Bulletin of the Chemists and Technologists of Macedonia, Vol. **14**, No. 1, p. 23 – 30 (1995)

GHTMDD – 246

ISSN 0350 – 0136

Received: November 12th, 1993

UDC 615. 2 : 54–32

Original scientific paper

pH INDEPENDENT CONTROLLED RELEASE MATRIX TABLETS WITH WEAKLY BASIC DRUGS AS ACTIVE SUBSTANCES. EFFECT OF INCORPORATED ACIDS

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The release of drug substance from controlled-release dosage forms is often pH-dependent, since most drugs are either weak acids or weak bases. A system that permits the drug release to be changed freely while maintaining pH-independent drug release (model drug was Verapamil hydrochloride) was developed. Powder mixture of drug and excipients was granulated in a fluid-bed apparatus using plasticized ethyl cellulose solutions in absolute ethanol as a granulation fluid. Different granulation levels (15%, 35% and 55%) were examined using DTA analysis and X-ray diffraction studies. An improvement in release (pH independent release) was achieved incorporating acids in the granulations prior compression and preparation of non disintegrating matrix tablets. Comparison of dissolution rates between formulations containing acid and acid-free formulations was made. Stability studies showed that acid addition does not affect stability of prepared dosage forms, as there were no changes in the physical parameters tested during stability studies and also no changes appeared in HPTLC studies and dissolution rate studies during twelve months real time studies.

Key words: Controlled-release; pH independent release; Verapamil hydrochloride; fluid-bed granulation; ethyl cellulose; matrix tablets

INTRODUCTION

The release of weak basic drugs from controlled-release matrix tablets in the increasing pH milieu of gastrointestinal fluid is problematical. Precipitation of poorly soluble free base may occur within the formulation in the intestinal fluid followed by an interruption of drug release from controlled-release formulation [1, 2]. There have been some reports of 15–85% of non-released drug remained inside the tablets, depending on the thickness of the diffusion layer [3]. The availability of drug substance from the controlled-release dosage form is one of the most significant parameters for their quality evaluation. Promising attempts for ensuring pharmaceutical availability of drugs from controlled-release dosage forms may be development of a system that permits drug release rate to be changed freely while maintaining pH-independent release. In the present study non-disintegrating matrix tablets composed of different fractions of fluid-bed prepared granulations using plasticized ethyl-cellulose binding solution in absolute ethanol with Verapamil HCl as model drug substance, were developed. As the solubility of active substance at higher pH values drops from 0.156 g/cm^3 to 0.025 and 0.010 g/cm^3 (37 °C) at pH 5.0, 6.0 and 7.0, respectively, problems of release from the prepared controlled release dosage forms at higher pH values were expected [4]. Prepared non-desintegrating matrix tablets really experienced problems with release of drug substance, showing slow and non quantitative release at higher pH values. Incorporation of different percentages of acid in the granulations prior to compression permits the drug release rate to be changed freely while maintaining pH-independent release.

EXPERIMENTAL

Materials

Verapamil hydrochloride and Norverapamil (Fischer Chemicals AG, Germany), Ethyl cellulose 10 cp (Ethocel® 10 cp, Colorcon Limited, U.K.), Microcrystalline cellulose (Avicel® PH 101, FMC Corp., U.S.A.), Diethylphtalate (Merck, Germany), Tartaric acid (Merck, Germany), Citric acid (Merck, Germany), Fumaric acid (Merck, Germany) and Itaconic acid (Merck, Germany).

Methods

Fluid-bed granulation process and granulation's characterization

Fluid-bed granulation process was used for governing the blending of the drug and excipients mixture prior to granulation, granulation and drying in a single operation (apparatus Glatt AG, Schweiz). The granulation process was performed up to 15%, 35% and 55% level, relative to the drug and excipients

charge. A final drying for 5 min was than carried out in the fluidized bed. After each granulation run the granules were sieved using 2 mm sieve. The undersize fractions (<2 mm) were used for further granulation and in the final size study. Sieve analysis was performed to determine particle size distributions of the granulations (Erweka Sieve Analyzer, Type GSA). Granulation's flow properties were tested on Erweka Granulate Flow Tester, Type GWF. Granules of different granulation levels (15%, 35% and 55%) were examined using DTA analysis (apparatus NETZCH Geratebau GmbH Selb, STA 409) and X-ray diffraction studies (Jeol diffractometer, model JDX-7E, goniometer model DX-60-F).The operating conditions in granulation process are presented in Table I.

Table I

Operating conditions in granulation

Composition of a spray solution	(Absolute ethanol was used as a solvent)
Ethyl cellulose (%)	3.5
Diethylphtalate (%)	20 (related to ethyl cellulose quantity)
Drug-excipients charge	(Initial charge was 2000 g)
Verapamil hydrochloride (%)	50
Microcrystalline cellulose (Avicel PH 101) (%)	20
Sucrose powder (%)	30
Operation conditions	(Apparatus Glatt AG, Schweiz)
Inlet air temperature (°C)	70
Outlet air temperature (°C)	28–32
Spray rate (ml/min)	30
Spray pressure (kPa)	304
Inlet air pressure (kPa)	35.5–40.5
Nozzle diameter (mm)	1.2
Granulation level	(percents, related to drug and excipient charge)
A	15
B	35
C	55

Preparation of matrix tablets

Granulations were blended with 5% talcum and different percentages of acid prior to tableting and compressed on a single punch tablet machine (Corsch, Berlin) to prepare non-disintegrating matrix tablets of 18.00 ±3.00 kp hardness (Erweka Hardness Testing System, Type TBH28 MDR). A die with an internal diameter of 13 mm and a flat-faced punch were used. The acid contents in the tablets which were prepared using granules of different granulations levels are presented in Table II. Acid-free tablets were also prepared to compare the effect of different granulation levels on the drug release rate and to evaluate the effect of acid incorporation. Erweka Tablet Friability Tester, Type TAD was used for evaluating the mechanical strength of prepared tablets. The theoretical quantity of drug substance in the tablets used to be 240 mg.

Table II

The acid content in tablets prepared with granulations of different granulation levels

	Granulation level (%)		
Incorporated acid	15	35	55
Citric acid	3	5	10
Tartaric acid	3	5	10
Itaconic acid	3	5	10
Fumaric acid	3	5	10

Determination of Verapamil hydrochloride content

For each granulation level, Verapamil HCl content and possible decomposition that may have occurred during the process of granulation was determined using the HPTLC method. The mean drug content for granulations of different granulation levels was determined and expressed for 0.7 g product.

Verapamil hydrochloride content and possible decomposition that may have occurred during preparation and stability evaluation of the matrix tablets was also evaluated using the HPTLC method (Camag applicator, Camag scanner II, plates Silica gel $60F_{254}$). The plates were developed using solvent system of cyclohexane : diethylamine 85 : 15. The detection was carried out at 278 nm. Verapamil hydrochloride and Norverapamil were used as standard substances.

Dissolution rate studies

Matrix tablets were tested for dissolution rate studies in 1000 ml buffer solutions with pH 1.5; composed of NaCl and HCl and pH 6.8 composed of KH_2PO_4 and NaOH (USP XXII rotation basket method, apparatus Erweka DZT, at 100 rpm). Also, a half-change dissolution method was carried out with the samples during 24 hours, changing pH of the medium from 1.2 (during one hour), 2.5 (for two hours), 5.5 (for two hours) and 7.5 until the end of the dissolution test [5]. The drug content in the withdrawn aliquots was analyzed spectrophotometricaly at 278 nm (Pye Unicam PU 8610).

Analysis of drug release data

The controlled-release behavior was analyzed using coupled diffusion-relaxation model [6–8] or coupling Fickian and non-Fickian mechanism using equations [9]:

$$M_t/M_\infty = k_1 t^m + k_2 t^{2m} \quad (1)$$

where the first therm on the right-hand side is the Fickian contribution and the second therm being the Case II relaxational contribution. With comparison of simple exponential relation $M_t/M_\infty = kt^n$ with Eq. 1 it is concluded that $m = n$ when relaxational mechanism is negligible. Equation 2:

$$F = \frac{1}{1 + k_2 \backslash k_1 t^m} \quad (2)$$

which leads to the percentage of drug release due to Fickian mechanism, and equation 3:

$$R\backslash F = k_2 \backslash k_1 t^m \quad (3)$$

which leads to the ratio of relaxational over Fickian mechanism.

Stability studies

Stability studies were carried out during twelve months in Kottermann chamber (temperature 26 °C, relative humidity 65 per cent). Physical parameters testing, HPTLC studies and dissolution tests were carried out for characterization of tested formulations during twelve months real time studies.

RESULTS AND DISCUSSION

Granulation's properties

Examples of the granule size distributions determined by sieve analysis are given in Fig. 1. The granule size distributions for different granulation levels are significantly different. Specifically, the greater polymer mass sprayed onto the powder bed resulted with increased particle size of the granulations. For 15% granulation level sieve fraction of 0.8/0.63 mm passed/retained represents a fairly large proportion (50.82%) of the product.

As the granulation process proceeds to the higher granulation levels the coarsening of the particles was noticeable and the largest proportion for 55% granulation level was the sieve fraction of 1.00/0.8 mm passed/retained with 48.91%.

The granulation's properties, flow properties, compressibility (calculated assuming aerated and packed bulk density), and mean drug content per 0.7 g product are presented in Table III. The granulation level efficiency is noticeable by the expected drop of mean drug content for higher granulation levels. Also the mean drug content for different granulation levels was in a range of 96–101% of theoretical drug loading.

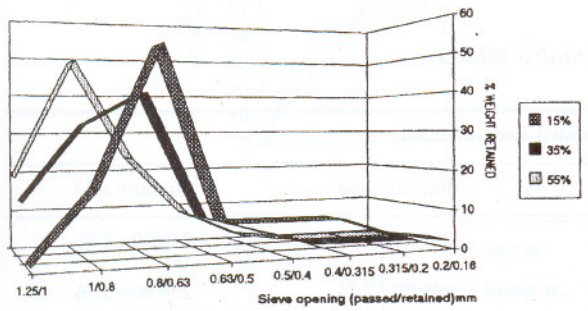


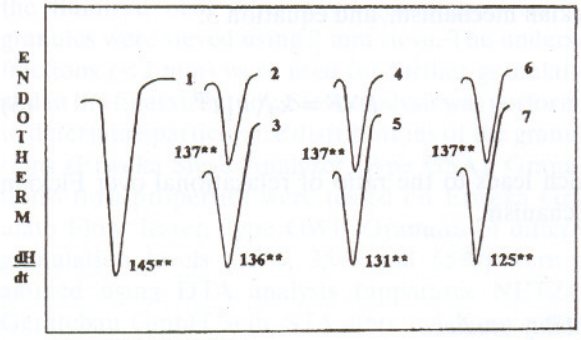
Fig. 1. Particle size distribution for granulations of different granulation levels (15%, 35% and 55%)

Table III

Granulation's properties

Granulations	Flow angle	Flow time s	Compressibility	Mean Verapamil HCl content (mg)± SD; 0.7 g product
A	24° 7'	4	13.3	240.00 ± 1.54
B	43° 8'	5	18.9	211.00 ± 2.05
C	57° 8'	6	23.9	186.00 ± 2.40

DTA analysis showed different decreasing of melting point temperature of Verapamil HCl at different granulation levels considering physical mixtures and granulations. The drop of the melting point temperature of Verapamil HCl for 12 °C was noticed with granulations of 55% granulation level compared with the melting point of Verapamil HCl in physical mixture composed of same quantities of drug substance and ingredients as the 55% level granulation. No significant difference considering Verapamil. HCl melting point temperature in 15% level granulation and it's physical mixture was noticed. DTA analysis are shown in Fig. 2. X-ray diffraction studies points to non disrupted crystalinity of Verapamil HCl in granulations. Differences in the X-ray diffractograms appeared regarding to enlarged quantity of non crystal material (ethyl cellulose) in granulations at higher granulation levels. X-ray diffraction studies are presented in Fig. 3.



** Peak temperature (°C)

Fig. 2. DTA curves of Verapamil HCl (1), physical mixture of granulation A (2), granulation A (3), physical mixture of granulation B (4), granulation B (5), physical mixture of granulation C (6) and granulation C (7).

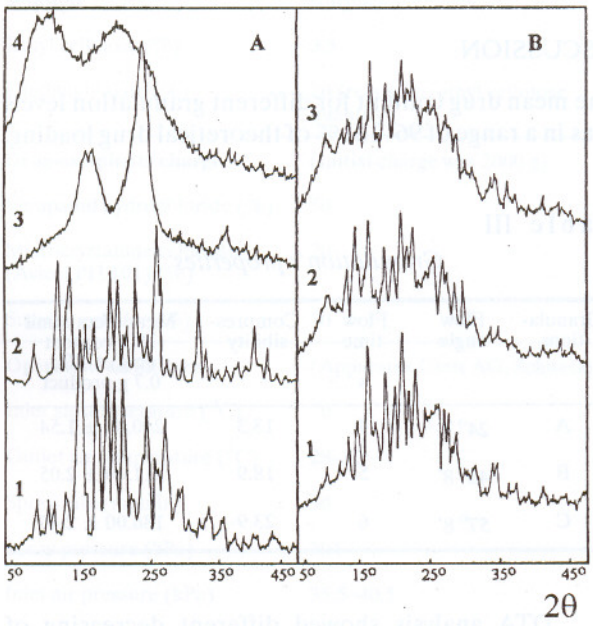


Fig. 3. X-ray diffractograms of: A – Verapamil HCl (1), Sucrose powder (2), Microcrystalline cellulose (3), Ethyl cellulose (4); B – Granulation A (1), granulation B (2) and granulation C (3)

Tablet evaluation

Verapamil HCl content in matrix tablets obtained by HPTLC method is presented in Table IV. Possible decomposition or chemical changes that may have occurred during the preparation of matrix tablets was eliminated as no new peaks were detected in HPTLC study.

The results of dissolution tests (half-change method) for matrix tablets are presented in Fig. 4 (55% granulation level, acid content 10% and acid free tablets) and Fig. 5 (35% granulation level, acid content 5% and acid free tablets) and Fig. 6 (15% granulation level, acid content 3% and acid free tablets).

In conditions of increasing pH values (half-change dissolution test) acid-free tablets showed slow and non-quantitative drug release. In an attempt to increase the drug release rate at higher pH values a number of experiments with incorporation of different amounts of citric, tartaric, fumaric and itaconic acid in the matrix tablets were performed. Quantitative drug release from matrix tablets of different granulation levels with different acid content was noticed during 12h or 24 hours (Fig. 4, 5 and 6)

To further investigate the effect of incorporated acid, dissolution tests at pH 1.5 and 6.8 were done. The release rates at pH 1.5 compared with release rates at pH 6.8 showed no significant differences for all types and percentages of incorporated acids except for formulations which contain fumaric acid. For all acid free formulations the release rate at pH 6.8 was very low compared with formulations containing acids. The drug release rate at low pH values (pH 1.5) where the high solubility of drug substance as a weak base is expected, was easily influenced by the different granulation levels or different acid content. Complete different picture appeared when pH 6.8 was taken into consideration. As was expected, the release rate of the active substance was highly influenced by both factors, granulation levels and percentage of incorporated acid. This effects can be explained if we take into consideration the decrease of drug solubility at higher pH values from 0.156 g/cm^3 at pH 5.0 to 0.025 and 0.010 g/cm^3 at pH 6.0 and 7.0, respectively, and

Table IV

Verapamil HCl content in matrix tablets

acid content and granulation level	Incorporated acid (mg±SD)			
	Citric acid	Tartaric acid	Itaconic acid	Fumaric acid
10%ac., 55% g.l.	239.00±1.32	239.00±2.52	237.00±2.36	240.00±2.36
5% ac., 35% g.l.	242.00±2.03	239.00±2.56	239.00±2.36	238.00±3.56
3%ac., 15%g.l.	242.00±2.56	240.00±1.32	239.00±2.70	241.00±2.36

*g.l. – granulation level

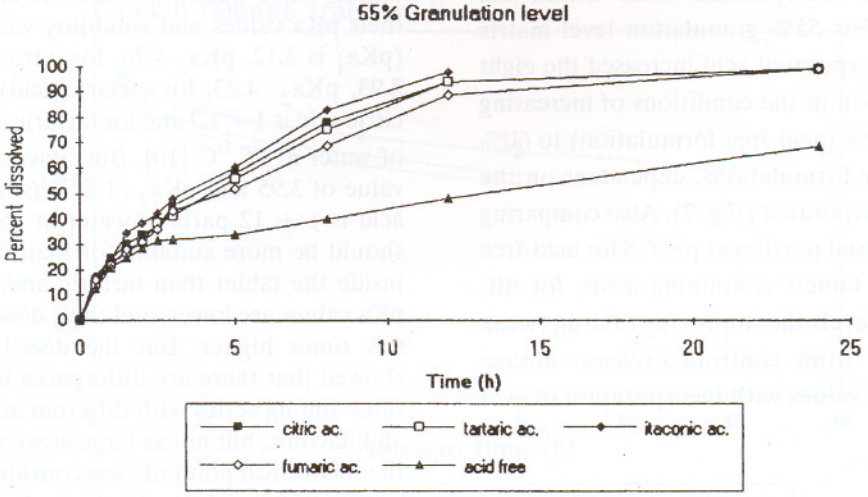


Fig. 4. Dissolution tests (half-change method) for matrix tablets of 55% granulation level with 10% acid (citric, tartaric, itaconic, fumaric acid) content including acid-free tablets

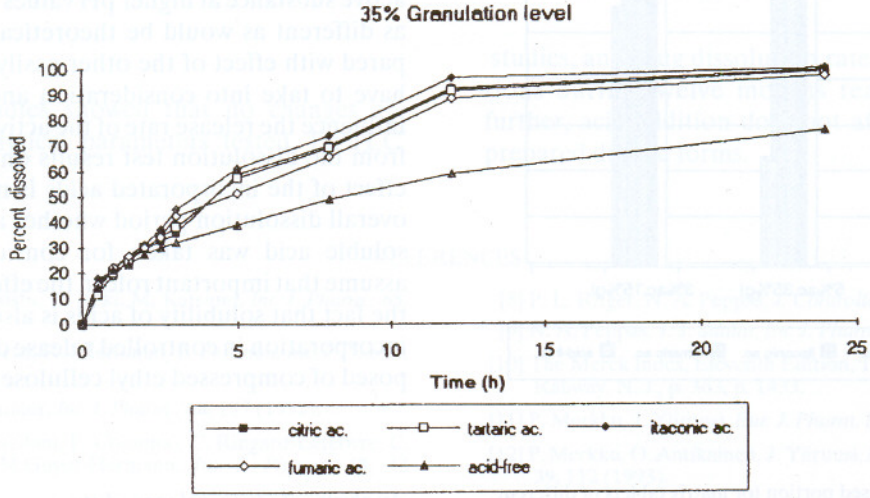


Fig. 5. Dissolution tests (half-change method) for matrix tablets of 35% granulation level with 5% acid (citric, tartaric, itaconic, fumaric acid) content including acid-free tablets

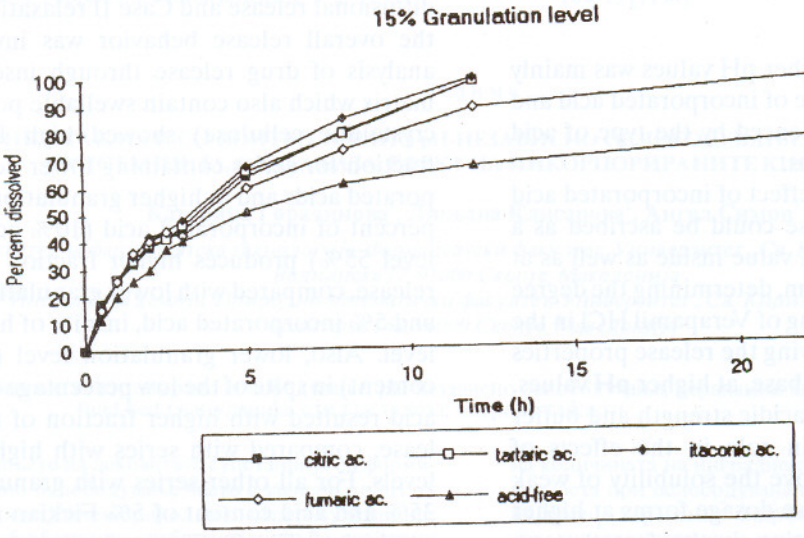


Fig. 6. Dissolution test (half-change method) for matrix tablets of 15% granulation level with 3% acid (citric, tartaric, itaconic, fumaric acid) content including acid-free tablets

buffering effect of incorporated acids within the dosage forms [4]. For 55% granulation level matrix tablets, 10% of incorporated acid increased the eight hour released portion in the conditions of increasing pH values, from 20% (acid-free formulation) to 60% and nearly 70% for formulations, dependent on the type of the acid incorporated (Fig. 7). Also comparing the eight hour released portion at pH 6.8 for acid-free tablets and matrix tablets containing acids, for different granulation levels the improving of drug (weak base) release rate from controlled-release dosage forms at higher pH values with incorporation of acid is obvious (Fig. 7).

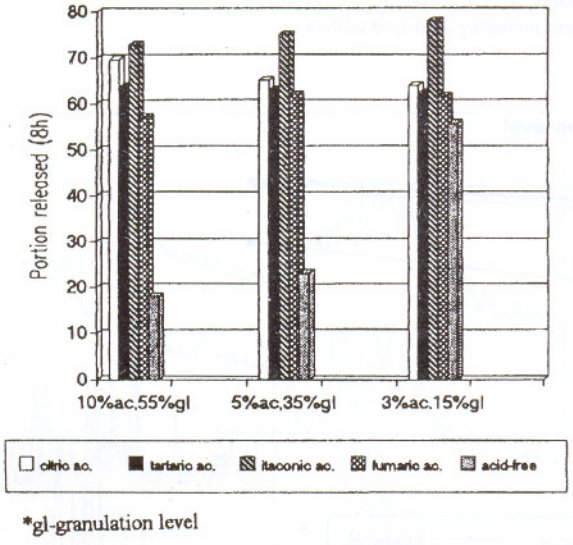


Fig. 7. Eight hour released portion for matrix tablets of different granulation levels, different content of citric, tartaric, itaconic and fumaric acid, including acid-free formulations (pH 6.8)

The release rate at higher pH values was mainly controlled by the percentage of incorporated acid and pH independence was influenced by the type of acid incorporated in formulations.

It is possible that the effect of incorporated acid and pH independent release could be ascribed as a consequence of reduced pH value inside as well as at the surface of the dosage form, determining the degree of ionization and partitioning of Verapamil HCl in the ethyl cellulose walls, improving the release properties of the drug substance, weak base, at higher pH values. So solubility of acids, their acidic strength and buffer capacity will play the main role in the effects of incorporated acids to improve the solubility of weak bases from controlled-release dosage forms at higher pH values. As a confirmation is the fact that no significant differences were noticed among series containing same quantities of citric and tartaric acid as their pKa values and solubility values are very close (pKa_1 is 3.12, pKa_2 4.76, for citric acid, and pKa_1 is 2.93, pKa_2 4.23, for tartaric acid); the solubility of citric acid is 1 + 1.7 and for tartaric acid is 1 + 0.7 parts of water at 25 °C [10]. But, itaconic acid with pKa_1 value of 3.95 and pKa_2 of 5.50 (solubility of itaconic acid is 1 + 12 parts of water at 25 °C) theoretically should be more suitable for maintaining an acid pH inside the tablet than tartaric and citric acid, whose pKa values are lower, and their dissociation constants few times higher. But the dissolution test results showed that there are differences in drug dissolution rates among series with different acids, citric, tartaric and itaconic, but not as large as we would expect from the theoretical point of view considering higher buffer capacity of itaconic acid. Assuming this fact and the results that fumaric acid (pKa_1 value is 3.03 and pKa_2 is 4.54) in spite of its low solubility in water (1 + 150 parts of water at 25 °C) improves the release of the active substance at higher pH values with the effect not as different as would be theoretically expected compared with effect of the other easily soluble acids, we have to take into consideration another factors that influence the release rate of the active substance. Also, from the dissolution test results one can see that the effect of the incorporated acids is noticed during the overall dissolution period whether an easily or hardly soluble acid was taken for consideration. We can assume that important role in the effect of acids occupy the fact that solubility of acids is also affected by their incorporation in controlled release dosage forms composed of compressed ethyl cellulose coated granule.

Analysis of drug release data

The importance of the two mechanisms (Fickian diffusional release and Case II relaxational release) in the overall release behavior was investigated. The analysis of drug release through insoluble polymer matrix which also contain swellable polymers (microcrystalline cellulose) showed high Fickian release fraction for series containing lower percent of incorporated acids and at higher granulation levels. Higher percent of incorporated acid (10% acid, granulation level 55%) produces higher fraction of relaxational release, compared with lower granulation level of 35% and 5% incorporated acid, inspite of high granulation level. Also, lower granulation level (15%, 3% acid content) in spite of the low percentage of incorporated acid resulted with higher fraction of relaxational release, compared with series with higher granulation levels. For all other series with granulation levels of 35% and acid content of 5% Fickian release fraction was higher (Fig. 8). The analysis of drug release data for acid free series showed that Fickian release mechanism predominates.

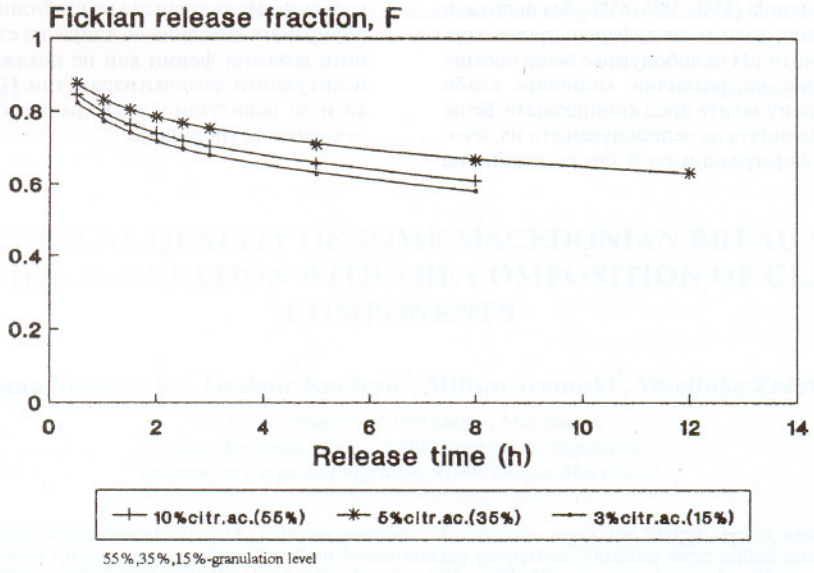


Fig. 8. Fickian release fraction, F, for series of 55% granulation level and 10% acid-content, 35% granulation level and 5% acid content and 15% granulation level, 3% acid content

Stability studies

Stability studies showed that no changes appeared in the physical parameters tested, HPTLC studies, and drug dissolution rate for tested formulations during twelve months real time studies, so further, acid addition does not affect the stability of prepared dosage forms.

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Резиме

МАТРИКС-ТАБЛЕТИ СО КОНТРОЛИРАНО pH-НЕЗАВИСНО ОСЛОБОДУВАЊЕ НА ЛЕКОВИТАТА СУПСТАНЦИЈА, СЛАБА БАЗА. ЕФЕКТ НА ИНКОРПОРИРАНИТЕ КИСЕЛИНИ

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Клучни зборови: контролирано ослободување; pH-независно ослободување; Верапамил хидрохлорид; fluid-bed гранулација; етил целулоза; матрикс-таблети

Ослободувањето на лековитата супстанција од формите со контролирано ослободување често е зависно од pH на средината, бидејќи најголем број од лековитите супстанции претставуваат слаби бази или слаби киселини. Во овој труд беше формулирана дозажна форма со контролирано ослободување чија што брзина може да се променува со промената на количината на ингредиентите без да се наруши pH-независноста при ослободувањето (модел на лековита супстанција беше Верапамил хидрохлорид). Прашкастата смеса од лековитата супстанција и ингредиентите беше гранулирана во fluid-bed апаратура со употреба на раствор на етилцелулоза во апсолутен етанол како средство за гранулација. Раз-

личните нивоа на гранулација (15%, 35%, 55%) беа испитани со дифракција со X-зраци, како и со диференцијална термичка анализа. Независното pH ослободување беше постигнато со инкорпорирање на различни количини слаби органски киселини во гранулатите пред компресијата. Беше направена споредба на брзината на ослободувањето на лековитата супстанција од формулации со и без содржина на киселина. Испитувањата на стабилност покажаа дека инкорпорираната киселина не влијае на стабилноста на подготвените дозажни форми кои не покажаа никакви промени во испитуваните физички параметри, HPTLC-испитувањата, како и во испитувањата на брзината на ослободувањето на лековитата супстанција.