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DEVELOPMENT OF SUSTAINED RELEASE MATRIX TABLET FORMULATION AND EVALUATION OF AMBROXOL HYDROCHLORIDE

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ABSTRACT

Ambroxyl is a Mucolytic expectorant. Ambroxyl has short half life (3-4hrs) makes the development of sustained release forms extremely advantageous, Ambroxyl is a weak acidic pka 4.5 – 6, it has pH dependent solubility, characterized in low pH condition present in stomach, Which consequently delayed in onset of action, Formulation of SR tablet is effective approach for mucolytic expectorant it gives maximum action with prolong drug concentration due to sustained release from tablet matrix. Different formulation (F1 – F7) designed with HPMC K100, HPMC 5CPS, Povidone K30, MCCP. pre and post -compression parameters for all formulation were studied. Batch F7 selected as optimized batch on the basis of dissolution profile.

KEYWORDS: Ambroxy, HPMC, MCCP, Dissolution, 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.

MATERIALS AND METHODS

Materials

Ambroxol HCL BP WAS OBTAINED AS A GIFT SAMPLE FROM REMIDEX PHARMA PVT LTD. Micro Crystalline Cellulose Plain, Povidone K-30, Hydroxy Propyl Methyl Cellulose (K 100M), Hydroxy Propyl Methyl Cellulose (5 CPS), Colloidal Silicon Dioxide, Magnesium Stearate

Methods

Drug - Excipient Compatibility Studies

In the tablet dosage form the drug and the excipients are in extreme contact with one another. The Excipient have an important role in the stability of the drug. So the drug - excipient interaction study is very useful for the formulator in selection of proper excipients.

Drug Profile

Ambroxol HCl BP (British Pharmacopoeia 2009)

Storage **:** Store in tightly closed, light resistant container.

General Description : Ambroxol HCl (group of benzilamides) is an N-desmethyl metabolite of Bromhexine. It expectoration enhancer and mucolytic agent used in the treatment of acute and chronic pulmonary disorders characterized by the production of

Molecular Formula **:** $C_{13}H_{18}Br_2N_2O$. HCl

Molecular Weight **:** 414.57.

Chemical Name **:** *Trans*-4-[(2-Amino-3,5dibromobenzyl)amino] cyclohexanolhydrochloride(http://chemicalland21.com).

Description **:** White or yellowish crystalline powder.

Solubility **:** Slightly soluble in water, ethanol; soluble in dimethyl lformamide, methanol; insoluble in chloroform and benzene.

Melting Point **:** 235-240°C.

PH **:** 4.5-6.

Loss on drying : Maximum 0.5 per cent.

Stability : Stable under ordinary conditions.

EVALUATION OF PHYSICAL PROPERTIES

Bulk Density

Bulk density is the ratio of the weight of the powder to the bulk volume it occupies. It is expressed in gm/ml. Weighed quantity of powder were transferred into a 50 ml measuring cylinder without tapping; the volume occupied by the powder was measured. Bulk density was measured by using formula.

$$\mathbf{B.D = M/V_o}$$

Where,

B.D = Bulk density

M = Mass of the powder

V_o = Untapped Volume

Tapped Density

Weighed quantity of powder was taken in a 50 ml measuring cylinder, volume occupied by powder was noted down. Then cylinder was subjected to 500 taps in tapped density tester (Electro Lab USP II), the % Volume variation was calculated by following formula.

$$\mathbf{T.D = m/V_t}$$

Where,

T.D = Tapped density,

m = Mass of the blend,

V_t = Tapped volume.

Compressibility Index

Compressibility is the ability of powder to decrease its volume under pressure. Using tapped density and untapped density the percentage compressibility of granules can be determined, which is given as Carr's compressibility index.

$$\mathbf{C.I = [V_t - V_0 / Vt] \times 100}$$

Formulation of Tablet

The Sustained Release Was Achieved By Means Of A Polymeric Matrix For Sustained Release Tablets It Tends To Swell And Slowly Erode Rather than Disintegratting

Formulation Development And Evaluation Of Ambroxol Hydrochloride Sustained Release Matrix Tablets By Following Steps

Sifting

The following ingredients were sifted through # 40 mesh in the order Ambroxol HCl, Microcrystalline cellulose Plain, HPMC K100M, HPMC 5CPS, Povidone K30 and Aerosil in a tray. Magnesium stearate is sifted through # 60 mesh.

Dry Mixing

All the sifted ingredients except the binder (Povidone K 30) were mixed thoroughly for 10 mins in rapid mixer granulator.

Binder Preparation

The weighed amount of Povidone K30 was completely dissolved in purified dematerialized water in a beaker.

Granulation

The binder solution containing Povidone K30 in water was added slowly to the above ingredients and mixed at slow speed. After the complete addition of binder solution mix well to get the granules. The wet granules were passed through #12 mesh sieve.

Drying

The wet granules were loaded in a rapid dryer and dried at 60^{o} C till the moisture content of granules are less than 1%. The dried granules are passed through #20 mesh sieve and loaded in a planatary mixer.

Pre lubrication

Sifted HPMC K100M, HPMC 5CPS, and Aerosil is mixed to the above blend and mix for 15 mins at slow speed.

Lubrication

Finally Magnesium stearate already passed through #60 mesh sieve were loaded in planetary mixer and mixed well for 2mins at slow speed**.**

Compression of tablets

The quantity of dried granules was loaded into the hooper of a Table top compression machine. The compression is done by using 9.5×9.5 mm normal concave plain punches. The target weight of tablet was fixed at 250mg, hardness 4kg/cm^2 and thickness 3.6 to 4mm.

Formulation for Ambroxol Hydrochloride Sustained Release Tablets

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7
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

EVALUATION OF SUSTAINED RELEASE TABLETS

Appearance

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

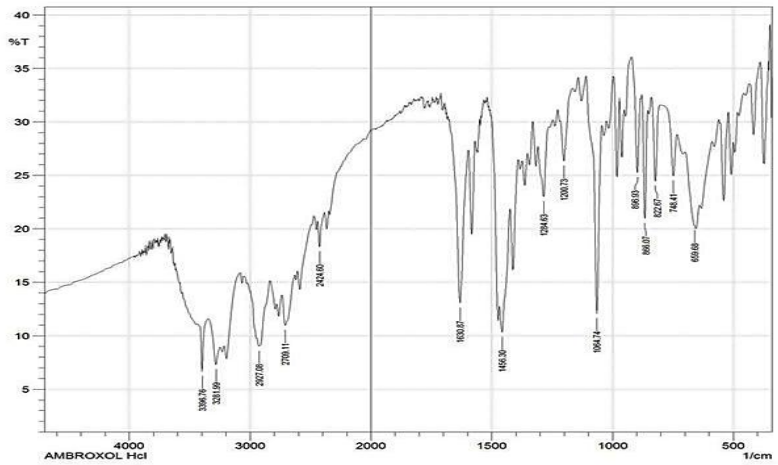
Particle size analysis

Data for particle size analysis

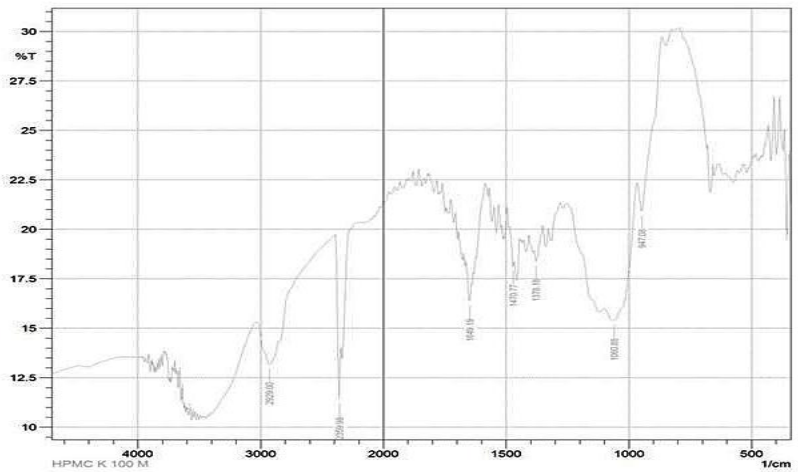
Seive No. passed/ retained	Arithmetic mean size of opening (µm) (Xi)	Weight retained on sieve (gm)	Percent weighed retained (%) Fi	Weight size XiFi
14/16	1350	0.0345	0.35	472.5
16/22	1355	0.9836	10.15	13753.25
22/44	517.5	2.7379	28.26	14624.55
44/85	180	2.8761	29.69	5344.2
85/100	36.5	3.0542	31.53	1150.84

Drug – Excipient compatibility study (Physical observation)

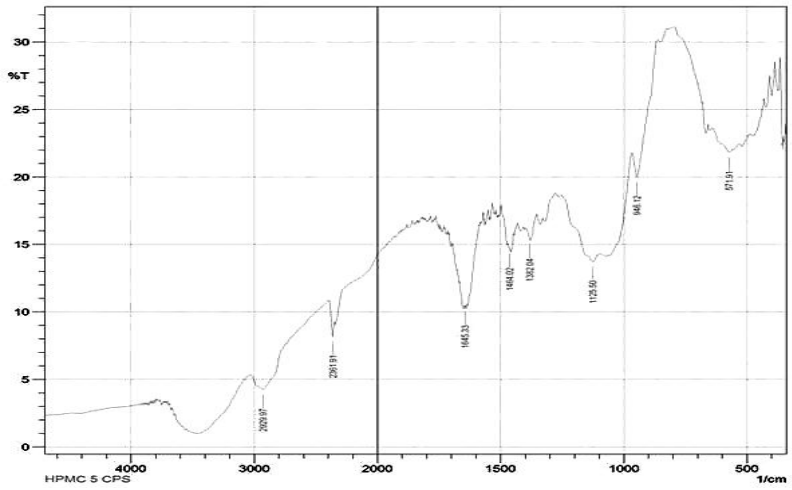
SL No	Drug+Excipient	Parameter	Initial Value of Parameter	Condition		Comments
				RT40°C±2°C/75% ±5%RH		
				15 days	30 days	
1	Ambroxol HCl	Any colour change	Yellowish white colour	No colour change	No colour change	Compatible
2	Ambroxol HCl + HPMC K100M	Any colour change	White colour	No colour change	No colour change	Compatible
3	Ambroxol HCl + HPMC 5CPs	Any colour change	White colour	No colour change	No colour change	Compatible
4	Ambroxol HCl + MCCP pH102	Any colour change	Light yellow colour	No colour change	No colour change	Compatible
5	Ambroxol 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



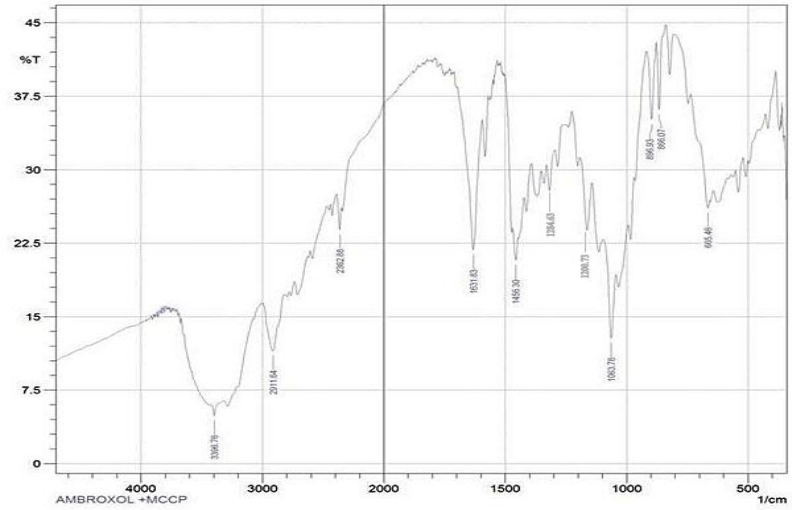
IR Spectrum of HPMC K 100 M



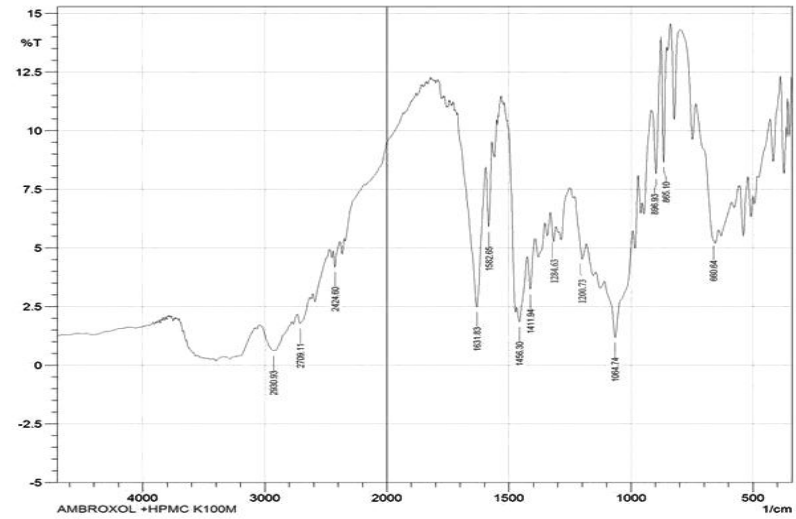
IR Spectrum of HPMC 5CPS



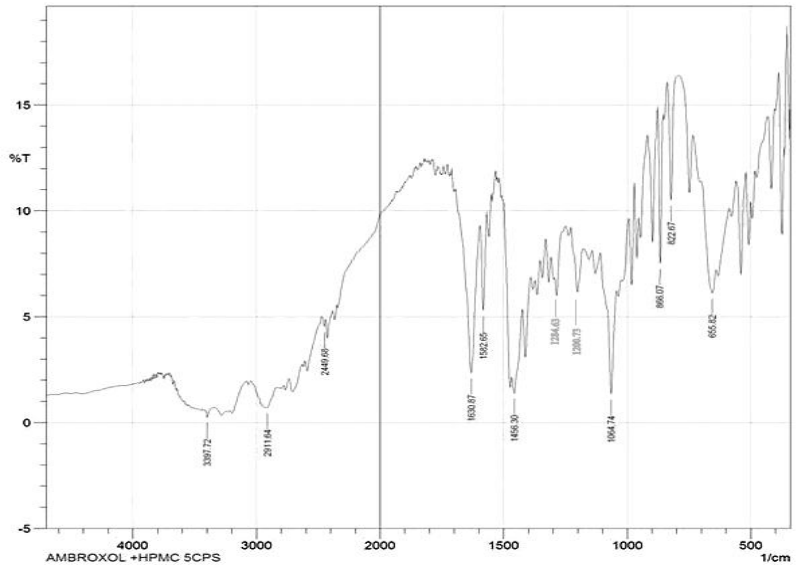
IR Spectrum of physical mixture (Ambroxol HCl+ MCCP).



IR Spectrum of physical mixture (Ambroxol HCl+ HPMC K 100 M)



IR Spectrum of physical mixture (Ambroxol HCl + HPMC 5CPS)



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^{o} ± 0.01	0.476 ± 0.03	0.567 ± 0.03	16.05 ± 0.03	1.191 ± 0.04
F2	33.67^{o} ± 0.03	0.475 ± 0.01	0.553 ± 0.02	14.40 ± 0.02	1.16 ± 0.03
F3	33.46^{o} ± 0.03	0.477 ± 0.03	0.547 ± 0.04	12.79 ± 0.02	1.14 ± 0.02
F4	34.78^{o} ± 0.02	0.476 ± 0.02	0.539 ± 0.03	11.68 ± 0.01	1.13 ± 0.02
F5	26.43^{o} ± 0.01	0.478 ± 0.03	0.543 ± 0.01	11.97 ± 0.04	1.13 ± 0.04
F6	28.68^{o} ± 0.02	0.474 ± 0.02	0.526 ± 0.02	10.01 ± 0.01	1.09 ± 0.02
F7	28.53^{o} ± 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

Physical Characteristics of Ambroxol HCl sustained release Tablet

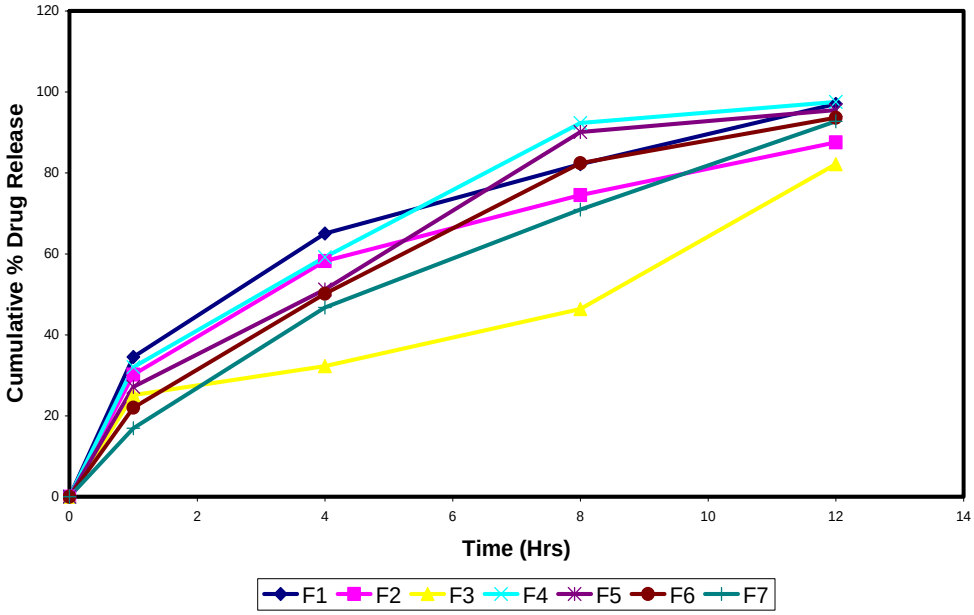
Formulation	Weight variation in mg ± SD	Thickness in mm ± SD	Diameter in mm ± SD	Hardness in Kg/cm^2 ± SD	Friability (%)
F1	249.4 ± 1.31	3.7 ± 0.02	9.47± 0.034	4.5 ± 0.16	0.22
F2	251.1 ± 1.24	3.8 ± 0.01	9.48 ± 0.027	4.2 ± 0.13	0.41
F3	248.9 ± 1.13	3.7 ± 0.01	9.45 ± 0.045	5.5 ± 0.12	0.15
F4	249.8 ± 1.21	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

In Vitro release profile of Ambroxol HCl Sustained release matrix tablet

Time in (Hrs)	Limits	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 inhours specification.

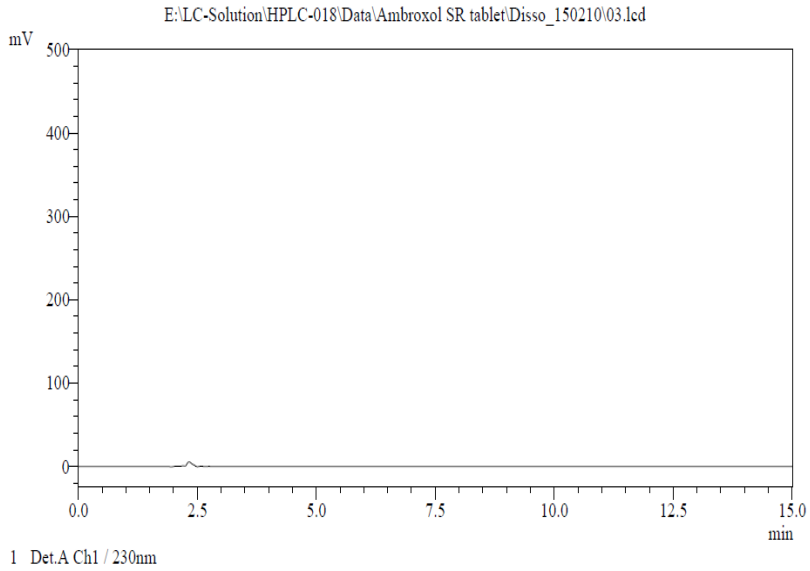
In-vitro drug release profile for formulation F1-F7



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.

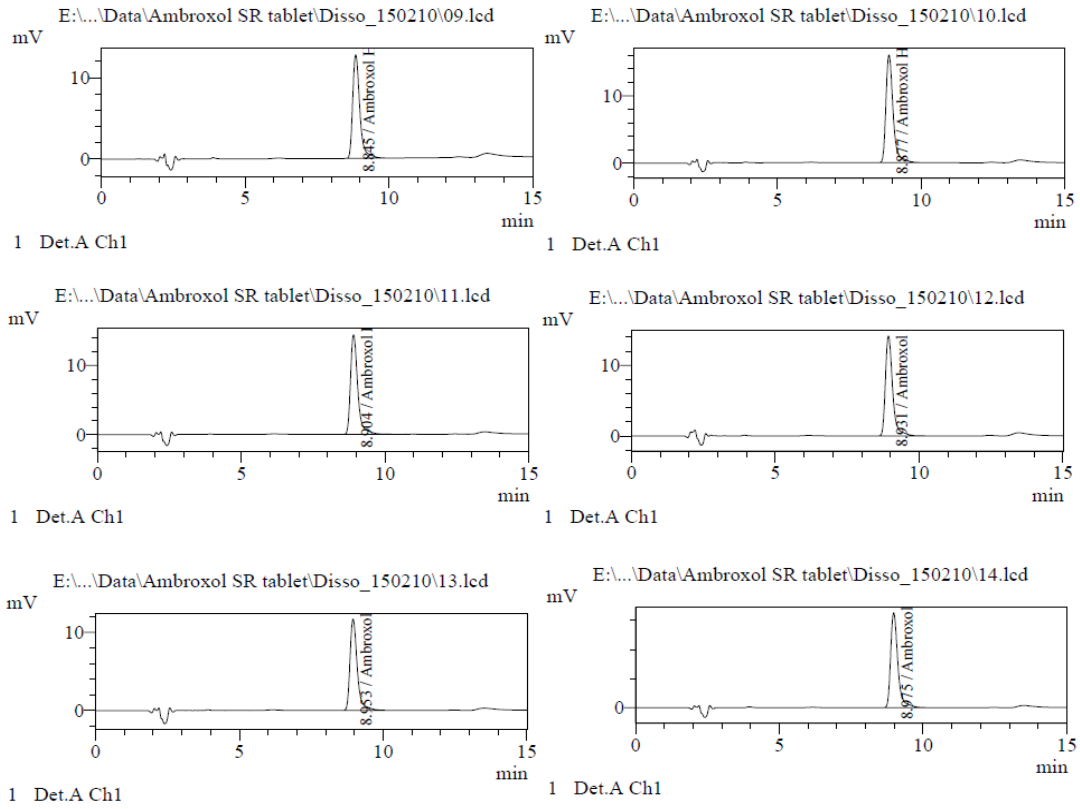
CHROMATOGRAM FOR BLANK



CHROMATOGRAM FOR FIRST HOUR

Sample Information E:\LC-Solution\HPLC-018\Data\Ambroxol SR tablet\Disso_150210\09.lcd

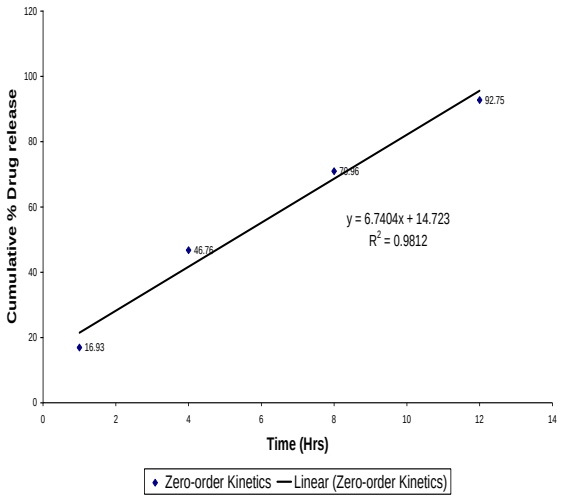
Sample Name	: Anbroxol HCL SR Tab .
Sample ID	: Ambroxol_1 Hour_D1
Method Filename	: Ambroxol Disso..lcm
Data Filename	: 09.lcd
Batch Filename	: Disso_150210.lcb
Vial#	: 3
Injection Volume	: 20 µL



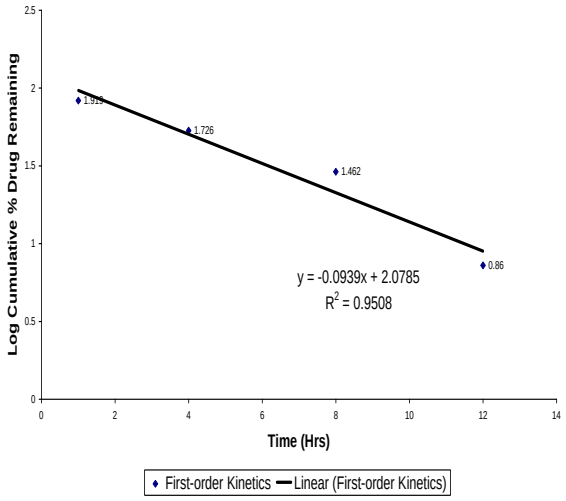
Kinetic studies of optimum formulation F7

Time in hours	√ T	Log T	Cumulative % drug release	Log Cumulative %drug release	Amount of drug release	Cumulative %drug remain	Log Cumulative %drug remain
1	1.0	0	16.91	1.228	12.68	83.09	1.919
4	2.0	0.602	46.72	1.669	35.04	53.28	1.726
8	2.828	0.903	70.73	1.849	53.04	29.27	1.466
12	3.464	1.079	92.13	1.964	69.09	7.87	0.895

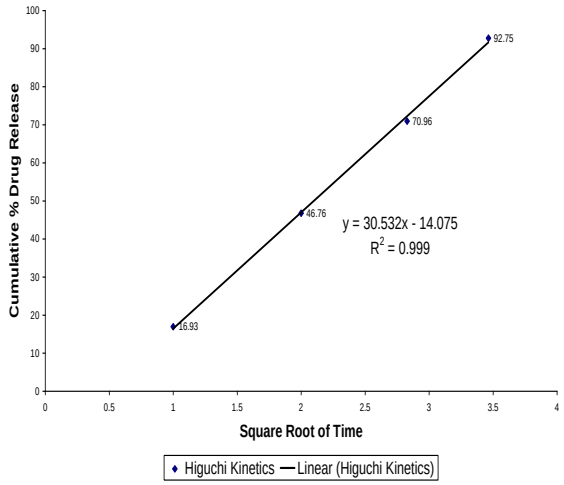
Kinetic plots for formulation F7



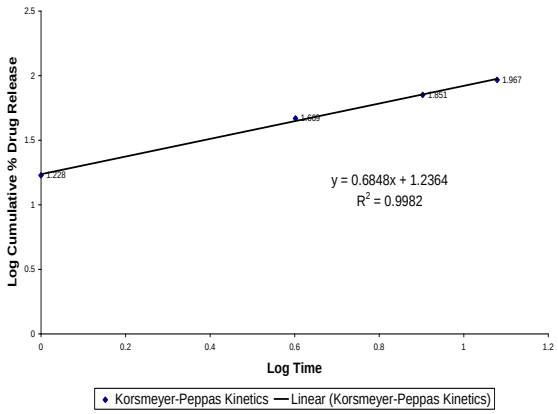
Zero order plot of F7



First order plot of F7



Higuchi plot of F7



Korsmeyer-Peppas plot of F7

Kinetic Values Obtained From F7 Plot Formulation of Ambroxol SR Tablets

Formulation	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer -Peppas R^2	n	Mechanism Of drug release
F7	0.981	0.950	0.999	0.998	0.684	Zero order non Fickian diffusion

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.

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 limits.

- Solution properties i.e pH 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. InfraRed spectrum of Ambroxol HCl matches with the standard spectrum as well as there was not any additional peak formation with the excipients.
- All 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 ^{o}C $\pm$ 2 ^{o}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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