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Research Article

Evaluation of quality control parameters on various brands of pediatric Paracetamol Suspension

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ABSTRACT

Paracetamol (Acetaminophen) is a widely used OTC Analgesic, antipyretic medicine available as compressed tablets, suspension, and emulsion. It is also very commonly used for children and is available without a prescription. It is marketed and manufactured by a number of pharmaceutical companies worldwide. In the present study we randomly selected three brands of Paracetamol suspension (Brand X, Brand Y and Brand Z) used for Pediatric purpose. Further, various quality control tests of suspensions were performed like, Appearance, Sedimentation volume, Particle size determination, Drug content, Dissolution studies as per the official monographs B.P, U.S.P to evaluate & compare these three different brands. As a result was this study we found that all the three brands met the specifications laid down in the official monographs. They differ only slightly in terms of various quality control parameters, however brand Y had faster dissolution rate and drug content, its % drug release was more, its sedimentation volume was also higher reflecting better physical stability than the other two brands at the same time.

Keywords: Dissolution studies; Drug content; Particle size determination; Paracetamol suspension; Pediatric use; Quality control tests; Sedimentation volume.

INTRODUCTION

Paracetamol (Figure 2) is an over-the-counter non-steroidal anti-inflammatory drug (NSAID) which is commonly used as an analgesic and antipyretic agent but has weak anti-inflammatory effects since it has poor ability to inhibit cyclooxygenase (COX) in the presence of high concentration of peroxides, as are found at sites of inflammation. It is used to relieve mild to moderate pain from headaches, muscle aches, menstrual periods, colds and sore throats, toothaches, backaches, osteoarthritis, and reactions to vaccinations (shots), and to reduce fever.(Royal Children, 2013).

It is available in a tablet, capsule, suspension or solution (liquid), drops, extended-release (long acting) tablet, orally disintegrating tablet, suppository, intravenous, and intramuscular form. Paracetamol is generally safe and well tolerated for human use at recommended doses. It also has a low incidence of gastrointestinal side effects at therapeutic doses in contrast to the NSAIDs (AK Nayak, 2010). Besides its use for adults, it is also very commonly used for children and often without prescription. Raised temperature is not always a bad thing as it helps to strengthen the immunity but it makes children feel very uncomfortable.

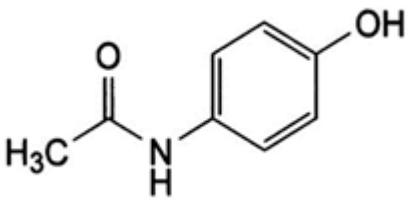

Figure 1: Structure of Paracetamol

Posology and method of administration

For oral administration only

3- 12 months	2.5- 5ml
1- 5 years	5- 10ml
6- 12 years	10- 20ml

These doses may be repeated every 4- 6 hours when necessary with a maximum of 4 doses in 24 hours.

Adults and children over 12:- 20- 40ml every 4- 6 hours to a maximum of 4g daily.

If pyrexia develops after immunization, a child can be given a dose of Paracetamol followed, if necessary, by a second dose 4- 6 hours later. The dose of Paracetamol for post immunization pyrexia in an infant aged 2-3 months is 60mg (2.5ml of the 120mg/5ml presentation); an oral syringe can be obtained from any Phar-

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macy to give the small dose volume required. The parents should be warned that if the pyrexia persists after the second dose medical advice should be sought. (B.P, 2001)

Interaction with other medicinal products and other forms of interaction

The hepatotoxicity of Paracetamol, particularly after over dosage, may be increased by drugs which induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants and alcohol. The speed of absorption of Paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of Paracetamol with increased risk of bleeding; occasional doses have no significant effect. Regular use of Paracetamol possibly reduces metabolism of antiviral drug Zidovudine (increased risk of neutropenia).

Classification/types of suspensions

Pharmaceutical suspensions may be defined as coarse dispersions in which insoluble solids are suspended in a liquid medium. The liquid medium is usually water or a water based vehicle. The insoluble solid may have size range from 10 to 1000µm. Suspensions are also called heterogeneous systems, or more precisely biphasic systems. They can be classified as under:-

1) Based on proportion of solid particles a) Dilute suspensions (2 to 10% w/v solid) b) concentrated suspensions (50% w/v solid)

2) Based on electrokinetic properties of solid particles a) flocculated suspensions b) deflocculated suspensions.

3) Based on general classes a) oral suspensions b) externally applied suspensions c) parenteral suspensions

Assesment of quality control parameters

Quality is a combination of all the characteristics of a product that determine the degree of acceptability of the product. The PMA (Pharmaceutical Manufacturing Association) says that the quality of a product is its degree of possession of those characteristics designed and manufactured with and which contribute to the performance of extended functions when the product is used as directed. The central idea of Quality Control is that quality must be built into the product during research and development and production. It the responsibility of pharmaceutical company to design tests and procedures to produce dosage form that contains exact quantity and quality of drugs, which is acceptable, reproducible, convenient and elegant. (Lachman L et al., 2012). It was found that only a small fraction of drugs marketed and utilized as therapeutic agents in children are actually clinically evaluated. The majority of other drugs are either not labeled or inadequately labeled, for use in pediatric patients. Thus the absence of critically safe, suitable medicine poses significant risk to a large vulnerable population. The pediatric population is made up of a large range of individuals with varied physical size, weight and stage of physiological development (USP, 2003). Thus it becomes even more necessary to evaluate the formulations for children as sometimes even the excipients may even become unsuitable for children. The present study evaluates and compares the various quality control parameters for three marketed formulations of Paracetamol suspension which are very commonly prescribed by physicians. For the purpose of study they were labeled as Brand X, Y, and Z (Terry B.Ernest et al., 2007)

MATERIAL AND METHODS:-

Study design

Three commercially available Paracetamol suspensions, 5ml of which contains 250 mg of Paracetamol I.P, were assessed for *in-vitro* quality control parameters like Sedimentation volume, Particle size determination, Drug Content, Dissolution, Viscosity. The study was done by performing various test procedures associated to assess the quality of suspensions. All the brands were purchased from the various retail pharmacies in Lucknow area.

Instruments used

Dissolution: Dissolution apparatus II i.e. paddle apparatus Veego, VDA-6DR UV-Spectrophotometer: Model UV-1800, Shimadzu corporations Kyoto Japan.

Viscosity: Brookfield Viscometer, Model No-DV III Ultra

Analytical balance: Sartorius, BT 2245.

For ethical and legal purposes the randomly selected samples of Pediatric Paracetamol Suspension were codified as X, Y, Z so that the identity of the manufacturer and marketing company could not be revealed.

Appearance

The sample was observed for uniformity, any coagulated materials, flocculation etc.

Sedimentation volume

20 ml of suspension was taken in a measuring cylinder. The particles were allowed to sediment and measuring cylinder left undisturbed. The weight of the sediment was observed and it was noted after every 10 minutes till the sediment height ceases to change. Sedimentation Volume was calculated as under. This procedure was repeated for all the three brands of test suspensions.

$$Sedimentation\ Volume = \frac{Ultimate\ height\ of\ sediment\ (V_u)}{Initial\ height\ of\ suspension\ (V_0)}$$

Particle size distribution

1. A drop of suspension was placed at the center of the glass slide and a drop of water was mixed to it.

2. The slide was mounted on the microscope and observed with a calibrated eye-piece micrometer.
3. The particle diameter (for circular particles) and particle length & width (for asymmetric particles) was measured and recorded for at least 300 particles.
4. The data was represented as size-frequency distribution curve and the average particle size was calculated.

Calibration of eye-piece micrometer

1. The eye piece micrometer and the stage micrometer were mounted on microscope.
2. The first line of both eye-piece and stage micrometer should coincide by visualizing and were so adjusted.
3. The number of divisions of both the micrometers between the coinciding points was counted.
4. The Least Count of the instrument was calculated.

Dissolution

Dissolution test was conducted using a six flask bath dissolution apparatus. The medium used was phosphate buffer (900ml at 37±0.5°C) of pH 7.4. Rotational speed of the apparatus was held constant at 100 revolutions per minute. 10ml of sample was withdrawn at a predetermined time intervals (10, 20,30,45,60 minutes) and after the necessary dilutions the sample was analyzed for Paracetamol by measuring their absorbance at 254 nm. This procedure was repeated for all the three brands of suspensions.

Drug content

1 ml of suspension was withdrawn and the volume was made up to 10 ml with buffer. 0.1 ml of the above solution was taken and its volume was made up to 100ml. Further 1ml of this solution was made up to 10 ml. Absorbance was measured at 254 nm. Percentage drug content was calculated for all the three brands of suspensions.

Viscosity measurement

The Viscosity was calculated using Brookfield Viscometer. Spindle no 31 was selected, sample was then placed in Sample cup. Spindle was dipped in the sample. At rpm 25 to 30 motor reading were noted for all the three brands of suspensions.

RESULTS AND DISCUSSIONS

Appearance

All the three suspensions were uniform, no breaks or coagulated particles were seen.

Sedimentation volume

The sedimentation volume of the formulations were calculated and were compiled as in Table 1

Particle size determination

Calibration of eye-piece micrometer

1 div. of eye-piece micrometer = 1.33 divisions of stage micrometer.

Particle size determination of various formulations

Particle size determination of various formulations were calculated and the results were compiled as in Table 2. A graph was plotted between mean particle size and the formulations as shown in Figure 3.

Drug content determination

Calibration curve of Paracetamol

Calibration curve of Paracetamol was tabulated as in Table 3 and the calibration curve was plotted as shown in Figure 4.

Drug content determination in various formulations

The % Drug content determination was done in various formulations and the results were compiled as in Table 4. The figure to depict the same is shown in Figure 4.

Drug dissolution determination

The percentage release of Paracetamol was determined in different formulations and the result were compiled as in Table 5. The % drug release with time was plotted as a graph and the results were shown in Figure 4

Viscosity determination

The viscosity of different formulations were calculated in centipoise and the results were compiled in Table 6.

Paracetamol 120mg/5ml Oral Suspension contains the active ingredient Paracetamol, which is an analgesic (relieves pain) and an antipyretic (lowers your temperature when you have a fever). Paracetamol 120mg/5ml Oral Suspension is used to treat mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains, and aches and pains. It may also be given to bring down fever and to help relieve the symptoms of cold and flu. The various Quality Control tests are:- Appearance, Photo microscopic examination, Color, odor and taste, Density, pH value,Clarity testing, Pourability, Viscosity,Rheology, Zeta potential measurement, Drug content uniformity, Particle size measurement, Sedimentation rate and sedimentation volume, Redispersibility,Potency test, Preservative effectiveness, Compatibility with primary container-closure system(AK Nayak, 2010; ML Elaine et al., 2011)

Appearance:- The appearance in a graduated glass cylinder or transparent glass container is noted. It is checked for Uniformity of color and appearance of the sediment, any breaks or air pockets in the sediment,any coagulated material adhering to the inside wall of the container. Photo microscopic examination:- The microscope can be used to estimate and detect changes in particle size distribution and crystal shape.

Table 1: Determination of sedimentation volume of formulations

S.No.	Brand	V_u	V_0	$F= V_u/ V_0$
1	X	1 ml	10 ml	0.1
2	Y	3 ml	10 ml	0.3
3	Z	1 ml	10 ml	0.1

Table 2: Particle size determination of various formulations

S.No.	Class Interval	Frequency (N)			Midpoint of Class interval (X)			N*X		
		Brand X	Brand Y	Brand Z	Brand X	Brand Y	Brand Z	Brand X	Brand Y	Brand Z
1	**31-60**	105	105	100	45.5	45.5	45.5	4777.5	4777.5	4550
2	**61-90**	85	80	82	75.5	75.5	75.5	6417.5	6040	6191
3	**91-120**	85	95	91	105.5	105.5	105.5	8967.5	10022.5	9600.5
4	**121-150**	25	15	20	135.5	135.5	135.5	3387.5	2032.5	2710
5	**151-180**	0	5	7	165.5	165.5	165.5	0	827.5	1158.5
ΣN=		300	300	300						
ΣNX=								23550	23700	24210
Mean Size (µm) = ΣNX/ ΣN								78.5	79	80.7

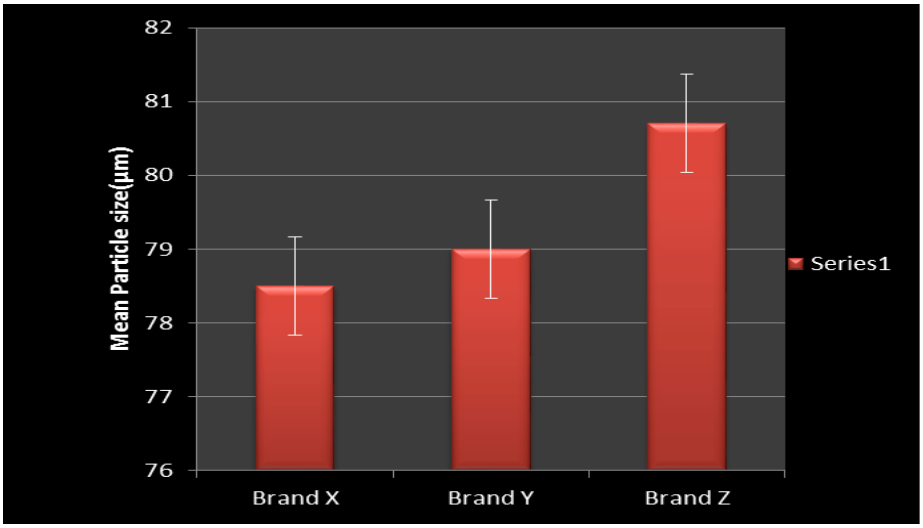

Figure 2: Comparison of particle size of various formulations

Table 3: Calibration curve of Paracetamol

S.No.	Concentration (µg/ml)	Absorbance
1	2	0.166
2	4	0.268
3	6	0.312
4	8	0.408
5	10	0.500
6	12	0.640
7	14	0.730
8	16	0.880
9	18	0.965
10	20	1.009

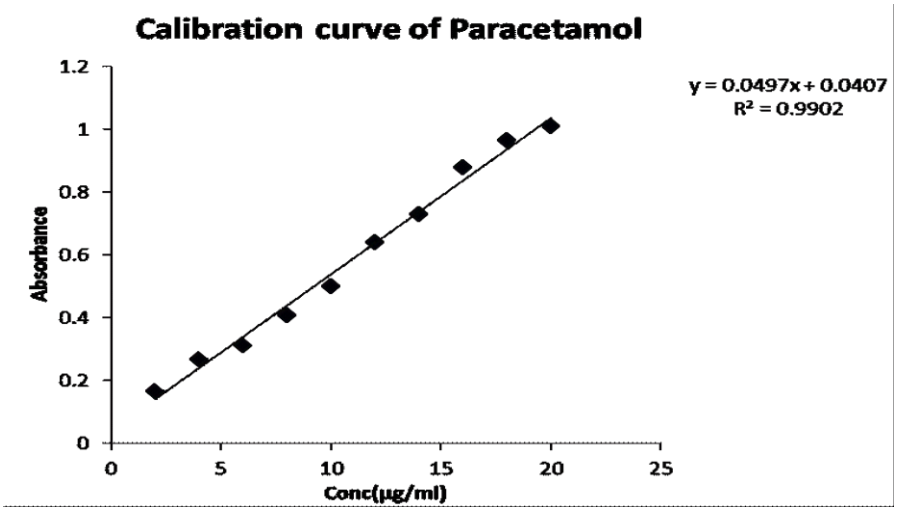

Figure 3: Calibration curve of Paracetamol

Table 4: Drug content determination in various formulations

S.No	Brand	Absorbance recorded	Conc(µg/ml)	%Drug Content
1	X	0.127	1.77	73%
2	Y	0.135	1.938	80%
3	Z	0.132	2	80%

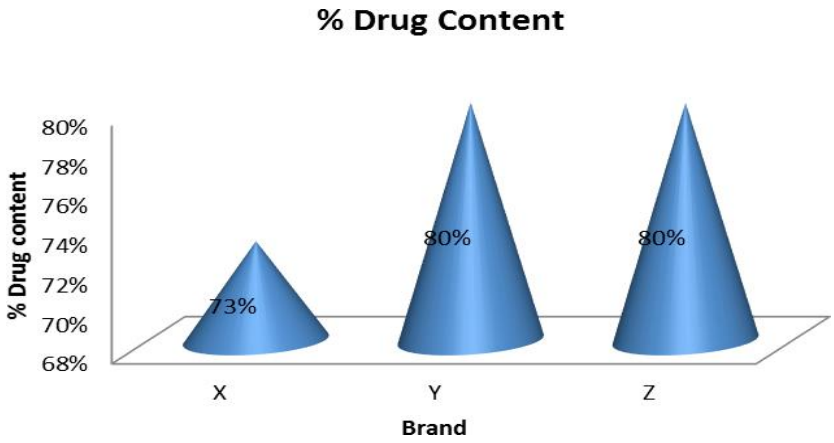

Figure 4: Drug content determination in various formulations

Table 5: Drug dissoluton determination in various formulations

Time (min)	% release of Paracetamol		
	Brand X	Brand Y	Brand Z
10	42.97	45.61	47.07
20	49.43	47.75	58.48
30	63.21	66.73	61.71
40	81.12	82.95	81.40
50	81.42	83.72	81.40
60	85.21	88.34	85.10

Its usefulness can be enhanced by attaching a Polaroid type camera to the microscope to permit rapid processing of photomicrographs. This can be used to distinguish between flocculated and non-flocculated particles and to determine changes in the physical properties.

Color, odor and taste:- These characteristics are especially important in orally administered suspensions. Variation in color often indicates poor distribution and/or differences in particle size. Variation in taste, especially of active constituents can often be attributed to changes in particle size, crystal habit and

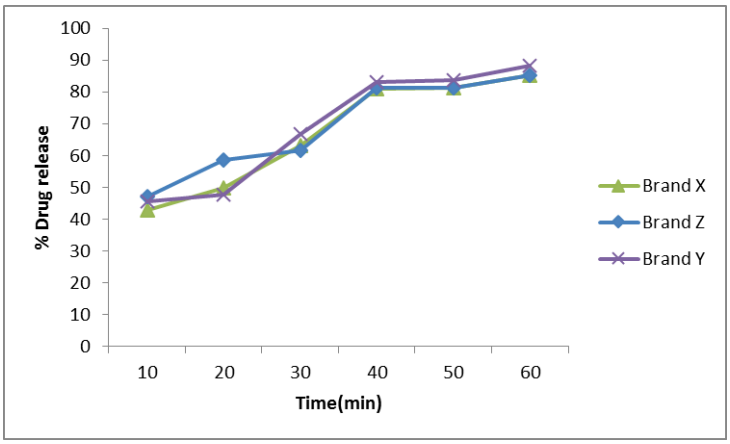

Figure 5: Drug dissolution determination in various formulations

Table 6: Viscosity determination in various formulations

S.No	Viscosity (Centipoise)	Shear stress	Shear R	Torque	Viscosity (Centipoise)
1	Brand X	64 D/cm^2	10.21/sec	64 %	621 cp
2	Brand Y	101 D/cm^2	10.21/sec	91.4%	983 cp
3	Brand Z	61.5 D/cm^2	10.21/sec	60 %	598 cp

subsequent particle dissolution. Changes in color, odor and taste can also indicate chemical instability.

Density: Specific gravity or density of the suspension is an important parameter. Decrease in density indicates the presence of entrapped air with in the structure of the suspension. Density measurements at a given temperature should be made using well-mixed uniform suspension. Hydrometers are used to measure the density.

pH value: pH of the phases of suspension also contributes to stability and characteristics of formulations. So pH of the different vehicles, phases of suspension before mixing and after mixing are monitored and recorded time to time to ensure optimum pH environment being maintained. **Clarity testing**:- Clarity testing is carried out to check the particulate matter in the sample.

Pourability: This test is carried out on the phases of suspension after mixing to ensure that the final preparation is pourable and will not cause any problem during filling and during handling by patient **Viscosity**:- Stability of a suspension is solely dependent on the sedimentation rate of dispersed phase which is dependent on the viscosity of the dispersion medium. So this test is carried out to ensure optimum viscosity of the medium so a stable, redispersible suspension can be formed. The viscosity can be measured by a) Cup and Bob viscometer (destructive method) b) cone and plate viscometer (destructive method).

Rheology: Rheology is the science that concerns with the flow of liquids and the deformation of solids. Brookfield viscometer is used to evaluate the rheological properties and behavior of settling of suspensions (C.V.S. Subrahmanyam**,** 2013).

Zeta potential measurement: Zeta potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and electro-neutral region of the solution. Value of zeta potential reflects the future stability of suspension so it is monitored time to time to ensure optimum zeta potential. The flocculated suspension is one in which zeta potential of particle 20 is to +20 mv.

Drug content uniformity: For proper dosing of the dosage form it is necessary that the active ingredient is uniformly distributed throughout the dosage form, so samples are withdrawn from the dispersed phase after micronization and after mixing with dispersion medium, assayed to find out degree of homogeneity.

Particle size measurement: Particle size can be measured by a) optical microscopy b) sedimentation method c) conductivity method (coulter counter method) .Optical microscopy Particle size in the range of 0.2 to 100µm can be measured by optical microscopy. This method directly gives number distribution.

Sedimentation volume: It is the ratio between ultimate volumes of sediment to initial volume of the suspension. F=Vu/V0=ultimate volume of the sediment by initial volume of the suspension .The F value is between the limits 0 to 1. The higher the sedimentation volume the better is the physical stability.

Redispersibility: If the particles settle they should be easily redispersible by a moderate amount of shaking.

CONCLUSION

As a result of this study we have concluded that all the three brands of Paracetamol suspension meet the criteria laid in the official monographs (Singh SK et al.,2016; Standing JF et al., 2005) and though they differ slightly in terms of various *in-vitro* quality control

parameters like Sedimentation volume, Particle size determination, Drug Content, Dissolution, Viscosity, however, brand Y had faster dissolution rate and drug content,its % drug release was more, its sedimentation volume was also higher showing that its particle settle more gradually thus reflecting better physical stability than the other two brands at the same time.

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