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FORMULATION AND EVALUATION OF DOXOPHYLINE SUSTAINED RELEASE TABLETS USING DIFFERENT POLYMERS

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ABSTRACT

Doxophylline, a xanthine derivative, is commonly used for the treatment and prevention of asthma due to its bronchodilator properties. The present study focuses on the formulation and evaluation of sustained-release tablets of doxophylline using different polymers. Two formulations were prepared: F1 by direct compression (slugging method) and F2 by wet granulation method. Both formulations contained doxophylline (650 mg), microcrystalline cellulose (MCC PH102), and hydroxypropyl methylcellulose (HPMC K100M) in varying proportions, along with talc and magnesium stearate. Preformulation studies indicated favorable physicochemical properties such as good solubility, bulk density, and compressibility. Granules were evaluated for angle of repose, bulk density, Carr's index, and Hausner's ratio, revealing excellent flow properties especially after lubrication. Tablets were assessed for weight variation, hardness, friability, disintegration, and drug content uniformity. The results showed that both formulations complied with standard pharmacopoeial limits and exhibited good mechanical strength and controlled release characteristics. The study demonstrates that HPMC K100M-based sustained-release tablets can effectively deliver doxophylline, enhancing therapeutic efficacy and patient compliance.

KEYWORDS: Doxophylline, Sustained Release Tablets, HPMC K100M, Direct Compression, Wet Granulation, Asthma Therapy.

1. INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by bronchoconstriction, wheezing, coughing, and shortness of breath. It affects millions of people worldwide and significantly impacts the quality of life and daily activities of patients. The management of asthma involves both immediate relief of symptoms and long-term control of airway inflammation. Bronchodilators and anti-inflammatory drugs are commonly used to achieve these goals.

Doxophylline, a xanthine derivative, is an effective bronchodilator used in the treatment of asthma. It offers several therapeutic advantages over traditional xanthines such as theophylline, including fewer side effects and better tolerability. Doxophylline exhibits bronchodilatory action by relaxing bronchial smooth muscles and improving airflow in the respiratory tract. It is available in conventional dosage forms such as tablets and capsules, but frequent dosing may lead to reduced patient compliance and fluctuating plasma drug levels.

Sustained-release (SR) drug delivery systems are designed to release medication at a predetermined rate, maintaining constant therapeutic levels over an extended period. SR tablets can improve patient compliance, reduce dosing frequency, minimize side effects, and enhance therapeutic efficacy. Various hydrophilic and hydrophobic polymers such as hydroxypropyl methylcellulose (HPMC), microcrystalline cellulose (MCC), and other matrix-forming agents are used to control drug release.

The present study aims to formulate and evaluate sustained-release tablets of doxophylline using different polymers and manufacturing methods, including direct compression and wet granulation. The formulated tablets were evaluated for pre-compression and post-compression parameters such as angle of repose, bulk density, Carr's index, hardness, friability, disintegration time, and drug release. This research intends to develop a stable and effective sustained-release formulation of doxophylline to improve therapeutic outcomes and patient adherence in asthma management.

2. DRUG PROFILE

Xanthenes Derivatives: (*Doxophyline)*

Doxophylline (also known as doxophylline) is a xanthine derivative drug used in the treatment of asthma.

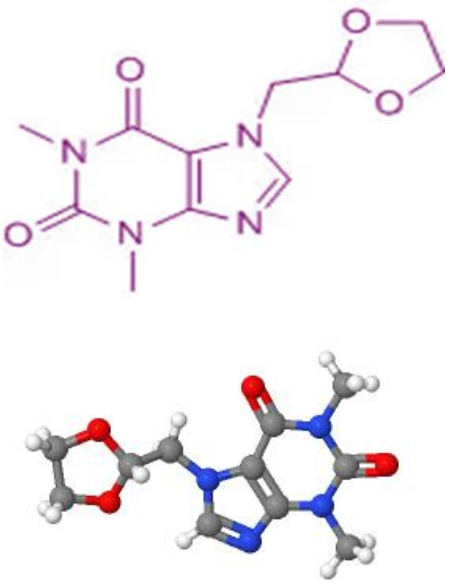

Fig. 1: Structure of Doxophyline.

Table 1: Physio – Chemical Properties of Doxophyline.

IUPAC Name	7-(1,3-dioxolan-2-ylmethyl)theophylline
Chemical Formula	C11H14N4O4
Water Solubility	Freely soluble in water
Molecular Weight	266.25 g/mol
Melting Point	217-219°C
Bioavailability	60-80%
Protein Binding	60%
Metabolism	Liver (CYP enzyme mainly CYP1A2)
Biological Half Life	6-8 Hours
Clearance	80-90 ml/min
Excretion	Renal (60-70%), Feces(20-30%).

3. MATERIALS AND METHODS

3.1 Methodology

Table 2: Formulation Table.

INGREDIENT	F1	F2
Doxophyline	650	650
MCCPH102	150	150
HPMCK100M	150	100
TALC	18	18
Mg Stearate	07	07
Total(mg)Weight	975	975

Procedure

Method 1: Preparation Of Tablets By Direct Compression (Slugging): The formulations (F1) of Doxophylline sustained release tablets were prepared by passing drug, polymer, Mcc101 through a no.30 mesh sieve. And dry mix for 10mins and blend with talc no.40 mesh sieve for 2mins. Finally lubricate with Mg. Stearate through a no.40 mesh sieve. The blend was compressed in a cadmach tablet compressing machine filled with biconvex punches (19.5mm+8.2mm). And then collect the tablets, mill through 1.2mm screen in multi-mill and further the milled granules was compressed in a cadmach tablet compressing machine filled with biconvex punches (19.5mm+8.2mm). Finally the tablet weight was adjusted to 975mg. The composition of core tablet is given in table-1.

Method 2: Preparation Of Tablets By Wet Granulation Method: The formulations (F2) of Doxophylline sustained release tablets were prepared by passing drug, polymer, Mcc101 through a no.40 mesh sieve, and dry mix for 10mins. Then granulated with pvpk90 solution and dried. The dried granules were sifted through no.20 mesh sieve and lubricated with HPMC K100M, talc, magnesium stearate. The granules were compressed in a cadmach tablet compressing machine filled with biconvex punches (19.5mm+8.2mm). Finally the tablet weight was adjusted to 975mg. The composition of core tablet is given in table-1 Construction of Calibration Curve for Doxophylline. The Calibration curve of Doxophylline was constructed by preparing three stock solutions. Preparation of 0.1M HCl 1.2 pH. An accurately measured 8.5ml of concentrated HCl was added to 1000ml to make 0.1M HCl. The resulting solution pH was measured by pH meter and it was recorded as 1.2 pH.

3.2 Evaluation Parameters

- Angle of Repose
- Bulk Density
- Carr's Compressibility Index

- Hausner's Ratio
- Thickness
- Weight Variation
- Hardness
- Friability
- Drug content uniformity
- Disintegration time
- Dissolution
- Stability

4. RESULTS AND DISCUSSION

4.1 Angle of Repose By Funnel method

Table 3: Angle of Repose by Funnel method.

Before Lubrication				
S.NO	**Height(h)**	**Radius(r)**	**TanØ=h/r**	**Ø=*Tan* (h/r)**
1.	1.2 cm	2.7 cm	0.476	25°45′
2.	1.3 cm	2.2 cm	0.590	30°54′
3.	1.8 cm	2.6 cm	0.692	34°68′
Avg	1.43 cm	2.5 cm	0.586	30°22
After Lubrication				
S.NO	**Height(h)**	**Radius(r)**	**TanØ=h/r**	**Ø=*Tan* (h/r)**
1.	1.2 cm	2.6 cm	0.461	24º74′
2.	1.2 cm	2.5 cm	0.480	25º64′
3.	1.4 cm	2.4 cm	0.583	30º24′
Avg	1.26 cm	2.5 cm	0.508	26º87′

Discussion: The Angle of Repose for the prepared mesalamine granules were measured by Funnel method. The values observed shows that the granules have good flow property and after lubrication it has got excellent flow property which is required for the proper filling of the granules in the dies**.**

4.2 Bulk Density

Table No: 4 Bulk Density.

		S.No	**Mass Of Granules**	**Bulk Volume After Tapping**	**Bulk Density (gm/cm³)**
FORMULATION I	**Before lubricant**	**1.**	43.5g	87	0.5
		2.	43.5g	86	0.50
		3.	43.5g	85	0.511
	After lubricant	**1.**	47.8g	83	0.575
		2.	47.8g	80	0.597
		3.	47.8g	78	0.612
	Avg	0.575 + 0.597 + 0.612⁄3 = 0.594gm/cm³			
FORMULATION II	**Before lubricant**	**1.**	49g	107	0.457
		2.	49g	106	0.462
		3.	49g	108	0.453
	After lubricant	**1.**	52.6g	100	0.526
		2.	52.6g	96	0.547
		3.	52.6g	94	0.559
	Avg	0.526 + 0.547 + 0.55⁄3 = 0.544gm/cm³			

Discussion: The Bulk Density for the granules was measured using 100 ml glass measuring cylinder. The readings for bulk density observed in the normal range. Bulk density is also measured inorder to ensure drug content uniformity and uniform mixing of the drug and the excipients.

4.3 Carr's Compressibility Index & Hausner's Ratio

Table No. 5: Carr's Compressibility Index & Hausner's Ratio.

Carr's Compressibility Index & Hausner's Ratio	
FORMULATION: 1	**FORMULATION: II**
I = 1 - (V/Vo) * 100 = 1 - (12/14) * 100 = 1 - 0.8571 * 100 = 14.29	I = 1 - (V/Vo) * 100 = 1 - (12/14) * 100 = 1 - 0.8571 * 100 = 14.29

Discussion: Compressibility index and Hausner's ratio are measures of the propensity of a powder to be compressed. They are measures of the relative importance of interparticulate interactions.

4.4 Pre-formulation Studies

Table No. 6: Pre-formulation Studies.

S. No	Parameters	Observation
1.	**Solubility**	Freely soluble in water, slightly soluble in ethanol (95%), partially insoluble in chloroform and in ether
2.	**Bulk density**	0.714gm/ml
3.	**Tapped density**	0.66gm/ml
4.	**% Compressibility**	6.7%

4.4 Weight Variation Analysis

Table No. 7: Weight Variation Analysis.

Profile	S. No.	Table Weight(gm)	S. No.	Table Weight(gm)
Formulation-I	**1.**	1.015	**11.**	1.048
	2.	0.986	**12.**	1.025
	3.	0.990	**13.**	0.982
	4.	1.019	**14.**	0.974
	5.	1.035	**15.**	0.981
	6.	0.971	**16.**	1.054
	7.	0.936	**17.**	1.027
	8.	0.976	**18.**	0.997
	9.	1.010	**19.**	1.046
	10.	1.030	**20.**	1.057
Formulation-II	**1.**	1.034	**11.**	0.993
	2.	0.940	**12.**	0.987
	3.	0.999	**13.**	0.979
	4.	0.960	**14.**	1.017
	5.	1.014	**15.**	1.026
	6.	0.946	**16.**	0.977
	7.	0.921	**17.**	0.998
	8.	0.970	**18.**	0.996
	9.	0.968	**19.**	1.032
	10.	1.041	**20.**	1.050

Discussion: A table designed to contain a specific amount of the drug in a specific amount of tablet formula.

4.4 Friability Test

Table No. 8: Friability Test.

S. No.	Formulation	Weight of Tablets		Weight Loss
		Before Friability	After Friability	
1.	I	20.237	20.179	0.058 (0.2866 %)
2.	II	19.582	19.523	0.059 (0.3%)

4.6 Hardness Test

Table No. 9: Hardness Test.

Profile	Hardness Value	
	Initial Value	Final Value
Formulation -I	2.5	12.5
	2.5 – 12.5 = 12 10 × 975 = 9750 = 9.7 kg	
Formulation-II	2.0	12.0
	2.0 – 12.0 = 12 10 × 975 = 9750 = 9.7 kg	

Discussion: Hardness test is routinely carried out during tablet punching in order to confirm die filling and compaction of tablets. In this, the tablet passes the limit range during tablet formation.

4.7 Disintegration Test

Table No. 10: Disintegration Test.

S. No.	Profile	No. of Tablets	Time Measured
1.	Formulation-I	6	21 Minutes
2.	Formulation-I	6	23 Minutes

4.8 Weight Variation Analysis

Table No. 11: Weight Variation Analysis.

S. No.	Number of Tablets	F1	F2
1.	1	59	64
2.	2	58	59
3.	3	60	60
4.	4	60	57
5.	5	58	61
6.	6	60	61
7.	7	61	62
8.	8	60	62
9.	9	60	60
10.	10	58	57
11.	11	61	60
12.	12	60	58
13.	13	58	60
14.	14	57	58
15.	15	60	62
16.	16	59	61
17.	17	60	64
18.	18	61	58
19.	19	58	62
20.	20	59	57
	Average Weight	0.607	0.611

DISCUSSION

This work has been done after a brief review of literature about the asthma disease that affects most of the people around the world. It has been recommended that, Doxophylline, a Xanthine derivative is one of the best drugs of choice for the treatment and prevention of severe asthmatic condition.

Patients suffering from various Etiological conditions related to asthma and wheezing need a immediate relief from the signs and symptoms. The drug to be administered should have immediate onset of action. Doxophylline is an anti-asthmatic drug available in various dosage forms such as Tablets, Capsules, etc., which will act in the Respiratory system. Doxophylline available as 200mg and 400 mg dose tablets. Doxophylline tablet granules were prepared by Wet granulation method. The prepared granules were evaluated before and after lubrication. Evaluation parameters include Angle of Repose, Bulk Density, Carr's Compressibility index and Hausner's ratio.

The prepared granules were compressed into compact tablets in the tablet punching machine. In-process Evaluation such as Weight variation analysis, Hardness test, Friability test and Disintegration Tests were carried out. It was observed after seeing the results, that, the Formulated tablet with coating showed good drug release after analysis. In future, the Doxophylline tablets can be formulated and manufactured with suitable polymers and thereby efficacy of the drug can be enhanced.

5. CONCLUSION

The study successfully formulated sustained-release Doxophylline tablets using different polymers and manufacturing methods. Both formulations (F1 and F2) met the required preformulation and post-compression evaluation parameters including angle of repose, bulk density, Carr’s index, hardness, friability, and weight variation. The wet granulation (F2) and direct compression (F1) methods produced tablets with satisfactory mechanical strength and sustained drug release profiles. The use of HPMC K100M as a polymer effectively controlled the release of doxophylline, potentially improving therapeutic outcomes and patient compliance in asthma management. Future work may focus on optimizing polymer concentration and performing in-vivo studies to further validate sustained release behavior.

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