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Nonaqueous Enteric Coating Application of HPMC and Eudragit L100 on Hard Gelatin Capsules: Designed to Achieve Intestinal Delivery

Swamykannu Dinesh Mohan[1], V. R. M. Gupta[2], Harika yasam[1], Yamini jampani[1], Manaswini Yalamanchili[1]

[1]Department of Pharmaceutics, Vishnu Institute of Pharmaceutical Education and Research, Narsapur, Medak (DT) Hyderabad – 502313, India.
[2]Department of Pharmaceutics, Pulla Reddy Institute of Pharmacy, Annaram, Jinnaram (M) Hyderabad -502313, India.

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ABSTRACT

Omeprazole (OMZ) is a weak base proton pump inhibitor and it can be easily broken down in the acidic location before reaching to the small intestine where it is absorbed. Therefore, the main aim of this investigation is to protect the drug in the stomach environment with the object of exhibiting 100% drug release at the site of absorption. Prior to coating all the capsules were filled with API and other suitable excipients then placed on to the lab model conventional coating pan. Two different polymers such as (HPMC) and Eudragit L 100 were selected for this study. First, the pre coating solution (HPMC) was employed after drying enteric coating solution (Eudragit L 100) was applied under suitable coating parameter finally over coating solution of (HPMC) was applied and kept for drying. Different coating thickness ranges from 38.33 to 89.75% was observed by Scanning electron microscopy and tested for acid uptake test, disintegration and dissolution tests in pH 1.2 HCl media for 2 hours and pH 6.8 phosphate buffer solution. Less coating thickness capsules were allowed to penetrate the acid and the capsules were ruptured in an acid environment, therefore early drug release was occurred in acid media. Whereas capsules with high coating thickness of 89µm were not allowed acid to penetrate this indicates that the drug could be protected from degradation in the gastric environment.

INTRODUCTION

An enteric coating is a polymer applied to solid oral medications such as tablets, pills and pellets. This barrier helps by protecting drugs from the acidic pH of the stomach (Lachman *et al.,* 1987). Enteric coatings are pH-dependent to exploit this pH progression in the GI tract in order to prevent gastric irritation or delay the release of drugs that are inactivated by the gastric acid in the stomach. In addition, such coatings may be applied to facilitate delivery of a drug to its optimal absorption site in the intestine, provide delayed action, or for delivering the drug to its local site of action in the intestine (United States Pharmacopeia, 1983). Omeprazole is a weak base proton pump inhibitor, chemically known as 6-methoxy-2-[(4-methoxy-3, 5-dimethylpyridin-2-yl) methylsulfinyl] -1Hbenzimidazole. Which stopsthe stomach from producing acid by inhibiting the gastric H+/K+ATPase (hydrogen-potassium adenosine tri phosphatase) at the secretory surface of the gastric parietal cell (Stenhoff et al., 1999), Omeprazole is acid labile substance itself broken down in acid and therefore the drug generally has an enteric coating around it either as a granule in the capsules or as a granule in the dispersible form when administered orally (Singh *et al.,* 2012). Therefore, in order for it to reach the small intestine where it is absorbed, it must be protected from gastric fluid (Jérômeaubert *et al.,* 2011).

* *Corresponding Author*
Swamykannu Dinesh Mohan, Asst.Professor, Dept of Pharmaceutics
Vishnu Institute of Pharmaceutical Education & Research Vishnupur, Narsapur – 502313 Medak District Telangana, India.
Email: dineshmohan.s@viper.ac.in

Commercially omeprazole available in the form of pellet which is filled into conventional hard gelatin capsule preparation of pellets is a complicated, expensive and time consuming process (Sirisha *et al.*, 2013). The coating process of gelatin capsules is very sensitive, especially when aqueous dispersions are used, resulting in shell softening and capsule sticking due to the interaction of water and gelatin (Cole *et al.*, 2002). To overcome these problems the non aqueous coating solutions were used (Felton *et al.*, 1995). Accordingly the purpose of this invention was to coat hard gelatin capsule by using non aqueous enteric polymer. There are clear advantages resulting from the ability to coat a capsule and provides the possibility to deliver drugs to the intestine. The main aim of this study was to investigate the suitability of Eudragit L 100. One of the most important properties of the modified release item is its resistance against gastric conditions. It requires that no more than 10% drug degradation would occur after 2 h in 0.1N HCl solution (Murat *et al.*, 2014). Therefore the main objective and purpose of the present research work is to provide a new process for enteric coated hard gelatin capsule shells containing a drug omeprazole which exhibit 100% release at the site of absorption. The coated capsules were evaluated for coating thickness by scanning electron microscopy and dissolution tests in different pH media.

MATERIALS AND METHODS

Materials

All the materials including hard gelatin capsules, omeprazole, microcrystalline cellulose and disodium hydrogen phosphate were kindly supplied as a gift sample by Yeluri formulations Hyderabad, India. Coating polymers Eudragit L100, HPMC, PEG6000 and organic solvents like isopropanol, acetone, ethanol and methylene chloride were gifted from Bioleo analytical laboratory Hyderabad, India.

Methods

Capsule preparation and characterization

First, the drug omeprazole 20.0 gm and inert fillers of 46.3 gm of microcrystalline cellulose, 12 gm of di sodium hydrogen was mixed in a poly bag separately. Next 2.4 gm of magnesium stearate was added into the mixture and mixed thoroughly for 15 min, then 2.4 gm of aerosil was added into the blend and mixing was continued further 10 min, finally the blend was filled into 100 piece size '0' of hard gelatin capsules (HGC) by a semi automated / manual capsule filling machine (Model-Ecofill). The filled capsule weights are shown in Table 1.After filling, 20 capsules were randomly selected for weight uniformity and drug content analysis (for each test 10 capsules were used). The capsules were open and the powder blend was transferred into volumetric flask and dissolved in 100ml of methanol. The solution was diluted to mark with the same solvent and filtered through Whatman filter paper. (No.41) the aliquot portion of this solution was diluted to get a suitable concentration of omeprazole. Absorbance of the sample solutions was recorded, at 302 nm by UV Spectrophotometer (Lambda 25, Perkin Elmer, Wellesley, (USA). The drug content was determined by following validated formula (Bioleo analytical laboratory, Hyderabad) and the results were described in Table 1 and 2.

Table 1: Formulation of 20 Mg of Omeprazole capsule.

Ingredients	Formula for 100 capsules	
	Mg / Capsule	Percentage
Drug	20	4.04
MCC	463.2	93.53
Magnesium stearate	0.024	0.008
Aerosil	0.024	0.008
Disodium hydrogen phosphate	12	2.4
Total	495.02	99.98

$$\frac{\text{Sample Absorbance}}{\text{Standard Absorbance}} \times \frac{\mathbf{WSTD}}{100} \times \frac{2}{100} \times - \frac{100}{\mathbf{WSPL}} \times \frac{100}{2} \times \frac{100}{LC} \times A.Wt$$

W_{STD} = Weight of the omeprazole working standard taken (mg)
W_{SPL}. = Weight of the sample taken (mg)
A. Wet = Average weight of a Tablet (mg)
LC=Label claim

Preparation of pre coating and over coating solution

Coatings on the gelatin capsules often suffer from insufficient adhesion between the shell and the coating. Therefore, previous workers in the field of enteric coating have found it necessary to pre-coat gelatin capsules with a cellulose derivative; either to promote adhesion of polymers or improve gastro-resistance (Ewart *et al.*, 2002). Consequently, we have used three different coating steps in this investigation, namely pre coat, protective coat or enteric coat and overcoat.

Accurately weighed 12.68 gm of HPMC were dissolved in two third of mixed solvents of Ethanol and Methylene chloride 130 ml (1:1 ratio) with gentle starring and mixed for 30 minutes. Finally the remaining organic solvent was added then the mixture is stirred until a clear solution was obtained. The same procedure was followed for over coating solution. Table 2

Table 2: Evaluation of Uncoated Capsule.

Capsule No	Weight of the Capsule (mg)	Theoretical content of OMZ (mg)	Practical content of OMZ (mg)	Practical content of OMZ (%)
1	490	20	19.7	98.5
2	491	20	19.8	99
3	487	20	19.6	98
4	494	20	19.9	99.5
5	490	20	19.7	98.5
6	495	20	20	100
7	486	20	19.6	98
8	489	20	19.7	98.5
9	492	20	19.5	97.5
10	480	20	19.3	96.5

Preparation of enteric coating solution

Accurately weighed 105.6 gm Eudragit L 100 was dissolved in 80 ml of 1:1 ratio of isopropanol and acetone on a magnetic stirrer. Then PEG 6000 (14% based on the film former) and talc (6.0%) was added into the above solution, stirring was continued until a clear solution was obtained Table 3

Table 3: Coating Composition.

S. No	Name of the materials	Pre coat	Enteric coat	Overcoat
1	HPMC	12.68gm	-	12.68gm
2	Ethanol+Methylene chloride (1:1 ratio)	130 ml	-	130 ml
3	Eudragit L100	-	105.6gm	-
	PEG 6000	-	13.3gm	-
5	Talc	-	5.71gm	-
6	Isopropyl alcohol	-	40ml	-
7	Acetone	-	40ml	-

Preparation of Eudragit L 100 -coated capsules.

Uncoated capsules are placed in a lab model conventional coating pan (PCP-12" Prism Pharma machinery, Ahmadabad, India) and then the pre coating solution are sprayed on capsules at the rate of 4.2 gm/minutes. The temperature is set at 35° C and the coating time is about 45 minutes. The coated capsules were allowed to tumble in the warm air 35 °C until the capsules were free of all organic solvents. Next the enteric coating solution was sprayed on the capsules tumbling in the coating pan. The atomizing air pressure and capsule bed temperature were maintained at 1.3 bar and 25-27ºC respectively, while the capsules were being sprayed.

The enteric coating solution was sprayed on the capsules at the rate of 4.2gms/minutes. The capsules are allowed to tumble slowly until thoroughly dry. During storage of the film coated capsules, adhesion which sometimes occurs can be prevented by an overcoat. Use of an overcoat also improves the appearance of the capsules and can have a positive effect on the stability of the product (Murthy *et al.,* 1988). Coating parameters were presented in Table 4

Table 4: Coating Parameters.

	Parameters	Value		
		Pre coating	Enteric coating	Over coating
1	Nozzle diameter	0.5mm	0.5mm	0.5mm
2	Speed of RPM	12rpm	12rpm	12rpm
3	Atomizing air pressure	1.3 bars	0.8 bars	1.3 bars
4	Inlet air temperature	35°C	35°C	35°C
5	Outlet air temperature	25-30°C	25-30°C	25-30°C
6	Temp of capsule bed	25-27°C	25-27°C	25-27°C
7	Spray rate	4.2gm/min/kg	4.2gm/min/kg	4.2gm/min/kg
8	Coating time	45 min	100 min`	45 min

Evaluation of coated capsules

Scanning electron microscopy (SEM)

To characterize the surface properties, uniformity of film thickness and appearance of the outer surface of the hard gelatin capsule coated with HPMC and Eudragit L100 was examined by scanning electron microscopy (SEM) (JEOL JSM – 6490 LA, Japan) at the body and domed end of the capsule.

Test for gastric resistant and disintegration test

In order to evaluate the percentage of gastric resistant on coated HGCs, disintegration tests were performed according to the United States Pharmacopoeia (USP XXIII, 1995) (Oliveira et al.,). In this test uncoated and coated capsules were placed in baskets separately and immersed in 0.1 N HCl solution at 37 ^{o}C in the disintegration apparatus for 2 hours. The capsules were then carefully removed from the basket assembly for visual inspection of any defects (bloating or swelling). The surface was gently blotted dry with a lint-free wipe. Capsules were then individually reweighed. The percent weight increase was reported as acid uptake (%). Intact capsules were further returned to the disintegration basket and exposed to a phosphate buffer of pH 6.8 at 37°C to determine the total time for disintegration. Percent acid uptake was calculated by using the following equation (Rege *et al.,* 2005).

$$\% \text{ Acid uptake} = \frac{\text{Capsule weight (After acid)} - \text{Capsule weight (Initial)}}{\text{Capsule weight (Initial)}} \times 100$$

In vitro dissolution test

Dissolution of coated HGC was performed by using USP Type II Dissolution apparatus (Lab India). Initially the capsules were kept in 900 ml in 0.1N HCl under the specific conditions of paddle speed of 50 RPM and the temperature of 37°C.At the end of 2h period 0.1N HCl was withdrawn and drug content in the solution was determined spectrophotometrically at 302nm for omeprazole. The remaining solution was discarded and the vessel was replaced by 900ml of pH 6.8 phosphate buffer at same condition. Sample aliquots were withdrawn at the specific interval time and sink condition was maintained by constantly replenishing with the same volume of fresh buffer solution. Each time 5 ml of the solution was withdrawn and filtered through the whatman filter paper and the sample was analyzed by the validated UV detector at 302nm using the same buffer solution of pH 6.8 phosphate buffer as blank. The same procedure was followed for uncoated capsule. (Colorcon, 2009). The dissolution amount of drug was determined by the following validated formula (Bioleo analytical laboratory, Hyderabad).

$$\frac{\text{Sample absorbance}}{\text{Std absorbance}} \times \frac{\text{Std. wt}}{\text{Std dilution}} \times \frac{\text{Sample dilution}}{\text{Sample wt}} \times \frac{Stdpurity}{Lableclaim} \times Avg.Wt$$

RESULTS AND DISCUSSION

Uncoated hard gelatin capsules were indicated in Table 2. The drug content found to be between 96.5 % to 100% of the theoretical amount for all the formulations respectively, weight variation laid between 480 mg to 495 mg obtained values is in accordance within United states Pharmacopoeial limits. In this present work 90 hard gelatin capsules, previously filled with drug and excipients, sealed by using a drop of 1% hydro alcoholic solution to prevent the separation of cap and body inside the coating pan while rolling. They were then coated with the coating solutions of HPMC and Eudragit L 100 by maintaining a significant distance between the coating pan and spray nozzle to avoid the loss of coating material.

Processing problems like; capsule sticking and separation of cap and body have not been found. The coated capsules were shown in Fig.1 A sample of 20 capsules were withdrawn and studied further for surface morphology and thickness by SEM. The

results confirmed that a uniform coating thickness around the domed end and flat surface of the capsule and also no pores and cracks were seen on the capsule surface as shown in Fig.2A and 2B. This could be achieved by a well controlled coating process.
Based on the SEM analysis, we have chosen four different thicknesses of capsules (low-medium-high) for further evaluation like; disintegration, acid uptake and dissolution.

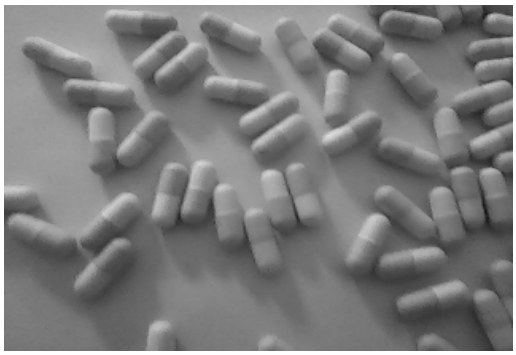

Fig.1: Coated capsules.

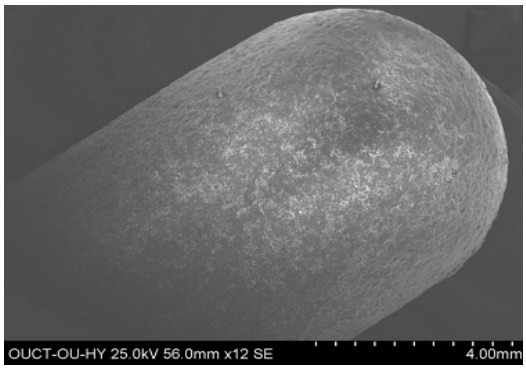

Fig. 2: Coated surface of the capsules.**(A) :** Domed surface of the capsule.

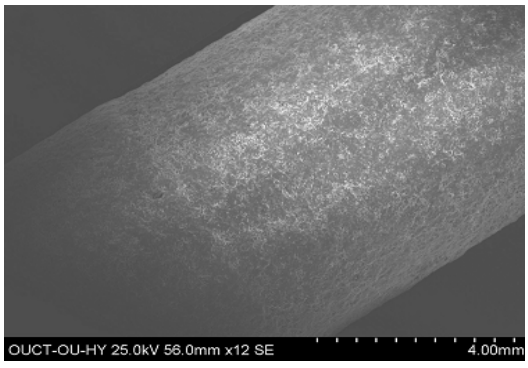

Fig. 2B: Flat surface surface of the capsule**.**

The effort of this research work was to resist the disintegration and dissolution of enteric-coated capsules in an acidic environment. The disintegration of the capsules coated with HPMC and Eudragit L100 was performed for 2 h in acid media and later in PBS. For this evaluation, we have selected one low, two medium and one high weight capsules. It was found that no disintegration occurred in coated capsules, but the capsule weight was increased negligibly as shown in Fig.3 and Table 5. Disintegration of coated capsules was observed only in the phosphate buffer solution as shown in Table 6. Whereas, the rapid disintegration occurred in uncoated capsules within 5 min in acidic media as represented in Fig.4. Hence we found 40% drug release within 5 min and 95% of the drugs were released at the end of 30 min

Table 5: Acid uptake test for uncoated and enteric coated capsules in 0.1NHCl

Capsule No	Initial weight (mg± SD) n=3	Final weight (mg± SD)n=3	Acid uptake in (%± SD) n=3	Disintegration time (min)
1	480±0.57	525±1.15	8.5±0.15	Nil
2	486±1.52	527±1.52	7.7±0.30	Nil
3	490±0.57	514±1.15	4.6±0.25	Nil
4	495±1.73	508±0.57	2.5±0.20	Nil
Uncoated capsule	494±1.52	-	-	5

Table 6: Disintegration time of coated capsules in ph **6.8** phosphate buffer solution.

Initial weight (mg± SD)n=3	Disintegration time in 6.8 PBS (min± SD)n=3
525±1.15	24±0.57
527±1.52	32±0.57
514±1.15	40±1.52
508±0.57	45±0.57

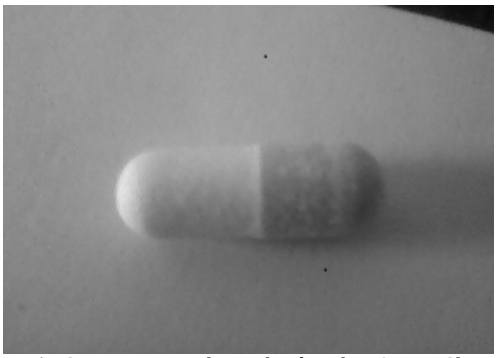

Fig. 3: Enteric coated capsule after 2h in 0.1N HCl.

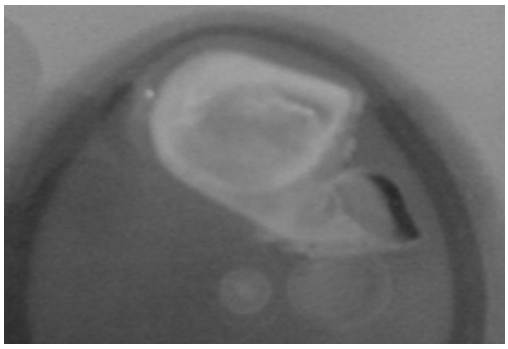

Fig. 4: Disintegration of uncoated capsules in 0.1N HCl.

No omeprazole was released over 2 h at pH 1.2 from the capsules coated with higher coating thicknesses of 89µm whereas, low and medium thickness capsules (38µm, 58µm and 67µm) Fig.5 were released the drug in the percentage between 0.55 - 58%. The reason could be less polymer thickness around the outer

surface of the gelatin capsule due to that it allows to penetrate the dissolution medium.

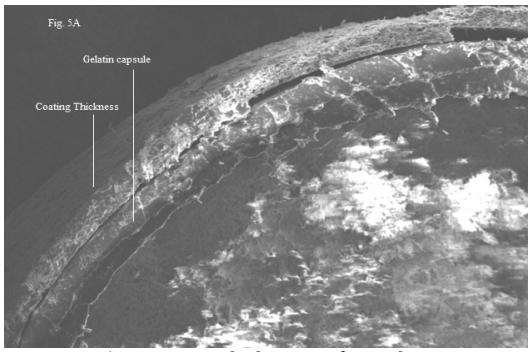

Fig. 5: various thicknesses of capsules .
Fig. 5: (**A)** Coated capsule a thicknesses of 38µm.

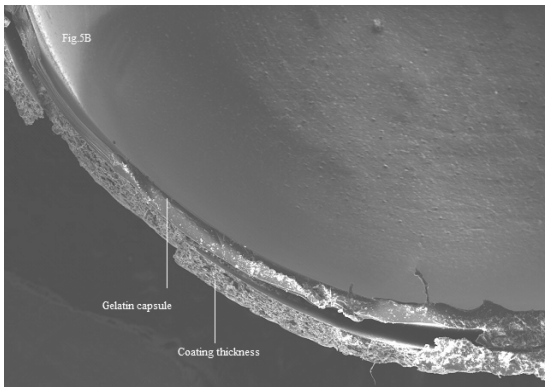

Fig. 5 B : Coated capsule a thicknesses of 67µm.

Those three capsules were not selected for further dissolution test in pH 6.8 PBS solution because enteric coated formulations require not more than 10% drug degradation in 0.1N HCl solution. omeprazole release were rapid from the capsules coated with higher coating thicknesses of 89 µm at pH 6.8 Fig.6.

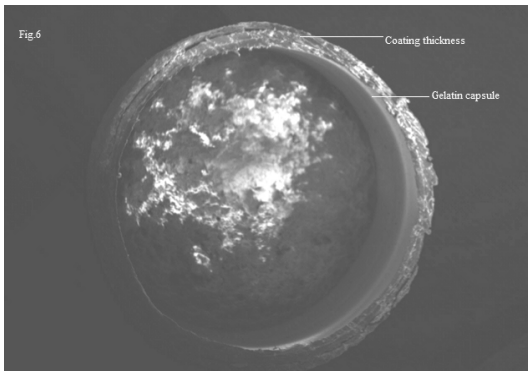

Fig.6 : Coated capsule a thicknesses of 89µm

At this condition dissolution medium of pH 6.8 PBS was penetrated through the polymers and enters between the body and cap and dissolved the gelatin. This led to the dissolution of the drug, where maximum amount of drug was released in pH 6.8 PBS solution. Fig.7 and Table 7 From this experiment, it was concluded that this method offers a novel and better way to prepare enteric coated capsules of acid labile drugs like omeprazole or new drugs to deliver to the absorption site resisting the drug release in the acid environment.

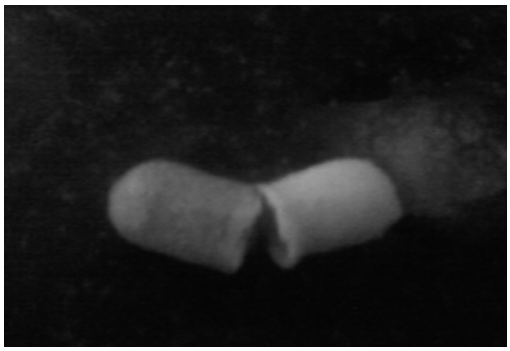

Fig. 7: Capsule disintegration and drug dissolution at pH 6.8 PBS (Capsule of 89 µm thicknesses).

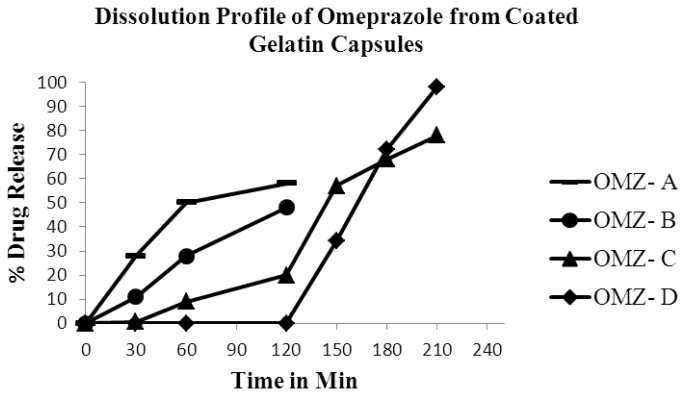

Fig. 8: OMZ-A Thickness of 38µm, OMZ-B Thickness of 58µm, OMZ-C Thickness of 67µm and OMZ-D Thickness of 89µm

Table 7: Dissolution Profiles Of Coated Capsules.

Coating Thickness	Amount of drug released in different dissolution media					
	pH 1.2			pH 6.8		
	(Time in Min± SD) n=3			(Time in Min± SD) n=3		
	30	60	120	150	180	
38.33±5.12	28.69±0.06	50.46 ±0.10	58.62 ±0.01	-	-	-
58.66± 6.02	11.61±0.03	28.79 ±0.03	48.54 ±0.02	-	-	-
67.25± 5.66	0.55± 0.00	8.95± 0.03	20.23 ±0.01	57.10 ±0.04	68.70 ±0.06	78.56 ±0.03
89.75± 7 .25	0.00±0.0 0	0.00± 0.00	0.00± 0.00	34.46 ±0.03	72.90 ±0.04	98.77 ±0.03

CONCLUSION

Hard gelatin capsules containing omeprazole have been successfully enteric coated with non aqueous method by using HPMC and Eudragit L100 polymers in a conventional coating pan. Capsules coated with a high polymer thickness provide enough protection and resistance to the drug in acidic media of pH0.1N HCl. Uniform coating thicknesses of the polymeric film around the capsule play a significant role that providing good gastric protection to the drug. In conclusion, this could be a good alternative of enteric coated tablets.

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