Formulation and *In Vitro* Evaluation of Theophylline Sustained Release Tablet from Hydrophobic Matrix

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Abstract

In the present study theophylline sustained release tablet matrix was prepared by utilizing the spray dried powder grade polymer kollidon SR (polyvinyl acetate and Povidone based matrix retarding hydrophobic polymer) by direct compression method. Different amount of kollidon SR was used to develop matrix builder in the five proposed formulations (F-1 to F-5) for the study of release rate retardant effect at 10%, 12%, 15%, 18% and 20% of total weight of tablet matrix respectively. The *in vitro* dissolution study of kollidon SR based tablet matrices of those proposed formulations were carried out in the simulated gastric medium (pH 1.3) for first two hours and then in the simulated intestinal medium (pH 6.8) for 6 hours using USP dissolution apparatus II (paddle method). The formulation F-3 (using 15% polymer) and F-4 (using 18 % polymer) met the optimum release of theophylline for 8h period dissolution study. The drug release kinetics was plotted against zero order, first order and Higuchi release kinetics to assess the release mechanism of theophylline from the formulated tablet matrix. The release kinetics of formulation F-3 and F-4 was very closely followed by Higuchi kinetic order than first order and zero order kinetics that reflected the type of drug release from the tablet matrix by diffusion and erosion mechanism.

Key Words: Theophylline, Direct compression, Controlled release, Kollidon SR, Tablet matrix.

1. Introduction

Theophylline is a naturally occurring alkaloid and it is one of the most widely prescribed drugs for the treatment of airway diseases worldwide, where the major use is in the treatment of asthma and chronic obstructive pulmonary disease (COPD). According to recent international guidelines, theophylline has been relegated to third-line therapy in asthma (Global Initiative for Asthma Guidelines, 2002) and COPD (Goodman and Gilman's, 2001). Theophylline sustained release tablet matrix was prepared by direct compression method by utilizing Kollidon SR. These polymers are hydrophobic in nature and can hold active ingredients firmly that depends on the concentration or ratio of the polymers used (Longer et al., 1990). Oral sustained release dosage form by direct compression technique is a very simple approach of drug delivery systems that proved rational demand in the pharmaceutical arena as its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms . Sustained or controlled drug delivery occurs while embedded with a polymer that may be natural or semisynthtic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a redesigned fashion and released the drug at constant rate for desired time period (Lordi, 1992). There are a number of techniques applied in the formulation as well as in the manufacturing of sustained release dosage form however the matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. Direct compression method has been applied for preparation of tablet matrix that involved simple blending of all ingredients used in the formulations and then under went direct compression. It required fewer unit operations, less machinery, reduced number of personnel and reduced processing time, increased product stability and faster production rate (Shangraw et al.,). A wide array of polymers has been employed as drug retarding agents each of which

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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 and are classified as plastic matrix systems. The second class represents hydrophobic and water-insoluble materials, which are potentially erodable and the third group behaves hydrophilic properties (Reza *et al.,* 2003).

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. The release of drug from the tablet matrix depends on the nature of polymer. Kollidon SR is hydrophobic polymer that becomes hydrated, swollen and facilitates to diffuse the drug. In the present study an attempt has been made to formulate theophylline sustained release tablet matrix with the addition of release retarding polymers kollidon SR and to evaluate the effect of kollidon SR to sustain the release of theophylline from the theophylline sustained release tablet matrix by direct compression and determine the type of polymer exhibit better sustained release of theophylline and drug release mechanism from the tablet matrix (Bidah *et al*.,).

2. Materials and method

2.1. Materials

Theophylline (Merk, Germany); Kollidon SR (BASF, Germany); Microcystalline Cellulose (Avicel-101) (Hanau Chemicals Ltd, Japan); Polyvinnyl Pyrrolidone (Povidone K-30) (Hanau Chemicals Ltd, Japan); Colloidal Anhydrous Silica (Aerosil 200) (Hanau Chemicals Ltd, Japan); Magnesium Stearate (Hanau Chemicals Ltd, Japan); Hydrochloric acid (Merk, Germany)**;** Sodium Hydroxide (Merk, Germany)**;** Ortho phosphoric acid (Merk, Germany) were used. **Equipments:** Single Punch Tablet Press**;** Simadzu UV Spectophometer**;** Digital pH meter**;** Electronic Hardness tester (Ereweka, Germany)**;** Electrolab Tablet Dissolution Test machine (XXII)**;** Sartorius Electronic Balance.

2.2. Preparation of dissolution medium

For dissolution simulated gastric medium (pH 1.3) and intestinal medium (pH 6.8) were required. a) **Preparation of gastric medium (0.1 N HCl pH 1.3)**: For 0.1N HCl, 11.4 ml of Hydrochloric acid (32% w/v) was diluted with sufficient water to produce 1000 ml. b) **Preparation of intestinal medium (Buffer pH 6.8)**: 20 ml Sodium Hydroxide (25%) was diluted with 0.1 N Hydrochloric acid to 1000 ml adjusting pH 6.8 by addition of 1.2 ml of ortho-phosphoric acid.

2.3. Preparation of tablet

Drug, polymer and other excipients were weighed separately for 20 tablets per formulation as per proposed formulations. The proposed formulations were coded as F-1, F-2, F-3, F-4, and F-5. The amounts of drug and excipients are expressed in milligram. Then active ingredient, microcrystalline cellulose, povidone K-30, polymer and aerosil were blended for 15 minutes and then magnesium stearate was added and further blended for another 1 minute. Blended mass was taken in the hopper and then die and punch were adjusted to get the desired weight of the tablet (500 mg). After compression the tablets were weighed and tablet weight was found 495 mg-505 mg. The tablets were prepared by direct compression using kollidon SR (Table1).

2.4. In vitro dissolution study of tablet

Dissolution studies were conducted according to USP method (USP XXII) using apparatus II paddle at a speed of 100 rpm and the temperature was maintained at 37.0±0.5^{o} C. The total duration of dissolution was 8 hours in which the first 2 hours the tablet matrices were subjected to simulated gastric media (0.1 N HCl pH 1.3) and the later six hours the tablet matrices were subjected to simulated intestinal media (Buffer pH 6.8). **Acid stage**: 900 ml of 0.1 N HCl was placed in each vessel and the apparatus was assembled. Six tablets from each formulation were weighed and placed in the baskets. The operation in the acid stage was carried out for 2 hours. After each hour 10 ml of sample solution was withdrawn and filtered. The released drug was assayed by using UV spectrophotometer at 272 nm. **Buffer stage**: After 2 hours operation in the acid stage, 20 ml NaOH (25%) was added to the previous fluid. The pH (6.8 ±0.05) was adjusted with addition of 1.2 ml ortho-phosphoric acid. The operation was continued for 10 hours. After each one hour interval 10 ml of dissolution solution was sampled and filtered and the released drug assayed by using UV spectrophotometer at 272 nm. At each withdrawal 10 ml of fresh dissolution medium was added.

2.5. Kinetic analysis of release data

The release of drug from sustained release dosage form is controlled by several processes. These

are extraction or diffusion of drug from matrix and erosion of matrix; alternatively the drug may be dissolved in the matrix material and then released by diffusion through membrane. In some cases, drug may be released by osmotic process. Different kinetic equations (Zero order, First order, and Higuchi's equation) were applied to interpret the release rate from the tablet matrix. The best fit of higher correlation ($R^2 > 0.98$) was found with well-known Higuchi equation.

Higuchi derived the rate of release of drugs dispersed in an inert matrix system.

Higuchi equation is -

$$dM/dh = Co.dh - Cs/2$$

Where,

dM = Change in the amount of drug release per unit area

dh = Change in the thickness of the zone of matrix that been depleted of the drug

Co = Total amount of drug in a unit volume of the matrix

Cs = Sustained concentration of the drug within the matrix

3. Results and discussion

In this study Kollidon SR (the spray dried powder grade polymer) was used for the development of theophylline sustained release tablet matrix by direct compression method. The effect of Kollidon SR on theophylline sustained release dosage form was assessed. As it contains no ionic groups it shows no interaction with most of the commonly used APIs and excipients (Arthur, 2000). Different percentage of kollidon SR (10%, 12%, 15%, 18% and 20% of total weight of tablet matrix) containing tablet matrices were added in the dissolution media according to design of study. The percent release from all the respective polymer matrix systems were plotted against time to observe drug release pattern. It was seen that percent of drug release was increased by decreasing the amount of kollidon SR in the proposed formulations (Table1) and from the release kinetics. (Table 2-4). The variable ranges of kollidon SR were selected by considering physicochemical behavior of the polymer in the physiological fluid and physicochemical properties of the drug. According to USP, for an ideal sustained release dosage form, the percent release in 1st hour should be not more than 30% and in 10th hour not less than 80% (USP 29th Edition, 2006). The release pattern of theophylline from the proposed formulation F-3 (15% kollidon SR) and proposed formulation F-4 (18% kollidon SR) met the desired sustained release pattern (Table 5). This indicated that at minimum percent i.e. 15% of kollidon SR met the desired sustained release of theophylline by direct compression method from 1st hour to 8th hour *in vitro* dissolution studies.

Determination of release mechanism from multiple coefficients

The drug release data proposed formulations F-1, F-2, F-3, F-4, and F-5 were treated in different kinetics orders such as Zero Order, First Order and Higuchi kinetics and their correlation coefficients were determined graphically to identify their release mechanism. The drug percent release was plotted against time to get zero order release kinetics, log% remaining against time to get first order release kinetics and the percent release versus square root of time to get Higuchi release kinetics and from correlation coefficient we can determine the mechanism of release kinetics. The correlation coefficient getting close to 1.0, the release kinetics will be followed that order of the proposed formulations. From the Table 5, it was observed that proposed formulations F-3 and F-4 followed Higuchi release mechanism (Higuchi *et al*.). The proposed formulations F-1, F-2, F-3, F-4 and F-5 although followed first order and Higuchi release kinetics as shown in the Table 4 & Table 5, however, the release kinetics was very close to 1 in case of Higuchi plot than other kinetic orders that indicated Higuchi release kinetics was predominant here.

4. Conclusion

Theophylline is widely used against asthma and COAD, which is a very common disease where the patients take medicine regularly. Sustained release dosage form of theophylline can provide better patient compliance and prolonged action against asthma and COAD. The half life of theophylline is 8 hour in adults although there is large intra and inter individual variation, and also varies greatly with age being approximately 30 hours in premature neonates, 12 hours within the first 6 months, 5 hours up to the first year of life and approximately 3.5 hours up to the age of 20 gradually increasing again there after. Due to its rapid 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-sustained release with addition of release retarding polymer kollidon (Lee *et al.,*). From the study it was concluded that at least 18% Kollidon SR showed desired sustained release tablet matrix by direct compression. We also observed that Higuchi release kinetics was the predominant release kinetics among all the release kinetics. The use of direct compression method may increase high production, performance, save valuable time in manufacturing plan, less involvement of labor, reduce cost and increase profit. The proposed formulations (F-3 and F-4) may be used for the development of theophylline sustained release matrix and meet the patient's demand in order to combat against asthma and COAD more precisely.

Table 1: Proposed formulations of Theophylline suatained release matrix tablets

Proposed Formulation	Theophy Lline (mg)	Kollidon SR(mg)	Avicel (mg)	Povidone K-30 (mg)	Magnesium Stearate (mg)	Aerosil (mg)	Total wt.(mg)	Kollidon SR (%)
F-1	300	50	115	25	5	5	500	10
F-2	300	60	105	25	5	5	500	12
F-3	300	75	90	25	5	5	500	15
F-4	300	90	75	25	5	5	500	18
F-5	300	100	65	25	5	5	500	20

Table: 2. Effect of kollidon SR on theophylline from proposed formulations in gastrointestinal fluid and intestinal fluid

% release of drug					
Time (hours)	F-1 (10%)	F-2 (12%)	F-3 (15%)	F-4 (18%)	F-5 (20%)
0	0	0	0	0	0
1	20.14	16.63	16.15	13.68	13.62
2	29.09	26.13	22.63	19.6	18.15
3	53.88	48.93	43.55	37.92	33.12
4	60.47	51.43	48.36	42.08	37.33
5	74.69	70.68	56.32	45.88	40.16
6	80.14	73.4	65.48	49.6	48.31
7	83.54	78.21	71.08	53.84	52.53
8	85.26	82.32	74.25	60.21	55.14

Table 3: Effect of kollidon SR on theophylline from proposed formulations 1-5 in gastrointestinal fluid and intestinal fluid (First Order Plot)

Log % of remaining					
Time (hours)	F-1 (10%)	F-2 (12%)	F-3 (15%)	F-4 (18%)	F-5 (20%)
0	0	0	0	0	0
1	1.90	1.92	1.92	1.93	1.93
2	1.85	1.86	1.88	1.90	1.91
3	1.66	1.70	1.75	1.79	1.82
4	1.59	1.68	1.71	1.76	1.79
5	1.40	1.46	1.64	1.73	1.77
6	1.29	1.42	1.53	1.70	1.71
7	1.21	1.33	1.46	1.66	1.67
8	1.16	1.24	1.41	1.59	1.65

Table 4: Effect of kollidon SR on theophylline from proposed formulations 1-5 in gastrointestinal fluid and intestinal fluid (Higuchi Plot)

% release of drug					
SQRT (hours)	F-1 (10%)	F-2 (12%)	F-3 (15%)	F-4 (18%)	F-5 (20%)
0	0	0	0	0	0
1	20.14	16.63	16.15	13.68	13.62
1.41	29.09	26.13	22.63	19.6	18.15
1.73	53.88	48.93	43.55	37.92	33.12
2	60.47	51.43	48.36	42.08	37.33
2.23	74.69	70.68	56.32	45.88	40.16
2.44	80.14	73.4	65.48	49.6	48.31
2.64	83.54	78.21	71.08	53.84	52.53
2.82	85.26	82.32	74.25	60.21	55.14

Table 5: Multiple coefficients of determination data of Theophylline matrix tablets

Formulation code	Multiple coefficient of determination (R^2)		
	Zero Order	First Order	Higuchi
F-1	0.92	0.91	0.96
F-2	0.87	0.92	0.96
F-3	0.88	0.96	0.98
F-4	0.89	0.95	0.98
F-5	0.92	0.97	0.97

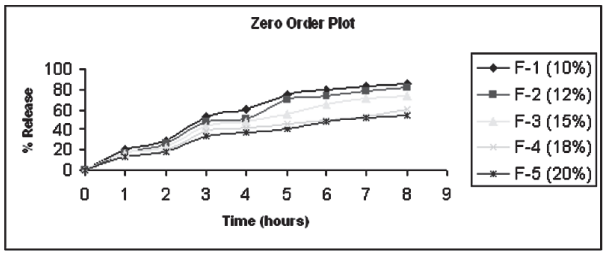

Fig 1: Effect of kollidon SR on theophylline from proposed formulations in gastrointestinal fluid and intestinal fluid (Zero Order Plot)

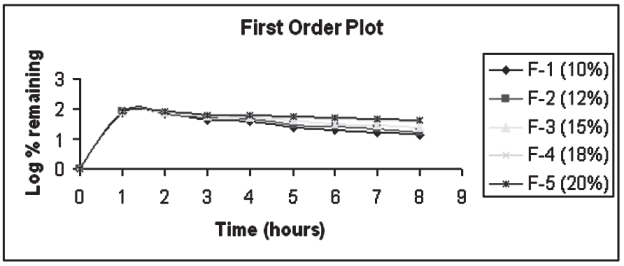

Fig 2: Effect of kollidon SR on theophylline from proposed formulations in gastrointestinal fluid and intestinal fluid (First Order Plot)

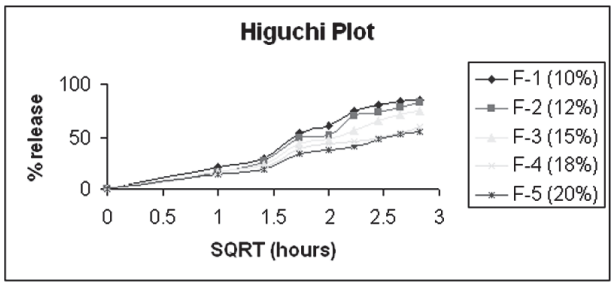

Fig 3: Effect of kollidon SR on theophylline from proposed formulations in gastrointestinal fluid and intestinal fluid (Higuchi Plot)

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