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Research

Formulation and Evaluation of Sustained Release Matrix Tablets Containing Ambroxol Hydrochloride

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Abstract

The evolution of pharmaceutical drug delivery systems has witnessed a shift towards novel technologies, replacing conventional dosage forms with innovative approaches. Among these advancements, oral administration remains paramount due to its patient acceptance, ease of use, and cost-effectiveness. However, conventional dosage forms often necessitate frequent dosing, leading to fluctuating blood levels and potential therapeutic failures or toxicities. Sustained release formulations emerge as a solution to this challenge, offering prolonged and controlled drug release to maintain therapeutic levels over time. This study focuses on formulating sustained release matrix tablets of Ambroxol HCl, a mucolytic agent used in respiratory conditions. By utilizing polymers like HPMC K100M and HPMC 5CPS, the aim is to develop tablets capable of sustaining drug release, thereby improving patient compliance and therapeutic outcomes. The significance lies in addressing the therapeutic relevance of Ambroxol hydrochloride by providing a consistent dosage regimen. Evaluation of these matrix tablets will contribute to advancing drug delivery systems, optimizing treatment efficacy, and enhancing patient care.

Keywords: Ambroxol Hydrochloride, Matrix tablet, Sustained release.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed. All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid) must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. Sustained release system includes any delivery system that achieves release of drug

over an extended period of time. If the system at maintaining constant drug level in the blood of target time, it is considered a controlled release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered a prolonged release system (Chien Y.W 1992).

Tablets

Pharmaceutical tablets are one of the important dosage forms for drug delivery. They are manufactured by compressing dry powder blends consisting of several of components with different functions in a die. By the use of advanced technology and increased knowledge on modification in standard tablet to achieve better acceptability as well as bioavailability, newer and more efficient tablet dosage forms are being developed. The main reasons of formulating different types of tablets are to develop a drug delivery system that is very simple and less expensive to manufacture, provide the dosage form that is convenient for the patient's and utilize an approach that is unlikely to add complexity during regulatory approval process.

Matrix System

The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied. To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. Hence the following must be considered (Lachman Leon, Liberman H.A etal 1991).

- The chemical nature of support (generally, the support are formed by polymeric net)
- The physical state of drug (dispersed under molecular or particulate form or both)
- The matrix shape and alteration in volume as a function of time.
- The route of administration (oral administration remains the most widely used but other route are adaptable)
- The release kinetic model.

MATERIALS AND METHODS

Materials Used

The materials used for the formulation and evaluation of Ambroxol HCl SR tablets are listed in the below table:

Table 1: List of Materials and Suppliers

Sl. No	Materials	Manufacturers/ Suppliers
1.	Ambroxol HCL BP	Remidex Pharma
2.	lline Cellulose Plain	Reliance Cellulose Products Ltd
3.	Povidone K-30	Ninhang Ltd, Kawarlal & CO
4.	Purified Water	-
5.	ydroxy Propyl Methyl Cellulose (K 100M)	Colorcon Asia Ltd,
6.	droxy Propyl Methyl Cellulose (5 CPS)	Colorcon Asia Ltd,
7.	Colloidal Silicon Dioxide	Wacker Silicons
8.	Magnesium Stearate	Amishi Drugs & Chemicals LTD

METHODS

Preformulation study of Ambroxol HCl BP

Preformulation study is the first step in the formulation of a new drug delivery system. The study focuses on the physico chemical properties of the new compound that affect the drug performance and development of an efficacious dosage form. The overall aim of the preformulation study is to generate useful information to the formulator to develop a stable and bioavailabe dosage form useful for human. The preformulation study of Ambroxol HCl was done as per BP 2009. The following test were conducted for Ambroxol HCl.

Table 2: Formula For Ambroxol Hydrochloride Sustained Release Tablet

	F1 Per tablet in mg	F2 Per tablet in mg	F3 Per tablet in mg	F4 Per tablet in mg	F5 Per tablet in mg	F6 Per tablet in mg	F7 Per tablet in mg
Ambroxol HCl	75.308	75.308	75.308	75.308	75.308	75.308	75.308

Hydroxy propyl methyl cellulose K100M	62.5	75	87.5	87.5	87.5	92.5	100
Hydroxy propyl methyl cellulose 5CPS	-	-	-	25	12.5	12.5	12.5
Povidone K30	5	5	5	5	5	5	5
Microcrystalline cellulose Plain	102.192	89.692	77.192	55.192	67.692	62.692	55.192
Colloidal Silicon Dioxide	2	2	2	2	2	2	2
Magnesium stearate	3	3	3	3	3	3	3
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Average Weight	250	250	250	250	250	250	250

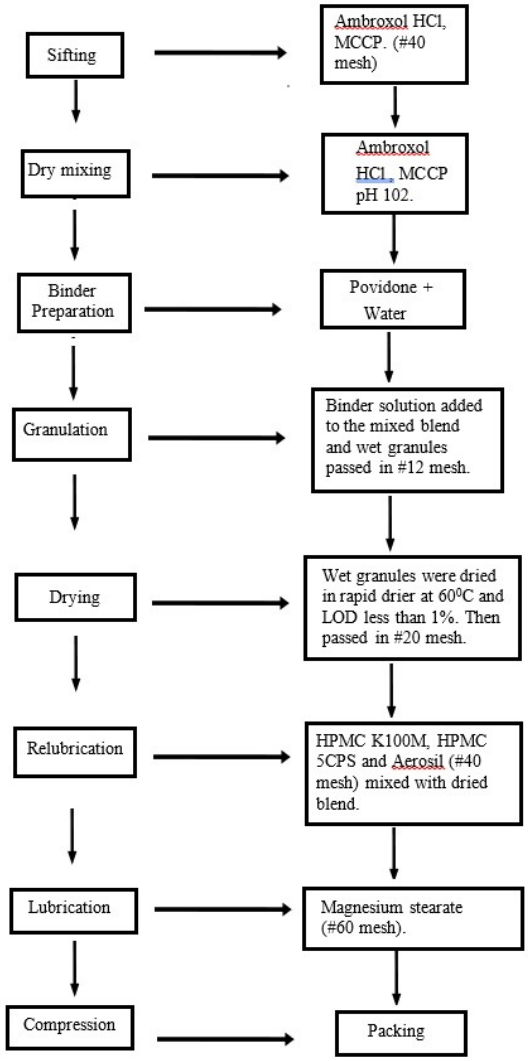

Fig 1: Flow chart of the Manufacturing process

RESULTS AND DISCUSSION

In the present study seven formulations (F1- F7) were prepared by using HPMC of different viscosity grades viz; (K100M and 5CPS) MCC pH102, and PVPK-30. To know the mechanism of drug release from these formulations, the data were fitted in various kinetic models like Zero order plot, First order plot, Higuchi's and Korsmeyer equation.

Preformulation Studies

Table 3: Appearance

Test	Specification	Observation
Physical Appearance:	White or Yellowish Crystalline powder.	White crystalline powder.
Taste	Bitter	Bitter
Odour	Nil	Nil.

Loss on Drying

This test was done as per BP specification.

Table 4: Observation for Drying

Test	Specification	Observations
Loss on drying	Not more than 0.5% $^{w}/_{w}$	0.13% $^{w}/_{w}$

Melting point determination

Melting point of Ambroxol HCl was done as per BP specification and found to be following.

Table 5: Observation for melting point

Test	Specification	Observation
Melting point	235-240°C	239°C

Particle size analysis

Table 6: Data for particle size analysis

Seive No. passed/ retained	Arithmetic mean size of opening (µm) (Xi)	Weight retained on sieve (gm)	Percent weighed retained (%) Fi	Weight size XiFi
14/16	1350	0.0345	0.35	472.5
16/22	1355	0.9836	10.15	13753.25
22/44	517.5	2.7379	28.26	14624.55
44/85	180	2.8761	29.69	5344.2
85/100	36.5	3.0542	31.53	1150.84

ΣFi = 99.98, ΣXiFi = 35345.34

$$\text{Mean particle size} = \frac{\Sigma XiFi}{\Sigma Fi} = \frac{35345.34}{99.98} = 353.52\mu m\ (0.353mm)$$

pH

Table 7: pH

Test	Specification	Observation
pH	4.5 – 6.0	5.30

The pH of the drug complies with B.P specification.

Solubility

Ambroxol HCl is sparangly soluble in water, freely soluble in methanol, practically insoluble in methylene chloride.

Assay or percentage purity of drug

Table 8: Assay

Test	Specification	Result
Assay on dried basis.	99.0 – 101.0 % $^{W}/_{W}$	99.90 % $^{W}/_{W}$

Percentage purity of Ambroxol was determined as per procedure given in BP and found to be 99.90% $^{W}/_{W}$. which complies with B.P specification.

Compatibility studies

Compatibility studies were performed by physical observation and FT-IR Spectrophotometer. Physical observation was performed in a stability chamber at 40ºC ± 2ºC / 75 ± 5% RH and 15 days and 30 days. The FT-IR spectrum of pure drug was compared with FT-IR spectrum of physical mixture of *Ambroxol*, HPMC K100M, HPMC 5CPS, MCC pH102.

Table 9: Drug – Excipient compatibility study (Physical observation)

SL No	Drug+Excipient	Parameter	Initial Value of Parameter	Condition RT40°C±2°C/75% ±5%RH		Comments
				15 days	30 days	
1	Ambroxol HCl	Any colour change	Yellowish white colour	No colour change	No colour change	Compatible
2	ımbroxol HCl + HPMC K100M	Any colour change	White colour	No colour change	No colour change	Compatible
3	mbroxol HCl + HPMC 5CPs	Any colour change	White colour	No colour change	No colour change	Compatible
4	mbroxol HCl + MCCP pH102	Any colour change	Light yellow colour	No colour change	No colour change	Compatible
5	ɔroxol HCl + Povidone	Any colour change	White colour	No colour change	No colour change	Compatible
6	Ambroxol HCl + Colloidal Silicon Dioxide	Any colour change	White colour	No colour change	No colour change	Compatible
7	Ambroxol HCl + Magnesium stearate	Any colour change	White colour	No colour change	No colour change	Compatible

From the available excipients, the excipients given in the above table showed more compatibility with the drug.

IR spectra of pure Ambroxol HCl showed the major bands at 1284 for secondary amines, 1200.73 primary amines, 3396.76 for C-OH group, 1064 for C-O group and 650.5 for C-Br of dibromobenzene (Robert M. Silverstein, Francis X. Webster 2005). The results of IR spectra of active ingredient and excipients also revealed that there was no considerable change observed in bands of Ambroxol HCl. This shows the absence of any interaction between the drug, polymer and excipients used.

Evaluation of Ambroxol HCl granules

Flow Properties

The flow properties were determined as per procedure given in material method part. The results are illustrated in following tables.

Table 10: Flow properties of pure drug

Formulation	Angle of repose± SD	Bulk density (gm/ml) ± SD	Tapped density (gm/ml) ± SD	Compressibility index (%)± SD	Hausner's Ratio ± SD
F7	37.56° ± 0.04	0.481 ± 0.02	0.601 ± 0.01	19.96 ± 0.04	1.24 ± 0.03

The flow property of Ambroxol HCl API was found to be fair from the above table.

Table 11: Physical characteristics of Ambroxol HCl granules

Formulation	Angle of repose ± S.D	Bulk density (gm/ml) ± S.D	Tapped density (gm/ml) ± S.D	Compressibility index (%) ± S.D	Hausner's ratio ± S.D
F1	35.70° ± 0.01	0.476 ± 0.03	0.567 ± 0.03	16.05 ± 0.03	1.191 ± 0.04
F2	33.67° ± 0.03	0.475 ± 0.01	0.553 ± 0.02	14.40 ± 0.02	1.16 ± 0.03
F3	33.46° ± 0.03	0.477 ± 0.03	0.547 ± 0.04	12.79 ± 0.02	1.14 ± 0.02
F4	34.78° ± 0.02	0.476 ± 0.02	0.539 ± 0.03	11.68 ± 0.01	1.13 ± 0.02
F5	26.43° ± 0.01	0.478 ± 0.03	0.543 ± 0.01	11.97 ± 0.04	1.13 ± 0.04
F6	28.68° ± 0.02	0.474 ± 0.02	0.526 ± 0.02	10.01 ± 0.01	1.09 ± 0.02
F7	28.53° ± 0.01	0.476 ± 0.01	0.528 ± 0.03	9.84 ± 0.03	1.09 ± 0.04

The flow parameters of the pure drug showed that the flow was in fair condition. So after adding the other excipients the flow of the granules was excellent.

Evaluation of sustained release matrix tablets of Ambroxol HCl

Table 12: Physical Characteristics of Ambroxol HCl sustained release Tablet

Formulation	Weight variation in mg ± SD	Thickness in mm ± SD	Diameter in mm ± SD	Hardness in Kg/cm^2 ± SD	Friability (%)
F1	249.4 ± 1.31	3.7 ± 0.02	9.47± 0.034	4.5 ± 0.16	0.22
F2	251.1 ± 1.24	3.8 ± 0.01	9.48 ± 0.027	4.2 ± 0.13	0.41
F3	248.9 ± 1.13	3.7 ± 0.01	9.45 ± 0.045	5.5 ± 0.12	0.15
F4	249.8 ± 1.21	3.6 ± 0.02	9.44 ± 0.032	4.5 ± 0.14	0.36
F5	250.1 ± 1.36	3.9 ± 0.03	9.49± 0.021	5.5 ± 0.13	0.43
F6	251.2 ± 1.12	3.6 ± 0.02	9.48 ± 0.019	4.6 ± 0.14	0.17
F7	249.9 ± 1.23	3.7 ± 0.01	9.49± 0.015	4.5 ± 0.12	0.11

The weight variations for all the formulation F1 to F7 were within the in- house specification. Thickness of all the formulation F1 to F7 was in the range 3.6 -4.0 mm. Hardness of all formulation F1to F9 was in range of 4-10 kg/cm^2. Diameter of all formulation F1 to F9 was in the range of 9.40-9.50 mm. Friability of all formulation was not more than 0.8%.

Assay

Table 13: Assay of Ambroxol HCl SR tablets

FORMULATION	ASSAY (%)
F7	99.06

Assay of tablet was performed by HPLC and found to be 99.06 % $^{w}/_{w}$.

In Vitro release profile of Ambroxol HCl Sustained release matrix tablet:

Table 14: Formulation F1-F7

Time (Hrs)	imi ts me	Cumulative % drug release of F1	Cumulative % drug release of F2	Cumulative % drug release of F3	Cumulative % drug release of F4	Cumulative % drug release of F5	Cumulative % drug release of F6	Cumulative % drug release of F7
1	NMT 25%	34.51±0.34	30.14±0.13	25.10±0.42	32.01±0.13	27.14±0.41	22.02±0.15	16.91±0.21
4	30 – 50%	65.01±0.23	58.21±0.21	32.26±0.32	59.19±0.32	51.21±0.63	50.13±0.24	46.72±0.32
8	50 – 80%	82.15±0.12	74.53±0.42	46.35±0.21	92.32±0.51	90.10±0.52	82.41±0.53	70.90±0.35
12	NLT 80%	97.02±0.43	87.52±0.51	82.17±0.34	97.51±0.43	95.53±0.16	93.64±0.14	92.13±0.27

The in-vitro drug release profile reveals that the formulation F7 shows better release within the inhouse specification.

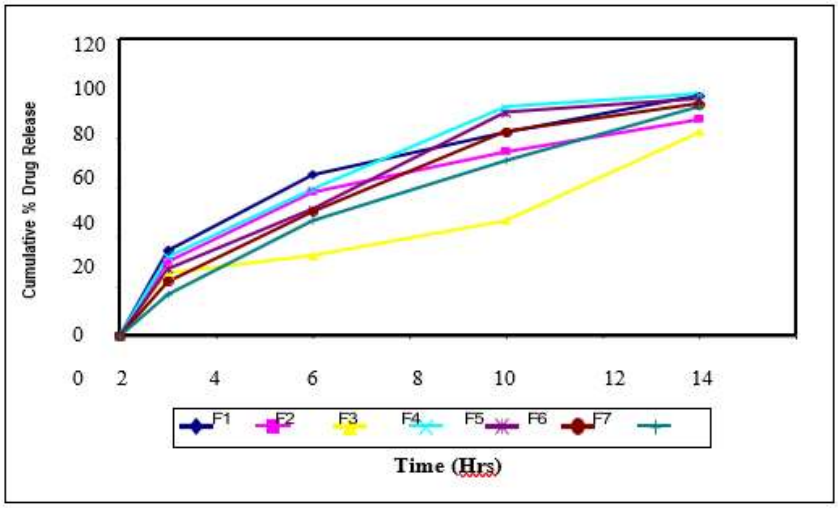

Fig 9: In-vitro drug release profile for formulation F1-F7

The in-vitro dissolution study of sustained release matrix tablets from each batch (F1-F7) was carried out in phosphate buffer 6.8 for 12 hrs using basket type dissolution apparatus. The chromatogram is obtained from HPLC and the values obtained as per USP specifications which are mentioned above. Cumulative % drug release Vs time were plotted. From the in vitro dissolution data, it was found that the drug release from formulations containing HPMC K100M (F1-F3) showed 97%, 87%, 82% drug release after 12 hrs respectively. Formulation containing HPMC K100M and HPMC 5CPS (F4-F7) showed 97%, 95%, 93% and 92.13% drug release after 12 hrs respectively.

The comparative release of all formulations showed the improvement in sustaining property of drug release. Increasing the HPMC K100M concentration (from 37% - 40%) and decreasing HPMC 5CPS concentration (from 10% - 5%) in formulation F7 showed more sustained action and optimum release than all other formulations. This shows that concentration of polymer influences the drug release. Thus the optimized formulation F7 was successful in the study.

Mechanism of drug release

In order to understand the complex mechanism of drug release from the matrix system, the in vitro release rate were fitted to Korsmeyer-peppas model and interpretation of release exponent value (n) enlighten in understanding the release mechanism from the dosage form. The release exponent value (n) obtained thus obtained was 0.682. The F7 formulation thus exhibited anomalous (non Fickian) diffusion mechanism. The drug release was diffusion controlled as plot of higuchi's model was found to be linear.

These formulations also showed highest R^2 values of zero order kinetics indicating the amount of drug from the matrix system were by both diffusion and erosion.

Table 15: Characterization of drug release mechanism

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous(Non- Fickian) diffusion
0.89	Case II transport
n>0.89	Super case II transport

Selection of optimized batch

The F7 of sustained release matrix tablet was chosen as optimized formulation because it showed more linearity between the cumulative percentage release of Ambroxol verses time, as indicated by the highest value of the correlation coefficient in all selected models, among all sustained release matrix tablets and best fitted for both Korsmeyer-peppas (0.684) and zero order (0.988) model.

Stability Studies

The selected formulation was evaluated for stability studies. The formulation were stored at 40° C at 75% RH for 1 month and analyzed for their physical parameters and drug content at every one month interval. Stability studies were performed for the formulation F- 7 for 1 month at 40°C±2°C/75%RH±5%Rh at walk-in stability chamber. The tablets were analysed for appearance, weight variation, drug content and *in vitro* drug release. The overall results showed that the formulation is stable at the above mentioned storage conditions.

Fig 1 0 : Circular Biconvex un-coated tablets of Ambroxol HCl SR tablets 75mg.:

SUMMARY AND CONCLUSION

In this project work, an attempt has been made to design sustained release matrix tablets of Ambroxol Hydrochloride, by using hydrophilic polymers HPMC K100M and HPMC 5CPS employed for mucolytic activiy in various pulmonary disorders. The matrix tablets were prepared by wet granulation technique. Based on studies of the API organoleptic properties were complied with the BP specification. Physical properties such as bulk density and tapped density, angle of repose, carrs index, hausners ratio were within the in house tentative specification in case of granules ready for compression than that of Ambroxol raw powder. Sieve analysis and melting point determination were given the information about particle size distribution and purity of the drug powder respectively. Loss on drying was within the B.P limit. Solution properties i.e pH of the solution and solubility were evaluated, results were complied with the pharmacopoeial specification. Assay of Ambroxol Hydrochloride was carried out by HPLC method and was found to be 99.90%. The physical compatibility evaluation was performed in visual basic and FT- IR. The study implies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description. Infra Red spectrum of Ambroxol HCl matches with the standard spectrum as well as there was not any additional peak formation with the excipients. ll the formulations were evaluated on the basis of pharmacopoeial specification. Shape of the tablets was round biconvex, hardness, diameter, thickness, weight variation, and in-vitro dissolution test were carried out. Assay was carried out for formulation F7 and was formed to be 99.06%. Stability studies of the selected formulated tablets were charged at 40 °C $\pm$ 2 °C/ 75 $\pm$ 5 % RH for accelerated study. All the parameters were

within the limit after one month analysis. In the kinetic study drug release from the matrix system is revealed, the in vitro release rate were fitted to Korsmeyer-peppas model. The release exponent value (n) obtained thus obtained was 0.684. The F7 formulation thus exhibited anomalous (non Fickian) diffusion mechanism. The drug release was diffusion controlled as plot of higuchi's model was found to be linear.Further continuation of real time stability and In-vivo studies should be progressed.

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