*Bangladesh Pharmaceutical Journal* ***28****(1): 105-113, 2025 (January)*

# Feasibility Study for the Development of Combination Dosage Form Containing Aspirin and Omeprazole for Treating Cardiovascular and Cerebrovascular Events

**Maniza Muni[1], B. K. Sajeeb[2], Sumaiya Sharmin Mou[2], Adeeba Jaheen Faruqui[2] and Md. Elias Al-Mamun[2]**

[1]Department of Pharmacy, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh
[2]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka
Dhaka-1000, Bangladesh

**(Received: November 5, 2024; Accepted: January 12, 2025; Published (web): January 29, 2025)**

**Abstract**

Cardiovascular and cerebrovascular diseases are two of the major reasons of morbidity and mortality worldwide, hence require proper treatment and secondary prevention. Aspirin is a first line treatment option for the patients suffering from aforementioned issues and is usually co-administered with omeprazole to lessen the gastrointestinal side effects. A survey was done among patients, doctors, pharmaceuticals and retailers to explore the feasibility of developing a combination bilayer dosage form of aspirin and omeprazole so that the complications of co-administration can be minimized. Data were collected through direct interview and online questionnaire, and statistical significance was determined using independent sample t-test. The study showed that drug utilization pattern of 85% of patients contain aspirin and omeprazole in the same prescription. Statistical data supported that both doctors and patients prefer the dose to be 75 mg for aspirin and 20 mg for omeprazole. More than 60% of each stakeholder showed their preference for the combination dosage form. Almost 50% of the doctors and patients preferred it for ease of consumption while retailers and manufactures considered the sales aspect. Moreover, ease of remembering, lesser number of pills consumption and lower price of the combination than the individual formulations came out to be the reasons for expecting availability of the combination among 68.82% of patients. As the demand of the combination and the market prediction of the pharmaceuticals matched, so introduction of fixed dose aspirin-omeprazole bilayer combination in Bangladesh can be beneficial overall.

**Key words:** Cardiovascular, cerebrovascular, aspirin, omeprazole, combination.

## Introduction

Cardiovascular disease (CVD) refers to a wide variety of disease conditions related to the arteries supplying blood to the brain, heart, lungs, muscle and other organs; veins carrying blood to the heart, heart muscle and valves (Mendis *et al.*, 2011). Cerebrovascular diseases are a type of disease in which vessels supplying blood to the brain are affected (Capildeo *et al.*, 1978). CVD is the topmost cause of death in the whole world (Zhang *et al.*, 2007). Internationally, the CVD burden per capita is highest in Eastern Europe and then in Central Asia but Asia and South Asia are known as the largest total CVD burden region because of the 78.1 million CVD disability adjusted life-years (DALYs) and 65.6 million CVD DALYs in 2016 respectively (Roth *et al.*, 2015). Heart failure (HF) is also a common disease in Bangladesh. Government has developed National NCD Strategy and planned to manage NCDs, especially CVDs. WHO as well as other non-

**Corresponding author:** Md. Elias Al-Mamun; E-mail: elias_0276@yahoo.com; Tel: 880-2-9661900
DOI: https://doi.org/10.3329/bpj.v28i1.79470

government institutions are performing important parts in this play (Islam *et al.*, 2016).

Aspirin at a low dose is recommended as it lowers the possibility of cardiovascular events and myocardial infarction (MI) by 15% and 30% respectively (Sanmuganathan *et al.*, 2001). A 2009 review stated that low dose aspirin used daily caused 19% reduction of threatening cardiovascular events in patients with a history of acute MI or ischemic stroke, but 0.19% increase in the risk of bleeding and damage in the gastrointestinal tract (Rothwell *et al.*, 2018). Dyspepsia is another common side-effect of aspirin, mostly at higher dosage (Yeomans, 2011). Every year 0.1-3% of patients who take low dose aspirin suffer from serious GI bleeding (Yeomans, 2011).

As omeprazole is commonly co-prescribed with aspirin to combat its side effects, the concept of developing a combination dosage form of these two were developed eventually. American company Aralez Pharmaceuticals Inc. first launched aspirin-omeprazole combination in the form of delayed release tablets and named it as Yosprala which was approved by US Food and Drug Administration (FDA) on 15 September 2016 (Sachs *et al.*, 2006). The advantages of bilayer combination tablets include lower cost, easier large-scale production, greater stability, highest dose precision, lowest content variability, patient compliance and extension of product lifecycle by renewing patent (Kumar *et al.*, 2013).

Gathering public opinion about a drug's necessity is an important part of the total feasibility study. Thus we conducted our survey and analysis to understand the usage of aspirin and omeprazole among Bangladeshi patients and to quantify the demand for aspirin-omeprazole combination drug among different stakeholders and their overall idea about the benefits of such combination drug.

## Materials and Methods

*Stakeholders:* Our stakeholders were categorized into four groups, namely patients, doctors, pharmaceutical professionals and retailers of pharmacies. We collected data of the retailers from some of the drug stores of Dhanmondi, Shahbagh and Polashi area of Dhaka; patients from online and Dhaka Medical College Hospital; doctors from different private and public hospitals and online; pharma professionals from online and different companies.

*Sample size determination:* We obtained qualitative as well as quantitative data from the participants of each group of stakeholders. Using Cochran's formula of sample size for categorical data and considering error level as 5%, we got the sample size of our experiment.

Sample size $n = \{z^2_{\alpha/2}pq\}/ d^2$

Here, $z_{\alpha/2} = 1.96$; $p = 0.5$, $q = (1-0.5) = 0.5$

d is the margin of error, that is 0.05 (5%)

α is the significance level which is assumed as 5%

p is the value of proportion, which is taken as 0.5 in a standard sample determination process.

So, $n = \{z^2_{\alpha/2}pq\}/ d^2$

$= \{1.96^2 \times 0.5 \times 0.5\}/ 0.05^2$

= 384.16, which is equivalent to 384

We earnestly tried to keep our data close to the standard value. But due to the nature of the experiment and lower density of the suitable subjects within the population, we could manage only 231 respondents' data in our survey.

*Study method:* We followed a questionnaire-mediated survey method which is quantitative in nature. This method provided us with frequency data. Further evaluation of the obtained data has been done with descriptive and inferential statistical tools.

*Data collection:* To fulfill our study objective, we collected data both from the field and from online. 4 sets of questionnaires were prepared and sent to patients, doctors and pharma professionals virtually through Google Form. The responses of the retailers, some pharmaceutical professionals and some doctors were collected manually by visiting them. The retailers were asked questions personally on relevant issues and their responses were recorded by the collector manually. The questions followed a common pattern that consisted of demographic characteristics, multiple choice questions and their recommendation on various issues. After receiving

all the responses, the data were arranged and analyzed precisely without changing any of their answers.

*Data analysis:* We processed our data through MS WORD, MS Excel and SPSS that helped to deal with the descriptive and inferential data. Data collected from the survey work were further analyzed and represented via several tables and graphs. Microsoft Office Excel 2010 was used in this regard.

*Time frame of the study:* It took around 2-3 weeks to plan the research by reviewing papers relevant to the study and one month to prepare the questionnaires. The data collection took about three months and organization took 15 days. The total work started from February 2022 and continued till June 2022. The analysis and further addition of some data were done in the month of July 2022.

## Results and Discussion

*Findings from the analysis of data relevant to aspirin and omeprazole utilization pattern in Bangladesh:* The study targeted the patients suffering from cardiovascular and cerebrovascular diseases from Dhaka medical college hospital and few from outsides. 71.15% of the patients of the study were from urban area and their age group was in between 40-60 years old and 60 above. 70.19% of the patients were male. The demographic data is shown in table 1.

**Table 1. Demographic data of the patients**

| Characteristics | | Frequency (n) (Total = 104) | Percentage (%) |
|---|---|---|---|
| Age | <18 | 1 | 0.96 |
| | 18-25 | 17 | 16.35 |
| | 25-40 | 21 | 20.19 |
| | 40-60 | 43 | 41.35 |
| | >60 | 22 | 21.15 |
| Gender | Male | 73 | 70.19 |
| | Female | 31 | 29.81 |
| | Others | 0 | 0 |
| Area of residence | Urban | 74 | 71.15 |
| | Rural | 30 | 28.85 |
| Monthly income (BDT) | <20 thousand | 52 | 50 |
| | 20-40 thousand | 35 | 33.65 |
| | 40-60 thousand | 10 | 9.62 |
| | 60-80 thousand | 4 | 3.85 |
| | 80 thousand-1 lakh | 3 | 2.88 |
| | >1 lakh | 0 | 0 |

Among the 104 patients, 79 (76%) used aspirin as a drug to manage their conditions. Majority of them used 75 mg dose (n=72), others used 100 mg (n=4),150 mg (n=2) & 500 mg (n=1) dose respectively. All these responses are shown in Figure 1(a) and figure 1(b). Concurrently the data from the doctors showed that, all of the 42 doctors prescribed aspirin to the patients suffering from cardiovascular and cerebrovascular diseases. As per the doctors' response, which is delineated in figure 1(c), 76.19% of them prescribe aspirin and PPI (Proton pump inhibitor) in the same prescription.

Moreover, it can be an impactful finding that the doctors and the patients preferred 75 mg of aspirin and 20 mg of omeprazole among all the strengths. To

find out the association between their responses statistical analysis was done. The Chi-square test presented in table 2 and table 3 show the statistical association among the responses.

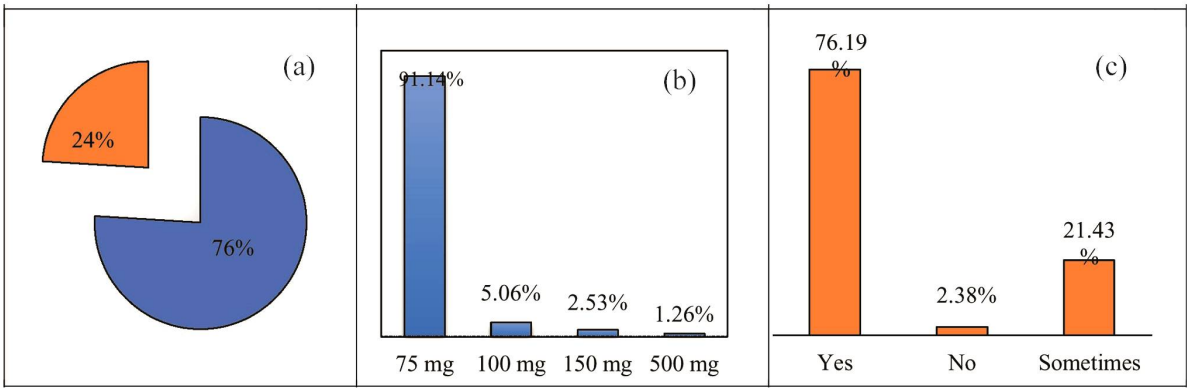


Figure 1. Aspirin and PPI utilization pattern in Bangladesh. (a). Distribution of patients taking aspirin. (b). Dosage of aspirin utilized by patients. (c). Doctors prescribing aspirin and PPIs in the same prescription.

**Table 2. Statistical analysis of preferred dose of aspirin by majority of doctors and patients (independent samples test).**

| | | Levene's test for equality of variances | | *t-test for equality of means* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | F | Sig. | t | df | Sig. (2-tailed) | Mean Diff. | Std. Error Diff. | 95% Confidence Interval of the Diff. | |
| | | | | | | | | | Lower | Upper |
| Aspirin dose | Equal variances assumed | 6.094 | .015 | -1.264 | 119 | .209 | -13.480 | 10.668 | -34.603 | 7.644 |
| | Equal variances not assumed | | | -1.153 | 65.209 | .253 | -13.480 | 11.693 | -36.831 | 9.872 |

(sig=significance, df=degrees of freedom, diff=difference, std=standard)

**Table 3. Statistical analysis of preferred dose of omeprazole by majority of doctors and patients (Independent Sample Test).**

| | | Levene's test for equality of variances | | *t-test for Equality of Means* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | F | Sig. | t | df | Sig. (2-tailed) | Mean Diff. | Std. Error Diff. | 95% Confidence interval of the difference | |
| | | | | | | | | | Lower | Upper |
| Omeprazole dose | Equal variances assumed | 2.760 | .100 | .812 | 107 | .419 | .839 | 1.033 | -1.209 | 2.886 |
| | Equal variances not assumed | | | .867 | 103.513 | .388 | .839 | .968 | -1.081 | 2.758 |

(sig=significance, df=degrees of freedom, diff=difference, std=standard)

The analysis stated above considers the equal variance not to be assumed and for that the significance is got .253>.05 (p Value). So, the Null hypothesis cannot be rejected and the response of the doctors and the patients regarding the usage of a particular dosage of omeprazole along with aspirin is same. It is evident that, 75 mg of aspirin is the preferred one in case of co-prescription with omeprazole.

The analysis stated above considers the equal variance to be assumed and for that the significance got was .419>.05 (p Value). So, the Null Hypothesis

cannot be rejected and the response of the doctors and the patients regarding the usage of a particular dosage of omeprazole along with aspirin is same. Therefore, it may be recapitulated that, 20 mg of omeprazole is the preferred one in case of co-prescription with aspirin.

It was clearly analyzed from the data that, 48% (n=20) of the doctors preferred omeprazole over other PPIs and 33% (n=14) of the doctors preferred omeprazole in some cases but not all. 19% (n=8) of the doctors preferred other PPIs like pantoprazole or esomeprazole over omeprazole. Figure 2 shows all the responses.

Focusing on the reasons behind the co-prescription of PPIs along with aspirin, some questions were set for the stakeholders. The patients reported that they faced some sort of side effects when they took aspirin without PPIs. Among 79 of them, 26.37% faced no side effect. But the rest experienced at least one side effect which are shown in the bar chart of figure 3.

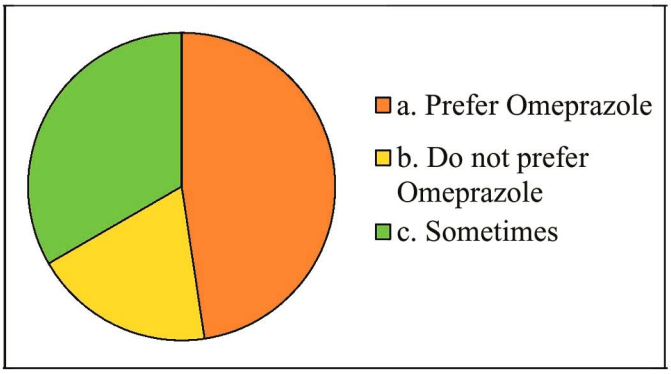


Figure 2. Preference of omeprazole for co-medication with aspirin over other PPIs.

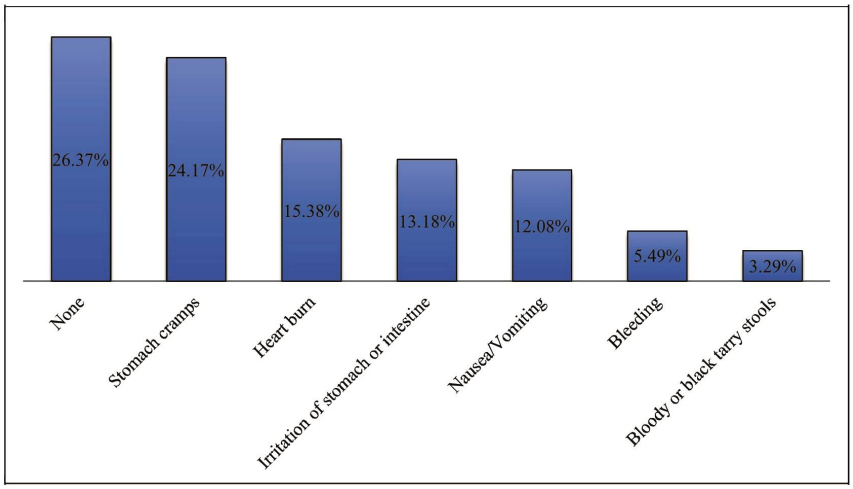


Figure 3. Side effects faced by patients using aspirin without PPIs.

*Justification of aspirin and omeprazole combination in Bangladesh medicine market:* The side effects faced by patients taking aspirin without PPIs might be the root cause of prescribing them together in a prescription. The study was aimed at finding the feasibility of the aspirin-omeprazole combination dosage form. For this reason, the preference of the combined dosage form of these two

co-prescribed medicines for cardiovascular and cerebrovascular disease was analyzed. After getting responses from all the stakeholder groups, a comparative study among them showed that most of them preferred the aspirin-omeprazole combination in Bangladesh. In the study the data of 73.53% of the patients, 64.28% of the doctors, 68.29% of the pharmaceutical professionals and 79.54% of the retailers showed their preference regarding the combination dosage form shown in figure 4. All the stakeholders showed higher positivity towards the combination to be made available in Bangladesh market.

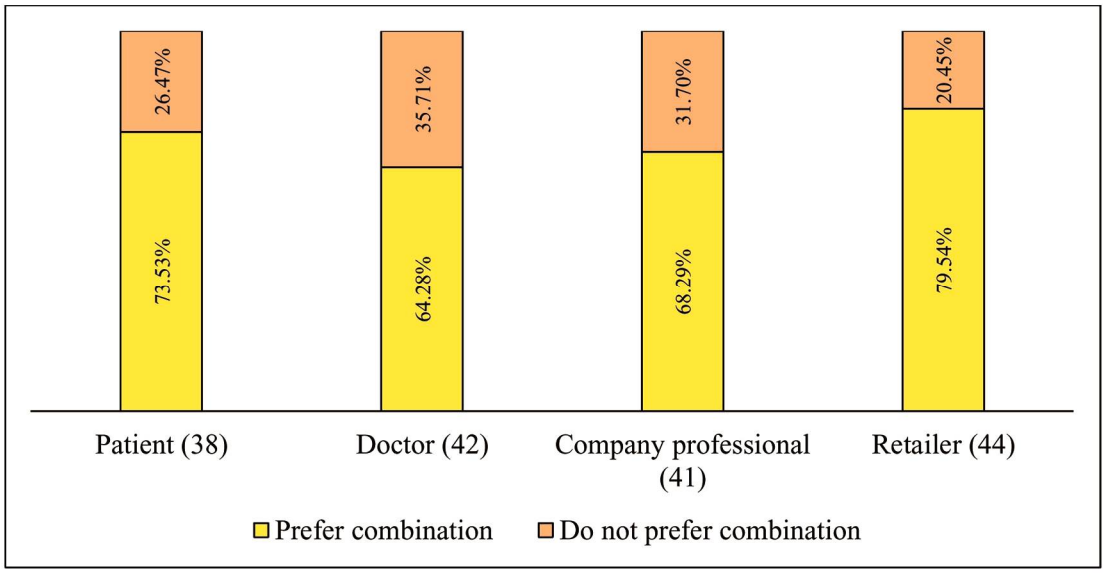


Figure 4. Correlational study of the opinions of stakeholders regarding the combination dosage form of aspirin and omeprazole.

It is established through studies that, aspirin and omeprazole are prescribed together to mitigate the gastrointestinal (GI) complications in case of patients with cardiovascular diseases (Elmasry *et al*., 2022). So, combining them together will open up so many wings for the patients as well as for other group of stake holders. Also, adherence with a treatment is necessary to get optimum therapeutic effect. But sometimes critical patients do not stick to the treatment guideline properly. This creates so many problems for their physical condition. Non adherence is a common issue for aspirin takers. Therefore, aspirin adherence rate in case of more than 70% patients remains suboptimal (Howden, 1991). For this, combination therapy might be beneficial.

The benefits that can be obtained from the combination were also analyzed. As per the stakeholders there may be many reasons to have their positive attitude towards the aspirin-omeprazole combination. The highest response was got for few of the reasons like- ease of medication intake, decrease in pill burden, reduced cost, less chance of skipping dose and ease of remembrance of their medications. All of these are shown in figure 5. In most of the cases, patients suffering from the cardiovascular and cerebrovascular complication fall into the age group of 40-60 years old. This is a finding from the demographic data of the patients of the study showed in table 1, therefore, their convenience of taking medicine is being reflected by their reasoning behind preferring combination dosage form.

*Findings from the medicine market based on the response of retailers and manufacturers*: The pharma professionals' data showed significance when their combination preference and their market acceptance perception were tested statistically (Table 4). So, the

field data from the patients are associated with the data from the pharmaceutical professionals. 54% of the companies also agreed to manufacture the combination which is visualized in figure 6.

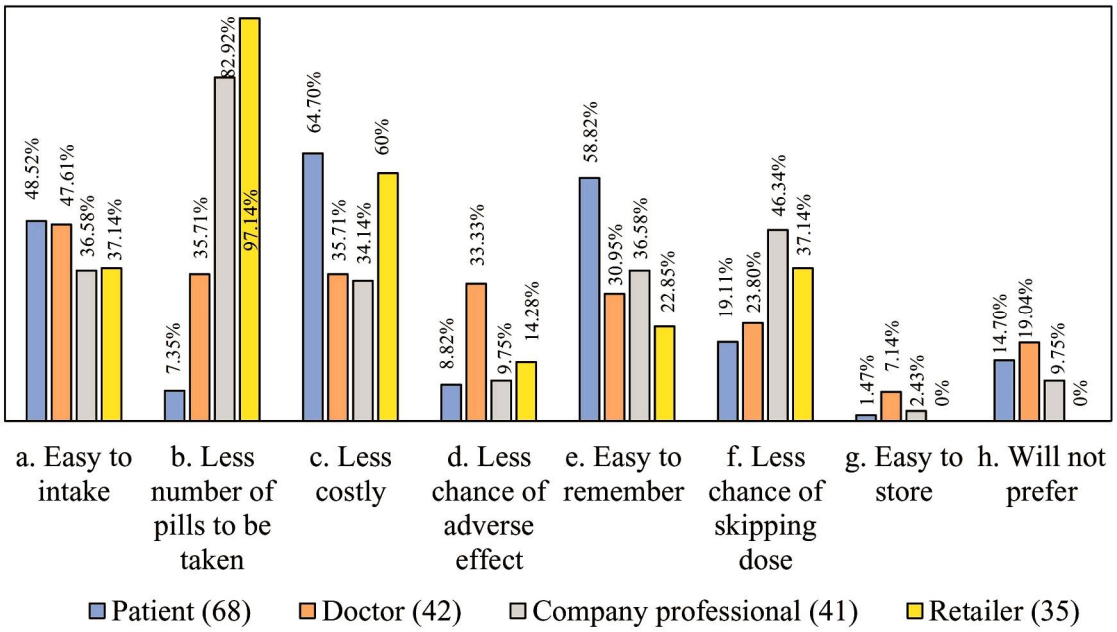


Figure 5. Reasons behind preferring the combination in a single dosage form.

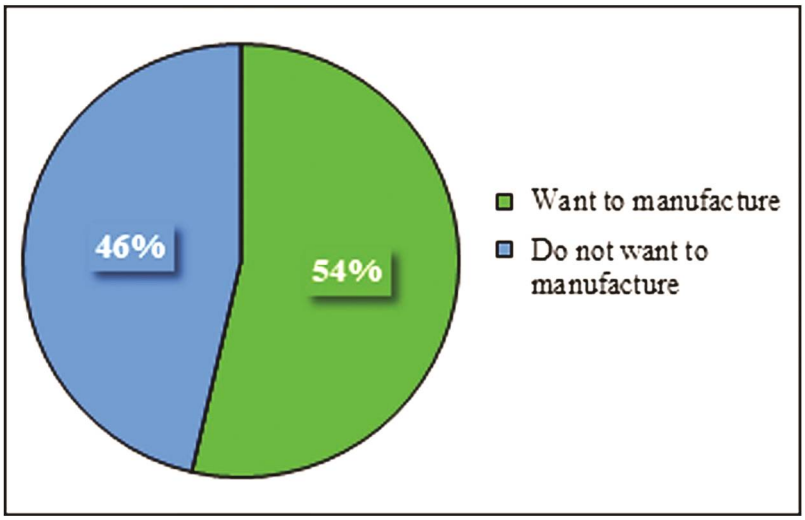


Figure 6. Future plan of companies regarding aspirin-omeprazole combination.

Three types of chi-square tests were performed to find out if the pharma professionals who predicted that market demand of aspirin-omeprazole combination is high also wanted to manufacture the combination formulation in near future (Table 4) as well as to know retailers' view about purchase of omeprazole with aspirin and supporting aspirin-omeprazole combination (Table 5).

Six cells (60.0%) have expected count less than 5. The minimum expected count is 1.85.

Here, considering the Fisher Exact value .130> .05 (p value), The Null hypothesis cannot be rejected. So, the opinion of the pharma company regarding the market demand is similar to the actual market demand of aspirin and omeprazole combination if it is introduced. The pharma professional opting to manufacture the combination and their market analysis delineates the same proportion.

**Table 4. Statistical analysis between pharma professionals' prediction of combination market and their future prospect regarding this: Chi-Square tests.**

| | Value | df | Asymp. Sig. (2-sided) | Exact Sig. (2-sided) |
|---|---|---|---|---|
| Pearson Chi-Square | 6.902[a] | 4 | .141 | .153 |
| Likelihood ratio | 7.272 | 4 | .122 | .190 |
| Fisher's exact test | 7.038 | | | .130 |
| N of valid cases | 41 | | | |

(asymp. sig.= asymptotic significance, df=degrees of freedom).

**Table 5. Statistical analysis between retailers' view about purchase of omeprazole with aspirin and supporting aspirin-omeprazole combination: Chi-Square Tests.**

| | Value | df | Asymp. Sig. (2-sided) | Exact Sig. (2-sided) |
|---|---|---|---|---|
| Pearson chi-Square | 2.796[a] | 3 | .424 | .480 |
| Likelihood Ratio | 4.106 | 3 | .250 | .362 |
| Fisher's Exact Test | 2.748 | | | .427 |
| N of Valid Cases | 44 | | | |

(asymp. sig.= asymptotic significance, df=degrees of freedom)

Five cells (62.5%) have expected count less than 5. The minimum expected count is 1.23.

Here the chi-square tests are done to find out if the retailers who thought majority of the patients buying aspirin also buys omeprazole are also those who thought aspirin-omeprazole combination should be available. The analysis stated above indicates a large exact value than the p value, so the Null hypothesis cannot be rejected. So, the proportion of the retailers supporting the combination and those who said that maximum patients buy aspirin with omeprazole is same. So, combination can be a good choice as per the retailers' perception.

## Conclusion

This study gives a realistic idea about the situation of drug market aspirin and omeprazole as well as their combination in Bangladesh. From this knowledge, we would be able to decide whether we should proceed with making the combinations and in which factors we should emphasize on while continuing the process. The limitation of the study is that it was conducted among a small group of people, and as there were four types of stakeholders, finding similar number of participants from each group was difficult. Due to these reasons, showing statistical significance among the data obtained from different groups was not possible in some cases. So, there is scope for further and more widespread study to achieve more significant results.

## Acknowledgments

This work was financially supported by the Centennial Research Grant (CRG), University of Dhaka (Project Ref. No.: Reg./Admin-3/47854, dated: 03-06-2021).

## References

Capildeo, R., Haberman, S. and ROSE, F.C., 1978. The definition and classification of stroke: a new approach. QJM: *An Int. J. Med*. **47**, 177-196.

Elmasry, M.S., Hassan, W.S., El-Mammli, M.Y. and Badrawy, M., 2022. Earth friendly spectrophotometric methods based on different manipulation approaches for simultaneous determination of aspirin and omeprazole in binary mixture and pharmaceutical dosage form: comparative statistical study. *Spectrochimica Acta Part A: Mol. Biomol. Spectrosc.*. **266**, 120436.

Howden, C.W., 1991. Clinical pharmacology of omeprazole. *Clin. Pharmacokinet.*. **20**,.38-49.

Islam, F.M.A., Bhuiyan, A., Chakrabarti, R., Rahman, M.A., Kanagasingam, Y. and Hiller, J.E., 2016. Undiagnosed hypertension in a rural district in Bangladesh: The Bangladesh Population-based Diabetes and Eye Study (BPDES). *J. Hum. Hypertens*. **30**, 252-259.

Kumar, A.H., Kavitha, K., Kumar, S.A., Kumar, M.R. and Singh, S.D., 2013. Novel approach of bilayer tablet technology-a review. *Int. J. Pharm., Chem. Biol. Sci.* **3**(3).

Mendis, S., Puska, P., Norrving, B.E. and World Health Organization, 2011. Global atlas on cardiovascular disease prevention and control. *World Health Organization.*

Roth, G.A., Forouzanfar, M.H., Moran, A.E., Barber, R., Nguyen, G., Feigin, V.L., Naghavi, M., Mensah, G.A. and Murray, C.J., 2015. Demographic and epidemiologic drivers of global cardiovascular mortality. *New Engl. J. Med*. **372**, 1333-1341.

Rothwell, P.M., Cook, N.R., Gaziano, J.M., Price, J.F., Belch, J.F., Roncaglioni, M.C., Morimoto, T. and Mehta, Z., 2018. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *The Lancet* **392**, 387-399.

Sachs, G., Shin, J.M. and Howden, C.W., 2006. The clinical pharmacology of proton pump inhibitors. *Aliment. Pharm. Ther.* **23**, 2-8

Sanmuganathan, P.S., Ghahramani, P., Jackson, P.R., Wallis, E.J. and Ramsay, L.E., 2001. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart* **85**, 265-271.

Yeomans, N.D., 2011. Aspirin: old drug, new uses and challenges. *J. Gastroenterol. Hepatol.* **26**, pp.426-431.

Zhang, X.H., Guan, T., Mao, J. and Liu, L., 2007. Disparity and its time trends in stroke mortality between urban and rural populations in China 1987 to 2001: changing patterns and their implications for public health policy. *Stroke* **38**, 3139-3144.