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Study of Formulation of Mild Pharmaceutical Forms of Paracetamol in Medical Practice

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ORIGINAL PAPER

ABSTRACT

Introduction: Paracetamol is one of the most used antipyretic- analgesic preparation, which can be found in different pharmaceutical forms and in different doses. Due to its wide utilization 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. Material and methods: Study has included two formulations of paracetamol suppositories with doses of 125 mg widely used in the paediatric practice. Suppositories prepared according to these two formulations by the melting method and spilling into forms was subject to the quality control by implementing a series of trials and analyses for that aim, such are: reactions of identification, average mass, disintegration time, and homogeneity whilst quantitative determination was performed by applying two methods of instrumental analyze: spectrophotometry in UV zone and cromatography in liquid phase with high pressure. **Results and discussion:** Results of these analyses, performed immediately following the preparation and 3 months after the preparation, showed that content of paracetamol in both of two formulations is within the norms of Pharmacopoeia. Suppositories of paracetamol in doses of 125 mg prepared as per formulation 1 are to be considered as more appropriate because it contains semi synthetic glycerides as excipient which has better features than other suppository excipients.

Key words: Paracetamol suppositories (125 mg).

1. INTRODUCTION

Paracetamol is one of the most used antipyretic - analgesic preparation, which can be found in different pharmaceutical forms and in different doses. It has an antipyretic and analgesic effects but it does not manifest any anti-inflammatory effect (1).

Currently, in clinical practice, paracetamol is a safe alternative for substitution of the acetoacetic acid and of phenacetin. Due to its wide utilization 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).

Different methods for quality control of pharmaceutical products of paracetamol are used as described in literature. According to the monography of the paracetamol in British Pharmacopoeia, 2 basic methods of analyzing the paracetamol are described; spectrophotometric method for determination of paracetamol and HPLC method for determination of 4-aminophenol. Meanwhile, in the mon-

ography as per USP 30, the HPLC method is described for paracetamol, but with no described methods for testing of the impurity of preparation (3).

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) (4).

Process of producing the tablets requires a strict control of each individual phase of this process (processing of material, grinding, granulation, admixture, sieving, and tableting). Granulation increases the size of granules in order to supply, in a uniform manner, the proper equipment for preparation of tablet matrix. This results in uniform pressure of product granules and it enables tablets to be uniform one as far as heft and consistency of physical-chemical properties of the pharmaceutical product are concerned (hardness, incoherence).

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) (5, 6).

In our pharmaceutical market, formulations of paracetamol of different manufacturers are also present, and therefore, analyses of these formulations are important regarding medical practice and scientific pharmaceutical community in our country.

Aim of this research was to analyze the formulation, preparation, quality control, and follow-up of the stability of two formulations of paracetamol suppositories through HPLC and spectrophotometry methods in the UV zone, presentation and analyses of these results commensurate to regulative of International Pharmacopoeias.

2. MATERIAL AND METHODS

Paracetamol suppositories of 125 mg of two formulations were analysed regarding the content of acting substance with methods of instrumental analyze. Suppositories were analyzed immediately following the preparation and after 3 months of storing.

Results of determining of the content of paracetamol in suppositories by spectrophotometry in UV zone

Results of the paracetamol content in two formulations of these suppositories and statistic processing of results are provided in Tables 1, 2 and Graph 1. These results represent the mean arithmetical of determining.

Formulation 1

Paracetamol (micronized)	125.00 mg
Colloidal dioxide silica	4.38 mg
Microcrystal cellulose	87.50 mg
Semi synthetic glycerides	833.12 mg

Formulation 2

Paracetamol (micronized)	125.00 mg
Colloidal dioxide silica	1.40 mg
Witepsol H15	698.16 mg
Witepsol W35	225.44 mg

Formulation	Average mass (mg)		
	Minimal	Maximal	Mean
1	1.030	1.062	1.050
2	1.035	1.058	1.050

Table 1. Results of determining of the average mass of paracetamol suppositories of 125 mg in two different formulations

From the above table, it can be seen that average mass of paracetamol suppositories of 125 mg complies with the theoretical mass of both formulations (mass which derives from tabulation of paracetamol's dose for 1 suppository (125 mg) with the mass of excipients used to obtain suppository).

From the Table 2, it can be seen that content of paracetamol in two formulations of suppositories of 125 mg complies with requirements of official pharmaceutical literature (95.0 – 105.0%).

From the determination of paracetamol's content in two formulations of suppositories 125 mg, as per method of spectrophotometry in the zone, 3 months after the preparation, it is obvious that content of paracetamol in suppository has not changed, which speaks about the well known

Statistical indexes	Formulation 1	Formulation 2
Average (°)	98.92	99.85
Standard deviation (°)	0.682	0.565
Coefficient of variation (CV%)	2.02	1.87

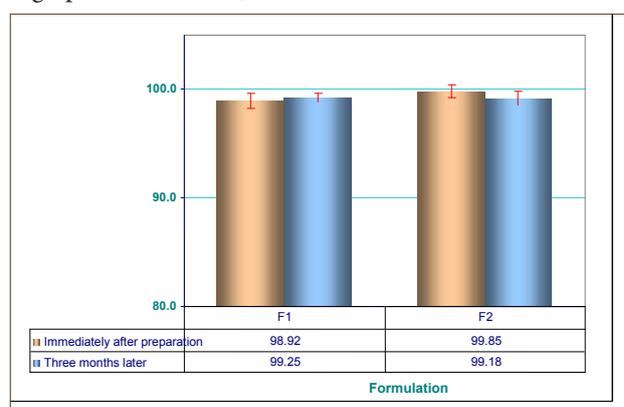
Table 2. Results of statistic data processing for content of paracetamol, in two different formulations of suppositories 125mg (immediately after preparation)

Statistical indexes	Formulation 1	Formulation 2
Average (°)	99.25	99.18
Standard deviation (°)	0.397	0.615
Coefficient of variation (CV%)	1.95	2.12

Table 3. Results of statistic data processing for content of paracetamol, in two different formulations of suppositories 125mg (3 months after preparation)

mentioned fact regarding tablets and syrup also in terms that this substance is quite stable.

Results of determining of the content of paracetamol in suppositories by cromatography in the liquid phase with high pressure (HPLC)



Graph 1. Average content of the paracetamol in two different formulations of suppositories 125 mg (within three months following the preparation). Determination with spectrophotometry in UV zone

Results of this determination are provided in Tables 4, 5 and Graph 2.

Statistical indexes	Formulation 1	Formulation 2
Average (°)	99.76	99.82
Standard deviation (°)	0.715	0.615
Coefficient of variation (CV%)	1.92	2.22

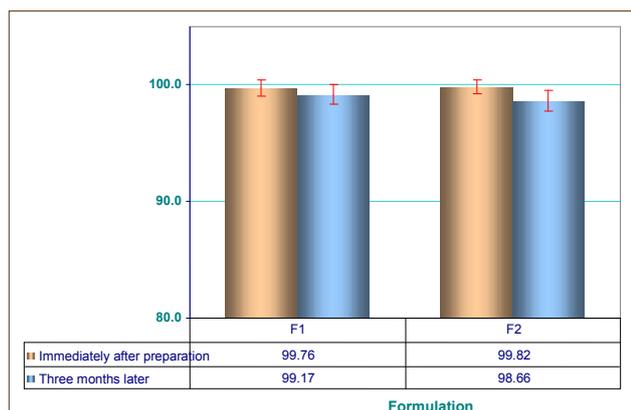
Table 4. Results of statistic data processing for content of paracetamol, in two different formulations of suppositories 125mg (immediately after preparation)

These results indicate that the content of paracetamol in suppositories of 125 mg is within norms (95.0 – 105.0%).

Statistical indexes	Formulation 1	Formulation 2
Average (°)	99.17	98.66
Standard deviation (°)	0.823	0.924
Coefficient of variation (CV%)	1.43	1.85

Table 5. Results of statistic data processing for content of paracetamol, in two different formulations of suppositories 125mg (3 months after preparation)

Content of paracetamol in suppositories of 125 mg has not changed, which is also proved with statistical indexes represented in the above table. Obtained results from the statistical



Graph 2. Average content of the paracetamol in two different formulations of suppositories 125 mg (within three months following the preparation). Determination with chromatography in liquid phase with high pressure (HPLC)

data processing, emphasized also in cases of paracetamol syrup and tablets, speaks also for the precision of analytical methods applied by us. From both experimented formulations, we think that formulation 1 are to be considered as more appropriate because it contains semi synthetic glycerides used as excipient described in most of recent years pharmacopoeias.

3. DISCUSSION

Results of our research were compared with conditions, respectively criteria, set by International Pharmacopoeia, respectively British Pharmacopoeia (BP) and American Pharmacopoeia (USP) (7, 8, 9). Permitted limit of mass deviation, as per BP, lies within a range of $\pm 5\%$ of the declared mass. In our research, average mass of the analyzed formulations has not exceeded this limit set as per BP (10).

Time of absorption was also analyzed in our research as per conditions set by BP. Time of disintegration for all of the formulations was within defined limits by BP, 1998, and it was less than 15 min, respectively it was comparable to results of other authors (11, 12). Thus author Roohullah et al. has defined the paracetamol absorption time in different percentages in temperature of $37 \pm 1^\circ\text{C}$ in accordance to the method described in British Pharmacopoeia, 1998, whilst the process of defining the absorption was realized in the same conditions in terms of temperature according to the method also described in British Pharmacopoeia and it was realized in the Erweka-DT equipment (13).

Regarding stability of paracetamol formulations in our research, in a period following 3 months, no evident influential changes were seen in the content of these formulations.

Other authors also has ascertained that there were seen no significant changes in physical-chemical properties and dissolution velocity of paracetamol, provided that suppositories were stored in defined conditions within summarized requirements of British Pharmacopoeia. In the market there are many boxes for dispensing of medicines to patients that enables protection of suppositories against air, humidity, and light by increasing the overall medicine compliance. Results of a research conducted by Haywood and associates showed that paracetamol suppositories can be repacked and stored in a dispensing box for medicines at 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 suppositories (14). Therefore, generally paracetamol suppositories indicate a high scale of stability. Results of our research enabled us an detailed reflection of qualitative and quantitative content of two formulations of paracetamol found in our country pharmaceutical market and indicated an high scale of compliance in between 2 methods of instrumental analyse: spectrophotometry in UV zone and cromatography in liquid phase with high pressure (HPLC).

4. CONCLUSIONS

Two different formulations of paracetamol suppositories in doses of 125 mg, which are used in the paediatric practice, were experimented. Suppositories prepared according to both formulations by the melting method and spilling into forms was subject to the quality control by implementing a series of trials and analyses, such are: reactions of identification, average mass, disintegration time, and homogeneity. Quantitative determination of paracetamol in suppositories, as in the case with tablets, was performed by applying two methods of instrumental analyze: spectrophotometry in UV zone and cromatography in liquid phase with high pressure (HPLC). As in the case with paracetamol tablets, results of defining the content of paracetamol by both analytical methods, immediately following the preparation and 3 months after preparation, have indicated that content of the acting matter in both two formulations is within the norms of specialty literature. Even in the case of suppositories, changes in the results of analyses between two analytic methods were inconsiderable. Paracetamol suppositories in doses of 125 mg as per formulation 1 are to be considered as more appropriate because they contains semi synthetic glycerides as excipient with better features than other suppository excipients.

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