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FORMULATION AND EVALUATION OF BILAYER TABLETS OF MONTELUKAST SODIUM IMMEDIATE RELEASE AND DOXOFYLLINE SUSTAINED RELEASE

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ABSTRACT

The aim of the study was to develop a bilayer tablet formulation for the treatment of chronic obstructive pulmonary disease (COPD) using a new polymer Polyethylene (oxide) as a matrix for sustained release layer and Doxofylline and Montelukast sodium as model drugs. The sustained release layer was formulated by the direct compression method and the immediate release layer was prepared by the wet granulation method. Bilayer tablets were evaluated for hardness, thickness and friability. *In-vitro* release studies were carried for both the layers. For sustained release layer, water was used as dissolution medium and release pattern of the drug from the new polymer was evaluated by using a UV spectrophotometer. For immediate release layer pH6.8 buffer medium was used and the drug release was evaluated by using HPLC. *In-vitro* release studies reveal that the new polymer releases the drug Doxofylline in a mixed orderly manner that is swelling, erosion and dissolution. The study reveals that the new polymer Polyethylene (oxide) was used as an alternative to hydroxy propyl methyl cellulose in lower concentration.

Key Words: COPD, Doxofylline, Montelukast sodium, Polyethylene (oxide), Cros Carmellose Sodium, Hydroxy Propyl Cellulose.

INTRODUCTION

Oral drug administration has been the predominant route for drug delivery. An ideal drug delivery system provides a therapeutic amount of the drug to the proper site in the body to achieve the desired drug concentration. An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desired therapeutic concentration of drug in plasma or at the site of action and maintains the concentration for the entire duration of treatment. In short, managing of spatial placement and temporal delivery is an important criterion for an ideal dosage regimen. Tablets can be defined as a solid pharmaceutical dosage form containing the medicament alone or in combination with additive /excipients and prepared either by compression or molding. Sustained release preparation provides an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic level for an extended period of time. The therapeutic activity of Doxofylline, [7-(l, 3-dioxolane-2-methyl) theophylline] has been evidenced in clinical trials made with asthmatic patients or individuals with **Chronic obstructive pulmonary disease** (**COPD) [**[2]**.** COPD is defined by its characteristically low airflow on lung function tests. In contrast to asthma, this limitation is poorly reversible and usually gets progressively worse over time. Doxofylline[[3]] has demonstrated to have bronchodilator activity equal or superior to that of theophylline in spite of its inferior affinity for adenosine receptors, A l and A2. Doxofylline does not produce any cardiac side effects and this major advantage for heart disease patients with asthmatic conditions.

Montelukast sodium[[4]] is a leukotriene antagonist with high affinity and selectivity to the CysLT1 receptor used for bronchodilatation. For immediate onset of action Montelukast is used as an immediate release layer. Doxofylline is rapidly absorbed and has high tissue diffusion. When administered orally, the observed half-life is 6-7 hours and for this reason several administrations are required during a 24 hour period. In sustained release, it is possible to obtain a bioequivalent concentration with 650mg of Doxofylline to exert the bronchodilator effect. Montelukast is rapidly and completely absorbed following oral administration. The observed half-life is 2-5 hours and more than 99% bound to plasma protein. The dosage for adults is 10 mg. The present study is aimed to prepare and optimize bilayer tablets with a sustained release matrix layer of Doxofylline and an immediate release layer of Montelukast sodium.

For the formulation of SR layer Poly (ethylene) oxide [PEO] [5] {POLYOX WSR 303 (7 500–10 000)} was used as matrix former. It is a

white, free flowing hydrophilic powder. It is currently used as an alternative to HPMC. A hydrophilic polymer such as PEO rapidly hydrates and produces a gel barrier around the outer part of the matrix. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix

approach. It has been shown to be an excellent mucoadhesive polymer. Polyethylene oxide films demonstrate good lubricity when wet. The objective of this study was to develop a bilayer tablet with a sustained release, hydrophilic Poly (ethylene) oxide matrix formulation of Doxofylline 650 mg and immediate release Montelukast sodium 10mg in order to increase the patient compliance.

MATERIALS AND METHODS:

Doxofylline was purchased from Biocon Limited, Bengaluru and Montelukast sodium from Unimark Remedies Ltd, Gujarat. Polyethylene (oxide) polymer was provided by Colorcon Asia Limited, Goa. Poly (ethylene) oxide POLYOX WSR 303 (7 500–10 000) grade was used as a matrix former. Other materials used for this study was gifted by Fourrts (India) Laboratories Pvt. Ltd., Chennai.

Methods:

The sustained release layer was formulated by direct compression method[6] and the immediate release layer was prepared by wet granulation method[7]. Immediate release layer was prepared by the wet granulation method with Cros Carmellose Sodium[8] as Superdisintegrant. Three formulations were formulated and the optimized formulation was selected for formulating bilayer tablets. Sustained release layer was optimized by preparing the tablets by the direct compression method. Four formulations were formulated with various concentrations of polymer, PEO, ranging from 25%-10%. The tablet compositions for immediate release and sustained release are shown in Table I and II respectively. The superdisintegrant and polymer concentrations are shown in Table III and 1V respectively.

TABLE*:* I For Immediate release layer

S.No	Materials (mg)	M-1	M-2	M-3
1.	Montelukast sodium	10.5	10.5	10.5
2.	Microcrystalline cellulose	40	40	40
3.	Lactose	42.75	40.75	8.75
4.	Cros carmellose sodium(**granulation**)	1	2	3
5.	Hydroxyl propyl cellulose (Klucel)	1.75	2	2
6.	Cros carmellose sodium(**mixing**)	2	3	4
7.	Iron oxide yellow	0.5	0.5	0.5
8.	Magnesium stearate	1.25	1.25	1.25

Table II Superdisintegrant concentration

Formulation	Concentration of superdisintegrant (%) to the average weight
M-1	3
M-2	5
M-3	7

TABLE: III For sustained release layer: Direct compression

Materials(mg)	Formulations			
	F-1	F-2	F-3	F-4
Doxofylline	**650**	**650**	**650**	**650**
Poly (ethylene)oxide Polyox WSR 303	**180**	**135**	**90**	**110**
Microcrystalline cellulose 102	**60**	**105**	**150**	**130**
Colloidal silicon dioxide	**5**	**5**	**5**	**5**
Magnesium stearate	**5**	**5**	**5**	**5**

TABLE: IV Concentration of polymer in percentage

Formulation	Polymer (Polyox) concentration (%) to the average weight
F-1	**20**
F-2	**15**
F-3	**10**
F-4	**12**

Evaluation parameters[9]:

Thickness and diameter were measured using vernier caliper. Hardness of the prepared formulations was determined using a Monsanto hardness tester. Friability of the tablets was determined using Roche friabilator. UV spectrophotometric method was used to estimate the Doxofylline content from the

prepared tablets. HPLC analytical method was used to estimate the Montelukast content.

Twenty tablets were accurately weighed and the average weight was calculated. Tablets were crushed to fine powder. The accurately weighted amount of the powder equivalent to 325mg of Doxofylline was taken, dissolved in water, diluted and estimated at 274nm by UV spectrophotometer. The content of Doxofylline was calculated by comparing with a standard solution. The accurately weighted amount of the powder equivalent to 10mg of Montelukast sodium was dissolved in Acetonitrile: water (13:7), sonicated for half an hour, and diluted. 20 µl of the resulting solution was injected and the responses were measured as peaks.

***In-vitro* release studies:**

The release of Montelukast sodium was determined using USP type II (paddle) dissolution apparatus under sink condition. The dissolution medium was 900 ml of pH 6.8 buffer solution at 37^0C with the stirring speed 50 rpm. The release study was carried out for 30 min. The release of Doxofylline was determined using USP type II (paddle) dissolution apparatus under sink condition.

The dissolution medium was 900 ml of water at 37^0C and the stirring speed was 100 rpm. The absorbance of the solutions was recorded at 274 nm. The *In-vitro* release studies were carried out for 12 hours.

Stability studies[10]:

Stability studies were carried out according to ICH guidelines. All formulations were packed in blister packing. Samples were kept in humidity chamber at 40^0C and 75 % RH for 3 months. At periodical intervals, samples were analyzed for drug content, hardness, and *in-vitro* dissolution studies.

RESULTS AND DISCUSSION:

Raw material analysis:

The drugs were analyzed for solubility and loss on drying. Doxofylline is freely soluble in chloroform and dichloromethane, Soluble in water. Montelukast sodium is freely soluble in ethanol and methanol. Loss on drying for the drugs Doxofylline and Montelukast sodium were 0.3%w/w and 0.9%w/w respectively. These were within the specified limit.

Micromeritics studies:

The quality of final products is generally dictated by the quality of physico-chemical properties of the granules. There are many formulation and process variables involved in manufacturing and all these can affect the characteristics of the final product produced. The various physical characteristics of granules such as Bulk density, Tap density, Hausner ratio and Angle of repose were determined.

For immediate release layer Formulation M-3 shows satisfactory results when compared to that of the other formulations. Bulk density of M-3 was found to be 0.412±0.0036g/cm^3, Tap density- 0.458±0.0036 g/cm^3, compressibility index-10.04±0.0750% Hausner ratio-1.1116±0.001and finally Angle of repose - 25.03±0.7303^o. For sustained release layer F-4 shows good results when compared to other 3 formulations. Precompression parameters such as Bulk density, Tap density, Hausner ratio, Compressibility index, and Angle repose were found to be 0.610±0.011g/cm^3, 0.678±0.0122 g/cm^3, 1.1112±0.002, 10.01±0.036%, 24.95±0.325^o respectively.

Evaluation of tablets:

The disintegration time of M-3 (IR layer) as 3min 4sec with a 7% concentration of Cros Carmellose sodium. The drug content was calculated as 99.67**±**0.2443%w/w. Doxofylline content was 100.46± 0.5%w/w.

***In-vitro* evaluation:**

In-vitro release of Montelukast sodium was 98.15±0.3%w/w. *In-vitro* release of Doxofylline was 93.59±0.2%w/w at the end of 12th hour. Studies carried out revealed that the formulations containing 12% polymer shows a good release pattern. On the other hand other formulations F-1 and F-2 showed an unsatisfactory release pattern with the polymer concentration of 25% and 20% respectively. F-3 containing 15% polymer concentration showed more than 96.27%±0.3 of drug release at the end of 12th hour. F-4, which contains 12% polymer concentration, showed 93.27% release at the end of 12th hour. The results of *in-vitro* release are tabulated in Table V and VI.

TABLE: V Drug release profile for Montelukast sodium (IR)

S.No	Time (min)	M-1*	M-2*	M-3*
1.	10	30.26±0.3	38.12±0.3	48.99±0.2
2.	20	82.15±0.2	80.15±04	85.42±0.3
3.	30	95.94±0.4	96.77±0.2	98.15±0.3
*** Mean ±SD (n=6)**				

TABLE: VI Drug release profile for Doxofylline (SR)

Time (H)	F-1*	F-2*	F-3*	F-4*
2	19.51±0.3	26.07±0.4	44.38±0.5	35.51±0.3
6	32.75±0.1	57.79±0.2	83.98±0.6	67.16±0.1
9	77.42±0.3	75.34±0.2	90.01±0.3	86.49±0.2
12	81.92±0.8	88.58±0.4	96.27±0.3	93.59±0.2
*** Mean ±SD (n=6)**				

Graphical representations are shown in Figure I and II.

To know the mechanism of drug released from these formulations, the data were treated in different modes.

As observed in the graphs III to VII, F-4 did not follow zero order release. When the data were plotted in the first order equation it showed linearity with regression values 0.963 which indicate that the formulation did not follow first order. When the data plotted in Higuchi's equation, it showed good linearity with regression values of 0.996. The slope of Higuchi equation was more than one, which indicates that it follows Higuchi kinetics[11] of release. For further confirmation the data were fitted to Hixson-Crowell equation. The plot showed linearity with regression values of 0.993 for F-4.This indicates the complex release pattern of swelling, diffusion and erosion for the formulation F-4. The 'n' value, an exponent of Peppas equation[12] was found to be 0.853 (more than 0.5). From this it was concluded that the drug release follows non-Fickian diffusion or anomalous release (0.5<n<1). It can be inferred that the release was dependent on both drug diffusion and polymer relaxation[13]. Kinetics plots are shown in Figure III, IV, V, VI, and VII.

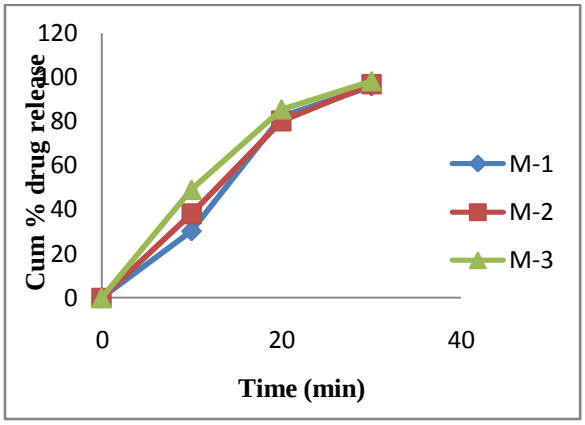

FIGURE: I Release profile for Montelukast sodium as immediate release

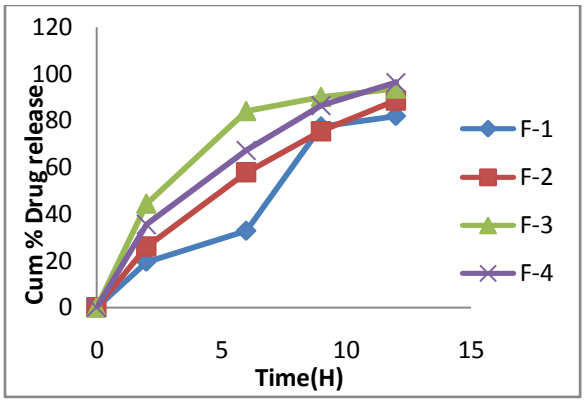

FIGURE: II Release profile for Doxofylline as sustained release

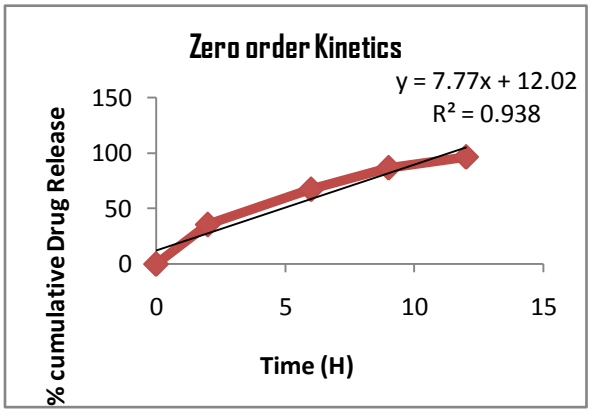

FIGURE: III Zero order release kinetics

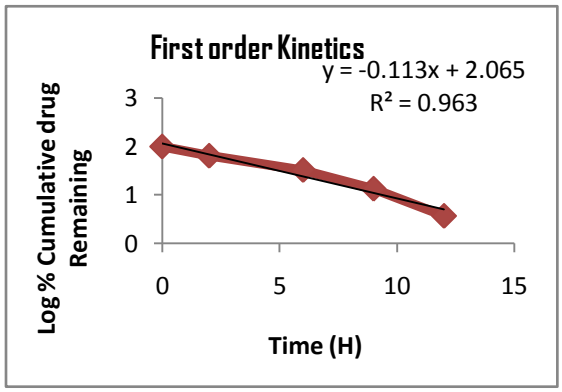

FIGURE: IV First order release kinetics

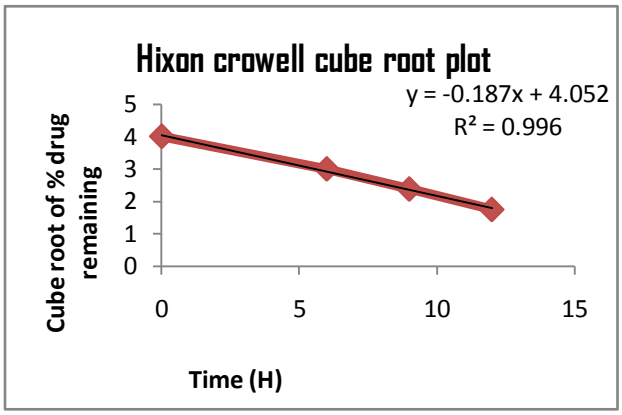

FIGURE: VII Hixon crowell release kinetics

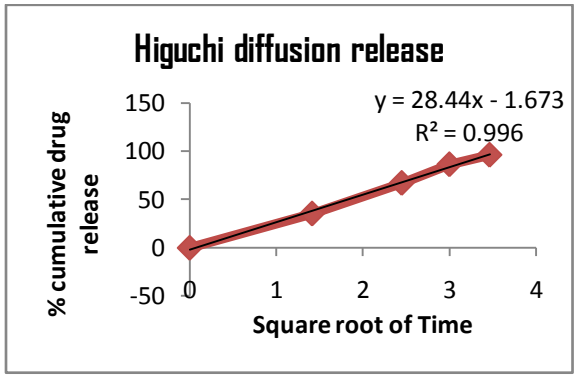

FIGURE: V Higuchi release kinetics

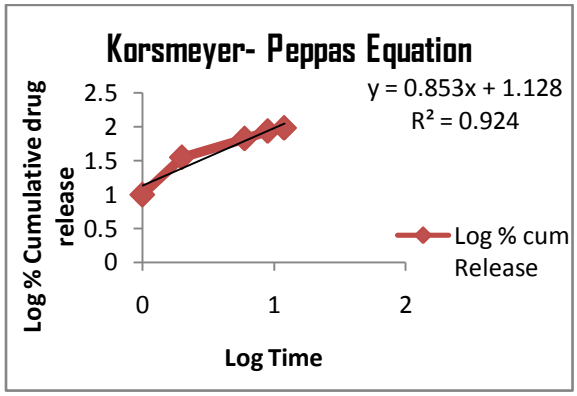

FIGURE: VI Korsmeyer- Peppas release kinetics

Stability studies:

The stability study15 of the bilayer tablet also showed a desired release pattern. Other parameters like hardness, thickness, assay, friability of the formulation were satisfactory. The results are shown in Table VII.

TABLE: VII In-vitro release studies of bilayer tablets (stability samples)

IMMEDIATE RELEASE LAYER			
TIME (MIN)	**ONE MONTH**	**TWO MONTHS**	**THREE MONTHS**
10	91.67±0.033	90.74±0.124	90.67±0.097
20	94.9±0.010	94.16±0.139	93.76±0.028
30	96.95±0.079	97.25±0.149	97.47±0.008
SUSTAINED RELEASE LAYER			
TIME (HRS)	**ONE MONTH**	**TWO MONTHS**	**THREE MONTHS**
2	35.02±0.285	35.15±0.117	35.07±0.146
6	65.51±0.202	65.25±0.109	65.25±0.141
9	85.21±0.160	84.73±0.187	85.23±0.172
12	95.0±0.206	95.12±0.121	95.36±0.105
*** Mean ±SD (n=6)**			

CONCLUSION

It was concluded that Formulation F-4 designed with 12% Concentration of Poly (ethylene) oxide shows a satisfactory dissolution profile up to 12 hours, and for immediate release Formulation M -3 containing 7% cros carmellose sodium as a super disintegrant was optimized. The formulated once daily bilayer tablet with Montelukast sodium 10mg and Doxofylline 650 mg can be used for COPD to improve the patient compliance with least formulation variables.

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