The Pharma Innovation Journal 2018; 7(8): 187-191

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(8): 187-191

www.thepharmajournal.com
Received: 17-06-2018
Accepted: 19-07-2018

Komal Pangavhane
Department of Quality Assurance Techniques, R.G. Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India

Ravindranath Saudagar
Department of Pharmaceutical Chemistry, R.G. Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India

Correspondence
Komal Pangavhane
Department of Quality Assurance Techniques, R.G. Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India

Formulation, development and evaluation of controlled porosity osmotic tablet of Vildagliptin

Komal Pangavhane and Ravindranath Saudagar

Abstract
The present work aims towards the development of controlled release formulation of water soluble drug Vildagliptin based on osmotic technology by using controlled porosity approach. Vildagliptin is anti-diabetic drug with short half-life, makes the development of controlled release dosage forms extremely advantageous. A present work comprises a drug Vildagliptin, NaCl, HPMC, Magnesium Stearate, Lactose, PVP K30, Talc, Cellulose acetate, PEG 400. 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 (F8) exhibited zero order kinetics with a drug release of 98.84% in 24hrs. Scanning electron microscope study showed the formulation of pores in membrane. It was concluded that release of Vildagliptin was significantly controlled from controlled porosity osmotic drug delivery system.

Keywords: Osmotic technology, osmogent, optimization, pore former, Vildagliptin

Introduction
The oral drug delivery systems are mostly used techniques in administration of drugs. In case of long term treatment of chronic disease conditions conventional tablets are required to be administered in multiple doses and also provides an immediate release of drug which does not control the release of the drug and does not maintain effective concentration at target site for a longer period of time. Hence to avoid this problem there is development of various controlled drug delivery systems. Among these osmotically controlled oral drug delivery system is the one which utilizes osmotic pressure for controlled delivery of active agent. The release of drug from osmotic drug delivery system follow zero order kinetics [1, 2].

The controlled porosity osmotic tablet concept was developed as an oral drug delivery systems by Zentner et.al. The controlled-porosity osmotic tablet 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 the membrane. The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by a 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 [3].

Diabetes mellitus is a metabolic disorder characterized by hyperglycemic, glycosuria etc. Type I-Insulin dependent diabetes mellitus, Type II-Non-insulin dependent diabetes mellitus, Vildagliptin comes under Type II diabetes mellitus and act as Dipeptidyl peptidase-4 (DDP-4) inhibitor. This enzyme destroys the in cretin harmone GLP-1, which helps the body to produce more insulin when it is needed. GLP-1(Glucose like peptidase-1) and GIP (Glucose dependent insulinotropic peptidase) harmones are release from intestine. They act by reduced blood glucose by increasing the production and release of insulin from the pancreas [4, 5].

Thus, there is a strong clinical need and market potential for a dosage form that will deliver Vildagliptin in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance.

Materials and Method

Materials

Vildagliptin was obtained as a gift sample from Alembic pharmaceutical, Vadodara, HPMC K100M was gift sample of Colorcon Asia Pvt Ltd Goa. Sodium chloride, PVP K30, lactose, magnesium stearate, PEG 400, cellulose acetate, acetone, alcohol were purchased from Research-lab Fine Chem. Industry-Mumbai.

Method

Formulation of Vildagliptin core tablet

A core tablet of Vildagliptin was prepared by wet granulation method. The composition of core tablets is given in table no 1. Vildagliptin was mixed with Sodium chloride, Lactose, and HPMC 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 °C for 2 hrs. Dried granules were lubricated with magnesium stearate and talc. Lubricated blend was evaluated for powder characteristics and flow properties like bulk density, tapped density, Carr index, Angle of repose, and Hausner's ratio. Then desired amount of blend was compressed in to the tablet using Rimek tablet punch machine equipped with 8 mm punch, Weight of the tablet was kept to 250mg.

Table 1: Composition of Controlled porosity osmotic pump tablet as per 3^2 Full Factorial Design (All values are expressed in mg)

Ingredients	Formulation code								
Quantity(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Vildagliptin	50	50	50	50	50	50	50	50	50
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
Lactose	125	110	95	120	105	90	115	100	85
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Total Weight (mg)	250	250	250	250	250	250	250	250	250

Coating of Vildagliptin Osmotic Core Tablets

The core tablets of Vildagliptin were coated with 5% w/v Solution of cellulose acetate in acetone: alcohol (1:1). Cellulose acetate was used as a semipermiable membrane provider. PEG 400 15% v/v was used as plasticizer. The tablets were warmed to 40±2°c before applying coating solution. The composition of coating solution used for coating of core tablets are given in table 2. Dip coating technique was used for the coating of osmotic tablet [6].

Table 2: Coating composition

Ingredients	Quantity for 100 ml
Cellulose Acetate	5 %
Polyethylene glycol 400	1 %
Acetone: Alcohol (1:1)	50:50 ml

Evaluation Parameters

Evaluation of Granules

Bulk Density

Bulk density was determined by measuring the volume known mass of granules sample that has been passed through a screen into a graduated cylinder [7, 8].

$$\text{Bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of powder}}$$

Tapped Density

Tapped density was achieved by mechanically tapping, a measuring cylinder containing granules sample and was allowed to drop under its own weight using suitable mechanical tapped density tester that provided, a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute [7,8].

$$\text{Tapped density} = \frac{\text{Total weight of powder}}{\text{Total volume of tapped powder}}$$

Angle of repose (θ)

Angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles. The angle of repose (θ) for powder was determined by placing the powder in a funnel [7, 8].

$$\tan\theta = \frac{h}{r}$$

Where, θ = Angle of repose, h = height of the powder pile and r = radius of base of cone.

Compressibility Index (CI) and Hausner's Ratio (HR)

The CI & HR are measure of propensity of a powder to be compressed. As such they are measures of relative importance of inter-particulate interactions [7, 8].

$$\text{Compressibility Index} = \frac{\text{Tappeddensity} - \text{Bulkdensity}}{\text{Tappeddensity}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{Bulk density}}{\text{Tapped density}}$$

Evaluation of Precoated Tablet

Thickness

The uniformity of thickness was measured using varnier caliper. The average thickness of tablet was calculated [7, 9, 10].

Hardness

The hardness of the tablets was measured using Monsanto hardness tester. Tablet was placed between the plungers, and was tightened from one end, and pressure required to break tablet diametrically was measured. The hardness was measured in terms of kg/cm^2 [7, 9, 10].

Uniformity of Content

Twenty tablets were weighed individually and powdered in pestle mortar, 50 mg of Vildagliptin was in 100 ml of

phosphate buffer pH 6.8. The solution was filtered and the content of Vildagliptin in the solution was determined by measuring absorbance on double beam UV spectrophotometer (Shimadzu 1800 Series) at 207nm after suitable dilution [7,9,10].

Weight uniformity

Twenty 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 using the following formula [11].

% Deviation= (Individual weight - Average Weight /Average weight) x 100

Friability

In this test 20 tablets were weighed and placed in a Roche Friabilator test apparatus, and then the tablets were subjected to rolling ad replaced shocks, resulting from free falls within the apparatus from the height of 6 inches. 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 [7, 9, 10].

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

Evaluation of Coated Tablet

Thickness of tablet

All tablets were initially subjected for thickness measurement by using digital vernier caliper after coating to assess thickness of coat. All the measurements were made in triplicate [7, 11].

Thickness of film

Thickness of film was calculated by considering difference between coated tablet and uncoated tablet [7, 11].

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

Weight Uniformity

Weight variation was calculated as per method described in Indian pharmacopoeia. 20 tablets were weighed individually and the average weight was calculated [7, 11].

Scanning electron microscopy (SEM)

The aqueous pores of coating were determined using scanning electron microscopy (SEM). Tablet before and after dissolution was taken and scanned.

Dissolution test

s 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°C. The dissolution medium (900ml) was 0.1N HCL for the first 2hrs 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 [12,13].

Dissolution Kinetics

In order to investigate the mode of release from the tablets the release data were analyzed with the zero order, first order, higuchi model, korsmeyer-peppas model [14].

Stability study

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 Vildagliptin formulation was assessed at 40±2 ^{0}c/ 75±5% RH as per ICH Guidelines. Tablets were packed in aluminium foil and stored for 3 months. Samples were analyzed after 3 months for physical appearance, drug content, and *in vitro* dissolution profile [15].

Result and Discussion

Evaluation of Granules for Tablets

The angle of repose of all the formulations were within the range of 26˚- 29˚, indicative of excellent flow ability. The bulk density of granules was found to between 0.24-0.29gm/cm^3. The values indicates good packing capacity of granules. The tap density of granules were found in the range of 0.26-0.31gm/cm^3. The bulk density and tap density was used to calculate the percent compressibility of the granules. The carr's index of granules was observed in range of 6% to 10%, indicating excellent compressibility of the granules. The values of Hausner's ratio were found to be in the range of 1.05 to 1.11, indicating excellent flowability. Data summerized in table 3.

Table 3: Evaluation of Granules 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	27.84±0.64	0.2651±0.004	0.2912±0.005	7.681±1.27	1.07±0.014
F2	27.63±1.05	0.2603±0.004	0.2885±0.005	10.64±0.53	1.11±0.007
F3	27.81±0.25	0.2526±0.003	0.2721±0.004	9.164±0.49	1.09±0.007
F4	26.39±1.15	0.2793±0.004	0.3094±0.005	6.521±0.12	1.06±0.023
F5	29.84±1.41	0.2821±0.004	0.2943±0.009	6.899±0.28	1.07±0.023
F6	29.98±0.65	0.2473±0.004	0.2672±0.004	7.466±0.11	1.07±0.012
F7	28.34±0.83	0.3007±0.005	0.3184±0.005	6.312±0.07	1.05±0.014
F8	29.25±0.15	0.2914±0.005	0.3091±0.005	6.521±0.12	1.07±0.017
F9	29.78±0.75	0.2541±0.003	0.2679±0.005	7.493±0.16	1.05±0.018

Evaluation of Tablets

Pre-coating evaluation

All formulated uncoated osmotic tablet batches were evaluated for Weight variation, Hardness, Thickness, friability and Drug content and found within the range. Evaluated data is shown in table 4.

Table 4: Pre-coating 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	249.05±0.94	0.32	3.51±0.14	3.47±0.038	0.227±0.022	96.83±0.057
F2	248.81±1.14	0.36	3.90±0.14	3.33±0.025	0.134±0.022	96.82±0.076
F3	248.94±1.11	0.40	3.91±0.14	3.48±0.025	0.120±0.04	97.83±0.057
F4	248.45±1.42	0.50	3.74±0.26	3.35±0.041	0.340±0.046	98.49±0.054
F5	249.50±1.60	0.52	3.91±0.15	3.39±0.034	0.067±0.023	98.16±0.050
F6	248.76±1.31	0.44	3.74±0.21	3.43±0.03	0.243±0.04	96.66±0.050
F7	249.16±1.20	0.33	3.92±0.14	3.32±0.01	0.120±0.04	97.99±0.029
F8	249.10±1.12	0.32	3.90±0.07	3.33±0.015	0.216±0.047	99.32±0.041
F9	249.23±1.43	0.45	3.81±0.15	3.38±0.033	0.233±0.063	97.33±0.076

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. Evaluated data is shown in table 5.

Table 5: 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	259.95±1.18	0.594	4.10±0.015	0.313±0.014
F2	261.60±0.99	0.323	4.13±0.025	0.400±0.010
F3	258.45±1.10	0.361	4.09±0.022	0.306±0.021
F4	258.60±1.05	0.338	4.11±0.026	0.380±0.008
F5	259.05±1.10	0.320	4.12±0.026	0.365±0.025
F6	260.10±0.97	0.410	4.14±0.020	0.355±0.013
F7	261.80±0.98	0.306	4.12±0.015	0.401±0.005
F8	259.63±1.04	0.449	4.12±0.020	0.393±0.007
F9	258.31±1.12	0.380	4.14±0.015	0.378±0.010

SEM of Coating (before and after dissolution)

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 shown in Fig 1.

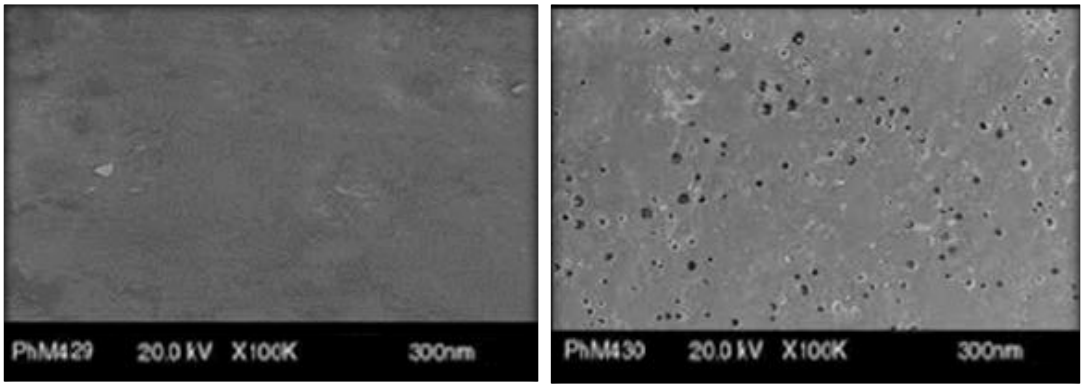

Fig 1: Scanning Electron Microscopy (SEM) of coating layer a) before dissolution b) After dissolution

Dissolution Test

The dissolution test showed 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 Vildagliptin for the duration of about 24 hrs. On the basis of *In–vitro* drug release profile the optimum formulation F8 was selected as it releases 98.84% drug within 24 hrs.

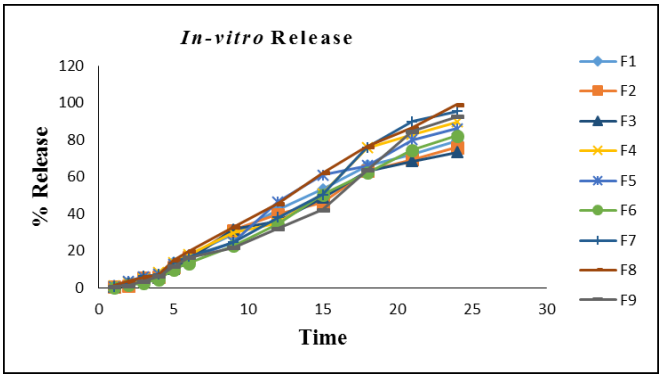

Fig 2: Dissolution Profile of Formulation Batches (F1-F9)

Dissolution Kinetics

Release kinetics studies

Different kinetic treatments (zero order, first order, Higuchi's square root equation and Korsmeyer treatment) were applied to interpret the release of Vildagliptin from different matrices. All batches follow zero order release kinetics, for F8 formulation drug release was found to be 98.84% upto 24 hrs. Other batches also follows 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=0.996. So, the drug release is of fickian release.

Table 6: Kinetic treatment of prepared Vildagliptin osmotic tablet formulations

Formulation code	Coefficient of determination (R^2)			
	Zero order	First order	Higuchi square root	Korsmeyer plot
F1	0.994	0.976	0.967	0.784
F2	0.990	0.968	0.965	0.797
F3	0.981	0.910	0.967	0.843
F4	0.990	0.898	0.942	0.895
F5	0.977	0.958	0.942	0.826
F6	0.984	0.893	0.959	0.766
F7	0.982	0.851	0.924	0.858
F8	0.996	0.774	0.960	0.840
F9	0.971	0.831	0.905	0.799

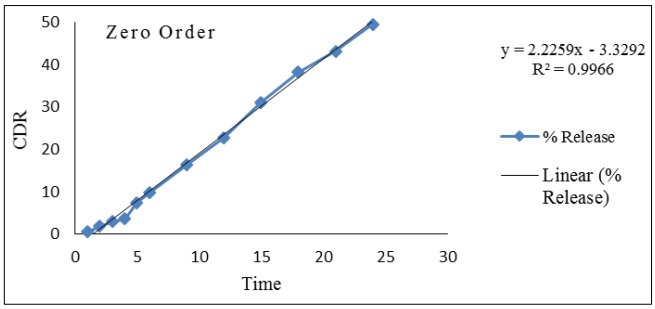

Fig 3: Model Graph for Evaluation of Zero Order Release Kinetics

Stability Study

Table 7: Characteristics of optimized formulation F8 after 3 months storage

Parameter	Initial sample of optimized formulation	After storage at 40±2 ºC / 75±5% RH, for 3 months
	F8	F8
Color	White	White
Drug content	99.32%	99.21%
% Drug Released (After 24 hrs.)	98.84%	98.45%

Conclusion

The present work of controlled release formulation of Vildagliptin 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. The experimental results proved that the granules of Vildagliptin showed excellent flow properties, tablet evaluation tests before and after coating are within the acceptable limits. In-vitro dissolution of osmotic tablet was performed for 24hr and for optimized formulation drug release was found 98.84%. 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˚±2˚, 75% ±5% RH for 3 months. Finally, It is concluded that release of Vildagliptin is significantly controlled from the controlled porosity osmotic delivery system.

References

1. Edavalath S, Rao BP. A Review on Controlled Porosity Osmotic Pump Tablets, International Journal for Pharmaceutical Research Scholars. 2013; 2(4):565-574.
2. Shah N, Patel K. Design and Development of Controlled Porosity Osmotic Tablets of Captopril, Journal of Pharmaceutical Science and Bio scientific Research. 2013; 3(4):145-150.
3. Babu A, Rao MP. Controlled porosity Osmotic Pump Tablets- An Overview. Journal of pharmaceutical research and health care. 2010; 2(1):114-126.
4. Tripathi KD. Essential of Medical Pharmacology, Edn 6th, Jaypee brothers medical pulisher, 2006, 254-274.
5. Handan He, Phi Tran, Hequn Yin. Absorption, Metabolism, and Excretion of [14C] Vildagliptin, a Novel Dipeptidyl Peptidase 4 Inhibitor, in Humans. The American Society for Pharmacology and Experimental Therapeutics. 2009; 37:536-544.
6. Patel H, Patel MM. Formulation and Evaluation of Controlled Porosity Osmotic Drug Delivery System of Metoprolol Succinate. International Journal Pharmaceutical Sciences and Research. 2012; 3(6):1761-1767.
7. Mahalpure N, Gondkar SB, Saudagar RB. Development of control porosity osmotic pump tablet of linagliptin, World journal of pharmacy and Pharmaceutical science. 2017; 6(6):765-775.
8. Shingala K, Singh C, Dumaniya D, Patel B. Formulation Development and Evaluation of Immediate Release Tablet of Poorly Soluble Candesartan Cilexetil. Journal of Pharmaceutical Science and Bio scientific Research. 2013; 3:77-90.
9. Thakkar HP, Pancholi N, Patel V. Development and Evaluation of a Once Daily Controlled Porosity Osmotic Tablet of Tapentadol Hydrochloride, American association of Pharmaceutical Sciences. 2016; 17(5):1248-1260.
10. Chinmaya KS, Nalini KS, Surepali RM. A Review on Controlled Porosity Osmotic Pump Tablets and Evaluation, Bulletin of faculty of pharmacy, Cairo University. 2015; 53:195-205.
11. Andhale S, Gondkar SB. Development of Osmotically controlled Release tablet of Quetiapine Fumarate. Invent rapid Pharm Tech. 2014; 3:1-12.
12. Leon Lachman, Herbert Libermann. The Theory and Practice of Industrial Pharmacy, CBS Publisher, Indian edition, 2009, 293-308.
13. Controlled release formulation, Patent EP 2046299 A1
14. Dash S, Murthy PN, Nath L. Kinetic Modeling on Drug Release from Controlled Drug Delivery Systems, Acta Poloniae Pharmaceutica-Drug Research. 2010; 67(3):217-223.
15. Carstensen JT, Rhodes CT. drug Stability Principles and Practices, Edn 3rd, Revised and expanded. 107:446-450