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FORMULATION AND EVALUATION OF SUBLINGUAL TABLETS OF ISOSORBIDE DINITRATE

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ABSTRACT

The aim of the present research was to formulate and evaluate sublingual tablets of Isosorbide Dinitrate, belonging to the class of anti-angina drug. The tablets were prepared by direct compression technique. The surfactants in the formulation include the Croscarmellose Sodium, Sodium starch glycolate, crospovidone in different ratios. The polymer used in the formulation includes the poloxamer that act as a surfactant and also the wetting agent that causes the rapid and effective disintegration of the tablet and the other excipients. The formulation (F5) was found to disperse at the least time of 5±.02 seconds and the total time for disintegration was found to be 3 ± .14 minutes. The drug content was found to be 99.19%. The tablets were showing hardness of 3±.5. The tablets was found to show the friability of .52±.03 %. In-vitro study profile of the formulation proves that all the formulations showed the optimal release within specific time duration. The release kinetic study revealed that formulationF5 showed non fickian release mechanism and show zero order kinetic. According to the evaluations done on the various formulations it was observed that the formulation number 5 (F5) showed the best result as the disintegration time required was less as compared to other formulations.

KEYWORDS: Croscarmellosee sodium; Sodium Starch Glycolate; crospovidone; Non Fickian diffusion; zero order release.

1. INTRODUCTION

Among the various types form of tablets available, sublingual tablets are among one of the forms available to the patients. The entail of the Sublingual tablets emanate to provide

immediate onset pharmacological effect. Sublingual tablets come into existence for the pediatric and geriatric patients and also for patient compliance in the people suffering from dysphasia, mentally retarded, uncooperative, nauseated or unconscious.[1-4]

The absorption is affected by the lipid solubility and accordingly the permeability of the solution frequently known as osmosis, the ionization, and the molecular weight of the drug. The cells of oral epithelium soak up the drug by the process of endocytocis. It is improbable that the same mechanism is observed throughout the stratified epithelium. Although, it is believed that acidic stimulation of the salivary glands, accompanying vasodilatation, facilitates absorption and uptake into the circulatory system. The mouth is lined with a mucous membrane which is covered with squamous epithelium and contains mucous glands. The sublingual mucosal tissue is similar to that of buccal mucosa.[5-7] The salivary glands consist of lobules of cells which secrete saliva through the salivary ducts into the mouth. The three pairs of salivary glands are the parotid, the submandibular and the sublingual which lies on the floor of the mouth. The more acidic the taste, greater the stimulation of salivary output; serving to avoid potential harm to acid-sensitive tooth enamel by bathing the mouth in fulsome neutralizing fluid. The sublingual artery travels forward to the sublingual gland, it supplies the arterial branches to the neighboring muscles and to the mucous membranes of the mouth, tongue and gums. Two symmetrical branches travel behind the jawbone under the tongue to meet and join at its tip. Another branch meets and anastomoses with the submental branches of the facial artery. The sublingual artery stems from the lingual artery – the body's main blood supply to the tongue and the floor of the mouth – which arises from the external carotid artery. The proximity with the internal carotid artery allows fast access to its route supplying the greater part of the cerebral hemisphere.[8,9]

2. MATERIAL AND METHOD

Isosorbide dinitrate was received as a gift sample from IPCA Dehradun, India and all the othe excipients used were received from Central drug house Pvt. Ltd. Delhi (IND).

2.1. Method

Tablets containing 5 mg of Isosorbide dinitrate were prepared by direct compression method. Three different superdisintegrants were used for the formulation were Croscarmellose Sodium, Soduim starch glycolate, crospovidone. Poloxamer was used as a polymer that act as a surfactant and wetting agent . the other excipients used in the formulation include aspartame, lactose, talc, mannitol, magnesium sterate.

Table 1: Composition of all batches of sublingual tablets of Isosorbide Dinitrate.

S.No.	Ingredients	F1	F2	F3	F4	F5	F6
1.	Isosorbide Dinitrate	5	5	5	5	5	5
2.	Croscarmellose Sodium	30	25				
3.	Sodium Starch Glycolate			30	25		
4.	Crospovidone					30	25
5.	Poloxamer	10		10		10	
6.	Aspartame	5	5	5	5	5	5
7.	Lactose	10	20	10	20	10	20
8.	Talc	20	25	20	25	20	25
9.	Mannitol	15	15	15	15	15	15
10.	Magnesium sterate	5	5	5	5	5	5

Average weight of each tablet= 100 mg

2.2. Pre Compression Parameters[10-15]

A. Angle of repose (θ): angle of repose is defined as the maximum angle between the surface of the pile of the powder and the horizontal plane. It is used to measure the frictional force of the powder.

B.

$\tan \theta = h/r$ **$\theta = \tan^{-1} h/r$**

where θ = angle of repose , h = height of the cone formed, r = radius of the cone base

C. Bulk density: bulk density is defined as the ratio of the mass of the powder to its bulk volume. The bulk density of the powder predominantly depends on the particles size, shape, distribution, and there tendency to adhere to one another.

Bulk density = M / V_0

Where, M = mass of powder taken V_0 = apparent volume

D. Tapped density: tapped density as the name signifies is achieved by mechanical tapping the graduated cylinder filled with the powder sample. Tapped density was calculated using the following formula:

Tapped density = Mass of powder/ Tapped volume

E. Carr's compressibility index: the compressibility index measures the proclivity of the powder to be compressed. It is specified by the Carr's compressibility index (CI)

CI = {(Tapped density – Bulk Density) / Tapped Density} *100

F. Hausner ratio: the Hausner ratio is the ratio of the tapped density to the bulk density of the powder substance under investigation. Hausner ratio can be calculated by the formula:

Hausner ratio = (Tapped Density / Bulk Density)*100

2.3. Post compression parameters for tablets[16-25]

A. General appearance: All the ingredients used in the formulation were white in color so there must be no change in the color of the tablet in all the formulations. It proves that all the excipients used in the formulation are compatible and are not causing any chemical reaction that could alter the properties of the formulation.

B. Weight variation:. Ten tablets were taken randomly from the batches and weighed on digital weighing balance machine. The average weight was determined.

C. Uniformity of thickness: The thickness of the individual tablet were measured by using Vernier Caliper, that measures the thickness. 6 tablets were randomly selected from the batch and were evaluated for thickness using Vernier Caliper. The average was calculated.

D. Hardness: Hardness of the tablet is evaluated so as to check the loss like chipping, abstraction or breakage that are more likely to occur. Monsanto hardness tester was used to check the hardness. And the average hardness was calculated in kg/cm^2.

E. Friability: Friability of the tablets is evaluated to check its mechanical strength. Roche friabilator is used to determine the friability using the following procedure. 20 pre weighed tablets were placed in the cleaned friabilato. The loss in the weight of the tablets is the measure of friability and expressed in percentage as following:

% friability = {(initial weight – final weight) / initial weight}*100

% Friability of tablets less than 1% is considered as acceptable.

F. Disintegration time: disintegrants are added in the formulation with the aim to facilitate the breakup of the tablet upon its exposure to water. For testing the disintegration time disintegration apparatus was used. Saline phosphate buffer of pH 6.8 was used as medium. The temp was set up at 37± 2° C. The time taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

G. Drug content: weight accurately a portion of the powder, equivalent to about 5mg of Isosorbide Dinitrate. Add exactly 50 mL acetic acid, shake for 15 minutes, filter, and use this filtrate as the sample solution. Separately weigh accurately about 0.09 gm of dried potassium nitrite, dissolve in 5 mL of water make up the volume from the acetic acid upto 100 mL. separate out 10 mL of this solution, and make the volume upto 100 mL using acetic acid, use this solution as the standard solution.

Measure exactly 2mL of the sample solution and the standard solution; add exactly 2.5 mL of salicylic acid to each. Shake well; allow standing for 15 minutes, and adding 10 mL of water.

Make them alkaline with about 12 mL of solution of sodium hydroxide while cooling in an ice bath; add water to make exactly 50 mL measure the absorbance at 405 nm.

H. In vitro study: In-vitro release rate of tablet were carried out using Paddle apparatus method. The dissolution test was carried out using 900 mL of 6.8 pH phosphate buffer, at 37± 0.5º C and 50 rpm. A required quantity of sample solution was withdrawn from the dissolution apparatus at a specific time intervals and the withdrawn volume was replaced with fresh dissolution media. The % release of drug was calculated.

3. RESULT AND DISCUSSION

3.1. Result of bulk powder study.

A. Identification: the procured drug sample as Isosorbide Dinitrate was identified by Organoleptic properties and FTIR spectra of the drug sample.

Table 2. Result of Organoleptic properties.

S.No.	Organoleptic properties	
1.	Description	Crystalline Powder
2.	Color	White
3.	Odor	Odorless
4.	Taste	Tasteless

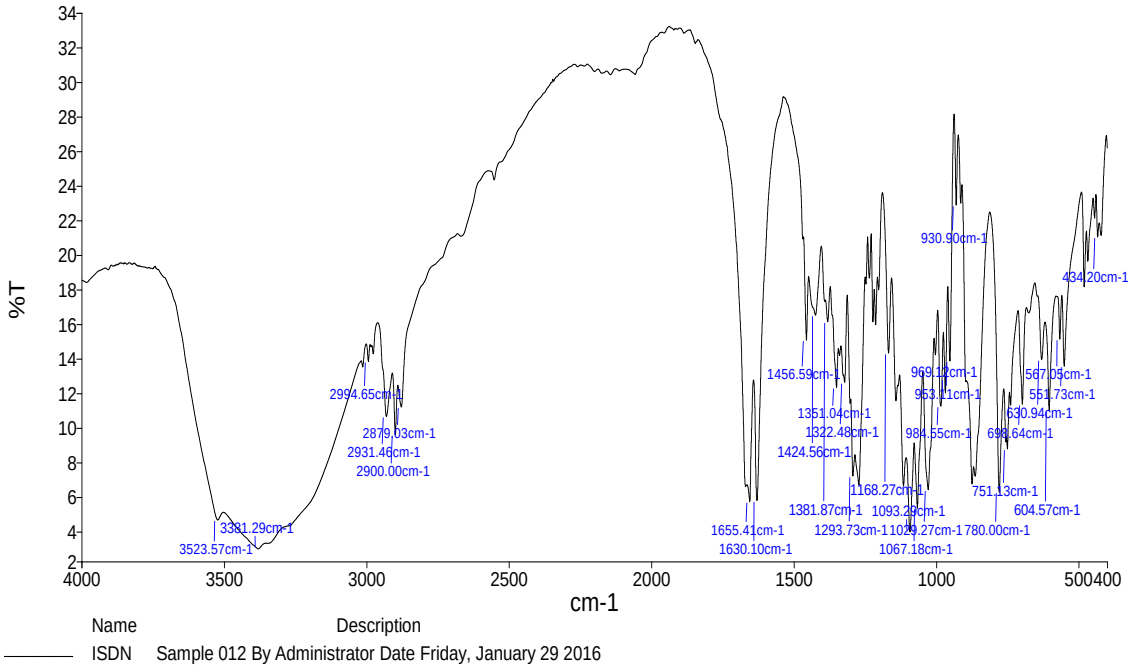

Fig 1: FTIR of Isosorbide Dinitrate.

B. Solubility analysis: Preformulation solubility analysis was done to select the suitable solvent system to dissolve the drug and also to test solubility in dissolution medium that are to used. Result of the analysis are shown in table 3.

Table 3: solubility analysis.

S.No.	Solvent	Solubility
1.	Acetone	Very soluble
2.	Chlololform	Freely soluble
3.	Toulene	Freely soluble
4.	Methanol	Soluble
5.	Ethanol	Soluble
6.	Diethyl Ether	Soluble
7.	Water	Sparingly soluble

C. Melting point determination: Melting point of the drug was determined by using the capillary method. Fine powder of the drug was filled in a capillary tube, previously sealed at one end. The capillary tube was inserted at the sample holder of the melting point apparatus with a thermometer placed in the apparatus. The temperature at which the powder of the drug starts to melt was found to be 70- 72 º C. The melting point value of the sample was found to be nearly as mentioned in the standard reference 70 º C.

D. UV Spectroscopy: The UV spectroscopy of Isosorbide Dinitrate performed at the absorbance of 405 nm and the beers range of 2-12 µg/ml.. The calibration curve thus obtained is shown in figure 4. Absorbance of each concentration plotted by taking absorbance on y-axis and concentration on x-axis.and the regression equation was calculated.

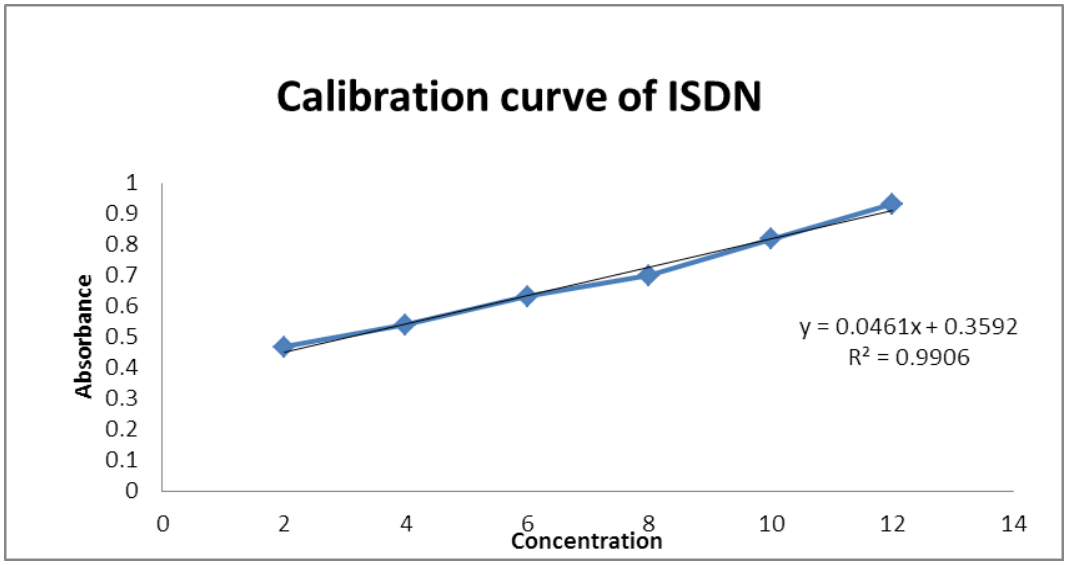

Fig 2. Calibration curve of Isosorbide Dinitrate.

3.2. Result of pre-compression parameters.

The bulk of the drug sample containing (Isosorbide Dinitrate) as the active pharmaceutical ingredient that were ready to be mould undergo the following pre compression evaluation so as to achieve optimized product. The evaluations showed the following results.

A. Angle of repose (θ): The obtained value for the angle of repose of Isosorbide Dinitrate was found to be in the range of 25-30 that revealed that the drug shows good flow property. The result of the observation is shown in the table 4.

B. Bulk density: The bulk density was found in the range of 0.25 – 0.26. The result obtained was shown in table 4.

C. Tapped density: The tapped density was found in the range of 0.29 – 0.30. The result obtained was shown in table 4.

D. Carr's Index: The Carr's index was found to be in the range of 13-16 %. The value proves the powdered drug showed good flow property. The result obtained was shown in table 4.

E. Hausner Ratio: The Hausner ratio was found to be less than 1.25 % proving the good flow property. The result obtained was shown in table 4.

Table 4: Pre-compression parameters.

Drug	Angle of repose	Bulk density	Tapped density	Carr's ratio	Hausner ratio
Isosorbide Dinitrate	28.27	.25	.29	13.79	1.16
	29.02	.25	.30	16.66	1.2
	28.84	.26	.30	13.33	1.15
	Avg= 28.71	Avg= .25	Avg= .29	Avg=14.59	Avg= 1.17

The pre compression study of the sample showed that the drug powder to have a good flow property. All the parameters that were included in the study of the bulk powder showed the standard range to prove themselves as a good flow able powder. Hence, it can be concluded that the powder was a good flowing powder.

3.3. Result of post compression parameters

A. General appearance: Around 20 compressed tablets from each batch of formulation were examined. No variation in the color, shape was observed, and no identifying marks were noticed. All the tablets were white in color and with a flat surface.

B. Weight variation: 10 tablets were selected from every batch of the formulation and were evaluated for the weight variation. The tablets showed the variation under the limits as per described in IP. The result is shown in table 5.

C. Thickness: 6 tablets were selected from every formulation batch and were evaluated for thickness using Vernier caliper. The tablets deviation in the range of 0.01- 0.05 mm. The result of the thickness are showed in table 5.

D. Hardness: 6 tablets were selected from the formulation batches and were evaluated for the hardness parameters using Monsanto hardness tester. The tablets showed variation under the limits as per described in IP. The results are shown in table 5.

E. Friability: 20 pre weighed tablets were selected from every batch of the formulation and then were evaluated for the friability. The tablets show the result under the limits as per described in IP. The result of the test is shown in table 5.

F. Disintegration time: 6 tablets were selected from the batches of formulation and were evaluated. The result for the disintegration is shown in table 5.

G. Drug content: powder containing drug equivalent to 5 mg of the drug and various solutions were prepared. The result is shown in table 5

H. In vitro study: the in vitro studies were conducted taking tablet from the batches. The result of the evaluation of formulations F1 to F6 are give from table 6. Table 7 shows the various release kinetic. Fig 3-6 shows the graphical representation of relaase of formulation.

Table 5: Post compression parameters.

Parameters	F1	F2	F3	F4	F5	F6
Weight variation (mg) n=10	100± .12	100±. 08	100± .18	99±.89	100± .23	100± .16
Thickness (mm) n=6	3.2±.02	3.1± .08	3.2±.03	3.3±.04	3.3±.01	3.2± .01
Hardness (kg/cm^2) n=6	3± .3	3± .4	3± .3	3± .2	3± .5	3± .3
Friability (%) n=20	.53±.02	.51±.04	.60±.03	.59±.01	.52±.03	.55±.02
Dispersion time (sec) n=6	5± .01	6± .02	6± .02	7±.01	5±.02	6±.02
Disintegration time (min) n=6	3± .7	3±.22	4± .19	5± .11	2±.14	3±.01
Drug content (%)	97.12	97.80	95.59	96.92	99.19	99.88

Table 6: In- vitro profile of formulations (F1-F6).

S.No.	Time	%CR F1	%CR F2	%CR F3	%CR F4	%CR F6	%CR F7
1	2	26.20	27.17	16.10	19.67	19.84	25.61
2	4	39.81	46.44	20.79	28.35	33.13	41.67
3	6	49.73	54.03	47.07	49.39	47.07	56.54
4	8	67.09	68.85	62.67	63.49	58.96	73.19
5	10	83.83	81.60	79.29	80.32	76.57	81.76
6	12	93.84	90.10	82.02	89.00	91.74	91.50

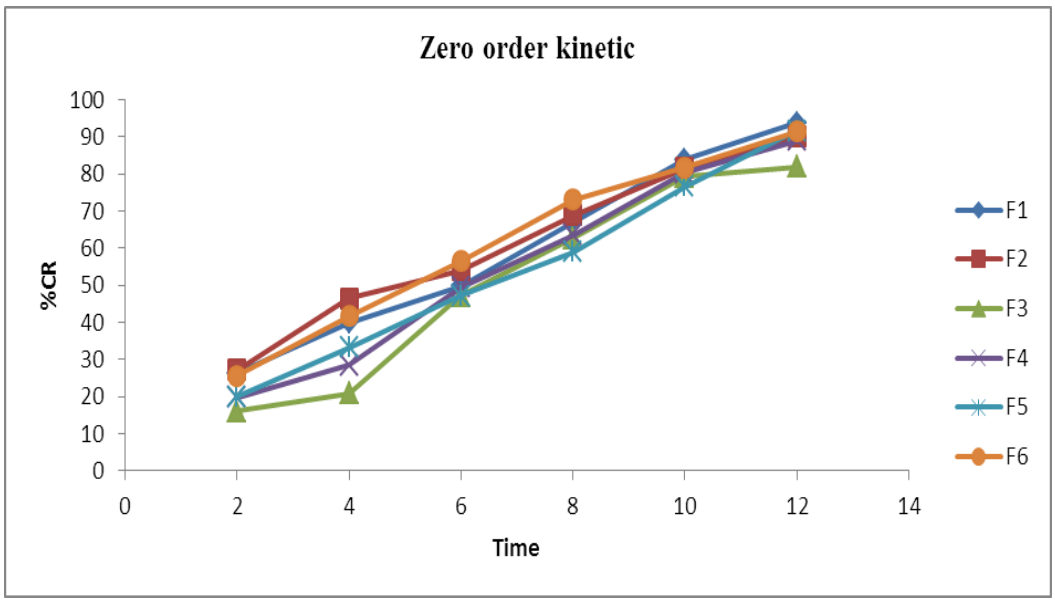

Fig. 3: Release kinetics following zero order kinetic.

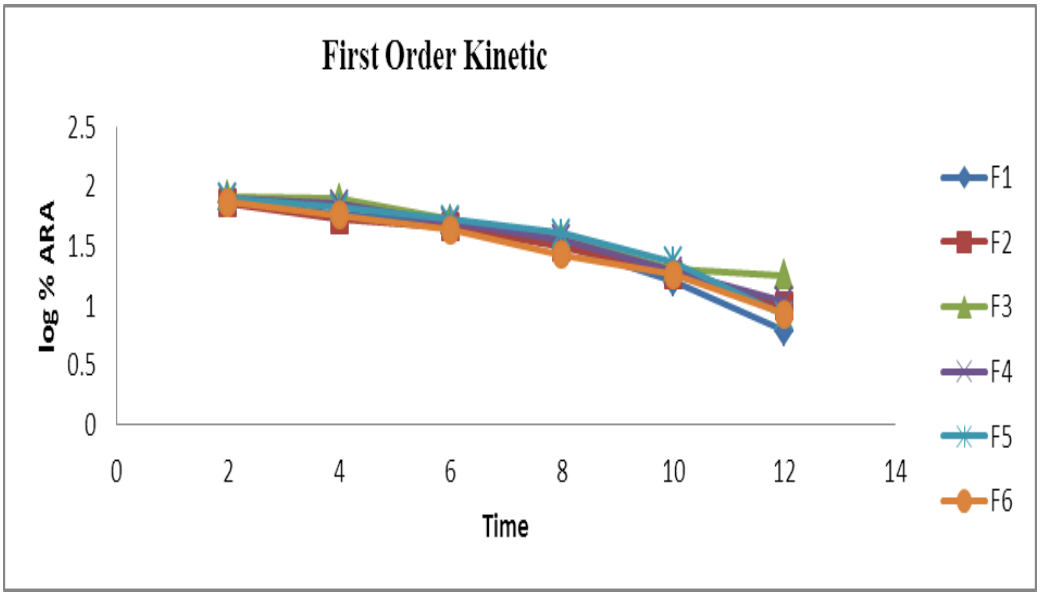

Fig. 4: Release kinetics following first order kinetic.

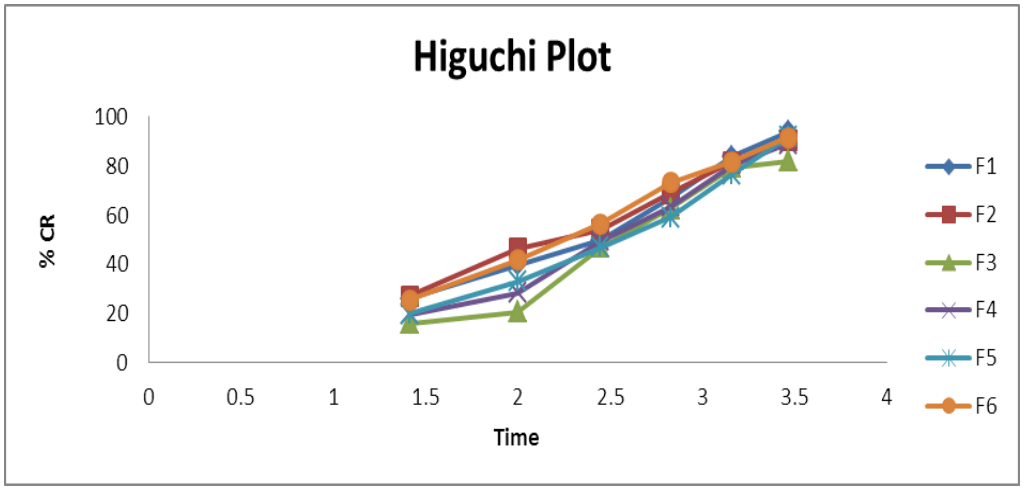

Fig. 5: Release kinetics following Higuchi plot.

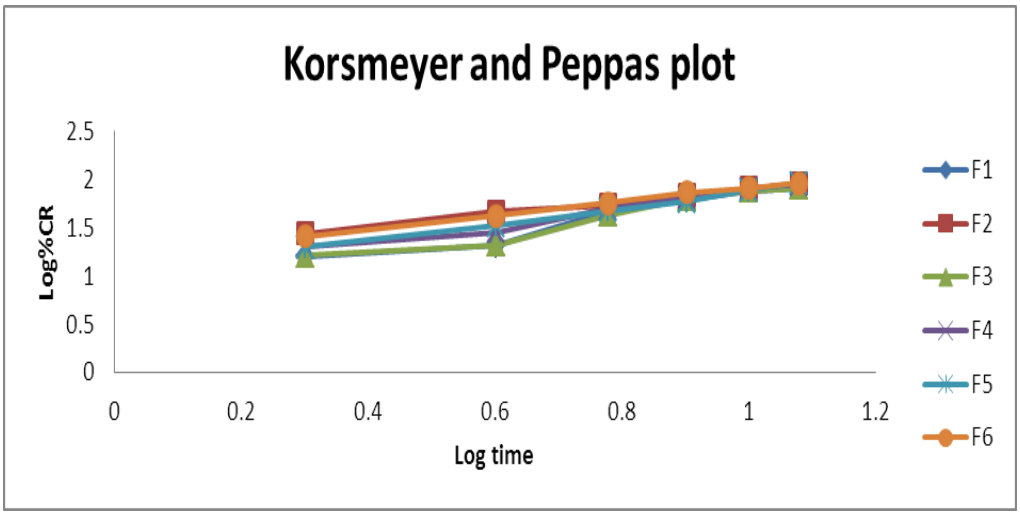

Fig. 6: Release kinetics following Korsmeyer and Peppas plot.

Table 7: Table for correlation factor.

Formulation code	Correlation Factor			Korsmeyer and Peppas (N)	Mechanism of release	Best fit model
	Zero (R^2)	First (R^2)	Higuchi (R^2)			
F1	.993	.902	.972	1.017	Super case II	Zero order
F2	.987	.955	.990	.660	Non Fickian	Higuchi
F3	.957	.961	.953	1.010	Super case II	First order
F4	.988	.951	.975	.895	Non Fickian	Zero order
F5	.996	.879	.977	.850	Non Fickian	Zero order
F6	.958	.963	.995	.724	Non Fickian	Higuchi

4. CONCLUSION

In-vitro study profile of the formulation proves that all the formulations showed the optimal release within specific time duration. The release kinetic study revealed that the two

formulations (F1,F3) among the 6 formulated batches showed super case II mechanism of release, while the other formulation (F2, F4,F5,F6) showed non fickian release mechanism.
The kinetic study revealed that each formulation follow different model. Formulation 1 (F1) follow zero order kinetic. Formulation 2 (F2) follow Higuchi model. Formulation 3 (F3) follow first order kinetic. Formulation 4 (F4) follows zero order kinetic. Formulation 5 (F5) follow zero order kinetic. Formulation 6 (F6) follow Higuchi model.

According to the evaluations done on the various formulations it was observed that the formulation number 5 (F5) showed the best result. The formulation (F5) was found to disperse at the least time of 5±.02 seconds and the total time for disintegration was found to be 3 ± .14 minutes. The drug content was found to be 99.19%. The tablets were showing hardness of 3±.5 that passes the limits as per described in the reference standard was taken from IP. The tablets was found to show the friability of. 52±.03 %.

The reason for the formulation no 5 being the best can be justified as due to the presence of the polymer poloxamer that decreased the disintegration time and the dispersion time of the tablets. As the main requirement of the sublingual dosage form was that the time of disintegration and dispersion should be less. The other factor to be considered include the weight variation, thickness, hardness, friability and drug content. The formulation F5 passes all the criteria as per the standard reference from IP.

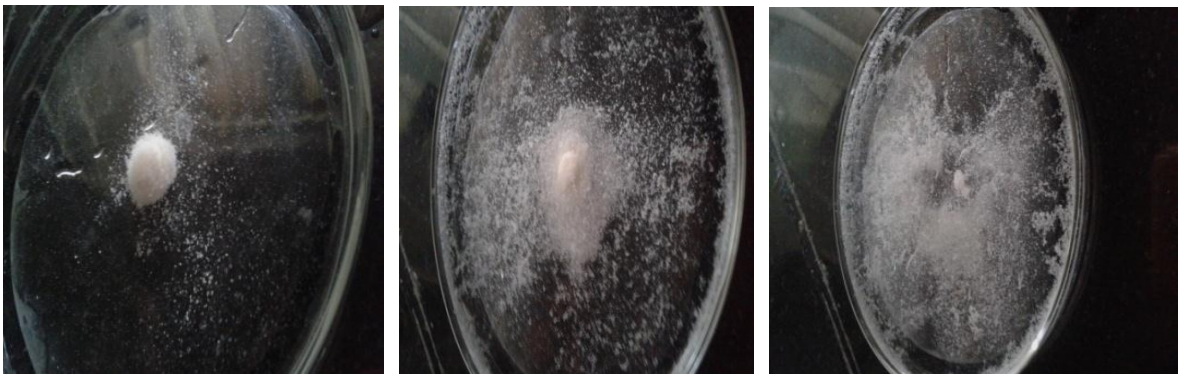

Fig.7. Disintegration of formulation F5.

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