International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304
Vol.8, No.6, pp 147-155, 2015

Effect of diluent types and soluble diluents particle size on the dissolution profile of trimetazidine dihydrochloride and caffeine from Kollidon SR matrix tablets

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Abstract: Effect of different diluents types on the dissolution profile of trimetazidine dihydrochloride and caffeine from Kollidon SR matrix tablets was investigated using microcrystalline cellulose (Avicel PH-101), calcium hydrogen phosphate dihydrate (Emcompress) and sorbitol (Neosorb P100T). The decreasing of mentioned diluents possibility to slow down of model substances dissolution kinetics (at pH 6.8) had follow sequence: Avicel PH-101 >Emcompress>Neosorb P100T.Effect of soluble diluents particle size on dissolution profile of trimetazidine dihydrochloride and caffeine from Kollidon SR matrix tablets was investigated using sorbitol (Neosorb P100T, Neosorb P60 W and Neosorb P30/60) and lactose monohydrate (Sorbolac 400, Granulac 200 and Capsulac 60). The particle size increasing of lactose monohydrate from 11 to 251 μm and sorbitol from 110 to 513 μm decreased dissolution kinetics of model substances from Kollidon SR matrix tablets.
Keywords : matrix tablets, Kollidon SR, caffeine, trimetazidine, diluent, particle size.

Introduction

Sustained release oral matrix tablet is a popular dosage form using which could be achieved the desired in vitro drug release, and corresponding in vivo therapeutic concentration of drug. Therefore, investigation of factors that influence the drug in vitro release kinetics is an important task.

Kollidon SR is one of the insoluble matrix formers that could be used for matrix tablets formulation. The main mechanism of release from insoluble matrix is diffusion. Thus Higuchi equation derived from Fick's law of diffusion[1, 2] and Lapidus and Lordimodification of Higuchi equation that includes matrix structure factors (porosity and tortuosity) [3]could be used for insoluble matrix:

$$\frac{M_t}{A} = \sqrt{D\frac{\varepsilon}{\tau} C_s (2C_0 - C_s) t} \qquad \text{(Equation)}$$

whereM_t is the total mass released up to time t; A is the total area of tablet; $D$is the diffusion coefficient of the drug in the material; $\varepsilon$and τ correspond to the matrix porosity and tortuosity; C_0 andC_S correspond to initial concentration of drug in matrix and drug solubility in matrix.

There are some publications where effect of different diluent types was investigated on soluble matrix tablets and lack of publications with insoluble matrix tablets. Effect of insoluble calcium hydrogen phosphate dehydrate (Emcompress) and soluble lactose monohydrate in concentration 30 % was investigated using tetracycline hydrochloride (100-30 mg/ml aqueous solubility) matrix tablets with40 % of hypromellose

(Methocel K4 M) asmatrix former [4]. Effect of soluble lactose monohydrate, swellable insoluble microcrystalline cellulose (Avicel PH-101) and Emcompress in concentration 65 % was investigated using diltiazem hydrochloride (50 mg/ml) matrix tablets with 18 % hypromelose (Methocel K15M) as matrix former [5]. Established that hydration dynamic, swelling front movement and erosion was faster using lactose. The dissolution kinetics decreased in the follow sequence: lactose monohydrate >Avicel PH-101>Emcompress. Comparative effect of lactose monohydrate, microcrystalline cellulose and soluble swellable partially pregelatinized starch (Starch 1500) in concentration 50 %was investigated using chlorpheniramine maleate(>100 mg/ml) and theophylline (8 mg/ml) matrix tablets with 20 % hypromelose (Methocel K4M)asmatrix former. Using of Starch 1500 significantly decreased dissolution rate of model substances comparing to lactose monohydrate and microcrystalline cellulose. The dissolution kinetics decreased in the follow sequence: lactose monohydrate > microcrystalline cellulose >Starch 1500 [6]. The influence ofhypromelloseto anhydrous dibasic calcium phosphate ratio on dissolution profile of soluble drug also investigated [7].

Effect of soluble particle size on dissolution profile from insoluble matrix was discussed in some publications. The dissolution kinetics was decreased with decreasing of soluble KCl particle size in insoluble acrylic copolymer (Eudragit RS-PM) matrix. This result was explained by more small and regular clusters forming [8]. The authors also observed zero order release kinetic after burst effect that was explained by KCl saturated concentration in matrix pores. It was stated tablets with bigger KCl particles lead to bigger clusters that resulted in faster depletion and shorter dissolution profile part of zero order release [9].Established that Higuchi equationdon't work at conditions close to percolation threshold because decreasing of drug availability and incomplete release due to blocking of some drug particles in closed clusters [10]. The quantity of closed clusters decreased with particles size decreasing [11]. Established that percolation threshold correspond to 30-40 % of NaCl in insoluble Eudragit RS 100 matrix. It was illustrated by significant decreasing of conductivity and incompleteNaCl release [12]. After this linear dependence between drug particle size and percolation threshold was shown for insoluble matrix tablets [13]. Using ethylcellulose and niflumic acid particle size variation was stated that excipient-excipient and drug-excipient connections have the main effect on dissolution kinetics from insoluble matrix tablets [14].Thus initial particle size of excipients and drugs has main influence on insoluble matrix tablet formation and predetermines diffusion ways formation and dissolution kinetics [15, 16].

The aim of this work is investigation of different diluent types effect and soluble diluent particle size effect on TMZ•2HCl and caffeine release from Kollidon SR matrix tablets.

Objects and Methods:

The objects of study were Kollidon SR matrix tablets with trimetazidinedihydrochloride (TMZ•2HCl) or caffeine model substance and different types of diluents or different particle size of soluble diluents.

Materials: trimetazidinedihydrochloride(TMZ•2HCl from Sochinaz SA, Switzerland); caffeine (BASF SE, Germany); microcrystalline cellulose (Avicel PH-101from FMC Corporation, USA);calcium hydrogen phosphate dihydrate ($CaHPO_4$•$2H_2O$;Emcompress from JRS Pharma, Germany); sorbitol (Neosorb P100T,Neosorb P60 W and Neosorb P30/60 from Roquette, France); lactose monohydrate (Sorbolac 400, Granulac 200 andCapsulac 60 from Meggle AG, Germany); spray dried physical mixture of polyvinyl acetate and polyvinylpyrrolidone (8:2) (Kollidon SRfrom BASF SE, Germany); colloidal silicon dioxide (Aerosil 200 Ph. from Evonik AG, Germany); sodium stearylfumarate (Pruv from JRS Pharma, Germany).

The shake-flask method was used for model substances and diluents aqueous solubility determination. The excess of tested substance was added to the 50 ml of medium (0.1 N HCl or PBS pH 6.8). The equilibrium concentration was achieved in three days. The substance solubility calculated after drying of known quantity of aliquot to constant weight at 105°C.

Laser scattering particle size distribution analyser (Coulter LS 230, Coulter Electronic, Germany) was used to determine average particle size and standard deviation, D_{10}, D_{50} and D_{90}.

Direct compression method was applied to obtain 200 mg biconvex tablets with 8 mm diameter according to the formulation presented in Table 1 using a mixer (Turbula T2F, Willy A. Bachofen AG, Switzerland) and eccentric tablet press (Korsch EKO, Korsch AG, Germany).

The drug release from tablets was investigated in a paddle apparatus (Vankel VK 300, Vankel Industries, Edison., NJ, USA) at following conditions: 900 ml of 0.1 N HCl or PBS pH 6.8, 100 rpm, 37°C; ($n \geq 3$). Samples were withdrawn at predetermined time points, filtered through 0.35 µm filters and measured UV-spectrophotometrically at λ=269 nm (pH 1: y=0.0022x, R2=0.9999; pH 6.8: y=0.0022x+0.0276, R2=0.9993). The cross-section and surface of some tablets was additionally observed under the optical microscopeafter preliminary treating with methylene blue solution.

Table 1. Formulations of tablets, %

Ingredients	Formulations								
	F 1	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**	**F 7**	**F 8**	**F 9**
TMZ•2HCl	17,5	17,5	17,5	17,5	17,5	17,5	17,5	17,5	48,8
Caffeine	-	-	-	-	-	-	-	-	-
Avicel PH-101	31,3	-	-	-	-	-	-	-	-
Emcompress	-	31,3	-	-	-	-	-	-	-
Neosorb P100T	-	-	31,3	-	-	-	-	-	-
Neosorb P60 W	-	-	-	31,3	-	-	-	-	-
Neosorb P30/60	-	-	-	-	31,3	-	-	-	-
Sorbolac 400	-	-	-	-	-	31,3	-	-	-
Granulac 200	-	-	-	-	-	-	31,3	-	-
Capsulac 60	-	-	-	-	-	-	-	31,3	-
Kollidon SR	50,0	50,0	50,0	50,0	50,0	50,0	50,0	50,0	50,0
Aerosil 200 Ph	0,2	0,2	0,2	0,2	0,2	0,2	0,2	0,2	0,2
Pruv	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0

Table 1. Formulations of tablets, % (continuation)

Ingredients	Formulations								
	F 10	**F 11**	**F 12**	**F 13**	**F 14**	**F 15**	**F 16**	**F 17**	**F 18**
TMZ•2HCl	-	-	-	-	-	-	-	-	-
Caffeine	17,5	17,5	17,5	17,5	17,5	17,5	17,5	17,5	48,8
Avicel PH-101	31,3	-	-	-	-	-	-	-	-
Emcompress	-	31,3	-	-	-	-	-	-	-
Neosorb P100T	-	-	31,3	-	-	-	-	-	-
Neosorb P60 W	-	-	-	31,3	-	-	-	-	-
Neosorb P30/60	-	-	-	-	31,3	-	-	-	-
Sorbolac 400	-	-	-	-	-	31,3	-	-	-
Granulac 200	-	-	-	-	-	-	31,3	-	-
Capsulac 60	-	-	-	-	-	-	-	31,3	-
Kollidon SR	50,0	50,0	50,0	50,0	50,0	50,0	50,0	50,0	50,0
Aerosil 200 Ph	0,2	0,2	0,2	0,2	0,2	0,2	0,2	0,2	0,2
Pruv	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0	1,0

Result and Discussion:

TMZ•2HCl and caffeine model substances were chosen for experiment because of different aqueous solubility (tab. 2).

Table 2.Aqueous solubility of ingredients,mg/ml(n=3, SD ≤ 5 %)

Ingredients	Solubility at pH corresponding to	
	stomach	small intestine
TMZ•2HCl	620 (pH 0.6)	340 (pH 6.7)
Caffeine	20 (pH 1.0)	20 (pH 6.9)
Lactose monohydrate	210 (pH 0.9)	210 (pH 6.5)
Sorbitol	>4000 (NA*)	>4000(NA*)
Calcium hydrogen phosphate dihydrate	200 (pH 1.0)	0 (pH 6.8)

* Impossible to determine pH because of high concentration

Soluble Neosorb P100T, insoluble at pH 6.8 but soluble at pH 1 Emcompress, insoluble Avicel PH-101were chosen for investigation of different diluent type effect on TMZ•2HCl and caffeine dissolution profile fromKollidon SR matrix tablets.

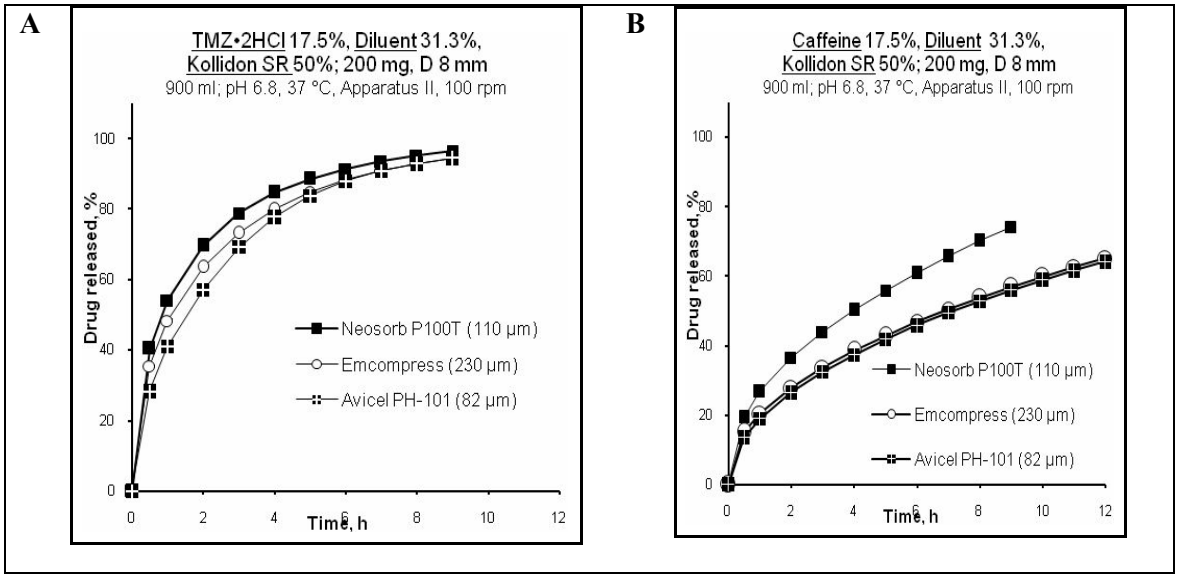
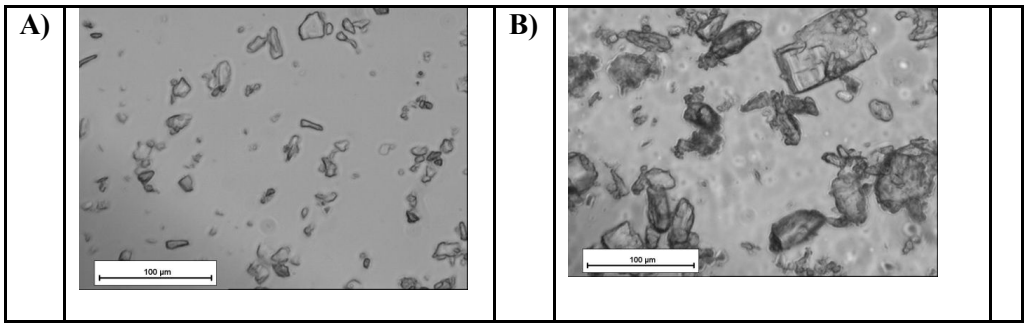


Figure 1:Effect of diluent type on dissolution profile from Kollidon SR matrix tablets: A) TMZ•2HCl; B) caffeine

The decreasing of possibility of mentioned diluents to slow down of model substances dissolution kinetics had follow sequence: Avicel PH-101 >Emcompress>Neosorb P100T (fig. 1).



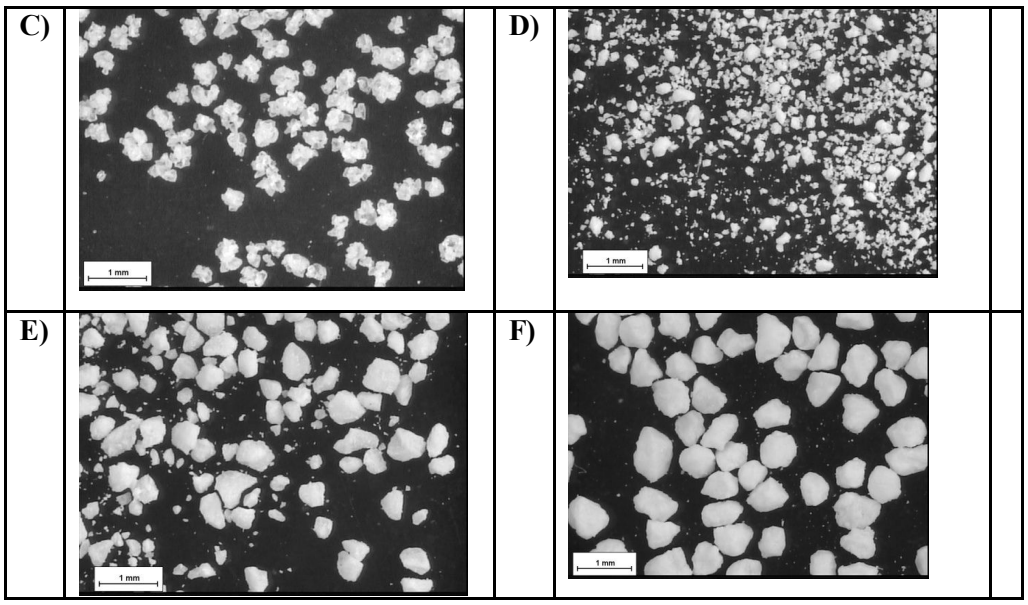


Figure 2: Microscopy of diluents: A) Sorbolac 400; B) Granulac 200; C) Capsulac 60; D) Neosorb P100T; E) Neosorb P60; F) Neosorb 60/30

Different grades of lactose monohydrate (Sorbolac-400, Granulac-200, Capsulac-60) and sorbitol (NeosorbP100T, P60 W, P30/60)were used to investigate the soluble diluent particle size effect on TMZ•2HCl and caffeine dissolution profile from Kollidon SR matrix tablets (fig. 2, 3, tab. 3).

Table 3.Particle size distribution, µm

	Ingredients	Av.	S.D.	D_{10}	D_{50}	D_{90}
2	Kollidon SR	86,6	45,1	29,1	83,1	150,0
4	TMZ•2HCl	20,9	12,5	6,1	19,2	38,4
5	Caffeine	23,9	19,3	2,7	19,2	53,4
6	Sorbolac 400	10,5	7,7	1,24	9,3	21,4
7	Granulac 200	16,7	12,2	2,6	14,1	35,7
8	Capsulac 60	250,7	88,0	144,7	245,2	368,7
9	Neosorb P60 W	299,0	183,0	72,1	281,0	553,0
10	Neosorb P30/60	513,0	158,0	331,0	509,0	715,0
11	Avicel PH-101	82,2	55,3	22,7	71,4	156
12	Emcompress	229,5	116,1	96,2	210,5	394,4
13	Pruv	14,9	10,2	2,7	13,2	29,6

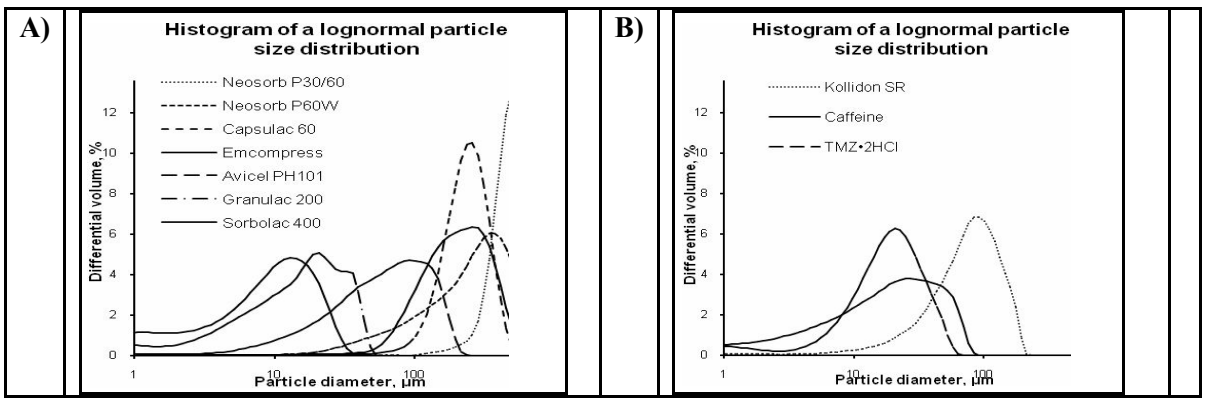


Figure 3. Particle size distribution: A) diluents; B) model substances and Kollidon SR

Increasing diluent particle size from 21 µm(Granulac-200) to 110 µm (Neosorb P100T) slightly decreased TMZ•2HClrelease from Kollidon SR matrix tablets (fig. 4 A). Increasing of sorbitol particle size from 110 to 299 and 513 µm had no significant effect on TMZ•2HCl dissolution kinetics. Increasing the particle size of lactose monohydrate (from 11 to 251 µm) and sorbitol (from 110 to 513 µm) decreased caffeine release from Kollidon SR matrix tablets (fig. 4 B).

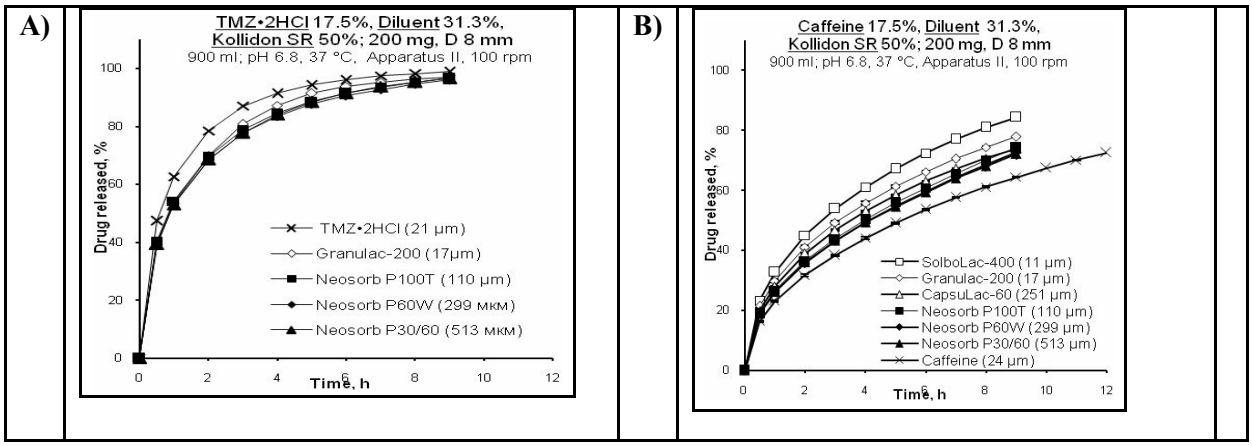
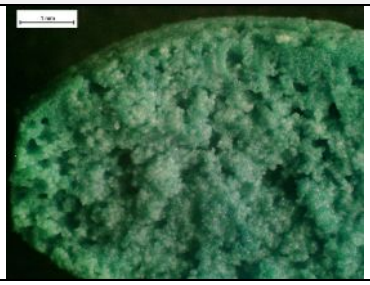
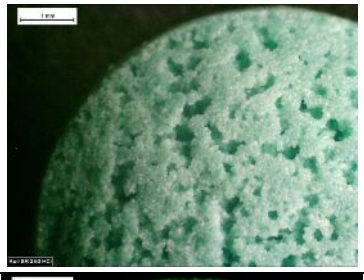
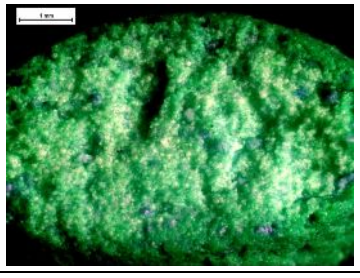
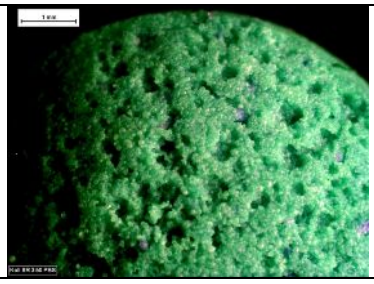


Figure 4. Effect of soluble diluents particle size on dissolution profilefrom Kollidon SR matrix tablets: A) TMZ•2HCl B) caffeine

Matrix tablet structure had one of the main roles in both cases when used different diluent types and soluble diluents with different particle size. In every formulation Kollidon SR as insoluble swellable matrix former had 50 % of matrix formulation and formed continuous phase. Depending on model substance-diluent composition and their particles sizes corresponding matrix structure was formed (F 1-18).Soluble diluents and model substances are form porous matrix structure during dissolution. At pH 6.8 Emcompress crystals are insoluble and block some percolation ways but at pH 1 have behavior like soluble ingredient (fig 5). The particles of Avicel PH-101 are swelling inside percolation wayswhich leads to a denser structure compared tosoluble diluents andEmcompress. This leads to the idea that the swollen cellulose is swollen polymer complicates the diffusion of fluid into the tablet and slows down the release.

Using soluble diluents with different particle size leads to form corresponding porous matrix structure during dissolution test, smaller particles formed smaller pores (fig. 6).In addition to the pores formed by diluent tablets contain pores formed by model substances: TMZ•2HCl with average particle size 21 µm and caffeine – 24 µm.

Formulation: used diluent and conditions	**Cross-section**	**Surface**
F2:Emcompress (230 µm) after0.1 N HCl medium (pH 1)		
F2: Emcompress (230 µm) after PBS medium (pH 6.8)		

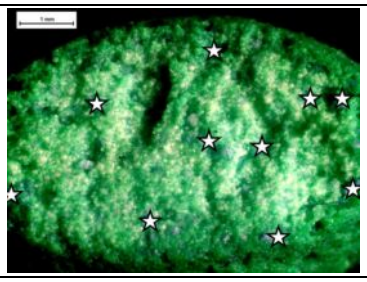
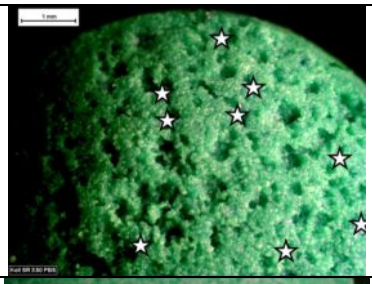
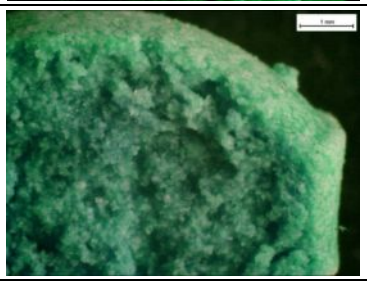
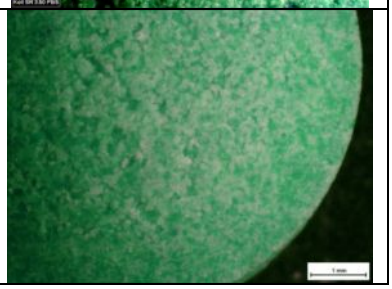
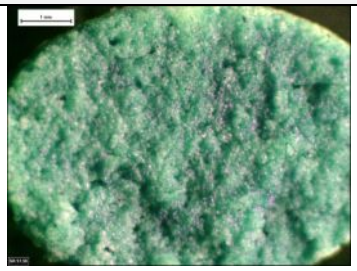
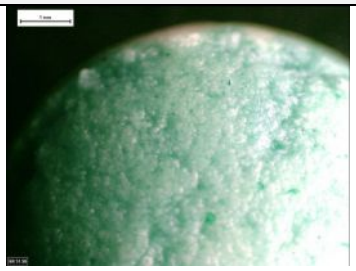
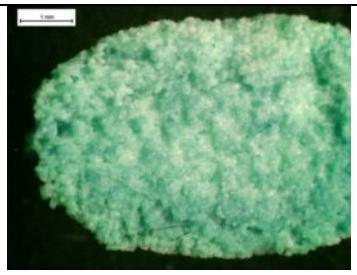
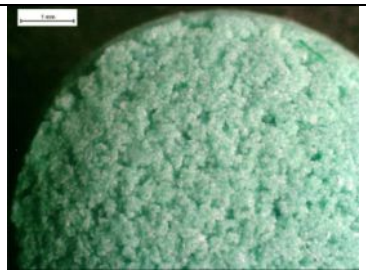
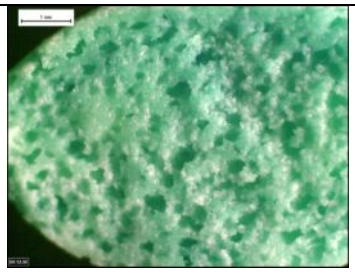
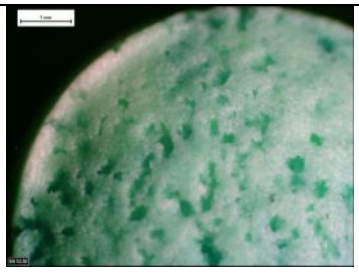
F2: Emcompress (230 µm) after PBS medium (pH 6.8) with marked Emcompress crystals		
F1: Avicel PH-101 (82 µm) after PBS medium (pH 6.8)		

Figure 5. Effect of different diluents type on microstructure of Kollidon SR matrix tablet surface and cross-section after dissolution test

All these pores played the role of percolation ways for soluble ingredients. It's interestingto note that increasing of soluble diluents average particle size from 11 to 110 µm had much mort effect than particle size increasing from 110 to 513 µm.

Formulation: used diluent and conditions		**Cross-section**	**Surface**
Lactose monohydrate	F 6: Sorbolac 400 (11 µm)		
	F 7: Granulac 200 (17 µm)		
	F 8: Capsulac 60 (251 µm)		

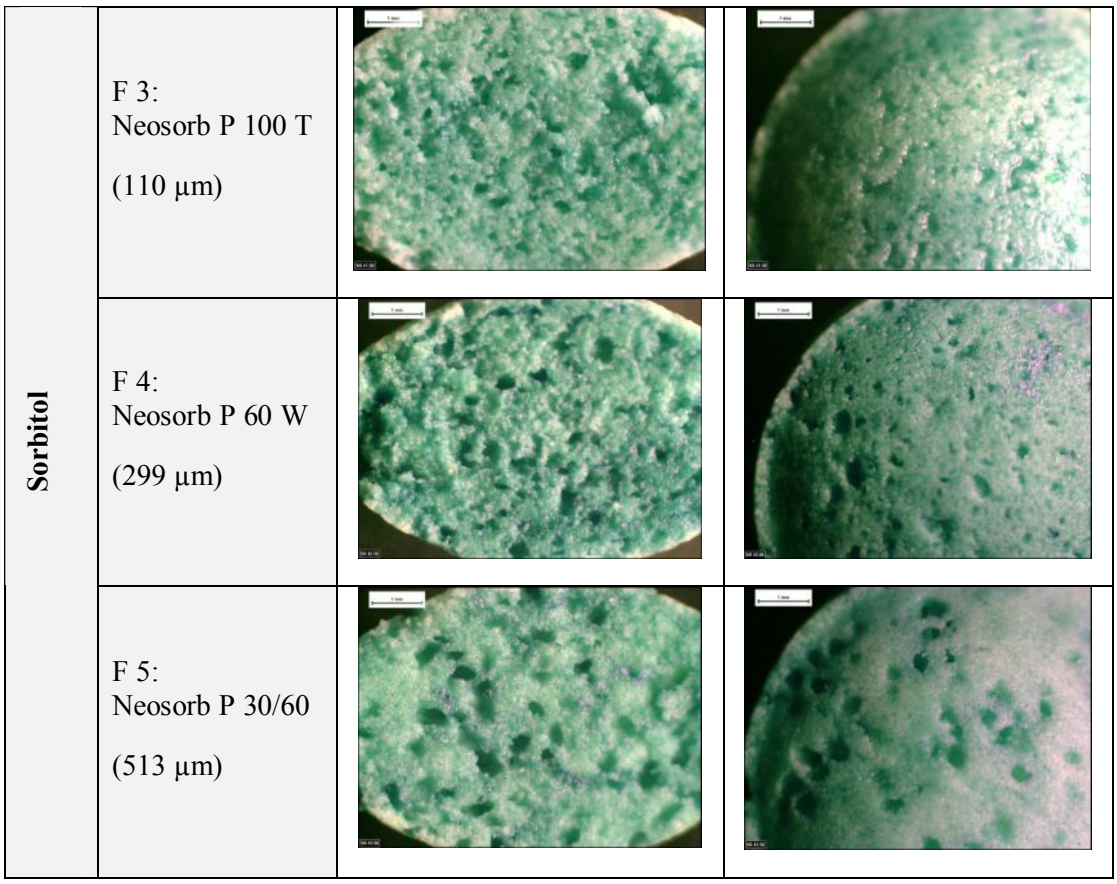


Figure 5. Effect of soluble diluents with different particle size on microstructure of Kollidon SR matrix tablet surface and cross-section after dissolution test

It seems that it could be linked with forming a plurality of branched percolation pathways when useddiluent particle that equal and smaller thanNeosorb P 100 T.At the same time holes in tablet structure formed after particles that equal and bigger than Capsulac 60 looks like isolated from the contact with holes with same size that in agreement with small difference of dissolution profiles of caffeine andTMZ•2HCl matrix tablets prepared using soluble diluents with average particle size bigger than 251 µm.

The dissolution kinetic of caffeine in all comparable cases was slower than kinetic of TMZ•2HCl (fig. 1, 4). Taking in account comparable particle sizes of model substances is interesting to pay attention on significant difference ofTMZ•2HCl (F 9)and caffeine (F 18) dissolution kinetics from matrix tablets without diluents (fig. 4 A, B).Slower dissolution kinetic of caffeine coincides with its lower aqueous solubility comparing to TMZ•2HCl.

Conclusion:

Comparing different diluent types was established that dissolution kinetic of model substances from Kollidon SRmatrix tablets (at pH 6.8) was faster with sorbitol than with Emcompress orAvicel PH-101. Using Emcompress (at pH 6.8) provided fasterdissolution kinetic comparing toAvicel PH-101, thatcould be linked withKollidon SR and Avicel PH-101 swelling.In the dissolution medium at pH 1Emcompress provide porous matrix structure as soluble diluent.

Establishedthat particle size increasing of lactose monohydrate from 11 to 251 µm and sorbitol from 110 to 513 µm decreased dissolution kinetics of caffeine andTMZ•2HCl from Kollidon SRmatrix tablets. Obtained results are in agreement with tablets structure and percolation theory.Dissolution kinetics of model substances from Kollidon SRmatrix tablets were increased with its solubility increasing from caffeine to TMZ•2HCl.

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