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Original Research Article

Dissolution rates of various brands of proton pump inhibitors in combination with domperidone: an in vitro study

Shibendu Ghosh[1], Sandip Kumar Das[2], Krishna C. V.[3], Ritwik Banerjee[3]*

[1]Jagannath Gupta Institute of Medical Sciences, Kolkata, West Bengal, India
[2]Rehab Polyclinic, Burdwan, Burdwan, West Bengal, India
[3]Dr Reddy's Laboratories, Hyderabad, Telangana, India

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***Correspondence:**
Ritwik Banerjee,
Email: ritwikbanerjee@drreddys.com

ABSTRACT

Background: Drug solubility, bioavailability, and dissolution rates are important in establishing in vivo efficacy. Eight brands of domperidone proton pump inhibitor combination drugs were compared to enable physicians to take an informed decision regarding the dissolution rates of various domperidone-PPI combinations available in the Indian market to allow identification and prescription of the drug with better bioavailability.
Methods: The in vitro dissolution rate of a combination of domperidone-PPI drugs was measured using the United States Pharmacopeia dissolution paddle apparatus. Each flask of the dissolving testing apparatus contained one tablet and 900 mL of the media, which was dissolved in pure water with 1% Tween® stored at 37.4°C. At regular intervals, aliquots were removed, filtered, and the amount of drug released was measured. The cumulative drug release was calculated using a standard formula.
Results: P04 and P07 had the fastest and the slowest onsets of action, respectively. P01 (Omez DSR) and P08 exhibited the longest and the shortest durations of action, respectively. The P05, P06, and P08 formulations had greater particulate matter than the other formulations. Under in vitro conditions, the bioavailability of Omez DSR was nearly two-fold higher than P07 and five-fold higher than P08.
Conclusions: Although P04 exhibited the fastest onset of action, Omez DSR had the longest duration of action, superior bioavailability, and ensured the rapid and continuous release of domperidone. Omez DSR demonstrated superior properties compared with other brands.

Keywords: Domperidone, Proton pump inhibitors, Omeprazole, Esomeprazole

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common chronic condition caused by the abnormal retrograde flow of gastric contents into the esophagus, oral cavity, or lungs. It has an estimated worldwide incidence of up to 20%, making it the most encountered disease in gastroenterology.[1] Bhatia et al conducted a multicenter healthcare facility-based study and estimated a prevalence of 7.6% of GERD in Indians. Another study reported a high prevalence of GERD (28.5%) among employees of a tertiary hospital in southern India.[2] This increase can also be attributed to changes in people's lifestyle, diet, medication, and smoking habits, which have led to an increased incidence of GERD symptoms. In terms of treatment, antacids were the primary treatment in the 20th century, followed by the introduction of histamine 2 receptor antagonists (H2RAs) in the 1970s. The H2RAs reduce the acidity of gastric fluid and esophageal refluxate. In the 1980s, proton pump inhibitors (PPIs) were developed, which have been widely used in most countries to reduce gastric acid production.[1] Proton pump inhibitors belong to a group of antisecretory drugs.[3] They selectively

block H+/K+ Adenosine triphosphatase pumps, which permanently inhibit the release of stomach acid.[4] With the acid–base dissolution constant (pKa) values ranging from roughly 4.0 (omeprazole) to 5.0, they are weak acids (rabeprazole). Those PPIs with higher pKa values have a more rapid commencement to the protonation process and accumulate more in parietal cells.[3] The rate of delivery of the active component into the body, by an orally administered product, is crucial.[5] Omeprazole has poor solubility in water, which contributes to low dissolution rates and hence low bioavailability. Omeprazole's S-enantiomer is stable and optical in humans,[6] is eliminated more slowly, and is metabolized more rapidly than the R-enantiomer.[3] Pantoprazole has a bioavailability of approximately 77%, a half-life of 1-2 hours, and a maximal plasma concentration (tmax) of 2-4 hours.[7] Rabeprazole sodium dissolves rapidly at an acidic and neutral pH. To prevent degradation at a lower gastric pH, rabeprazole sodium is presently available as delayed-release capsules and enteric-coated tablets. With a tmax of 3.5-4.[5] hours, enteric-coated rabeprazole drugs generally have a much-delayed pharmacokinetic onset time.[8] In comparison with delayed release omeprazole formulations, it has been observed that immediate-release omeprazole preparations stabilized with bicarbonate buffers enable faster absorption and initiate gastric acid suppression. Additionally, the rates of absorption vary significantly between PPI preparations.[9] Understanding each PPI's dissolution profile is critical for developing effective and safe formulations that ensure consistent drug delivery. The enzymes cytochrome (CYP) 3A4, CYP450, and CYP2C19 are responsible for the hepatic metabolism of most PPIs. Different patients may respond differently to identical drug doses, according to observations.[7] Combining PPI and domperidone is a successful treatment option for patients with GERD, especially omeprazole's efficacy in treating excess acid and domperidone's ability to prevent poor acid suppression by promoting rapid transport to the upper intestine. It provides synergistic therapeutic benefits with no significant interactions.[4,10] Domperidone is a dopamine (D2) receptor antagonist that exerts its action by blocking dopamine receptors in both the brain and the gastrointestinal tract. It reverses the dopaminergic inhibition of gastric motility mediated via the chemoreceptor trigger zone, which leads to symptoms such as bloating, pain, nausea, and vomiting. By blocking dopaminergic receptors, domperidone increases the release of acetylcholine, which in turn facilitates gastrointestinal motility, thereby improving these symptoms. Domperidone does not cross the blood–brain barrier, thus avoiding central nervous system side effects.[11] Its plasma protein binding and bioavailability are 91%-93% and 13%-17%, respectively. Its low water solubility results in low bioavailability.[12] The advantages of combining domperidone with other PPIs on pharmacokinetics have been well investigated. Ndraha and colleagues evaluated the impact of domperidone on the therapeutic efficacy of omeprazole. They observed that patients who received both omeprazole and domperidone responded more favorably than those who received omeprazole alone.[13] Coadministration of domperidone and omeprazole induces a rapid onset of action and greater sustained suppression of acid with adequate bioavailability than omeprazole alone. Omeprazole 40 mg has been observed to be significantly superior compared with omeprazole 20 mg in the control of intragastric pH.[10] Drugs of different brands exhibit minor and predictable variability that is not clinically significant.[14] Some pharmaceutical brands may use excipients for improving the drug's effectiveness, stability, or patient acceptability.[15] Hydroxypropyl methylcellulose (HPMCs) is a pharmaceutical excipient recognized for its capacity to regulate drug release, improve bioavailability, and improve patient compliance. For controlled-release dosage forms with HPMC as a polymer, the drug is released at a constant pace to maintain a constant dose and eventually establish a stable equilibrium.[12] A drug's dissolution profile is an important characteristic in its pharmaceutical development as it determines the rate and degree of absorption of the drug, which impacts its efficacy and safety.[17] The dissolving rate is affected by both intrinsic (solid state qualities of pure substance, such as particle size, surface area, crystal habit, and distribution) and extrinsic (hydrodynamics and test conditions) components. The bioavailability of orally delivered drugs is determined by their ability to be absorbed via the gastrointestinal tract.[18] Predictive in vitro dissolution testing is a useful method for formulation development as it delivers discriminative in vitro data that can guide the selection of desirable formulation features.[9] Comprehension of the pharmacokinetic benefits of combining domperidone with different PPIs can aid in selecting optimal drug combinations and dosing regimens for managing acid related disorders. The objective of this in vitro study was to assess the dissolution rates of PPIs when combined with domperidone, aiming to provide clinicians with valuable information about the appropriate use of this drug combination. At present, there exists a dearth of research on the concomitant use of domperidone and PPIs. As the first study of its kind, the results of this investigation have significant implications for clinical decision-making and future research in this field. The findings offer valuable insights into the safety and effectiveness of combining domperidone and PPIs, thereby filling an important gap in the existing literature.

METHODS

Domperidone dissolution

Eight combinations of domperidone with PPIs of several brands were acquired from a pharmacy. They included P01=Omez DSR (30 mg of domperidone and 20 mg of omeprazole), P02 (30 mg of domperidone and 20 mg of rabeprazole), P03 (30 mg of domperidone and 40 mg of esomeprazole), P04 (30 mg of domperidone and 40 mg of pantoprazole), P05 (30 mg of domperidone and 40 mg of pantoprazole), P06 (30 mg of domperidone and 40 mg of esomeprazole), P07 (30 mg of domperidone and 40 mg of pantoprazole), and P08 (10 mg of domperidone and 20 mg

of omeprazole). All the drugs were masked at the time of the study and revealed later. The United States Pharmacopeia dissolution paddle apparatus 2 was utilized to assess the in vitro dissolution rate for the combination of domperidone-PPI brands at a rotation speed of 50 rpm. Each dissolving testing apparatus flask held one tablet and 900 ml of the dissolution media (purified water with 1% Tween®) at a temperature of 37.4°C; 24 hours were allotted for the experiment. At regular intervals, aliquots (5 ml) were taken out, filtered, and the amount of drug released was examined. The volume of the media was adjusted by the addition of the same amount of media after each sampling. The following equation computed the overall drug release:

$$Amount\ of\ drug\ release\ (mg) = Concentration \times dilution\ factor \times volume\ of\ media/1000$$

$$Drug\ release\ (\%) = Amount\ drug\ release\ (mg) \times 100/\ Dose\ (mg)$$

Domperidone calibration curve

Methanol was used to dissolve domperidone and prepare a stock solution with a concentration of 100 g/ml. Working solutions (2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 g/ml) from the stock solution were prepared by diluting it in dissolution media. After filtering each solution, the absorbance at 284 nm was calculated. Moreover, high-performance liquid chromatography was carried out using a Phenomenex-C18 (4.6 mm id, 250 mm, 5 m) column with a mobile phase of methanol: 0.1% orthophosphoric acid in water (55%:45% v/v) at a flow rate of 1.0 ml/min. At 284 nm, domperidone was identified, and a concentration vs. absorbance standard curve was plotted.

Statistical analysis

Statistical analysis was conducted to evaluate the significance of differences between the data sets. The data were analyzed using GraphPad Prism software, employing a one-way analysis of variance followed by a post hoc Tukey test. The level of significance was set at $p<0.05$, with a 95% confidence interval.

RESULTS

The comparative dissolution profiles of drugs P01 to P08 are provided in (Table 1). The (Figure 1) is a graphical representation of the comparative dissolution behavior of different brands of PPIs in combination with domperidone. The dissolution profiles of various drugs are represented by different colored lines.

The area under the curve (AUC) and t-max of the drugs P01 to P08 are given in (Table 2).

The sustained release properties of different brands of PPIs in combination with domperidone are depicted in (Figure 2). The (Figure 3) demonstrates the rapid-release properties of different brands of PPIs in combination with domperidone.

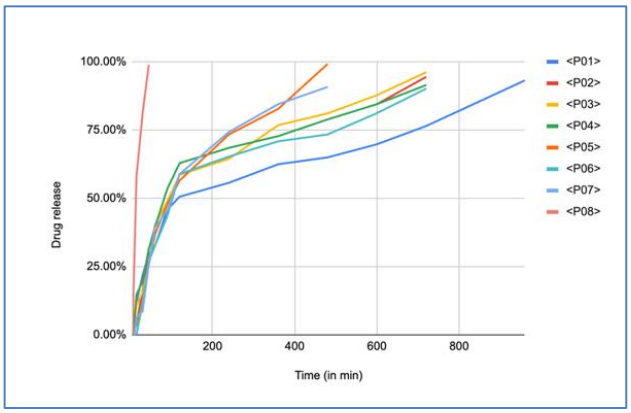

Figure 1: Comparative dissolution profile of marketed proton pump inhibitors.

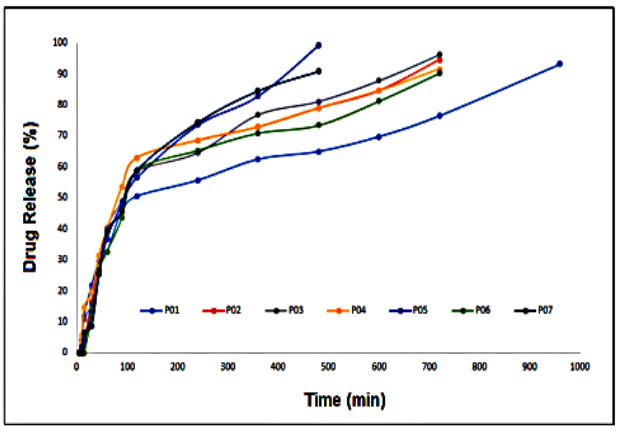

Figure 2: Sustained release properties of drugs P01 to P07.

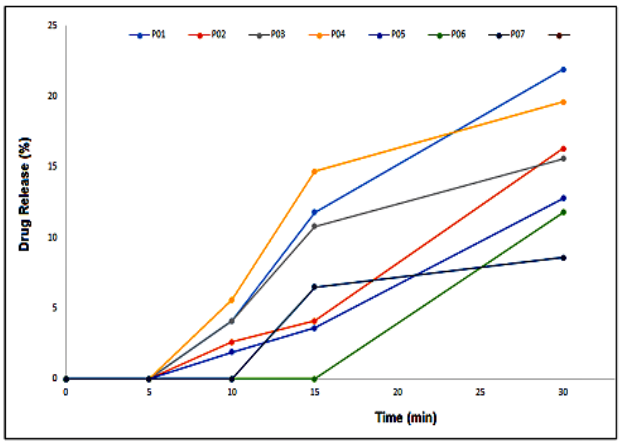

Figure 3: Rapid release properties of drugs P01 to P07.

Table 1: Comparative dissolution profiles of marketed proton pump inhibitors and percentage of domperidone release.

Time (minutes)	P01 (%)	P02 (%)	P03 (%)	P04 (%)	P05 (%)	P06 (%)	P07 (%)	P08 (%)
5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	4.10	2.60	4.10	5.60	1.90	0.00	0.00	28.50
15	11.80	4.10	10.80	14.70	3.60	0.00	6.50	58.00
30	21.90	16.30	15.60	19.60	12.80	11.80	8.60	81.20
45	29.50	31.40	25.70	31.40	25.50	26.80	25.70	98.90
60	32.50	39.40	40.20	39.40	36.70	32.60	39.20	
90	45.90	53.50	48.90	53.50	48.00	43.50	45.70	
120	50.60	62.90	58.60	62.90	56.50	58.90	58.90	
240	55.70	68.50	64.50	68.50	73.40	65.30	74.30	
360	62.50	72.80	76.80	72.80	82.80	70.90	84.50	
480	65.00	78.90	81.10	78.90	99.20	73.40	90.80	
600	69.80	84.50	87.80	84.50		81.20		
720	76.50	94.50	96.20	91.50		90.20		
960	93.20							

P01: Omez DSR (30 mg of domperidone and 20 mg of omeprazole); P02: 30 mg of domperidone and 20 mg of rabeprazole; P03: 30 mg of domperidone and 40 mg of esomeprazole; P04: 30 mg of domperidone and 40 mg of pantoprazole; P05: 30 mg of domperidone and 40 mg of pantoprazole; P06: 30 mg domperidone and 40 mg esomeprazole; P07: 30 mg domperidone and 40 mg pantoprazole; P08: 10 mg domperidone and 20 mg omeprazole.

Table 2: Comparison of AUC of drugs P01 to P08.

Parameters assessed	P01	P02	P03	P04	P05	P06	P07	P08
AUC 0–t µg/ml/min	62126.8	50212.5	50510.5	50203.0	31819.3	47402.0	31770.3	12350.0
T-max (h)	8	6	6	6	4	6	4	1/2

AUC: Area under the curve; Tmax: Time to maximum concentration.

Study observations

Onset of action: This indicates the time taken by a drug to exhibit effects after administration. In a dissolution study, the onset is determined by the time at which drug release begins or, if the time is kept constant, then the amount of drug released at the first instance is calculated. The results demonstrate that the onset of action follows a decreasing order as depicted in (Table 1). P04>P01=P03>P02>P05> P06=P07 (P04 exhibiting the fastest onset of action and P07 exhibiting the slowest onset of action). The data indicated that the drug release at 30 minutes for P01 was significantly higher than that for P05 ($p<0.001$), P06 ($p<0.001$), P07 ($p<0.001$), P02 ($p<0.05$), and P03 ($p<0.05$) but it was not significantly different from that for P04. Drug release at 10 minutes and 15 minutes for P01 was significantly higher than that for P02 ($p<0.001$), P05 ($p<0.001$), P06 ($p<0.001$), P07 ($p<0.001$) but not it was significantly different from that for P03 and P04. The P08 formulation, an immediate-release formulation, exhibited the fastest onset of action with 28.5% of the drug released in 10 minutes. Despite P08 having immediate-release properties, it does not provide sustained therapeutic effects. This highlights the need for alternative drug formulations or dosing strategies that can provide both immediate and sustained release.

Duration of action: This indicates the sustained release property of the formulation and under *in vivo* conditions, it represents the maximum duration for which the drug shows its effect. In dissolution studies, it is determined by the length of the graph or the duration for which the drug is released. The results showed that the duration of action follows the order shown below (Table 1). P01>P02=P03= P04=P06>P05=P07>P08 (P01 exhibiting the longest duration of action and P08 exhibiting the shortest duration of action). The t-max in dissolution is determined as half of the total time for drug release. The t-max value (Table 2) indicated the superior sustained release behavior of P01 compared with that of other brands. As expected, P08 being an immediate-release agent showed the shortest duration of action with a complete drug release in 45 minutes and exhibited the lowest tmax of 30 minutes among the PPIs.

Equivalence/bioavailability: *In vivo* bioavailability represents the fraction of the oral drug that reaches the systemic circulation and is responsible for the pharmacological response. For dissolution, the equivalence is determined by calculating the AUC for the dissolution graph obtained from time 0 to the time of complete drug release. The bioavailability of the drugs is illustrated in (Figure 1). P01>P03>P02>P04>P06>P05> P07>P08 (P01 exhibiting the highest bioavailability and P08 exhibiting the lowest bioavailability). Under *in vitro* conditions, the bioavailability of P01 is nearly two-fold that of P07 and is five-fold that of P08.

Particulate matter: Particulate matter in dissolution studies is the quantity of a substance that is yet to completely dissolve. The P05, P06, and P08 formulations had greater particulate matter than other products. The particulate matter weight that remained after dissolving for P01, P02, P03, P04, and P07 was not considerably different from one another. The P05 and P06 formulations may have more particle matter as they comprise tablets that have a greater amount of excipient, which does not dissolve. The excessive particulate matter observed in P08 results from the coating that failed to dissolve.

Study inference

All the tested formulations, except P08, include 30 mg of domperidone formulated for a prolonged effect. The quick-release domperidone 10 mg in P08 exhibited a total drug release in 45 minutes. When compared against each other, sustained-release drug brands (P01 to P07), such as Omez DSR's unique pellet technology, enabled an initial rapid drug release of up to a 30-minute time point followed by excellent sustained-release property. Figure 2 demonstrates the superior sustained properties of P01. Figure 3 demonstrates the rapid-release properties of drugs P01 to P07. A permeable coating of HPMC and Eudragit-coated domperidone in each Omez DSR capsule enabled the rapid release of 10 mg (or 30%) of domperidone and a continuous release of the remaining 20 mg of domperidone. A comparison of the AUCs of P01 to P08 drugs has been depicted in (Table 2).

DISCUSSION

The instability of PPIs in an acidic environment is one of the greatest challenges encountered during their pharmacological development. Omeprazole was the first PPI developed and commercialized. Even though there are various PPIs available now, omeprazole remains the most mentioned PPI in scientific research.[3] In the present study, P04 exhibited a faster onset of action than all other brands even when the P07 drug combination had the same composition. A study by Chishty et al also observed a similar outcome. In the study, the effectiveness of several commercially available brands of pantoprazole sodium sesquihydrate and domperidone formulations manufactured by various national companies was evaluated. Six distinct brands were randomly chosen from pharmacies and quantifiable differences exist between the brands. The formulation excipients that are added to the drug during the manufacturing process differ amongst manufacturers, which could cause variation in the observed dissolving profiles. Proton pump inhibitors are manufactured as enteric-coated capsules or tablets as they are particularly unstable at a low pH. Any defect in the enteric coating, caused by the coating material's concentration, type, solvent, or curing time, may cause the drug to release into an acidic environment where it will degrade in the liberated amount. A defective coating can lead to a failure in meeting the parameters of disintegration and dissolution standards.[19] The current study is related to a previous study that examined the effectiveness of two brands of commercially available pantoprazole and domperidone drug combinations in vitro. One drug combination disintegrated more slowly than the other per the analysis of the dissolution profile.[20] The outcomes from the present study are also consistent with research that evaluated the in vitro dissolving profile of several brands of pantoprazole sodium tablets manufactured by various pharmaceutical companies under various trade names. Heterogeneity was observed in the dissolving profiles and is attributed to the fact that different manufacturers use different pharmaceutical production procedures, varied tablet formulation additives, and distinct physical forms.[21]

In the present study, Omez DSR showed the longest duration of action and better in vitro bioavailability compared with other brands. Similarly, an assessment of the in vitro dissolution and degradation characteristics of three omeprazole brands indicated that these products were not considered interchangeable due to differences in their physical and physicochemical properties. However, in contrast with the outcomes of the current study, an in vitro study that evaluated the stability of the enteric coating of pellets in capsules of three distinct omeprazole brands concluded that all three brands of the drug demonstrated similar stability.[22] The interaction of excipients with drug components and physiological parameters at the absorption site are the two dosage form factors that might impact a drug's bioavailability. Excipients can also affect drug bioavailability through physiochemical interactions that affect drug absorption.[23] Domperidone had better clinical efficacy and does not cross the blood–brain barrier, according to research by Quratulain et al. on the effectiveness of the combination of 30 mg of domperidone with fixed dose esomeprazole. They concluded that this combination is effective and well tolerated in adult patients suffering from dyspepsia caused by GERD.[24] The effectiveness and safety of omeprazole–domperidone combination therapy compared with those of omeprazole monotherapy in GERD were studied by Marakhouski et al. They were able to determine that omeprazole–domperidone was more efficient than omeprazole alone.10 Omeprazole is metabolized almost entirely by CYP2C19, hence providing the highest potential for interaction with other drugs compared with other PPIs.[25] The ability of esomeprazole to suppress the production of intragastric acid increased with the exposure level. A greater AUC was associated with greater efficacy.[26] Proton pump inhibitors, such as rabeprazole, that are metabolized by nonenzymatic processes are less likely to be susceptible to isoenzyme polymorphism and result in a lower potential for drug-drug interactions than other PPIs.[3] Chaturvedi et al. indicated that solid domperidone dispersion using 2-hydroxypropyl-beta-cyclodextrin (2-HPCD) considerably increased solubility and dissolution in a study on enhancing the solubility and dissolution of domperidone by kneading.[27] There exists evidence of the greater efficacy of omeprazole coupled with domperidone when compared with that of PPIs such as lansoprazole, pantoprazole, and

esomeprazole. This might be because omeprazole works faster and has a longer duration of action in decreasing acid secretion and treating symptoms of GERD. The formulations P05, P06, and P08 had a higher particulate matter level than the other formulations in the present study. It has been found that 40% of the drugs that are now being prescribed to patients in pharmacies are thought to have poor water solubility. These drugs require functional excipients to compensate for their poor physicochemical properties.[28]

The brand Omez DSR formulation has domperidone coated with a permeable coating of HPMC and Eudragit. Omez DSR's special pellet technology offered a rapid drug release of around 30 minutes initially and a superior sustained-release feature. Eudragit has been used in varying formulations, including tablets, microspheres, micro sponges, nanoparticles, and liposomes. It has been used for many applications, including enteric coating, sustained release, insulin permeation, and enhancing bioavailability.[29] The pharmaceutical industry is well recognized for using Eudragit, which includes a sequence of poly(meth)acrylates to enable the active ingredients in solid dosage forms to function throughout the passage of the human body. The appropriate drug release profile is achieved at the desired site and time because different polymers can be combined in a variety of ways.[30] Omez DSR's distinctive pellet technology improved the drug's site-specific delivery.[31] Omez DSR outperformed other pharmaceutical formulations.

CONCLUSION

Identifying the appropriate domperidone and PPI combination is essential for successfully managing gastrointestinal disorders. The drug P04 demonstrated the fastest onset of action, making it an excellent option for immediate symptom relief. The formulation P07 exhibited the slowest onset of action and is beneficial for patients who need sustained symptom relief over a prolonged period. The drug Omez DSR demonstrated both immediate and sustained relief and a greater bioavailability and minimal particulate matter. Each Omez DSR capsule comprises domperidone that is coated with Eudragit and a permeable layer of HPMC. The coating enables the continuous release of the remaining 20 mg of the domperidone while facilitating the fast release of 10 mg. Due to its rapid release, domperidone in Omez DSR may provide instant relief for patients from nausea and vomiting. Moreover, it can offer relief from symptoms of GERD all day long due to its prolonged release.

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