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Research Article

# DESIGN AND DEVELOPMENT OF AMBROXOL HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLETS

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**ABSTRACT**

In the present investigation, an attempt was made to formulate the oral sustained release matrix tablets of Ambroxol HCl in order to improve efficacy, reduce the frequency of administration, and better patient compliance. Ambroxol Hydrochloride is a potent mucolytic agent capable of inducing bronchial secretions used in the treatment of respiratory disorders. Differential scanning calorimetric analysis confirmed the absence of any drug polymer interaction. Matrix tablets of Ambroxol Hydrochloride were formulated employing hydrophilic polymers HPMC K100M, Carbopol 934P and hydrophobic polymer Ethyl cellulose as release retardant polymers. The powder blend was evaluated for micromeritic properties. The sustained release matrix tablets were prepared by direct compression technique. The tablets were evaluated for thickness, diameter, weight variation test, hardness, friability, and drug content. The *in vitro* drug release characteristics were studied in simulated gastric fluid (2 hours) and intestinal fluid for a period of 10 hours using USP type II dissolution apparatus (total 12hours). The results of dissolution studies indicated that formulation F7 (drug to polymer 1:0.26), the most successful of the study and exhibited satisfactory drug release in the initial hours and the total release was very close to the theoretical release profile. Matrix tablet containing Ethyl cellulose (F7) formulation were found to show good initial release 24.24% at 2 hrs and at the end of 12 hrs the drug release was found to be 96.86%. The n value for F7 obtained from Korsmeyer – peppas model confirmed that the drug release was anomalous diffusion mechanism.

**Keywords:** Ambroxol HCl, Hydroxypropyl methylcellulose, Carbopol 934P, Ethyl cellulose, Matrix tablet.

## INTRODUCTION

Oral administration of drugs has been known for decades as the most common and preferred route for delivery of most therapeutic agents via various pharmaceutical products of different dosage forms. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods, as well as traditional belief that by oral administration the drug is as well absorbed and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other tablets [1, 2].

Sustained release drug delivery aimed at controlling the rate of release as well as maintains desire drug level in the blood that is therapeutically effective and non toxic for extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects. It provides prolonged but not necessarily uniform release of the drug. The rationale for development of a sustained release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effect while improving the management of the diseased condition [3, 4].

Ambroxol is a metabolite of bromhexine with similar actions and uses. It is chemically described as Trans-4-[(2-amino-3, 5-dibromobenzyl) amino]-cyclohexanol. Ambroxol hydrochloride is an expectorant improver and a mucolytic agent used in the treatment of respiratory disorders such as, bronchial asthma, chronic bronchitis characterized by the production of excess or thick mucus . Ambroxol hydrochloride has also been reported to have a cough suppressing effect and anti inflammatory action. It has been successfully used for decades in the form of its hydrochloride as a secretion releasing expectorant in a variety of respiratory disorders. Its short biological half life (4 hrs) that calls for frequent daily dosing (3 to 4 times) and therapeutic use in chronic respiratory diseases necessitates its formulation in to sustained release dosage forms [5, 6].

## MATERIALS AND METHODS

Ambroxol Hydrochloride was received as a gift sample from Kaushik Pharmaceuticals, Chennai).HPMC K100M, microcrystalline cellulose (AVICEL PH 101), were procured from Milton drugs Pvt. Ltd., (Pondicherry, India). Carbopol 934P, ethyl cellulose, Aerosil, Magnesium stearate was purchased from Loba chemie pvt. Ltd, (Mumbai ,India).

### Differential scanning calorimetry (DSC)

The DSC analysis of pure drug, drug+ HPMC K100M, Drug+ Carbopol 934P and Drug+ Ethyl cellulose were carried out using a Shimadzu DSC 60, (Japan) to evaluate any possible drug-polymer interaction. The 2 mg sample were heated in a hermetically sealed aluminum pans in the temperature range of 40-300ºC at heating rate of 10ºC /min under nitrogen flow of 20 ml/min [7, 8].

### Micromeritic properties

The physical mixture of the drug with different excipients was prepared by triturating drug and additives in a dried mortar for 5 min.

### Angle of repose

The angle of repose, which signifies the flow properties of powder blends was determined by the funnel method. The accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of powder. The powders were allowed to flow through the funnel freely onto a clean surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation[9].

$$\tan \theta = h/r$$

where h is the height of powder cone and r is the radius of the powder cone.

### Bulk density and tapped density

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. Both bulk density (BD) and tapped bulk density (TBD) of powder blends were determined using the following formulae[10].

BD = Weight of the powder/Volume of the powder
TBD = Weight of the powder/Tapped volume of the powder

**Table 1: Results of study of Physical Parameters of powders**

| Formulation code | Angle of repose (⁰)* | Loose bulk density(g/ml)* | Tapped bulk density(g/ml)* | Hausner ratio * | Carr's index* |
|---|---|---|---|---|---|
| F1 | 28.02±0.8 | 0.354±0.00 | 0.412±0.00 | 1.16±0.00 | 14.18±0.00 |
| F2 | 25.12±0.6 | 0.358±0.00 | 0.442±0.00 | 1.23±0.00 | 14.63±0.00 |
| F3 | 27.18±1.1 | 0.355±0.00 | 0.406±0.00 | 1.14±0.00 | 12.45±0.00 |
| F4 | 25.05±0.97 | 0.365±0.00 | 0.418±0.00 | 1.16±0.00 | 12.76±0.00 |
| F5 | 28.26±0.31 | 0.360±0.00 | 0.420±0.00 | 1.14±0.00 | 13.09±0.00 |
| F6 | 26.11±0.48 | 0.348±0.00 | 0.403±0.00 | 1.15±0.00 | 13.51±0.00 |
| F7 | 29.52±0.55 | 0.359±0.00 | 0.415±0.00 | 1.16±0.00 | 12.66±0.00 |
| F8 | 29.33±0.34 | 0.360±0.00 | 0.412±0.00 | 1.15±0.00 | 13.68±0.00 |
| F9 | 28.09±0.47 | 0.353±0.00 | 0.405±0.00 | 1.14±0.00 | 12.94±0.00 |

*All the values are expressed as mean± SE, n=3.

**Table 2: Composition of sustained release tablet formulations**

| S.no | Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Ambroxol HCl | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 |
| 2. | HPMC K100M | 20 | 30 | 40 | _ | _ | _ | _ | _ | _ |
| 3. | Carbopol 934 P | _ | _ | _ | 20 | 30 | 40 | _ | _ | _ |
| 4. | Ethyl cellulose | _ | _ | _ | _ | _ | _ | 20 | 30 | 40 |
| 5. | PVP K-30 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| 6. | Microcrystalline cellulose | 275 | 265 | 225 | 275 | 265 | 225 | 275 | 265 | 225 |
| 7. | Aerosil | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 8. | Magnesium stearate | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |

**Table 3: Results of study of physical parameters of tablets**

| Formulation Code | Thickness (mm)* | Weight variation (%) | Hardness (kg/cm²)* | Friability (%) | Drug content (%) # |
|---|---|---|---|---|---|
| F1 | 4.34±0.06 | 0.721±0.52 | 7.42±0.53 | 0.1 | 100.63±0.57 |
| F2 | 4.38±0.04 | 0.516±0.33 | 7.38±0.21 | 0.2 | 100.67±0.07 |
| F3 | 4.24±0.05 | 0.673±0.74 | 8.16±0.21 | 0.07 | 100.76±0.12 |
| F4 | 4.27±0.04 | 0.685±0.39 | 7.72.±0.39 | 0.0 | 100.79±0.22 |
| F5 | 4.30±0.75 | 0.284±0.31 | 8.05±0.15 | 0.02 | 100.32±0.44 |
| F6 | 4.24±0.09 | 0.631±0.48 | 7.15±0.24 | 0.22 | 100.31±0.30 |
| F7 | 4.39±0.04 | 0.227±0.37 | 8.05±0.15 | 0.14 | 100.76±0.56 |
| F8 | 4.41±0.05 | 0.405±0.25 | 8.02±0.23 | 0.05 | 99.90±0.15 |
| F9 | 4.44±0.07 | 0.466±0.33 | 8.10±0.35 | 0.02 | 99.93±0.91 |

*All the values are expressed as mean± SE, n=10; #All the values are expressed as mean± SE, n=3.

**Carr's compressibility index**

The compressibility indices of the formulation blends were determined using following Carr's compressibility index formula[11].

*Carr's Compressibility Index (%) = [(TBD-BD)/ TBD] x100*

**Hausner ratio**

Hausner ratio is the ratio between tapped density and bulk density.

*Hauser's ratio = Tapped density/poured density.*

Hausner ratio less than 1.25 indicates good flow properties while Hausner ratio greater than 1.5 shows poor flow of powder. Hausners ratio between 1.25 to 1.5 can be improved by addition of glidants[12].

**Preparation of matrix tablets**

Matrix tablets containing 75mg of Ambroxol Hcl along with various amount of polymers such as HPMC K100M, EC, Carbopol and other inactive ingredients were mixed and tablet were prepared by direct compression technique. In the first step, active and inactive ingredients (except Magnesium stearate) weighed accurately and were screened through a 40-mesh sieve. Required materials except lubricant were then combined and passed through 40-mesh sieve. Mixing of powders was performed by geometric dilution method in polythene bag. In the screened powder following the addition of given amount of lubricant powder was again mixed. Before compression, the surfaces of the die and punch were lubricated with Magnesium stearate, and then desired amount of blend was directly compressed (11mm diameter, biconcave punches) using a single punch tablet compression machine (Cad mach, Ahmadabad, India). All the preparations were stored in airtight containers at room temperature for further study [13, 14].

***In vitro* drug release studies**

The release rate of Ambroxol Hcl from matrix tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus II (paddle method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed using 900 ml of pH 1.2 for the first 2 hrs and phosphate buffer pH 6.8 from 2-8hrs at 37 ± 0.5°C and 100 rpm. A sample (2ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted suitably; Absorbance of these solutions was measured at 244.5 nm using a Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer [15, 16].

**Drug release kinetics**

For finding out the mechanism of drug release from tablets, the dissolution data obtained from the above experiments were treated with the different release kinetic equations [17, 18].

Zero order release equation: Q = K0 t,

First order equation: Q = Kf t

Higuchi's square root of time equation: Q = KH t ½

Korsmeyer and Peppas equation: F = (Mt / M) = Km tn

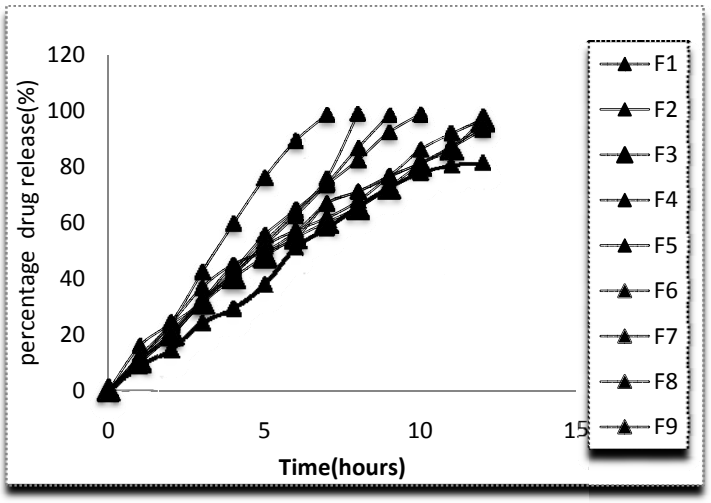


**Fig. 1: *In-Vitro* drug release of formulation F1 to F9**

**Table 4: Dissolution kinetics of Ambroxol Hcl matrix tablets**

| Code | Zero order | | First order | | Higuchi | | Peppas | | Best fit model |
|---|---|---|---|---|---|---|---|---|---|
| | $R^2$ | $K_0$ (mg/h$^{-1}$) | $R^2$ | $K_1$ (h$^{-1}$) | $R^2$ | K (mg h$^{-1/2}$) | $R^2$ | n | |
| F1 | 0.9922 | 11.230 | 0.7411 | 0.2955 | 0.9090 | 26.058 | 0.9967 | 0.651 | Peppas |
| F2 | 0.9886 | 10.326 | 0.8586 | 0.2703 | 0.9408 | 26.904 | 0.9990 | 0.673 | Peppas |
| F3 | 0.9901 | 08.284 | 0.8907 | 0.1807 | 0.9585 | 23.737 | 0.9974 | 0.693 | Peppas |
| F4 | 0.9968 | 14.469 | 0.8624 | 0.3995 | 0.9242 | 31.691 | 0.9975 | 0.614 | Peppas |
| F5 | 0.9992 | 10.698 | 0.8180 | 0.2680 | 0.9257 | 26.357 | 0.9990 | 0.612 | Zero order |
| F6 | 0.9847 | 08.421 | 0.9429 | 0.1773 | 0.9632 | 24.190 | 0.9948 | 0.582 | Peppas |
| F7 | 0.9780 | 08.752 | 0.9185 | 0.2033 | 0.9726 | 25.235 | 0.9976 | 0.548 | Peppas |
| F8 | 0.9794 | 08.495 | 0.9625 | 0.1763 | 0.9664 | 24.452 | 0.9941 | 0.582 | Peppas |
| F9 | 0.9893 | 07.624 | 0.9799 | 0.1369 | 0.9392 | 21.724 | 0.9957 | 0.573 | peppas |

**RESULTS AND DISSCUSSION**

The prepared powder blend of the different formulations was evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, and Hausner ratio. The prepared matrix tablets were evaluated for thickness, weight variation, hardness, friability, drug content, in vitro drug dissolution studies and stability studies. All the studies were performed in triplicate, and results are expressed as mean ± SD.

**Characterization of powder blend**

The powder blend prepared for compression of Matrix tablets were evaluated for their flow properties. Angle of repose was in the range of 26.11±0.48 to 29.52°±0.55 which indicates good flow of all formulations. The bulk density of the powder formulation was in the range of 0.348±0.00 to 0.365±0.00 g/ ml; the tapped density was in the range of 0.405±0.00 to 0.445±0.00 g/ ml, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 12.45±0.00 to 14.63±0.00, which indicates good flow of the powder for all formulation. Hausner ratio was found to be in the range of 1.14±0.00 to 1.23±0.00, these values indicate that the prepared blend exhibited good flow properties.

Differential scanning calorimetry studies showed that there is no any drug polymer interaction.

**Evaluation of matrix tablets**

The results of physicochemical characterizations are shown in Table 3. The thickness of matrix tablets was measured by vernier caliper and was ranged between 4.24±0.09and 4.44±0.07 mm for all formulation. The weight variation for different formulations (F1 to F9) was found to be 0.227±0.37% to 0.721 ±0.52%, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of tablet is indicative of crushing strength to withstand handling during packaging and transportation. The hardness of the matrix tablets was measured by Monsanto tester and was controlled between 7.15±0.24 and 8.16±0.21 kg/cm$^2$. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability of formulation was below 1%, indicating that the friability was within the prescribed limits, which is an indication of good mechanical resistance of the tablet. Good uniformity in drug content was found among the formulations, and percentage of drug content was more than 95%. All the tablet formulations showed acceptable pharmacotechnical properties.

***In vitro* drug release study**

The *In vitro* dissolution studies of all the formulations of matrix tablets of Ambroxol HCl were carried out in pH 1.2, pH 6.8 buffer solution. The study was performed for 12 hours, and percentage drug release was calculated at 1 hours time intervals. The results of *in- vitro* dissolution studies of all formulations were shown in Figures 2 to 4.The drug release from formulation F1 to F3 containing HPMC K100M at three different concentration levels of 5%, 7.5%, 10% were found to be 98.95±0.05, 98.70±0.20 and 96.64±0.02 at the end of 8$^{th}$ hr, 10$^{th}$ hr, 12$^{th}$ hr respectively . The drug release from formulation F4 to F6 containing Carbopol 934P at three concentration level of 5%, 7.5%, 10% were found to be 98.52±0.02,98.42±0.03,94.42±0.06 at the end of 7$^{th}$ hr, 9$^{th}$ hr, 12$^{th}$ hr respectively . The drug release from formulation F7 to F9 containing Ethyl cellulose at three different concentration levels of 5%,7.5%,10% were found to be 96.86±0.04, 93.28±0.00 and 81.095±0.11 respectively at the end of 12 hrs (2 hrs in 0.1N Hcl and 10 hrs in Ph 6.8).

When % drug release plotted vs. time showed in figure 1 for F1 to F9 and it was observed that, for three of the polymers used, an increase in polymer concentration induce a decrease in the release rate. The drug release rate from HPMC K100M matrix was found to be higher as compared to Ethyl cellulose. Formulation F1 to F3 failed to

generate sustained release of drug up to 12 hrs and drug was completely released at 8 hrs. Whereas formulation containing Carbopol 934P (F4 to F6) also gave higher drug release as compared to formulations containing HPMC K100M (F1toF3) and ethyl cellulose (F7 to F9). This is due to less degree of swelling of Carbopol 934P in acidic media as compared with Carbopol 934P, the dissolution medium can penetrate fast and deep in to the glossy core and the drug is released faster. Formulation containing Ethyl cellulose (F7) was showed better retardation as compared to formulation containing HPMC K100M (F1to F3) and Carbopol 934P (F4 to F6). The formulation F7 which consisted of the drug: polymer Ethyl cellulose ratio of 1:0.26, gave satisfactory release profile in a sustained manner for 12 hrs among all formulations.

Based on the *in- vitro* drug release data the $t_{50\%}$, $t_{90\%}$ parameters were calculated. It was found that as the concentration of polymer increases, the values of t50 and t90 increased. Ethyl cellulose polymer formulation was selected as the optimized formulation among all other formulations. Ethyl cellulose (EC) is a non-toxic, stable, compressible, inert hydrophobic polymer that has been widely used to prepare pharmaceutical dosage forms. Increasing the concentration of EC showed more retardation in the release of the drug.10% ethyl cellulose tablet showed a very much sustained profile of the release, which was not suitable. The 5% of ethyl cellulose was used to retard the release to maximum rate, when comparing the HPMC K100M which thereby produced an appropriate retardation only at the rate of 10% of HPMC K100M polymer .From the commercial point of view, EC is more economical than HPMC and Carbopol. Thus considering the release retardation, cost effectiveness of the polymer (only 5% of ethyl cellulose was sufficient to retard maximum release) reduces the toxicity of the formulation and ethyl cellulose is the water insoluble polymer which favours the water soluble drug category. From these parameters, the formulation F7 (Ethyl cellulose) showed the maximum retardation of drug release (10.9 hours to release the 90% of drug) and it shows anomalous diffusion mechanism, for these reasons, it was considered that the formulation F7 was best formulation among all the nine formulations. Ethyl cellulose could make sustained release Ambroxol Hydrochloride tablets, with amount as little as 5% in formulation.

**Kinetic analysis of dissolution data**

The linear regression analysis is given in Table 4. The kinetic data of formulations F1 to F9 except F5 showed good fit in the Korsmeyer-Peppas model ($R^2$: 0.9794 to 0.9968) when compared with other kinetics model (first order, zero order, Higuchi). Formulation F5 showed high linearity with the zero order kinetics ($R^2$: 0.9992). Drug release data was also fitted to peppas model, which showed the slope (n) value (0.582 to 0.693) in case of formulations F1 to F9 .From the release exponent in the Korsmeyer-Peppas model, it can be suggested that the mechanism that led to the release of Ambroxol HCL was an anomalous non-Fickian diffusion transport, which indicates that the drug release occurred through diffusion in the hydrated matrix and polymer relaxation.

**CONCLUSION**

This study deals with the investigation carried out with the objective of developing oral sustained release formulation of Ambroxol Hcl using HPMC K100M, Carbopol 934P and Ethyl cellulose. Preparation of matrix tablet by direct compression technique was found to be more successful in sustaining the release of drug. Based on the *in- vitro* drug release data the formulation F7 was concluded as best formulation. Although all the polymers studied could slow down the release of Ambroxol HCl from the matrices, Ethyl cellulose showed the best results. This is due to hydrophobic nature of EC, seems to have contributed toward reduction in the penetration of the solvent molecules in to the matrix. Thus EC helped in retaining the drug in the matrix and did not allow rapid diffusion of soluble drug from the matrix and gives better retarding property to give desire dissolution profile. In turn, it may enable to release the drug in a sustained manner for prolonged time and thereby accompanying some of the benefits like reduction in total dose, frequency of administration, dose related side effects and better patient compliance. The drug release from the tablets was sufficiently sustained and anomalous diffusion mechanism of the drug from tablets was confirmed. In conclusion the present study demonstrated the successful preparation of sustained release matrix tablet of Ambroxol hydrochloride.

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