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PHYSICOCHEMICAL CHARACTERIZATION AND EVALUATION OF MUCOADHESIVE TABLETS OF OMEPRAZOLE FOR LOCAL ACTION

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Abstract:
In the present work, we developed an effective mucoadhesive tablets of omeprazole(Di-omeprazole magnesium powder and omeprazole pellets) by direct punch method with excellent mucoadhesive force using three mucoadhesive polymers namely hydroxyl propyl methyl celluloseK4M, sodium carboxy methyl cellulose, carbopol934p and water insoluble polymer ethyl cellulose which can be attached with the intestinal mucosa. Mucoadhesive tablets are coated with respective polymer and prepared them enteric coated tablets by coated with Eudragit L100. Tablets were evaluated in three mediums like 0.1N HCl for 2hr, pH 6.5 phosphate buffer solution for 10hr. and 7.8 phosphate buffer solution for 12hr. Sodium carboxy methyl cellulose showed above 90% release for 10hr. where carbopol934p provided slow release 100% over a period of 12hr. but Ethyl cellulose containing tablets showed less than 68% release and release was diffusion and erosion controlled and followed Zero order kinetics. Thus, the present study concluded that, Carbopol934p containing mucoadhesive tablets of Omeprazole pellets and Di-Omeprazole magnesium powder can be used for local action in the intestine as well as for Oral Controlled Release Drug Delivery.
Key words:Cellulose, Diffusion, Erosion, Kinetic.

Introduction

Omeprazole **(**5-methyl-2-{[(4-methoxy-3, 5-di-methyl-2-pyridinyl) methyl] sulfonyl}-1H-benzimidazole**)**, a substituted benzimidazole, exhibits potent and long lasting inhibition of gastric acid secretion by selectively interacting with the gastric proton pump (K^+/H^+-ATPase) in the parietal cell secretory membrane[1, 2]. The enteric coated mucoadhesive sustained release tablets were prepared by mucoadhesive polymer such as hydroxypropylmethylcellulose, sodiumcarboxymethylcellulose, carbopol 934p and water insoluble polymer ethylcellulose. These individual polymers are used for the preparation of mucoadhesive tablets of omeprazole pellets and omeprazole powder using direct compressible diluents dibasic calcium phosphate (DCP) and lubricant as talc. These mucoadhesive tablets were coated with respective polymer (normal coating) and also coated with enteric polymer Eudragit L100. Reason behind this investigation, Omeprazole is slightly soluble in water and very soluble in alkaline conditions [3]and the stability of omeprazole decreases with a corresponding decrease in the pH of the media with which it comes in contact. Therefore exposure of omeprazole to the acidic content of the stomach would lead to significant degradation of the drug and hence reduced bioavailability and short biological half life 0.5-3hr [4]. Due to its low bioavailability, short biological half life and hepatic first pass metabolism, various oral formulation of omeprazole such as enteric coated granules[5, 6] and tablets[7, 8] have been developed with a subsequent 40% increase in oral bioavailability[9] of omeprazole but have a wide individual variation of plasma concentration in human[5-8]. To overcome this problem, alternative dosage forms such as rectal suppository[10] and buccal adhesive tablets[11] were developed. But all the dosage form of omeprazole gives systemic

effect so, attempts have been made to develop enteric coated mucoadhesive sustained release product with prolonged residence time by attaching with the intestinal mucosa for long time and may give local effect, reduced drug loss and reduced dosing frequency.

Material and Method

An Omeprazole pellet was a gift sample from Diamond Drugs Pvt. Ltd., Kolkata and Di-omeprazole magnesium powder was a gift sample from Ranbaxy Laboratories Ltd. Baddi, Eudragit L100 was a gift sample from Zydus Cadila;Sikkim. Hydroxypropyl methylcellulose K4M (HPMC -K4M) and Sodium carboxymethyl cellulose were supplied by Loba Chemie Pvt.Ltd., Mumbai and Visco industry, Houra, respectively. Ethyl cellulose- LR (EC-LR) and Carbopol 934p were supplied by S.D. Fine- Chem. Limited, Mumbai.

Drug–Polymer Interaction study

Drug and polymer interaction study was carried out by using Fourier Transform Infrared (FTIR–8400S, Shimadzu Corporation, Japan). Samples were triturated with Potassium bromide and transformed into disk. Disk was applied to the centre of the sample holding device and scanned between 4000–400cm^{-1} at a resolution of 2 cm^{-1}. The IR scans were processed using IR Solution and represented as percentage transmittance (%T) on a common scale [3].

Preparation of mucoadhesive tablet

Measure amount of Omeprazole pellets are mixed with the respective polymer for formulation F1, F2, F3 and F4. Formulations (F5, F6, F7 and F8) are prepared using di-Omeprazole magnesium powder. Diluents are mixed with formulations in desired amount and blended for 30 min. Finally mixed the talc used as a lubricating agent just prior to tablet punch. 200mg tablets were manufactured as per the formula given in table 1 using an instrumented tablet compression machine (Rimek Mini Press-I, Shakti Engineering).

Preparation of coated tablets

Each formulation was coated with 0.5% coating solution of respective polymer as well as make them enteric coated by 0.5% coating solution of Eudragit L100. Coating was done by dipping the tablets into the 0.5% solution and immediately dried under the hot air flow [12].

Physicochemical evaluation

Thickness and diameter, hardness and friability was carried out before and after coating using the instrument slide calipers, Monsanto hardness tester and Roche friabilator respectively. Swelling index [12-14], Drug content [12, 14, 15], Bioadhesive strength and in-vitro release rate were also studied which are discussed below-

Measurement of bioadhesive strength

The bioadhesive strength of the tablets was measured using a modified physical balance. Goat intestine was used as a model membrane for measurement of bioadhesive strength and phosphate buffer pH6.5 and pH 7.8 as a moistening fluid. The surface of the mucosal membrane was first blotted with a filter paper and then moistened with 2-3 drops of buffer solution pH 6.5 and pH 7.8. The tablets were tied with thread and attached with the intestine. Anather end of thread tied with one side of the physical balance. The weight required to detach the tablet from the mucosal surface was taken as the measure of bioadhesive strength [12, 14, 16].

In-vitro drug release studies

The release rates of prepared enteric coated mucoadhesive tablets of Omeprazole were studied using the Veego dissolution test apparatus (USP II) rotating paddle method under sink conditions at 37±0.5ºc and 50 rpm. The tablets were placed in the basket and tested for drug release for 2hr. in 0.1N

Table I: - Composition of mucoadhesive tablets of Omeprazole pellets and powder

mg/tablet	F1	F2	F3	F4	F5	F6	F7	F8
Omeprazole pallet	91.4	91.4	91.4	91.4	---	---	---	---
Omeprazole powder	---	---	---	---	60	60	60	60
HPMC	45.7	---	---	---	30	---	---	---
SCMC	---	45.7	---	---	---	30	---	---
EC	---	---	45.7	---	---	---	30	---
Carbopol 934p	---	---	---	45.7	---	---	---	30
Dibasic calsium phosphate	60.9	60.9	60.9	60.9	108	108	108	108
Talc	2	2	2	2	2	2	2	2

a) HPMC- Hydroxy Propyl Methyl Cellulose
b) SCMC- Sodium Carboxy Methyl Cellulose
c) EC- Ethyl Cellulose

HCl solution and tested for drug release for 12hr. in pH 6.5 and 7.8 phosphate buffer solution [12-15].

Result and Discussion

Using the mucoadhesive polymer hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose, carbopol934p and water insoluble polymer ethyl cellulose with a coat consisting of respective polymer and Eudragit L100, we prepared enteric coated mucoadhesive tablets of Omeprazole pellets and Di-Omeprazole magnesium powder by direct compression method. Afterthat drug-polymer interaction study was done. The principal IR absorption peaks of omeprazole pallets at 1016, 1205 and 1627 cm^{-1} were obtained in the spectra of the pure drug as well as different drug –polymer complex indicating that no chemical interaction occurred between the omeprazole pallets and the polymer used. The principal IR absorption peaks of omeprazole powder at 1014, 1199 and 1624 cm^{-1} were obtained in the spectra of the pure drug as well as different drug –polymer complex indicating that no chemical interaction occurred between the omeprazole powder and the polymer used [3].

The formulation had low tablet weight variation (% deviation < 0.6). Hardness of the tablets was in the range 6 to 7 and percentage weight loss in the friability test was ≤ 0.09 in all the batches. Drug contents of the tablets in all the batches showed 54mg to 57mg instead of 60mg. Overall, the prepared tablet batches were of good quality with regard to hardness, friability, weight uniformity and drug content. Enteric coating trials yielded tablets without edge defects or surface imperfections.

Detachment force measurement method is used for the determination of mucoadhesive strength of different formulations and it was observed that the carbopol 934p had the highest bioadhesive strength (between 31-34gm) and sodium carboxy methyl cellulose(between 24-25gm) is a good bioadhesive material but ethyl cellulose did not contain any bioadhesive property when compared with non mucoadhesive material.

The release of omeprazole from the tablets was studied in phosphate buffer solution of pH 6.5 and 7.8 for a period of 12hr in prescribed dissolution apparatus USP II. Mucoadhesive tablets containing hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose, carbopol 934p alone gave

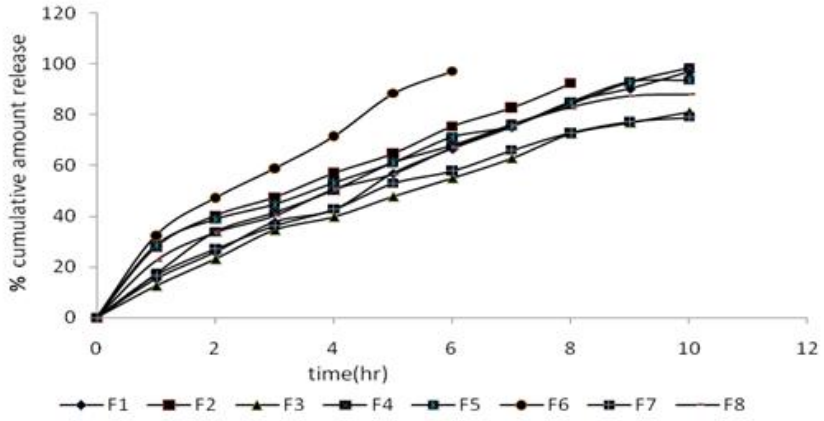

Figure 1: - In-vitro release profile of mucoadhesive tablets in pH 6.5 phosphate buffer solution.

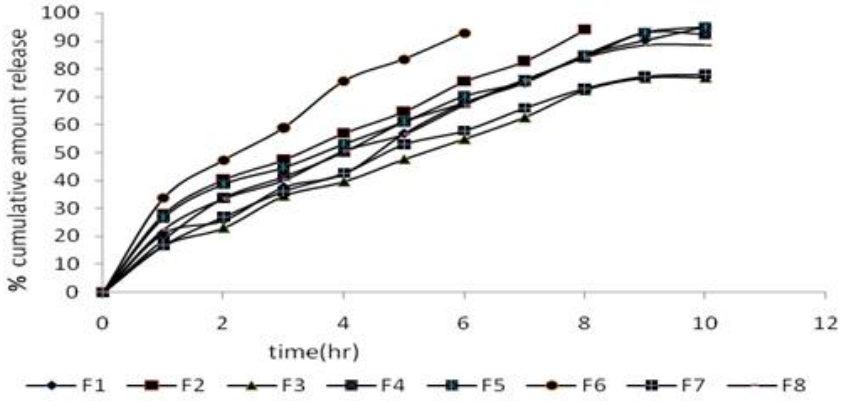

Figure 2: - In-vitro release profile of mucoadhesive tablets in pH 7.8 phosphate buffer solution.

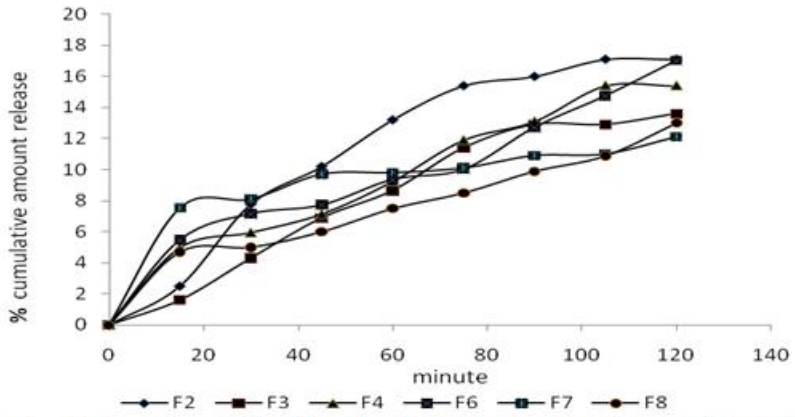

Figure 3: - In-vitro release profile of coated and enteric coated mucoadhesive tablets in 0.1 N HCL medium.

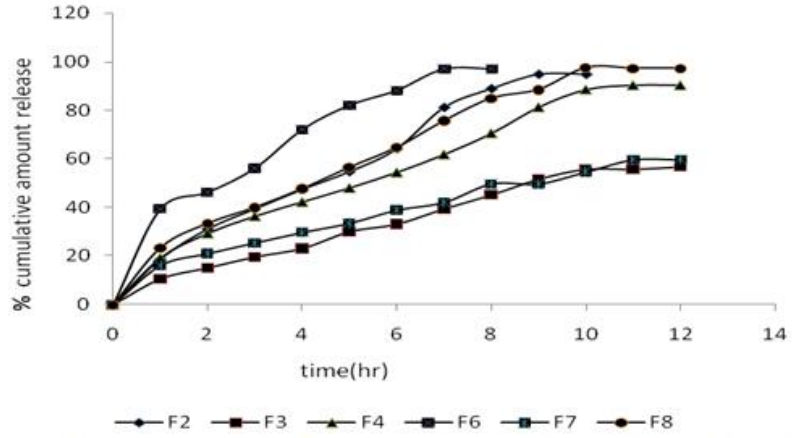

Figure 4: - In-vitro release profile of coated mucoadhesive tablets in pH 6.5 phosphate buffer solution.

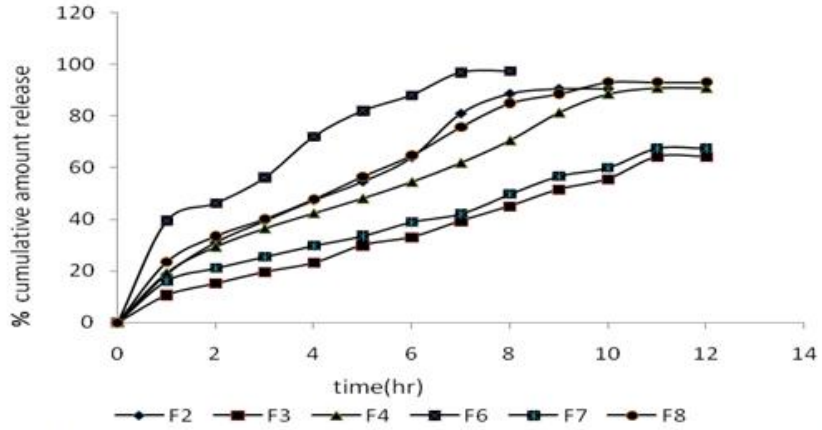

Figure 5: - In-vitro release profile of coated mucoadhesive tablets in pH 7.8 phosphate buffer solution.

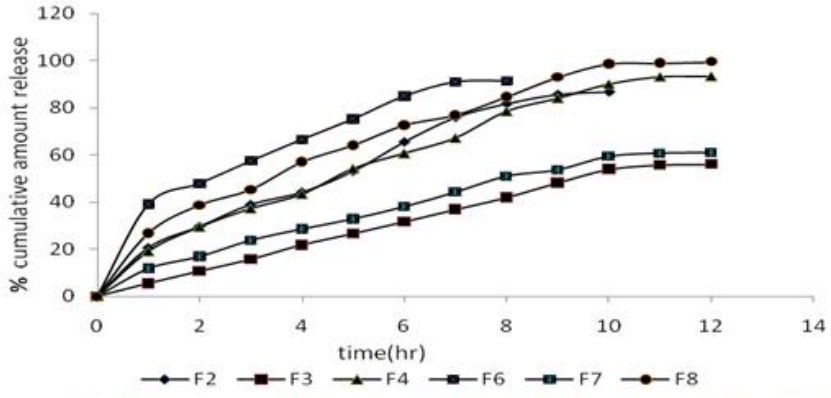

Figure 6: - In-vitro release profile of enteric coated mucoadhesive tablets in pH 6.5 phosphate buffer solution.

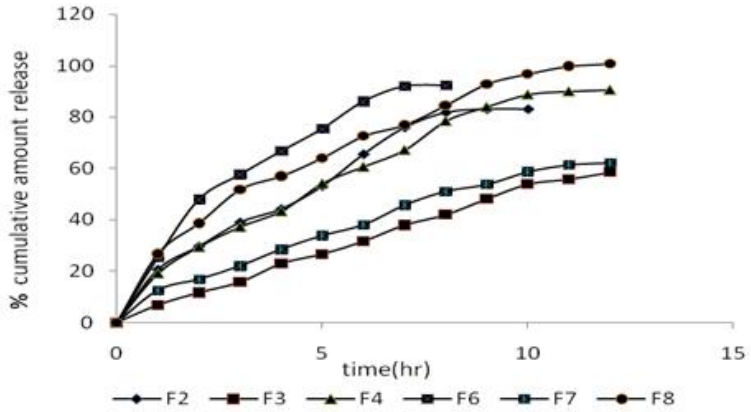

Figure 7: - In-vitro release profile of enteric coated mucoadhesive tablets in pH 7.8 phosphate buffer solution.

slow release over a period of 10hr, 6-8hr and 10hr respectively. By comparing all the data of two formulations (hydroxy propyl methyl cellulose, carbopol 934p) indicated that the tablets have similar release pattern. But water insoluble polymer ethyl cellulose containing tablet release the drug maximum 81% over a period of 10hr. Release profile of mucoadhesive tablets is shown in Figure 1 and 2. Coated as well as enteric coated tablets were prepared and evaluated the release profile in three mediums like 0.1N HCl, pH 6.5 and 7.8 phosphate buffer solution. But due to some process variables the hydroxy propyl methyl cellulose containing formulation was discarded. Coated and enteric coated tablets were prepared acid resistance but normal coated tablets were gave somewhat more release than enteric coating polymer in 0.1N HCl medium but these formulation were readily dissolved in pH 6.5 and 7.8 phosphate buffer solution. The percent of omeprazole release in 0.1N HCl medium showed in Fig.3 not exciding 17% over 2 hr. The tablets containing Di-Omeprazole magnesium powder were gave somewhat more release than tablets containing Omeprazole pellets in phosphate buffer solution but release rate spread over a period of 12hr. From release profile data it was found that sodium carboxy methyl cellulose containing tablets give minimum 82% release over a period of 8-10 hr. carbopol 934p containing tablets were release the drug near about 100% over a period of 12hr. and ethyl cellulose containing tablets were release the drug in very less amount not more than 67% over a period of 12hr. Release profile of coated and enteric coated mucoadhesive tablets is shown in Fig.4-7. The release profile of each formulation was fitted into different release model and Peppas and Korsmeyer equation was used to determine the mechanism of rate of release of drug.

Conclusion

In the present study, Carbopol 934p containing tablets showed 100% release completely within 12hr. and had good mucoadhesive property and drug release was controlled by Diffusion as well as Erosion mechanisms followed by Zero order kinetics. Thus, the result of the present study concluded that, Carbopol 934p containing mucoadhesive tablets of Omeprazole pellets and Di-Omeprazole magnesium powder can be used for local action in the intestine as well as for Oral Controlled Release Drug Delivery.

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