Abstract

Drugs that are easily absorbed from the GI tract and have a short half-life are eliminated quickly from the bloodstream, requiring frequent dosing. To avoid this problem, the oral controlled release formulations are being developed. Gastro-retentive dosage forms have the potential from use as controlled release systems. The purpose of this research is to develop the gastro retentive drug delivery system of centrally acting alpha adrenergic agonist cyclobenzaprine Hydrochloride (cyclobenzaprine HCl). It is well absorbed from the upper part of the GIT, due to short gastric residence time the bioavailability is low and hence it is need to develop a dosage form that releases the drug in stomach using gastro retentive system. Different formulations of cyclobenzaprine HCl gastro-retentive floating tablets were prepared by wet granulation method using various concentrations of HPMC K4M / HPMC K100M and combination of Psyllium husk and HPMC K100M as matrix forming agent. Sodium bicarbonate and citric acid were used as a gas generating agent that helps in maintaining the buoyancy. The prepared cyclobenzaprine HCl gastro-retentive floating granules were subjected to pre-compression properties to comply with pharmacopeial limits and the prepared gastro-retentive floating tablets were characterized for weight variation, hardness, thickness and friability drug content, swelling studies. The floating lag time of all formulation is good and the Total floating time of all the formulations was >12 hours. The tablets were evaluated for in vitro release characteristics for 12hrs in 0.1N HCl at 37°C and from this in vitro release studies the formulations F-5, F-9 and F-15 exhibited good controlled release profile of about 96.0%, 94.5% and 95.0% when compared with other formulations while floating on the dissolution medium.

Introduction

Many of the drug delivery systems, available in the market are oral drug delivery systems. Oral drug delivery systems have progressed from immediate release to site-specific delivery over a period of time. Every patient would always like to have an ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action. An orally administered controlled drug delivery system encounters a wide range of highly variable conditions, such as pH, agitation intensity, and composition of the gastrointestinal fluids as it passes down the G.I tract. Considerable efforts have been made to design oral controlled drug delivery systems that produce more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, like inability to retain and localize the drug delivery system within desired regions of the G.I tract and highly variable nature of the gastric emptying process. An important factor, which may adversely affect the performance of an oral controlled drug delivery system, is the G.I transit time. The time for absorption in the G.I transit in humans, estimated to be 8-10 hr from mouth to colon, is relatively brief with considerable fluctuation. G.I transit times vary widely between individuals, and depend up on the physical properties of the object ingested and the physiological conditions of the gut. One of the important determinants of G.I transit is the residence time in the stomach.

Methods and Materials

Majority of the drugs are well absorbed from all the regions of the G.I tract while some are absorbed only from specific areas, principally due to their low permeability or solubility in the intestinal tract, their chemical instability, the binding of the drug to the gut contents, as well as to the degradation of the drug by the microorganisms present in the colon.

Therefore, in instances where the drug is not absorbed uniformly over the G.I tract, the rate of drug absorption may not be constant inspite of the drug delivery system delivering the drugs at a constant rate into the G.I fluids. More particularly, in instances where a drug has a clear cut absorption window. It is due to the relatively brief gastric emptying in humans, which normally averages 2-3 hrs through the major absorption zone. It may cause incomplete drug release from the dosage form at absorption sites leading to diminished efficacy of the administered dose. It is apparent that for a drug having such an absorption window an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for a long period of time. For this drug, increased or more predictable availability would result if controlled release systems could be retained in the stomach for extended periods of time.
Evaluation of cyclobenzaprine HCl gastroretentive floating tablets:

The prepared cyclobenzaprine Hydrochloride floating tablets were evaluated for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation:

To study the weight variation, ten tablets from each formulation were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula:

\[
\% \text{ deviation} = \left( \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \right) \times 100
\]

The average weight for tablets in each formulation was calculated and presented with standard deviation.

| Average weight of tablets (mg) (LP) | Average weight of tablets (mg) (U.S.P) | Maximum percentage difference allowed |
|-----------------------------------|----------------------------------------|--------------------------------------|
| Less than 80                      | Less than 130                          | 10                                   |
| 80 – 250                          | 130 – 324                              | 7.5                                  |
| More than 250                     | More than 324                          | 5                                    |

Pharmacopeial specifications for tablet weight variation.

Results

Standard graph of cyclobenzaprine Hydrochloride was plotted as per the procedure in experimental method and its linearity is shown in table 7 and graph 15. The standard graph of cyclobenzaprine Hydrochloride showed good linearity with \( R^2 \) of 0.9998 which indicates that it obeys “Beer-Lambert’s” law.

Standard graph of cyclobenzaprine Hydrochloride in 0.1N HCl buffer

| Concentration(µg/ml) | Absorbance |
|----------------------|------------|
| 0                    | 0          |
| 4                    | 0.2        |
| 8                    | 0.313      |
| 12                   | 0.587      |
| 16                   | 0.778      |
| 20                   | 0.99       |
| slope                | 0.050x     |
| \( R^2 \)            | 0.9998     |

Flow properties of cyclobenzaprine HCl gastroretentive floating granule mixture.

| Formulation code | Angle of repose (°) | Bulk density (gm/cc) | Tapped density (gm/cc) | Carr’s index (%) |
|------------------|---------------------|----------------------|------------------------|------------------|
| F-1              | 27.12 ±1.13         | 0.28±0.11            | 0.34±0.09              | 19.753±0.05      |
| F-2              | 26.12±0.13          | 0.29±0.15            | 0.32±0.11              | 14.088±0.12      |
| F-3              | 25.12±0.13          | 0.27±0.05            | 0.35±0.16              | 17.796±0.17      |
| F-4              | 29.56±1.46          | 0.28±0.08            | 0.36±0.06              | 18.844±0.11      |
| F-5              | 27.11±1.14          | 0.30±0.12            | 0.39±0.03              | 19.743±0.01      |
| F-6              | 29.56±1.86          | 0.31±0.14            | 0.37±0.14              | 21.641±0.19      |
| F-7              | 29.13±1.26          | 0.29±0.05            | 0.34±0.08              | 20.105±0.10      |
| F-8              | 24.64±1.35          | 0.28±0.17            | 0.33±0.12              | 15.225±0.09      |
| F-9              | 27.12±1.22          | 0.29±0.11            | 0.32±0.17              | 18.348±0.05      |
| F-10             | 25.45±1.19          | 0.28±0.12            | 0.34±0.15              | 13.687±0.02      |
| F-11             | 29.86±1.35          | 0.27±0.11            | 0.36±0.13              | 20.145±0.18      |
| F-12             | 23.35±1.46          | 0.29±0.05            | 0.39±0.04              | 16.389±0.17      |
| F-13             | 26.19±1.28          | 0.28±0.19            | 0.37±0.07              | 19.621±0.13      |
| F-14             | 29.64±1.54          | 0.27±0.02            | 0.36±0.11              | 15.987±0.12      |
| F-15             | 24.89±1.22          | 0.28±0.13            | 0.33±0.13              | 14.258±0.04      |
| F-16             | 28.35±1.55          | 0.28±0.13            | 0.32±0.17              | 17.458±0.01      |

Data represents mean ± SD (n=3).

Physical properties of prepared granule mixture

Physical properties of all prepared powder blends are within the limits as per USP. It means the flowability of powder blends is excellent. The granules prepared by wet granulation, direct compression had shown good flow properties with angle of repose values ranging from 25 to 30. Carr’s index values indicate that all the formulations had good flow properties.

The percentage swelling obtained from the water uptake studies of the formulations is shown in Figure 14, 15 and 16. The formulations with HPMC K4M, HPMC K100M and psyllium husk showed the swelling and tablet integrity. The change in sodium bicarbonate concentration did not show any effect on swelling of the tablet. Complete swelling was achieved at the end of 8 h, then diffusion and erosion takes place. The formulation F11 containing K100M shows the higher swelling compared to that of the formulations containing K4M, psyllium husk. The swelling index of the tablets increases with an increase in the polymer viscosity grades.

The release of cyclobenzaprine Hydrochloride was studied using USP dissolution apparatus II. The dissolution media were 900 ml 0.1 N HCl maintained at 37 ± 0.5°C with rotation speed of 50 rpm. Aliquots of 5 ml was collected at predetermined time intervals and replenished with equivalent volume of fresh medium. The samples were diluted to a suitable concentration with 0.1N HCl and were analyzed by using UV/VIS double beam spectrophotometer at 320 nm. The results are expressed as mean±S.D (n=3).

Conclusion

An attempt was made to develop matrix type floating drug delivery system of cyclobenzaprineHCl with acceptable physical characteristics to increase gastric residence time and thereby improve its bioavailability.
Cyclobenzaprine HCl floating tablets were successfully formulated by wet granulation method using cellulose polymers like HPMC K4M, HPMC K100M and Psyllium Husk. Formulated tablets gave satisfactory results for various evaluation parameters like tablet dimensions, hardness, weight variation, tablet hardness, thickness, floating lag time, total floating time, content uniformity and in vitro drug release. From the in vitro studies it was concluded that the formulations F-5, F-9 and F-15 showed better controlled drug release in comparison to the other formulations. The drug release from above formulation followed zero order profile and the mechanism of drug release from floating tablets followed non-fickian diffusion or anomalous diffusion. FTIR studies of optimized formulation showed there were no drug-polymer interactions. Further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies in humans. In conclusion, development of matrix type floating drug delivery system of cyclobenzaprine HCl is a good approach to improve its bioavailability for efficient treatment.

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