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INCREASING THE BIOAVALILABILITY OF MEBENDAZOLE I. INFLUENCE OF CROSCARMELLOSE ON DISSOLUTION RATE, EXTENT AND MECHANISM IN SIMULATED GASTRIC MEDIUM

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ABSTRACT: The objective of the research presented in the paper was the obtaining of mebendazole tablets with increased bioavailability. Five solid formulations containing croscarmellose, an internally cross-linked sodium carboxymethylcellulose as superdisintegrant in 1%, 2 %, 3 %, 4 % and 5 % concentrations were prepared by direct compression and characterized in accordance with USP specifications. For the mebendazole quantitative analysis a HPLC method with UV detection was developed and validated. The effect of croscarmellose on rate, extent and mechanism of release of mebendazole from resulted formulations was studied. In vitro release kinetics was evaluated using USP Apparatus 2, in acidic medium (0.1N HCl) containing 1% sodium lauryl sulfate (SLS). The release of mebendazole was complete within 120 minutes. Rate and extent of release increased with croscarmellose concentration. The release mechanism was diffusion controlled, application of Higuchi law being excellent both in pre and post-disintegration phases. Peppas and Weibull models proved to be also applicable.

Keywords: mebendazole tablets, croscarmellose, bioavailability, diffusion controlled release

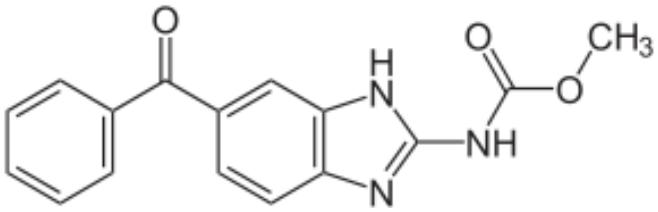
INTRODUCTION:

Bioavailability of oral administered drugs is determined by several factors, most important being water solubility and intestinal permeability, which define their belonging in one ofthe four classes of the Biopharmaceutical Classification System (Amidon et al., 1995). Further, based on observation that solubility and permeability are correlated with bioavailability, metabolism and elimination, Wu and Benet (Wu and Benet, 2005) introduced the Biopharmaceutics Drug Disposition Classification System (BDDCS). Particularly, highly permeable class I and class II BCS active substances are substrate of the metabolizing enzymes within hepatocytes. So that it becomes obvious that class I and class II compounds are eliminated via metabolism while class III and class IV compounds are eliminated unchanged into urine and bile.

Most of the drugs follow this correlation but there are also some exceptions. Mebendazole is predominantly eliminated in the unchanged form in the urine and bile. Lindenberg et al (Lindinberdg et al., 2004) considered mebendazole as either class II or class IV so that its classification is a problem.

BCS class IV drugs due to their low solubility and low permeability have a poor bioavailability and a high variability. Class II drugs, with a low solubility and a high permeability have a high variability but usually a good bioavailability. In the case of mebendazole, whatever its classification, it is characterized by a low bioavailability and a high variability, leading to the necessity to increase its solubility and dissolution rate in the gastrointestinal fluids.

Mebendazole (MBZ), chemically methyl-5-benzoyl benzimidazole-2-carbamate, has a broad-spectrum anthelmintic drug for infections with ascaris, threadworms, hookworms and whipworms.



Low water solubility is considered the main cause in implying low oral bioavailability. On other hand, great increase of bioavailability and consequently of plasma levels could lead to appearance of adverse effects such as liver damage and anemia. (Dayan, 2003).

Improving the solubility of poorly soluble drugs administered orally is a challenge for research and formulation specialists (Fricker et al., 2010). A lot of methods have been conceived increase solubility to of poorly soluble drugs, based on physical modification as for example drug embedding in a carrier (Butu et al, 2015; Ortan et al., 2015; Dinu-Pirvu et al., 2013),

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micronization (Müller et al., 1995), or chemical modification such as complexation (Challa et al., 2005; Loftsson and Brewster 1996), salt formation (Martins et al., 2012) or miscellaneous methods such as co-solvent (Uivarosi et al, 2013; Anuta et al., 2014), use of surfactants (Jafvert et al., 1994) etc.

In particular, several practical methods have been applied to increase the solubility and availability of mebendazole such as administration as prodrug (Nielsen et al., 1994), preparation of solid dispersions (Chiba et al., 1991; Yellanki et al., 2010), crystal engineering, (Chen et al., 2012) complexation (Shehatta, 2002), Self-Micro-emulsifying Drug Delivery System (Hussein, 2017), micronization (Gemmell et al., 1985), salt formation (Brusau et al., 2008) etc. Some of these strategies tried to increase solubility and bioavailability (Kiran et al., 2010; Ortan et al., 2009), others looked for increase dissolution rate by optimization of the formulation and preparation method (Carlert et al., 2012). The aim of the present paper is to present a research concerning development of mebendazole formulations containing different concentrations of Ludiflash as liant and disintegrant and croscarmellose as superdisintegrant, testing in vitro dissolution of resulted tablets and estimation of mechanism of release kinetics.

MATERIALS AND METHODS:

Materials

Mebendazole was a gift sample from Iraqi Pharmaceutical Industry (IPI) Company (Baghdad – Iraq). Croscarmellose, an internally cross-linked sodium carboxymethylcellulose, superdisintegrant in pharmaceutical formulations was in 1%, 2%, 3 %, 4% and 5% concentrations (Table 1).

Tab. 1
Composition of mebendazole tablets

Mebendazole ODT formulations		Formulation 1		Formulation 2		Formulation 3		Formulation 4		Formulation 5	
		Amount		Amount		Amount		Amount		Amount	
Nr	Raw ingredients	mg/tablet	%	mg/tablet	%	mg/tablet	%	mg/tablet	%	mg/tablet	%
1	Mebendazole	100.0	16.7	100.0	16.7	100.0	16.7	100.0	16.7	100.0	16.7
2	Ludiflash(Basf)	482.0	80.3	476.0	79.3	470.0	78.3	464.0	77.3	458.0	76.3
3	***Croscarmellose sodium***	***6.0***	***1.0***	***12.0***	***2.0***	***18.0***	***3.0***	***24.0***	***4.0***	***30.0***	***5.0***
4	Talc	6.0	1.0	6.0	1.0	6.0	1.0	6.0	1.0	6.0	1.0
5	Magnesium Stearate	6.0	1.0	6.0	1.0	6.0	1.0	6.0	1.0	6.0	1.0
Total amount		**600.0**	**100.0**	**600.0**	**100.0**	**600.0**	**100.0**	**600.0**	**100.0**	**600.0**	**100.0**

Ludiflash (BASF) contains manitol 90 % as filler, Kollidon CL-SF 5% disintegrant and Kollicoat SR 30 D as water insoluble binder which accelerates disintegration.

Methods

Tablets were controlled using USP methods in terms of content in active substance and physico-chemical properties. For the assay of mebendazole a HPLC method with UV detection was developed and validated. Mebendazole release kinetic was measured using USP Apparatus 2, in acidic medium containing (HCl 0,1 N) with addition of Sodium Lauryl Sulfate 1% [HCl+ SLS], 900 ml, 75 rpm.

RESULTS AND DISCUSSIONS:

Design, optimization, preparation and evaluation of mebendazole tablets using croscarmellose and Ludiflash.

Five solid formulations containing croscarmellose sodium and Ludiflash (BASF) were prepared. The required quantity of mebendazole was slowly mixed with croscarmellose in a 2 kg double cone mixer at 10 revolutions per minute for 15 minutes. After the first dilution, the quantities of Ludiflash and talcum were added and the mixing procedure was repeated for 15minutes.

The next powdering step was blending the mix with magnesium stearate for 3 minutes. This 3 minutes time interval was found to be a critical parameter, Lubrication of the mixture more than 3 minutes lead to segregation of the mixture in the tableting machine. After blending the mixture was sifted through a 200 mesh sift. Tablets were obtained by direct compression, using an eccentric tablet press single punch, equipped with a 12 mm diameter set punch. The machine weight screw was adjusted so that the compressed tablets had an average weight of 600 mg.

The pressing force screw was adjusted at a tension optimal for tablet compression. The pressure required to compress the tablets was quite low thanks to good compressibility of the Ludiflash.

The tablets where clean, no sticking to the faces of the punches. The inside pressure of the tablets and the plasticity of the material was good as no capping effect was observed.

In vitro drug release

Multiple phases release of mebendazole. Whatever the composition of the tablets release was characterized by two different main phases: pre and post disintegration (Mircioiu et al., 2012; Preda et al., 2012). In the first phase of the dissolution experiment tablets were swollen by water, doubling their volume, as can be seen in figures 1a and 1b.

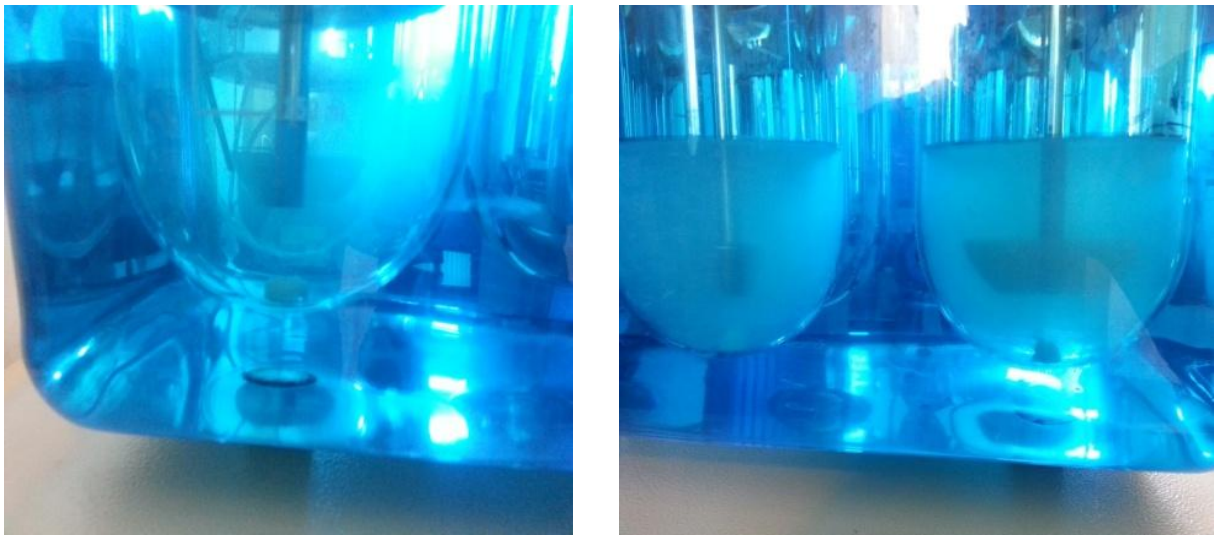

Fig.1 Absorption of dissolution medium in tablets: 1a. tablet before absorption, 1b. Swelled and superficially disintegrated tablet.

After this time interval appeared disintegration in many particles, visible at direct visual analysis (Figure 2).

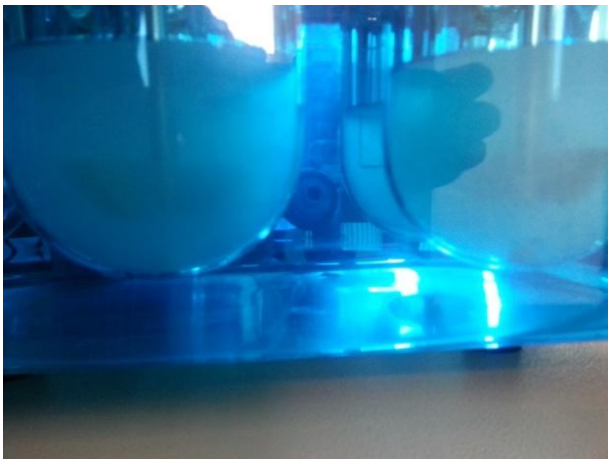

Fig. 2. Final disintegration of tablets in small particles

After 2 hours, release was complete in HCl and sodium lauryl sulfate 1 %. As can be seen in Figure 3, the cluster of entire set of curves (n= 15) is homogeneous distributed in space with exception of a single curve.

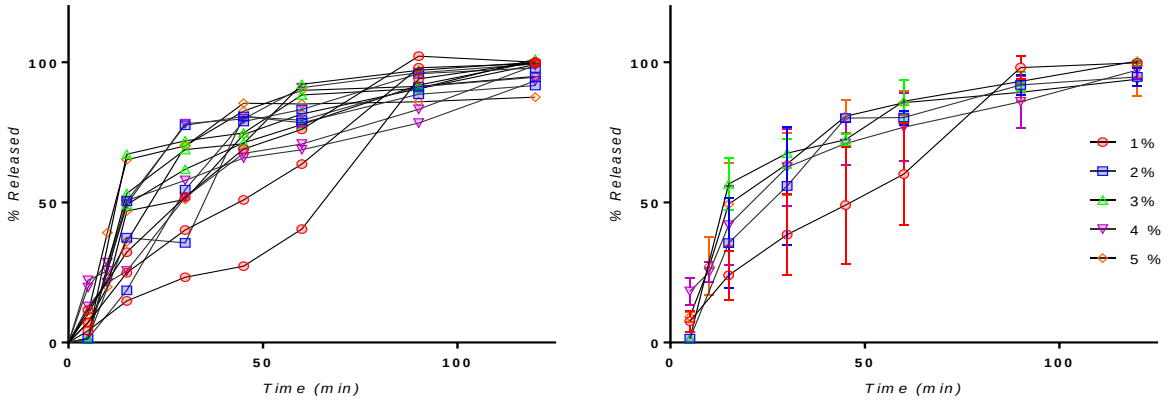

Fig. 3. Dissolution curves. 3a entire set of curves, 3b. Mean curves for the five CC concentration

The mean dissolution curves corresponding to different concentrations of croscarmellose are presented in Fig. 3. Excepting the first curve (CC 1%) the rest of the 4 mean curves appeared as similar even at a shallow visual inspection. This can be seen more in detail in table 2 with the resulted f2 factors in comparison of pairs of curves

$$f2 = 50 \times \log \frac{100}{\sqrt{1 + \frac{\sum_{i=1}^{n} (T_i - R_i)^2}{n}}}$$

where R and T refers to one curve considered as reference and another considered as tested release curve, measurements being performed in n time points.

If the factor f2 is greater than 50 it is accepted that release profiles are similar. If profiles are identical f2=100.

Tab. 2.
Similarity factor F2 between curves

f2	1%	4,00%	5,00%	2%	3%
1%	100	37	32	38	32
4,00%	37	100	57	52	50
5,00%	32	57	100	56	61
2%	38	52	56	100	50
3%	32	49	61	49	100

It appears that formulation F1 is dissimilar compared to all curves. The rest of curves are similar one-by one, value of f2 factor being more than 50.

Release extent, defined as Area Under Dissolution Curve (AUDC) increased approximately linear following the increase of croscarmellose concentration, as can be seen in Figure 4.

In the 3 - 5 % concentration of crosscarmelose interval a saturation of the effect on the rate and extent of dissolution could appear.

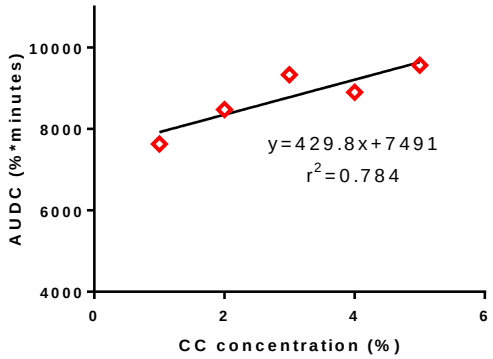

Fig. 4. Areas under mean dissolution curves corresponding to different CC concentrations

In conclusion the release in acidic medium is complete in a 2 – 3 hours interval.

DISCUSSION:

Dissolution and release mechanism.

Croscarmellose and Ludiflash action mechanism. Ludiflash (BASF) contains manitol 90 % as filler, Kollidon CL-SF 5% as disintegrant and Kollicoat SR 30 D as water insoluble binder which accelerates disintegration. The cross-linking reduces water solubility while still allowing the material to swell (like a sponge) in a formed hydrophilic network and absorb many times its weight in water. As a result, it provides superior drug dissolution and disintegration characteristics, thus improving formulas′ subsequent bioavailability by bringing the active ingredients into better contact with bodily fluids. (Swarbrick and Boylan, 1990).

After swelling a three-dimensional network of hydrophilic cross-linked polymer is formed, which becomes a hygrogel containing three different domains: “glass” (mostly hydrogel), “tough rubber” (significant proportion of water and hydrogel) and “soft rubber” (mostly water) (Omidian and Park, 2008).

Croscarmellose sodium is a very commonly used (Mumoliet al., 2011) pharmaceutical additive approved by FDA. Association of croscarmellose sodium (7.5%) with pregelatinized starch (6%) as superdisintegrants, positively influenced the dissolution properties of loratadine (5%) from orally fast dispersable tablets. (Ciurba et al., 2017). Souto et al (Souto et al., 2005) evaluated the application of croscarmellose sodium in increasing the dissolution rate of hydrochlorothiazide.

Later, in the second phase, tablets disintegrated the and a further release occurred across a much higher

surface, i.e. the total surface of particles resulted from disintegration.

In absence of a disintegrant in the tablet formulation, the dissolution was governed by the erosion-diffusion process. Even for a highly soluble drug a super-disintegrant is needed in the formulation to overcome the diffusion layer limitation and change the dissolution mechanism from erosion-diffusion to disintegration. (Desai et al., 2015)

Release kinetic modeling

Concomitant swelling and diffusion Polymer swelling, drug dissolution, drug diffusion, matrix erosion and disintegration are the basic phenomena leading to the drug release from swellable matrices. (Conti et al., 2007; Colombo et al., 1996). The model considers that the front ofsolvent is moving slowly inside the tablet determining the the apparition of a network of water channels.

Formulations contain both soluble and insoluble polymers. Consequently, a much larger swelling of the insoluble polymer takes place after partial dissolution of polymers and drug. A network of pores, of water channels, or even large cavities full of liquid through which the drug diffuses is formed very quickly.

Mebendazole concomitently dissolves in water and diffuses across a limit layer from solid network of the tablet. Since solubility of mebendazole is low it can be assumed that, at the channel wall the concentration reaches saturation or even supersaturation (Figure 5).

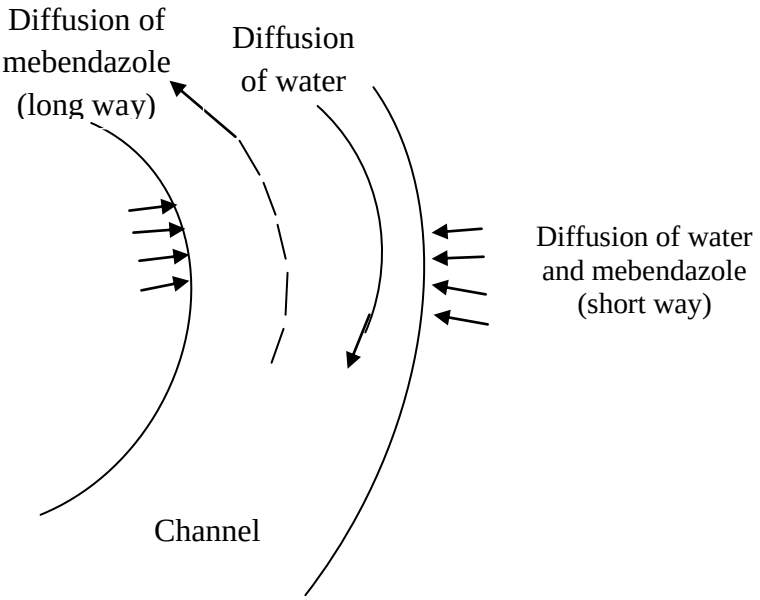

Figure 5. Concomitant swelling of tablets and release of mebendazole by diffusion

During the swelling of the tablet at least three different diffusion processes can be considered: a) diffusion of mebendazole from tablet surface to dissolution medium, b) dissolution of mebendazole from wall of channel to water (a short way diffusion) and c) diffusion in water along channel and diffusion from channel to the surrounding medium (the long way diffusion).

Initial and boundary conditions differ for the three diffusion domains. Water from channels is very different from continuously stirred water from the surface of tablet.

The general process of diffusion with swelling has been considered by many authors, starting with of Hopfenber et al. in 1978 (Hopfenber and Hsu, 1978), the researchers tried to understand the concomitant swelling and diffusion and to predict and control the drug release (Peppas, 1984), but it was very rapidly understood that the problem is much complex to be easy solved (Peppas N.A. *et al.*, 1985). Swelling means a continuous change in the boundaries which makes mathematical treatment infeasible (Bakhouya-Sabbahi N. *et al.*, 1994)). The diffusivity becomes concentration dependent, increasing with time and, with the concentration of the liquid. (Bakhouya N. *et al.*, 1999)).

"Marginal" models, in function of preponderant processes, were developed (Brazel C.S. *et al.*, 1999; Brazel C.S. *et al.*, 2000).

1. When the drug is not highly soluble and the quantity of penetrated liquid is small, the saturation concentration is reached, resulting time and space dependent of the boundary conditions for diffusion. Consequently a strong dependence of the amount of released drug on the amount of penetrated liquid it is to be expected, which could be our case since the areas under dissolution case is linearly dependent on the quantity of croscarmellose , which is further proportional with embedded water.

2. When the rate of entering diffusion of the liquid into the dosage form is much larger than the rate of diffusion of the drug out of the dosage form, the release kinetics is controlled by swelling process.

Transport from swellable systems may often lead to release under conditions that do not agree with Higuchi's or the Fickian behavior (Davidson III G.W.R. *et al.*, 1986a; Davidson III G.W.R. *et al.*, 1986b; Klier J. *et al.*, 1988; Korsmeyer R.W. *et al.*, 1986b; Korsmeyer R.W. *et al.*, 1986a; Lustig S.R. *et*

al., 1987; Peppas N.A. *et al.*, 1987)). For dosage forms of typical shapes, an anisotropic behavior toward diffusion could also be seen, as was shown with rubber discs (Azaar K. *et al.*, 2002).

Alfrey, Gurnee and Lloyd proposed (Alfrey T. *et al.*, 1966) an useful classification in terms of relative rates of diffusion and polymer relaxation:

(i) case I or Fickian diffusion in which the rate of diffusion is much less than that of relaxation;

(ii) case II diffusion, the other extreme in which diffusion is very rapid compared with the relaxation processes;

(iii) non-Fickian or anomalous diffusion which occurs when the diffusion and relaxation rates are comparable.

Case I systems are controlled by the diffusion coefficient.

In Case II the parameter is the constant velocity of the advancing front which marks the innermost limit of penetration of diffusant and is the boundary between swollen gel and glassy core.

A simple expression of this observation can be written by adding the diffusion controlled and relaxation controlled drug delivery

$$M_t / M_\infty = k_1 t + k_2 \sqrt{t}$$

In practice frequently is followed a power law

$$M_t / M_\infty = k t^n$$

The generalized expression similar to that from Crank, was introduced later in pharmaceutical literature and is known as the "Peppas equation". The power law was used extensively describe the first 60 % of the release curves. (Colombo et al., 1995, 1996; Ferrero et al., 2000; Bettini et al., 2001).

Square root release model.

Dependence of released amount of M on the square root of time is graphically present in Figure 6.

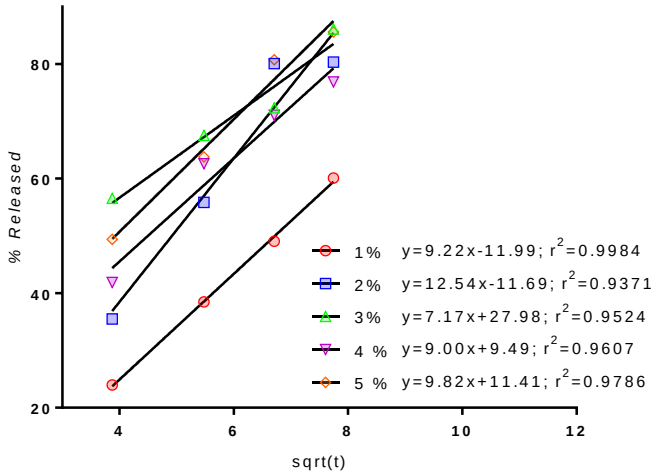

Figure 6. Linear dependence of the % of released mebendazole on the square root of time

Linear correlation is excellent but it is important to make some observations. First of all it is to note that representation of data starts from 5 minutes in case of formulation F1 and from 15 minutes in case of the rest of formulations. These time lags correspond to first phase, when release medium enter and swell the tablets but release is not yet significant.

Second observation is that the model describes usually release of 60 – 70 % of active substance. After this diffusion – controlled release appear other processess connected with disappearance of the structure of tablets or other formulations. As can be seen in figure, the diffusion phase lasted , in case of all formulations excepting F1 , even by 80 - 90 % release of mebendazole.

Since the release curves coresponding to concentrations 2, 3, 4 and 5% proved to be similar, the square root law of Higuchi was tested aldo for the mean of these curves. Then, since observation of transformation of tablets during release put in evidence a predisintegration and a postdisintegration phase, in was tested a biphasic linear fitting also for the mean curve. As can be seen in Figure 7, two excellent linear correlations between released amount and square root of time in the intervals 5 min – 45 min and 45 min – 180 min were obtained. Curve 1 could be fitted with the square root law only in the 5 min – 45 min.

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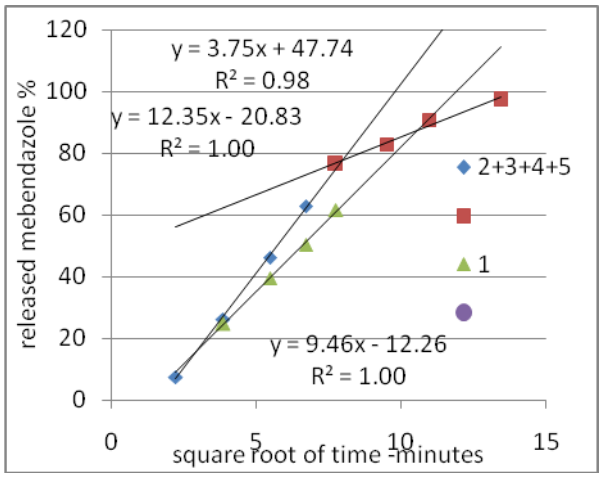

Fig. 7. Application of Higuchi model for describing release kinetics for curves corresponding to F1 and mean of F2- F5 curves

In case of several HPMC-based matrix tablets, it was demonstrated (Rinaki et al., 2003) that square root laws describes the entire drug release profile. Much more, the authors found a theoretical justification for existence of cases where equation can really be extended to all release data. Hypothesis based on the nonclassical diffusion of the solutes in the HPMC matrices as disordered media is used to interpret the successful use of the power law in describing the entire release profile. Simulation of drug release in fractal matrices (Bunde et al., 1985) or percolation model (Leuenberger et al., 1987) were used in case of HPMC matrix as disordered medium.

Keeping in mind that concomittent time course of swelling and diffusion it was considered necessary to to try also a fitting with the power law model of Peppas. Nor in the first, nor in the second phase it was not obtained a better linear correlation than in case of square root laws so that the higuchi model remains the preferred model.

A more general model introduced in natural science by Weibull (Weibull, 1951) is based mainly on the assumption that the process evoluate in more steps which are independent, run with equal rates and cumulative probability of the observed event at step n is conditioned by probabilities to observe the event at previous steps $(1-P_n)=(1-P)^n$. In case of dissolution P will be the probability that mebendazole molecule to remain within the formulation. (Langenbucher, 1972).

Time course of % released quantity R could be described by Weibull distribution function in the form $R(t) = 100 * (1 - e^{-\alpha t^{\beta}})$ or in equivalent form $\ln(-\ln(1 - R(t)/100) = \ln\alpha + \beta \ln t$

Macheras extended theory in describing escape of particles from devices of fractal geometry. When the molecule is all the time moving it obtains the equation characterizing diffusion. (Kosmidis et al., 2003a, b; Landau and Binder 2000; Bunde et al., 1985).

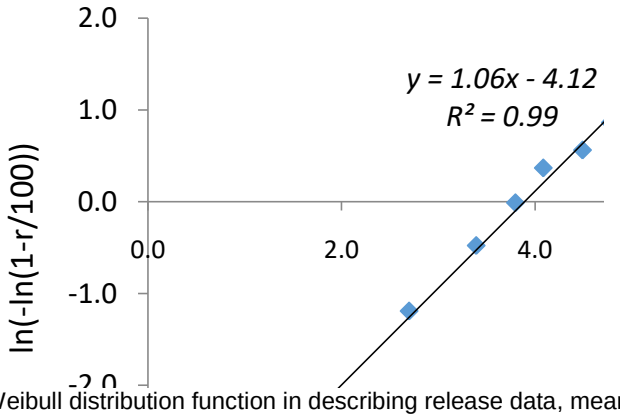

Figure 8. Application of Weibull distribution function in describing release data, mean of F2 – F5 curves

Making a vast number of simulations concerning power laws and Weibull function (Kosmidis et al., 2003) and fitting of experimental data concerning release of diltiazem and diclofenac Papadopoulou et al. concluded that in case of polymer matrices the value of the exponent β is an indicator of the mechanism of transport of the drug through the polymer matrix: $\beta \leq 0.75$ indicates Fickian diffusion in either fractal or Euclidian spaces while a combined mechanism (Fickian diffusion and swelling controlled transport) is associated with β values in the range $0.75 < \beta < 1$. For values of β higher than 1, the drug transport follows a complex release mechanism (Papadopoulou et al., 2006).

In conclusion, croscarmellose has the effect of increasing the release of mebendazole from tablets. Since in similar conditions an increased oral bioavailability measured by the amount of absorbed drug (AUC and C(max)) was obtained following solubilization by complexation with povidone (Daniel-Mwambete et al., 2004) it is to suppose that the effect of croscarmellose observed *in vitro* implies an increase of bioavailability of mebendazole *in vivo.*

CONCLUSIONS:

Formulations with mebendazole as active substance, with Ludiflash as disintegrant and croscarmellose as superdisintegrant are feasible as tablets. The experimental tablets corresponded in regard to uniformity of weight, hardness, friability, drug content, disintegration time and dissolution properties.

Release of mebendazole was increased approximately linearly by addition of croscarmelose. Increase of the area under release curves as function of croscarmelose concentration as metrics of the effect, was linear **.**

Release of mebendazole from tablets followed a two phase time course: a slow release in the first 10 – 15 minutes during swelling of polymeric matrix and a more rapid release from particles resulted after disintegration.

In both phases, in spite of concomitant swelling and to concomitant diffusion toward and inside channels as well as diffusion at the interfaces with release medium in very different initial and boundary conditions, the release was described very well by square root laws, in both pre- and post-disintegration phases.

Application of Peppas law for the case of intermediary case between diffusion and swelling controlled mechanism didn't improved the fitting in comparison with square root law fitting.

As usual in release experiment, application of more general Waloddi Weibull distribution function lead to an unique theoretical curve describing all data, but this function is less discriminative in terms of the release mechanism. It is to underline that the obtained value – 1 for β parameter suggests towards a preponderant but complex, diffusion controlled mechanism. (Higuchi 1961; Krosmeyer et al., 1983).

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