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Formulation and evaluation of fast dissolving oral wafers of linagliptin

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***Abstract*---**Wafers are modern oral dosage forms which are commonly used by patients worldwide. Also, in acute pain, these dosage types can be used to get immediate relief. These oral sublingual wafers are nothing more than a thin oral stripe which dissolves immediately due to the presence of saliva in the mouth when placed in the sublingual cavity by releasing medication within a short span of time. The faster dissolution can be achieved by using different superdisintegrants in different concentrations and a comparative study of different superdisintegrants has been carried out. Present investigation aims to formulate fast dissolving wafer of linagliptin using different film forming agents. From the latest research it can be inferred that fast-dissolving oral films of drug release are preferable. The films prepared by HPMC K4 and K15 and CCS and CP had shown strong mechanical power, release of narcotics, period for disintegration and analysis of dissolution. F7 formulation is considered the better with less disintegrating time and release in 10 min according to the results obtained. Percent drug release and disintegration time was taken as responses for study which were found within the accepted ranges. Linagliptin administered in the form of fast dissolving films will be potential novel drug dosage form for pediatric, geriatric and also for

general population by providing faster release and better patient compliance

Keywords---Wafers, Linagliptin, Sublingual wafers, polymers.

Introduction

Wafer – A novel oral dosage form

- Quick dissolving wafers are modern oral dosage forms which are commonly used by patients worldwide. Also, in acute pain, these dosage types can be used to get immediate relief. [1]
- These oral sublingual wafers are nothing more than a thin oral stripe which dissolves immediately due to the presence of saliva in the mouth when placed in the sublingual cavity by releasing medication within a short span of time. [2]
- Sublingual wafers tend to be of highly advantageous dosage during flight, as they do not require water for swallowing. Also, rapid onset of action is achieved as this dosage type is highly successful in preventing metabolism from the first step. [3]
- Wafers are administered sublingually to increase the onset of action, decrease the dosage and increase the effectiveness of the drug, it is more stable, durable and quicker dissolving than other conventional dosage forms, an oral wafer helps to enhance bioavailability of the drug. [4,5]

Ideal properties of the Wafer forming polymers [6,7]

- Non-toxic, nonirritant and devoid of leachable impurities,
- Good wetting and good shelf life,
- Pleasant mouth feels
- Devoid of secondary infections in the oral mucosa or dental regions,
- Local enzyme inhibition action along with penetration enhancing property.

Materials and Methods

The drug Linagliptin is used for the preparation of oral wafers. The formulation is to be prepared in such a way that the tablets will disintegrate very fast and make the drug present in the formulation to be ready for the dissolution. The faster dissolution can be achieved by using different superdisintegrants in different concentrations and a comparative study of different superdisintegrants has been carried out. Present investigation aims to formulate fast dissolving wafer of linagliptin using different film forming agents.

Formulation development of oral wafers of Linagliptin

Table no 1. Selection and optimization of wafers forming agents

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6	F7	F8	F8
Linagliptin	60	60	60	60	60	60	60	60	60

HPMC K4	50	100	150				25	50	75
HPMC K15				50	100	150	25	50	75
PEG-400	50	50	50	50	50	50	50	50	50
SSG	50	100		-	-	-	25		25
CCS	-	-	50	100	-	-	25	25	
CP	-	-	-	-	-	-	-	25	25
Mannitol	50	50	50	50	50	50	50	50	50
Citric acid	30	30	30	30	30	30	30	30	30
DM water qs to (ml)	30	30	30	30	30	30	30	30	30

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm^2 wafers present whole plate = 12
- Each wafer contains 5 mg of drug.
- 12 no. of wafers contains mg of drug = 5×12 = 60mg
- The amount of Linagliptin added in each plate was approximately equal to 60mg.

Results

1. Pre-formulation study

1.1 Results of Organoleptic characteristics

S. No.	Properties studied	Results
1.	Color	White
2.	Odor	Odorless
3.	Taste	Bitter
4.	Appearance/Morphology	Crystalline powder

1.2 Results of solubility

Solvents	Results of Solubility
Methanol	Soluble
Ethanol	Sparingly soluble
Chloroform	Soluble
Distilled water	Soluble
Phosphate buffer pH 6.8	Soluble
0.1 N HCl	Sparingly soluble
0.1 N NaOH	Sparingly soluble

1.3 Results of loss on drying

Results of Loss on drying of Linagliptin was found 0.147±0.005%.

1.4 Results of melting point

The Melting point of Linagliptin was found 194-196 ºC.

1.5 Results of FTIR spectra of Linagliptin

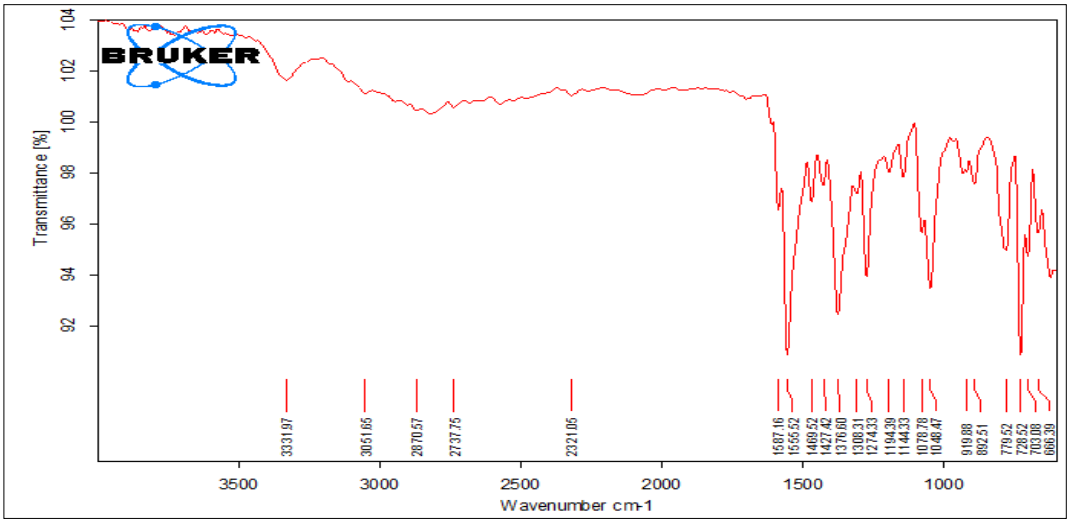

Fig no 1: FTIR spectra of Linagliptin

1.6 Results of UV analysis

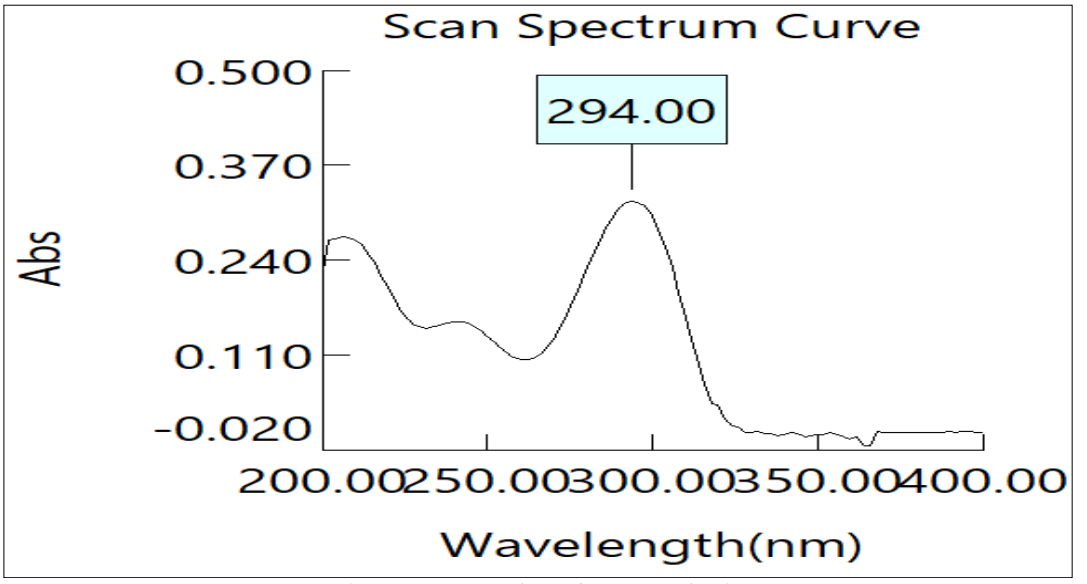

Fig no 2: Results of UV analysis

Table no 2: Results of UV analysis

S. No.	Concentration (µg/ml)	Absorbance
1.	5	0.136
2.	10	0.251
3.	15	0.369
4.	20	0.477
5.	25	0.596

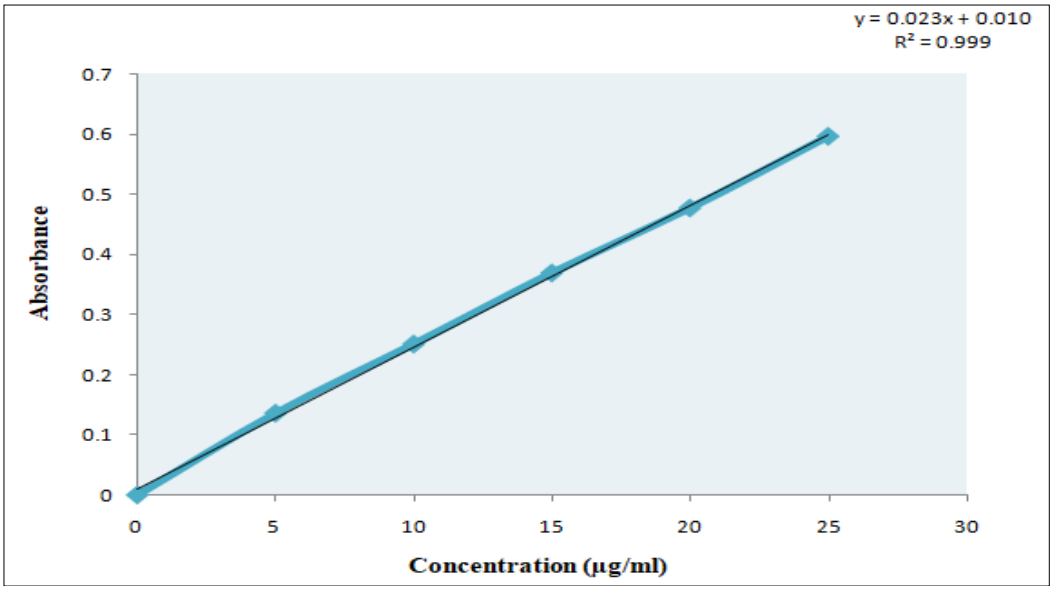

Fig no 3: Results of UV analysis

2. Evaluation parameter of prepared wafers

2.1 Evaluation of prepared wafers for general appearance, thickness and weight

Formulation code	General Appearance	Thickness* (µm)	Weight* (mg)
F1	Transparent	43±3	78±4
F2	Transparent	45±2	75±6
F3	Transparent	48±5	85±5
F4	Transparent	42±4	74±2
F5	Transparent	43±3	76±1
F6	Transparent	46±2	79±4
F7	Transparent	42±5	82±2
F8	Transparent	45±4	85±3
F9	Transparent	47±2	89±4

*Average of three determination (n=3±SD)

2.2 Result of Folding Endurance, Disintegrating time, Tensile strength, Percentage Moisture Content and % Assay

Formulation code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength in kg/cm^2	Percentage of Moisture Content	% Assay
F1	125±5	45±5	0.98±0.8	9.25±0.12	98.78±0.45
F2	136±7	35±4	0.85±0.9	7.32±0.25	99.12±0.62
F3	123±8	25±6	1.05±0.5	7.65±0.32	98.98±0.25
F4	129±6	20±2	0.95±0.06	7.25±0.28	98.85±0.36
F5	133±5	23±5	0.85±0.08	6.74±0.36	98.74±0.65
F6	135±8	20±7	0.74±0.07	7.12±0.45	97.98±0.58
F7	178±6	14±4	0.65±0.05	5.65±0.65	99.47±0.78
F8	136±8	22±5	0.84±0.07	6.85±0.25	98.85±0.85
F9	145±4	23±2	0.81±0.04	7.42±0.52	98.75±0.25

***2.3 In-vitro* drug release study of Formulation F1-F9**

Time (Min.)	Cumulative % Drug release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	Pure Drug
1	32.25	33.25	26.65	29.98	24.45	26.65	35.56	30.14	28.89	11.12
2	46.65	42.23	45.58	49.95	39.98	45.56	52.26	48.85	45.65	16.65
4	59.98	56.65	63.32	62.26	49.95	52.25	69.98	65.58	62.23	22.25
6	72.23	76.65	82.23	75.56	68.85	69.98	79.98	79.98	75.65	28.89
8	81.14	83.32	89.98	86.65	75.65	79.98	89.98	92.26	85.56	35.56
10	95.56	96.65	97.74	98.12	92.23	94.45	99.48	96.65	92.23	45.56

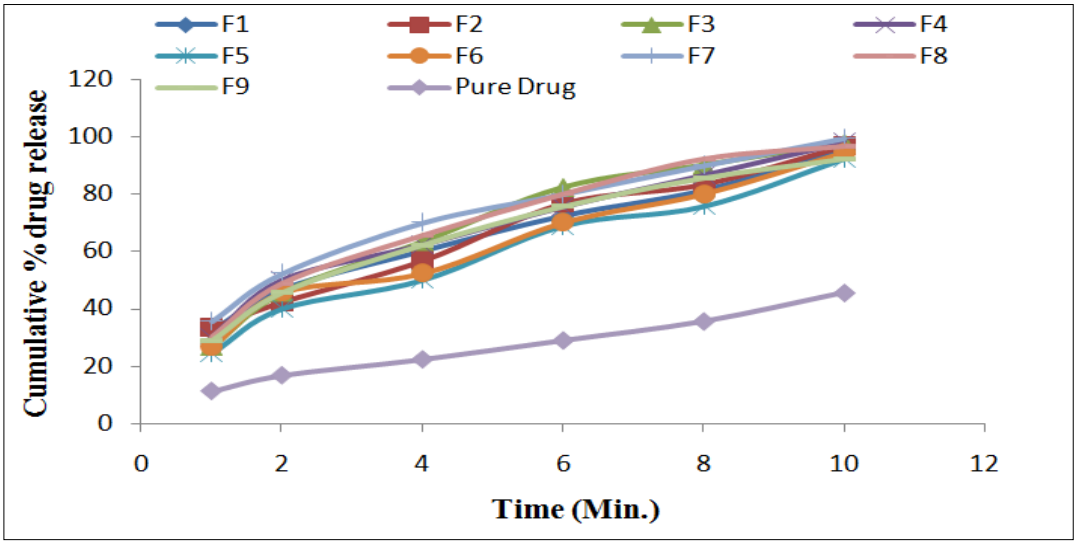

Fig no 4 In-vitro drug release study of Formulation F1-F9

2.4. Results of *in-vitro* release kinetics of optimized formulation F7

Time (min.)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative %Drug Remaining	Log Cumulative % Drug Remaining
1	1.000	0.000	35.65	1.552	64.35	1.809
2	1.414	0.301	58.89	1.770	41.11	1.614
4	2.000	0.602	73.32	1.865	26.68	1.426
6	2.449	0.778	89.98	1.954	10.02	1.001
8	2.828	0.903	94.65	1.976	5.35	0.728
10	3.162	1.000	99.12	1.996	0.88	-0.056

2.5 Regression coefficient for selection of optimized batch

Zero order		**First order**	**Higuchi**	**Peppas model**
r^2	0.952	0.814	0.992	0.993

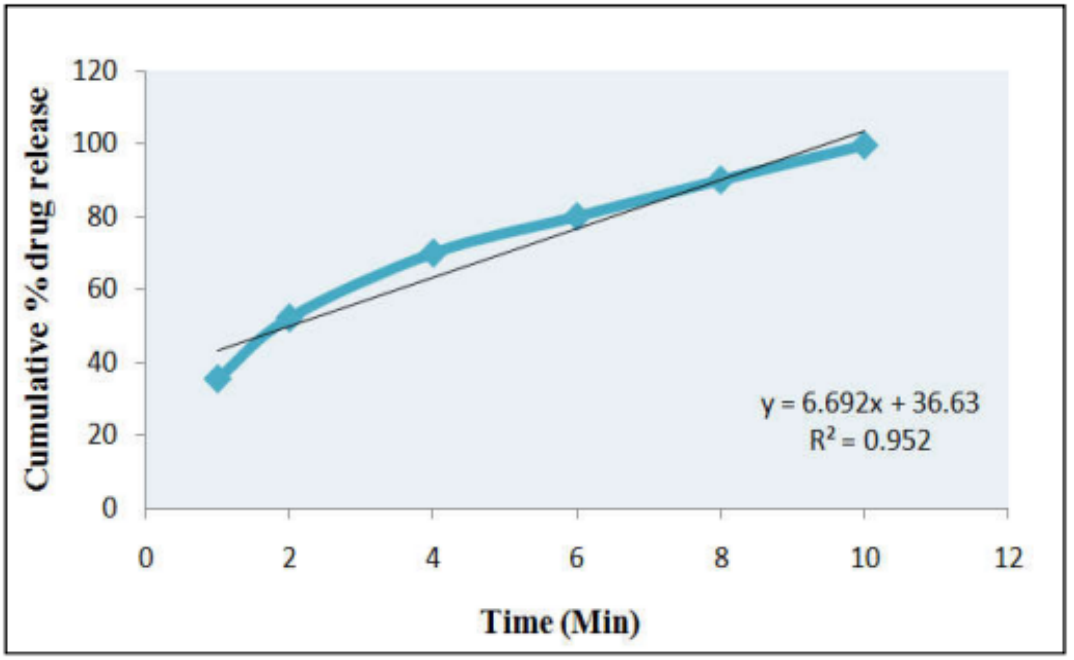

Fig no 5 Zero order release Kinetics (Cumulative % drug released Vs Time)

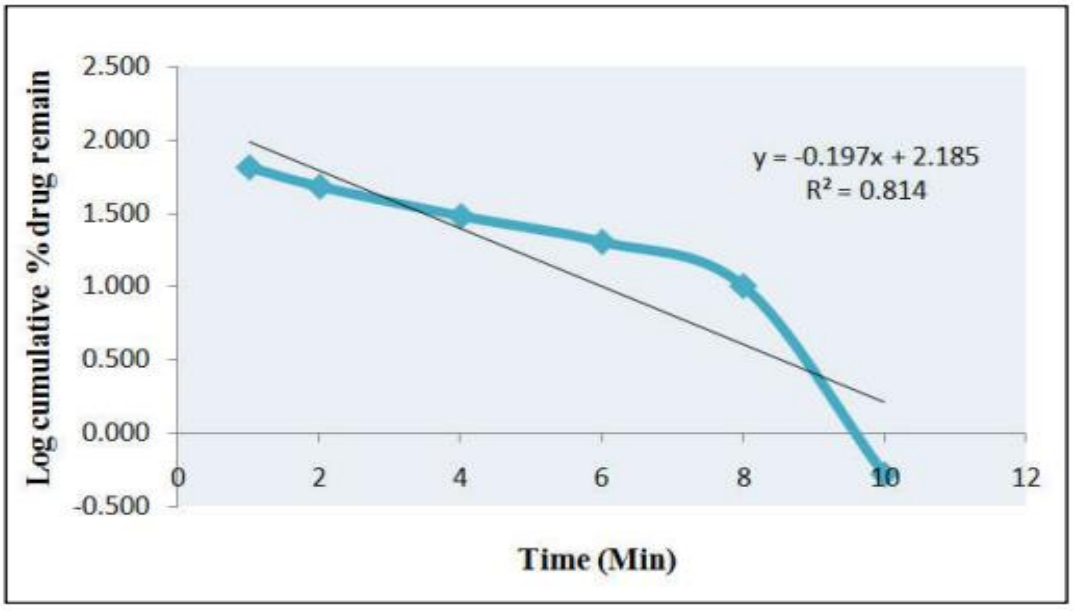

Fig no 6 First order release kinetics (Log cumulative % drug remaining Vs Time)

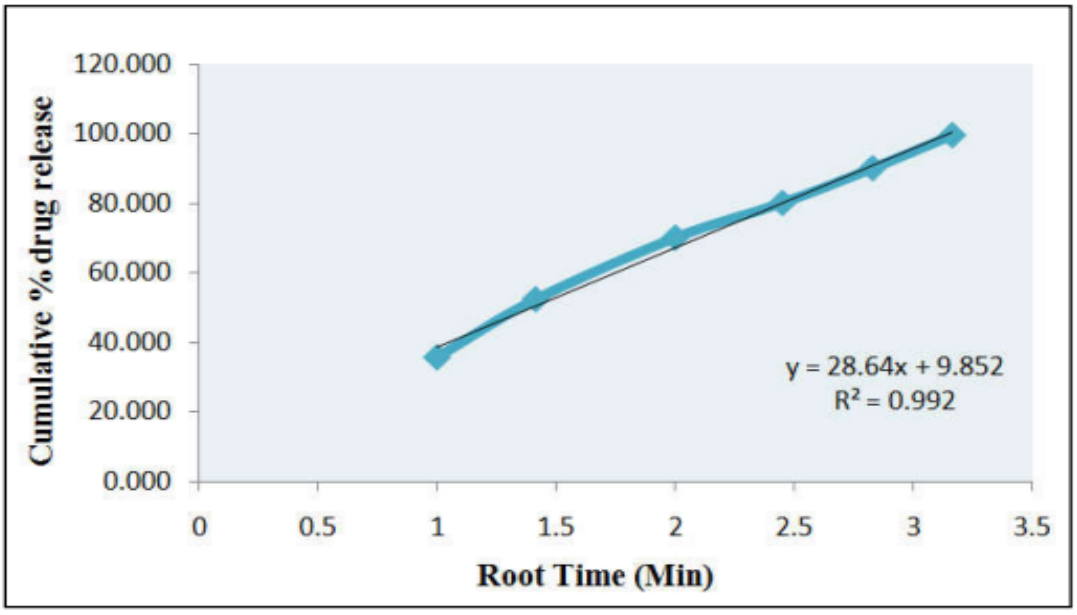

Fig no 7 Higuchi release kinetics (Cumulative % drug release Vs Root Time)

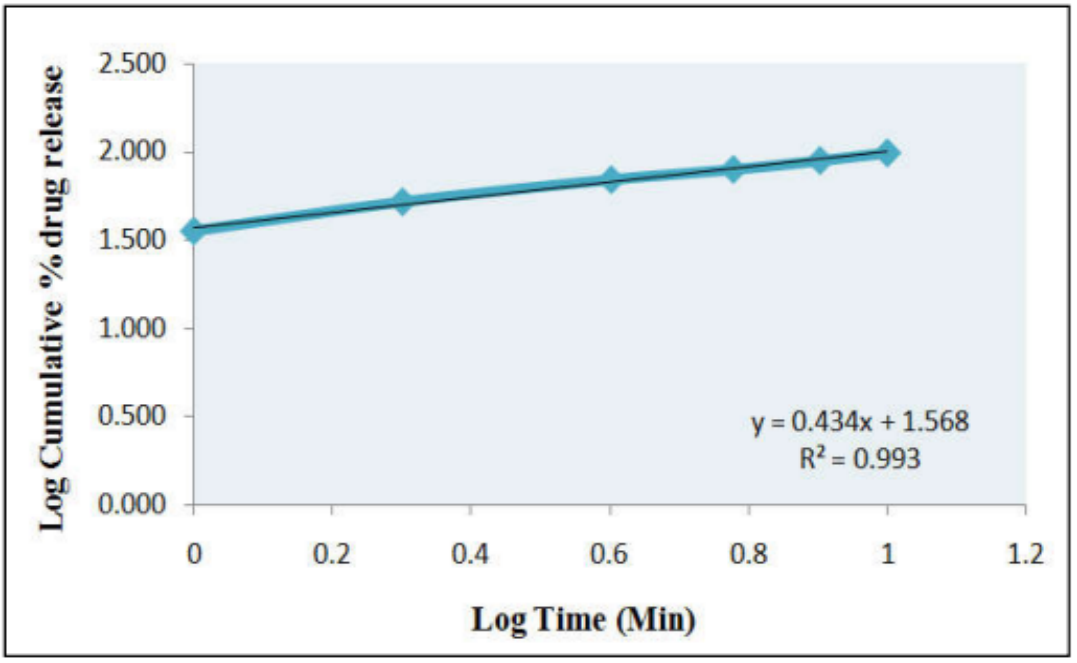

Fig no 8: Peppas release kinetics (Log cumulative % drug release Vs Log Time)

2.6 Characterization of stability study of optimized formulation

Characteristic	Time (Month)			
	Initial	1 Month	2 Month	3 Month
% Assay*	99.48±0.25	99.12±0.14	98.85±0.85	98.50±0.74

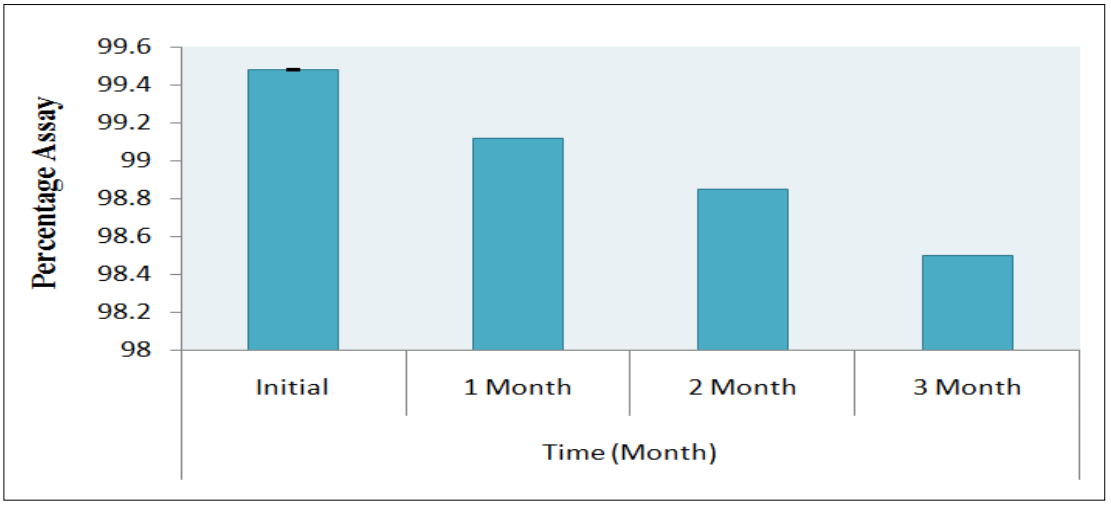

Fig no 9 Graph of stability study

Conclusions

From the latest research it can be inferred that fast-dissolving oral films of drug release are preferable. The films prepared by HPMC K4 and K15 and CCS and CP had shown strong mechanical power, release of narcotics, period for disintegration and analysis of dissolution. F7 formulation is considered the better with less disintegrating time and release in 10 min according to the results obtained. Percent drug release and disintegration time was taken as responses for study which were found within the accepted ranges. Linagliptin administered in the form of fast dissolving films will be potential novel drug dosage form for pediatric, geriatric and also for general population by providing faster release and better patient compliance

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