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FORMULATION AND EVALUATION OF SUSTAIN RELEASE TABLETS OF AMBROXIL HCL

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ABSTRACT

In the present investigation, an attempt was made to design and develop of Sustained Release Ambroxol Hydrochloride Matrix Tablets using the combination HPMC k 4 100 and carbopol 940, 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. The Sustained release matrix tablets containing Ambroxol hydrochloride were developed using different drug: polymer ratios. Sustained release matrix tablets were prepared by wet granulation method. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The prepared tablets were further evaluated for uniformity of weight, hardness, friability, thickness, content uniformity, In-vitro dissolution, drug-excipients interactions. The FT-IR studies revealed that there was no chemical interaction between drug and excipients. In-vitro release studies were carried out using USP XXII type II (paddle method) dissolution apparatus at 50 rpm by taking 900 ml of 0.1 N HCl (pH 1.2) as dissolution medium for first 2 hours and later replacing it with 900 ml pH 6.8 phosphate buffer solution for rest of the time period at 37 ± 0.50C. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order, and Zero order to evaluate the kinetics and mechanism of the drug release. Among all the formulations, F 3 shows 98.97 % better controlled release at the end of 11 hr.

KEYWORDS: Ambroxol Hydrochloride, Matrix tablet, Sustained release, carbopol 940, Wet Granulation.

INTRODUCTION

Dosage forms are designed to deliver optimum dose of drug to the site of action to produce desired pharmacological action and also to achieve the effective drug concentration over the preferred period of time. Oral drug delivery system is the most commonly used route of administration when compared to all other routes for various pharmaceutical products of different dosage forms. Easy administration, high patient compliance, avoiding tough sterile standards, and relatively cheap and easy formulation makes the oral dosage form as the first priority.[1]

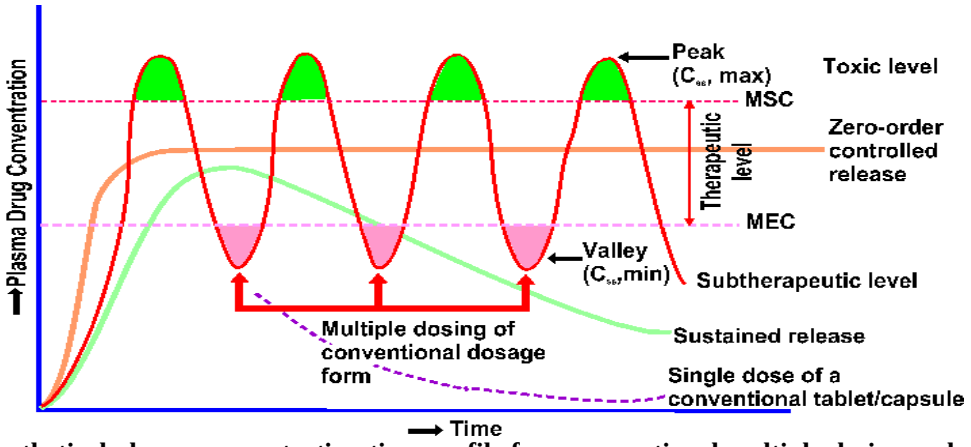


Fig. 1. A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration).[2-4]

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits. Ambroxol is an active N-desmethyl metabolite of the mucolytic bromhexine. Although its mechanism of action has not been fully defined, it may increase the quantity and decrease the viscosity of tracheobronchial secretions. It may also act as an expectorant, increasing mucociliary transport via stimulation of cilliary motility. Ambroxol hydrochloride has also been reported to have a cough suppressing effect and anti inflammatory action.[5-8] 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] The aim of present study is to develop sustained release matrix tablets of Ambroxol hydrochloride using the combination hpmc k4 100 and carbopol 940.

MATERIALS AND METHODS

Materials HPMC K4 100, Polyvinyl Pyrrolidone K 30, Lactose and Talc were purchased from SD Fine Chem. Limited, Mumbai. Carbopol were purchased from Research Lab Fine Chem Industries, Mumbai. Ambroxol Hydrochloride was obtained from hetero labs hyderabad. Magnesium stearate were purchased from Loba Chemie Pvt. Ltd, Mumbai.

METHODOLOGY

Construction of Standard Graph of Ambroxol hydrochloride

Accurately weighed amount of 100 mg ambroxol hydrochloride was transferred into a 100ml volumetric flask. 20 mL of 0.1N hydrochloric acid (HCl) was added to dissolve the drug and volume was made up to 100 mL with the same HCl. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'. From this stock solution 10ml was taken and diluted to 100 mL with 0.1N HCl which has given the solution having the concentration of 100 mcg/mL. Necessary dilutions were made by using this second solution to give the different concentrations of ambroxol hydrochloride (5 to 35 mcg/mL) solutions. The absorbances of above solutions were recorded at $_{max}$ (248 nm) of the drug using double beam UV-Visible spectrophotometer.

Preparation of 0.1 N HCl: Accurately measured 8.5 mL of concentrated hydrochloric acid was added to 1000 mL of distilled water.

Preparation of pH 7.4 phosphate buffer: Accurately measured 50 mL of 0.2 M potassium dihydrogen orthophosphate was transferred to a 200mL volumetric flask and 39.1 mL of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 mL with distilled water, mixed and pH was adjusted to 7.4 with 0.2 M sodium hydroxide or 0.2 M othophosphoric acid.

Preparation of 0.2 M potassium dihydrogen phosphate solution: Accurately weighed 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

Calculation of Sustained-Release Dose and Theoretical Release Profile of Ambroxol hydrochloride

The total dose of ambroxol hydrochloride for twice-daily SR formulation was calculated by Robinson Eriksen.[9-11] equation using available pharmacokinetic data.[33]

The zero-order drug release rate constant (k_0) was calculated using following equation

$k_0 = DI \times k_e$

where DI is the initial dose (i.e., conventional dose = 10 mg) and k_e is first-order rate constant for overall elimination.

$k_e = 0.693 / t_{1/2}$
where $t_{1/2}$ = Biological half-life of timolol maleate = 4 h

Therefore $k_e = 0.693 / 4$
= 0.1732 mg/h.

Availability rate $R = k_e \times DI$
= 0.1732 x 75
= 12.99mg/h.

Loading dose = $D_L = DI - R \times t_{max}$
where t_{max} = 2 h

Therefore D_L = 75-(12.99x 2)
= 49.02 mg.

Maintenance dose = $D_M = R \times H$
where H = Number of hours for which sustained action is desired after initial release.

Therefore D_M = 12.99x 12
= 155.88 mg.

Total dose required = $D_T = D_L + D_M$
= 49.02+155.88
= 204.9 mg
205 mg

Hence an oral controlled release formulation of ambroxol hydrochloride should contain a total dose of 205 mg.

Preparation of Ambroxol hydrochloride Matrix Tablets

All the matrix tablets, each containing 205 mg of ambroxol hydrochloride, were prepared by wet granulation method.

Wet granulation: Drug and the diluent (MCC) were sifted through sieve No. 40 manually and mixed well to ensure the uniformity of premix blend. Several drug-diluent premixes were then mixed with the selected ratio of polymer(s), previously sifted through sieve No. 40, for 5 minutes. Premix blend was wet granulated with 1% w/v solution of PVP K-30 in a mortar.[36] The wet mass was passed through No.18 sieve. The wet granules were dried at 55°C ± 5°C for 1 hour in a hot-air oven and the dried granules were sieved through No.22 sieve.

These granules were blended with lubrication mixture (magnesium stearate and talc) and compressed using 16 station rotary tableting machine, equipped with flat-faced, round punches of 6-mm diameter.

Formulations

In the formulations prepared, the release retardants included was hydroxypropylmethylcellulose (HPMC K100M CR) and microcrystalline cellulose (MCC) was used as diluent. Magnesium stearate (MS) and talc was used as lubricant and glidant. 1% w/v solution of polyvinylpyrrolidone (PVP-K30) in isopropyl alcohol (IPA) was used as binder. Compositions of formulation was given in the following Table1.

* qs = quantity sufficient

Table 1. Composition of Matrix Tablets.

F.Code	AMB HCL (mg)	HPMC K100M (mg)	CARBOPOL 940 (mg)	MCC (mg)	PVP-K30 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F1	75	37.5	-	74.5	10	Qs	4	4	205
F2	75	56.5	-	55.5	10	Qs	4	4	205
F3	75	75	-	37	10	Qs	4	4	205
F4	75	-	37.5	74.5	10	Qs	4	4	205
F5	75	-	56.5	55.5	10	Qs	4	4	205
F6	75	-	75	37	10	Qs	4	4	205

Evaluation of Precompression Blend[12-14]

a) Angle of Repose

The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

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

where h and r are the height and radius of the powder cone, θ is the angle of repose.

Angle of repose values less than 25, 25-30, 30-40 and more than 40 indicates excellent, good, passable and poor flow properties respectively.

b) Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density and the tapped density were calculated using the following formulae.

Bulk density = W/V_0

Tapped density = W/V_f

where, W= Weight of the powder

V_0 = Initial volume

V_f = final volume

c) Compressibility Index (Carr's Index)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is.

CI = (TD-BD) x 100/TD

where, TD is the tapped density and BD is the bulk density.

d) Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index

Evaluation of Matrix Tablets[15-18]

i) Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper. Average thickness and standard deviation values were calculated.

ii) Hardness
Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

iii) Friability Test
From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

Note: No tablet should stick to the walls of the apparatus. If so, brush the walls with talcum powder. There should be no capping also.

% friability was calculated as follows

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

where W_1 = Initial weight of the 20 tablets.
W_2 = Final weight of the 20 tablets after testing.
Friability values below 0.8% are generally acceptable.

iv) Weight Variation Test
To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\% \text{ weight variation} = (W_A - W_I) \times 100/ W_A$$

As the total tablet weight was 120 mg, according to IP 1996, out of twenty tablets ±7.5% variation can be allowed for not more than two tablets.

According to USP 2004, ±10% weight variation can be allowed for not more than two tablets out of twenty tablets.

vi) In -Vitro Drug Release Characteristics
Drug release was assessed by dissolution test under the following conditions: n = 3, USP type II dissolution apparatus (paddle method) at 100 rpm in 500 mL of 0.1N HCl for first 2 hours and the phosphate buffer pH 7.4 from 3 to 12 hours, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatmann filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 248 nm.

vii) Kinetic Analysis of Dissolution Data
To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq.(1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannou *et al*., 1993). The first order Eq.(2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq.(3) The Hixson-Crowell cube root law Eq.(4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.[13-15]

$$C = K_0 t \qquad (1)$$

where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log}C = \text{Log}C_0 - K_1 t / 2.303 \qquad (2)$$

where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \qquad (3)$$

where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \qquad (4)$$

where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data.

Cumulative % drug release vs. time (Zero order kinetic model);
Log cumulative of % drug remaining vs. time (First order kinetic model);
Cumulative % drug release vs. square root of time (Higuchi model);
And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

viii) Mechanism of drug release
Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \qquad (5)$$

where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table16, for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Peppas, 1985).

RESULTS AND DISCUSSION

Standard Graph of Ambroxol hydrochloride

The standard graph of Ambroxol hydrochloride ((Table. 17) has shown good linearity with R^2 values 0.973 and 0.9968 in 0.1 N HCl (Fig. 3) and pH 7.4 buffer (Fig. 4) respectively, which suggests that it obeys the "Beer-Lambert's law".

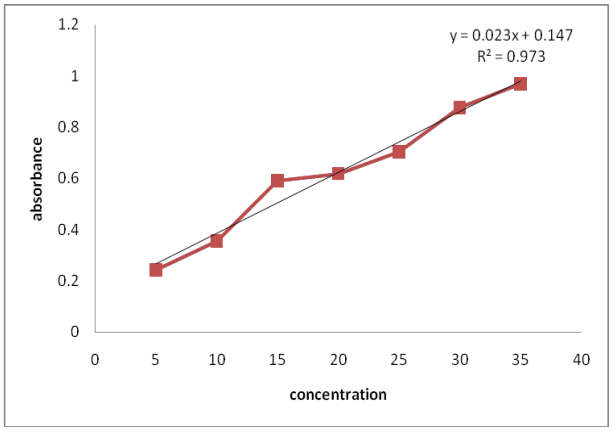


Fig 2. Standard Graph of Ambroxol hydrochloride in 0.1N Hcl.

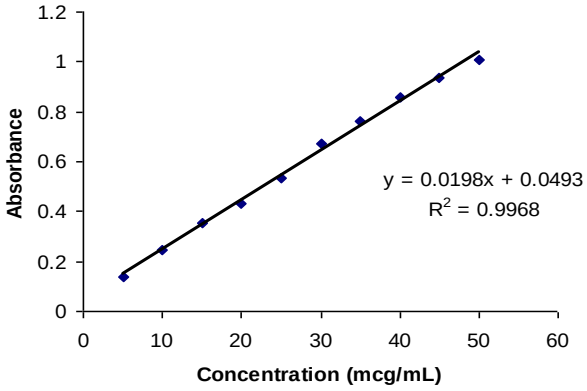


Fig 3: Standard graph of Ambroxol hydrochloride in 7.4 pH buffer.

Characterization of Granules

The granules for matrix tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and drug content (Table 19). Angle of repose was less than 29° and Carr's index values were less than 16 for the granules of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.19 for all the batches indicating good flow properties.

Table 2: Physical Properties of Precompression Blend

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	26.56	0.422	0.506	16.60	1.19
F2	28.75	0.481	0.572	15.90	1.18
F3	29.05	0.276	0.322	14.28	1.16
F4	26.97	0.341	0.388	12.11	1.13
F5	27.34	0.510	0.591	13.70	1.15
F6	28.77	0.533	0.617	13.61	1.15

Physical Evaluation of matrix tablets

The results of the uniformity of weight, hardness, thickness, friability and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 203.4 and 205.6 mg. The hardness of the tablets ranged from 5.08 to 6.28 kg/cm^2 and the friability values were less than 0.8% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 3.08 to 3.33 mm. Thus all the physical attributes of the prepared tablets were found be practically within control.

Table 3: Physical Evaluation of Matrix Tablets.

F.Code	Hardness (kg/cm^2)	Thickness (mm)	Weight variation v (mg) ‡	Friability (%)
F1	5.50 ±0.44	3.22±0.17	204.8±1.48	0.36
F2	5.50±0.31	3.37±0.25	205.4±0.54	0.39
F3	6.28±0.40	3.22±0.80	204.6±0.41	0.13
F4	6.16±0.55	3.20±0.20	203.8±1.64	0.11
F5	5.25±0.57	3.08±0.66	205.6±1.14	0.54
F6	5.08±0.30	3.33±0.25	204.2±0.83	0.58

In-Vitro Drug Release Studies

Low molecular weight HPMC is used predominantly for tablet film coating, while high molecular weight HPMC is used as rate-controlling polymer to retard the release of drugs from a matrix at levels of 10% to 80% w/w in tablets and capsules . Results for the drug release from HPMC K100M matrices showed in Table 4 and Figure 4. Formulations containing HPMC K100M (F3) have shown initial burst release and extended the release for 8 to 12h.

The drug release was slower from matrices containing HPMC K100M compared to caarbopol 940.This may be due to structural reorganization of HPMC. Increase in concentration and viscosity of HPMC may result in increase in the tortuosity or gel strength of the polymer. When HPMC is exposed to aqueous medium, it undergoes rapid hydration and chain relaxation to form viscous gelatinous layer. Failure to generate a uniform and coherent gel may cause rapid drug release. Similar findings were reported by Amelia and Vikram, 2007 and Basak et al, 2006. They revealed that 30-40% HPMC K100M was able to extend the release of water soluble drugs for more than 8 h.

Table 4: In -Vitro Release Data of Ambroxol hydrochloride.

Time (hours)	F1	F2	F3	F4	F5	F6
1	26.2	24.4	22.93	22.16	21.25	22.82
2	35.7	28.5	39.86	31.08	32.28	36.71
3	49.5	41.2	46.82	42.58	43.88	46.36
4	60.71	58.3	55.87	57.73	56.46	57.83
6	84.43	76.9	79.89	73.83	74.25	76.25
8	95.29	94.6	87.07	80.87	83.89	85.93
10	-	98.3	91.97	90.14	90.63	93.06
12	-	-	98.97	92.22	93.55	-

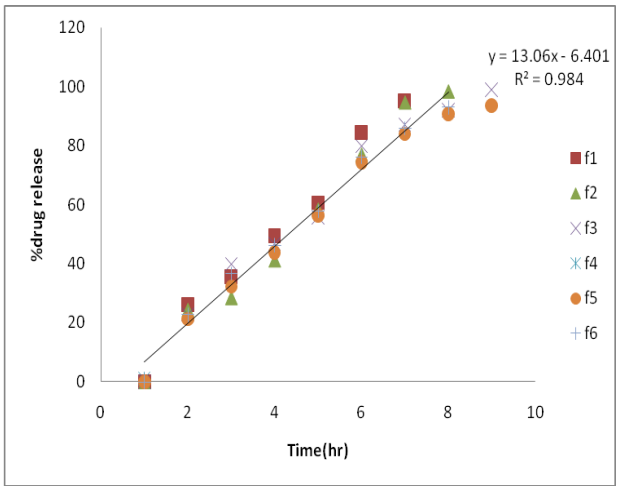


Fig 4: dissolution % drug release graphs for formulations.

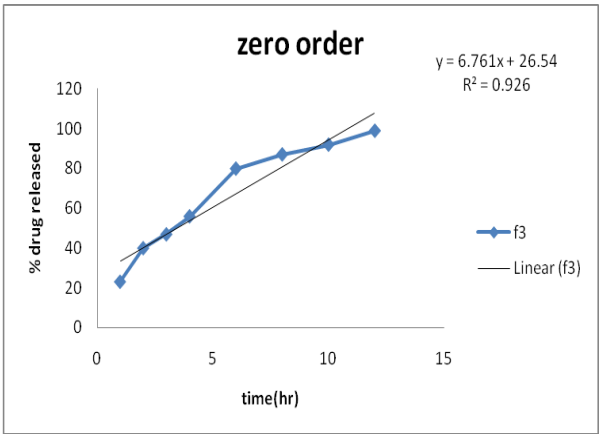
Kinetic analysis of dissolution data

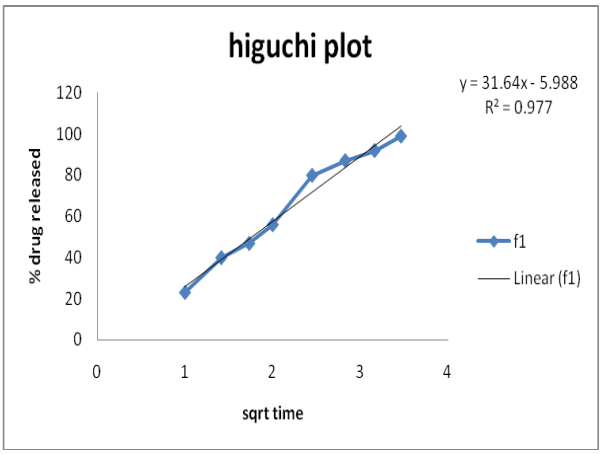
As shown in Figures 4, drug release data was best explained by first order equation, as the plots showed the highest linearity (r^2 = 0.9688), followed by Higuchi's equation (r^2 = 0.984). As the drug release was best fitted in first order kinetics, indicating that the rate of drug release is concentration dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases.

Table 6: Drug Release Kinetics of Batch (F12) Matrix Tablets*

Zero order	First order	Higuchi	Korsmeyer-Peppas	
r^2	r^2	r^2	r^2	N
0.926	0.821	0.977	0.981	0.59

* r^2 = Correlation coefficient ; n= Diffusional exponent.





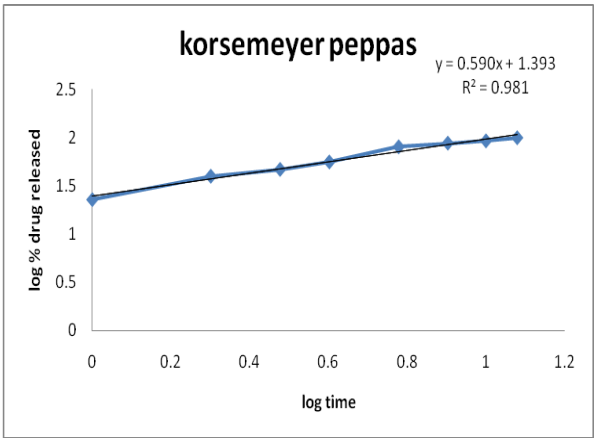


Figure 9: dissolution kinetics Graph of Optimized Formulation (F3).

CONCLUSION

Sustained release tablets were compressed without any problem and do not require any change in ratio of excipients in formulation. Results of the present study demonstrated that polymers could be successfully employed for formulating sustained-release matrix tablets of ambroxol hydrochloride. All the formulations containing drug to polymer ratio and MCC as a diluent extended the drug release for 8 to 12 hours. The drug release rate was slower with the tablets containing hydrophilic HPMC K100M compared to with that of carbopol 940.Majority of formulations have released the drug by non-Fickian diffusion.Optimized formulation F3 which includes HPMC K100M has successfully sustained the drug release for 12 hours.The release process involves anomalous diffusion mechanism or diffusion coupled with erosion, as indicated by the n value of 0.59 in Korsmeyer's plot.

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