Perindopril Sublingual Tablets: Formulation and Evaluation

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Abstract: *The objective of the present study was to develop and optimize a sublingual tablet of Perindopril which is effective in the treatment of hypertension. Perindopril tablets were prepared by direct compression method using different ingredients Sodium starch glycolate, Spray dried lactose, Starch, Talc and Magnesium stearate. The compressed tablets were evaluated for physical properties including hardness, weight variation, thickness, friability, drug content, wetting time, water absorption ratio, in-vitro disintegration time, in-vitro dissolution study and drug release kinetic study. All the physical properties evaluated for the compressed tablets have shown the results within the acceptable range of Pharmacopoeia limits.* F_{10} *was considered as the optimized formulation, which provided short wetting time of 64 sec, water absorption ratio of 66 and In-vitro disintegration time of 65 sec. From the above results, it indicated that the amount of super disintegrant i.e. Sodium starch glycolate was significantly affected the dependent variables like wetting time, water absorption ratio and in-vitro disintegration time.* F_{10} *has shown the best in-vitro drug release profile i.e., 97.83% during the end of 10 min. The in-vitro drug release data of all Perindopril sublingual tablets were subjected to testing by linear regression analysis according to Zero order equation, first order equation, Higuchi's equation and Korsmeyer-Peppas equation to comprehend the mechanism of drug release. According to the results the drug release followed First order release kinetics with Non-Fickian diffusion mechanism.*

KEYWORDS: *Perindopril; Sublingual; Sodium starch glycolate; Wetting time; In-vitro dissolution study.*

1. INTRODUCTION

Tablets that disintegrate or dissolve quickly in the patient's mouth are useful for young children, the elderly, and patients who have swallowing problems, as well as in cases where potable liquids are unavailable. Limited amounts of saliva are normally enough to lead the disintegration of tablets into the oral cavity for these formulations. The drug can either be absorbed partially or completely into the systemic circulation via blood vessels in the sublingual mucosa, or it can be swallowed as a solution and absorbed via the gastrointestinal tract. The sublingual route typically results in a quicker onset of action than orally administered tablets, and the portion absorbed through sublingual blood vessels sidesteps the hepatic first-pass metabolic processes.

Perindopril is used in the treatment of hypertensive and congestive heart failure, as Angiotensin converting enzyme inhibitor. It is quickly absorbed in the mouth, when given orally, because of its minimal biological half-life (0.8-1 h), repeated dosing is necessary [1]. Secondly, the drug is subjected to the metabolism of the first hepatic transfer. Different methods may be used to formulate tablets that quickly decompose or dissolve. Direct compression is one of the strategies requiring super disintegrants or the use of high-water soluble excipients for fast disintegration of the compressed tablets [2]. The faster disintegration of tablets would be required to increase drug release from tablets for rapid sublingual mucosal blood vessels absorption. Perindopril was determined to be formulated as a potential emergency for high blood pressure in quickly disintegrating tablets for sublingual administration [3].

2. MATERIALS AND METHODS

2.1. MATERIALS

Perindopril was gifted by Apotex Research Pvt.Ltd, Lactose was obtained from Finar chemicals, Sodium starch glycolate from LOBA chemie laboratory, PVP K30, starch, Magnesium stearate and Talc were obtained from Central drug house.

2.2. METHODS

2.2.1. Pre-formulation studies

Pre-formulation studies were carried out to know and understand the physical and chemical behavior of a drug and also to know the drug-excipient compatibility using FTIR **[4]**.

2.2.2. Solubility studies

Solubility was evaluated by accurately weighing 1 g of the drug and transferring it into 5 distinct 10 mL volumetric flasks containing different solvents (water, ethanol, methanol, DCM, and 0.1N HCl).

2.2.3. FTIR studies

It is often used to detect organic, inorganic, and polymeric materials present in the dosage form, as well as to analyze pure drug formulations, polymer, and drug-loaded polymer formulations, and to determine functional groups. At ambient temperature, the spectra were scanned in the 3600–400 cm^2 wave number range [5].

2.2.4. Micromeritic properties of powder blend

Angle of repose: It is the maximum angle formed between the surface of a pile of powder and its horizontal plane. It is determined by pouring the powder through a funnel and allowing it to fall freely onto the surface. The height and diameter of the resultant cone are then calculated using the equation $\tan \Theta = h/r$, Where, Θ is the angle of repose, h = height of the pile and r = radius of the pile.

Bulk density and tapped density*:* A predetermined amount of powder blend from each formulation was placed in a 10 mL graduated cylinder and gently shaken to break up the agglomerates [6]. After the measurement, the initial volume of the bulk density of the powder was estimated using the formula

Bulk density = (weight of the powder)/(bulk volume of the powder)

The cylinder containing the sample was tapped with a mechanical tapped density tester (Electrolab), which delivers a fixed drop of 142 mm at a nominal rate. The cylinder tapping was maintained until no more

changes in volume were detected and was estimated using the formula Tapped density= (weight of the powder)/(tapped volume)

Compressibility index and Hausner's ratio: They were measured using the following formula.

Carr's index = Tapped density-Bulk density x 100/ Tapped density;

Hausner's ratio=Tapped density/Bulk density

2.2.5. Analytical method for calibration curve of Perindopril:

The maximum wavelength of Perindopril was measured using UV-visible spectroscopy which was found to be 216 nm. The secondary stock solution (100 µg/mL) was prepared from the primary stock solution (1 mg/mL) with 6.8pH buffer. Further dilutions were made from the secondary stock solution to obtain 2–10 µg/mL [7]. The absorbance of each aliquot was measured at 216 nm against 6.8 pH buffer as blank. Then, a graph of concentration of drug versus absorbance was plotted by applying linear regression analysis.

2.2.6. Formulation of Perindopril tablets

Perindopril sublingual tablets were prepared by the direct compression method using different excipients concentrations. All the ingredients of the sublingual tablets of Perindopril were weighed and mixed in mortar with the help of pestle. Then the blended material was slightly compressed on the7 mm flat–biconvex punch using rotary tablet punching machine. The total weight of the formulation was maintained 150 mg.

Table 1. Formulation of Perindopril sublingual tablets

Ingredients	Formulation Code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Perindopril	8	8	8	8	8	8	8	8	8	8
PVP-K30	10	10	10	10	10	-	-	-	-	-
Starch	-	-	-	-	-	5	5	5	5	5
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Spray dried lactose	123	120	117	114	111	128	125	122	119	116
Sodium starch glycolate	3	6	9	12	15	3	6	9	12	15
Talc	3	3	3	3	3	3	3	3	3	3
Total weight (mg)	150	150	150	150	150	150	150	150	150	150

2.2.7. Post Formulation Studies

Perindopril sublingual tablets have been evaluated through standard procedures. The following are the parameters evaluated [8].

Weight variation test*:* The weight variation test was performed according to standard procedures by Weighing 20 tablets from each formulation (F1 to F10) using an electronic balance and average weights were calculated which were compared with an individual weights of the tablets.

Hardness and Thickness: Hardness is the tablet's ability to withstand mechanical shock during handling. It is determined with Monsanto hardness tester by random selection of three tablets from each formulation, which are measured in terms of kg/cm^2. Tablet thickness was determined randomly by selecting three discs from each formulation using vernier calipers expressed in mm. The deviation of the tablet formulation should not exceed the limit of ± 5% of the specified values.

Friability: The friability was measured using a Roche Friabilator. Tablets were rotated at 25 rpm for 4 minutes or up to 100revolutions. The tablets were taken out, dedusted and reweighted. The percentage

friability was calculated from the loss in weight as given in equation below. The weight loss should not morethan1%.

$$\%\text{Friability} = \frac{(\text{Initial Weight} - \text{Final Weight}) \times 10}{(\text{Initial Weight})}$$

Drug content Uniformity: Ten tablets were placed in a mortar and crushed to a fine powder. Accurately weighed powder equivalent to 100 mg of Perindopril was transferred into a 100 mL volumetric flask containing 100 mL of 6.8pH buffer and the absorbance was measured at 215 nm relative to the blank [9].

Wetting Time: The tablet was positioned in the center of two layers of absorbent paper in a dish. Excess water was drained from the dish after thoroughly wetting the paper with distilled water. A stopwatch was then used to record how long it took for the water to diffuse from the wetted absorbent paper throughout the entire tablet.

Water absorption ratio: A piece of tissue paper folded twice was placed in a small Petri-dish containing 6 mL of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio (R) was determined using following equation

$$R = 100 \times W_a - W_b / W_a$$

Where W_a = Weight of tablet after water absorption, W_b = Weight of tablet before water absorption

In-vitro disintegration time: The disintegration time of sublingual tablets were measured using a USP tablet disintegration apparatus and a phosphate buffer with a pH of 6.8 as the medium. The medium volume was 900 mL, and the temperature was adjusted to 37±2 °C. The time in seconds required for full disintegration of the tablets with no palatable mass left in the instrument was recorded.

In-vitro drug release study: The in vitro release rate of Perindopril sublingual tablets was determined using a USP Type II dissolution apparatus (paddle type) [10]. The dissolution test was conducted using 900 mL of 6.8 pH phosphate buffer at 37±2˚C and 50 rpm. At the time intervals of 2, 4, 6, 8, 10 minutes a sample (5 mL) of the dissolution medium was withdrawn from the dissolving equipment and was replaced with equal quantity of fresh dissolution medium. After suitable dilution, the samples were filtered using Whatman filter paper No 40 and tested for Perindopril using a UV spectrophotometer at 216 nm [11,12]. An equation derived from the calibration curve was used to compute the percentage drug release.

Drug release kinetics: Various kinetic models are used to describe the total release of drugs from the dosage form. It is always desirable to develop the tools that facilitate the development of products by reducing the need for biological research, since the qualitative and quantitative changes in the preparation may change the release of drugs and the performance in *in- vivo*. In this regard, the use of data on drug solvents in *In-vitro* for predicting the biological performance in *In-vivo* can be regarded as the reasonable development of the gradual preparation. The method of the approaches used to investigate the kinetics of drug release from the controlled release formulation is model dependent methods such as Zero order, First order, Korsmeyer-Peppas, Higuchi etc [13].

3. RESULTS & DISCUSSION

Perindopril sublingual tablets were prepared by direct compression method. Various evaluation parameters were measured [14]. From the solubility studies, it was found that Perindopril was practically soluble in water, alcohol, Dichloro methane and chloroform. A standard calibration curve for Perindopril was acquired by measuring the absorbance at 216 nm in 6.8 pH buffer and by plotting the graph of absorbance against concentration (Table. 2). The standard plot of Perindopril was shown in Fig. 1.

Table 2. Standard curve of Perindopril

Conc(µg/mL)	Absorbance (nm)
0	0
2	0.09
4	0.163
6	0.238
8	0.314
10	0.375

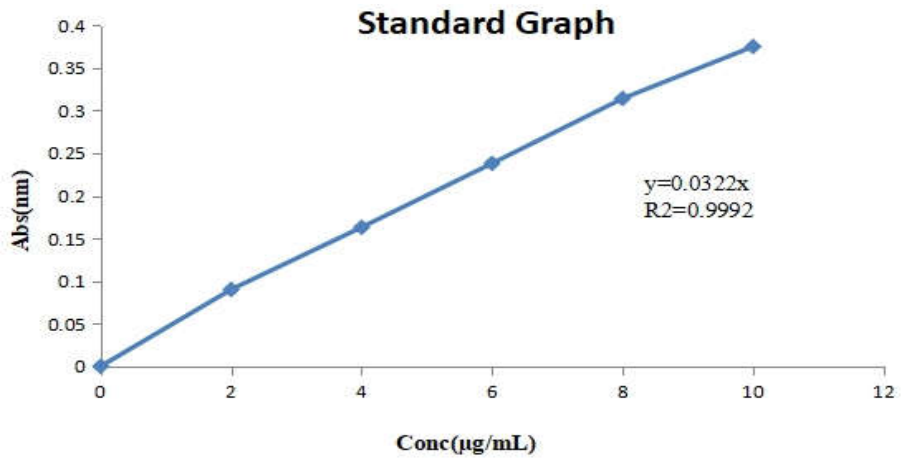

Figure 1. Standard calibration curve of Perindropril

Parameters such as the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were evaluated to determine the flow properties of the prepared powder mixture [15]. The angle of repose and compressibility index for the formulations (F6-F10) were found to be in the range of good flow properties, whereas the formulations (F1-F5) were found to be poor due to binder effect which led to gummy nature of the powder blend [16,17]. So the results of formulations (F1-F5) were excluded.

It was observed that the tablets of formulation (F6-F10) passed the test for weight variation, which were within acceptable pharmacopeia limits and these formulations possessed good mechanical strength with sufficient hardness in the range of 2.5-3 kg/sq.cm. The tablet mean thickness was almost uniform in (F6-F10) formulations, which varied between 2.9 to 3.2 mm. The friability varied between 0.24 to 0.48 %. The friability values between 1% were an indication of good mechanical resistance of tablets. The drug content in the formulations (F6 to F10) was highly uniform and in the range of 98.82 to 100%. The wetting time was found to be in the range of 64 sec to 155 sec. The water absorption ratio was found to be in the range of 25 to 66. The disintegration time was observed within fraction of second i.e., in the range of 65 to 155 sec.

Table 2. Evaluation parameters of Perindopril sublingual tablets

Evaluation Parameters	Formulation codes				
	F6	**F7**	**F8**	**F9**	**F10**
Weight variation(mg)	147.2	149.8	150.5	148.5	150.7
Friability(%)	0.37	0.24	0.38	0.48	0.26
Thickness(mm)	3	3.1	29	3.2	29
Diameter(mm)	7.1	6.99	6.98	7.1	6.99
Hardness(Kg/cm^2)	2.5	3	2	2.5	3
Drug content(%)	98.2	99.8	99.2	100.2	98.8
Water absorption ratio	25	37	36	57	66
Wetting time(sec)	155	122	105	90	64
***In-vitro* disintegration time(sec)**	137	106	95	76	65
***In-vitro* drug release (%)**	96.08	98.18	95.38	98.52	97.83

Different ratios of super disintegrating agent and diluents were added and formulated into tablets to optimize the formulation [18].

***In-vitro* dissolution studies**

Drug release from Perindopril sublingual tablets was studied for about 10 min in 6.8 pH buffer as shown in Fig. 2. Total 10 formulations were prepared, F1-F5 formulations contain PVP-K30 as binder, whereas the formulations F6-F10 were formulated with Starch as binder. Different ratios of super disintegrating agent and diluent were added and formulated into tablets in order to optimize the formulation [19,20]. During the study of trials, it was concluded that the addition of PVP-K30 to the formulations lead to sticking of the tablets due to gummy nature of the blend. So the results of formulations (F1-F5) were not included. It was observed that as the concentration of sodium starch glycolate increases, disintegration time decreases significantly (Table 2).

Table 3. *In-vitro* dissolution studies of Formulations (F6-F10)

TIME (min)	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	35.29	38.08	43.67	50.66	55.55
2	45.07	43.67	51.36	76.16	83.15
4	61.14	51.36	59.05	81.06	84.55
6	70.57	75.12	82.10	93.28	97.48
8	88.04	92.24	95.03	95.48	97.56
10	93.08	95.18	96.38	96.52	97.83

The percentage of drug release for all the formulations were observed to be maximum by the end of 10 min as shown in Table 3. From the above studies, it was observed that increase in concentration of super disintegrant i.e. sodium starch glycolate, the percentage of drug release also increased in all formulations [21,22]. Among all the formulations (F6-F10), the best in-vitro drug release was observed for the formulation F10 with 97.83%, as increase in the concentration of sodium starch glycolate that lead to rapid disintegration.

The drug release data was performed to examine the kinetics and mechanism of drug release, Perindopril sublingual tablets were fitted into several mathematical models (zero order, first order, Higuchi, Korsmeyer-Peppas) [23,24,25]. The model with the highest R^2 value for the release data is considered the best fit (Fig 2-6).

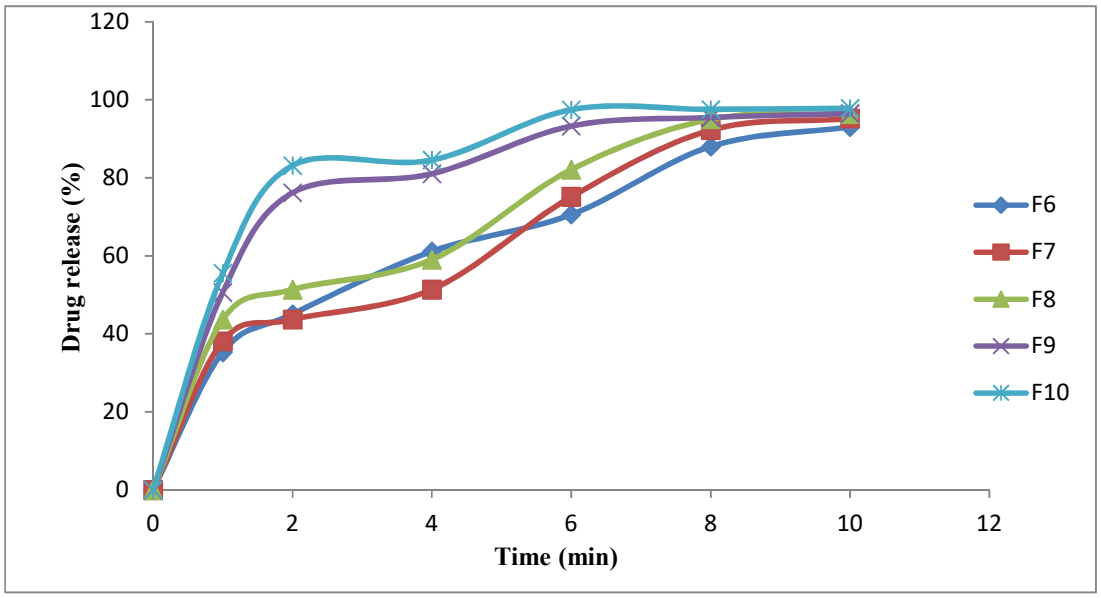

Figure 2. In-vitro dissolution time of Perindopril tablets (F6-F10)

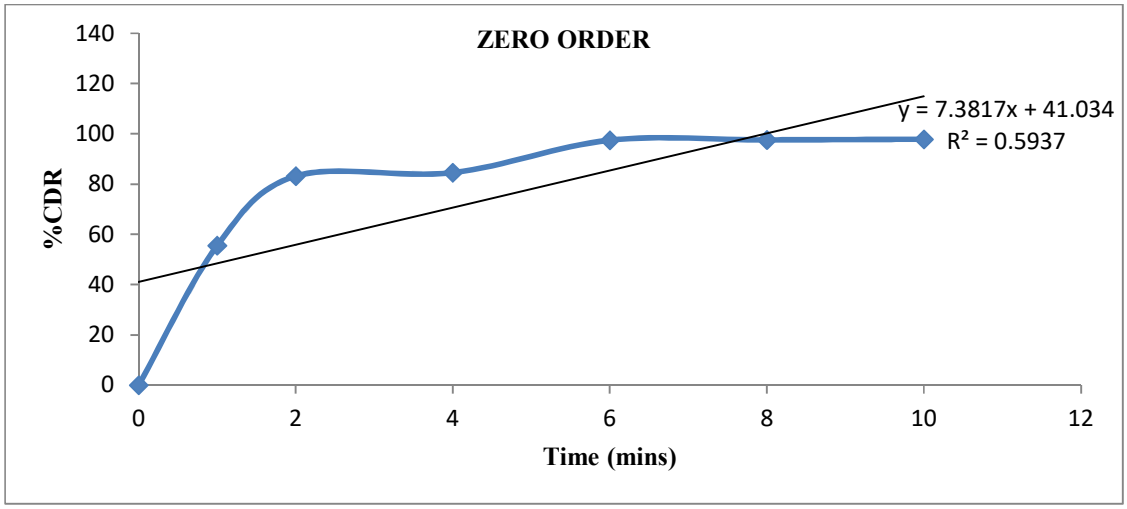

Figure 3. Zero order release plot formulation (F10)

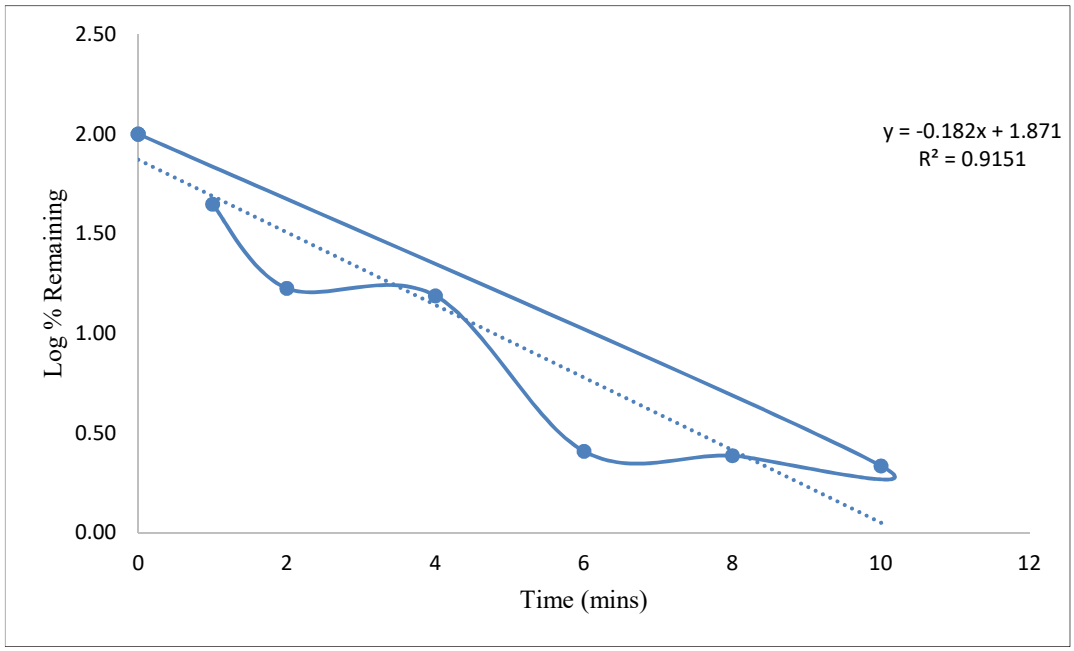

Figure 4. First order release plot formulation (F10)

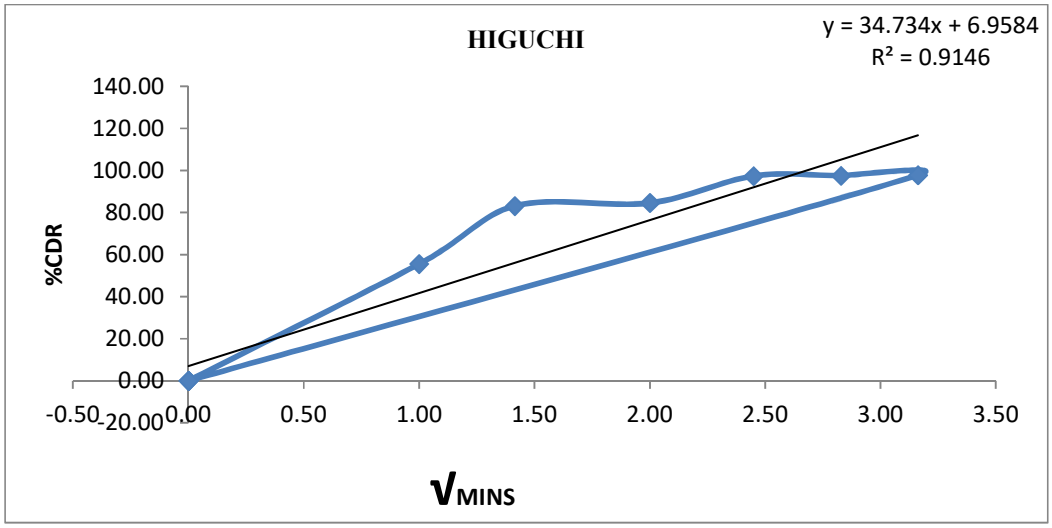

Figure 5. Higuchi order release plot formulation (F10)

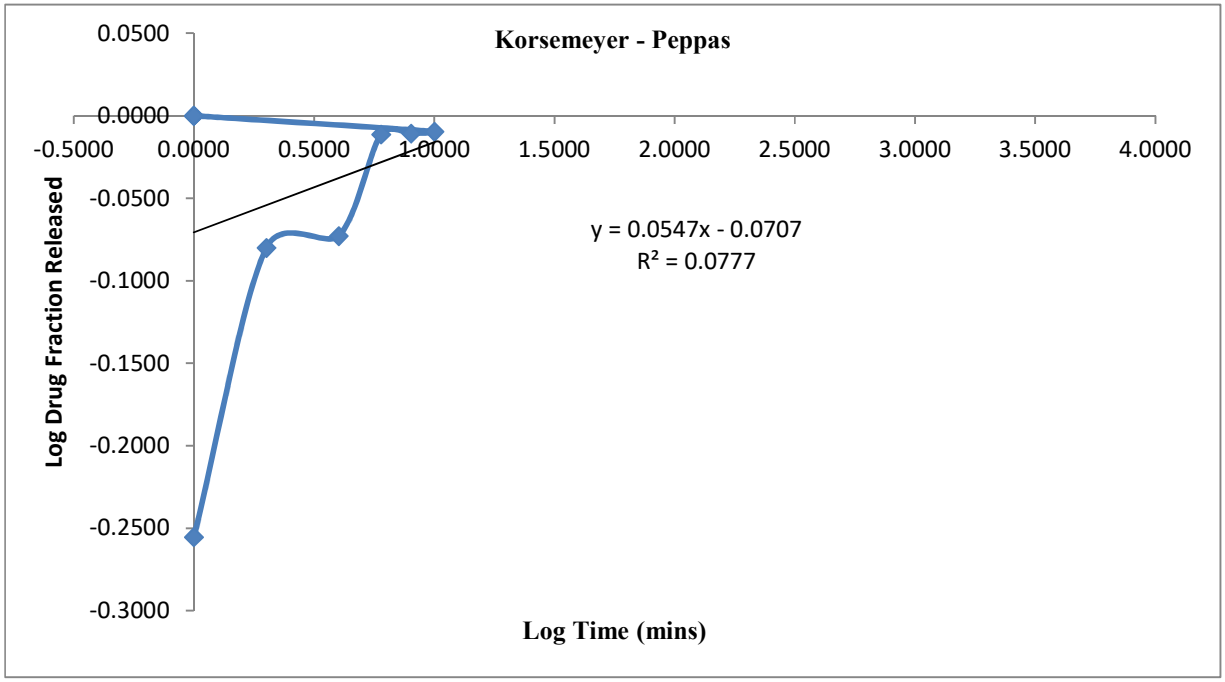

Figure 6. Korsemeyer peppas order release plot formulation (F10)

Conclusion

Perindopril sublingual tablets were prepared using various concentrations of sodium starch glycolate by the direct compression method. The best *in-vitro* drug release was observed for the optimized formulation F10 with 97.3%. From the present study it was concluded that among all the other formulations F10 was considered best as it has exhibited good wetting time, water absorption ratio, faster disintegration time and also with desired drug release kinetics, which especially follows first-order release kinetics with Non-fickian diffusion mechanism.

References:

1. N.S. Gadekar, S.M. Gaikwad, "Katkar SB. Review on Sublingual Tablet", *Int J Res Appl Sci Eng Technol*. 2024 Jan;12(1).
2. R.S. Nikam, R.P. Jadhav, P.D. Jadhav, V.D. Yadav, "Sublingual Tablets: An Overview", *Int J Sci Res Sci Technol*. 2019;6(5):181-187.
3. P. Prathusha, P. Kamarapu , "A Review on Sublingual Tablets", *J Formul Sci Bioavailab*. 2017; 1:1.
4. K. Parmar, M.B. Patel, "A review on sublingual spray: novel drug delivery system" *Int J Pharm Sci Res*. 2017;8(11):4533-4539.
5. T. Ashok, M. Nawaz, C. Madhavi, K. Nandini, S. Sirisha, D. Spandana, "Sublingual Tablets - An Updated Review", Asian J Pharm Res. 2019;9(2):97-103.
6. S.B. Bhaja, P. Ellaiah, "Formulation and evaluation of Perindopril sublingual tablets", *Int J res pharm biomed sci*. 2011; 2(3): 1193-1198.
7. D. Pratiksha, D.M. Avish, "Review on orodispersible tablet: Recent trends of manufacturing of orodispersible tablet", *Res J Pharm Technol*. 2022; 14(2): 177-172.
8. Pathak, Kaushal, "Analytical techniques for the estimation of Perindopril Erbumine: A Review", *Curr Pharm Anal*. 2021; 17(2): 185-193.
9. V. Rashmitha, S. Pavani, "Formulation and evaluation of Fenoverine floating tablets", *Asian J Pharm Clin Res*. 2021; 14(4): 175-180.
10. Perindopril/Indopamide/Amlodipine in Hypertension: A profile of its use. *Am J Cardiovas Drugs*. 2022; 22: 219-230.
11. E.J. Henderson, M. Achison, "Effect of Perindopril or Leucine on physical performance with sarcopenia: The LACE randomized controlled trial", *J Cachexia Sarcopenia Muscle*. 2022; 13(2): 858-871.
12. P.M. Bhagwat, B.B. Shyamila, "A Review on mouth disintegrating tablets", *Int J Res Rev*. 2021; 2(11): 367-372.
13. S.A. Hamad, H.A. Mohammad, "Formulation of sublingual Promethazine hydrochloride tablets for rapid release of motion sickness", Saudi Pharm J. 2021; 29(5). 478-486.
14. J. Ashok, C. Madhavi, "Sublingual Tablets-An updated Review", *Asian J Pharm Res*. 2019; 9(2): 97-103.
15. Manish Kumar Gupta, Saurabh Sharma (MK Gupta, S Sharma), "Formulation and evaluation of fast dissolving tablets", *Int J Curr Pharm Rev Res*. 2021; 13(3): 13-19.
16. K.C. Panda, M. Habibuddin, "Formulation and evaluation of vilazodone sublingual tablets by using Lyophilization technique", *Res J Pharm Technol*. 2018; 11(1): 267-274.
17. B. Bhupinder, J. Sarita, "Formulation and evaluation of fast dissolving sublingual films of Rizatriptan benzoate", *Int J Drug Dev Res*. 2012; 4(1): 133-143.
18. M.D. Nehal Siddiqui, G.A. Garima, "Short Review on a novel approach in oral fast dissolving drug delivery system and their patents", *Adv Biol Res*. 2011; 5(6): 203-291.
19. S. Somya, B. Ashutosh, "Sublingual Tablets: An overview", *Indian J Pharm Biol Res*. 2016; 4(2): 20-26.

20. P. Kundan, T. Umes, “Formulation and evaluation of fast dissolving sublingual tablets of Amlodipine besylate”, *Der Pharma Sinica*. 2014; 5(4): 1-9.
21. P. Prathyusha, K.A. Praneeth, “Review on sublingual tablets”, *J Formul Sci Bio*avail. 2017; 1(1): 1-2.
22. A. Sindhu, B.V. Basavaraj, “Formulation and optimization of sublingual tablets of Rabeprazole sodium”, *J Pharm Sci Rev Res*. 2010; 5(2): 50-54.
23. B. Vineet, S. Vikesh, “Formulation and evaluation of fast disintegrating sublingual tablets of Amlodipine besylate using different superdisintegrants”, *Int J Pharm Pharma Sci*. 2010; 2(3): 89-92.
24. S. Rajat, G. Alka, “Formulation and evaluation of disintegrating sublingual tablets of Glipizide: An attempt to treat Diabetic coma”, *Int J Chemtech Res*. 2010; 2(4): 2026-2033.
25. R. Ferrari, G. Pasanisi, “Specific properties and effect of Perindopril in containing the Renin-angiotensin system”, *Am J Hypertens*. 2005; 18(9): 1425-1545.