RESEARCH ARTICLE

In-vitro Evaluation and Optimization of Sacubitril and Valsartan Floating Tablet using Natural Polymer

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Received: 16th September, 2023; Revised: 14th October, 2023; Accepted: 24th November, 2023; Available Online: 25th December, 2023

ABSTRACT

Oral systems have become gradually extensive for human consumption because of their numerous advantages, such as formulation efficiency, cost-effectiveness, and patient safety compliance. These systems offer a versatile platform for controlled drug release, allowing precise targeting of absorption site in the gastrointestinal tract. Accomplishing ideal therapeutic results for certain medications often requires precise control of drug release at specific locations within the gastrointestinal tract. In this study, our goal was to create a floating drug delivery system for two vital cardiovascular medications, sacubitril and valsartan. Our specific objectives were to extend floating time, prolong stomach residency, and reduce floating lag time. The strategy involved harnessing the synergistic potential of natural polymers in optimal proportions to enhance drug activity. Following the principles of quality by design (QbD), we systematically explored various formulation factors to optimize the drug delivery system. Analysis of tablet characteristics revealed significant variations in key parameters, such as swelling index, floating lag time (FLT), total floating time (TFT), and drug content for both sacubitril and valsartan. The enhanced formulation (F12) stood out with a remarkable swelling index of 93.4%, a floating lag time of 6.7 seconds, and an impressive total floating time of 12 hours. Furthermore, high drug content percentages were achieved, with sacubitril at 98.70% and valsartan at 94.65%. The successful development and optimization of the floating tablet formulation carry substantial clinical implications. The extended gastric retention, controlled drug release, and high drug content of the optimized formulation suggest enhanced bioavailability and therapeutic efficacy for both sacubitril and valsartan. The prolonged total floating time offers convenience to patients, potentially improving medication adherence in managing cardiovascular diseases. In conclusion, this study highlights the formulation and optimization of floating tablets as a noteworthy advancement in drug delivery technology, promising improved therapeutic outcomes and enhanced patient convenience.

Keywords: Sacubitril, Valsartan, Buoyancy studies, Natural polymer, Gastric residence time, *In-vitro* study.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.4.51

How to cite this article: Goyal AK, Kumar V. *In-vitro* Evaluation and Optimization of Sacubitril and Valsartan Floating Tablet using Natural Polymer. International Journal of Drug Delivery Technology. 2023;13(4):1454-1458.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Oral systems are now the favored method for human intake due to various benefits, such as ease of administration, formulation flexibility, cost-effectiveness, convenient storage and transportation, and increased patient compliance. This preference has transformed the pharmaceutical landscape, providing a versatile foundation for the controlled release of drugs and allowing accurate targeting of specific absorption sites in the gastrointestinal tract.[1,2] For certain drugs, achieving optimal therapeutic outcomes relies on precise control over their release at specific sites along the gastrointestinal tract. One promising approach involves the use of low-density drug delivery systems, where the overall density of dosage is lower than gastric fluid, facilitating gastric retention until the complete release of drug content. This controlled release approach holds tremendous potential in ensuring continuous drug delivery across the critical "absorption window."[3]

Over the past few decades, the development of gastroretentive drug delivery systems (GRDDS) has been explored extensively in pharmaceutical literature. Density-controlled devices have emerged as promising candidates for prolonging drug residence in the stomach.[4,5] Within the realm of density-controlled systems, both effervescent and non-effervescent floating systems, swelling systems, and raft-forming systems have garnered significant attention. Floating systems, in particular, offer a remarkable advantage by remaining buoyant in gastric for extended periods without impeding gastric emptying. This is primarily attributed to their less bulk density related to gastric fluid.[6,7]

However, while floating systems have several advantages, these include insufficient floatation when gastric fluid levels are low and the potential for dosage forms to be propelled towards the pylorus by forceful housekeeping waves, leading to reduced buoyancy time and diminished drug retention. To

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address limitations, advanced approaches have been pursued, incorporating mucoadhesive properties into floating systems to secure dosage form adherence to the gastric mucous lining. This augmentation significantly extends drug residence in the GIT, thereby enhancing drug absorption and oral bioavailability.[8,9]

In the background of research work, we endeavor to formulate a floating drug delivery system for two vital cardiovascular medications, sacubitril and valsartan, with the specific goal of extending the floating time, prolonging stomach residency, and reducing floating lag time. Our approach harnesses the synergistic potential of natural polymers, judiciously selected and utilized in optimal proportions, to enhance the therapeutic activity of these drugs.

METHOD AND MATERIALS

Materials

Sacubitril Valsartan trisodium hemipentahydrate, were provided by Alembic Pharmaceuticals. HPMC K4M, HPMC K100M, Polyox, and other excipients were acquired from Rankem, India. Guar Gum was procured from local market.

Methods

Formulation of sacubitril and valsartan floating tablets[10,11]

Sacubitril and valsartan floating tablets were manufactured employing a direct compression process with excipients and polymers to provide controlled drug release after ingestion. Excipients were weighed out precisely, added to a mortar, and blended gradually while being constantly kneaded to produce a homogeneous material. After passing through sieve number 40, the uniform powder was kept on sieve number 100. Talc and magnesium stearate were then used to lubricate the powder. On a tablet punching machine, the powder was then immediately compressed into tablets. Refer Table 1 for the formulation composition of sacubitril and valsartan floating tablets.

Quality target product profile and critical quality attributes

The QbD-based approach to drug product development led to the establishment of the quality target product profile (QTPP), which includes an overview of the quality attributes of the drug product for attaining the targeted GR drug delivery to get the best therapeutic effect. To reach the QTPP, a number of patient-centric critical quality attributes (CQAs) were developed that related to the finished product's quality. The extra material included an explanation of the primary QTPP components for making floating tablets along with the necessary rationale for the CQAs.[12]

Tables 2 and 3 represent the design matrix for floating matrix tablets including information on the coded factor levels (X1 for HPMC K4M and X2 for Guar Gum). A methodical investigation of the formulation space was made possible by the coded factor levels, which reflected the high and low values for each factor. The factorial design method was usually used to determine the levels, which were chosen in accordance with experimental design principles.

The predicted range of concentrations that are likely to affect the response (tablet characteristics or performance) and the requirement for a well-balanced and informative experimental design are generally used to calculate the levels. When examining the impact of HPMC K4M and guar gum on tablet characteristics, for instance, the high and low levels may be associated with the maximum and minimum concentrations of these ingredients that are realistically achievable in the formulation.

Table 1: Formulation composition

Ingredients	*Amount*
Sacubitril + Valsartan	53
HPMC K4M	20–100
Polyox	20
HPMC K100M	10–40
Guar gum	20–100
Sodium bicarbonate	10–18
Citric Acid	10–18
MCC	q.s
Talc	4
Magnesium stearate	2
Total (mg)	220

Table 2: Translation of level of codes

Level of codes	*Low*	*Intermediate*	*High*
X_1 (HPMC K4M)	0	50	100
X_2 (Guar gum)	0	50	100

Table 3: Design matrix for floating matrix tablets

Formulation ID	*Factor levels of codes*	
	X_1	X_2
F-1	1	-1
F-2	1	-1
F-3	-1	0
F-4	-1	-1
F-5	-1	-1
F-6	-1	-1
F-7	-1	1
F-8	-1	1
F-9	-1	0
F-10	-1	0
F-11	-1	-1
F-12	-1	0
F-13	0	0
F-14	0	1
F-15	0	1
F-16	1	-1
F-17	0	-1
F-18	0	-1
F-19	1	-1
F-20	0	-1

Characterization of Floating Tablet of Sacubitril and Valsartan

Swelling index

To assess the swelling index of tablets, they were deep in a 100 mL beaker containing HCl solution (pH 1.2), and the medium was kept at a temperature of 37 ± 0.5°C. After an 8-hour period, each beaker with a tablet was retrieved, cleaned with tissue paper to eliminate excess water, and then weighed using an analytical scale. The swelling of the tablet was ascertained by comparing its weight before and after immersion in the HCl solution (pH 1.2). The swelling index was evaluated using the following formula.[13]

$$\text{Swelling index} = \frac{W_t - W_0 \times 100}{W_o}$$

In-vitro floating lag time study

The period it takes for a tablet to rise to the surface of a dissolving liquid is referred as buoyancy lag time (BLT). The total duration for which the dosage remains consistently afloat on the surface of the liquid is termed as the total floating time (TFT).[14]

Table 4: Evaluation of formulated tablet

Batch	*Swelling Index (%)*	*FLT (sec)*	*TFT (hour)*	*Sacubitril (%)*	*Valsartan (%)*
F-1	83.2	4.3	7	--	--
F-2	81.9	3.2	9	--	--
F-3	94.2	4.9	8	--	--
F-4	63.8	6.1	8	--	--
F-5	72.8	5.3	7	--	--
F-6	84.6	5.4	8	89.8	92.4
F-7	89.4	5.9	7	87.7	94.6
F-8	95.6	6.5	10	94.5	91.2
F-9	86.1	6.9	8	85.6	89.5
F-10	76.9	10.7	9	94.7	92.3
F-11	86.8	5.4	12	91.5	96.8
F-12	93.4	6.7	12	98.7	94.65
F-13	87.7	3.2	8	95.8	90.5
F-14	89.2	4.7	11	91.6	84.1
F-15	92.3	5.8	8	92.8	96.59
F-16	89.6	5.7	8	94.65	94.26
F-17	91.4	5.6	9	95.47	91.25
F-18	88.3	5.8	11	94.69	92.35
F-19	90.5	6.5	10	96.32	93.57
F-20	84.3	6.8	9	94.87	96.54

*F1-F5 are the dumpy samples without drug API

In-vitro floating studies

To evaluate the *in-vitro* buoyancy of the manufactured floating tablet, determine both the floating lag time and the total floating time. The tablet underwent testing in a 100 mL beaker containing HCl solution (pH 1.2), maintained at a constant temperature of 37 ± 0.5°C throughout the test. The total floating time represents the duration the tablet remains buoyant in the solution, while the floating lag time is the interval between the tablet's introduction and its attainment of buoyancy in the HCl solution (pH 1.2).[14]

RESULTS

The formulated floating tablets of sacubitril and valsartan were evaluated on the parameters of swelling index, floating lag time, total floating time and drug content of sacubitril and valsartan. The results of the evaluation of formulated tablet are mentioned in Table 4.

Desirability

Table 5 represents the experimental findings for drug formulations with different concentrations of guar gum and hydroxypropyl methylcellulose (HPMC) K4M, assessing their effects on swelling index (Figure 1), floating lag time

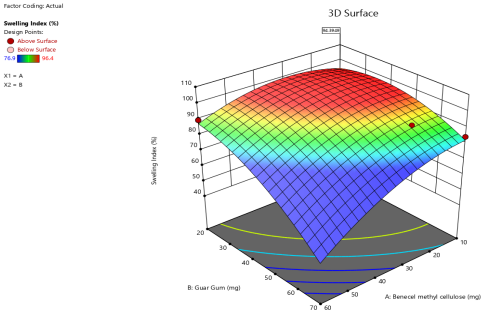

Figure 1: QbD central composite design graph of swelling index

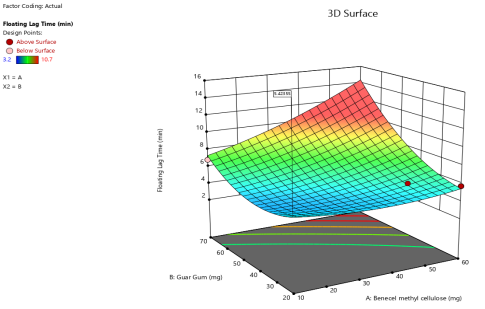

Figure 2: QbD central composite design graph of floating lag time

Table 5: Desirability of QbD

No.	*HPMC K4M*	*Guar Gum*	*FLT*	*Swelling Index*	*TFT*	*Drug Content Sacubitril*	*Drug Content Valsartan*	*Desirability*	
1	10.000	60.000	5.424	94.395	9.338	93.607	90.987	0.724	
2	0.064	59.184	6.500	88.971	10.398	96.212	94.425	0.952	Selected
3	21.264	59.073	6.500	89.000	10.390	96.232	94.426	0.421	

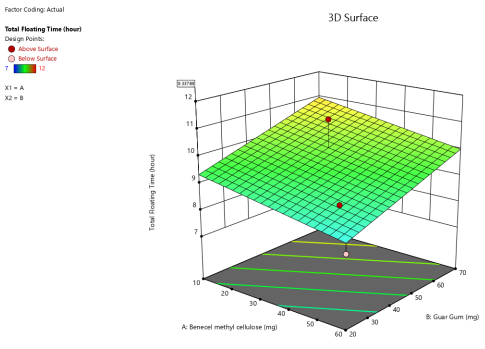

Figure 3: QbD central composite design graph of total floating time

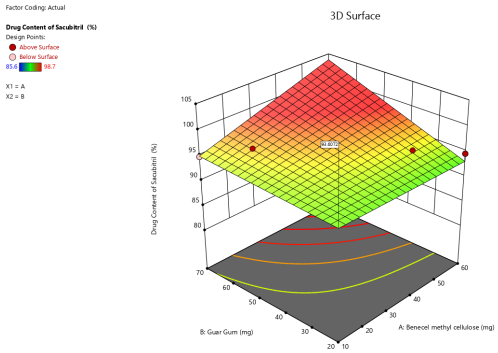

Figure 4P: QbD central composite design graph of sacubitril

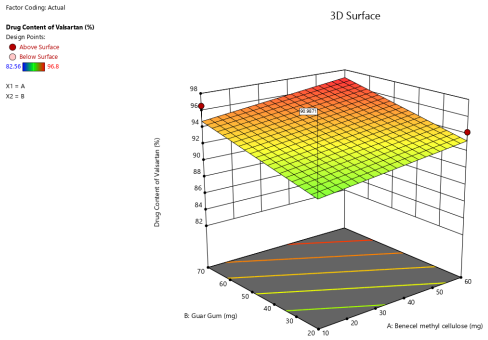

Figure 5: QbD central composite design graph of valsartan

(Figure 2), total floating time (Figure 3), and drug content of Sacubitril (Figure 4) and Valsartan (Figure 5). Notably, the formulation with a desire of 0.952 shows an ideal polymer concentration balance, which leads to a longer total floating period, a shorter floating lag time, and a high drug content for both components. The formulation that has a desirability of 0.952 indicates that polymer concentrations have a significant impact on formulation qualities, making it a viable option for creating a pharmaceutical dosage form with effective floating and drug release capabilities.

DISCUSSION

The formulation of floating tablets for the co-administration of sacubitril and valsartan represents a promising approach to enhance the bioavailability and therapeutic efficacy of these cardiovascular medications. This discussion delves into the key findings and implications of the study, including the evaluation of tablet characteristics, the influence of formulation factors, and the optimization of the final formulation.

The study evaluated several crucial tablet characteristics, including swelling index, FLT, TFT, and drug content of both sacubitril and valsartan. These characteristics are indicative of the tablet's performance in terms of gastric retention and drug release. The swelling index of the tablets, an important parameter for controlled drug release, ranged from 63.8 to 95.6%. Notably, formulation F8 exhibited the highest swelling index at 95.6%, suggesting that this tablet swells significantly in the gastrointestinal environment, facilitating drug release. The FLT, which represents the time taken for the tablet to emerge on the surface of the dissolution medium, ranged from 3.2 to 10.7 seconds. Formulation F13 exhibited the lowest floating lag time at 3.2 seconds, indicating rapid buoyancy. Total floating time, the duration during which the tablet remains buoyant in the dissolution medium ranged from 7 to 12 hours. Formulations F11 and F12 demonstrated the longest total floating times, both extending to 12 hours, which is particularly significant for controlled drug release. The drug content of sacubitril and valsartan within the tablets ranged from 84.1 to 98.7% and 84.1 to 96.8%, respectively. Formulation F12 exhibited the highest drug content for both drugs, with sacubitril at 98.7% and valsartan at 94.65%. Influence of Formulation Factors: The formulation variables, including HPMC K4M, guar gum, citric acid, and sodium bicarbonate, were systematically assessed using a QbD-based approach. The desirability function was employed to optimize the formulation. Among the evaluated formulations, F2 emerged as the selected formulation based on the desirability criteria. This formulation consisted of 0.064 mg HPMC K4M, 59.184 mg Guar Gum, 6.5 seconds of FLT, 88.971% swelling index, and 10.398 hours of total floating time. F2 was chosen as the final formulation for further analysis. The study culminated in the identification of an optimized final formulation, denoted as F12. This formulation incorporated key ingredients, including guar gum (60 mg), citric acid (12 mg), and sodium bicarbonate (18 mg). F12 exhibited favorable tablet characteristics, with a swelling index of 93.4%, a floating lag time of 6.7 seconds, and an impressive total floating time of 12 hours. Additionally, the drug content analysis revealed high drug content percentages for both sacubitril (98.70%) and valsartan (94.65%). The successful development and optimization of floating tablet formulation for sacubitril and valsartan hold substantial clinical implications. The extended gastric retention, controlled drug release, and high drug content of the optimized formulation (F12) suggest improved bioavailability and therapeutic efficacy for both sacubitril and valsartan. The prolonged total floating time of 12 hours ensures convenience for patients by reducing the frequency of dosing, potentially improving medication adherence in the management of cardiovascular conditions. The use of natural polymers and a QbD-based approach offers formulation flexibility and a systematic framework for the development of other gastro-retentive drug delivery systems.

CONCLUSION

In conclusion, the formulation and optimization of floating tablets for sacubitril and valsartan represent a significant advancement in drug delivery system. The results underscore the potential of controlled-release formulations to improve the therapeutic outcomes of cardiovascular medications while addressing patient convenience and compliance.

ACKNOWLEDGMENT

We express our gratitude to L.B.S. College of Pharmacy, for providing various resources and facilities used during the research study.

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