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A review article on Sustained Release tablets of Theophylline & Etophylline and its formulation Aspects

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ABSTRACT-The sustained release matrix tablet of Theophylline and Etophylline in Different grades of hydroxypropyl methyl cellulose were evaluated for gel forming properties. Differential Scanning Calorimeter (DSC) study shows that drug and other excipients are compatible with each other. The effects of polymers concentration on drug release profile were investigated. A 32 full factorial design was applied to systemically optimize the drug release profile. The amounts of HPMC K-4M (X1) and HPMC K-100M (X2) were selected as independent variables. Cumulative percentage release of drug for 1st hour and 8th hour were selected as dependent variables. The results of the full factorial design indicated that a low amount of HPMC K-100M and a high amount of HPMC K-4M favors sustained release of Theophylline from matrix tablet. Accelerated stability study was also performed for three months indicated that optimized formulation was stable. Finally, process optimization was carried out to optimize the process parameters like kneading time, mixing time, thickness of the tablet and lubrication time.

Keywords: Sustained release, Theophylline, Etophylline Matrix tablet, HPMC(Hydroxy propyl Methyl cellulose).

I. INTRODUCTION

Sustained release formulation – an initial release of drug sufficient to provide a therapeutic dose soon after administration and then a gradual release over a extended period ,describe the slow release of a drug substance from a dosage form to maintain therapeutic response for extended period for about 8-12 hr of time with minimum side effects[1] .
Sustained generally do not follow zero order kinetic pattern, usually do not contain mechanical to provide localization of the drug at active site.

Basic concept of sustained release- The concept of sustained release formulation can be divided into 2 consider

1- Release rate-
2- Dose consideration

Advantage-

1- Reduction in frequency
2- Reduction in healthcare cost
3- Reduce nursing and hospitalizing time
4- Reduction in blood level fluctuation of the drug ,thus the better management of disease
5- Maximum bioavailability with minimum dose
6- Minimizes the accumulation of drugs with chronic disease
7- Reduction in healthcare cost

Disadvantage-

1- Reduced potential for dose adjustment of drug normally administered in varying strength
2-Cost of the single unit dosage form is higher than that of conventional dosage form
2- Increased potential for first-pass metabolism
3- Requirement of additional patient education for proper medication
4- Retrieval of drugs is difficult in case of toxicity poisoning and hypersensitivity reaction

Therapeutic uses of Theophylline & Etophylline-

Theophylline is used to treat lung diseases such as asthma and COPD (Chronic obstructive Pulmonary Disease). It must be used regularly to prevent wheezing and shortness of breath.
Dose- 300-400 mg per day

Factor influencing sustained release-

1- Drug properties
2- Route of drug delivery
3- Target site
4- Acute or chronic therapy
5- The disease
6- Patients[3]

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The desired biopharmaceutical properties of a drug to be used in a sustained drug delivery system are discussed below:-

Molecular weight: Lower the molecular weight faster and more complete will be the absorption. For the drugs absorbed by the pore transport mechanism, the molecular size threshold is 150 Daltons for spherical compounds and 400 Daltons for linear compounds. The upper limit for the molecular size is 600 Daltons for passive diffusion.

Aqueous solubility of the drug: Drugs with good aqueous solubility are good candidates for sustained release dosage form rather than the candidates having poor aqueous solubility.

The apparent partition coefficient of the drug: Greater the apparent partition coefficient of the drug, the greater is the rate and extent of absorption.

Drug pk_a and ionization at physiological pH: The pka range for acidic drugs is 3.0-7.5 and that for basic drugs is 7.0-11.0. The aqueous solubility of weak acids and bases is governed by the PKA of the compound and the pH of the medium. According to pH theory, the absorption of acidic drugs is favored in an acidic environment and that of basic drugs in a basic environment. Hence, the release of the ionizable drugs must be programmed in accordance with pH variations across the GIT. So, the drugs that exist largely in ionized form serve as poor candidates for sustained-release dosage form

Drug stability: Drugs unstable in the GI environments are poor candidates for oral sustained release systems.

Biopharmaceutical aspects of the route of administration: Oral and parental (i.m.) routes followed by transdermal are the most popular. Routes of minor importance in sustained drug delivery are buccal/sublingual, nasal, rectal, ocular, and pulmonary Detailed knowledge of ADME characteristics of the drug is essential in the design of sustained-release products. An optimum range of given pharmacokinetic parameter of a drug is necessary beyond which controlled/sustained delivery is difficult[2,4] .

Parameters-

Parameters	Criteria
Molecular size	Less than 600 Daltons
Aqueous solubility	More than 0.1mg/ml
Partition coefficient Ko/w	1-2
Dissociation constant pka	Acidic drugs, pka>2.5 Basic drugs, pka<11.0
Absorption mechanism	Passive
Stability in GI milieu	Stable at both gastric and intestinal pH
Ionization at physiological pH	Not more than 95%

Table 1. Physicochemical parameters for drug selection

Parameters	Comment
Elimination half life	Between 2-6 hrs
Absolute bioavailability	> 75% or more
Absorption rate constant (Ka)	High
Metabolism Rate	Not too High
Total clearance	Should not depend on dose
Therapeutic concentration (Css)	Lower Css and small Vd

Table 2. Pharmacokinetic parameters for drug selection

Matrix Tablet

Matrix tablet is defined as an "Oral solid dosage form in which active pharmaceutical ingredient is uniformly dispersed throughout polymeric matrices (hydrophilic or hydrophobic) which retards the drug release rate.

This approach is widely used for formulating sustained-release tablets. The mechanism involved in the drug release is either dissolution-controlled or diffusion controlled [4].

Advantages of matrix system:

- Easy to manufacture.
- Cost effective.
- Improved patient compliance.
- Sustained release formulations avoid the high blood concentration.
- Reduce drug toxicity by slowing down drug absorption.
- Enhanced drug stability in GI milieu.
- Minimize the local and systemic side effects.
- No see-saw fluctuations in plasma drug concentration profile.
- Less amount of drug is required.

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• Temporal effects can be provided. e.g. morning relief of arthritis through bed time dosing.

Disadvantages of matrix tablets:
• Matrix needs to be removed after drug release.
• Costly in comparison to conventional dosage form.
• Presence of food and gut transition time can affect the release rate .

Classification of Matrix Tablets-
On the basis of the retardant material used matrix can be divided into 5 types:

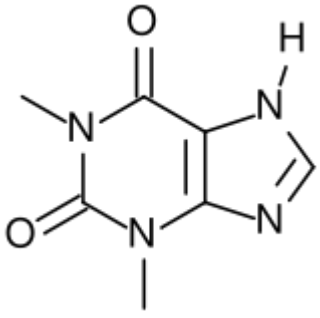
1- Hydrophobic matrices (plastic matrices):
In this technique, hydrophobic inert polymers are used as release retarding matrix material. The drug is mixed with the hydrophobic inert polymer (e.g. polyethylene, polyvinyl chloride, ethyl cellulose) and then compressed into a tablet. The drug is entrapped between the network channels of polymer particles thereby sustaining the release of the drug.

2- Lipid matrices:
Lipid material is used as a release retardant (e.g. carnauba wax in combination with stearyl alcohol). The mechanism involved in drug release includes both pore diffusion and matrix erosion.

3- Hydrophilic matrices:
In this type of system, a variety of hydrophilic polymers can be used, such systems are also known as swellable matrices. These polymers are preferred over former ones as they are cost-effective and a desirable drug profile can be easily obtained.

Classification of hydrophilic polymer matrices:
• **Cellulose derivatives:** Methylcellulose 400 and 4000cPs; Hydroxy ethyl cellulose, Hydroxy propyl methyl cellulose (HPMC) 25, 100, 4000, and 15000cPs, and Sodium carboxy methyl cellulose.
• **Non-cellulose natural and semi-synthetic polymers:** Agar-Agar; alginates; carob gum; molasses; polysaccharides of galactose and mannose; chitosan and modified starches.
• **Polymer of acrylic acid:** carbopol-934.
4- Biodegradable polymers: These consist of biodegradable polymers that are degraded either by enzymatic or nonenzymatic process into products that are excreted out from the body e.g. Polyanhydrides, proteins, polysaccharides.
5- Mineral matrices: Species of seaweeds like alginic acid are used as release retardants

DRUG PROFILE[5]
1. THEOPHYLLINE CHEMISTRY

Structure		
IUPAC NAME	1,3-dimethyl-7H-purine-2,6-dione	
Formula	$C_7H_8N_4O_2$	
Mol. mass	180.164 g/mol	

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PHARMACOKINETIC DATA

Bioavailability	100%
Protein binding	40%, primarily to albumin
Metabolism	hepatic to 1-methyl uric acid
Half life	8 hours

Physicochemical Characteristics

A white crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids.

Stability.

Alcohol-free theophyline liquid repackaged in clear or amber polypropylene oral syringes could be stored at room temperature under continuous fluorescent lighting for at least 180 days without significant change in the concentration of theophyline. However, it was recommended that solutions be protected from the light because of the potential for discoloration.

Extemporaneous oral preparations of theophylline 5 mg/mL in commercial suspension vehicles were found2 to be stable for up to 90 days in amber plastic bottles stored at 23 degrees to 25 degrees[6,7].

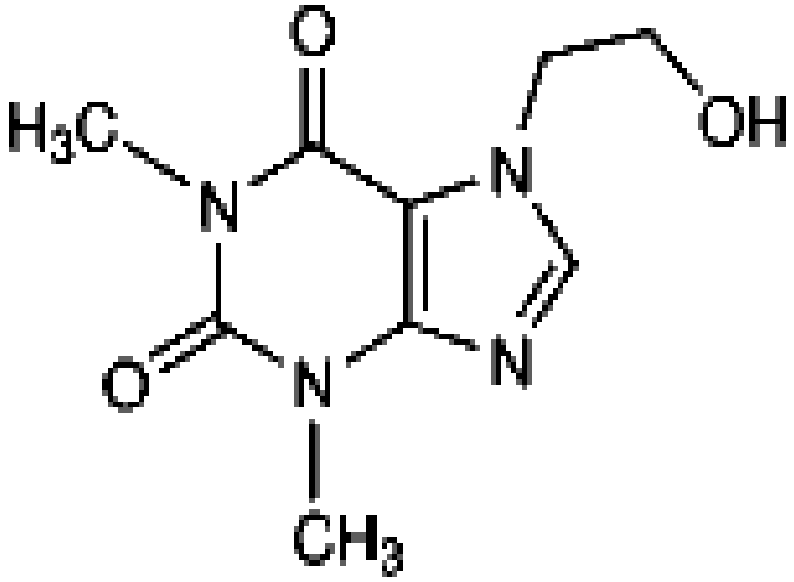
2. ETOPHYLINE CHEMISTRY[8]

Synonyms.Aethophyllinum**;** Hydroxyethyltheophyllinum**;** Oxyetophylline.

Chemical name: 7-(2-Hydroxyethyl)-1,3-dimethylxanthine; 3,7-Dihydro-7-(2-hydroxyethyl)-1,3-dimethyl-1H-purine-2,6-dione; 7-(2-Hydroxyethyl)theophylline

Molecular formula: $C_9H_{12}N_4O_3$ =224.2

Chemical Structure of Etophylline



- A white crystalline powder. Soluble in water; slightly soluble in alcohol. Protect from light.
- M.p. 161° to 166°.
- Freely soluble in water; moderately soluble in ethanol; sparingly soluble in chloroform; practically insoluble in ether.

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- Partition Coefficient**.** - Log P(octanol/water), −0.8.
- Etophylline is a derivative of theophylline that is an ingredient of preparations promoted for respiratory and cardiovascular disorders. It does not liberate theophylline in the body.
- Etophylline nicotinate has also been used.

II. MATERIALS AND METHODS

(1) MATERIALS:-

A. Drug: ETOPHYLINE & THEOPHYLINE was obtained from Arbro Pharmaceuticals Ltd, New Delhi.

B. Chemicals: Chemicals and reagents used for the preparation of buffers, analytical solutions and other experimental purposes are listed in table no 1.

S. No.	Chemicals	Grade	Manufacturer / Supplier
1.	Acetonitrile	HPLC	Merck, Germany
2.	Ammonium thiocynate	AR	S.D. Fine Chemicals
3.	Ammonium di-hydrogen phosphate	AR	S.D. Fine Chemicals
4.	Cobalt(II) Chloride	AR	S.D. Fine Chemicals
5.	Glacial acetic acid	HPLC	Merck, Germany
6.	Methanol	HPLC	Merck, Germany
7.	Ortho-Phosphoric Acid	AR	Ranbaxy Lab. Ltd.
8.	Potassium dihydrogen phosphate (KH_2PO_4)	HPLC	Merck Limited, India
9.	Sodium acetate	HPLC	Merck Limited, India

C. Excipients: - the excipients used in formulation development are listed in table.no 2

S. No.	Excipients	Brand Name	Grade	Supplier/ Manufacturer
1. .	Hydroxy propyl methyl cellulose	Methocel	K 100M Premium	Colorcon, India
2. .	Sodium Alginate	-	-	-
3. .	Colloidal Silicon Dioxide	Aerosil	Aerosil 200	-
4. .	Magnesium Stearate	-	-	-

METHODOLOGY FOR DEVELOPMENT OF SUSTAINED RELEASE TABLET:-

(2.1) Pre formulation studies:

Pre formulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bio available dosage forms that can be man produced.[9-A]

(2.1.1) Organoleptic properties:

- **Colour:** A small quantity of ETOPHYLINE & THEOPHYLINE powder was taken in butter paper and viewed in well-illuminated place.
- **Taste and odour:** Very less quantity of ETOPHYLINE & THEOPHYLINE was used to get taste with the help of tongue as well as smelled to get the order[9]**.**

(2.1.2) Physical characteristics:

- **Loss on drying:**

Determine on 1.000 g by drying in an oven at 100°C to 105°C for 3 hours. Mix and accurately weigh the substance to be tested. If the sample is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Tare a glass stoppered, shallow weighing bottle that

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has been dried for 30 minutes under the same conditions to be employed in the determination. Put the sample in the bottle, replace the cover, and accurately weigh the bottle and the contents. By gentle, sidewise shaking, distribute the sample as evenly as practicable to a depth of about 5 mm. Place the loaded bottle in the drying chamber. Dry the sample at the specified temperature for constant weight. Upon opening the chamber, close the bottle promptly, and allow it to come to room temperature in a desiccator before weighing.
The difference between successive weights should not be more than 0.5 mg.
The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2 - W3)}{(W2 - W1)} \times 100$$

Where, W1 = Weight of empty weighing bottle
W2 = Weight of weighing bottle + sample
W3 = Weight of weighing bottle + dried sample

Flow properties:

The flow properties of powders are critical for an efficient tabletting operation. A good flow of powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. If a drug is identified at the pre formulation stage to be "poorly flowable", selecting appropriate excipients can solve the problem. In some cases, drug powders may have to be pre-compressed or granulated to improve their flow properties. During pre formulation evaluation of drug substance, therefore, its flowability characteristic should be studied, especially when the anticipated dose of the drug is large.

Procedure:

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of sample powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction. The height of the heap was measured by using scale. The values of angle of repose are calculated by using the following formula:

$\tan \theta = h/r$

$\theta = \tan^{-1} h/r$

Where, h: height of the heap
r: radius of the heap

For most pharmaceutical powders, the angle of repose values range form 25 to 45, with lower values indicating better flow characteristics. Values of angle of repose ≤ 30 usually indicate a free flowing material and angle ≥40 suggest a poorly flowing material.

Assay of Etophyline & Theophyline Powder (HPLC method):

Assay or percentage purity of the Etophyline & Theophyline is done by HPLC method.

Chromatographic conditions:

- Mobile phase: 1.35 gm of Sodium acetate in 925 ml with 5 ml of glacial acetic acid and 70 ml acetonotrile.
- Column used: L-1
- Wavelength: 273 nm
- Flow rate: 2.0 ml/min
- Injection vol.: 20 µL

The calculation of assay was done with the help of graph obtained and using the formula;

$$\% \text{ purity} = \frac{\text{Ave. sample area}}{\text{Ave. standard area}} X \frac{\text{Standard dilution}}{\text{Sample dilution}} X \frac{\text{Standard purity}}{100} X100$$

Evaluation of Uncoated Sustained Release Matrix Tablets:

1. Weight Variation Test:

Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated. As per Indian Pharmacopoeial Specification, tablets with an average weight between 80 – 250 mg, the percentage deviation should not more than ± 7. 5 % and tablets with an average weight more than 250 mg should not be more than ±10 %.

2. Friability Test:

Weighed amount of 20 dedusted tablets were subjected to rotating drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The apparatus was operated for 4 minutes and reweighed the tablets. Friability was calculated by the following formula.

$$F = 100\left[\frac{W_0 - W}{W}\right]$$

F = Friability, W = Final weight, Wo = Initial

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weight

3. Hardness Test:

The hardness of tablet was carried out by using Monsanto type hardness tester. The hardness of the tablet (kg / cm²) was measured.

4. Thickness, width and length:

Control of physical dimension of the tablets such as thickness, width and length is essential for consumer acceptance and to maintain tablet to tablet uniformity. The dimensional specifications were measured using digital micrometer calipers. The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter.

5. Dissolution Study:

Medium :900 ml of 0.1 M HCl, for ½ and 1 hour 900 ml phosphate buffer pH 6.8 for 2,4 and 6 hours.
Apparatus: USP I (basket)
Speed: 50 rpm
Temperature : 37 ± 0.5 °C
λ max: 273 nm

Place one weighed tablet in to each of six dissolution vessel of the dissolution apparatus as per the above mentioned condition. After half and one hour withdraw ten ml and centrifuge. Decant the 0.1 N HCl and incorporate 900 ml phosphate buffer pH 6.8 and run the apparatus for five hours[10].

III. SUMMARY

In present work attempts have been made to formulate sustained release matrix tablet of Etophyline and Theophyline by using hydrophilic polymer, which is preferably used in asthma.

Matrix tables were prepared using polymer with HPMC K 100m and Sodium alginate in different concentration by wet granulation technique. Etophyline and Theophyline gives all the ideal characteristic with HPMCK 100m but not with sodium alginate.

Under pre formulation study the organoleptic properties were complied with USP specification. Physical properties such as bulk density and tapped density were more incase of granules ready for compression then that of Etophyline and Theophyline raw powder. Loss on drying was with in the USP limit.

Solution properties i.e. pH of the solution and solubility were evaluated, results were complied with the paharmacopocial specification.

The compatibility evaluations were performed by FTIR spectroscopy .

Both studies implies the drug and polymers are compatible with each other. There were no interaction found between polymers and drugs.

The final formulation were evaluazted on the basis of pharmacopoeial specification. The physical parameters like length, width, and thickness, hardness, friability and weight variation is carried out.

Assay were carried out for finally selected formulation and the result were found to by 98.0% (Etophyline) & 101.1% (Theophyline) by HPLC.

Stability by studies were carried out by keeping the tablets at room temperature (25^{o}C $\pm$ 2^{o}C / 60% $\pm$ 5% RH) and at accelerated temperature (40 ^{o}C $\pm$ 2 ^{o}C / 75% $\pm$ 5% RH) in stability chamber for 90 days. The result of stability studies conducted on F-3 reveled no change in physical appearance, hardness drug content and in vitro distribution profile whereas IR spectrum attained exhibits no incompatibility. Hence F-3 formulation was found to be stable at tested temperature.

The mechanism of drug release from matrix tablet is through diffusion due to soluble nature of drug. In all formulation F1 to F5 Except F3 that % drug release in out of the specified range in comparison to that of the innovator sample of German Remedies, Deriphyline SR 300 mg tablet.

IV. CONCLUSION

SR matrix tablets of Etophyline and Theophyline were prepared by direct compression. In vitro study showed formulation F3 were well suited to be extended release formulation.

Final selected formulations were found to be nearly zero to zero order drug release, governed by diffusion through swollen matrix and erosion of the matrix, showing anomalous diffusion of non fickian transport.

From the results obtained, it can be concluded that formulation F-3 has achieved the objective of sustained drug release, patient convenience and cost effectiveness as a single daily dose of the drug and appears to be assessed further by conducting bioavailability studies in human volunteers and long term stability testing.

Further, in vivo and continuation of stability studies are recommended.

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