FORMULATION AND CHARACTERIZATION OF CHEWABLE TABLETS OF PARACETAMOL AND METOCLOPRAMIDE HYDROCHLORIDE

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The present study was aimed to formulate and characterized chewable tablets of Paracetamol and Metoclopramide hydrochloride. Paracetamol and Metoclopramide hydrochloride is an oral fixed dose combination for the preparation of chewable tablets used to treat the symptoms of migraine as it comply with physicochemical properties require to improve the effectiveness of therapeutic agent, better bioavailability, improved patient acceptance (especially pediatrics) through pleasant taste, patient convenience; need no water for swallowing, fasten the absorption of drug and for rapid onset of action. The investigation was carried out to study the effect of different proportion of Avicel 101, Avicel 102 and moringa gum, which are superdisintegrating agents. The chewable tablets of Paracetamol and Metoclopramide hydrochloride were prepared by wet granulation method. Several physicochemical parameters like thickness, diameter, hardness, %weight variation, %loss in weight, drug content, disintegration time, in vitro dissolution studies, kinetics of drug release and stability studies for all the formulations were studied and were found within the acceptance limits. Formulation F7 (containing moringa gum 1%) showed the best cumulative drug release and disintegration time of 56 secs.

Key words: Paracetamol; Metoclopramide hydrochloride; chewable tablets Moringa gum.

INTRODUCTION

Administration of drugs through oral route is the most common and the easiest way to administer a drug. However, pediatric, geriatric and bedridden patient shows inconvenience swallowing conventional tablets or capsules due to difficulties in swallowing with lesser amounts of water with the medication, unable to tolerate the taste of many drugs when formulated as liquid dosage forms, resulting in poor patient compliance. The rationalized approach in case of medication leads to the development of chewable tablets. The advantages of chewable tablet include palatability, stability, precise dosing, portability and ease of dosing.[1]

Chewable tablets have been designed so that they may be chewed in the mouth producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter a unpleasant taste. Chewable tablets are the dosage forms, which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing of drugs. Successfully tablet formulation development involves the careful selection of ingredients in order to manufacture a robust solid dosage form. Choosing the appropriate excipients to perform a specific function in a tablet formulation, such as disintegration or lubrication can be critical to achieving acceptable manufacturing performance. Sweeteners, both naturally occurring and synthetic, are one type of functional excipients commonly used in chewable tablet formulations to mask unpleasant tastes and facilitate pediatric dosing.

Paracetamol and Metoclopramide hydrochloride is an oral fixed dose combination for the preparation of chewable tablets used to treat the symptoms of migraine as it comply with physicochemical properties require to improve the effectiveness of therapeutic agent, better bioavailability, improved patient acceptance (especially pediatrics) through pleasant taste, patient convenience; need no water for swallowing, fasten the absorption of drug and for rapid onset of action.[2]

MATERIAL AND METHODS

Metoclopramide hydrochloride, moringa gum, tartrazine, aspartame and vanilla flavor were purchased from Balaji drug, Gujrat,lactose, maize starch, citric

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acid, sodium starch glycolate, magnesium stearate and talc were purchased from Central Drug House (P) Ltd. New Delhi, Paracetamol, Avicel 101 and Avicel 102 were purchased from Sanjay Biological Museum, Amritsar and mannitol was purchased from Rankem, New Delhi.

Preparation of chewable tablets containing Paracetamol and Metoclopramide hydrochloride:

Chewable tablets containing 325 mg Paracetamol and 5mg Metoclopramide hydrochloride were prepared with a total weight of 500 mg by wet granulation method of different homogeneous blends containing Avicel 101, Avicel 102 and moringa gum in different ratios individually in order to achieve the desire drug release profile. Drug and other excepients were sieved and mixed in a pestle and mortar. Maize starch and tartrazine (coloring agent) were dissolved in purified water to get a starch paste. Drug mix was added to starch paste and obtained wet mass, which was sieved form # 10 mesh sieve. The obtained granules were dried in oven. After drying the granules were passed through # 16 mesh sieve. Then added magnesium stearate and talc as lubricant and glident and thoroughly blended for 3 mins. The tablets were compressed using rotary punching machine using 11 mm punch. Compression force of machine was adjusted to obtain the hardness for each formulation.[3-4]

Table:1 Formulation composition of chewable tablets containing Paracetamol & Metoclopramide hydrochloride

Ingredients	**Formulation code**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Paracetamol	325	325	325	325	325	325	325	325	325
Metoclopramide hydrochloride	5	5	5	5	5	5	5	5	5
Avicel 101	5	10	15	---	---	---	---	---	---
Avicel 102	---	---	---	5	10	15	---	---	---
Moringa gum	---	---	---	---	---	---	5	10	15
Lactose	75	70	65	75	70	65	75	70	65
Mannitol	50	50	50	50	50	50	50	50	50
Maize starch	15	15	15	15	15	15	15	15	15
Citric acid	2	2	2	2	2	2	2	2	2
Sodium starch glycolate	3	3	3	3	3	3	3	3	3
Tartrazine	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Aspartame	10	10	10	10	10	10	10	10	10
Vanilla flavour	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation of chewable tablets containing Paracetamol and Metoclopramide hydrochloride:

Pre-Compression Parameters [5]

Angle of repose

In order to determine the flow property, the angle of repose was determined using the standard procedure. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plane. $\theta = \tan^{-1}\frac{h}{r}$

Determination of bulk density and tapped density

A quantity of 5gm of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals.

The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulae -

Bulk density = W / V_o Tapped density = W / V_f

Where, W = weight of the powder, V_o = Initial volume, V_f = Final volume

Compressibility index (Carr's index)

It was identified using the formula,

$$C.I = 100 (V_0 – V_f) / V$$

Hauser's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hauser's Ratio = $(W / V_f) / (W / V_0)$

Where, W / V_f= Tapped density, W / V_0 =Bulk density

Post compression parameters:[5--7]

Shape of Tablets

The Compressed tablets were examined under the magnifying lens for the shape of the tablet.

Tablet dimensions

Thickness and diameter were measured using a calliberated vernier caliper. Five tablets of each formulation were taken randomly and thickness was measured individually.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablet was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Five tablets were randomly picked and hardness of the tablet was determined.

Friability Test

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (w_0 initial) and transferred into friabilator was operated at 25rpm for 4 mins or run up to 100 revolutions. The tablets were weighed (w).

The friability was then calculated by

$$Friability = 100 (1-w/w_0)$$

Weight variation test

Twenty tablets were selected at random and the average weight was determined.

% Maximum positive deviation = (WH –A/ A) x 100

% Minimum negative deviation = (A-WL/ A) x 100

Where, WH = Highest weight in mg, WL=Lowest weight in mg, A= Average weight of tablet.

Drug content estimation

Five tablets were weighed individually and powdered. The powder equivalent to average weight of the tablet was weighed and drug was extracted in 0.1(N) HCl pH 1.2, the drug content was determined measuring the absorbance at 249 nm and 310 nm after suitable dilution using UV visible spectrophotometer.[1]

Disintegration test

Disintegration test was carried out by using disintegration test apparatus. One tablet is placed in each tube, and the basket rack was positioned in a 1 ltr beaker of water, at 37°C ±2°C. A standard motor-driven device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per mins. The time taken for the tablet to disintegrate completely was noted.[7]

In vitro drug release study

In vitro drug release studies were performed to provide the amount of drug that is released at a definite time period. In these release studies for all formulations were carried out using tablet dissolution USP type II (paddle method). The dissolution media used was 0.1(N) HCl, pH 1.2 maintained at $37±0.5^0$C and rotated 50 rpm. Aliquots were withdrawn at different time intervals and the same volume of fresh medium was replaced to maintain sink conditions. The samples were analysed against 0.1(N) HCl pH 1.2 as blank at λ max 249 nm and 310 nm using UV spectrophotometer.[8]

RESULTS & DISCUSSION

The diameter of all formulations ranged between 6.20±0.05 to 6.80±0.05 mm and thickness was in the range of 1.60±0.03 to 2.00±0.32 mm. All the batches showed hardness in the range 3.75±0.42 to 4.64±0.64 Kg/cm^2. The friability was found to be below 1% ensuring that all the formulations were mechanically stable. Uniformity of weight and drug content was evaluated usually by weight variation and content uniformity test. The variations in weight were within the

range of -0.143±0.31 to 0.654±1.32% complying with Pharmacopoeia specifications (±7.5 %). The range of drug content for Paracetamol was 95.385±0.006 to 98.256±0.005% and for Metoclopramide hydrochloride was 95.319±0.020 to 99.574±0.032% for all formulations. For all formulations disintegration time was in the range of 56±0.07 to 156±0.01 secs. The results were shown in Table No-5 to 6.

Table 2: Pre-formulation parameter of Paracetamol

Parameters	**Inference**	
Appearance	White or almost white	
Melting point	169±1.15^{0}C	
Solubility	In water	Partially Soluble
	In methanol	Freely Soluble
	In Hcl	Spraingly Soluble
Flow properties	Angle of repose	25.25±0.02
	Bulk density	0.5±0.02 gm/cc
	Tapped density	0.66±0.02 gm/cc
	Carr's index	24.24±0.05
	Hausner's ratio	1.32±0.01
Assay	98.4%	

All the 9 formulations of prepared chewable tablets of Paracetamol and Metoclopramide hydrochloride were subjected to *in vitro* release studies. The results obtaining *in vitro* release studies were plotted in different model of data treatment. The release data obtained for formulations F1 to F9 were showed in Figure No-1 to 2. In the present study Paracetamol and Metoclopramide hydrochloride chewable tablet by wet granulation method using polymers like Avicel 101, Avicel 102 and moringa gum was developed. Formulation F7 containing Moringa gum 5% showed best cumulative drug release and disintegration time of 56 secs, emerging as best formulation.

Table 3: Pre-formulation parameter of Metoclopramide hydrochloride

Parameters	**Inference**	
Appearance	Ligh yellowish	
Melting point	183±1.10°C	
Solubility	In Acetone	Soluble
	In methanol	Partially Soluble
	In Hcl	Soluble
Flow properties	Angle of repose	27.85±0.05
	Bulk density	0.45±0.02 gm/cc
	Tapped density	0.62±0.04 gm/cc
	Carr's index	23.20±0.03
	Hausner's ratio	1.25±0.03
Assay	99.5%	

Table 4: Flow properties of granules of formulations F1-F9

Formulation Code	**Bulk density* (gm/cm^3)**	**Tap density* (gm/cm^3)**	**Carr' index* (%)**	**Hausner's ratio***	**Angle of repose* (θ)**
F1	0.50±0.03	0.50±0.01	6.25±1.04	1.07±0.05	27.54±0.89
F2	0.50±0.05	0.50±0.03	12.50±1.13	1.14±0.04	27.93±1.45
F3	0.53±0.04	0.53±0.02	6.67±0.97	1.07±0.07	28.46±1.32
F4	0.47±0.03	0.47±0.01	11.76±1.32	1.13±0.02	27.87±0.84
F5	0.43±0.05	0.43±0.02	16.22±0.87	1.19±0.03	26.55±0.62
F6	0.43±0.01	0.43±0.05	16.22±1.15	1.19±0.02	27.43±0.23
F7	0.53±0.01	0.53±0.02	10.00±0.20	1.11±0.02	27.48±1.20
F8	0.40±0.02	0.40±0.01	17.50±0.67	1.21±0.02	28.76±1.23
F9	0.40±0.03	0.40±0.03	15.00±0.35	1.18±0.07	28.32±0.87

Table 5: Diameter, thickness, hardness and %loss in weight of formulation F1-F9

Batch Code	Diameter* (mm)	Thickness* (mm)	Hardness* (kg/cm^2)	%Loss in wt.**
F1	6.80±0.01	1.60±0.03	4±0.56	0.117±0.07
F2	6.20±0.05	1.80±0.06	4.32±0.14	0.056±0.04
F3	6.20±0.04	1.80±0.04	4.64±0.64	0.226±0.09
F4	6.40±0.01	2.00±0.32	4.62±0.87	0.423±0.17
F5	6.80±0.02	2.00±0.03	4.55±0.43	0.439±0.05
F6	6.80±0.05	1.80±0.22	3.75±0.42	0.2±0.18
F7	6.80±0.01	2.00±0.05	4.25±0.21	0.436±0.07
F8	6.80±0.04	2.20±0.16	4.52±055	0.112±0.03
F9	6.80±0.05	2.20±0.24	4.5±0.48	0.534±0.21

Table 6: %Weight variation, disintegration time, drug content of Paracetamol and drug content of Metoclopramide of formulation F1-F9

Formulation Code	%Weight variation**	Disintegration time (in sec)	Drug content** of Paracetamol	Drug content** of Metoclopramide
F1	-0.123±1.22	105±0.02	98.256±0.005	95.319±0.020
F2	0.235±1.56	90±0.01	96.821±0.010	97.872±0.005
F3	0.386±0.09	110±0.04	97.867±0.006	96.596±0.008
F4	0.256±1.24	145±0.05	96.205±0.007	99.574±0.032
F5	0.654±1.32	134±0.01	95.385±0.006	98.298±0.004
F6	-0.056±1.24	156±0.01	96.615±0.008	96.596±0.002
F7	0.116±1.52	56±0.07	95.795±0.007	95.787±0.008
F8	-0.143±0.31	62±0.01	96.615±0.017	96.340±0.003
F9	0.237±0.03	70±0.05	96.205±0.002	97.574±0.010

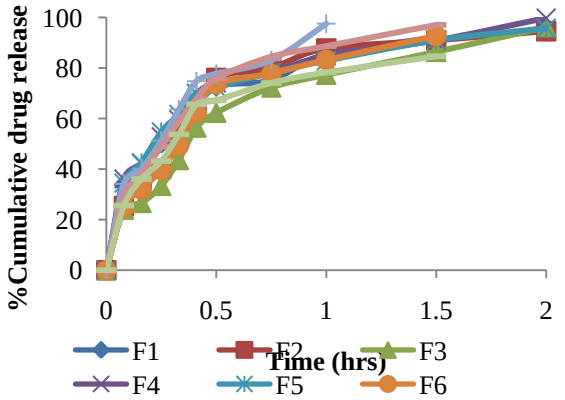

Fig. 1: Comparison graph of *in vitro* drug release profile of formulations F1-F9 containing Paracetamol

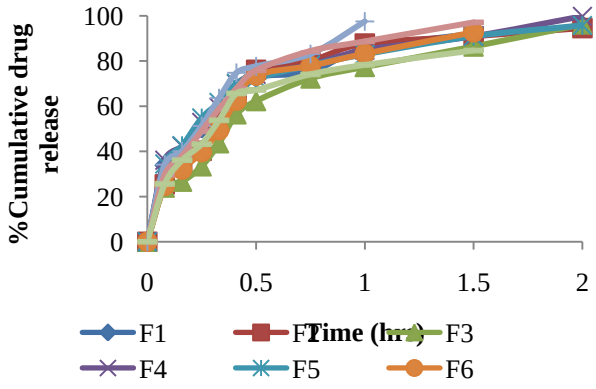

Fig. 2: Comparison graph of *in vitro* drug release profile of formulations F1-F9 containing Metoclopramide hydrochloride

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