Optimizing Drug Delivery Vehicle with Multi-Criteria Decision Making (MCDM) - Based Excipient Selection

Ibrahim Omodamilola Omoyayi[1]*, Süleyman Aşır[1], Abdullahi Umar Ibrahim[1]

[1] Department of Biomedical Engineering, Faculty of Engineering, Near East University, Nicosia, Mersin 10, Turkey.

ABSTRACT

Excipients are used in drug delivery systems as a means of effectively delivering drugs to their target site. Multi-criteria decision-making (MCDM) methods are tools for decision-making that consider multidimensional factors. Such methods are a comparative technology used in medicine that combines individual criteria into the total assessment of selected alternatives. This study aims to enhance the solubility and bioavailability of drugs through the application of MCDM-based excipient selection. By incorporating the Preference Ranking Organization Method for Enrichment Evaluations (PROMETHEE), various excipients can be evaluated and ranked based on their suitability for specific applications, considering parameters related to drug solubility and bioavailability. The results highlight the potential of cyclodextrins (net flow: 0.0023) and Eudragit polymers (net flow: 0.0016) as preferred options for drug carriers, while Poloxamer 188 (P188) (net flow: -0.0030) is identified as the least preferred option. This study demonstrates the effectiveness of the PROMETHEE method in improving the performance of poorly soluble and bioavailable drugs, ultimately contributing to the development of new drug delivery systems. The findings have significant implications for therapeutic outcomes in the treatment of diseases.

Keywords: Multi-criteria decision making (MCDM), Drug Carrier excipient, Solubility, Bioavailability.

1.0 INTRODUCTION

The selection of suitable drug carrier excipients in drug delivery systems plays a crucial role in enhancing the solubility and bioavailability of drugs (1). BCS (as seen in Fig 1) is a scientific classification system used for grouping drug products according to their water solution solubility and intestinal permeability. Excipients play a significant role in improving the solubility and permeability of desired drugs. Using several enhancing techniques, drug carrier polymers such as Eudragit, HPMC, Soluplus, HPC, PVP, and many others have proven to improve the apparent solubility and bioavailability of class II and IV drug compounds. Multi-criteria Decision-Making (MCDM) methods provide a robust framework for decision-making processes, considering multiple factors and criteria in the evaluation of selected alternatives. Several authors, such as Alaa Aziz and Fraj Abudayah, have explored the opportunity of drug delivery for treating diseases (2). In the pharmaceutical field, MCDM-based approaches have shown promise in streamlining the excipient selection process, reducing screening time, and optimizing drug delivery vehicles for improved therapeutic outcomes. The motivation behind this study is to leverage the potential advantages of MCDM in pharmaceutics and drug delivery technologies. By employing the Preference Ranking Organization Method for Enrichment Evaluations (PROMETHEE), this research aims to identify and rank various excipients based on their suitability for enhancing drug solubility and bioavailability. The application of fuzzy logic in PROMETHEE facilitates handling complex and uncertain decision-making scenarios, making it well-suited for

Corresponding author: Ibrahim Omodamilola Omoyayi
omodammy@gmail.com
Received: 31/08/2023 Accepted: 12/11/2023.
DOI: https://doi.org/10.35516/jjps.v17i1.1692

pharmaceutical applications where several criteria need to be considered (2). While excipient selection is a critical aspect of drug development, limited research has focused on the potential advantages of Multi-Criteria Decision-Making (MCDM) methods in this domain. Traditional approaches to excipient selection often involve time-consuming and resource-intensive experimental screenings. This research novelly employs the MCDM-based fuzzy Preference Ranking Organization Method for Enrichment Evaluation (PROMETHEE) for excipient selection, providing a systematic and efficient means of identifying optimal drug carriers.

The proposed methodology integrates the fuzzy sets approach, which allows the inclusion of expert knowledge and linguistic variables in the decision-making process. This enables a more realistic representation of human judgment, making decision outcomes more relevant and applicable to real-world scenarios. This study uniquely combines the benefits of both MCDM and fuzzy sets to optimize the selection of drug delivery vehicles using fuzzy PROMETHEE.

The primary contribution of this study lies in demonstrating the effectiveness of the fuzzy PROMETHEE method for selecting drug carrier excipients to enhance drug solubility and bioavailability. This research provides a comprehensive evaluation of various excipients based on multiple criteria. To the best of our knowledge, this is the first study to innovatively use the fuzzy PROMETHEE method to evaluate drug carrier excipients. No other study in existing literature has compared drug carrier excipients using this methodology.

This research offers pharmaceutical scientists and decision-makers a valuable tool for informed decision-making in drug delivery system design. The potential advantages of MCDM-based excipient selection include reduced screening time and efforts, cost-effectiveness, and improved therapeutic outcomes. Additionally, the application of fuzzy logic in PROMETHEE allows for handling uncertainties and ambiguities often encountered in pharmaceutical decision-making processes. The findings of this study hold significant implications for drug development and therapeutic advancements in the treatment of diseases, including oncology and rare genetic conditions.

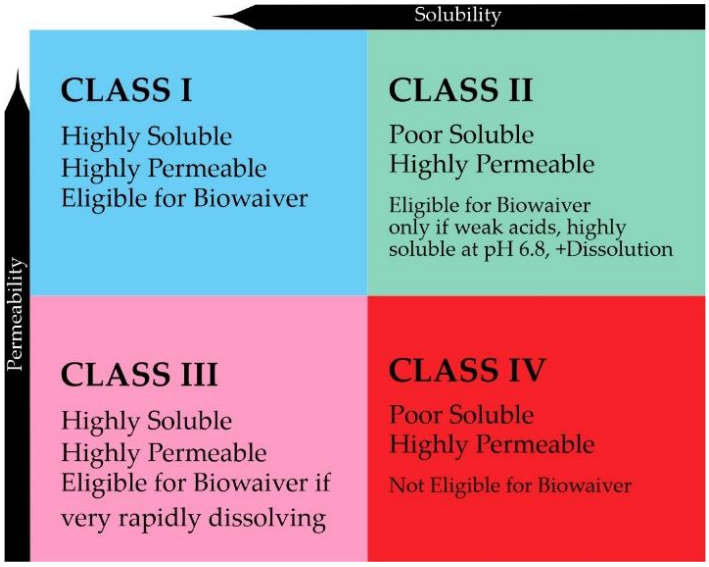

Figure 1: BCS Classification of drug (Author, 2023)

This current study focuses on frequently used drug carrier excipients over the past 10 years. The selected excipients have varied properties, disparate chemical compositions, and diverse means of drug delivery.

1.1 Cyclodextrins

Cyclodextrins are ring-shaped oligosaccharides naturally produced when bacteria act upon cellulose. They are composed of larger glucose molecules joined together by α-1,4 glycosidic bonds. While some types may possess as many as 6 units of glucose, others bear 7 to 8 units (β-, and γ- cyclodextrins, respectively) (Fig 2a). Cyclodextrins can encapsulate drugs and release them at the site of absorption (Fig 2b), thereby enhancing the solubility and bioavailability of the drug. Their applications include the crosslinking of water-soluble cyclodextrin with hyaluronic acid for targeted drug delivery for wound treatment (3).

Figure 2a: Chemical structure of alpha, beta, and gamma cyclodextrins (Nikitenko et all, 2013)

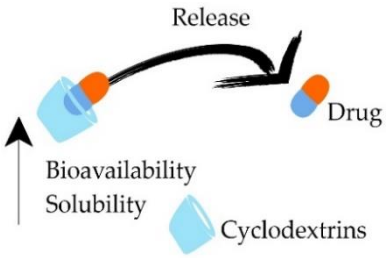

Figure 2b: Cyclodextrins as a drug carrier (Author, 2023)

1.2 Soluplus

The application of these polymers in enhancing technologies such as amorphous solid dispersions aim to maintain the supersaturation of the drug molecules by forming micelles around the poorly soluble drugs thereby inhibiting recrystallization of the drug. The stability of enhanced drugs by amorphous solid dispersions by micelles continues to be a concern as the micelle's formations do not stay around the drugs indefinitely.

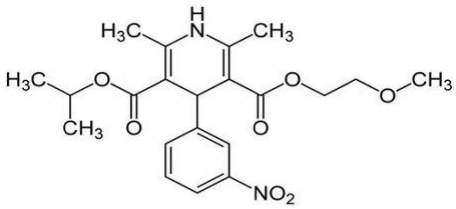

Figure 3a: Chemical Structure of Soluplus (PCL-PVAc-PEG) (Alsheyyab et all, 2019)

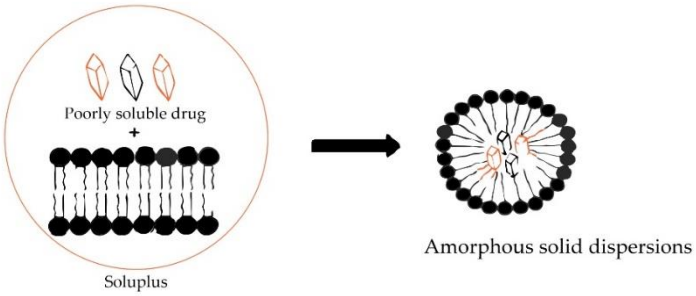

Figure 3b: Soluplus Polymeric Micells (Author, 2023)

1.3 Hydroxypropyl methylcellulose (HPMC)

HPMC, or Hydroxypropyl Methylcellulose, is a hydrophilic polymer used in the production of orally based drug delivery systems. It possesses significant properties such as high swelling capability and delayed release characteristics. Hydroxypropyl methylcellulose is a semi-synthetic, inert, viscoelastic polymer. Several formulations based on HPMC have been synthesized and evaluated for use as gastro retentive drug delivery systems, including tablets, capsules, pellets, and microparticles.

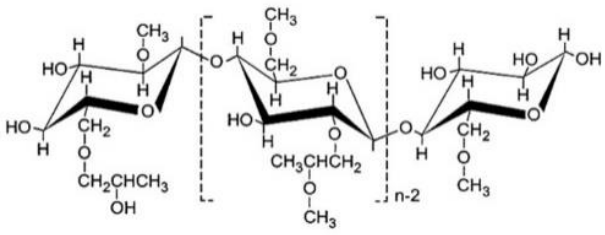

Figure 4: Chemical structure of Hydroxypropyl methylcellulose (Azad et all, 2019)

1.4 Poly (vinyl pyrrolidone) PVP

Polyvinylpyrrolidone (PVP), also known as Povidone, is a water-soluble material obtained through the polymerization of the monomer N-vinyl-pyrrolidone (Fig 5). PVP can encapsulate both hydrophilic and lipophilic drugs. Its inert and non-toxic properties, temperature resistance, and stability across various pH ranges contribute to its selection as a choice ingredient in drug delivery systems.

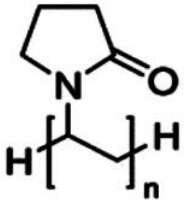

Figure 5: Chemical structure of Polyvinylpyrrolidone (Sigma Aldrich, 2023)

1.5 Poloxamers

Poloxamers are used as carriers to improve the solubilization and stability of compounds. They can form micelles and act as nanocarriers of drugs to the site of action. The surfactant property of poloxamer allows it to be inserted into lipid monolayers, thereby promoting the solubility and bioavailability of drugs.

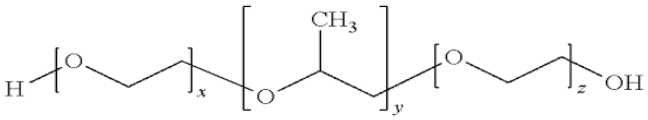

Figure 6: Chemical structure of Poloxamer (Specialized RX, 2023)

1.6 Eudragit Polymers

Eudragit polymers offer a wide range of polymers with enhancing characteristics to optimize the bioavailability, stability, and drug load of the final product. Eudragit is prepared by the polymerization of acrylic and methacrylic acids, or their esters, as seen in Figure 7.

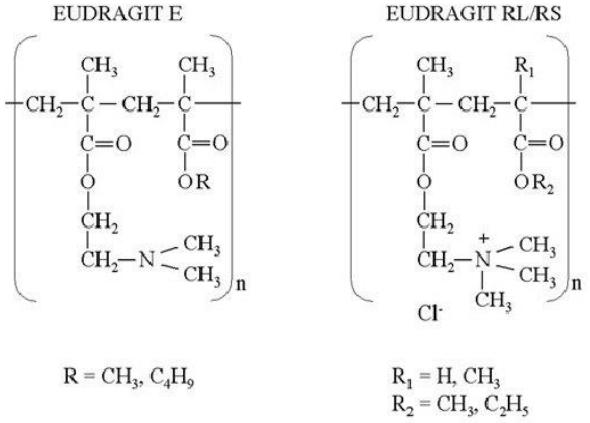

Figure 7: Chemical Structure of Eudragit (Nguyen et all, 2006)

2.0 Multi Criteria Decision Making (MCDM)

The diversity of Multi-Criteria Decision-Making (MCDM) methods ensures that decision-makers have a wide range of tools at their disposal to handle various decision-making challenges effectively. In this study, the fuzzy Preference Ranking Organization Method for Enrichment Evaluations (PROMETHEE) method has been deployed to evaluate the available alternatives based on selected and weighted parameters. The use of MCDM has gradually gained traction with agencies for healthcare technological advancement, and its incorporation is progressively occurring across Europe. It's vital to carefully select the MCDM method that aligns with the complexity of the problem, data availability, and the level of ambiguity present. It's important to note that no single MCDM method is innately more valuable than the others, as their significance depends on the specific problem context and the decision-maker's preferences and priorities.

2.1 Fuzzy PROMETHEE

The PROMETHEE method is one of the most recent Multi-Criteria Decision Analysis (MCDA) methods. It was developed by Brans (1982) and later expanded by Vincke and Brans (1985). PROMETHEE is a tool used for sorting a number of closely related alternatives from which selections are ranked and chosen based on clearly stated criteria. Fuzzy PROMETHEE is an extension of the traditional PROMETHEE method that incorporates fuzzy logic to handle uncertainties and linguistic variables. It allows for more flexible and realistic decision-making, making it suitable for situations with imprecise or ambiguous data (4).

Several studies have utilized the fuzzy PROMETHEE technique in the field of medicine. For example, a study by Ozsahin (2022) (5) used the fuzzy PROMETHEE technique for the selection of radiopharmaceutical tau PET tracers to significantly improve the diagnosis and treatment accuracy of neurodegenerative diseases for targeted and personalized imaging based on precision. Another study by Uzun (2023) (6) used fuzzy PROMETHEE to evaluate machine learning models used for the real-time detection of brain tumors, facilitating early diagnosis and effective management of brain cancer. Similarly, Onakpojeruo (2022) (7) compared the treatment alternatives for spinal cord tumors using the same MCDM technique, contributing to the existing body of knowledge that prioritizes the treatment approaches for spinal cord tumors. These studies and many others demonstrate the effectiveness of MCDM methods in decision-making, particularly in the healthcare field.

3.0 METHODOLOGY

Before proceeding with the implementation of fuzzy PROMETHEE, we simplified the process by assigning relative weights to each of the criteria, as shown in Table 1. The weighted average scores of all the criteria used to rank the various options are displayed in Table 2. Additionally, we used the Yager index to remove any ambiguity that may have resulted from the data used. The Yager index is a promising candidate for defuzzification, as it comprehensively covers all potential set points, making it an ideal choice for this process. During the analysis process, we utilized a Gaussian preference function to make decisions regarding the PROMETHEE strategy.

Putting a numerical value on each criterion is a common approach to prioritize different criteria and draw attention to their relative importance. When using the fuzzy PROMETHEE method, the order in which various options are ranked depends on distinct factors. These factors include the criteria used, the considered alternatives, the weights assigned to different criteria, and the preset preferences. To correctly assign criteria, it is necessary to conduct a thorough analysis of the relevant literature and consult field experts.

Table 1. Linguistic variables and assigned fuzzy numbers with their corresponding priority weight.

Linguistic scale	Fuzzy Number/criteria weight	Rating of criteria
Very high (VH)	(0.75, 1.00, 1.00)	Solubility, Bioavailability
High (H)	(0.50, 0.75, 1.00)	side effect
Moderate (M)	(0.25, 0.50, 0.75)	Food effect, Stability of Drug Product, Drug Load, Dosage Form, Manufacturing Cost.
Low (L)	(0, 0.25, 0.50)	Ease of Manufacturing, Formulation Technology Selection
Very low (VL)	(0, 0, 0.25)	Sustained or Delayed Release Modification of Drug

Table 2. Drug carrier parameters evaluated with visual PROMETHEE values

criteria/alternatives	Aim	Weight	Cyclodextrins	Soluplus (PCL-PVAc-PEG)	Hydroxypropyl methylcellulose (HPMC)	Poly (vinyl pyrrolidone) (PVP)	Poloxamer	Eudragit Polymers
Solubility	Max	VH (0.92)	H	VH	M	H	H	VH
Bioavailability	Max	VH (0.92)	M	H	M	H	H	VH
Food effect	Min	M (0.50)	L	M	L	M	M	M
Stability of Drug Product	Max	M (0.50)	L	L	H	M	L	M
Sustained or Delayed Release Modification of Drug	Max	VL (0.08)	H	L	VH	L	L	VH
Drug Load	Max	M (0.50)	H	M	M	M	M	M
Dosage Form	Max	M (0.50)	VH	H	L	M	L	M
Side Effect	Min	H (0.75)	L	M	M	M	M	M
Manufacturing Cost	MIn	M (0.50)	L	M	H	L	M	M
Ease of Manufacturing	Max	L (0.25)	H	VH	H	H	L	VH
Formulation Technology Selection	Max	L (0.25)	VH	VH	L	H	L	H

3. RESULT AND DISCUSSIONS

In this study, drug carrier excipients, including cyclodextrins, soluplus (PCL-PVAc-PEG), hydroxypropyl methylcellulose (HPMC), poly(vinyl pyrrolidone) (PVP), poloxamer, and Eudragit polymers, were evaluated using a combination of fuzzy and PROMETHEE methods. The evaluation utilized criteria such as enhancements in solubility, bioavailability, the food effect, drug stability, drug load, manufacturing cost, side effects, manufacturing ease, ability to sustain or delay drug release, swallowability, and taste masking. Relative weights were assigned to each criterion, and their weighted average scores were used to rank the various options. The Yager index was employed to clarify any potential confusion caused by the data.

The drug carriers and their excipients were ranked according to their net flow scores, which took into account both the positive and negative flows between various criteria. The PROMETHEE method used in the study generates an important output known as the NetFlow score. This score represents the difference between the positive "outranking" flow and the negative "outranking" flow for each evaluated option—essentially, it measures the degree to which an option outperforms the other options.

Within this investigation's context, the NetFlow score provides a quantitative indication of the overall ranking of various drug carriers and excipients. Alternatives with higher positive NetFlow scores are considered the best choices as they exhibit a higher degree of preference compared to other options within the set. Conversely, options with negative NetFlow scores are viewed as less desirable alternatives due to their lower ranking. Therefore, NetFlow scores' significance lies in their ability to establish a distinct ranking of drug carriers and excipients, based on each option's overall preference concerning the evaluation criteria.

The findings from the investigation, as shown in Table 3, indicate that cyclodextrins ranked first with a net flow score of 0.0023, followed by Eudragit polymers with a net flow score of 0.0016. Soluplus (PCL-PVAc-PEG) came in third with a net flow score of 0.0011, and Polyvinylpyrrolidone (PVP) was fourth with a net flow score of 0.0005. The Hydroxypropyl Methylcellulose (HPMC) drug carrier excipient ranked fifth, with a negative net flow score of -0.0025, indicating it held a lower rank than the other excipients used in drug carriers. Poloxamer, with a net flow score of -0.0030, came in sixth and was considered the least desirable drug carrier excipient according to the criteria used in the analysis.

It's important to underscore the significance of a drug's property in its carrier selection. We used the graphical PROMETHEE rainbow to assess how well each potential drug carrier aligned with the criteria, showcasing the positive and negative attributes. Based on the considered criteria and their respective weights, Figure 8 shows that cyclodextrins are the most advantageous and preferred drug carrier excipient, while poloxamer ranked last.

3.1. Further Discussions

This study used a unique methodology that integrated fuzzy logic and the PROMETHEE method to evaluate and rank drug carrier excipients based on their ability to improve medication solubility and bioavailability. The careful selection of suitable drug carriers is a crucial component in the development of effective drug delivery systems. Various factors, including solubility, bioavailability, food effect, medication stability, and production cost, significantly impact drug carrier effectiveness. However, offering a qualitative assessment of the optimal excipient selection lacks methodological rigor. The current study seeks to overcome this limitation by providing a quantitative and systematic evaluation of diverse drug delivery systems.

To ensure clarity, we assigned relative weights to each criterion according to their respective importance. The weights were derived using linguistic variables and fuzzy numbers, which served as a medium to convert expert opinions from qualitative to quantitative forms. The selected criteria were pivotal in assessing the excipients.

The PROMETHEE approach was used for a thorough evaluation of the drug carriers, in line with the determined criteria. As explained earlier, the net flow scores acquired from the PROMETHEE analysis represent the collective preference of each drug carrier, considering both positive and negative flows. Positive NetFlow scores indicate a greater level of preference compared to other options within the group, while negative NetFlow scores suggest lesser desirability.

When examining the results, it was observed that cyclodextrins demonstrated the most advantageous characteristics, as evidenced by achieving the highest NetFlow score (0.0023). In contrast, Poloxamer obtained the lowest NetFlow score (-0.0030), indicating its status as the least preferred excipient. The obtained results establish a definitive hierarchy among the drug carriers, as determined by their overall preference concerning the defined parameters.

This research's novelty lies in its innovative application of Multi-Criteria Decision Making (MCDM) methodologies, namely fuzzy logic and PROMETHEE, within the field of medicine, specifically for excipient selection. Traditional approaches often depend on subjective assessments, lacking a rigorous scientific foundation. Our approach addresses this constraint by quantifying qualitative factors and providing a structured, scientifically determined evaluation of drug carriers, utilizing a comprehensive set of criteria.

Table 3: PROMETHEE results for drug carriers excipients

Rank	Drug carriers	Outranking NetFlow	Phi+ NetFlow	Phi- NetFlow
1	Cyclodextrins	0,0023	0,0035	0,0012
2	Eudragit Polymers	0,0016	0,0023	0,0007
3	Soluplus (PCL-PVAc-PEG)	0,0011	0,0021	0,0010
4	Poly(vinyl pyrrolidone) (PVP)	0,0005	0,0014	0,0010
5	Hydroxypropyl methylcellulose (HPMC)	-0,0025	0,0014	0,0040
6	Poloxamer	-0,0030	0,0004	0,0034

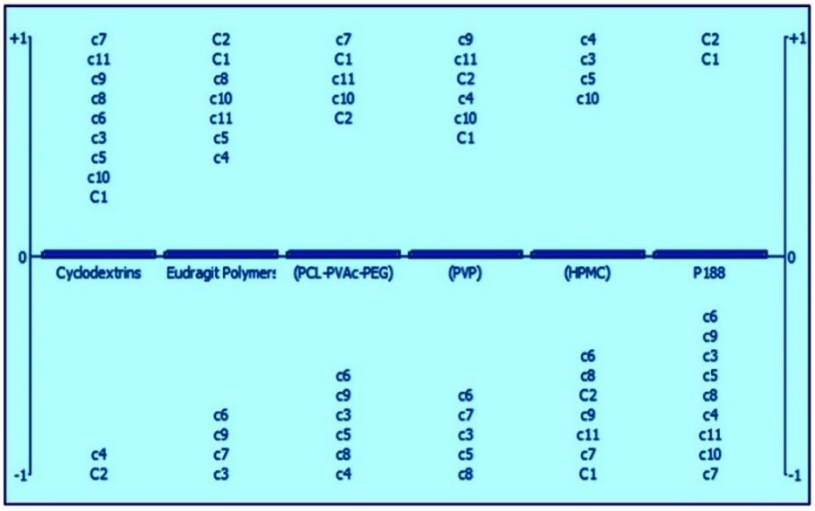

Figure 8: PROMETHEE rainbow of positive and negative aspects of the drug carriers

NB: C1= Solubility, c2 = Bioavailability, c3 = Food effect, c4 = Stability of Drug Product, c5 = Sustained or Delayed Release Modification of Drug, c6 = Drug Load, c7 = Dosage Form, c8 = Side Effect, c9 = Manufacturing Cost, c10 = Ease of Manufacturing, c11 = Formulation Technology Selection

4. CONCLUSION

Solubility and bioavailability continue to present major challenges in drug delivery. To increase a drug's efficacy, a drug carrier excipient is often used. However, the selection of this carrier is based on a multitude of factors, which can make choosing the optimal carrier quite difficult. In this study, we evaluated the most frequently used excipients in the pharmaceutical industry and ranked them in order according to their PROMETHEE values. This straightforward yet efficient technique allows for swift screening of suitable excipients among a vast array of choices. This time-saving method can also be extended to a more extensive selection of excipients, yielding similar results.

While we acknowledge that every drug molecule is unique and may respond differently to drug carriers, the MCDM tool serves as a robust guide in screening and reducing the need for multiple experimental runs, thereby saving time, money, and resources. The results from the analysis show that cyclodextrins are the preferred drug carrier excipients, followed by Eudragit polymers and then Soluplus, while Poloxamer is the least preferred alternative based on the evaluation criteria.

Future research should focus on validating the results through experimental trials, investigating how the chosen excipients perform concerning actual drug delivery and bioavailability enhancement. Additionally, integrating more complex criteria and refining the linguistic variables could further improve the accuracy and applicability of the method.

The findings of this study hold significant implications for drug development and therapeutic advancements in pharmaceutical research and development. Researchers, pharmaceutical scientists, and decision-makers can leverag these findings to make informed choices in drug delivery system design, thus positively impacting the field.

Conflict of Interest

The authors declare no conflict of interest.

Funding

The authors received no funding for this research.

REFERENCES

1. Chavda H.V, Patel C.N and Anand I.S. Biopharmaceutics Classification System. *Sys Rev Pharm*. 2010;1.
2. Alaa Aziz, Fraj Abudayah. Implication of Nanotechnology for Pulmonary Delivery of Docetaxel. *Jordan j. pharm. sci*. 2023;16(2), Supplement 1, 470.
3. Fedaa Adaileh. Crosslinking of Water-Soluble Cyclodextrin with Hyaluronic Acid for Targeted Drug Delivery. *Jordan j. pharm. sci*. 2023;16(2), Supplement 1, 458.
4. Zimmermann, H., J. Description, and optimization of fuzzy systems. *Inter-nat. J. General Systems*. 1976;209-215.
5. Ozsahin, I. Identifying a personalized anesthetic with fuzzy PROMETHEE. *Healthcare Informatics Research*. 2020; 26(3):201-211.
6. Uzun Ozsahin, D., Onakpojeruo, E. P., Uzun, B., Mustapha, M. T., & Ozsahin, I. Mathematical Assessment of Machine Learning Models Used for Brain Tumor Diagnosis. *Diagnostics*. 2023; 13(4): 618.
7. Onakpojeruo, E. P., Uzun, B., Ozsahin, I., & Ozsahin, D. U. Evaluation of the Treatment Alternatives for Spinal Cord Tumors Using Analytical Evaluation Models; 2011.
8. Nikitenko, Natalia & Prassolov, Vladimir. Non-Viral Delivery and Therapeutic Application of Small Interfering RNAs. *Acta naturae*. 2013;5:35-53. 10.32607/20758251-2013-5-3-35-53.
9. Alsheyyab, Rawda & Obaidat, Rana & Al Tall, Yara & Abuhuwaij, Rana & Ghanma, Rand & Ailabouni, Anoud & Mashaqbeh, Hadeia & Al-Haj, Shayma. Solubility enhancement of nimodipine through preparation of Soluplus ® dispersions ARTICLE INFO. *Journal of Applied Pharmaceutical Science*. 2019.9:30-037. 10.7324/JAPS.2019.90905.
10. Azad, Obyedul & Kang, Wie & Lim, Jung & Park, Cheol. Bio- Fortification of Angelica gigas Nakai Nano-Powder Using Bio-Polymer by Hot Melt Extrusion to Enhance the Bioaccessibility and Functionality of Nutraceutical Compounds. *Pharmaceuticals*. 2019; 13. 3. 10.3390/ph13010003.
11. Polyvinylpyrrolidone Image accessed from https://www.sigmaaldrich.com/US/en/product/sial/81440 [accessed 1 Oct 2023]
12. Poloxamer Image accessed from https://specializedrx.com/products/poloxamer-407-nf-micronized-pluronic-f-127 [accessed 1 Oct 2023]
13. Nguyen, Cung & Konan-Kouakou, Yvette & Allémann, Eric & Doelker, Eric & Quintanar, David & Fessi, Hatem & Gurny, Robert. Preparation of surfactant-free nanoparticles of methacrylic acid copolymers used for film coating. *AAPS PharmSciTech*. 2006;7:63. 10.1208/pt070363.
14. Baki, G., Bajdik, J. And Pintye Hodi, K. Evaluation of powder mixtures and hydrophilic gastroretentive drug delivery systems containing zinc acetate and sodium bicarbonate. *J. Pharm. Biomed*. Anal; 2011;54(4): 711-716.
15. Bartlett and Parelukar, Breast cancers are rare diseases—and must be treated as such. *npj Breast Cancer*. 2017;3:11; doi:10.1038/s41523-017-0013-y.
16. Behzadian, M., Kazemzadeh, R.B., Albadvi, A., Aghdasi, M. PROMETHEE: A comprehensive literature review on methodologies and applications. *European Journal of Operational Research*. 2010; 200:198–215.
17. Boldhane, S. P. And Kuchekar, B. S.Development and optimization of metoprolol succinate gastroretentive drug delivery system. *Acta. Pharm*. 2010;60(4):415-425.
18. Dong, B., Lim, L. M. And Hadinoto, K. Enhancing the physical stability and supersaturation generation of amorphous drug-polyelectrolyte nanoparticle complex via incorporation of crystallization inhibitor at the nanoparticle formation step: a case of HPMC versus PVP, Eur. *J. Pharmaceut. Sci*. 2019;138:105035, https://doi.org/10.1016/j.ejps.2019.105035;
19. Dorozynski, P., Kulinowski, P., Mendyk, A., Jachowicz, R. Gastrorentetive drug delivery systems with L-dopa based on carrageenans and hydroxypropylmethylcellulose. *Int. J. Pharm*. 2011; 404: 169-175.
20. Duwa, B., Onakpojeruo, E. P., Uzun, B., Ozsahin, I., & Ozsahin, D. U. Comparative Evaluation of 3D Filaments, Used in Additive Manufacturing of Biomedical Tools; Using Fuzzy Promethee. 2022

21. Fitch C, Keim KS. Position of the Academy of Nutrition and Dietetics: use of nutritive and nonnutritive sweeteners. *J Acad Nutr Diet*. 2012; 112(5):739–758.
22. Gaikwad, D., Shewale, R., Patil, V., Mali, D., Gaikwad, U. And Jadhav, N. Enhancement in in vitro anti-angiogenesis activity and cytotoxicity in lung cancer cell by pectin-PVP based curcumin particulates, *Int. J. Biol. Macromol*. 104:656–664, https://doi.org/10.1016/j.ijbiomac . 2017; 2017.05.170;.
23. Gajbhiye, V., Escalante, L., Chen, G., Laperle, A. And Zheng, Q. Drug-loaded nanoparticles induce gene expression in human pluripotent stem cell derivatives. *Nanoscale*. 2014;6:521-531.
24. Giri, T.K., Saurabh Verma, S., Ajazuddin, Alexander, A., Badwaik, H. and Tripathi, D.K. Prospective and New Findings of Hydroxypropyl Methylcellulose (HPMC) as a Potential Carrier for Gastrorententive Drug Delivery Systems. *Drug Delivery Letters*. 2012;2:98-107.
25. Gottwald, S. On the existence of solutions of systems of fuzzy equations. *Fuzzy Sets and Systems.* 1984;12:301-302.
26. Gu, J. H., Ge, J.B., Li M., Xu, H. D., Wu, F. And Qin, Z. H. Poloxamer 188 protects neurons against ischemia/reperfusion injury through preserving integrity of cell membranes and blood brain barrier. *PLoS One*. 2013;16:8(4): e61641. doi: 10.1371/journal.pone.0061641.
27. Hao, Y., Shih, H., Munoz, Z., Kemp, A., Lin, C. C. Visible light cured thiol-vinyl hydrogels with tunable degradation for 3D cell culture. *Acta Biomater*. 2014;10: 104-114.
28. Hascicek, C. Rossi, A. Colombo, P. Massimo, G. Strusi, O.L. Colombo, G. Colombo, G. Assemblage of drug release modules: effect of module shape and position in the assembled systems on floating behavior and release rate. *Eur. J. Pharm. Biopharm*. 2011; 77(1):116-121.
29. Hu, L.D. Xing, Q.B. Shang, C. Liu, W. Liu, C. Luo, Z.L. Xu, H.X. Preparation of rosiglitazone maleate sustained-release floating microspheres for improved bioavailability. *Pharmazie*. 2010;65(7):477-480.
30. Hughey, J. R., Kean, J. M., Miller, D. A., Brough, C. And McGinity, J. W. Preparation and characterization of fusion processed solid dispersions containing a viscous thermally labile polymeric carrier, *Int. J. Pharm*. 2012; 438:11-19.
31. Koczkur, K. M., Mourdikoudis, S., Polavarapu, L., Skrabalak, S. E., Koczkur, K. M., Mourdikoudis, S., Polavarapu, L., Skrabalak, P. Pvp, R.S. Chem, Polyvinylpyrrolidone (PVP) in nanoparticle synthesis, R. Soc. *Chem*. 2015;44:17883–17905.
32. Li, B., He, M., Li, W., Luo, W., Guo, Y., Li, Y., Zang, C., Wang, B., Li, F., Li, S. and Ji, P. Dissolution and pharmacokinetics of baicalin–polyvinylpyrrolidone coprecipitate. *J. Pharm. Pharmacol*. 2013; 65:1670-1678.
33. Linkov, I. And Moberg, E. Multi-Criteria Decision Analysis: Environmental Applications and Case Studies. Boca Raton, FL: CRC Press, Taylor & FrancisGroup. 2011
34. McKinnon, D. D., Brown, T. E., Kyburz, K. A., Kiyotake, E. And Anseth, K. S. Design and characterization of a synthetically accessible, photodegradable hydrogel for user-directed formation of neural networks. *Biomacromolecules*. 2014; 15:2808-2816.
35. Miller, D. A., DeNunzio, J. C., Hughey, J. R., Williams III, R. O. and McGinity, J. W. Kinetisol: A new processing paradigm for amorphous solid dispersion system. *Drug Development & Delivery*. 2012: 30-39.
36. Miller, D. J., Kasemset, S., Wang, L., Paul, D. R. And Freeman, B. D. Constant flux crossflow filtration evaluation of surface-modified fouling-resistant membranes. *Journal of Membrane Science*. 2014; 452:171-183.
37. Moloughney, J. G., And Weisleder, N. Poloxamer 188 (p188) as a membrane resealing reagent in biomedical applications. *Recent Pat Biotechnol*. 2016; 6(3):200-11.
38. Moreno, M., Zurita, E. And Giralt, E. Delivering wasp venom for cancer therapy. *J Control Release*. 182: 13-21.
39. Mori F., Barni S., Pucci N., Rossi ME., de Martino M., Novembre E. Cutaneous adverse reactions to amoxicillin-clavulanic acid suspension in children: the role of sodium benzoate. *Curr Drug Saf*. 2012; 7(2):87–91.
40. Omodamilola, Omoyayi Ibrahim, and Abdullahi Umar Ibrahim. CRISPR technology: advantages, limitations and future direction. *J Biomed Pharm*. 2018; 1.115: 2.

41. Portran, D.). Micropatterning Microtubules. Methods in Cell Biology. Matthieu P, Manuel T (Editors). Academic Press, USA. 2014: 39-51.
42. Qin X. Etiology of infl ammatory bowel disease: a unified hypothesis. *World J Gastroenterol*. 2012; 18(15):1708–1722.
43. Santos, J. L., Cordeiro, P. and Temtem, M. Scale-up of spray dried amorphous solid dispersions. *Eur. Indust. Pharm*. 2013; 19:4-8.
44. Setthacheewakul, S., Kedjinda, W., Maneenuan, D., Wiwattana-patapee, R. Controlled release of oral tetrahydrocurcumin from a novel self-emulsifying floating drug delivery system (SEFDDS). *AAPS. Pharm. Sci. Tech*. 2011; 12(1):152-164.
45. Shah, N., Iyer, N. R. M., Mair, H, G., Choi, D. S., Tian, H., Diodone, R., Fahnrich, K., Pabst-Ravot, A., Tang, K., Scheubel, E., Grippo, J. F., Moreira, S. A., Go, Z., Mousakountakis, J., Louie, T., Ibrahim, P. N., Sandhu, H., Rubia, L., Chokshi, H., Singhal, D. and Malick W. Improved human bioavailability of vemurafenib, a practically insoluble drug, using an amorphous polymerstabilized solid dispersion prepared by a solvent controlled co-precipitation. *J. Pharm. Sci*. 2013; 102:967-981.
46. Teodorescu, M., Bercea, M. And Morariu, S. Biomaterials of PVA and PVP in medical and pharmaceutical applications: perspectives and challenges, Biotechnol. *Adv*. 2019; 37:109–131. https://doi.org/10.1016/j.biotechadv.2018.11.008.
47. Thokala, P., Devlin, N., Marsh, K., Baltussen, R., Boysen, M. And Kalo, Z. Multiple criteria decision analysis for health care decision making—an introduction:report 1 of the ISPOR MCDA emerging good practices task force. *Value Health*. 2016; 19:1–13. doi: 10.1016/j.jval.2015.12.003.
48. Tong X. and Yang F. Engineering interpenetrating network hydrogels as biomimetic cell niche with independently tunable biochemical and mechanical properties. *Biomaterials*. 2014; 35:1807-1815.
49. Uzun Ozsahin, D., Onakpojeruo, E. P., Uzun, B., Mustapha, M. T., & Ozsahin, I. Mathematical Assessment of Machine Learning Models Used for Brain Tumor Diagnosis. *Diagnostics*. 2023; 13(4): 618.
50. Wieduwild, R., Lin, W., Boden, A., Kretschmer, K., Zhang, Y. A repertoire of peptide tags for controlled drug release from injectable noncovalent hydrogel. *Biomacromolecules*. 2014; 15:2058-2066.
51. Xu, J., Feng, E, And Song, J. Bioorthogonally Cross-Linked Hydrogel Network with Precisely Controlled Disintegration Time over a Broad Range. *J Am Chem Soc.* 2014; 136: 4105-4108.
52. Yu X, Buevich AV, Li M, Wang X, Rustum AM A compatibility study of a secondary amine active pharmaceutical ingredient with starch: identification of a novel degradant formed between desloratadine and a starch impurity using LC-MS(n) and NMR spectroscopy. *J Pharm Sci*. 2012; 102(2):717–731.
53. Zardavas, D., Baselga, J. & Piccart, M. Emerging targeted agents in metastaticbreast cancer. 2013. *Nat. Rev. Clin. Oncol*. 10:191–210

تحسين وسيلة توصيل الدواء باستخدام اختيار المواد المساعدة المبني على قرارات متعددة المعايير (MCDM)

إبراهيم أوموداميلولا أومويايي[1*]، عبد الله عمر إبراهيم[1]، سليمان آشير[1]

[1] قسم الهندسة الطبية الحيوية، كلية الهندسة، جامعة الشرق الأدنى، نيقوسيا، مرسين 10، تركيا.

ملخص

تُستخدم المواد المساعدة في أنظمة توصيل الدواء كوسيلة لتوصيل الأدوية بفعالية إلى موقعها المستهدف. تُعد طرق اتخاذ القرار متعددة المعايير (MCDM) أدوات لاتخاذ القرارات التي يمكن أن تضع في الاعتبار العوامل متعددة الأبعاد بالإضافة إلى التكنولوجيا المقارنة المستخدمة في الطب مع مزيج من المعايير الفردية في التقييم الكلي للبدائل المختارة. تهدف هذه الدراسة إلى تحسين الذوبانية والتوافر الحيوي للأدوية من خلال تطبيق اختيار المواد المساعدة المستند إلى MCDM. من خلال دمج طريقة ترتيب التفضيلات لتقييمات التحسين (PROMETHEE الضبابي)، يمكن تقييم المواد المساعدة المختلفة وترتيبها بناءً على مدى ملاءمتها للتطبيق المحدد، مع الأخذ في الاعتبار المعايير المتعلقة بذوبانية الدواء وتوافره الحيوي. تسلط النتائج الضوء على إمكانات السيكلودكسترين (صافي التدفق: 0.0023) وبوليمرات اليودراجيت (صافي التدفق: 0.0016) كخيارات مفضلة لحاملات الدواء، بينما يتم تحديد بولوكسامر 188 (P188) (صافي التدفق: −0.0030) كأقل خيار مفضل. تُظهر هذه الدراسة فعالية طريقة PROMETHEE الضبابي في تحسين أداء الأدوية ذات الذوبانية والتوافر الحيوي المنخفض، مما يساهم في النهاية في تطوير أنظمة توصيل الدواء الجديدة. تتمتع النتائج بأهمية كبيرة للنتائج العلاجية في علاج الأمراض.

الكلمات الدالة: اتخاذ القرار متعدد المعايير (MCDM)، مادة مساعدة حاملة للدواء، الذوبانية، التوافر الحيوي.

[*] ***المؤلف المراسل إبراهيم أوموداميلولا أومويايي***

omodammy@gmail.com

تاريخ استلام البحث: 2023/08/31 وتاريخ قبوله للنشر 2023/11/12.