Original Research Article

Microbial and physicochemical analysis of non-sterile pharmaceutical liquid products in Karachi Pakistan.

1. ABSTRACT

The pharmaceutical products and their therapeutic efficacy were comprised' due to the involvement of both physicochemical and microbial characteristics of the pharmaceuticals. However, liquid preparations are highly at risk due to the high percentage of sucrose contains that is beneficial for the growth of microbes. The inspection was to find to judge the microbial and physicochemical qualities of samples of paracetamol and cetirizine sold in Karachi, Pakistan. Three hundred fifty (350) pharmaceuticals brand were investigating; their organoleptic properties such as density, color, pH, test and total content of active ingredients, total viable count, and type of microbe of samples. These tests were conducted followed by the standard techniques and procedure. Assess the brands of paracetamol and cetirizine samples were meet the standard microbial specifications. The result of the organoleptic test was sweet, according to the color sample was found green, pink, red, yellow, and transparent liquids. The density of samples fluctuated between (1.150 - 1.390) g/ml. Similarly, the pH of the samples was recorded between (4.72 - 6.10). The active ingredient concentration of both samples was observed, ranging from 99% - 104%. The microbial limit many tests were conducted for the observation; the absence of 5 specified microbes in non-sterile pharmaceutical preparation. Pseudomonas sp. Escherichia coli (E-coli), salmonella spp, Staphylococcus spp, and Candida Albicans. All the samples of paracetamol and cetirizine were found contaminated under the acceptable limit. This observation

explained that the ten brands of paracetamol and cetirizine sold in the pharmacy of Karachi Pakistan were complying with specifications of pharmacopeia, about both physicochemical and microbial characteristics analyzed dosage form fit for used and acceptable for pediatric and geriatric patients.

Keywords; Microbial control; Microbial contamination; Pharmaceutical product; Consumer safety; Non-sterile pharmaceuticals

2. INTRODUCTION

The numerous pharmaceutical brands and their dosage forms are available for selling on the pharmacy outlets. These pharmaceutical brands have been many applications and goal plans, such as diagnosis, prevention, and treatment of diseases **[1,2]**. Pharmaceutical surveillance is playing an important role to help out for the avoidance from patients at risk due to inadequate safety, efficacy, and quality of pharmaceuticals and ensure they are fit for use. Many studies show that drug-borne diseases worldwide are associated with contaminated pharmaceutical dosage forms **[3,4]**. The presence of microbes in pharmaceutical products are not only hazardous for the consumer but may also change or lose physicochemical and organoleptic properties of the formulation, such as fermentation of syrups, and change in color, phase separation of emulsions, changes in thickness, odor, and color of creams, cake formation in suspensions, they are converted into toxic products **[5]**. To determine the source of contamination single step of manufacturing from starting to the final stage of manufacturing should be monitored critically of bio-burden **[6]**. The presence of microbial contamination in the pharmaceutical product may cause secondary infection in patients **[7]**. The use of these contaminated pharmaceutical products can cause alteration of therapeutic effect of drugs and may cause financial loss to the industrialist **[8]**. Mostly formulation ingredients on the risk of microbial attacks, such as active pharmaceutical ingredients, polymers, oils,

sweetening agents, surface-active agents, coloring agents, and preservatives **[9]**. Development of pharmaceutical dosage form is complex and various step processes, every step can cause physical, chemical, and microbiological contamination in the product. Other sources of microbial contamination are mainly considered, such as raw materials, Instruments, air sources, workers, and technicians **[16]**. The level of contamination can be minimized; during the manufacturing of pharmaceuticals by adopting some measures, like proper cleanliness of equipment and glassware used in manufacturing units and following guidelines of regulatory agencies such as proper hygiene condition of personals working in the manufacturing area **[10]**.

3. METHODOLOGY

3.1 Sample collection

A total of three hundred fifty (350) samples of paracetamol suspension and cetirizine syrups of different batches which purchased equally from drug stores by randomly selected from ten different pharmaceutical companies of seven districts; [Karachi central; Karachi East; Karachi South; Karachi West; Korangi; Malir; and Kemari]. In each district, thirty-five paracetamol suspension samples and thirty-five cetirizine syrups samples were collected **[11]**.

3.2 Preparation of pharmaceutical samples

All the samples were prepared accordingly to El-Housseiny et al., the physical characteristic of the product is the major factor for the method of sample preparation for testing of the product all containers will be swabbed with ethanol 70% v/v externally before opening. Overall, takes equal to 1 ml (liquids) samples or 1 g (solids or semisolids) will test for each product. The volume dilution will prepare by the ratio (1:10) in any one of sterile Trypticase Soy Broth and Sabourand Dextrose Broth (SDB) **[12].**

3.3 Total viable aerobic count (TVAC)

The test of total viable aerobic count (TVAC) provides the approximation of viable aerobic microorganisms such as bacteria and fungus in the non-sterile pharmaceuticals. Preparation of Trypticase soy agar Petri plate dishes with the 9cm diameter, added 1ml of sample on 20ml liquefied Trypticase soy agar and the preparation of Sabouraud dextrose agar plate added 1ml of sample on 15ml of liquefied Sabouraud dextrose agar in Petri dishes. This test was performed by using the spread-plate technique. The total bacterial count on the Trypticase soy agar plate was incubated for three days at 35°C, while the count of total fungus, Sabouraud dextrose agar plate was incubated for five days at 25°C. The counting of colony-forming unit (CFU) per ml on each plate and multiplied by the dilution factor **[13, 14, 15]**.

3.4 Isolation and identification of specified microbial contaminants

To observation, the safeness of non-sterile pharmaceuticals, **(Sandle, T., 2015)** prescribes the microbial limit tests, which were conducted for the observation for the absence of 5 specified microbes in non-sterile pharmaceutical preparation. Pseudomonas sp, Escherichia coli (E-coli), salmonella spp, Staphylococcus spp, and Candida Albicans. For the isolation of microbes, the sample was placed on various media such as Trypticase Soy Agar (TSA), Sabouraud dextrose agar(SDA), MacConkey agar, Cetrimide agar, mannitol agar, and Xylose lysine deoxycholate then incubated. For the identification of microbes, many biochemical tests were performed such as catalase testing, coagulase testing, starch hydrolysis, Citrate use, novobiocin sensitivity, Triple Sugar Iron Agar, Eosin methylene blue agar, urease production test, and oxidase production test **[16, 17,18]**.

4. Physico-chemical examination of samples;

4.1 Chemical examinations of Paracetamol and Cetirizine

The content of Paracetamol (PCM) in paracetamol liquid, suspension, and cetirizine syrup samples was evaluated by UV/Visible spectrophotometer **[19, 20].**

4.2 Standard solution preparation

The official methods were repeated for different weights of paracetamol working standard solution containing (P1= 120mg/5ml), (P2= 250mg/5ml), (P3= 120mg/5ml), (P4= 250mg/5ml), and (P5= 250mg/5ml), On the other Hand cetirizine standard solution containing (C1= 1mg/1ml), (C2= 1mg/1ml), (C3= 1mg/1ml), (C4= 1mg/1ml), and (C5= 1mg/1ml) respectively. One of all paracetamol and cetirizine weight was added to 50ml of 0.1M (NaOH) and diluted to 200ml with Distal Water in a 200ml measuring flask. Finally, 1ml of the above solution was added to 10ml of 0.1M (NaOH) and diluted with DW to 100ml in a measuring flask **[19,20]**.

4.3 Preparation of sample solution

Added 5ml from each paracetamol and cetirizine sample into 50ml of 0.1M (NaOH) and diluted to 200ml with distal water in a 200ml measuring flask. 1ml of the above solution was added to 10ml of 0.1M (NaOH) and diluted with distal water to 100ml in a measuring flask **[19,20].**

4.4 UV/Visible Spectrophotometer for samples assayed

The absorbance of UV in the prepared paracetamol solutions (standard and sample) were measured in a UV/Visible Spectrophotometer (Germany EMC-32PCS-UV) model (V-1100) with bandwidth (2.0nm), connected to a hp Compaq computer loaded with software, at a wavelength of 257nm and 230nm using a mixture of 10ml of 0.1M (NaOH) and 90ml of DW as a blank. For measuring the absorbance of all the paracetamol and cetirizine solution Quartz cells, were used. This method is recommended **[19,20]**.

5. Data analysis

Each of the above results was performed for statistical purposes. The obtained data were subjected to statistical analysis of mean, standard deviation, and analysis of variance (ANOVA) using IBM SPSS Statistics software (version 21.0, 2020). Illustrations of generated data were also calculated with Microsoft Office Excel 2010. Differences in microbial count mean for CFU/ml and isolated microbial contaminants were compared ANOVA test. Spearman test for correlation coefficient was carried out. Values of $P<0.01$ were considered statistically significant

6. RESULTS

6.1 Physical appearance and taste of Samples

In the physical examinations, the appearance of suspensions and syrups was assessed in each sample by visual examination to determine the color. The observation of taste was assessed by using the appropriate relevant sense organs. All the samples of paracetamol and cetirizine meet the specification. The appearance of three paracetamol samples showed clear red (P1, P2, P5), While the remaining two types (P3 and P4) of paracetamol samples were yellowish, similarly in the count of test all the paracetamol sample sweet in the test. At the same time, the four types of cetirizine samples (C1, C2, C3, and C5) were clear Transparent, and (C4) the sample was green in color, while all the cetirizine samples were sweet in the test.

Table (1): Contain appearance, and taste results from analyzed samples.

S.No	Type of samples	Product Code	Sample Size	Physical examination		Comply with USP 2019 Specification			
						Comply		Non-Comply	
				Appearance	Test	No	%	No	%
1	Paracetamol suspension	P1	35	Red	Sweet	35	100	0	0
2		P2	35	Red	Sweet	35	100	0	0
3		P3	35	Red	Sweet	35	100	0	0
4		P4	35	Yellowish	Sweet	35	100	0	0
5		P5	35	Yellowish	Sweet	35	100	0	0
6	Cetirizine	C1	35	Transparent	Sweet	35	100	0	0

7	Syrup	C2	35	Transparent	Sweet	35	100	0	0
8		C3	35	Transparent	Sweet	35	100	0	0
9		C4	35	Green	Sweet	35	100	0	0
10		C5	35	Transparent	Sweet	35	100	0	0

*Appearance limit: clear, Taste limit: sweet or bitter according to (USP 2019).

6.2 Density of Samples

The density was measured by the density instrument (NDJ-8S digital rotational viscometer-China) model (NDJ-8S). The paracetamol suspension density results of samples had a different range according to the product (P1= 1.182-1.185g/ml), (P2= 1.153-1.160g/ml), (P3= 1.150-1.157g/ml), (P4= 1.171-1.175g/ml), and (P5= 1.160-1.168g/ml) were recorded. Similarly cetirizine syrups the density results were observed (C1= 1.19–1.239g/ml, (C2= 1.205–1.210g/ml), (C3= 1.180–1.191g/ml), (C4= 1.216-1.219g/ml), and (C5= 1.225–1.234g/ml).

6.3 pH value of samples

The pH value for each sample was measured once and determined using an instrument (Pen Type Digital pH Meter Model SK-661PH Japan) model (SK-661PH) pH meter with a glass electrode. pH test results showed that all the samples of paracetamol and cetirizine complied with the standards. The pH values in the paracetamol suspension samples were recorded (P1= 5.51–5.59), (P2= 4.72–4.77), (P3= 5.31–5.39), (P4= 5.15-5.25), and (P5= 5.05–5.10). At the same time, the pH level of cetirizine syrup samples; (C1= 4.91–4.97), (C2= 5.18–5.23), (C3= 5.08–5.15), (C4= 4.75-4.85), and (C5= 6.01–6.10) were reported.

6.4 Drug contents uniformity

The test results showed that all paracetamol and cetirizine samples were compiled to official standards. The drug contents values in the paracetamol and cetirizine samples were recorded (P1= 99.5%– 102%), (P2= 100% – 103%), (P3= 98% – 102.5%), (P4= 100% – 102.5%), and (P5=

99.5% – 103%). At the same time, the cetirizine syrup samples; (C1= 101% – 103%), (C2= 99% – 102%), (C3= 97% – 102%), (C4= 100% - 103%), and (C5= 101% – 104%) were reported.

6.5 Total microbial count results from analyzed samples

In this study mostly isolated organisms was Pseudomonas sp and Staphyloccus spp, the paracetamol samples was observe, the total bacterial count <10cfu/ml recorded in (P1= 33(94%),(P2= 31(89%), (P3= 32(91%), (P4= 30(86%), and (P5= 28(80%), while the total bacterial count was <100cfu/ml recorded in (P1= 2(6%), (P2= 4(11%), (P3= 3(09%), (P4= 5(14%), and (P5= 7(20%). The results reported that the total fungal count was ≤10cfu/ml in all samples of paracetamol samples (P1, P2, P3, P4, and P5).

Furthermore, the total bacterial count in cetirizine samples was <10cfu/ml recorded in (C1= 33(94%), (C2= 34(97%), (C3= 31(89%), (C4= 30(86%), and (C5= 29(83). Also, the total bacterial count was <100cfu/ml reported in (C1= 2(6%), (C2= 1(3%), (C3= 4(11%), (C4= 5(14%), and (C5= 6(17%). Similarly the total fungal count was recorded ≤10cfu/ml in all samples of (C1, C2, C3, C4, and C5). All total microbial count of microorganism results of all samples were 100% corresponding to the microbial limit specifications.

Table 2 : Microbial count

S.No	Sample type	Product Code	Sample Size	Total Microbial Count												Comply to USP (2019) specification			
				Total Bacterial Count (cfu/ml)							Total Fungal Count (cfu/ml)					Comply		Non-Comply	
				<10		<100		≤100		P Value	≤10		>10						
				No	%	No	%	No	%		No	%	No	%		No	%	No	%
1	Paracetamol suspension	P1	35	33	94	2	6	0	0	>0.01*	35	0	0	0		35	100	0	0
2		P2	35	31	89	4	11	0	0		35	0	0	0		35	100	0	0
3		P3	35	32	91	3	9	0	0		35	0	0	0		35	100	0	0
4		P4	35	30	86	5	14	0	0		35	0	0	0		35	100	0	0
5		P5	35	28	80	7	20	0	0		35	0	0	0		35	100	0	0
6	Cetirizine Syrup	C1	35	33	94	2	6	0	0	>0.01*	35	0	0	0		35	100	0	0
7		C2	35	34	97	1	3	0	0		35	0	0	0		35	100	0	0
8		C3	35	31	89	4	11	0	0		35	0	0	0		35	100	0	0

9		C4	35	30	86	5	14	0	0		35	0	0	0	35	100	0	0
10		C5	35	29	83	6	17	0	0		35	0	0	0	35	100	0	0

*The P-value is not significant at the 0.01 level.
Cfu /ml= Colony Forming Units Per Milliliter.
USP., (2019) limits not more than 100cfu/ml for the total bacterial count.
USP., (2019) limits not more than 10cfu/ml for the total fungal count.

Table 3 : Microbial load in the oral suspensions and syrups tested

S No	Sample Type	Sample Code	pseudomonas spp	E-coli	Salomonella Spp	Staphyloccus spp	Candida Albican
1	Paracetamol Suspension	P1	-	-	-	+	-
2		P2	+	-	-	+	-
3		P3	-	-	-	+	-
4		P4	+	-	-	-	-
5		P5	-	-	-	-	-
6	Cetirizine Syrups	C1	+	-	-	+	-
7		C2	+	-	-	-	-
8		C3	-	-	-	+	-
9		C4	-	-	-	-	-
10		C5	+	-	-	+	-

+ Presence of bacteria, - Absence of bacteria

7. Discussion

In this study, three hundred fifty (350) samples of paracetamol and cetirizine were collected from seven districts of Karachi, and ten different pharmaceutical brands were investigated for their physicochemical and microbial qualities. The product code is applied to find the result instead of the brand name. These will be locally manufactured and consist of multinationals and national products. One hundred seventy-five samples of the paracetamol [P1, P2, P3, P4, and P5] and one hundred seventy-five samples of the Cetirizine [C1, C2, C3, C4, and C5] were analyzed their

microbial and physicochemical qualities. The official specification recommended that the TVAC acceptance limit be less than 10^2cfu/ml in the total bacterial count and not more than 10^1cfu/ml in the total fungal count for the non-sterile oral pharmaceutical syrups, liquid drops, a suspension, etc. The TVAC results confirmed that all the samples investigated in this examination were contaminated much less than the permissible limit for the non-sterile oral pharmaceutical syrups, liquid drops and, suspension complied with specification **[21]**. In this study, that observed the total bacterial count <10cfu/ml in 158(90.02%), and 156(89.14%), and <100cfu/ml in 17(09.71%), and 19(10.85%) samples of paracetamol and cetirizine syrups respectively, while the total fungal count was ≤10cfu/ml recorded in all the 350 (100%) samples of paracetamol and cetirizine syrups **[22]**. This study observed the physicochemical properties of all the paracetamol and cetirizine samples, and they are meet the official specification. The physical examinations, the appearance of suspensions, and syrups were assessed in each sample by visual inspection to determine the color. The visual inspection found that all the samples, comply with USP specification no samples founded discolored. All the samples examined, taste properties have judged the use of appropriate, relevant sense organs. The entire sample to pass this test found sweetens. The density of samples was measured by the density instrument (NDJ-8S digital rotational viscometer-China) model (NDJ-8S). The pH test results show that all the paracetamol and cetirizine samples complied with USP standards. The pH of both samples was under the acceptable limit, slightly acidic. In this study, all the samples were met, with the USP standard, in the count of drug uniformity test. The tested samples of paracetamol and cetirizine content, the drug concentration between (95% to 105%). In this study, no samples were found; below or above the acceptable limit of drug concentration in the dosage form **[23,24,25,26]**.

8. Conclusion

This study concludes that the pharmaceutical brands of paracetamol and cetirizine sold in Karachi, Pakistan, have to clear the official specification for microbial quality of samples. Furthermore, the color, taste, pH, density, and active ingredients content are under the acceptable limit. sAt the same time, results showed red, yellow, pink, green, and transparent colors with sweet taste show more acceptable for the pediatric patient. The microbial growth also blows the maximum microbial contamination, which is helpful to control the drug from spoilage. It is suggested that improve the quality of non-sterile dosage forms to control microbial contamination and physicochemical properties; for the more suitable for pediatric and geriatric patients. That's should be improved by adopting Good Manufacturing Practices and proper treatment of air and water; improvement of production personnel (personnel hygiene) and official treatments of natural materials be enforced and maintained.

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