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IN-VITRO STUDY OF FORMULATED PARACETAMOL PLUS CAFFEINE TABLET WITH DIFFERENT BRANDS AVAILABLE IN BANGLADESH

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Abstract

This study aimed to formulate paracetamol with caffeine tablets and comparing them with four local marketed paracetamol with caffeine coated tablets. Different batches numbers selected the samples randomly and the physicochemical experiments were done according to monographs. The tablets were prepared by using wet granulation method. All the coated tablets passed weight variation test as the percentage of weight variation was within USP limits of ± 5% of the average weight. The chemical assay test of all the tablets showed that none had potency less than the required specifications of USP. The in vitro dissolution test results were found within the BP recommended limits for paracetamol 500 mg & caffeine 65mg film coated tablets. The comparative in-vitro study of F_{P+C} with four different brands showed that F_{P+C} has almost comparable characteristics with these brands. This study also proved the physicochemical equivalency of the four different brands.

If any one brand is not available in the market then other three brands can be taken in place of that unavailable brand.

Keywords: *Paracetamol, caffeine, In-vitro study, Dissolution, Physicochemical equivalency*.

Introduction

Paracetamol or acetaminophen is a widely used over-the-counter analgesic and antipyretic drug [1]. It has both analgesic and antipyretic properties and is used for the treatment of mild and moderate pain. Although the precise mechanism of paracetamol has not been established, data suggests that central prostaglandin synthetase inhibition plays a large role [2]. Unlike NSAIDs, paracetamol does not inhibit the peripheral generation of prostaglandins and exhibit a clinical anti-inflammatory effect. Paracetamol does not alter the generation of prostaglandins in gastric mucosa [3] and, therefore, it is particularly suitable for patients with a history of GI disease or on concomitant medication where peripheral prostaglandin inhibition would be undesirable. At present, beside paracetamol, a new paracetamol/caffeine formulation is designed to deliver faster dissolving and more quickly absorbed drug product [4]. Along with paracetamol, the combination product is also available and well established medicine in Bangladesh due to patients' acceptability [5].

Caffeine is a common adjuvant for analgesic drugs such as paracetamol or acetylsalicylic acid [6-9]. The mechanism of action of caffeine is not fully understood, but involves nonselective antagonism of adenosine receptors [10], e.g., by counteracting adenosine, caffeine reduces resting cerebral blood flow between 22% and 30% [10]. Study suggests that caffeine induces changes in mood [11] which are probably due to its psychotropic actions and which may influence pain perception. Recently it has been demonstrated in an experimental pain model that the addition of caffeine 130 mg enhances and prolongs the analgesic effect of paracetamol 1000 mg [12]. Moreover, solubility of paracetamol is increased in the presence of caffeine [13]. Caffeine also accelerates the absorption of paracetamol and therefore provides enhanced and prolonged analgesic activity [14].

The clinical effectiveness exerted by tablet formulation depends on at least two factors such as, the drug must be present in the labeled amount and its availability to the body [15]. The main objective of an oral tablet is to deliver the drug to the human body at certain and defined amount through the gastro-intestinal system for producing therapeutic effect [16]. The formulation of the drug product can have a significant effect on the quality parameters such as weight variation, hardness, friability, disintegration time, dissolution profile etc. This also includes the physiochemical properties of the active ingredients and excipients as well as the procedures used in the manufacturing process [17-18].

Quality of medicine is an absolute necessity in terms of both therapeutic efficacy and safety of the patients. World Health Organization claimed that the manufacturers must undertake responsibility for the quality of the medicines that they manufacturing [19]. About 300 pharmaceutical companies are manufacturing variety of medicines in Bangladesh. Only 3% of the medicines are imported, the remaining 97% come from local companies [20]. Bangladesh has made agreeable positive developments in the pharmaceutical sector. As a result it is now exporting drugs to many countries across the world including the United States [21]. The principal criteria for a quality medicine product are safety, potency, efficacy, and stability [22].

This work will increase awareness among the health practitioners and medicine control authority so that, pharmaceutical manufacturers are forced by them to manufacture quality medicine. Therefore the present study was designed to formulate paracetamol plus caffeine tablet and its in vitro study with currently marketed other different available brands.

Methods

Materials

Paracetamol powder, Caffeine powder was received as a gift from Desh Pharmaceuticals ltd., Mirpur, Dhaka. Poly vinyl pyrrolidone - PVP K30 (Yuking Chemtech Co. Ltd., China), Microcrystalline cellulose (Avicel PH 102; Mingtai Chemical Co Ltd., Taiwan), Sodium starch glycolate (Yung Zip Chemical Industries, Taiwan), Magnesium stearate (Coin Chemical Industrial Co. Ltd., Taiwan), Talcum (Micron, Pakistan), Colloidal silicon dioxide (Cab-O-Sil; Cabot Corporation, Germany), Hydroxy propyl methyl cellulose (DOW Chemicals, Japan),Titanium dioxide (Shanghai Hychem Co., Ltd, China) , Isopropyl alcohol (Lee Chang Yung Chemical

Industry Corporation, Taiwan), Methylene chloride (ICI, UK.).

Different brands of Paracetamol with Caffeine Tablet

Four different brands of Paracetamol with Caffeine film coated tablets as shown in Table: 1 were evaluated.

Methods:

Formulation of Paracetamol with Caffeine tablets

Paracetamol with Caffeine tablets were prepared by wet granulation method according to the formulation given in Table 2. The self-designed formulation was coded as **F_{P+C}**.

Method used for tablet formulation

The active pharmaceutical ingredient (API) and all the excipients were weighed accurately. Paracetamol powder was passed through oscillating granulator having stainless steel mesh # 16. PVP K_{30} & Maize starch was used as a binder solution for granulation and dissolved in sufficient quantity of purified water. Paracetamol, half part of Avicel pH102 & starch glycolate powder was granulated by using PVP K_{30} & starch binder solution. The wet mass obtained from granulation was passed through rotary granulator having mesh # 8. These granules were then dried in a hot air circulation oven at about 50°C. The dried granules were passed through oscillating granulator-having mesh # 12. These granules were mixed with rest part of sodium starch glycolate, avicel pH 102 passed through mesh # 16 and finally lubricated with magnesium stearate, talcum & Caffeine passed through mesh # 40. The powder blend was mixed well for about 15 minutes.

Evaluation of powder blend

The prepared powder blend was evaluated for following different parameters.

Bulk density

Bulk density (ρb) indicates the ratio of total mass of powder to the bulk volume of powder. It was determined by pouring the accurately weighed amount (M) of the powder blend into graduated cylinder and the initial volume of packing also called as bulk volume (Vb) was measured. The bulk density was then calculated by the following formula [23]

$$\rho b = M / Vb$$

Tapped density

Tapped density (ρt) indicates the ratio of total mass of the powder to the tapped volume of powder.

It was determined by using method described by Levis [23]

$$\rho t = M / Vt$$

Carr's compressibility index

Carr's compressibility index is used to indicate the compressibility of a power. It is named after the scientist Ralph J. Carr, Jr.

It was calculated by the formula given below:

$$\text{Carr's Index} = [(\rho t - \rho b) / \rho t] \times 100$$

Hausner's ratio

Hausner's ratio (H) indirectly expresses an ease of flow of powder blend.

It was calculated by the formula given below:

$$\text{Hausner's ratio (H)} = \rho t / \rho b$$

Carr's compressibility index and Hausner's ratio were determined by using standard method [24].

Angle of repose

The angle of repose (θ) is used to measure the friction forces in the powder blend or granules. It indicates the maximum angle which is possible between the surface of the pile of powder blend or granules and the horizontal plane.

Related to

-The density,

-surface area,

-shapes of the particles, and

-The coefficient of friction of the material.

The angle of repose can range from 0° to 90°.

It was determined by using method described by Wells [25].

Angle of repose was calculated by the formula given below:

$$\tan \theta = h/r$$

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

Moisture content

The moisture content of the powder blend was determined by placing a specific quantity (5 gm) of the powder blend in the moisture analyzer (MA-45, Sartorius) at 105°C.

Compression of granules:

The granules were compressed on rotary press machine ZP-19 (Model No. ZBC92005, China) having 12 mm concave punches. Round biconvex shaped core tablets were produced with an average hardness of 10 kg/cm2, friability 0.4% and disintegration time 5 minutes.

Film coating of core tablets:

Paracetamol plus caffeine core tablets were film coated according to the formulation given in Table: 3.

Procedure of film coating:

HPMC and talcum were added to isopropyl alcohol under constant stirring and mixed for about 15 minutes. PEG & Titanium dioxide was dissolved in small quantity of isopropyl alcohol and filtered into solution containing the coating material. Finally Methylene chloride was added to this solution and mixed well. The core tablets of **F_{P+C}** were put into the coating pan and heating was started with hot air. Coating was done by spraying the coating solution on core tablets with continuous heating.

Evaluation of F_{P+C} film coated tablets:

The film coated tablets of formulation **F_{P+C}** and the selected brands were evaluated according to specifications of U.S.P.

Thickness and diameter test

The thickness and diameter of the tablets were determined by using slide calipers. Thickness and diameter of ten tablets was determined randomly. It was expressed in mm.

Hardness test / crushing strength

The crushing strength was determined with a tablet hardness tester (Monsant, U.K). Five tablets from **F_{P+C}** and each brand were selected randomly and then the pressure at which each tablet crushed was recorded and the hardness value obtained [26].

Weight variation test

10 tablets from each brand and **F_{P+C}** tablet was weighed individually with an analytical weighing balance. The average weights for each effervescent tablet and the percentage deviation from the mean value were obtained [27].

Friability test

The Roche Friabilator consists of a plastic chamber divided into two parts and revolves at 25 rpm. A fixed number of tablets are weighed, placed in the tumbling chamber and rotated for four minutes of 100 revolutions. During each revolution the tablets fall from a distance of six inches to undergo shock. After 100 revolutions the tablets are again weighed. The loss in weight indicates the friability [28].

Disintegration test

The disintegration test was carried out in accordance to **USP 30** specifications by using Disintegration Tester (Model No.DT-122, Galvano Scientific, Pakistan). Six tablets from **F_{P+C}** and each brand were subjected to disintegration test. One tablet was placed in each of the six tubes of the basket. Then disks were added to each tube of the basket. The temperature was maintained as a motor driven device helps to move the basket up down through a distance of 5-6 cm at a rate of 28-32 cycles per minutes.

The time taken for the last tablet to disintegrate completely was recorded in minutes.

Chemical assay

The chemical assay of film coated tablets of **F_{P+C}** and each brand was carried out according to USP 30 by using UV-Visible Spectrophotometer (Model No. 1800, Shimadzu, Japan). The assay was performed in triplicate.

Procedure:

a) Paracetamol

Sample Preparation:

Grind 10 tablets into fine powder. Take 26 mg of this powder in a 250 ml separating funnel, add 25 ml water and 10 ml of 0.1M sodium hydroxide and mix well. Extract with four 25-ml quantities of chloroform, washing each extract with the same two 10-ml quantities of 0.1M sodium hydroxide. Collect both of aqueous and organic layers separately. Take the aqueous layer in a 100ml volumetric flask and add 0.1M sodium hydroxide up to the volume. Mix, filter and take 5 ml filtrate in a 100 ml volumetric flask. Add 0.1M sodium hydroxide up to volume and mix well. This is sample solution.

Standard Preparation:

Take 20mg standard Paracetamol in a 100ml volumetric flask and add 0.1M sodium hydroxide up to the volume and mix. Take 5ml of this solution in a 100ml volumetric flask, add 0.1M sodium hydroxide up to volume and mix well. This is standard solution.

Measure the absorbance of sample and standard solution at 257 nm of an UV-Visible spectrophotometer using 0.1M sodium hydroxide as blank solution.

Calculate the amount of Paracetamol in test sample by using the following equation

$$Q = \frac{A \times Cst \times P \times W}{Ast \times C} \text{ mg}$$

Where,

Q = Amount of Paracetamol in tablet.

A = Absorbance of sample solution.

Ast = Absorbance of standard solution.

C = Concentration of sample solution.

Cst = Concentration of standard solution.

P = Potency of standard.

W = Average weight of tablet.

b) Caffeine

Sample Preparation:

Grind 10 tablets into fine powder. Take 250mg of this powder in a 250 ml separating funnel, add 25 ml water and 10 ml of 0.1M sodium hydroxide and mix well. Extract with four 25-ml quantities of chloroform, washing each extract with the same two 10-ml quantities of 0.1M sodium hydroxide. Collect both of aqueous and organic layers separately. Take chloroform layer in a 100 ml volumetric flask, add chloroform up to the mark and mix. Take 2ml from this solution in a 50 ml volumetric flask, add chloroform up to mark and mix well. This is sample solution.

Standard Preparation:

Take 25mg standard Caffeine in a 100 ml volumetric flask, add chloroform up to the mark and mix. Take 2ml of this solution in a 50 ml volumetric flask, add chloroform up to mark and mix well. This is standard solution.

Measure the absorbance of sample and standard solution at 276 nm of an UV-Visible spectrophotometer using chloroform as blank solution. Calculate the amount of caffeine in test sample by using the following equation:

$$Q = \frac{A \times Cst \times P \times W}{Ast \times C} \text{ mg}$$

Where,

Q = Amount of Caffeine in tablet.

A = Absorbance of sample solution.

Ast = Absorbance of standard solution.

C = Concentration of sample solution.

Cst = Concentration of standard solution.

P = Potency of standard.

W = Average weight of tablet.

In-vitro Dissolution Studies

Medium : Phosphate Buffer pH 5.8, 900 ml

RPM : 50

Apparatus : Dissolution Test Apparatus USP

Time : 45 minutes

ISSN: 1827-8620

Procedure: Introduce 900 ml of Phosphate Buffer pH 5.8 into every of the six of the apparatus. Warm the dissolution medium to between 36.5°C and 37.5°C.

Place one tablet each in six of the vessels in the six vessels. Allow the tablet to sink to the bottom of the vessel prior to rotation of the paddle. Operate the apparatus immediately at the rotation specified above. Take samples after 45 minutes. Withdraw the samples from a point halfway between the surface of the dissolution medium and the top of the rotating blade, not less than 10 mm from the wall of the vessel. Filter the samples at 36.5°C to 37.5°C. Filter the resulting solution through a filter paper rejecting the first 25ml (approx.) of filtrate.

[**Buffer preparation:** Take 2.5L of 0.1N sodium hydroxide in a large beaker. Adjust the pH of the solution at 5.8 by adding Phosphoric Acid drop wise simultaneous stirring the solution with a stirrer.]

[**For Paracetamol**]

Take 2 ml of the filtrate sample in 100 ml volumetric flask, dilute to 50 ml with Phosphate Buffer pH 5.8, and shake well & up to volume.

[**For Caffeine**]

Take 20 ml of the filtrate sample in 100 ml volumetric flask, dilute to 50 ml with Phosphate Buffer pH 5.8, and shake well & up to volume.

Standard Solution: [Paracetamol]

Weigh accurately 50mg of Paracetamol WS in a 100 ml volumetric flask. Add 70 ~ 80 ml of Phosphate Buffer pH 5.8. Shake to dissolve and sonicate for 5 minutes. Dilute to volume with the same and mix well.

Transfer 2 ml of this solution to 100 ml volumetric flask, dilute to with the same solvent. This is standard solution.

Standard Solution: [Caffeine]

Weigh accurately 28mg of Caffeine WS in a 100 ml volumetric flask. Add 70 ~ 80 ml of Phosphate Buffer pH 5.8. Shake to dissolve and sonicate for 5 minutes. Dilute to volume with the same and mix well. Transfer 5 ml of this solution to 100 ml volumetric flask, dilute to with the same solvent. This is standard solution.

Calculation:

[**For Paracetamol**]

The chromatographic conditions described under Assay for paracetamol may be use. [BP]

Calculate the dissolution tolerance of each of the sample using the following formula:

$$\% = \frac{Au}{As} \times \frac{900 \times 100}{500 \times 2} \times \frac{50 \times 2}{100 \times 100} \times Pst \times 100$$

Where,

A_s = Absorbance of the sample solution

A_{st} = Absorbance of the standard solution

P_{st} = Potency of paracetamol working standard

Calculation:

[**For Caffeine**]

The chromatographic conditions described under Assay for caffeine may be use. [BP]

Calculate the dissolution tolerance of each of the sample using the following formula:

$$\% = \frac{Au}{As} \times \frac{900 \times 50}{65 \times 10} \times \frac{28 \times 5}{100 \times 100} \times Pst \times 100$$

Where,

A_s = Absorbance of the sample solution

A_{st} = Absorbance of the standard solution

P_{st} = Potency of caffeine working standard

Results and discussion:

Paracetamol is a widely used for the treatment of mild and moderate pain. At present a new paracetamol plus caffeine formulation is designed to deliver faster dissolving and more quickly

absorbed drug product by using wet granulation method.

The self-designed formulation was coded as F_{P+C}. The prepared granules blend was evaluated for different parameters before compression. Table 4 shows the results of evaluation parameters of powder blend of F_{P+C}.

The angle of repose less than 30° indicates good flow properties while an angle of more than 40° shows poor or absent flow [29]. The result of angle of repose (29.23°) indicated good flow properties of the powder blend. There is no large difference in the values of bulk density and tapped density of the powder blend. The data of both bulk and tapped densities was used to calculate Carr's compressibility index and Hausner's ratio. Lower Carr's index (<20%) indicates better flow properties of the powder blend than higher ones (>20%) [30]. Lower Hausner's ratio (<1.25) indicates better flow properties of the powder blend than higher ones (>1.25)[31]. The compressibility – flow ability correlation data indicated good flow of the powder blend with less moisture content.

The lubricated powder blend was compressed on compression machine. The core tablets were film coated. The film coated tablets of **F_{P+C}** and four different brands were evaluated for various parameters according to USP. All the tablets of **F_{P+C}** and different brands were four within the acceptable range of USP for different quality control tests.

The average hardness of tablets was determined by using Monsanto hardness tester. The tablets of **F_{P+C}** and different brands possessed good mechanical strength with sufficient hardness. The maximum hardness (14.26 Kg/cm2) was observed for Paracetamol Extra while minimum hardness (9.74 Kg/cm2) was shown by Ace plus as in Table 5.

Uniformity of weight does serve as a pointer to good manufacturing practices (GMP) as well as amount of the active pharmaceutical ingredient (API). Paracetamol with caffeine contained in the formulation. All the brands complied with the compendia specification for uniformity of weight, which states that for tablets weighting less than 730 mg, weight of not more than two tablets should not differ from the average weight by more than 5%. From the all brand result and Formulated **F_{P+C}** tablet are all comply with monograph requirement. In USP pharmacopeia tablet must not be above 110% or below 90% of the average weight and from (table 5), the deviation percent is more indication for content uniformity and all brands comply content uniformity and Formulated **F_{P+C}** tablet too.

The compendia specification for friability is 1% friability for all the brands was below 1% and from (table 5), all the brands comply with monograph[32]

Disintegration is the breakdown process of a tablet into smaller particles and is the first step towards dissolution. It could be directly related to dissolution and subsequent bioavailability of a drug. A drug in corroborated in a tablet is released rapidly as the tablet disintegrates a critical step for immediate release dosage forms because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine. All the brands complied with compendia specifications for disintegration. The BP specification is that uncoated tablets should disintegrate within 15 min and film coated tablets should disintegrate within 30min while USP specifies that uncoated and film coated tablets should disintegrate within 30min. The disintegrate of four brands & Formulated **F_{P+C}** of Paracetamol with Caffeine was determined and the observed results are shown in the table-5.

Similarly the chemical assay of tablets was carried out in accordance to USP 30. There was no considerable difference in chemical assay of **F_{P+C}** and the four brands. The results of chemical assay paracetamol were in the range of 100.49% (Ace plus) to 99.60% (Pyrenol) and Caffeine were in the range of 99.85% (Ace plus) to 99.50% (Pyrenol).

The in vitro dissolution test was carried out in accordance to USP 30. There was no considerable difference in dissolution data of **F_{P+C}** and different brands. The maximum average dissolution (Paracetamol: 99.11%) & (Caffeine: 99.28%) was observed for Ace plus while the minimum average dissolution (Paracetamol: 96.54%) & (Caffeine: 96.25%) was shown by Paracetamol Extra (Tab.5). It has been reported that dissolution rate has a direct effect on the bioavailability profile of tablet dosage

forms because it can be used to determine the pattern of drug release in vivo.

Conclusion

The monitoring and quality control test of medicines in pharmacies randomly to ensure the good storaging conditions and to ensure drug's effectiveness and patient confidence.

The comparative in-vitro study of the self-designed formulation F_{P+C} with four different brands namely Ace plus®, Pac®, Paracetamol Extra®, Pyrenol® showed that F_{P+C} has almost comparable characteristics with these brands. The study also proved the physicochemical equivalency of the four different brands.

So if one brand is not available in the market then any of the other three brands can be taken in place of that unavailable brand.

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Table 1: Four different brands of Paracetamol with Caffeine film coated tablets.

Brand name	Manufacturer	Batch No.	Expiry date	Max. Retail Price per unit [Tk]
Pyrenol tablet	Delta Pharmaceuticals ltd.	3052	March, 2020	2.50
Paracetamol Extra Tablet	Albion Lab. Ltd	4476	August, 2020	2.50
Pac Tablet	IBN Sina	9046	July, 2020	2.50
Ace plus Tablet	Square Pharmaceuticals Ltd.	1560	June, 2020	2.50

Table 2: Formulation ($\mathbf{F_{P+C}}$) of Paracetamol with Caffeine tablets

Ingredients	**Quantity/tablet (mg)**
Paracetamol BP	500.00 mg
Caffeine BP	65.00 mg
Maize Starch BP	70.45 mg
Poly vinyl pyrrolidone BP	3.00 mg
Methyl paraben sodium BP	0.50 mg
Propyl paraben sodium BP	0.05 mg
Sodium starch glycolate BP	5.00 mg
Magnesium stearate BP	2.00 mg
Purified Talc BP	4.00 mg

Table 3: Formulation of film coating material.

Hydroxy propyl methyl cellulose (HPMC) BP	3.00 mg
Titanium dioxide BP	1.50 mg
Purified Talc BP	1.00 mg
Isopropyl alcohol BP/Ph. Grade	55.00 mg
Methylene chloride BP/Ph. Grade	70.00 mg
PEG -6000 BP	1.00 mg

Table 4: Evaluation of powder blend of $\mathbf{F_{P+C}}$

Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hauser's ratio	Moisture content (%)
29.23	0.682	0.749	8.945	1.098	2.2

Table 5: compression of quality control test between four brands of paracetamol + caffeine with formulated paracetamol + caffeine [$\mathbf{F_{P+C}}$] tablets

Name of Brand	Average hardness (Kg/cm2)	Average Weight	Friability [%]	Average disintegrate time (min)	Dissolution data (%)		Assay [%]	
					Paracetamol	Caffeine	Paracetamol	Caffeine
Formulated [F_{P+C}] Tablet	10.25	720	0.94	14.25	97.25	96.35	100.02	99.59
Pyrenol Tablet	13.31	680	0.86	11.56	96.70	97.51	99.60	99.50
Paracetamol Extra Tablet	14.26	740	0.67	10.24	96.54	96.25	100.09	99.52
Pac Tablet	11.25	715	0.83	11.12	99.06	98.98	99.75	99.57
Ace plus Tablet	9.74	650	0.24	13.74	99.11	99.28	100.49	99.85