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ORIGINAL PAPER

Study of Formulation of Pharmaceutical Solution Form of Paracetamol in the Pediatric Clinical Practice

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Aim of the study was selection of 2 different formulations of paracetamol of 2.5% (125 mg/5 mL) in the Pediatric practice. Paracetamol is widely used in the form of the syrup, with usual percentage of acting ingredient of 125mg/5mL. **Material and methods:** Both samples of the paracetamol syrup were monitored each day regarding organoleptic features (potential changes in color, smell, transparency, crystallization, etc.), whilst in monthly intervals (1 month, 2 months, 3 months, 4 months and 5 months) content of the paracetamol was analyzed, with the spectrophotometric method (HPLC). **Results and Discussion:** Content of the paracetamol in both syrup formulations has not incurred any change even after a period of 6 months of storage, which showed that these two formulations are appropriate ones. From six different formulations of the paracetamol syrup in percentage of 2.5% (125 mg/5ml) as more appropriate are: fifth formulation which can be considered, without no doubt, as most appropriate one because of its relatively low cost, an stabilized pH, a quite likeable taste and as such also consequently acceptable in the pediatric practice. In some cases, mainly during the winter, the crystallization of the paracetamol in the lid, walls and bottom of the bottle was ascertained also. **Conclusion:** Syrup of paracetamol 2.5% (125mg/5mL) as per the formulation 5 experimented by our side can be recommended as most appropriate to be produced in industrial conditions for purposes of pediatric practice. **Key words: Solutio paracetamol 2.5% (125 mg/5 mL).**

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1. INTRODUCTION

Paracetamol is a preparation of antipyretic and analgesic effects but it does not manifest any anti-inflammatory effect (1). In today's time, in clinical practice, paracetamol is a safe alternative for substitution of the acetoacetic acid and the phenacetin. Due to its wide administration in the clinical practice, determination of paracetamol in pharmaceutical formulation is of a great importance since that over dosage with paracetamol may cause the hepatic fulminant necroses and other toxic effects (2).

Decrease in use of the acetominophen and reduction of the administration of the phenacetin derives as a result which relies on some scientific researches which have researched the action of phenacetin to kidneys and have assumed the possibility of the connection of the administration of the phenacetin with the increased incidence of tumor manifestation (3, 4). Nevertheless, scientific community could not develop a convincing animal model of the research in order to prove the nephrotoxic effect of the phenacetin, and the mechanism of manifestation of these effects remains yet unexplained.

Acetominophen as a primary metabolite of the phenacetin, does not manifest cancerogenesis effects, but in acute doses may cause bulbar centrilobular necrosis in humans and experimental animals (5).

Therefore, a great importance today is paid to the pharmaceutical products of paracetamol. According to the British Pharmacopoeia, 2 basic methods of paracetamol analyses are described: spectrophotometric method for determination of paracetamol and HPLC method for determination of 4-aminophenol. Meanwhile, in the monography as per USP 30, the HPLC method is described for paracetamol, but with no described methods for testing of the impurity of preparation (6).

Nevertheless, many methods of defining the paracetamol in pharmaceutical preparation are published in the professional scientific literature and some of them determine also the percentage of 4-aminophenol in simultaneous manner (RP-HPLC, liquid microemulsion cromatography, capillary electrophoresis, spectrophotometric electrophoresis UV) (7).

This is why pharmaceutical industry usually utilizes granulates of the substance with narrow distribution (small difference in the size of particles comparing to average size of granulate) (8, 9). In our pharmaceutical market, formulations of paracetamol by different producers are also present and therefore analyses of these formulations are important regarding medical practice and scientific pharmaceutical community.

Aim of this research was the analyses of formulation, preparation, quality control, and monitoring the stability of six formulations of paracetamol syrups through HPLC and spectrophotometry methods with the UV zone, presentation and commensurate analyses of these results to regulative of International Pharmacopoeias.

2. MATERIAL AND METHODS

Experimental work was done in the laboratory for research at the pharmaceutical factory "Farmakos"–Prizren. Prepared samples of the paracetamol syrup 2.5% (125mg/5mL) were analyzed in terms of their organoleptic features (potential changes in color, smell, transparency, crystallization, etc.), and the chemical stability (decrease of the content of paracetamol).

Samples of the paracetamol syrup 2.5% were monitored each day related to their organoleptic features, while content of the paracetamol was analyzed in the monthly intervals.

Careful examination of the samples of the syrup for a time period of 6 months showed no change of their organoleptic features.

Results of analyses regarding content of paracetamol in different formulations is presented in the tables below. See formulations 1, 2, 3, 4, 5 and 6.

Formulation 1

Paracetamol	25 g
Alcohol	100 mL
Sorbitol	357 g
Glycerin (85%)	450 g
Nipagin	0.8 g
Nipazol	0.2 g
Distilled water up to	1000 mL

Formulation 2

Paracetamol	25 g
Sugar syrup	400 mL
Sorbitol syrup 70%	200 mL
Propilenglycol	90 g
Alcohol	50 mL
Cherry essence	1 mL
Lemon essence	0.1 mL
Citrus essence	0.1 mL
Mint essence	0.01 mL
Nipagin	1 g
Nipazol	0.1 g
Distilled water up to	1000 mL

Formulation 3

Paracetamol	25 g
Sugar	500 g
Sorbitol syrup 70%	200 mL
Propylene glycol	100 g
Alcohol	100 mL
Mint alcohol	1.65 mL
Peach essence	0.75 mL
Vanilla	0.2 g
Nipagin	1.2 g
Nipazol	0.2 g
Distilled water up to	1000 mL

Formulation 4

Paracetamol	25g
Alcohol	100 mL
Glycerin (85%)	450 g
Sorbitol syrup 70%	500 g
Distilled water up to	1000 mL

Formulation 5

Paracetamol	25 g
Glycerin	200 g
Propylene glycol	100 g
Alcohol	100 mL
Nipagin	0.9 g
Nipazol	0.1 g
Monobasic sodium phosphate	15 g
Dibasic sodium phosphate	2.5 g
Sugar	300 g
Distilled water up to	1000 mL

Formulation 6

Paracetamol	25 g
Alcohol	357 mL
Sorbitol	100 g
Glycerin (85%)	450 g
Nipagin	0.8 g
Nipazol	0.2 g
Sodium saccharin	1 g
Distilled water up to	1000 mL

Results gained from spectrophotometric definition of the paracetamol in two different syrup formulations (125mg/ml), 1 month, 2 months, 3 months, 4 months and 5 months following the preparation are presented in the tables 1, 2, 3, 4, 5, 6 and 7 and the figure 1. Results indicate that content of the active ingredient (paracetamol) has not incurred any change, which shows the best that both proposed and prepared formulations entirely fulfill requirements of the existing literature.

While analyzing the results of the content of paracetamol in two different syrup formulations (125mg/mL; formulation 5 and 6), 6 months following the preparation, we can conclude that even after this period of storage, proposed and prepared formulations have not incurred any change in the percentage of paracetamol.

It is a well known fact that industrial preparation should have a storage time term (administration time term, validity time term) of at least 24 months, but time frame for this magistral work of 6 months is sufficient enough to form an opinion regarding lasting of the active ingredients within the different pharmaceutial preparations, respectively of the paracetamol in syrup. As notable, value of this coefficient is relatively small , which means that changeability of the results of the analyses from one sample to another is barely negligible.

As far as two studied formulation are concerned (formulation 5 and 6) we think that formulation 5 is more appropriate in terms of applying it in the practice, because it has a lower cost than other formulation, an stabilized pH by the phosphatic buffered system (mixture of the monobasic phosphate with the dibasic phosphate) and a quite likeable and kids acceptable taste

Results presented in the below tables indicate that content of paracetamol in two formulations (5 and 6) are within the forecasted norm.

Statistical indicators	Formulation 5	Formulation 6
Average () Standard deviation () Coefficient variation (CV%)	24.78 0.3545 1.43	24.88 0.478 1.92

Table 1. Results of the statistical processing of data regarding content of the paracetamol (in percentage), in two different syrup formulations (2.5%) (Immediately after preparation).

Statistical indicators	Formulation 5	Formulation 6
Average () Standard deviation () Coefficient variation (CV%)	25.05 0.327 1.306	25.02 0.387 1.546

Table 2. Results of the statistical processing of data regarding content of the paracetamol

(in percentage), in two different syrup formulations (2.5%) (1 month after preparation).

Statistical indicators	Formulation 5	Formulation 6
Average ()	25.08	24.97
Standard deviation ()	0.285	0.497
Coefficient variation (CV%)	1.14	1.99

Table 3. Results of the statistical processing of data regarding content of the paracetamol (in percentage), in two different syrup formulations(25mg/mL) (2 months after preparation).

Statistical indicators	Formulation 5	Formulation 6
Average ()	24.98	25.015
Standard deviation ()	0.33	0.452
Coefficient variation (CV%)	1.33	1.81

Table 4. Results of the statistical processing of data regarding content of the paracetamol, in two different syrup formulations (25mg/mL) (3 months after preparation)

Statistical indicators	Formulation 5	Formulation 6
Average ()	25.078	25.081
Standard deviation ()	0.318	0.445
Coefficient variation (CV%)	1.27	1.77

Table 5. Results of the statistical processing of data regarding content of the paracetamol, in two different syrup formulation s(25mg/mL) (4 months after preparation)

Statistical indicators	Formulation 5	Formulation 6
Average ()	25.075	24.89
Standard deviation ()	0.422	0.45
Coefficient variation (CV%)	1.68	1.803

Table 6. Results of the statistical processing of data regarding content of the paracetamol, in two different syrup formulations (25mg/mL) (5 months after preparation)

Statistical indicators	Formulation 5	Formulation 6
Average ()	25.063	25.07
Standard deviation ()	0.367	0.405
Coefficient variation (CV%)	1.464	1.62

Table 7. Results of the statistical processing of data regarding content of the paracetamol, in two different syrup formulations (25mg/mL) (6 months after preparation)

3. RESULTS AND DISCUSSION

The results of our research were compared to the conditions, respectively criteria, set by International Pharmacopeia, respectively British Pharmacopeia (BP) and American Pharmacopeia (6, 10, 11).

Permitted limit of mass deviation, as per BP, lies within a range of ±5% of the declared mass. In our research, average mass of the analyzed formulations has not exceeded this limit set as per BP (10).

Paracetamol is a product of the metabolism of 4-aminophenol (*p*-aminophenol; AP) which has significant nephrotoxic and teratogenic effect, therefore presence of this metabolite according to the British Pharmacopoeia should not exceed the rate of 0.005% in the active substance of paracetamol (10). Whereas, presence of 4-aminophenol in the pharmaceutical formulation of paracetamol may vary; in the monography of the paracetamol in British Pharmacopoeia allowed amount of aminophenol in paracetamol tablet is 0.1% (10,12,13).

Permitted limit of presence of other substances, respectively of different excipient substances in different pharmaceutical forms, usually is not described in a strict manner because they do not derive from the disintegration of the basic active substance, but their quantity is determined in pharmacopoeias of many different countries. On the other side, we are convinced that even after the expiry of the 6 months of storage, content of the paracetamol can hardly be subject to any reduction. In addition to this, it is well known that content of the active ingredient reduces by 10% (achieves an value of 90% of initial content, or of the nominal value declared in the label), pharmaceutical preparations are considered to be stable and practically usable. In our case, paracetamol syrup can be considered stable and consequently approved legally to be administered, even though content of the paracetamol would not be 25mg/mL or (22.5mg/mL).

Regarding the accuracy of the implemented analytical method, besides values of the standard deviation, the calculated values of the coefficient of the variation provided in the table speaks also (1, 2, 3, 4, 5, 6 and 7). It is known that this statistical indicator (coefficient of the variation) assesses the rate of the changeability of the values of results of analyses in some of the repeated proofs. Lesser the value of it, lesser is also the difference of the repeated analyses results in some parallel samples, thus these results are much reliable (14). In our case, this coefficient varies from 1.14% up to 1.68%, with an average value of 1.374%.

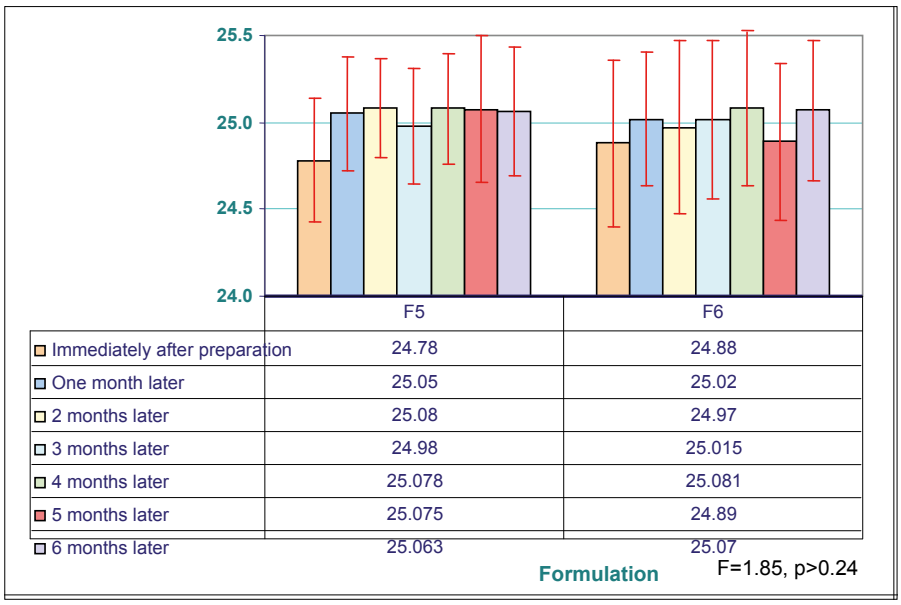
Thus, author Roohullah et al. has defined the paracetamol disintegration time in different percentage of polyvinylpolividon in the temperature of 37 ± 1°C in accordance to the method described in British Pharmacopoeia, 1998, whilst the process of defining the dissolution was realized in the same conditions in terms of temperature according to the method also described in British Pharmacopoeia and realized in the Erweka-DT equipment (15).

In this research also time of disintegration was less than 15 minutes and authors concluded a positive correlation in between the time of disintegration and connective substance.

While disintegration time of all the formulations, as per abovementioned authors, in T_{45} minutes was from 95 – 99.2%, whereas disintegration time of these formulations was from 15 minutes up to 135 minutes. Authors in question have concluded that there is no correlation in between concentration of connective substance and disintegration time (16). In our research, only 2 of first formulations have met conditions of velocity of dissolution as per BP whereas 2 last formulations have not met them.

Amount of dissolution of active substance in the solution (after 45 minutes) was not less than 70% of overall quantity of active substance. Amount of active substance of paracetamol in pharmaceutical formulations of paracetamol should be within limits of 95 – 105% of the defined amount in the quantitative content of the pharmaceutical form (17, 18, 19).

Physical properties that have an important role in defining of the dissolution velocity are size of granules, molecular weight, hydrophilicity and crystal structure (20). Regarding stability of paracetamol formulations in our research, in a period following 3 months, no evident influential changes were observed in the content of these formulations. Other authors also has ascerted that there were observed no significant changes in physical-chemical properties and dissolution velocity of paracetamol, provided that it was stored



Graph 1. Average content of the paracetamol in two different formulations of syrup 2.5% (within six months after preparation)

in defined conditions within summarized requirements of British Pharmacopoeia. In the market there are many boxes for dispensing medicines to patients which enable protection of the paracetamol from air, humidity, and light by increasing the overall medicine compliance. Results of a research conducted by Haywood and associates showed that paracetamol can be repacked and stored in a dispensing bottle for medicines to patients for a period of 6 weeks and to provide adequate protection against air, humidity, and light by preserving physical-chemical properties of the paracetamol (21).

Therefore, generally paracetamol syrup indicates a high scale of stability. Results of our research enabled us an detailed reflection of qualitative and quantitative content of 6 formulations of paracetamol that are in the pharmaceutical market and indicated a high rate of compliance in between 2 methods of instrumental analyse: spectrophotometry in UV zone and cromatography in liquid phase with high pressure (HPLC).

4. CONCLUSIONS

From six different formulations of syrup of paracetamol in a percentage of 2.5% (125mg/5mL), reviewed by our side, we have selected two formulations, as more appropriate ones in terms of cost, simplicity and taste. Both selected formulations were placed in a bottle of the polyethylene with 100 mL and were stored in appropriate conditions, as per recommendations of the existing literature. Syrups prepared as per both formulations resulted as stable regarding organoleptic features, which even with the expiry date (at least 6 months) have not undergone any change. Content of the paracetamol, defined by spectrophotometric method in the UV zone, in both formulations of the paracetamol syrup has not incurred any change even after time term storage of 6 months. From both experimented formulations, we think that formulation 5 is more appropriate one, because it has a lower cost, a very stable pH and quite likeable taste and as such is acceptable in the pediatric practice.

Conflict of interest: none declared.

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