MS.ID-IJPBS-0844
International Journal of Pharmacy and Biological Sciences-IJPBS® (2023) 13 (3): 106-115
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Formulation and Evaluation of Fast Dissolving Oral Films of Sitagliptin Phosphate by Solvent Casting Method

M. Shobana[1] and R. Parthibarajan [2]

[1]Assistant Professor, Department of Pharmaceutics, Cherraaan's College of Pharmacy, Telungupalayam, Coimbatore - 641039.

[2]Associate Professor, Department of Pharmaceutics, PSV College of Pharmaceutical Science and Research, Krishnagiri - 635108.

Received: 28 Mar 2023 / Accepted: 24 Apr 2023 / Published online: 1 Jul 2023
***Corresponding Author Email:** shobanapsaravanan@gmail.com

Abstract

The aim of this research work was to formulate fast-dissolving oral films of sitagliptin phosphate for the treatment of diabetes mellitus. The fast dissolving films of sitagliptin phosphate were prepared by solvent casting method using film forming polymers HPMC E 15 and HPMC E 50 cps and PEG and propylene glycol are used as plasticizers. All the films prepared were evaluated for weight variation, thickness, folding endurance, percentage elongation, tensile strength, drug content, *In*-vitro disintegration time, in-vitro dissolution test, SEM analysis and stability studies. All the results were found to be satisfactory. Among all the formulations F3 was showed a disintegration time of 20 sec and 99 % of drug released in 3 minutes respectively. Based on the above results it can be concluded that the fast dissolving oral films of Sitagliptin phosphate may produce the rapid action thereby enhance the absorption by avoiding the first pass effect[1].

Keywords

Sitagliptin phosphate, HPMC E15, HPMC E50, PEG, Solvent casting method.

*****

INTRODUCTION:

Oral films are the newer technologies in the manufacturing of oral disintegrating dosage forms. They are thin elegant films of edible water soluble polymers of various sizes and shapes like square, rectangle or disc. The stripes may be flexible or brittle, opaque or transparent. They are designed to provide rapid disintegration on the tongue without the need for the water[2,3]. Fast disintegrating films (FDF s) have a large specific surface area for disintegration. Fast disintegrating film is placed on the patient tongue are mucosal tissue, which gets instantly wetted by saliva. The film hydrates rapidly and adheres onto the site of application. It then rapidly disintegrates and dissolves to release drug for oral mucosal absorption, or for gastric absorption on swallowing.

Novelty behind this research work is following:

- No Marketed Sitagliptin Phosphate film is available in India.
- Less excipients are required to manufacturing of film, ultimately cost of film decreases.
- Specially intended for geriatric patients who have problems of dysphagia. Administered without water, anywhere, any time (after or before meal). Avoid the problem of disintegration.

MATERIALS AND METHODS:

Sitagliptin phosphate was obtained as a gift sample from by Dr. Reddy's laboratory, Hyderabad. HPMC, PEG-400, Propylene glycol were obtained from SD fine chemicals, Mumbai. All the chemicals were of analytical grade[4,5].

FORMULATION DEVELOPMENT OF SITAGLIPTIN PHOSPHATE ORAL FILMS

	Formulation trials								
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Sitagliptin phosphate (g)	0.625	0.625	0.625	0.625	0.625	0.625	0.625	0.625	0.625
HPMC E15 (g)	1.0	1.25	1.5	-	-	-	1.25	-	1.25
HPMC E50 (g)	-	-	-	1.0	1.25	1.5	-	1.25	1.25
PEG 4000 (g)	1.5	1.25	1.0	-	-	-	-	1.25	-
Propylene glycol (ml)	-	-	-	1.5	1.25	1.0	1.25	-	-
Citric acid (g)	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Sodium saccharin (g)	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
Flavor (g)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Distilled water (ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Fast Dissolving

PROCEDURE:

The water soluble polymers and plasticizers were dissolved in distilled water. The solution is stirred up for 2 hours in the magnetic stirrer and kept aside to remove all air bubbles entrapped. Meanwhile, the excipients and drug were dissolved and stirred well for 30 min, after the completion of stirring both the solutions are mixed together. Finally, the solution is cast on a suitable petri plate to form a film. The plates were kept in a hot air oven at 60° c for 1 hour. The dried film was gently separated from the glass plate and cut into a desired sizes[6,7].

Dose calculations

Length of glass plate =10 cm.
Width of glass plate =10 cm.
Area of the plate =100 cm^2.
No. of 4 cm^2 films present whole plate =100/4 =25 films.
Each films contains 25 mg of drug.
25 films contain 625 mg drug (25×25).
Labelled claim= 25 mg

Standard Graph of Sitagliptin Phosphate

Stock solution was prepared by 50 mg of sitagliptin phosphate in 100 ml of water. From this stock solution 10 ml was withdrawn and diluted up to 100 ml using water. Calibration curve was prepared by using different concentration (20 µg/ml-100 µg/ml) by appropriate dilution of stock solution. The absorbance was measured at 267 nm[8].

Compatibility Studies

FTIR study was carried out to check the compatibility of drug with polymers. Infrared spectrum of

sitagliptin phosphate was determined on Fourier transform Infrared spectrophotometer using KBr dispersion method. The baseline correlation was done using dried potassium bromide. Then the spectrum of dried mixture of drug and Potassium bromide was run followed by drug with various polymers by using FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum[9,10].

EVALUATION OF ORAL FILM

Thickness

A micrometer screw gauge was used to measure the film thickness. In order to obtain uniformity of film, thickness is measured at 5 different locations. The thickness of the film should be less than 5 %.

Weight variation

Ten films were randomly selected and their average weight was weighed. Individual films were weighed and compared with the average weight for the deviation[11].

Folding endurance

To determine folding endurance, a film is cut and rapidly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance. Topical folding endurance for film was between100-150[12].

Percentage elongation

It was calculated by

$$\text{Percentage elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the formula

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{strip width}}$$

***In-vitro* disintegration**

Disintegrating time is defined as the time (sec) at which a film breaks when brought in contact with water or saliva[13].

Petri dish method

2 ml of distilled water was placed in the petri dish and one film was added on the surface of water and the time measured until the oral film was dissolved completely[14, 15].

***In-vitro* dissolution**

900 ml of o.1 N HCL was used as a media, at was maintained at 37 +0.5 °c while the basket was set at 100 rpm. A film sample of 4 cm^2 (2×2 cm) was cut and taken into the basket. 5 ml of the sample were taken every 2 minutes and the same amount was replaced with fresh 0.1 N HCL. The withdrawn samples were filtered and analyzed using a UV spectrometer at a wavelength of 267 nm.

Drug content

This test was performed by dissolving a 4 cm^2 area of film in 50 ml of 0.1 N HCL with stirring. This solution was filtered using a Whatman filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analysed using UV spectrometer[18, 19].

Stability studies

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized F3 formulation was sealed in Aluminum packing laminated with polyethylene. Samples were kept at 40 c and 75% RH for 3 months. At the end of study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics[20-24].

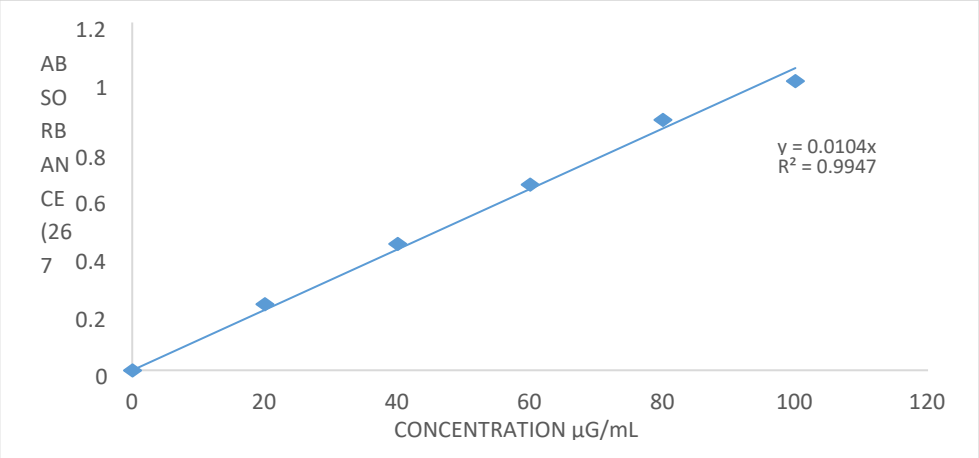
SEM analysis

The morphological study of oral strip was done by the scanning electron microscopy (SEM) at a definite magnification. Study refers the difference between upper and lower side of the films. It also helps in determination of the distribution ofAPI[25-27].

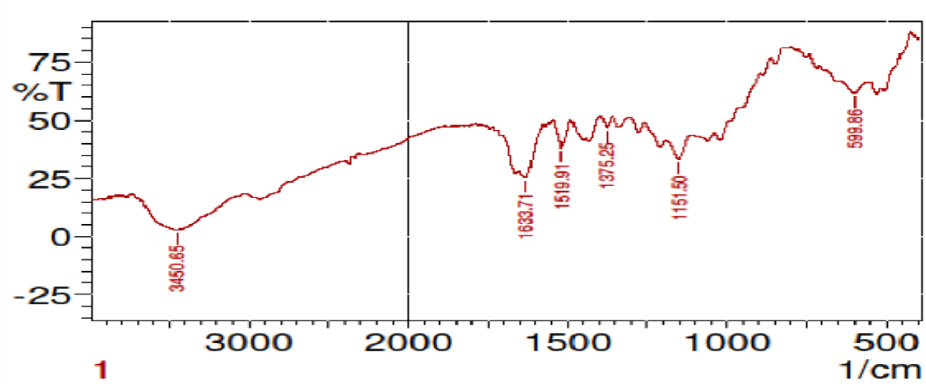
RESULTS AND DISCUSSION:

Standard graph of Sitagliptin phosphate

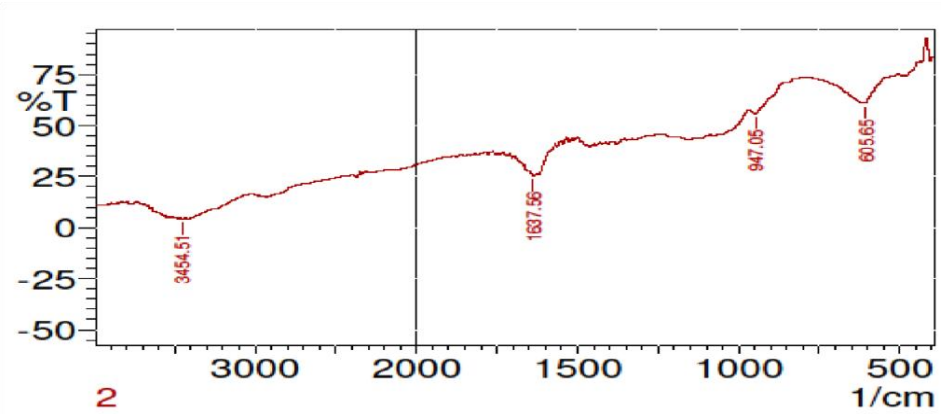
S. No	Concentration µg/ml	Absorbance (267 nm)
1	20	0.228
2	40	0.436
3	60	0.641
4	80	0.864
5	100	0.998



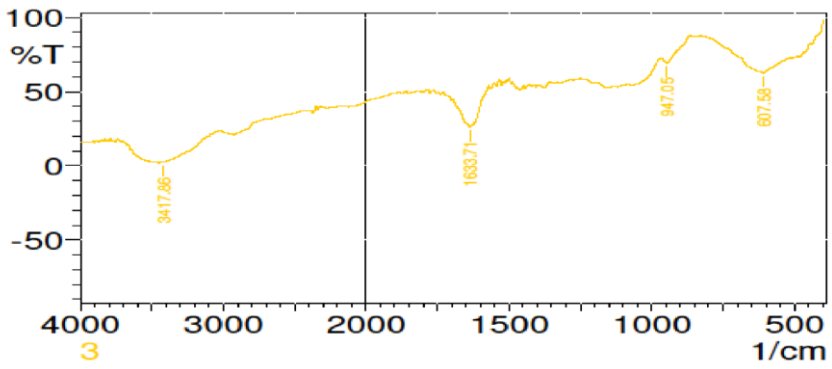
Standard graph of sitagliptin phosphate



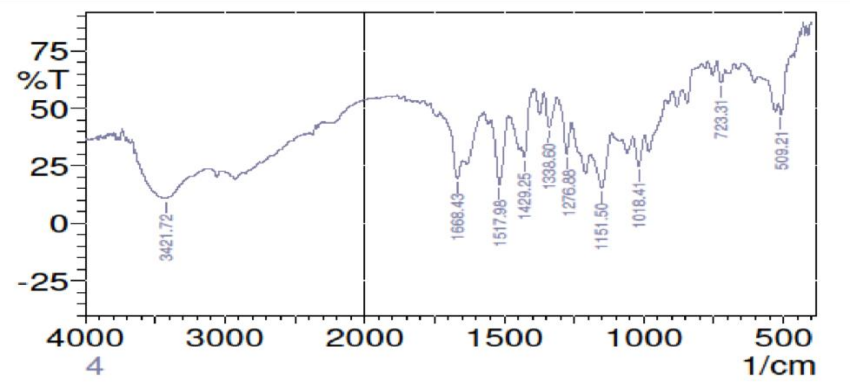
IR spectrum of Sitagliptin phosphate



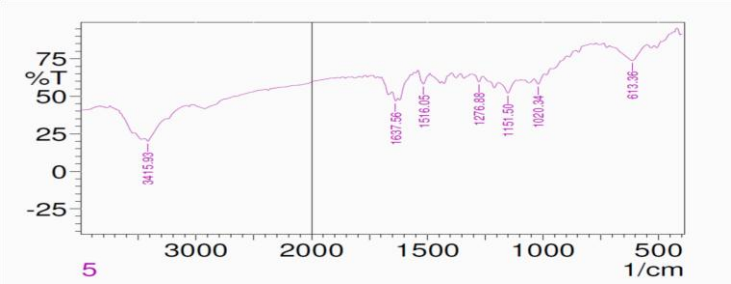
IR spectrum of HPMC E15



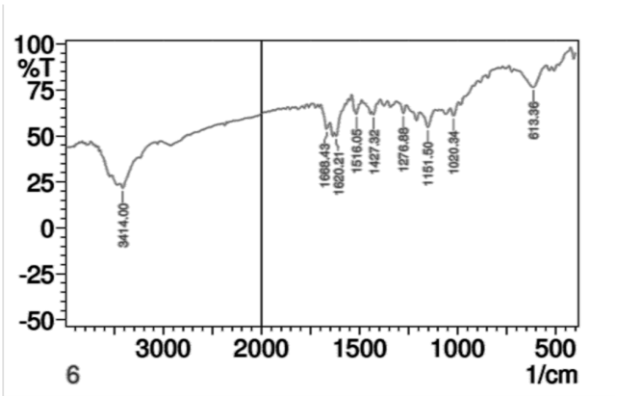
IR spectrum of HPMC E50



IR spectrum of sitagliptin phosphate & HPMC E15



IR spectrum of sitagliptin phosphate &HPMC E50

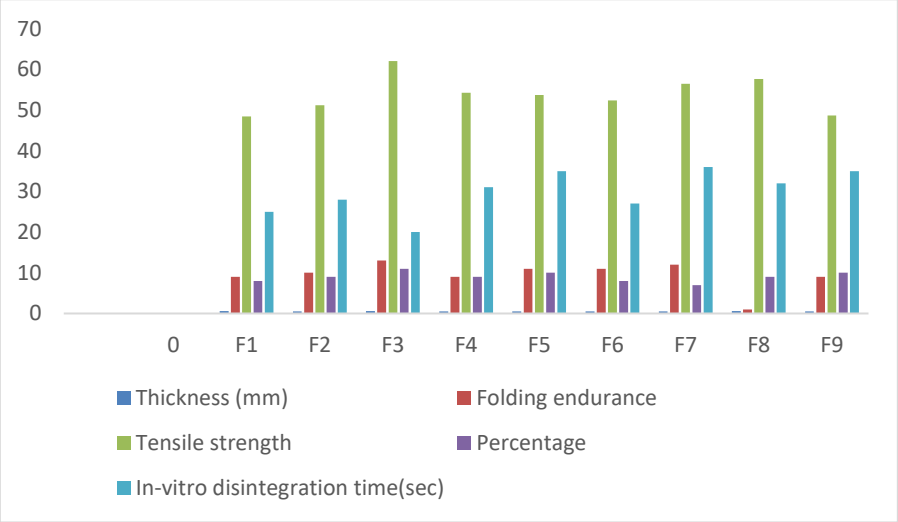


IR spectrum of sitagliptin phosphate &HPMC E15 & HPMC E50

Evaluation parameters

Formulations	Thickness (mm)	Folding endurance	Tensile strength (g/cm ^{2})	Percentage elongation	*In-vitro* disintegration time(sec)
F1	0.58	9	48.41	8	25
F2	0.55	10	51.18	9	28
F3	0.59	13	62.04	11	20
F4	0.51	9	54.25	9	31
F5	0.53	11	53.68	10	35
F6	0.52	11	52.33	8	27
F7	0.55	12	56.45	7	36
F8	0.57	1.0	57.62	9	32
F9	0.53	9	48.63	10	35

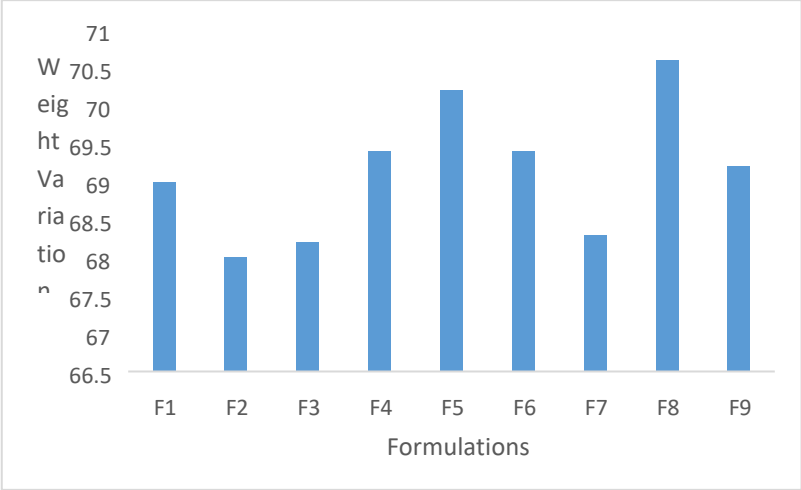
Bar chart of evaluation parameters



Weight Variation

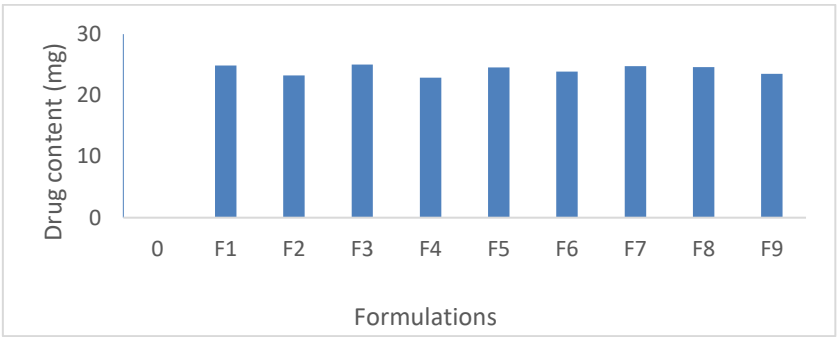
Formulations	Weight variation (mg)
F1	69
F2	68
F3	68.2
F4	69.4
F5	70.2
F6	69.4
F7	68.3
F8	70.6
F9	69.2

Bar chart of weight variation



DRUG CONTENT

Formulations	Drug content (mg)
F1	24.86
F2	23.25
F3	25.01
F4	22.91
F5	24.55
F6	23.88
F7	24.78
F8	24.63
F9	23.52

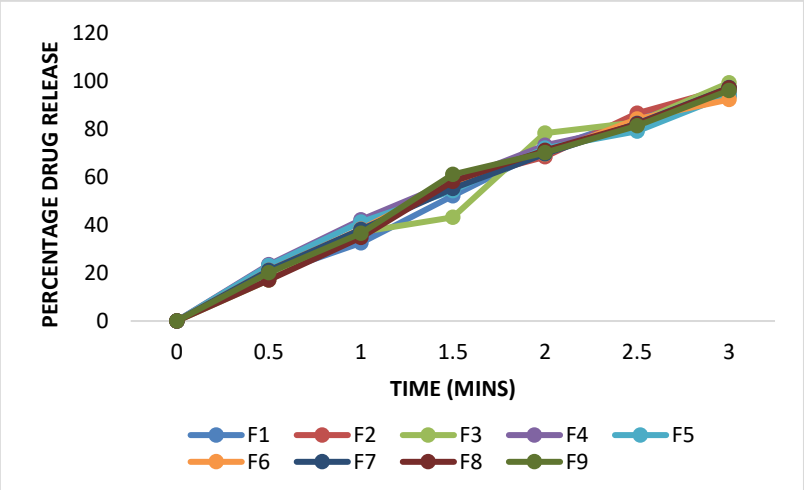


IN-VITRO DISSOLUTION

***In-vitro* dissolution profile data of formulations F1-F9**

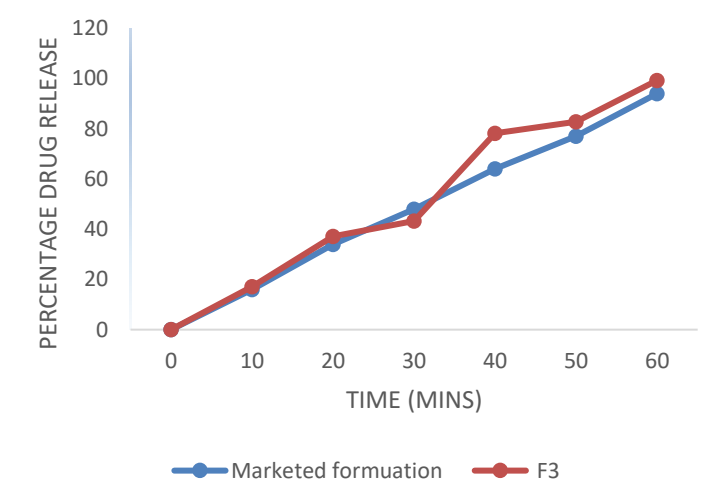
Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	19.21	21.12	17.08	23.45	23.03	21.11	21.02	17.12	20.12
1.0	32.54	36.33	37.12	42.17	41.18	38.23	38.17	34.78	36.55
1.5	52.11	58.17	43.22	58.09	54.30	57.37	55.25	58.10	61.01
2.0	71.34	68.44	78.25	73.23	72.05	69.42	69.67	71.05	70.12
2.5	84.67	86.56	82.78	81.51	79.11	84.19	82.25	82.05	81.34
3.0	93.67	97.23	99.26	95.47	94.33	92.29	97.17	97.11	96.08

All values expressed as mean ± SD (n=3), F = Formulation batch



***In-vitro* drug release data of marketed formulation Vs Formulation 3**

Percentage drug release			
Time (mins)	**Marketed formulation**	**Time (mins)**	**F3**
10	16	0.5	17.08
20	34	1.0	37.12
30	48	1.5	43.22
40	64	2.0	78.25
50	77	2.5	82.78
60	94	3.0	99.26



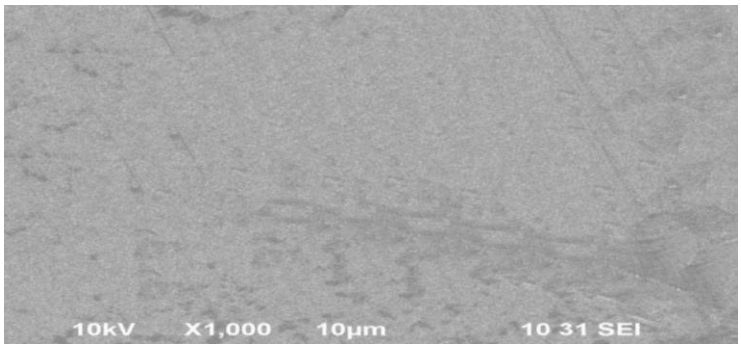
STABILITY STUDIES

Stability studies [Condition (40°C/75%RH)]

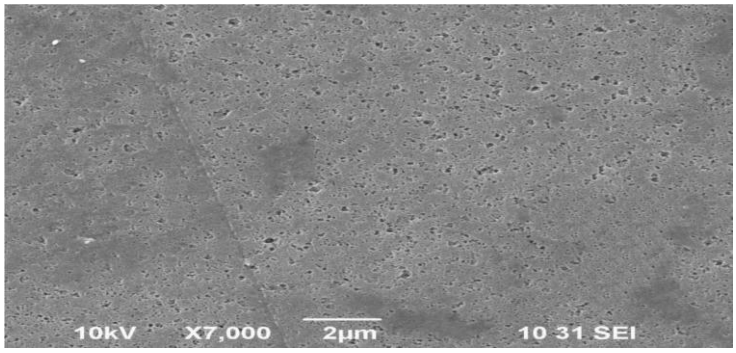
Parameters	**Initial**	**1 month**	**3 months**
Thickness (mm)	0.59	0.59	0.59
Folding endurance	13	13	12
Tensile strength (gm/cm^2)	54.25	54.25	53.01
in-vitro disintegration time (sec)	20	20	22
in-vitro dissolution (%)	99.26	99.26	99.06

SEM ANALYSIS

The morphological study of oral strip was done by the scanning electron microscopy (SEM) at a definite magnification. Study refers the difference between upper and lower side of the films. It also helps in determination of the distribution of API.



SEM analysis of formulation 3 under 1000 magnification



SEM analysis of formulation 3 under 7000 magnification

DISCUSSION:

The present investigation was undertaken to formulate Sitagliptin phosphate oral films for the treatment of Diabetes mellitus. F1-F3 were carried out with HPMC E15 cps, PEG 400, sodium saccharin, citric acid and flavor. The films were clear and transparent. The thickness also uniform. The flexibility also good. The films shown good mechanical properties. According to the assay result the drug was properly loaded in the film. F4-F6 were carried out with HPMC E50, propylene glycol, sodium saccharin, citric acid and flavor. The films shows good appearance. The thickness also not uniform. The flexibility of the film was not good. The percentage drug release was found to be. F7 was formulated with HPMC E15, propylene glycol, sodium saccharin, citric acid and flavor. The appearance of the film was also good but the thickness and disintegration time was more. F8 was formulated with HPMC E50, PEG 400, sodium saccharin, citric acid and flavor. F9 was formulated with HPMC E15 & E50 without the addition of plasticizers. The formulated films were more brittleness. Among all the formulations F3 shown good mechanical properties and less disintegration time of 20 seconds. All the parameters of film were found to be satisfactory. And the dissolution profile was found to be desirable and reproducible. The morphological study (SEM) of F3 shows more porous. Therefore rapid drug release was achieved for the immediate onset of action. The stability studies were performed for about 1 month and 3 months. No significant changes were observed in the thickness, tensile strength, in-vitro disintegration and in-vitro drug release. The film (F3) samples evaluated gave maximum release within 3 minutes indicating the rapid drug release profile which entails in faster onset of action for the medicament. Therefore the oral films have considerable advantage over the conventional dosage forms.

CONCLUSION:

The primary objective of this work was to develop a mouth dissolving film with Sitagliptin phosphate, along with basic ingredients like polymers, plasticizers, sweetener, saliva stimulating agent and flavor.

The films were prepared by solvent casting method.

HPMC E50 cps, which was not able to impart thickness to the film. HPMC E15 shown good flexibility.

The plasticizer propylene glycol which was not able to impart flexibility and folding endurance to the

film. PEG 400 produced good folding endurance, tensile strength and percent elongation.

The optimized formulation (F3) was shown good mouth feel, folding endurance, instant drug release as well as good mechanical properties.

The F3, shown less disintegration time of 20 seconds and 99% drug released within 3 minutes while the marketed formulation took 1 hour.

Therefore rapid drug release was achieved for immediate onset of action which is beneficial when compared to conventional tablet dosage form.

REFERENCES:

1) Lavanya A et.al "Formulation and In Vitro Evaluation of Fast Dissolving Sublingual Films of Agomelatine" IJPBS, 2019, vol 9 (4): p.no 232-238.
2) Bhusnure O.G et.al "Formulation and evaluation of oral fast dissolving film of gabapentin by QBD approach"IJPBS, 2018, vol 8 (2)p.no 426-437.
3) Syed Abdul Azeez Basha et.al "Formulation, In Vitro Evaluation and Stability Studies of Oral Disintegrating Films of Candesartan Cilexetil" IJPBS, (2019) vol 9 (4): 239-249.
4) M. Sunitha Reddy et.al "Formulation development and evaluation of immediate release Anti-coagulant drug Rivaroxaban film coated tablets" IJPBS, 2018, vol 8 (4) p.no 369-378.
5) Abdul Mannan et.al "Formulation Development and Evaluation of Ciprofloxacin HCl Transfersomes" IJPBS, 2019, vol 9 (4) p.no 364-373.
6) G.Kadhe and R.E Arasan 'Advances drug delivery of oral hypoglycemic agents' Current science, vol 83 (12), 2002, p.no 1539-1543.
7) Helen M colham et.al 'primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes study' Fast track articles, 2004, vol 364 (9435), p.no 685-696.
8) Jigisha patel et.al, ' Dyslipedimia in diabetes mellitus' BMJ clinical evidence, 2008.
9) Dysphagia: Merck manual of patient symptoms in the Merck manuals online medical library.
10) Expert committee on the diagnosis and classification of diabetes mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes care 1997, vol.20: 1183-1197.
11) Drucker DJ et.al 'the efficiency and safety of incretin system: glucagon like peptide-I receptor agonists and dipeptidase-4 inhibitors in type 2 diabetes, 2006, vol 36, p.no 695-705.
12) Wale Kiran K et.al 'Formulation, development and in-vitro evaluation of immediate release tablet of sitagliptin phosphate monohydrate, WJPR 2014, vol 3 (3), p.no 4945-4957.
13) Abbaraju Prasanna Lakshmi et.al 'Formulation and evaluation of taste masked orally disintegrating tablets of sitagliptin phosphate monohydrate' Int Re Jr Ph 2012, vol 3(9), p.no 305-308.
14) Hemanth Kumar G et.al 'Formulation and in-vitro evaluation of bilayer floating tablets of metformin hydrochloride and sitagliptin phosphate' Ini J Ad Ph 2012, vol 2 (2), p.no 64-81.
15) Gnanachaithanya N et.al 'Formulation and evaluation of fast disintegrating tablets of sitagliptin phosphate' Int J Ph W Res 2012, vol 3 (3) p.no 1-12.
16) Handbook of pharmaceutical excipients by Raymond C Rowe.
17) Bentley's, Rawlins EA, textbook of pharmaceutics 8 th edition, 2003, 270-281.
18) Lachman L, theory andpractice of industrial pharmacy, vargheese publication house, 1990, vol 3, p.no 317-319.
19) Aulton ME, Wells TI, pharmaceutics: the science of dosage from design. London, England: churchil; livingstone; 1998.
20) Leon lachman, Herbert A, liberman and joseph L.King: the theory and practice of industrial pharmacy p.no 293-303.
21) Desai.P et.al 'Design and evaluation of fast dissolving film of Domperidone' Int Res Jr Ph 2012, 3(9), P.NO 134-135.
22) Julie Mariam Joshua et.al 'Formulation of propranolol hydrochloride oral thin films for migraine prophylaxis' Int Jr Ph Sci Rev &Res, 2017, vol 42 (1) p.no 8-14.
23) Farhana Sultana et.al 'Preparation and evaluation of fast dissolving oral thin films of caffeine' Int Jr Ph &Bio Sci, 2013, vol 3(1) p.no 152-161.
24) Thonte S. S et.al 'Formulation and evaluation oral fast dissolving films of glipizide' W Jr Ph Res, 2017, vol 6 (7) p.no 1279-1297.
25) Pravin Kumar Sharma et.al 'Development and evaluation of fast dissolving oral film of poorly water drug Felodipine' A Jr Ph, 2018, vol 12(1) p.no 256-267.
26) Rajeshwar V et.al 'Formulation and evaluation of rapid dissolving films of pravastatin sodium' Int Jr Biomed & Adv Res, 2015, vol 6(8) p.no 594598.
27) Priyanka S Patil et.al 'Formulation and evaluation of fast mouth dissolving films of metoprolol succinate' W Jr Ph &Ph Sci, 2017, vol 6 (7) p.no 657-669.