A review: Pharmaceutical excipients of solid dosage forms and characterizations

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Article History:
Received on: 20.09.2019
Revised on: 15.12.2019
Accepted on: 21.12.2019

Keywords:
Solid Dosage Form, Excipients, Functions, Characteristics

ABSTRACT
Excipients play an important role in formulating dosage forms. Exertion is empowered to help manufacture, provide, or collect dosage forms. Although considered pharmacological, excipients may consider a drug, due to chemical or physical interactions with the composition of the drug. Excipients have many functions in pharmaceutical dosage forms, including enhancing active ingredients in dosage forms, assisting active ingredients, disintegration, lubricants, binders, and suppliers. Each excipient has different characteristics. In this review, a library of studies is provided relating to the function, and content of solid excipients in a solid dosage form. Various choices can be used on different compositions; resulting, this difference is also different. In this example, describe the types of excipients that can be used for various components in solid preparations that can be used in the formulation of solid preparations and select the right type of excipient according to the character of the desired solid preparation. In this review also presented a method combining in and characterizing solid excipients to find out its quality. The most commonly used methods for analysis of solid excipients are flow properties, compressibility index, Hausner index ratios, and angle of repose, while the instrumentation commonly used is Fourier transform infrared spectroscopy (FTIR), H and C-Nucleo magnetic resonance (H-CNMR), scanning electron microscopy (SEM), Particle size analysis (PSA), X-ray diffraction (XRDP) and differential scanning calorimeter (DSC).

INTRODUCTION
Excipients in pharmaceuticals are substances other than the pharmacologically active drug or active ingredients that are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form. The excipient has many functions in the form of a pharmaceutical preparation, including solubility modulation & API bioavailability, enhancing the stability of active ingredient in the dosage forms, helping the active ingredient maintains preferred polymorphic forms or conformations, disintegrant, lubricant, binder, and filler. In selecting pharmaceutical excipients, dosage forms and drug products the excipient must have a
standard to assure the consistent quality and functioning of the excipient. In the solid dosage form, the drug is in intimate contact with one or more excipient; the latter may affect the stability of the drug. Knowledge of drug excipient interaction is very useful for formulators in choosing the right excipients. This information may already exist for known drugs (Patel et al., 2011).

Excipients are not pure. It virtually of minerals, synthetic, semi-synthetic or natural manufacture involves the use of starting materials, reagents, and solvents. (Fathima et al., 2011). Excipient similarity tests permit us to decide excipient interactions that can be either kept away from or can be adjusted to use in an effective way, which helps in limiting the hazard related to the excipients. Excipient determination must be finished on the premise of qualities an excipient offers. An excipient must be chemically steady, non-responsive, low hardware and process sensitive, inert to the human body, non-toxic, acceptable as to organoleptic attributes, economical, and having effectiveness in respects with the expected utilize (Madhav et al., 2017).

**Binding agents (Binder)**

The binding agent (Binder) is the material necessary to maintain the strength structure of the tablet preparations required during the manufacturing process until packaging. The binding agent will increase the tablet’s inter particulate bonding strength (Shailendra et al., 2012). The binding agent works by improving the flow qualities for granule formulation with the desired hardness and size. Examples of these binding agents are Acacia, Carboxymethylcellulose, gelatin, polyvinylpyrrolidone, povidone, and starch paste (Chaudhari and Patil, 2012).

Historically on the development of new drug products, formulations containing the original corn starch are widely used as both binding and disintegrating agents in paste form. Due to flow and compressibility problems, it is necessary to examine alternative excipients and other combined excipients (Labella and McDougal, 2006). Different binding agents can produce various mechanical strengths of tablets and drug release properties, depending on the intended use. Natural polysaccharides are also used as excipients widely in the pharmaceutical industry because they have low toxicity, biodegradable, safer, and economical. Starch, mucilage, gum, and also dried fruits have several other properties such as disintegrant, filler, and sustained release other than as binding agents, and they also used to modify drug release so they can affect the bioavailability of the introduced drug and its absorption, acting as a vehicle transporting the drug incorporated into the absorption site, as well as to ensure the accuracy and precision of the dose, the stability, and to enhance the organoleptic properties of the drug thus improving patient compliance (Pfiferi et al., 1999).

Haroon Rahim et al., in his research in 2014, evaluated the potential binder in the Na Diclofenact tablets formulation by wet granulation method. The binder used is Gum Prunus domestica and PVP K30 as standard. Evaluation is done in the form of examination of powder flow properties such as Carr Index, density, tapped density, Hausner ratio, rest angle as tablet compression’s physical parameters that are in the form of hardness, fragility, thickness and time of disintegration. The characterization performed in the form of analysis using FTIR spectroscopy shows that the formulations containing Gum correspond to other drugs and excipients used in tablet formulations, so it can be concluded that this plant is a potential binder and is better than PVP K30 (Rahim et al., 2014).

Synthesis polymers are widely used as bonding agents. However, its use has several disadvantages, which can cause difficulties in the manufacturing process, sometimes causing the hardening of the tablets. Besides, the strong disintegrant addition is no longer used as it should (Shailendra et al., 2012). The bonding properties of this binding agent have various parameters, one of which is the compression parameter of the powder material and its formulation, which can be explained using Heckel and Kawakita equations. Bond strength size, tensile strength (T), and fragile index (tablet fragility level) are the characterization used in addition to compression properties (Odeku and Itiola, 2002).

In a study conducted by Odeku and Itiola, they characterized the nature of the binding agent Khaya Gum comparing with the characterization profiles of Polyvinylpyrrolidone (PVP) and Gelatin on PCT tablets. The result of the test is that Khaya Gum has better formulation characterization in its use as a commercial binding agent because it also has a destructive activity of microorganism contaminants (Odeku and Itiola, 2002). Albizia gum is claimed as one of the binding agents that can improve the ingredient’s softness, provide higher plasticity, and has a greater reduction in the viability of Bacillus subtilis spores, compared with gelatin. Tablets that contain Albizia gum were also found to have higher tensile strength than tablets that contain synthetic binding gels, resulting in tablets with good mechanical strength (Ayorinde et al., 2011).

Types of characteristics that can be performed on
binding agents in solid preparations are Hardness, Tensile strength, friability, compressibility, dissolution profile, disintegration time, and conformity analysis of the binder agent with the drug or substrate. Compressibility power can be explained by this equation,

\[
\% \text{ Index of Carr} = \frac{TD - BD}{TD} \times 100\%
\]

\[
The \text{ ratio of Hausner} = \frac{TD}{BD} \times 100\%
\]

Where, Tapped density (TD) is density after the process of tapping as much as 50 times from its initial mass, whereas Bulk density (BD) is the bulk mass density (Enauyatifard et al., 2012). Stephen O. Majekodunmi and Stanley Makper conducted a study of the content of the binding agent Raphia hookeri Gum on PCT tablets. The flow index indicates that Raphia hookeri Gum has no better flow properties than gelatin, but is still within acceptable limits on Carr’s Index and Hausner ratios. However, in terms of tablet strength, tablets with Raphia hookeri Gum, when compared to gelatin-containing tablets as binding agents, have longer disintegration times, less fragility, and also have better mechanical properties (Majekodunmi and Makper, 2016).

Jena et al. in a research in 2014 also characterizes the Gum Odina binder agent, which determines the percentage of purification results (70%), pH determination (4.68) using pH meter, Swelling Index (S = 6), and percentage of water solubility (70%). Evaluations were also performed on Gum Odina, including using FTIR on pre-compression evaluation, microscopic studies, and Postnostic evaluation, such as disintegration time, drug release kinetics, friability, hardness, in vitro dissolution test, thickness, and weight variation. The evaluation result is Gum Odina has better characterization value compared to the use of Starch so that the required usage is also less than the use of Starch as the binding agent (Jena et al., 2014).

Disintegrant

Disintegrator or super disintegrant is one of the tablet excipients that serves as a tablet-breaking agent when entering the digestive tract (Table 1). Examples of disintegrant include starch-based or cellulose-based excipient (e.g., microcrystalline cellulose), sodium starch glycolate (SSG) tab, crospovidone. SSG and crospovidone are examples of super disintegrant, the disintegrant that has been developed with structural modification (Desai et al., 2012).

Good disintegrant characteristics include, not having a tendency to form complexes with drugs in tablet, have good hydration capacity, have good compressibility and flow ability. For disintegrant to work properly, the desired concentration of disintegrant, type of disintegrant and tablet hardness should be considered (Varma, 2016).

Potato starch is one of the common excipient used as a disintegrant and filler agent. Potato starch is commonly used as a disintegrant with a concentration of 3-15%. High compression pressure will cause the tablets are formed more compact so that when the tablets enter the digestive tract, the power to swell the tablet will be higher. Swelling high by tablet also causes the tablet to have a high dissolution rate (Szabo-Revesz et al., 2009).

SSG has synonyms include primojel, explotab, or sodium carboxyl methyl starch. Description of SSG is white to colorless, odorless, tasteless, the powder easily flowing, and consist of oval or round shape granules. SSG is stored in sealed containers to avoid caking. (Edge et al., 2002). SSG is commonly used as a disintegrant in tablet and capsule formulation with a concentration of 2-8% (Varma, 2016).

SSG can be synthesized from potato starch by crosslinking with starch esterification agent (e.g., sodium trimethaphosphate or phosphorus oxychloride in alkaline suspension). A large number of hydrophilic carboxymethyl group introduction aims to disrupt the hydrogen bonds in the structure. It is thus allowing the polymer to absorb more water without forming a gel that can slow the dissolution rate (Mohanachandran et al., 2011).

To identify the truth of material, it is necessary to test to see the difference of each material of the characteristic. The test can be done by checking the organoleptic materials, characterization of granules with SEM (scanning Electron Micrograph) (Abegunde et al., 2013), X-ray diffraction and particle size distribution (Szepes et al., 2014), H and C NMR, FT-IR Spectroscopy. The following is an example of characterizing various starch and SSG using SEM (Figures 1 and 2)

Lubricant

Lubricants are active substances added in the formulation to curb friction occurring in the manufacturing process. Lubrication is often used to reduce friction between manufacturing landing surfaces and organic solids in the formulation process such as mixing, roller compaction, tablet making, and tablet filling. Lubricants are substances added in pharmaceutical preparations such as tablets and capsules in very small amounts (typically 0.25% -5.0%, w/w)
Table 1: Disintegration versus super disintegrant

| Type of Disintegrant | Advantages                                                                 | Disadvantage                                                                 |
|---------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Disintegrant (starch) | Commonly used multifunctional excipient                                     | Unstable in high temperature in high concentration increase the fragility (Hartesi et al., 2016). |
|                     | Stable in dry form and will last a long time                                |                                                                              |
| Superdisintegrant (SSG) | Rapid disintegration does not form agglomerate during the disintegration generally compatible with other excipients (Mohanachandran et al., 2011). | Tablets are fragile tablet easily degraded by temperature, humidity (Immadi et al., 2017). |

Figure 1: SEM starch granules from various cultivars show diversity of shapes and sizes. (A) Muxuan no.1 (x3500); (B) Xicheng shu 007(x1000); (C) Xushu 28 (x600); (D) Xushu 18 (x3500); (E) Chuan shu 34 (x3500); (F) Xushu 27 (x1000); (G) Xushu 27 (x600); (H) Shi 5 (x3500).

Figure 2: results of SEM type of SSG: (A) explotab; (B) primioge; (C) vivastar P
to improve the powder formulation properties of the powder. Lubricants also serve to reduce shear stress and reduce internal friction between powder particles (Li and Wu, 2014).

Lubricants are one type of pharmaceutical excipient which is useful to improve the quality and efficiency of making solid dosage. This is due to its characteristics that can serve to improve fluidity, filling properties, as well as to prevent powder adhesion. In general, the use of hydrophobic lubricants is more effective than hydrophilic lubricants. However, the use of hydrophobic lubricants may also alter the physicochemical properties of tablets, such as tablet hardness, tablet disintegration time, and drug release. It also has an impact on the lubrication process that occurs. The lubrication process is a combination of factors that include the lubricant used, the formulation process and the mechanical process to produce the final dosage form (Bastos et al., 2008).

Lubricants are one type of pharmaceutical excipient, which is Sodium stearyl fumarate is one type of lubricant that is effectively used regards dosage tablets. Sodium stearyl fumarate used as much as 0.5 - 1.5% in the formulation can produce good flow properties. Outside the 1.5% lubricant concentration, the powder flow properties in terms of compressibility index are found to be poor. Tablets containing sodium stearyl fumarate have a smaller impact on violent variations. Similarly, sodium stearyl fumarate tablets have less disintegration time and release the drug faster than magnesium stearate and talcum. Besides, sodium stearyl fumarate is inert, hydrophilic lubricant for all forms of dense oral dosage and plays a very important role in all types of immediate-release preparations, oral disintegrating and mouth dissolving tablets (Abhishek, 2013).

Magnesium stearate is one of the most commonly used lubricants in pharmaceutical tablets preparation formulations. This is due to the hydrophobic lubricant properties and its ability to reduce friction between tablets and dead walls during the ejection process. The usual concentration is 0.25 - 5%. It appears in the form of different crystals, showing the size and shape of different particles, and occurs in some form of hydrate (Kanher et al., 2017).

Magnesium stearate has a form of crystal plates or often called stacked lamellae. The higher concentration of Magnesium Stearate used or the longer the mixing process is done will result in the closer the particle layer occurs. This is because when the mixing process takes place, the plates continue to cut and coat adjacent particles. The process will cause the preparation to have a low coefficient of friction and a high cover potential. The lubricant efficiency depends on the length of mixing the mass of the tablet with Magnesium Stearate because of its laminar structure (Kanher et al., 2017).

The use of magnesium stearate in a solid dosage form also has some disadvantages. The more concentrations of magnesium stearate used in the formulation will cause problems in manufacturing processes such as decreased tablet strength, longer disintegration time and inhibition of dissolution rate. To overcome this, some substances such as sodium stearyl fumarate, sucrose fatty acid ester, hexagonal boron nitride magnesium lauryl sulfate, hydrophobic organic material and inorganic materials are used as a lubricant in solid dosage form (Bani-Jaber et al., 2015).

One of the lubricant alternatives evaluated in the International Journal of Pharmaceutics is the use of chitosan conjugate with lauric acid (CS-LA). The use of CS-LA may also increase the pressure transmission ratio in the presence of additional CS-LA concentrations used. Also, adverse characteristics such as reduction of tablet mechanical strength, prolonged disintegration time, or slow dissolution profiles do not occur in CS-LA use, which increases its concentration as a lubricant (Bani-Jaber et al., 2015).

One of the parameters used to assess lubricant quality is the value of Carr’s Index (CI). The Carr (CI) index is a parameter used to measure the flow properties of the powder, obtained from bulk and incompressible density. The smaller the CI indicates, the better the flow properties. Carr’s Index value is in the range 5% - 23%. If a CI value close to 5% indicates a very good flow, and when a value approaching 23% indicates a poor flow (Halaçoğlu and Üğurlu, 2015).

Hexagonal boron nitride was found to be the most effective lubricant at 0.5% - 1% concentration. Based on the disintegration time and Heckel analysis, hexagonal boron nitride is better than magnesium stearate. Hexagonal boron nitride can also be used as a lubricant indirect or wet granulation (Halaçoğlu and Üğurlu, 2015).

Magnesium stearate showed a rapid decline and had a minimum cohesion index value with an increase in lubricant concentration. Hexagonal boron nitride showed similar cohesion index values but slightly better than 59.58, 52.48, 33.75 and 50.88 compared with magnesium stearate. The phenomenon of low cohesion index for Hexagonal boron nitride and magnesium stearate causes the lowest compressibility value at lubricant concentration levels 2 and 4% (Ügurlu and Turkoğlu, 2008).
In an era of importance to the quality of formulations, the type of lubricants and the optimal amounts used in tablet formulations should be made based on systematic evaluations. The efficiency of magnesium stearate lubrication is the highest. However, magnesium stearate has a deficiency of a distant magnesium stearate bond that causes a decrease in the strength of the resulting tablet. Therefore, the slightly elevated sodium stearyl fumarate concentrations are also equally effective for magnesium stearate but do not reduce other important tablet properties, including tablet strength, hardness, and disintegration (Paul and Sun, 2018).

Sodium benzoate is used as a water-soluble lubricant. Sodium benzoate is used both as a lubricant and glidant. The granular glidency is facilitated well during material flow, removes a binding to the die and minimizes picking and attaches to surface punch-face compression. Compared with other lubricants, both disintegration time and effervescent tablet dissolution were 98.6% for 03 h in pH 6.8. When a single effervescent tablet is dropped into a glass of water, it dissolves completely without scumming or agglomeration or sediment and the clear solution is clear. The color display of the solution is good and the last drink of this effervescent dosage form tastes good. The study finally concluded that the sodium benzoate used in effervescent tablet formulations is the best lubricant among other lubricants used, such as Talc, magnesium stearate, and PEG (Dinesh and Mutahar, 2009).

**Filler**

The filler is usually added to dosage tablets that have a few API (Active Pharmaceutical Ingredient), so it can be an addition to a mass tablet. Moreover, it can improve compactibility and flow rate, especially on tablets made by a direct compression method (Hadisoewignyo et al., 2011). One of the commonly used fillers is microcrystalline cellulose. Microcrystalline cellulose is pure cellulose that isolated from α-cellulose, which is the purest quality of cellulose with cellulosic content greater than 92%. Microcrystalline cellulose is obtained by removing the amorphous microfibril fibers by dissolution using mineral acids, the microfibril fibers that can not be isolated to produce quality microcrystalline cellulose. Microcrystalline cellulose is hygroscopic, insoluble in water, but expands contact with water (Widia et al., 2017b).

Avicel® became the trade name of microcrystalline cellulose. In 1964, Avicel® PH was introduced by FMC Corporation to the pharmaceutical industry as an ingredient for direct compression tablets (Albers et al., 2006). Avicel PH 102 as an excellent dry binder (La et al., 2006). Moreover, Avicel PH 102 has better properties compared to Avicel PH 101 because it has a larger particle size. Avicel PH 102 has excellent compatibility and can cause interrelated changes, which is the bonding strength between particles. So, Avicel PH is good to use in the direct compression method (Lachman et al., 1986).

Characteristics of microcrystalline cellulose can be determined by performing some tests (Widia et al., 2017a):

1. **Organolectic test**, good microcrystalline cellulose has organoleptic powder crystal, white, odorless, tasteless.
2. **Qualitative analysis using iodized zinc chloride will produce blue-violet.**
3. **Starch test using iodine reagent does not produce blue color** (does not contain starch).
4. **Solubility test was performed on four different solvents, i.e., water; 95% alcohol, 2N HCl, NaOH 1N and ether.**
5. **Good microcrystalline cellulose solubility is insoluble in water, not in 95% alcohol, insoluble in 2N HCl, insoluble in 1N NaOH, and insoluble in ether.**
6. **pH test; Good microcrystalline cellulose has a pH range of 5-7.5.**
7. **Test of power flow and angle of silence; A good microcrystalline cellulose has a resting angle that belongs to a very easy flowing molecule.**
8. **Test the compressibility by calculating the compressibility index value. Good microcrystalline cellulose will have a true density value of 1.512-1.668 g / cm3, bulk density of 0.337 g / cm3, and a compressive density of 0.478 g / cm3.**
9. **FTIR, with a spectrum measured at wavenumbers 4000-400 cm-1.** Good microcrystalline cellulose will show the presence of a major uptake in wavenumbers 3344, 2884, 1426, 1316, and 1024 cm-1 indicating the presence of OH groups, hydrogen bonds, C-H alkanes, C-O ether bonds, and alcohols.
10. **SEM-EDS, microcrystalline cellulose with 170 times magnification of the actual size, the particle size can be estimated between 2.94-117.6 μm has irregular shapes as well as uneven surface textures in the form of spiky and dull angles.**
11. X-ray Diffractometer, the emergence of three specific strongest peaks at 2θ, i.e., 14; 116°, 16; 502°, and 22; 359°.

Cellulose has been developed in the form of nanocrystal, commonly known as nanocrystalline cellulose, which is a renewable, sustainable, environmentally friendly, and extremely wide-ranging bionanomaterial (Anwar et al., 2016) that has many uses in applications such as biotechnology, composites, adsorbents, emulsions and dispersions, and biomedicine (Effendi et al., 2015). Microcrystalline cellulose can be used as a filler, binder, and disintegrant in the manufacture of a direct compression tablet because it has good flow characteristics and properties. Whereas in nanocrystal, cellulose can be used as a filler and binder on tablets by giving the release of drugs that are slowed (Sumaiyah, 2015). Several methods for the synthesis of nanoselulose, namely mechanical methods (ultrasonication and high pressure), chemistry (hydrolysis of strong acids, organosolv, alkaline solvents, oxidation, and ionic liquids), and biologically (using enzymes) (Effendi et al., 2015).

Based on tests by Sumaiyah with the source of cellulose derived from sugar palm bunches. 10% of nanocrystal cellulose is formulated into diclofenac sodium tablets by direct compression method, and the reference tablet used Voltaren®. The nanocrystalline cellulose form of sugar palm (Selulosa nanokristal tandan aren, SNTA) spherical form with a diameter of 15-20 nm and a particle size distribution of 257.2 - 395.8 nm. SNTA has a crystalline form of cellulose II with a degree of crystallinity of 97.57%. The SNTA degradation was performed thermogravimetric analysis (TGA) occurred at 173°C with leaving a solid mass residue of 11.25% at 800°C. The flow rate and compressibility of SNTA are good enough and can be used as fillers and binders on tablets. Diclofenac sodium tablet formulated with SNTA (F5) has a disintegrating time, lower friability, and higher hardness when compared to diclofenac sodium tablet formulated with microcrystalline cellulose (SMTA) (F6) and Avicel PH 102 (F7). The F5 tablet has a slower release rate than tablets, F6, F7, and Voltaren®. In a medium with pH 6.8, the drug release kinetics of F5 tablets are order 1 and Higuchi, and in medium with pH changing is the kinetics of Higuchi release (Sumaiyah, 2015).

CONCLUSION

Excipients play an important role in the manufacture of pharmaceutical dosage forms; the function of each excipient depends on the amount. Excipients of tablet formulations include binder agents, fillers, crushers, lubricants, and lubricants. Each excipient has its respective advantages and disadvantages, therefore to cover the deficiency, the excipient is further developed both chemically and physically. Each excipient has different characteristics, to test these characteristics can be tested by using SEM, X-ray diffraction, etc.

REFERENCES

Abegunde, O. K., Mu, T. H., Chen, J. W., Deng, F. M. 2013. Physicochemical characterization of sweet potato starches popularly used in Chinese starch industry. Food Hydrocolloids, 33(2):169–177.

Abhishek, Y. K. 2013. Evaluation and Comparison of Highly Soluble Sodium Stearyl Fumarate with Other Lubricants In Vitro. Indo American Journal of Pharmaceutical Research, 3(5):24–30.

Albers, J., Knop, K., Kleinebude, P. 2006. Brand-to-brand and batch-to-batch uniformity of microcrystalline cellulose in direct tabling with a pneumohydraulic tablet press. Pharmazeutische Industrie, 68(12):1420–1428.

Anwar, B., Bundjali, B., Arcana, I. M. 2016. Isolasi Nanokristalin Selulosa Bacterial Dari Jus Limbah Kulit Nanas: Optimasi Waktu hidrolisis. Jurnal Kimia Dan Kemasan. 38(1):7.

Ayorinde, J. O., Itiola, O. A., Odeku, O. A., Odeniyi, M. A. 2011. Influence of binder type and process parameters on the compression properties and microbial survival in diclofenac tablet formulations. Brazilian Journal of Pharmaceutical Sciences, 47(4):845–854.

Bani-Jaber, A., Kobayashi, A., Yamada, K., Haj-Ali, D., Uchimoto, T., Iwao, Y., Itai, S. 2015. A newly developed lubricant, chitosan laurate, in the manufacture of acetaminophen tablets. International Journal of Pharmaceutics, 483(1-2):49–56.

Bastos, M., De, O., Friedrich, R. B., Beck, R. C. R. 2008. Effects of filler-binders and lubricants on physicochemical properties of tablets obtained by direct compression: A 22 factorial design. Latin American Journal of Pharmacy, 27(4):578–583.

Chaudhari, S. P., Patil, P. S. 2012. Pharmaceutical Excipients : A review. International Journal of Advances in Pharmacy, 1(1):21–34. Biology and Chemistry.

Desai, P. M., Liew, C. V., Heng, P. W. S. 2012. Understanding Disintegrant Action by Visualization. Journal of Pharmaceutical Sciences, 101(6):2155–2164.
Dinesh, B. M., Mutahar, R. K. M. 2009. Compatibility studies of intrinsic lubricants for effervescent tablets: Formulation and in vitro evaluation. *Biomedical and Pharmacology Journal, 2*(1):21–29.

Edge, S., Belu, A. , Potter, U. , Steele, D. , Young, P. , Price, R., Staniforth, J. 2002. Chemical characterisation of sodium starch glycolate particles. *International Journal of Pharmaceutics, 240*(1-2):109–115.

Effendi, D. B., Nurul, H. R., Asep, B. D. N., Ahmad, M. 2015. Review: Sintesis Nanoselulosa. *Jurnal Integrasi Proses, 5*(2):61–74.

Enauyatifard, R., Azadbakht, M., Fadakar, Y. 2012. Assessment of Ferula gummosa gum as a binding agent in tablet formulations. *Acta Poloniae Pharmaceutica - Drug Research, 69*(2):291–298.

Fathima, N., Mamatha, T., Qureshi, H. K., Anitha, N., Rao, J. V. 2011. Drug-excipient interaction and its importance in dosage form development. *Journal of Applied Pharmaceutical Science, 1*(6):66–71.

Hadisoewignyo, L., Teny, G. F., Handayani, E. T., Yunita, B. 2011. Pengaruh bahan pengisi pada tablet ibuprofen dengan metode cetak langsung. *Majalah Farmasi Indonesia, 22*(4):279–285.

Halaçoğlu, M. D., Üğurlu, T. 2015. Compression parameters of hexagonal boron nitride on direct compression mixture of microcrystalline cellulose and modified starch. *Pharmaceutical Development and Technology, 20*(2):747–754.

Hartesi, B., Sriwidodo, Abdassah, M., Chaerunisa, A. Y. 2016. Starch as a pharmaceutical excipient. *International Journal of Pharmaceutical Sciences Review and Research, 41*(2):59–64.

Immadi, H. P., Kala, S. L. J., K. S. R., Manikiran, S. S., Rao, N. R. 2017. Comparative study of Natural and Synthetic Superdisintegrants in the Formulation of Oral Fast Disintegrating Tablets Using Levofoxacin HCl as Model Drug. *International Journal of Pharmacy & Pharmaceutical Research, 10*(2):121–138.

Jena, A. K., Das, M., De, A., Mitra, D., Samanta, A. 2014. Determination of efficacy of a natural tablet binder: Characterization and in-vitro release study. *Asian Journal of Pharmaceutical and Clinical Research, 7*(3):164–168.

Kanher, P. R., Bakhle, S. S., Upadhye, K. P., Dixit, G. R. 2017. Lubricants In Pharmaceutical Solid Dosage Forms”. *World Journal of Pharmaceutical Research, 6*(9):131–146.

La, L. R. D., Medina, M., Kumar, V. 2006. Evaluation of cellulose II powders as a potential multifunctional excipient in tablet formulations. *International Journal of Pharmaceutics, 322*(1-2):31–35.

Labella, G., McDougal, M. 2006. Multifunctional Excipients. *Excipients, pages 26–28.

Lachman, L., Lieberman, H. A., Kanig, J. L. 1986. The Theory and Practice of Industrial Pharmacy, 3rd Edition. page 902, New York. Marcel Dekker, Inc.

Li, J., Wu, Y. 2014. Lubricants in Pharmaceutical Solid Dosage Forms. *Lubricants, 2*(1):21–43.

Madhav, N., Abhijeet, O., Shubhamtyagi, Vedprakash, G., Upendra, R. 2017. Significance of Pharmaceutical Excipients - A review. *Innovat International Journal of Medical & Pharmaceutical Sciences, 2*(6):128–132.

Majekodunni, S., Makper, S. 2016. Development and Evaluation of the Binding Properties of Raphia hookeri (Fam. Palmaceae) Gum in Pharmaceutical Tablet Formulations. *British Journal of Pharmaceutical Research, 14*(3):1–9.

Mohanachandran, P. S., Sindhumol, P. G., Kiran, T. S. 2011. Superdisintegrants: An overview. *International Journal of Pharmaceutical Sciences Review and Research, 6*:105–109.

Odeku, O. A., Iitiola, O. A. 2002. Characterization of Khaya Gum as a Binder in a Paracetamol Tablet Formulation. *Drug Development and Industrial Pharmacy, 28*(3):329–337.

Patial, H., Shah, V., Upadhyay, U. 2011. New Pharmaceutical Excipients in Solid Dosage Forms - A review. *International Journal of Pharmacy & Life Sciences, 2*(8):1006–1019.

Paul, S., Sun, C. C. 2018. Systematic evaluation of common lubricants for optimal use in tablet formulation. *European Journal of Pharmaceutical Sciences, 117*:118–127.

Pifferi, G., Santoro, P., Pedrani, M. 1999. Quality and functionality of excipients. *II Farmaco, 54*(1-2):101–104.

Rahim, H., Khan, M. A., Badshah, A., Chishti, K. A., Khan, S., Junaid, M. 2014. Evaluation of Prunus domestica gum as a novel tablet binder. *Brazilian Journal of Pharmaceutical Sciences, 50*(1):195–202.

Shailendra, P., Shikha, A., Singh, L. B. 2012. Natural Binding Agents in Tablet Formulation. *International Journal of Pharmaceutical & Biological Archives, 3*(3):466–473.

Sumaiyah 2015. Pembuatan dan Karakterisasi Selulosa Mikrokristal dan Nanokristal Tandan Aren (Arenga pinnata (Wurmb) Merr) dan penggunaannya sebagai Eksipien Dalam Tablet Natrium Diklofenak.

Szabo-Revesz, Piroska, Szepes, A. 2009. Potato
Starch in Pharmaceutical Technology. *Food*, 3(2):109–117.

Szepes, A., Szabó-Révész, P., Bajdík, J., Kása, P., Neményi, M., Pap, R., Pintye-Hódi, K. 2014. Characterization and Utilization of Starches Extracted from Florencia and Waxy Maize Hybrids for Tablet Formulation: Compaction Behaviour and Tablet Properties. *American Journal of Plant Sciences*, 05(06):787–798.

Ugurlu, T., Turkoglu, M. 2008. Hexagonal boron nitride as a tablet lubricant and a comparison with conventional lubricants. *International Journal of Pharmaceutics*, 353(1-2):45–51.

Varma, K. 2016. Excipients Used in the Formulation of Tablets. *Research and Reviews: Journal of Chemistry*, 5(2):143–154.

Widia, I., Marline, A., Anis, Y. C., Taofik, R. 2017a. Karakterisasi Serbuk Selulosa Mikrokristal Asal Tanaman Rami (Boehmeria nivea L. Gaud). *Farmaka*. 15(4):37–46.

Widia, I., Nasrul, Wathoni 2017b. Review Article Selulosa Mikrokristal: Isolasi, Karakterisasi, dan Aplikasi Dalam Bidang Farmasetik. *Farmaka. Suplemen*, 15(2):127–143.