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Research paper

Designing robust immediate release tablet formulations avoiding food effects for BCS class 3 drugs

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A B S T R A C T

Food induced viscosity in the gastrointestinal tract is reported to reduce the bioavailability of tablets containing BCS class 3 drugs, mainly by retarding their disintegration and dissolution of the active pharmaceutical ingredient. The role of formulation factors in minimizing this negative food effect is largely unknown. Combinations of disintegrants were studied together with soluble and insoluble fillers and trospium chloride as model drug substance. Different batches of tablets were compressed at 10 kN and 30 kN, by incorporating different combinations of croscarmellose sodium (CSS), cross-linked (CPD) and sodium starch glycolate (SSG) at low level i.e, 2% + 2% and high level i.e, 4% + 4% of compressional weight, while taking lactose as a soluble filler and dibasic calcium phosphate (DCP) and microcrystalline cellulose (MCC) as insoluble fillers. Under low viscous conditions, disintegration of DCP based tablets was faster compared to lactose based tablets, but under high viscous conditions, simulating the effect of an ingested FDA meal, the disintegration behavior was reverted. Increased compressional force prolonged the disintegration of lactose and DCP based formulations under fasted conditions. However, when evaluated under food viscosity conditions, DCP based tablets compressed at higher force showed rapid disintegration while no effect of increased compressional force in lactose based tablets was observed. MCC based tablets in particular showed largely prolonged disintegration times in viscous media irrespective of the disintegrant type and levels investigated. Disintegrant combinations possessing wicking ability with minimum or no gelling were found to reduce disintegration times. The disintegrant combination of CPD + CCS was effective in reducing disintegration and enhancing dissolution besides not being affected by changes in compressional force and their total proportion in the tablet. In conclusion, it is recommended to evaluate formulations under increased viscosity conditions during the development phase of tablets with an objective to minimize the negative effect of food viscosity on disintegration and dissolution.

1. Introduction

Delayed and reduced absorption of active pharmaceutical ingredients has been reported for immediate release tablets, in particular for those containing BCS class III compounds, when the medication was taken together with food. This “negative food effect” may be attributed to delayed gastric emptying but evidence has been generated that the phenomenon can also be partly ascribed to slow tablet disintegration and dissolution - imparted by food induced viscosity - as shown by *in vitro* and *in vivo* studies [1–3]. One of the reasons of this slow disintegration is the formation of a layer around the tablet in the presence of food components, which was strong enough to reduce the water penetration into the tablet and possibly also hindering the particles to move away from the tablet surface. In one study this layer was postulated to act similar to an extended release coating [4], while another study has revealed that food effects can cause an immediate release tablet to perform as if it was an enteric coated tablet [5].

Delayed disintegration and dissolution in this regard emphasize the use of disintegrants in order to prevent the negative effect of increased medium viscosity. We have reported earlier that, despite of the use of single disintegrants, differences between the respective disintegration times (DTs) and mean dissolution time (MDTs) were high, when results obtained under non viscous and viscous conditions were compared. These differences were attributed to the functionality of the disintegrants [6]. It is worth mentioning that the majority of studies pertaining performance of disintegrants focused on the use of single disintegrants, whereas the role of disintegrant combinations was not investigated noticeably. Besides the increase in viscosity by solid meals and its influence on tablet disintegration, also the existence of a potentially significant interference of alcohol with the disintegration phenomenon has been shown recently, suggesting that the concomitant administration of tablets and intake of alcoholic beverages may affect, in some cases, tablets disintegration [18].

The composition of a tablet matrix especially the solubility of the filler is among the most important decisive parameters that determines the disintegration of a tablet. A quick disintegration was observed in tablets containing insoluble fillers [7]. While, a higher dissolution rate was obtained from the tablets when soluble fillers were used [8]. However, these and similar other results are based on the evaluation of tablets in 0.1 N HCl or water, where the impact of food-induced higher

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viscosity was not considered.

The current study focusses on the impact of fillers and the role of disintegrants and their possible synergism in reducing the disintegration time under food induced viscosity conditions. A recent review has underlined the role of disintegrants in a typical tablet dosage form [19]. Various disintegrants, i.e, croscarmellose sodium (CSS), cross-linked polyvinylpyrrolidone (CPD) and sodium starch glycolate (SSG), and their respective combinations, were evaluated in the current study. The influence of the presence of functionally different fillers, i.e, lactose as soluble, dibasic calcium phosphate (DCP) as non-soluble and microcrystalline cellulose (MCC) as swellable and insoluble filler, was also assessed. The overall objective of this study is to devise a formulation strategy towards robust immediate release formulations which will be least affected by food induced viscosity.

2. Materials and methods

2.1. Materials

Trospium chloride (purity – 99.9%), gifted by Dr. R. Pfleger GmbH, Germany, was used as a model drug (BCS class III). Methyl hydroxypropyl cellulose E4M, obtained from Synopharm (Germany) was used for the preparation of viscous medium for disintegration/dissolution studies. Primellose® (Croscarmellose Sodium, DFE Pharma, Germany), Primojel® (Sodium Starch glycolate, DFE Pharma, Germany) and Kollidon® CL-SF (Crospovidone, BASF, Germany) were used as superdisintegrants. Tablettose® 80 (Lactose, Meggle, Germany), Dibasic Calcium Phosphate dihydrate (Merck, Germany) and VIVAPUR®, Type 102 (Microcrystalline cellulose, JRS Pharma, Germany) were utilized as soluble, insoluble, and swellable fillers, respectively. As binder and lubricant, PVP K-30 (Polyvinylpyrrolidon, Carl Roth GmbH, Germany) and magnesium stearate (Fagron GmbH, Germany) were incorporated in the direct compression tablet formulations, respectively.

2.2. Tablet formulation and preparation

In order to assess the role of single disintegrants, each disintegrant i.e, CCS, CPD and SSG was used at the level of 4% of compressional tablet weight. Evaluation of disintegrant combinations was done by using their respective combinations i.e, CPD + CCS, SSG + CCS and SSG + CPD in a 1:1 ratio either at low level (4% of total tablet weight) or at a high level (8% of total tablet weight) according to the scheme presented in Table 1. Three formulations having the single disintegrant, six formulations having the combination of disintegrants and one formulation without any disintegrant were formulated. Therefore, 10 formulations each were prepared while taking lactose, DCP and MCC as fillers, respectively.

Each blend of the formulations also contained Trospium chloride as model drug (40 mg/tablet), Polyvinylpyrolidone (K – 30) as binder (2.5%, w/w) and magnesium stearate as lubricant (0.5% w/w). All constituents of each formulation, except the lubricant, were blended in a mixer (Turbula® T2F type, Switzerland) for 15 min. Magnesium stearate, which was screened through a 60-mesh sieve, was then added and mixed for further 2 min. Round shaped tablets with a compressional weight of 250 mg, were compressed on a manual hydraulic press (Specac®, USA – 25 tons), by filling the exactly weighed quantity of powder mixture. Each formulation was compressed at 10 kN and 30 kN with a dwell time of 10 s by using a 9 mm die and a flat-faced with beveled edge punch assembly.

2.3. Media composition simulating fasted and fed viscosity state

Fasted state was simulated by preparing simulated gastric fluid without enzymes (SGF, USP). Media viscosity in fed state was simulated by 1.4% aqueous solution of Hydroxypropylmethyl cellulose (HPMC E4M) having a pH value of 3.0 as reported earlier [9,6].

2.4. Disintegration studies

Disintegration tests were carried out in a tablet disintegration tester (Pharma Test, Type PTZ 2EH, Germany) in 800 ml of simulated medium at 37 °C without disks. Six tablets, one per vessel, were used for each test. Disintegration times (DT) for individual tablets were noted when no residue remained on the mesh.

2.5. Dissolution studies

Dissolution studies in viscous and non-viscous media were performed in USP apparatus II (Erweka DT 7R, Germany) using 500 ml of media at 50 rpm. All experiments were conducted at 37 ± 0.5 °C. 5 ml samples were withdrawn at predetermined time intervals of 5, 10, 15, 30, 45, and 60 min and 5, 10, 15, 30, 45, 60, 90 and 120 min in simulated fasted condition and in simulated fed conditions, respectively, and replaced by an equal volume of medium. Their absorbance was recorded UV-photometrically (Lambda 35 UV/Vis Spectrophotometer, Perkin Elmer, USA) at 210 nm after filtration and proper dilution [9]. Calibration curves for Trospium chloride were constructed ranging from 2 mcg/ml to 50 mcg/ml for non-viscous and 5 mcg/ml to 30 mcg/ml for viscous medium, respectively. No interference from tablet excipients was noted. Calibration curves were linear ($R^2 > 0.999$) and coefficients of variation were < 5% for the higher concentrations and < 10% for the lower concentrations. Cumulative dissolution versus time profiles were constructed. The mean dissolution time (MDT) was calculated by the following equation:

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}.\ \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$

where j is the sample number, n is the number of dissolution sample times, $\hat{t}$ is the time at midpoint between tj and tj − 1 (calculated with the expression ((tj + tj − 1)/2)) and ΔM is the additional amount of drug dissolved between tj and tj − 1.

2.6. Texture analysis

The development of disintegration force and related parameters were studied by using the texture analyzer (TA. XT plus, Stable microsystems, UK) following the procedure explained in a previous

Table 1
Composition of formulations showing the varying levels of disintegrant combinations.

Disintegrant combination	Sodium Starch Glycolate (SSG) %	Crospovidone (CPD) %	Croscarmellose Sodium (CCS) %
CPD + CCS (Low level)	0	2	2
SSG + CCS (Low level)	2	0	2
SSG + CPD (Low level)	2	2	0
CPD + CCS (High level)	0	4	4
SSG + CCS (High level)	4	0	4
SSG + CPD (High level)	4	4	0

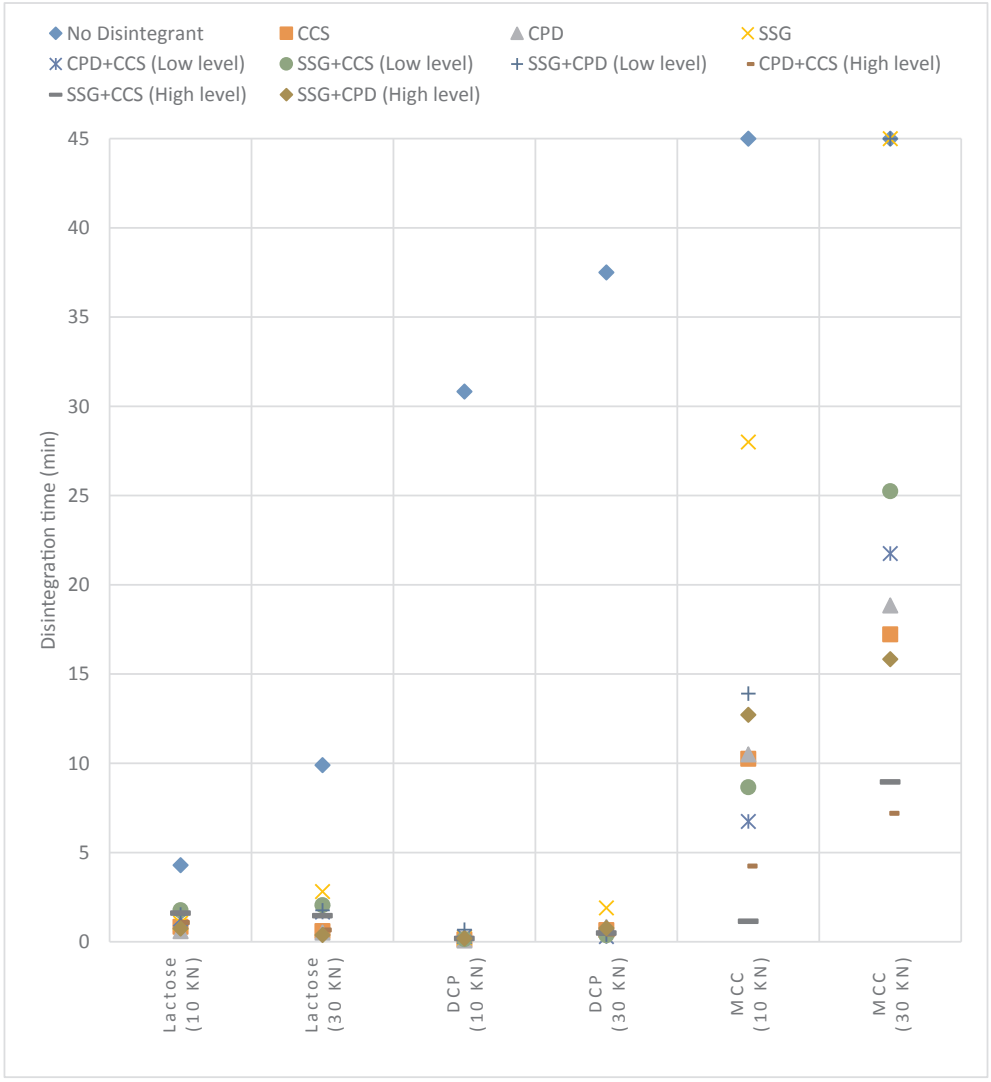

Fig. 1. Summary of disintegration times in fasted state. CCS – Croscarmellose sodium, CPD – Crospovidone, SSG – Sodium starch glycolate, DCP – Dibasic Calcium Phosphate, MCC – Microcrystalline cellulose.

publication [6]. Pre-test speeds of 1.0 mm/s, trigger force of 0.049 N and data acquisition rate of 10 data points per second were employed. Data obtained was analyzed by using the software Exponent, TA (XT plus stable microsystems, UK).

3. Results

3.1. Disintegration studies

Disintegration times of immediate release tablets was strongly dependent on the tablet composition and on the viscosity of the media, as shown in Figs. 1 and 2. Under low viscous conditions, average disintegration times for tablets without disintegrants ranged from 4.3 (lactose as filler) to 40 min (MCC as filler) and from 9.9 (lactose) to 40 min (MCC) for tablets compressed at 10 and 30 kN, respectively. In general, among the formulations without disintegrant, only lactose based tablets disintegrated within 10 min, while disintegration of DCP and MCC based tablets took more than 30 min. The good aqueous solubility of lactose may account for the relatively rapid disintegration. Disintegration times strongly decreased when disintegrants were present in the formulations and ranged from 0.1 (DCP + CPD 4%) to 14 min (MCC + SSG/CPD low) and from 0.3 (DCP + CPD/CCS high) to 40 min (MCC + SSG/CPD low) for the tablets with different compression strengths. The importance of a disintegrant in the formulation in reducing disintegration time is thus evident. Furthermore, it was noticed, that, in particular for tablets containing DCP as filler, the addition of disintegrants caused a rapid disintegration with minimum variation. This may be ascribed to the hydrophilic nature of DCP that helped in the rapid uptake of disintegration medium through capillary action into the pores where disintegrant particles reside. In lactose based tablets on the other hand, the solubilization of lactose may have caused an elevation of localized viscosity within the tablet pores that have resulted in a slight delay in disintegration time. In case of MCC based tablets, disintegration time was very dependent on the nature of disintegrants used in the tablet formulation.

When evaluated under fed state viscous conditions, lactose based tablets without disintegrant did disintegrate within 7 min, which is only slightly higher than the disintegration time obtained under fasted conditions (4.3 min). On the other hand DCP and MCC based formulations having no disintegrant failed to disintegrate within the test duration of 45 min. Among the formulations containing disintegrants, lactose based tablets have provided rapid disintegration with little variation also in viscous media. On the other hand, disintegration times associated with DCP based tablets varied noticeably depending on the amount and types of disintegrant used in the formulations. In addition, the compressional force played its role in this variation. It is in contrast

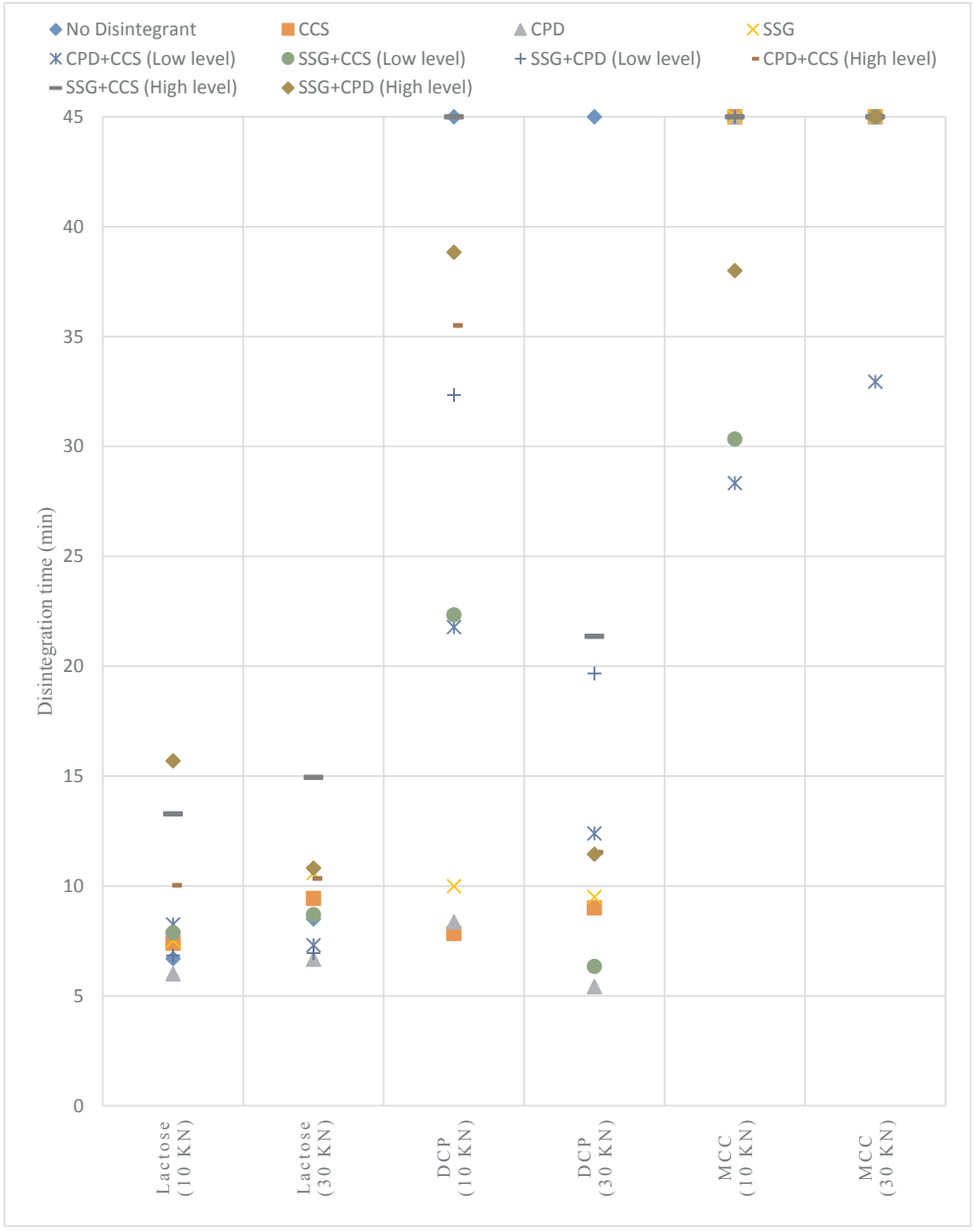

Fig. 2. Summary of disintegration times in fed state. CCS – Croscarmellose sodium, CPD – Crospovidone, SSG – Sodium starch glycolate, DCP – Dibasic Calcium Phosphate, MCC – Microcrystalline cellulose.

with the results obtained under low viscous conditions where DCP based tablets demonstrated rapid disintegration with little variation. Most of the MCC based tablets failed to disintegrate within the test duration of 45 min, while such MCC based tablets which have disintegrated within 45 min resulted in disintegration time of 25 min or higher.

3.2. Dissolution studies

Lactose-based tablets: When tested in low viscosity media, most of the formulations showed very rapid dissolution, i.e. > 85% of API was released within 15 min, except for the high level of CPD + CCS (10 kN) and low level of the same combination compressed at 30 kN. Both of these formulations complied with the criterion for rapid dissolution though, i.e. > 80% of API released within 30 min. Overall, drug release was slower when the formulations were tested under high viscous conditions. Less than 60% of drug was released within 30 min and no formulation complied with “very rapid dissolution” nor “rapid dissolution” criteria in simulated fed state. Dissolution profiles of lactose-based formulations under viscous and low viscosity conditions are shown in Figs. 3a and 3b.

DCP-based tablets: When tested under simulated fasted conditions, most of the formulations compressed at 10 kN showed very rapid dissolution behavior, and some compressed at 30 kN behaved similarly. Generally, all of the formulations complied with the criterion for rapid dissolution i. e. more than 80% of API was released within 30 min (Fig. 4a).

Release of trospium was found to be slower when the formulations were tested under simulated fed conditions. Less than 60% of API was released within 30 min. Therefore, no formulation complied neither with “very rapid dissolution” nor with “rapid dissolution” criteria in fed state (Fig. 4b). Generally, formulations containing low levels of disintegrant were found to release more drug within the test duration of 120 min.

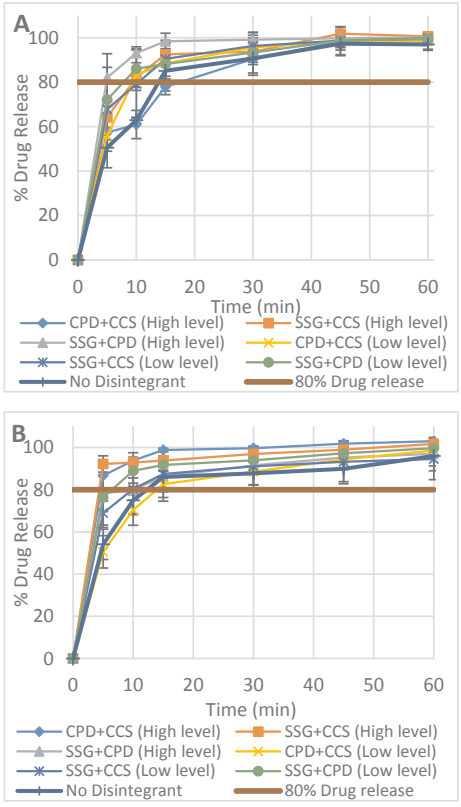

Fig. 3a. Effect of compression force, combination of disintegrants and their levels on % drug release from lactose based Trospium chloride formulations, in low viscosity media (Mean ± SD; n = 4) A – Formulations compressed at 10 kN, B – Formulations compressed at 30 kN. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

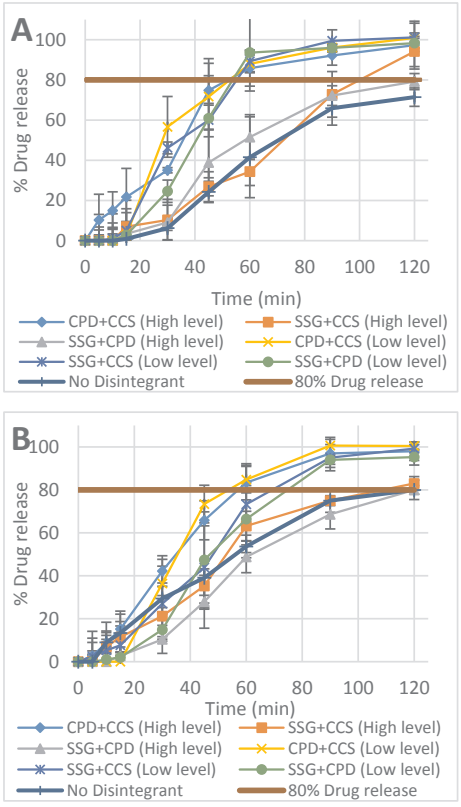

Fig. 3b. Effect of compressional force, combination of disintegrants and their levels on % drug release from lactose based Trospium chloride tablets, in high viscous media (Mean ± SD; n = 4) A – Formulations compressed at 10 kN, B – Formulations compressed at 30 kN. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

CMC-based tablets: When tested under low viscosity conditions, only the formulations at low levels of disintegrant combination of CPD + CCS and SSG + CCS (10 kN) showed "very rapid dissolution". Interestingly, no other formulation complied even with the "rapid dissolution' criterion. Moreover, when compressed at 30 kN, all formulations except two (low level of SSG + CPD and high level of SSG + CCS) meet the criterion for "rapid dissolution (Fig. 5a).

Similar to the results obtained with lactose and DCP as fillers, release of drug was found to be slower when the formulations were tested at high viscous conditions. Less than 20% of drug was released within 30 min. Therefore, formulations complied neither with "very rapid dissolution" nor "rapid dissolution" criteria in fed state (Fig. 5b). Generally, formulations containing low level of disintegrant were found to release more drug within the test duration of 120 min. Fig. 5b, also reveals that higher compressional force noticeably impeded the release of API at earlier time points.

3.3. Texture analysis

The development of sufficient disintegration force upon access of water to the tablet is required to overcome the internal bonding as well as resistance offered by the boundary layer around the tablet. For tablets with sufficiently rapid disintegration times, the F_{max} values generally were low, indicating that the internal bonding forces of the tablet components readily were broken down upon access of water, subsequently followed by rapid disintegration. As an example, the relationship between disintegration times and maximum disintegration forces for a series of formulations containing single disintegrants at a level of 4% is shown in Fig. 6.

Furthermore, the time required to reach maximum disintegration force (T_{max}) is the time after which disintegration force starts to decline; therefore, shorter T_{max} is generally associated with rapid degeneration of disintegration force. The disintegration force development rate (DFDR) is the result of a complex interplay of formulation variables i.e. disintegrants, binders and filler with the water that is accessing the tablet. In this study a rapid DFDR generally worked in favor of short T_{max} (data not shown) and short disintegration times, as shown in Fig. 7.

Under fed conditions, a general increase in the values of F_{max} and T_{max} and a decrease in DFDR was observed, in particular with an increase in the level of disintegrant combinations as well as compressional force. Particularly for formulations containing MCC high values of T_{max} and slow DFDR in conjunction with long disintegration times were recorded.

4. Discussion

In a previous communication, we have analyzed the effect of medium viscosity on the disintegration and dissolution characteristics of tablets containing various BCS class III drugs [9]. Longer disintegration times of tablets in high viscous media representing the fed state after ingestion of the FDA recommended breakfast were associated with slower water diffusivity and lower water uptake rates into the tablets [10]; direct measurements of water diffusivity in various media helped to correlate water diffusivity and water uptake with tablet disintegration times [11]. In the present manuscript, we have expanded this investigation to the screening of formulation factors that may affect the performance of immediate release tablets under fed and fasted viscosity conditions with the aim of making recommendations on their design and manufacture. A tablet formulation that would demonstrate

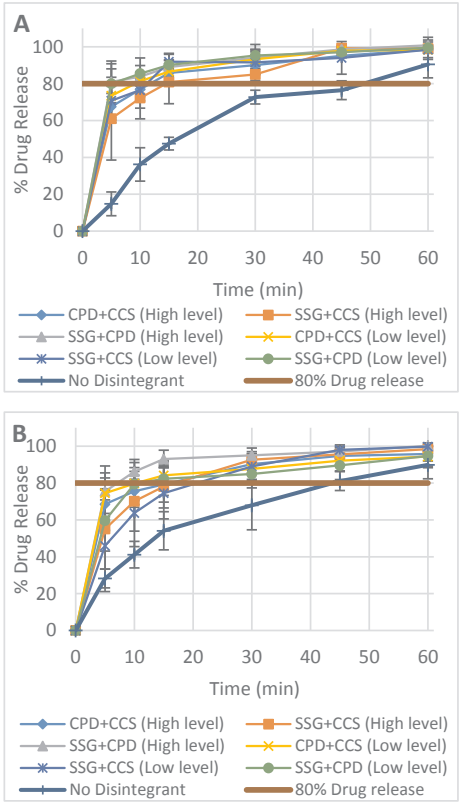

Fig. 4a. Effect of compressional force, combination of disintegrants and their levels on % drug release from Dibasic Calcium Phosphate based Trospium chloride formulations, in simulated fasted state (Mean ± SD; n = 4) A – Formulations compressed at 10 kN, B – Formulations compressed at 30 kN. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

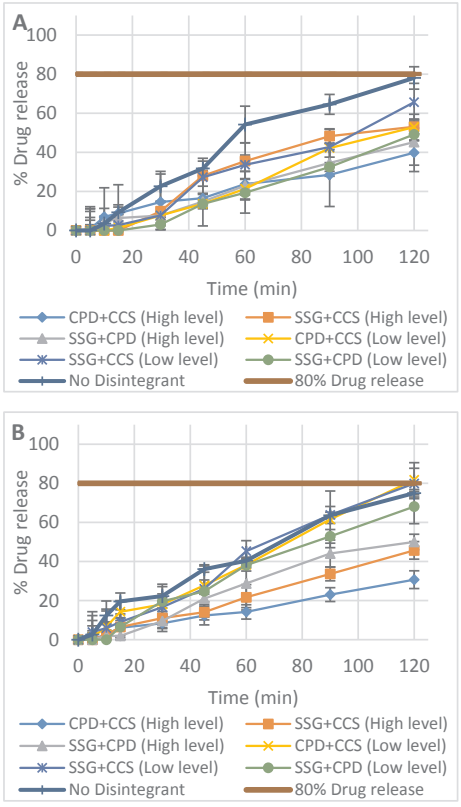

Fig. 4b. Effect of compressional force, combination of disintegrants and their levels on % drug release from Dibasic Calcium Phosphate based Trospium chloride formulations, in simulated fed state (Mean ± SD; n = 4) A – Formulations compressed at 10 kN, B – Formulations compressed at 30 kN. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

fast disintegration under both fed and fasted state conditions was generally favored. During the development phase, formulators generally evaluate the formulations under non viscous conditions. However, it will be difficult to develop robust formulations with an objective to minimize the negative food effect, if only these results are considered. The current study has disclosed contrasting observations obtained under fasted and fed conditions, therefore strongly suggesting testing and optimization of tablet formulations under conditions simulating food viscosity as well as under low viscosity conditions.

MCC, lactose and DCP as fillers were combined in this study either with single disintegrants (CPD, SSG and CCS) or their binary combinations. As can be seen from Figs. 1 and 2, the nature of the filler in the tablet formulation plays a dominant role with respect to tablet disintegration times. Whereas in low viscous media lactose and DCP based tablets combined with disintegrants showed rapid disintegration, this was not the case for MCC based tablets. Most probably, the strong binding of wetted and partially swollen tablet cores prevented rapid deaggregation and dissolution of the tablet when MCC was present. The scenario became extreme, when the tablets were tested in viscous media where all MCC based tablets except for one showed disintegration times above 30 min.

An interesting scenario was revealed when the disintegration times of various lactose and DCP based formulations, containing combinations of disintegrants, obtained under fasted and fed conditions were compared (see Figs. 8 and 9).

In lactose based tablets, rapid disintegration was achieved when disintegrant combinations were used at higher level under fasted conditions, while under fed conditions the use of higher level of disintegrant combination provided prolonged disintegration times. Moreover, under fasted conditions increased compressional force reduced the disintegration time of lactose based tablets, when disintegrant combinations were used at higher level, while higher compressional force has prolonged the disintegration of these tablets when disintegrant combinations were used at lower levels. However, under fed conditions no such relationship of disintegration time with compressional force was established.

Similarly, when evaluated under fasted conditions, compression of DCP based tablets at higher compressional force generally provided prolonged disintegration especially when disintegrant combinations were used at low level. On the contrary, when evaluated under fed conditions, relatively rapid disintegration of DCP based tablets was obtained when compressed at higher compressional force.

The nature of the filler played an important role on the overall effect of compressional force on the disintegration times both in fasted and fed state. In DCP based tablets compressed at higher compressional force, even the low content of disintegrant, particularly that having swelling tendency was sufficient to cause rapid disintegration. This is due to the fact that at higher compressional force, particles are packed in close proximity and swelling disintegrants like SSG are expected to exert their immediate effect on adjacent particles, provided that water penetration is adequate. Due to its hydrophilicity, the larger pore space of DCP based tablets compressed at 10 kN, may have been filled with the viscous medium. Thus it may take more time until the disintegrant particles can overcome this viscous medium in addition to the bonding of tablet constituents and surrounding boundary layer. Similarly, when a higher proportion of disintegrants is used, the gel forming disintegrants will form more gel which is acting against the disintegration forces. Depending upon the gelling tendency of the disintegrant combination, it may or may not be sufficient to block the pores. Therefore, due to subsequent blockade of pores not only the disintegration but the

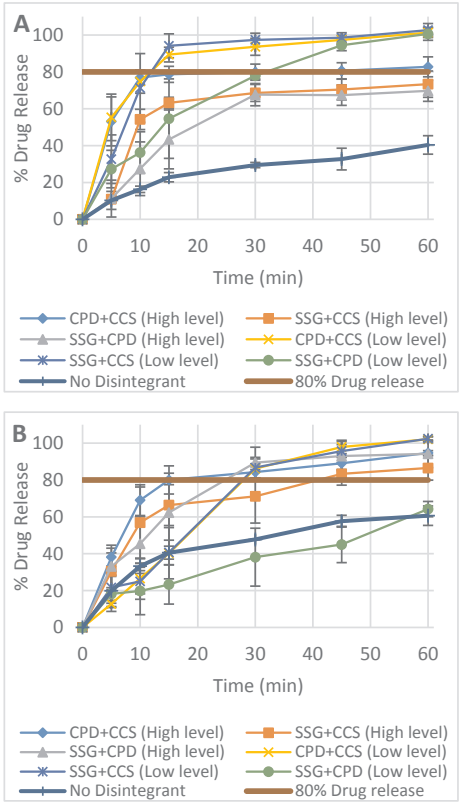

Fig. 5a. Effect of compressional force, combination of disintegrants and their levels on % drug release from Microcrystalline cellulose based Trospium chloride formulations, in simulated fasted state (n = 4) A – Formulations compressed at 10 kN, B – Formulations compressed at 30 kN. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

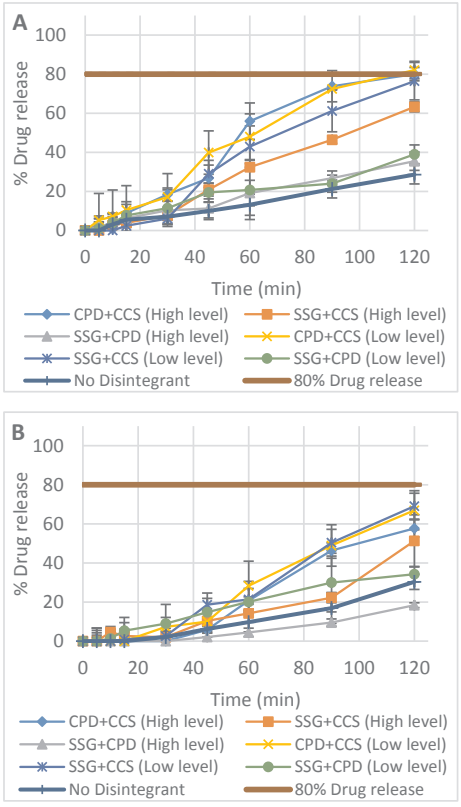

Fig. 5b. Effect of compressional force, combination of disintegrants and their levels on % drug release from Microcrystalline cellulose based Trospium chloride formulations, in high viscous media (n = 4) A – Formulations compressed at 10 kN, B – Formulations compressed at 30 kN. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

dissolution could also be impaired. In addition to the afore mentioned factors, the lack of any active mechanism of disintegration of DCP results in larger DT at lower compressional force. When liquid penetrates into the tablet pores, it can either dissolve or dislodge the particles comprising the pore wall, causing the porosity of the tablet to change, which itself influences the disintegration process [12]. This phenomenon needs to be considered in lactose based tablets, where solubilization of lactose may also be contributing to the elevation of localized viscosity in the porous structure of tablets. In tablets with low porosity, the development of this localized viscosity in small pores where disintegrant particles reside might be sufficient for narrowing/blocking of these pores. Factors i.e, localized viscosity and changes in porous system will affect the continuous penetration of liquid, ultimately affecting the process of disintegration/dissolution.

Although in DCP based formulations, T_{max} values were lower while DFDR values were higher as compared to lactose based formulations under fed conditions, disintegration and dissolution turned out to be rapid in lactose based formulations. Shorter T_{max} and rapid DFDR might be due to the fact that owing to the hydrophilicity of DCP the dissolution medium was readily available for the disintegrant particles to provide their effect [13]. Nevertheless, due to the non-disintegrating nature of DCP, the disintegration force was not dissipated accordingly, which lead to slow disintegration and dissolution [14]. An overall smaller magnitude of F_{max} was observed in lactose based formulations, where, after coming in contact with dissolution medium, lactose particles start leaving the compact due to both their intrinsic solubility and the influence of disintegrant particles. Apparently, this simultaneous dissipation of disintegration force will keep the magnitude of F_{max} lower in addition to causing the relatively rapid disintegration and dissolution in lactose based tablets.

SSG exerts its disintegrant action through a strong increase in the volume of its particles upon contact with water. But the hydration of SSG particles coupled with swelling results in an increase in the viscosity of the medium surrounding the disintegrant particles, which may form a gel layer [15]. Therefore, any factor contributing to potentiate the viscous barrier needs to be limited, when devising a strategy for robust formulations that are insensitive towards food-induced viscosity. Thus the inclusion of SSG in such formulations should be avoided.

The combination of CPD + CCS was found to give the most rapid dissolution among all the tested formulations under fed conditions. In lactose based tablets the performance of this combination was not influenced by changes in the levels of compressional force and disintegrant combinations, respectively. In DCP based tablets however, more rapid dissolution was obtained when the said combination was used at low level and the tablet was compressed at 30 kN. In order to understand the impact of the combination of CPD + CCS on the disintegration of tablets their mechanism of disintegrant action should be considered. Swelling of CCS with moderate gelling and presumed shape recovery mechanism of CPD without gelling may be accounted in this regard [16,17]. CPD present in the combination, due to its wicking action, apparently assists to maintain an adequate water penetration thereby counteracting the gelling potential of CCS. This may explain the rapid disintegration and dissolution associated with this combination of disintegrants, among all other tested combinations.

5. Conclusion

The current study provides substantial evidence that commonly used tablet excipients behave differently when evaluated under enhanced viscosity conditions. Although a negative effect of food induced

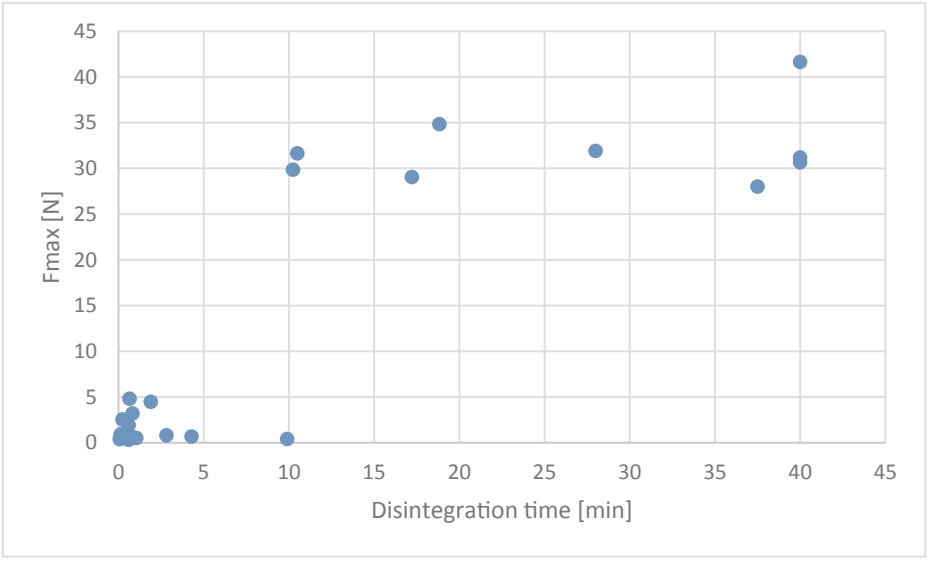

Fig. 6. Relationship between maximum force developed as demonstrated by texture analysis and mean disintegration time in low viscous media for lactose, DCP and MCC based formulations containing single disintegrants at a level of 4%.

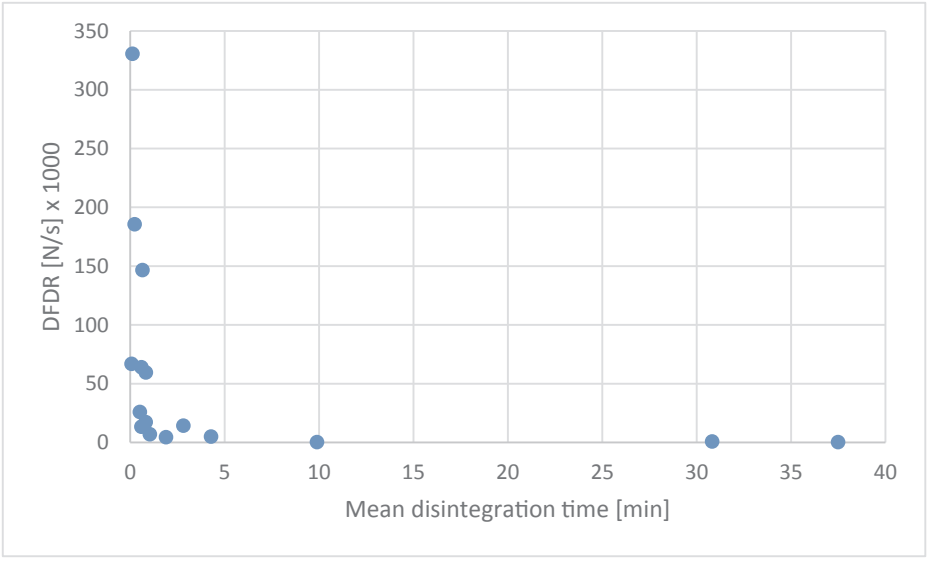

Fig. 7. Relationship between disintegration force development rate (DFDR) and mean disintegration times demonstrated by texture analysis in low viscous media for lactose, DCP and MCC based formulations containing single disintegrants at a level of 4%.

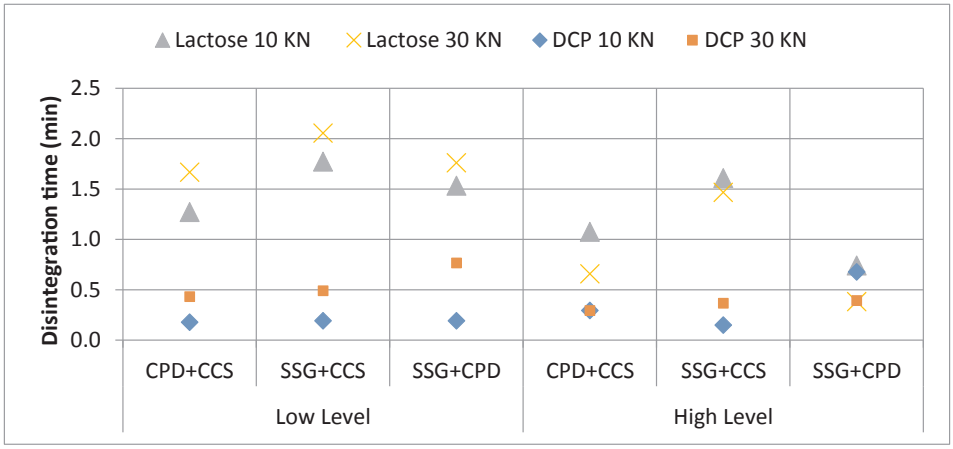

Fig. 8. Influence of levels of disintegrant combinations and compressional force on the disintegration times of lactose based and DCP based tablets under fasted conditions. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

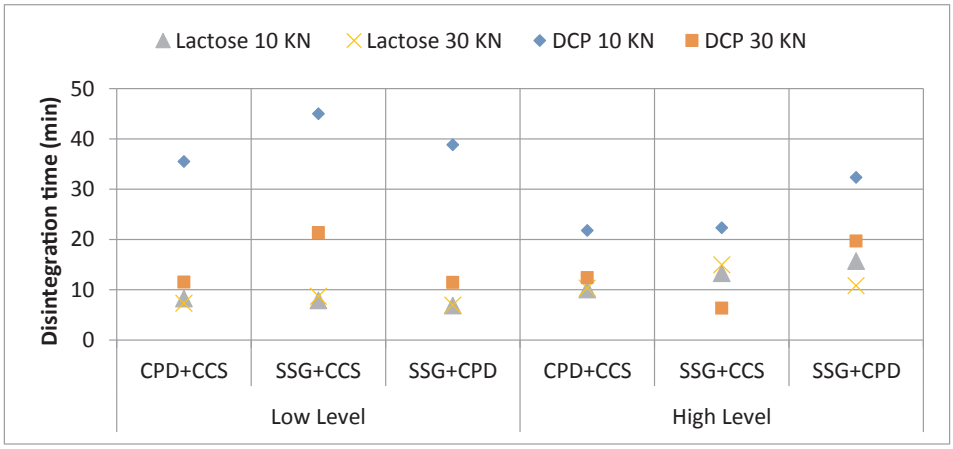

Fig. 9. Influence of levels of disintegrant combinations and compressional force on the disintegration times of lactose based and DCP based tablets under fed conditions. CCS – Croscarmellose Sodium, CPD – Crospovidone, SSG – Sodium Starch Glycolate.

viscosity on disintegration and dissolution cannot completely be avoided, a combination of disintegrants, when used in an appropriate ratio, may surrogate the development of different formulation strategies for soluble and insoluble fillers. Therefore, while optimizing the formulations, which will be least affected by food-induced viscosity, formulators may consider suitable proportions of the combination of CCS and CPD in not more than 4% of the compressional weight of the tablet. When DCP comprises the major proportion of the tablet formulation, the use of higher compressional force is encouraged. Finally, the use of MCC as soluble and swellable filler is discouraged.

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References

[1] S. Anwar, J. Fell, P. Dickinson, An investigation of the disintegration of tablets in biorelevant media, Int. J. Pharm. 290 (2005) 121–127.
[2] S. Cvijić, J. Parojčić, P. Langguth, Viscosity-mediated negative food effect on oral absorption of poorly-permeable drugs with an absorption window in the proximal intestine: in vitro experimental simulation and computational verification, Eur. J. Pharm. Sci. 61 (2014) 40–53.
[3] K. Kelly, B. ÓMahony, B. Lindsay, T. Jones, T.J. Grattan, A. Rostami-Hodjegan, H.N. Stevens, C.G. Wilson, Comparison of the rates of disintegration, gastric emptying, and drug absorption following administration of a new and a conventional paracetamol formulation, using gamma scintigraphy, Pharm. Res. 20 (2003) 1668–1673.
[4] B. Abrahamsson, T. Albery, A. Eriksson, I. Gustafsson, M. Sjöberg, Food effects on tablet disintegration, Eur. J. Pharm. Sci. 22 (2004) 165–172.
[5] J. Brouwers, B. Anneveld, G.-J. Goudappel, G. Duchateau, P. Annaert, P. Augustijns, E. Zeijdner, Food-dependent disintegration of immediate release fosamprenavir tablets: in vitro evaluation using magnetic resonance imaging and a dynamic gastrointestinal system, Eur. J. Pharm. Biopharm. 77 (2011) 313–319.
[6] K. Zaheer, P. Langguth, Formulation strategy towards minimizing viscosity mediated negative food effect on disintegration and dissolution of immediate release tablets, Drug. Dev. Ind. Pharm. 44 (2018) 444–451.
[7] F. Ferrari, M. Bertoni, M. Bonferoni, S. Rossi, A. Gazzaniga, U. Conte, C. Caramella, Influence of porosity and formula solubility on disintegrant efficiency in tablets, STP Pharm. Sci. 5 (1995) 116–121.
[8] M.S. Gordon, V.S. Rudraraju, K. Dani, Z.T. Chowhan, Effect of the mode of super disintegrant incorporation on dissolution in wet granulated tablets, J. Pharm. Sci. 82 (1993) 220–226.
[9] A. Radwan, G.L. Amidon, P. Langguth, Mechanistic investigation of food effect on disintegration and dissolution of BCS class III compound solid formulations: the importance of viscosity, Biopharm. Drug. Dispos. 33 (2012) 403–416.
[10] A. Radwan, M. Wagner, G.L. Amidon, P. Langguth, Bio-predictive tablet disintegration: effect of water diffusivity, fluid flow, food composition and test conditions, Eur. J. Pharm. Sci. 57 (2014) 273–279.
[11] A. Radwan, S. Ebert, A. Amar, K. Münnemann, M. Wagner, G.L. Amidon, P. Langguth, Mechanistic understanding of food effects: water diffusivity in gastrointestinal tract is an important parameter for the prediction of disintegration of solid oral dosage forms, Mol. Pharm. 10 (2013) 2283–2290.
[12] W. Lowenthal, Disintegration of tablets, J. Pharm. Sci. 61 (1972) 1695–1711.
[13] M. Jivraj, L.G. Martini, C.M. Thomson, An overview of the different excipients useful for the direct compression of tablets, Pharm. Sci. Technol. Today 3 (2000) 58–63.
[14] C. Caramella, P. Colombo, U. Conte, F. Ferrari, A.L. Manna, H. van Kamp, G. Bolhuis, Water uptake and disintegrating force measurements: towards a general understanding of disintegration mechanisms, Drug. Dev. Ind. Pharm. 12 (1986) 1749–1766.
[15] M. El-Barghouthi, A. Eftaiha, I. Rashid, M. Al-Remawi, A. Badwan, A novel superdisintegrating agent made from physically modified chitosan with silicon dioxide, Drug. Dev. Ind. Pharm. 34 (2008) 373–383.
[16] P.M. Desai, C.V. Liew, P.W.S. Heng, Understanding disintegrant action by visualization, J. Pharm. Sci. 101 (2012) 2155–2164.
[17] D.A. Khairnar, S.P. Anantwar, C.S. Chaudhari, P.A. Shelke, Superdisintegrants: An emerging paradigm in orodispersible tablets, Int. J. Biopharm. 5 (2014) 119–128.
[18] L. Bisharat, H.S. AlKhatib, S. Muhaissen, J. Quodbach, A. Blaibleh, M. Cespi, A. Berardi, The influence of ethanol on superdisintegrants and on tablets disintegration, Eur. J. Pharm. Sci. 129 (2019) 140–147.
[19] P.M. Desai, C.V. Liew, P.W.S. Heng, Review of Disintegrants and the Disintegration Phenomena, J. Pharm. Sci. 105 (2016) 2545–2555.