Formulation and evaluation of Benazepril pulsatile drug delivery system

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ABSTRACT

The purpose of this research is to prepare enteric coated tablets consisting of disintegrants and Benazepril by Direct compression method and to evaluate their quick disintegration and release properties. To the optimized formulation enteric coat is usually given by various enteric polymers. The effect of various excipients and process variables on the particle morphology, micromeritics properties, *in vitro* release behavior, etc., was studied.

KEY WORDS: Pulsatile drug delivery, Benzapril, disintegrants.

1. INTRODUCTION

Numerous drug entities based on oral delivery have been successfully commercialized, but many others are not readily available by oral administration, which are incompatible with the physical and/or chemical environments of the upper gastrointestinal tract (GIT) and/or demonstrate poor uptake in the upper GI tract. Due to lack of digestive enzymes, colon is considered as suitable site for the absorption of various drugs. Over the past two decades the major challenge for scientists is to target the drugs specifically to the colonic region of GIT. Previously colon was considered as an innocuous organ solely responsible for absorption of water, electrolytes and temporary storage of stools. But now it is accepted as important site for drug delivery.

Colonic drug delivery is a relatively recent approach for the treatment of diseases like ulcerative colitis, Crohn's disease, colorectal cancer and amoebiasis. Colon-specific delivery systems are also gaining importance for the systemic delivery of protein and peptide drugs. Due to negligible activity of brush border membrane peptidase activity and less activity of pancreatic enzymes, the colon is considered to be more suitable for delivery of peptides and protein in comparison to small intestine. Besides this low hostile environment, the colonic transit time is long (20-30 hrs.) and the colonic tissue is highly responsive to the action of absorption enhancers. The longer residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancers make the colon a promising site for the delivery of proteins and peptide drugs for systemic absorption. Colonic delivery can be accomplished by oral or rectal administration. Rectal dosage forms such as suppositories and enemas are not always effective since a high variability in the distribution of these forms is observed. Suppositories are only effective in the rectum because of the confined spread, and enema solutions can only offer topical treatment to the sigmoid and descending colon. Therefore, oral administration is preferred, but for this purpose, physiological barriers have to be prevail over. Absorption or degradation of the active ingredient in the upper part of the GI tract is the major obstacle and must be circumvented for successful colonic drug delivery. The scientific frame work required for development of a successful oral controlled drug delivery dosage form consists of an understanding of three aspects of the system. Namely, The physicochemical characteristics of the drug, Relevant GI anatomy and physiology, Dosage form characteristics.
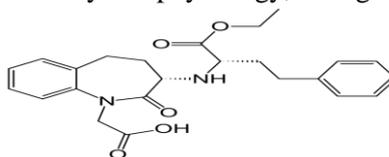

Figure.1.Structure of Benazepril

2. MATERIALS AND METHODS

Benazepril, A gift sample from Aurobindo pharmaceuticals, HPMC E15 and Eudragit L 100 from Qualikem fine chemicals Ltd, Chloroform AR and Methanol AR Merck Ltd, Mumbai, Polyethylene glycol, Potassium dihydrogen phosphate and Sodium hydroxide from Finar chemicals limited, Ahmedabad.

Preformulation studies, Weight variation, friability, disintegration test and compatibility studies using FTIR and dissolution studies were conducted as per the standard procedures given in pharmacopoeias.

Table.1.Formulation table of Benazepril tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Benazepril	20	20	20	20	20	20	20	20	20
SSG	6	-	-	8	-	-	-	-	-
Cross povidone	-	6	-	-	8	-	-	-	-
Pre gelatized starch	-	-	6	-	-	8	-	-	-
Pectin	-	-	-	-	-	-	20	40	60
Micro crystalline cellulose	71	71	71	69	69	69	57	37	17
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100

3. RESULTS AND DISCUSSION
FTIR Studies
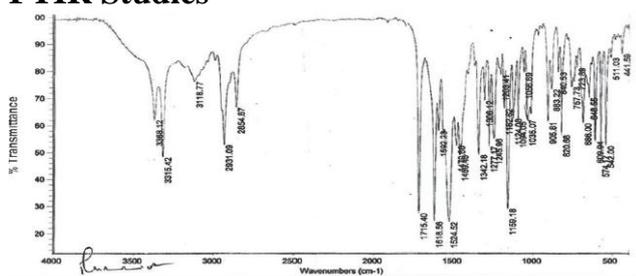
Figure.2.FTIR spectra of Benazepril
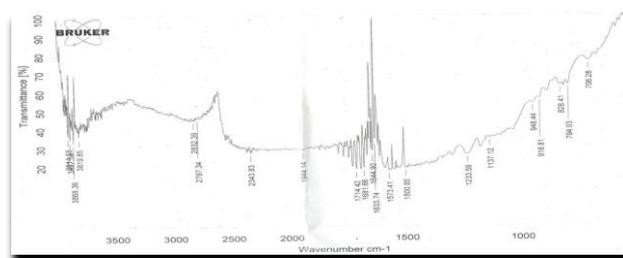
Figure.3.Drug with HPMC K15
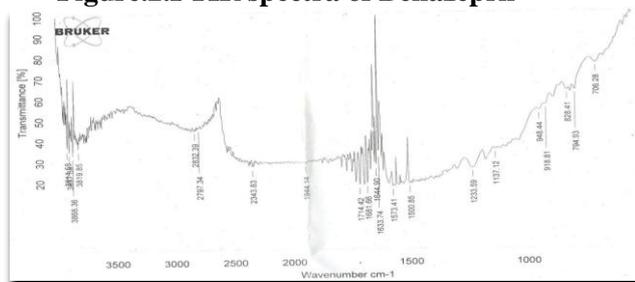
Figure.4.Optimized formulation
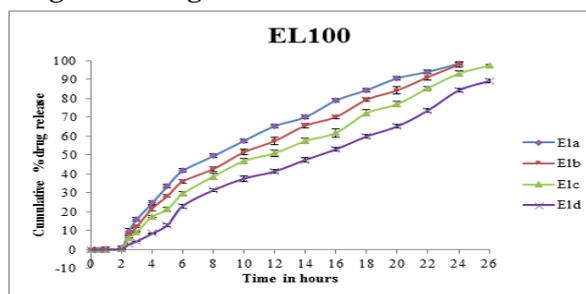
Figure.5.*In vitro* **drug release profiles of tablets coated with EL- 100**
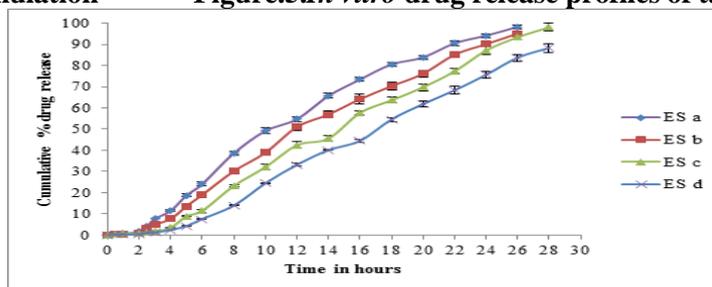

Figure.6.*In vitro* **drug release profiles of tablets coated with Eudragit S- 100**

Discussion: The aim of the present study was to formulate HPMC matrix tablets coated with Eudragit S 100 and Eudragit L 100 for site-specific delivery of Benazeprilfor treating absence seizures. Initial Benazepril release fastly with HPMC K15 than the HPMC K100 and pectin is a time dependent polymer.The use of enteric polymer Eudragit S 100 coated matrix tablets makes them able to release the drug at the particular pH of colonic fluid.

FT IR analysis shows that the drug Benazeprilis compatible with the polymers used. There was no drug-excipient interaction in the physical mixture. It also suggests that the drug did not undergo any degradation or interaction through the whole of the coating process.

The method employed for tableting in this study was direct compression for which the powder blend should possess good flow. The optimum value for Carr's index (%) is upto 15%. Values for angle of repose (θ) less than or equal to 25 generally indicate free flowing material. By means of pilot studies it was found that pure Benazepril exhibited angle of repose value of 23.21± 0.52 indicating good flow property. It was further supported by high Carr's index value of 17.24 ± 0.27. The tablet powder blend Possessed good flow properties. Since, the flow properties of the powder mixture are important for the uniformity of dose of the tablets. The tablets of different batches showed varied thickness (2.72±0.1 to 2.80±0.2), and hardness (5.47±0.45 kg/cm^3 to 6.17 ± 0.29). The friability (0.12 to 0.19 %) and weight variation (%deviation: 99.5±1.36 to 101.35±1.63) of different batches of tablets were found within the prescribed limits. The drug content was found to be uniform (> 98%) within the batches of different tablet formulations.

The evaluation of release profile is recommended as an important tool in the development and optimization of drug formulations. Release studies of core tablet were carried out in pH 7.4 phosphate buffer.

The second part of the formulation focused on the pH dependent polymeric coating of the tablets. The coating polymers were, Eudragit S-100 and Eudragit L-100, dissolves above pH 7.0 and pH 6 respectively, thereby protecting the drug from releasing from the core before reaching the colonic region. Once the enteric coating dissolves, it is expected that drug release would be by HPMC K15. Taking into account the dissolution profile of Benazepril tablets, the F2 was an optimized formulation as its dissolution profile was according to the expected requirements of the study. 6% of Eudragit S 100 and Eudragit L 100 are enteric coated to achieve 5, 10, 15, 20% weight gain separately. The weight variation, hardness and the drug content of all the formulations was found to be within the official limit. From the dissolution data it was observed that all the formulations showed

little or no significant release at pH 1.2 (i.e., <1% drug release). Release started in pH 6.8 buffer for all the formulations. This may be attributed to the fact that the threshold pH (pH at which dissolution occurs) of Eudragit L-100 is 6. The lag time for drug release in pH 6.8 buffer was found to be dependent on the level of coating 5, 10, 15 and 20% (coating level in TWG) corresponding to batches EL a, EL b, EL c and EL d respectively showed significant drug release (i.e., >20%) after a lag time of 4 hr., 5 hr., 5.5 hr. and 6 hr. respectively and drug release in pH 7.4 is >90% for EL a, EL b, in 24 hours and >90% for EL c in 26 hours and <90% for EL d in 26 hours.

Formulations coated with ES-100 TWG 15% and 20% showed no release in pH 6.8 buffer (i.e., <1% drug release). However the release for formulations coated with ES 100 TWG 5%, 10% started in 7.4 buffer. Also the lag time for drug release in pH 6.8-7.4 buffer was found to be dependent on the level of coating. 5, 10, 15, 20% (coating level in TWG) corresponding to batches ES a, ES b, ES c and ES d showed significant drug release (i.,e < 25%) after a lag time of 5 hr. (in pH 6.8 medium). Drug release in pH 7.4 buffer is >90% for ES a, ES b in 24 hours, >90% for ES c in 28 hours and <90% for EL d in 28 hours.

Formulation ES c coated with 15% TWG of Eudragit S- 100 showed the most desirable properties. EL c also performed better *in vitro* but ES c was considered more superior because of the former's dependence of GI transit for drug release and was not specific to pH of the colon. Hence ES c was considered as the optimized formulation for colonic drug delivery.

The release mechanism is also influenced by porosity and tortuosity of the matrix. In this study, drug release kinetics was evaluated by fitting with different models, zero-order, first-order, Higuchi, or Korsmeyer-Peppas. According to the Table 32, it is observed that ES c formulation was best fitted with zero order model indicating their release kinetics is not dependent on the concentration of drug in the depot. The drug release data were fitted to the power law or the Korsmeyer–Peppas equation. In this study, the Benazepril.Benazeprilrelease, in neutral medium, from Xanthum gum tablets showed a good fit into the Korsmeyer-Peppas equation, indicating combined effect of diffusion and erosion mechanisms for drug release. It exhibited a correlation coefficient (r^2) greater than 0.98. In the case of matrix tablets, $0.45 < n$ corresponds to a Fickian diffusion mechanism and $n = 0.89$ indicates a purely relaxed controlled delivery which is referred to as Case II transport. Intermediate values $0.45 < n < 0.89$ indicate an anomalous behavior (non-Fickian kinetics corresponding to coupled diffusion/polymer relaxation). Occasionally, values of $n > 0.89$ have been observed, which has been regarded as Super Case II kinetics. The mechanisms of drug release is (super case-II), since they fitted well with Korsmeyer–Peppas models as their r^2 values in the range of 0.999 with n value above 1. This indicates that the drug release depends on swelling, relaxation and erosion of polymer with zero order release kinetics.

4. CONCLUSION

A successful colon drug delivery requires that the triggering mechanism in the delivery system only respond to the physiological conditions particular to the colon. Due to the lackofdiscontinuity in physiological parameters along the GI tract, few mechanisms can be incorporated into a delivery system to effect in colon-specific drug release. So far, four approaches were proposed for colon-specific drug delivery: prodrugs, pH- and time-dependent systems and microflora-activated systems. F6was the optomised formulation. Based on the different ratios of coating FS3d was optimized and it is better than the pectin which is Time (Delayed release) dependent polymer. For further confirmation invivo studies to be done.

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