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Formulation design and *in-vitro* release profile evaluation of Theophylline hydrochloride sustained release tablet using different polymer at different concentration

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ABSTRACT

The aim of the work was to develop Theophylline hydrochloride sustain release tablet using Methocel k 15 MCR, Methocel K100M CR premium and Methocel K4M CR premium in blending and granulation stage of processing and evaluate their physico-chemical properties and also compared the dissolution profile with the marketed drugs.Tablets were prepared by wet granulation method. The active ingredient, release retardants, diluents, fraction of polymer are mixed together to make wet mass for granulation. The rest of the polymer was mixed in the blending stage. The effect of polymer on drug release was studied with other physicochemical properties. Formulations (F-4) containing Methocel k 15 MCR met the desired sustained release pattern as per USP specification (30th edition, 2006) from 1st hour to 8th hour as per in-vitro dissolution studies. The another test trial containing double polymer Methocel K100M CR premium and Methocel K4M CR premium also showed desired release pattern slightly deviated from compendia limit against specified time for 1st and 2nd hour. At the same time we also compared the dissolution profile of two marketed product with our test product. In that case the marketed product showed irregular dissolution profile in 6 th and 8 th hour in some cases.

Key words: CR, Premium, COPD, dissolution and Higuchi

INTRODUCTION

Theophylline hydrochloride was used as model drug in this experiment. Theophylline Hydrochloride is used in a therapy for respiratory disease. The main therapeutic uses of theophylline are chronic obstructive diseases of the airways,chronic obstructive pulmonary disease (COPD),bronchial asthma and infant apnea etc .The main mechanism of action of theophylline is that of adenosine receptor antagonism. Theophylline is a non-specific adenosine antagonist, antagonizing A1, A2, and A3 receptors almost equally, which explains many of its cardiac effects and some of its anti-asthmatic effects [1]. The goal of any drug-delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration [2-3]. Most conventional drug products, such as tablets and capsules, are formulated to release the active drug immediately to obtain rapid and complete systematic absorption of the drug. In recent years, various modified drug products have been developed to release drug products are designed for different routes of administration based on

the physicochemical, pharmacological, and pharmacokinetic properties of the drug. Sustained release, sustained action, prolonged action, controlled release, extended action, time release, depot and respiratory dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose[3-5]. In the case of injectable dosage forms; this period may vary from days to months. In the case of orally administered forms, however, this period is measured in hours and critically depends on the retention time of the dosage form in the GI tract.

Depending on the route of administration, a conventional dosage form of the drug e.g. solution, suspension, capsule, tablet etc produce a drug blood level time profile which does not maintain within the therapeutic range for longer periods by, for example increasing the dose of an intravenous injection, toxic levels may be produced at any time. An appropriately designed controlled-release drug-delivery system can be a major advance toward solving this problem. An alternative is to administer the drug repetitively using a constant dosing interval. Controlled released drug delivery system may have the profound advantage to address this purpose Controlled release (CR) technology actively explored in the pharmaceutical industries for prolonged therapeutic action, reduced cost and commercial advantages [6-7].

Now days a great deal of attention has been paid to such system in both industrial and academic laboratories due to therapeutic, economic and commercial advantage. Sustained release dosage formulations by wet granulation processes are traditional system in order to achieve prolonged action without avoiding multiple doses taking which is commonly needed for maintaining therapeutic action of the drug for a stipulated period. This type of dosage form can be defined as “the drug delivery system that is designed to have a prolonged therapeutic effect by continuously releasing the active ingredient over an extended period of time after administration of a single dose [8].

Sustained or controlled drug delivery occurs while embedded with a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously combined with a drug or other active ingredients in such a way that the active agent is released from the material in a redesigned fashion. The main target was that the active agent must be released at constant rate over a stipulated period of time. In most cases, the purpose of controlling or sustaining the drug delivery is to achieve more effective therapeutic action with eliminating the potential for both under and overdosing. There are a number of techniques applied for the formulation as well as in the manufacturing of sustained release dosage form. A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. Polymers that primarily forming insoluble or skeleton matrices are considered as the first category of retarding materials are classified as plastic matrix systems. The second class represents hydrophobic and water-insoluble materials, which are potentially erodible and the third group behaves hydrophilic properties [11-12].

The hydrophobic and waxy materials, on the other hand, are potentially erodible and control the release of drug through pore diffusion and erosion. Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, does not disintegrate, but immediately hydrated with aqueous fluid and form viscous gelatinous surface barrier that control release of drugs and allowed liquid penetration into the center of the matrix system [9,13-14].

During recent years there has been an upsurge of research into providing sustained release formulations. An appropriate designed sustained release drug delivery system can be major advantages toward solving the problems of conventional dosage forms. In the last two decades, sustained-release dosage forms have made significant progress in terms of clinical efficacy, patient compliance and cost effective. Theophylline Hydrochloride is used mainly in a therapy for respiratory disease. 250-500 mg is considered therapeutically effective every twelve hours and for child over 6 years 125-250 mg every 12 hours as well. In this study an attempt was made to prepare sustained release 300 mg tablet of Theophylline Hydrochloride with desired drug release pattern [15-16].

EXPERIMENTAL SECTION

Drug and other materials used to perform this study are given in below table -1

Table- 1: List of Drug and other materials used to perform this study

Sl. No.	Type of Materials	Name	Source or Origin
1	**Drug**	Theophylline Hydrochloride	Abbott Logistics B.V
2	**Polymer**	Hydroxypropyl methylcellulose-Methocel K15M Premium USP/EP	Gift from Square pharma
3		Hydroxypropyl methylcellulose-Methocel K100 MCR Premium USP/EP	Gift from Incepta pharma
4		Methocel K4 MCR premium	Colorcon Asia Pvt. Ltd.
5	**Excipients**	Microcystalline Cellulose (Avicel-101)	Comprecel 101, Mingtai Chemical Co. Ltd., Taiwan
6		Polyvinnyl Pyrrolidone (Povidone K-30)	BASF, Southeast Asia Pvt. Ltd
7		Colloidal Silicon Dioxide (Aerosil 200)	Deggusa AG, Germany
8		Magnesium Stearate	Chemical Management Co., Germany
9		Lactose	The Lactose Co. Newzeland
10		Dibasic Calcium Phosphate	Sunny Pharmaceutical Ltd., China
11	**Solvents and Reagents**	Sodium dihydrogen orthophosphate	BDH, U.K
12		Disodium phosphate dibasic	BDH, U.K
13	**Equipments**	Clit Tablet Press	India
14		Shimadzu UV Spectophometer	Shimadzu, Japan
15		Digital pH meter	Done from Square pharma
16		Electronic Hardness tester	Erweka, Germany
17		Electrolab Tablet Dissolution Test machine (XXII)	Done from Square pharma
18		Sartorius Electronic Balance	Germany
19		Mettler Toledo Moisture Analyzer	Switzerland
20		Pharmatest Friabilitator	Germany

Preparation of Matrix Tablet:

Tablets were prepared by the method of wet granulation. The active ingredient, release retardants, diluents, fraction of polymer are mixed together and are made wet mass for granulation. After sieving through 30 mesh granules are formed. The Loss On Drying (LOD) of the granules are maintained within 0.70% to 1.00%. Lubricant, the rest of polymers and flow promoters were blended together by dry mixing with the dried granules and made into tablets by compression at a fixed compression force. The formulation perspective parameters and quantity are presented in table 3.2. In all cases, the amount of the active ingredient (theophylline hydrochloride) is 300 mg/tab. Properly weighed materials were blended in a laboratory for 10 minutes. Particular attention has been given to ensure through mixing and phase homogenization. The appropriate amounts of the mixture were then compressed using a Clit compression machine equipped with a 12.5 mm faced punch and die set. The hardness was in between 120 N to 150 N. All the preparations were stored in airtight containers at room temperature for further study. This method of tablet production has previously been reported & provided reproducible experimental results in terms of in vitro release. However, this process of tablet manufacturing differs from practical condition to a large extent and does not consider some critical tabletting parameters such as porosity, tablet hardness and versatility of process conditions. Data generated from such systems require sufficient scaling up and should not be directly extrapolated to commercially prepared controlled release tablets. Different features of the formulations are shown in the following tables. Formulation of matrix tablet of Theophylline hydrochloride is given in table -2 and 3

Table-2: Formulation of matrix tablet of Theophylline hydrochloride using single polymer (Methocel K 15 M CR)

Name of ingredients	Formula 1 mg/tab	Formula 2 mg/tab	Formula 3 mg/tab	Formula 4 mg/tab
Granulation Stage				
Theophylline anhydrous	300	300	300	300
Microcrystalline Cellulose(Avicel PH 101)	84.75	84.75	84.75	84.75
Dibasic calcium Phosphate	76.5	76.5	76.5	76.5
Povidone k 30	7.5	7.5	7.5	7.5
Methocel K 15 M CR	10	10	10	10
Blending Stage				
Methocel K 15 M CR	10	12.5	14	15
Purified Talc	7.5	7.5	7.5	7.5
Magnesium stearate	3.75	3.75	3.75	3.75
Total tablet Weight	500 mg	500 mg	504 mg	505 mg

Table-3 Formulation of matrix tablet of Theophylline hydrochloride using double polymer (Methocel K100M CR premium and Methocel K4M CR premium,)

Name of ingredients	Formula (F-5) (mg/tab)
Mixing and preliminary Blending Stage	
Theophylline anhydrous	300
Lactose	120.25
Methocel K100M CR premium	15
Methocel K4M CR premium	20
Purified talc	1
Magnesium stearate	3
Crosscarmellose sodium	2
Granulation and final blending stage	
Methocel K100M CR premium	10
Maize Starch	10
Povidone K-30	5
Magnesium stearate	3.75
Purified water	0.40
Total tablet Weight	490 mg

Evaluation of Tablet

Loss on drying: 20 Tablets were taken in a clean dry mortar and crushed to make fine powder. 10 gm of powder was weighed and moisture content was measured at 105 °C for 05 minutes with Mettler Toledo moisture analyzer.

Hardness and thickness: Six tablets of each formulation were taken and hardness and thickness were measured with Erweka hardness tester. Average value of hardness and thickness was calculated in neuton (N) and mm respectively.

Friability: 10 Tablets of each formulations were taken and weighed. Tablets were taken in the rotating disc of a friability tester, Pharmatest friabilitator. It was allowed to rotate at 25 rpm for 4 minutes. At the end of the rotation, tablets were collected, dedusted and re-weighed. The friability was calculated as a percent of weight loss.

In vitro dissolution study of the matrix tablet

Preparation of dissolution medium: Dissolution medium was prepared according to the USP method. This was Preparation of phosphate buffer at pH 7.5 . For Phosphate buffer solution preparation, 6.8 g of monobasic potassium phosphate was dissolved in 250 ml of water. 190 ml of 0.2 N sodium hydroxide was added in 400 ml of water, the pH was adjusted with 0.2 N sodium hydroxide to a pH of 7.5 ± 0.1 which was diluted with water to 1000 ml, and mixed.

Dissolution test: In-vitro drug release study from the prepared matrix tablets were conducted for a period of 8 hours using as a Medium of Phosphate buffer solution; 900 ml and Apparatus-2 for 50 rpm. The amount of theophylline was determined by employing UV absorption at the wavelength of maximum absorbance at about 278 nm on filtered portions of the solution under test, suitably diluted with medium, and, in comparison with a Standard solution having a known concentration of USP verapamil hydrochloride as RS in the same medium. As per compendia times and the percentages of release of the labeled amount of theophylline dissolved at the times specified was conformed to accept Table -4.

Table -4: Drug release percentage with specified time

Time (hours)	Amount dissolved
0 (After 1st Hour)	between 3% and 30%
2	between 15% and 50%
4	between 45% and 80%
6	NLT (not less than) 70%
8	NLT 85%

Drug content assay:

Drug content of the sample solution i.e. the quantity of the drug release was determined by spectrophotometric analysis and the absorbance measured at 276 nm by using Shimadzu UV spectrophotometer. The water bath was checked, if necessary, water was added to maintain the desired water level. The dissolution medium was introduced in each of the six vessels. The thermostat was adjusted at 37.8^0C. After attaining this temperature the rotation was

adjusted at 50 rpm. One tablet was placed in each of the five vessels and in the 6th vessel place 240 mg Theophylline hydrochloride. The apparatus was operated for one hour. After 1st hour 10 ml solution was taken from each of the vessels and filter. 50 ml 2M sodium hydroxide was added in each of the vessels and p^H was checked. The p^H was adjusted at 7.5 by using 2M sodium hydroxide and 1M phosphoric acid. The instrument was run for further seven hours. After an hour 10 ml solution was taken from each of the vessels and filter. At the same time this volume was adjusted by adding 10 ml fresh phosphate buffer p^H 7.5 in the vessels.

The filtrate was collected. The procedure was repeated after 4th hour and 8th hour. Every time the absorbance was measured at 278 nm of an ultraviolet spectrophotometer. The % dissolution was calculated by using the following equation

$$\% \text{ Dissolution} = \frac{As \times P \times 100}{Ast}$$

where, As = absorbance of the sample solution.
Ast = absorbance of the standard solution.
P = potency of standard Theophylline hydrochloride.

The average % release of six tablets of each proposed formulation was calculated.

Analysis of release data:
The release data obtained were treated according to zero- order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of drug remaining versus square root of time) and Korsmeyer-peppas (log cumulative percentage of drug released versus log time) equations model.

RESULTS AND DISCUSSION

For the development of Theophylline hydrochloride sustained release dosage form three different grades of cellulose derivative; HPMC-Methocel K15M CR and Methocel K100M CR premium and Methocel K4M CR premium were used by wet granulation method. Four dosage forms were developed by using HPMC-Methocel K15M CR and another dosage form was developed by using double polymer Methocel K100M CR premium and Methocel K4M CR premium.
The effect of three different grades of hydroxypropyl methylcellulose (HPMC) as HPMC-Methocel K15M CR, Methocel K100M CR premium and Methocel K4M CR premium on theophylline hydrochloride sustained release dosage was assessed. Four formulations (F-1, F-2, F-3 and F-4) containing different percentage of hydroxypropyl methylcellulose-Methocel K15 MC R in blending and granulation stage were subjected to various evaluation tests such as LOD, content uniformity, hardness and friability. The result is showed in table 5. Another trial formulation (F-5) containing different percentage of hydroxypropyl methylcellulose- Methocel K100M CR premium and Methocel K4M CR premium was subjected to dissolution study to compare the polymer effect on drug release profile.

The dissolution study of different formulations (F-1, F-2, F-3, F-4 and F-5) based tablet matrices were added in simulated intestinal fluid for 8 hours period. The percent releases from different formulas (F-1, F-2, F-3, F-4) based polymer matrix were summarized on the table 6. The percent release of formula containing Methocel K100M CR premium and Methocel K4M CR premium is summarized on the table -6.

Table- 5: Summary of LOD, Assay, Average Wt, Standard deviation, Friability and Hardness

Parameter	F-1	F-2	F-3	F-4
LOD (%)	4.46	4.38	4.58	4.30
Assay (mg)	287.53	286.20	288.00	289.30
Average Wt (mg)	500	501	500	502
Standard deviation	3.6	4.40	3.6	2.9
Friability (%)	0.62	0.40	0.40	0.35
Hardness (N)	131N-150N	135N-149N	147N-150N	115N-137N

Table- 6: Effect of HPMC-Methocel K15 MCR on dissolution profile of Theophylline hydrochloride sustain release tablet from formulations F-1 to F-4

Time (hours)	% of drug released			
	F-1	F-2	F-3	F-4
0(3-30%)	40%	32%	30%	29%
2(15-50)%	68%	56%	50%	45.00%
4(45-80)%	80%	86%	75%	65.00%
6(NLT 70%)	85%	90%	89%	85.00%
8(NLT 85)%	96%	98%	95%	101.00%

Drug release data obtained were extrapolated by zero-order, first-order, Higuchi and Korsmeyer-peppas model to analyze the pattern of release. The release pattern was shown in the figure 1, 2, 3 and 4 respectively.

Fig-1: Zero-order plot of release kinetics of four different formulations

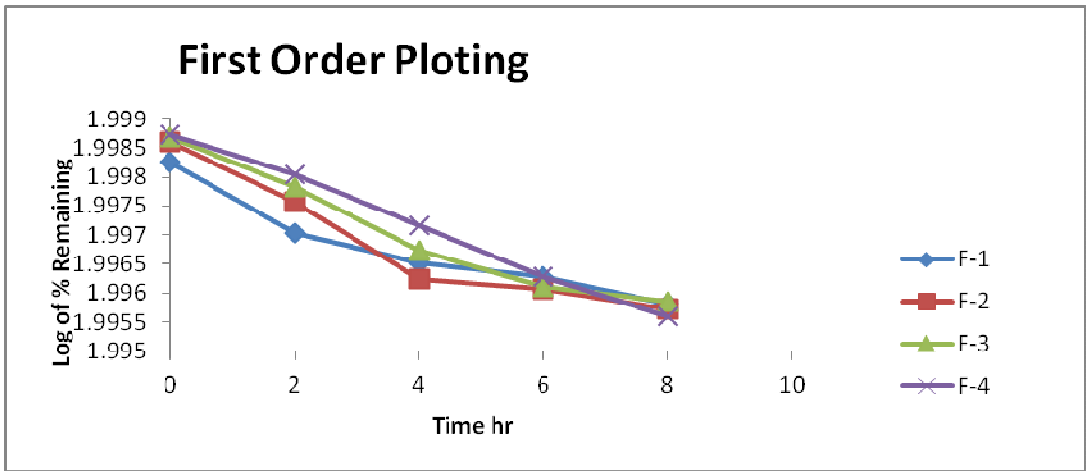

Fig-2: First- order plot of release kinetics of four different formulations

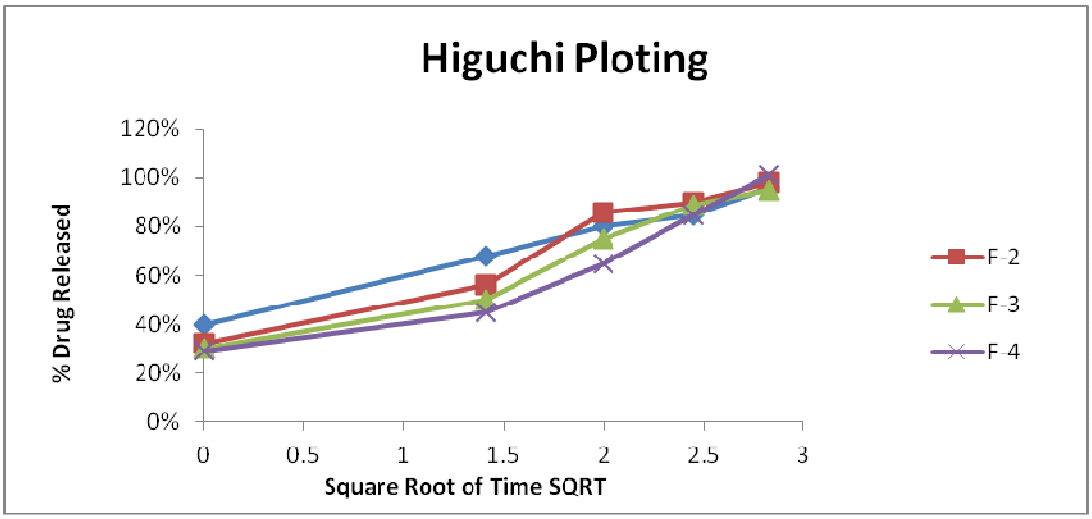

Fig-3: Higuchi plot of release kinetics of four different formulations

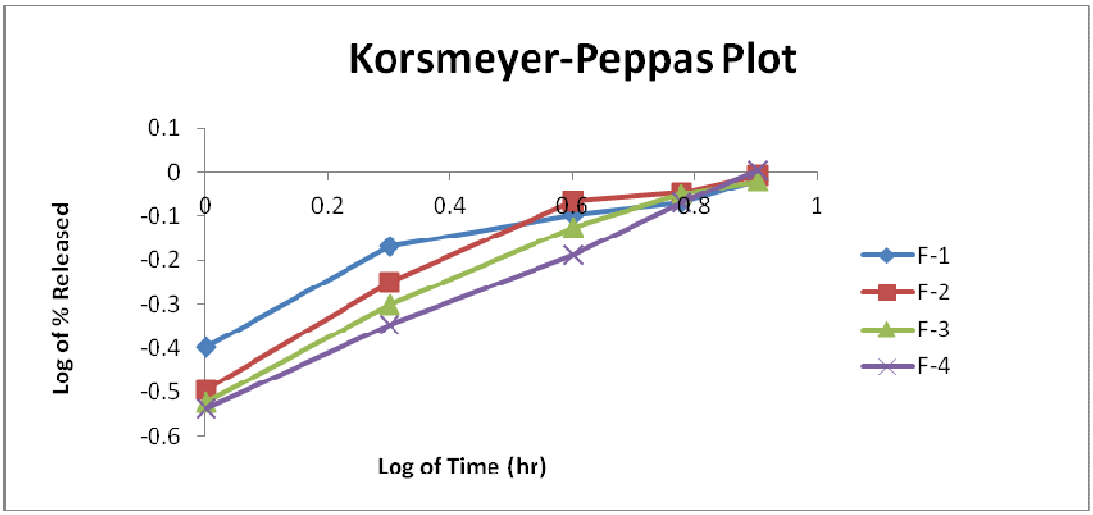

Fig-4: Korsmeyer- Peppas plot of release kinetics of four different formulations

Four formulation F-4 containing hydroxypropyl methylcellulose-Methocel K15 MC R in blending and granulation stage were subjected to comaparison evaluation tests of release with two available market preparation denoted as MP-1 and MP-2.These were also analyzed for zero-order and first-order release kinetics. The data and figure were shown in table 7 and figure 5 & 6 respectively.

Table -7: Comparative evaluation of dissolution profile of Theophylline hydrochloride sustain release tablet using single layer polymer HPMC-Methocel K15 MCR with two available market products denoted as MP-1 & MP-2

Time (hours)	% of drug released		
	F-4	MP-1	MP-2
0(3-30%)	29%	27%	28%
2(15-50)%	45.00%	42%	44%
4(45-80)%	65.00%	67%	60%
6(NLT 70%)	85.00%	70%	75%
8(NLT 85)%	101.00%	82%	84%

**MP: Market Product*

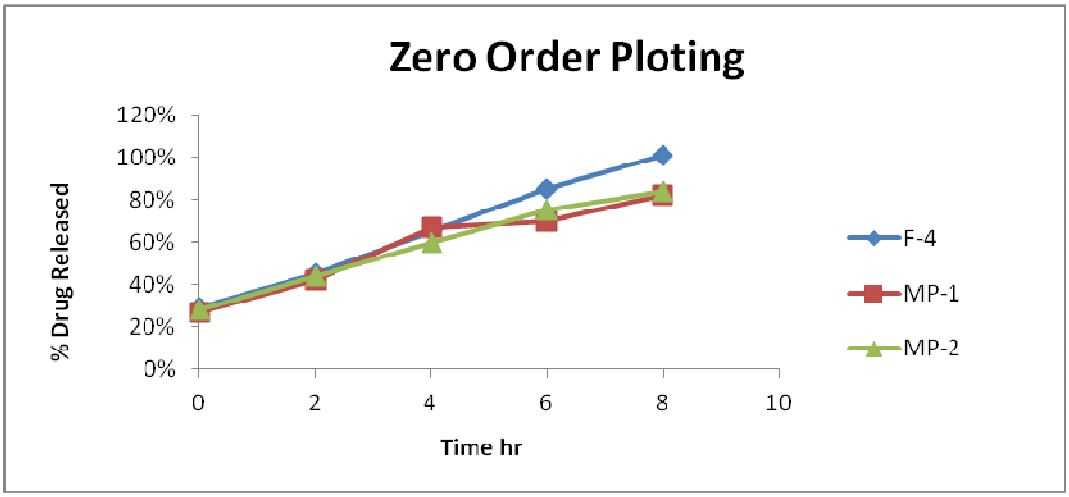

Fig-5: Zero-order plot of release kinetics of formulation F-4 and MP-1 & MP-2

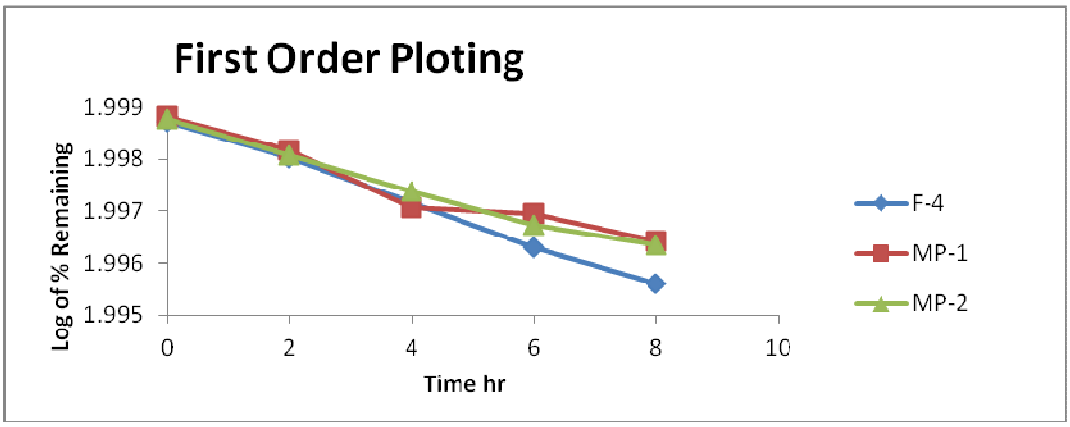

Fig-6: First-order plot of release kinetics of formulation F-4 and MP-1 & MP-2

Another formulation containing Methocel K100M CR premium and Methocel K4M CR premium which met all the tabletting parameter and release profile as per table no. 3.4. Formulation F-5 was also subjected to release kinetics of zero-order, first-order, higuchi and korsmeyer model to evaluate release pattern. The data and figure was shown in table 8 and figure 7, 8, 9 and 10 respectively.

Table -8: Effect of double polymer HPMC-Methocel K100M CR premium and Methocel K4M CR premium on dissolution profile of Theophylline hydrochloride sustain release tablet of formulation F-5

Time (hours)	% of drug released
	F-5
0(3-30%)	43%
2(15-50)%	55.50%
4(45-80)%	69.08%
6(NLT75%)	84.10%
8(NLT85)%	99.00%

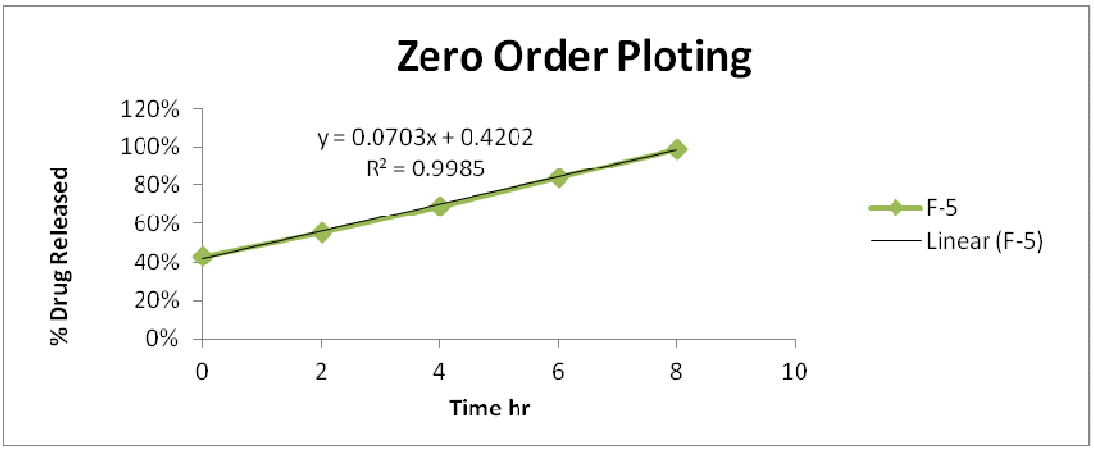

Fig-7: Zero-order plot of release kinetics of formulation F-5

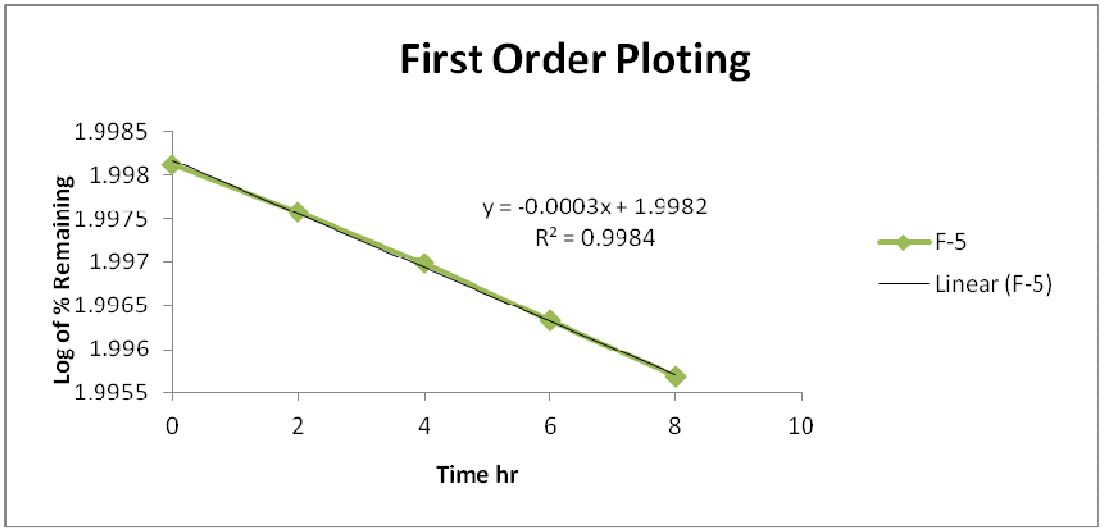

Fig-8: First-order plot of release kinetics of formulation F-5

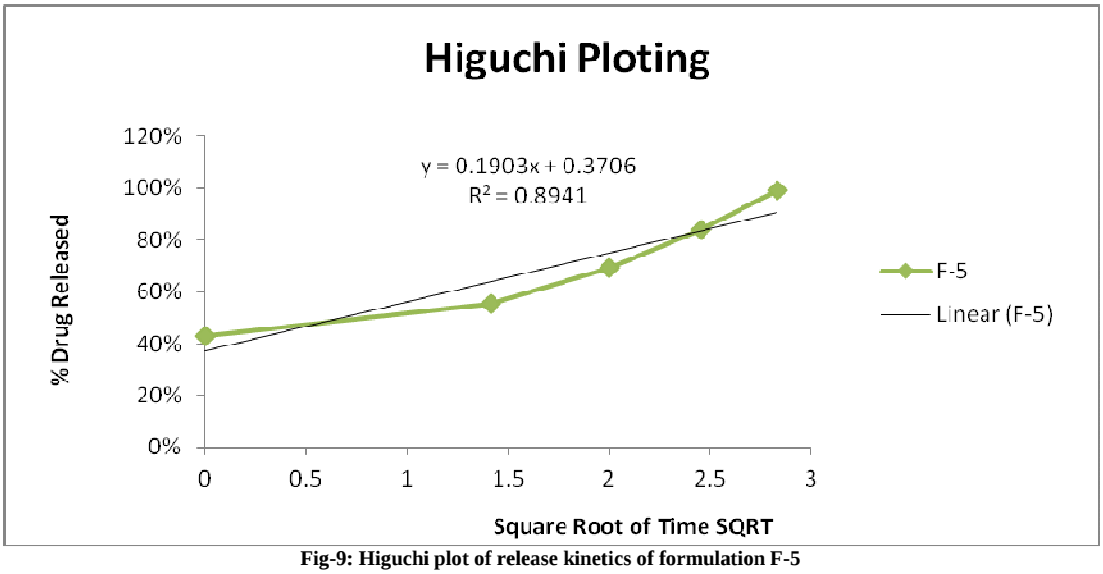

Fig-9: Higuchi plot of release kinetics of formulation F-5

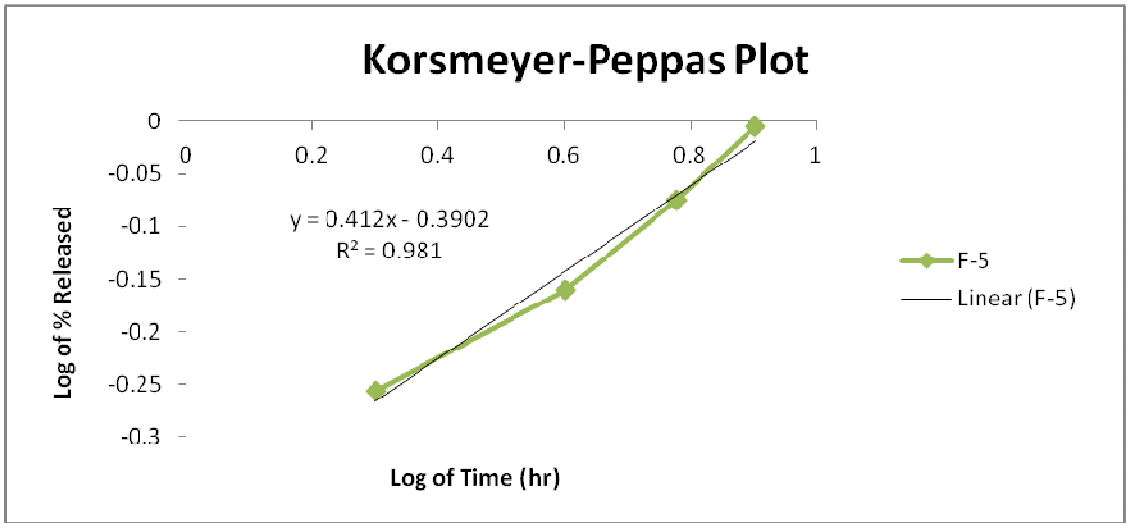

Fig-10: Korsmeyer-peppas plot of release kinetics of formulation F-5

Release profile of formulation F-4 was also compared with the release pattern of formulation F-5 containing double polymer HPMC-Methocel K100M CR premium and Methocel K4M CR premium. The release data and zero-order and first-order release kinetics were shown in table 9 and figure 11 and 12.

Table -9: Comparison of Effect of single layer polymer HPMC-Methocel K15 MCR against double polymer HPMC-Methocel K100M CR premium and Methocel K4M CR premium on dissolution profile of Theophylline hydrochloride sustain release tablet of formulations denoted as F-4 to F-5

Time (hours)	% of drug released	
	F-4	F-5
0(3-30%)	29%	43%
2(15-50)%	45.00%	55.50%
4(45-80)%	65.00%	69.08%
6(NLT75%)	85.00%	84.10%
8(NLT85)%	101.00%	99.00%

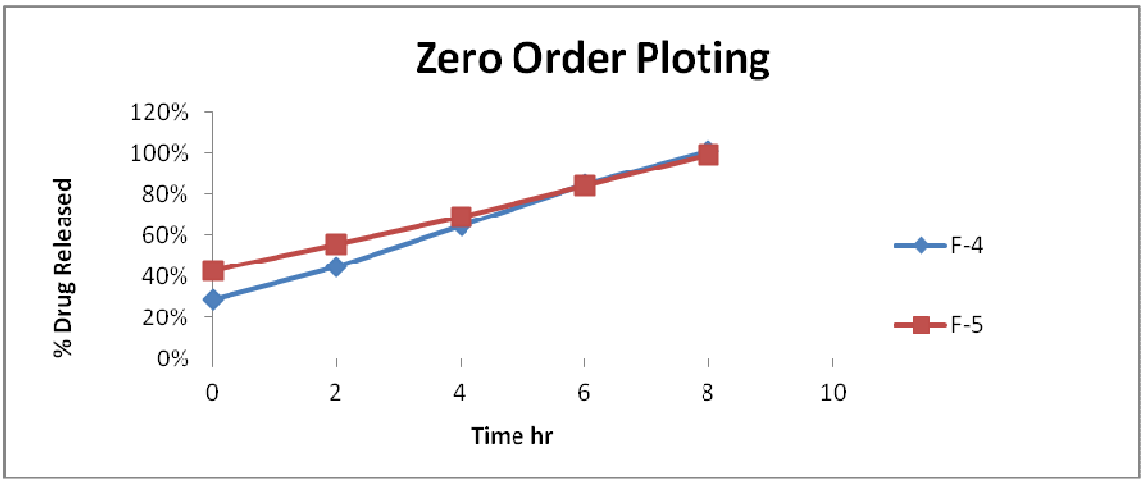

Fig-11: Zero-order plot of release kinetics of formulation F-4 and F-5

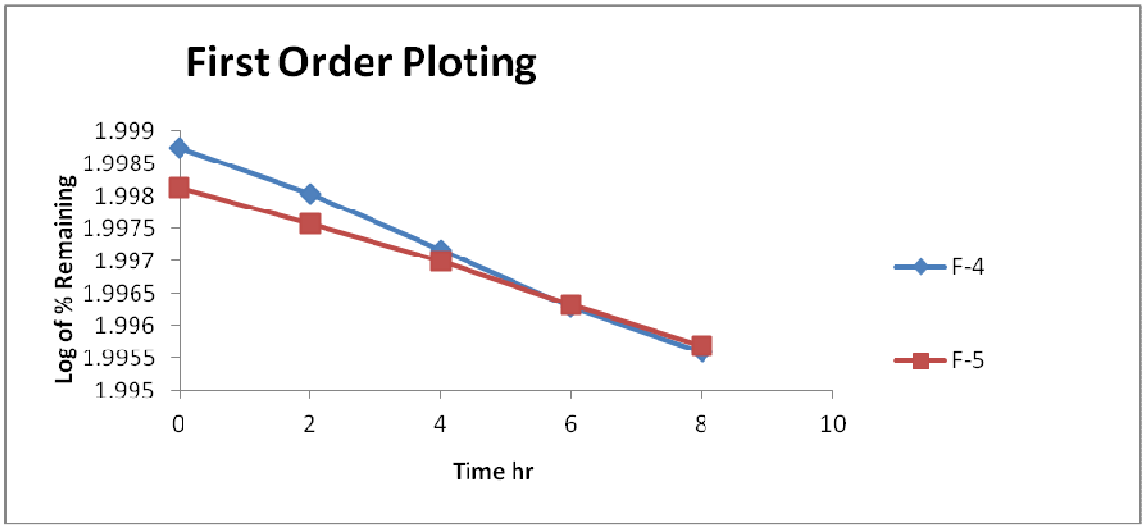

Fig-12: Zero-order plot of release kinetics of formulation F-4 and F-5

From the following release profile it was observed that above proposed formulations (F-4) met the desired sustained release pattern as per USP specification (30th edition, 2006). This indicated that blends of Methocel K15 M CR met desired sustained release of theophylline hydrochloride by wet granulation method from 1st hour to 8th hour *in vitro* dissolution studies.

At the same time we have compared the dissolution profile of a marketed product with our test product (Formula 1, 2, 3, 4). In that case the marketed product showed irregular dissolution profile in sixth and eighth hour. Marketed product was randomly collected two batches from different medicine shop to ensure the representative of whole batch. On the other hand the test trial containing Methocel K100M CR premium and Methocel K4M CR premium also showed deviated release pattern, moreover it may require higher cost due to using double polymer with other excipients and processing complexity. Although the release kinetics of formulation F-5 showed good zero-order and first-order kinetics but it showed deviated poor release pattern as per Higuchi plotting and Korsmeyer-peppas plotting.

CONCLUSION

Theophylline hydrochloride is a dimethylxanthine, is a methylxanthine drug, used widely in the treatment of respiratory disease. The half life of Theophylline Hydrochloride is 5-8 hours for oral dosage. Due to its elimination and posology, this drug is a suitable candidate to be formulated into sustained release dosage forms. The present study was investigated in order to formulate Theophylline hydrochloride sustained release tablet dosage form with addition of release retarding double polymer HPMC-Methocel K15M CR and HPMC-Methocel K100 M CR and HPMC-Methocel K4 M CR. From the study it was concluded the formulation F-5 showed partially deviated regular release profile. Although it complied zero order and first order kinetics but does not meet the specified release pattern for Higuchi plotting and Korsmeyer-peppas plotting as per specification in compendia.

From the above comparative study it may be concluded that formulation containing single polymer can replace the formulation containing double polymer if any chance of dose dependent complication is absent which can be investigated by under clinical trial. In addition, it will reduce the cost, processing time. Overall it will offer cost effective treatment. Wet granulation method may increase high production, performance, save valuable time in manufacturing plan, less involvement of labour, reduce cost and increase profit. However, The proposed formulations (Formula F-4) may be used for the development of Theophylline hydrochloride sustained release matrix and meet the patient's demand in order to combat against ulcer more precisely. Further study may be required to establish firmly the proposed formula with double polymer containing Methocel K4M CR and Methocel K100 M CR premium at different concentration other than formula F-5.

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