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Research Article

# Preparation and Evaluation of Matrix Tablets Containing Ambroxol Hydrochloride

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## ABSTRACT

Purpose: This study aimed to formulate Ambroxol hydrochloride SR matrix tablets using xanthan gum (natural polymer) and to elucidate the release kinetics of Ambroxol hydrochloride from xanthan gum-matrices. Methods: controlled release matrix tablets of ambroxol hydrochloride, a mucolytic expectorant were prepared by wet granulation method using xanthan gum as natural hydrophilic polymer in three different ratios (Drug : Polymer 1:1(F-1), 1:1.5(F-2), 1:2(F-3)). The prepared granules of three different formulations were evaluated for angle of repose, bulk density (BD), tapped density (TD) and compressibility index (CI), hausners ratio. The prepared tablets were tested for physical parameters like weight variation, hardness, friability, content of active ingredient and In-vitro drug release studies. Results: The results obtained were within the prescribed limits. The release of ambroxol from the matrix tablets was sustained up to 12hrs. The cumulative percentage of drug release was decrease with increase in polymer concentration. Among the three formulations F-3 gave the release profile close to the commercially available marketed sample of ambroxol Hcl (A-MS).The results indicate that the drug release from the matrix tablets followed Zero order kinetics. The dissolution data was fitted to Korsmeyer equation which is used to describe the drug release behaviour from polymeric systems. All the formulations showed diffusion co-efficient value (n) greater than 0.43 but less than 0.85 after fitting to the Korsmeyer equation. So, it indicates Non-Fickian transport mechanism. Therefore the drug release is by diffusion and erosion mechanism. Conclusion: Matrix tablets of Ambroxol Hydrochloride using xanthan gum prepared by wet granulation method were found to be good in appearance. The drug-polymer ratio was found to influence the release of drug from the formulations. Formulation F-3 i.e. (1:2 drug: polymer) exhibited the similar In-vitro drug release rates as that of the marketed sample.

**Keywords:** Ambroxol hydrochloride, xanthan gum, Micro crystalline cellulose, Starch, Talc, Magnesium stearate

## INTRODUCTION

For many decades treatment of acute diseases or chronic illnesses have been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, suppositories, creams, ointments, liquids, aerosols and injectables. Even today these conventional dosage forms are the primary pharmaceutical vehicles commonly seen in the prescription and over the counter drug market. The oral conventional types of drug delivery systems are known to provide a prompt release of the drug. Therefore to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This results in a

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significant fluctuation in drug levels often with a sub-therapeutic and or toxic levels and wastage of drug. Recently several technical advancements have resulted in the development of new systems of drug delivery capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drug to a tissue [1]. The term controlled release implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and a known mechanism of release. This means that the release of drug ingredient(s) from a controlled release drug delivery system proceeds at a rate that is not only predictable kinetically but also reproducible from one unit to another. In other words, the system attempts to control drug concentration in the target tissue. This correctly suggests that there are sustained-release systems that cannot be considered controlled-release systems. On the other hand the term sustained-release is usually used to describe a pharmaceutical dosage form formulated such that the liberation of the drug in the systemic circulation is prolonged over time resulting in plasma profile, which is sustained in duration [2]. Repeat-action tablets are an alternative method of sustained release in which the multiple doses of the drug are contained within a dosage form and each other released at a periodic interval. Delayed release system in contrast, may not be sustaining, since often the function of the dosage form is to maintain the drug within the dosage form for some times before release. Commonly the release rate of drug is not altered and does not result in sustained delivery once drug release has began [3]. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

Controlled release drug delivery systems are designed by different techniques like enteric coating, osmotic pump, prodrugs, transdermal patches and matrix tablets. Among the various techniques used, recently the attention of pharmaceutical researchers has been attracted by the matrix tablets because of their ease of manufacturing. Different types of polymers are used to control the release of drugs from the dosage forms for absorption by the body. Though a variety of polymeric substances are available to serve as release retarding matrix materials there is a continued need to develop new, safe and effective release retarding materials for matrix tablets. Natural gums and polysaccharides and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms due to their non-toxicity, low cost and free availability. Natural gums and hydrophilic polymers and where in contact with water, their hydrated to form a gel. Because of this property natural gums like gum karaya, xanthan gum and olibanun gum have been reported as good matrix materials for sustained release dosage forms.

Xanthan gum is compatible with variety of active ingredients and other excipients and readily hydrates, absorb water and swell quickly. Because of their hydrophilic nature and highly cross-linked structure they are more suitable candidates for use in controlled release drug delivery systems.

Ambroxol is a metabolite of bromohexine with similar action and uses. It is chemically described as trans-4[(2-amino-3, 5-dibromo benzyl)] amino]-cyclohexanol. It has been successfully used for decades in the form of its hydrochloride as a secretion-releasing expectorant in a variety of respiratory disorders. It's short biological half life (4hrs) that calls for frequently daily dosing (2 to 3 times) and therapeutic use in chronic

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respiratory diseases necessitates its formulation into sustained release dosage form.

The objective of the present study was to formulate Ambroxol hydrochloride SR matrix tablets using xanthan gum (natural polymer) and to elucidate the release kinetics of Ambroxol hydrochloride from xanthan gum-matrices. Here, an attempt was made to develop sustained release Ambroxol hydrochloride matrix tablets

Hence, the objectives of the present work include

1. Preparation of ambroxol hydrochloride matrix tablets using xanthan gum in three different drug to polymer ratios [1:1 (F-1), 1:1.5 (F-2), 1:2 (F-3)] by wet granulation method.
2. Preformulation testing of the prepared granules for bulk density, tapped density, compressibility index, angle of repose and Hausners ratio
3. Evaluation of the prepared matrix tablets includes

a) Physical parameters like hardness, friability, weight variation and drug content estimation.
b) In-vitrodissolution studies

## MATERIALS AND METHODS

Table-1 List of materials used in the present work

| S.NO | Materials used | Source |
|---|---|---|
| 1. | Ambroxol hydrochloride | Hetero laboratories,Hyderabad |
| 2. | Xanthan gum | Hetero laboratories,Hyderabad |
| 3. | Micro crystalline cellulose | Aurobindo Pharma Pvt Ltd,Hyderabad |
| 4. | Starch | Aurobindo Pharma Pvt Ltd,Hyderabad |
| 5. | Talc | Trident Pharma,Hyderabad |
| 6. | Magnesium stearate | Trident Pharma,Hyderabad |

Table-2 List of Instruments used in the present work

| S.no | Equipments | Source |
|---|---|---|
| 1 | Tablet punching machine | SECOR,INDIA |
| 2 | Tablet dissolution apparatus | SECOR,INDIA |
| 3 | Hardness tester, pfizer | SECOR,INDIA |
| 4 | Friabilator | SECOR,INDIA |
| 5 | Double beam UV- VIS Spectrophotometer | SYSTRONICS |
| 6 | pH meter | DIGI SUN ELECTRONICS (model 152-R) |
| 7 | Balance | DHONA,200D |
| 8 | Hot air oven | SISCO |

## EXPERIMENTAL WORK

**Preparation of standard curve of Ambroxol HCl**

Preparation of Reagents[4]

**Preparation of 0.1N HCL:** Dissolve 8.5ml of HCL in sufficient quantity of distilled water in volumetric flask and make up the volume up to 1000ml.

**Preparation of phosphate buffer pH 6.8**: Dissolved 50.0ml of 0.2M potassium dihydrogen phosphate in 200ml volumetric flask. 39.1ml of 0.2M Sodium hydroxide was added and the volume was made upto 200 ml with distilled water.

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**Standard plot of Ambroxol hydrochloride with 0.1N HCL**

100mg of Ambroxol hydrochloride was dissolved in 0.1N Hcl and make up the volume upto 100ml. From this stock solution pipette out 1ml and make up to 100ml from this solution 1, 1.5, 2, 2.5, 3, 3.5, 4ml was pippeted out and the volume was made up to 100ml with 0.1N Hcl. This gives the concentrations of 10, 15, 20, 25, 30, 35, 40 µgm/ml. The absorbances of the solutions were measured at 244nm using ELICO UV-Visible spectrophotometer.

**Standard plot of Ambroxol hydrochloride with pH6.8**

100mg of Ambroxol hydrochloride was dissolved in pH6.8 and make up the volume upto 100ml, from this stock solution pipette out 1ml and make up to 100ml. From this solution 1, 1.5, 2, 2.5, 3, 3.5, 4ml was pippeted out and the volume was made up to 100ml with pH6.8. This gives the concentrations of 10, 15, 20, 25, 30, 35, 40 µgm/ml. The absorbance of the solutions were measured at 244nm using ELICO UV-Visible spectrophotometer.

**Granulation Properties**

Certain methods are used to measure granulation characteristics in order to monitor granulation suitability for tableting. Good flow properties are essential for the transport of the material through the hopper into and through the feed frame and in to dies.

**Angle of repose** [5]

The frictional force in a loose powder can be measured by the angle of repose θ. It is defined as, the maximum angle possible between the surface of the pile of the granules and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. The angle of repose was determined by the funnel method suggested by Newman. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated using the following formula

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

Therefore: $\theta = \tan^{-1}(h/r)$

Where,

θ = Angle of repose

h = Height of the cone

r = Radius of the cone base

Table-3 Flow Properties and Corresponding Angle of Repose

| Flow Property | Angle of Repose (Degrees) |
|---|---|
| Excellent | 25 – 30 |
| Good | 31 -35 |
| Fair (aid not needed) | 36 – 40 |
| Passable (may hang up) | 41 – 45 |
| Poor (must agitate, Vibrate) | 46 – 55 |
| Very poor | 56 – 65 |
| Very, Very poor | > 66 |

**Bulk Density** [5] Density is defined as weight per unit volume. Bulk density $P_b$ is defined as the mass of the powder divided by the bulk volume and is expressed as $gm/cm^3$. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. There are two types of bulk density.

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The particles are pack in such a way so as to leave large gaps between their surfaces resulting up in light powder of low bulk density. Here the smaller particles shift between the large particles resulting in heavy powder of high bulk density. Bulk density is very important in the size of containers needed for handling, shipping and storage of raw material and blend. It is also important in size blending equipment Apparent bulk density ($P_b$) was determined by pouring blend into a graduated cylinder. The bulk volume ($V_b$) and weight of the powder (M) was determined. The bulk density was calculated by using the following formula

$$P_b = M / V_b$$

Where,
$P_b$= Bulk Density
M = Weight of sample in gm
$V_b$= Final volume of blend in $cm^3$

**Tapped Density** [5]
It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. The tapped density was calculated by using the following formula

$$P_t = M / V_t$$

Where,
$P_t$= Tapped Density
M= Weight of the sample in gm
$V_t$= Tapped volume of blend in $cm^3$

**Compressibility Index and Hausners ratio**[6]
In recent years, the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and the Hausner ratio are determined by measuring both the bulk volume and tapped volume of a powder.

**Basic methods for the determination of compressibility Index and Hausner Ratio** [5]
While there are some variations in the method of determining the compressibility index and Hausner ratio, the basic procedure is to measure the unsettled apparent volume ($V_0$), and the final tapped volume ($V_f$), of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner ratio are calculated as follows

$$Compressibility\ Index = 100 \times \frac{V_0 - V_f}{V_0}$$

$$Hausner\ Ratio = \frac{V_0}{V_f}$$

Alternatively, the compressibility index and Hausner ratio may be calculated using measured values of bulk density and tapped density as follows ,

Compressibility Index= 100 × Tapped density / Bulk density

Hausner Ratio= Tapped density/ Bulk density

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to, the change in volume that occurs on tapping. For the compressibility index and the Hausner ratio, the generally accepted scale of flow ability is described by carr. The values are tabulated in the below table – 4.

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Table: 4 Scale of Flow ability

| Compressibility Index (%) | Flow Character | Hausner Ratio |
|---|---|---|
| 1 – 10 | Excellent | 1.00 – 1.11 |
| 11 – 15 | Good | 1.12 – 1.18 |
| 16 – 20 | Fair | 1.19 – 1.25 |
| 21 – 25 | Passable | 1.26 – 1.34 |
| 26 – 31 | Poor | 1.35 – 1.45 |
| 32 – 37 | Very Poor | 1.46 – 1.59 |
| > 38 | Very, Very Poor | > 1.60 |

**Preparation of Matrix Tablets**

Matrix tablets of Ambroxol Hcl using xanthan gum in different proportions were prepared by wet granulation method using 1:1 ratio of methanol and water mixture microcrystalline cellulose (MCC) was used as diluent. The composition of different formulations used in the study is given in table-5. The weighed quantities of medicaments and matrix materials were mixed thoroughly in a mortar by following geometric dilution technique. The 1:1 ratio of methanol and water mixture was added and mixed thoroughly to form a wet mass. The mass was passed through a sieve no.16 to obtain wet granules. The wet granules were dried at 50ºC for 30 minutes. Dried granules were passed through sieve no.21 to remove the aggregates. These granules were lubricated with a mixture of talc and magnesium stearate (2:1). The lubricated granules were compressed into tablets on a rotary multi-station tableting machine with required hardness using 9 mm round and flat punches.

Table 5: Formula for formulation of matrix tablets

| S.NO | INGREDIENTS | F-1 (1:1) | F-2 (1:1.5) | F-3 (1:2) |
|---|---|---|---|---|
| 1. | Ambroxol Hcl | 75mg | 75mg | 75mg |
| 2. | Xanthan gum | 75mg | 112.5mg | 150mg |
| 3. | Microcrystalline cellulose | 80mg | 42.5mg | 5mg |
| 4. | Starch | 12.5mg | 12.5mg | 12.5mg |
| 5. | Talc | 5.0mg | 5.0mg | 5.0mg |
| 6. | Magnesium stearate | 2.5mg | 2.5mg | 2.5mg |
| | Total Weight | 250mg | 250mg | 250mg |

**Evaluation of Tablets**

The prepared matrix tablets were evaluated forGeneral appearance, thickness, hardness, weight variation, friability and drug content.

**General appearance**

The tablets prepared were white, round, spherical shape. They were smooth, uniform and free from cracking and chipping.

**Hardness test** [7]

Hardness (diametral crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The permissible limit for hardness is 4-7kg/cm$^2$. Thehardness was tested usingMonsanto tester. “Hardness

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factor", the average of the five determinations was determined and reported.

**Uniformity of weight (Weight variation test)** [8]

This is an important In-process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablet (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weight. 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (7.5%). The percent deviation was calculated using the following formula.The limits are mentioned in the below table as per Indian pharmacopoeia (I.P)

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

| Average weight | Percent difference |
|---|---|
| 130mg or less | 10 |
| More than 130mg but less than 324mg | 7.5 |
| More than 324mg | 5 |

**Friability test** [8]

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This In-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Five tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability wasdetermined using the following formula

$$(W_1 - W_2)/W_1 \times 100$$

Where,

$W_1$ = weight of the tablets before test

$W_2$ = weight of the tablets after test

**Content of active ingredient** [8]

To ensure the consistency of dosage units, each unit in a batch should have active substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of an active substance in each dosage unit.

Ten tablets from each formulation were powdered. The powder equivalent to 100 mg of ambroxol was weighed and dissolved in phosphate buffer pH 6.8 in 100 ml standard flask. From this 10 µg/ml, equivalent solution was prepared and analyzed at 244 nm using UV-visible Spectrophotometer. Generally, the drug content in any formulation should fall within the limit of 90 – 110%.

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***In-vitro* drug release studies** [8]

In-vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 12hrs, at 100 rpm, 0.1 N HCL was used as a dissolution medium for first 2hrs followed by pH 6.8 ± 0.2 phosphate buffer for further 10hrs. 10ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and concentration of drug in each sample was analyzed by UV/Visible Spectrophotometer at 244 nm and cumulative percent drug release was calculated. The study was performed in triplicate .The commercial Ambroxol SR tablets were used as the reference formulation, and were also subjected to In-vitro drug release studies.

The results of *In-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows.

1. Log cumulative percent drug remaining versus time (firstorder kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchis model)
3. Log cumulative percent drug release versus time (zero order kinetic model)
4. Log cumulative Percent Drug released versus log time (korsmeyers model)

**Drug release kinetics-model fitting of the dissolution Data** [9-17]

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Nowadays the pharmaceutical industry and the registration authorities focus on drug dissolution studies. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some analyticaldefinitionsof the Q (t) function are commonly used such as zero order, first order, Higuchi, korsmeyers models. Other release parameters, such as dissolution time ($t_{x\%}$), dissolution efficacy (ED), difference factor ($f_1$), similarity factor ($f_2$) can be used to characterize drug dissolution / release profile.

**Zero-order kinetics:**

A zero-order release would be predicted by the following equation:

$At = A_o - K_o t$ ..... 1

Where,

At = Drug release at time t

$A_o$ = Initial drug concentration

$K_o$ = Zero-order rate constant (hr)

When the data is plotted as cumulative percent drug release versus time if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to $k_o$

**Use**: This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in case of some transdermal systems etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

**First-order kinetics:**

A first order release would be predicted by the following equation:

$Log\ C = Log\ Co - K_t / 2.303$ ..... 2

Where

C = Amount of drug remained at time t

$C_o$ = Initial amount of drug

K = First-order rate constant

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line indicating the release follows first-order kinetics, the constant k can be obtained by multiplying 2.303 with slope values

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**Use:** The pharmaceutical dosage forms containing water-soluble drugs in porous matrices, follows this type of dissolution profile. The release of the drug is proportional to the amount of drug remaining in its interior so that the amount of drug release by unit of time diminishes.

**Higuchi model**

Drug release from the matrix devices by diffusion has been described by following higuchis classical diffusion equation.

$Q = [DE/ \tau(2A- ECs) C_{st}]$ ..... 3

Where

Q = Amount of drug release at time t

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

$C_s$ = The solubility of the drug in the matrix

E = Porosity of the matrix

T = Time in hrs at which q is the amount of drug is release

Equation-3 may be simplified if one assumes that D, Cs and A are constant. Then equation-3 becomes

$Q = K_t ½$

When the data is plotted according to equation-4 i.e. cumulative drug release versus Square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to k.

**Use**

The relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in case of some water soluble drugs

**Korsmeyer model**

In order to understand the mode of release of drug from swellable matrices, the data were fitted to the following equation

$$M_t / M_á = Kt^n$$

Where,

$M_t / M_á$ = The fraction of drug released at time't'

K= Constant incorporating the structural and geometrical Characteristics of the drug / polymer system.

n= Diffusion exponent related to the mechanism of release.

The above equation can be simplified by applying log on both sides we get

$\text{Log } M_t / M_á = \text{Log } K + n \text{ Log } t$

When the data is plotted as a log of drug released versus log time, yields a straight line with a slope equal to n and the k can be obtained from y- intercept.

The value of n for a cylinder is <0.45 for fickian release, > 0.45 and < 0.89 for non-fickian release, 0.89 for the case 2 release and > 0.89 for super case2 type release.

**RESULTS**

Table -6: Standard plot of Ambroxol Hcl in 0.1NHCL Buffer at λmax 244nm

| S.NO | CONCENTRATION (µgm/ml) | ABSORBANCE nm |
|---|---|---|
| 1. | 10 | 0.340 |
| 2. | 15 | 0.511 |
| 3. | 20 | 0.672 |
| 4. | 25 | 0.847 |
| 5. | 30 | 1.021 |
| 6. | 35 | 1.204 |
| 7. | 40 | 1.352 |

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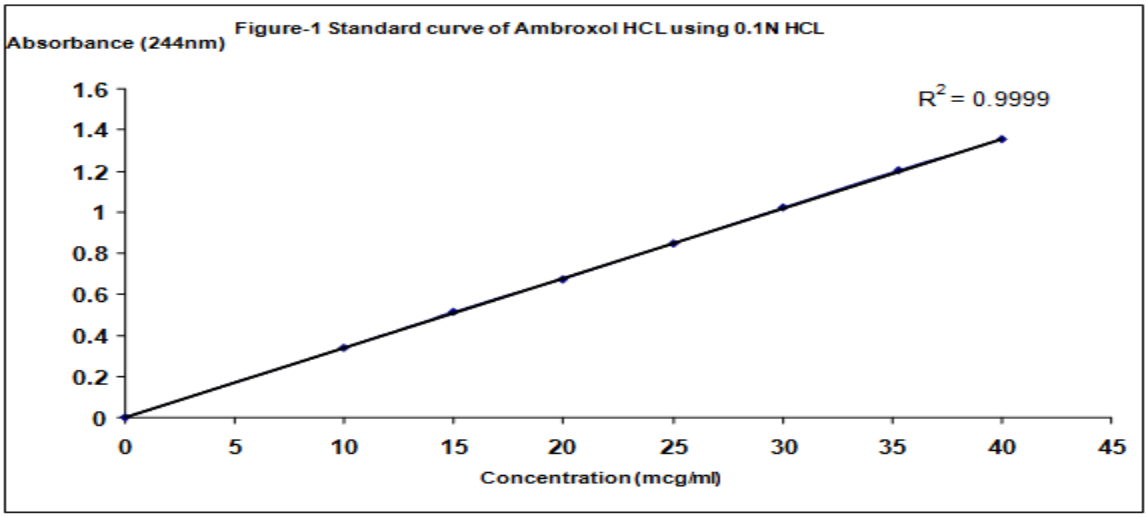


Table – 7: Standard plot of Ambroxol Hcl in pH6.8 Buffer at λmax 244nm

| S.NO | CONCENTRATION(µgm/ml) | ABSORBANCE nm |
|---|---|---|
| 1. | 10 | 0.385 |
| 2. | 15 | 0.576 |
| 3. | 20 | 0.770 |
| 4. | 25 | 0.960 |
| 5. | 30 | 1.146 |
| 6. | 35 | 1.342 |
| 7. | 40 | 1.526 |

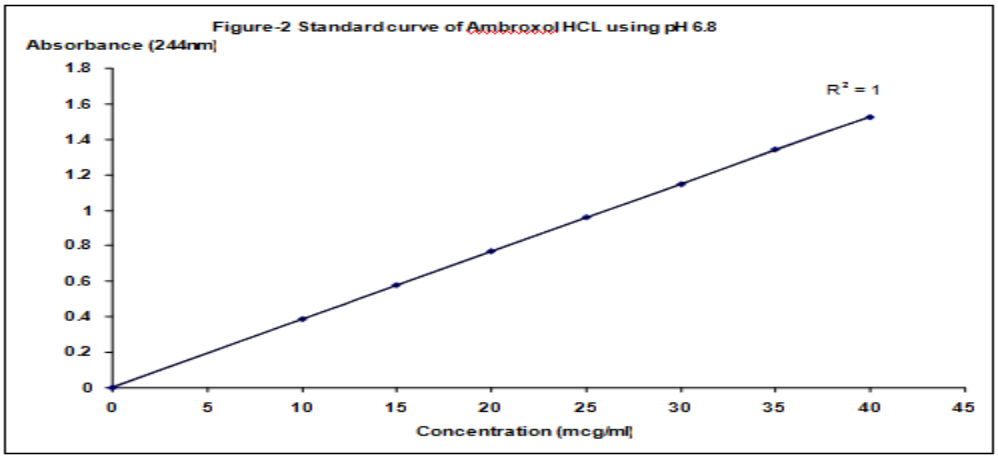

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Table-8 Micrometric Properties of Granules

| Formulation code | Angle of Repose | Bulk Density (g/ml) | Tapped Density (g/ml) | Hausners Ratio | Compressibility Index (%) |
|---|---|---|---|---|---|
| F – 1 | 27.22 ± 1.86 | 0.336 ± 0.037 | 0.352 ± 0.009 | 1.15 ± 0.026 | 12.88 ± 1.54 |
| F – 2 | 27.09 ± 1.77 | 0.524 ± 0.008 | 0.516 ± 0.058 | 1.14 ± 0.020 | 13.13 ± 0.88 |
| F - 3 | 27.33 ± 1.212 | 0.432 ± 0.009 | 0.576 ± 0.014 | 1.15 ± 0.021 | 12.42 ± 1.52 |

*****Average of three observations
*All the values are expressed as mean ± SE

Table-9 Physico-Chemical Evaluation of Tablets

| Formulation Code | Weight Variation (mg) (n=20) | Hardness ($kg/cm^2$) (n=5) | Friability (%) (n=5) | Content of the Active Ingredient (%) (n=5) |
|---|---|---|---|---|
| F – 1 | 248.6 ± 1.52 | 4.5 ± 0.14 | 0.6 ± 0.14 | 97.1 ± 0.5 |
| F – 2 | 248.0 ± 1.414 | 4.9 ± 0.09 | 0.4 ± 0.353 | 98.5 ± 0.98 |
| F – 3 | 250.1 ± 1.01 | 5.3 ± 0.070 | 0.1 ± 0.152 | 99.4 ± 0.92 |

All the values are expressed as mean ± SE

Table-10 *In-Vitro* Drug Release Profile of Ambroxol hydrochloride Matrix Tablets

| S.No | Time (hrs) | Cumulative Percentage Drug Release | | | |
|---|---|---|---|---|---|
| | | F -1 | F - 2 | F - 3 | A - MS |
| 1. | 00.30 | 23.14 ± 0.43 | 21.33 ± 0.48 | 17.46 ± 0.60 | 15.86 ± 0.20 |
| 2. | 01.00 | 26.54 ± 0.35 | 28.33 ± 0.20 | 25.50 ± 0.35 | 26.10 ± 0.45 |
| 3. | 01.30 | 35.60 ± 0.20 | 34.53 ± 0.35 | 31.27 ± 0.35 | 28.15 ± 0.31 |
| 4. | 02.00 | 40.01 ± 0.56 | 40.24 ± 0.35 | 35.50 ± 0.54 | 33.24 ± 0.24 |
| 5. | 03.00 | 42.72 ± 0.35 | 41.45 ± 0.31 | 39.50 ± 0.30 | 40.09 ± 0.07 |
| 6. | 04.00 | 48.93 ± 0.31 | 48.09 ± 0.17 | 46.41 ± 0.02 | 46.11 ± 0.41 |
| 7. | 05.00 | 57.22 ± 0.31 | 53.69 ± 0.31 | 52.15 ± 0.32 | 51.78 ± 0.22 |
| 8. | 06.00 | 61.96 ± 0.29 | 60.66 ± 0.18 | 59.60 ± 0.32 | 58.99 ± 0.51 |
| 9. | 07.00 | 68.20 ± 0.36 | 66.64 ± 0.36 | 65.25 ± 0.26 | 65.28 ± 0.32 |
| 10 | 08.00 | 74.39 ± 0.31 | 72.82 ± 0.32 | 70.92 ± 0.52 | 71.25 ± 0.01 |
| 11 | 09.00 | 80.67 ± 0.31 | 78.46 ± 0.03 | 76.49 ± 0.46 | 77.50 ± 0.25 |
| 12 | 10.00 | 86.96 ± 0.31 | 85.48 ± 0.46 | 83.08 ± 0.47 | 84.13 ± 0.36 |
| 13 | 11.00 | 92.62 ± 0.30 | 91.95 ± 0.04 | 89.13 ± 0.27 | 89.18 ± 0.54 |
| 14 | 12.00 | 99.23 ± 0.27 | 98.35 ± 0.19 | 97.02 ± 0.31 | 97.30 ± 0.03 |

*A-MS : Ambroxol Marketed Sample
*All the values are expressed as mean ±SE, n=3

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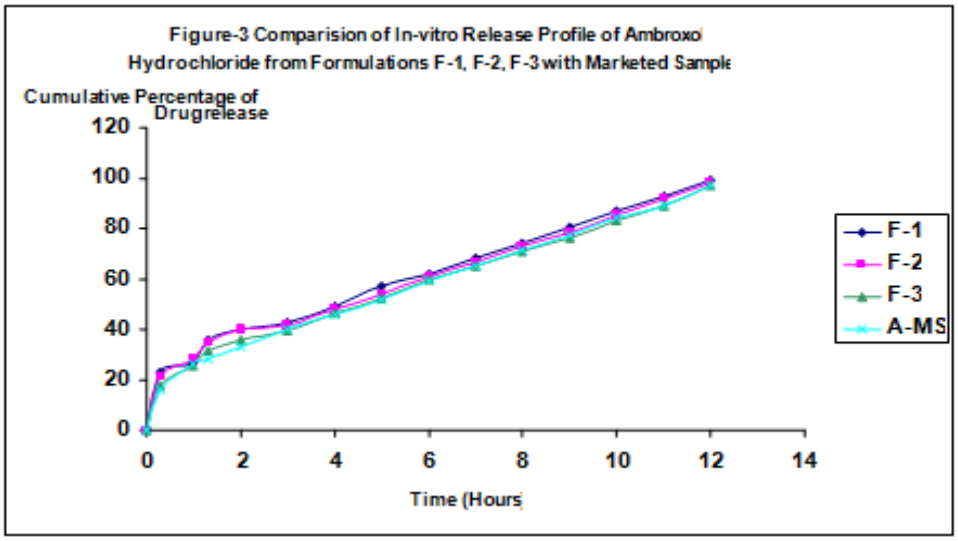


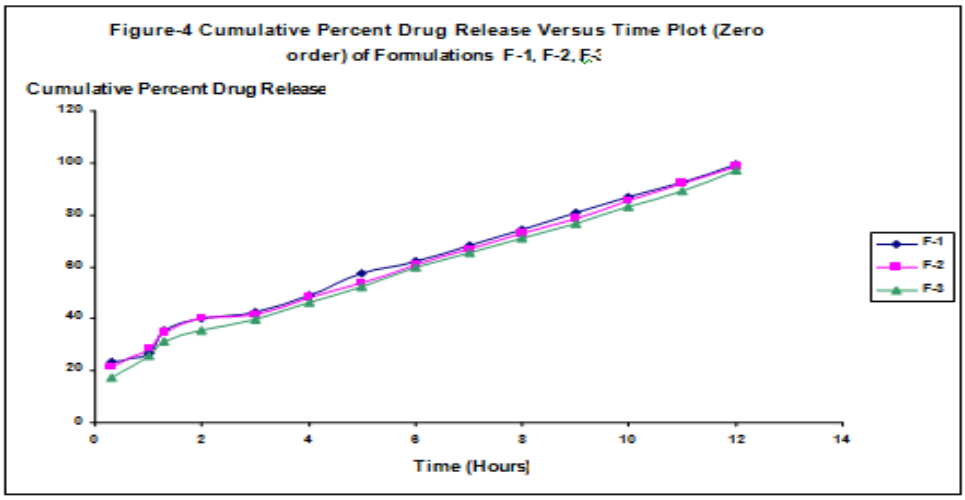


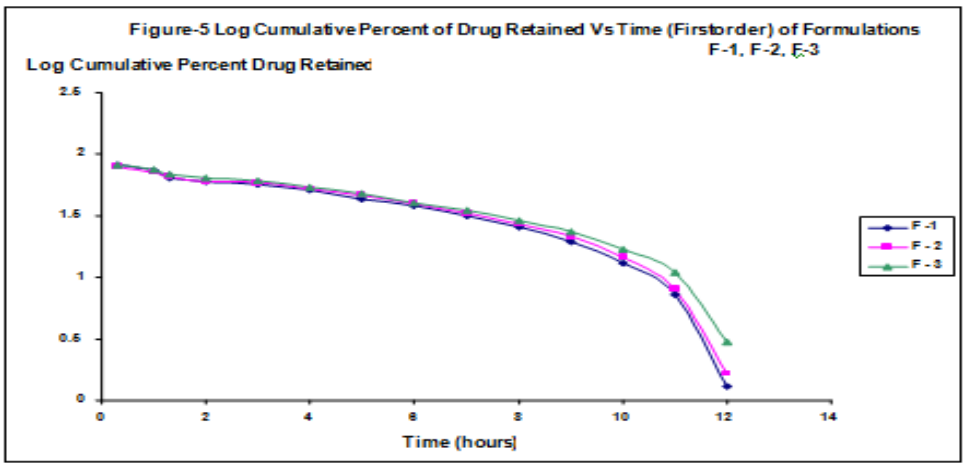

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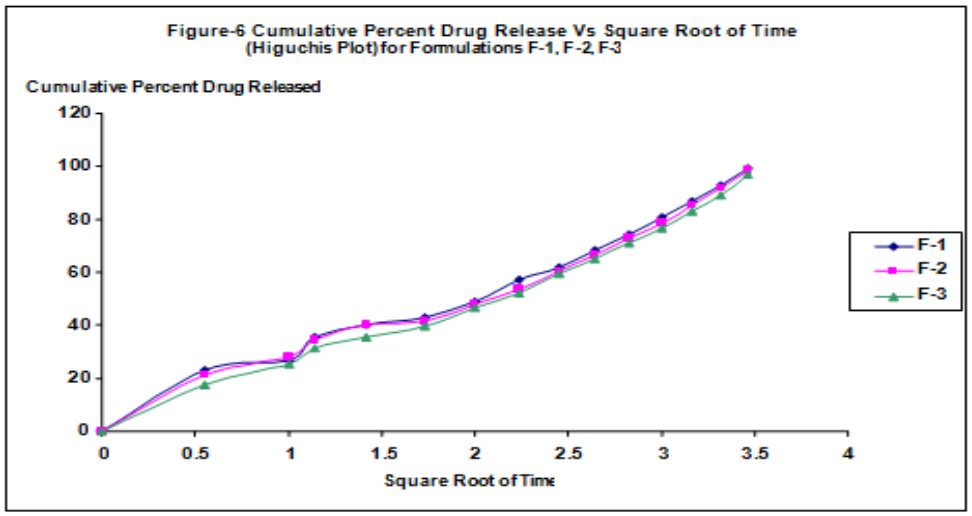


Table -11: Mathematical modeling and drug Release Mechanisms of Ambroxol Hcl Matrix Tablets [Formulated and Marketed Sample]

| Formulation code | Correlation Coefficient (r) Value | | | Korsmeyers – Peppas Plot | |
|---|---|---|---|---|---|
| | Zero order | First order | Higuchi equation | Slope (n) | Correlation Co-efficient |
| F – 1 | 0.9540 | 0.7442 | 0.9727 | 0.501 | 0.7419 |
| F – 2 | 0.9950 | 0.7864 | 0.9786 | 0.523 | 0.7386 |
| F – 3 | 0.9661 | 0.8302 | 0.9760 | 0.701 | 0.7205 |
| A – MS | 0.9718 | 0.8443 | 0.9796 | 0.706 | 0.5034 |

*A-MSAmbroxol hydrochloride Marketed Sample.

## DISCUSSION

In the present work, an attempt has been made to prepare controlled release matrix tablets of ambroxol hydrochloride, a mucolytic expectorant by wet granulation method using xanthan gum as natural hydrophilic polymer in three different ratios (Drug : Polymer 1:1, 1:1.5, 1:2)

The prepared granules of three different formulations were evaluated for angle of repose, bulk density (BD), tapped density (TD) and compressibility index (CI), hausners ratio. This was further supported by lower compressibility index values table-8. Generally CI values up to 15% results in good to excellent flow properties

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The prepared tablets were tested for physical parameters like weight variation, hardness, friability, content of active ingredient and *In-vitro* drug release studies. The results of all these evaluation are tabulated in the table-9. The results obtained were within the prescribed limits.

The release of ambroxol from the matrix tablets was sustained up to 12hrs. The cumulative percentage of drug release from the different formulations of F-1, F-2 and F-3 was shown in the table-10. The cumulative percentage of drug release was decrease with increase in polymer concentration. Among the three formulations F-3 gave the release profile close to the commercially available marketed sample of ambroxol Hcl (A-MS).

The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. Increase in the concentration of the polymer results in a decrease in cumulative percentage drug release. This may be due to structural reorganization of hydrophilic xanthan gum polymer. Increase in concentration of Xanthan gum may result in increase in the Tortuosity or gel strength of the polymer. Failure to generate a uniform and coherent gel may cause rapid drug release.

The release data of matrix tablets were fitted into various mathematical models (Zero order, First order, Higuchi equation and korsmeyersequation) to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation co-efficient(r) value in various models. The model that gives high "r" value is considered as the best fit of the release data. The "r" values for zero order, first order, Higuchi model and korsmeyers plot are given in table-11. The results given in table-11 indicate that the drug release from the matrix tablets followed Zero order kinetics.

Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. To evaluate drug release mechanism from the tablets, plots of percent released versus square root of time as per Higuchi's equation were constructed. All the formulations show better linearity for Higuchi release kinetics with ($r^2$>0.97). It indicates that the drug release is by diffusion mechanism.

The dissolution data was fitted to Korsmeyer equation which is used to describe the drug release behaviour from polymeric systems. Plots of Log cumulative percent drug release versus log time gives $r^2$ values. The values of n<0.43 indicates Fickian release, >0.45 but <0.85 indicates Non-Fickian release. All the formulations showed diffusion co-efficient value (n) greater than 0.43 but less than 0.85 after fitting to the Korsmeyer equation as shown in the table-12. So, it indicates Non-Fickian transport mechanism. Therefore the drug release is by diffusion and erosion mechanism.

## CONCLUSION

From the present study, the following conclusions are drawn. Matrix tablets of Ambroxol Hydrochloride using xanthan gum prepared by wet granulation method were found to be good in appearance. The granules showed satisfactory flow properties and compressibility index. Quality control tests were performed for prepared tablets and they are within the prescribed limits as per I.P specifications. The drug content was uniform in all the formulations of tablets prepared. The results indicate uniform distribution of drug within the matrices. The drug-polymer ratio was found to influence the release of drug from the formulations. As the polymer level is increased, the drug release rates were found to be

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decreased. Drug release was found to follow zero order kinetics and the mechanism of drug release was found to be diffusion and erosion. Formulation F-3 i.e. (1:2 drug: polymer) exhibited the similar *In-vitro* drug release rates as that of the marketed sample.

## FUTURE PROSPECTS

Comparative study of natural polymers such as xanthan gum, guar gum, olibanum resin can be performed; Scope for further *In-vitro* studies and *Invitro-Invivo* correlation, Stability studies can be performed.

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