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RESEARCH ARTICLE

Tabletting Properties and Physical Interaction of Microcrystalline Cellulose With Magnesium Stearate in a Mixture Under Compression

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Tabletting Properties and Physical Interaction of Microcrystalline Cellulose With Magnesium Stearate in a Mixture Under Compression

SUMMARY

Micro-crystalline cellulose from Rice straw was evaluated next to PH 101and PH102 types of micro-crystalline cellulose for its tabletting properties and interaction with magnesium stearate in a mixture under compression. The result showed that processed cellulose produced tablets of enhanced mechanical properties. However, the disintegration and dissolution rates of the produced tablets were slow. Under compression, a physical interaction took place between magnesium stearate and cellulose particles and a particulate system comprising of cellulose core firmly attached to a magnesium stearate out layer was produced. The isolated particulate system was elastic and its fracture under compression was less. The production of fine particles having contact points and new sites and surfaces for bonding was reduced. Powder consolidation decreased and the mechanical properties of the corresponding compacts were negatively affected. Processing excipients from the available valueless crude materials may support the economy of the developing countries.

Key Words: *Tabletting properties, Cellulose/ magnesium physical interaction, Isolated cellulose particulates.*

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Mikro-kristalin selülozun tabletleme özellikleri ve basım sırasında karışımın magnezyum stearat ile fiziksel etkileşimi

ÖZET

Pirinç kabuğundan elde edilen mikro-kristalin selüloz, tabletleme özellikleri ve basım sırasında magnezyum stearat ile etkileşimi açısından mikro-kristalin selüloz PH 101 and PH102 ile kıyaslanmıştır. Sonuçlar işlem görmüş selüloz ile elde edilen tabletlerin mekanik özelliklerinin iyileştiğini, bunun yanı sıra tabletlerin dağılma ve çözünme hızlarının daha yavaş olduğunu göstermiştir. Basım sırasında, magnezyum stearat ve selüloz partiülleri arasında fiziksel bir etkileşim meydana gelerek, çekirdeği selülozdan dış tabakası ise magnezyum stearattan oluşan partiküler bir sistem oluşmuştur. İzole edilen bu partilüler sistemin elastik olup ve basım esnasında kırılma özelliği daha azdır. Bu sayede değme açıları, bağlanma için yeni bölümleri ve yüzeyleri olan çok ince partiküllerin oluşumu azaltılmıştır. Toz konsolidasyonu azalmış, bahsi geçen oluşumların mekanik özellikleri ters yönde etkilenmiştir. Yararsız atıkların işlenmesiyle elde edilen yardımcı maddelerin kullanımıı gelişmekte olan ülkelerin ekonomilerini desteklemesi açısından faydalı olabilir.

Anahtar kelimeler: *Tabletleme özellikleri, selüloz/magnezyum fiziksel etkileşim, İzole edilmiş selüloz partikülleri.*

INTRODUCTION

A great deal of attention was directed to bio-technology as a means to process economically valuable materials such as paper pulp (1), ethanol (2-6) and micro-crystalline cellulose (MCC) from valueless agro-residues (7-9). MCC has tabletting properties close to optimal. It has high degrees of compressibility, compactibility and high dilution potential. The physico-chemical properties of a processed MCC vary according to the source used in processing (8,9). It was reported that MCCs processed from bagasse or corn cobs showed better compressibility than the celluloses extracted from rice husks and cotton linters, respectively (9). Lubricants are essential additives in tablets and capsules formulations. They improve the flow of the powder formulations during compression and reduce the die-wall friction to facilitate tablet ejection after compression (10). Magnesium stearate (MS) is the most widely used lubricant because of its low friction coefficient and high covering potential. MS however, imparts adverse effects on the compactibility and compressibility of tablet excipients and on the mechanical properties, disintegration and dissolution behaviors and the stability of the corresponding tablets (11). The concentration and duration of mixing were reported as factors controlling these adverse effects (12-15). In Egypt, processing microcrystal-

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line cellulose from rice straw may resolve the issue of the impact of burning tons of rice straw annually on the environment and other threatened ecosystems. As a cellulose based material, rice straw represents a potential source for in-expensive MCC since it is abundant and accessible, and the production is simple and economical. Such industrial projects may substantially support the economy of the country.

The objectives of this work were to evaluate the tabletting properties of microcrystalline cellulose extracted from rice straw (CCR) and explore the mechanism of the adverse effects imparted by MS on cellulose excipients and their corresponding tablets. Standard PH101 and PH102 types of micro-crystalline cellulose were employed as reference materials, respectively.

MATERIALS AND METHODS

Materials

Rice straw was collected from the Egyptian Organization of Crops, EOC, Cairo, Egypt. The analytical grade chemicals namely: Hydrochloric acid (37.5%) obtained from Scharalab, S.L., Gato Prez, Spain; sodium hydroxide pellets; glacial acetic acid, formic acid and sodium hypochlorite powder and ethanol 90% purchased from Pvt. Ltd. Mumbai, India, were used in this investigation, respectively. MS (Scharalab, S.L., Spain), PH101 and PH102 types MCC denoted as (CC1) and (CC2) were given by Krishna Chemicals, Mumbai-40078, Maharashtra, India.

Methods

Processing of CCR

CCR was extracted as follows: A 500 g straw sample was washed , dried and milled using a suitable laboratory grinder. A 250 g sample of the powder was soaked in a fresh 800 ml of 2% w/w sodium hydroxide solution for 48h then was boiled in a fresh 800 ml the sodium hydroxide solution for 6 h. The pulp was washed, neutralized and boiled in 500ml of 9% w/w HCl solution for 15 min to hydrolyze the cellulose. The mass was thoroughly washed with distilled water and wet milled using the laboratory grinder. It was successively boiled in 2 liters of 3% w/w of formic acid and in 6% w/w of acetic acid for 3h in order to remove the heavy metals. The yielded mass was washed from the acid, neutralized and bleached with 3 liters of 6% w/w sodium hypochlorite solution for 2 h. The produced mass was thoroughly washed with distilled water, neutralized, dried, pulverized and kept in screw capped powder bottles till use.

Evaluation of CCR

Chemical properties and characterization

CCR solubility in water and common solvents, pH, degree of polymerization, DP, and percent sulfated ash, % SA, were determined using the BP 2010 official methods.

IR spectrum of a cellulose sample was carried out as described by Rojas et al (9) using 100 mg KBr pellets containing 1 mg the cellulose sample .

CCR physical properties

The shape of CCR particles was characterized by using a scanning electron microscope, SEM. Sieving technique was employed to determine the effective mean particle diameter and size distribution of CCR in a given powder sample. The - 63µm / pan powder fraction was used to carry out all the tests. The apparent particle density, ρ, was determined using the liquid displacement technique, the bulk and tap densities, flow rate and the repose angle were determined as shown earlier (16). The moisture content (dry weight basis) of a cellulose powder sample was determined by drying.

Determination of percent of elastic recovery (%R)

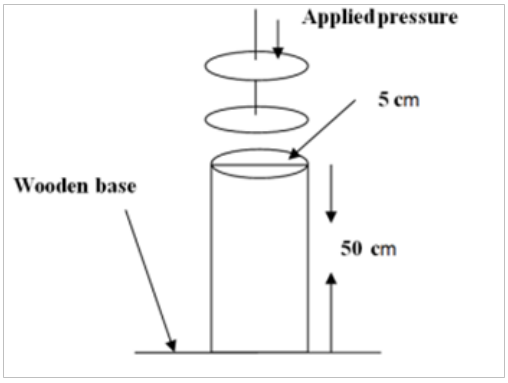

Figure 1. The locally assembled apparatus used to measure the elastic recovery, %R, of the tested powders

%R was determined using a locally assembled apparatus shown Fig.1. The initial volume of a given powder was precisely recorded as v_o. A pressure was gradually applied on the powder till no change in the volume was attained and the new volume was recorded as v_1. The pressure was released and the powder in the cylinder was equilibrated over silica gel for 24 h prior to measuring the final volume recorded as v_2. This is to allow the elastic recovery to take place and avoid the falsely yield value. The % R was calculated as:

$$\% R = (v_1 - v_2) / (v_o - v_1) \times 100. \quad \text{Eq.1}$$

The mean of such five determinations was taken as % R of the given powder.

Formulation, compression and evaluation of cellulose tablets

The multi-stage mixing technique was employed to prepare a 1 % w/w tartrazine/ cellulose powder mixture. The mixtures prepared with CCR, CC1 and CC2 were each subjected to the uniformity of content test using the spectrophotometric method of analysis as described below and the obtained result was satisfactory (99.5 ± 0.7, 99.1 ± 0.4 and 98.9 ± 0.6 % w/w for CCR, CC1 and CC2 mixtures, respectively). A given mixture was sub-divided into sub-batches lubricated with increasing concentrations of MS. A single punch tabletting machine (F3 Manesty Machines ltd., Liverpool, UK.) fitted to flat faced punches of 9.5 mm diameter was used to compress the sub-batches into tablets. The machine settings were adjusted to produce tablets of 0.25± 0.05 g mean weight, 5 kg mean crushing strength, H, and of the least friability, F, level that could be achieved from the un-lubricated sub-batch formulated with CC2. This sub-batch could not be compressed. CC2 sub-batch lubricated with 0.5% w/w MS was used instead to adjust the machine settings. The settings were kept constant throughout compressing all the prepared sub-batches. Altogether 1000 tablets were compressed from each batch. The compressed tablets were evaluated for the uniformity, H, F, and porosity, ε. The detachment and recovery and isolation intensity indexes of the lubricated powders were determined as shown earlier (16). The disintegration behaviors of the compressed tablets were also studied.

Uniformity of content test for a tartrazin/cellulose powder mixture

An accurately weighed 5mg of a given powder mixture was shaken with 100ml of freshly prepared 0.1N HCL solution for 15 min. The suspension was carefully filtered and one ml aliquot sample was withdrawn from the filtrate and transferred into a 100 ml measuring flask. The volume was adjusted with the freshly prepared 0.1N HCL solution.

The absorbance of the sample read at 420 nm was used to calculate the dye in the sample with a reference to a calibration curve constructed using a pure tartrazine dye sample as used in formulation.

Study of the dissolution behavior of cellulose tablets

A USP dissolution rate test apparatus (DT D Erweka Apparatabeau, Frankfurt, FRG) was employed to study the dissolution profiles of the produced tablets. The dissolution medium used was 900 ml 0.1N HCl maintained at 37±0.5^{O} C. The apparatus was monitored at 100 rpm. All the USP requirements for the test were kept constant. At a predetermined time interval accommodated with the disintegration time of the tablet batch under the test, a 5 ml aliquot sample was withdrawn from the dissolution chamber and immediately substituted by equal volume of a fresh 0.1N HCl maintained at 37±0.5^{O} C. The absorbance of a withdrawn sample read at 420 nm was employed to calculate the percent of the liberated dye with reference to a calibration curve constructed using a pure sample of the dye sample taken from the same lot as used in formulation. The mean of such three analyses was used as a point on the dissolution curve.

RESULTS AND DISCUSSION

Chemical properties of cellulose powders

The celluloses under investigation were insoluble in water and in the common solvents. Table I shows some chemical properties of the powders such as pH, DP and % SA determined using the official methods mentioned in BP 2010. The IR spectra of the tested cellulose powders seen in Fig.2 declares that the celluloses are chemically similar No new peaks suggesting the presence of new or different material were seen.

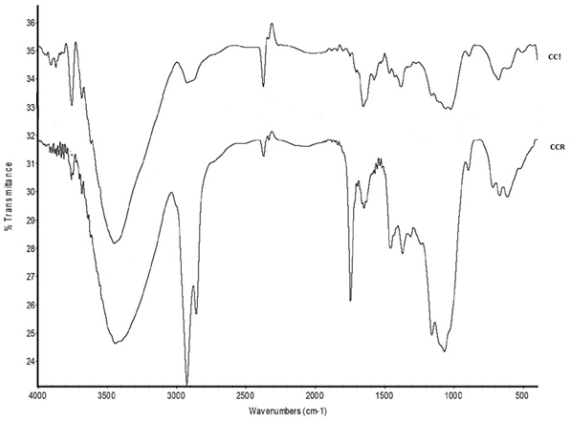

Figure 2. FTIR spectra of CCR and CC1

Table 1. Some chemical properties of the studied cellulose powders

Cellulose investigated	pH	Degree[1] polymerization	% w/w[1] sulphated ash
CC1	6.88	265	0.021
CC2	6.85	273	0.033
CCR	6.83	278	0.281

1) The mean of 3 determinations

CCR physical properties

Table 2 shows that the flow rates and repose angles of the tested celluloses ranged from 1.1 to 1. 1.3 gs^{-1} and from 50 to 53^{o}, respectively. Lubrication with MS increased the flow rate from 2.7 gs^{-1} and decreased the

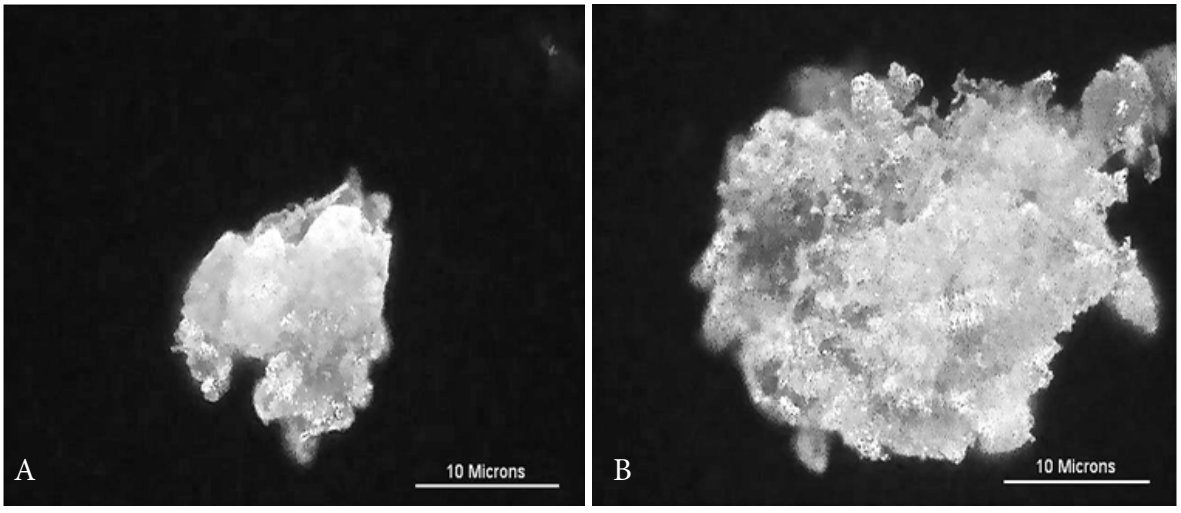

Figure 3.(A,B) Micro-photographs for CCR particles (A) plain and (B) particles claimed from tablets lubricated with 2.5%w/w MS and shaken with ethanol 90% for 15 min.

repose angle to 32°, respectively. The microphotograph of CCR particle is seen in Fig. 3(a,b). The particles were long and amorphous. Such particles like to intermesh and create a resistance against flow (17). Upon mixing MS with a cellulose powder, an isolating layer film of MS covering the particles surface was formed. This layer film reduced the inter-particle friction and improved the flow properties of the cellulose powder. In addition, this layer film increased the elasticity of the powder. % R and the recovery modulus (RM) calculated from

$$\% R = \% R^{O} + RM \cdot C \qquad \text{Eq.2}$$

where % R^{O} stands for the percent recovery of a cellulose powder before lubrication increased. CCR and CC2 generated very close RM values (1.43 and 1.32, respectively). CCR and CC2 generated more or less equal compactibility (δ) values (see Table 2). The physical properties of the compressed cellulose tablets are given in Table 3. The produced tablets were uniform according to BP 2010 specifications. Due to the isolation effect of MS layer film, the crushing strength of the tablets compressed from a lubricated formulation decreased. The percent reduction in the height of a powder column of the lubricated formulation due to compression

Table 2. Effect of varying concentrations of MS on the physical properties of the tested cellulose powders.

Cellulose. Lubricated with C% w/w MS		Flow[1] Rate, g/s⁻ Mean ±(CV%)		Repose[1] angle, degree mean	± (CV%)	Density, g/cc true[2]	loose[1]	tap[1]	Elastic[2] recov. %R Mean	± (CV%)
	0.0	1.1	(1.3)	51	(6.1)	1.52	0.92	0.34	3.80	(1.1)
	0.5	1.4	(8.6)	43	(9.1)	---	0.92	0.33	4.90	(1.2)
CC1	1.0	1.7	(4.7)	41	(7.9)	---	0.94	0,34	5.20	(2.4)
	2.0	2.2	(3.9)	33	(3.9)	---	0.94	0,34	6.30	(3.4)
	2.5	2.5	(6.9)	31	(6.1)	---	0.94	0.32	7.00	(6.9)
	0.0	1.3	(3.2)	50	(3.3)	1.51	0.93	0.34	3.60	(1.1)
	0.5	1.4	(2.2)	45	(2.7)	---	0.93	0.33	4.30	(3.1)
CC2	1.0	1.8	(9.4)	37	(5.3)	---	0.94	0.33	4.80	(2.7)
	2.0	2.4	(6.7)	33	(9.9)	---	0.94	0.34	5.90	(3.4)
	2.5	2.7	(8.4)	30	(7.8)	---	0.94	0.34	7.10	(4.5)
	0.0	1.1	(4.8)	53	(9.4)	1.53	0.93	0.35	3.55	(1.1)
	0.5	1.3	(8.7)	47	(7.9)	---	0.94	0.34	4.60	(5.5)
CCR	1.0	1.7	(5.9)	39	(9.9)	---	0.94	0.34	4.78	(7.6)
	2.0	2.1	(3.7)	36	(8.1)	---	0.94	0.33	6.32	(5.4)
	2.5	2.3	(8.5)	32	(6.9)	---	0.94	0,34	7.30	(8.1)

1) Mean of 10 determinations, 2) Mean of 5 determinations

Table 3. Physical properties of tablets compressed from different cellulose powder and lubricated with increasing C of MS

Cell-ulose used	MS C% w/w	Weight[1] (g) Mean	±CV%	Thickness[1], (mm)[1] Mean	±(CV%)	Crush.stren.[1] H, (kg) Mean	(±CV%)	Reduction in the height of the powder column, mm	%	x10^{-2}	Friab.,F, loss % w/w, Mean	(±CV%)	Disint. time[3] x10^{-2} (min) Mean	(± CV%)
	0.5	0.254	22.1	0.301	16.7	5.3	9.2	8.24	100		1.2	15.9	12.5	21.8
	1.0	0.258	20.3	0.305	12.8	4.1	16.3	8.25	100		1.2	12.5	15.8	9.4
CC1	1.5	0.263	18.5	0.311	10.6	3.2	11.1	7.49	90		1.6	12.8	19.3	12.5
	2.0	0.271	13.9	0.328	10.2	2.9	8.2	6.60	75		2.1	11.7	22.8	9.7
	2.5	0.273	12.6	0.339	8.9	2.5	7.6	5.49	63		2.8	7.9	30.5	5.6
	0.5	0.254	16.1	0.302	12.4	5.0	19.2	7.73	100		1.0	11.9	12.5	21.8
	1.0	0.253	12.3	0.306	10.6	4.0	6.3	6.71	86		1.2	8.5	14.8	9.4
CC2	1.5	0.265	11.5	0.319	13.4	3.0	9.1	6.85	87		1.4	2.9	20.3	12.5
	2.0	0.271	10.9	0.328	9.1	2.7	10.2	6.55	84		1.9	6.3	26.8	9.7
	2.5	0.273	16.6	0.341	11.9	2.3	9.6	5.64	72		2.4	10.9	35.5	5.6
	0.5	0.251	12.1	0.301	10.4	5.1	12.2	7.40	100		1.1	16.9	11.5	31.8
	1.0	0.253	10.4	0.304	11.6	3.7	16.3	7.00	95		1.3	18.5	16.8	7.4
CCR	1.5	0.260	9.7	0.314	12.4	3.1	8.1	6.67	90		1.6	12.9	22.3	13.5
	2.0	0.270	12.3	0.327	19.3	2.6	11.2	6.54	88		1.9	9.3	26.8	8.7
	2.5	0.273	10.5	0.339	6.9	2.1	7.6	5.44	74		2.7	11.9	35.5	6.6

1) Mean of 20 readings 2) Mean of 10 readings 3) Mean of 3 readings

also decreased i.e. lubrication increased the elasticity of cellulose powders. The friability of the tested cellulose tablets increased and their disintegration rates decreased, respectively.

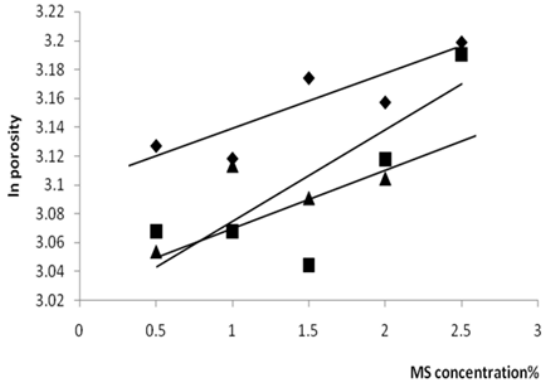

Figure 4. ln porosity vs MS concentration for the studied cellulose tablets. Key: ♦ CC1, ■ CC2 and ▲CCR

Fig. 4 shows that ε minimally expanded as MS concentration increased in a given tablet. The formation of layer film around cellulose particles represents the first step of MS mode of action. In the second step which proceeded under compression, the MS particles underwent a physical interaction with cellulose particles and produced isolated cellulose particulates (ICPs) comprising of a cellulose core (formed by interlocking bonding mechanism) firmly attached to and surrounded by MS layer (developed via asperite melting bonding mechanism under the effect of compression heat) by bridging bonding mechanism was developed. The variations in the size, shape, density and melting point of MS and cellulose particles played the vital role in tailoring ICPs structure. The consolidation of the ICPs was poor and the strength of particles bonding was weak. The values of the detachment and recovery index (DRI), Isolation intensity index (ISI) and porosity expansion index (PI) calculated for the studied celluloses are given in Table 4. CCR generated higher values i.e. it is more sensitive to MS. The amorphous shape and large size of CCR parti-

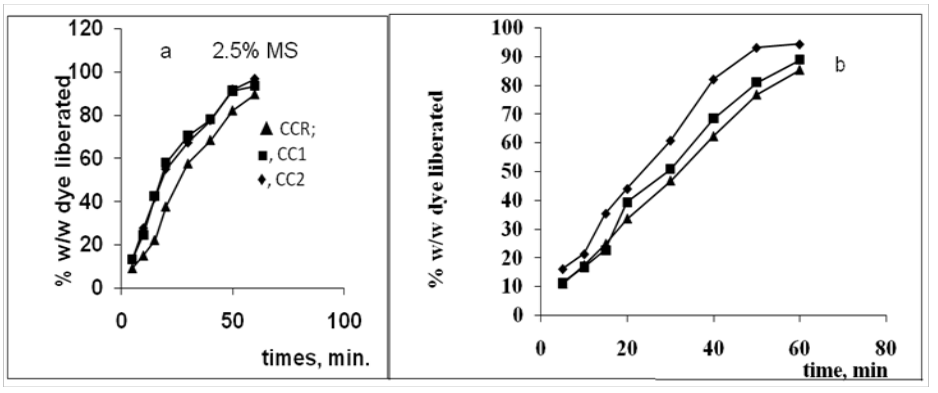

Figure 5. 5 (a,b) The dissolution profiles of tablets made from different celluloses and lubricated with increasing concentrations of MS

Table 4. Some parameters indicative of the compressional and disintegration behaviours of the studied celluloses.

Cellulose used	Detach. &recov Index, DRI[1]	Isolat. intens. index, ISI[1]	Poros. expan. index, PI x10^{-2}	RM[1] (slope)	1/MR compactibility	R^{o1} Intercept	Correl. Coeff. (r)	k^{o}_{disin} x 10^{-2}	RI x 10^{-2}	$t_{50\%}$(min) for tabs.lubricated with MS 1.0 % w/w	2.5 % w/w
CC1	-0.36	-0.37	3.1	1.19	0.84	4.01	0.989	-35.7	- 2.3	21.3	28.0
CC2	-0.46	-0.39	5.9	1.32	0.76	3.57	0.989	-29.8	- 2.2	19.3	30.0
CCR	-0.54	-0.43	5.2	1.43	0.70	3.57	0.989	-49.7	- 2.6	21.0	33.0

1) calculated using the least squares fit of the expression mentioned in Eq.1 .

cles were the cause of its higher sensitivity towards MS. This agrees with the early made conclusion (15). The concept of developing ICPs is supported by the eroded surface seen as opaque area in the photomicrograph of CCR particles (see Fig 3b) claimed from tablets lubricated with 2.5% w/w MS and shaken with a suitable volume of 90% ethanol for 10 min.. The relationships existing between DRI value and ISI, PI and RI (RI is the retardation index which is the ability and the extent of a lubricant in a tablet batch to retard its disintegration) support this concept. As DRI decreased, the ISI , PI and RI increased (see Table 4).

Disintegration and dissolution behaviors of cellulose tablets

Lubrication with MS negatively affected the disintegration and dissolution behaviours of the tested cellulose tablets. The disintegration rate constant, k_{disint}, (gs^{-1}) of a tested tablet batch was found to fit into the expression:

$$k_{disint} = k^{o}_{disint} - \exp. x_d . C \qquad \text{Eq.3}$$

where k^{o}_{disint} stands for the disintegration rate constant of the control (un-lubricated) tablet batch. The slope x_d or RI stands for the retardation index induced by MS. MS generated larger RI value (-2.60) with CCR while it generated almost equal RI values (-2.31and -2.20),with CC1 and CC2, respectively. Fig.5 (a,b) shows that slow release profiles were recorded for the tablets made by CCR or lubricated with large concentration of MS. This is confirmed by the data obtained on the times of the release of 50%w/w of the dye from a given tablet batch as seen in Table 4.

CONCLUSION

Economically valuable pharmaceutical excipients meeting the pharmacopoæial standards can be locally manufactured from economically abundantly available valueless crude materials. Utilizing the back log of the agro-residues to process pharmaceutical excipients via bio-technology represents the best solution for the issue of the impact of burning these residues or damping it in water resources on the environment and other threatened ecosystems. The lubricant mode of action of MS was two step mechanism. Under compression, ICPs was developed as a result of physical interaction of magnesium stearate with a cellulose excipient. Several physical parameters related MCC and MS contributed to tailor the structure of ICPs.

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