pH-INDEPENDENT CONTROLLED RELEASE SWELLABLE MATRIX TABLETS
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ABSTRACT
The aim of this study was to overcome pH-dependent release of weakly basic drug and to achieve pH-independent drug release. An anti-hypertensive drug, Propranolol hydrochloride was chosen due to its pH-dependent solubility. One of the approaches to solve the problem of pH-dependent release of weakly basic drug has been done in this work. The water soluble and highly swellable HPMC was used as a matrix former and organic acids Citric acid and Succinic acid were added to the drug polymer system in different formulations in varying proportions (at 10, 20, 40 and 80mg) as release modifiers. The addition of organic acids was found to maintain an acidic micro environmental pH inside the polymer matrices during drug release in phosphate buffer pH 7.4. On the other hand, the amount of each organic acid added to the system had no effect on the drug release in acidic solution 0.1N HCL. So the micro environmental conditions for the dissolution and diffusion of drug were almost kept constant. Thus, the release of Propranolol hydrochloride from tablets containing HPMC and organic acids was found to be pH-Independent. Between the two organic acids, Succinic acid showed slightly better release when compared to Citric acid.

KEYWORDS: pH-independent, weakly basic drug, HPMC, solubility and swell-ability of HPMC.

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INTRODUCTION
Many drugs are weak bases or salts thereof and thus demonstrate pH dependent solubility in the pH range of the GI tract. With controlled release dosage forms, a possible pH-dependent release could result in in-vivo variability and bioavailability problems. Hence pH-independent drug release is desirable to better assure a reliable drug therapy and to build a greater control into a dosage form.

Several attempts to overcome the problem of pH dependent solubility of weakly basic drugs have been published. They are mostly based on the presence of acidic Excipients such as water-soluble or insoluble polymers or organic acids that either increases the permeability of the drug delivery system by leaching out at higher pH-values or which keep the pH within the system in the intestinal pH-range low and thus the solubility of the drug high.

The objective of this study is to achieve a pH-independent release of a weakly basic drug from matrix tablets consisting of HPMC, a swellable and water-soluble polymer. One of the approaches to overcome the problem of pH-dependent drug release has been demonstrated in this work, i.e., using organic acids (Citric acid, Succinic acid) to create an acidic micro-environmental pH inside the polymer matrices. Propranolol HCl is an adrenergic blocking agent, effective in treatment of hypertension and angina. Propranolol HCl has short plasma half-life of 3-5hrs owing to which, multiple doses are needed to maintain therapeutic concentration of the drug in plasma for better therapeutic response and improved patient compliance. Therefore, it is necessary to develop sustained release preparations with extended clinical effects.

MATERIALS AND METHODS
The materials used were procured from the following sources: Propranolol hydrochloride (Zydus Cadila Pharmaceuticals ltd. -Bangalore), Hydroxy propyl methyl cellulose (HPMC, Methocel®, K-15M, BPRL Pvt. Ltd. Bangalore), Magnesium stearate (Loba chemie -Mumbai), lactose (Fast flow, Pharmatose, Nice chemicals) citric acid, Succinic acid (Nice chemicals-Cochin) and all the other reagents used were laboratory grade. Magnesium stearate was used as lubricant. After evaluating the pre-compression parameters the lubricated granules were compressed using 10-station Rimek mini-
press RSB-4 tablet punching machine using 8mm diameter concave punches. The total weight of the tablet was maintained at 250mg. The hardness of all the tablets was maintained to 4kg/cm².

**Formulation of tablets**

Weighed quantity of drug, polymer, organic acids (citric acid and Succinic acid) and diluents (lactose) were passed through sieve # 80 and mixed in geometric proportion using a mortar and pestle followed by lubrication using Magnesium stearate (0.5 %)(table 1). 250 mg of the lubricated physical mixture were compressed using a 10- station ‘Remek’ mini-press tablet punching machine using flat punches (8mm diameter)3,8,9,10. Characteristics of the blend such as bulk density, compressibility index, and angle of repose were determined for each formulation1,11,12.

Weight variation test was conducted as per specifications of IP. Hardness of the tablet was kept constant (approximately 4 kg/cm²) for all the formulations.

**Evaluation of tablets:** The tablets were subjected to various evaluation tests such as

1. **Weight variation test:** The tablets complied with the I.P. requirements in the test for weight variation.

2. **Friability test:** less than 0.1%

3. **Drug content determination:**
   The tablets were powdered, the tablet triturate equivalent to 40mg of propranolol HCl was taken in 100 ml volumetric flask, dissolved and volume was made up to the mark with simulated gastric fluid. From this solution, 0.5 ml was pipetted into a 50 ml volumetric flask and volume was made up to 50 ml with simulated gastric fluid. The absorbance was measured at 216 nm against reagent blank (0.1 N HCl) using UV (Elico-SL159) spectrophotometer. The procedure was repeated for four more tablets of the same formulation and the average value of all five tablets was calculated. The drug content was calculated using the following equation.

\[
\text{Amount of drug present} = \frac{\text{Absorbance} \pm \text{Intercept}}{\text{slope} \times \text{Dilution Factor}}
\]

**In-vitro dissolution profile**

Dissolution studies were carried out by USP-Type II method at 37°C ± 0.5°C. The paddle was set to rotate at 50 rpm. One tablet, previously weighed, was kept in the dissolution media. The dissolution media, acidic buffer pH 1.2 for 12 hours and Phosphate buffer, pH 7.4 for 12 hours were used. 5ml of samples were withdrawn at each hour with replacement and diluted to 50ml and absorbance was measured at 216nm in a UV (Elico-SL159) spectrophotometer.13,14,15

**RESULTS AND DISCUSSION**

Propranolol HCl is a useful model drug to test the formulation concept because of its distinct pH-dependent solubility (µg).

The solubility of Propranolol HCl at pH 2.0 is 120.5224mg/ml; at pH 3.6 it is 71.2462mg/ml, at pH 6.0 it decreases to about 63.5386 mg/ml and at basic pH 8.0 it reduces to 63.0042 mg/ml. Due to this pH-dependent solubility a remarkable difference in the resulting drug release from HPMC tablet was observed in 0.1N HCl and in Phosphate buffer pH 7.4 solutions.

Hydroxy Propyl Methyl cellulose polymer was used as a matrix former in which the drug Propranolol HCl was embedded. The drug: polymer ratio were 1:1,1:1.5,1:2,1:2.5,1:3 for Hydroxy propyl methyl cellulose polymer. The drug: polymer ratio of 1:3 was selected as an optimised formula. To this optimised formula, organic acids such as citric acid and Succinic acid were added.

In the case of highly swellable HPMC matrix tablets (Table-I formulation No. 5), approximately 7.7% and 4.6% of the drug was released after 1 hour in 0.1N HCl and Phosphate buffer respectively. After 8 hours, 48% of the drug was released in 0.1N HCl versus only 20% was released in Phosphate buffer solution, pH 7.4. (Shown in graph 1).

The reason for this behaviour is that HPMC swells to a significant extent upon contact with the release medium. The drug is not predominantly released by diffusion through water-filled pores but by diffusion through the swollen polymer network. In addition the swelling of HPMC polymer matrix also plays an important role. Hence the approach to adjust the release profile of weakly basic drugs in Phosphate buffer to that in 0.1N HCl was based on the addition of organic acids to create a constant acidic microenvironment inside the tablets. Ideally, these acids should dissolve rather slowly to remain within the tablet during the entire period of drug release independent of the pH value of the dissolution medium, the pH inside the tablet matrix was expected to be acidic and thus the solubility of the weakly basic drug to be high. In this case, drug release should be pH-independent. For this purpose, substances with high acidic strength (low pKa value) and relatively low solubility in 0.1N HCl are suitable. Citric acid and Succinic acids were selected. In addition, the organic acids can act as pore-formers at high pH values.

The addition of organic acids to HPMC-based matrix systems significantly increased the drug release in Phosphate buffer (pH 7.4) with increasing amount of organic acids (10 to 80 mg). The resulting release profiles almost overlapped with the ones in 0.1N HCl.
This is in good agreement with above described hypothesis of a constant micro-environmental pH within the tablets.

The amount of organic acids added to the system had no effect on the drug release rate in 0.1N HCl. The explanation for this phenomenon might be as follows. The polymer HPMC swells to a significant extent upon contact with release medium and hence the water filled pores are rapidly closed due to the swelling of the hydrogel. But the amount of imbibing bulk fluid is much higher in case of Phosphate buffer pH 7.4; this leads to higher amount of hydroxide ions entering the tablet, resulting in higher micro environment pH values lead to higher solubility of the organic acids. Hence creation of additional water filled pores and thus to higher force for diffusion with increasing amount of incorporated organic acids (The formation of water-filled pores increases and the resulting release rate increases). Furthermore, the effect of the organic acid was investigated. In all the case the addition of organic acid lead to a significant increase in drug release in Phosphate buffer pH 7.4. However, when compared to citric acid, Succinic acid based formulation shows slight increase in the drug release rate, which may be attributed to the lower pKa value of Succinic acid.

CONCLUSION

The use of HPMC matrices makes possible a sustained release of Propranolol hydrochloride with coupled dissolution mechanism of diffusion and essentially independent of pH. The addition of Succinic acid resulted in a slight increase in the drug release in phosphate buffer pH 7.4 when compared to citric acid, which could be attributed to the lower pKa value of Succinic acid.

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<th>Formulation Code</th>
<th>Propranolol Hydrochloride</th>
<th>HPMC 4000 CPS</th>
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<th>Citric acid</th>
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*All quantities are in milligrams/tablet

REFERENCES


Table 1: Tablet formulations

Graph 1
IN VITRO RELEASE PROFILE OF FORMULATION F5 - pH 1.2 & 7.4

Graph 2
IN VITRO DISSOLUTION PROFILE OF FORMULATIONS FS10, FS20, FS40, FS80

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