugs, except those drugs that are applied at the site of action, or those that are intravenously injected. After oral administration (gastro-intestinal route), many factors determine the bioavailability (fraction of drug reaching the systemic circulation). Since only dissolved drug can pass the gastro-intestinal membrane, dissolution is one of those factors. In the recent past several novel technologies have emerged with improved performance, improved patient compliance and reduced adverse effects. One such approach is to formulate mouth-dissolving tablet or mouth-disintegrating tablets which are dissolves rapidly in saliva without the need of water within few seconds due to the action of superdisintegrant in the formulation.[8,9] The demand for mouth dissolving tablets has been growing over the other oral dosage forms (such as tablets, capsule, dry syrups, chewing gums/chewable tablets) among pediatric, geriatric, dysphasic, psychotic and non-cooperative patients and travelers.

The primary advantage of the fast melt dosage forms is that they do not need to be chewed because they disintegrate quickly and completely in the small amount of saliva in the mouth. This makes them easy to swallow, avoiding the need to take them with water. It is estimated that 25% of the population find it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by doctors, resulting in ineffective therapy. However hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and in case of uncooperative patients, the problem of swallowing is common phenomenon, which leads to poor patient compliance. To overcome these drawbacks, mouth dissolving tablets or orally disintegrating tablets has emerged as alternative oral dosage forms. These are novel types of tablets that disintegrate/dissolve/disperse in saliva within few seconds. According to European

pharmacopoeia, the oral disintegrating tablets should disperse/disintegrate in less than three minutes.[4]

MATERIALS AND METHODS

Materials

The following drug excipients, chemicals and instruments were used for the formulation and evaluation studies.

Table 1: Materials used

S.NO	CHEMICAL/DRUG	COMPANY
1.	Promethazine	Meridian pharmaceuticals , Solan
2.	Camphor	Meridian pharamaceuticals , Solan
3.	Cross carmellose	Meridian pharmaceuticals, Solan
4.	Sodium starch glycolate	S. D. Fine Chemicals Ltd., Mumbai, India.
5.	Mannitol	S. D. Fine Chemicals Ltd., Mumbai, India.
6.	Talc	S. D. Fine Chemicals Ltd., Mumbai, India.
7.	Sodium saccharine	Meridian pharmaceuticals, Solan
8.	Magnesium stearate	S. D. Fine Chemicals Ltd., Mumbai, India.
9.	Raspberry flavour	Meridian pharmaceuticals, Solan
10.	Crosspovidone	R.M remedies, Solan
11.	Aspartame	Meridian pharmaceuticals, Solan.
12.	Plantago ovata seed mucilage	GI products, Delhi

Preparation of standard curves of Promethazine in 0.1N HCl and 6.8 pH phosphate buffer

In 0.1N HCl: 8.5 ml of conc. hydrochloric acid was diluted up to 1000 ml with distilled water, gives 0.1N solution. Stock solution was prepared by dissolving 100.0 mg of drug (promethazine) in 100.0 ml of 0.1 N HCl solutions, which was further diluted to give the solutions of concentration 1, 2, 3, 4,5,6 and 7 µg/ml respectively. Absorbance of these solutions were measured on UV spectrophotometer at their respective wavelengths (249.6nm) and plotted against the concentration to give the standard curve.

In 6.8 pH phosphate buffer

Dissolve 28.80g of disodium hydrogen phosphate and 11.45g of potassium dihydrogen phosphate in sufficient water to produce 1000ml. Stock solution was prepared by dissolving 100.0 mg of drug (Promethazine) in 100.0 ml of 6.8 pH phosphate buffer solutions, which was further diluted to give the solutions of concentration 1, 2,3, 4,5,6 and 7 µg/ml respectively. Absorbance of these solutions were measured on UV spectrophotometer at their

respective wavelengths (249.6nm) and plotted against the concentration to give the standard curve.

Partition coefficient

A measurement of a drug's lipophilicity and an indication of its ability to cross cell membranes is the oil/water partition coefficient in systems such as octanol/water and chloroform/water. The partition coefficient is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium.

$$\text{Partition coefficient} = \frac{\text{concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}}$$

For series of compounds, the partition coefficient can provide an empiric handle in screening for some biologic properties. For drug delivery, the lipophilic/hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption. Although partition coefficient data alone does not provide understanding of in vivo absorption, it does provide a means of characterizing the lipophilic/hydrophilic nature of the drug.

PRECOMPRESSION STUDIES

Determination of λmax.

Stock solution (1000µg/ml) of promethazine hcl was prepared in 0.1N HCl. This solution was apparently diluted with same solvent to obtain concentration of 100 µg/ml. The resultant solution was scanned in the range of 200-400 nm on double beam UV-spectrophotometer. The resultant was plotted with respect to the values calculated.

Methodology for isolation of mucilage

For the isolation of mucilage, seeds of Plantago ovata were used. They were soaked in distilled water for 48 h and then boiled for 1 h for complete release of mucilage into water. The material was filtered by squeezing in a muslin cloth to remove marc.

Then equal volume of acetone was added to filtrate to precipitate the mucilage. The mucilage was separated and dried in oven at a temperature less than 60°, powdered (mesh), weighed and stored in desiccator until further use.

Fourier Transfer Infrared spectrophotometer (FTIR)

The FTIR studies were carried for the drug, the polymers and the drug-polymer physical mixture in the ratio 1:1 were mixed separately with IR grade KBr in the ratio of (100:1) and corresponding discs were prepared by applying 5.5 metric ton of pressure in a hydraulic press using FTIR Spectrophotometer. The disks were scanned over a wave number range (4000 - 400cm).

(1) Angle of repose

Angle of repose method, is most closely mimic the manufacturing situation, in which powder is in motion. They are particularly sensitive to changes in particle size distribution and to moisture content and they provide rapid means of monitoring significant batch difference in these respects.

Angle of repose was determined by using funnel method. The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The value of angle of repose are calculated by using the following formula,

The value of angle of repose are calculated by using the following formula,

$\tan \theta = h/r$ $\theta = \tan^{-1} (h/r)$

Where, θ = Angle of repose,

h = height of the heap

r = radius of the heap

Compressibility index and Hausner ratio

The compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting granules flow characteristics. The compressibility index and Hausner ratio were determined by measuring both the Bulk density and tapped density of granules.

Compressibility index = Tapped density − Bulk density/ Tapped density X 100

Hausner ratio = Tapped density/ Bulk density.

EVALUATION OF TABLETS PREPARED BY DIRECT COMPRESSION TECHNOLOGY

Low cost, direct compression method was employed to develop a rapidly disintegrating tablet with a taste and texture acceptable to patient and with sufficient structure integrity. Tablet

(200 mg) were prepared from control formulation, using various concentration of superdisintegrant plantago ovate used as natural polymer to enhance the characteristics of drug used. Mixed blend of drug and excipient was compressed on single punch tablet machine. Tablet, each weighing 200 mg was prepared. Similarly tablets was prepared by the combinations of drug and superdisintegrant were subjected to evaluate official and non official specifications.

POST COMPRESSION EVALUATION OF TABLET

Weight variation

With a tablet designed to contain a specific amount of drug in a specific amount of formula, the weight of a tablet being made is routinely measured to ensure that a tablet contains proper amount of drug.

Procedure

First weight of 20 tablets was determined. From that average weight was calculated. Then individual tablets were weighed and the individual weight was compared with an average weight.

Hardness and Friability

Tablets required certain amount of strength, or hardness and resistance to friability. It is necessary or important to withstand mechanical shocks of handling in manufacture, packaging and shipping.

Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance. More recently relationship of hardness to tablet, disintegration and dissolution of drug had become apparent. Monitoring of tablet hardness is especially important for drug products that possess real bioavailability problems and or those which are sensitive to altered dissolution profile as the function of compressive force employed. Using tablet hardness tester(monsanto), hardness of the tablet was checked. Using Roche Friabilator friability of the tablet was checked. This device subjects tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves. Preweighted weight of 10 tablets was placed in the Friabilator, which was then operated for 100 revolutions. Tablets were dusted and weighed. The friability was determined using following formula.

Friability = [(Initial weight- Final weight) / (initial weight)] x 100%

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

R = 100 × Wa –Wb/Wa

Where, Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption.

In- vitro dispersion time

Tablet was added to 10 ml Phosphate buffer solution, pH 6.4 at 37± 2ºC. Time required for complete dispersion of a tablet was measured.

In-vivo dispersion time

In-Vivo dispersion time of a tablet was checked in healthy human volunteers by putting a tablet on tongue and required for complete dispersion of a tablet was checked.

Uniformity of content

The test is applicable for tablets that contain less than 10 mg or less than 10% w/w of active ingredients. The test for uniformity of content should be carried out only after the content of active ingredient in a pooled sample and tablets has been shown to be within acceptable limits of the started content. Ten tablets were taken and their content was determined by UV spectrophotometer.

Dissolution study

Dissolution rate was studied by using USP type II apparatus under following experimental condition:

- 50 rpm
- 900 ml of buffer 6.8 as dissolution medium
- 37 ± 0.5ºC as a temperature of dissolution medium.

Aliquot equal to 10 ml of dissolution medium was withdrawn at specific time interval and it was filtered. Absorption of filtered solution was checked by UV spectroscopy at 276.5 nm and drug content was determined from the standard calibration curve. The dissolution testing was carried out in triplicate.

The fast dissolving tablets of Promethazine HCl were prepared using camphor as subliming agent in three different proportions of 2%, 5% and 10%. Sodium starch glycolate, crosscarmellose and tulsion ingredients. Each of these were used in different concentrations of 5% and 10%. Mannitol is used as diluents in quantity sufficient; talc is used as flow promoter and magnesium state as lubricant. All the ingredients will be passed through mesh screen and weighed in geometrical order. All the materials were directly compressible so this uniformly mixed blend was compressed into tablets using single tablet punching machine (cadmach).

Sublimation will be performed from tablets by keeping them in hot air oven at 60ºC for 1 hour. Six formulations will be prepared for the whole procedure that will be performed during the complete process.

In addition to all other ingredients we are using a additional natural polymer known as plantago ovata as a Superdisintegrant used as mucilage during the formulation of tablet. This mucilage is most commonly used as adjuvant in the manufacturing of different pharmaceutical dosage forms. They possess a variety of pharmaceutical properties, which include binding, disintegrating, suspending, emulsifying and sustaining properties at different proportion in different pharmaceutical dosage forms.

RESULTS AND DISCUSSION

The results of the tablet that was formulated are being discussed in this chapter. This chapter has very important significance in this research work as the basis and the major platform that has been laid down depending upon the work and the experimental study done in the vast field of pharmaceutical sciences.

Determination of maximum wavelength of Promethazine in 0.1 N HCl:

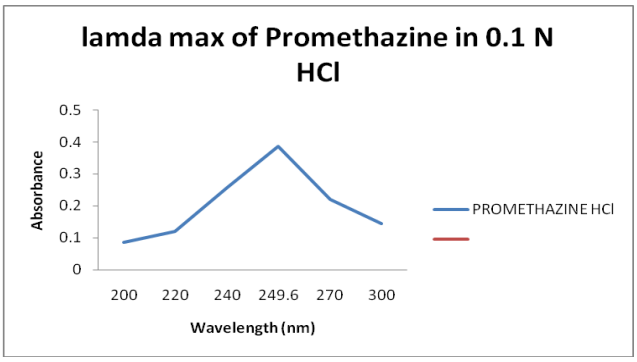

Figure 1: Graph showing the maximum wavelength of promethazine in 0.1N HCL.

FT-IR spectroscopy was employed to ascertain the compatibility between Promethazine hydrochloride and the selected polymer (plantago ovata) that is being used in our research work.

FTIR spectra of Promethazine HCl

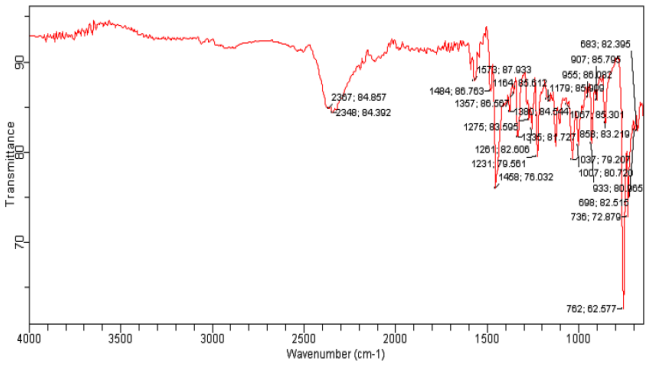

Figure 2: Graphical representation of promethazine/ FTIR spectrum.

FTIR spectra of natural polymer Plantago ovata is shown in graph as shown below.

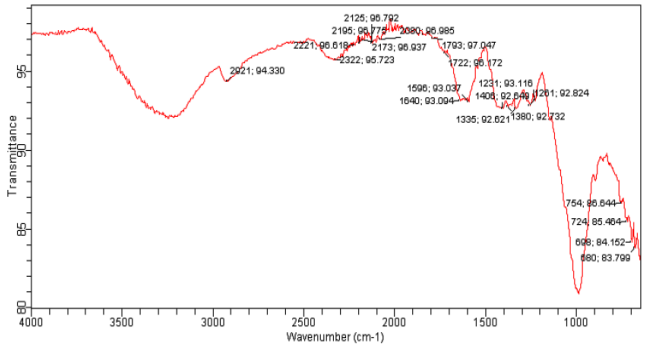

Figure 3 Graphical representation of plantago ovata/ FTIR spectrum.

FTIR spectra of promethazine in combination with natural polymer Plantago ovata is shown in graph as shown below.

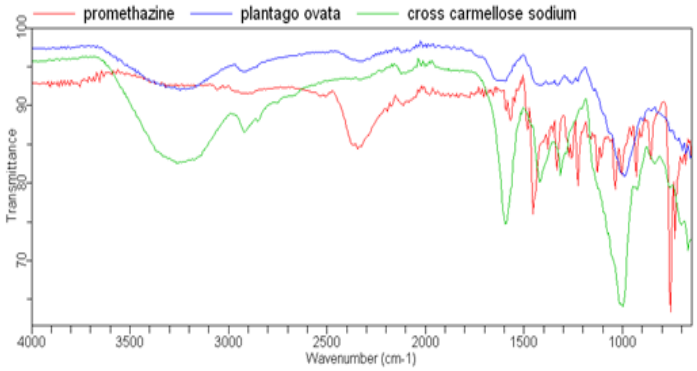

Figure 4: Graph showing the spectrum analysis of promethazine plantago ovata and ingredient used cross carmellose sodium.

DRUG IDENTIFICATION TEST

Spectrophotometric study: for this the graph obtained is shown below.

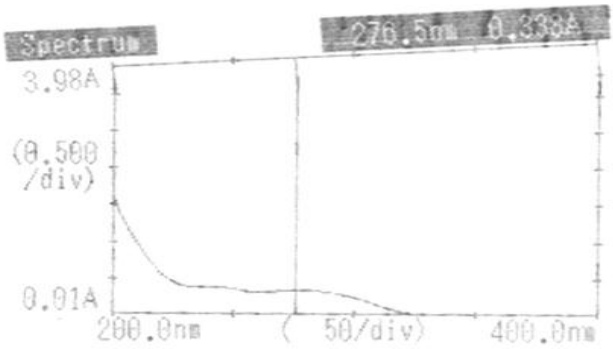

Figure 5: Spectroscopic studies of Promethazine.

Identification of drug by infra-red spectrum

The IR spectrum of promethazine was determined and recorded; it was matched with literature image of drug and found that there were no any extra peaks.

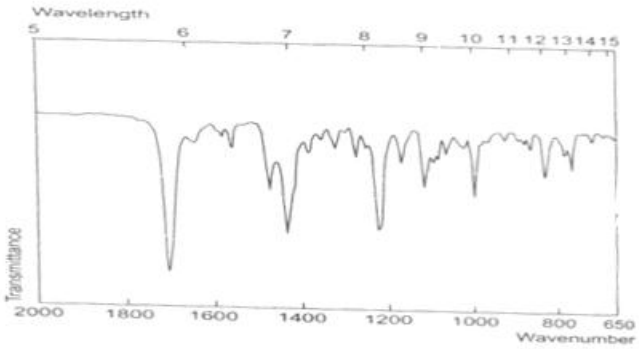

Figure 6: Reference IR-spectrum of promethazine drug.

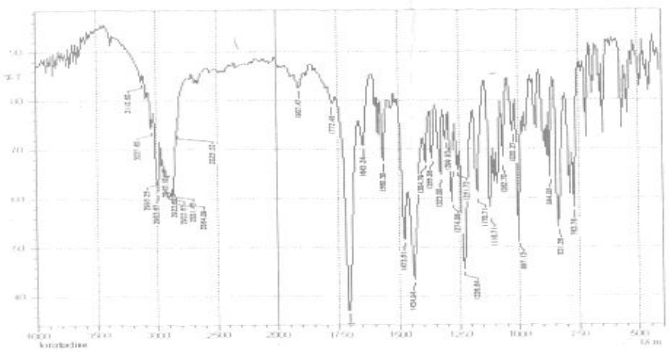

Figure 7: IR-Spectrum of sample drug promethazine.

EVALUATION OF TABLETS PREPARED BY DIRECT COMPRESSION TECHNOLOGY

Table 2: Specification as per IP

Average Weight of tablet	% Deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

The calibration curves were plotted between absorbance versus concentration. These curves plotted are shown in the figures below.

Table 3: Absorbance data of promethazine in phosphate buffer at Ph 6.8.

Sr. no.	Concentration (µg/ml)	Absorbance
1.	1	0.079
2.	2	0.173
3.	3	0.267
4.	4	0.359
5.	5	0.439
6.	6	0.538
7.	7	0.608

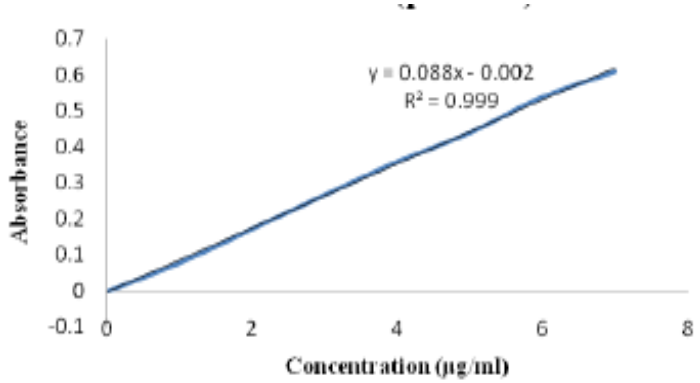

Figure 8: Calibration curve of promethazine in phosphate buffer at Ph 6.8

Table 4: Absorbance data of promethazine in water.

Sr. no.	Concentration (µg/ml)	Absorbance
1.	1	0.088
2.	2	0.157
3.	3	0.256
4.	4	0.351
5.	5	0.453
6.	6	0.512
7.	7	0.621

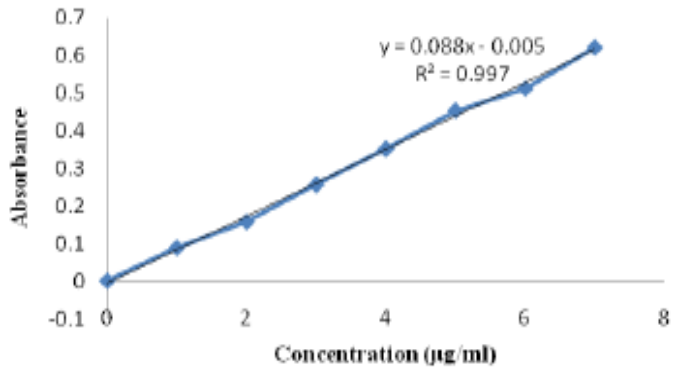

Figure 9: Calibration curve of promethazine in water.

Table 5: Absorbance data of promethazine in 0.1N Hcl.

Sr. no.	Concentration (µg/ml)	Absorbance
1.	1	0.097
2.	2	0.171
3.	3	0.258
4.	4	0.345
5.	5	0.435
6.	6	0.517
7.	7	0.604

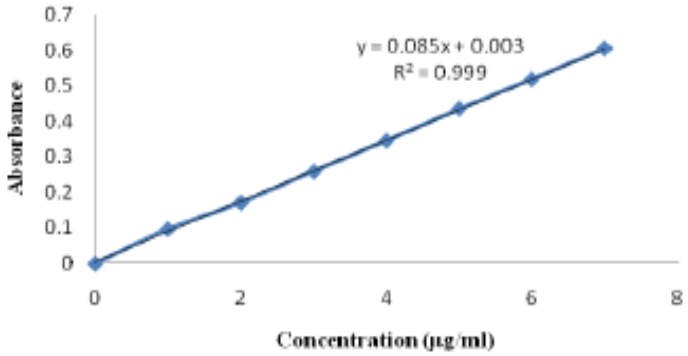

Figure 10: Calibration curve of promethazine in 0.1N Hcl.

Table 6: FORMULATION USING SUPERDISINTEGRANT

	F1	F2	F3	F4	F5	F6	F7	F8
PROMETHAZINE DRUG (mg)	25	25	25	25	25	25	25	25
CAMPHOR(mg)	40	30	20	10	40	20	30	20
CROSS CARMELLOSE(mg)	20	30	40	30	10	40	30	20
P.OVATA SEED ETRACT (mg)	_	_	_	60	40	30	30	50
MANNITOL(mg)	120	120	120	80	90	90	90	100
MAGNESIUM STEARATE (mg)	5	5	5	5	10	5	5	2
SODIUM SACCHARINE(mg)	5	5	5	7	2	5	5	2
TALC (mg)	5	5	5	3	3	5	5	1
TOTAL (mg)	220	220	220	220	220	220	220	220

TABLET PREPARED BY USING PLANTAGO OVATA

Powder containing Formulation for plantago ovata

From table shown it was observed that powder blend containing plantago ovata as superdisintegrant has shown angle of repose between 25.43-28.23^0 and carr's index between 20-26.47%, which indicate that all powder, had good flowability.

Table 7: Powder properties of formulation containing Plantago ovata (F5-F8)

Formulation properties	F5	F6	F7	F8
Angle of repose (^{o})	28.23	25.43	26.64	27.23
Bulk density (g/cm^3)	0.28	0.27	0.25	0.28
Tapped density (g/cm^3)	0.35	0.36	0.34	0.36
Carr's index	20	25	26.47	22.22
Fowability	Good	Good	Good	Good

Evaluation of physical properties of tablet using plantago ovata

Table 8: Physical properties of tablets with using plantago ovata.

Formulation properties	F5	F6	F7	F8
Weight variation	Passes	Passes	Passes	Passes
Hardness(kg/cm^2)	3.5	3.0	3.5	3.5
Friability (%)	0.64	0.60	0.70	0.62
Uniformity of Content (%)	98.65	98.08	99.86	100.5
Water absorbption Ratio(%)	60.2	65.68	69.8	72.3
Wetting time(sec)	26	22	18	16
Disintegration Time(sec) in vitro	38	35	37	33
In vivo	55	51	44	48

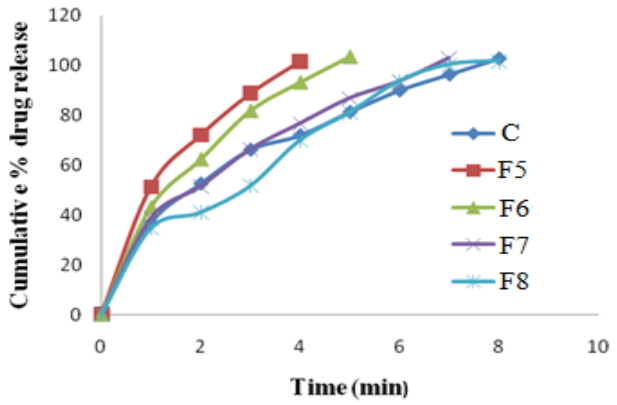

Figure 11: A comparative study of In-vitro drug release of tablet by using Plantago ovata.

In the present dissertation work, mouth dissolving tablets of promethazine were prepared using Superdisintegrant plantago ovata seed mucilage. The frabicated tablets were evaluated

for their physical characteristics such as weight variation, friability, content uniformity, hardness, water absorption ratio, wetting time disintegration time in vitro and in vivo and dissolution. The hardness of tablet prepared without superdisintegrants means control tablet have hardness 3.5 $Kg/cm^2$and friability 0.65% The hardness of tablet prepared by using natural polymer plantago ovata as shown from table tabulated above the graph are also 3-3.5 Kg/cm^2.

The wetting time and water absorption ratio which are the important criteria for determining the capacity of disintegrants to swell in presence of little water was found have been evaluated for each batch as indicated that the water absorption ratio for control tablet was 45.23% and wetting time was 53. It was more in comparisonas there was no superdisintegrants.

Tabulated results indicated using Superdisintegrant plantago ovate tablet batch F6 was the best prepration and it shown the water absorption ratio and wetting time was 76.1% and 14 seconds.

Plantago ovata superdisintegrant and the 5% concentration of this gave the less disintegration time in comparison to formulation without Superdisintegrant which was found 42 seconds, because of viscous plug formation have been take place in higher concentration. Dissolution rate studies show that about 95-100% drug release within the 2 to 7 minutes for all formulation. When the tablet was prepared with using the superdisintegrants then according the tabulated results for control tablets shows that the complete release of drug was found within the 2-4 minutes.

Thus we can say that we have met our goals for achieving the best possible results by using plantago ovata seed mucilage as a natural Superdisintegrant in our oral drug formulation futher improving its overall characteristics.

CONCLUSION

Fast disintegrating tablets of promethazine were prepared by direct compression method employing *Plantago ovata* mucilage as super-disintegrant in different ratios along with different ingredients. Directly compressible mannitol was used as a diluent to enhance mouth feel. A total of various formulations with without super-disintegrant were formulated. As the blends were free flowing (angle of repose <30°, and Carr's index <15%) tablets obtained

were of uniform weight (due to uniform die fill), with acceptable variations as per IP specification i.e., below ±7.5%. Drug content was found to be in the range of 95 to 101%, which is within acceptable limits. Hardness of the tablets was found to be about 2.63 kg/cm^2. Friability below 1% was an indication of good mechanical resistance of the tablets. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrant to swell in presence of little amount of water were found to be in the range of 50-86% and 11-47 s, respectively. Among all the designed formulations, two formulations, were found to be promising and displayed an *in vitro* dispersion time ranging from 8 to 10 s, which facilitates their faster dispersion in the mouth.

Overall, the formulation one containing 8% w/w of *Plantago ovata* mucilage found to be promising and has shown an *in vitro* dispersion time of 8 s, wetting time of 11 s and water absorption ratio of 86% when compared to formulation without Superdisintegrant for various different parameters that were incorporated within the evalauation The experimental data also reveals that the results obtained from the *Plantago ovata* mucilage are comparable and even slightly better than those without disintegrant.

SUMMARY

Research work done in this project work has been summarised as we have prepared the tablet of promethazine using the natural polymer as plantago ovata and hence enhanching the overall characteristics of the tablet formulated. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio and in vitro dispersion time. The basic approach used in development of mouth dissolving tablet is the use of superdisintegrants, which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drug that pass down into the stomach.

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