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EFFECT OF COMPRESSION AND DILUENT ON DRUG RELEASE FROM MASTIX MATRIX TABLETS. A STATISTICAL ANALYSIS

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ABSTRACT

The effect of compression (30-150 kp/cm^2) and diluent (PVP, lactose) on the in vitro release of PASNa from matrix tablets of mastix was evaluated on the basis of different mathematical models. The Higuchi and the exponential model were proved to be the best statistically. It seems that the use of lactose causes an increase on drug release. Also the relationship between the compression and the packing fraction of the tablets was examined. There seems to be a limit point above which no changes in packing fraction occure.

INTRODUCTION

For the preparation of matrices, many materials as cellulose (methylcellulose, hydroxyethylcellulose), polysaccharides (agar, gummi arabi-

* Part of Thesis

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cum), acrylic acid, polymers (carbopol, polyethylene polyvinyl chlorate), have been used (1,2). Recently, investigations are focused on mastix and its properties as a media for the preparation of matrix tablets (3). Mastix is a natural resin collected from Pistacia Lentiscus L. var. Chia. In the present work the effect of compression and some diluent on the in vitro release of sodium p-aminosalicylic from matrix tablets of mastix have been studied.

MATERIALS AND METHODS

Materials

Sodium p-aminosalicylic (PASNa) powder (Fluka A.G.), mastix free of its essential oil (production year 1984), lactose monohydrate (BDH Ltd.), polyvinylpyrrolidone PVP (BDH Ltd.), aceton (Mallincrodt) and Magnesium stearate (BDH Ltd) were used.

Apparatus

Spectrophotometer Hitachi 200, continuous flow dissolution apparatus Desaga D (Heidelberg), Turbula mixer 12C (Switzerland), sieves (DIN 4188), pycnometer (Beckman 930), hydraulic press with 13 mm flat faced punches and die.

Preparation of granules

PASNa powder (fraction 0.160/0.125 mm passed/retained) was sprayed with a solution of mastix in acetone (10% w/v). The wet mass was granulated through a sieve 0.800 mm and the granules dried for 24 hours at 25°C to constant weight and stored in glass jars. The size distribution was determined by sieve analysis. The fraction 0.850/0.710 mm (passed retained) was used. The true granule densities were also determined with a Beckman air comparison pycnometer.

Preparation of matrix tablets

Tablets were prepared according to the following formula:

PASNa	295 mg	(59%)
Mastix/diluent	200 mg	(40%)
Mg-Stearate	5 mg	(1%)

The diluent and Mg-stearate were mixed with the granulated PASNa

TABLE I

The Mastix/Diluent Ratios in Tablet Lots T_{13}-T_{20}

Tablet	Mastix %	PVP %	Lactose %
T_{13}	4	36	
T_{14}	12	28	
T_{15}	20	20	
T_{16}	30	10	
T_{17}	4		36
T_{18}	12		28
T_{19}	20		20
T_{20}	30		10

in a Turbula mixer for 20 min and compressed in a hydraulic press using 13 mm flat faced punch and die. Compression pressures of 30-150 Kp/cm^2 (lots T1 - T12, Table II) were applied for 20 sec to the upper punch. PVP was used as diluent and the proportion of mastix/PVP was 20/20. There were also prepared four lots of tablets (T13 - T16) with different proportions of mastix/PVP at a standard compression pressure of 50 Kp/cm^2 as well as four lots (T17 - T20) using lactose instead of PVP (Table I).

Each tablet was individually weighed to the nearest 0.1 mg and its apparent volume was determined geometrically. The tablets packing fraction was calculated from the granule density and the tablets apparent volume.

Dissolution procedure

PASNa release rates were determined for 6 hours using Desaga apparatus of continuous flow, at the flow rate of 8 ml/min. The dissolution medium used for the first 2 hours was artificial gastric fluid of pH 1.2 ± 0.1 (2.0 g Nacl, 7.0 ml HCl ad 1000 ml water), and for the next four hours artificial enteric fluid of pH 7.4 ± 0.1 (250

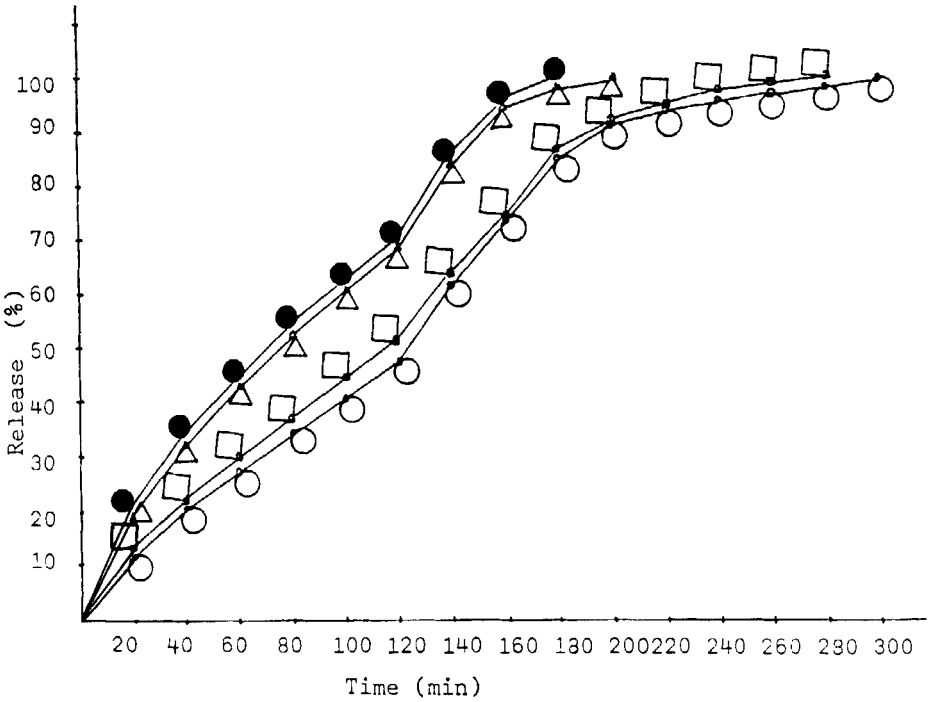

FIG. 1 Release (%) vs time at compression pressures of 30(●) 50(○), 90(△) and 150(□) kp/cm^2.

ml KH_2PO_4 0.2M, 175 ml NaOH 0.2M ad 1000 ml water). The solution was maintained at 37°C ± 0.1. Samples were withdrawn from the system at measured time intervals (every 20 min). The concentration of drug in solution was measured spectrophotometrically at 299 nm. Each experiment was run 4 times.

RESULTS AND DISCUSSION

The dissolution profiles of matrix tablets prepared at different compression pressures are shown in Fig. 1. It can be seen that the compression load applied during tableting does not have

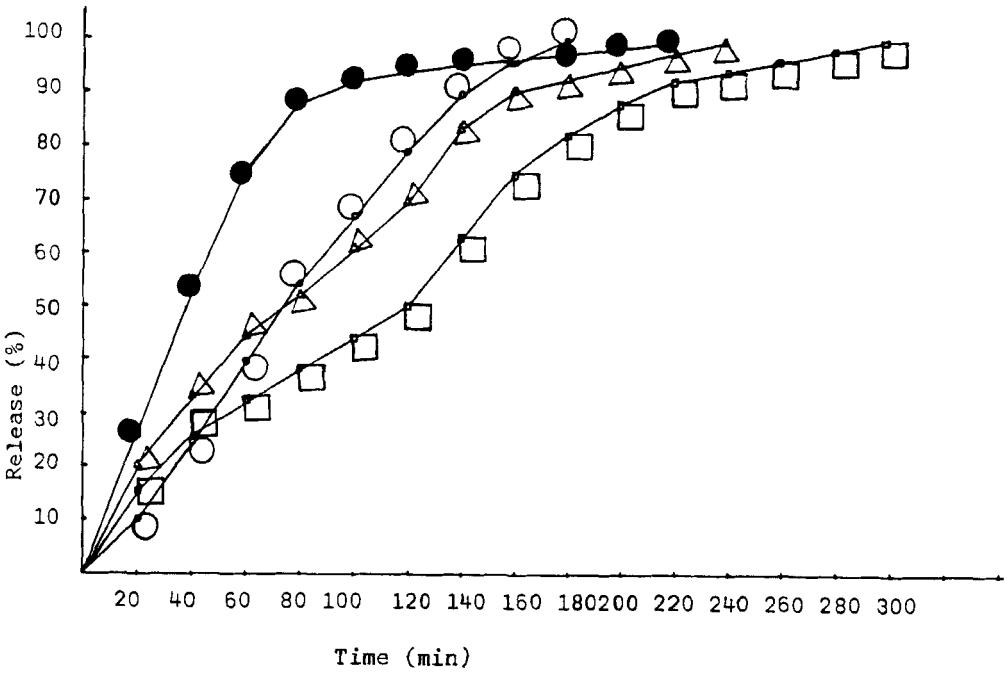

FIG. 2 Release % vs time at the compression pressure of 50 kp/cm^2 for PVP [4% mastix (△),20% mastix(□)] and lactose [4% mastix(●),20% mastix(○)]

very significant effect on the release of drug although it seems to have two limit points; one at 50 Kp/cm^2 and one at 90 Kp/cm^2 as it is also shown in Fig. 3. The release rates of PASNa from matrices with different diluent and different ratios of mastix/diluent at the compression pressure of 50 Kp/cm^2 are shown in Fig. 2. It can be seen that PVP compared to lactose causes a significant retardation of the release rate of the drug due to its binding properties.

Generally, one of the following process could be rate determining for the release of the drug from insoluble matrices: a) the

permeation pf the solvent, b) the dissolution of the drug in the penetrating solvent, c) the diffusion of the dissolved drug through the coating film and d) the Higuchi's porous penetration (4,5). In order to determine the effect of compression and diluent on the release rate, we ploted the percentage of drug undissolved (m) vs time (t), and tested the fit of the release data with the following mathematical models:

1) Zero order kinetics:

$$100-m = k_o t \qquad (1)$$

2) Exponential model:

$$\ln m = -k_1 t \qquad (2)$$

3) Cube root equation:

$$\sqrt[3]{100} - \sqrt[3]{m} = k_2 t \qquad (3)$$

4) Higuchi's model (square root of time equation):

$$100-m = k_3 \sqrt{t} \qquad (4)$$

If the release of the drug is dictated by the actual dissolution of the drug then a cube root relationship should hold. If it is dictated by porous penetration then eqn 4 should hold, whereas in other cases (a, c) we should expect an eqn of type 2.

The goodness of the fit is evaluated for pH 1.2 ± 0.1 and pH 7.4 ± 0.1 individually. Table II shows the lots of tablets T1 - T12, the compression loads, the packing fractions as well as the rate constants and the correlation coefficients of the exponential and the Higuchi models which were found to fit better in this case.

Results of the release rates and correlation coefficients for the tablets T13 - T16 and T17 - T20 are shown on Tables III and IV respectivelly.

In Fig. 3 we ploted the release rate constant (exponential model) vs the compression load of the tablets and in Fig. 4 we ploted the percentage of drug undissolved (m) vs time (t) according to the exponential model. The tablets compressed at 50 Kp/cm^2

TABLE II

Packing Fraction, Release Rates and Correlation Coefficients for Matrices at Different Compression Loads on the Basis of the Exponential and the Higuchi Models (pH 1.2±0.1).

Tablet	Compression load kp/cm^2	p.f.	Exponential model $k_1(h^{-1})$	r	Higuchi's model $k_3(h^{-\frac{1}{2}})$	r
T_1	30	0.84	0.021	0.999	17.47	0.999
T_2	50	0.96	0.012	0.999	12.66	0.999
T_3	60	0.99	0.12	0.999	13.03	0.997
T_4	70	0.99	0.015	0.997	14.43	0.998
T_5	80	1	0.017	0.999	15.91	0.999
T_6	90	1	0.021	0.999	17.22	0.999
T_7	100	1	0.020	0.999	16.71	0.999
T_8	110	1	0.019	0.999	16.71	0.999
T_9	120	1	0.019	0.998	16.97	0.998
T_{10}	130	1	0.019	0.999	16.58	0.999
T_{11}	140	1	0.016	0.999	14.39	0.999
T_{12}	150	1	0.012	0.999	12.59	0.999

TABLE III

Release Rates and Correlation Coefficients on the Basis of the Exponential and Higuchi's Models for the Tablet Lots T_{13}-T_{16}.(pH 1.2±0.1)

Tablet	Mastix %	PVP %	Compression load kp/cm^2	Exponential model $k_1(h^{-1})$	r	Higuchi's model $k_3(h^{-\frac{1}{2}})$	r
T_{13}	4	36	50	0.021	0.998	17.29	0.999
T_{14}	12	28	50	0.017	0.995	15.84	0.996
T_{15}	20	20	50	0.011	0.998	19.73	0.953
T_{16}	30	10	50	0.011	0.998	12.5	0.999

TABLE IV

Release Rates and Correlation Coefficients on the Basis of the Exponential, Higuchi's and Cube Root Equation Models for the Tablet Lots T_{17}-T_{20}. (pH 1.2±0.1)

Tablet	Mastix %	PVP %	Compression load kp/cm^2	Expon.model $k_1(h^{-1})$	r	Cube root eq. $k_2(h^{-1})$	r	Higuchi's model $k_3(h^{-\frac{1}{2}})$	r
T_{17}	4	36	50	0.061	0.992	0.05	0.980	24.94	0.970
T_{18}	12	28	50	0.127	0.933	0.048	0.999	23.21	0.985
T_{19}	20	20	50	0.023	0.984	0.039	0.994	23.03	0.995
T_{20}	30	10	50	0.015	0.999	0.020	0.999	16.21	0.997

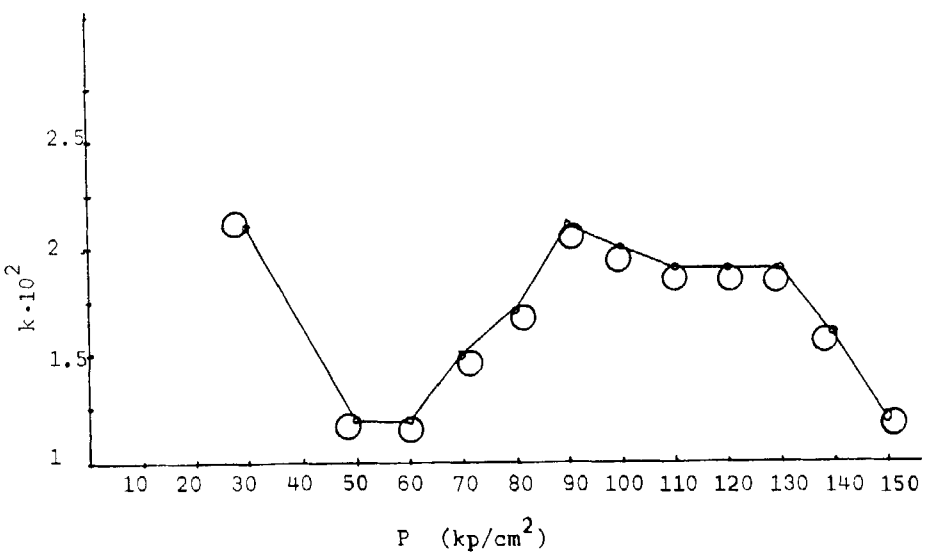

FIG.3 Release rate constant (exponential model) vs the compression pressure (mastix 20%).

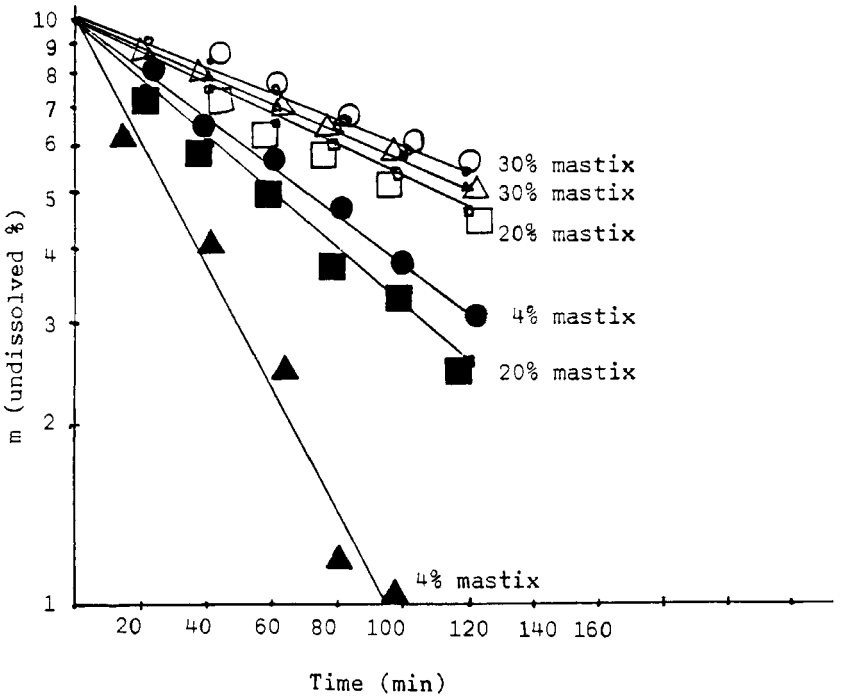

FIG.4 Percentage of drug undissolved (m) vs time.

Compression pressure 50 kp/cm^2

PVP (○,□,●),lactose (△,■,▲).

TABLE II$_A$

Release Rates and Correlation Coefficients for Tablet Lots T_1-T_{12} on the Basis of the Exponential,Higuchi's and Cube Root Equation Models(pH 7.4±0.1)

Tablet	Compression load kp/cm^2	Exponential model $k_1(h^{-1})$	r	Higuchi's model $k_3(h^{-\frac{1}{2}})$	r	Cube root equation $k_2(h^{-1})$	r
T_1	30	0.11	0.951	7.36	0.842	0.14	0.982
T_2	50	0.05	0.998	14.26	0.909	0.036	0.973
T_3	60	0.06	0.996	16.56	0.933	0.043	0.992
T_4	70	0.088	0.975	12.02	0.900	0.06	0.999
T_5	80	0.11	0.991	14.32	0.919	0.07	0.998
T_6	90	0.068	0.794	4.88	0.769	0.047	0.947
T_7	100	0.044	0.948	7.00	0.836	0.024	0.905
T_8	110	0.015	0.946	9.52	0.813	0.15	0.994
T_9	120	0.14	0.989	15.96	0.921	0.10	0.996
T_{10}	130	0.10	0.932	10.02	0.847	0.10	0.998
T_{11}	140	0.14	0.955	10.98	0.836	0.11	0.997
T_{12}	150	0.06	0.985	15.63	0.948	0.045	0.999

TABLE III_A

Release Rates and Correlation Coefficients for Tablet Lots T_{13}-T_{16} on the Basis of the Exponential, Higuchi's and Cube Root Equation Models (pH 7.4±0.1).

Tablet	Mastix %	PVP %	Compression load kp/cm^2	Exponential model $k_1(h^{-1})$	r	Higuchi's model $k_3(h^{-1/2})$	r	Cube root eqn. $k_2(h^{-1})$	r
T_{13}	4	36	50	0.02	0.896	6.41	0.822	0.015	0.824
T_{14}	12	28	50	0.04	0.889	7.53	0.760	0.018	0.788
T_{15}	20	20	50	0.04	0.995	13.93	0.937	0.029	0.980
T_{16}	30	10	50	0.08	0.977	13.02	0.951	0.045	0.983

TABLE IV_A

Release Rates and Correlation Coefficients for Tablet Lots T_{17}-T_{20} on the Basis of the Exponential, Higuchi's and Cube Root Equation Models (pH 7.4±0.1).

Tablet	Mastix %	Lactose %	Compression load kp/cm^2	Exponential mod. $k_1(h^{-1})$	r	Higuchi's mod. $k_3(h^{-1/2})$	r	Cube root eqn. $k_2(h^{-1})$	r
T_{17}	4	36	50	0.066	0.919	2.88	0.998	0.033	0.891
T_{18}	12	28	50	0.08	0.987	2.19	0.991	0.09	0.951
T_{19}	20	20	50	0.22	0.996	9.23	0.973	0.12	0.974
T_{20}	30	10	50	0.204	0.972	14.73	0.913	0.092	0.984

exhibited greater release prolongation than those compressed at 90 Kp/cm^2.

The release enhancement due to pressure increase is probably caused by the greater fragmentation of the drug particles. The fragmentation results an additional release of drug due to the increased surface. In higher pressures (more than 90 Kp/cm^2) a release prolongation is observed. This could be explained as follows: The amorphous (x-ray analysis) and macromolecular character of mastix yields thermoplastic properties. Due to these properties, the percentage of mastix surrounding

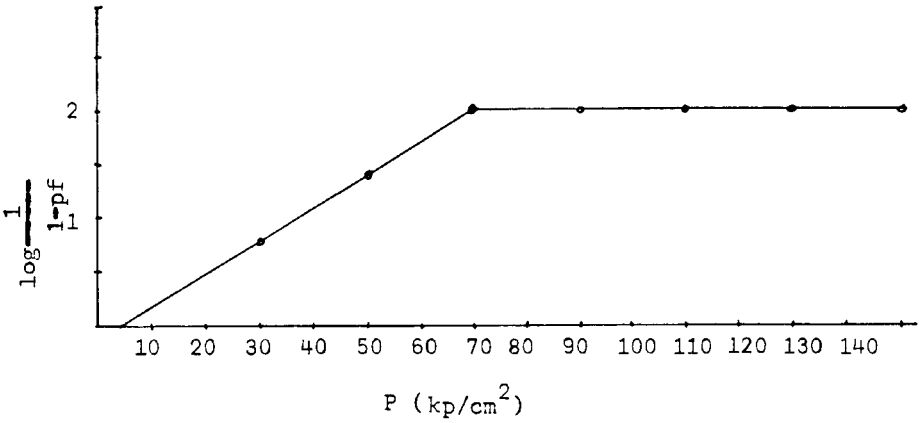

FIG. 5

the granules yields a sponge-like matrix (3). In higher pressures, because of the increase of the temperature in the punch and die, presumably mastix becomes more plastic and less friable. When lactose is used as diluent (Table IV), the release data fit better to the cube root eqn model. When PVP is used (Table III), the release data fit better to the exponential model. As shown in Fig 4, for the same lots of tablets the substitution of PVP with lactose, exhibits release enhancement. This may be due to the solubility of lactose. The difference between the two diluents is greater when the tablets contain small percentages of mastix.

As it is shown in Tables IIa, IIIa, IVa, the release data fit better to the cube root eqn model, for the different compression loads, while for the different diluents to the exponential model (PVP) and to the Higuchi model (lactose).

Fig. 5 shows the relationship between the compression loads of the tablets and the packing fraction. It seems to be a limited pressure of 70 kp/cm² up to which the relationship follows the equation

$$\log 1/1\text{-pf} = aP + b \qquad (5)$$

P: the compression load

pf: the packing fraction

a,b: constants

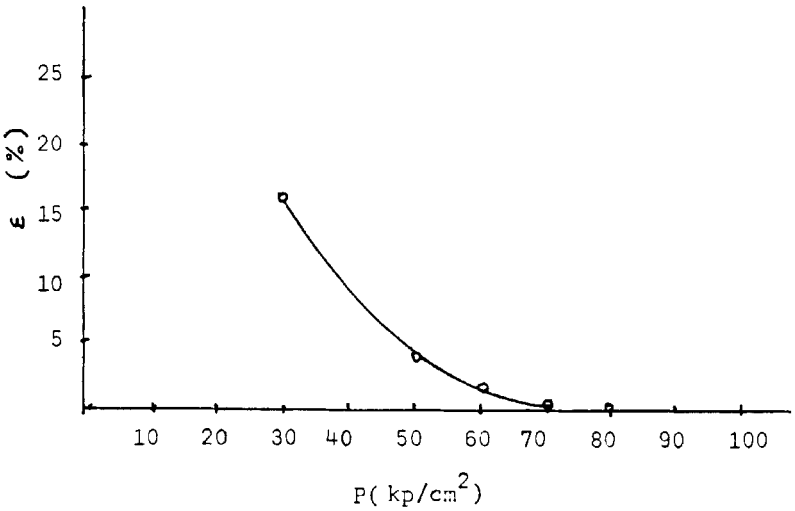

FIG.6

Regression analysis (up to 70 Kp/cm^2) gave for equation (5) the following values: a: 0.03, b:-0.1, r: 1.00. The packing fraction of the tablets at the pressure of 70kp/cm^2 becomes 1 due probably to the thermoplasticity of mastix. Further increase of the pressure does not affect packing fraction. From Fig. 6 it can be also seen that pressures greater that 70 Kp/cm^2 have not any effect on the porocity (ε) of the tablets.

CONCLUSIONS

The effect of compression pressure on mastix matrix tablets does not seem to be significant for the release rate of the drug. It shows, however, two limit points.

When lactose is used as diluent, an increase in release rate is observed in comparison with PVP. Data statistical analysis showed that when PVP is used as a diluent, the release rate at pH 1.2 + 0.1 and 7.4 + 0.1 follows the exponential model. In case that lactose is used, the release rate follows the cube root eqn (for pH 1.2 + 0.1) and the Higuchi model (for pH 7.4 + 0.1).

It was also found that the packing fraction of the tablets increases at higher compression pressures and that it has a limit point at 70 Kp/cm² at which it becomes 1. Further increase in pressure does not effect packing fraction.

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