

ORIGINAL PAPER

Study of Formulation of Pharmaceutical Forms of Paracetamol in Medical Practice

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It is a well-known fact that tablets are the most ordinary medicines in daily practice, which along with capsules represents about 70% of pharmaceutical preparations. Experimenting with paracetamol tablets of 500 mg dose was scope of this study. Study of formulation, preparation, quality control, and follow-up of the paracetamol stability in tablets was conducted. Carefully analyzing the physical – chemical properties of the paracetamol, in particular to the high number of excipients utilized in the preparation of tablets (diluting, connective, analyzing, and lubricant excipients), and by researching an considerable number of bibliographic sources, we have conceived four different formulations of the paracetamol tablets 500 mg. Preparation of tablets was realized by the humid method of granulation. Quality control of the paracetamol tablets was performed by implementing a series of trials and analyses forecasted in latest editions of most recognized pharmacopoeias. From these trials and analyses, we can mention as follows: reactions of identification, diameter, and average mass, time of analysis, velocity of dissolution and determination of 4-aminophenol. Requirements deriving from the abovementioned trials and analyses were accomplished, excluding the velocity of dissolution that was not accomplished in two of the last formulation (3 and 4). Since this trial is very important in regard to the quality of solid pharmaceutical forms, two of the abovementioned formulations are considered as inappropriate to be used in practice. From the four formulations of paracetamol tablets, results shows that 1st and 2nd are most appropriate formulations due to its simplicity in preparation and practice to be produced industrially. Defining of the timely depending content of the paracetamol in tablet was performed by the implementing of two contemporary methods of spectrophotometry in UV zone and chromatography in the liquid phase with high pressure (HPLC). Just as it was expected, results of these analyses showed that acting substance did not incur any alteration during the period of storage and that alterations of the analyses results in between these two methods are almost inconsiderable ones. **KEY WORDS:** PARACETAMOL TABLET (500 MG).

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1. INTRODUCTION

Paracetamol (PCT) is a preparation of acetylated aromatic amid group, for the first time presented by *Von Mering*

in the year of 1893. Paracetamol is one of the most used antipyretic- analgesic preparation, which can be found in different pharmaceutical forms and in dif-

ferent doses. It has an antipyretic- 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 the 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).

4-aminophenol (*p*-aminophenol; AP) is a product of the paracetamol metabolism, which have 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 (3). 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% (4, 5, 6).

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.

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, two basic methods of ana-

lyzing the paracetamol are described; spectrophotometric method for determination of paracetamol and HPLC method for determination of 4-aminofenolit. 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 (7).

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 chromatography, capillary electrophoresis, spectrophotometric electrophoresis UV) (8)

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).

Moisture of granulated material depends on size of the particle component, intensity of particle distribution, shape of the particle, tablet surface harshness, and humidity of the ingredient. As a rule, smooth particles with a high rate of relation of "surface towards heft" are more cohesive in comparison to particles with harsh surface.

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 (9, 10).

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

Aim of this research was the analyses of formulation, preparation, quality control, and follow-up of the stability of four formulations of paracetamol tablets through HPLC and spectropho-

tometry methods in the UV zone, presentation and analyses of these results commensurate to regulative of International Pharmacopoeias.

2. MATERIAL AND METHODS

Experimental work was done in the laboratory for research at the medicine factory 'Farmakos', Prizren. (See formulations 1, 2, 3, 4; graph: 1, 2).

Formulation 1

Paracetamol	0.5 g
Lactose	0.03 g
Amidon	0.07 g
Talc	0.02 g
Magnesium stearate	0.0025g
Gel	0.0075g

Formulation 2

Paracetamol	0.5 g
Lactose	0.03 g
Amidon	0.07 g
Talc	0.002 g
Magnesium stearate	0.0025 g
Alcoholic solution polyvinylpolividon	10%

Formulation 3

Paracetamol	0.5 g
Microcrystal cellulose	0.028 g
Gel	0.02 g
Talc	0.058 g
Magnesium stearate	0.05 g
Colloidal dioxide silica	0.0012 g

Formulation 4

Paracetamol	0.5 g
Microcrystal lactose	0.028 g
Alcoholic solution polyvinylpolividon	10%, as sufficient
Talc	0.0058 g
Magnesium stearate	0.005 g
Colloidal dioxide silica	0.0012 g

3. RESULTS AND DISCUSSION

Results of our research was compared with conditions, respectively criteria, set by International Pharmacopeia, respectively British Pharmacopeia (BP) and American Pharmacopeia (USP) (3,6,7).

In the process of analyzing the mass of the paracetamol 500 mg tablets, evident importance has content of the excipient substances that determines the disintegration properties and velocity of

tablet dissolution.

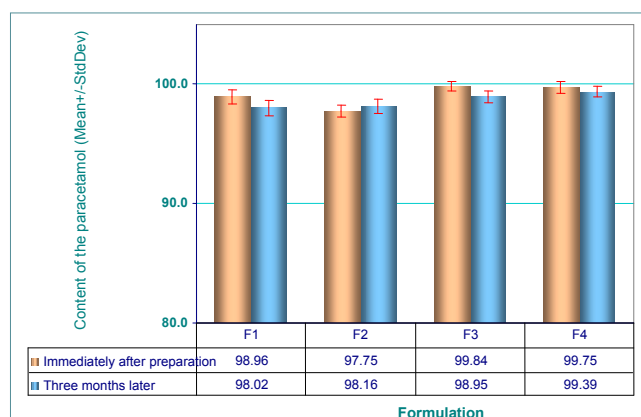
Permitted limit of mass deviation, as per BP, lies within a range of $\pm 5\%$ of the declared mass. In our research, average mass of the analyzed formulations has not exceeded this limit set as per BP (3).

Author Roohullah with bp. has analyzed physical-chemical properties of the Paracetamol tablets that have polyvinylpolividon as a connective substance in their content. Polividon and polyvinylpolividon in the pharmaceutical industry are used as diluents, connective substance, disintegrating substance, and covering in the pharmaceutical technology of tableting. Therefore, usage of connective substances has importance in the process of defining of physical-chemical properties of tablets. In our elaboration, this preparation was used in the formulation 2.

These authors have presented that mass of the tablet in all of the formulations was in the range of 539 – 573 mg and it was within permitted limits as per BP ($\pm 5\%$). Mass of the tablets according to these authors has been significantly higher at formulation of paracetamol tablets that contained polyvinylpolividon. Meanwhile, powder of the amidon was usually used due to its disintegrator effect, whilst talc and magnesium stearate due to their lubricant properties (see formulation 1).

Time of disintegration of tablets 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.

Disintegration of tablets in conditions determined by British Pharmaco-



GRAPH. 1. Average content of the paracetamol in four different formulations tablets 500 mg (within three months following the preparation). Determination with spectrophotometry in UV zone

poeia should not exceed 15 minutes (11).

Thus, author Roohullah with bp has defined the paracetamol tablets disintegration time in different percentage of polyvinylpolividon in the temperature of $37 \pm 1^\circ\text{C}$ 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 (12).

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

Whilst 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 of tablets (13).

Velocity of tablet dissolution depends on properties of medicine itself and medium in which dissolution of tablet takes place (14,15).

Physical properties that have an im-

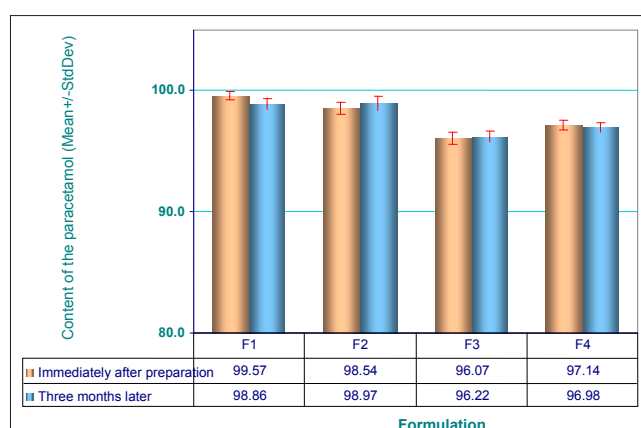
portant role in defining of the dissolution velocity are as follows: size of granules, molecular weight, hydrophilicity and crystal structure (16).

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).

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 ascer-



GRAPH. 2. Average content of the paracetamol in four different formulations of tablets 500 mg (within 3 months following the preparation).

Determination with chromatography in a liquid phase with high pressure (HPLC)

tained that there were seen no significant changes in physical-chemical properties and dissolution velocity of paracetamol tablets, provided that tablets were stored in defined conditions within summarized requirements of British Pharmacopoeia.

In the market there are many of boxes for dispensing of medicines to patients that enables protection of tablet against air, humidity, and light by increasing the overall medicine compliance. Results of a research conducted by Haywood and associates showed that paracetamol tablets can be re-packed 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 tablets (20).

Therefore, generally paracetamol tablets indicate a high scale of stability. Results of our research enabled us an detailed reflection of qualitative and quantitative content of 4 formulations of paracetamol that are in our country pharmaceutical market and indicated an high scale of compliance in between 2 methods of instrumental analyse: spectrophotometry in UV zone and chromatography in liquid phase with high pressure (HPLC).

4. CONCLUSIONS

- 4 different formulations were selected for preparation of paracetamol tablets 500 mg, and preparation of these tablets was done by the method of humid granulation.
- Tablets prepared according to four formulations were subject to the quality control by implement-

Statistical index	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Average	98.96	97.75	99.84	99.75
Standard deviation	0.593	0.462	0.398	0.537
Coefficient variation	1.78	1.86	1.92	1.54

TABLE 1. Content of the paracetamol (in percentage), in four different formulations of tablets 500 mg (immediately following the preparation)

Statistical index	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Average	98.02	98.16	98.95	99.39
Standard deviation	0.624	0.568	0.497	0.415
Coefficient variation	1.64	1.75	1.96	1.87

TABLE 2. Content of the paracetamol (in percentage), in four different formulations of tablets 500 mg (3 months following the preparation)

Statistical index	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Average	99.57	98.54	96.07	97.14
Standard deviation	0.353	0.513	0.476	0.394
Coefficient variation	1.48	1.82	1.57	1.19

TABLE 3. Content of the paracetamol (in percentage), in four different formulations of tablets 500 mg (immediately following the preparation)

Statistic index	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Average	98.86	98.97	96.22	96.98
Standard deviation	0.457	0.583	0.398	0.416
Coefficient variation	1.52	1.93	1.74	1.44

TABLE 4. Content of the paracetamol (in percentage), in four different formulations of tablets 500 mg (3 months following the preparation)

ing a series of trials and analyses, such as: reactions of identification, diameter, average mass, disintegration time, dissolution velocity, defining of 4 – aminophenol. All of the four formulations meet requirements of official pharmaceutical literature, excluding the dissolution velocity that was not met in two formulations (3 and 4). Therefore, these two formulations are considered as inappropriate.

- Quantitative determination of paracetamol in tablets was realized by applying two contemporaneous methods of instrumental analyzes: spectrophotometry in UV zone and chromatography in liquid phase with high pressure (HPLC).
- Results of defining the content of paracetamol in tablets by aforementioned analytical methods, immediately following the preparation and 3 months after preparation, have indicated that content of the acting matter in all four formulations is consistent with pharmacopoeias requirements. Changes in the results of analyses between two applied methods were inconsiderable.
- * In our opinion, formulation 1 stand as more appropriate formulation for paracetamol tablets, because it is simpler in terms of preparation, even though formulation 2 also meets requirements

of official literature of specialty.

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