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THEOPHYLLINE CONTROLLED RELEASE MATRIX TABLETS USING GUAR GUM

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ABSTRACT

The aim of the present work is to prepare and evaluate theophylline-controlled release matrix tablets using guar gum. Theophylline controlled release tablets can help control asthma throughout the sleep by releasing the drug for up to 12 hours. Natural polymers like guar gum are used because they are safe, cost effective, and easily available. The main criteria for the selection of guar gum is that this is a natural polymer which is safe, easily available and cost effective and theophylline is an bronchodilator which is prescribed to the patients with breathing problems. The combination of this theophylline and guar gum is used to develop controlled release tablets which provide a long lasting more reliable release of the drug in GIT.

KEYWORDS: Theophylline, Controlled release, Matrix tablets, Guar gum, Asthma.

INTRODUCTION

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. About 70% of the total medicines are dispensed in the form of tablets which are most popular dosage form. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms. Solid dosage forms like tablets are prepared from the dry powders which contains API and also excipients which include Diluents, binders, lubricants, glidants, disintegrating agents, coloring agents, flavoring agents, sweeteners etc. In market most of the drugs are found in the form of tablets. According to Indian Pharmacopoeia pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or mixture of drug with or without excipients which vary in shape and differ greatly in size and weight depending on the amount of medical substances and mode of administration. Oral administration is the most popular route for systemic effects and most importantly it does not

require sterile conditions and are therefore, less expensive to manufacture. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and case of administration lead to high levels of patient's compliance. The oral route is considered the ideal method for administering therapeutic agents due to its cost effectiveness and ability to promote high patient compliance.

Controlled release system aims to deliver a consistent supply of active ingredients, ideally at a zero-order rate, by releasing the medication continuously over a predetermined period. This ensures that the amount of drug released is equivalent to the amount eliminated by the body, maintaining a steady therapeutic level. An ideal controlled drug delivery system is one the releases medication at a predetermined rate, targeting either local or systemic areas, for a precise duration. Controlled release products are formulated to sustain a consistent therapeutic drug concentration in the plasma within the therapeutic range for extended durations.

DRUG PROFILE

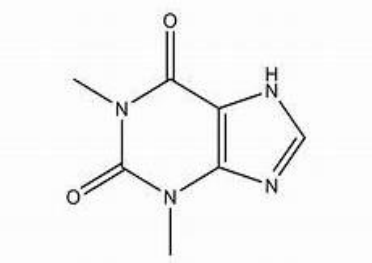
Theophylline:

Chemical Profile:

- **IUPAC Name:** 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione
- **Molecular Formula:** $C_7H_8N_4O_2$
- **Molecular Weight:** 180.16 g/mol

Chemical Structure

- Theophylline is a xanthine alkaloid and a methylated derivative of the purine nucleobase, theobromine. It contains a purine ring system (a two-ring structure with nitrogen atoms), which is further methylated at positions 1 and 3.



EXCIEPIENT PROFILE

Guar Gum

- **Chemical Name:** Guar gum (Galactomannan polysaccharide)
- **Source:** Extracted from the seeds of the guar plant (*Cyamopsis tetragonoloba*).
- **Molecular Structure:** Guar gum is a polysaccharide consisting of a linear chain of β-D-mannopyranose units linked by β-1,4-glycosidic bonds, with α-D-galactopyranose units attached to the mannose backbone in a 2:1 ratio.
- **Molecular Weight:** 200,000 to 2,000,000 g/mol (varies depending on the grade)

Functionality as an Excipient

Binder: In tablet formulation, it acts as a binder to hold the ingredients together.

Lactose Monohydrate

- **Chemical Name:** Lactose monohydrate ($C_{12}H_{22}O_{11}\cdot H_2O$)
- **Source:** Derived from milk, a disaccharide of glucose and galactose.
- **Molecular Weight:** 360.31 g/mol

Functionality as an Excipient

1. **Filler/ Diluent:** Commonly used as a filler in tablet and capsule formulations.
2. **Binder:** Provides some binding properties in tablet formulations.
3. **Taste Masking:** Often used in formulations to mask the taste of bitter active ingredients.
4. **Stabilizer:** Helps in stabilizing powder blends and improving flow properties in tablet manufacturing.

Polyvinylpyrrolidone (PVP) K30

- **Chemical Name:** Polyvinylpyrrolidone, K30 $(C_6H_9NO)_n$
- **Molecular Weight:** Approximately 40,000 – 70,000 g/mol (depending on the polymer chain length).
- **Structure:** A water-soluble synthetic polymer composed of repeating N-vinylpyrrolidone monomers.

Functionality as an Excipient

1. **Binder:** Commonly used as a binder in tablet formulations to improve cohesion of ingredients.
2. **Disintegrant:** Helps tablets break apart during dissolution by promoting rapid water uptak
3. **Film-Forming Agent:** Used in coatings for controlled-release formulations, as well as in topical preparations.

Magnesium Stearate

- **Chemical Name:** Magnesium stearate ($Mg(C_{18}H_{35}O_2)_2$)
- **Molecular Weight:** 591.26 g/mol

Physical Properties

Functionality as an Excipient

Lubricant: Magnesium stearate is primarily used as a lubricant in tablet

Isopropyl Alcohol

- **Chemical Name:** Isopropyl alcohol (IPA) or 2-propanol (C_3H_8O)
- **Molecular Weight:** 60.1 g/mol

Functionality as an Excipient

Solvent: Isopropyl alcohol is widely used as a solvent for both active pharmaceutical ingredients (APIs) and excipients due to its ability to dissolve a variety of compounds, including oils, resins, and non-polar substances.

MATERIALS

The materials are used in this tablet preparation are as follows, Theophylline, Guar gum, Magnesium, Lactose monohydrate, Polyvinyl pyrrolidone, isopropyl alcohol.

METHODS

Table 1: Composition of Theophylline CR matrix tablets (mg/tablet)

Ingredients (mg)	Theophylline: Guar Gum (1:1)	Theophylline: Guar Gum (1:2)	Theophylline: Guar Gum (1:3)
Theophylline	2g	2g	2g
Guar Gum	2g	4g	6g
Lactose monohydrate	5.92g	3.92g	1.92g
Polyvinyl pyrrolidone K30 (PVP K30)	0.04g	0.04g	0.04g
Magnesium stearate	0.04g	0.04g	0.04g
Iso propyl alcohol (IPA)	q.s	q.s	q.s

(1;1), (1:2) & (1:3) are drug: polymer ratio

These tablets are prepared by using wet granulation technique. Theophylline controlled tablets are prepared by using Guar gum and other ingredients are as follows in above table. Firstly PVP K-30 is dissolved in isopropyl alcohol then Theophylline, guar gum and lactose monohydrate are mixed together into a powder, now this powder is mixed with the mixture of isopropyl alcohol and PVP K-30 forms into a coherent mass. Then it is passed through sieve no.16 then the resulted granules were dried at 40 degrees Celsius for 2 hours. These dried granules were passed through sieve no.20.Then these granules are evaluated before turned into tablets. Now magnesium stearate is added to granules for lubrication then, then lubricated granules were compressed into tablets weighing 250mg.

EVALUATION GRANULES

The granules are evaluated are as follows:

Angle of Repose: -

The angle of repose, or critical angle of repose,[1] of a granular material is the steepest angle of descent or dip relative to the horizontal plane on which the material can be piled without slumping. At this angle, the material on the slope face is on the verge of sliding. The angle of repose can range from 0° to 90°.

Formula:- $\tan(\theta) = h/r$ R= radius of the cone

RELATIONSHIP BETWEEWN θ AND POWDER FLOW

Bulk Density

Bulk density is the mass of a material divided by its total volume, including the spaces between particles and the voids within particles.

Formula: - $pb = M/V$

Where, pb =Bulk density, M =Weight of powder

V =volume of powder.

Tapped Density

Tapped density is the mass per unit volume of a powder after it has been tapped to remove air gaps and voids between particles.

Formula: - $pt = M/Vt$

Where, pt = tapped density M=weight of powder

And Vt = minimum volume occupied after tapping.

COMPRESSIBILITY INDEX

The compressibility index, also known as the Carr index, is a measurement of how easily a powder can be compressed. It's calculated using the tapped and bulk densities of a powder, and is expressed as a percentage:

Formula: - compressibility index = 100*(p tapped density -p bulk density /p tapped density).

HAUSNER RATIO

The Hausner ratio (HR) is a measurement of how easily a powder or granular material flows. It's calculated by dividing the tapped density of a powder by its bulk density:

Formula: -

Hausner ratio =(p tapped density/p bulk density).

ESTIMATION OF FLOW PROPERTIES

Flow	Angle of repose	Carr's index	Hausner's ratio
Excellent	25 - 30	<10	1.0 -1.11
Good	31 - 35	Nov - 15	1.12 -1.18
Fair	36 - 40	16 - 20	1.19 -1.25
Possible	41 - 45	21 - 25	1.26 -1.34
Poor	46 - 55	26 - 31	1.35 -1.45
Very poor	56 - 65	32 - 37	1.46 -1.59
Very very poor	>66	>38	>1.60

EVALUATION OF TABLETS

To design tablets and tablet production quality test, the formulated tablets were evaluated for thickness and diameter (using a vernier caliper), hardness test (using Monsanto hardness tester)10 and friability (using Roche friabilator)11. For weight variation test12, 20 tablets of each formulation were selected at random and weighed individually. The individual weights were compared with average weight for determination of weight variation. The results were expressed in table-3. For content uniformity test13, ten tablets were powdered in a mortar. The powder equivalent to 100mg of theophylline was weighed and transferred to 100ml volumetric flask. It was dissolved in pH 7.4. From this appropriate dilution were made and the absorbance was analyzed at 277nm using UV double beam spectrophotometer.

DISINTEGRATION

The rate and extent of drug release form the tablet is estimated by dissolution test. Different types of apparatus are used to study the dissolution test of the tablet. As per IP apparatus "A" (paddle) and apparatus "B" (basket) are used. called basket dissolution apparatus and paddle dissolution apparatus.

Disintegration apparatus

Tablets after disintegration

DISSOLUTION

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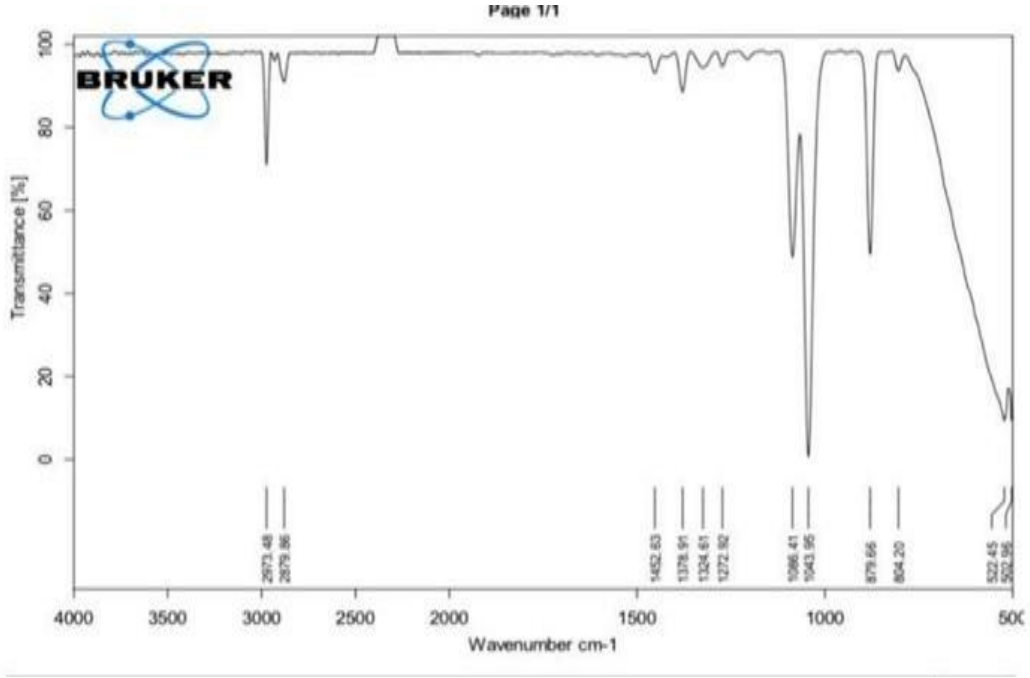
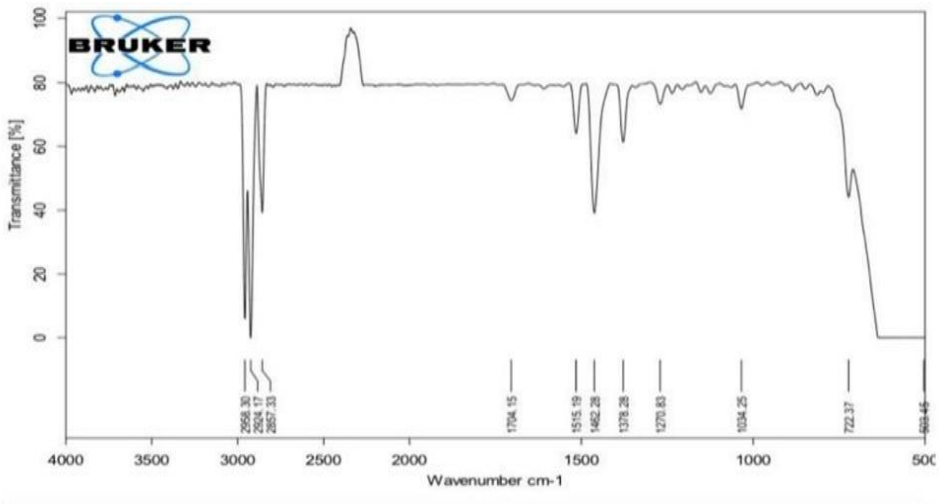
Dissolution apparatus

FT - IR STUDIES

It was used to study the interactions between the drug and polymer. The drug and polymer must be compatible with one another to produce a stable product. Drug and polymer interactions were studied by using FTIR (Shimadzu, Japan model – 8400S) as per the method described by Pathra et.al14. IR spectral analysis of pure theophylline, guar gum and theophylline with guar gum (1:2) were carried out. The peak and patterns produced by the pure drug were compared with combination of pure drug and polymer.



Graph-1.



Graph-2.

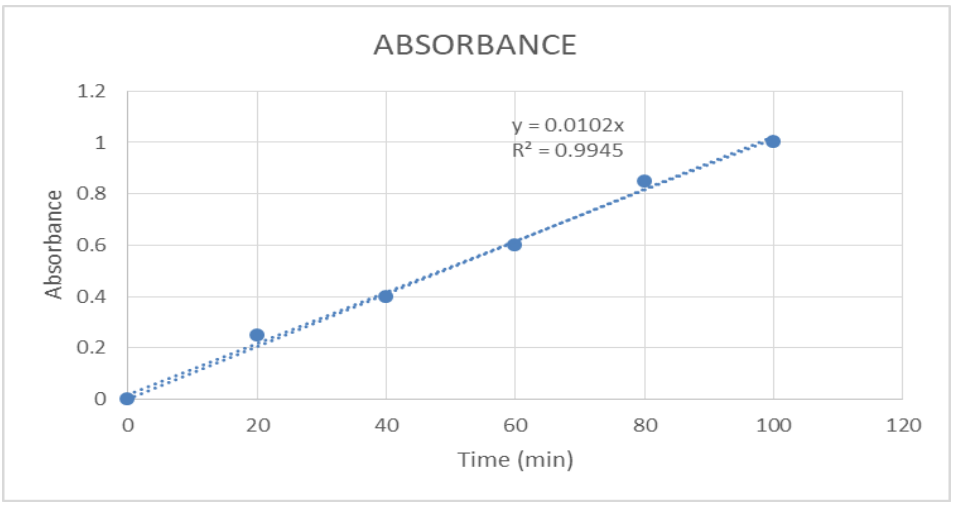
RESULT AND DISCUSSION

Table 2: Evaluation of theophylline matrix granules.

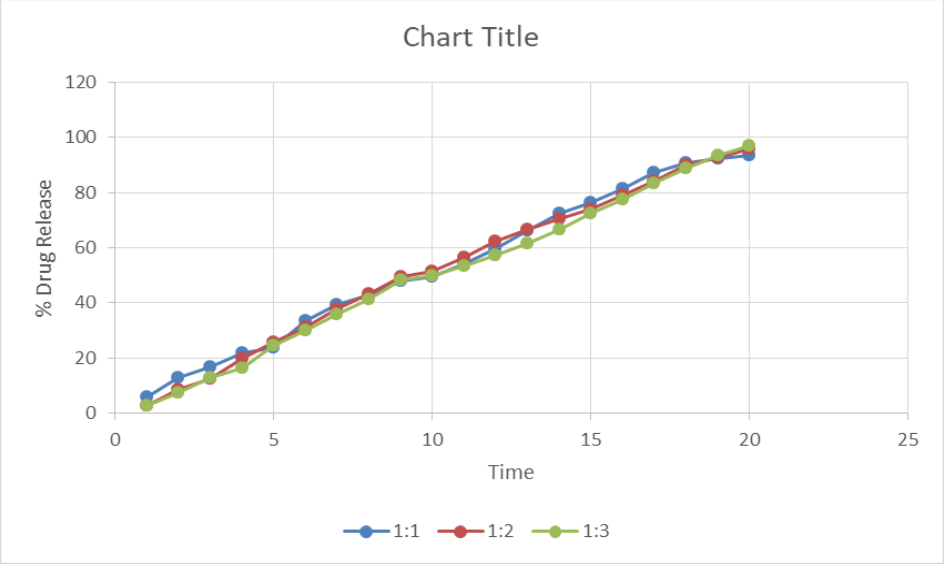
Parameters	**1:1**	**1:2**	**1:3**
Angle of Repose (θ)	0.71 35.37°	0.69 34.6°	0.63 32.21°
Bulk Density (gm/cc)	0.375	0.370	0.36
Tapped Density (gm/cc)	0.44.	0.43	0.41
Compressibility (%)	1.477	1.395	1.219
Hausner Ratio	1.173	1.162	1.138

Table 3: Evaluation of theophylline matrix tablets.

Parameters	**1:1**	**1:2**	**1:3**
Hardness (kg\cm2)	5.3	5.9	6.0
Uniformity of Weight (mg)	2510	2490	2520
Friability (%) Before After Duration	 2.570 2.490 0.79 %	 2.490 2.465 1.00 %	 2.520 2.503 0.67 %
Disintegration Time (min)	27	27.9	29
Thickness (mm)	3	2.9	2.5
Diameter (mm)	9.5	9.5	9



Graph 3: Standard graph of Theophylline Gaur gum of controlled release tablets.



Graph 4: Comparison of invitro drug release study of theophylline controlled release formulations.

The graph Time (x-axis) vs % drug release (y-axis) is plotted for above 3 formulations they are (1:1, 1:2, 1:3). In these formulations 1:3 is comparatively produces more drug release than other.

CONCLUSION

The above study concluded that the polymer ratio and tablet hardness significantly influence the release of theophylline from the controlled release matrix tablets prepared with guar gum. As the polymer ratio and tablet hardness increased, the drug release rate was prolonged. Specifically, the formulation with a higher guar gum content (1:3 ratio) exhibited the most prolonged drug release, indicating that the higher polymer concentration slows down the drug's release over time.

The controlled release properties of the formulations are crucial for applications like asthma treatment, where theophylline can provide sustained therapeutic effects for up to 12 hours, ensuring continuous bronchodilation during the night. The use of guar gum, a natural, cost-effective, and readily available polymer, proves to be an effective excipient in the preparation of these tablets. The study also highlights the importance of optimizing the polymer-to-drug ratio to achieve the desired drug release profile, which is essential for improving patient compliance and therapeutic outcomes.

Further investigations into the stability and long-term efficacy of these formulations could be beneficial to confirm their performance under varying environmental conditions.

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