Bangladesh Pharmaceutical Journal ***16****(2): 177-183, 2013*

Release Profile of Losartan Potassium from Formulated Sustained Release Matrix Tablet

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Abstract

The present study was undertaken to develop sustained release (SR) matrix tablets of Losartan potassium, an angiotensin-II antagonist for the treatment of hypertension. The tablets were prepared by direct compression method along with Kollidon SR and Methyl Cellulose as release retardant polymers. The evaluation involves two stages- the physical properties studies of tablets and *in vitro* release kinetics assessment. The USP paddle method was selected to perform the dissolution test and 900 ml phosphate buffer of pH 6.8 was used as dissolution medium at 50 rpm at 37^0C. The release kinetics were analyzed. All the formulations followed Higuchi release kinetics. When the release data was plotted into Korsmeyer-Peppas equation, then it was confirmed that F-1, F-2, F-3, F-4 and F-5 exhibited non-fickian type drug release whereas F-6 exhibited fickian type drug release from the tablet matrix. The *in-vitro* release studies revealed that the formulation F-2 can be taken as an ideal or optimized formulation of sustained release tablets for 24 hours release as it fulfills all the requirements for sustained release tablet. Furthermore, when the tablets were preheated at different temperature (30^0C, 45^0C, 60^0C) before dissolution they showed decrease in drug release compared with ambient temperature.

Key words: Losartan Potassium, Kollidon SR, Matrix Tablets, Methyl Cellulose, Ambient Temperature

Introduction

The oral route is the most often used route for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. Sustained drug delivery involves the application of physical and polymer chemistry to produce well characterized and reproducible dosage forms, which control drug entry into the body within the specifications of the required drug delivery profile (Alderman, 1984). Typically, sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Lachman *et al.,* 1986). The use of polymers in controlling the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Sustained release can be achieved by formulating drugs as matrix devices using HPMC, Sodium CMC and other swellable polymers.

Hydrophilic polymers with high gelling capacity are of particular interest in the field of controlled release drug delivery. In contact with aqueous medium they hydrate at solid-liquid interface and form a viscous layer which retards the release of the drug. The aims of the present study were to investigate the role of hydrophilic polymers in sustaining the release of drugs in tablet dosage form, and to study the effects of proportion of polymers, diluent and drug solubility on drug dissolution characteristics. The release kinetics and mechanism of drug release were also investigated by using various release kinetics model equations (Chien, 1992).

Materials and Methods

Materials: The Losartan potassium was kindly supplied by Globe Pharmaceuticals Limited, Noakhali, Bangladesh, as a gift sample. Kollidon SR was procured from BASF, Bangladesh Limited. Potassium di-hydrogen phosphate (Merck, Germany) and Sodium hydroxide (Merck, Germany) were used as dissolution medium. Magnesium stearate and Lactose were obtained from Novo Pharmaceuticals Limited, Bangladesh and Methyl cellulose was procured from local market. Solvents and all other chemicals were of analytical grade.

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Preparation of matrix tablet: Various methods are available for producing sustained release Losartan potassium tablet preparation. In our experiment, direct compression technique was followed to prepare sustained release Losartan potassium matrix tablet using the following formulations:

Table 1. Proposed formulations for sustained release Losartan potassium matrix tablet.

Ingredients	Amount (mg)					
	F-1	F-2	F-3	F-4	F-5	F-6
Losartan potassium	100	100	100	100	100	100
Kollidon SR	300	350	100	100	350	0
Methyl cellulose	100	100	300	350	0	350
Lactose	100	50	100	50	150	150
Mg stearate	5	5	5	5	5	5
Total	605	605	605	605	605	605

The active ingredient (Losartan potassium), release retardant (Kollidon SR), polymer (Methyl cellulose), filler (Lactose) and lubricant (Magnesium stearate) were blended together by dry mixing in a mortar using a pestle. The dried granules were then sieved through mesh 40. Then the granules were made into tablets by direct compression.

Evaluation of tablets

Length, width, size and shape: The length and width of tablets depend on the die and punches selected for making the tablets. The tablets of various sizes and shapes are prepared but generally they are circular with either flat or biconvex faces. Here, we prepared round cylindrical shape tablets.

Thickness: The thickness of a tablet can vary without any change in its weight. This is generally due to the difference of density of granules, pressure applied for compression and the speed of compression. The thickness of the tablets was determined by using a Digital Caliper (range 0-150 mm).

Uniformity of weight: It is desirable that every individual tablet in a batch should be in uniform weight and weight variation within permissible limits. If any weight variation is there, that should fall within the prescribed limits (generally, USP/ BP recommends ±10% for tablets weighing 130 mg or less, ±7.5% for tablets weighing 130 to 324 mg and ±5% for tablets weighing more than 324 mg) (Gupta, 1994).

The weights of 10 tablets of each batch were taken at individually and calculate the average weight of 10 tablets. The weights were determined by using an electronic balance (Adventurer TM electronic balance, Model AR2140, Capacity (Max) - 210 gm, Readability 0.0001 gm). Then determine the percentage of weight variation of each tablet by using the following formula.

Percentage of weight variation: (Average weight – Individual weight)/ Average wt. ×100

Friability: Friability test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The instrument used for this test is known as 'Friability Test Apparatus' or 'Friabilator'. Ten tablets were weighed (W_1) and placed in the tumbling chamber which was rotated for four minutes or for 100 revolutions. During each revolution the tablets fall from a distance of six inches to undergo shock. After 100 revolutions the tablets were again weighed (W_2) and the loss in weight indicates the friability. The acceptable limits of weights loss should not be more than 1 percent (USP, Gupta, 1994).

$$\text{Friability} = [(W_1 - W_2)/W_1] \times 100$$

Hardness: The hardness of the tablets was determined by using a hand operated hardness tester apparatus (Electrolab EH-01P). A tablet hardness of about 6-8 kg-ft was considered for mechanical stability (British Pharmacopoeia, 2000). If the finished tablet is too hard, it may not disintegrate in the required period of time and if the tablet is too soft it may not withstand the handling during packing and transporting. Therefore it is very necessary to check the hardness of tablets when

they are being compressed and pressure adjusted accordingly on the tablet machine.

Assay of Losartan potassium

Preparation of sample solution: 605 mg of crushed tablet powder (equivalent to 100 mg of active drug) was dissolved in phosphate buffer solution and made the volume up to 100 mL. The solution was diluted 100 times and absorbance was taken.Then the percentage of potency was calculated by the following equation:

$$\% \text{ of potency} = \frac{\text{Aspl x Wstd x Pstd x Average weight}}{\text{Astd x Wspl x Label claimed value}}$$

Where,

A_{spl} = Absorbance of sample

W_{std} = Weight of standard

P_{std} = Potency of standard

A_{std} = Absorbance of standard

W_{spl} = Weight of sample

***In vitro* Release Studies**

Dissolution study procedure: The *in vitro* dissolution studies were performed using USP type-II dissolution apparatus (Rotating Peddle method) at 50 rpm. The dissolution medium consisted of potassium di-hydrogen phosphate buffer of pH 6.8 up to 900 mL, maintained at 37°C ± 0.5°C. An aliquot (5 mL) was withdrawn at specific time intervals which replaced by equivalent amount of buffer solution. The drug content was determined by UV-visible spectrophotometer (SHIMADZU UV-1800 spectrophotometer) at 205 nm. The release studies were conducted in triplicate.

Analysis of release data: The release data obtained were treated according to zero-order (cumulative amount of drug release versus time in hr, Higuchi (cumulative percentage of drug release versus square root of time in hr, Korsmeyer-Peppas (log cumulative percentage of drug release versus log time in hr and Hixson-Crowell (cubic root of percentage drug release versus time in hr equation models. Dissolution data were also fitted according to the well-known exponential equation, which is often used to describe the drug release behavior from polymeric systems introduced by Korsmeyer *et al.* (1983).

$$M_t / M_\infty = k\, t^n$$

Where, M_t is the amount of drug release at time t, M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusional exponent indicative of the mechanism of drug release. A value of $n \leq 0.45$ indicates Fickian (case I) release, > 0.45 but < 0.89 for non-Fickian (anomalous) release and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Korsmeyer *et al.,* 1983; Shato *et al.,* 1997).

Results and Discussion

Drug content and physical evaluation of losartan potassium matrix tablets: The prepared tablets were subjected to preliminary characterization for physical parameters (thickness, length, width, hardness and friability) and weight uniformity. The values shown in Table 2 also express the drug content of these tablets.

All the batches showed uniform thickness and diameter. The average percentage deviation of 10 tablets of each formulation was less than (5%), and hence all formulations passed the test for uniformity of weight as per official requirements (USP). The hardness of all the formulations was within the range of limit. The use of Kollidon SR and Methyl cellulose has facilitated the compression of the tablets and made it possible to impart proper hardness settings. Tablets hardness is, however, not an absolute indicator of strength. The percentage of friability of the tablets of all the formulations were also within the range. In the present study, the percentage friability for all formulations was below 1% w/w, indicating that the friability is within the prescribed limits. So, all the tablet formulations showed acceptable pharmacopoeia properties and complied with pharmacopoeias specifications for weight variation and friability. All the formulations showed good uniformity in drug content and the percentage of drug content was 99.7±1.2, 99.33±0.7, 101.52±1.5, 99.75±0.9, 98.41±0.8 and 101.24±1.1, respectively for formulations F-1 to F-6.

In vitro drug release studies

The dissolution data (from the values of 0 to 8 hours drug release) of all formulations were fitted into various mathematical models (Zero-order, Higuchi, Korysmeyer-Peppas model, Hixson-Crowell plot) to know which mathematical model will best fit the obtained release profile. From all dissolution data the plotted figure are presented in figure 1 and the release kinetics of all formulations is presented in table 3.

Based on highest regression coefficient value (r^2) the best-fit model for all formulations was Higuchi model. When the data where plotted according to a Higuchi equation, the formulations F-1, F-2, F-3, F-4, F-5 and F-6 showed a fair linearity, with regression values 0.938, 0.955, 0.969, 0.951, 0.954 and 0.956, respectively.

Table 2. Physical parameters and drug content of Losartan potassium from proposed formulation.

Code	Weight variation*(%) ±SEM	Thickness (mm)** ±SEM	Length (mm)** ±SEM	Width (mm)** ±SEM	Hardness (Kf)** ±SEM	Friability (%) **	Drug content** (%) ±SEM
F-1	605.88±1.16	8.28±0.23	17.6±0.41	5.05±0.44	6.37±0.01	0.25	99.7±1.2
F-2	605.78±0.68	8.30±0.26	17.5±0.52	5.03±0.53	6.82±0.17	0.33	99.33±0.7
F-3	605.59±0.35	8.31±0.19	17.49±0.59	5.04±0.65	6.34±0.29	0.73	101.52±1.5
F-4	605.92±0.52	8.30±0.22	17.55±0.37	5.06±0.44	6.52±0.37	0.45	99.75±0.9
F-5	605.72±0.79	8.32±O.33	17.5±0.61	5.05±0.57	6.65±0.19	0.39	98.41±0.8
F-6	605.85±0.59	8.29±0.36	17.48±0.49	5.04±0.68	6.72±0.25	0.49	101.24±1.1

*and ** indicate n=10 and n=3 respectively

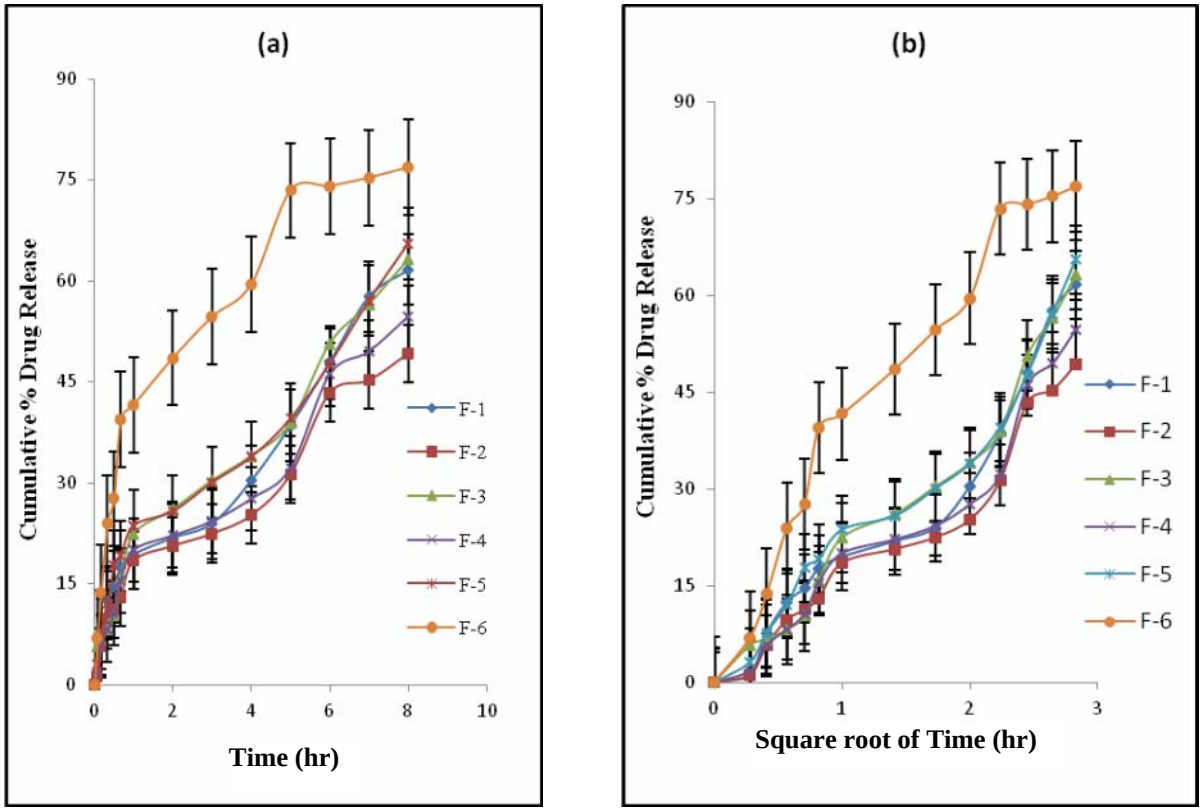

Figure 1. Release model of Losartan poatssium sustained release formulations (a) Zero-order release model and (b) Higuchi release model.

Table 3. Release kinetics of designed sustained release matrix tablets of Losartan potassium.

Code	Zero-order (r^2)	Higuchi (r^2)	Korsmeyer's-Peppas (r^2)	Hixson-Crowell (r^2)
F-1	0.954	0.938	0.875	0.654
F-2	0.946	0.955	0.845	0.649
F-3	0.964	0.969	0.902	0.680
F-4	0.948	0.951	0.836	0.667
F-5	0.943	0.954	0.870	0.626
F-6	0.833	0.956	0.957	0.508

Table 4. *In vitro* drug release mechanism for proposed formulations of Losartan potassium sustained release matrix tablet using Korsmeyer-Peppas model.

Code	Release rate constant (k)	Diffusion exponent (n)	Release type
F-1	1.195	0.596	Non-Fickian
F-2	1.186	0.503	Non-Fickian
F-3	1.287	0.505	Non-Fickian
F-4	1.218	0.506	Non-Fickian
F-5	1.297	0.490	Non-Fickian
F-6	1.602	0.324	Fickian

Time Required for 25%, 50% and 75% Drug Release According to Higuchi Equation

After 8 hours percent of drug release were 61.62, 49.17, 63.13, 54.63, 65.47 and 76.82 from F-1 to F-6 formulation respectively. Among the formulations, F-2 is the best formulation, in which the ratio of polymer is 3.5:1 (Kollidon SR: MC). Figure 2 shows the effect of polymer on drug release rate. From this figure it can be clearly identified that increase is polymer decreases drug release. F-1 to F-6 formulations contain polymer (Kollidon SR:MC) of different ratio as 3:1, 3.5:1, 1:3, 1:3.5, 3.5:0, 0:3.5. Based on the 'n' values from the table 4. Drug release for F-6 was found to follow Fickian release and for F-1 to F-5 was found to follow anomalous or non-Fickian release. This value indicates a coupling of the diffusion and erosion mechanism and indicates that the drug release was controlled by more than one process. This finding was in accordance with other reported works. (Shato *et al.*, 1997; Reza *et al.,* 2002; Goodhart *et al*., 1974; Peterlin, 1980).

Based on highest regression coefficient value (r^2) the best-fit model for all formulations was Higuchi model. Time required for 25%, 50% and 75% of drug release was corrected using linear equation of Higuchi plot. From this study, it was observed that formulated tablets of formulation 2 were released 75% in 21.25 hours. So, it was concluded that more than 24 hours required for 100% release.

Table 5. Time required for 25, 50 and 75% drug release according to Higuchi equation.

Code	$t_{25\%}$	$t_{50\%}$	$t_{75\%}$
F-1	1.78	6.734	14.75
F-2	2.53	9.61	21.25
F-3	1.69	6.2	13.62
F-4	2.22	8.24	17.98
F-5	1.56	6.15	13.76
F-6	0.44	2.49	6.25

Effect of annealing temperature on drug release mechanism: With an aim to demonstrate the effect of temperature in drug release mechanism, release rate, formulation-2 was placed in different temperature condition (30ºC, 45ºC and 60ºC) for two hours in oven before dissolution. *In-vitro* release data presented in figure 3 shows that drug release was faster from the tablet in which temperature was not applied, but it continuously decreased for tablets which are placed in 30ºC, 45ºC and 60ºC for two hours before *in-vitro* dissolution study, respectively and they follow zero order kinetics. Figure 4 shows the overall effect of temperature on the release rate of drug. From this figure it can be clearly identified that

increase of temperature decreases drug release rate. Statistical significant ($p \leq 0.05$) difference in drug release was observed in case of the tablets preheated 60^0C while it compared with ambient temperature. It is reported that amorphous polymer heated to temperature above glass transition temperature because the changes in mechanical properties of the polymer specially increase the density of the polymer and decreases the rate of stress relaxation, increase the ability of film formation and this could decrease the rate of drug release from the matrix (Omelczuk *et al.,* 1993). Formulation-2 is kollidon SR based matrix, as Kollidon SR is amorphous polymer, we are predicting the same phenomenon in this study to cause the less drug release at higher temperature.

Higuchi release rate of Losartan potassium from different formulation

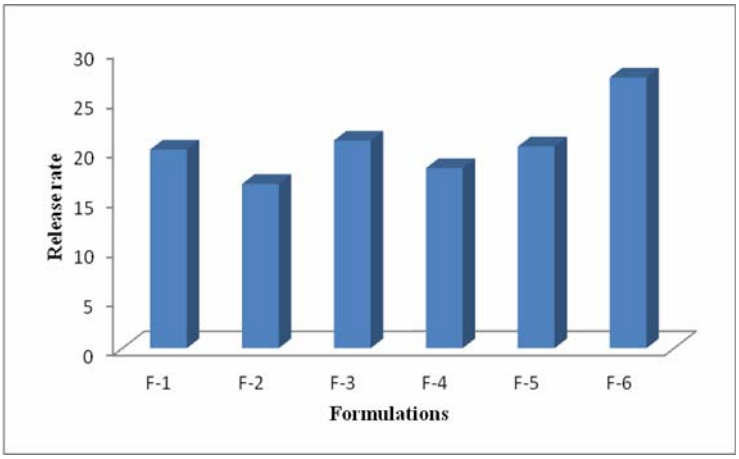

Figure 2. Effect of polymer content on release rate (Higuchian release)

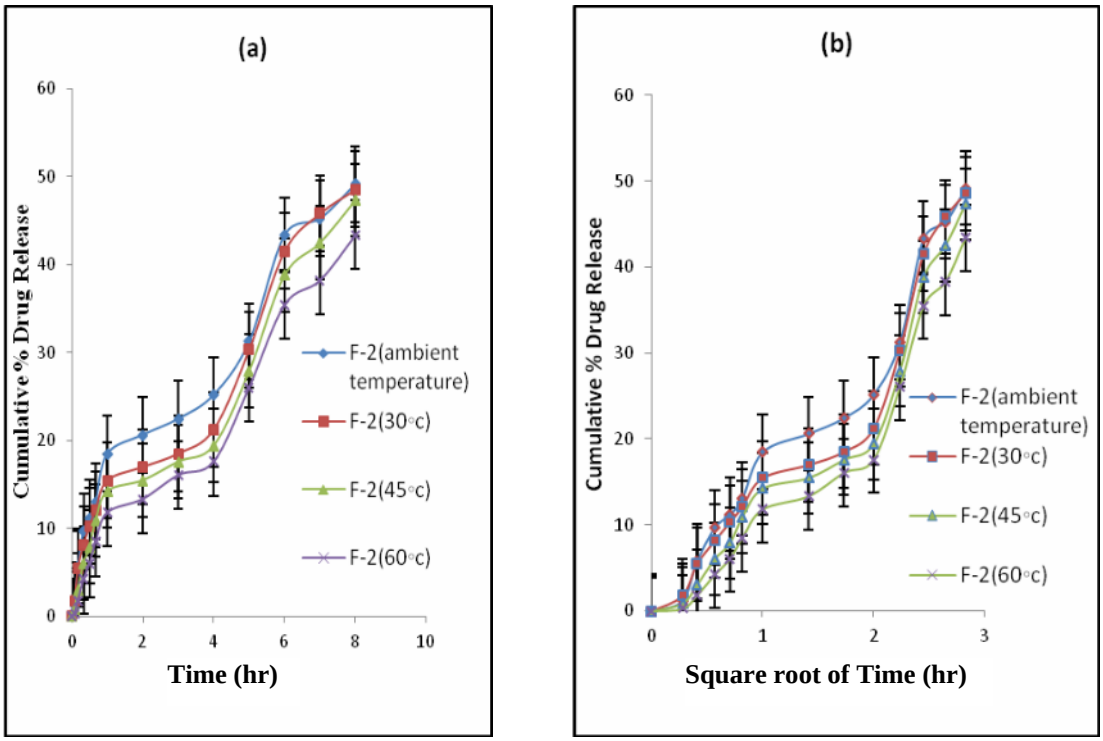

Figure 3(a) Zero-order release profile of Losartan potassium sustained release formulations in different annealing temperature (b) Higuchi release profile of Losartan potassium sustained release formulations in different annealing temperature.

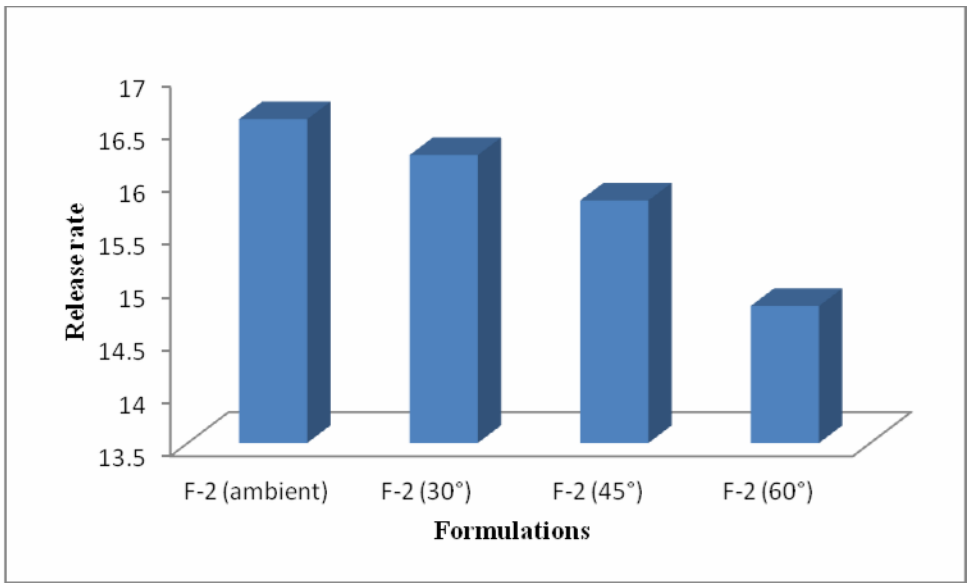

Figure 4. Effect of annealing temperature on release rate (Higuchian release).

Conclusion

From the study, it is possible to conclude that the proposed tablet formulations were suitable for direct compression method. The incorporation of Kollidon SR and Methyl cellulose as a polymer entails the stronger rate-retarding agents. According to the release studies, it was observed that the rate of drug release increases with decrease in total polymeric content of the matrix. According to Higuchi release rate, the formulated tablets of formulation 2 sustained the release effects up to 24 hours. However, further investigation is required to establish *in-vivo-in-vitro* correlation to reveal the accurate pattern of drug release during *in vivo* environment from this polymeric system.

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