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Development of a Novel Co-processed Excipient Comprising of Microcrystalline Cellulose, Xylitol, Mannitol, and Crospovidone for Orally Disintegrating Tablets

Kai Bin Liew[1]*, Hiu Ching Phang[1], Zhi Qi Ng[1], Yik Ling Chew[2] and Siew-Keah Lee[3]

[1]Faculty of Pharmacy, University of Cyberjaya, 63000 Cyberjaya, Selangor, Malaysia
[2]Department of Pharmaceutical Chemistry, UCSI University, Kuala Lumpur, Malaysia
[3]M. Kandiah Faculty of Medicine and Health Sciences, UniversitiTunku Abdul Rahman, Selangor, Malaysia
*Corresponding author: liewkaibin@cyberjaya.edu.my

Abstract

Co-processing an excipient is categorized as a novel methodology applied in the preparation of tablet dosage forms. The main objective of this novel technique is to enhance the flow property of excipients commonly used in the production of tablets which correlates to the direct compression method of tablet production which is highly influenced by the powder characteristics such as dilution potential, compressibility or even flowability. Oral disintegrating tablets (ODT) is becoming a preferred choice in solid dosage form due to its benefits to the patient. It offers a rapid onset of action, improved bioavailability, ease of administration, and improvement in patient compliance to medication, ideal for individuals such as adolescents or elderly that have difficulty in swallowing medications. Although ODTs offers a myriad of merits, there are still some niches where further research may be conducted to improve the formulation, these includes optimizing stability condition, as well as improving mechanical strength of the formulation. The most common method to produce ODTs is through direct compression. Corresponding to the discussion points above, this study was carried out to formulate a novel co-processed excipient that consists of microcrystalline cellulose (MCC), xylitol, crospovidone, and mannitol as an orally disintegrating tablet dosage form. The study was conducted in 2 stages. The first stage involves developing 6 different formulations of ODTs that differs in the percentage of co-processed excipients such as crospovidone or croscarmellose sodium. Following Stage 1 will be the characterization tests. These includes pre-, and post- compression tests respectively to evaluate the standard of each formulation. Formulation 3 that consist of 72% MCC, 10% xylitol, 10% mannitol, and 8% crospovidone was selected as the optimum co-processed excipient formulation as it achieved fastest disintegration time in comparison to the remaining formulations and was tested with dissolution test to identify the efficiency of drug release. Besides, Formulation 3 also portrayed desired results in other evaluation tests such as friability test weight variation test and hardness test. Co-processed excipient that is characterized by an improve in functionality and disintegration process is beneficial in the application of oral disintegration tablets.

Keywords: Co-processed excipient; formulation; oral disintegrating tablets; optimization

Introduction

ODT as defined by the U.S. Food and Drug Administration (FDA) is a dosage form that can disintegrate within seconds in contact with saliva in the oral cavity (1).The aim of ODT primarily targets patients that have dysphagia specifically, geriatrics,

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pediatrics, bedridden, psychiatrics, and nauseated patients with the intention to reduce any possible risk of chocking. ODT formulations also provides an avoidance in first pass metabolism which subsequently enhances the bioavailability of the drug, reducing dosing frequency and side effect of respective medication. There are many formulation methods that may be used to produce an ODT and method has respective advantages and drawbacks, while the most used method will be direct compression as it has low handling cost, and comparatively simple stages involved with near to zero losses (2).

One of the main focuses in production of tablets will be the choice of excipients. Each excipient carries respective pros and cons and could play a variety of role in the formulation process. Excipients may be co-processed to enhance functionality of individual excipients and assist in overcoming straggles during the formulation process of ODTs. Co-processed excipients are described as a combination of two or more excipients which is developed to alter respective physical properties in a way that is unachievable with the conventional way such as mixing and without considerable changes in chemical property. This technique aims to improve the overall flow property of the excipients in comparison to when used individually, which usually gives an enhancement of the binding and blending property of the excipients during the production process. Hence, co-processed excipients play a significant role in the formulation process, making the production of ODTs significantly simpler, hence concurrently optimizes the benefits of ODT and attain the qualities of an optimum ODT formulation (3).The high demand of multifunctionality excipients calls out the need to develop a new excipient and this is achievable by either creation of a completely new excipient or by developing a co-processed excipient with the existing excipients. The latter is favored as it is comparably more cost effective. An example of multifunctional co-processed excipient is microcrystalline cellulose (MCC) and starch. MCC is a poor tablet disintegrant however, it has an exceptional compaction property, while starch is a common disintegrant with poor flow and compaction. This combination often results in brittle tablets, hence the formulation of co-processed MCC and starch synergists each other and produces a robust tablet with desired mechanical and dissolution properties (4).The main objective of this study is to identify the ideal composition of co-processed excipients comprised of xylitol, MCC, mannitol, crospovidone and croscarmellose sodium (CCS) to produce an optimum ODT which will be loaded with the drug memantine hydrochloride to test the dissolution efficacy of the drug.

Memantine hydrochloride is a subtype of glutamate receptor and categorized as an antagonist of N-Methyl-D-Aspartate (NMDA) receptor, and it is indicated for moderate to severe Alzheimer's Disease and other neurodegenerative diseases. Memantine hydrochloride is available, as capsules, tablet, and solution form and it is important to take the entire solid dosage form content as a whole for optimum efficiency. However, due to rapid deterioration of motor function, and presence of dementia in Alzheimer's Disease individuals, it is often a challenge for this population to consume medication. Hence the presence of oral disintegrating tablets (ODT) fits as a solution to cater this problem as it offers fast disintegration without usage of any water within 60 seconds in the oral cavity. Testing of the co-processed excipient formulated ODT with memantine hydrochloride brings multiple beneficial for future development and discovery. The benefits of co-processed excipients are displayed in which it plays a crucial role in the production process as well as in improving the ODT formulation characteristics.

Materials and Methods

Materials used for this study includes croscarmellose sodium and

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crospovidone purchased from Merck KGaA; magnesium stearate and sodium chloride from R&M Chemicals; mannitol from Systerm; microcrystalline cellulose from Daily Chem; xylitol from MH Food; and 0.1N hydrochloric acid from Chemiz.

Equipment utilized in this study include digital balance from Mettler Toledo; Dissolution Tester and UV Spectroscopy from AHS Laboratory Supplies; disintegration tester, friability tester, tap density tester, and hardness tester from Electrolab and multiple punch tablet press from Karnavati.

Formulation of Oral Disintegrating Tablets (ODTs) with Co-Processed Excipient

Table 1 shows the formulation design for the preparation of ODT. First, all ingredients are weighed and grounded into fine powder using separate pestle and mortar. Next, suitable quantity of water, only enough to dissolve both excipients was added to xylitol and mannitol respectively to dissolve them. The water added should be less than half the amount of MCC to prevent the resulting mass from being excessively wet. Xylitol and mannitol were combined to form a granulating fluid and the combination was added to MCC, memantine hydrochloride, and crospovidone or CCS. A No. 12- sized mesh was used to sieve the resulting wet mass to obtain granules which were then allowed to dry for two hours within the incubator at a temperature not exceeding 50°C. The granules were subsequently passed through a No. 20-sized mesh after drying and finally subjected to compression into ODTs with the multiple punch tablet press.

Evaluation of Blend

Angle of Response

A method known as fixed funnel was applied in the following test. Granular materials are poured at a specific height from a funnel on to the base and stopped when it reaches a particular width or heigh. Next, information regarding conical shape's radius and maximum height were obtained.

Angle of repose was calculated with the following formula (5).

$Tan\theta = h/r$

h = Height of the cone

r = Radius of the cone

Compressibility Index and Hausner Ratio

Measurements regarding the powder's initial apparent volume (Vo) and the final tapped volume (Vf) after tapping the material until maximum volume change were obtained. The following formulas were applied to identify the compressibility index and Hausner ratio:

Compressibility Index (%):
100 × (VO - Vf)/VO
Hausner Ratio: Vo/Vf

Evaluation of Oral Disintegrating Tablets
Hardness Test

Hardness test was conducted by selecting ten blank tablets from each formulation randomly and subject the tablets to testing through the hardness tester.

Table 1: Formulation of Orally Disintegrating Tablets with Co-Processed Excipients

Excipient	F1	F2	F3	F4	F5	F6
MCC	77%	75%	72%	77%	75%	72%
Crospovidone	3%	5%	8%	-	-	-
CCS	-	-	-	3%	5%	8%
Xylitol	10%	10%	10%	10%	10%	10%
Mannitol	10%	10%	10%	10%	10%	10%

CCS = croscarmellose sodium.
MCC = microcrystalline cellulose

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Weight Variation

Twenty tablets from each formulation were selected randomly and weighed. The mean was identified, and all tablets weight are to be within the calculated upper limit and lower limit range. The following formula was applied in calculating the weight variation.

Weight Variation (%) =
[(Individual weight – Average weight)/ Average weight] × 100%

Friability Test

Roche friability tester was used to identify the friability of twenty randomly chosen tablets with a speed of 25rpm. The weight of the tablets before the test and after the test were identified to calculate the loss limit of each formulation. The following formula was used to determine the percentage of friability:

Friability (%) = [(W1 – W2) × 100] / W1
W1= Total weight of tablet before test
W2= Total weight of tablet after test

Disintegration Test

Disintegration test was conducted by randomly selecting six tablets from each formulation and place them in the six tubes of the disintegration time tester basket. The basket rack was positioned in a 1-L beaker container containing distilled water as the disintegration medium and maintained at 37°C which portrayed the human normal body temperature. The time for all six samples in the basket to distort in shape was observed and collected.

Selection of Optimum Formulation

The formulation that comprises of the fastest disintegration time with dominant pre- and post- compression test results is identified as the ideal formulation of memantine hydrochloride ODT. To achieve a complete formulation, the optimal formulation was subjected for dissolution test to identify the drug-release characteristics and consistency of the active component.

Dissolution Test

The test was conducted USP Apparatus 1 at 100rpm and 37°C. Six randomly selected tablets from the optimum formulation were dissolved in 900mL of 0.1N hydrochloric acid and 2g/L of sodium chloride in water. The solution is pH – adjusted with HCL to a pH of 1.2. 10mL of the sample was obtained at 10, 20, and 30 minutes respectively.

Results and Discussion

Evaluation of Blend

Angle of repose

Based on Figure 1, all formulations subjected to angle of repose test displayed excellent flowability which ranges within 25° to 30°. Among all formulations, Formulation 4 portrayed the best flowability as it has the lowest angle of repose (26.6°). Formulation 4 consists of 10% xylitol and mannitol, 77% of MCC, 3% of CCS, and 10mg of memantine hydrochloride. On the other hand, Formulation 1 depicted the highest angle of response, despite interpretated as having excellent flowability.

Angle of repose test is tightly correlated with the flow characteristics and stability of the granules produced (6). Excellent angle of repose suggests that aid may not be needed for the formulation process. The improvement in powder flow is due to increased particle size or spherical shape of the granules that occurred during co-processing. Hence, modification of particle size has a great impact on the flowability and compressibility of the excipients (7).

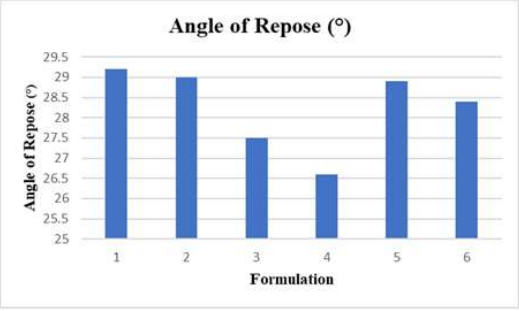

Figure 1: Results of Angle of Repose

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Compressibility Index and Hausner Ratio

According to Figures 2 and Figure 3 displayed in the appendix session, all formulations have good compressibility and flowability as they are all within a range of 11% to 15% and also within a Hausner ratio ranging from 1.12 to 1.18. Among all formulations, Formulation 4 displayed explicit flowability as it has the lowest Compressibility Index of 12.9% and Hausner ratio of 1.13. This formulation consists of 10% xylitol and mannitol, 72% of MCC, 8% of Crospovidone, as well as 10% of memantine hydrochloride.

In relation to the Compressibility Index and Hausner ratio results, it shows that the co-processed excipients lead to an improvement in terms of compressibility, which supports one of the studies reported Ludipress, a co-processed excipient has better compressibility in comparison with physical mixtures of their constituent excipient (3).

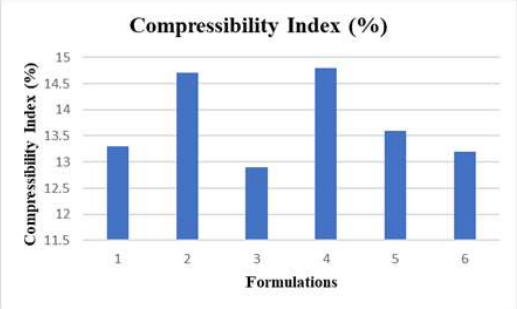


Figure 2: Results of Compressibility Index

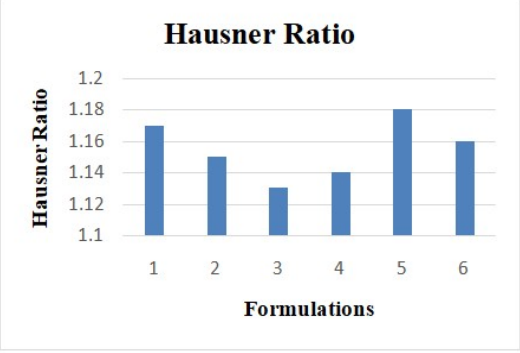


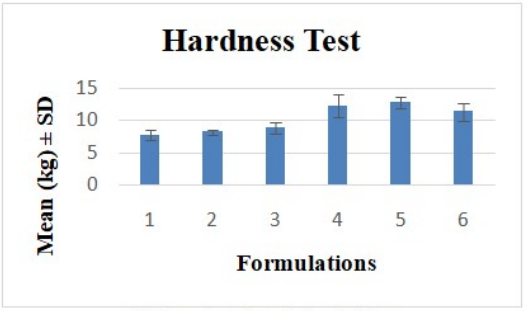
Figure 3: Results of Hausner Ratio

Several criteria are to be adhered to obtain a satisfactory result on the Compressibility Index and Hausner ratio. The amount of water added into the formulation during wet granulation process was increased in comparison to the amount mentioned in the reference article, however, the temperature and drying time was maintained as suggested to increase the moisture content of the granules which will ultimately lead to an improvement of flowability and compressibility since a large percentage of formulations consisted of MCC.

It was shown in research that the moisture content of MCC greatly affects the compaction, tensile, and viscoelastic properties of material. Moisture content in the pores of MCC serves as an internal lubricant and is important in lowering frictional forces, promoting slippage and plastic flow. The lubricant characteristics of water may further lessen variation in tablet weight by enhancing the passage of the compression force through the compact and reducing the adherence of the tablet weight. Generally, when the moisture content of MCC increases, relative compaction pressure required for formation of particular porosity reduces (8).

Evaluation of Oral Disintegrating Tablets
Hardness Test

Figure 4 shows the test of normality from Kruskal-Wallis test. Based on the obtained results, $p<0.001$ ($p<0.05$). A p value



SD = standard deviation

Figure 4: Results of hardness test

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less than 0.05 indicates that there was a statistically significant difference in hardness between the different formulations of ODTs containing memantine hydrochloride.

The results from Bonferroni post-hoc test shows that there was significant difference between Formulation 1, and Formulation 4,5,6; between Formulation 2, and Formulation 4,5,6; and between Formulation 3, and Formulation 4,5,6.

According to the United States Pharmacopoeia (USP), a satisfactory tablet hardness range from 5kg to 10kg. Based on the reference, only tablets from Formulation 1,2, and 3 passed the hardness test (9). Hardness from Formulation 4,5, and 6 exceeded the limit of 10kg and is not desired for ODT formulations. The difference between Formulation 1,2 and 3 with Formulation 4,5, and 6, were the super-disintegrants used. Formulation 1,2, and 3 contained Crospovidone, while Formulation 4,5, and 6 contained CCS which had variation in terms of porosity and might contribute to the difference in tablet hardness.

A study by Fathollahi et.al (2020) stated that CCS has high compressibility. The property of high-compressibility materials include that they are considerably densified upon pressure without significant elastic recovering. This indicates that the internal voids of highly compressible materials will be permanently destroyed as a result of rearrangement and shear when in contact with high pressure (10). Hence, this is why the type of super disintegrant may have an impact on the hardness, friability, as well as disintegration, absorption, and dissolution of the drug (11).

Weight Variation

Figure 5 shows the test of normality from Kruskal-Wallis test. Based on the obtained results, p=0.463 (p<0.05). A p value more than 0.05 indicates that there is no statistically significant difference in weight variation between the different formulations of ODTs containing memantine hydrochloride.

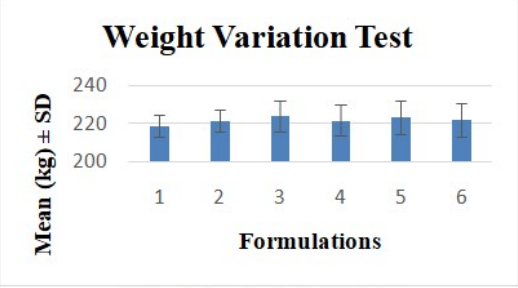

Figure 5: Results of Weight Variation Test

The formulated weight of memantine hydrochloride ODT in this study was 300mg. According to United States Pharmacopoeia (USP) standards, for tablets weighing between 130mg to 324mg, the weight variation readings of the tablets should be within a percentage deviation of ± 7.5%. Table 4 shows that all formulations are within the upper and lower limit of ± 7.5% and thereby achieved uniformity in weight. The tableting process was done manually where each blend was carefully weighed to 300mg before pouring the blend into the die. This is important to ensure the uniformity of each batch, that each batch of drug contains equal amount of API, and that ultimately the end users receive the correct dosage of medication (12).

Friability Test

The acceptance loss limit for friability test is that it should not exceed one percent. All formulations passed the friability test and were within a loss limit range of 0.22% to 0.24%. Friability is a crucial criteria as easily damaged tablets would lead to variations in weight, and uniformity of dosing of the API. It would be a problem for storage and transport of product as well. It is important to conduct this test to ensure strength and hardness of the tablets to conclude that all tablets are capable of withstanding abrasion during handling, packaging, or delivery of the product (13).

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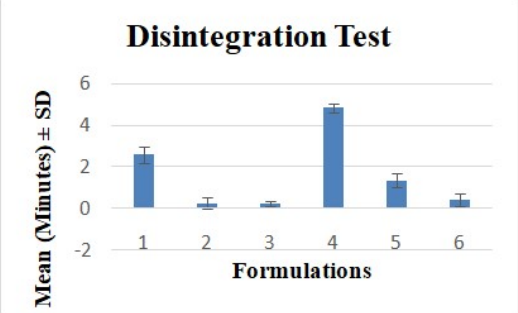
Disintegration Test

Figure 6 shows the test of normality from Kruskal-Wallis test. Based on the obtained results, $p<0.001$ ($p<0.05$). A p value less than 0.05 indicates that there is a statistically significant difference in disintegration profile between the different formulations of ODTs containing memantine hydrochloride.

The results from Bonferroni post-hoc test shows that there were differences between Formulation 3 and the remaining Formulations, except for Formulation 6; between Formulation 6, and Formulation 1, 4; between Formulation 2 and 4; and lastly between Formulation 5 and 1.

The ideal disintegration time for ODT is within 3 minutes (14).The results in Table 6 shows that all formulations meet the requirement for disintegration time and Formulation 3 stands the fastest disintegration time as it contains highest percentage of super disintegrant-crospovidone. Formulation 6 portrayed slower disintegration time in comparison to Formulation 3 as the super disintegrant used in this formulation is CCS (15). CCS has the tendency to form a viscous gel layer and prevent the disintegration medium from penetrating farther opposing the disintegration weight of the tablet. It is important to correlate the hardness result of Formulation 6 with Formulation 3 as well. Formulation 6 has a significantly higher hardness which will impact on the disintegration time as well since they are directly correlated (16). Finally, the poring of CCS differs with crospovidone as well. When hardness increases, pore distance reduces, which subsequently will lead to reduction in water permeability hence influencing the disintegration time of the tablets (17).



SD = standard deviation

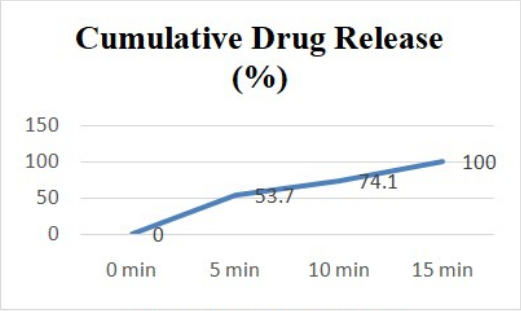
Figure 6: Results of Disintegration Test

Selection of Optimum Formulation

Conclusively, Formulation 3 which consists of 10% xylitol and mannitol, 72% MCC, 8% crospovidone, and 10mg memantine hydrochloride was chosen as the optimum formulation for the manufacturing of memantine hydrochloride ODT (18). This formulation stands out as it acquires the fastest disintegration time, with acceptable level of hardness, weight variation, and friability. In additionally, it also exhibits excellent flowability and good compressibility (19).

Dissolution Test

Figure 7 shows a line graph of the cumulative drug release profile of an optimum formulation of ODT containing memantine hydrochloride. The results shows that the drug content in the formulation was released slow and steadily reached full release profile at the 15th minute of the test. According to FDA, a minimum requirement of 85% API release is to be released within 30 minutes of dissolution test, Hence, this formulation of memantine hydrochloride ODT meets the specifications of the dissolution test (20).



SD = standard deviation

Figure 7: Dissolution profile of orally disintegrating tablets for formulation 3

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Conclusion

In conclusion, a co-processed excipient provides an improved functionality overall and has can be a potential trend in the pharmaceutical industry. In this study the four ingredients involved in the formulation of the co-processed excipients were xylitol, mannitol, MCC, and crospovidone or CCS. Ultimately, 10% xylitol, 10% mannitol, 72% MCC, and 8% Crospovidone were found to be the optimum composition as co-processed excipient and it shows acceptable results for all pre- and post-compression tests, displaying excellent disintegration time which is desired in an ODT formulation. Extension of study regarding taste masking of ODTs are highly recommended to expend the unlimited potential of discovery in the pharmaceutical field.

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