Formulation and Development of Floating Capsules of Celecoxib: In Vitro and In Vivo Evaluation

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ABSTRACT

The objective of the present study was to develop a hydrodynamically balanced system for celecoxib as single-unit floating capsules. Various grades of low-density polymers were used for formulation of these capsules. The capsules were prepared by physical blending of celecoxib and the polymer in varying ratios. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in citrate phosphate buffer pH 3.0 (with 1% sodium lauryl sulfate). Capsules prepared with polyethylene oxide 60K and Eudragit RL100 gave the best in vitro percentage release and were used as the optimized formulation. By fitting the data into zero-order, first-order, and Higuchi models, we concluded that the release followed zero-order kinetics, as the correlation coefficient (*R* value) was higher for zero-order release. For gamma scintigraphy studies, celecoxib was radiolabeled with technetium-99m by the stannous reduction method. To achieve the maximum labeling efficiency the process was optimized by studying the reaction at various pH conditions and stannous concentration levels. The radiolabeled complex was added to the optimized capsule, and dissolution studies were performed to ensure that there was no leaching of radioactivity from the capsules. Gamma imaging was performed in rabbits to assess the buoyancy of the optimized formulation. The optimized formulation remained buoyant during 5 hours of gamma scintigraphic studies in rabbits.

KEYWORDS: Celecoxib, single-unit floating capsules, gastroretentive systems, gamma scintigraphy.

INTRODUCTION

Unpredictable gastric residence time (GRT) of a controlled release dosage form leads to interest in targeting and retaining the dosage form in the stomach for a prolonged period of time. Drug absorption from the gastrointestinal (GI) tract is a complex procedure subject to many variables. It is widely acknowledged that the extent of GI tract drug absorption is related to contact time with the small intestinal mucosa.[1]

The pH of the stomach in the fasting state is ~1.5 to 2 and in the fed state is 2 to 6. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6 to 9, and the stomach does not have time to produce sufficient acid to dissolve the drug before the liquid is emptied. In addition the meal also brings pH differences according to the type of meal consumed. Hence, in general, basic drugs have a better chance of dissolving in a fed state than in a fasting state.[1]

Use of a hydrodynamically balanced system (HBS) is desirable where a prolonged GRT is required. The underlying principle of an HBS is that such a dosage form would swell to create a gel-like structure after administration and attain a density less than that of gastric fluids.[2]

Many approaches have been reported in the literature for the formulation of gastroretentive systems: mucoadhesion,[3,4] flotation,[5] sedimentation,[6,7] expansion,[8,9] and modified shape systems.[10,11] Both single-unit systems (tablets or capsules) and multiple-unit systems (multiparticulate systems) have been reported in the literature.[12]

Celecoxib, a Biopharmaceutics Classification System class II drug, is reported to be 22% to 40% bioavailable by conventional capsule dosage form.[13] Paulson et al reported that if the GRT of celecoxib could be prolonged, its absorption could be enhanced. In the present study we aimed to prolong the GRT of celecoxib by designing an HBS in the form of a single-unit floating capsule that would be retained in the stomach because it would attain a density less than that of gastric fluids.[13]

MATERIALS AND METHODS

Materials

Celecoxib was obtained as a gift sample from M/s Unichem Lab Ltd (Mumbai, India). Different grades of polyethylene oxide (PEO) (grades WSR 1105, WSR 301, WSR 303, WSR 60K, and WSR N80; Amerchol, Edison, NJ), hydroxypropyl

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Table 1. Composition of 100 mg Celecoxib Hydrodynamically Balanced System Capsules*

	Quantity/Capsule Formulation Number							
Ingredients	I	II	III	IV	V	VI	VII	VIII
HPMC K4M	75 mg	100 mg	150 mg	200 mg				
PEO 60K					100 mg	120 mg	150 mg	200 mg
Eudragit RL100						50 mg		

*Each formulation contained magnesium stearate 0.5%. HPMC indicates hydroxypropyl methylcellulose; PEO, polyethylene oxide.

methylcellulose (HPMC) K4M, and Eudragit RL100 were obtained as gift samples from M/s Ranbaxy Research Laboratories (Gurgaon, India).

Technetium-99m (99mTc) was obtained from the Regional Center for Radiopharmaceuticals, Board of Radiation and Isotope Technology, Department of Atomic Energy (Delhi, India). In vivo study permission was granted by the institutional ethical review board.

Methods

Preparation of Capsules

Single-unit capsules were formulated with the help of different low-density polymers, which upon administration would attain a density of less than that of the gastric fluids and therefore would float. Exactly 100 mg of celecoxib was weighed and physically blended with polymers in a glass mortar and pestle and filled in a hard gelatin capsule # 0. The drug and polymer blend was transferred into the empty capsule shells manually. The polymer and drug mixture was blended for 10 minutes in a double cone blender (lab scale Kalweka apparatus of 4-kg capacity, Karnavati, Gujarat, India). The composition of the HBS capsules is given in Table 1.

In Vitro Buoyancy Studies

The capsules were immersed in 900 mL of citrate phosphate buffer pH 3 (simulating the pH of the gastric contents in the fed state) contained in a US Pharmacopeia (USP) paddle-type apparatus where the speed of rotation was maintained at 50 rpm.

The amount of time during which the capsules remained buoyant was the floating time. The polymer that showed the best floating behavior was used for in vitro release studies.

In Vitro Release Studies

Based on the buoyancy period, various ratios and combinations of low-density polymers were used with 100 mg of celecoxib. Celecoxib and HPMC K4M were used in 4 ratios (1:0.75, 1:1, 1:1.5, and 1:2). Similarly, celecoxib and PEO 60K were used in 4 ratios (1:1, 1:1.2, 1:1.5, and 1:2) to optimize the formulation on the basis of release studies.

In vitro release studies of the HBS capsules (n = 6) were performed in a USP paddle-type apparatus at 50 rpm using 900 mL of citrate phosphate buffer pH 3 (containing 1% sodium lauryl sulfate). Five-milliliter samples were withdrawn at regular intervals and replaced with buffer. The samples were evaluated spectrophotometrically at 257 nm (λ_{max}).

Analysis of In Vitro Drug Release Data

To analyze the mechanism of drug release from the capsules, the in vitro dissolution data were fitted to the zero-order,[14] first-order,[15] Higuchi release,[16] cube root,[17] and

Table 2. Pharmacokinetic Models for Analysis of In Vitro Dissolution Data

Serial No	Model	Equation	Reference
1	Zero order	$F = k \times t$	14
		(where F is the fraction of drug release, k is the release constant, and t is the time)	
2	First order	$\ln F = k \times t$	15
		(where F is the fraction of drug release, k is the release constant, and t is the time)	
3	Higuchi	$F = k \sqrt{t}$	16
4	Cube root	$F = 100(1 - (1 - kt)^3)$	17
5	Korsmeyer-Peppas	$F = kt^{n*}$	18-21

*Different n values of Korsmeyer-Peppas equation indicate different mechanism of drug release. If the n value is around 0.5 then Fickian diffusion is apparent, if the n value ranges from 0.5 to 1.0 it represents anomalous diffusion transport and if the n value reaches 1 and above then case II and Super case II transport is indicated which shows that the release is following Zero order.[21]

Table 3. Effect of $SnCl_2$ Concentration on Labeling Efficiency Keeping Other Reaction Conditions Constant

Amount of $SnCl_2$ (μg)	% Free 99mTc	% Reduced/Hydrolyzed Tc_{99m}	% 99mTc-Celecoxib
50	21.5	3.50	75.0
100	1.60	3.40	95.0
200	0.80	12.0	87.2
500	0.50	34.5	65.0
1000	0.10	54.4	45.5

Korsmeyer-Peppas[18-21] models. The equations for the models are given in Table 2.

For the cube root model, the difference between the cube root of the initial amount of the drug (M_0) and the cube root of the amount of drug remaining at time t (M_t) was plotted against time.

For the Korsmeyer-Peppas model, the fraction of drug remaining at time t was determined for every time interval log (M_t/M_∞) and plotted against the log of time t. The slope of the line was taken as the value of n.[22]

Gamma Scintigraphy Studies

In vivo buoyancy of the formulation was evaluated by gamma scintigraphy using rabbits. Permission was obtained from the institutional ethical review board.

Radiolabeling of Celecoxib

Celecoxib was labeled with 99mTc by the stannous reduction method.[23] The 99mTc was chosen for the radiolabeling of celecoxib because of its short half-life (6 hours) and because it allows very little electron emission. It can be administered in millicurie amounts, resulting in a very low radiation dose to the patient. Moreover, 99mTc is readily available in a sterile, pyrogen-free, and carrier-free state.

For the radiolabeling of celecoxib, 2 mCi of 99mTc was taken in a sealed vial, and 100 μL of stannous chloride (1 mg/mL) in 0.1 N HCl was added to reduce 99mTc to its lower valence state. One milliliter of celecoxib solution (2 mg/mL) was added to the reduced 99mTc solution, and the contents were mixed thoroughly in a glass vial for 30 seconds. The pH was adjusted to 6.5 using 0.5 M sodium bicarbonate solution. This mixture was allowed to incubate at room temperature for 10 minutes.

Radiochemical Purity

The radiochemical purity of 99mTc-labeled celecoxib was assessed by using ascending instant thin layer chromatographic (ITLC) plates using silica gel–coated fiber glass sheets (Gelman Sciences Inc, Ann Arbor, MI) and a dual solvent system (100% acetone and a solvent mixture of pyridine:acetic acid:water [5:3:1.5 vol/vol]). The radioactive contaminates were identified as reduced/hydrolyzed 99mTc and free 99mTc pertechnetate.[23]

Effect of pH and Stannous Chloride Concentration

The effect of varying the pH of the reaction mixture on the labeling efficiency was studied to optimize the pH for the reaction by keeping the concentration of stannous chloride constant at 100 μL.

In another experiment, the pH of the reaction mixture was kept constant at 6.5 and the quantity of stannous chloride was varied from 50 to 200 μL. The labeling efficiency of celecoxib was measured using ascending ITLC plates[24] (Tables 3 and 4).

In Vitro Stability

The in vitro stability of the radiolabeled complex was assessed by ascending ITLC plates. Exactly 100 μL of the radiolabeled complex was mixed with 2 mL of physiological saline, that is, 0.9% NaCl. ITLC plates were used to examine the labeling efficiency after incubation at 37ºC at different time intervals (Table 5).

Comparative Dissolution Studies

A comparative dissolution study was performed with optimized capsules with and without radioactivity to ensure

Table 4. Effect of pH on Labeling Efficiency Keeping Other Reaction Conditions Constant ($SnCl_2$ Concentration at 100μ)

pH	% Free Tc_{99m}	% Reduced/Hydrolyzed Tc_{99m}	% Tc_{99m}-Celecoxib
5	11.5	1.50	87.0
6.5	1.40	3.20	95.4
7.5	7.80	22.0	70.2

Table 5. In Vitro Stability of the Radiolabeled Complex

Incubation Time (h)	% Free Tc_{99m}	% Reduced/Hydrolyzed Tc_{99m}	% Tc_{99m}-Celecoxib
0	1.5	3.5	95.0
1	1.6	3.4	95.0
2	1.6	4.0	94.4
3	2.0	4.2	93.8
4	2.0	4.1	93.9
5	2.1	4.1	93.8
24	4.2	7.5	88.3

that there was no leaching out of radioactivity from the capsules and to correlate the drug release. Exactly 0.2 mL of the 99mTc-labeled celecoxib solution was added to the contents of the optimized capsules. The capsules were subjected to in vitro dissolution studies in citrate phosphate buffer pH 3.0, and the release was compared with the release from the capsule without radioactivity (Figure 1).

Gamma Imaging in Rabbits

The scintigraphy was performed in 6 healthy male New Zealand albino rabbits weighing 2.5 to 4 kg. The oral dose was based upon the weight of the individual rabbit, and the capsule was orally administered (with 0.2 mL of radiolabeled celecoxib). Ten minutes before imaging, the animal was anesthetized by Calmpose injection, with each 2 mL ampoule composed of 10 mg diazepam, 1.5% vol/vol benzyl alcohol, 0.035% benzoic acid, and 0.38% sodium benzoate (Batch No 9063100, M/s Ranbaxy). The animal was fixed on a board in the posterior position, and imaging was performed using a gamma camera (Siemens Private Ltd, Munich, Germany). The scans obtained at successive intervals are shown in Figure 2.

Results and Discussion

In Vitro Buoyancy Studies

From the in vitro buoyancy studies it was observed that PEO WSR 60K–, PEO WSR 301–, and HPMC K4M–containing formulations showed good buoyancy, with floating up to 12 hours on the dissolution medium (citrate phosphate buffer with 1% sodium lauryl sulfate) (Figure 3). Sinkers (helix-like wire used to hold the capsules below the paddle during dissolution in the USP type 2 apparatus) were used for the preliminary in vitro buoyancy studies, and the capsules floated after a period of 15 minutes, but the swelling of the capsules was hindered significantly. Therefore, we decided to carry out the study without the sinkers.

In Vitro Drug Release Studies

In vitro drug release studies revealed that the formulation containing celecoxib and PEO WSR 301 (1:1 ratio) had a relatively low percentage drug release, with only 30% release in 8 hours. Therefore, different ratios of drug with HPMC and drug with PEO WSR 60K were used to optimize the drug release from the capsules. It was observed that the

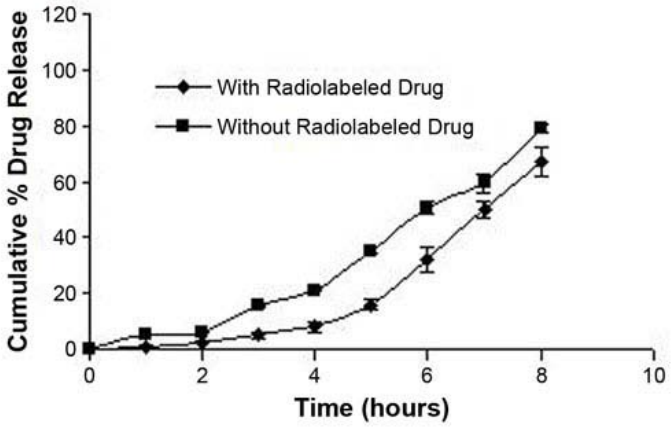

Figure 1. Comparative in vitro drug release profile of the optimized capsule formulation of celecoxib (with and without radioactivity).

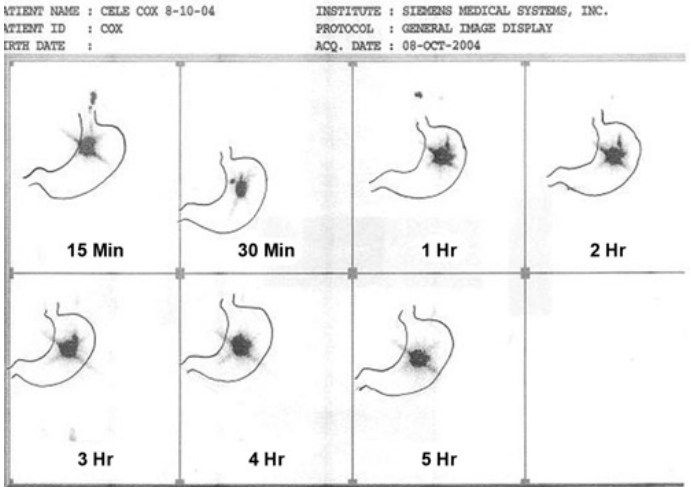

Figure 2. Gamma scintigraphy images of stomach taken at periodic intervals.

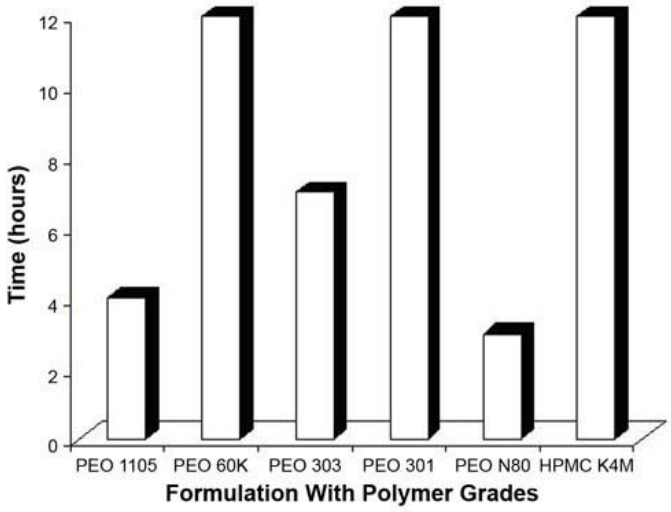

Figure 3. Bar chart indicating in vitro buoyancy time for various polymers studied. PEO indicates polyethylene oxide; HPMC, hydroxypropyl methylcellulose.

formulation containing HPMC released drug at a slower rate compared with the formulation containing PEO 60K. This was in agreement with a Maggi et al study where it was concluded that a slower release rate could be obtained from plain matrices containing HPMC than from those containing PEO.[25] In another study it was reported that PEO has a higher affinity for water than HPMC does.[26] Drug release from the HPMC matrix was shown to be by a swelling-controlled diffusion process, and it was concluded, as part of this study, that the overall release rate of PEO is faster than that of HPMC. The release rate from PEO matrices is inversely proportional to PEO's molecular weight (approximate molecular weight of PEO 60K is 20 000 000, and for PEO 301 it is 40 000 000) (Figures 4 and 5). The formulation containing 100 mg of celecoxib, 120 mg of PEO WSR 60K, 50 mg of Eudragit RL100, and 0.5% magnesium stearate had an in vitro drug release of 78.97% in 8 hours (Figure 6).

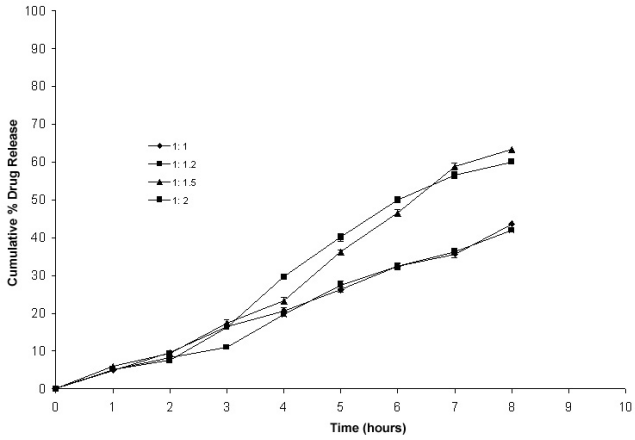

Figure 4. In vitro drug release profiles for various celecoxib formulations containing polyethylene oxide.

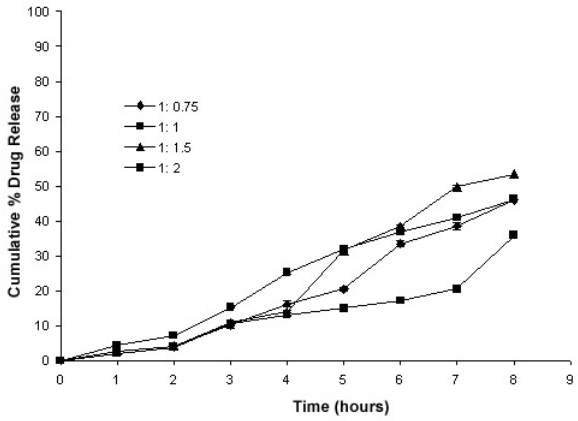

Figure 5. In vitro drug release profiles for various celecoxib capsule formulations containing hydroxypropyl methylcellulose.

Analysis of In Vitro Drug Release

By fitting the in vitro dissolution data into zero-order and first-order equations, we concluded that the release followed the zero-order model, as the coefficient for correlation—that is, the *R* value—for zero-order release was higher than the *R* value of the Higuchi model. *R* values of around 0.80 were obtained after application of the Higuchi model. *R* values of above 0.95 were obtained by fitting the data to the cube root model, which indicated an erosion-based mechanism.[27]

Value of n above 1 was obtained after the application of Korsmeyer and Peppas model that supports Super case II transport. (Tables 6, 7, and 8).

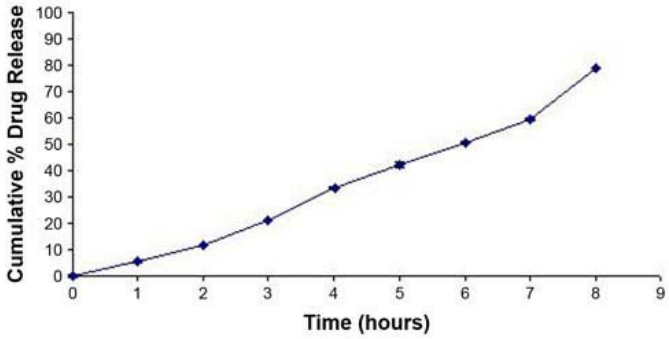

Figure 6. In vitro drug release profiles for optimized capsules of celecoxib capsule formulation.

Table 6. Dissolution Parameters for Various Release Models for Celecoxib/PEO Capsules

Zero Order		
Ratio	Slope of Release (%/h)	*R* (Correlation Coefficient)
1:0.75	5.139	0.931
1:1	5.894	0.982
1:1.5	6.210	0.912
1:2	3.446	0.888
First Order		
Ratio	**Slope of Release (%/h)**	***R* (Correlation Coefficient)**
1:0.75	0.028	0.890
1:1	0.032	0.974
1:1.5	0.036	0.869
1:2	0.017	0.836
Higuchi		
Ratio	**Slope of Release (%/h)**	***R* (Correlation Coefficient)**
1:0.75	11.66	0.702
1:1	13.70	0.826
1:1.5	14.04	0.681
1:2	7.86	0.687
Cube Root		
Ratio	**Slope of Release (%/h)**	**R (Correlation Coefficient)**
1:0.75	0.104	0.900
1:1	0.106	0.979
1:1.5	0.116	0.885
1:2	0.058	0.853
Korsmeyer-Peppas		
Ratio	**Slope of Release (%/h)**	**R (Correlation Coefficient)**
1:0.75	1.649	0.952
1:1	1.475	0.975
1:1.5	1.548	0.957
1:2	1.213	0.977

Optimization of Radiolabeling Method

For the optimization of the radiolabeling method, the best results were obtained with 100 μL of stannous chloride. At pH 6.5, 95% of the drug could be radiolabeled and the complex was stable for up to 24 hours (Tables 4, 5, and 8). By varying the stannous chloride concentrations but keeping the other reaction conditions unchanged, we found that maximum labeling was achieved with 100 μg of stannous chloride. Furthermore, increasing the stannous chloride concentration led to a decrease in the yield of radiopharmaceutical and an increase in the corresponding reduced/hydrolyzed 99mTc. By varying the pH of the reaction mixture, we observed that maximum yield was achieved at pH 6.5. The radiolabeled complex was incubated for up to 24 hours in saline and was found to be stable with 88% 99mTc-celecoxib complex and only 7.5% reduced/hydrolyzed 99mTc. In the comparative in vitro dissolution study between the capsules with and without radiolabeled celecoxib, a good correlation (*R* value of 0.975) and f2 value (similarity factor of 50) were attained; hence, it was concluded that the radioactivity does not leach out from the capsule in citrate phosphate buffer pH 3.0 (Figure 1).

Gamma Scintigraphy Studies

Gamma scintigraphy studies revealed the location of the capsule in 6 healthy rabbits. Posterior whole body images at various time intervals (15 minutes, 30 minutes, and 1, 2, 3, 4, and 5 hours) showed the retention of the capsules in the stomach for more than 5 hours, as shown in in vitro studies (Figure 2).

CONCLUSION

It was concluded on the basis of buoyancy and in vitro release kinetics that the formulation containing 100 mg of celecoxib, 120 mg of PEO 60K, and 50 mg of Eudragit

Table 7. Dissolution Parameters for Various Release Models for Celecoxib/Polyethylene Oxide Capsules

Zero Order		
Ratio	Slope of Release (%/h)	*R* (Correlation Coefficient)
1:1	5.299	0.977
1:1.2	7.669	0.967
1:1.5	7.595	0.965
1:2	5.167	0.983
First Order		
Ratio	**Slope of Release (%/h)**	***R* (Correlation Coefficient)**
1:1	0.028	0.981
1:1.2	0.047	0.939
1:1.5	0.048	0.902
1:2	0.028	0.967
Higuchi		
Ratio	**Slope of Release (%/h)**	***R* (Correlation Coefficient)**
1:1	12.38	0.856
1:1.2	17.68	0.782
1:1.5	17.42	0.759
1:2	11.98	0.814
Cube Root		
Ratio	**Slope of Release (%/h)**	**R (Correlation Coefficient)**
1:1	0.093	0.988
1:1.2	0.148	0.951
1:1.5	0.148	0.925
1:2	0.091	0.973
Korsmeyer-Peppas		
Ratio	**Slope of Release (%/h)**	**R (Correlation Coefficient)**
1:1	1.040	0.997
1:1.2	1.319	0.965
1:1.5	1.222	0.978
1:2	1.074	0.969

RL100 gave the best in vitro release of 78.97% in 8 hours in citrate phosphate buffer pH 3.0 (with 1% sodium lauryl sulfate). The release of celecoxib from the matrix formulation followed zero-order release kinetics.

HPMC K4M formed a hard, swollen matrix through which drug release occurred slowly. Addition of Eudragit RL100 to the PEO 60K–containing formulation enhanced the water permeability of the swollen matrix and thus led to increased drug release.

Gamma scintigraphic studies revealed that the optimized HBS capsule was retained in the gastric region (stomach) for a prolonged period.

Table 8. Dissolution Parameters for Optimized Capsules

Model	Slope of Release (%/h) or Diffusional Exponent (n)	*R* (Correlation Coefficient)
Zero order	8.77	0.971
First order	0.061	0.837
Higuchi	20.18	0.775
Cube root	0.189	0.895
Korsmeyer-Peppas	1.35	0.979

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