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Development and characterization of sitagliptin smart film tablets

S.Sanjeev*, C.Santhosh Kumar

Srikrupa Institute of Pharmaceutical Sciences, Siddipet, Telangana: 502277
***Corresponding Author: S.Sanjeev**

ABSTRACT

The possibility to compress ordinary paper into tablets was systematically investigated in this study. The model drug Sitagliptin loaded in to the paper and studied various tableting characters. The drug-loaded tablets were produced by direct compression method without using and additives. Results proved that tablets can be made from paper, independent of the type of paper used. The tablets appear shiny and with a smooth surface. The pharmaceutical quality was acceptable, i.e. all tablets fulfilled the requirements for tablets according to the Indian Pharmacopeia. However, the uncoated tablets possessed fast disintegration, i.e. intense swelling upon contact with water. To tablets were successfully coated with a polymer film, leading to a delay the disintegration in simulated gastric fluid. In Post-compression characterization, coated and uncoated, drug content was found to be in the range of 95 to 99% with round shape and having hardness of 2.15-5 kg/cm2. Percent weight variation was observed between 4.0 and 6.1 with friability of between 0.34 to 0.66%. The disintegration time of uncoated tablets prepared by direct compression were found to be in the range of 19-20 seconds and the coated tablet 6.2-12.1 min. The drug loaded tablet made by facial tissue paper (uncoated tablet F2 and coated tablet F7) showed highest time duration for disintegration. In fact, tablets made from paper are a novel and promising strategy for improved oral drug delivery. They can be easily produced without any further excipients and possess pharmaceutical quality according to the Indian pharmacopeia.

Keywords: Tablets, Paper, Drug release, Oral drug delivery, Individualized therapy

INTRODUCTION

The most agreeable route for the patients is oral route preferred by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form (Maniruzzaman et al., 2012). Peroral dosage form can be distinguish as solid or liquid oral dosage form in which prior fall in the category of pills, capsules, granules and powders while the latter include solution, suspension or emulsions offering more advantages over monolithic dosage from (Patel et al., 2011).

Generally, thin films can be referred as a thin and flexible layer of polymer with or without a plasticizer (Maniruzzaman et al., 2012).Since they are thin and flexible by their nature, it can be perceived to be less obtrusive and more acceptable

by the patient (Patel et al., 2011). The thin film is polymeric matrices that meet many requirements for being used efficiently as a drug release platform (Borges et al., 2015). Fundamentally, thin films are excellent candidates for targeting sensitive site that may not be possible with tablets or liquid formulations (Sharma et al., 2015). Thin films have shown the capabilities to improve the onset of drug action, reduce the dose frequency and enhance the drug efficacy (Barbu et al., 2006).Similarly, thin films may be useful for eliminating side effects of a drug and reducing extensive metabolism caused by proteolytic enzymes (Castro, Kang et al.,2015,2014). Ideal thin films need to exhibit desirable features such as sufficient drug loading capacity, fast dissolution rate or long residence time at the site of administration, and acceptable formulation stability. They should also be non-toxic, biocompatible and biodegradable (Kang, Achouri et al., 2006,2013). Compared with the existing traditional dosage forms, it stands out to be superior in terms of enhanced bioavailability, high patient compliance, and patent extension of active pharmaceutical ingredients (API) (Hearnden et al., 2012). Furthermore, thin film formulations offer several advantages, including (a) convenient administration through non-invasive routes, (b) ease of handling during manufacture and transportation, and (c) cost effectiveness in the development of formulations (Achouri, Janßen ,Morales et al.,2013,2013,2011).The availability of a wide array of suitable polymers and the paradigm shift in manufacturing technology have made possible to develop a wide range of thin films (Nair et al.,2013) Therefore, a thin film is gaining popularity and acceptance in the pharmaceutical arena as a novel drug delivery dosage form.

MATERIALS AND METHODS

Materials

Different types of papers were obtained from a local store and were used to produce Tablets which includes Napkin paper ,Facial tissue paper (Presto, India), Note book paper, Bond paper, and Whatman filter Grade 1 For the production of drug-loaded tablets Sitagliptin the API was gifted from Caplin point laboratories (Pondicherry, India). Eudragit L100 used as coating material an purchased from (Yarrow Chemical, Mumbai). All solvents used in this study were of pharmaceutical grade.

Preformulation Studies

Preformulation study is the identification of physicochemical properties of a drug substance. It can be said that it is the initial stage in the design of dosage form of any type.

Drug authentication study

Solubility

A semi quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute of vice versa. After each addition, the system is vigorously shaken and examined visually for any un dissolved solute particles.

Organoleptic properties

The Organoleptic properties of sitagliptin phosphate were recorded using descriptive terminology.

Melting point determination

It is one of the parameters to judge the purity of crude drug. In case of pure Chemicals, melting points are very sharp and constant. A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and thetemperature when all the powder gets melted was recorded. This was performed in triplets and average value was reported. The results are shown in results anddiscussion.

Fourier transform infra-red (FTIR) spectroscopy

Sitagliptin phosphate disc were created by compressing the Sitagliptin with KBr and the spectra was scanned in the range between 4000 to 400 cm-1. Perfect operational conditions were maintained.

ANALYTICAL METHOD DEVELOPMENT

Estimation of Sitagliptinin phosphate buffer pH-6.8

Preparation of phosphate buffer pH-6.8

- **Preparation of 0.2 M potassium dihydrogen ortho phosphate:** 27.218 gm 0fKH2PO4 was dissolved in distilled water and made up the volume to 1000 mlwith distilled water to produce 0.2 M potassium dihydrogen ortho phosphate:
- **Preparation of 0.2 M sodium hydroxide:** Sodium hydroxide was dissolved in water to produce a 40 to 60 % w/vsolution and allowed to stand .taking precautions to avoid absorption of carbondioxide siphoned off the clear supernatant liquid and diluted with carbondioxide free water a suitable volume of the liquid to contain 8 gm of sodiumhydroxide to 1000 ml.
- **Mixing of standard solution:** placed 50 ml of 0.2 M potassiumdihydrogen ortho phosphate in a 200 ml volumetric flask and added thespecified volume of 0.2 M sodium hydroxide as per shown in below tableand make up the volume with distilled water.

Construction of Standard Graph of Sitagliptin Phosphate

- Accurately weighed amount of 100 mg of Sitagliptin was transferred into a 100ml volumetric flask. 20 ml of 0.1N hydrochloric acid (HCl) was added to dissolve the drug and volume was made up to 100 ml with the same HCl. The resulted solution had the concentration of 1mg/ml which was labelled as 'stock'.
- From this stock solution 10ml was taken and diluted to 100 ml with 0.1NHCl which has given the solution having the concentration of 100 mcg/ml.
- Necessary dilutions were made by using this second solution to give thedifferent concentrations of Sitagliptin (5 to 50 mcg/ml) solutions.
- The absorbances of above solutions were recorded at λmax (nm) of thedrug using double beam UV-Visible spectrophotometer. Standard graphwas plotted between the concentration (on X-axis) and absorbance (on Yaxis).Similarly, standard graph was plotted with 6.8 pH phosphate buffer.

Table 1: Formulation table of Sitagliptin phosphate tablet

INGREDIENTS	Uncoated tablet					Coated tablet				
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Sitagliptin (mg)	50	50	50	50	50	50	50	50	50	50
Ethanol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Napkin paper	200	--	--	--	--	200	--	--	--	--
Tissue paper		200	--	--	--	--	200	--	--	--
Whatsmen filter paper	--	--	200	--	--	--	--	200	--	--
Notes paper	--	--	--	200	--	--	--	--	200	
A4 paper	--	--	--	--	200	--	--	--	--	200
Total weight	250	250	250	250	250	250	250	250	250	250

RESULT & DISSCUSSION

Solubility

Sitagliptin phosphate was freely soluble in water and ethanol and phosphate buffer pHslightly soluble in methanol, completely soluble in phosphate buffer pH6.8.

Organoleptic properties

- Odour : Odourless
- Colour : A White amorphous powder TasteMetallic taste

Determination of Melting Point

Melting point of Sitagliptin phosphate was determined by open capillary method using digital melting point apparatus. The melting point of Sitagliptin phosphate was found to be 216.33°C. The value meets the standard value i.e., 216-219ºC,

which is an indicative of its purity of the substances

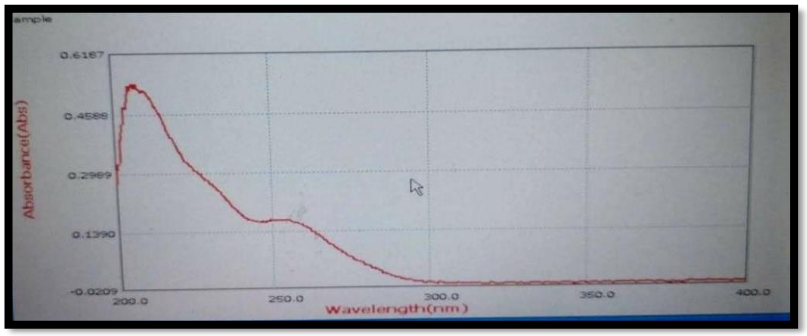

Figure 1: UV- spectrum of Sitagliptin phosphate pH 6.8

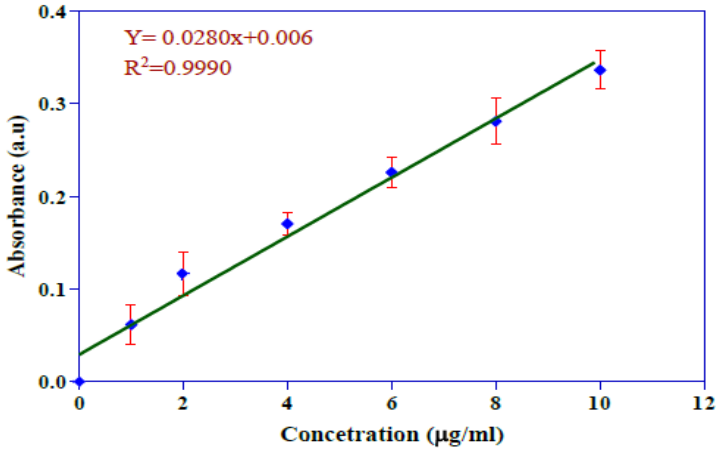

Figure 2: Calibration Curve of Sitagliptin phosphate buffer Ph6.8

Identification of drug and excipients by FTIR analysis

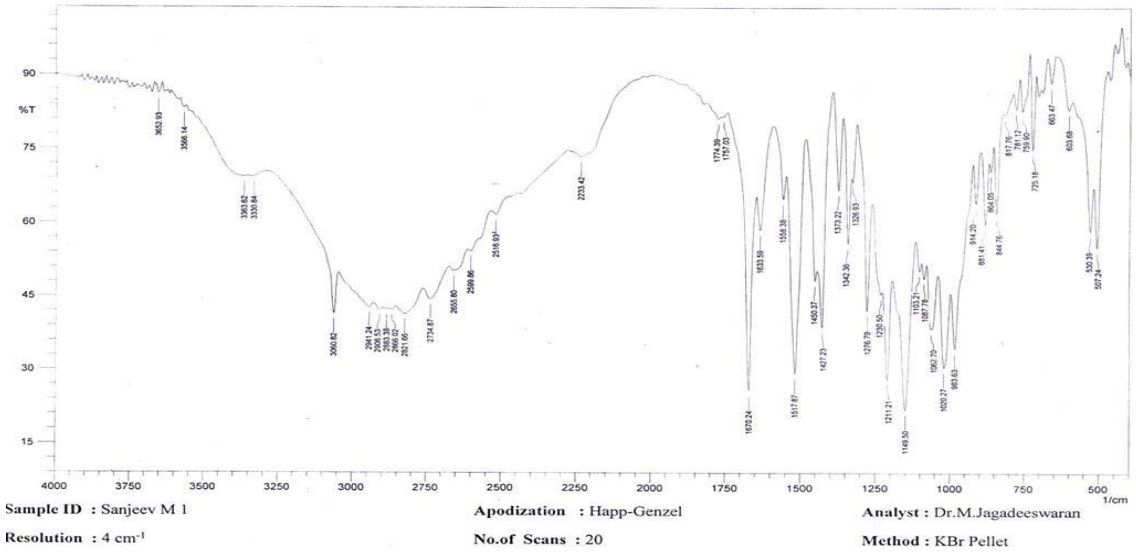

Figure 3: FTIR spectra of Sitagliptin phosphate

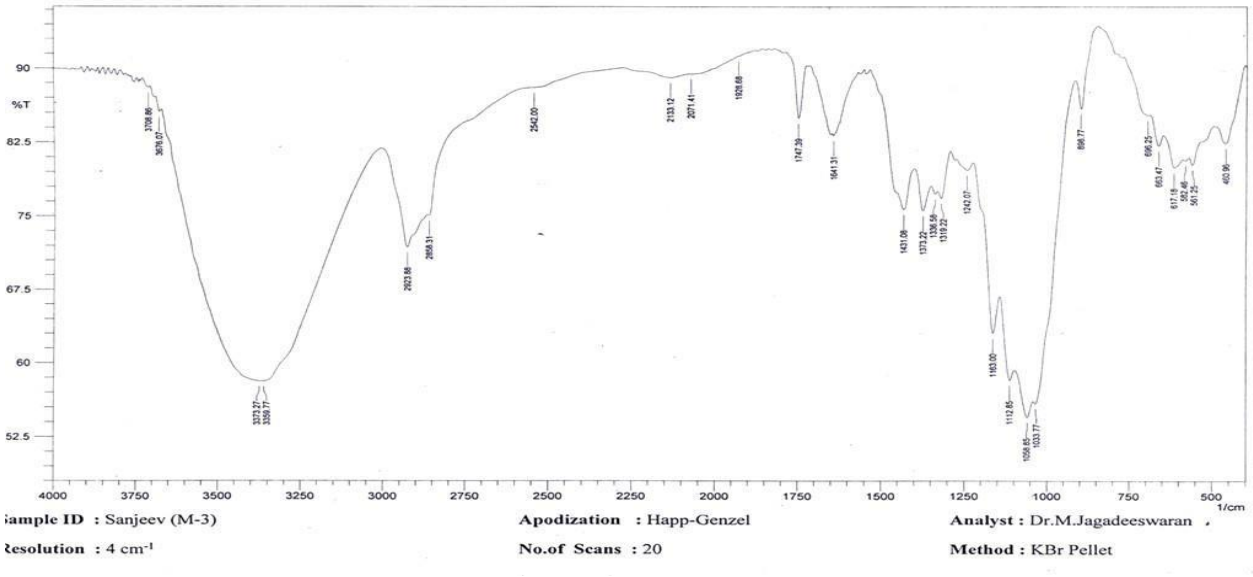

Figure 3: FTIR spectra of tissue paper

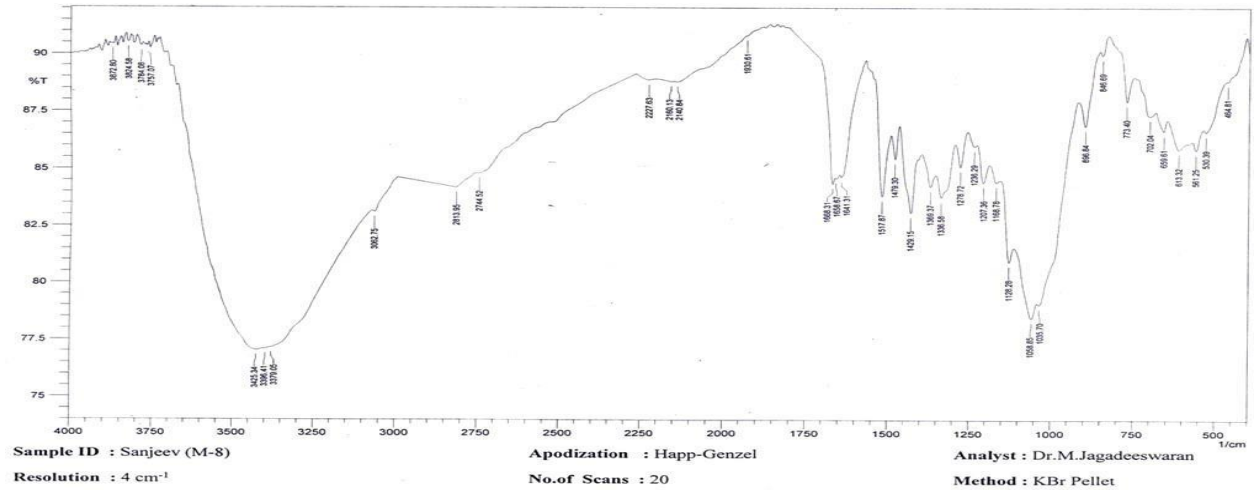

Figure 3: FTIR spectra of tissue paper with Sitagliptin phosphate

Table: 2 Infrared band assignment for papers

S.No	Functional groups	Wave number (cm^{-1})observed	Wave number (cm^{-1}) Reported
1	-OH	3428	3550-3450
2	Primary alcohol (-OH)	1050	1050
3	Ether linkage (C–O–C)	1150	1150-1160

Table: 3 Infrared band assignment Eudragit L100

S.No	Functional groups	Wave number (cm^{-1}) observed	number (cm^{-1}) Reported
1	C=O	1718	1725-1700
2	C-O	1265	1250-1270
3	C(CH3)	1367	1380-1370

Table: 4 Physicochemical analyses of commercially available papers

S.No	Types of paper	Thickness(µm)	Folding endurance	pH	Alkali reservemol/kg
1.	Napkin paper (NP)	30.2 ± 3.2	125 ± 23	8.1	0.043
2.	Facial tissue (FTP)	35.2 ± 1.6	174 ± 18	7.6	0.022
3.	Note book paper (NBP)	60.4 ±2.2	220 ±	8.7	0.047
4.	Bond paper(BP)	80.1 ± 3.2	> 300	8.4	0.045
5.	Whatman filter paper (WFP)	127.6± 3.3	> 300	7.9	0.027

Table: 5Physical evaluation of Sitagliptin phosphate tablet

S.No	Types of tablet	Formulation code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Content uniformity (%)	Disintegration time
1.	Jncoated tablet	**F1**	6.3 ± 0.3	2.5 ± 0.2	0.51 ± 0.4	248 ± 2.1	98.2 ±1.06	19±0.5*
2.		**F2**	6.4 ± 0.5	2.7 ± 0.4	0.47 ± 0.2	249 ± 1.5	97.8 ±1.28	21±0.2*
3.		**F3**	6.2 ± 0.7	2.4 ± 0.5	0.54 ± 0.1	251 ± 1.1	98.7 ±0.58	18±0.3*
4.		**F4**	6.6 ± 0.5	2.5 ± 0.7	0.61 ± 0.5	248 ± 1.3	98.3 ±1.91	20±0.1*
5.		**F5**	6.7 ± 0.8	2.3 ± 0.9	0.66 ± 0.6	250 ± 1.7	97.8 ±1.38	15±0.4*
6.		**F6**	7.13 ± 0.2	4.5 ± 0.2	0.41 ± 0.2	278 ± 1.5	99.2 ±1.28	8.7± 1.7$^{\#}$
7.	Coated tablet	**F7**	7.43 ± 0.5	5.0 ± 0.4	0.39 ± 0.5	267 ± 1.6	99.2 ±1.04	12.1± 1.2$^{\#}$
8.		**F8**	7.10 ± 0.6	4.0 ± 0.6	0.44 ± 0.3	271 ± 3.7	95.2 ±1.28	8.2 ± 1.1$^{\#}$
9.		**F9**	7.23 ± 0.7	4.5 ± 0.3	0.52 ± 0.4	274 ± 3.3	98.6 ±1.27	9.5±0.13$^{\#}$
10.		**F10**	7.80 ± 0.9	3.3 ± 0.4	0.55 ± 0.2	279 ± 2.8	99.6 ± 1.14	6.2 ±0.43$^{\#}$

INVITRO DISSOLUTION STUDY

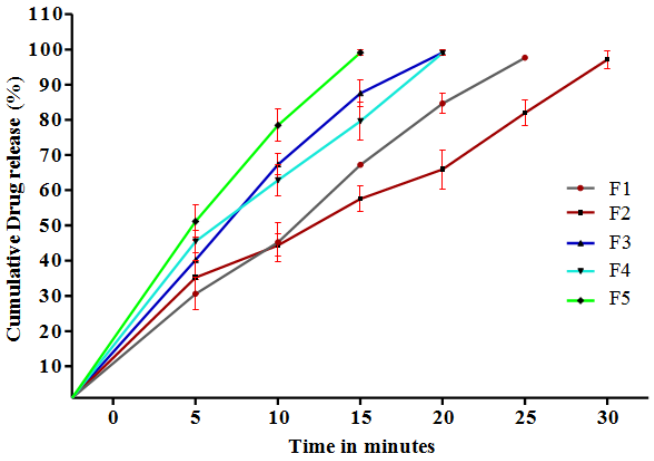

Figure 4: Comparison of cumulative drug release profiles of uncoated Sitagliptin phosphate tablets F1-F5

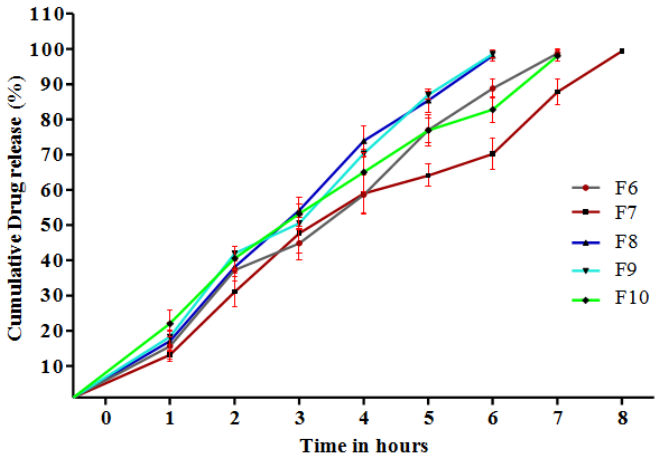

Figure 5: Comparison of cumulative drug release profiles of Eudragit L100coated Sitagliptin phosphate tablets F6-F10

DISCUSSION

Oral drug delivery is only successful if the active pharmaceutical ingredient (API) can be successfully released from the oral dosage form and can dissolve in the body fluid, because only dissolved API can be taken up from the body. Unfortunately, today most of the new chemical entities (NCE) possess solubility problems.

Therefore, sophisticated drug delivery systems are needed to increase the solubility of these NCE. The smart Film technology uses ordinary paper as matrix in which APIs are loaded in amorphous state Smart Films can be obtained by dissolving the poorly soluble API in a solvent and by adding this mixture to commercially availablepaper.

The five types drug loaded paper prepared by direct compression method without adding any additives. Tablets prepared by direct compression methods were found to be good without any sticking, picking, capping and chipping. The formulated tablets was coated with enteric coating agent Eudragit.

In Post-compression characterization, coated and uncoated, drug content was found to be in the range of 95 to 99% with round shape and having hardness of 2.15-5 kg/cm^2. Percent weight variation was observed between 4.0 and 6.1 with friability of between 0.34 to 0.66%.

The disintegration time of uncoated tablets prepared by direct compression were found to be in the range of 19-20 seconds and the coated tablet 6.2-12.1 min. The drug loaded tablet made by facial tissue paper (uncoated tablet F2 and coated tablet F7) showed highest time duration fordisintegration

Results of dissolution study uncoated tablet showed that more than 50% of the drug was released within the first 10 minutes. The F2 release entire drug content with in 30 min other formulation release the drug > 20min.

This indicates highly porous nature of the paper conventional tablet, which suggested the rapid penetration of water that resulted in rapid wetting, disintegration, and dissolution.

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