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FORMULATION AND EVALUATION OF GASTRO INTESTINAL RESISTANT MICROPOROUS MEMBRANE PERMEATED DRUG DELIVERY SYSTEM OF VILDAGLIPTIN

Srilakshmi N[1*], P Srinivasa Babu[2], M Bhagavan Raju[3], G Kishore Babu[2], T Praveen Kumar[4]

*[1]Malla Reddy Pharmacy College, Hyderabad
[2]Vignan Pharmacy College, Guntur
[3]Gland Institute of Pharmaceutical Sciences, Hyderabad
[4]Martinsynge Pharma Sciences Pvt Ltd

***Author for Correspondence: Srilakshmi N**
Malla Reddy Pharmacy College, Hyderabad

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ABSTRACT

The purpose of the present study is to obtain an oral controlled release formulation for highly water soluble drugs which have shorter half-life. In this study Vildagliptin has been used. Vildagliptin belongs to a class of orally active anti-diabetic drug which inhibits dipeptidyl peptidase-4(DPP-4) and potentiates the secretion of insulin in the β-cells, thereby decreasing blood glucose level. The desired effect is obtained by preparing matrix tablets and applying a coat of gasto-intestinal resistant micro-porous membrane on the core tablet. Core tablet is obtained by wet granulation and compression method. Core tablets are tested for dissolution studies and the best formulation has been chosen for further studies. Optimized core tablet has been coated with ethyl cellulose in which sodium lauryl sulphate was dispersed. Effect of formula compositions of core tablets and coating suspensions on the pharmaceutical characteristics, such as drug release kinetics and membrane stability of the coated tablets was investigated *in vitro*. Vildagliptin released from the coated tablets at a zero-order rate in a pH-independent manner. This independency of Vildagliptin release to pH change from 1.2 to 7.2 is favorable for the controlled oral drug delivery, since it will produce a constant drug release in the stomach to intestine regardless of the pH change in the GI tract. Drug release could be extended upto 10 h according to the coating condition. The release rate could be controlled by changing the formula compositions of the core tablets and coating suspensions, coat weight per each tablet, and especially ethyl cellulose/sodium lauryl sulphate ratio in the coating suspension. Among the prepared formulations, formulation C12 (optimized formula with ethyl cellulose 5% and sodium lauryl sulphate 2%) was the optimized one and it showed non-fickian transport and korsmeyer peppas mode and is concluded as the best formulation.

KEYWORDS: Vildagliptin, Anti-diabetic drug, Wet granulation, Ethyl cellulose, Sodium lauryl sulphate.

INTRODUCTION

Diabetes Mellitus is a chronic metabolic disorder characterized by hyperglycaemia, altered metabolism of lipids, carbohydrates and proteins because of a lack of or ineffective use of the hormone insulin and associated with reduced life expectancy, significant morbidity due to specific diabetes related micro vascular complications and diminished quality of life.[1,2] Vildagliptin belongs to a class of orally active antidiabetic drugs (DPP-IV inhibitors) that appear to have multiple functional benefits beyond simple blood-glucose control. One of these is a potential protective effect on pancreatic beta cells, which deteriorate in diabetes. It appears to be safe, very well tolerated, and efficacious. Following a meal, gut incretin hormones are released. The most important incretin hormones are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). These hormones, secreted in the human small intestine, are responsible for insulin release due to increased glucose levels. In contrast to agents that promote insulin secretion via glucose-independent mechanisms, GLP-1's dependence on glucose concentration is considered beneficial due to a lower risk of hypoglycemia. GLP-1 also inhibits glucagon secretion and increases beta cell mass by stimulating proliferation and neogenesis. However, the clinical utility of GLP-1 is limited by its short half-life (2 minutes). GLP-1 is rapidly degraded by the proteolytic enzyme DPP-IV. To enhance GLP-1 activity, inhibition of the DPPIV enzyme is emerging as a novel therapeutic approach in the treatment of diabetes. Administration of vildagliptin enhances GLP-1's ability to produce insulin in response to elevated concentrations of blood glucose, inhibit the release of glucagon following meals, slow the rate of nutrient absorption into the bloodstream, slow the rate of gastric emptying, and reduce food intake.[3,4] As there is difficulty in developing new and new drugs for

the diseases, more and more emphasis has been put on developing new drug delivery systems for the available existing drugs and new chemical entities. Drugs can be delivered to patients by several routes and several dosage forms. Though dosage form and drug delivery system is used interchangeably, "drug delivery system" refers as a technology that has been used to deliver a drug to the desired body site for drug release with a predetermined rate. Among all the drug delivery systems oral controlled release formulations are most widely used in the pharmaceutical industry. Delayed release, sustained release and repeat action formulations are the most widely used controlled release formulations. The aim of any drug delivery system is to provide therapeutic amount of drug to appropriate site in the body to achieve immediate therapeutic response and to maintain the desired drug concentration. Diffusion controlled formulations are another type of controlled release formulations where the drug diffuses through the polymer membrane or a polymer matrix into the environment. Depending on the type of diffusion systems they are classified as reservoir systems and monolithic systems. In nonporous reservoir systems drug molecules will diffuse through the polymer membrane and in microporous reservoir systems, drug molecules are diffused through the micopores which are generally filled with either water or oil. Apart from these both the nonporous and microporous, diffusion monolithic systems are further classified depending upon the concentration of loaded drug. The monolithic system is called monolithic solution if the drug is loaded into a soaking polymer matrix in the drug solution. In this type the drug loading is equal to the drug's solubility. In monolithic dispersion type of systems the drug loading is higher than the solubility of the drug.[5]

MATERIALS AND METHODS

Preparation of the Core tablets

Wet granulation method was employed for tablet compression. Initially all the quantities required for tablet are weighed and are mixed together in geometric dilutions. Later small granules are prepared by using water. After preparation of the granules it's dried in an oven at a temperature of 45^{o}C until the granules get dried. Later the granules are passed through the sieve #10.The passed granules are later compressed using the compression machine. These tablets are used for further extensive studies. Quantities of all ingredients are tabulated in Table 1.

Table 1: Composition of core tablets

Ingedients	F1	F2	F3	F4	F5	F6
Vildagliptin	100	100	100	100	100	100
Eudragit S100	50	75	100	-	-	-
HPMC K 15	-	-	-	50	75	100
Pregelatinised Starch	90	65	40	90	65	40
PGS	50	50	50	50	50	50
Aerosil	5	5	5	5	5	5
Talc	5	5	5	5	5	5
TOTAL Wt.	300mg	300mg	300mg	300mg	300mg	300mg

Coating of the core tablet

The core tablet which has been optimized (F6) is used for further studies. Initially required quantity of ethyl cellulose as mentioned in the Table 2 was taken into the beaker and later required quantity of methanol was added to it and initially stirred. Later this mixture is sonicated until the solution becomes transparent. Add the remaining components such as Sodium lauryl sulphate, Titanium di oxide and Castor oil to the sonicated mixture and sonicate it again for fifteen minutes. The core tablets have been coated by using the Spray coating technique. The prepared coating solution has been filled in the sprayer. The tablets to be coated are placed in the pan. Coating solution is sprayed on to the bed in the rotating pan. Randomly tablets are taken and are checked for its weight increase. After attaining the desired weight the pan is stopped and the tablets are removed and used for the further analysis.

Table 2: Ingredients of Coating Solution

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Ethyl cellulose	15	15	15	15	10	10	10	10	5	5	5	5
Sodium lauryl sulphate	0.5	1.0	1.5	2.0	0.5	1.0	1.5	2.0	0.5	1.0	1.5	2.0
Titanium Di Oxide	2	2	2	2	2	2	2	2	2	2	2	2
Castor Oil	2	2	2	2	2	2	2	2	2	2	2	2
Methanol	q.s	q.s	q.s.	q.s.	q.s.	q.s.	q.s	q.s	q.s.	q.s.	q.s.	q.s.

*All the ingredients mentioned above are in the terms of "percentages."

Evaluation

Precompression Parameters: Precompression parameters like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose were evaluated and the results are given in Table 3.

1. Bulk density (D_b)[6,7]: It is the ratio of total mass to the bulk volume. It was measured by pouring the weighed sample into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by:

$$D_b = \frac{M}{V_0}$$

Where, M is the mass
V_0 is the bulk volume

2. Tapped density (D_t)[6,7]: It is the ratio of total mass to the tapped volume. The volume was measured by tapping for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. It is expressed in g/cc and is given by:

$$D_t = \frac{M}{V_1}$$

Where, M is the mass
V_t is the tapped volume

3. Carr's index (%)[6,7]: The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

$$\text{Carr's index} = 100 \times \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}}$$

4. Angle of repose (θ) [6,7]: It is defined as the maximum angle possible between the surface of a pile and the horizontal plane.

$\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose
h is the height in cms
r is the radius in cms

5. Hausners' Ratio: It is the ratio of tapped density and bulk density.

Post compression Parameters: Post compression parameters were evaluated for both core and coated tablets and they tabulated in Table 4 & 5.

Hardness[8]

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted.

Friability Test[8]

This test is performed in Roche friabilator and %friability was calculated as follows:

%Friability = (W1 – W2) x 100/W1

Where,
W1 = Initial weight, W2 = Final weight

Weight Variation Test[8]

To study weight variation individual weights of 20 tablets from each formulation were noted. Their average weight was calculated. Percent weight variation was calculated.

***In -Vitro* Drug Release Studies**

Dissolution of the core and coated tablets are performed by employing 0.1 N HCl for first two hours and later the dissolution is continued using phosphate buffer pH 6.8 maintained at 37°C ± 0.5°C. At appropriate time intervals samples were extracted from the apparatus (each of 5 ml) and the content of the drug was analyzed by using Elico SL 210 UV/Vis spectrophotometer and absorbance was measured at 210 nm. Dilutions were performed as necessary using the dissolution medium. The extracted samples were replaced by 5 ml of fresh dissolution medium in an attempt to maintain sink conditions. The results were fitted into different kinetic models. Results wre given in Table 6, 7 and 8.

RESULTS AND DISCUSSION

Pre compression properties were assessed and angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio of formulated granules were calculated. All these physical parameters were found to be within acceptable limits. All the post compression parameters were found to be within limits.

Table 3: Precompression parameters of the core tablet

Parameter	F1	F2	F3	F4	F5	F6
Bulk Density (gm/ml)	0.53±0.042	0.490±0.081	0.55±0.023	0.52±0.049	0.51±0.011	0.54±0.032
Tapped Density (gm/ml)	0.59±0.065	0.533±0.032	0.63±0.051	0.63±0.018	0.59±0.018	0.64±0.048
Compressibility index	10.16±0.29%	8.06±0.108%	12.69±0.47%	13.6±0.37%	13.5±0.21%	15.6±0.71
Angle of repose	20.65±0.21	21.54±0.62	20.01±0.34	21.24±0.31	24.84±0.44	26.4±0.29
Hausner's Ratio	1.113±0.04	1.087±0.04	1.145±0.02	1.21±0.05	1.15±0.02	1.18±0.04

Table 4: Post compression parameters of the core tablet

Parameter	F1	F2	F3	F4	F5	F6
Weight variation(g)	0.301±0.02	0.299±0.12	0.304±0.009	0.303±0.024	0.299±0.01	0.302±0.031
Hardness (Kg/cm^2)	4.6±0.2	5.0±0.1	4.9±0.3	4.8±0.2	5.1±0.4	5.0±0.2
Friability (%)	0.76±0.021	0.74±0.015	0.68±0.025	0.76±0.034	0.72±0.015	0.74±0.017

Table 5: Post compression parameters of the coated tablet:

Formula	Parameter		
	Friability (%)	Hardness (Kg/cm^2)	Weight variation (g)
C1	0.24±0.01	7.1±0.3	0.314±0.02
C2	0.21±0.04	7.1±0.1	0.315±0.03
C3	0.19±0.08	7.0±0.1	0.315±0.02
C4	0.20±0.04	7.2±0.2	0.313±0.04
C5	0.27±0.02	6.8±0.1	0.314±0.02
C6	0.26±0.03	6.6±0.4	0.314±0.04
C7	0.28±0.01	6.5±0.3	0.313±0.02
C8	0.29±0.04	6.6±0.2	0.314±0.02
C9	0.29±0.08	6.5±0.1	0.313±0.04
C10	0.31±0.05	6.4±0.1	0.314±0.01
C11	0.29±0.04	6.4±0.2	0.313±0.02
C12	0.30±0.03	6.6±0.4	0.314±0.01

Table 6: Dissolution data of the core tablet formulations

Time (min)	Cumulative Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	47.86	23.98	11.41	31.55	37.42	41.93
15	56.4	27.36	16.91	36.43	42.63	47.83
30	59.95	38.63	19.63	46.92	54.72	55.67
60	71.03	42.17	28.55	58.61	66.8	69.72
90	78.12	51.36	31.48	67.92	78.22	82.23
120	91.54	67.24	36.17	78	86	94

Based on the release studies formulation F6 was optimized and was used for coating.

Table 7: Dissolution data for coated tablet formulations

Time (min)	Cumulative % drug release											
	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
0	0	0	0	0	0	0	0	0	0	0	0	0
15	0.03	0.08	0.13	0.19	0.07	0.29	1.02	1.59	0.53	0.91	1.05	2.88
30	0.12	0.17	0.25	0.31	0.11	0.61	2.72	3.01	0.81	1.08	2.55	4.87
60	0.19	0.24	0.38	0.48	0.26	0.93	3.95	5.16	1.21	1.87	5.29	10.54
120	0.28	0.39	0.51	0.65	0.35	1.15	4.8	6.93	1.94	2.87	7.38	15.66
180	0.35	0.53	0.72	0.81	0.47	1.82	7.17	8.48	3.65	4.14	9.1	19.85
240	0.49	0.64	0.99	1.1	0.59	3.1	8.35	10.59	4.91	6.57	12.22	24.67
300	0.61	0.73	1.07	1.19	0.71	6.82	10.68	12.8	5.88	8.98	15.37	29.56
360	0.75	0.86	1.26	1.38	0.88	8.21	12.64	14.77	7.43	11.49	17.43	33.65
420	0.89	1.08	1.33	1.42	1.02	10.29	15.82	17.32	9.48	15.75	20.98	39.81
480	1.05	1.3	1.47	1.89	1.24	14.28	19.88	23.42	11.84	18.85	26.45	43.74

Table 8: Peppas data for coated tablet formulations

log Time	log % dissolved											
	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
0	0	0	0	0	0	0	0	0	0	0	0	0
1.17	-1.52	-1.09	-0.88	-0.72	-1.15	-0.53	0.008	0.20	-0.27	-0.04	0.02	0.45
1.47	-0.92	-0.76	-0.60	-0.50	-0.95	-0.21	0.43	0.47	-0.09	0.03	0.40	0.68

1.77	-0.72	-0.61	-0.42	-0.31	-0.58	-0.03	0.59	0.71	0.082	0.27	0.72	1.02
2.07	-0.55	-0.40	-0.29	-0.18	-0.45	0.06	0.68	0.84	0.28	0.45	0.86	1.19
2.25	-0.45	-0.27	-0.14	-0.09	-0.32	0.26	0.85	0.92	0.56	0.61	0.95	1.29
2.38	-0.30	-0.19	-0.00	0.04	-0.22	0.49	0.92	1.02	0.69	0.81	1.08	1.39
2.47	-0.21	-0.13	0.02	0.07	-0.14	0.83	1.02	1.10	0.76	0.95	1.18	1.47
2.55	-0.12	-0.06	0.10	0.13	-0.05	0.91	1.10	1.16	0.87	1.06	1.24	1.52
2.62	-0.05	0.03	0.12	0.15	0.008	1.01	1.19	1.23	0.97	1.19	1.32	1.59
2.68	0.02	0.11	0.16	0.27	0.09	1.15	1.29	1.36	1.07	1.27	1.42	1.64

Scanning electron microscopy images of the optimized coated tablet

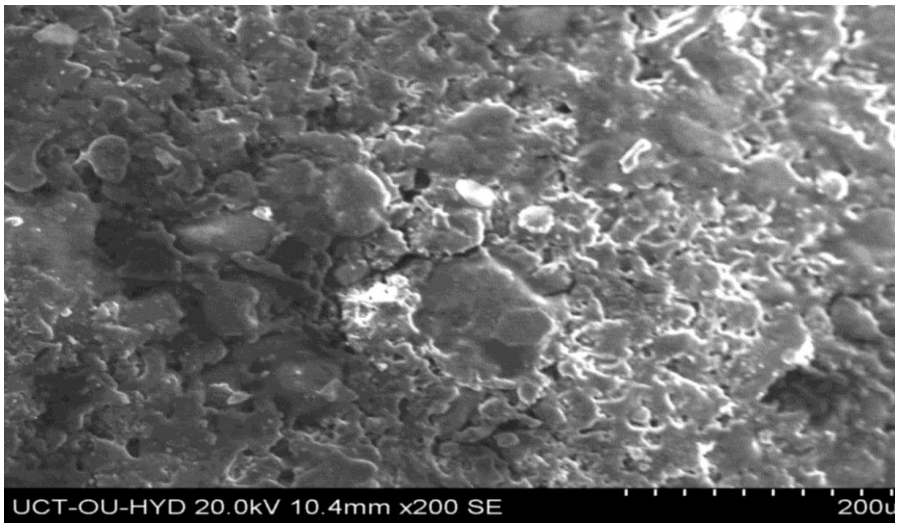

Figure 1: Scanning electron microscopy image of tablet before dissolution

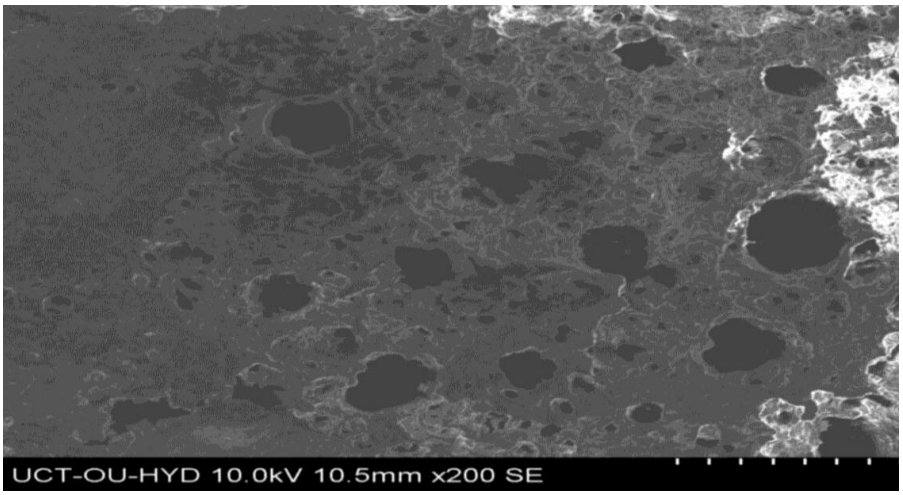

Figure 2: Scanning electron microscopy image of tablet after dissolution

CONCLUSION

The objective of the present study is to sufficiently control the drug release of water soluble drug Vildagliptin. A novel microporous permeation controlled gastro intestinal resistant method is developed using Ethyl cellulose and Sodium lauryl sulphate. The characterization and evaluation of tablets by drug dissolution studies and SEM studies conclude the effect of pore forming material SLS on the drug release. The diameter of the pore increases with SLS concentration and it is observed that a drug dissolution is much faster with increased pore diameter. The formulation of tablets doesn't require advanced equipments, a simple coating process can be used to develop the formulations. Among the prepared formulations, formulation "C12" was the optimized one and it showed non-fickian transport and korsmeyer peppas mode; and is concluded as the best formulation.

REFERENCES

1. Elas JL and Longo N. Glucose transporters. Annu Rev Med, 1992; 43: 377-93.

2. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia, World Health Organization, 2006: 1-46.
3. U.S.P. Convention Krowcyzynski, L., extended release dosage forms, CRS press, Inc. Florida, 1987: 4.
4. DRUG BANK http://www.drugbank.ca/drugs/DB00661.
5. Lee, V.H., Robinson, J.R., in "Sustained and controlled release drug delivery systems" Marcel Dekker, New York, 71-121.
6. Cooper J, Gunn C, Powder flow and compaction, In; Carter SJ, eds, Tutorial Pharmacy. New Delhi, India: CBS Publishers and distributors; 1986; 211-233.
7. Aulton ME, Wells TI, Pharmaceutics: The science of dosage form design, England: Churchill Livingstone; 1988.
8. Reddy et al, World journal of pharmacy and pharmaceutical sciences, 2015; 4(10).