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Microcrystalline Cellulose isolated from Rami (*Boehmeria nivea* L. Gaud) used as a disintegrant in Dimenhydrinate tablets

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ABSTRACT

Microcrystalline cellulose was isolated from rami (Boehmeria Nivea L. Gaud), and applied as disintegrant in tablets of dimenhydrinate, made by direct compression and wet granulation. The aim of this study is to produce dimenhydrinate tablets with Microcrystalline Cellulose Rami (MCC Rami) isolated from Rami (Boehmeria Nivea L. Gaud), as a disintegrant and assess the effect of MCC Rami and Granulation technique on physical properties of drug such as, disintegration time, drug release and dissolution. Formulations of dimenhydrinate 100mg tablets were prepared with a combination of mannitol and lactose as a filler and MCC Rami as disintegrant in a concentration of 10-20%. The formulas were directly compressed or were compressed into tablets after wet granulation. The mechanical properties, drug release, physical properties and effects of process parameters, methods of applying disintegrant in tablet formulas were examined. A significant difference in disintegration time of tablets that were produced by direct compression and wet granulation was seen, that can be attributed to the porous structure of granules that enhanced fast disintegration, which had eventually improved dissolution and drug release. F1 and F2 with MCC Rami and physical mixture of MCC Rami with crosspovidone as a disintegrant that were directly compressed disintegrated in 79 and 72 seconds respectively thats not a significant difference, however when MCC was applied in an intragranular way its disintegration time is 67 seconds. The results showed that the method of disintegrant application and press of tableting has a significant effect on drug release and dissolution.

Keywords: Microcrystalline Cellulose, wet granulation, disintegrant, *Boehmeria Nivea* L. Gaud.

1. Introduction

Microcrystalline cellulose (MCC) is so versatile that has a widespread application in many fields from food to pharmaceuticals. MCC is becoming more popular now because of its increasing number of alternatives made by co-processing it or either making bio-composites of MCC (1). In pharmaceutical department it has been considered for last fifty years as diluent in direct compression (DC) of tablets, its compactibility, tabletability, easy supply, inertness, compatibility and availability makes it popular. MCC is a partially depolymerized cellulose that is achieved by acid application on cellulose obtained from fibrous plants and wood (2). There are a number of studies that have prepared MCC from different raw materials but all of them have used the same method of acidic hydrolysis; such as Dutta Kalita et al have extracted microcrystalline cellulose from fodder grass that is very cheap and environmental friendly and has applied as a drug delivery vehicle for isoniazid (3). Kale et

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al also reported ectraction of microcrystalline cellulose from cotton silver (4).

MCC is mostly applied as a filler in tableting due to its good binding properties it is a preferred filler for direct compression, moreover it has self-disintegrating properties although it doesn't take away the need of using a disintegrant but it can promote disintegration (5). Therefore, the disintegrating properties of MCC has been neglected that we aim to assess in current study. However, studies have shown that combining MCC with superdisintegrants have complementary effects on enhancing disintegration (6). MCC has high porosity that gives a surface area of 90-95% approximately (7), that would promote disintegration by swelling and the penetration of water into the hydrophilic tablet matrix with help of capillary action of the pores (8).

Disintegration properties of tablet can be improved by different process methods, one of which is wet granulation as it creates granules that are porous and will help in water uptake that will improve disintegration of tablets, that was studied by Ramana et al in producing pioglitazone fast disintegrating tablets (9). Despite of the increased focus and in the area of targeted drug delivery system in recent years, tablet dosage forms that are intended to be swallowed whole, disintegrate, and release their medicaments rapidly in the gastrointestinal tract still remain the formulation of choice from both a manufacturing as well as a patient acceptability point of view (10). Thus, a drug given in the form of a tablet must undergo dissolution before being absorbed and eventually transported into systemic circulation. For most of the tablet dosage forms, disintegration precedes drug dissolution. MCC is economical and is used in large batches of tablet production by DC, it is one of the best tablet diluents, and thus we try to explore its disintegration properties as well that will eventually promote better drug dissolution.

2. Method

2.1 Material and Instrument

Dimenhydrinate (Central Laboratory, UNPAD), Lactose (Formulasi dan Teknologi Farmasetika LAB), Mannitol, Microcrystalline Cellulose Rami (MCC Rami was prepared in Central Lab UNPAD), Crosspovidone (JRS Pharma), Tapped density tester (Erweka SVM 221) Rotary Tableting Machine, Dissolution Tester (Zotax), Disintegration tester (Metlertoledo), Hardness Tester (Metlertoledo), Friability Tester (Erweka).

2.2 Preformulation parameter study

Physical properties of Isolated MCC from Rami and its prepared co-processed disintegrant and formulation of tablets were studied by evaluating Angle of repose, Tapped and bulk density, Hausner's Ratio and Carr's Index by procedures given below (11);

2.3 Angle of repose

Flowing properties of Isolated MCC from Rami and its prepared co-processed disintegrant were evaluated with help of Flow Rate analyzer Metler Toledo. The sample was poured through the funnel until the apex of the conical pile touched the tip of the funnel. The angle of repose was calculated using the formula tan **α** = H/R, where **α** is the angle of repose and R is the radius of the conical pile.

Table 1. Angle of repose and flow properties of powder

Flow property	Angle of Repose (Degrees)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very Poor	56-65
Very, very Poor	>66

2.4 Determination of tapped and bulk density, Hausner's Ratio and Carr's index

The powder property tester was used to determine the bulk (ρb) and tapped (ρta) densities for the compressibility studies. Compressiblity was reflected by Hausner ratio. Bulk density was measured by pouring samples through a vibrating metal funnel into a measuring cylinder until it was full. The

volume of the cylinder was exactly 100 cm^3 and pre-weighted as m_0.

$$\rho ta = m_2 - m_0 /100 \qquad (1)$$

After the excessive powder was scraped off, the weight of the cylinder containing powder was recorded as m1. The bulk density was calculated by Eq.1 ρb ¼ m1 m_0 (1)Tap density was obtained by pouring more samples into the cylinder until an appropriate height with aid of a glass sleeve. Tapping was carried out for 5 min. After the excessive powder was scraped off, the weight of the cylinder containing sample was recorded as m2. The tap density and Hausner ratio were calculated by Eqs.1 and 2, respectively (12).

$$\rho b = m_2 - m_0 /100 \qquad (2)$$

Carr's 'percent compressibility and the Hausner ratio were calculated using the equation Dt – Db/Dt x 100 and t/ b respectively. t and b are respectively the tapped and bulk densities (13).

Table 2. Carr's Index value

Carr's Index (%)	Type of flow
5-15	Excellent
12-18	Good
18-23	Fair to passable
23-35	Poor
35-38	Very poor
>40	Extremely poor

2.5 Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Hausner ratio} = Dt/Db$$

Where, Dt is the tapped density, and Db is the bulk volume. The inter relationship between angle of repose and flow properties of powders is shown in table 3.

2.6 Preparation of dimenhydrinate Tablets

Tablets containing 100 mg of dimenhydrinate were prepared by direct compression and wet granulation method and the various formulas used in the study are shown in the table 4. For direct compression the required amounts were weighed and mixed well and directly compressed. For wet granulation the drug and diluent, disintegrant (and superdisintegrant) in required quantities and properly mixed and granules were prepared by using ethanol as a binder solution (14). The cohesive mass was passed through mesh number 20 and dried at temperature of 40˚C in oven. The dried mass was sieved. Then lubricants and glidants (Magnesium stearate, and talc) were added mixed well and then compressed into tablets. The tablets were prepared by rotary die compression machine (15).

2.7 Evaluation of prepared tablets (post-compression parameters)

2.7.1 Weight variation and Tablet Hardness and thickness

The formulated tablets were tested for weight uniformity, hardness and thickness. For this 20 tablets were weighed individually in metller toledo chemical balance. Thickness and hardness of tablets was measured using Metller Toledo hardness tester. The mean and Standard Deviation of hardness values were calculated (16).

2.7.2 Friability

Friability of the tablets was determined by using Metller Toledo friabilator. The weight of 20 tablets (initial weight) was subjected to friabilator at 25 revolutions per 4 min. Tablets were then dedusted, reweighed (final weight) and percentage loss was calculated (17).

Friability is obtained by the following formula:

$$\%\text{friability} = \text{Initial weight} - \text{Final weight} / \text{Initial weight} * 100$$

Table 3. Hausner ratio

Hausner ratio	Type of flow
<1.25	Good
1.25-1.5	Moderate
>1.5	Poor

2.7.3 Wetting time and Water Absorption Ratio

A double folded tissue paper was placed in a Petri dish. 10 mL of water containing a water-soluble dye was added to the Petri dish. A tablet (pre-weighed) was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time. The wetted tablet was then weighed and the water absorption ratio (R) was determined by using the equation:

$$R = (Wb-Wa) / Wb *100 \quad (3)$$

Where Wa and Wb are the weights of tablet before (dry weight) and after water absorption (wet weight) respectively (18).

Table 4: Formulation of Dimenhydrinate Tablets

Ingredients (mg)	F1*	F2**	F3***
Dimenhydrinate	100	100	100
Mannitol	100	100	100
PVP	15	10	40
MCC Rami	30	30	30
Crosspovidone	-	-	3
Talc	3	2	3
Mg stearate	2	2	2
Flavorant	1	1	1
Lactose	q.s to 600mg	q.s to 600mg	q.s to 600mg

*Directly compressed, ** MCC Rami with Crosspovidone applied intragranularly in Tablets, *** Physical mixture of MCC Rami with Crosspovidone directly compressed.

2.7.4 In vitro Disintegration Study

The disintegration time of tablet was determined using disintegration apparatus in distilled water as disintegration medium maintained at 37˚C. When all the six tablets are completely disintegrated, the time was noted (19).

2.7.5 Determination of maximum absorption wavelength of Dimenhydrinate

Maximum absorption wavelength (λ max) for dimenhydrinate, a 10µg/ml solution of dimenhydrinate was prepared in Simulated Gastric Fluids later its absorbance would be determined by UV spectrophotometer (16).

2.7.6 Calibration Curve

Calibration Curve of dimenhydrinate was prepared in Simulated Gastric Fluids (Hydrochloric acid buffer pH 1.2) with concentrations from 10µg/ml until 30µg/ml. After recording λ max calibration curve was drawn in Excel program (20).

2.7.7 In vitro Dissolution Study

Dissolution studies were conducted to determine the release pattern of the drug from the product. Dissolution test for dimenhydrinate tablet was carried out as per USP method for dissolution test for tablets and capsules using apparatus II (paddle type). Dissolution medium used was 900 mL of SGF, agitation speed at 50 rpm at 37±0.5˚C. An aliquot sample of 5 mL was withdrawn at different time periods and replaced with fresh medium. These samples were filtered and diluted suitably. Absorbance of the resulting solution was measured at 267 nm. Percentage cumulative drug release was calculated (21).

3. Results

3.1 Flow Properties

Microcrystalline cellulose was isolated from fiber of *Boehmeria Nivea* L. Gaud called Rami in Indonesia. MCC Rami used was available in Faculty of Pharmacy, Universitas Padjadjaran that was isolated and characterized before (22), since flow properties are of significance in

uniformity of tablets mass, we further evaluated the flow properties of MCC Rami and Formulations intended to be directly compressed in to tablets, the results are given in table 5. Results revealed that F1 and F2 have angle of repose 36 and 30, Carr's Index 37.7 and 35.8, Hausner's ratio 1.41 and 1.55 that shows they doesn't have good flow properties that come in range of poor to moderate, therefore in direct compression there were some problems thus we intend to granulate the formulas first and then compress them into tablets.

Table 5: Flow Properties (n=3)

Parameters	MCCRami	F1	F2
OD	6.4%	-	-
Bulk Density	0.4g/cm^3	0.52g/cm^3	0.377g/cm^3
Tapped Density	0.5g/cm^3	0.83g/cm^3	0.588g/cm^3
Hausner Ratio	1.25	1.41	1.55
Carr's Index	20	37.7	35.8
Angle of Repose	24	36	30

3.2 Evaluation of Tablets

3.2.1 Weight variation and Hardness

Results of tablets weight uniformity, thickness and hardness are in acceptable range.

3.2.2 Wetting time and water absorption ratio

They show the capacity of disintegrant that how much water it can take into tablet, where water absorption ratio was 17% for tablets with MCC Rami as a disintegrant, and increased to 25% when MCC Rami was applied intragranularly and further increased to 27% when physical mixture of MCC Rami is used with Crosspovidone. Wetting time results were the same it decreased from MCC Rami to PM of Crosspovidone and MCC Rami.

3.2.3 Disintegration Time

F1 and F2 with MCC Rami as a disintegrant have disintegration time of 79 and 72 seconds respectively that is considered a very good disintegration time, as shown in table 6.

Table 6: Tablet Characterization (n=3)

Parameters	F1*	F2**	F3 ***
Weight variation(mg)	595±3	611±3	598±8.6
Thickness(mm)	5±0.03	5±0.03	5.10±0.03
Hardness(N)	45.50±8	65.70±4	44.85±7
Diameter (mm)	13±0.01	13±0.01	13.02±0.02
Friability%	13%	3%	0.7%
Disintegration(s)	79 ±24	72s ±11	67s ±13
Waterabsorption ratio%	17%	25%	24%
Wetting time (s)	79s	72s	78s

*Directly compressed, ** Physical mixture of MCC Rami with Crosspovidone directly compressed, *** MCC Rami with Crosspovidone applied intragranularly in Tablet

3.2.4 In-Vitro Dissolution Test Results

Maximum absorption wavelength of dimenhydrinate was determined in SGF, that was 267nm for dimenhydrinate. Standard calibration curve was prepared in the same media that is shown in figure 1. As shown in figure 2, 80% of the drug is released in 10 minutes.

Microcrystalline cellulose shows promising properties of disintegration. According to USP and BP for conventional tablets acceptable disintegration time is 15 minutes and for dispersible tablets is less than 3 minutes. Since

disintegration time of dimenhydrinate tablet with MCC Rami as a disintegrant is 79 seconds that's even less than 3 minutes for dispersible tablets, it reveals good disintegration properties of MCC Rami and it can be used even in dispersible tablets. In order to compare the disintegration effect of MCC with crosspovidone in F3 a physical mixture of both was applied in a ratio of 10:1 respectively.

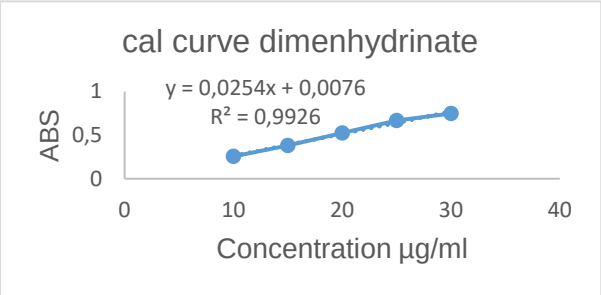

Figure 1: Calibration curve of Dimenhydrinate in Gastric media

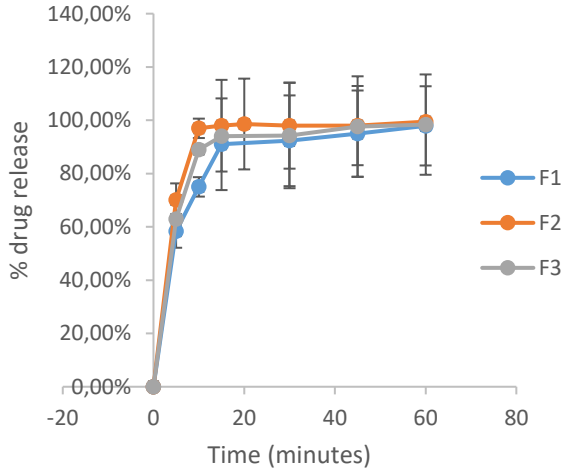

Figure 2: Cumulative drug release

Disscusion

On the basis of results shown in table 6 disintegration time decreased that is attributed to addition of crosspovidone that increases water uptake, swells and tends to disintegrate fast. This result is in consistence with work done by Setty as they also concluded that disintegration time was decreased if tablets were produced by wet granulation due to having porous structure that was further decreased by using superdisintegrant (23). Disintegration time for tablet with crosspovidone in Setty et al was 12s because they had used 25mg crosspovidone per tablet which is quite high quantity in comparison to our study where crosspovidone is just 2% of formulation 3mg and disintegration time is 67s that is a good disintegration time for conventional tablets. In the same research article one formula was produced with microcrystalline cellulose 78mg/tablet as a diluent with a mixture of mannitol that is quite similar to formualtions used in our study without any superdisintegrant, and disintegration time was 3minutes, and hence if we compare the disintegration of MCC Rami with Microcrystalline Cellulose used in study done by Setty et al shows much better properties as a disintegrant.

Another study by Ramana et al, reported formulation of pioglitazone fast disintegrating tablets prepared by direct compression and wet granulation, where one of the superdisintegrant applied was crosspovidone that were similar to our study, and formula with 6mg of crosspovidone per tablet that was directly compressed had disintegration time of 69seconds less than formulas done by wet granulation that is 45 seconds (9). So it can be seen that wet granulation can have significant effects on tablet disintegration.

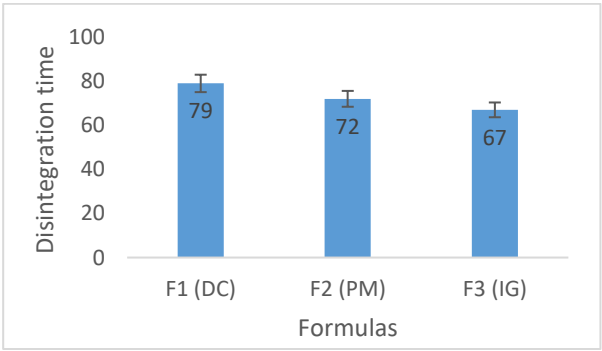

Figure 3: Disintegration time

According to USP tolerance for dimenhydrinate dissolution test results is not less than 75% of the labeled amount is dissolved in 45 minutes and in the figure we can see that 80% of drug is release in course of 10minutes, thus we can conclude that because of low disintegration time drug dissolution can be enhanced that would resultantly increase the bioavailability of drug (10).

4. Conclusion

It is concluded from the current study that Microcrystalline Cellulose Rami (MCC Rami) has appreciable disintegrant properties that can be even applied in dispersible tablets due to its fast disintegration properties that happens in less than one and half minute. Moreover, wet granulation is a good technique to overcome preformulation problems and can contribute to better disintegration due to porous structure of granules that will eventually enhance the dissolution and bioavailability of drug, as shown in the results where disintegration time of F3 is 78s, although for immediate release tablets disintegration time can be up to 15min. Further research is needed to assess the disintegration properties of MCC Rami.

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