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Effect of Superdisintegrants on Physical Attribute and Release Profile of Metformin HCl Immediate Release Tablets

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ABSTRACT

An immediate action of Metformin HCl is essential for emergency treatment of diabetes. With an objective of finding the best suitable disintegrant for immediate release tablet of Metformin HCl, different formulations were prepared by incorporating varying ratios of three widely used superdisintegrants both by intra and extra granularly. Wet granulation method was adopted to formulate the tablets by using Maize Starch as diluent; Povidone k-30 as binder; Sodium Starch Glycolate/Kollidon CL/Crosscarmellose Sodium as superdisintegrants in different concentration (2-3.5%), Aerosil-200 as flow promoter and Magnesium Stearate as lubricant. To evaluate the rheological properties of powdered blend, some pre-compression characteristics including bulk and tapped densities, compressibility index, Hausner's ratio, angle of repose were studied. The compressed tablets were evaluated for hardness, thickness, diameter, friability, drug content, weight variation, *in vitro* dispersion time, *in vitro* disintegration time, *in vitro* wetting time and finally for *in vitro* dissolution studies. It was found that wetting time, dispersion time and the disintegration time of the tablets were governed by the type and quantity of the superdisintegrants. *In vitro* drug release data obtained at phosphate buffer at pH 6.8 also found reliant on successful incorporation of right disintegrating agent. Higher the disintegrant ratio in the formulation, lower the disintegration time and hence, higher percentage of drug release was obtained. Based upon results of different studies, Sodium Starch Glycolate has been proven successful in rapid disintegration of tablets and enhancing dissolution behavior.

Keywords: Superdisintegrants, wetting time, dispersion time, Hausner's ratio, compressibility, flow promoter.

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INTRODUCTION

Oral route is probably the most versatile, convenient and commonly employed pathway of drug delivery for systemic action. Various dosage forms are administered orally; the tablet is one of the most preferred dosage forms amongst them because of its ease of manufacturing, convenience in administration, accurate dosing, unit packing and stability when compared with oral liquids and capsules. The bioavailability of drug is dependent on *in vivo* disintegration, dissolution and various physiological factors [1].

Disintegration is the doorway for dissolution of solid dosage forms and hence, the key for *in vivo* drug absorption and performance. Since it is the essential step for a drug to release from the dosage form, it has drawn a particular attention from the scientists around the globe. Particularly the drugs that required immediate action such as pain killers, cardiac drugs and anti-diabetic drugs highlighted the importance of the relatively rapid disintegration of a tablet as a criterion for ensuring uninhibited drug dissolution behavior. Choosing the right disintegrating agents is thus become very important issue in formulating the dosage form.

Disintegrants are substances or mixture of substances added to the drug formulations that facilitate dispersion or breakup of tablets and contents of capsules into smaller particles for quick dissolution [2]. Disintegrants promote the breakup of the tablet or capsule or their slugs into smaller fragments in an aqueous environment, thereby increasing the available surface area and persuading a more rapid release of the drug substance. In the past, non-modified disintegrants such as alginates, starches, ambrelite resins, cellulosic materials, pectins etc. were used to accelerate disintegration process [3].

In the same way, superdisintegrants are those substances that facilitate the faster disintegration with smaller quantity in contrast to disintegrants. These substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Three classes of superdisintegrants are commonly used: modified cellulose, crosslinked polyvinyl-pyrrolidone and modified starch. Disintegrants usually act by different mechanisms like rapid swelling by water insoluble agents (starch), capillary actions by usually aqueous soluble materials and combination of those (crospovidone).

Metformin HCl is an oral anti-hyperglycemic drug, belonging to the biguanide class. It is the first-line drug for the treatment of type-II diabetes, since Metformin is not associated with weight gain; it is the hypoglycemic agent of choice for the treatment for this kind of diabetic patients [4]. Metformin is slowly and partially absorbed from an oral dose when taken in the form of oral

tablets of 500 and 850 mg. The absolute bioavailability of a 500 mg immediate release tablet is about 50 to 60%; the half-life is 2 to 6 hr and the maximum plasma concentration is reached after 2.5 hr, the drug being excreted through the urinary tract unaltered [5]. An immediate release preparation of Metformin HCl might be more advantageous in proper management of diabetes.

The objective of this study was to prepare immediate release tablets containing different types of superdisintegrants via wet granulation, in order to compare their impacts on disintegration and dissolution profiles. Metformin HCl was used as a model drug for immediate release tablets. Another aim of this study was to find a suitable superdisintegrants having excellent disintegrating properties.

MATERIALS AND METHODS

Materials

Metformin HCl, sodium starch glycolate, croscarmellose sodium and Kollidon CL were obtained as gift samples from ACI Pharmaceutical Ltd, Bangladesh. All necessary ingredients and reagents were of analytical grade and purchased from local market.

Preparation of granules

First of all, the active ingredient, Starch, and ¾ of stated amount of superdisintegrants were weighed by electronic balance and passed through a '40' mesh sieve in a mortar to obtain fine particles as per Table 1. The obtained granular materials were then mixed together for 10 min. The binding solution was prepared by dissolving povidone k-30 in sufficient amount of water. This solution was then added drop by drop to the dry mixture in the mortar. During this addition, the mixture was continuously stirred in clockwise direction and stirring was continued for a further 10 mins after all the binding solution had been added. A uniform wet mass was obtained after completion of mixing stage.

Table 1: Formulations of Metformin HCl immediate release tablets (in mg).

Sl. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Metformin HCl	500	500	500	500	500	500	500	500	500
2	Starch	27.2	23.2	19.2	27.2	23.2	19.2	27.2	23.2	19.2
3	Povidon K-30	30	30	30	30	30	30	30	30	30
4	SSG	12	16	20	-	-	-	-	-	-
5	Kollidon Cl	-	-	-	12	16	20	-	-	-
6	Croscarmallose sodium	-	-	-	-	-	-	12	16	20
7	Aerosil 200	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8
8	Magnesium stearate	6	6	6	6	6	6	6	6	6
	Total weight (mg)	578	578	578	578	578	578	578	578	578

The wet mass was dried in an oven for 30 min at 60^0 C. Again the dry mass was passed through a '16' mesh sieve to get smaller granules. The obtained small granules were mixed with Aerosil-200, remaining part of superdisintegrant and magnesium stearate to obtain granules with adequate flow property.

Evaluation of granules

The flow properties of the powder blend (before compression) were characterized in terms of angle of repose, Carr's index and Hausner's ratio. Angle of repose (θ) was measured by using the funnel method [6] and calculated by via the following equation:

$$\text{Tan } \theta = h/r$$

Bulk density (BD) and tapped density (TD) are the ratio of total mass of powder to the bulk and tapped volume of powder respectively. BD and TD were calculated using following equations.

BD = Weight of the powder/volume of the packing

TD = Weight of the powder/tapped volume of the packing

Compressibility index [7] of the powder blend and their Hausner's ratio [6] were determined using bulk density and tabbed density via following equations:

$$\text{Carr's index (\%)} = [(TD - BD) \times 100] / TD$$

$$\text{Hausner's ratio} = TD/BD$$

Compression of tablets

The blended granules were then compressed using single punch KBr-Press laboratory scale hydraulic press tablet machine to produce round flat faced tablets with a diameter of 13 mm. Compression stage was controlled enough to produce a 10-15 kg/cm^2 tablet crushing strength. Die and punch were lubricated each time before compression. Tablets of each batch were stored in airtight container at room temperature in a desiccators.

Evaluation of tablets

The prepared tablets were evaluated for quality control tests; hardness, thickness, diameter, friability, drug content, weight variation, *in vitro* dispersion time, *in vitro* disintegration time, *in vitro* wetting time and finally for *in vitro* dissolution studies. The results are summarized in the Table 3.

Thickness and diameter

The thickness and diameter of the tablets was measured using digital slide calipers and expressed in mm. Randomly selected 10 tablets of each batch were tested for thickness and diameter.

Tablet hardness

Hardness is the crushing strength of tablet which determines the ease of handling and rigors of

the transportation. Those 10 tablets that previously undergo thickness and diameter test were used in the study. The hardness of each tablet was determined by Monsanto hardness tester and expressed in kg/cm^2.

Weight variation test

Twenty tablets from each batch were individually weighed and their average weight was calculated. From the average weight of the prepared tablets, the standard deviation was determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Friabilator (Veego, India) was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. The tablets that undergo weight variation test were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dedusted and reweighed. The percent friability was measured using the formula:

$$\% F = \{1- (W_t/W)\} \times 100$$

Where, %F= friability in percentage

W = Initial weight of tablet

W_t = weight of tablet after revolution

***In vitro* disintegration time**

One tablet was placed in each of six tubes of the Electrolab disintegration tester ED-2L. The test was carried out in 800 ml of phosphate buffer of pH 6.8 at 37 ± 0.5^0C [6]. Average disintegration time of six tablets was determined.

Drug content determination

Drug content determination was performed as per method described by Sravani *et al.*, 2012 [8]. Ten tablets of each formulation were powdered by mortal-pestle. Grinded powder equivalent to 500 mg of Metformin HCl was weighed and transferred to 100 ml volumetric flask, initially about 50 ml of phosphate buffer 6.8 was added and the flask was shaken thoroughly and the volume was made up to 100 ml with the buffer solution. The resulting solution was filtered. From this 5 ml was taken and diluted to 100 ml. 2 ml of this solution was taken and diluted up to 100 ml. From the resulting solution drug content was estimated at 233 nm using UV spectrophotometer taking phosphate buffer as blank.

***In vitro* wetting time**

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of distilled water. A tablet was put on the paper and the time required for complete wetting was measured [9]. The experiment was done triplicate for each formulation.

***In vitro* dispersion time**

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 10 ml of pH 6.8 [9]. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was observed.

Preparation of dissolution media

1.19 gm of disodium hydrogen orthophosphate dihydrate ($Na_2HPO_4.2H_2O$) and 8.25 gm of potassium dihydrogen Orthophosphate (KH_2PO_4) were required to prepare 1 liter of phosphate buffer of pH 6.8. The required amounts of salts were accurately weighed, dissolved and the volume was adjusted to the required amount by distilled water. If necessary, the pH was attuned by using sodium hydroxide.

***In vitro* dissolution studies**

The *in vitro* dissolution study was carried out in dissolution test apparatus (USP XXII) Type 2 (paddle) using pH 6.8 phosphate buffer; 900 ml. The paddle rpm was maintained at 100 while the temperature maintained always at 37 ± 0.5^0C [10]. 10 ml aliquots were withdrawn at each 5 min interval up to 30 minutes and the volume was kept constant by replacing immediately the same amount with fresh dissolution medium to maintain the sink condition. The dissolution was carried out for 30 min. The aliquots were filtered, suitably diluted and analyzed at 233 nm using UV spectrophotometer (Shimadzu, Japan). The amount of drug release was calculated with the help of a straight line equation obtained from the standard curve of Metformin HCl at the same wavelength.

RESULTS AND DISCUSSION

Immediate release tablets of Metformin HCl were prepared with varying concentrations (2.08%, 2.77% and 3.46%) of three superdisintegrants: sodium starch glycolate, Kollidon CL, croscarmellose sodium (Table 1). Prior to compression of the tablets, the powder blends were subjected to various physical tests including determination of angle of repose, estimation of bulk density & tapped density and compressibility index of the blend. The angle of repose was determined by fixed funnel and free standing cone method [6]. Using bulk and tapped density data, Hausner's ratio and compressibility index were also calculated.

Flow properties of the powder, resistance to particle movement can be judged from the angle of repose. This measurement gives a qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external loading that might be applied in mixing and tabletting [11]. Values for angle of repose were found in the range of 27.47^0 to 34.56^0. This indicated to fairly good flow properties of the granules for all the formulations. The set of formulation containing Kollidon CL showed relatively uniform and lesser value of the angle. As per USP-33 NF 28 general chapter <1174> Powder Flow, an angle of repose of 25^0-30^0 indicates excellent flow property and 31^0-35^0 stands for good flow of materials. Therefore, all of the granules from each batch yielded a good to excellent flow characteristics.

Bulk densities of the blended powder mix were found in the range of 0.270-0.412 g/ml and the tapped densities between 0.322-0.533 g/ml. F1 & F7 gave the highest value of bulk density and again F7 showed highest value of tapped density (Table 2). By calculating the densities, Hausner's ratio was calculated for all the batches and found from 1.19 to 1.31. As per USP-33 NF 28 general chapter <1174> Powder Flow, Hausner's ratio ranging from 1.19 to 1.25 indicates fair flow and 1.26 to 1.34 refers to passable type of powder flow characteristics. Furthermore, from the Table 2, the granules of all the formulations gave a compressibility index ranging from 16.15% to 23.70%. A compressibility Index of greater than 25% is considered to be an indication of poor flow ability and below 15% an indication of good flowability of granules [3]. Thus the results obtained from the compressibility index indicated a reasonable flow property of the granules obtained for each batch. The findings also match with results of angle of repose and Hausner's ratio. Among the three sets of formulations, the group of Kollidon CL showed better flow property by having angle of repose below 30^0 and lower value of compressibility index. Whereas, those containing croscarmellose sodium as disintegrant (formulation F7, F8 and F9), showed relatively poor flow characteristics.

Table 2: Characterization of powdered blend.

Sl	Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Bulk density (g/ml)	0.412	0.396	0.380	0.380	0.317	0.270	0.412	0.400	0.396
2	Tapped density (g/ml)	0.501	0.487	0.465	0.456	0.387	0.322	0.533	0.512	0.519
3	Compressibility index (%)	17.76	18.69	18.28	16.67	18.09	16.15	22.70	21.88	23.70
4	Hausner's ratio	1.22	1.23	1.22	1.20	1.22	1.19	1.29	1.28	1.31
5	Angle of repose	29.25	32.62	30.96	27.47	29.25	29.26	34.25	33.89	34.56

The compressed tablets were assessed by different physical and analytical tests including thickness, diameter, hardness, friability, drug content, weight variation, *in vitro* dispersion time, *in vitro* disintegration time, *in vitro* wetting time and finally *in vitro* dissolution studies.

The description of tablets of each batch was simply the same as a white to off-white flat tablet. The thickness and diameter of all batches were found alike with little variation. Hardness of the tablets of different formulations varied slightly ranging from 11.42-11.93 kg/cm^2 that is an indication of good binding capacity of the granules (Table 3). Literally the average weight of the tablets of the different formulations should be 578 mg (Table 1). The average weight of the tablets was found remarkably consistent with the theoretical weight. From the Table 3, the tablets were found to have average weight within 576 mg to 579 mg. Correspondingly, friability of the tablets of different formulations remains within the acceptable range and were found in between 0.14% to 0.32%. It again indicates that the granules of each batch were capable of forming tight bonds and hence, become able to withstand shocks. Friability below 1% was an indication of good mechanical resistance of the tablets. [12]

Table 3: Characterization of Metformin HCl tablets.

Sl	Evaluation	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Thickness (mm)	3.22±0.1	3.30±0.1	3.41±0.1	3.42±0.1	3.69±0.0	3.46±0.1	3.36±0.1	3.46±0.1	3.67±0.0
2	Diameter(mm)	13.1±0.1	13.1±0.1	13.1±0.0	12.9±0.1	13.0±0.1	13.0±0.1	13.1±0.0	13.0±0.2	13.0±0.1
3	Hardness (kg/cm^2)	11.93±0.5	11.63±0.8	11.53±0.4	11.42±0.5	11.53±0.6	11.63±0.8	11.42±0.6	11.53±0.7	11.63±0.5
4	Weight variation (mg)	578±1.0	576±1.1	578±2.0	576±1.5	579±1.2	579±0.8	576±1.4	579±0.5	578±1.8
5	Friability (%)	0.22	0.26	0.25	0.17	0.14	0.15	0.19	0.32	0.27
6	Wetting time (min)	1.6±0.5	1.4±0.2	1.2±0.1	1.8±0.4	1.7±0.1	1.4±0.4	1.5±0.3	1.5±0.1	1.3±0.4
7	Dispersion time (min)	2.6±0.8	2.5±0.4	2.3±0.5	3.1±0.4	2.9±0.4	2.6±0.3	3.0±0.6	3.1±0.4	2.8±0.1
8	Drug content (%)	99.10%	98.45%	99.24%	99.02%	98.67%	98.79%	99.39%	98.98%	99.01%

In vitro wetting time is an important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water[12]. The wetting time were found to be in the range of 1.2 to 1.8 min. Among all the designed formulations, formulation F3 was found to be promising and displayed an *in vitro* wetting time of 1.2±0.4 min, which facilitates faster dispersion and induction of swelling by the disintegrant. *In vitro* dispersion is another special parameter in which the time taken by the tablet to produce complete dispersion is measured. The time for all the nine formulations varied between 2.3 to 3.1 min. Tablets were prepared of sodium starch glycolate showed faster dispersion time when compared to those made of Kollindon CL and croscarmellose sodium. The lower value of wetting time may contribute to the quick dispersion time of the formulation F3. Lower wetting time makes the tablet granules possible to be wetted and allow the polymer to swell remarkably and hence, the disintegration time has also been reduced. In the drug content analysis, all the formulations revealed good uniformity and had yielded results from 98.45% to 99.39% of the theoretical claim.

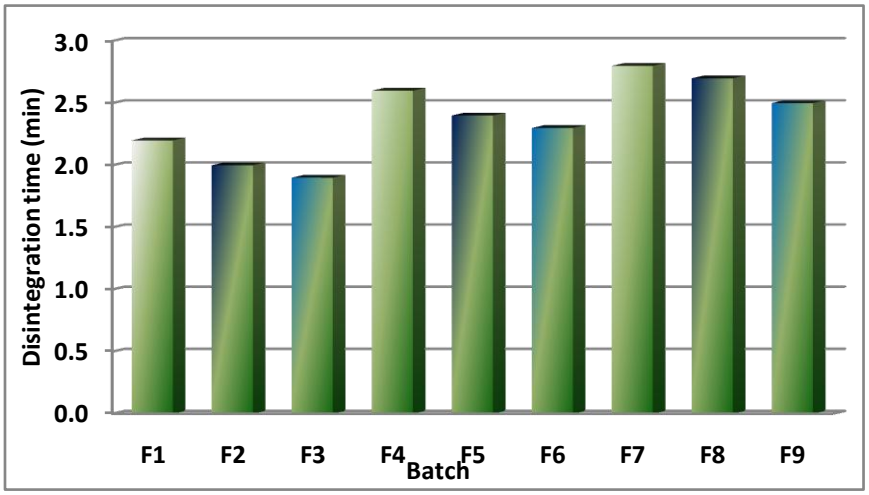

Figure 1: Disintegration time (min) of tablets of different formulations of Metformin HCl.

The *in vitro* disintegration time of all nine formulations were found within only 3 min (Figure 1). Formulation F3 containing 3.46% sodium starch glycolate was found to have lowest disintegration time of 1.9 min. Lower wetting time and quick dispersion time of the formulation might contribute to the faster disintegration of tablet. Each set of formulation showed a gradual decrease in disintegration time on incorporating higher amount of disintegrant. Using Kollidon CL at the ratio of 2.08% showed at disintegration time of 2.6 min, 2.77% concentration produced 2.4 min and finally concentration of 3.46% turned out a DT of 2.3 min. Parallel scenario was demonstrated by formulations of croscarmellose sodium; F7, F8 and F9 produced a disintegration time of 2.8, 2.7 and 2.5 min respectively. Sodium starch glycolate showed the lowest values of disintegration time in all three ratios. It might be due to the higher swelling characteristics of sodium starch glycolate compared to Kollidon CL and croscarmellose sodium.

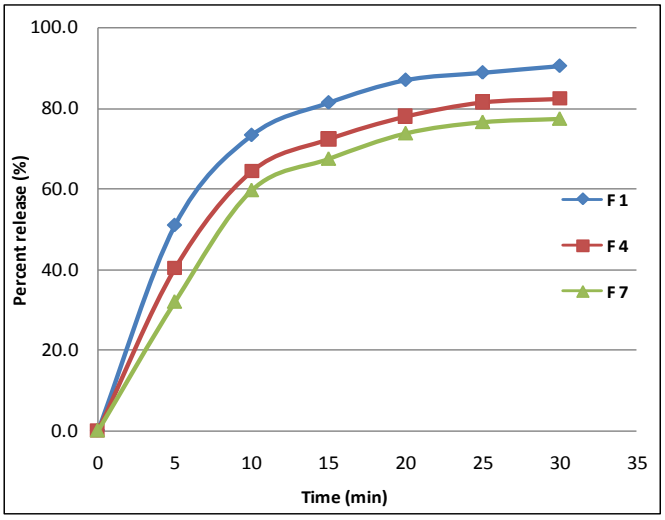

Figure 2: Percent drug release from formulation F1, F4 and F7 containing different superdisintegrants 12 mg per tablet.

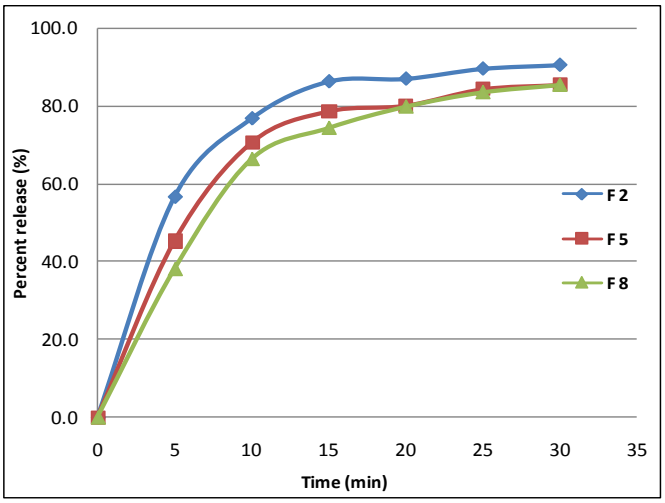

Figure 3: Percent drug release from formulation F2, F5 and F8 containing different superdisintegrants 16 mg per tablet.

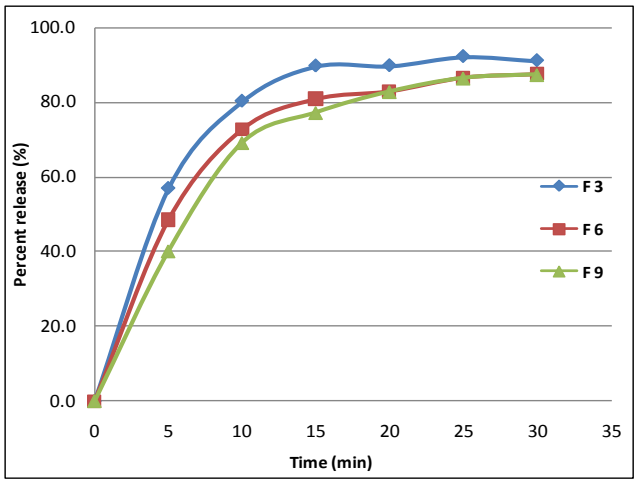

Figure 4: Percent drug release from formulation F3, F6 and F9 containing different superdisintegrants 20 mg per tablet.

To explore the effect of superdisintegrants on release pattern of the formulations, six tablets of each batch were undertaken to *in vitro* dissolution study (Figure 2, 3 and 4). A gradual increase in the percent release of the tablets was revealed upon addition of more disintegrating agents. Formulation F4, F5 and F6 were found to release 82.47%, 85.63% and 87.63% of incorporated drug on account of having 2.08%, 2.77% and 3.46% Kollidon CL in the formulation. The higher extent of drug release might be resulted from faster wetting time, quick disintegration time and rapid dispersion time achieved by the greater amount of polymer. Among the three groups of formulations, tablets made of sodium starch glycolate showed higher drug release at each incorporated ratio. Kollidon Cl might take the second position in terms of drug release but showed similar efficacy to croscarmellose sodium when used at higher ratio. 82.46% and 77.38% drug release were obtained by using Kollidon CL and croscarmellose sodium at 16 mg per tablet

ratio (F4 and F7); while 87.63 % and 87.39% drug release were found using them 20 mg per tablet (F6 and F9). However, it seems that Kollidon CL is relatively more effective than croscarmellose sodium when incorporated at lower ratio.

From the accumulated data on *in vitro* wetting time, dispersion time, disintegration time and dissolution study, a comparison between the three superdisintegrants can be drawn. At each concentration ratio, sodium starch glycolate has been proven most successful in every testing parameter. Remarkable swelling capacity in water probably makes it capable of rapid disintegration. It swells to up to 300 times of its volume [13]. Other contributing factors for rapid disintegration are the swelling pressure & volume of disintegrant, hydrophilic behavior, available pores within the tablet & their sizes, water absorbing rate & capacity, mechanical properties of the tablet and properties of other excipients used.

Kollidon CL on the other hand, is a cross linked water insoluble polivinylpyrrolodone that act as disintegrant by absorbing water and subsequent swelling. And croscarmellose sodium is a cross linked polymer of carboxy methyl cellulose sodium. It is insoluble in water but rapidly swells to 4-8 times of its original volume on contact with water. To conclude, it can be summarized that though the all three superdisintegrants act by rapid water intake and swelling, speed of disintegration not only depend on swelling but other factors mentioned above can play significant role. However, based on the various parameters, the sequence of efficiency as disintegrant can be expressed as per below order:

Sodium starch glycolate>Kollidon CL >croscarmellose sodium

CONCLUSION

With an aim to find out a suitable disintegrant for immediate release tablets of Metformin HCl, different formulations were prepared by wet granulation technique having different proportions of both intra and extra granular superdisintegrants. The disintegrants were found to influence various properties of tablet such as wetting time, dispersion time and disintegration time. Disintegration time was found governed by type and quantity of superdisintegrants. Disintegration time was decreased with the increase of disintegrant content in the formulation. Similarly high concentration of superdisintegrants caused high percentage of drug release from the tablet. All three superdisintegrants were found capable of preparing pharmaceutical equivalent dosage form that meet the pharmacopial requirements. Sodium starch glycolate was found most effective in reducing disintegration time and improving dissolution of drug in consequence.

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