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Preparation and Evaluation of Combination Tablet Containing Paracetamol and Ginger Powder and Its Extract.

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ABSTRACT

The present study has been aimed to develop a tablet containing paracetamol in which ginger is incorporated to prevent the side effect of paracetamol like nausea and vomiting. In addition ginger contains starch, which acts as disintegrant. Granules were prepared by inclusion of ginger extract in A and B formulation and while ginger powder is present in C and D formulations. Granules were evaluated for particle volume, density and flow properties. Granules were compressed and tablets were evaluated for thickness, hardness, friability, and disintegration studies. The tablet hardness were generally higher with the ginger starch, an indication that lower concentration of ginger could be used to achieve the same level of binding. Tablets were further tested for dissolution studies, which showed better release of drug and drug content. Formulation C was found to be most effective as it decreases the concentration of starch, talc and magnesium stearate requirements.

INTRODUCTION

Paracetamol is an analgesic, antipyretic used to treat minor pain and in combination with NSAID's for treatment of cancer pain. Although paracetamol is safe drug upto 2 g per day, overdose leads to gastrointestinal tract complications such as stomach bleeding, swollen pancreas, asthma, eczema and liver failure. Normal dose of paracetamol in hypersensitive patients leads to emesis and vomiting causing patient noncompliance. It is also known that paracetamol has an extremely bitter taste which can make it particularly unpleasant to take orally.

Paracetamol based compositions are often used as "cold remedies". Such compositions may not cure the underlying condition, but may treat or alleviate the symptoms of colds or influenza, including headaches, fever, rhinitis and general aches and pains. Formulation were made [1] with sweeteners such that the bitter taste of the paracetamol is masked. These sweeteners are sucrose, aspartame and saccharin. The sweeteners present in the composition make the composition overpoweringly sweet. Reducing the amount of sweeteners can overcome this problem, but then the bitter taste of the paracetamol is insufficiently masked. Such formulation cannot be used for diabetic patients.

Therefore there is a need of taste masking agent, which is devoid of sweetness. In present study preparation of tablet containing paracetamol and ginger in its extract form and plain powder form is made to avoid the side effects of paracetamol.

The rhizomes of ginger have been reported to contain up to 56.0% starch. Ginger contains major active constituents such as gingerol, shogaols and dehydrogingerdiones. Since ginger has antibacterial, antioxidant, [2,3] anti-allergic, cardiotoxic [4] antitumor [5, 6], antiinflammatory [7], hepatoprotective [8] and antiemetic [9] activities. Ginger can be given safely upto 2-4 g per day dose. Ginger accelerates gastric emptying. So the ginger was used in combination to have dual action such as to prevent the side effects of paracetamol and its starch content as disintegrant.

EXPERIMENTAL METHODS

Preparation of extract

Coarsely powdered dried ginger below 45°C is extracted with ethyl ether by percolation method. The drug is extracted exhaustively and extracts were combined. The solvent removed by distillation under reduced pressure to prevent decomposition of active ingredients. To his concentrated extract was added the ethanolic solution of polyvinylpyrrolidone (PVP) and stirred well. It is known from the PCT application WO99/32130 to use polyvinylpyrrolidones in order to improve the release of valueable ingredients of dry extracts of medicinal plants. This was then vacuum dried below 45°C to get a paste, which was then added to the formulation.

Preparation of granules by wet granulation method

Wet granulation method was used for all tablet production. Calculation was made for 24 tablets in each batch. In each case, accurately weighed quantities of paracetamol, lactose and ginger extract or powder were mixed in a mortar and the binder solution PVP was added to obtain composition. Therefore use of suitable stabilizing agents in formulation is desired for long shelf life of the medicament.

Polyvinylpyrrolidone act as a binder and forms a cohesive mass, which imparts better flow properties and better compression of the tablet. PVP also improves the release of ingredients due to surface area enlargement. PVP also act as capturer and prevent the protonation and dehydration of the gingerols.

Concentration of Polyvinylpyrrolidone was varied from 3 to 16 %w/w in accordance with the quantity of ginger extract or powder. Ginger extract requires less quantity while ginger powder requires higher quantity of polyvinylpyrrolidone to form a damp coherent mass. The damp mass was sieved with 1.7 mm sieve and dried below 45°C for overnight. The dried granular mass was passed through a 1.0 mm sieve to obtain uniform sized granules. Granules were analyzed for their flow properties, bulk density, tapped density and Carr's index. The different batches of the granules were then mixed with calculated equal quantities of magnesium stearate using mixing bottle, and then compressed into tablets under constant pressure with a Manesty single punch (Type F3, England) tableting machine. The punch size and volume of fill were carefully adjusted to give the required tablet size and weight. Tablet was made of 250 mg of paracetamol, a batch of 24 tablets is made by taking 6 g of paracetamol and varying quantities of ginger, PVP, lactose, starch, talc and magnesium stearate.

Table 1: Formulation of tablet

Ingredient	A	B	C	D
Paracetamol	6 g	6 g	6g	6g
Ginger	1 g (extract)	1 g (extract)	6 g (powder)	2 g (powder)
Polyvinylpyrrolidone	0.8 g	1 g	2 g	1 g
Lactose	2g	2g	1.2 g	1.2 g
Magnesium stearate	0.2 g	1.2 g	0.2 g	0.2 g
Talc	2 g	0.2 g	0.4 g	1 g
Starch	2 g	2 g	0.8 g	1 g
Theoretical weight per tablet	0.583 mg	0.558 mg	0.691 mg	0.516 mg

Evaluation of tablet

The tablets were evaluated for hardness, friability, weight uniformity, disintegration and dissolution.

Hardness test

Five tablets were selected at random from each batch to perform this test. Monsanto harness tester (Manesty machines Liverpool, England) was used to measure the hardness. Tablet was placed between spindle and anvil of the tester and the calibrated length adjusted to zero. The knob was then screwed to apply a diametric compression force on the tablet and the position on the calibrated length at which the tablet broke was recorded in kg/cm² units. A mean hardness was calculated for each batch and thus their standard deviations and coefficient of variations were calculated.

Weight uniformity test

Twenty tablets from each batch were selected randomly and weighed individually using a highly sensitive electronic balance. Their mean weights were calculated; deviations and coefficients of variation for each batch were calculated.

Friability test

Roche friabulator was used to carryout this test. Ten tablets were selected at random, dusted and weighed together using the electronic balance and then placed in the Roche friabulator. The machine was operated for 4 min at 120 rev/min and then stopped. The tablets were dusted again and reweighed. The percentage losses were calculated for each batch of the tablets.

Disintegration time

The method specified in the Indian Pharmacopiea was used. The machine used was Electrolab multiple disintegration unit. Disintegration medium used was 900 ml of buffer pH 7.8 maintained at temperature between 35 and 39°C throughout the experiment. Six tablets selected at random from each batch were placed one in each of the cylindrical tubes of the basket but no disc was used. The time taken for each tablet to break up into small particles and pass out through the mesh was recorded. Mean disintegration time was calculated for each batch.

Calibration curve for paracetamol

A stock solution of 100 mg% of paracetamol (API) was prepared by dissolving 100 mg of the drug in 100 ml of buffer pH 7.8. Various dilutions of the stock were made so as to obtain 0.01, 0.02, 0.04, 0.06, 0.08, 0.10 and 0.12 mg% with buffer pH 7.8. The absorbance of the various dilutions were then taken at 249 nm using a UV-VIS spectrophotometer. A plot of absorbance against concentration (mg%) of the drug was made from which the calibration curve was determined from the slope of the graph.

Dissolution test

Using 900 ml of phosphate buffer pH 7.8 as the medium and rotating paddle at 50 rpm for 30 min. withdraw a suitable volume of sample and filter promptly through the membrane filter disc of an average pore diameter NMT 0.1 µm. Reject the first few ml of the filtrate and dilute a suitable volume of the filtrate with the same solvent. Measure the absorbance of the resulting solution at the maximum of about 249 nm using a UV-VIS spectrophotometer.

Assay of Paracetamol

Dissolve 50 mg in sufficient methol to produce 100 ml, to 1ml of this solution add 0.5 ml of 0.1 M HCl and dilute to 100 ml with methanol. Protect the resulting solution from bright light and immediately measure the absorption at maximum at about 249 nm.

Stability studies

Tablets made by using extract and powders were kept for room temperature (27 °C), refrigerator temperature (8°C) and 45 °C for 4 weeks. Assay of paracetamol was performed after 14 days and 28 days further test was extended for 3 months.

RESULTS AND DISCUSSION

Formulation C contains amount of pracetamol and ginger powder in 1:1 ratio. This will benefit reducing the side effect of paracetamol effectively. Better granules were obtained when PVP was used in 12 to 15 %w/w concentration. Granules were found to be free flowing and have good compressibility as angle of repose is below 30° while Carr's index is below 15 %.

Table 2: Granule properties

Formulation	A	B	C	D
Volume (cm ³)	28	32	34	35
Density (g/cm ³)	0.27	0.25	0.32	0.34
Tap density (g/cm ³)	0.3	0.26	0.33	0.36
Angle of repose (°)	21.87	18.66	20.55	21.77
Carr's Index	7.33	1.7	3.03	5.25

Hardness of tablet was well within the accepted limit of 4 to 7 kg/cm². Tablets are comparatively harder in case of ginger powder formulations (C, D) where higher concentration of binder PVP is used.

The low tapped densities of ginger extract formulation (A, B) indicate that both materials are not highly porous and have poor flowing powders. The low bulk density results when the void spaces created by larger powder particles are not filled by smaller particles in distribution leading to consolidation of powder particles.

Mean of disintegration was within acceptable range, was found to be within 30 minutes. Disintegration study shows formulation C and D have higher disintegration time as compared to formulation A and B. This could be due to higher quantity of binder used for these formulations.

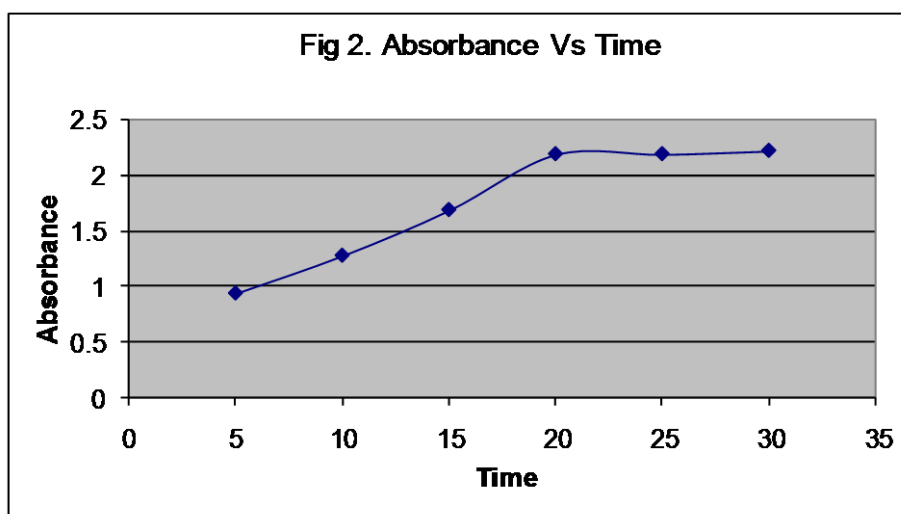
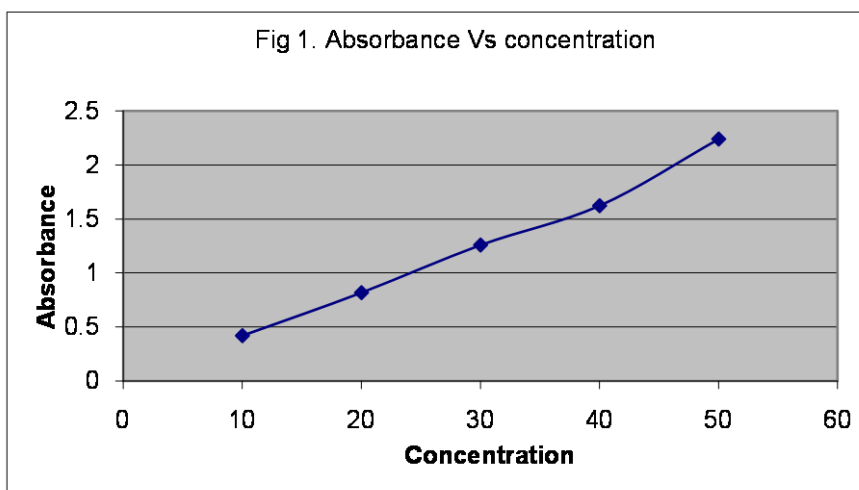
Table 3: Evaluation of tablet

Formulation	A	B	C	D
Hardness (kg/cm ²)	5	6	7	6
Friability (%)	2.8	2.7	1.2	1.9
Mean Disintegration time (min)	5	4	8	7

Ginger powder formulations (C, D) have lower friability than the ginger extract formulation. Formulation C shows near to acceptance limit of below 1.0% friability. Variations in weight uniformity were less with tablets prepared using ginger powder formulations (C, D).

Dissolution test shows the release of paracetamol well within specified time. Graph of concentration Vs absorbance shows rate of release of paracetamol in specified time limit.

Fig 1. shows calibration curve for standard paracetamol while Fig 2. shows graph of absorbance Vs time i.e release of paracetamol in specified time. Percentage content of paracetamol tablet by dissolution test was found to be 90.72 %. This shows ginger powder formulation where ginger does not hinder the release of paracetamol.



Stability studies show that drug content did not change within first 14 days and even after 3 months. Tablets made of ginger extracts were more stable.

CONCLUSION

Ginger powder can be used instead of ginger extract with additional benefits. Ginger powder shows better compressibility as well as rapid disintegration thus allowing paracetamol to release faster.

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