

Effect of Hydrophilic Matrix on The Release Behavior of Ambroxol Hydrochloride

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Abstract: The sustained release (SR) tablets of Ambroxol Hydrochloride were prepared by wet granulation method. The effect of hydrophilic matrices on the behavior of Ambroxol Hydrochloride using different polymers and their combinations. The prepared tablets were evaluated for physical characteristics such as Hardness, Thickness, Friability, Weight variation, Content uniformity and In-vitro release behavior. The drug release from the optimized formulation was found to follow zero order kinetics. It was also found linear in Higuchi's plot. Thus the phenomenon of drug release showed that the release of optimized formulation is controlled by diffusion. It is concluded that as compare to other formulations, optimized formulation fulfilled all criteria for SR tablet dosage form.

Keywords: Sustained release (SR), Ambroxol Hydrochloride, Matrices

Introduction

The advantages of sustained release (SR) tablets or capsules are that they can often be taken less frequently than instant release formulations of the same drug, and that they keep steadier levels of drug in the blood stream. SR tablets are formulated so that the active ingredients are embedded in a matrix of insoluble substance (some acrylics, chitin, often patented). So that the dissolving drug has to find its way out through the holes in the matrix. In some SR formulations the matrix physically swells up to form a gel, so that the drug has to first dissolve in matrix, then exit through the outer surface¹.

Ambroxol is a metabolite of bromohexine which possess mucokinetic and secreteolytic properties. It is used in the treatment of respiratory tract disorders such as chronic bronchitis and management of cough. Adverse effects produced such as gastrointestinal disorder, headache, dizziness, sweating, rhinorrhoea, lacrymation and allergic reactions. Due to short biological half-life (4-6hr),

frequent daily dosing (2-3 times) of Ambroxol hydrochloride is required². Therefore its formulation in SR dosage form is advantages.

The simplest and least expensive way to control the release is to dispense it with in an inert polymeric matrix³. The hydrophilic matrices are an interesting option when SR formulations are done for a drug. The development of SR formulation of Ambroxol hydrochloride is therefore of therapeutic relevance and can be used to provide a consistent dosage through a sustaining an appropriate level of the drug over a time.

Based on this, an attempt was made through investigate and to formulate the effect of hydrophilic matrices on the release behavior of Ambroxol Hydrochloride using different polymers and their combinations. The prepared tablets were evaluated for physical characteristics such as Hardness, Thickness, Friability, Weight variation, Content uniformity and In-vitro release characteristics.

Material & Methods

Ambroxol Hydrochloride (a gift sample from Kaushik Pharmaceuticals, Chennai), HPMC- K15M, SCMC, Sodium alginate, Microcrystalline cellulose (MCC), PVP (all the above obtained from S.D. Fine chemicals Ltd, Mumbai). All the chemicals were of analytical grade.

Preparation of Sustained Release (SR) tablets of Ambroxol Hydrochloride:

Sustained Release tablets of Ambroxol Hydrochloride were prepared by wet granulation method⁴ according to the formula given in Table -1. Ambroxol hydrochloride, HPMC – K15M, SCMC and MCC were accurately weighed and mixed thoroughly in a mortar, PVP solution was added drop wise until suitable mass of granulation is obtained. The coherent mass was passed through sieve # 20. The granules were dried at room temperature for 1hr and the dried granules was passed through sieve #100 and finally lubricated with lubricants. Tablets were compressed using concave 16 station rotary tablet compression machine having a punch size of 12 mm³.

Evaluation of Granules:

Granules were evaluated for Tap density, Hausner ratio and Carr's index as given Table – 2.

Evaluation of Tablets:

Thickness and diameter of tablets were carried out using Vernier caliber, Hardness and friability of the tablet were determined by using Monsanto hardness tester and Roche friabilator respectively⁵. Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation. For content uniformity the tablets were taken in a mortar and crushed to powders. A quantity of powder weighed equivalent to 100mg of Ambroxol Hydrochloride was taken in a 100ml volumetric flask and 7.4 pH buffer added. It was then heated at 60°C for 30 minutes. The solution was filtered using membrane filter (0.45µm) and then its absorbance was measured at 278 nm.

Dissolution Studies:

Dissolution apparatus USP XIII Type-I model was used for carrying out in-vitro release studies. 900ml of 0.1N HCL was used as dissolution medium⁶. The basket was rotated at 100 rpm. After 2 hours, the dissolution medium was changed to 7.4 pH buffer and continued the dissolution upto 12 hours. The temperature of dissolution fluid was maintained at 37 °C ± 1°C throughout the study. 5ml of the sample was withdrawn at every hour. The drawn samples were made upto 10ml with respective medium.

Stability studies:

Stability studies were carried out for optimized formulation. The tablets were packed in aluminium foil placed in air tight container and kept at 4°C in refrigerator, 40°C/ 75 % RH in stability chamber and 55°C incubator for 3 months at the interval of 30 days the tablets were withdrawn and evaluated for physical properties, in-vitro drug release⁷.

TGA and DTA studies:

Thermal behavior of the drug and formulation were studied by TGA and DTA. DTA exhibits melting of the drug and in mixture was about at the same point. The shape of TGA of pure drug and mixture are almost similar in the thermo gram. This indicates that there was no interaction occurs between drug and excipients.

Kinetics of Drug Release⁸:

The optimized formulation AMB 6 is subjected to graphical treatment to assess the kinetics of drug release. A rapid first- order release of part of the dose followed by a zero- order release for an extended period of time was observed.

The release from the dosage form occurred in two ways. First, a fraction of the total dose is released for immediate availability to be absorbed by a first-order process and the remaining fraction is released at a constant rate (i.e.) a slow zero- order process over a prolonged time period. Hence, the release is considered to follow zero- order kinetics with exception of initial 1 hour.

The result data was fitted into the zero- order equation $\alpha = K^{\circ} t$

Where,

α - The amount of drug released at time 't'.

K° - Release rate.

Higuchi's Plot:

The graph was plotted between cumulative percentage release and square root of time. The regression values for drug release profile of formulation AMB 6 was found to be 0.9892. This indicates that the diffusion is the mechanism of drug release from the system.

Result and Discussion

The SR tablets of Ambroxol hydrochloride were prepared by wet granulation. AMB 6 is considered to be optimized formulation with desired drug release rate (97%) for 12 hours and complied with the all the evaluated parameters. Stability studies of optimized formulation AMB 6 at 4° C, 40° C/ 75% RH, 55° C for 3 months did not show any variation in tested parameter and release also. The TGA / DTA analysis showed that no interaction occurred between

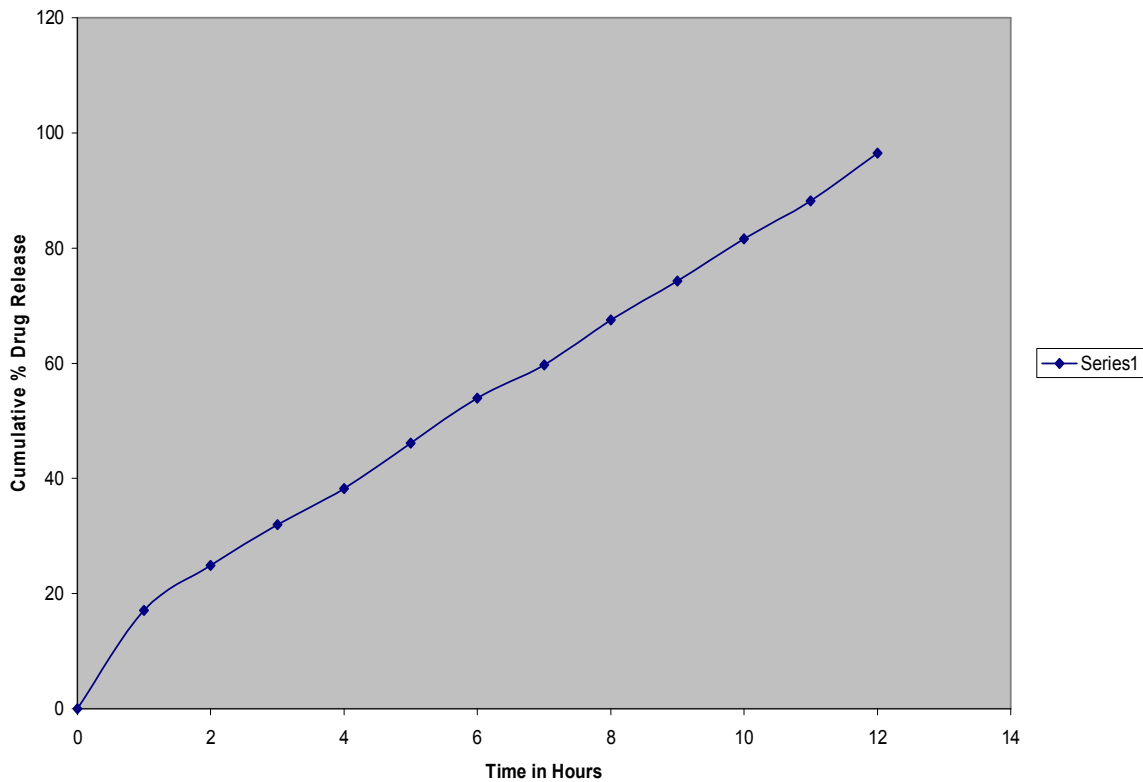
drug and excipients. The drug release from AMB 6 formulation was found to follow zero- order kinetics. It was also found linear in Higuchi's plot. Thus the phenomenon of drug release showed that the release of

optimized formulation AMB 6 is controlled by diffusion. From the above information it is concluded that as compared to other formulations, AMB 6 fulfilled all criteria for SR tablet dosage form.

Formulation code: AMB 1

S.No.	Ingredients	Quantity required per tablet					
		AMB 1	AMB 2	AMB 3	AMB 4	AMB 5	AMB 6
1.	Ambroxol Hydrochloride	75mg	75mg	75mg	75mg	75mg	75mg
2.	HPMC K4M	84mg	-	126mg	-	-	-
3.	HPMC K15M	-	84mg	-	126mg	126mg	126mg
4.	SCMC	-	-	-	-	-	29.4mg
5.	MCC	231mg	231mg	189mg	189mg	159.6mg	159.6mg
6.	Sodium Alginate	-	-	-	-	29.4mg	-
7.	PVP	10mg	10mg	10mg	10mg	10mg	10mg
8.	Talc	10mg	10mg	10mg	10mg	10mg	10mg
9.	Magnesium Stearate	10mg	10mg	10mg	10mg	10mg	10mg
	Total	420mg	420mg	420mg	420mg	420mg	420mg

Invitro Drug release Data for Formulation AMB 6



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