www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2015; 4(10): 27-30

www.thepharmajournal.com
Received: 22-10-2015
Accepted: 23-11-2015

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Development of composition and technology for effervescent tablets containing salts of zinc

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Abstract
WHO recommendations for use of zinc salts as anti-diarrheal remedy for children were issued in 2006. We have carried out a study on development of a domestic product that meets the requirements of these recommendations.
A complex work for creating a formulation containing zinc salts in an amount of 10 mg, in terms of zinc in the form of effervescent tablets has been carried out. The technological characteristics of the resulting compositions have been studied. The studies are summarized as a block diagram of the technological process.
The compositions of effervescent tablets have been developed and their technological quality indicators have been studied. The features of the dosage form with zinc manufacturing process have been outlined.

Keywords: effervescent tablets, technology development, zinc, WHO recommendations, diarrhea.

1. Introduction
It is currently believed that the use of zinc in the treatment of acute diarrhea affects immune function or intestinal structure or function and recovery of epithelial process in diarrhea. It is known that zinc plays a crucial role in the metal-enzymes, polyribosomes cell membrane and cellular function and also plays an important role in cell growth and immune system function. Loss of intestinal zinc during diarrhea aggravates pre-existing zinc deficiency.
Convincing evidence of the clinical significance of zinc were obtained by randomized controlled trials evaluating the effect of zinc supplementation during acute and persistent diarrhea. In 2001 WHO convened a meeting of experts in New Delhi, India, to review the results of these studies [1].
The experts concluded that the zinc supplement given in an amount of 10-20 mg per day for 10-14 days, is an effective means of significantly reducing the severity of diarrhea and the duration of the disease [1].
WHO recommendations for use of zinc salts as anti-diarrheal remedy for children were issued in 2006. We have carried out a study on the development of a domestic product that meets the requirements of these recommendations. The research included the development of both solid and liquid dosage forms.
The analysis of the antidiarrheal action drugs in Ukrainian market has revealed the predominance of solid dosage forms. But these drugs are not intended for use in pediatrics. There was a need for a drug which parameters would satisfy the WHO recommendations. To solve this problem the works on the creation of effervescent tablets have been performed.
The advantages of instant formulations include high bioavailability, ease of application and dosing, the possibility of combining the inter-reacting components and the correction of unpleasant organoleptic properties of drug substances.
Among the group of instant dosage forms special place belongs to effervescent preparations. The technology of such drugs requires special conditions of production and additional studies of shelf life [1, 2].
The aim of this research was to develop a formulation ensuring the implementation of the WHO recommendations to creation of tablets, containing zinc salts.
To achieve this aim it was necessary to complete the following tasks:

1. To develop the optimum composition of effervescent tablets, and also offer the technology of their production.
2. To find out the effect of different technological characteristics on the quality of effervescent tablets.
3. To develop an optimal composition of effervescent tablets, based on compliance with the

requirements of the State Pharmacopoeia of Ukraine and WHO recommendations.

2. Materials and Methods

The object of research were tablets with zinc acetate.

As an active substance in our study used zinc acetate salt. The amount of zinc salt has been calculated based on the conversion to pure zinc 20 mg and 10 mg, and was 0.0677 grams and 0.03385 grams of salt, respectively [2, 3].

According to the requirements of the State Pharmacopoeia of Ukraine effervescent tablets are uncoated tablets, which usually contain acidic substances and carbonates or hydrogen carbonates, reacting rapidly in water with release of carbon dioxide. They are intended to dissolve or disperse a drug in water just before use.

According to WHO the quantity of water which dissolves the tablet should not exceed 5 ml and a dissolution time should be not more than one minute. The resulting solution must meet taste requirements [1].

The technique of effervescent tablets disintegration has been designed to meet the requirements of the State Pharmacopoeia of Ukraine and WHO recommendations. Disintegration test was conducted under normal conditions (temperature from 15 °C to 25 °C). One tablet was placed in a 10 ml cylinder containing water P - in a 5 ml. The tablet considered disintegrated, if after termination of gassing around tablet or its fragments it dissolved or dispersed in water without the agglomerates of particles. Repeat the procedure on the other five tablets. The disintegration time should not exceed 60 seconds. The test is considered passed if each of the six tablets disintegrated in the above manner [1, 4].

The choice of excipients was conducted from the list of excipients which are used for the manufacture of solid dosage forms (Table 1) allowed in pediatrics and registered in Ukraine, and are also used in oral rehydration therapy for the treatment of diarrhea in children [1, 5].

Table 1: The list of excipients.

Name of substance	Technological functions	Solubility in water
Potato starch	Binder	Insoluble
Microcrystalline cellulose	Binder	Insoluble
Sodium croscarmellose	Binder	Insoluble
Polyvinylpyrrolidone	Binder	Insoluble
Sorbitol	Sweetening agent, sweetener, sugar substitute	Soluble
Glucose	Sweetening agent, sweetener, sugar substitute	Soluble
Fructose	Sweetening agent, sweetener, sugar substitute	Soluble
Sodium saccharin	Sweetening agent, sweetener, sugar substitute	Soluble
Sodium bicarbonate	Blowing	Soluble
Citric acid	Blowing	Soluble
Magnesium stearate	Glidant, free flowing agent	Insoluble
Talc	Glidant, free flowing agent	Insoluble

Results and Discussion

As the result of the studies it has been found that the presence of potato starch and magnesium stearate in the tablets by dissolution leads to supersaturated suspension forming a glidant film on the surface of the solution, which does not comply with organoleptic characteristics shown to the dosage form.

This was the reason the tablet weight was reduced to 0.2 g by excluding starch from the tablet mass composition.

Magnesium stearate, due to its structure, has advantages over btalc as a glidant, but forms a film on the water surface. Therefore, the prepared model compositions of tablet masses containing zinc acetate dehydrate, microcrystalline cellulose, sodium bicarbonate and citric acid were very hygroscopic and sticked to the operating parts of tablet press.

Based on these results, in the tablet mass introduced polyvinylpyrrolidone as a binder and talc as a glidant.

To improve the taste characteristics of the resulting suspension it was advisable to introduce, as a filler - sugar, besides having a good solubility instead of insoluble microcrystalline cellulose.

In the preparation of the tablets to the composition of powdery mass introduced sorbitol which, when used in direct compression technology has several advantages over glucose and fructose by hygroscopicity and solubility percentage.

Based on studies, we have developed a composition which is given in Table 2.

have been produced pilot samples

Table 2: Recommended composition of tablets with zinc acetate.

Number	Name of component	Quantity in g	Quantity in%
1	Zinc acetate dehydrate	0,03385	16,925
2	Sorbitol	0,06015	30,075
3	Sodium hydrocarbonate	0,0400	20,00
4	Citric acid	0,0600	30,00
5	Polyvinylpyrrolidone	0,0040	2,00
6	Talc	0,0020	1,00
	Total:	0,2000	100,00

By the method of direct compression for further technological and analytical studies [6, 7, 8].

Figure 1 shows a block diagram of technological process of effervescent tablets containing zinc salts production. The gray color indicates critical stages and points in the production process.

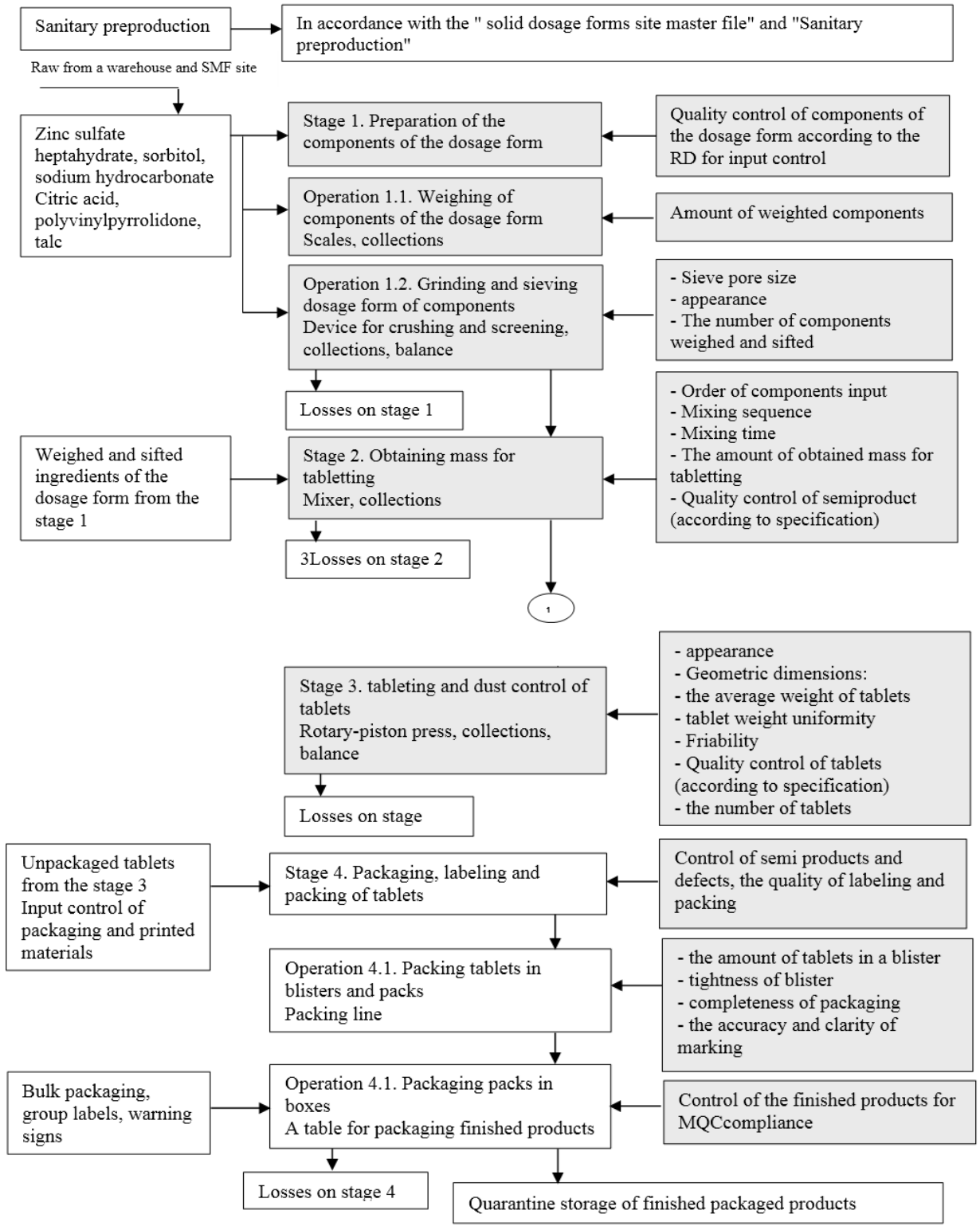

Fig1: A block diagram of the technological process of effervescent tablets production

As a result, we have obtained effervescent tablets of plain cylindrical shape, with a notch, a diameter of 7 mm. Technological characteristics of the obtained sample are shown in Table 3.

Table 3: The technological characteristics of the developed composition.

Indicator	Criteria	Results
m, g	0.20 g	0,20
d, mm	7 mm	7 mm
h, mm	2.5 - 3.0 mm	3 mm
The strength of crush, kgf	2,04 – 2,1 кгс	3,5 – 7,8 кгс
Disintegration, min	1 min (in 5 ml of water)	50 sec
Friability, %	Not more than 1%	0,8 %

The quality of resulting tablets meets both the requirements of the State Pharmacopoeia of Ukraine and WHO recommendations [1, 3].

Description of technological process comprises classical tableting by direct compression steps, but in steps 2, 3 and 4 specific production conditions should be used to avoid excessive moisture ingress into the process [4, 5].

Conclusions

As a result of the studies, we have conducted complex research work on creation of preparation containing zinc salts in an amount of 10 mg, in conversion to zinc in the form of effervescent tablets. The technological characteristics of the resulting compositions have been studied. The studies conducted have been summarized in the form of a block diagram of the technology development that can easily be repeated on pharmaceutical enterprises of Ukraine.

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