Archives of Pharmaceutical Sciences and Biotechnology Journal

Volume 4 Issue 2 December, 2024 ISSN: 2971_611X

https://doi.org/10.47514/10.47514/APSBJ.2024.4.2.005

APSBJournal

Page 48 - 57 Submitted 30/10/2024 Accepted 2/1/2025

ARCHIVES OF PHARMACEUTICAL SCIENCES AND BIOTECHNOLOGY JOURNAL

VOLUME 4 ISSUE 2, December 2024

ISSN 2971 – 611X

Archives of Pharmaceutical Sciences and Biotechnology Journal

Volume 4 Issue 2 December, 2024 ISSN: 2971_611X

https://doi.org/10.47514/10.47514/APSBJ.2024.4.2.005

APSBJournal

Page 48 - 57 Submitted 30/10/2024 Accepted 2/1/2025

Published by the Faculty of Pharmaceutical Sciences, Kaduna State University, Kaduna

EVALUATION OF THE EFFECT OF VARIOUS SUPERDISINTEGRANTS ON THE DRUG RELEASE PROFILE OF OMEPRAZOLE CORE TABLETS

M.U. Nzekwe[1]*, A.K. Olowosulu[1], Y.E. Apeji[1], T.O. Olurishe[2]

[1] Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria

[2] Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria, Nigeria

*Corresponding author Tel.: +234 8033207301 E-mail:kokonzekwe@gmail.com

ABSTRACT

Background: Superdisintegrants play a crucial role in enhancing tablet disintegration and, consequently, drug release. Omeprazole, a proton pump inhibitor used in treating gastroesophageal reflux disease (GERD), will benefit from rapid disintegration and dissolution to ensure prompt therapeutic action.

Aim: The study investigated the influence of three distinct superdisintegrants—croscarmellose sodium, sodium starch glycolate, and crospovidone—on the physical and functional properties of omeprazole core tablets.

Methods: Tablets were formulated with varying concentrations of each superdisintegrant, and the effects on disintegration time, dissolution rate, and mechanical strength were evaluated. **Results:** Each superdisintegrant imparted unique characteristics to the tablets: croscarmellose sodium facilitated faster disintegration due to its high swelling capacity, while sodium starch glycolate provided moderated disintegration with enhanced stability. Crospovidone, known for its capillary activity, demonstrated rapid water uptake, resulting in faster disintegration but lower mechanical strength. Among the three, crospovidone sodium achieved the most efficient balance of disintegration and mechanical integrity, making it favourable for rapid drug release without compromising tablet durability.

Conclusion: These findings emphasize the importance of selecting an optimal superdisintegrant to tailor drug release profiles in omeprazole formulations, potentially improving therapeutic efficacy and patient compliance.

Keywords: Omeprazole; Core tablets; Super disintegrants; GERD

INTRODUCTION

The oral route of drug administration remains one of the most convenient and widely used methods due to patient compliance, ease of use, and cost-effectiveness (1). Among oral dosage forms, tablets are preferred for their stability, dosing accuracy, and efficiency in mass production. However, achieving rapid disintegration and dissolution, particularly for drugs requiring fast action, is a challenge in tablet formulation (2). This is especially relevant for drugs like omeprazole, a proton pump inhibitor (PPI) extensively used for the management of gastroesophageal reflux

Archives of Pharmaceutical Sciences and Biotechnology Journal

Volume 4 Issue 2 December, 2024 ISSN: 2971_611X

https://doi.org/10.47514/10.47514/APSBJ.2024.4.2.005

APSBJournal

Page 48 - 57 Submitted 30/10/2024 Accepted 2/1/2025

disease (GERD), peptic ulcers, and related acid-related disorders. Omeprazole (OMP) is sensitive to acidic environments, and its efficacy depends on timely release in the intestine, where pH levels are more favourable (3). To address these requirements, formulating omeprazole core tablets with optimized disintegration properties is essential, as these cores will later be used in pressure-coated tablets designed for targeted release.

The disintegration and dissolution rates of tablets can be significantly enhanced by incorporating superdisintegrants, which facilitate tablet breakup upon exposure to gastrointestinal fluids. Superdisintegrants are crucial in overcoming the resistance to disintegration posed by tablet formulation factors, leading to a faster onset of action (4). Among the most commonly used superdisintegrants are croscarmellose sodium, sodium starch glycolate, and crospovidone, each offering distinct mechanisms for accelerating tablet disintegration. Croscarmellose sodium (CCS) works primarily through a swelling mechanism, allowing the tablet to rapidly break apart as it absorbs water. Sodium starch glycolate (SSG), on the other hand, swells and also contributes to disintegration through a wicking action, pulling liquid into the tablet matrix. Crospovidone (CP) operates primarily by capillary action, rapidly absorbing water without substantial swelling, enabling quick disintegration with minimal impact on tablet size and density. The efficacy of these superdisintegrants is influenced by their concentration within the tablet and by the overall composition of the formulation, as factors like binder type and compression force may alter their performance (4). Factors such as the degree of cross-linkage, particle size, and hygroscopicity influence their effectiveness necessitating the use of specific concentrations for different formulations (5). This study focuses on evaluating the effect of croscarmellose sodium, sodium starch glycolate, and crospovidone on the properties of omeprazole core tablets. The core tablets are intended for further use in the production of pressure-coated tablets, a specialized form designed to provide targeted release in specific areas of the gastrointestinal tract. Pressure coating is a dry-coating process advantageous for moisture-sensitive drugs like omeprazole, offering additional protection while allowing controlled release. However, for pressure-coated tablets to perform optimally, the core tablet must possess well-balanced disintegration properties to ensure rapid drug release once the coat dissolves or breaks down in the targeted environment.

By evaluating the three superdisintegrants in omeprazole core tablet formulations, this study aims to identify which disintegrant best balances rapid disintegration with adequate mechanical strength, both being essential properties for pressure-coated systems. Parameters such as tablet hardness, friability, disintegration time, and dissolution profile will be assessed to determine the most suitable superdisintegrant for omeprazole core tablets. Additionally, the impact of each superdisintegrant on the physicochemical stability of omeprazole, which is prone to degradation in acidic conditions, will be considered. Findings from this research will provide valuable insights into optimizing

Archives of Pharmaceutical Sciences and Biotechnology Journal

Volume 4 Issue 2 December, 2024 ISSN: 2971_611X

https://doi.org/10.47514/10.47514/APSBJ.2024.4.2.005

APSBJournal

Page 48 - 57 Submitted 30/10/2024 Accepted 2/1/2025

core tablet formulation for omeprazole and potentially guide the selection of an appropriate superdisintegrant for other acid-sensitive drugs in pressure-coated tablet formulations. This will contribute to more efficient and effective treatment options, enhancing the therapeutic outcomes for patients requiring proton pump inhibitors (PPIs) and similar medications.

MATERIALS AND METHODS

Materials

Omeprazole powder (CDH Chemicals, India) croscarmellose sodium (Vivasol® JRS Pharma, India), sodium starch glycolate (Vivastar®JRS Pharma, Germany), crospovidone (Vivapharm® PVPP XL-10, JRS Pharma, Germany), Prosolv®NF (PROSOLV® SMCC HD 90 JRS Pharma, Germany). All other reagents used were of analytical grade.

Methods

Compression of Omeprazole Core Tablet

The immediate release core tablets were prepared by direct compression using the Single Stroke Tablet Press (Erweka AR 400 Germany) at a compression pressure of 5.5 KN using 8 mm punch and die assembly. Omeprazole was geometrically mixed with the DC excipient, Prosolv®) and superdisintegrant (croscarmellose sodium, sodium starch glycolate and crospovidone respectively), along with talc and magnesium stearate. The powder mix was then fed into the die and compressed into tablets according to the formula in Table1.

Table 1: Formula for Preparation of Omeprazole Core Tablet

S/N	Ingredients	Quantity per tablet (mg)
1	Omeprazole (20 %)	40
2	Prosolv (75 %)	150
3	Super disintegrant*(2.5 %)	5.0
4	Talc (1.25 %)	2.5
5	Magnesium stearate (1.25 %)	2.5
Total weight of tablet		200

Key: *croscarmellose sodium, sodium starch glycolate, crospovidone

Evaluation of Omeprazole Core Tablets

Evaluation of tablet properties of core tablets were carried out as stated in the general chapter of the United States Pharmacopoeia-National Formulary, (6).

- The weight variation of 20 core tablets was determined using a balance, followed by the calculation of the mean tablet weight.
- The diameter and average thickness of 10 core tablets were measured using digital vernier callipers (USA) TOH-700K (USA).
- The average crushing strength of 5 core tablets was determined using the

Archives of Pharmaceutical Sciences and Biotechnology Journal

Volume 4 Issue 2 December, 2024 ISSN: 2971_611X

https://doi.org/10.47514/10.47514/APSBJ.2024.4.2.005

APSBJournal

Page 48 - 57 Submitted 30/10/2024 Accepted 2/1/2025

Logan Instrument Corporation (HDT-300) hardness tester.

- The average friability of 10 core tablets was determined using the Logan Instrument Corporation (FAB-2S) Friability tester.
- The average disintegration time of 6 core tablets was determined using the Erweka Disintegration tester (ZT series GmbH, Germany).
- Dissolution studies were carried out in the dissolution apparatus (Erweka DT 128 light series, Germany) using the basket method, apparatus 1.
- Each evaluation was conducted three times (in triplicate).

Statistical Analysis

One-way ANOVA was employed to compare the tablet properties across various categories of data sets. Significant differences were identified for p-values less than 0.05.

RESULTS AND DISCUSSION

Evaluation of Omeprazole Core Tablets

The calculated average weight of the tablets across the 3 formulations (Table 2) was within compendial specifications for tablets weighing 130 mg – 324 mg, with no more than two individual weights differing from the average weight by ±7.5 % (USP 2023). The crushing strengths of tablets across the formulations were also all lower than 10 Kgf, but it was observed that the CP formulations had the lowest and that these values were not dependent on the concentration. The crushing strength of the SSG formulation showed a direct correlation with the concentration while an inverse relationship was observed with the CCS formulation. The higher crushing strengths of the SSG and CCS formulations is attributable to the formation of stronger bonds between the particles. The lower crushing strength of the CP formulation is desirable because it is envisaged that after compression coating of the core, its crushing strength should further increase. Maiti and Sa (7) in their study, adjusted manufacturing variables and kept the crushing strength of the core tablet constant, at 4 Kgf, for this same reason; excessive tablet hardness can also impact adversely on disintegration time. The friability values across the formulations show that the SSG formulations have the lowest tendency for weight loss with abrasion because of the relatively stronger bonds formed between the particles that prevented abrasion of the tablets. The disintegration time (DT) of all the formulations were fast, but CP was the fastest within the stipulated time. DT of CP batches is facilitated by high particle porosity (8) and the disintegrating functionality of SSG has been reported to be sensitive in some cases to the presence of magnesium stearate (9). It was observed that DT was inversely proportional to the concentration of superdisintegrant in this formulation (SSG). Drug release was fast and completed in under 30 minutes which is a desirable attribute because “burst release” of the drug is preferred ensuring that disintegration and dissolution do not play any role in the controlled release mechanism when the core tablet is compression-coated with the polymers, so that their release modifying properties can then be clearly evaluated. The *in-vitro* drug release profiles (Figures 1, 2 and 3) show that the tablets formulated with CP achieved the highest drug release, in phosphate buffer, pH 6.8. This is because CCS and SSG have been reported to be sensitive to pH; also have potential for interaction with drug substances, even weakly basic drugs (10). The drug content of all the core tablets was within a compendial limit of between 90 – 110% (USP 2023). The core tablets however did not show any significant difference ($p < 0.05$) in their properties.

Archives of Pharmaceutical Sciences and Biotechnology Journal

Volume 4 Issue 2 December, 2024 ISSN: 2971_611X

https://doi.org/10.47514/10.47514/APSBJ.2024.4.2.005

APSBJournal

Page 48 - 57 Submitted 30/10/2024 Accepted 2/1/2025

Figure 1: Transverse view of Core Tablets

Table 2: Properties of Omeprazole IR core Tablets

Formulations	Average weight (mg)	Diameter (mm)	Thickness (mm)	Crushing strength (Kgf)	Friability (%)	Drug content (%)	Disintegration time (sec)
SSG1	198±0.0	7.98±0.01	3.96±0.01	7.±0.17	0.41±0.01	100.4±0.05	20±0.0
SSG2	201±1.8	7.96±0.01	3.98±0.01	8±0.30	0.47±0.01	100.2±0.05	20±0.0
SSG3	198±0.8	7.96±0.005	3.96±0.01	8±0.30	0.49±0.01	100.4±0.05	20±0.0
SSG4	201±0.8	7.97±0.02	3.98±0.01	9.5±0.17	0.42±0.01	100.4±0.01	18±1.1
SSG5	197±0.8	7.98±0.01	3.96±0.0	9.5±0.17	0.46±0.01	100.1±0.02	18±0.0
CCS1	198±0.57	7.97±0.005	3.96±0.01	8±0.30	0.6±0.01	100.2±0.05	21±0.8
CCS2	198±0.0	7.9±0.07	3.96±0.0	8±0.30	0.69±0.02	100.4±0.05	20±0.57
CCS3	202±1.6	7.98±0.01	3.98±0.01	9±0.15	0.62±0.0	100.3±0.02	20±1.15
CCS4	197±0.57	7.98±0.01	3.96±0.01	6±0.15	0.58±0.02	100.1±0.01	18±1.15
CCS5	198±0.0	7.98±0.01	3.96±0.01	6±0.15	0.6±0.01	100.1±0.05	18±1.15
CP1	199±1.4	7.98±0.02	3.98±0.015	6±0.15	0.7±0.01	101±0.03	16±1.16
CP2	203±1.45	7.99±0.02	3.99±0.015	6±0.15	0.72±0.015	100.4±0.05	15±1.15
CP3	201±0.8	7.98±0.09	3.98±0.015	6±0.15	0.7±0.01	100.2±0.05	12±1.15
CP4	201±0.8	7.99±0.025	3.98±0.015	6.5±0.15	0.71±0.01	100.4±0.05	10±0

Key: SSG1, SSG2, SSG3, SSG4, SSG5 = Formulations containing sodium starch glycolate, 1, 2, 4, 6 and 8 %
CCS1, CCS2, CCS3, CCS4, CCS5 = Formulations containing croscarmellose sodium, 1, 2,3, 4 and 5 %
CP1, CP2, CP3, CP4 = Formulations crospovidone, 2, 3, 4 and 6 %

Archives of Pharmaceutical Sciences and Biotechnology Journal

Volume 4 Issue 2 December, 2024 ISSN: 2971_611X

https://doi.org/10.47514/10.47514/APSBJ.2024.4.2.005

APSBJournal

Page 48 - 57 Submitted 30/10/2024 Accepted 2/1/2025

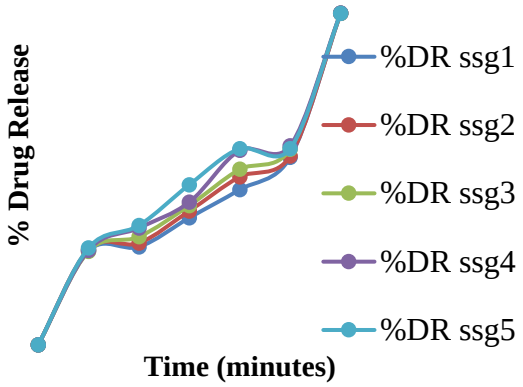

Figure 2: Graph of Drug release (DR) (%) versus time (min) of OMP core tablets formulated with sodium starch glycolate, PBS, pH 6.8

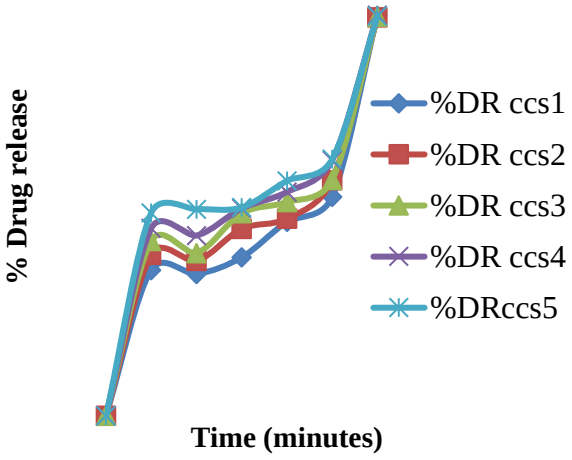

Figure 3: Drug release (DR) (%) versus time (min) of OMP core tablets formulated with croscarmellose sodium, in PBS pH 6.8

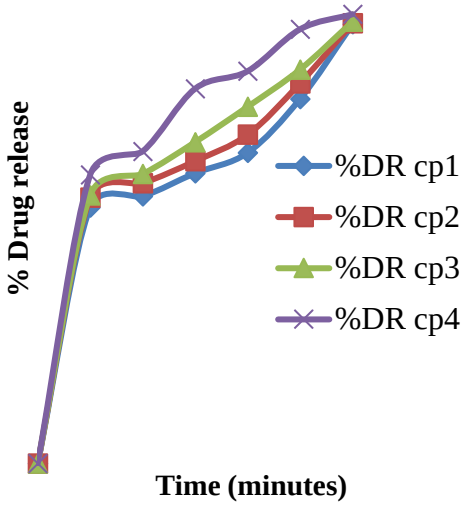

Figure 4: Graph of Drug release (DR) (%) versus time (min) of OMP core tablets formulated with crospovidone, in PBS, pH 6.8

Effect of Compression Pressure on Disintegration Time and Crushing Strength of Core Tablets

The amount of applied force affects disintegration time, crushing strength (11) and may even affect release properties (12). Crushing strength is indicative of the tablets ability to maintain its integrity throughout the chain from manufacturing to distribution and finally, use, and a range of 5 – 8 Kgf is considered acceptable (13). The graphs of crushing strength against compression pressure (Figures 4, 5 and 6) show the influence of change in compression force across the 3 formulations (Figures 4, 5 and 6). There was notable increase in the crushing

Archives of Pharmaceutical Sciences and Biotechnology Journal

Volume 4 Issue 2 December, 2024 ISSN: 2971_611X

https://doi.org/10.47514/10.47514/APSBJ.2024.4.2.005

APSBJournal

Page 48 - 57 Submitted 30/10/2024 Accepted 2/1/2025

strength of the tablets, irrespective of superdisintegrant type or concentration, with increasing compaction pressure, caused by increased particle rearrangement, fragmentation and finally, deformation (14). At higher compression force, there is also reduction in pore diameter and total porosity of the tablets (15). It was also observed that the action of superdisintegrants was able to overcome the influence of the change in compression pressure at higher superdisintegrant concentrations; the swelling and wicking action of the superdisintegrants as well as the elastic deformation of their particles prevailed in the formulations; this scenario was also reported by Maiti and Sa (7). At lower concentrations though, there was observed slight increase in disintegration times with increase in compression pressure across all formulations (Table 3); this is attributable to the formation of stronger bonds between the particles, which took more time to be disrupted, reduced tablet porosity which in turn reduces penetration of liquid (16).

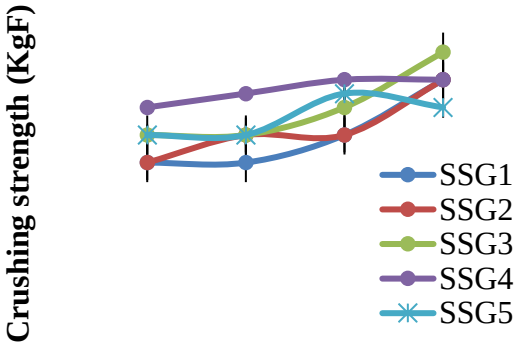

Figure 5: Graph of crushing strength versus compression pressure of core tablets prepared with sodium starch glycolate

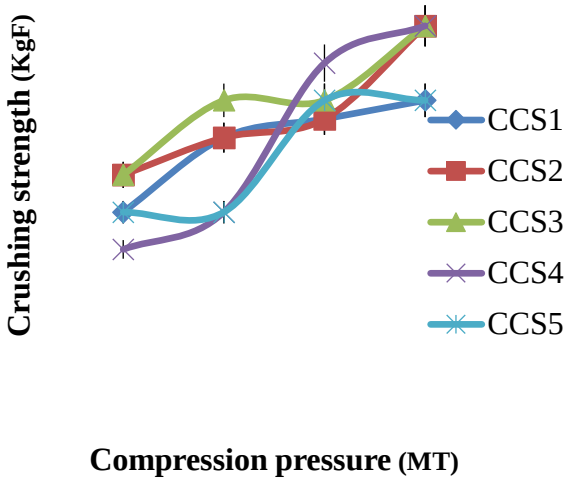

Figure 6: Graph of crushing strength versus compression pressure of core tablets prepared with cross carmellose sodium

Archives of Pharmaceutical Sciences and Biotechnology Journal

Volume 4 Issue 2 December, 2024 ISSN: 2971_611X

https://doi.org/10.47514/10.47514/APSBJ.2024.4.2.005

APSBJournal

Page 48 - 57 Submitted 30/10/2024 Accepted 2/1/2025

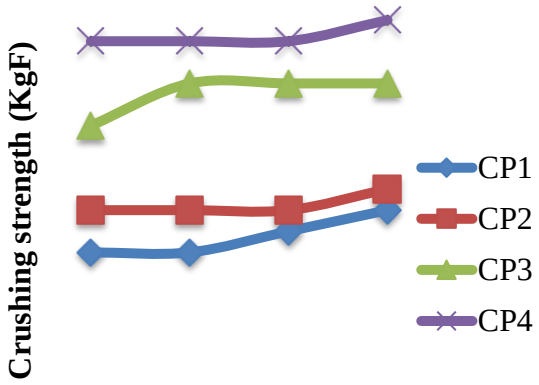

Figure 7: Graph of crushing strength versus compression pressure of core tablets prepared with crospovidone

Table 3: Disintegration Times of Core Tablets with Varying Compression Pressures

Compression pressure	Formulations/Disintegration time (sec)*				
	SSG1	SSG2	SSG3	SSG4	SSG5
5.5	18.00(±0.12)	18.00(±0.06)	20.00(±0.03)	20.00(±0.05)	20.00(±0.06)
6.0	20.00(±0.06)	20.00(±0.02)	20.00(±0.05)	20.00(±0.02)	20.00(±0.0)
6.5	20.00(±0.09)	20.00(±0.06)	22.00(±0.01)	20.00(±0.06)	20.00(±0.05)
7.0	25.00(±0.05)	25.00(±0.05)	22.00(±0.06)	20.00(±0.02)	20.00(±0.03)
	CCS1	CCS2	CCS4	CCS4	CCS5
5.5	18.00(±0.11)	20.00(± 0.02)	21.00(±0.01)	23.00(±0.08)	23.00(±0.04)
6.0	18.00(±0.03)	21.00 (±0.0)	20.00(±0.09)	20.00(±0.02)	18.00(±0.05)
6.5	20.00(±0.02)	23.00(± 0.04)	25.00(±0.06)	23.00(±0.11)	25.00(±0.06)
7.0	22.00(±0.01)	25.00(±0.03)	25.00(±0.01)	23.00 (± 0.0)	25.00(±0.02)
	CP1	CP2	CP3	CP4	
5.5	15.00(±0.02)	15.00(± 0.0)	12.00(±0.03)	10.00(±0.05)	
6.0	16.00(±0.06)	15.00(± 0.05)	12.00(±0.01)	10.00(±0.01)	
6.5	18.00(±0.05)	16.00(± 0.02)	15.00(±0.06)	12.00(± 0.0)	

Archives of Pharmaceutical Sciences and Biotechnology Journal

Volume 4 Issue 2 December, 2024 ISSN: 2971_611X

https://doi.org/10.47514/10.47514/APSBJ.2024.4.2.005

APSBJournal

Page 48 - 57 Submitted 30/10/2024 Accepted 2/1/2025

7.0	20.00(±0.05)	18.00(± 0.12)	18.00(±0.08)	16.00(±0.02)

*(mean±SD, *n=3*)

CONCLUSION

Core tablets were prepared by direct compression and were evaluated as stipulated in official monographs. The results from this study demonstrated the efficacy of formulating omeprazole tablets utilizing three distinct superdisintegrants: sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crospovidone (CP), among which the CP batch, formulation CP4 containing CP 6%, exhibited the most favourable characteristics. The enhanced disintegration properties, along with the improved drug release profile signify its potential to provide burst release making it the optimal choice for the preparation of compression coated tablets for the chrono-tailored management of GERD.

REFERENCES

1. Alqahtani M.S., Kazi M., Alsenaidy M.A., and Ahmad M.Z. (2021). Advances in oral drug delivery. *Frontiers in Pharmacology*, 12, 618411. https://doi.org/10.3389/fphar.2021.618411
2. Nagendra R., Anusha B. H., Venkatesh K., Hanumanthachar Joshi, and Tanuja A. J. (2024). Innovations In Fast Disintegrating Tablet Formulation: Harnessing the Power of Super Disintegrants for Rapid Oral Dissolution. *International Journal of Pharmaceutical Sciences*, 2(2), 380-391. DOI: 10.5281/zenodo.10673308
3. Mohylyuk, V., Yerkhova, A., Katynska, M., Sirko, V., and Patel, K. (2021). Effect of Elevated pH on the Commercial Enteric-Coated Omeprazole Pellets Resistance: Patent Review and Multisource Generics Comparison. *AAPS Pharmaceutical Science and Technology*, 22, Article 188. DOI: 10.1208/s12249-021-02038-2
4. Rani, N., Dev, D., and Prasad, D. N. (2022). Recent Trends in Developments of Superdisintegrants: An Overview. *Journal of Drug Delivery and Therapeutics*, 12(1), 145-152. DOI: 10.22270/jddt.v12i1.5148
5. Kute S.S., Sonwane S.S., Jadhav V.A. (2024). Super Disintegrants: An Overview. *International Journal of Pharmaceutical Sciences*: Vol 2, Issue 1, 77-89
6. United States Pharmacopoeia- National Formulary Online, 2023, general test methods in General chapters: United States Pharmacopeial Convention; 2023
7. Maity, S., and Sa, B. (2016). Compression-coated tablet for colon targeting: Impact of coating and core materials on drug release. *AAPS Pharmaceutical Science and Technology*, *17*, 504-515.
8. Shobana K., Subramanian L., Rajesh M. and Sivaranjani K. (2020). A review on superdisintegrants. *International journal of pharmaceutical sciences review and research;* 65(**2**):149-154
9. Dilebo J. and Gabriel T. (2019). An Overview of Factors Affecting Superdisintegrants Functionalities.*International Journal of Pharmaceutical Sciences and Nanotechnology;* Vol 12: Issue 1, pages 4355-4361

Archives of Pharmaceutical Sciences and Biotechnology Journal

Volume 4 Issue 2 December, 2024 ISSN: 2971_611X

https://doi.org/10.47514/10.47514/APSBJ.2024.4.2.005

APSBJournal

Page 48 - 57 Submitted 30/10/2024 Accepted 2/1/2025

10. Narang A.S., Desai D. and Badawy S. (2012). Impact of excipient interactions on solid dosage form stability. *Journal of pharmaceutical research*; 29(**10**): 2660-83
11. Wunsch I., Finke E., John E., Juhnke M. and Kwade A. (2021). Influence of particle size on the application of compression and compaction models for tableting. *International Journal of Pharmacy*; 599:120424. Doi: 10.1016/j.ijpharm.2021.120424
12. Adeleye, O. A., Femi-Oyewo, M. N., Odeniyi, M. A., &Ajala, T. O. (2019). Evaluation of Cissus populnea gum as a directly compressible matrix system for tramadol hydrochloride extended-release tablet. *Journal of Applied Pharmaceutical Science*, *9*(2), 105-111.
13. Dulla O., Sultana S., and Hosen S.M. (2018). *In-vivo* comparative quality evaluation of different brands of esomeprazole tablets available in selected community pharmacies in Dhaka, Bangladesh. *BMC Research Notes*; 11: 184. Doi: 10.1186/s13104-0218-3285-x
14. Ouazzou A.A., Harshe Y.M., Meunier V., Finke J.H., and Heinrich S. (2022). Influence of Process Parameters and Particle Size Distribution on Mechanical Properties of Tablets. *ChemieIngenieur Technik*; vol 95 (1-2): p. 168-177
15. Patere S.N., Kapadia C.J. and Nagarsenker M.S. (2015). Influence of Formulation Factors and Compression Force on Release Profile of Sustained Release Metoprolol Tablets using Compritol® 888ATO as Lipid Excipient. *Indian Journal of Pharmaceutical Sciences; 77*: 620 - 625.
16. Zheng, A.Y., Huang, W.W., Poon, L.Y.J., Wong S.E., Heng P.W.S. and Chan L.W. (2023). Examining the effect of spatial distribution of disintegrant particles on tablet disintegratability. *Journal of Pharmaceutical Investigation;* **54**: 195–207. https://doi.org/10.1007/s40005-023-00639-6