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DEVELOPMENT AND EVALUATION OF ANTIPYRETIC PAEDIATRIC FORMULATION

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ABSTRACT: Paracetamol (PCT), an analgesic and antipyretic drug commonly used and safe for children, was chosen as the model drug candidate to obtain a dosage form with improved palatability, enhanced bioavailability, attractive paediatric elegance and cost effectiveness. The present work was carried out to design and develop oral effervescent granules of Paracetamol, to be dispersed and then given with effervescence for children of age group 6-12 years. To increase the drug solubility, formulations were prepared with solid dispersion technique using PEG 6000. All formulations showed excellent flow properties and satisfactory organoleptic characteristics with *in vitro* effervescence time of 2-3 minutes and *in vitro* drug release more than 50% during 60 seconds of effervescence.
KEYWORDS: Paracetamol, PEG solid dispersion, Effervescent granules

INTRODUCTION AND EXPERIMENTAL

Granules are the dosage forms for administration of drugs with unpleasant taste. Solid drugs with large dose are difficult to present and in such situation tablets and capsules are impracticable due to their size and number required per dose. The liquid dosage forms are precluded because it depends on the stability of the drug in solution and also associated are the solubility problems if the drug is insoluble. Granulation allows addition of flavours, colours and also attractive form if effervescent characteristics are administered.

The objective of the present study is to design and develop oral preparations of Paracetamol for the age group 6 to 12 years in form of dispersible effervescent granules using solid dispersion technique so as to have rapid drug release and enhanced acceptance, palatability and ease of administration. Paracetamol (PCT) is an antipyretic and analgesic drug which is marketed as oral tablets, capsules, suspensions, solutions and dry syrup[1-6]. Hence it was chosen as the model drug candidate to present in a more elegant, palatable dosage form along with dispersible and effervescent characteristics and attractive paediatric elegance. This technology can also be used to obtain quick relief and for administration of bitter drugs meant for children[7-13].

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MATERIALS AND METHODS

Paracetamol was purchased from Research Fine Chemical Industries. Sodium bicarbonate was purchased from Swastik Pharmaceuticals; Tartaric acid was purchased from Loba Chemie Pvt. Ltd. and Citric acid was purchased from West Coast Laboratories. All other chemicals were of analytical grade and were purchased from Merck India

Preparation of Dispersible Effervescent Granules:

To increase the solubility and therefore dissolution of PCT, solid dispersion of PCT with PEG 6000 were made employing melt fusion technique in 1:0.5 ratio. PEG 6000 was melted and to the molten mass PCT was added when the temperature reached 50^0C. This dispersion was cooled to room temperature with constant stirring. The solid mass thus obtained was sieved through 60#. Solid dispersion of PCT (Dose 250 mg), citric acid and sodium bicarbonate along with other excipients were mixed by the method of geometric dilution (Table 1). The homogenous blend was heated in a crucible kept on a boiling water bath till a wet pliable mass was obtained. The mixture was pressed down until a damp coherent mass was obtained. The damp mass was then passed

through an 8# superposed upon 20#. These granules were then dried in the oven at a temperature below 50^0 C.
The dose of granules was kept 2.5 g of the dispersible effervescent granules equivalent to 0.25 g of PCT. Following variables were investigated (Table 1):

1. Concentration of effervescent agents
   a. Sodium bicarbonate: 15%, 22% and 25%
   b. Citric acid: 8%, 9%, 10%, 11%, 12%
   c. Tartaric acid: 8%, 9%, 10%, 11%, 12%
2. Concentration of sweetener

Physical characteristics of Dispersible effervescent granules:
Dispersible effervescent granules of PCT were evaluated for organoleptic properties, flow properties, pH, *in vitro* effervescence time, *in vitro* drug release along with specific gravity and weight per ml.

Flow Properties:
The flow properties of the granules were determined from the flow rate, angle of repose, bulk and tap density and % porosity.

Viscosity:
The viscosities of the formulations were determined using Oswald Viscometer.

Drug content estimation:
One dose of effervescent dispersible granules equivalent to one dose of PCT (2.5 gm of the dispersible effervescent granules equivalent to 0.25 gm of PCT) was dissolved in 100 ml of distilled water and the solution was filtered through nylon filter membrane (0.22 µm). 0.1 ml of the solution was further diluted to 10 ml with distilled water and absorbance of the solution was read at λmax 250 nm on Hitachi U-2800 UV spectrophotometer. The drug concentration was extrapolated from the calibration curve in distilled water.

***In vitro* effervescence time:**
One dose of effervescent dispersible granules (2.5 gm of the dispersible effervescent granules equivalent to 0.25 gm of PCT) was added in 50 ml of distilled water and the time for *in vitro* effervescence till it ceases was determined.

***In vitro* drug release:**
One dose of effervescent dispersible granules (2.5 gm of the dispersible effervescent granules equivalent to 0.25 gm of PCT) was added in 50 ml of distilled water and *in vitro* drug release was determined. 0.1 ml aliquot was withdrawn at the end of 60 seconds in presence of effervescence and diluted to 100ml with distilled water. The absorbance was read at λmax 250 nm on Cecil CE 2021 UV spectrophotometer.

RESULTS AND DISCUSSION

All the formulations designed showed excellent palatability without any bitterness, as granules as well as solutions in distilled water. The flow properties of the granules were satisfactory along with other properties evaluated (Table 2).
It was observed that the flow rate of the effervescent dispersible granules increased with decrease in the concentration of sucrose and increase in the concentration of effervescent agents. Granules showed excellent flow rate and the angle of repose increased with decrease in the concentration of sodium bicarbonate and increase in the concentration of tartaric acid. As the concentration of sodium bicarbonate increased effervescence increased but the effect decreased as the concentration was increased further. It was also observed that as the concentration of sodium bicarbonate increased drug release increased but the drug release decreased as the concentration was increased further.
All the formulations showed satisfactory organoleptic characteristics, flow properties with *in vitro* effervescence time of 2-3minutes and *in vitro* drug release more than 50% during 60 seconds of effervescence.
In conclusion, dispersible effervescent granules of PCT were successfully developed. Granules with enhanced acceptability, palatability and elegance were obtained without any bitter taste of the drug. Therefore a highly palatable formulation technique which can avoid bitter taste of drugs with enhanced ease of administration can be used within the existing machinery. It can also be concluded that this method may also be used to administer other bitter drugs especially for children for quick relief.

Table 1 shows Formulations of Dispersible Effervescent Granules of PCT Using Different Concentrations of Effervescent Agents

Formulations	F-I (%)	F-II (%)	F-III (%)	F-IV (%)	F-V (%)	F-VI (%)
PCT: PEG 6000	15.0	15.0	15.0	15.0	15.0	15.0
Sucrose	43.0	43.0	38.0	38.0	52.0	52.0
Sodium bicarbonate	22.0	22.0	25.0	25.0	15.0	15.0
Citric acid (monohydrate)	09.0	11.0	10.0	12.0	10.0	08.0
Tartaric acid	11.0	09.0	12.0	10.0	08.0	10.0
Colour (Tartrazine)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Flavour (Lemon)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2 shows Evaluation Data for Dispersible Effervescent Granules of PCT

Sr.No.	Evaluation Parameters	F-I	F-II	F-III	F-IV	F-V	F-VI
1.	Flow Properties:						
	a. Flow Rate (g/second)	166.66 ± 0.01	94.34 ± .01	500 ± 0.02	500 ± 0.01	300 ± 0.01	187 ± 0.01
	b. Angle of Repose (^{0})	26 ± 0.05	28.7 ± 0.02	28.7 ± 0.01	23.4 ± 0.02	27.3 ± 0.12	28.2 ± 0.11
	c. Bulk Density (g/cm^3)	0.41 ± 0.12	0.45 ± 0.11	0.45 ± 0.1	0.5 ± 0.02	0.36 ± 0.11	0.37 ± 0.01
	d. Tap Density (g/cm^3)	0.5 ± 0.1	0.55 ± 0.1	0.55 ± 0.1	0.55 ± 0.01	0.45 ± 0.1	0.47 ± 0.01
	e. Porosity (%)	16.66 ± 0.11	18.18 ± 0.12	18.18 ± 0.1	10 ± 0.2	19.11 ± 0.11	22.22 ± 0.1
2.	Drug Content (%)	100 ± 0.3	99 ± 0.4	99 ± 0.21	98 ± 0.5	99 ± 0.1	98 ± 0.1
3.	pH	6	6	6	6	6	6
4.	Viscosity (centipoises)	0.0095 ± 0.01	0.0094 ± 0.01	0.010 ± 0.02	0.0095 ± 0.01	0.010 ± 0.01	0.0098 ± 0.02
5.	*In Vitro* Effervescence time (seconds)	180 ± 0.01	132.6 ± 0.021	91.8 ± 0.11	150 ± 0.012	81 ±0.02	91.2 ±0.02
6	Specific gravity	1.02 ± 0.01	1.02 ± 0.02	1.01 ± 0.011	1.02 ± 0.011	1.01 ± 0.011	1.02 ± 0.02
7	Weight per ml (g/ml)	1.02 ± 0.01	1.02 ± 0.02	1.01 ± 0.011	1.02 ± 0.011	1.01 ± 0.011	1.02 ± 0.02
8	*In vitro* release in 60 seconds in presence of effervescence in 50 ml water (%)	92 ± 0.01	82 ± 0.02	73 ± 0.021	66 ± 0.011	57 ± 0.02	59 ± 0.01

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