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DEVELOPMENT OF CONTROLLED POROSITY OSMOTIC PUMP TABLET OF LINAGLIPTIN

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ABSTRACT

The major objective of this study was to develop controlled porosity osmotic pump tablets of linagliptin to be taken once daily. Unlike the elementary osmotic pump which consists of an osmotic core with the drug surrounded by a semi permeable membrane drilled with a delivery orifice, controlled porosity of the membrane is accomplished by the use of channeling agent in the coat. NaCl was used as an osmogent and HPMC K100M was used as a release retardant. Cellulose acetate was used as the semipermeable membrane and PEG 400 was used as pore forming agent. Optimization was done using 3^2 factorial design considering two independent variable at three levels. Optimized formulation exhibited zero order kinetics with a drug release of 98.43% in 24 hrs. Scanning electron microscope studies showed the formation of pores in membrane (Coat). It was concluded that release of linagliptin was significantly controlled from controlled porosity osmotic drug delivery systems.

KEYWORDS: Controlled porosity osmotic pump (CPOP), Linagliptin, Osmogent, Pore former.

INTRODUCTION[1,2,3,4,5]

Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia, glycosuria etc. Diabetes mellitus is divided into two types.

Type I- Insulin dependent diabetes mellitus (IDDM)
Type II- Non-insulin dependent diabetes mellitus (NIDDM)[1]

Linagliptin is under the type II diabetes mellitus and works by blocking the action of DPP-4. An enzyme that destroy the harmone GLP-1, which helps the body to produce more insulin when it is needed. GLP-1 and GLP-2 hormones are released from intestine. The act by reduced blood glucose by increasing the production and release of insulin from pancreas.[2]

Conventional drug delivery systems have little or no control over the drug release, and effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. Conventional preparation is usually administered two or three times a day, which leads to large fluctuation in drug plasma concentration and side effects on human body. Development of oral controlled release dosage forms. Various techniques have been used in the formulation of controlled release products. In general, controlled release formulations can be divided into different categories based on the mechanism of drug release. A number of design options are available to control or modulate the drug release from a dosage form. Osmotically controlled oral drug delivery systems are those which utilize osmotic pressure for controlled delivery of active agents.[3,4]

The controlled- porosity osmotic pump tablet concept was developed as an oral drug delivery systems by Zentner et al. The controlled-porosity osmotic pump tablet (CPOP) is a spray coated or coated tablet with a semipermeable membrane (SPM) containing leachable pore forming agents. They do not have any aperture to release the drugs; drug release is achieved through the pores, which are formed in the semipermeable wall in situ during the operation. In this system, the drug, after dissolution inside the core, is released from the osmotic pump tablet by hydrostatic pressure and diffusion through pores created by the dissolution of pore formers incorporated in a membrane. The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by tablet component, after water is imbibed across the semipermeable membrane. This membrane after formation of pores becomes permeable for both water and solutes. A controlled-porosity osmotic wall can be described as having a sponge like appearance.[5]

MATERIALS AND METHOD

Materials: Linagliptin was obtained as gift sample from Zydus cadila, Mumbai, hydroxypropyl methyl cellulose k100M (HPMC K100M) was gift sample of colorcon Asia

Pvt Ltd Goa. Sodium chloride, PVP K30, sodium lauryl sulphate, starch, cellulose acetate, polyethylene glycol 400 (PEG 400), acetone were purchased from Research-lab Fine Chem. Industry- Mumbai.

METHOD

Formulation of linagliptin core tablets: A core tablet of linagliptin was prepared by wet granulation method. Linagliptin was mixed with sodium chloride, HPMC, Starch, Sodium Lauryl Sulphate this powder blend was kneaded in the mortar and pestle for 15-20 min. The blend was granulated using PVP K30 as a binder in IPA. Wet mass was formed; resulting wet mass was passed through sieve #22. Granules were dried in oven at 50^0C for 2 hrs. Dried granules were lubricated with magnesium stearate and talc. Lubricated blend was evaluated for powder characteristics and flow properties. Then desired amount of blend was compressed in to the tablet using Rimek tablet punch machine equipped with 8 mm punch.

Table 1: Composition of Controlled porosity osmotic pump tablet as per Factorial Design. (All values are expressed in mg)

Ingredients	**Formulation code**								
Quantity(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Linagliptin	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium chloride	5	5	5	10	10	10	15	15	15
HPMC	50	65	80	50	65	80	50	65	80
PVP K30	15	15	15	15	15	15	15	15	15
Starch	127.5	112.5	97.5	122.5	107.5	92.5	117.5	102.5	87.5
Sodium Lauryl Sulphate	15	15	15	15	15	15	15	15	15
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Total weight (mg)	220	220	220	220	220	220	220	220	220

Coating of linagliptin core tablets: The coating solution was prepared by dissolving 5% w/v of cellulose acetate in acetone:alcohol (1:1). Add 1% v/v PEG 400 in the solution and solution was stirred for 20 min.

Coating method: The tablets were warmed to 40 ± 2^0C before applying coating solution. Dip coating technique was used for the coating of osmotic tablet. Tablet was dip into a coating solution and dried for 40^0C.

Characterization

A. Evaluation of Granules:[6,7] Flow properties of granules were evaluated by established methods. Angle of Repose was determined using funnel method. Bulk Density, Tapped Density, Compressibility index and Hausner's ratio were calculated.

B. Evaluation of Precoated Tablets:[8,9] The formulated core tablets were evaluated for different parameters like hardness, thickness, weight Variation, friability and drug content uniformity of tablet.

1. **Thickness:** The uniformity of thickness was measured using digital vernier caliper. The average thickness of the tablet was calcutated.
2. **Weight Variation Tests:**[10] 20 tablets were weighed individually average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits (±7.5%). The percent deviation was calculated.
3. **Hardness:**[11] the hardness of tablets was measured using Monsanto hardness tester. In this tablet was place between the plungers, and was tightened from one end, and pressure required to break tablet diametrically was measured.
4. **Friability:** In this test 20 tablet were weighed and placed in a roche friabilator test apparatus. After 100 revolutions the tablets were removed, de-dusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

$$\% \text{ friability} = \frac{\text{Initial weight of Tablet} - \text{Final weight of Tablet}}{\text{Initial weight of Tablet}} \times 100$$

5. **Uniformity of Content:**[12] Twenty tablet weighed individually and powdered in mortar; 2.5 mg of drug dissolved in the 100 ml of phosphate buffer 6.8. The solution was filtered and the content of linagliptin in the solution was determined by measuring absorbance on double beam UV spectrophotometer (Jasco V-630) at 293nm.

C. Evaluation of Coated Tablet:[10]

1. **Thickness of tablet:** All tablets were initially subjected for thickness measurement by using digital vernier caliper after coating to assess thickness of coat.
2. **Thickness of film**: Thickness of film was calculated by considering difference between coated tablet and uncoated tablet.

$$\text{Thickness of coat} = \frac{\text{thickness of coated tablet} - \text{thickness of uncoated tablet}}{2}$$

3. **Weight Variation Tests:** 20 tablets were weighed individually average weight was calculated from the total weight of all tablets. The individual weights were compared with

the average weight. The percentage difference in the weight variation should be within the acceptable limits (±7.5%). The percent deviation was calculated.

4. **Scanning Electron Microscopy:** The surface morphology of the tablet coating layer before and after dissolution was examined by scanning electron microscope
5. **In –vitro Release Studies:**[13,14] In vitro drug release of the formulation was carried out in a USP dissolution apparatus (paddle type) set at a rotating speed of 50 rpm and temperature of 37±2^{0}C. The dissolution medium (900ml) was 0.1N HCl for the first 2 hrs and phosphate buffer (pH 6.8) there after upto 24 hrs sample (5ml) were withdrawn at specific time intervals and the medium was replenished with fresh dissolution fluid.

6. **Dissolution Kinetics**[15]

In order to investigate the mode of release from the tablets the release data were analyzed with the zero order, first order, higuchi square root, korsmeyer plot.

7. **Stability study**[16, 17]

Stability study of optimized formulation was carried out to point out any visual physical or chemical changes made in the formulation after storing it at elevated temperature and humidity conditions. Chemical and physical stability of optimized linagliptin formulation was assessed at 40±2 ^{0}c/ 75±5% RH as per ICH Guidelines. Tablets were packed in aluminium foil and stored for 6 months. Sample was analyzed after 6 months for physical appearance, drug content and in vitro dissolution profile.

RESULT AND DISCUSSION

1. Evaluation of Granules

The angle of repose of all the formulations was within the range of 26^0-28^0 indicative of excellent and good flow ability. The bulk density of powder was found to be between 0.27-0.28gm/cm^3. The tapped density of the granules of batches was found in the range of 0.30.34gm/cm^3. The bulk density and tapped density was used to calculate the percent compressibility of the powder. The compressibility index of the powder was observed in range of 13-15. The Hausner's ratio was found to be the range of 1.11-1.18 indicating good and fair flow ability.

Table 2: Evaluation of Powder Bulk for Tablets

Formulation code	Angle of repose(θ°) Mean± S.D	Bulk density (gm/cm^3) Mean± S.D	Tapped density (gm/cm^3)Mean± S.D	Compressibility index (%)Mean± S.D	Hausner's ratio Mean± S.D
F1	28.62±0.43	0.2869±0.006	0.3204±0.016	14.92±0.55	1.14±0.027
F2	28.66±0.49	0.2895±0.015	0.3282±0.011	15.03±0.93	1.12±0.015
F3	26.57±0.61	0.2718±0.141	0.3278±0.010	14.51±0.15	1.13±0.026
F4	27.82±0.30	0.2784±0.004	0.3188±0.018	14.38±0.24	1.14±0.024
F5	26.42±0.16	0.2718±0.006	0.3147±0.007	13.97±0.21	1.18±0.022
F6	28.55±0.35	0.2822±0.008	0.3409±0.005	14.74±0.24	1.11±0.026
F7	27.29±0.37	0.2893±0.006	0.3312±0.003	14.48±0.19	1.15±0.010
F8	28.55±0.10	0.2811±0.007	0.3357±0.008	14.68±0.44	1.16±0.045
F9	27.37±0.33	0.2809±0.015	0.3214±0.014	14.63±0.60	1.15±0.031

Precoating Evaluation

All formulated uncoated osmotic tablet batches were evaluated for weight variation, Hardness, thickness, friability and drug content. Weight variation, hardness, thickness, friability, and drug content of uncoated tablets were found within the range.

Table 3: Precoating evaluation parameters of osmotic tablets.

Formulation Code	Average Weight (mg) Mean ± S.D	Weight variation %	Hardness ($kg/cm^{2)}$ Mean± S.D	Thickness (mm) Mean± S.D	Friability (%) Mean± S.D	Drug content (%) Mean± S.D
F1	219.03±1.81	0.58	3.03±0.24	3.28±0.04	0.321±0.006	96.98±0.003
F2	219.00±1.64	0.45	2.91±0.22	3.29±0.11	0.068±0.007	96.61±0.0017
F3	218.77±1.91	0.65	2.91±0.30	3.3±0.008	0.014±0.036	96.28±0.0015
F4	219.30±2.31	0.66	3.11±0.23	3.2±0.04	0.15±0.047	98.11±0.0067
F5	220.19±0.78	0.53	3.27±0.19	3.3±0.03	0.20±0.026	97.63±0.002
F6	220.12±1.56	0.53	3.10±0.21	3.34±0.01	0.11±0.034	97.39±0.0064
F7	219.80±1.87	0.65	2.88±0.27	3.29±0.13	0.18±0.022	98.95±0.0022
F8	219.00±1.33	0.45	3.21±0.20	3.3±0.034	0.27±0.050	99.32±0.0040
F9	220.35±1.53	0.56	3.02±0.30	3.30±0.02	0.15±0.021	98.58±0.0037

Post coating evaluation

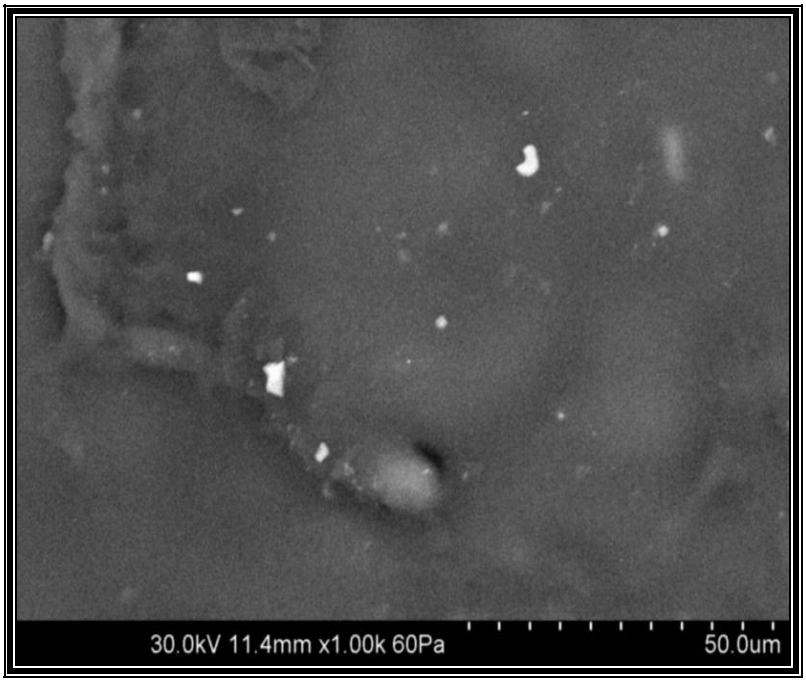
All formulated coated osmotic tablet batches were evaluated for Weight variation, thickness and film thickness. Due to uniform coating weight variation and thickness of coated tablets were found within the range. Thickness of film was measured by calculating the difference between thickness of coated tablet and uncoated tablet.

Table 4: Post coating evaluation parameters of osmotic tablets.

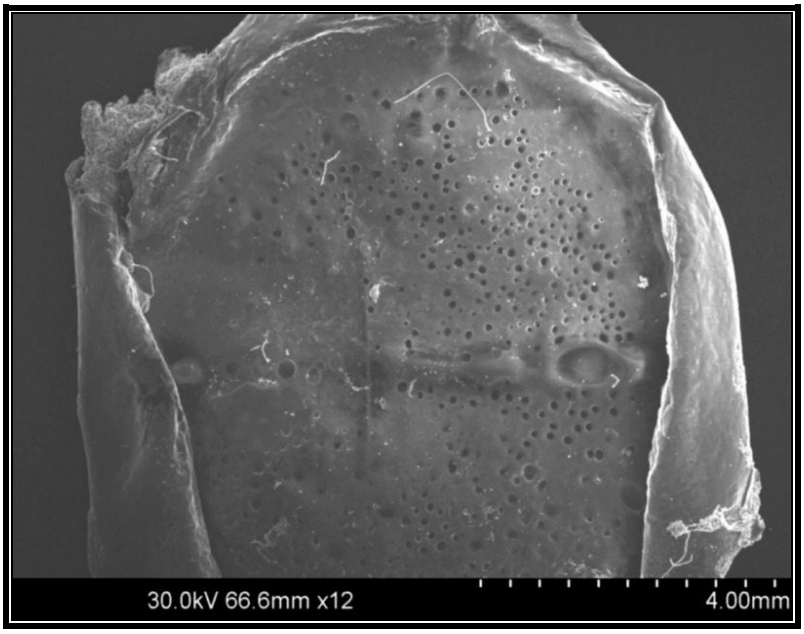
Formulation Code	Average Weight (mg) Mean± S.D	Weight Variation %	Thickness of coated tablet Mean± S.D	Thickness of film(mm) Mean± S.D
F1	229.6±0.35	0.6489	4.04±0.041	0.413±0.05
F2	231.2±0.89	0.6314	4.04±0.050	0.397±0.02
F3	230.9±1.08	0.8130	4.09±0.091	0.403±0.04
F4	233.8±0.56	0.7698	4.05±0.044	0.406±0.02
F5	234.4±1.12	0.6301	4.06±0.043	0.414±0.02
F6	231.1±1.74	0.6715	4.00±0.048	0.396±0.02
F7	228.3±0.66	0.6831	4.08±0.048	0.402±0.01
F8	229.9±0.39	0.4871	4.03±0.050	0.411±0.03
F9	231.7±1.64	0.5480	4.11±0.055	0.393±0.04

SEM of Coating (before and after dissolution)

Evaluation of coating layer before dissolution study and after dissolution study suggest that, aqueous pores were generated during testing through which the drug solution has passed across the Cellulose Acetate barrier after creation of osmotic pressure in the tablet core. This was confirmed by SEM Analysis of coating layer before and after dissolution testing.



a) Before Dissolution



b) After Dissolution

Figure 1: Scanning Electron Microscopy (SEM) of coating layer a) Before dissolution b) After dissolution.

In Vitro Dissolution study of formulation (F1-F9)

The result shows that with increase in concentration of sodium chloride (NaCl) and decreasing the concentration of HPMC the release rates gradually increases. The results showed that the osmotic tablet has the ability to extend the release of linagliptin for the duration of about 24 hrs. On the basis of In-vitro drug release profile the optimum formulation F8 was selected as it release 98.43% drug within 24 hrs shown in figure.

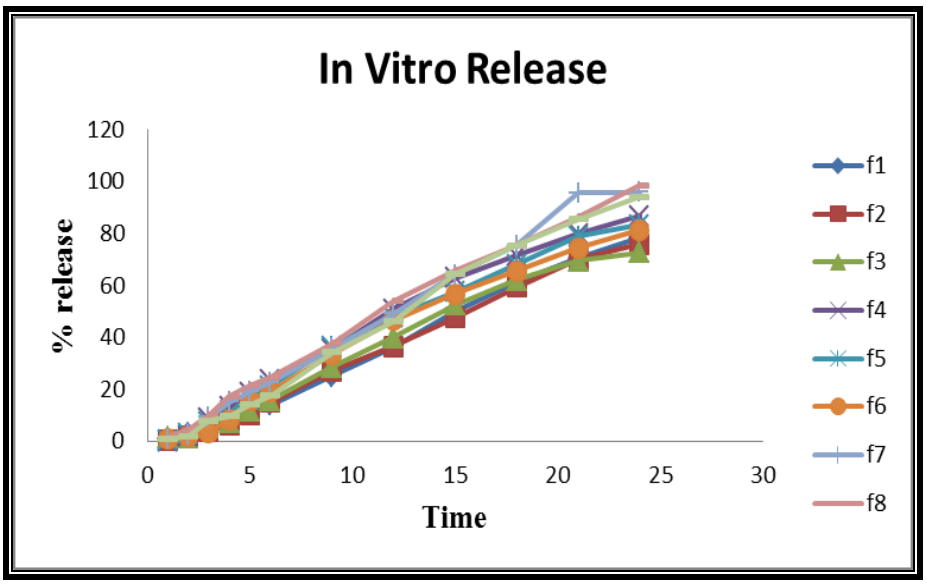


Figure 2: Dissolution Profile of Formulation Batches (F1-F9)

DISSOLUTION KINETICS

Release kinetics studies

All batches follow zero order release kinetics, for F8 formulation drug release was found to be 98.43% upto 24 hrs. Other batches also follow zero order release kinetics upto 24 hrs but their release was not upto 98-99%. Optimized formulation F8 follow Zero order kinetics with R^2=0.998. So the drug release is of fickian release.

Table 5: Kinetic treatment of prepared Linagliptin osmotic tablet formulations.

	Coefficient of determination (R^2)			
Formulation code	**Zero order**	**First order**	**Higuchi square root**	**Korsmeyer plot**
F1	0.995	0.737	0.960	0.96
F2	0.996	0.674	0.965	0.94
F3	0.988	0.750	0.973	0.96
F4	0.987	0.697	0.988	0.93
F5	0.990	0.741	0.985	0.97
F6	0.988	0.713	0.980	0.96
F7	0.992	0.586	0.972	0.88
F8	**0.998**	0.996	0.983	0.96
F9	0.994	0.685	0.968	0.94

Zero Order Kinetic Study

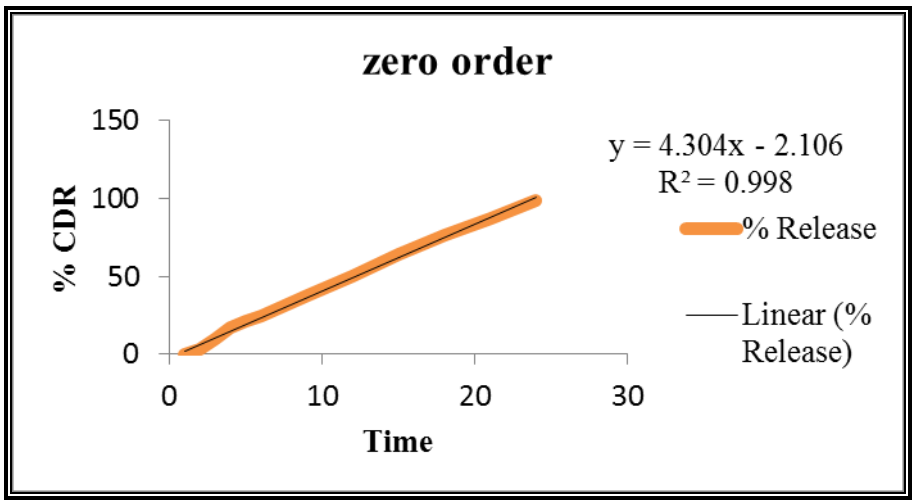


Figure 3: Model Graph for Evaluation of Zero Order Release Kinetics

Stability Study

Table 6: Characteristics of optimized formulation F8 after 3 months storage

Parameter	Initial sample of optimized formulation	After storage at 40±2°C / 75±5% RH, for 3 months
	F8	F8
Color	White to pale yellow	White to pale yellow
Drug content	99.32%	99.31 %
% Drug Released (After 24 hrs.)	98.43	98.02%

CONCLUSION

The present work of controlled release formulations of linagliptin was successfully prepared on the basis of osmotic technology. Formulation of osmotic tablet was designed using 3^2 full factorial design. Wet granulation method was used for preparation of granules and prepared granules were evaluated for various parameters, all parameters were found within the limit. Evaluation of osmotic tablet before coating was carried out for various parameters and these were found within the limits, coating of core tablet was done by dip coating method. After coating evaluation of osmotic tablets were evaluated for thickness of film and weight of variation, the results found were within limits. Evaluation of coating layer before and after dissolution was done by scanning electron microscope it was observed that aqueous pores were generated during dissolution test and drug solution has passed through the cellulose acetate barrier, after creation of osmotic pressure in the tablet core. In-vitro dissolution of osmotic tablet was performed for 24 hr and for optimized formulation drug release was found 98.43% within 24 hr. Drug release was directly proportional to the level of osmotic agent. Controlled porosity osmotic pump formulation (F8) was optimal formulation containing NaCl (15mg) and HPMC (65mg) in optimal level. Optimized formulation was stable for period of 6 months as there was no significant variation in the physical appearance, drug content and drug release of formulation.

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