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FORMULATION AND EVALUATION OF AMBROXOL HYDROCHLORIDE SUSTAINED RELEASE MICROSPHERES

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ABSTRACT

Sustained release microspheres of Ambroxol Hcl, It used as a Recipiratory Disease Ambroxol Hcl is water soluble drug, having low oral bioavailability (33-55%) due to complete metabolism of drug available in market were having daily administration. The present study was formulate and evaluate Ambroxol Hcl microspheres to increase oral bioavailability, decrease the frequency of drug administration, and improves patient compliance. In this study, Ambroxol Hcl microspheres was prepared by Ionotropic gelation technique using Sodium alginate, HPMC and Ethylcellulose as polymers and these prepared Ambroxol Hcl microspheres evaluated were percentage yield, particle size, drug entrapment efficiency and in vitro drug release studies. These microspheres results showed that percentage yield, entrapment efficiency, particle size and drug release studies were influenced mainly by concentration of polymer, type of polymer and stirring speed also. The results of in vitro drug release studies shows that the desired release rate is achieved by optimized formulation are releasing the drug up to 11 hrs. Optimized Ambroxol Hcl microspheres showing discrete, spherical microspheres.

KEYWORDS: Ambroxol Hcl, HPMC, Ethylcellulose, Ionotropic gelation technique.

INTRODUCTION

Ambroxol Hcl is a metabolite of bromohexine which possess mucokinetic and secreteolytic properties.[1] 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.[2,3] Due to short biological half-life (4-6 hr), frequent daily dosing (2-3 times) of Ambroxol

hydrochloride is required. Therefore its formulation in sustained microspheres is advantages.[4,5] The simplest and least expensive way to control the release is to dispense it with in an inert polymeric matrix.[6] Bitter after taste of many drugs which are orally administered often contributes to patient noncompliance in taking medicines.[8,9]

Microspheres are characteristically free flowing powders consisting of protein or synthetic polymers which are biodegradable in nature and ideally having particle size less than 1000µm[7]. Micro particles play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects.[10] The objective of the present study was to develop microspheres of Ambroxol Hcl by Ionotropic Gelation Technique using hydrophilic carrier to sustain the release so as to reduce the frequency of dosing and to improve patient compliance.

MATERIALS AND METHOD[11]

Materials

Ambroxol Hcl was obtained as gift sample from orchid pharma private limited, Chennai, Gelatin from aurobindo Pharma Pvt. Ltd., Hyderabad. HPMC, Sodium alginate from aurobindo Pharma Pvt. Ltd., Hyderabad. Methanol, Calcium chloride from AR chemicals.

Method

Ambroxol hcl Microspheres were prepared by using ionotropic gelation technique and by using Sodium alginate, Eudragit S100 and calcium chloride solution. Weighed Equal quantity of drug and polymer were added to 100 ml of sodium alginate solution with stirring at about 400 rpm.[12,13] The resultant solution was then added drop wise to 100 ml of calcium chloride solution under continuous stirring. Stirring was continued for 30 or 40 minutes. The obtained microspheres were filtered and washed with purified water and then dried for 6 hours at 40°C. Preparation of microspheres was optimized based on entrapment efficiency and drug release studies.[14]

Table 1: Formulation table of Glipizide microspheres.

Ingredients	F1	F2	F3
Drug	500	500	500
Sodium alginate	1000	1000	1000
HPMC	500	500	-
Ethylcellulose	-	500	500
Methanol	5	5	5
$Cacl_2$	2%	2%	2 %

Evaluation Parameters[15,16,17]

The prepared Ambroxol Hcl microspheres were evaluated for various parameters such as percentage yield, particle size, drug entrapment efficiency and in vitro drug release studies.

A. Yield of microspheres

The yield of microspheres was calculated from the amount of microspheres obtained divided by the total amount of all non-volatile components

$$\% \text{ Yield} = \frac{\text{Actual weight of the microspheres}}{\text{Total weight of all non-volatile components}} \times 100$$

B. Particle size and shape

The particle size of the microspheres was measured by optical microscopy. The eyepiece micrometer was calibrated using a stage micrometer and the calibration factor was used further in the calculation of the size of microspheres. The microspheres were finely spread over a slide and visualized under an optical microscope using an eyepiece micrometer. About 50 readings were taken at random and the mean ± standard deviation was calculated. The shape of the microspheres was visualized and the photographs were taken with the aid of a binocular microscope.

C. Surface morphology

The surface morphology of the prepared microspheres was examined with the aid of a Scanning Electron Microscope (SEM).

D. Drug entrapment efficiency (DEE)

The amount of drug entrapped was estimated by crushing 50 mg of microspheres using mortar and pestle, and extracting drug with aliquots of 7.4 pH buffer repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 7.4 pH buffer. The solution was taken in a beaker and sonicated in a bath sonicator for 2 hours. The solution was filtered and absorbance was measured after suitable dilutions spectro photometrically at 247 nm against an appropriate blank.

The amount of drug entrapped in the microspheres was calculated using the following formula –

$$DEE = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

E. In vitro drug release study

In vitro drug release studies were carried out for all formulations in Franz diffusion cell. Microspheres equivalent to 10 mg of Ambroxol Hcl were poured into 5 ml aliquots were withdrawn at a predetermined intervals and equal volume of dissolution medium was replaced to maintain sink conditions. The necessary dilutions were made with 7.4 pH buffer and the solution was analysed for the drug content spectrophotometrically using UV-Visible spectrophotometer at 247 nm against an appropriate blank. Three trials were carried out for all formulations. From this cumulative percentage drug release was calculated and plotted against function of time to study the pattern of drug release.

RESULTS AND DISCUSSION

The prepared sustained release microspheres were evaluated for various parameters such as yield, drug entrapment efficiency, particle size and in vitro drug release. And effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on particle size, yield, entrapment efficiency, and *in-vitro* release of Ambroxol Hcl from sustained microspheres were also studied.

Table 1: Evaluation parameters of microspheres.

Formulation code	%yield	Particle size	Drug Entrapment Efficiency	Drug release studies
F1	75.85	88.39	70.53	87.519
F2	79.55	93.64	82.22	*92.251*
F3	88.33	96.72	85.23	99.826

Here, keeping drug ratio constant and varied polymer ratio as the polymer concentration increases viscosity; this influences the interaction between disperse phase and dispersion medium that affects the size distribution of particle. And F3 formulation shows good results when compared to other formulations.

Table 2: Cumulative % drug release.

Time (hours)	F1	F 2	F3
0.5	63.519	35.185	37.449
1	69.471	52.680	53.109
2	75.628	76.452	57.949
3	86.990	84.521	63.232
4	91.907	85.845	65.664
5	94.432	87.997	68.725
6	97.520	90.159	70.979
7	99.826	91.508	73.656
8	----------	95.743	80.256
9	----------	96.707	92.243
10	----------	101.995	95.451
11	----------	----------	99.087
12	----------	----------	----------
13	----------	----------	----------

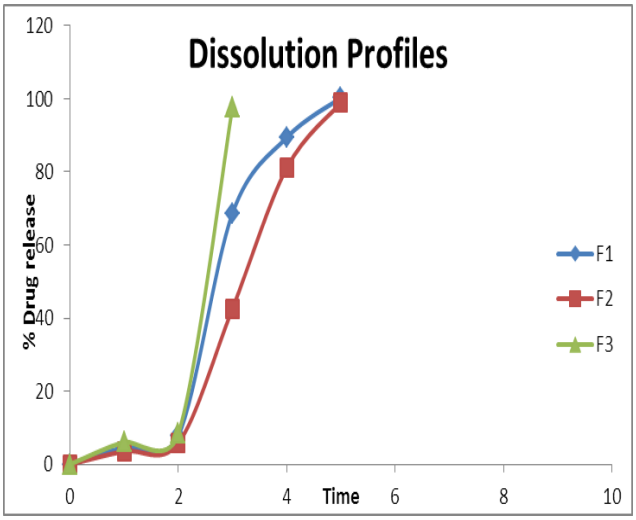


Figure 1: Percentage drug released Vs. Time Curves of microspheres F 1 – F 3 in P^H 7.4 buffer.

Conclusion: Above graph indicates that % Drug release of F3formulation shows better drug release when compared with other formulations.

Kinetic models

The mechanism of Ambroxol Hcl release from microspheres was studied by fitting the data obtained from *in-vitro* release studies into zero-order, first-order, Higuchi's, korsermeyer peppas kinetic models.

On application of different release kinetic models mentioned earlier, it was found that optimized formulations showed better fitting with the zero-order release and korsermeyer peppas model.

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Table 3: Kinetic Models.

S. no.	time	log T	Square root of Time	%CR	%Drug remaining	log %CR	LOG% Drug Retained	cube root of %drug remaining
0	0	0	0	0	100	0	2	4.642689
1	1	0	1	5.73	92.17	0.765668	1.973813	4.549564
2	2	0.30102	1.413214	6.21	94.79	0.857835	1.966501	4.527242
3	3	0.467121	1.632051	8.4	96.4	0.929417	1.961411	4.516064
4	4	0.60306	2	9.52	92.27	0.987566	1.954592	4.476037
5	5	0.69797	2.235068	10.31	88.6	1.013837	1.953792	4.37542
6	6	0.768151	2.44849	62.4	26.5	1.859729	1.440809	3.12206
7	7	0.835098	2.64751	79	10	1.94839	1.061393	2.23298
8	8	0.91329	2.828326	98.6	0.6	1.987259	-0.39674	0.736706

Table 4: Correlation coefficient values for release kinetics of sustained release microspheres.

Drug Kinetics	Optimised Formula
First-Order	0.689
Zero-Order	0.762
Higuchi	0.561
korsermeyer peppas	0.657

Zero Order Kinetics

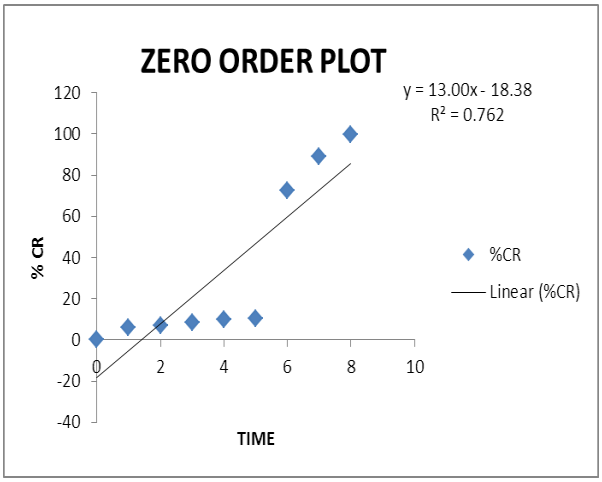


Figure 2: Zero Order Plot for Optimized Formulation.

First Order Kinetics

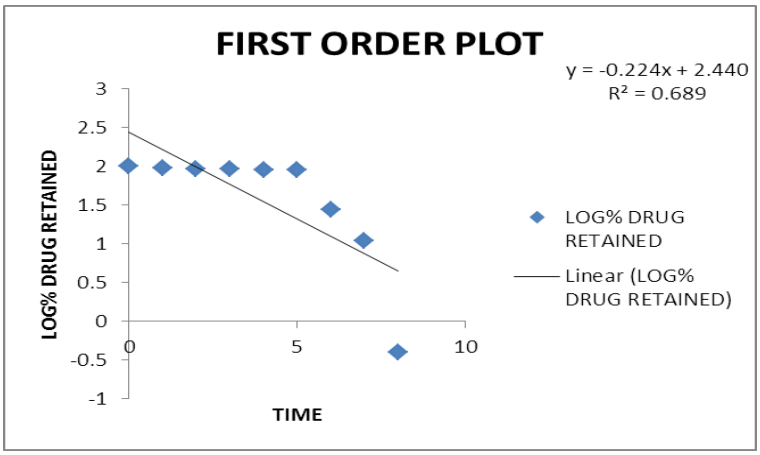


Figure 3: First Order Plot for Optimized Formulation.

Higuchi Model

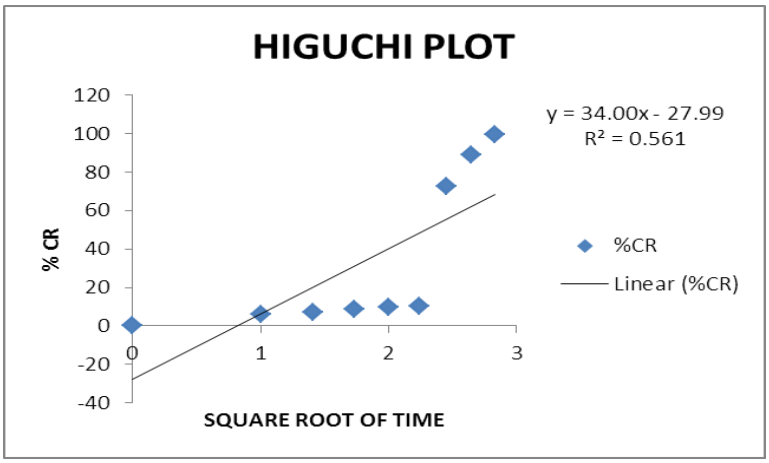


Figure 4: Higuchi Plot for Optimized Formulation.

Korsmayer Peppas Equations

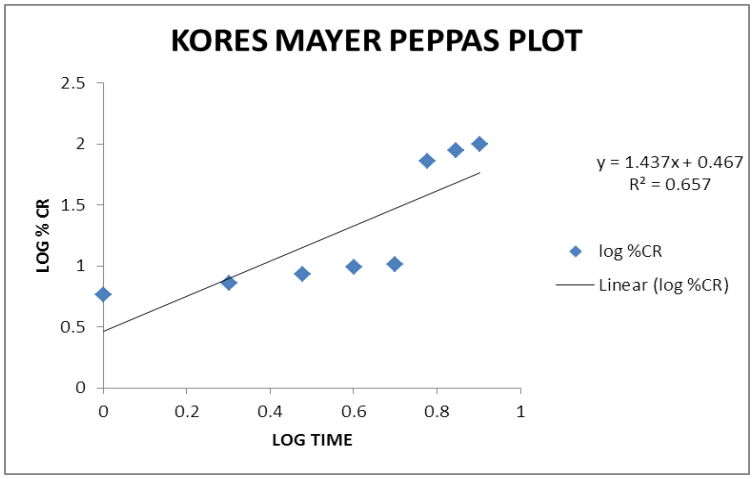


Figure 5: Kores Mayer Peppas Plot for Optimised Formulation.

Hixon Crowell erosion equation

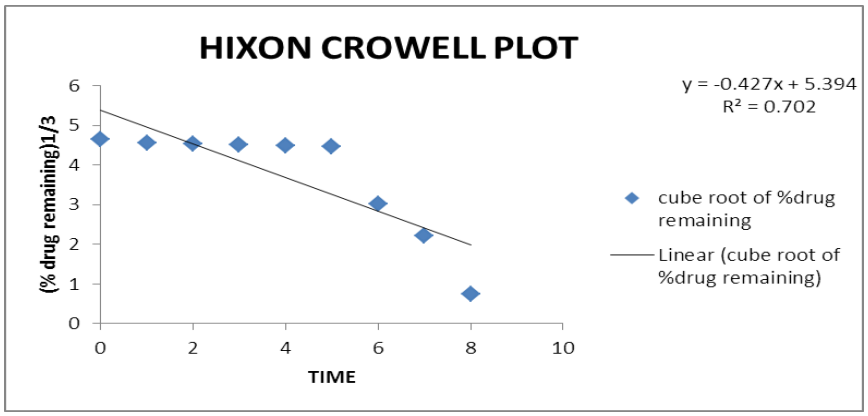


Figure 6: Hixson Crowell Plot for Optimized Formulation.

Stability Study

There was no significant change in physical and chemical properties of the of formulation F-3 after 3 Months. Parameters quantified at various time intervals were shown.

Table 5: Results of stability studies of optimized formulation F-3.

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	25^0C/60%RH % Release	99.61	99.52	99.52	99.50	Not less than 85 %
F-3	30^0C/75% RH % Release	99.46	99.54	99.53	99.50	Not less than 85 %
F-3	40^0C/75% RH % Release	99.60	99.55	99.54	99.75	Not less than 85 %
F-3	25^0C/60% RH Assay Value	99.85	99.87	99.73	99.80	Not less than 90 % Not more than 110 %
F-3	30^0C/75% RH Assay Value	99.78	99.88	99.82	99.92	Not less than 90 % Not more than 110 %
F-3	40^0C/75% RH Assay Value	99.97	99.85	99.74	99.95	Not less than 90 % Not more than 110 %

Table 6: Stability dissolution profile of F-3 for 1st, 2nd & 3rd months.

S. No.	Time(Hrs)	F-3 1M	F-3 2M	F-3 3M
1	0	0	0	0
2	1	5.73	4.70	5.68
3	2	7.22	6.30	6.20
4	3	8.6	8.27	8.54
5	4	9.62	9.76	9.75
6	5	10.2	11.26	10.34
7	6	72.3	73.36	72.30
8	7	79	87.8	84.4
9	8	98.55	98.52	96.52

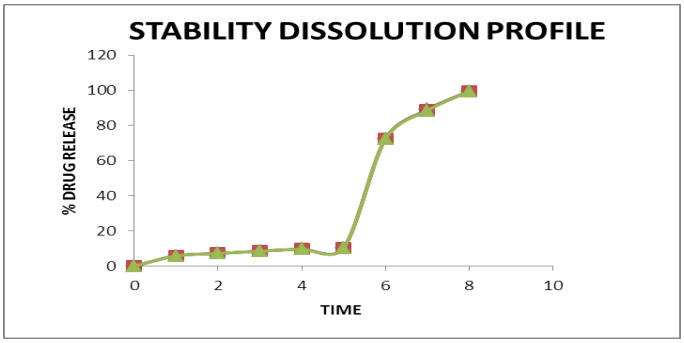
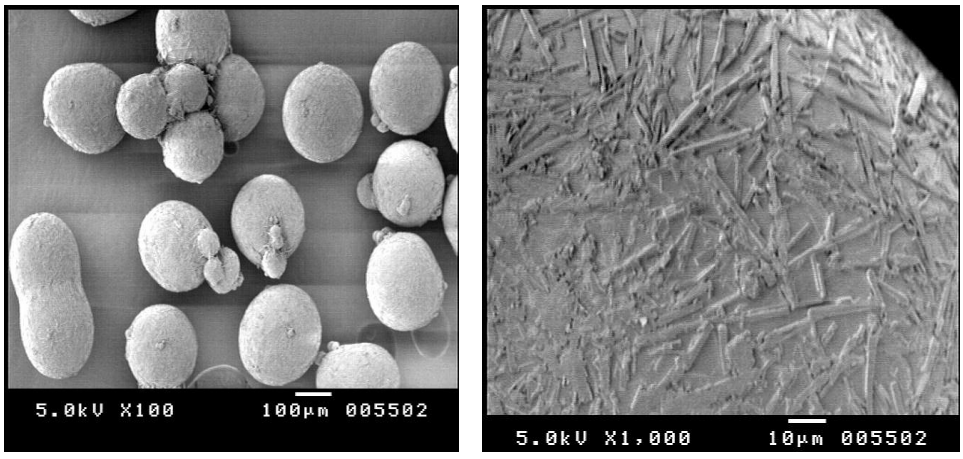


Figure 7: Stability dissolution profile of F-20 for 1st, 2nd & 3rd months.

Surface Topography by Scanning Electron Microscopy (SEM)

SEM photograph of optimized microspheres at 100× magnification, at 1000× magnification. SEM photographs showed discrete, spherical microspheres. SEM photographs also showed the presence of drug crystal on the surface of microspheres revealing that the microspheres were having some rough surface**.** The drug crystals on microspheres were may be due to the presence of entrapped drug in dispersion medium.



A. **B.**

Figure 8: SEM photograph of Ambroxol Hcl at 100x and 1000x magnification.

CONCLUSION

Rationale of the present study was to prevent extensive metabolism of the drug and consequently to increase the oral bioavailability of the drug in the form of sustained.

Attempt has been made to prepare sustained release microspheres of Ambroxol Hcl, a water soluble drug. The microspheres were prepared by Ionotropic gelation method using Ethylcellulose, Eudragit, Sodium alginate polymers as retarding polymers and evaluated for parameters like percentage yield, particle size, entrapment efficiency and the effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on evaluated parameters. Microspheres morphology was evaluated by SEM.

According to the results of SEM analysis, no drug interaction occurred with polymers and Ambroxol Hcl. And SEM photographs of optimized formulations showed discrete, spherical microspheres.

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