

DEVELOPMENT AND EVALUATION OF PARACETAMOL AND METOCLOPRAMIDE HYDROCHLORIDE CHEWABLE TABLETS**Dhruba Sankar Goswami*, Deepak Kumar**

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Goswami**S.D. College of Pharmacy,
Barnala, Punjab-148101.**ABSTRACT**

The present study was aimed to developed and evaluate 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 Aerosil, croscarmellose sodium, croscopolone and neem gum. Maize starch was used as binding agent. Tartrazine was used as coloring agent. Aspartame and Vanilla flavor were used as sweetening agent and flavoring agent respectively. 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 study for all the formulations were studied and were found within the acceptance limits. Formulation F10 containing neem gum (1%) showed best cumulative drug release for Paracetamol 99.550% and for Metoclopramide hydrochloride 98.587% and disintegration time of 40 ± 0.03 secs, emerging as best formulation.

KEY WORDS: Paracetamol, Metoclopramide hydrochloride, Neem 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 or 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, neem gum, croscarmellose sodium, croscopolone, tartrazine, aspartame and vanilla flavor were purchased from Balaji drug, Gujrat, lactose, maize starch, citric acid; sodium starch glycolate, magnesium stearate and talc were purchased from Central Drug House (P) Ltd. New Delhi, Paracetamol was purchased from Sanjay Biological Museum, Amritsar, mannitol was purchased from Rankem, New Delhi and Aerosil was purchased from Hi Media Laboratories (P) Ltd.

Preparation of chewable tablets containing Paracetamol and Metoclopramide hydrochloride

Chewable tablets containing 325 mg Paracetamol and 5 mg Metoclopramide hydrochloride were prepared with a total weight of 500 mg by wet granulation method of different

homogeneous blends containing Aerosil, croscarmellose sodium, croscopolone and neem gum in different ratios individually in order to achieve the desired drug release profile. Drug and other excipients 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 mixture was added to starch paste and obtained wet mass, which was sieved from # 10 mesh sieve. The obtained granules were dried in oven. After drying the granules were passed through # 16 mesh sieves. Then added magnesium stearate and talc as lubricant and glidant 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]

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.

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

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.

$$\text{Bulk density} = W / V_o$$

$$\text{Tapped density} = W / V_f$$

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

$$C.I = 100 (V_o - V_f) / V$$

Hauser's Ratio: It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

$$\text{Hauser's Ratio} = (W / V_t) / (W / V_0)$$

Where, W / V_t = 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 calibrated 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 again (w).

The friability was then calculated by

$$\text{Friability} = 100 (1 - w/w_0)$$

Weight Variation Test: Twenty tablets were selected at random and the average weight was determined.

$$\% \text{ Maximum positive deviation} = (WH - A / A) \times 100$$

$$\% \text{ Minimum negative deviation} = (A - WL / A) \times 100$$

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°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 analyzed against 0.1(N) HCl pH 1.2 as blank at λ max 249 nm and 310 nm using UV spectrophotometer.^[8]

RESULTS

TABLE: 1 Formulation composition of chewable tablets containing Paracetamol and Metoclopramide hydrochloride.

Ingredients	Formulation code					
	F1	F2	F3	F4	F5	F6
Paracetamol	325	325	325	325	325	325
Metoclopramide hydrochloride	5	5	5	5	5	5
Aerosil	5	10	15	---	---	---
Cros carmellose sodium	---	---	---	5	10	15
Lactose	75	70	65	75	70	65
Mannitol	50	50	50	50	50	50
Maize starch	15	15	15	15	15	15
Citric acid	2	2	2	2	2	2
Sodium starch glycolate	3	3	3	3	3	3
Tartrazine	1.5	1.5	1.5	1.5	1.5	1.5
Aspartame	10	10	10	10	10	10
Vanilla flavour	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Purified water	q.s	q.s	q.s	q.s	q.s	q.s

Table: 2 Formulation compositions of chewable tablets containing Paracetamol and Metoclopramide hydrochloride

Ingredients	Formulation code					
	F7	F8	F9	F10	F11	F12
Paracetamol	325	325	325	325	325	325
Metoclopramide hydrochloride	5	5	5	5	5	5
Cros povidone	5	10	15	---	---	---
Neem gum	---	---	---	5	10	15
Lactose	75	70	65	75	70	65
Mannitol	50	50	50	50	50	50
Maize starch	15	15	15	15	15	15
Citric acid	2	2	2	2	2	2
Sodium starch glycolate	3	3	3	3	3	3
Tartrazine	1.5	1.5	1.5	1.5	1.5	1.5
Aspartame	10	10	10	10	10	10
Vanilla flavour	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Purified water	q.s	q.s	q.s	q.s	q.s	q.s

Table: 3 Pre-compression parameters of Paracetamol.

Sl.No	Parameters	Inference	
1.	Appearance	White or almost white	
2.	Melting point	$169 \pm 1.15^{\circ}\text{C}$	
3.	Solubility	In water	Partially Soluble
		In methanol	Freely Soluble
		In Hcl	Spraingly Soluble
4.	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
5.	Assay	98.4%	

Table: 4 Pre-compression parameters of Metoclopramide hydrochloride.

Sl.No	Parameters	Inference	
1.	Appearance	Ligh yellowish	
2.	Melting point	$183 \pm 1.10^{\circ}\text{C}$	
3.	Solubility	In Acetone	Soluble
		In methanol	Partially Soluble
		In Hcl	Soluble
4.	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
5.	Assay	99.5%	

Table: 5 Flow properties of granules of formulations F1-F12

Formulation Code	Bulk density* (gm/cm ³)	Tap density* (gm/cm ³)	Carr's index* (%)	Hausner's ratio*	Angle of repose* (θ)
F1	0.42±0.01	0.42±0.02	15.79±1.12	1.19±0.03	26.62±0.45
F2	0.44±0.02	0.44±0.05	8.33±0.66	1.09±0.02	27.13±0.56
F3	0.53±0.04	0.53±0.04	13.33±0.35	1.15±0.07	26.65±1.23
F4	0.44±0.05	0.44±0.03	8.33±0.56	1.09±0.04	25.50±0.46
F5	0.43±0.01	0.43±0.02	13.51±1.24	1.16±0.05	26.91±1.45
F6	0.42±0.03	0.42±0.01	13.16±0.25	1.15±0.03	27.37±0.64
F7	0.44±0.05	0.44±0.02	16.67±1.23	1.20±0.07	26.70±1.30
F8	0.50±0.02	0.50±0.04	12.50±0.55	1.14±0.05	26.55±0.24
F9	0.50±0.04	0.50±0.04	6.25±1.11	1.07±0.04	27.32±1.10
F10	0.40±0.04	0.40±0.02	12.50±1.54	1.14±0.05	28.40±1.26
F11	0.44±0.01	0.44±0.01	16.67±1.42	1.20±0.03	27.21±0.54
F12	0.42±0.03	0.42±0.05	10.53±1.10	1.12±0.04	27.10±1.42

Table: 6 Diameter, thickness, hardness and %loss in weight of formulation F1-F12

Formulation Code	Diameter* (mm)	Thickness* (mm)	Hardness* (kg/cm ²)	%Loss in wt.**
F1	6.60±0.02	1.80±0.11	4.12±0.42	0.105±0.04
F2	7.00±0.05	1.80±0.21	3.91±0.14	0.215±0.15
F3	7.00±0.06	2.00±0.05	4.54±0.43	0.037±0.06
F4	6.80±0.04	1.60±0.05	4.43±0.16	0.165±0.20
F5	7.00±0.06	1.60±0.14	4.84±0.11	0.365±0.11
F6	6.80±0.05	1.60±0.04	4.27±0.28	0.234±0.30
F7	7.00±0.02	1.60±0.11	3.72±0.68	0.022±0.04
F8	7.00±0.05	1.60±0.24	4.3±0.34	0.014±0.06
F9	6.80±0.02	1.60±0.02	4.87±0.45	0.224±0.04
F10	6.20±0.06	1.60±0.06	4.36±0.64	0.078±0.03
F11	6.20±0.02	1.60±0.21	4.12±0.53	0.356±0.05
F12	6.40±0.04	1.60±0.05	4±0.36	0.213±0.15

Table: 7 %Weight variation, disintegration time, drug content of Paracetamol and drug content of Metoclopramide of formulation F1-F12

Formulation Code	%Weight variation**	Disintegration time (in sec)	Drug content** of Paracetamol	Drug content** of Metoclopramide
F1	0.231±1.11	125±0.03	96.410±0.009	97.447±0.00
F2	0.342±1.04	108±0.01	95.385±0.006	96.170±0.004
F3	0.465±0.34	143±0.04	97.087±0.011	99.640±0.003
F4	0.453±1.53	90±0.03	96.103±0.004	97.872±0.006
F5	0.53±1.10	85±0.05	95.795±0.003	98.723±0.005
F6	-0.075±1.38	110±0.03	97.846±0.018	98.979±0.002
F7	0.347±0.26	78±0.01	96.062±0.006	98.043±0.016
F8	0.642±1.43	74±0.04	97.846±0.031	96.213±0.004

F9	0.224±1.37	69±0.06	97.231±0.023	96.043±0.002
F10	0.456±1.04	40±0.03	98.667±0.006	99.660±0.017
F11	0.354±0.05	47±0.02	98.256±0.007	98.128±0.008
F12	0.335±1.07	55±0.04	97.026±0.005	95.830±0.006

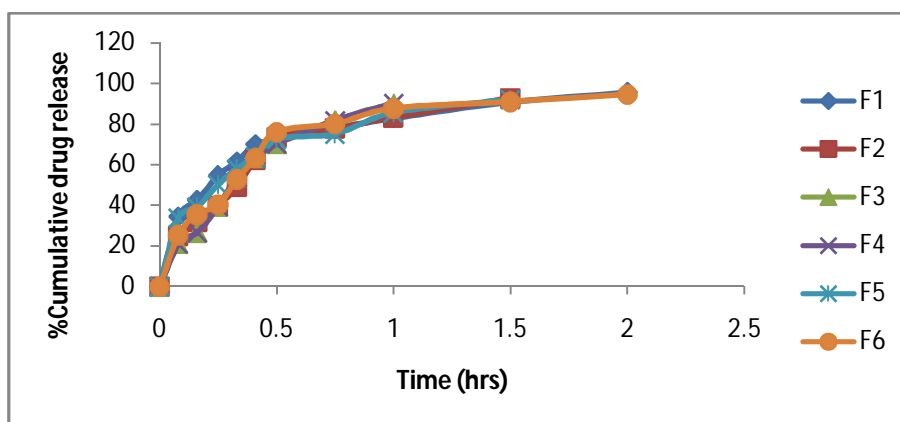


Fig. 1 Comparison graph of *in vitro* drug release profile of formulations F1-F6 containing Paracetamol

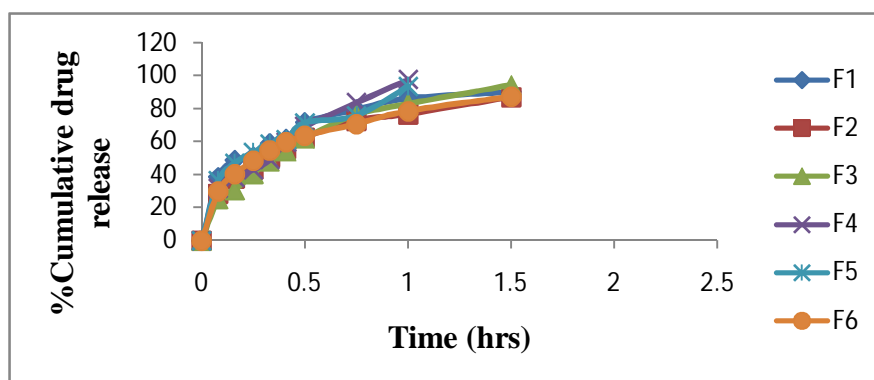


Fig. 2 Comparison graph of *in vitro* drug release profile of formulations F1-F6 containing Metoclopramide hydrochloride.

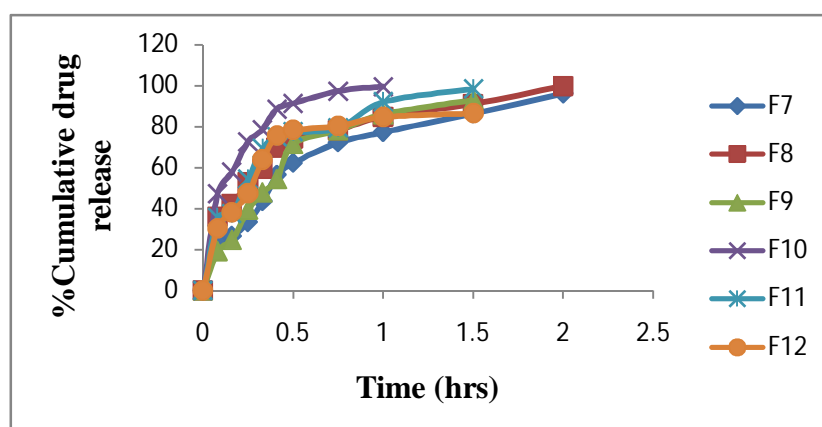


Fig. 3 Comparison graph of *in vitro* drug release profile of formulations F7-F12 containing Paracetamol.

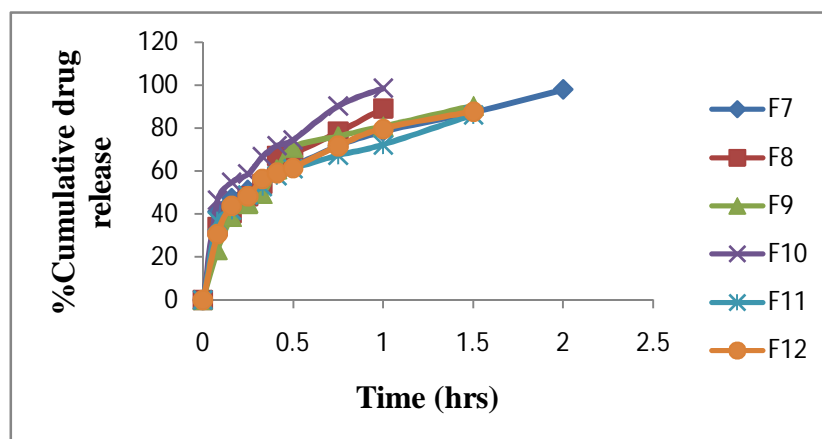


Fig. 4 Comparison graph of *in vitro* drug release profile of formulations F7-F12 containing Metoclopramide hydrochloride

DISCUSSION

The diameter of all formulations ranged between 6.20 ± 0.02 to 7.00 ± 0.06 mm and thickness was in the range of 1.60 ± 0.02 to 2.00 ± 0.05 mm. All the batches showed hardness in the range 3.72 ± 0.68 to 4.87 ± 0.45 Kg/cm². 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 -0.075 ± 1.38 to $0.642 \pm 1.43\%$ complying with Pharmacopoeia specifications ($\pm 7.5\%$). The range of drug content for Paracetamol was 95.385 ± 0.006 to $98.667 \pm 0.006\%$ and for Metoclopramide hydrochloride was 95.830 ± 0.006 to $99.660 \pm 0.017\%$ for all formulations. For all formulations disintegration time was in the range of 40 ± 0.03 to 143 ± 0.04 secs. The results were shown in Table No-6 to 7. All the 12 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 F12 were showed in Figure No-1 to 4. The %drug release of Paracetamol for all formulation was ranges from 86.581% to 99.794% and for Metoclopramide hydrochloride 86.206% to 98.587%.

CONCLUSION

In the present study Paracetamol and Metoclopramide hydrochloride chewable tablet by wet granulation method using polymers like Aerosil, croscarmellose sodium, croscopolvidone and neem gum was developed. Formulation F10 containing neem gum (1%) showed best cumulative drug release for Paracetamol 99.550% and for Metoclopramide hydrochloride 98.587% and disintegration time of 40 ± 0.03 secs, emerging as best formulation.

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