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DEVELOPMENT AND CHARACTERIZATION OF OSMOTIC DRUG DELIVERY SYSTEM OF MODEL DRUG

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ABSTRACT

Aim of present study is to develop osmotic controlled drug delivery of drug vildagliptin for controlling the release pattern of drug to achieve better efficacy. The clinical utility of GLP-1 is limited by its short half-life (2-3 hrs). GLP-1 is rapidly degraded by the proteolytic enzyme DPP-IV. To enhance GLP-1 activity, inhibition of the DPP-IV enzyme is emerging as a novel therapeutic approach in the treatment of diabetes. Osmotically controlled drug delivery systems (OCDDS) is one of the most promising drug delivery technology that use osmotic pressure as a driving force for controlled delivery of active agents. Osmotic tablet is prepared by core tablet and coating solution. core tablet consist of polymer (MCC), osmogen (KCl and NaCl) and other excipients. The tablets were coated by spray coating solution which is the mixture of Acetone and methanol in the ratio of 8:2 with cellulose acetate, pore forming agent is PEG 4000, and plasticizer is PEG 400. Different kinetic treatments were applied to interpret the release of Vildagliptin from different osmotic tablet. The r2 value of formulation batch F2C4 has highest value that was r2= 0.9720 than other of zero order kinetic of batches hence F2C4 batch of osmotic tablet was best and optimized formulation. Hence revealed that optimized formulation followed zero order drug release kinetics.

KEYWORDS: Vildagliptin, Osmotically controlled drug delivery systems, zero order.

1. INTRODUCTION

Novel drug delivery systems (NDDS) are the key area of pharmaceutical research and development.[1] In control release (CR) systems, there is maximum utilization of drug

enabling reduction in total amount of dose administered and possibility of delivering drugs having short biological half life.[2]

Majority of oral CR dosage forms fall in the category of matrix, reservoir or osmotic systems. Conventional matrix or reservoir type formulations exhibits problem of bioavailability fluctuations due to gastric pH variations. Moreover, the release of drugs from these systems is affected by the hydrodynamic conditions of the body. Osmotically controlled drug delivery systems (OCDDS) is one of the most promising drug delivery technology that use osmotic pressure as a driving force for controlled delivery of active agents. Drug release from OCDDS is independent of pH and hydrodynamic conditions of the body because of the semi permeable nature of rate- the controlling membrane and the design of deliver orifice used in osmotic systems, so a high degree of In vitro/In vivo correlation is achieved. It is also possible to obtain higher release rates through these systems than through other diffusion-based systems.[3]

Osmotic controlled drug delivery of drug Vildagliptin (Antidiabetic) for controlling the release pattern of drug to achieve better efficacy. The clinical utility of GLP-1 is limited by its short half-life (2-3 hrs). GLP-1 is rapidly degraded by the proteolytic enzyme DPP-IV. To enhance GLP-1 activity, inhibition of the DPP-IV enzyme is emerging as a novel therapeutic approach in the treatment of diabetes. Osmotic tablet is prepared by core tablet and coating solution. Core tablet consist of polymer (MCC), osmogen (KCl and NaCl) and other excipients Many innovative methods have been developed for obtaining controlled drug release. From the practical view point, controlled porosity osmotic pump tablet is one of the best approaches for developing controlled release dosage form.

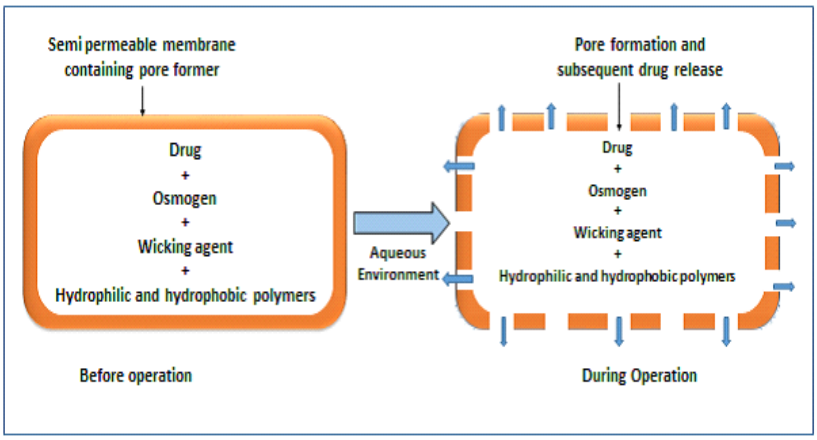

Fig. 1: Drug release mechanism of controlled porosity osmotic pump tablet.

Osmotically controlled drug delivery system osmotic devices are the most reliable controlled drug delivery system and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these types of systems to release the drug in a controlled manner. Controlled porosity osmotic pump tablet as shown in Figure 1 is a spray coated or coated tablet with a semipermeable membrane 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 membrane in situ during the operation. In this system, the drug, after dissolution inside the core, is released from the osmotic pump tablet by the hydrostatic pressure and diffusion through pores created by the dissolution of pore formers incorporated in the membrane. The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by the tablet component, after water is imbibed across the semipermeable membrane.[6,7]

2. MATERIALS AND METHODS

2.1. Reagents and Chemicals

Standard drugs of Vildagliptin were kindly supplied as a gift sample by Glenmark Pharmaceuticals Ltd. Mohol, Dist. Solapur. All the matrials used in the study are microcrystalline cellulose, cellulose acetate, PEG-400, PEG-4000, potassium chloride, sodium chloride, polyvinyl pyrilidone, acetone, methanol were purchased from Laboratory Reagent, Reaserch lab Mumbai, Thomas Baker Chemicals Ltd. Mumbai, MERCK Specialities Pvt, Ltd. Worali Mumbai, NICE Chemical(P) Kerala, India.

2.2. Instrumentation

The various apparatus used were like Mechanical Stirrer(Remi motors Ltd), Tablet Compression Machine(Model:H/416/95) Cadmach Machinary Co. Pvt. Ltd. Mumbai, Air Compressor (KDN compressor, Delhi), Coating Machine (Mixofil, Delhi.), Spray gun, Dissolution test apparatus (Electrolab, Mumbai), Friabilator (Roche Friabilator), Tablet hardness tester (Monsanto hardness tester), UV- Spectrophotometer(Agilent Cary 630 Spectrophotometer), FTIR (Agilent Resolutions Pro),etc.

2.3 Formulation of osmotic tablet

2.3.1 Selection of osmogent

According to literature review the variant amount of osmogents was selected like Potassium Chloride, Sodium Chloride on the basis of trial.

2.3.2 Selection of polymers

According to literature review the Cellulose acetate was taken as polymer in coating solution. The core tablet was prepared by granulation of various osmogent, MCC.

2.3.3 Selection of coating solution containing ingradient

According to literature review the mostly Cellulose acetated was taken to prepare coating solution as polymer, platicizer PEG 400, and pore forming agent Potassium chloride and PEG 4000 was taken to prepare Coating solution.

2.3.4 Method of preparation: All the ingredient of core tablet except PVP K30, Talc, Magnesium Stearate were passed through sieve #85.accurately weight to the quantities and thoroughly mixed required quantity of PVP K30 was weight and dissolved in sufficient quantity of isopropyl alcohol wet granulation technique was employed for granulation .Granules were dried at 50^0C for 1hr and passed through sieve #18. Talk, Magnesium stearate were blended with dry granules and compressed into tablet using Tablet machine fitted with 8 mm punch and set cavity of 190 mg.

Table. 1: Designed composition details of OCDDS batches.

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)
Vildagliptin	50	50	50
MCC	102	92	92
Potassium chloride	40	30	
Sodium Chloride	-	-	40
Polyvinyl pyrilidone	5	5	5
Talc	1.8	1.8	1.8
Magnesium Stearate	1.8	1.8	1.8

Table. 2: Designed formula for coating solution.

Ingredients	C1	C2	C3	C4
Cellulose acetate	2 gm	2gm	2gm	2gm
PEG400	20%	20%	20%	20%
PEG4000	40%	40%	30%	30%
Acetone	80ml	80ml	80ml	80ml
Methanol	20ml	20ml	20ml	20ml
Weight gain	4%	6%	4%	6%

2.3.5 Preparation of coating solution

Accurately weight all ingredient cellulose acetate as polymer, PEG 400 as plasticizer, PEG 4000 as pore forming agent. Firstly measure accurately Acetone and Methanol then add PEG 4000 it is 20% of Cellulose acetate. Stir it up to it get dissolves in solvent. then add a PEG

400 it is also 20% of Cellulose acetate stirrer it, add slowly and small quantity of Cellulose acetate. stir it by mechanical stirrer at 700 rpm. Then add sunset yellow color mix it properly to form clear sunset yellow color solution.

2.3.6 Coating on core tablet

The coating operation performed on 50 tablets batches in a conventional laboratory model stainless steel l20 cm pear shaped, baffled coating pan. The pan speed was 30 rpm and the coating solution as sprayed on tumbling bed of tablet with the help of Spray gun manually. The inlet air temperature was 40-45^{o}C and the manually the coating procedure was used was intermitted spraying and drying technique. Then weight tablets and thus coating thickness was controlled by percent weight gain of tablet with actual weight of core tablet .Coated tablet were allowed to dry completely in a hot air oven at 60 ^{o} C.

3. RESULTS AND DISCUSSION

3.1. IR analysis

3.1.1 FTIR study of Vildagliptin

FTIR of Vildagliptin exhibits characteristic Interpretation of C-H stretching having peaks at wave number (cm^{-1}) 2913.22, OH stretching =3293.79, C-N=2848.14, C-O=1653.81. which is match with standard FTIR of Vildagliptin exhibits characteristic Interpretation of C-H stretching having peaks at wave number (cm^{-1}) 2900.7, OH stretching =3300-2500, C-N=2294, C-O=1696.39.

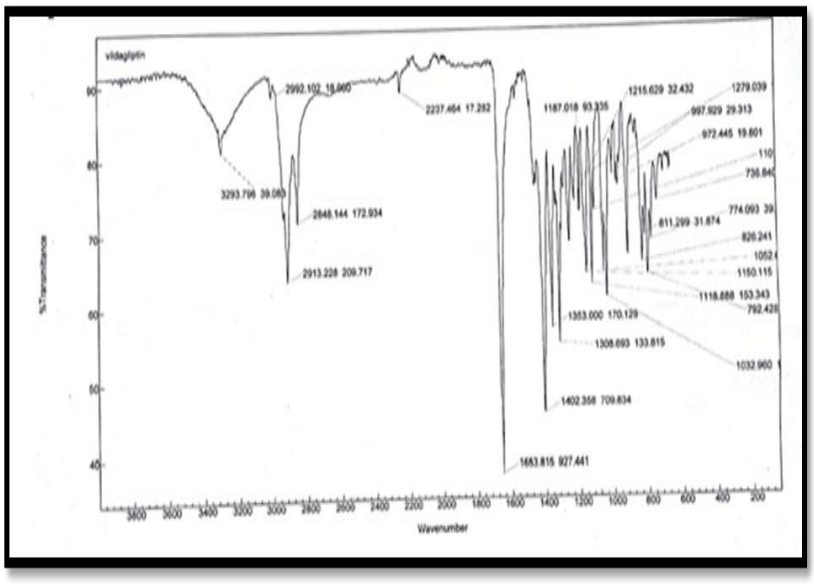

Figure. 2: FTIR spectrum of Vildagliptin.

3.1.2 Compatibility study between drug and osmogen FTIR spectrum of drug with Potassium Chlorideisshown in (Figure 3).

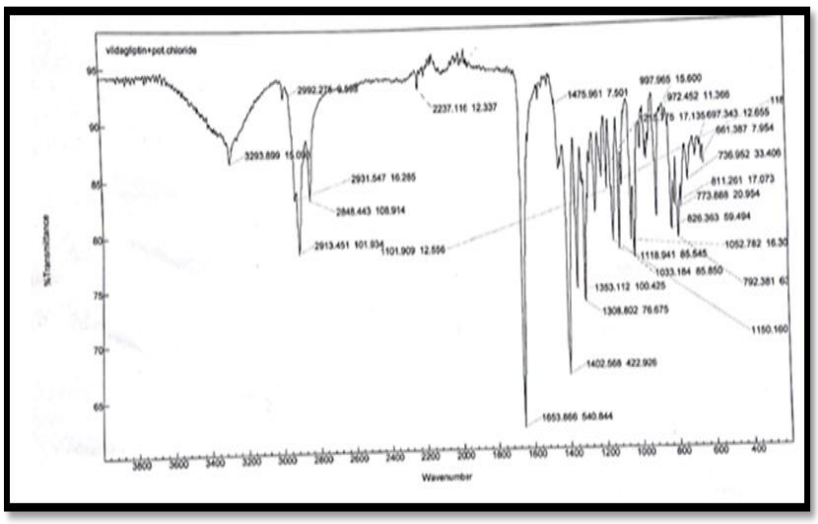

Figure. 3: FTIR spectrum of drug with Potassum Chloride.

3.2.3 In vitro drug release study of design formulations

The results of in vitro release of Vildagliptin from all formulations are shown in Figure 4,5,6.

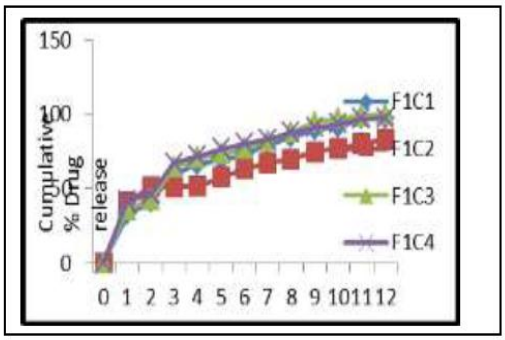

Fig 4: Drug release profile of F1C1 to F1C4

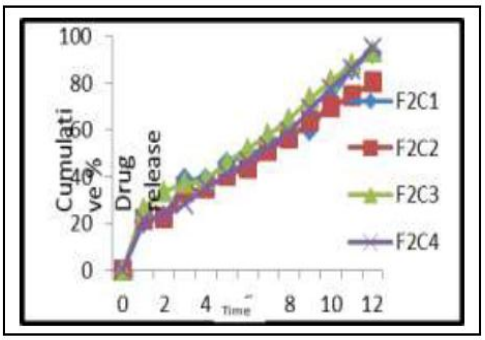

Fig 5 : Drug release profile of F2C1 to

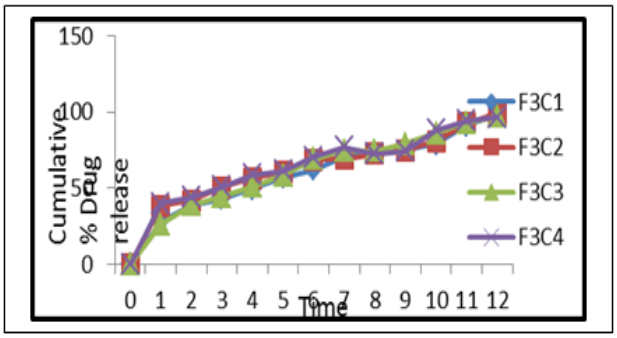

Fig 6: Drug release profile of F3C1 to F3C4

Table. 3: Kinetic release of prepared Vildagliptin osmotic tablet formulations.

Formulation Coad	Zero Order	First order	Hixon Crowell	Peppas Model	Higuchi Model
F1C1	0.867	0.465	0.656	0.232	0.986
F1C2	0.750	0.385	0.918	0.391	0.650
F1C3	0.867	0.465	0.656	0.232	0.986
F1C4	0.800	0.437	0.622	0.484	0.963
F2C1	0.940	0.5540	0.817	0.061	0.065
F2C2	0.924	0.554	0.501	0.061	0.778
F2C3	0.945	0.523	0.739	0.403	0.961
F2C4	0.973	0.592	0.834	0.259	0.941
F3C1	0.902	0.483	0.680	0.118	0.994
F3C2	0.602	0.483	0.918	0.167	0.993
F3C3	0.920	0.506	0.818	0.147	0.993
F3C4	0.920	0.4422	0.594	0.194	0.960

3.2.4 In vitro drug release study of Optimized Formulation F2C4

Table. 4: Cumulative % Drug Release of Optimized Batch.

Time (Hr)	Cumulative % Drug Release	Time (Hr)	Cumulative % Drug Release
1	21.54	**7**	52.71
2	23.50	**8**	58.96
3	28.38	**9**	68.94
4	35.66	**10**	77.42
5	40.88	**11**	85.93
6	46.54	**12**	94.93

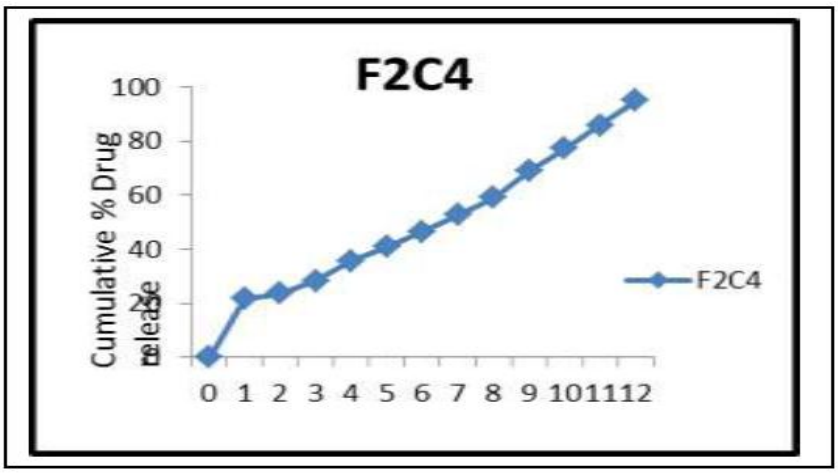

Fig. 7: In vitro release of Optimized formulation of F2C4.

3.3 Evaluation of Optimized Formulation F2C4

3.3.1 To study effect of pH on drug release of optimized formulation F2C4: The results of in vitro release of Vildagliptin from optimized formulation F2C4 are shown in Figure 5.

Table. 5: Cumulative % Drug Release of Optimised formulation to study effect of pH.

Time	Cumulative % Drug release		
	F2C4 0.1 N HCL	F2C4 pH 6.8	F2C4 pH 7.4
1	22.61	19.04	21.22
2	24.5	23.6	22.2
3	28.91	27.84	27.81
4	36.67	37.61	33.6
5	40.97	40.09	38.07
6	47.56	50.62	46.86
7	52.91	55.98	52.9
8	68.7	69.73	69.71
9	76.28	76.01	74.12
10	85.9	86.99	85.92
11	94.98	93.28	91.1
12	97.82	96.24	98.2

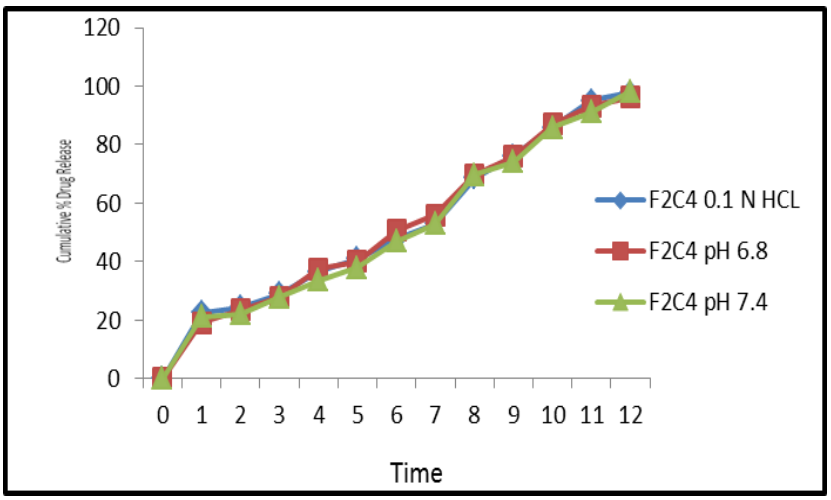

Fig. 8: In vitro release of Vildagliptin from F2C4 formulation in 0.1 N HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4.

It suggest that the dissolution data and dissolution profile of optimize formulation F2C4 in pH 1.2 hydrochloric acid, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer solutions respectively. The drug release rate in different dissolution media was almost similar. The pH of dissolution media has not significant impact on the drug release. So, the drug release from osmotic pump tablet was independent from pH.

3.3.2 To study effect of agitation intensity on drug release of optimized formulation F2C4: The results of agitation intensity on drug release of optimized formulation F2C4 on the 50 and 100 rpm to study the effect of agitation in Figure 5.

Table. No.6: agitation intensity on drug release of optimized formulation F2C4 on 50 and 100 rpm.

TIME (Hr)	Cumulative % Drug Release		TIME (Hr)	Cumulative % Drug Release	
	F2C4 50 rpm	F2C4 100 rpm		F2C4 50 rpm	F2C4 100 rpm
1	21.54	22.6	**7**	52.71	54.99
2	23.5	24.91	**8**	58.96	61.01
3	28.38	29.61	**9**	68.94	69.21
4	35.66	38.69	**10**	77.42	79.4
5	40.88	41.19	**11**	85.93	89.96
6	46.54	48.26	**12**	94.93	97.06

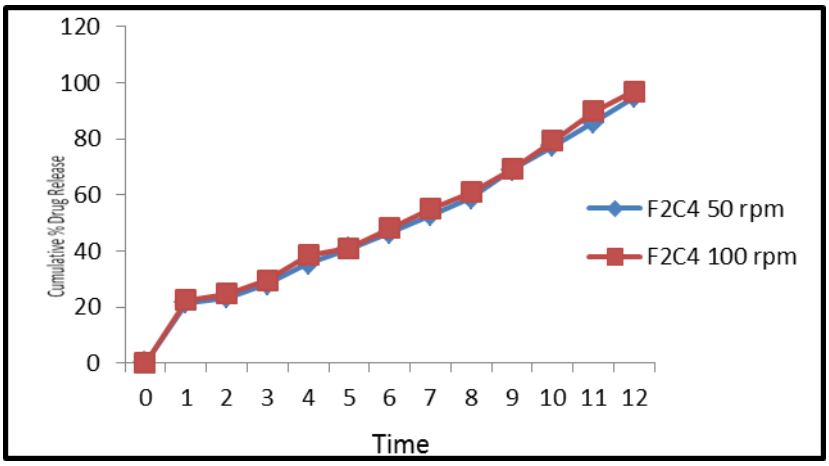

Figure 9: The results of agitation intensity on drug release of optimized formulation F2C4: It clearly evident that the dissolution data and dissolution profile of optimized formulation at 50 and 100 rpm. The drug release rate at different agitation speed was almost similar. The agitation speed of paddle has not significant impact on the drug release. So, the drug release from osmotic pump tablet was independent on agitation intensity. It could be expected that the release from the developed formulation will be independent of the hydrodynamic condition of the body.

3.3.4 Stability Study of Optimized Formulation F2C4

Short term stability studies were performed at temp of 40± 2°C/75± 5% RH over a period of one month (90 days) on the promising osmotic tablets of Vildagliptin (formulation F2C4). Sufficient number of tablets (15) were packed in amber colour rubber stopper vials & kept in stability chamber maintained at 40 ±2°C/75± 5% RH. Samples were taken at Three month interval. At the end of three month period, dissolution test was performed to determine the drug release profile.

Table. 7: The results of appearance and drug content.

Days	% Drug content
0	97.62±0.34
15	97.75±0.61
30	97.27±0.67

3.3.5 Results Stabilty Study of In vitro release of Vildagliptin from F2C4 formulation

Dissolution profiles before and after storage are nearly same. The developed dosage form passes stability study carried out for 90 days at 40± 2°C/75± 5% RH.

4. DISCUSSION

The semipermiable membrane formed by using cellulose acetate as a polymer and PEG 4000 as pore forming agent and PEG 400 as plasticizer gives plasticity and is selective in nature, which is essential for zero order release of drug.

In present investigation, batches F1C1 to F1C4 and F2C1 to F2C3 were prepared using 30mg and 40 mg KCl, 30 to 40% w/w PEG-4000 and 4 to 6% w/w weight gain of cellulose acetate and F3C1 to F3C4 were prepared by 30%-40% w/w PEG-4000 as pore former and 4%-6% weight gain of cellulose acetate. Among the batches, F2C4 batch containing 40 mg KCl, 40% w/w PEG-400, 40% PEG-4000 and 6% w/w weight gain of cellulose acetate gives Zero order release of drug 21.54% drug release after 1 hr and 94.93 % drug release after 12 hrs.

The release rate of drug from microporous membrane is at higher rate than as comparative to semipermiable membrane the rate of drug as vildagliptin can be increase by by using osmogent potassium chloride.

The release of drug from osmotic pump is inversely propotional to the membrane thicknesss, which can be related to the membrane weight.

By using the model fitting of drug release kinetic the zero order release can be predicted, the batch F2C4 shows higher value of r^2=0.973, hence it was optimized batch The release of drug from osmotic pump is unaffected by the environmental factor as pH of dissolution medium which was performed on different solution medium that is 0.1N HCL, pH 6.8 buffer, pH 7.4 buffer.

The release rate is also unaffected by intensity of agitation of dissolution fluid that was performed on different rpm that 50 and 100 rpm, shows no changes on drug release hence it can conclude that there is no effect of agitation on osmotic tablet.

The results of experimental studies of Vildagliptin osmotic tablets proved that the granules of Vildagliptin showed good flow properties, tablet evaluation tests are within the acceptable limits, IR spectral analysis proved that there was no drug-excipients interaction, the kinetic studies revealed that optimized formulation followed zero order drug release kinetics and stability studies revealed that all the formulations were found to be stable after storing at temperature of 45^{o}C± 2^{o}C, 75% ± 5% relative humidity for 1 months. Thus the results of the above study clearly indicated that Developed osmotically controlled release tablet of Vildagliptin provide release of drug at a predetermined rate and for a predetermined time in controlled manner.

Vildagliptin was successfully formulated as controlled porosity osmotic pump tablets to release drug at zero order release up to 12 hrs. The rate of drug release from the formulation increased with increased in concentration of osmogent, increased with increased in pore forming agent and increase with decrease in % weigh gain.

Finally, it can be concluded that preparation of osmotic pump tablet can be simplified by coating the core tablet with the a pore forming agent which is likely to be most cost-effective than laser drilling.

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