Research Article CODEN: IJPRNK Impact Factor: 5.567 ISSN: 2277-8713
Piyush Sharma, IJPRBS, 2016; Volume 5(4): 140-148 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

COMPARISION OF IN-VITRO DRUG RELEASE PROFILE OF THEOPHYLLINE FROM HYDROPHILIC AND HYDROPHILIC-HYDROPHOBIC COMBINED MATRIX

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Accepted Date: 16/08/2016; Published Date: 27/08/2016

Abstract: Theophylline is considered as one of the most useful bronchodilator in case of bronchospasm due to chronic obstructive pulmonary disorder (COPD) and asthma. Theophylline has a narrow therapeutive index and short half-life (3-5hrs), the regular monitoring of the serum Theophylline concentration become mandatory. Thus, sustained release formulation of Theophylline is a better approach to reduce and prevent the susceptible adverse effect due to fluctuation in plasma drug level. In this work, the attention is focused to compare the effect of the hydrophilic and hydrophilic-hydrophobic combined matrix on the *in-vitro* drug release profile of Theophylline from matrix type tablets which were prepared by wet granulation method. The method utilizes the hydroxyl propyl methyl cellulose (HPMC) as hydrophilic polymer and HPMC in combination of ethyl cellulose (hydrophobic polymer). The results revealed better sustained release profile can be achieved by using combination of hydrophilic and hydrophobic polymers as compared with hydrophilic matrix alone for the highly water soluble Theophyllin.

Keywords: Theophyllin, Therapeutive Index, HPMC, Half-life

PAPER-QR CODE

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Access Online On:

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How to Cite This Article:

Piyush Sharma, IJPRBS, 2016; Volume 5(4): 140-148

INTRODUCTION

The formulations of sustained-release drug delivery systems wish to achieve desired release rates, decrease the number of daily administrations, improve compliance and minimize side-effects[1]. Matrix is a well mixed composite of one or more drug with gelling agent i.e.-hydrophilic polymers. A hydrophilic matrix is one of sustained-release formulations. It is a homogeneous dispersion of drug molecules within a skeleton in which one or several of the excipients are present. HPMC is the most widely used as a drug release retardant excipient in hydrophilic matrices[2]. It is soluble in water, non-ionic, stable at a pH between 3.0 and 11.0 and resists enzyme attack. This sustained release system reduces drug toxicity and improving patient compliance by a prolonging dosing interval[3]. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network[4-8]. For such drugs it becomes essential to include hydrophobic polymers in the matrix system. Hence, in the present work, an attempt has been made to formulate the extended-release matrix tablets of Theophylline using hydrophilic matrix material in combination with hydrophobic ethyl cellulose.

Theophylline, also know as 1, 3-dimethylxanthine. It is a methyl xanthine drug, used as Bronchodilator and for pulmonary disease and asthma under a variety of brand names. It is a derivative of the xanthine; it shows structural and pharmacological activities similarity to caffeine and theobromine. Theophylline is naturally obtained from cocoa beans, amounts as high as 3.7mg/gm have been reported in Criallo cocoa beans. Theophylline is also obtained from brewed tea (approx. 1mg/l). Theophylline is one of three naturally occurring methylated xanthine alkaloids such as caffine, thiophylline and theobromine.

Material and method:

Sustained release matrix tablet were prepared by wet granulation. Both formulation were prepared according to the composition showed in table no.-1

Table 1: Formulation design of sustained release Theophylline matrix tablets.

	Quantity of Ingredient	
Name of Ingredient	Formulation 1	Formulation 2
Theophylline	75mg	75mg
HPMC	300mg	125mg
Ethyl Cellulose	----	25mg
PVP K30	40mg	25mg
Talc	2mg	2.5mg
Magnesium Stearate	2mg	2.5mg
Avg. of tablet	419mg	205mg

Procedure:

All Excipients were accurately weight and passed through the sieve no. 80. HPMC and drug were transferred in an air filled polybag and mixed by shaking it for 5 minutes. Then the mixture was transferred in a mortar pastel. PVP K30 was dissolved in isopropyl alcohol and a paste (10%) was made for the mixture. Prepared solution was slowly added in the mortal pastel, then mixture was triturated and the granules were formed. Granules were dried in hot air oven for 5 minutes below at 60°C. After half drying granules were passed through sieve no. 22. Then these granules were completely dried in oven. Sieve no. 22, 44 and collector was taken; dried granules were transfer in the sieve no. 22 and these sieves were shaken. Fine and coarse powder was collected. 70% of coarse and 30% of fine powder was taken and lubricated with the talc and magnesium stearate. Finally the granules were compressed in the form of tablets by using 16 station rotary compression machines.

Evaluation Test

To formulate tablet were evaluate for the following physiochemical characteristics[9-15].

General Appearance: Tablets was assessed for its general appearance.

Hardness: 10 tablets of each formulation were selected randomly and hardness of tablets was measured by using Monsanto hardness tester.

Friability: Friability of tablets was determined by using Roche friabilator. 10 tablets were selected from each formulation and weighed and tested at 25 rpm speed for 4 minutes. After removing the dust, tablets were reweighed and percentage friability was evaluated by this equation;

$$\% \text{ friability} = \frac{\text{Initial weight} - \text{final weight} \times 100}{\text{Initial weight}}$$

Weight variation: 10 tablets were accurately weight individually and average weight was calculated. Percent weight variation was calculated by this formula;

$$\%\text{weight variation} = \frac{\text{Average weight} - \text{Initial weight} \times 100}{\text{Average weight}}$$

Thickness: Thickness of tablets determine by using the vernier caliper scale.

Swelling index: Empty petridish was weighed. The individual tablets were weighed and transfer in the petridish. Petridish was filled up with water for 15 minutes. After 15 minutes water was removed. Petridish was completely dried with the help of tissue paper and then the weight was noted down. This procedure was repeated at a particular time intervals (15, 30, 60, 2 hours) until the tablet achieved a constant weight. Swelling index is calculated by this formula;

$$\% \text{ swelling index} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

***In-vitro* drug release study:** USP-type II dissolution apparatus was used for *in vitro* drug release study. Sustained release matrix tablet was transferred in the 900ml dissolution media (0.1N HCl) for 2 hours. Dissolution apparatus was operate at 50 rpm and temperature was set at 37° C. Samples were taken at 30, 60, 90,120 minutes intervals. After completing two hours, the dissolution media was replaced with pH 6.8 phosphate buffers. The temperature was maintained at 37° C and apparatus was operated at 50 rpm spee. Sample was taken at 60, 120, 180, 240 and 360 minutes intervals.

Drug release kinetics: The mechanism of drug release and rate kinetics were evaluated by the plotting the *in-vitro* release data in various kinetics models.

Zero order kinetics: when the rate of reaction is independent of the concentration of the reacting substance and therefore is considered to be zero order reaction.

First order kinetics: when the reaction rate depended on the first power of concentration of a single reactant, it is considered as to be first order reaction.

Higuchi kinetics: Drug release was proportional to the square root of time. Indicating that drug release is diffusion controlled.

Result and Discussion: Sustained release matrix tablet of Theophylline was formulated and evaluated using two different cellulose derivatives; HPMC (hydrophilic polymer) and HPMC-EC combination (hydrophilic-hydrophobic polymer) by wet granulation method. Both formulations have hardness, thickness, friability and weight variation within acceptable limits. Tablets were found to be satisfactory as per Indian pharmacopeia tolerance limit and both formulation were subjected to various parameter and the result obtained was within the range (Table-2).

Table 2: Physical evaluations of tablets.

Parameters	Formulation 1	Formulation 2
Thickness	4.7mm	4.3mm
Hardness	4.3kg/cm²	4.5kg/cm²
Friability	.502%	.394%
Avg. weight	416.37±3	250.28±4
Swelling index	0.512%	2.072%

In-vitro release studies were shown in (Table-3). Dissolution study of each formulation was conducted by using 0.1N HCl for first 2 hours. After completed two hours dissolution media was replaced with phosphate buffer pH 6.8. A graph was plotted between % drug release verses time (Fig 1). The *in vitro* data was fitted to different kinetic models by using BITSTAT software (Fig. 2 & Fig. 3). The results (Table 4) revealed that the formulation prepared with both HPMC & EC followed Higuchi kinetics as correlation coefficient is 0.94 and formulation prepared with HPMC alone followed the first order release kinetics with correlation coefficient 0.97.

Fig.1: Graph between % drug release verses time.

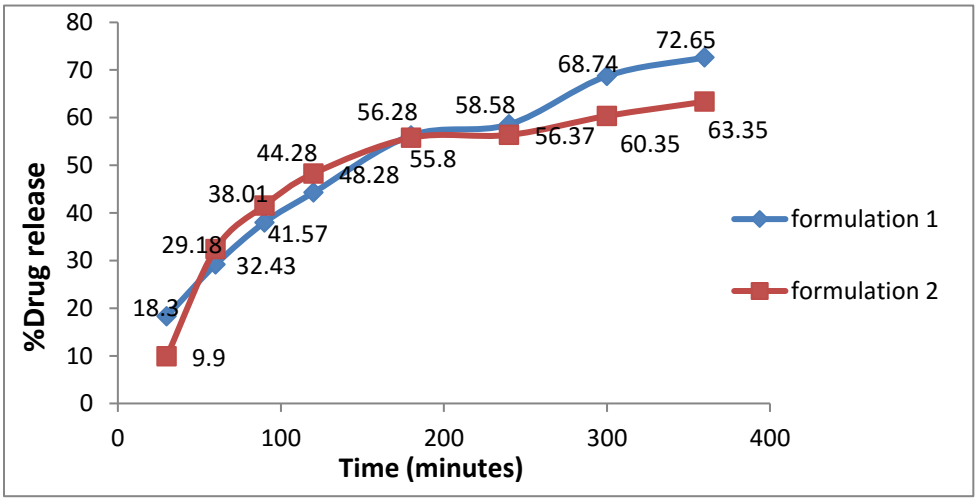

Table. 3: Comparative Dissolution data of Theophylline sustained release tablets

Time in minutes	% drug release	
	Formulation 1	Formulation 2
30	18.30%	9.90%
60	29.18%	32.43%
90	38.01%	41.57%
120	44.28%	48.28%
180	56.28%	55.80%
240	58.58%	56.80%
300	68.74%	60.35%
360	72.65%	63.35%

Figure: 2 Drug release Kinetics model of formulation 1.

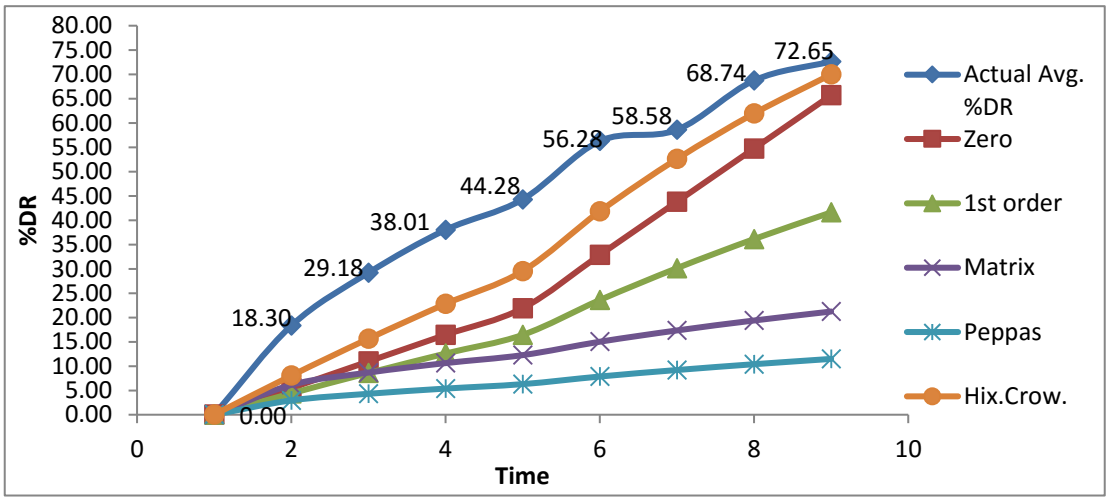

Figure: 3 Drug release kinetics model of formulation 2.

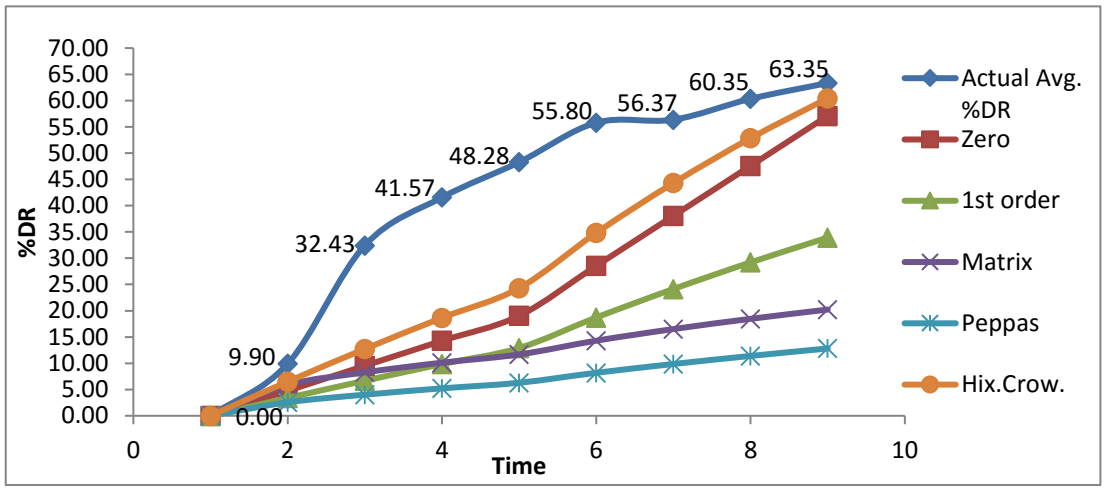

Table 4: In-vitro release kinetic of theophylline sustained release tablets with various polymers.

Formulation	zero order		First order		Higuchi kinetics	
	R^2	k	R^2	k	R^2	k
Formulation 1	.897	10.948	.976	-0.2064	.912	8.664
Formulation 2	.766	9.51	.858	-0.1591	.940	8.255

CONCLUSION: The sustained release formulations of Theophylline were studied in this work. We concluded that formulation containing hydrophilic-hydrophobic polymer (HPMC-EC) showed better sustained release rate as compared with hydrophilic polymer (HPMC) alone. Further it was concluded that by using the hydrophobic polymer reduction in concentration of hydrophilic polymer can leads to reduced tablet weight and cost. As the result revealed the weight of tablets having both HPMC & EC is approximately half as compared with the tablets having HPMC alone but more drug is sustained in later hours. There was no significant change in physical properties of matrix tablet with the change of sustained release polymers. The formulation prepared with both HPMC & EC followed Higuchi kinetics for drug release while formulation prepared with HPMC alone followed the first order release kinetics.

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