PROCESS OPTIMIZATION OF PREPARATION OF DICLOFENAC GASTRO- RESISTANT TABLETS

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Summary: A technological optimization of production process for manufacture of diclofenac sodium gastro-resistant tablets was explored. Tableting after granulation in fluidized bed conditions were examined as possible simplified methods for preparation of diclofenac-containing tablets. Single and double-layer enteric coating were proposed as suitable and less time consumable method for preparation of entero-solvent coating. Voltaren 50 mg was used as a reference drug product for evaluation of the factor of similarity.

Key words: diclofenac, tablets, gastro–resistant.

Introduction

Diclofenac is a nonsteroidal anti-inflammatory drug which possesses an inhibitory effect on both the cyclo-oxygenase and lipoxygenase pathways. It acts by potent cyclo-oxygenase inhibition (mainly on COX-2), reduction of arachidonic acid release, and enhancement of arachidonic acid uptake [1]. Following oral administration, diclofenac is rapidly absorbed, but it undergoes extensive first-pass effect, which limits its oral bioavailability (up to 50 – 60%) [2]. It is available in two enteral formulations - diclofenac potassium (formulated to dissolve under the acid conditions of the stomach) and diclofenac sodium, usually formulated in enteric-coated forms for delayed release of the drug in the duodenum.

Diclofenac sodium is poorly soluble in acidic conditions, but highly soluble in basic medium, so the change of pH in the gastro-intestinal tract (GIT) affects its solubility, absorption and efficacy [3]. The enteric coating of diclofenac formulations allows an unchanged drug's passage through the stomach and release in the intestine, ensuring better dissolution and absorption, and avoiding its irritating effect on gastric mucosa [4]. Enteric coating is achieved by polymers, such as cellulose acetate phthalate

and copolymers of methacrylic acid and its esters [5].

Diclofenac sodium is available on the market in both multiple-unit and single-unit dosage forms. Multiple-unit dosage forms (pellets, spheroids) have some advantages in comparison to the single-unit dosage forms. They disperse freely in the GIT, invariably maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects, without significant influence of drug bioavailability [6]. In the same time the production of multiple-unit dosage forms is more complicated in comparison to the single-unit dosage forms and usually requires specialized equipment. There are some reports in the scientific literature, related to the production of multiple-unit dosage forms using a standard granulating equipment [7]. Wet granulation method was used for preparation of enteric-coated diclofenac sodium granules, using solution of Eudragit L 100 as coating, binding and granulating agent. The authors show that the release of active substance satisfied requirements of USP only when plasticizer (PEG 400, di-n-butyl phthalate) was added.

However, enteric coated tablets are predominantly marketed. Their production is easier and does not require specialized equipment and the technologies are well known.

One of the main requirements for generic's drug production is related to the drug release - the generic analogue release profile should be similar to those of the original drug (similarity factor should be in the range 50-100) [8]. At the same time, the aim to reduce production costs, especially of generic products, goes through simplification of some of the technological processes. It is evident that technological processes can directly affect the biopharmaceutical characteristics (i.e. drug release properties), so the optimization of production should be done after careful consideration of all characteristics of the drug formulation. Almarzouki et al. investigated the importance of the method used for preparation by comparison of three marketed products, containing diclofenac [9]. It was determined that one of the brands showed low solidity, its disintegration time was not in compliance with the officially proved limits and showed an accelerated dissolution profile, compared to the original drug product Voltaren.

From a manufacturing point of view, granulation in fluidized bed has some advantages compared to granulation in a high-shear mixer granulator and subsequent drying of the granules. The granulation and drying processes are carried out in one apparatus, which reduces the number of machines used, shortens the production time and increases the efficiency of the production. In addition, although the short time of granulation process in the mixer granulator is achieved, this method is followed by a long period of cleaning, washing and proofing (with samples) of its physical and microbiological purity. The same applies to any other appliance, involved in the production process. The tablet's coating is another time-consuming stage in the manufacturing process. For example, for classic multi-layer tablet it could take 2-3 days. The shortening of this process would reduce production costs.

The main goal of this study was to investigate the possibility for production of diclofenac sodium tablets using tabletting after fluidized bed granulation. In addition, we investigated the possibility for replacement of the classical three-layer gastro-resistant coat to a single or double layer.

Materials and methods

Materials

Diclofenac sodium was purchased from Aarti drugs Ltd, India. Lactose monohydrate, Maize starch, PVP, Microcrystalline cellulose, Magnesium stearate, Silicon dioxide, HPMC E6, PEG 400, PEG 6000, Eudragit L30D, triethyl citrate, talc, iron oxide yellow, titanium dioxide meet the requirements of the European Pharmacopoeia (PhEur).

Qualitative and quantitative composition of diclofenac cores, used in the study, is given in Table 1.

Composition	Quantity (mg)
Active substance	
Diclofenac sodium	50.0
Excipients	
Lactose monohydrate	40.0
Maize starch	60.0
PVP	4.0
Microcrystalline cellulose	42.0
Silicon dioxide	1.0
Magnesium stearate	3.0
Total:	**200.0**

Table 1: Qualitative and quantitative composition of diclofenac cores (per tablet).

Methods

Granulation and mixing: Granulation and mixing processes were performed using fast speed mixer granulator (Oystar Huttlin Mycromix) and fluidized bed apparatus "Huttlin Unilab" provided with sprayer 1.2 mm.

Drying: Fluidised bed apparatus "Huttlin Unilab". Supply air temperature: 45-55ºC. Residual moisture of the product ≤ 2.0%.

Measurement of residual moisture: Scale "Precisa XM 50" in 105ºC.

Calibration of the finished granules: Sieves with a pore size of 1.5 mm.

Characterization of the finished granules: Tapping apparatus: "Sotax TD1", equipped with a measuring cylinder of 250 ml. The determination was made, according to the requirements of European Pharmacopoeia. The following indicators were monitored: bulk volume, volume after tapping, index of compression and Hausner's factor.

Tableting: The tablets (biconvex, 8 mm diameter) were prepared using a rotary tablet machine "Kilian Pressima".

Mechanical strenght: The measurement was conducted by using the apparatus for measuring of the mechanical strength "Sotax HT1". Ten tablets were used in the study.

Coating of the cores: Fluidized bed apparatus "Huttlin Unilab". Spray nozzle 1.2 mm. Supply air temperature: 45-55ºC. Inlet air - 500 m^3/h. Spray air 0.5 atm. Microclimate 0.1 atm. Product temperature 42ºC.

Disintegration of the tablets: Disintegration test of Ph. Eur., Gastro-resistant tablets.

Drug release study: Dissolution test, Delayed-release solid dosage forms, Method A of Ph. Eur. The study was carried out by using the "Sotax AT7 Smart " apparatus, equipped with 7 vessels (apparatus type II - Paddle method), at speed of 100 rpm. Buffer stage medium- 1000 ml phosphate buffer pH6.8. The samples were analyzed spectrophotometricaly - apparatus "Thermo Evolution 300" at a wavelength of 276 nm.

Requirement: more than 80% released drug after 60 min in buffer stage.

Factor of similarity: The calculation of the factor of similarity was made according to the requirements of Guideline on the investigation of bioequivalence (CPMP / EWP / QWP / 1401/98 / Rev1).

Results and discussion

Comparative composition of diclofenac tablets were prepared by the method of tableting after wet granulation, using a high speed mixer granulator. The active substance and the excipients were mixed until an uniform powder mixture was obtained. The uniformity of the powder was determined by analysis of three samples taken from different points in the mixer. The finished mixture was wetted with solution of PVP in distilled water and was granulated using mixer granulator`s high-shear chopper. Drying takes place in an fluidized bed-type dryer at a temperature of 50°C until a residual moisture below 2%. The granules were calibrated through a sieve with a pore size of 1.5 mm. The granules were characterized by good flow ability (index of compression 14.00 and factor of Hausner1.16) (Fig. 2). Tablets having a mechanical strength of about 100 N were prepared after powdering with 1.5% of magnesium stearate and 0.5% silicon dioxide.

Prepared tablet cores were then coated with three-layer gastro resistant coating, consisting of the a) film coat (3 mg HPMC E6 per tablet with 20% PEG 400 as a plasticizer), b) enteric coat (12 mg Eudragit L30D per tablet with 10% triethyl citrate as plasticizer and 50% talc as an anti-tacking agent) and c) color coat (3 mg iron oxide - yellow, 0.5 mg titanium dioxide, 0.4 mg HPMC E6 and 1.0 mg PEG 6000 as plasticizer per tablet).

The testing of the coated tablets showed that they met the Ph. Eur. requirements for disintegration of gastro- resistant tablets.

Thereafter, the drug release profile of the coated tablets was compared to those of the original medicinal product Voltaren 50 mg (diclofenac sodium). The results are presented in Fig. 1.

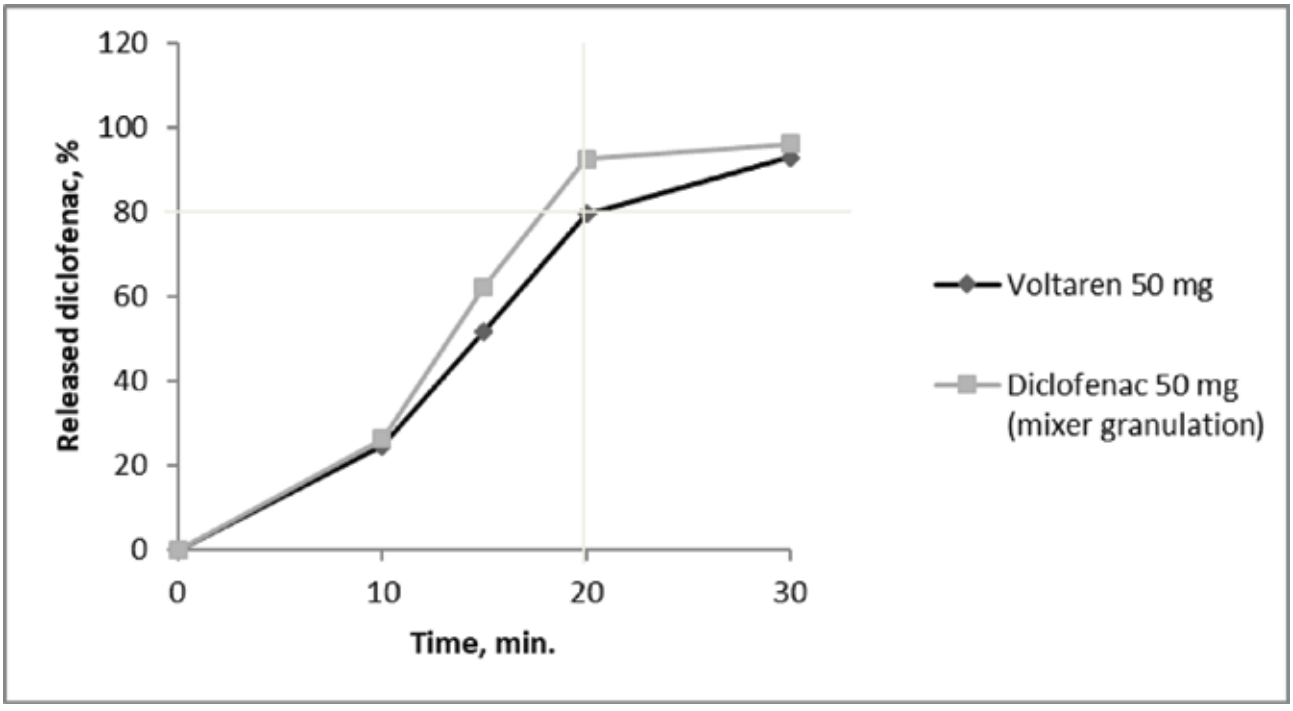

Figure 1: Release profiles of Voltaren 50 mg tablets and Diclofenac 50 mg tablets, produced by the method of tableting after mixer granulation. The study was conducted in phosphate buffer, pH = 6.8.

It was found that both tested formulations released more than 80% of the active substance within 20th minute. The factor of similarity was 53.2, i.e. the release profiles of both formulations (Diclofenac 50 mg test formulation and Voltaren 50 mg) were considered to be similar.

The next series of experiments were aimed to investigate the production of diclofenac-containing granules in a fluidised bed granulator. An achievement of this goal would avoid wet granulation stage in mixer granulator and would reduce production losses during the product manufacturing. For this purpose, we used a Hüttlin apparatus equipped with 1.2 mm sprayers.

The following granulation conditions were obtained in our preliminary experiments:

- Flow speed – 300 m^3/h
- Inlet air temperature – 45 ± 5^0C
- Temperature of the granules– 32 ÷ 36^0C

In preheated camera of the device homogenized mixture of diclofenac, lactose, and 70% of maize starch is transferred to.

After reaching the operating temperature (38°C), a solution of PVP in distilled water was added through the sprayer. All described parameters were not changed during inflowing of granulation solution. The granules were dried to residual moisture below 2% and were calibrated through a sieve of 1.5 mm. Finished granules characterizes with good flowability (index of compression 18.0, Hausner factor 1.22) (Fig. 2).

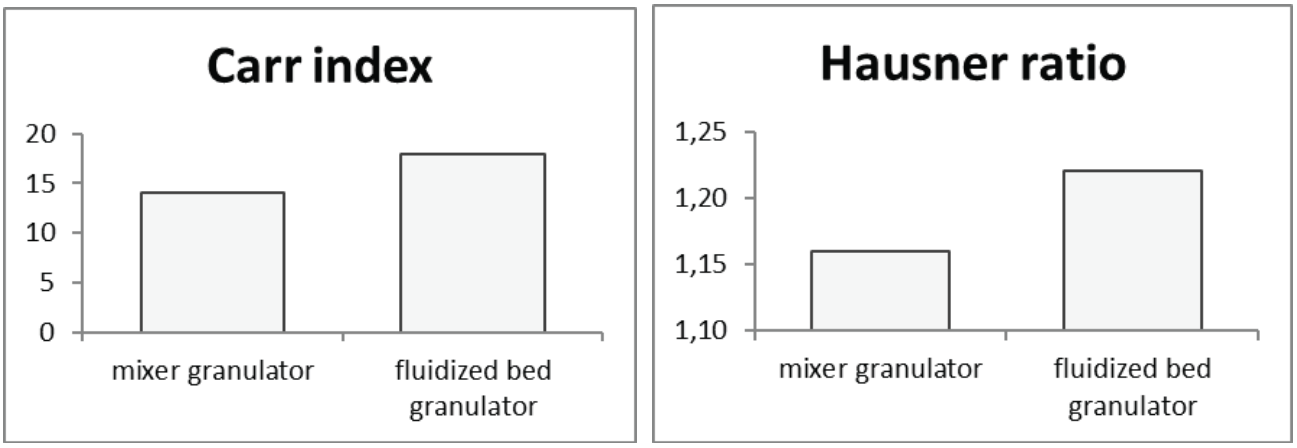

Figure 2: Carr`s index and Hausner`s ratio of granules, obtained by mixer granulation and fluidized bed.

Tablets with a mechanical strength of about 100 N were easily obtained after powdering the granules with the rest of maize starch, microcrystalline cellulose, silicon dioxide and magnesium stearate. The tablets were further coated with three-layer gastro-resistant shell, using the composition described above. A test to study the rate and speed of drug release was conducted and the test results are presented in Fig. 3.

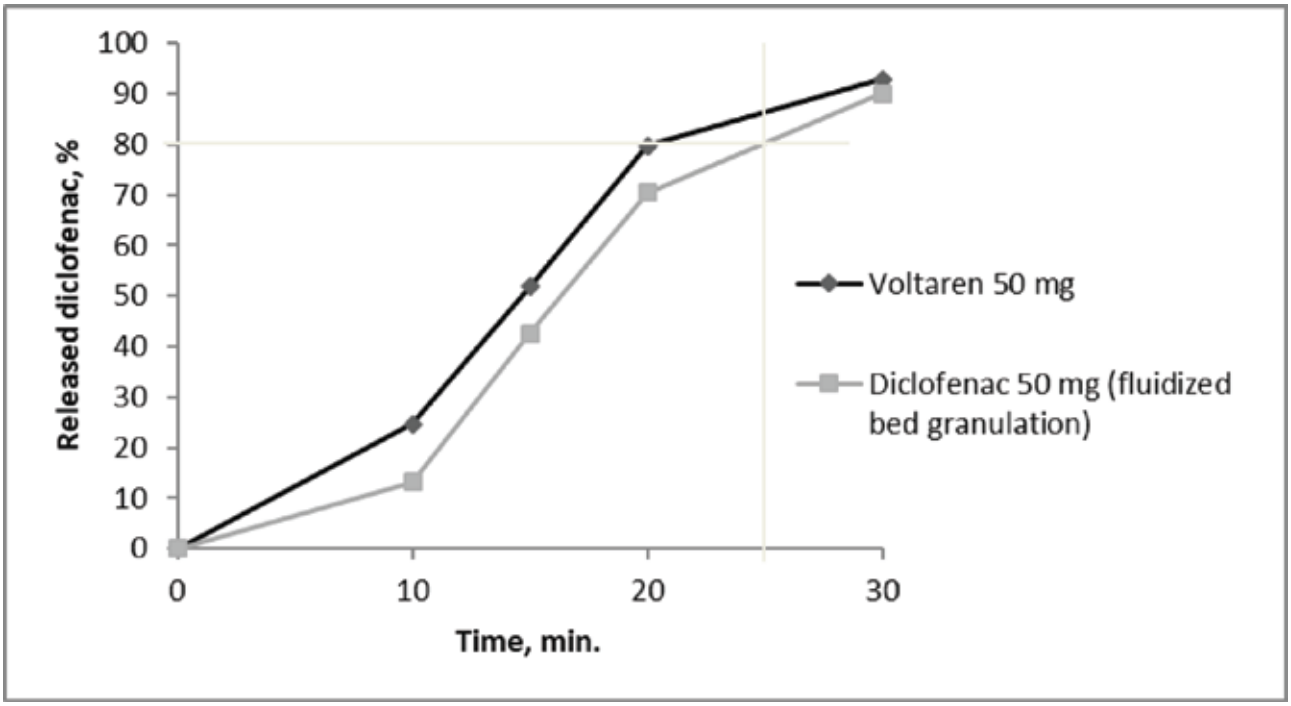

Figure 3: Release profiles of Voltaren 50 mg and Diclofenac 50 mg tablets, prepared by tableting after granulation in the fluidized bed. The study was conducted in an phosphate buffer medium, pH = 7.2.

The comparison between release profiles of tablets prepared after granulation in fluiduzed bed and original product Voltaren showed that over 80% of active substance was released at 25 min in both cases. The calculated factor of similarity was 52.62, i.e. release profiles were similar.

The three-layer coating technology is a classic and reliable coating method, but at the same time the technology is complicated and time-consuming. Under real manufacturing conditions, this procedure could takes 2 to 3 days per batch. Any simplification of the technology and shortening the technological time would lead to a reduction in the production costs. Therefore, in attempt to simplify the technology process, we decided to test the possibility for using a single- and double-layer coating. The produced coated tablets need to meet the requirements of Ph. Eur. for enteric-coated tablets and dissolution profile, similar to the referent product, as stated by Ph. Eur. .

In the initial experiments, we used a single layer coating having the following composition: Eudragit L30D 52.9%; Triethylcitrate 5.3%; Talc 26.4%; Iron oxide yellow 13.2%; Titanium dioxide 2.2%. The pigments were suspended in water, using Ultraturex and the resulting 30% suspension was added under constant stirring to Eudragit L30D. 10% suspension was obtained upon dilution with water. Film coating was carried out in Huttlin. Samples were tested according to Ph.Eur. requirements for delayed release solid dosage forms (Method A). Drug release measurements were made at the end of the residence time, in the acidic medium, and then, after 60 minutes in a phosphate buffer(Table 2).

Table 2. Quantity released diclofenac (%) from one-layer entero-solvent tablets. Dissolution test, delayed release, Method A of Ph. Eur.

	Coating weight, %	4.5	5.5	7.5	8.5	10.0
Diclofenac release, %	Acid buffer, 120 min	1.5	1.5	2.0	2.0	1.9
	Phosphate buffer, 60 min	73.2	91.5	92.8	95.8	99.9

Results from acid buffer measurements showed that the increase of the weight of entero-solvent coating practically did not influence the release rate of diclofenac. It was demonstrated, that even smallest coating weight (4.5%) ensures drug release lower than 10%, which meets the requirement of Ph. Eur. In the same time, in phosphate buffer, the increasing of the coating layer led to the increase of drug release rate. This tendency was very clearly expressed, so that the resulted tablets (4.5% coating weight) do not met the Ph. Eur requirements (not less than 80% released drug). These results showed that there is a negative interaction between tablet core and entero-solvent layer.

In order to minimize this negative interaction, we continue our experiments with production of series of two layer entero-solvent tablets. In this case, the tablet cores were sealed using HPMC E6/ PEG 400 coating layer prior to the entero-solvent coating (Table 3).

Table 3. Quantity released diclofenac (%) from two-layer entero-solvent tablets. Dissolution test, delayed release, Method A of Ph. Eur.

	Coating weight, %	5.0	6.5	7.5	8.5	10.0
Diclofenac release, %	Acid buffer, 120 min	2.0	2.0	2.0	1.9	1.9
	Phosphate buffer, 60 min	102.4	99.5	103.2	98.2	98.6

Based on the obtained data, no differences in drug release between one- and two-layer entero-solvent tablets were observed in acid buffer, so drug release met the requirements of Ph. Eur. Significant differences were observed in the dissolution profile of the drug formulation in phosphate buffer – as opposite to the results, obtained in acid buffer, in phosphate conditions

there was no entero-solvent coating weight variation in Diclofenac release. Moreover near 100% of the drug was released in all formulations.

In order to confirm the suitability of the coating process, we evaluated the process of release into the medium with pH = 6.8. We suppose, that the release profile in these conditions should be similar to the release profile of the original product Voltaren 50mg.

The drug release in a medium pH = 6.8 is presented in Figure 4.

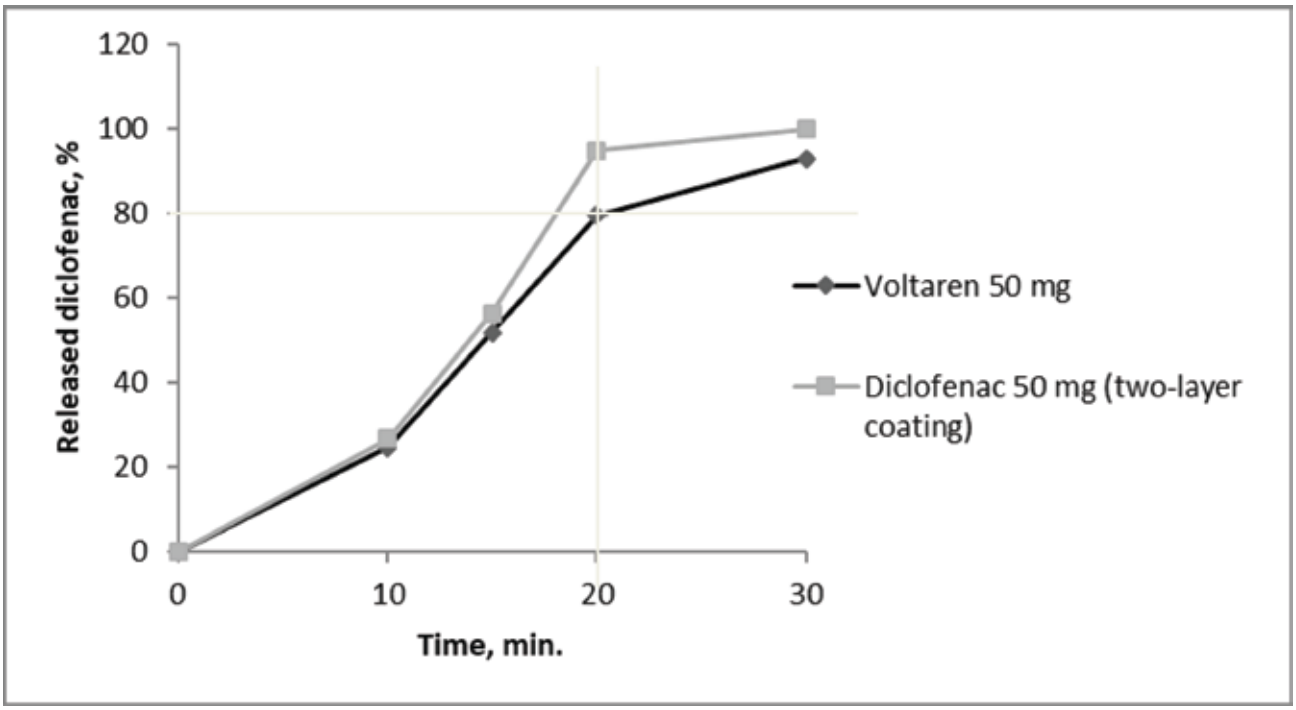

Figure 4: Release profiles of Diclofenac 50 mg coated tablets and Voltaren 50mg talets. The study was conducted in phosphate buffer, pH = 6.8.

The calculated factor of similarity had a value of 52.74 (acceptable values are in the range 50 ÷ 100), i.e. release profiles in a medium pH = 6.8 of both tested diclofenac 50 mg formulation and the original product (Voltaren 50 mg) can be considered as a similar.

Conclusion

Based on the results from our study, a technology-optimization of production of gastro-resistant tablets, containing Diclofenac sodium 50 mg was confirmed. The obtained data showed that the method of tableting after granulation in a fluidised bed is much promising. The obtained granules showed a good flowability and allowed preparation of cores with good mechanical properties. Resulted two-layer modified coating met the requirements of Ph. Eur. for gastro-resistant tablets. The suitability of the described technology for preparation of tablets Diclofenac 50 mg has also been proved by the obtained comparative results and similarity of the release profiles of diclofenac test formulation and Voltaren 50 mg.

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