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Research Article

# Pulsatile Drug Delivery Systems of Esomeprazole for Improved Therapeutic Efficiency: *In-vivo* Bioavailability Study and *In-vitro In-vivo* Correlation

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ABSTRACT

The prime objective was the development and pharmacokinetic characterization of pulsatile drug delivery systems (PDDS) to gain chronomodulated delivery of esomeprazole (EMP) suitable for combating nocturnal acid breakthrough (NAB). The analytical method by HPLC was developed for the quantification of EMP from the biological samples. *In-vivo* bioavailability testing was accomplished on Sprague–Dawley rats for the developed PDDS formulation. *In-vitro in-vivo* correlation (IVIVC) was carried out by the deconvolution method. The bioanalytical approach that was developed exhibited linearity within the range of 100 to 2000 ng/mL with a correlation coefficient of 0.999. The results of other method validation parameters were found satisfactory. The *in-vivo* studies on the PDDS specified that the EMP was released as two pulses at the desired times. The AUC and MRT from the PDDS were found to be increased by 3.02 times and 2.2 times, respectively in comparison with the marketed formulation. IVIVC revealed that a considerably good correlation was observed. The established bioanalytical approach proved to be appropriate for quantifying EMP in biological samples. The developed PDDS formulation of EMP was effective in combating the NAB condition.

## Introduction

About 70% of *Helicobacter pylori* affected ulcer patients experience NAB. [1-3] The NAB lowers stomach pH below 4 for at least 60 minutes in the nocturnal duration. Patients suffer severe pain when sleeping. Due to this chronophysiology, unique drug delivery methods that can sustain therapeutic plasma concentrations throughout potential NAB times are required.[4,5] When it comes to treating duodenal and stomach ulcers, proton pump inhibitors (PPIs) are the first class of medications.[6] Delayed release products of the PPIs are commonly found on the market. Enteric coating (EC) is used to create delayed-release products from these medications because the PPIs are unstable in the acidic milieu of the stomach.[7] These EC tablets or capsules release the drug immediately after reaching the small intestine (SI). Hence, these formulations are ineffective in treating the NAB condition. Considering the therapeutic need in the treatment of NAB, a novel drug delivery system that provides time-based or chronomodulated release of the PPI drug is much warranted. in order to achieve this chronomodulated delivery of drugs, pulsatile drug delivery systems (PDDS) are the first-choice approach. PDDS are the dosage forms that release the contained drug after a predetermined time lag after administration.[8,9] Several studies were reported on the efficiency of PDDS. Jagdale SC *et al.* [10] worked on the development of PDDS for releasing lisinopril in the next early morning after administering at night. The core tablet containing the drug was covered by buoyant layers by compression coating. Natural and synthetic polymers were

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used to make the tablet float in the stomach. The optimized tablets exhibited a delay of 4 hours before releasing the drug. Aceclofenac-coated tablets by compression were prepared for time-controlled release, as reported by Rashid R *et al.*[11] These authors reported that the matrix of HPMC and Eudragit combination could provide a lag time of upto 6 hours. Kharwade R *et al.* [12] prepared matrix tablets made up of EC, HPMC, and xanthan gum giving the required delay before the initiation of release of the drug. Research literature suggests that a matrix of a water-insoluble and a water-swellable polymer can effectively delay drug release. Single-unit dosage forms can fail due to coating breakage. Multi-particulate forms effectively give chronomodulated delivery without this drawback.[13,14]

Considering this research gap, it was aimed to develop PDDS containing multiparticulate units for delivering the loaded PPI as two pulses with a predetermined time gap between the doses. Esomeprazole (EMP) was taken as a model PPI drug in this work. The planned PDDS comprised of two doses of EMP, one dose as delayed immediate release (DIR) microparticles and the other as delayed extended-release (DER) microparticles. The release of one dose of the EMP from the DIR section microparticles was anticipated to occur around 2 hours after the PDDS capsule was administered, i.e., after reaching the SI. In contrast, the other dose from the DER portion microparticles was expected to be released with an additional lag o 4 hours. Hence, this PDDS, when administered at around 8 to 9 PM, the second dose was expected to be released at around 3 to 4 am thus providing the desired plasma drug concentrations to prevent the NAB condition.

Optimization of various formulation factors in achieving both DIR and DER portions microspheres of the PDDS was published by us elsewhere as Kurapati *et al.*[15] In this manuscript, mainly, *in-vivo* characterization of the finalized PDDS, including bioavailability testing and IVIVC development were presented. The data obtained from the bioavailability testing was analyzed using PK Solver software to quantify the bioavailability parameters.

## Materials And Methods

### Materials

EMP was procured from Mylan Laboratories Ltd., Hyderabad. All other compounds used were bought from Merck Specialities Pvt. Ltd.

### Development of Bioanalytical Method

In order to quantify the EMP from the *in-vivo* biological samples, a simple bioanalytical method using high-performance liquid chromatography (HPLC) was established with reference to a method reported earlier by Onal A *et al.* [16] with the required adjustments. HPLC with a Poroshell 120 EC-C 18; 4.6×100 mm column was employed. The column was kept at 35°C. The mobile phase flow rate of 1-mL/min was consistently maintained. The analyte was quantified utilizing a UV detector set at 205 nm. The internal standard (IS) used was lansoprazole. Acetonitrile (ACN) and phosphate buffer at a ratio of 60:40, with a pH of 7, was taken as the mobile phase. The following validation parameters were performed for the method.

### Validation Parameters

For testing linearity and range, concentrated solutions of EMP and the IS were made using ACN and then mixed with the mobile phase. Multiple dilutions of EMP ranging from 100 to 2000 ng/mL were made using the mobile phase. Throughout all of these linearity samples, the IS was consistently maintained at 800 ng/mL. The samples were mixed with plasma and extracted using the liquid-liquid extraction technique with ACN.

The other validation parameters like limit of detection (LoD), limit of quantification (LoQ), accuracy and precision testing were carried out with reference to the procedures reported by Krishna SR *et al.* [17] From the linearity curve, LoD and LoQ were estimated using the below formula,

$$LoD = \frac{3.3 * Standard\ deviation\ (SD) of\ the\ response}{Slope\ of\ linearity\ plot}$$

$$LoQ = 3 * LoD$$

For accuracy testing, three recovery levels of 50, 100, and 150% of the known concentration of EMP (500 ng/mL) were taken. The %RSD was computed by dividing the standard deviation by the response.[17-19] The precision was assessed by conducting six injections of the prepared sample. The responses were recorded and which mean, standard deviation and then the %RSD were calculated.[17-19]

### Preparation of PDDS of EMP

#### *Preparation of DIR portion microparticles*

The emulsion solvent evaporation approach[20] was employed to coat EMP with the enteric polymer Eudragit S100. An accurately weighed amount of 0.25 g of Eudragit S100 was dissolved in ethanol. In the resulting polymer solution, 0.5 g of EMP was dispersed. Span 20 at 0.2% v/v was added into another beaker containing liquid paraffin. The liquid was agitated at 550 rpm and maintained 45°C temperature. The EMP dispersion in the polymer solution was introduced slowly, drop by drop, into the liquid paraffin while stirring. The stirring process was continued until the solvent was completely evaporated over a period of roughly 3.5 hours. The obtained microparticles were filtered from liquid paraffin and cleaned with petroleum ether to remove paraffin. Subsequently, the microparticles underwent two rounds of water rinsing and were dried. The dried DIR microparticles of EMP were preserved for subsequent investigations.

#### *Preparation of DER portion microparticles*

This part of the microspheres was responsible for delaying the release for an extended time, even after reaching

the small intestine. Hence, these were manufactured in two different stages. In stage 1, fabrication of matrix microparticles was accomplished by utilizing a combination of a hydrophilic and a hydrophobic polymer. Later, in stage 2, enteric coating was applied to the above matrix microparticles to convert them into DER microparticles.

- *Stage 1*

The matrix microspheres were fabricated using the solvent evaporation. [21] Accurately weighed quantities of 0.66 g of Eudragit RSPO and 0.33 g of PEO N60K were dissolved in a 15 mL solvent mixture consisting of dichloromethane and methanol at equal proportions. One gram of EMP was added into the polymer solution mentioned above and mixed to dissolve using a cyclomixer. Span 20 at 0.2% v/v was added into another beaker containing 80 mL of liquid paraffin that was kept on a hot plate at 45°C. A mechanical paddle stirrer that was set at 550 rpm was submerged into the beaker. Subsequently, the above drug and polymer dispersion was gradually introduced as droplets into the liquid paraffin while maintaining continuous stirring. This resulted in the formation of small droplets of the volatile solvent that included drug-polymer monoliths. These droplets were dispersed in liquid paraffin in the form of an emulsion. The stirring process was maintained for a duration of 4 to 5 hours, ensuring that the solvent was removed entirely and the resulting droplets rigidized into microspheres. Next, the dispersion underwent filtering to separate microspheres, which were then washed to eliminate any attached paraffin. Subsequently, the microparticles were rinsed and, promptly dried and then properly preserved for future utilization.

- *Stage 2*

Eudragit S 100 was employed as the substance for generating the enteric film in this particular stage. The coating solution was prepared by adding 10 g of Eudragit S 100, 1.5 g of PEG 400, 0.1 g of Span 20 and 0.1 g of talc in 50 mL of isopropyl alcohol. The dispersion was placed on a cyclomixer for 10 minutes to produce a homogenous dispersion. A quantity of 100 g of the matrix microspheres was placed in the coating pan, which was set to rotate at 50 rpm. The temperature of the drying hot air was set to 40°C. The above polymer solution for coating was applied onto the microparticle in the pan at 5 mL/min. The obtained coated microparticles were inspected for any adhesion after drying.

### *In-vitro characterization of the DIR and DER portion microparticles*

The yield, entrapment efficiency (EE), and size of these microparticles were assessed using the previously reported methods for the microspheres' characterization.[22] Based on the EE values, each one dose (20 mg) equivalent DIR microparticles and DER microparticles was filled in a hard gelatin capsule for testing drug release. The drug release testing was conducted in two separate stages using the paddle apparatus that revolved at a speed of 100 rpm. The acid stage was conducted using 300 mL of a 0.1N HCl solution as the medium, whereas the buffer stage was carried out using 1000 mL of phosphate buffer with a pH of 6.8 as the medium.[23,24] Periodically, 5 mL samples were taken and put into sealed vails having 1-mL of 0.25M NaOH. These vials were then stored in a dark location till they could be analyzed spectrophotometrically.

### *In-vivo bioavailability studies*

The oral bioavailability study was performed (approved protocol number IAEC/XVIII/02/RIPER/2022) using male Sprague-Dawley rats of age 8 to 9 weeks and weighing between 250 to 280. The animals were maintained at a 12-hour light and dark cycle at 25°C and 50% RH. The rats were provided with normal laboratory meals. Water consumption was provided ad libitum. The trials were conducted on rats who had fasted overnight for 12 hours. The animals were categorized into three groups. Group 1 served as the control/placebo, group 2 received the marketed formulation of EMP as the reference product, and group 3 received the developed PDDS formulation of EMP as the test product. The selected formulations were administered orally to conscious rats by carefully inserting a gastric tube into their esophagus. The group-1 animals were not administered any dose. EMP at a dose of 4 mg/kg from the respective products was administered to the group 2 and the group 3 animals. [25] Two doses of the test product were provided, consisting of one dose of DIR microparticles and one dose of DER microparticles, in accordance with the work's objective. Nevertheless, the reference product was supplied as a single dosage due to its typical delayed release granules formulation, which is comparable to DIR microparticles. The blood samples (250 µL) were taken from the retro-orbital at various time intervals (1, 2, 2.5, 3, 4, 5, 6, 7, 8, 12, 18, and 24 hours) after administration. The collected samples were then placed into containers that contained heparin. To isolate plasma, the blood samples were centrifuged at 8000 rpm and at 4°C for a duration of 20 minutes. The analyte was extracted using acetonitrile following the addition of an internal standard solution to the plasma samples. To quantify, 20 µL of each extract was put into HPLC for quantification.

## Statistical Analysis

The bioavailability parameters of EMP were studied using non-compartmental analysis with PK Solver 2.0 software. [26] $C_{max}$ and $T_{max}$ were directly computed from the observed data. $AUC_{0-t}$ (area under the curve) was quantified using the trapezoidal rule. [27] Area under the first-moment time curve (AUMC) was quantified using statistical moments theory. Mean residence time (MRT) was quantified by dividing AUMC by AUC.

### *In-vitro In-vivo* Correlation

Level A or point-to-point IVIVC [28] was developed for the developed PDDS of EMP. For this purpose, the deconvolution method was employed. Firstly, the actual *in-vivo* plasma drug concentration data was deconvoluted into predicted %drug absorbed *in-vivo*. This was performed by using the Wagner-Nelson method. Later, this predicted *in-vivo* data was equated with %drug released *in-vitro*. This correlation was made as a linear regression model.

## Results and Discussion

### Bioanalytical Method and Validation Parameters

The HPLC spectra obtained is illustrated in Fig. 1 as the blank plasma spectrum was compared with those of a standard sample and a test sample. A peak at 3.76 minutes was observed for EMP and another peak at 4.51 minutes for the IS. These observations were correlated with the reference method.

The linearity was confirmed in the range of 100 to 2000 ng/mL of EMP. The obtained responses were made into a linearity plot, which is depicted in Fig. 2 and the linearity parameters are presented in Table 1. The observed correlation coefficient of 0.9998 demonstrated that the method showed good linearity. The results of LoD as well as LoQ are given in Table 1. The LoQ was found to be 110 ng/mL, which was almost close to the lowest concentration in the studied range. Hence, it can be inferred that this method could be used to quantify EMP from the biological samples containing as low as 110 ng/mL. [29]

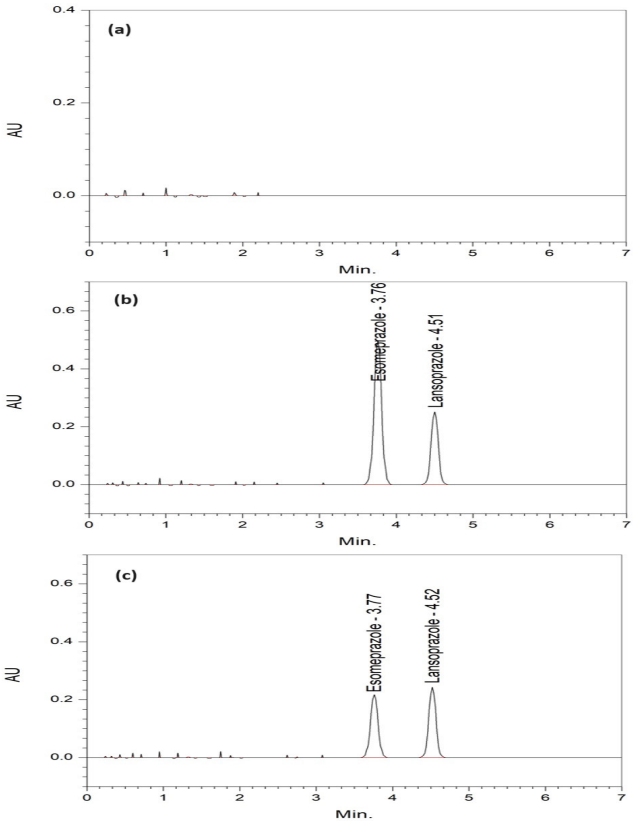


**Fig. 1:** Chromatograms of (a) Blank plasma; (b) Standard preparation and (c) Test sample showing esomeprazole and IS

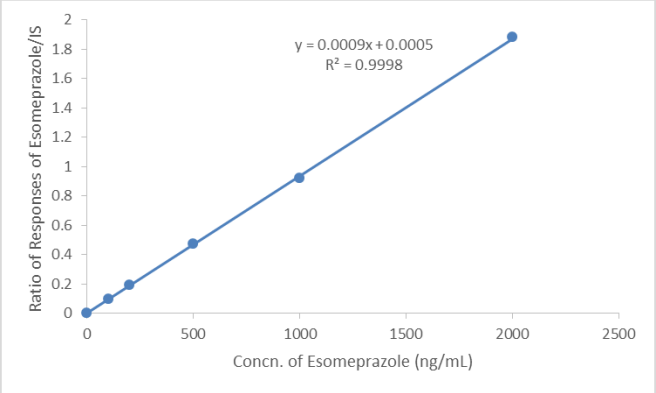


**Fig. 2:** Calibration curve of EMP in plasma

**Table 1:** Linearity test results including LoD and LoQ of estimation of EMP in plasma

| *S. No.* | *Parameter* | | *Result observed* |
|---|---|---|---|
| 1 | Concentration range (ng/mL) | | 100–2000 |
| 2 | Retention time (min.) | Esomeprazole | 3.76 |
| | | Lansoprazole (IS) | 4.51 |
| 3 | Regression equation | | y = 0.0009x + 0.0005 |
| 4 | Slope | | 0.0009 |
| 5 | Intercept | | 0.0005 |
| 6 | Correlation coefficient | | 0.999 |
| 7 | Standard deviation of the response | | 0.01 |
| 8 | LoD | | 36.67 |
| 9 | LoQ | | 110 |

**Table 2:** Accuracy test results of EMP

| *Test* | | *Observed result* | |
|---|---|---|---|
| | | *Mean recovered (%)* | *%RSD* |
| Accuracy | 50% Recovery level | 50.34 | 0.74 |
| | 100% Recovery level | 99.16 | 0.62 |
| | 150% Recovery level | 149.08 | 1.05 |

The results of the accuracy test are presented in Table 2. Three levels of the known concentrations of EMP as 50, 100 and 150%, were taken. The %recovery values were found to be the same to the added concentrations. The %RSD values in all three recovery levels was found to be not more than 2%. These findings signified that the method was accurate in quantifying the EMP.[30]

The standard concentration of 1000 ng/mL was taken for precision test. The mean and %RSD for the six replicas of the standard concentration were found to be 993.7 ng/mL and 0.59%. Hence, it can be inferred that the method was precise in quantifying EMP.

## *In-vitro* Characterization of PDDS of EMP

In the case of the DIR microparticles, the %yield obtained was found to be 83.6%. The mean size was 132.6 µm as determined by the microscopy method. The entrapment efficiency (EE) was observed to be 88.1%. In the case of the DER microparticles, the %yield obtained was found to be 85.9%. The mean size was 194.2 µm as determined by the microscopy method. The EE was observed to be 75.3%. These high yield and EE values of the microparticles signified that the process conditions adopted for their preparation were effective.[31] Besides, the high EE could impart an advantage of the requirement of less weight of the formulation. In addition to this, the smaller particle size of these microparticles occupy less bulk volume. Hence, they can be packed in suitably less size capsule.

*In-vitro* drug release studies were conducted after filling DIR DER microparticles of each one dose into a hard gelatin capsule. The drug release profile observed, as depicted in Fig. 3, demonstrated that only 5.6% of the total two doses was released in the acid stage. This demonstrates that both the DIR and DER microparticles have the ability to successfully inhibit the release of EMP in the stomach region owing to the outer enteric coat with Eudragit S 100.[32] In the buffer stage, 49.5% of the drug was released after one hour, potentially from the DIR microparticles. After arriving in the small intestine, one of the two doses of EMP was released in its entirety as a single pulse in the span of one hour. Additionally, following a specific delay of approximately four hours during the buffering phase, drug release was initiated from the DER microparticles as the second pulse and concluded within a 2 hour timeframe. This pattern of drug release could be attributed to the mixed polymer matrix of hydrophilic PEO and hydrophobic Eudragit RSPO.[33,34] Hence, the designed PDDS for EMP successfully achieved drug release in two distinct pulses as needed.

## *In-vivo* Bioavailability Studies on PDDS of EMP

The time *vs*. plasma concentration data obtained from both the test and reference products are shown in Fig. 4. The bioavailability parameters obtained after the non-compartmental analysis are displayed in Table 3.

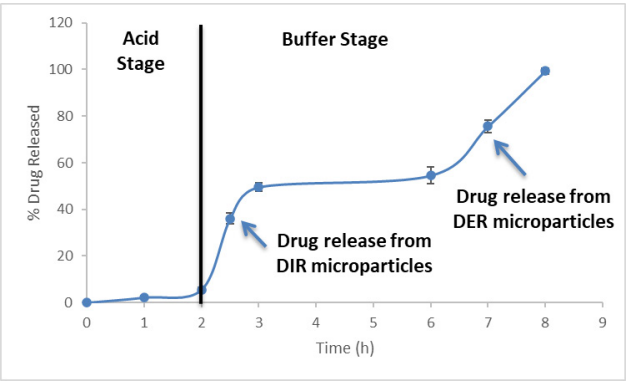


**Fig. 3:** Drug release pattern of EMP from the PDDS

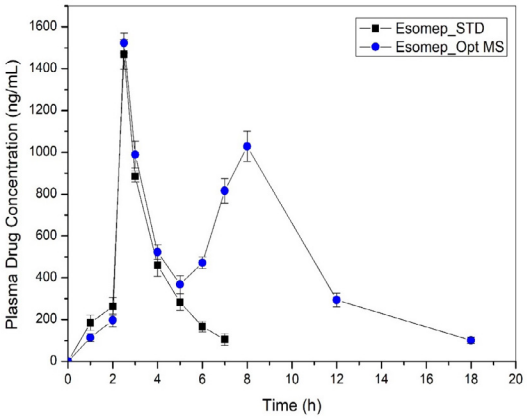


**Fig. 4:** Plasma drug concentration *vs*. time profiles of esomeprazole from the optimized microspheres and the marketed formulation

**Table 3:** Bioavailability parameters of esomeprazole from the optimized microspheres and the marketed formulation

| *Bioavailability parameter* | *Obtained values as Mean ± SD for n = 3* | |
|---|---|---|
| | *Esomep_STD* | *Esomep_PDDS* |
| $T_{max}$ (h) | 2.5 ± 0.0 | 2.5 ± 0.0 |
| $C_{max}$ (ng/mL) | 1468.0 ± 71.0 | 1523.0 ± 47.0 |
| $AUC_{0-t}$ (h.ng/mL) | 2743.5 ± 255.5 | 8287.0 ± 670.8 |
| AUMC ($h^2$.ng/mL) | 10085.1 ± 1345.3 | 66915.5 ± 6645.1 |
| MRT (h) | 3.7 ± 0.2 | 8.1 ± 0.2 |

* Results showed as average ± S.D for n = 3

The marketed formulation was taken as one dose and it showed a maximum concentration of 1468 ng/mL at 2.5 hours. $AUC_{0-t}$ of 2743 h.ng/mL with a mean residence time (MRT) of 3.7 hours. On the other hand, the AUC observed from the optimized formulations was 8287 h.ng/mL which is 3.02 times higher than that from the marketed formulation. As two doses of the optimized formulation was taken against one dose of the marketed formulation, the AUC was expected to be two times. But, it was found to be 3.02 times. This enhanced AUC might be due to the extended release of EMP from the DER portion microparticles. As evidenced by the literature from Bhalani DV *et al.*[35] and Liu *et al.*,[36] sustained release formulations, especially those containing hydrophilic carriers could improve the bioavailability of drugs. Further, the $AUC_{0-t}$ from both doses was found to be 8287 h.ng/mL with an MRT of 8.1 hours.

Importantly, the test formulation showed two peak concentrations at 2.5 and 8 hours. This could be due to the presence of two doses in the form of two different formulations. This further affirmed that one dose was released at 2.5 hours might be from the DIR microspheres. On the other hand, the release of the other dose was started from 6$^{th}$ hour and the peak was observed at 8 hours. This pattern could be due to the expected release

**Table 4:** Deconvoluted %drug absorbed *in-vivo* data along with the actual %drug released *in-vitro* data at common time points

| *S. No.* | *Time (hours)* | *%Drug released in-vitro* | *%Drug absorbed in-vivo* |
|---|---|---|---|
| 1 | 0 | 0.0 | 0.0 |
| 2 | 1 | 2.2 | 6.3 |
| 3 | 2 | 5.9 | 12.3 |
| 4 | 2.5 | 36.1 | 83.2 |
| 5 | 3 | 49.2 | 63.8 |
| 6 | 6 | 54.5 | 56.7 |
| 7 | 7 | 75.6 | 81.2 |
| 8 | 8 | 99.0 | 102.3 |

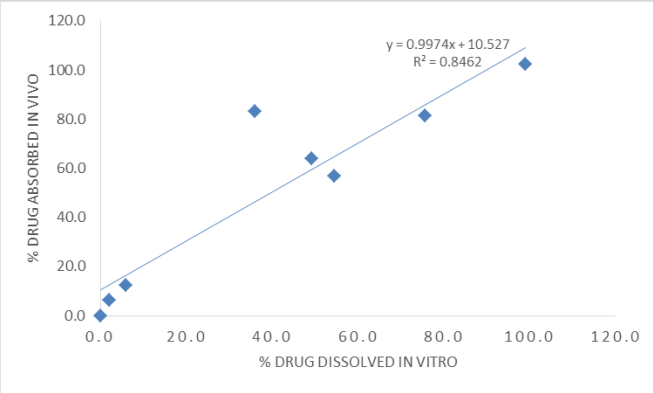


**Fig 5:** Level A correlation for the optimized microspheres of EMP PDDS

pattern of EMP from the DER microspheres. Hence, this result confirmed the ability of the optimized DER + DIR microspheres to produce the required two pulses of drug release as per the set objective.

### *In-vitro In-vivo* Correlation

The predicted %drug absorbed data obtained from the deconvolution of the *in-vivo* plasma data is presented in Table 4, along with the actual *in-vitro* %drug released data. This predicted *in-vivo* data and the actual *in-vitro* data at the same time points were fit into a linear regression model and the plot is presented in Fig. 5.

This plot illustrated that correlation with a linear regression coefficient of 0.85 and a correlation coefficient of 0.92 were achieved. These observations demonstrated that there could be a reasonably good IVIV from the optimized EMP microspheres.[32] On the other hand, the correlation could further be improved by obtaining the *in-vitro* data by performing the drug release test in relevant media instead of simple dissolution media. So, the developed IVIVC could possibly be used to predict the *in-vivo* bioavailability for low-dose formulations of PDDS, eliminating the need to perform actual *in-vivo* studies.

## Conclusion

PDDS were aimed to develop in this work with the objective of achieving the desired drug release so as to maintain therapeutic levels of EMP in the early morning to prevent NAB. An analytical method using HPLC was developed to quantify EMP in plasma samples. This method was proven to be accurate, precise and linear over the range of 100 to 2000 ng/mL of EMP. The PDDS was developed as two different formulations viz. DIR microparticles and DER microparticles. Matching with the objective, the DIR microparticles prevented the drug release in acidic media and released the total amount within 1-hour in the alkaline media. Whereas the DER microparticles delayed the drug release in acidic media and also up to 4 hours in alkaline media, that was summed to a total of 6 hours delay. *In-vivo* bioavailability tests were conducted on this PDDS system. The results revealed that the plasma concentrations were achieved as two peaks, with one at 2.5 hours and another at 8 hours, as anticipated in accordance with the set objective. The IVIVC was developed by deconvolution method revealing that a near-to-linear regression was present. Altogether, the results of the systematic experimental studies revealed that the developed PDDS was effective in providing the desired plasma drug concentration in the early hours to prevent NAB in ulcer patients.

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