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FORMULATION AND EVALUATION OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM OF AN ANTI-DIABETIC DRUG

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ABSTRACT

Saxagliptine has a relatively short elimination half-life (2.5 h), thereby requiring twice or thrice daily dosing in patients, which may lead to non-compliance. Extended release formulation of Saxagliptine based on osmotic technology was developed and evaluated. Controlled Porosity osmotic tablets of Saxagliptine were developed using Self Pore forming agent Mannitol. Prepared tablets were evaluated for their Flow property, weight variation, hardness, friability and content uniformity. Tablets were coated with a semi permeable membrane using 6% w/v cellulose acetate Phthalate (CAP) in isopropyl alcohol and Methylene chloride and Polyethylene Glycol-400 as plasticizer. Drug release rate was increased as the increase of Mannitol amount in Core Tablet. Drug release was inversely proportional to weight gain but directly proportional to the Self pore forming agent. The drug release from developed formulations was independent of pH and agitation intensity of release media. The DSC and FTIR studies demonstrated that there was no interaction between polymers and drug. The optimized formulation was stable after one months of accelerated stability studies.

KEYWORDS: "Saxagliptine**,** "Extended release", Osmotic technology.

INTRODUCTION

Osmotic drug delivery system utilizes the principle of osmosis for release of drug. Release of drug from osmotically controlled system is found to be independent of pH of the body fluid, presence of food in GIT, hydrodynamic conditions, and other body's physiological factors. Osmotic system has a high degree IVIVC, because release is found to be independent of the above mentioned factors, which are responsible for causing differences in release profile *in vivo* and *in vitro*.

The aim of the present study was to develop and optimize control porosity osmotic drug delivery system of Saxagliptine to give control release of drug by utilizing the osmosis principle with better patient compliance.

- **Experimental Material Method:-Preparation of Saxagliptine controlled porosity osmotic pump tablet.**
- **Experimental design**

A number of preliminary experiments were conducted to determine the formulation and parameters by which the process resulted in controlled porosity osmotic pump tablets. A full factorial 2^3 design was employed for the optimization procedure. The drug: osmogent ratio (X1), concentration of pore former (X2) and % weight gain (X3) were selected as the independent variables, whereas % Drug release and Hardness of Saxagliptine tablet (Y) was chosen as the dependent factor. Table no.26 summarizes these factors with corresponding levels and the responses studied, whereas experimental formulations are listed in Table. The factors were selected to measure the change in response from one extreme factor to another and for determining interactions, if any, among the factors with their best levels for optimizing the considered experimental responses.

- **Preparation of Factorials Batches**

A 2^3 factorial design was implemented for optimization of controlled release tablet formulation. According to the model it contained 3 independent variables at 2 levels, +1,-1. According to model total 8 formulations are possible, the composition of different formulation are shown in Table .The different independent variables, were presence or absence of The drug:osmogent ratio (X1), concentration of pore former (X2) and % weight gain (X3) were selected as the independent variables,. Dependent factors included % drug release at 12 hrs and Hardness of tablet.

Table No.01: Factorial design for preparation of batches.

Batches code	Variable Level In Coded Form		
	X1	X2	X3
F1	+1.00	-1.00	+1.00
F2	-1.00	-1.00	-1.00
F3	+1.00	+1.00	-1.00
F4	+1.00	+1.00	-1.00
F5	-1.00	+1.00	+1.00
F6	-1.00	-1.00	+1.00
F7	+1.00	-1.00	-1.00
F8	-1.00	+1.00	-1.00

Table No.02. Translation of Coded Value in Actual Unit.

Variable level	Low (-)	High (+)
X1= Drug:osmogent ratio	1:12	1:60
X2= Concentration of pore former	10 %w/w	20 %w/w
X3= (% wt gain)	8 %	10 %

Table No.03: Coating composition.

INGREDIENT	F1	F2	F3	F4	F5	F6	F7	F8
Instacoat (%w/v)	6	6	6	6	6	6	6	6
PEG 400(%W/W of dry polymer)	10	10	20	20	10	10	20	20
Isopropyl alcohol	9	9	9	9	9	9	9	9
Methylene chloride	85	85	85	85	85	85	85	85
% Weight gain	8	10	8	10	8	10	8	10

Table No.04: Composition of factorial design formulations for controlled porosity osmotic pump tablets.

Ingredients (mg)	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Saxagliptine	5	5	5	5	5	5	5	5
Mannitol	60	60	60	60	80	80	80	80
Lactose	20	20	20	20	20	20	20	20
Microcrystalline cellulose	50	50	50	50	30	30	30	30
PVP K30	18	18	18	18	18	18	18	18
HPMC K100M	40	40	40	40	40	40	40	40
Carbapol 934P	2	2	2	2	2	2	2	2
Gum Acacia	2	2	2	2	2	2	2	2
Starch	10	10	10	10	10	10	10	10
Magnesium Stearate	05	05	05	05	05	15	05	15
Talc	03	03	03	03	03	03	03	03
Aerosil	05	05	05	05	05	15	05	15
Total weight	220	220	220	220	220	220	220	220

RESULT AND DISCUSSION

✓ Drug selection

Antidiabetic drug like Saxagliptine has a relatively short elimination half-life (2.5 h).Thereby requiring twice daily dosing in large number of patients, which often leads to non-compliance. Saxagliptine with all evident advantages proved to be suitable candidates for development of a controlled-release dosage form. Treatment of hyperglycemia using conventional formulations of Antidiabetic drug is found to have many drawbacks such as adverse side effects (flushing, Dose dumping, interpatient variability, poor absorption of drug at GIT site) due to accumulation of drug in multi-dose therapy, and poor patient compliance. So, Controlled release once daily formulations of Saxagliptine can overcome some of these problems.

✓ Experimental Design for Controlled porosity osmotic pump tablet

A 2^3 full factorial design was design to estimated optimum concentration of drug:osmogent ratio (X1), concentration of pore former (X2) and % weight gain (X3) on evaluation parameter like drug release and Hardness. The drug containing tablet (Formulations F1-F8) was evaluated for appearance, solubility, melting point, compatibility study, drug content, drug release study. The drug release study reveals that ,as the proportion of drug:osmogent ratio increases drug release profile changes, there was remarkable changes in

concentration of pore former and % weight gain on drug release profile.

Drug like Saxagliptine, polymers like Carbapol 934p, and HPMC K-100M, Mannitol, Gum Accacia were chosen for the formulations for controlling the drug release. Carbapol 934p and HPMC K-100 M is a non toxic, biocompatible, cost effective and also reduce the risk of systemic toxicity due to dose dumping. HPMC K-100M also non-toxic, non allergic, non irritating, biocompatible, soluble at pH higher than 6.5. So it was used to control the release of the drug according to specification given in USP. Gum accacia and PVP-K30 is used in solid-dosage forms as a binder and disintegrant, in oral and topical products as a suspending, thickening, and stabilizing agent; and also as a controlled-release carrier. Tablets were prepared by wet granulation technique, to get required hardness and thickness with sufficient force.

The release of the drug in stomach was prevented by using acid resistance polymers like Cellulose acetate phthalate. Cellulose acetate phthalate is used for enteric coating to the core tablet. Hence by using the property of polymer CAP, the drug was made to release in the intestine (pH 6-7) by escaping acidic environment of stomach without degradation of drug and after passing the acidic environment drug release in intestine by generating pores at the semipermeable membrane by the osmotic pressure generate inside.

✓ **Melting Point Determination**

Melting point of Saxagliptine was determined by capillary method. The melting point of Saxagliptine was found to be in the range. This compiled with BP standards, indicating purity of the drug sample.

✓ **Solubility**

Saxagliptine was found to be more soluble in pH 6.8 phosphate buffer as compare to 0.2 N HCL , i.e. it has optimum solubility at pH 6.8 (4.67 mg/ml). The solubility decrease to about (2.56 mg/ml) at 0.2 N HCL

✓ **Compatibility Study**

It was observed that there were no changes in these main peaks in FTIR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.
The peaks obtained in the spectra's of each polymer correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

✓ **Flow Properties**

A flow property plays an important role in pharmaceuticals especially in tablet formulation because improper flow may cause more weight variation. Values of Carr's Index (Compressibility) below 15% usually give rise to good flow properties but readings above 25% indicate poor flow properties. It was found that the compressibility values of the powders were below 15% and hence they exhibit good flow characteristics.

Values of angle of repose are rarely 20^{o} and values up to 40^{o} indicate reasonable flow properties. Above 50^{o} however the powder flows only with great difficulties. Dynamic angle of repose measurements can be replicated with relative standard deviations of approximately 2%. They are particularly sensitive to changes in particle size distribution and to the moisture content, and they provide a rapid means of monitoring significant batch to batch differences in these respects.

The Carr's Index (Compressibility) of the powders was in the range of 7.14 to 14.62. The angles of repose of the powders were in the range of 29.74^{0} to 39.69^{0}, which indicate a good flow property of the powders. Here the angle of repose was found to be below 40o this shows that the reasonable flow property of powders.

❖ **Evaluation of Tablets**

- **Physical Parameters (Shape, Size, Hardness & Friability)**

The punches used to compress the tablets were 09 mm, round shaped. The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 4.2 to 16.85 Kg/cm2. It was within the range of monograph specification. Thicknesses of the tablets were found to be in the range of 3.78 to 3.96 mm. The friability of the tablets was found to be less than 1% and it was within the range of standard specification.

- **Weight Variation and Drug Content**

Weight variation test helps to check whether the tablet contain proper quantity of the drug. From each of the formulations ten tablets were randomly selected and weighed. The results are given in table no 43. The average weights of the tablets were found to be within the prescribed official limits (IP). Drug content for each of the formulations was estimated. The drug content for all the batches were found to be in the range of 93.77 to 98.43%.

- ***In-Vitro* Release Study**

All the formulation of prepared tablets of Saxagliptine were subjected to *in vitro* release studies, these studies were carried out using dissolution medium, (0.2 N HCL and Phosphate Buffer P^{H} 6.8) by using USP-1(Basket type) dissolution apparatus. The results were evaluated for 24 hours. As per the results of dissolution study formulations (Table no.44) F-1, F-2, F-3, F-4 shows 115.3%, 119.10%, 123.4%, 125.4% drug release up to 12 hrs. this is indicate that drug release in controlled manner dose not achieve and next batches F-5, F-6, F-7, F-8, F-9 shows 91.52%, 93.85%, 96.53%, 98.32%, and 98.86, release respectively over a period of 24 hours. Among all the formulation, F-8, showed 98.32 % i.e. prominent drug release for controlled release formulation for tablet, and these F-8 Batch selected for reproducible

formulation and these batch F-9 gives a 98.86% Drug release respectively at the end of 24 hours. The formulation F9 its release at the end of 24th hr is 98.86% also all other parameters like hardness, thickness, friability, and drug content and weight variation for this formulations were within the range. So, a formulation F-9 was selected as the optimized formulation.

- **Effect of weight gain**

To study the effect of weight gain of the coating on drug release, core tablets of Saxagliptine was coated so as to get tablets with different weight gain (08, 10, 12% w/w). Release profile of Saxagliptine from these formulations is shown in figure no 24**.** It clearly shows that drug release decrease with an increase in weight gain of membrane.

- **Effect of agitational intensity**

In order to study the effect of agitational intensity of the release media, release study of optimized formulation was carried out in dissolution apparatus at various rotational speeds. Dissolution apparatus used was USP I at 50, 100, 150 rpm/min. The data of the drug release profile of optimized batch tablets at different rpm conditions are shows that the release profile of Saxagliptine from the developed formulations is fairly independent of the agitational intensity of the release media and hence, it can be expected that the release from the developed formulations will be independent of the hydrodynamic conditions of the body.

Table No.05: Drug release profile of F1 –F9.

Sr.No	Time (hrs)	Formulation code (% Drug release)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
IN 0.2M(HCL)										
1	0	0	0	0	0	0	0	0	0	0
2	1	2.50	2.86	2.50	4.11	3.76	4.29	3.94	3.58	3.76
3	2	8.05	7.70	8.05	8.77	5.73	5.55	6.80	5.01	4.11
IN PHOSPHATE BUFFER pH (6.8)										
4	3	19.34	19.16	19.88	20.41	10.74	11.46	12.17	10.56	10.38
5	4	28.47	28.47	29.73	30.08	13.97	13.61	13.61	12.71	12.71
6	5	36.17	36.17	43.70	43.11	20.41	21.31	21.31	18.08	18.62
7	6	61.61	61.61	61.61	62.50	24.35	23.82	24.71	23.46	24
8	7	69.49	69.49	69.67	70.38	29.55	28.83	28.83	28.11	28.11
9	8	81.49	81.49	82.74	83.10	33.85	34.74	34.74	32.95	33.31
10	9	83.46	83.46	86.86	86.86	37.97	39.58	40.83	37.97	38.50
11	10	86.68	85.074	88.47	87.94	46.74	47.46	47.46	45.85	45.85
12	11	97.43	100.11	101.5	101.9	53.37	53.01	53.37	49.97	49.43
13	12	101.37	105.49	105.8	107.2	57.49	58.56	61.43	57.49	58.38
14	13	-	119.10	123.4	125.5	62.50	63.58	62.86	61.43	61.43
15	14	-	-	-	-	67.70	66.08	65.91	64.65	65.55
16	16	-	-	-	-	77.55	79.70	78.98	77.37	77.91
17	18	-	-	-	-	82.56	85.43	87.04	86.86	87.58
18	20	-	-	-	-	87.58	87.76	89.37	88.47	89.19
19	22	-	-	-	-	90.08	91.88	92.59	93.31	94.02
20	24	-	-	-	-	91.52	93.85	96.53	98.32	98.86

- **Kinetics**

Different models like Zero order, First order, Higuchi's, and Hixon-crowell model were drawn. The regression coefficient (R2) value for Zero order, First order, Higuchi's, and Hixon-crowell model (figure no. 20,21,22 and 23) for optimized formulation F-9 were found to be 0.985, 0.758, 0.920, 0.828.The regression coefficient (R2) of Higuchi plot of optimized formula F-9 is 0.920 that shows the drug releases through the controlled released mechanism. The regression coefficient (R2) value of zero order is 0.985 in. Thus, the drug release follows zero order release kinetics.

- **Scanning Electron Microscopy (SEM)**

In order to elucidate the changes in the membrane structure, SEM studies were conducted (both before and after dissolution studies). Figure no. 24 shows SEM micrographs of coating membrane (before (A) and after dissolution (B)) of optimized batch F-9 containing Instacoat (6% w/v cellulose acetate phthalate) and PEG 400 (20% w/w) as a plasticizer. It was expected that pores must be formed after dissolution.

In Figure (a), pores are visible as tiny spots, possibly due to stress, because it represents before dissolution. A perusal to Figure (b) indicated that pores were formed after dissolution and clearly visible and were large in number. This optimized formulation F-9 containing

Instacoat (6% w/v cellulose acetate phthalate) and PEG 400 (20% w/w) as a plasticizer in coating solution. The pores were circular. Further the coating surface becomes more rough (after dissolution) on account of leaching. The membrane becomes porous, presumably because of leaching of pore former, i.e. PEG 400. Finally, it can be concluded that leaching of pore former from the membrane had made membrane porous, through which drug release took place. The numbers of pores were directly proportional to the amount of pore former leached from the membrane. With this it can be concluded that the tablets prepared in this investigation were controlled porosity osmotic pumps.

In order to elucidate the changes in the membrane structure, SEM studies were conducted (both before and after dissolution studies) of optimized batch.

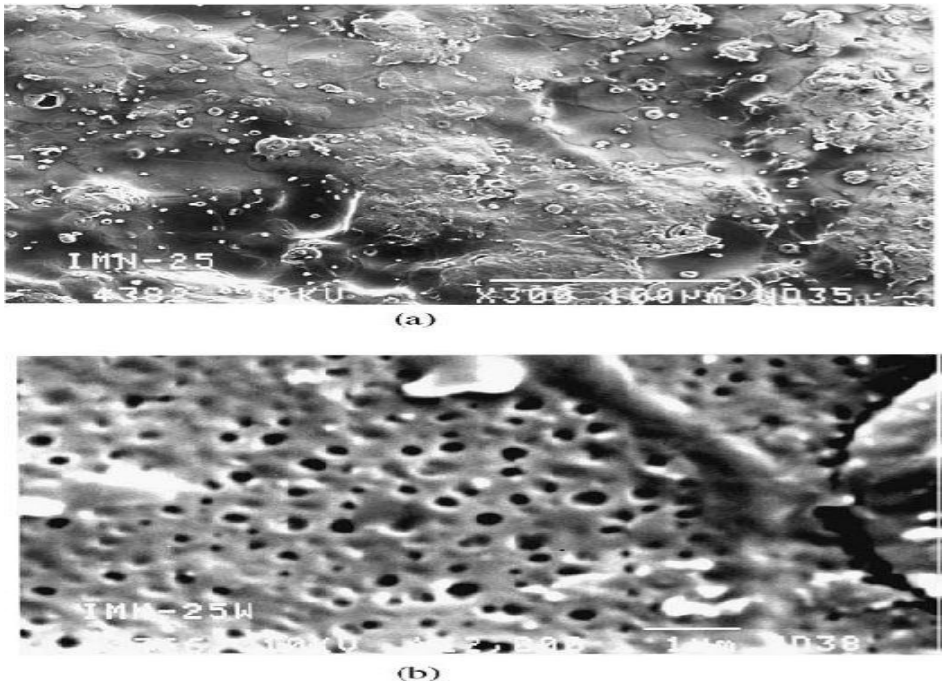

Figure No.01: SEM micrograph of coating membrane of batch F-9, containing PEG 400 (20% w/w) of in coating solution, before (a) and after dissolution (b)

- **FTIR Spectroscopy**

Drug polymer interaction was checked by comparing the IR spectra of the formulations with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectrums of the pure drug and also no additional peaks were seen in the selected optimized formulation. This confirms that no interaction between drug and excipients.

- **DSC Study**

DSC endotherm of Saxagliptine was observed at 99.03^{0}C. This endotherm was shifted to 166.24^{0}C in the DSC spectrum of physical mixture of Saxagliptine optimized formulation. This was due to Colligative property i.e formation of eutectic mixture of Saxagliptine with excipient used (i.e HPMC K 100, Mannitol, Carbapol 934^P, MCC, and Cellulose acetate Pthalate). Absence of any additional endotherm indicated that there was no any chemical interation between drug and excipient.

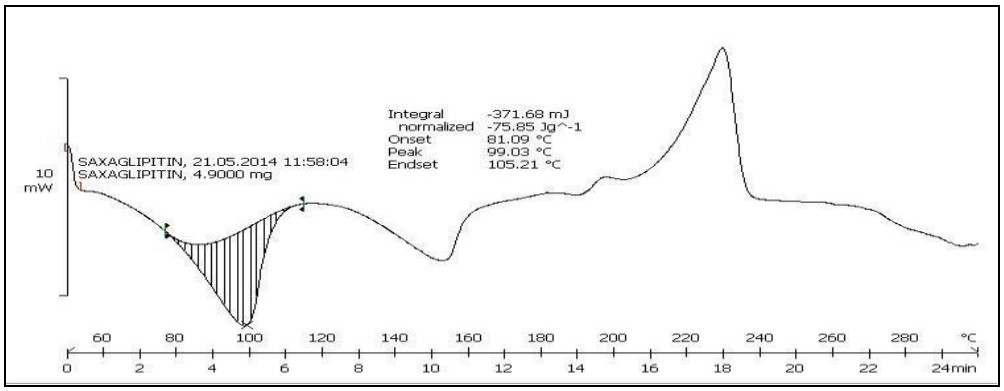

Figure No.02: DSC thermo gram of Saxagliptine pure drug.

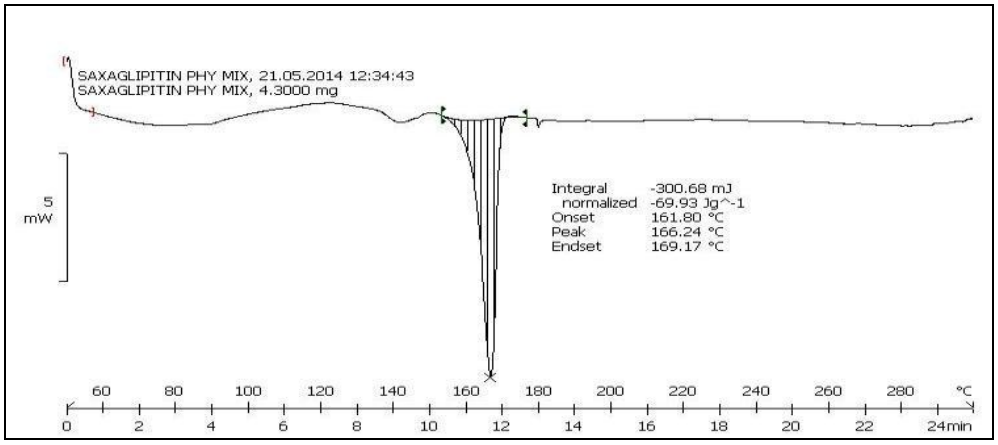

Figure No.03: DSC thermo gram of optimized formulation F9.

- **Stability Study**

Stability studies were carried out on selected formulations (F-9) as per ICH guidelines. Tablets of selected formulations (F-9) were kept for accelerated stability study at 40 + 2 °C and 75 + 5% RH for 1 month in the stability chamber. After a period of one month, the samples were observed for any change in physical parameters. It was observed that surface was devoid of any change in colour or appearance of any kind of spots on it. It was also noted that surface was free of any kind of microbial or fungal growth or bad odour. No changes in the smoothness of the tablets were noted. The formulations were found to be stable in terms of drug content and dissolution stability. By comparison, it was found that after a period of one month of storage there were no changes in the physical as well as drug release profiles of the tablets of optimize batch and was imitating the same drug release pattern.

CONCLUSION

The conclusions of this study indicated that the controlled porosity osmotic pump tablet of Saxagliptine developed and the results suggest that the developed controlled porosity osmotic pump tablets of Saxagliptine could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus the aim of this study was achieved. Further preclinical and clinical studies are required to evaluate the efficacy of these formulations of Saxagliptine in the management of hyperglycemia disorders.

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