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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING SUBLINGUAL FILM OF LINAGLIPTIN

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A B S T R A C T

Linagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolizes the naturally occurring incretins- like peptide-1 and glucose- dependent insulinotropic polypeptide resulting in enhanced glucose- dependent insulin secretion from the pancreas and decreasedhepatic glucose production. Mucoadhesive films for sublingual use were prepared by using polymers such as Polyvinyl alcohol, Hydroxy propyl methyl cellulose, Polyvinyl pyrrolidone, Mannitol, Polyethylene glycol 400 in different ratios by the solvent casting method. The IR Spectral studies showed no interaction between drug and polymer. The prepared formulations show satisfactory result, when subjected to various physicochemical tests such as uniformity of weight, thickness, Surface pH, folding endurance, uniformity of drug content, swelling index, bioadhesive strength. The formulations were also subjected to evaluation of in vitro drug release by using USP Dissolution Apparatus. Ex vivo drug release and permeation studies were also carried out using porcine membrane as the model. All the formulation showed 76.22-100.85% release within 5 min by the in vitro method. The stability studies conducted for a period of eight weeks showed that there was no appreciable change in drug content, surface pH and in vivo drug release when stored at refrigeration temp. 4-6^{0}C, room temp 28-30^{0}C and 40-45^{0}C.

INTRODUCTION

The sublingual mucosa is relatively permeable due to thin membrane and has a high degree of perfusion and hence, rapid drug absorption and instant bioavailability is possible and this leads to quick onset of drug action. Since the drug is directly absorbed into the systemic circulation, degradation in the GI tract and first pass effect can be avoided. Moreover better patient compliance is expected, because this system does not require being swallowed as in the case of conventional tablet, and therefore beneficial in patients with dysphagia or difficulty in swallowing[1]. The use of mucoadhesive polymers in the films will enable them to adhere to the sublingual mucosa for better retention and drug absorption[2]. Linagliptin is a powerful and potent antidiabetic drug used in the control of insulin secreation. It exhibits only 30% of oral bioavailability due to first pass metabolism and has a relative short half- life of 10-12 h. Linagliptin, is freely soluble in methanol and this makes it suitable for administration through sublingual route[1].

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There has been increased demand for the novel dosage form to gain more patient compliance. Fast dissolving films recently have acquired great importance in the pharmaceutical industry due to there unique properties and specific advantages like no need of water for disintegration, accurate dosing, rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance. Fast dissolving film is a type of drug delivery system, which when placed in the oral cavity it rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption, without chewing and intake of water. This technology evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers. These films have a potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also has been used for local action[1]. This type of technology offer a convenient way of dosing medication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population. The sublingual mucosa is relatively

permeable due to thin membrane and large veins. It gives rapid absorption and instant bioavailability of drugs due to high blood flow [2,3]. As the fast dissolving film is taken through the sublingual route, rapid absorption of drug is possible, which finally leads to quick onset of drug action and prevent the first pass-metabolism of the drug.

Diabetes mellitus (DM) is one of the ten most disabling disorders worldwide, and despite recent developments in the management of diabetes, it remains underdiagnosed and undertreated. Diabetes mellitus is as the heterogeneous metabolic disorder characterized by common feature of chronic hyperglycaemia with disturbance of carbohydrate, fats and protein metabolism. DM is a chronic metabolic disorder characterized by a high blood glucose concentration-hyperglycemia caused by insulin deficiency, often combined with insulin resistance. The symptoms include polyurea, polydipsia, polyphagia, weight loss, fatigue, cramps, constipation, blurred vision and candidiasis. Linagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. So orally fast dissolving sublingual films of Linagliptin prevents its first pass metabolism and eliminates the need of intake of water by the patient during diabetes mellitus and provide fast onset of action which would be beneficial to diabetes mellitus sufferers in resuming their functional abilities as soon as possible.

MATERIALS AND METHODS

Linagliptin was received as gift samples from Zydus Cadila pharmaceuticals Ltd., Mumbai, India. Hydroxypropyl methyl cellulose (E-15) was procured from the Loba Chemie, Mumbai, India. Polyvinyl alcohol was obtained from Reliance Cellulose, polyvinyl pyrrolidone was obtained from Evonik, Kolkata. Mannitol was purchased from Research-Lab Fine Chem. Industry- Mumbai.

Drug polymer compatibility studies

Drug polymer compatibility studies were carried out using FTIR. The sample was dispersed and analyzed. Spectra were obtained by powder diffuse reflectance on a FT-IR spectrophotometer type FT-IR Bruker Eco ATR.

UV Spectrum Analysis of Linagliptin

The solution was scanned in the range of 400 to 200 nm to fix the maximum wave length and UV spectrum was obtained.

Standard plot of Linagliptin in pH 6.8 Phosphate buffer

The standard plot of Linagliptin was prepared in pH 6.8 phosphate buffer. 10 mg of drug was weighed accurately and dissolved in 100 ml stock solution of phosphate buffer. Appropriate dilutions were made with buffer to obtain test solutions ranging from 5 µg/ml to 25 µg/ml. the absorbance of the drug in the buffer was then measured on a UV visible spectrophotometer at λ_{max} of 293 nm against the respective blank.

Standard plot of Linagliptin in methanol

The standard plot of Linagliptin was prepared in methanol. 10 mg of drug was weighed accurately and dissolved in 100 ml stock solution of methanol. Appropriate dilutions were made with methanol to obtain test solutions ranging from 5 µg/ml to 25 µg/ml. the absorbance of the drug in the methanol was then measured on a UV visible spectrophotometer at λ_{max} of 293 nm against the respective blank.

Standard plot of Linagliptin in 0.1 N HCL

The standard plot of Linagliptin was prepared in 0.1 N HCL. 10 mg of drug was weighed accurately and dissolved in 100 ml stock solution of 0.1 N HCL. Appropriate dilutions were made with 0.1 N HCL to obtain test solutions ranging from 5 µg/ml to 25 µg/ml. the absorbance of the drug in the 0.1 N HCL was then measured on a UV visible spectrophotometer at λ_{max} of 295 nm against the respective blank.

Method of preparation of fast dissolving sublingual film of Linagliptin

Fast dissolving film of Linagliptin was prepared by the solvent-casting method. In this method, three portions were made. In first portion the drug was dissolved in sufficient quantity of methanol, and in second portion weighed amount of PVP K-30, HPMC and mannitol were added in methanol. In third portion, the weighed quantity of PVA was dissolved in sufficient amount of distilled water with continuous stirring on magnetic stirrer. Now, this third portion was mixed with shaking in above two portions. At last calculated amount of PEG 400 and flavours were added to this drug polymeric solution. This solution was mixed thoroughly to obtain homogeneous solution. Methanol was finally added to make up the final volume. The homogeneous solution was put in to mould prepared from aluminium or glass (size 4-5 cm^2) and dried at 40-50^0 C. The film was carefully removed from the petri dish, checked for any imperfections, and cut according to the size required for testing (square film: 2 cm length, 2 cm width). The samples were stored in a glass container maintained at a temperature of 40^0±2^{0}C and relative humidity 75±5% until further analysis.

Evaluation

Thickness

Mechanical Properties [4,5]

Mechanical properties of the films are evaluated using Instron TA.XT2 texture analyzer equipment equipped with a 50 N load cell. Films are held between two clamps positioned between 3 cm. During measurement the strips were pulled at the rate of 2mm/sec. The force and elongation are measured when film breaks. Two mechanical properties namely tensile strength and % elongation are calculated.

Tensile strength [5,6]**:** Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. Tensile testing of the film was determined with digital tensile tester, which consists of two load cell grips. The lower one is fixed and upper one is movable. The test film of specific size was fixed between cell grips and force was gradually applied till the film breaks. Tensile strength is calculated by Formula;

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross sectional area of film in mm}^2}$$

Percent Elongation [7,8]**:** It is calculated by the distance travelled by pointer before the break of the film on the graph paper. When stress is applied, a film strip sample stretches and this is referred to as strain. Strain is basically the deformation of film strip divided by original dimension of the

sample. Generally elongation of strip increases as the plasticizer content increases. It is calculated as;

$$\% \text{ Elongation} = \frac{\text{Increase in length}}{\text{Original Length}} \times 100$$

Thickness of the Film [9,10,11]: The thickness of the drug loaded films was measured with the help of micrometer screw gauge at different strategic locations like four corners and centre of the each film. Mean SD is calculated. The standard range for film thickness should not be less than 5 %. This is essential to assure uniformity in the thickness of the lm as this was directly related to the accuracy of dose.

Weight variation of the film*[5,10]*: Weight variation is studied by individually weighing 10 randomly selected filmstrips and calculating the average weight should not deviate significantly from average weight. According to specifications given in I.P.2007 for 30 mg film standard deviation should not more than 10 %.

Folding endurance [6,10]: *It is measured manually for the prepared oral film. A film was repeatedly folded at the same place till until it breaks. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. This test should be performed on three films of each formulation and mean ±SD calculated.*

Surface pH[6]: *The film formulation has to be kept in the oral cavity, pH of the saliva ranging from 5.5-7.5. So, to dissolve and solubilise the drug in saliva present in the oral cavity the pH of film should keep near to neutral. Since acidic or alkaline pH may leads to irritation to the buccal mucosa.* The surface pH of the film is calculated in order to investigate any side effects in vivo. A combined pH electrode was used for this purpose. The film preparation to be tested was placed in nesseler cylinder and was slightly moistened with o.5 ml distilled water introduced drop wise. The pH is measured by bringing the electrode in contact with the surface of the oral film and allowing equilibrating for 1 min. The study performed on three films of each formulation & mean±SD calculated.

Differential Scanning Calorimetry (DSC)[10]: *The DSC thermograms of pure Linagliptin and sublingual film containing drug were measured using a differential scanning calorimetry. The samples of 3-5 mg were accurately weighted into solid aluminium pans with seals. The measurements were obtained by heating at every 10°C and flow rate of 15 ml/min.*
In-vitro disintegration time[10,12]: In vitro disintegration time was determined visually in a glass dish of 25 ml distilled water with swirling every 10 seconds. The test was performed in triplicate for each formulation. The disintegration is the time when film breaks or disintegrates. Superdisintegrants should be incorporated in the film formulation to improve disintegration rate. All the films were subjected to disintegration test and results obtained. In Indian pharmacopoeia limits for disintegration is 1-3 min for fast dissolving dosage forms.

In-vitro drug release study[6,12]: *The in vitro dissolution study was carried out in freshly prepared deionised simulated saliva solution pH 6.8 phosphate buffer using USP paddle apparatus at 37±0.5°C. Percent drug release was calculated for each formulation. Samples were withdrawn at every 1 min time interval within 5 min dissolution study. Samples were diluted by 6.8 phosphate buffer solution and analysed by UV-Visible spectrophotometer.*

Optimization study: Study is carried using design expert software 10.0 version. Statistics are apply to the results obtained from general factorial design in which two independent variables varied namely polyvinyl pyrrolidone (X1) and polyvinyl alcohol (X2) and their effect is recorded on dependent variable namely % drug release (Y1). Evaluation and interpretation of research findings are almost important and the p-value serves a valuable purpose in these findings.

Uniformity of Content[6,12]: The films were tested for content uniformity. Films of size 4 cm^2 was placed in 100 ml volumetric flask and dissolved in methanol, volume is made upto 100 ml with methanol (100µg/ml). Samples were suitably diluted by using methanol. The absorbance of the solution was measured at 293 nm in UV spectrophotometer. The acceptance value (AV) of the preparation 85-115%.

Morphology study: *The morphology of the films was studied using scanning electron microscopy (SEM), at a definite magnification. The external morphology of the formulation F1 was analysed using SEM to determine the drug distribution within the film.*

Accelerated Stability studies[13]: The standard test conditions for stability study were given in Table 1.

Table 1 Test conditions for stability study

Test Conditions	
Duration of study:	90 days
Temperature conditions:	40± 2°C
Relative humidity conditions:	75± 5%
Frequency of testing the samples:	30 days, 60 days, 90 days.

The Optimized formulation was evaluated mainly for its physical characteristics at the predetermined intervals of 30day, 60day and after 90 days like appearance (colour changes), pH, and drug content and disintegration time.

RESULTS AND DISCUSSION

UV Spectrum Analysis of Linagliptin

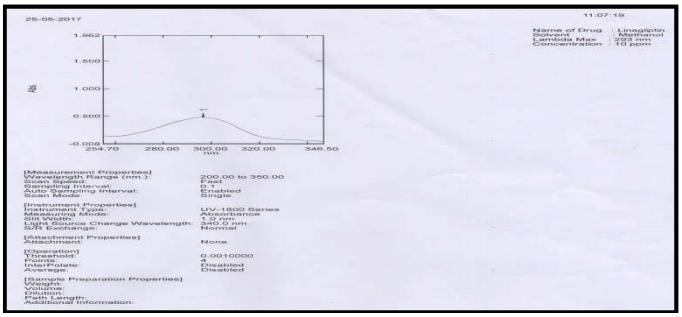

Figure 1 Scan of Linagliptin

Table 2 Standard curve of Linagliptin in pH 6.8 phosphate buffer at λ_{max} 293nm.

Sr. No.	Concentration (ppm)	Absorbance at 293nm
1	5	0.2433
2	10	0.3643
3	15	0.5150
4	20	0.6598
5	25	0.8145

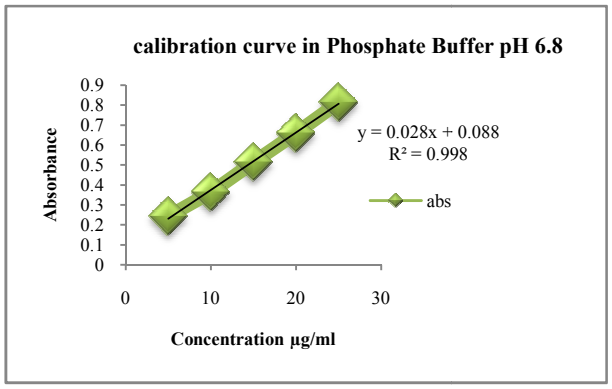

Figure 2 standard curve of Linagliptin in pH 6.8 Phosphate Buffer

Table 3 Standard curve of Linagliptin in 0.1 N HCL at λ_{max} 295nm

Sr. No.	Concentration (ppm)	Absorbance at 295nm
1	5	0.2965
2	10	0.5166
3	15	0.7425
4	20	0.9867
5	25	1.2317

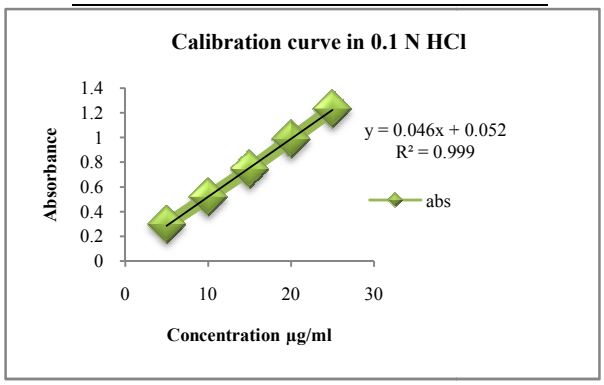

Figure 3 Standard curve of Linagliptin in 0.1 N HCL

Table 4 Standard curve of Linagliptin in Methanol

Sr. No.	Concentration (ppm)	Absorbance at 293nm
1.	5	0.1896
2.	10	0.4550
3.	15	0.6285
4.	20	0.8206
5	25	0.9902

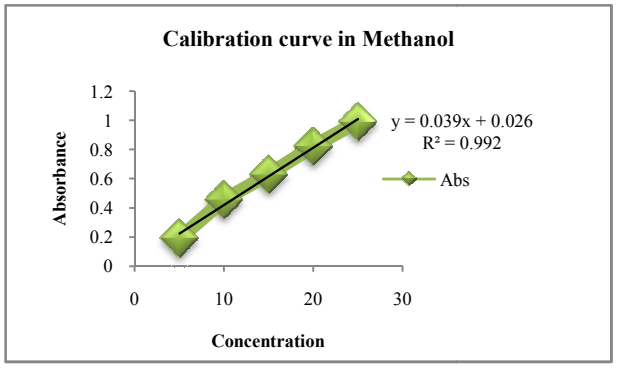

Figure 4 Standard curve of Linagliptin in Methanol

Drug polymer compatibility studies by FTIR

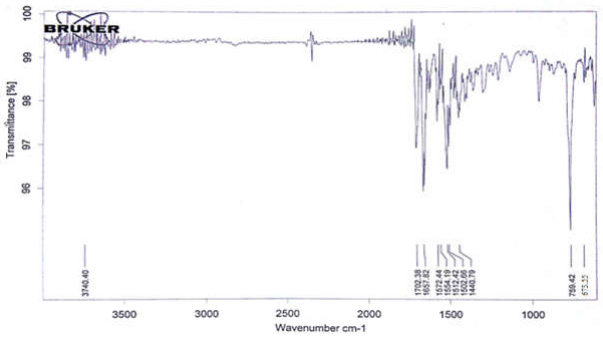

Figure 5 FTIR spectra of Linagliptin

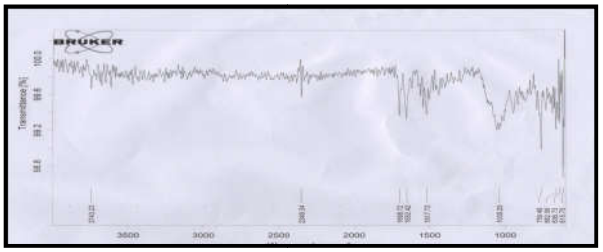

Figure 6 FTIR spectra of Linagliptin with polymer

DISCUSSION

Physical evaluation

Film thickness

As all the formulations contain different amount of polymers, hence the thickness was gradually increases with the amount of polymers. All the film formulations were found to have thickness in the range of 0.53 mm to 0.65 mm. the results are given in table 5.

Weight variations

The weight of each filmstrip is taken on Electronic analytical balance and the weight variation is calculated as mean SD. Weight variation varies from 24.3±0.421 to 30.1±0.461. the results are given in the table 5.

Surface pH

The surface pH of the films was ranging from 6.28-7.64 as shown in table 5. Since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity.

In vitro disintegration

It was observed that *in vitro* disintegration time varies from 32.4-42.9 sec for all the formulations. In *vitro* disintegration time of OFDFs containing HPMC E-15 as polymer was effected by the thickness of the film. In vitro disintegration time of the films was found to increased with increase in the amount of the polymer.

Determination of drug content of the films

The prepared film formulations were assayed for drug content. It was observed that all the formulations were satisfactory in uniformity of drug.

In-Vitro drug release tests

The *in vitro* drug release profiles of the formulations in pH 6.8 phosphte buffer show differences depending on their composition as given in table 7.

Table 5 Composition of Linagliptin fast dissolving films

Composition / Form. Code	Linagliptin (mg)	Polyvinylpyrr-olidone K-30 (mg)	Polyvinyl alcohol (mg)	Hydroxypr-opylmethylcellulose E-15 (mg)	Mannitol (mg)	Chitosan (mg)
F1	5	5	3	10	3.5	6
F2	5	5	4	10	2.5	6
F3	5	5	5	10	1.5	6
F4	5	4	3	10	4.5	6
F5	5	4	4	10	3.5	6
F6	5	4	5	10	2.5	6
F7	5	3	3	10	5.5	6
F8	5	3	4	10	4.5	6
F9	5	3	5	10	3.5	6

Table 6 Evaluation of physicochemical parameters of fast dissolving film of Linagliptin

Batch no.	Elongation at Break(%)	Thickness (mm)	Weight variation (mg)	Folding endurance	Surface pH
F1	24.74±1.250	0.59±0.0262	28.6±0.695	147±2.592	7.25±0.02618
F2	27.32±1.565	0.61±0.0531	29.3±0.324	172±1.885	7.34±0.02987
F3	36.68±0.650	0.57±0.0237	28.5±0.386	201±2.728	7.64±0.03525
F4	25.57±0.710	0.56±0.0245	28.3±0.235	158±1.414	6.89±0.02863
F5	28.35±0.780	0.63±0.6501	30.1±0.461	184±3.771	7.04±0.03747
F6	38.95±0.795	0.55±0.5672	25.2±0.322	217±2.828	7.25±0.05156
F7	27.25±0.635	0.53±0.0375	24.3±0.421	168±3.064	6.28±0.04532
F8	35.96±0.685	0.65±0.6432	31.8±0.512	196±2.121	6.48±0.04045
F9	46.54±0.665	0.62±0.0351	29.4±0.275	221±3.535	6.69±0.03218

Table 7 Drug content and disintegration time of fast dissolving films loaded with Linagliptin

Batch no.	% Drug content	Disintegration time (sec)
F1	99.63±0.05244	32.4±0.04786
F2	98.45±0.03921	38.7±0.03452
F3	98.65±0.07509	42.9±0.03625
F4	97.32±0.05737	40.2±0.0562
F5	97.54±0.08096	42.3±0.05667
F6	98.45±0.09263	44.8±0.03132
F7	97.57±0.06091	42.6±0.03218
F8	98.64±0.04328	46.4±0.06233
F9	99.69±0.07145	49.3±0.04169

A rapid dissolution of all the film preparations was observed by the dissolution test, in which approximately 100.85% of Linagliptin dissolved within 5 min. the formulations F1 showed approximately 100.85% drug release within 5 minutes. It was also observed that HPMC E-15 was able to modulate the Linagliptin release as higher amount of HPMC E-15 resulted in release of drug at slower rate.

Stability study

The stability study of the formulation F1 and F2 was carried out at normal room conditions and 40^0C/75% RH for a period of one month. The films does not show any change in appearance and flexibility. The drug content and surface pH was found almost constant for upto one month. The *in vitro* dissolution time of the films after the stability study was also not found to be affected.

Table 8 Comparative *in vitro* dissolution of formulations in pH 6.8 phosphate buffer

Time in Min	Cumulative drug release (%) ±SD								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	95.25 ±0.9452	82.13 ±0.4618	70.25 ±0.3987	73.26 ±0.3129	59.20 ±0.6124	70.50 ±0.5839	71.23 ±0.241	60.82 ±0.512	68.82 ±0.4623
2	96.35 ±0.8532	83.70 ±0.4525	73.43 ±0.7835	78.47 ±0.356	63.23 ±0.4365	72.76 ±0.4629	75.21 ±0.3286	63.93 ±0.468	70.89 ±0.152
3	97.57 ±0.7256	85.40 ±0.3863	75.55 ±0.9230	83.87 ±0.7122	70.78 ±0.4184	74.48 ±0.3412	79.62 ±0.756	66.55 ±0.2984	73.57 ±0.297
4	98.12 ±0.6298	86.76 ±0.2987	77.12 ±0.4523	90.78 ±0.4378	72.65 ±0.3985	77.50 ±0.491	85.73 ±0.267	70.77 ±0.7623	74.80 ±0.2854
5	100.85 ±0.5421	87.13 ±0.5154	80.45 ±0.4234	92.30 ±0.5314	81.12 ±0.4981	80.17 ±0.4715	87.50 ±0.484	75.25 ±0.3984	76.22 ±0.328

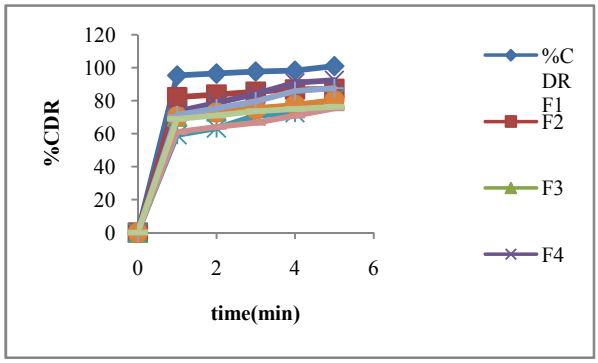

Figure 7 Comparative Evaluation of in-vitro drug release study of formulation

CONCLUSION

The results of the present study indicated that HPMC E-15 could be used as a film forming polymer for formulation of fast dissolving film containing Linagliptin. Acceptable mechanical properties were obtained for all the batches with in vitro disintegration time of 32.4 s. on the basis of data obtained from in vitro dissolution studies that F1 is promising formulation suitable for the immediate release of Linagliptin

for the systemic use since they exhibited maximum drug release . The formulation batch F1 was found to be stable for a period of one month at 40^0C/75%RH.

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