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Original Article

Superdisintegrant Efficiency in Acid Tolerance in Enteric Coated Diclofenac Sodium Tablets

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Abstract

Superdisintegrants are frequently used in tablet core formulations intended for enteric coating. The influence of superdisintegrant types and levels on the performance of enteric coated tablet formulations has been investigated. The core formulation markedly influences the functionality of a gastric resistant coat. A high water uptake of the core leads to increase in volume which in turn causes crack in the functional coat followed by increase in drug release. The application of an instant release sub-coat is appropriate for to prevent early drug release. This delays water permeation allowing MAE to take up water which acts as additional plasticizers.

Keywords: Superdisintegrants, diclofenac sodium, tablets, enteric coating, aqueous dispersion system, Kollicoat MAE 30DP.

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1. Introduction

Superdisintegrants are agents added to tablet formulations to promote the breakup of the tablet into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. The disintegrant can be incorporated either intragranularly, extragranularly or it can be distributed both intra and extragranularly .Superdisintegrants generally improve disintegration efficiency compared to traditional disintegrants. They are generally used at low levels in solid dosage forms, typically 1–10 % of mass relative to the total mass of the dosage unit. Examples of superdisintegrants are crosscarmellose sodium, sodium starch glycolate and crospovidone. The choice of superdisintegrant for a tablet formulation depends largely on the nature of the drug being used. For example, the solubility of the drug component could affect the rate and mechanism of tablet disintegration. Water-soluble materials tend to dissolve rather than disintegrate, while insoluble materials generally tend to disintegrate if an appropriate amount of disintegrant is included in the formulation. Superdisintegrants are frequently used in tablet core formulations intended for enteric coating. The influence of superdisintegrant types and levels on the performance of enteric

coated tablet formulations has been investigated.

Enteric film coating are intended to either protect the drug from the pH of the stomach (in the case of acid – vulnerable drugs) or protect the stomach from the irritant effect of certain drugs such as NSAIDs. This phenomenon can be achieved by using polymers formulations where these polymers are soluble at pH value in excess of 5-6. Indeed, polymer for enteric coating can be applied to a wide range of solid dosage forms including tablets, capsules, granules, or pellets, Several polymers are used as pH-sensitive enteric coating materials. Among these polymers cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid copolymers and acrylic copolymers were frequently recommended.

MAE (methacrylic ethyl acrylate copolymer) was considered as one of the most preferred materials for designing enteric coating formulations in terms of performance and global acceptability (BASF). In fact, MAE is commonly used in the pharmaceutical formulation polymer, especially as enteric coat for tablets and/or capsules. The aqueous based coating systems are preferred when compared with the organic solvent based systems.

Kollicoat MAE 30DP is an optimized, one-step, pigmented, aqueous polymer, providing an enteric, gastric resistant film coating for oral solid dosage forms. In fact, the obtained film coats resists to gastric juice but immediately starts to dissolve at a pH higher than 5.5. Kollicoat MAE 30DP is a special mixture of Methacryclic Acid – Ethyl Acrylate Copolymer (1:1), plasticizers and other components.

It offers consistent, reproducible enteric release characteristics which ensure the desired product performance. The obtained enteric coating support gastric guise as well as the severity of handling, packaging, transportation, and storage. Moreover, Kollicoat MAE 30DP is a cost effective option that uses simple coating pan and is both easy to prepare, and clean up. A subcoating layer is usually recommended to strengthen friable cores or to avoid incompatibilities between the pharmaceutical active ingredients and the enteric coat formulation. Indeed, the stability of alkaline drugs coated with acidic polymers, such as the case of acrylic polymers used in enteric coat, can be compromised due to acid base interaction between the acidic polymer and the alkaline drug.

When compared with almost all non-steroidal anti inflammatory drugs, diclofenac sodium causes gastric irritation which may results in ulceration by inhibiting the prostaglandins synthesis which has protective action on gastric mucosa. This cause of formation of ulcer at different levels of the gastrointestinal tract. Diclofenac sodium is an alkaline substance which may interact with acidic polymers used in enteric coating and thus may require a subcoating step to minimize this effect.

Developing a gastric resistant coating formulation can be quite demanding. The superdisintegrant functionality might interfere with the coating functionality. This work is to investigate the influence of the core formulation on the functionality of the applied coat of Methacryclic Acid – Ethyl Acrylate Copolymer.

MATERIAL AND METHODS

Materials

Diclofenac sodium (Aarti Drug Limited, India), lactose (Fastflo), microcrystalline cellulose (Vivapur 102; JRS, Germany),pregelatinised starch (Parachem, China), Aerosil (Evonik, Germany), croscarmellose sodium (DMV-Fonterra, Holland) and magnesium stearate (Magnesia, Germany). Sodium hydroxide (Merck, KgaA, and Darmstadt, Germany) monobasic potassium phosphate (Merck, KgaA, Darmstadt, Germany) and all the other chemicals used were of analytical grade and obtained from commercial sources. The enteric coating material was methacrylic acid copolymer based pigmented Kollicoat MAE 30DP white material was provided by BASF SE (Germany), Propylene Glycol (The Dow

Chemical Co.). Ethanol Internal (Gadot Chemical Co., Israel). Aluminum foil (Alufoil) and PVC (ACGpacks).

Instruments

UV-spectrophotometer (Shimadzu UV – 1700), Digital Balance (Adventure TM, OHAUS). Dissolution apparatus (Electrolab Tablet Dissolution USP TESTER (TDL 082). Hardness tester (Campbell Electronic Tablet Hardness Tester, (model HT50P). Friability Test Apparatus (Electrolab Dual Drum friability Tester USP (EF-2). Tablet compression machine (Adepth, 8 stations). Thickness (Electrolab Vernier calliper). Disintegration machine (Electrolab disintegration apparatus USP (Electrolab ED-2L). The tablet coating was performed in Becoater 12''coating pan (Betochem India) using external spray gun, dryer and (Type:Ceccato air compressor S.p.A, mod:8566 Mfg by CDA Engineering sdn Bhd-Malysia. Packing machine (ACG pampac, India).Humidity chamber for accelerated stability study (Memmert GmbH, Germany). Graphpad Instat 3.0

Preparation of uncoated Diclofenac sodium (75mg) Tablet

Diclofenac sodium and all other ingredients listed in Table 1, except sodium starch glycolate and magnesium stearate, were passed through a 30 mesh sieve. The mixture was then blended in a Cage blender for 5 minutes. Next, sodium starch glycolate was added and blending continued for 15 minutes. Finally, magnesium stearate (passed through a 60-mesh sieve) was introduced to the powder mixture and blended for an additional 5 minutes.

Table 1: Detailed composition of diclofenac sodium core tablets

Ingredients	CS6%	CS7%	CS8 %	SG7 %	SG7 %	SG8 %	CS6 %	CS7 %	CS8 %	SG7 %	SG7 %	SG8 %
Diclofenac Sodium	5	5	5	5	5	5	5	5	5	5	5	5
Pregelatinised Starch	4.2	1.9	9.6	4.2	1.9	9.6	4.2	1.9	9.6	4.2	1.9	9.6
Microcrystalline cellulose 102							03	03	03	03	03	03
Lactose anhydrous	03	03	03	03	03	03						
Sodium starch glycolate				3.8	6.1	8.4				3.8	6.1	8.4
Crosscarmellose sodium	3.8	6.1	8.4				3.8	6.1	8.4			
Aerosil												
Magnesium Stearate												
Total weight (mg)	30	30	30	30	30	30	30	30	30	30	30	30

Tablet Compression
Diclofenac tablets were compressed to a target tablet weight of 230 mg on an instrumented Adepth 8-station rotary tablet press equipped with 8mm standard, round, concave punch tooling and operated at 18 rpm.

Evaluation of Uncoated Tablets.
Tablet Physical Properties Testing

The hardness of the core tablets were measured on a Campbell Electronic Tablet Hardness Tablet Tester. Tablets friability was determined using Electrolab friabilator.

Uniformity of Dosage Units core tablets were carried out in accordance with the USP 2007 General Chapter: <905> Uniformity of Dosage Units. A sample of 10 tablets was assayed individually and the assay results were used to calculate the arithmetic mean, relative standard deviation (RSD).

Tablet Coating

Seal-Coating
Diclofenac tablets were seal-coated to a 3% weight gain with Instacoat Aqua III clear (reconstituted at 10% solids in purified water) using a side-vented 12" coating pan (Becoater, Betochem India). The coating process parameters employed in the coating operation are listed in Table 3.

Enteric coating of diclofenac sodium (75 mg/tablet)

Preparation of Kollicoat MAE 30DP for Enteric Coating
Mix propylene glycol with water and stir with Kollicoat MAE 30DP, stir for 2.5hours.
Suspend the talc, titanium
Uniformity of dosage units for diclofenac dioxide and yellow iron oxide colourants in water and homogenize in a colloid mill. Add the pigment suspension to the well stirred polymer suspension.

Spray the suspension obtained throughout the coating process.

Table 2: Parameters of coating formulation

Parameter	Coating
Theoretical weight gain (mg)	10%,12%,14% (w/w)
Polymer suspension	
Kollicoat MAE 30DP	50%(w/w)
Propylene Glycol	2.25% (w/w)
Water	32.25% (w/w)
Pigment suspension	
Titanium dioxide	0.5% (w/w)
Talc	4.0% (w/w)
Yellow iron oxide	0.5% (w/w)
Water	10.5% (w/w)

Coating:
Tablet coating was performed in a conventional coating pan with one spray gun. The coating pan was previously cleaned using alcohol 95%. A batch size of 1.0 kg diclofenac sodium core tablets was selected for coating. The core tablets were loaded into the coating pan. Tablet cores were pre-heated to about 40°C utilizing a dryer and air compressor (Type: Ceccato air compressor S.p.A, mod: 8566 Mfg by CDA Engineering sdn Bhd-Malysia). Warm air was introduced into the coating pan (up to 50–55°C) during the entire coating process. The spray gun was filled with Kollicoat MAE 30DP milky white aqueous dispersion and operated at a proper flow rate.
The pan was set into motion and seal coating dispersion was sprayed on to the falling cores under a suitable air pressure (25psi) 1.5 bar. The air heater was switched off and tablets were blow dried for 20-25 minutes after coating with Kollicoat MAE 30DP. . Always maintain a negative air pressure in the pan (more air out than in).After start-up, allow a minimum of 15 minutes for exhaust temperature to equilibrate before making.
Changes in fluid and/or air flows. To achieve highest enteric quality and adhesion between the core and enteric interface, the spray rate of Kollicoat MAE 30DP should be reduced by 15%, for the first 1% weight gain, if any tackiness or sticking is noticed. Once Kollicoat MAE 30DP delivery has begun, keep a constant

flow rate. Keep gun needles in an open position during the coating process (BASF).

Table 3: Parameters of coating process

Coating Process Parameters	Seal Coating	Enteric Coating
Equipment	Becoater 12''	Becoater 12''
Substrate	Diclofenac sodium 75mg tablets	Diclofenac sodium 75mg tablets
Pan charge	1.0kg	1.0kg
Dispersion solid content	10%	30%
Pan speed	4rpm	4rpm
Inlet Temperature	68	45
Outlet Temperature	55	35
Bed Temperature	45	30
Spray Rate	25g/min	20g/min
Distance between spray rate and gum	15cm	15cm
Pattern Air Pressure	27psi/1.7bar	15psi/1.1bar
Atomization Air Pressure	22psi/1.5bar	13psi/1.0bar
Coating time	45minutes	180minutes

Evaluation of diclofenac sodium (75 mg) coated tablets

Weight uniformity of coated tablets

Randomly selected twenty tablets were weighed individually and together. Average weight was calculated. Each individual tablet weight was compared against the calculated average.

Hardness

The hardness of the coated tablets was tested using a tablet hardness tester. This test was conducted according to the USP specification. 20 randomly selected tablets from each of study batches were tested at the different time intervals of the study.

Disintegration test.

The disintegration time of enteric coated diclofenac sodium 75 mg tablets was determined according to the procedure reported in USP (USP 2007). Six tablets of diclofenac sodium enteric coated tablets were weighed individually and placed in acid phase (0.1 N HCl) for 2 h in a USP basket rack assembly (Electrolab disintegration apparatus USP (Electrolab ED-2L) after which they were removed and inspected for cracking or disintegration. The same tablets were then placed in phosphate buffer, pH 6.8 and observed for disintegration.

Assay for enteric coated tablets

Drug assay was determined in accordance with the USP monograph for diclofenac sodium delayed release tablets.3 The USP 2007 specification states that the tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of diclofenac sodium

Acid uptake for enteric coated tablets

Diclofenac tablets (n=6) of each of the enteric coating weight gains were individually weighed and reciprocated for 2 hours in the test media, 0.1 N HCl and pH 4.5 acetate buffer solution in a USP 2007 disintegration apparatus at 37 ± 2^0C. At the end of this time interval, the tablets were removed from the disintegration bath and inspected for any defects (bloating or swelling). Any excess surface moisture was gently blotted dry using a paper towel, and the tablets reweighed individually. The percent liquid uptake for a tablet was calculated according to Equation 1. Historically, less than 10% liquid uptake has shown to correlate to acceptable enteric protection for tablets.

Liquid Uptake (%) = $[(T_f - T_i)/T_i] \times 100$.... Equation 1

Liquid Uptake (%): Percent liquid uptake

T_f: Final tablet weight (mg)
T_i: Initial tablet weight (mg)

Dissolution test of enteric coated tablets

Dissolution testing was carried out in accordance with the USP 2007 monograph for diclofenac sodium delayed release tablets. Drug release was determined using a USP compliant automated dissolution bath, Apparatus 2 (paddles) equilibrated to a temperature of 37±0.5°C at 50 rpm. Six tablets were introduced into the apparatus and the apparatus was run for 2 h .At the end of the acid stage, (2 hours in 900 mL 0.1 N hydrochloric acid), an aliquot was withdrawn and tested for the amount of diclofenac sodium released. The specification for the acid phase is not more than 10% diclofenac sodium released. The acid (0.1 N HCl) was then drained from the vessel, and replaced with pH 6.8 phosphate buffer. After the operation outlined above, an aliquot of the fluid was drawn, and the second stage (pH 6.8) was commenced. This last consisted of a phosphate buffer of pH 6.8 prepared by mixing 0.1 M hydrochloric acid with 0.20 M tribasic sodium phosphate (3:1). The apparatus was operated for a further 45 minutes The USP specification for the buffer phase is not less than 80% drug released after 45 minutes. At the end of the time period, an aliquot of the fluid was drawn. The samples were analyzed by UV spectrophotometer (UV 1700, Shuimadzu,) at wavelength 260 nm.

Stability Testing

Enteric coated diclofenac tablets were packaged in blistered PVC pack with plain alumium foil and stored for 6 months at accelerated conditions of 40^0C/75%RH. Stability was monitored via drug release, acid uptake and disintegration time of enteric coated tablets.

Statistical Analysis

Each tablet formulation was reared in duplicate and each analysis was duplicated. Each formulation variables on disintegration time, acid uptake and release parameters were tested for significance by using analysis of variance (ANOVA). Difference was considered significant when $P<0.05$.

RESULTS

The use of Kollicoat MAE 30DP white as enteric coating material gave successful results of enteric coating. In order to achieve good coating results, uncoated tablets should have good physical parameters to withstand the coating steps.

Physical Characterization of core tablets

The prepared tablets were free from defects such as capping and lamination. Tablets of good mechanical strength and low friability (a maximum loss of mass not greater than 1%) were manufactured.

Physical appearance, hardness, friability, weight variation and drug content evaluation of the uncoated tablets were found to be satisfactory under pharmacopoeial standards of tablet evaluation as shown in table4.

Table 4: Physical properties of Diclofenac core tablets

Test	Results
Weight variation test	Within the limits (±7.5%)
RSD (%)	0.45%
Friability test	Within the limits (0.3%)
Thickness (mm) (n=20)	4.42
Avg. Compression Force (kN)	17.77
Ejection Force (N)	143.61

	LACTOSE core Tablets			**MCC core Tablets**		
Superdisintegrant conc. (w/w)	CCS	SSG	Anova	CCS	SSG	Anova
4%	151.3(6.1)	156.8(6.9)	**P>0.05QS**	147.7(3.1)	181.2(4.4)	**P>0.0001ES**
6%	161.5(3.9)	158.2(5.7)	**P>0.05QS**	153.7(6.9)	178.8(5.1)	**P>0.0001ES**
8%	155.5(9.1)	162.4(0.5)	**P>0.05NQS**	155.3(5.7)	176.5(6.1)	**P>0.001ES**
ANOVA	**P>0.05NQS**	**P>0.05NQS**		**P>0.05NQS**	**P>0.05NQS**	

Mean of six readings. Values in parenthesis are positive standard deviations.

Assay and Uniformity of Dosage Units

The average assay results of diclofenac core tablets were within the range of 90% to 110% of the label claim (LC), and the RSD was less than 6%.. The assay results of diclofenac enteric coated tablets (Table 4b) were within the range of 90% to 110% of the label claim.

Table 6a- Assay and Uniformity of Dosage Units (Diclofenac Core Tablets)

Test	Results
Avg. Assay (% of LC)	100.4
RSD %	1.4

Table 6b: Assay and Uniformity of Dosage Units (Coated Tablets)

Coating weight gain	10	12	14
Avg. Assay	100	99.9	99.7
RSD %	1.67	1.37	123

	LACTOSE core Tablets			**MCC core Tablets**		
Medium	**Water**					
Superdisintegrant conc. (w/w)	CCS	SSG	Anova	CCS	SSG	Anova
4%	8.5(1.04)	9.7(1.37)	**P<0.05VS**	9.0(1.26)	8.8(0.75)	**P>0.05NS**
6%	7.8(1.17)	9.8(1.47)	**P<0.05VS**	8.2(1.47)	9.8(1.47)	**P<0.05VS**
8%	6.5(1.05)	10.3(1.03)	**P<0.05VS**	7.3(1.21)	10.2(1.17)	**P<0.05VS**
ANOVA	**P<0.05VS**	**P<0.05VS**		**P>0.05NS**	**P>0.05NS**	

Mean of six readings. Values in parenthesis are positive standard deviations N**S** → not significant, **NQS** → not quite significant, **S** → significant, **VS** → very significant, **ES** → extremely significant

Disintegration Time

Diclofenac core tablets disintegrated in pH 6.8 phosphate buffer media within 2-8 minutes. Results indicate that diclofenac tablets, enteric coated at higher coating weight gains, had longer disintegration times than those coated at lower levels. The longer disintegration times are attributed to the greater amount of polymer that must be dissolved at higher coating weight gains.

Table 8a: Disintegration time of Coated Tablet

LACTOSE Core TABLETS									
Test Medium	**PHOS[PHATE BUFFER pH 6.8**								
Coating weight gain	10%			12%			14%		
Superdisintegrant conc. (w/w)	CCS	SSG	Anova	CCS	SSG	Anova	CCS	SSG	Anova
4%	21(2.94)	21(4.87)	**P>0.05NS**	23(4.23)	26(4.09)	**P>0.05NS**	28(5.34)	30(5.34)	**P>0.05NS**
6%	18(3.89)	16(4.59)	**P>0.05NS**	20(4.78)	23(5.12)	**P>0.05NS**	24(5.23)	25(4.56)	**P>0.05NS**
8%	13(3.56)	12(3.89)	**P>0.05NS**	15(5.56)	19(4.11)	**P>0.05NS**	19(4.34)	20(5.98)	**P>0.05NS**
ANOVA	**P<0.05VS**	**P<0.05VS**		**P<0.05VS**	**P<0.05VS**		**P<0.05VS**	**P<0.05VS**	

Mean of six readings. Values in parenthesis are positive standard deviations **NS** → not significant, **NQS** → not quite significant, **S** → significant, **VS** → very significant, **ES** → extremely significant

Table 8b: Disintegration time of Coated Tablet

MCC Core TABLETS									
Test Medium	**PHOSPHATE BUFFER pH 6.8**								
Coating weight gain	10%			12%			14%		
Superdisintegrant conc. (w/w)	CCS	SSG	Anova	CCS	SSG	Anova	CCS	SSG	Anova
4%	20(3.27)	21(4.13)	**P>0.05NS**	21(3.84)	25(4.09)	**P>0.05NS**	25(4.62)	28(4.73)	**P>0.05NS**
6%	15(4.04)	16(3.78)	**P>0.05NS**	18(5.34)	20(4.27)	**P>0.05NS**	21(5.09)	23(5.23)	**P>0.05NS**
8%	11(4.35)	12(2.56)	**P>0.05NS**	13(5.11)	17(3.97)	**P>0.05NS**	16(4.29)	17(4.85)	**P>0.05NS**
ANOVA	**P<0.05VS**	**P<0.05VS**		**P<0.05VS**	**P<0.05VS**		**P<0.05VS**	**P<0.05VS**	

Mean of six readings. Values in parenthesis are positive standard deviations. **NS** → not significant, **NQS** → not quite significant, **S** → significant, **VS** → very significant, **ES** → extremely significant.

Assessment of Acid Uptake (AU)

At all the coating levels evaluated, tablets demonstrated very low liquid uptake (i.e less than 5%) in 0.1N HCL.

Table 9a: Assessment of Acid Uptake (AU) in 0.1 N HCl

LACTOSE Core TABLETS									
Test Medium	0.1N HCL								
Coating weight gain	10%			12%			14%		
Superdisintegrant conc. (w/w)	CCS	SSG	Anova	CCS	SSG	Anova	CCS	SSG	Anova
4%	4.8(0.64)	5.3(0.58)	**P<0.05VS**	4.5(0.57)	4.8(0.64)	**P<0.05VS**	4.0(0.8)	4.3(0.8)	**P<0.05VS**
6%	4.9(0.76)	5.2(0.45)	**P<0.05VS**	4.7(0.41)	5.0(0.54)	**P<0.05VS**	4.4(0.78)	5.1(0.62)	**P<0.05VS**
8%	5.0(0.56)	5.1(0.5)	**P<0.05VS**	4.9(0.83)	5.1(0.79)	**P<0.05VS**	4.6(0.11)	5.4(0.99)	**P<0.05VS**
ANOVA	**P>0.05NS**	**P>0.05NS**		**P>0.05NS**	**P>0.05NS**		**P>0.05NS**	**P>0.05NS**	

Mean of six readings. Values in parenthesis are positive standard deviations. **NS** → not significant, **NQS** → not quite significant, **S** → significant, **VS** → very significant, **ES** → extremely significant

Table 9b: Assessment of Liquid Uptake (LU) in 0.1 N HCl

MCC Core TABLETS									
Test Medium	0.1N HCL								
Coating weight gain	10%			12%			14%		
Superdisintegrant conc. (w/w)	CCS	SSG	Anova	CCS	SSG	Anova	CCS	SSG	Anova
4%	4.6(0.77)	4.5(0.58)	**P>0.05NS**	4.4(0.34)	4.3(0.64)	**P>0.05NS**	4.1(0.8)	4.2(0.11)	**P>0.05NS**
6%	4.8(0.39)	4.7(0.45)	**P>0.05NS**	4.6(0.28)	4.5(0.54)	**P.0.05NS**	4.5(0.86)	4.4(0.83)	**P>0.05NS**
8%	4.8(0.22)	4.7(0.5)	**P>0.05NS**	4.7(0.54)	4.6(0.79)	**P>0.05NS**	4.6(0.76)	4.5(0.66)	**P>0.05NS**
ANOVA	**P<0.05S**	**P<0.05S**		**P<0.05S**	**P<0.05S**		**P<0.05VS**	**P<0.05VS**	

Mean of six readings. Values in parenthesis are positive standard deviations **NS** → not significant, **NQS** → not quite significant, **S** → significant, **VS** → very significant, **ES** → extremely significant

Dissolution Profile

Table 10a: Dissolution profile of coated tablets in 0.1 N HCl

Lactose core Enteric coated Tablets : % Drug Release @ 120min									
Test Medium	0.1N HCL								
Coating weight gain	10%			12%			14%		
Super-disintegrant conc. (w/w)	CCS	SSG	Anova	CCS	SSG	Anova	CCS	SSG	Anova
4%	0.339(0.12)	0.262(0.03)	**P>0.05NS**	0.271(0.06)	0.379(0.04)	**P>0.05NS**	0.332(0.01)	0.372(0.07)	**P>0.05 NS**
6%	0.362(0.02)	0.321(0.07)	**P>0.05NS**	0.299(0.04)	0.324(0.08)	**P>0.05NS**	0.301(0.01)	0.265(0.03)	**P>0.05 NS**
8%	0.398(0.02)	0.333(0.02)	**P>0.05NS**	0.313(0.05)	0.358(0.05)	**P>0.05NS**	0.354(0.06)	0.330(0.06)	**P>0.05 NS**
ANOVA	**P>0.05NS**	**P>0.05NS**		**P>0.05NS**	**P>0.05NS**		**P>0.05NS**	**P>0.05NS**	

Mean of three readings. Values of parenthesis are standard deviation. **NS** → not significant, **NQS** → not quite significant, **S** → significant, **VS** → very significant, **ES** → extremely significant

Table 10b: Dissolution profile of coated tablets in 0.1 N HCl

MCC core Enteric coated Tablets : % Drug Release @ 120min									
Test Medium	0.1N HCL								
Coating weight gain	10%			12%			14%		
Superdisintegrant conc. (w/w)	CCS	SSG	Anova	CCS	SSG	Anova	CCS	SSG	Anova
4%	0.301(0.06)	0.348(0.02)	**P>0.05NS**	0.340(0.02)	0.373(0.04)	**P>0.05NS**	0.300(0.07)	0.422(0.02)	**P>0.05NS**
6%	0.313(0.05)	0.281(0.06)	**P>0.05NS**	0.354(0.06)	0.335(0.01)	**P>0.05NS**	0.359(0.02)	0.412(0.04)	**P>0.05NS**
8%	0.359(0.02)	0.402(0.04)	**P>0.05NS**	0.364(0.03)	0.436(0.01)	**P>0.05NS**	0.348(0.02)	0.354(0.04)	**P>0.05NS**
ANOVA	**P**	**P**		**P**	**P**		**P**	**P**	

	>0.05NS	**>0.05NS**		**>0.05NS**	**>0.05NS**		**>0.05NS**	**>0.05NS**	

Mean of three readings. Values of parenthesis are standard deviation. **NS** → not significant, **NQS** → not quite significant, **S** → significant, **VS** → very significant, **ES** → extremely significant

Table 10c: Dissolution profile of coated tablets in Phosphate buffer pH 6.8

Lactose core Enteric coated Tablets : % Drug Release @ 45min									
Test Medium	PHOSPHATE BUFFER pH 6.8								
Coating weight gain	10%			12%			14%		
Super-disintegrant conc. (w/w)	CCS	SSG	Anova	CCS	SSG	Anova	CCS	SSG	Anova
4%	97.96(0.4)	98.95(0.4)	**P<0.05VS**	98.82(0.5)	97.3(0.8)	**P<0.05VS**	97.66(0.4)	98.58(0.2)	**P<0.05VS**
6%	98.85(0.4)	99.41(0.2)	**P<0.05VS**	97.30(0.4)	98.54(0.4)	**P<0.05VS**	98.48(0.5)	98.06(0.8)	**P<0.05VS**
8%	99.18(0.4)	97.87(0.3)	**P<0.05VS**	98.14(0.6)	97.36(1.0)	**P<0.05VS**	98.02(0.6)	98.09(1.2)	**P<0.05VS**
ANOVA	**P>0.05NS**	**P>0.05NS**		**P>0.05NS**	**P>0.05NS**		**P>0.05NS**	**P>0.05NS**	

Mean of three readings. Values of parenthesis are standard deviation. **NS** → not significant, **NQS** → not quite significant, **S** → significant, **VS** → very significant, **ES** → extremely significant

Table 10d: Dissolution profile of coated tablets in Phosphate buffer pH 6.8

MCC core Enteric coated Tablets : % Drug Release @ 45min									
Test Medium	PHOSPHATE BUFFER pH 6.8								
Coating weight gain	10%			12%			14%		
CCS	SSG	Anova	CCS	SSG	Anova	CCS	SSG	Anova	CCS
98.49(1.1)	97.52(0.6)	**P<0.05VS**	98.81(0.6)	98.54(0.7)	**P<0.05VS**	97.77(0.3)	97.43(1.0)	**P<0.05VS**	97.77(0.3)
98.38(0.1)	98.60(0.2)	**P<0.05VS**	97.16(0.5)	98.37(1.1)	**P<0.05VS**	98.09(1.0)	97.97(0.6)	**P<0.05VS**	98.09(1.0)
98.53(0.9)	97.84(1.38)	**P<0.05VS**	97.83(0.6)	97.07(0.7)	**P<0.05VS**	97.43(0.8)	97.11(0.5)	**P<0.05VS**	97.43(0.8)
P>0.05NS	**P>0.05NS**		**P>0.05NS**	**P>0.05NS**		**P>0.05NS**	**P>0.05NS**		**P>0.05NS**

Mean of three readings. Values of parenthesis are standard deviation. **NS** → not significant, **NQS** → not quite significant, **S** → significant, **VS** → very significant, **ES** → extremely significant.

Stability Testing

Drug release testing indicates that the enteric coating (10% wg) continued to provide good protection in acid phase and greater than 80% release in 45 minutes when stored at 6 months for 40^0C/75%RH in a blistered foil pack. Similar results were obtained for the enteric coated tablets at 12% and 13% weight gain when stored for 6 months.

Table 11a: Disintegration time of Coated Tablet

Test Medium		**Phosphate Buffer pH 6.8**																	
Storage condition		**40^0C/75%RH**																	
		LACTOSE CORE COATED TABLETS																	
Superdisintegrant		**4%**						**6%**						**8%**					
Weight Gain		10%		12%		14%		10%		12%		14%		10%		12%		14%	
DT (minutes)		***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CC***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***
Stability time point	1st month	22	20	24	21	29	30	17	15	20	23	24	25	13	12	15	19	19	20
	2nd month	21	20	23	22	29	28	16	14	21	24	25	25	13	11	15	18	19	22
	3rd month	22	21	25	23	31	29	17	14	22	23	23	24	14	13	16	19	21	24
	6th month	23	22	22	21	30	28	16	15	21	24	25	26	13	12	14	20	22	23

Test Medium		**Phosphate Buffer Ph 6.8**																	
Storage condition		**40^0C/75%RH**																	
		MCC CORE COATED TABLETS																	
Superdisintegrant		**4%**						**6%**						**8%**					
Weight Gain		10%		12%		14%		10%		12%		14%		10%		12%		14%	
DT (minutes)		***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***
Stability time point	1st month	20	21	21	25	25	28	15	16	18	20	21	23	11	12	13	17	16	17
	2nd month	21	20	23	22	24	28	16	17	17	18	21	25	13	11	15	18	19	18
	3rd month	22	21	25	23	26	29	17	17	17	19	22	24	12	13	16	19	18	19
	6th month	23	22	22	21	26	29	16	16	16	18	21	23	13	12	14	19	17	19

Test Medium		**0.1N HCL**																	
Storage condition		**40^0C/75%RH**																	
		LACTOSE CORE COATED TABLETS																	
Superdisintegrant		**4%**						**6%**						**8%**					
Weight Gain		10%		12%		14%		10%		12%		14%		10%		12%		14%	
Acid uptake(%)		***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CC***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***
Stability time point	1st month	4.8	5.3	4.5	4.8	4.0	4.3	4.9	5.2	4.7	5.1	4.5	5.0	5.1	5.2	4.9	5.0	4.6	5.4
	2nd month	4.7	5.4	4.5	4.7	4.1	4.2	4.8	5.2	4.6	4.8	4.6	5.1	5.0	5.1	4.8	5.1	4.5	5.5
	3rd month	4.6	5.2	4.4	4.9	4.2	4.4	4.9	5.0	4.5	5.0	4.4	4.9	4.9	5.2	4.9	5.2	4.7	5.3
	6th month	4.9	5.3	4.6	4.7	4.1	4.4	4.6	5.1	4.8	4.9	4.3	5.2	4.9	5.0	5.0	5.0	4.6	5.5

Test Medium		**0.1N HCL**																	
Storage condition		**40^{0}C/75%RH**																	
		MCC CORE COATED TABLETS																	
Superdisintegrant		**4%**						**6%**						**8%**					
Weight Gain		10%		12%		14%		10%		12%		14%		10%		12%		14%	
Acid uptake(%)		***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***
Stability time point	1st month	4.5	4.4	4.5	4.4	4.1	4.3	4.7	4.5	4.5	4.3	4.4	4.2	4.6	4.4	4.6	4.4	4.3	4.2
	2nd month	4.6	4.6	4.6	4.2	4.2	4.4	4.8	4.7	4.3	4.2	4.4	4.3	4.8	4.5	4.6	4.3	4.4	4.3
	3rd month	4.7	4.4	4.5	4.1	4.2	4.3	4.9	4.6	4.5	4.4	4.3	4.1	4.7	4.6	4.5	4.4	4.5	4.4
	6th month	4.6	4.5	4.4	4.3	4.1	4.2	4.8	4.7	4.6	4.5	4.5	4.3	4.8	4.7	4.7	4.6	4.6	4.5

Test Medium		**Phosphate Buffer pH 6.8**																	
Storage condition		**40^{0}C/75%RH**																	
		LACTOSE CORE COATED TABLETS																	
Superdisintegrant		**4%**						**6%**						**8%**					
Weight Gain		10%		12%		14%		10%		12%		14%		10%		12%		14%	
Drug Release (%)		***CS***	***SG***	***CS***	***SG***	***CS***	***SG***	***CS***	***SG***	***C***	***SG***	***CS***	***SG***	***CS***	***SG***	***CS***	***SG***	***CS***	***SG***
Stability time point	1st month	6	6	6	6	5	6	6	6	6	7	8	6	8	7	6	7	6	6
	2nd month	8	7	7	8	6	7	7	7	8	8	7	7	6	8	7	8	7	7
	3rd month	6	6	6	7	8	7	7	8	6	8	8	6	7	6	7	6	7	6
	6th month	6	8	8	7	7	8	6	6	6	8	8	8	8	8	8	8	8	7

Test Medium		**Phosphate Buffer Ph 6.8**																	
Storage condition		**40^{0}C/75%RH**																	
		MCC CORE COATED TABLETS																	
Superdisintegrant		**4%**						**6%**						**8%**					
Weight Gain		10%		12%		14%		10%		12%		14%		10%		12%		14%	
Drug Release (%)		***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***	***CCS***	***SSG***
Stability time point	1st month	97	96	97	98	98	97	97	99	96	97	97	97	96	97	98	97	96	95
	2nd month	96	98	96	97	96	97	96	96	95	97	96	97	95	97	96	96	96	96
	3rd month	95	96	97	97	97	98	96	98	98	96	96	96	96	97	96	95	95	96
	6th month	96	97	96	99	98	96	96	97	98	97	97	95	95	97	98	96	96	97

GRAPHS

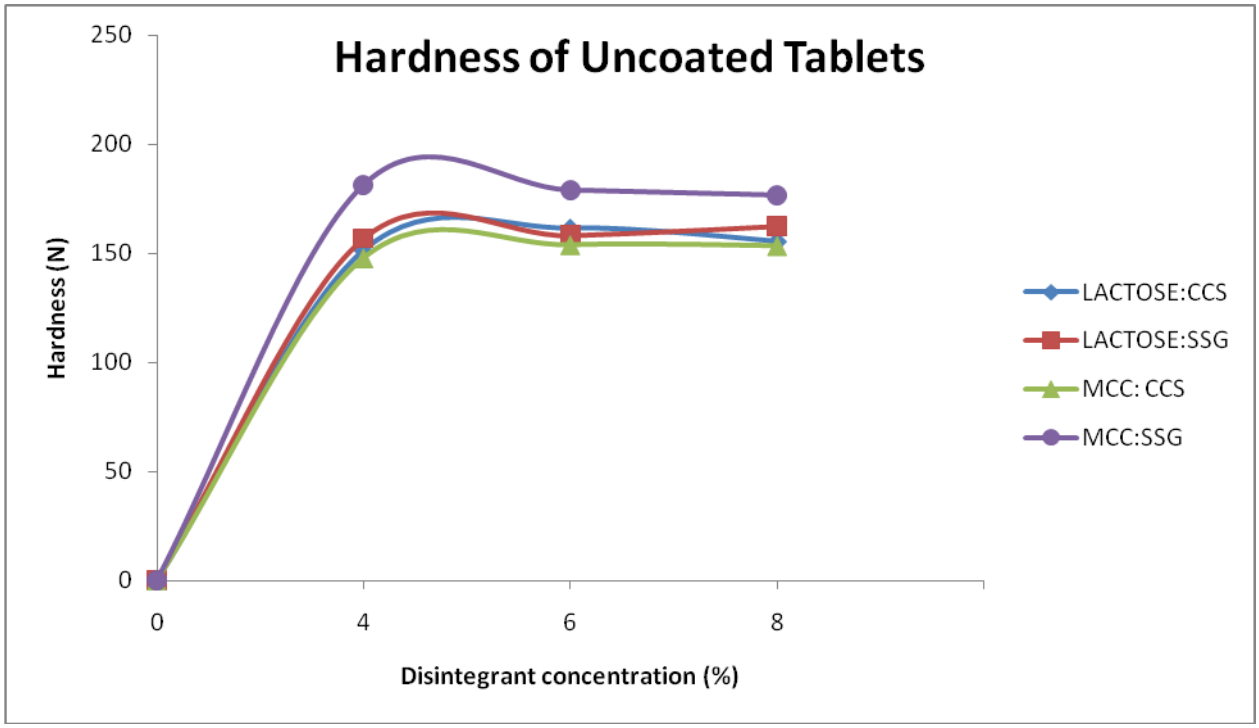

Fig 1: Hardness of Uncoated Tablets.

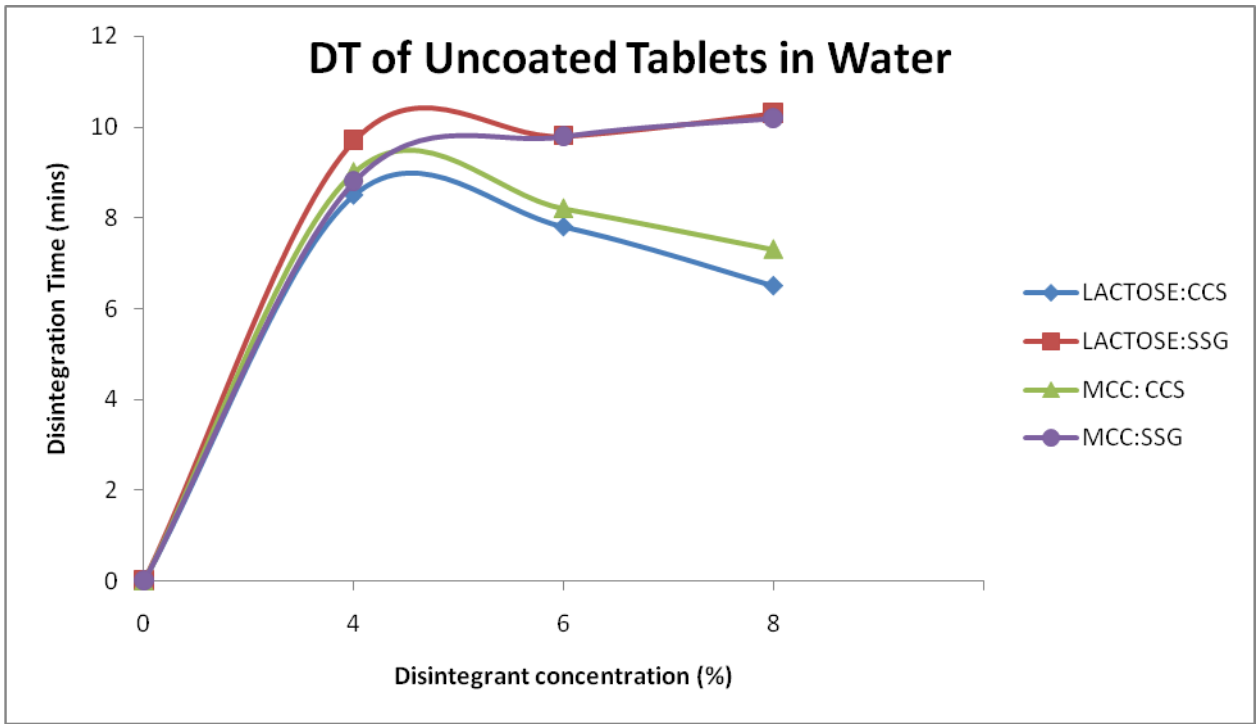

Fig 2: DT of Uncoated Tablets in Water.

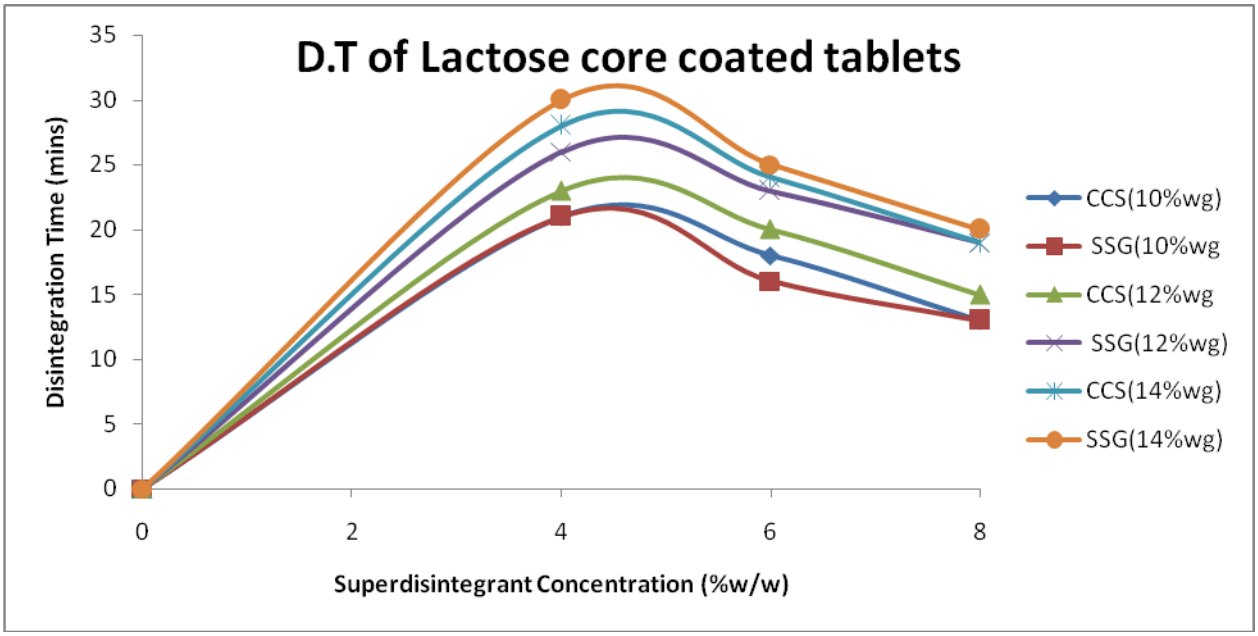

Fig 3: DT of Lactose core coated Tablets

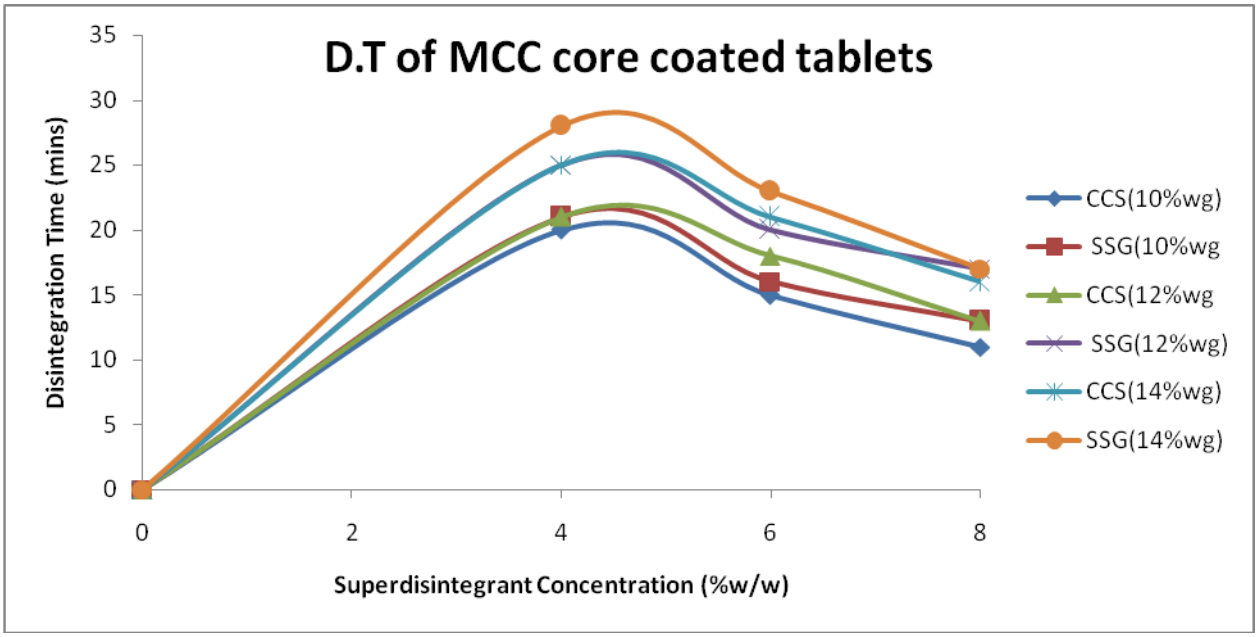

Fig 4: DT of MCC core coated Tablets.

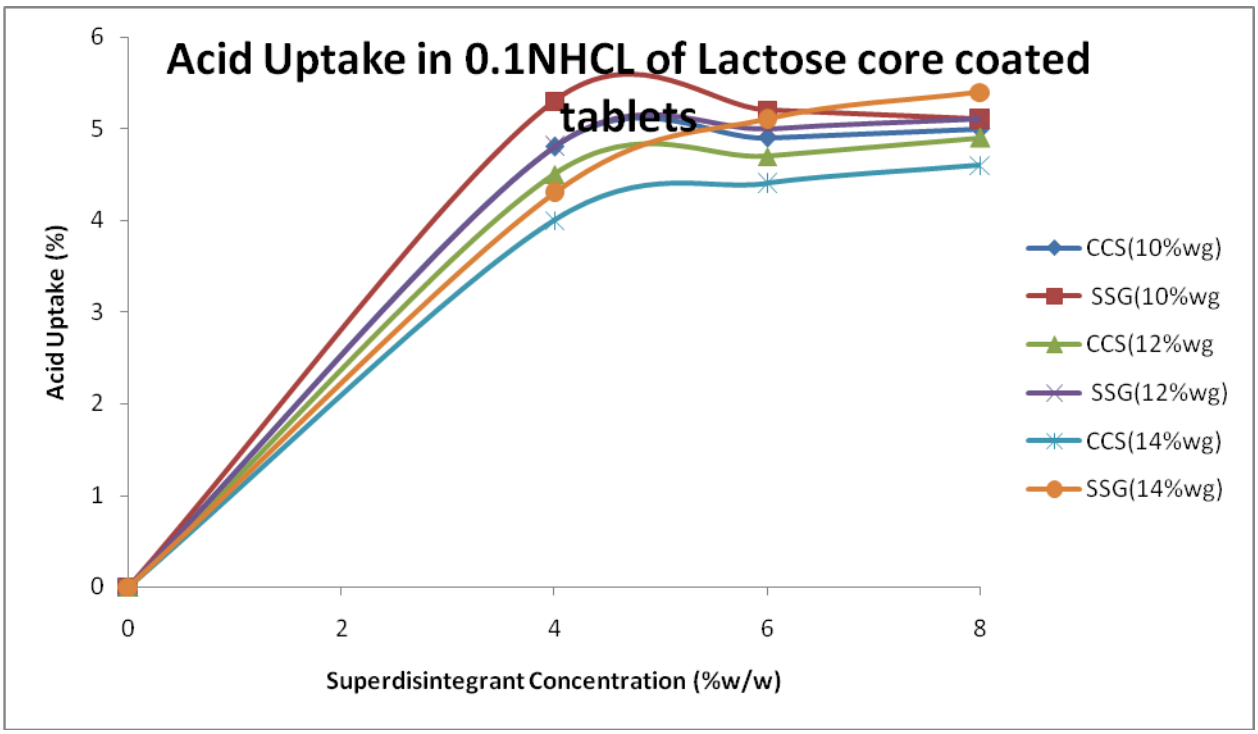

Fig 5:Acid uptake in 0.1N HCL of Lactose core coated tablets

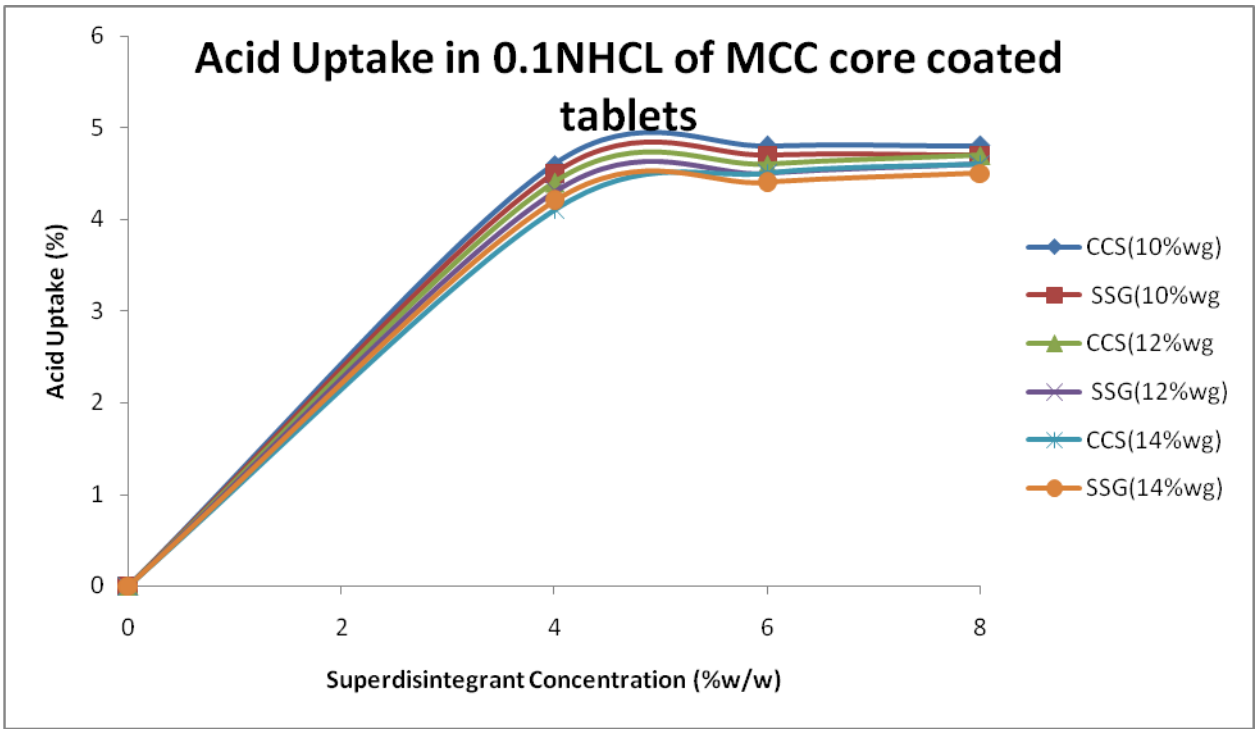

Fig 5:Acid uptake in 0.1N HCL of MCC core coated tablets

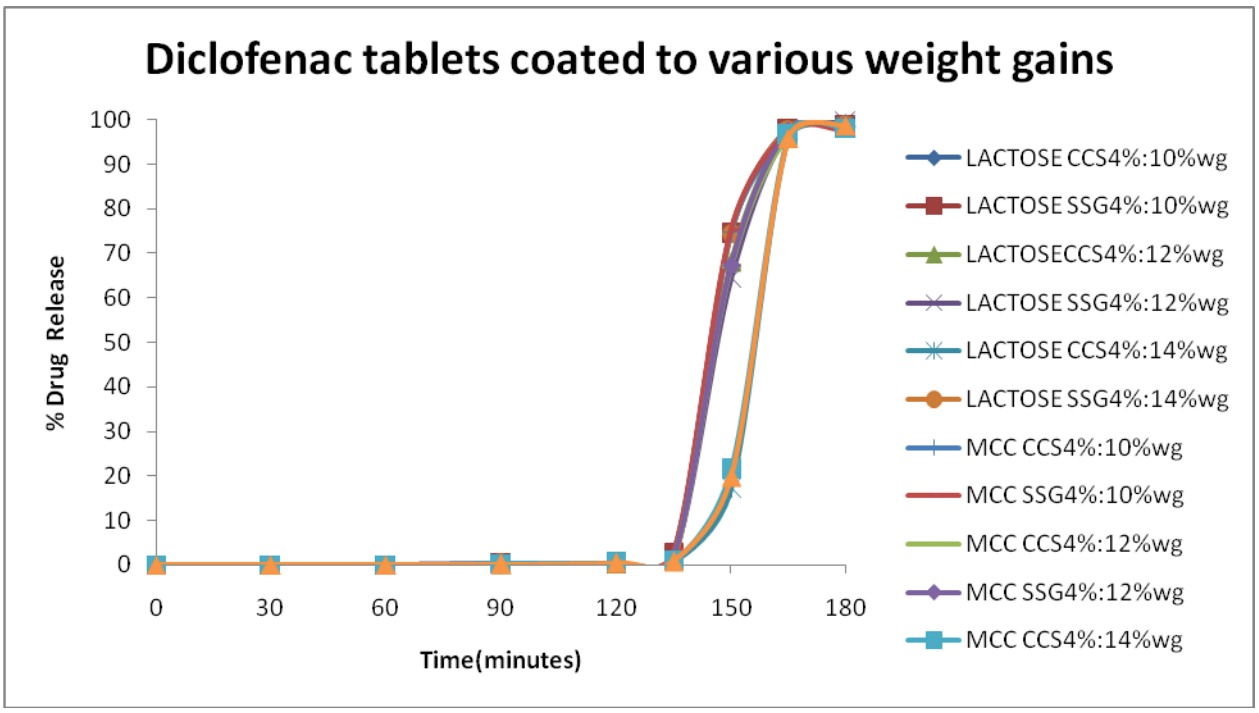

Fig 6: Drug release profile for 4% of coated tablets in acid and buffer phases.

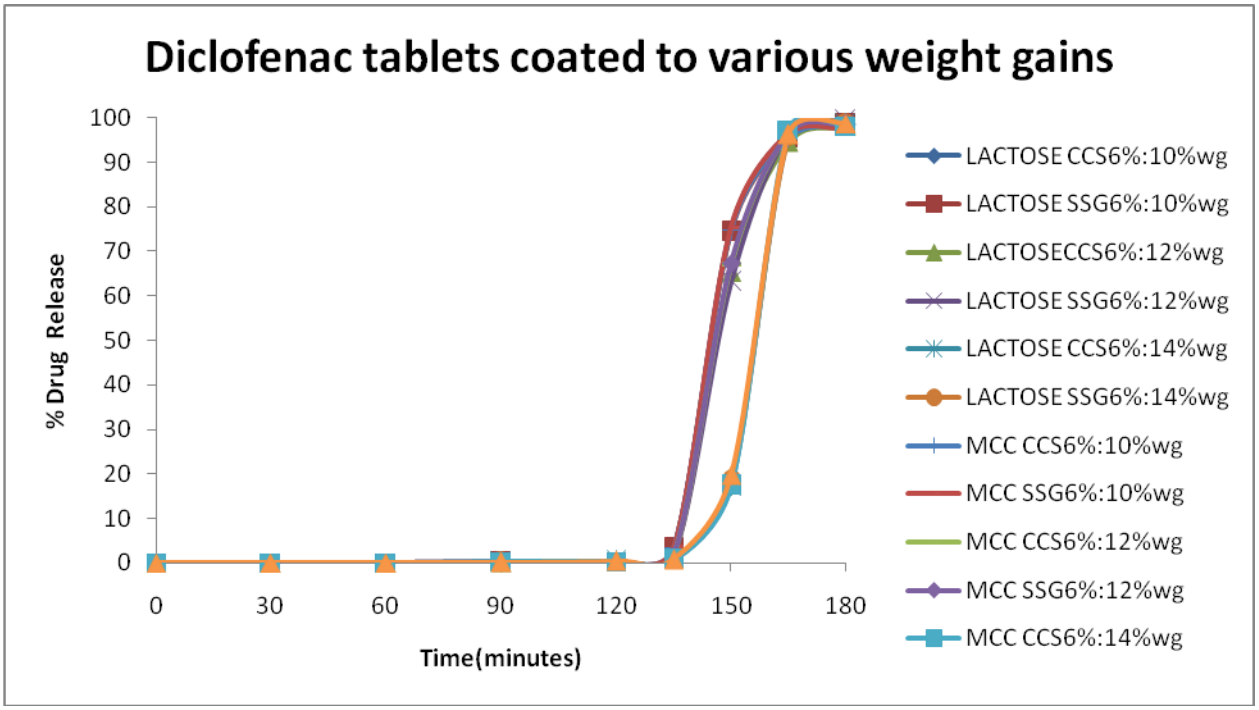

Fig 7: Drug release profile for 6%wg of coated tablets in acid and buffer phases.

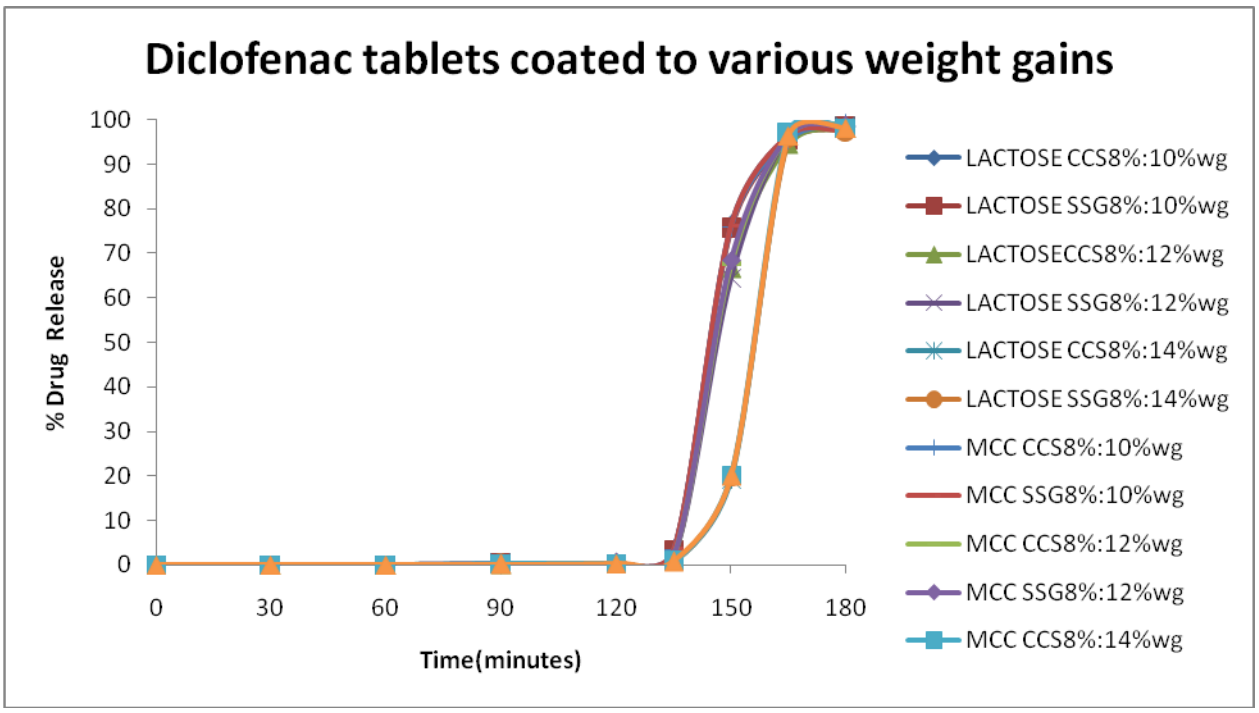

Fig 8: Drug release profile for 8%wg of coated tablets in acid and buffer phases.

Discussion

A tablet could deliver instant release functionality, even though coated with a functional polymer such as MAE. Reason for that is the core formulation. Formulation containing microcrystalline cellulose or high concentration of superdisintegrants attracts so much water in a short time that the functional coats crack. This is typically leading to instant release. The physical characteristics of the tablets (i.e. size, shape, hardness) remained unchanged when acid uptake was less than 10%. Tablets should show evidence of disintegration, cracking or softening, when acid uptake is greater than 10%. Therefore, acid uptake of less than 10% was considered acceptable. Adding superdisintegrant to tablets with a soluble filler (lactose) resulted in high acid uptake (>6%) across all superdisintegrant levels and all theoretical enteric weight gains (10-14%). Adding superdisintegrant to tablets with an insoluble filler (MCC) resulted in low acid uptake (<10%) across all superdisintegrant levels and all theoretical enteric weight gains (10-14%).

Conclusions

Acid resistance was lower in insoluble filler (MCC) when compared with soluble filler (Lactose).

- Tablets containing sodium starch glycolate had better acid resistance than that containing croscarmellose sodium.
- Increasing the weight gain of the enteric coating improved acid resistance regardless of filler type or superdisintegrant level.

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