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SCIENTIFIC PAPER

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COMPARISON OF DRUG RELEASE AND MECHANICAL PROPERTIES OF TRAMADOL HYDROCHLORIDE MATRIX TABLETS PREPARED WITH SELECTED HYDROPHILIC POLYMERS

Article Highlights

- HPMC and HPC were used for the preparation of sustained release matrix tablets
- Formulation and process parameters effects on tablet quality were evaluated
- Simulation of compaction profiles of large scale rotary tablet presses was used
- Proportion of tramadol HCl in tablet exhibits the most important influence on the drug release
- The type of filler had the most pronounced effect on tablet mechanical properties

Abstract

This study investigates the use of high molecular weight hydrophilic polymers, hypromellose and hydroxypropylcellulose, for the preparation of sustained release matrix tablets containing a high-dose highly soluble drug, tramadol HCl. The proportion of polymer, type of insoluble filler, proportion of tramadol HCl, amount of drug in the tablet and compression pressure were recognized as critical formulation and process parameters and their influence on drug release and tablet mechanical properties was evaluated. Tensile strength was used as an indicator of the mechanical properties of the tablets. Experiments were performed with utilization of a compaction simulator, a device that simulates compaction profiles of large scale rotary tablet presses. In formulations with both polymers, the proportion of tramadol HCl was the most critical formulation parameter, wherein increasing the proportion of tramadol HCl increased its release rate in the early stages of drug release. Regarding the tablet mechanical characteristics, the filler type had the most pronounced effect in formulations with both polymers. Higher tensile strengths were obtained with Avicel PH 102 as the filler in formulations with both HPMC and HPC.

Keywords: tramadol HCl, matrix tablets, hypromellose, hydroxypropylcellulose, drug release, tensile strength.

Hydrophilic polymers, such as hypromellose, polyethylene oxide, hydroxypropylcellulose, guar gum, carrageenan, xanthan gum, etc., are widely used in the formulation of hydrophilic matrices with controlled drug release. Formation of a gel layer in contact with surrounding media allows sustained drug release from such systems. Once the original protective gel layer is formed, it controls the further penetration of water into the tablet and release of drug [1]. The basic processes that determine drug release from hydrophilic matrix tablets are drug diffusion through the gel layer, as well as erosion of the swollen gel layer [2]. The solubility of the drug can significantly affect the mechanism of drug release. Release of a highly water-soluble drug from hydrophilic matrix system is mainly controlled by the diffusion through the swollen gel layer, whereas the release of poorly soluble drugs is predominantly controlled by the polymeric matrix erosion [3]. For prolonged release of high-dose, highly soluble drugs, it is necessary to use hydrophilic polymers of very high viscosity [4,5]. Quality by design (QbD) includes pro-

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cesses of determining critical quality attributes (CQA) of the drug product, as well as selecting the types and amounts of excipients to deliver drug product of the specified quality [6]. The most critical quality attribute in the development of sustained release hydrophilic matrix tablets is the drug release rate, which is predominantly determined by the properties of the polymer (type, concentration, solubility and viscosity) and drug (solubility and concentration). High proportions of both drug and matrix polymer can significantly affect mechanical properties that are considered as an important quality attribute of the hydrophilic matrix tablets. Therefore, in the formulation of hydrophilic matrix tablets, both the ability of the polymer to provide sustained drug release and the mechanical characteristics of the prepared tablets should be evaluated. The ability of the polymer to affect the release rate characteristics of high-dose, highly soluble drug can be evaluated in two ways: as the ability to prevent premature drug release in early stage of drug release, as well as the ability to maintain drug release with predictable kinetics in time points over a prolonged period of time. Mechanical properties of powder mixtures and compacts can be assessed through evaluation of compressibility (solid fraction *vs*. compaction pressure), compactibility (tensile strength *vs*. solid fraction) and tabletability (tensile strength *vs*. compaction pressure). Compression and compaction properties of hypromellose were evaluated with the influence of particle size, moisture content, compression force, compression speed, viscosity grade and substitution level of free OH-groups [7]. Mechanical properties and drug release characteristics of directly compressible controlled release matrix systems containing high viscosity hydroxypropylcellulose and highly or sparingly soluble model drug were evaluated for different types of fillers [5]. Tablet geometry plays also important role in drug release kinetics for diffusion-controlled systems and it has been studied in detail by Siepmann *et al*. [8]. Effect of a tablet surface/tablet volume ratio (SA/Vol) on the drug release from hydrophilic matrices was investigated for hypromellose matrix tablets [9] and for hydroxypropylcellulose matrix tablets [10]. Most of the studies that investigated mechanical characteristics of hydrophilic matrix tablets were conducted on either excenter tablet presses or instrumented small rotary presses. Using compaction simulator enables thorough studies of compaction characteristics of materials, as well as evaluation of the influence of different process variables of the compaction phase on tablet properties, determination of scale-up parameters, and creating database of the compaction properties of new active pharmaceutical ingredients (APIs) or excipients [11]. Compaction simulators are useful as the tools for evaluation and comparison of powder mechanical properties in simulated production conditions. Mathematical models, such as force-time, force-distance, and die-wall force parameters can be used to describe work of compaction, elasticity, plasticity, and time dependent deformation behavior of pharmaceuticals. Parameters such as the bonding index, brittle fracture index and strain index can be used to predict compaction related problems [12]. This study investigates the performance of two selected high viscous hydrophilic polymers, hypromellose and hydroxypropylcellulose in the formulation of hydrophilic matrix tablets with tramadol-hydrochloride, as a model of high-dose, highly soluble drug. The influence of the selected formulation and process variables on drug release characteristics and tablet mechanical properties was evaluated.

EXPERIMENTAL

Materials

The following materials were used: hypromellose, type 2208 (Metolose 90SH-100000, Shin-Etsu Chemical Co., Ltd, Tokyo, Japan), hydroxypropylcellulose (Klucel HXF, Hercules Incorporated Aqualon Division, Wilmington, DE, USA), microcrystalline cellulose (Avicel PH 102, FMC Biopolymer, USA), partially pregelatinised maize starch (Starch 1500, Colorcon, Dartford, UK), colloidal silicon dioxide (Aerosil 200 Pharma, Degussa), magnesium stearate, (Mallinckrodt, St. Louis, MO, USA). Tramadol HCl (Hemofarm A.D., Vršac, Serbia) was used as model of high dose, highly water-soluble drug.

Experimental design

In the first part, experiments were conducted according to 2^{5-2} fractional factorial design (Table 1) for each polymer, in order to evaluate the influence of different formulation (proportion of polymer, type of insoluble filler, proportion of tramadol HCl, amount of drug in tablet) and process input variables (compression pressure) on tramadol HCl release from compressed matrices. Percentages of drug released from matrix tablets after 30 and 240 min were selected as responses. Using this design type it is possible only to recognize factors that have the highest impact on the response variable, having in mind that effects that are small relative to the noise of the process will be confounded. Therefore, the applied design type was used for screening purposes in order

Table 1. Experimental matrix according to 2^{5-2} experimental design with obtained responses

Formulation	Proportion of polymer, %	Filler type[a]	Proportion of tramadol HCl, %	Compression pressure, MPa	Tramadol HCl per tablet, mg	HPMC matrix tablets			HPC matrix tablets		
						SA/Vol	Q_{30}[b]	Q_{240}[c]	SA/Vol	Q_{30}[b]	Q_{240}[c]
F1	25	Starch 1500	55.6	300	200	0.894	27.5	78.7	0.883	28.5	82.6
F2	35	Starch 1500	55.6	150	100	1.047	28.4	78.7	1.037	28.7	83.3
F3	25	Avicel PH 102	55.6	150	200	0.896	28.0	83.0	0.891	28.1	82.8
F4	35	Avicel PH 102	55.6	300	100	1.056	30.3	82.2	1.048	26.7	80.8
F5	25	Starch 1500	27.8	300	100	0.896	26.2	75.5	0.898	26.2	73.3
F6	35	Starch 1500	27.8	150	200	0.709	20.8	69.9	0.710	23.1	70.5
F7	25	Avicel PH 102	27.8	150	100	0.930	22.5	71.9	0.920	26.8	72.4
F8	35	Avicel PH 102	27.8	300	200	0.750	20.3	65.8	0.736	21.9	68.1

[a]Starch 1500 - partially pregelatinized maize starch; Avicel PH 102 - microcrystalline cellulose; [b]normalized percentage of drug release after 30 min; [c]normalized percentage of drug release after 240 min

to select factor that have pronounced influence on the selected response variable.

The effects of the input variables on responses were compared for each polymer. In order to eliminate the influence of tablets geometry on drug release, normalization of the percentage of drug released after 30 and 240 min, was performed by dividing obtained drug released percentages with surface area per volume ratio (SA/Vol) of tablets.

In the second part of the study, 2^3 full factorial design was used to evaluate the influence of the matrix polymer proportion, type of filler and drug proportion on the tablet mechanical properties (Table 2). From this point forward, two experimental sets according to 2^3 design was applied, for each polymer separately. Tensile strength (σ_t) was used as an indicator of tablets mechanical properties, enabling comparison of mechanical properties of tablets with different dimensions. Tensile strength was calculated according to the following equation:

$$\sigma_t = \frac{2F}{\pi dh} \quad (1)$$

where F is the crushing force, d is the tablet diameter and h is the tablet thickness.

Statistical software Design Expert 7.0 (StatEase, Inc.) was used throughout the study.

Tablets preparation

Powder mixtures for compression were prepared by using a Turbula® shaker-mixer (Glen Mills Inc., Clifton, NJ, USA). Tablets were compressed with direct compression method by using of Presster™ single station compacting simulator (Metropolitan Computing Corporation, East Hanover, NJ, USA). Simulation of the rotary tablet press Korsch PH336 was used, with simulated die table speed of 30 rpm which conforms to 65,000 tablets per hour and dwell time of 20 ms. Tablets were prepared using punches with diameters of 7, 10 and 13 mm, while tablet masses were 180, 360 and 720 mg, respectively, according to the experimental design. Compression pressure was calculated from the measured compaction force per cross-sectional area of tablets. Tablets were compressed on different compaction pressures in the range of 100 to 500 MPa with simul-

Table 2. Experimental matrix according to 2^3 experimental design with obtained responses

Formulation	Proportion of polymer[a], %	Filler type[b]	Proportion of tramadol-HCl, %	σ_t / N cm^{-2}			
				HPMC matrix tablets		HPC matrix tablets	
				120 MPa	250 MPa	120 MPa	250 MPa
F1	25	Starch 1500	55.6	75	105	95	130
F2	35	Starch 1500	55.6	115	180	107	140
F3	25	Avicel PH 102	55.6	145	195	145	201
F4	35	Avicel PH 102	55.6	170	213	130	182
F5	25	Starch 1500	27.8	60	95	75	130
F6	35	Starch 1500	27.8	85	130	95	135
F7	25	Avicel PH 102	27.8	295	360	253	305
F8	35	Avicel PH 102	27.8	245	330	205	265

[a]Proportion of polymer refers to a quantity of HPMC or HPC depends on experimental design; [b]Starch 1500 - partially pregelatinised maize starch; Avicel PH 102 - microcrystalline celullose

ation of the compaction profile of the Korch PH336 rotary tablet press. Tensile strength was calculated from measured hardness and tablet dimensions. Influence of the selected input variables on the tablet tensile strength was analyzed.

Drug release testing

Drug release test was performed using rotating basket apparatus (Sotax, Allschwil, Switzerland) during 8 h (rotational speed 75 rpm, medium volume 600 ml, temperature 37 °C). Drug release testing procedure was developed as a part of in-house testing. Samples were taken after predefined time intervals: 30, 120, 180, 240, 360 and 480 min and the amount of dissolved tramadol HCl was determined spectrophotometrically at $\lambda = 271$ nm. The data collected up to 240 min were selected for modeling of drug release. During the drug release testing, the pH of the medium was changed by adding buffer solutions as follows: in the first 30 min, pH 1.2; from 30–120 min, pH 2.3; from 120-180 min, pH 6.8; from 180-240 min, pH 7.2. Artificial gastric juice, pH 1.2, as well as two buffer solutions, were used for changing the pH during the dissolution test:

Buffer 1: K_2HPO_4, 63 g/100 ml (6 ml at 31 min)

Buffer 2: NaOH 15 g/100 ml (6 ml at 121 min and 3 ml at 181 min).

Mechanical characterization of tablets

Tablet hardness was measured using an 8M tablet hardness tester (Dr. Schleuniger Pharmatron, Thun, Switzerland) and tablet dimensions were measured with digital caliper. Tensile strength was calculated from dimensions of tablets and measured hardness, according to Eq. (1).

RESULTS AND DISCUSSION

Evaluation of drug release from hypromellose (HPMC) and hydroxypropylcellulose (HPC) matrices

Tramadol HCl release profiles from HPMC matrices and analogue formulations with HPC (formulation F1-F8) are presented in Figure 1a and b, respectively.

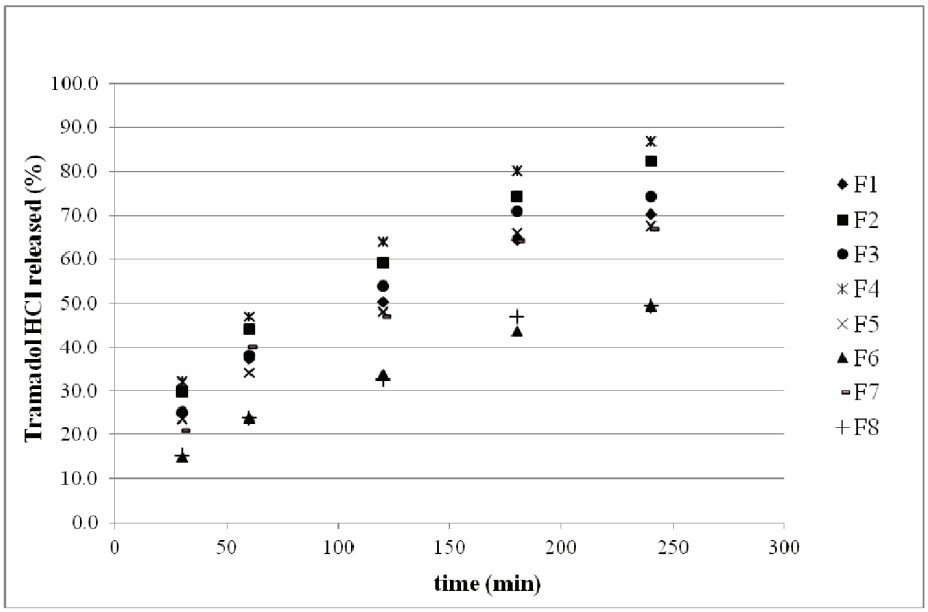
Since in the hydrophilic matrices with high viscosity polymers and highly water-soluble drug diffusion release mechanism is predominant in respect to erosion, drug release process follows Higuchi's model. There is linear relationship between drug release and the square root of time for both HPMC and HPC matrices (Figure 2a and b, respectively) in certain time intervals and it is related to the geometry characteristics of the matrix tablets. The calculated determination coefficients values (R^2) for all formulations were above 0.95, indicating good fitting to the Higuchi model.

One of the prerequisites for formulation of matrix tablets with extended drug release is that premature drug release should not happen. Percentages of tramadol HCl released after 30 and 240 min were selected as indicator of polymer ability to prevent premature drug release and enable sustained release of drug (Table 1). Furthermore, both time points are within the interval in which drug release follows Higuchi's model. Normalized values of drug released percentages were used in order to eliminate the influence of geometrical characteristics on drug release rate. Normalization was performed by dividing the percentage of drug released with surface area per volume ratio (SA/Vol) of the matrix tablets containing HPMC or HPC as the release rate control polymer (Tables 3 and 4).

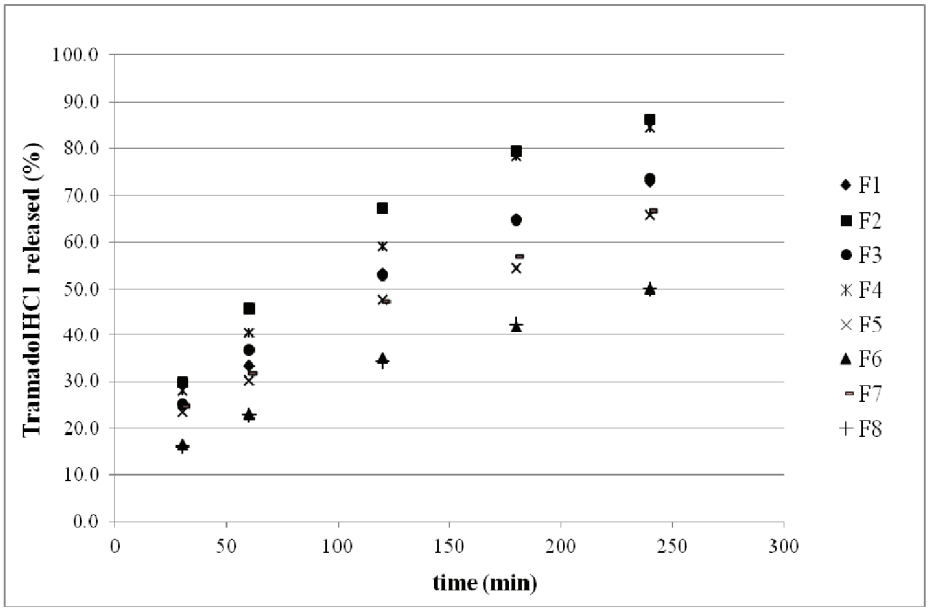
The influence of selected formulation and process parameters (proportion of polymer, type of insoluble filler, proportion of tramadol HCl, amount of drug in tablet and compression pressure) on normalized percentage of drug released at 30 and 240 min was analyzed and calculated factor effects are summarized in Table 3.

From the obtained results it can be concluded that in formulations containing HPMC as release rate control polymer, only the proportion of drug in tablet exhibits statistically significant effect on the percentage of drug release after 30 min ($p < 0.05$). By increasing the proportion of drug in the tablet, the drug release rate is increased. Other formulation and process variables in selected range have no statistical significant influence on tramadol HCl released rate. For the drug release at a later time point, 240 min, none of the examined factors exhibit statistically significant influence on drug release.

Contrary to HPMC matrix tablets, statistically significant effects of the proportion of tramadol HCl, proportion of polymer and amount of tramadol HCl in the tablet on the normalized percentage of drug released after 30 min were observed for HPC matrix tablets. The proportion of tramadol HCl exhibits the highest effect on the drug release in the early stage (30 min), and with its increase, the drug release rate increased. The proportion of the HPC polymer has the opposite effect on the drug release, wherein its increase led to slower drug release rate. Quantity of drug per tablet also showed a statistically significant effect for the early stage of drug release, indicating that there could be difference in drug release between tablets containing different amounts of the drug. For the normalized value of drug released at 240 min, the



a)



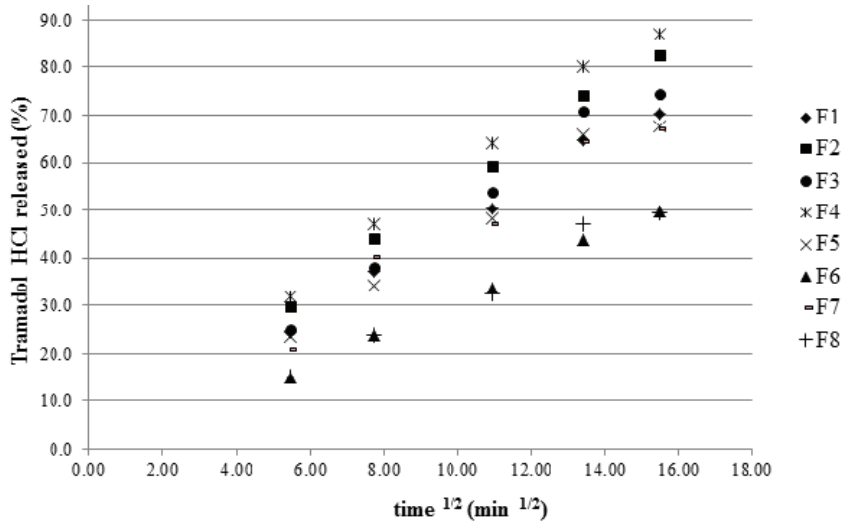
b)

Figure 1. Tramadol HCl release profiles from HPMC (a) and HPC (b) matrix tablets.

same formulation and process variables including type of filler had statistically significant effects. It was found that the proportion of tramadol HCl has the largest effect on the normalized percentage of drug release after 240 min. Increase in proportion of tramadol HCl results in the increase in percentage of drug release after 240 min, the same as after 30 min. Other input variables did not have statistically significant influence on the release of tramadol HCl.

Mechanical characterization of matrices with HPMC and HPC

Full factorial design was performed in order to evaluate the influence of input variables (proportion of polymer, type of filler and proportion of tramadol HCl per tablet) on mechanical characteristics of matrix tablets. Due to different tablet dimensions, tensile strength was used for evaluation of mechanical characteristics of matrix tablets. Profiles of tensile strength



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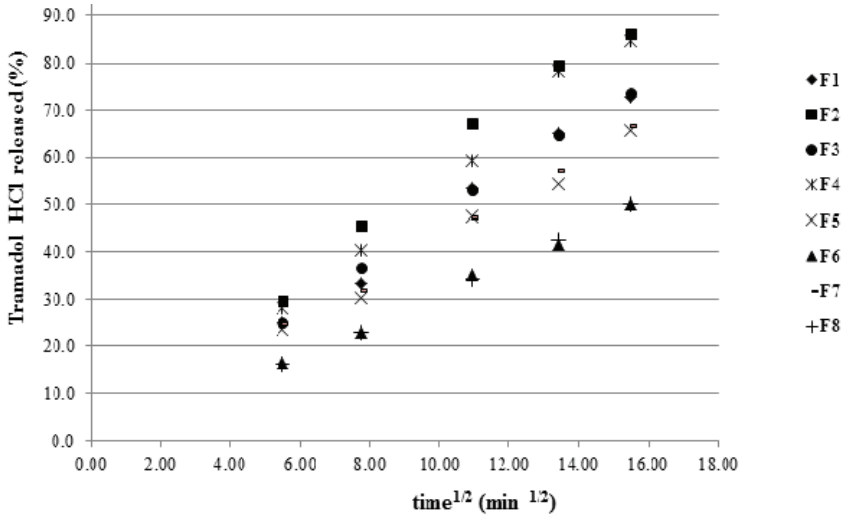


(b)

Figure 2. Tramadol HCl released per square root of time for HPMC (a) and HPC (b) matrix tablets.

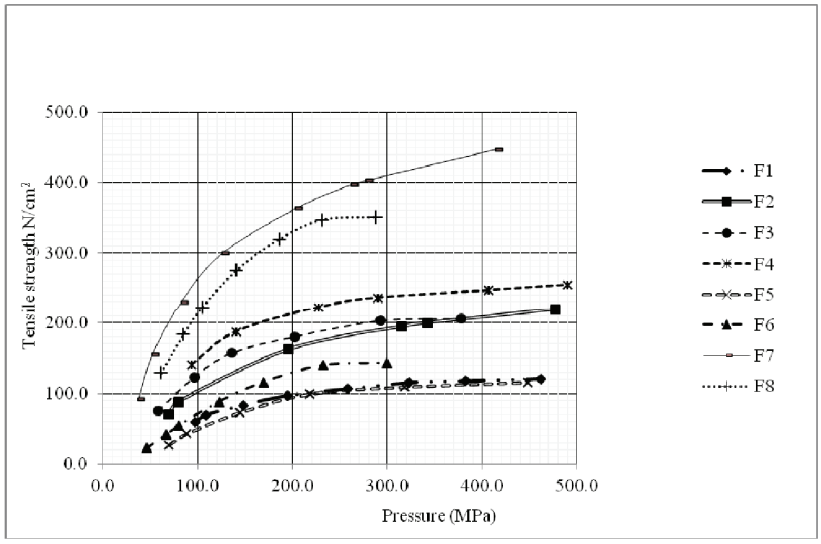
*Table 3. Calculated effects of the formulation and process parameters on normalized percentage of drug release after 30 and 240 min; * - statistically significant effects*

Parameter	HPMC matrix tablets		HPC matrix tablets	
	Q_{30}[a]	Q_{240}[b]	Q_{30}[a]	Q_{240}[b]
Proportion of polymer	-0.9099	-1.1403	-7.1839*	-7.6050*
Filler type	-0.3721	0.0091	-2.3426	-5.0700*
Proportion of Tramadol HCl	5.0441*	3.6032	10.9322*	40.9222*
Compression Pressure	-0.9509	0.1186	2.6549	3.8025
Tramadol HCl per tablet	2.2326	0.9943	5.3099*	5.2511*

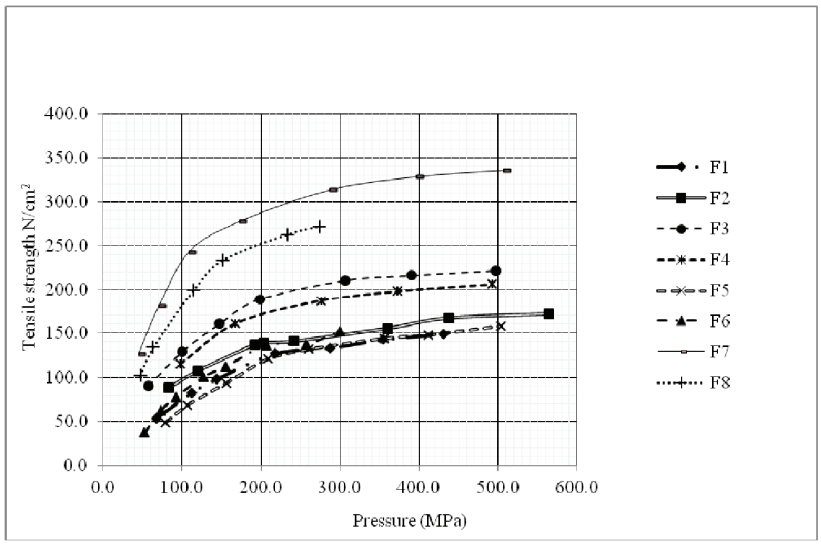
[a]Normalized percentage of drug release after 30 min; [b]normalized percentage of drug release after 240 min

versus compaction pressure (tabletability profiles) for the matrix tablets with HPMC and HPC are presented in Figure 3a and b, respectively.

Compression of tablet mixture was performed with compression force up to 40 kN, since with punch face diameter of 13 mm and compression pressure ofabout 300 MPa compression the force is near to the maximum possible force that could be achieved on the compaction simulator. Tensile strengths of matrix tablets on compaction pressures of 120 and 250 MPa were analyzed and compared as output variables (Table 2).



a)



b)

Figure 3. Profiles of tensile strength versus compaction pressure for HPMC (a) and HPC (b) matrix tablets.

The values of tensile strength were extracted from trend lines of tabletability profiles for matrix tablets with HPMC and HPC (Figure 3a and b, respectively). Values for compaction pressure of 120 MPa correspond to values of tensile strength in the ascending part of the tabletability profiles diagrams in all trials, while the compression pressure of 250 MPa corresponds to the part where the profile reaches a plateau. The higher values of tensile strength were obtained when Avicel PH 102 was used as the filler compared to Starch 1500 in formulations with both polymers. In the range of the lower compression pressure (120 MPa) for matrix tablets with both polymers, none of the evaluated formulation variables including interaction between them have a statistically significant influence on the output variable, *i.e.*, variation of either of the evaluated variables in the evaluated range did not exhibit statistically significant effects on the tensile strength (Table 4).

On the contrary, in the range of the higher compression pressures, ~250 MPa, for matrices formulated with HPMC all formulation variables including interaction between them except proportion of HPMC polymer and interaction between proportion of HPMC polymer and proportion of Tramadol HCl had significant effects on the tensile strength. The most pronounced effect is achieved with variation of the type of filler, where matrix tablets containing Avicel PH102

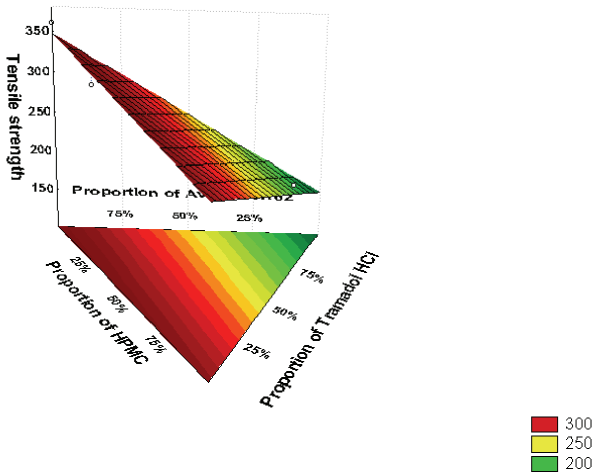
*Table 4. Calculated effects of the formulation and process parameters on tablet tensile strength; * - statistically significant effects*

Parameter	HPMC matrix tablets		HPC matrix tablets	
	120 MPa	250 MPa	120 MPa	250 MPa
Proportion of polymer	0.6667	12.2500*	-0.7561	-2.7500
Filler type	8.6667	73.5000*	8.8049	26.1250*
Proportion of Tramadol HCl	-3.0000	-27.7500*	-3.6829	-11.3750
Proportion of polymer×Filler type	-1.5000	-15.2500*	-2.3171	-4.6250
Proportion of polymer×Proportion of tramadol HCl	1.5000	11.0000	0.6098	1.6250
Filler type×Proportion of tramadol HCl	-4.5000	-42.7500*	-5.2439	-12.0000

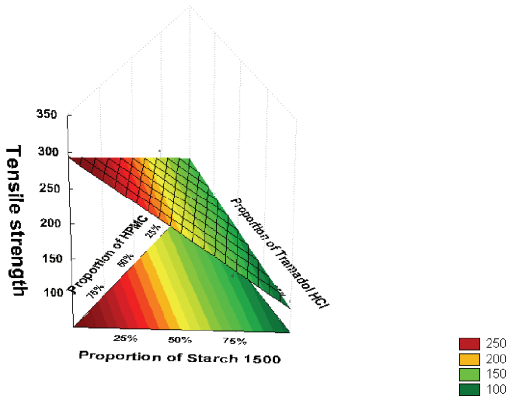
had much higher tensile strengths compared to matrices formulated with Starch 1500 as the filler. Increasing of the proportion of Tramadol HCl had a negative influence on the tensile strength, as well as the combination of using Starch 1500 with increasing proportion of Tramadol HCl, and the combination of the same filler with increasing proportion of HPMC polymer.

In the case of matrix tablets formulated with HPC and with higher compression pressure, only the type of filler had a statistically significant effect on the tensile strength. Same as with HPMC as a polymer, matrix tablets containing Avicel PH102 has much higher tensile strengths compared to matrices formulated with Starch 1500 as filler.

Influence of proportions of polymer, filler and drug (comprising 100% of tablet) on tensile strength for matrix tablets with HPMC polymer, is presented in Figure 4a and b for Avicel PH 102 and Starch 1500, respectively, as well as for the matrix tablets with



(a)



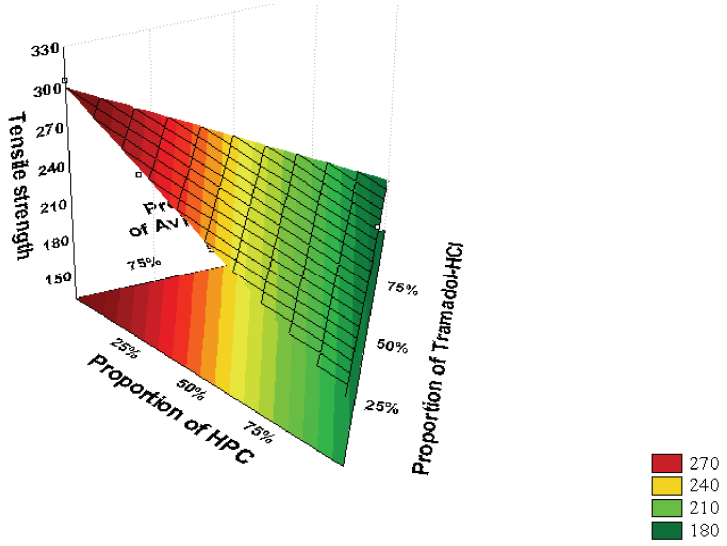
(b)

Figure 4. Influence of proportions of polymer (HPMC), filler and drug (comprising 100% of tablet) on tensile strength of tablets prepared with Avicel PH 102 (a) and Starch 1500 (b).

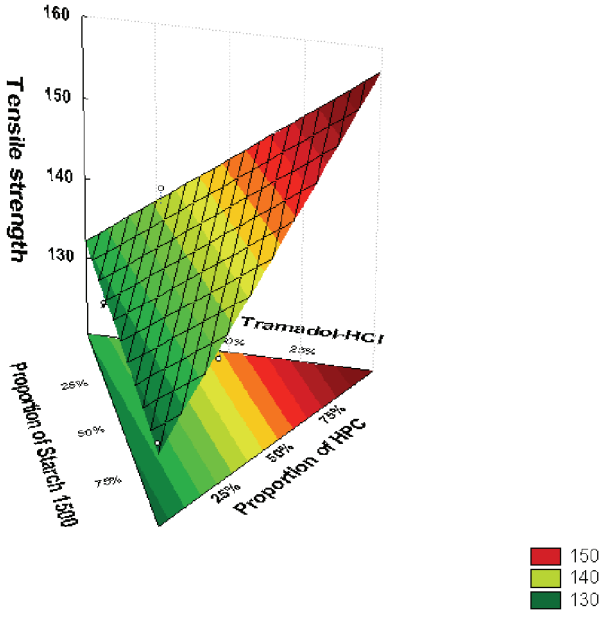
HPC polymer in Figure 5a and b for both fillers in the same order.

CONCLUSION

A comparison of hydrophilic polymers as matrix forming materials was made with respect to drug release modification abilities, as well as mechanical properties with the selected high-dose highly soluble model drug, tramadol HCl. Formulations with both polymers, HPMC and HPC, had similar characteristics with respect to sensitivity of drug release rate on the variation of proportion of the tramadol HCl in early stages of drug release. Increasing of the proportion of tramadol HCl in formulation resulted in higher amounts of drug released. Regarding the mechanical properties of tablets, the type of filler had the most critical effect on the powder mixture tabletability in formulations with both polymers. Mechanical properties of matrix tablets were significantly better with microcrystalline cellulose compared to partially pregelatinised starch. These findings could be useful in selection of the polymer and optimization of formulation of sustained release matrix tablets with high dose, highly soluble model drug.



(a)



(b)

Figure 5. Influence of proportions of polymer (HPC), filler and drug (comprising 100% of tablet) on tensile strength of tablets prepared with Avicel PH 102 (a) and Starch 1500 (b).

Acknowledgements

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NAUČNI RAD

POREĐENJE OSLOBAĐANJA TRAMADOL--HIDROHLORIDA I MEHANIČKIH KARAKTERISTIKA MATRIKS TABLETA IZRAĐENIH SA ODABRANIM HIDROFILNIM POLIMERIMA

U ovom radu ispitivana je mogućnost primene hipromeloze i hidroksipropilceluloze, kao hidrofilnih polimera velike molekulske mase, za izradu matriks tableta sa produženim oslobađanjem, sa visoko rastvorljivom, visoko doziranom lekovitom supstancom tramadol-hidrohloridom. Udeo hidrofilnog polimera, vrsta nerastvorljivog sredstva za dopunjavanje, udeo tramadol-hidrohlorida, količina lekovite supstance u pojedinačnoj tableti i pritisak kompresije su prepoznati kao kritični parametri formulacije i procesa i u radu je ispitivan njihov uticaj na oslobađanje lekovite supstance i mehaničke karakteristike izrađenih tableta. Zatezna čvrstina tableta je korišćena kao indikator mehaničkih karakteristika tableta. Svi eksperimenti su vršeni korišćenjem simulatora kompakcije, koji omogućava simuliranje profila kompakcije rotacionih tablet mašina velikog kapaciteta. Kod formulacija izrađenih sa obe vrste polimera, udeo tramadol-hidrohlorida se pokazao kao najkritičniji faktor formulacije, pri čemu je povećanje udela tramadol-hidrohlorida dovelo do povećanja brzine oslobađanja ove lekovite supstance u početnim fazama oslobađanja lekovite supstance. Vrsta sredstva za dopunjavanje je pokazala najveći uticaj na mehaničke karakteristike izrađenih tableta, kod formulacija izrađenih sa oba tipa hidrofilnih polimera. Više vrednosti zatezne čvrstine tableta su postignute kod formulacija izrađenih korišćenjem Avicel PH 102 kao sredstva za dopunjavanje, bez obzira da li je u sastav tableta kao matriks polimer ulazila hipromeloza ili hidroksipropilceluloza.

Ključne reči: tramadol-hidrohlorid, matriks tablete, hipromeloza, hidroksipropilceluloza, brzina oslobađanja lekovite supstance, zatezna čvrstina.