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TAILORED OSMOTIC DELIVERY OF NIFEDIPINE: A FORMULATION AND EVALUATION APPROACH

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Abstract

Nifedipine is used as an antianginal (especially in Prinzmetal's angina) and antihypertensive. The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilatation and consequently a reduction in peripheral vascular resistance. The primary objective of controlled drug delivery system is to ensure safety and to improve the patient compliance as well as efficacy of the drugs and this can be achieved by less frequent dosing and better control of drug plasma level.

***Keywords*:** Nifedipine, antianginal, antihypertensive, drug delivery system.

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Introduction

Nifedipine is used as an antianginal (especially in Prinzmetal's angina) and antihypertensive, although a large number of other indications have recently been found for this agent, such as Reynaud's phenomenon, premature labor, and painful spasms of the esophagus in cancer and tetanus patients. It is also commonly used for the small subset of pulmonary hypertension patients whose symptoms respond to calcium channel blockers

The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilatation and consequently a reduction in peripheral vascular resistance. The increased peripheral vascular resistance, an underlying cause of hypertension, results from an increase in active tension in the vascular smooth muscle. Studies have demonstrated that the increase in active tension reflects an increase in cytosolic free calcium.

The binding of nifedipine to voltage-dependent and possibly receptor-operated channels in vascular smooth muscle results in an inhibition of calcium influx through these channels. Stores of intracellular calcium in vascular smooth muscle are limited and thus dependent upon the influx of extracellular calcium for contraction to occur reduction in calcium influx by the nifedipine causes arterial vasodilation and decreased peripheral vascular resistance which results in reduced arterial blood pressure.

The dose of nifedipine extended release is 10-40 mg twice daily or 20-90 mg once daily. In angina pectoris-extended release dose is 10-40 mg twice daily or 30-90 mg once daily.

Advantages

There is various numbers of advantages which have been listed below[14, 15]

- Decrease frequency of dosing.
- Reduce the rate of rise of drug concentration in the body.
- Delivery may be pulsed or desired if required.
- Delivery ratio is independent of pH of the environment.

The primary objective of controlled drug delivery system is to ensure safety and to improve the patient compliance as well as efficacy of the drugs and this can be achieved by less frequent dosing and better control of drug plasma level.

The aim of the present work is to formulate and evaluate the extended release tablets of nifedipine. A dose of 20mg is selected for the extended release osmotic drug delivery. In a bilayer osmotic drug delivery systems a drug layer and a push layer exists, which are prepared separately by

using granulation technique. Both are compressed together to form bilayer tablet. Coating of these tablets is done which controls the release. *In-vitro* drug release studies are performed to confirm the extended zero order release.

This invention relates to an osmotic dispenser and more especially to an osmotically dispenser capable of releasing drug or active ingredient to its outside environment, at an osmotically controlled rate over a prolonged period of time. ALZA Corporation pioneered the development of osmotic drug delivery systems. They deliver the drug at a zero-order profile. The specific objective of the present work includes:

- To carry out preformulation studies.
- To develop analytical method.

To formulate drug layer and push layer by using Glatt powder coater granulator (GPCG) and compress to form bilayer tablet.

Methodology

Physico Chemical Properties Of Drug:

Table: 01 FORMULATION OF DRUG LAYER BY USING GPCG

S.No	Ingredients	mg/tablet
1	Nifedipine	22
2	Poly ethylene oxide WSR N 80	82.2
3	Hydroxy propyl cellulose	6.66
4	Purified water	6
5	Isopropyl alcohol	54
6	Magnesium stearate	0.466

Procedure

1. Nifedipine and poly ethylene oxide WSR N80 were co sifted through sieve#16 and mixed properly.
2. Preparation of binder solution: Hydroxyl propyl cellulose was dissolved into mixture of purified water and iso propyl alcohol under stirring to get a clear solution
3. Material of step 1 was loaded into glatt powder coater granulator fitted with top spray bowl, 1mm nozzle gun and granulation was performed.

Mechanism of granulation by wurster process

Granulation in the fluid bed is a modern method of creating granulates from powder using liquid bridges. The sprayed liquid can be either water or an organic solvent, a powder dissolved in solution or another binder. The moist granulates are dried and, if necessary, cooled.

Table: 02 formulation of Push Layer by Using GPC

S.No	Ingredients	mg/tablet
1	Hydroxy propyl cellulose	3.2
2	Purified water	2.66
3	Isopropyl alcohol	24
4	Poly ethylene oxide WSR coagulant	36.33
5	Sodium chloride	15.33
6	Iron oxide	0.266
7	Magnesium stearate	0.023

Hydroxy propyl cellulose was dissolved into mixture of purified water and isopropyl alcohol under stirring to get a clear solution.Poly ethylene oxide coagulant was sifted through sieve#20. Granules obtained from the above step were sifted through sieve#20 and required quantity of magnesium stearate (sifted through sieve#60) was added and mixed properly.

Compression: The drug layer and push layer was compressed into bilayer tablets using 7.3mm round punch plain on both sides using compression machine. The target weight of bilayer tablet is 166.66mg

Coating

Table: 03 Formula for coating of different formulations

S.No	Ingredients	F1 (100:0)	F2 (97.5:2.5)	F3 (95.25:4.75)	F4 (90:10)
1	Cellulose acetate	50	48.75	47.626	45
2	Poly ethylene glycol 4000	0	1.25	2.374	5
3	Acetone	912	912	912	912
4	Water	38	38	38	38

From each formulation different % weight gains were collected at different intervals

SEM Analysis

Scanning Electron Microscopy (SEM) is an important tool for measurement of pore diameter in osmotic systems and membrane thickness in coating. SEM analysis can provide high magnification, high resolution images of samples at magnifications up to 50,000xs. The pore diameter and coating thickness of the formulation was examined by scanning electron microscope..Scans were taken at an excitation voltage of 20 KV in a JSM-840A scanning electron microscope fitted with JFC-1100E ion sputtering device (Jeol, Japan).

Results and Discussion

Solubility of Nifedipine

Table: 04 Solubility of Nifedipine

Medium	Solubility (mg/ml)
0.1N HCL	0.005
Ph 6.8 Phosphate buffer	0.00428
pH 6.8 with 0.5% tween80	0.0709
pH 6.8 with 2% tween80	0.2337
pH 6.8 with 3% tween 80	0.3771
pH 7.5 Phosphate buffer	0.00309
pH4.5 Acetate buffer	0.00608
Water	0.00584

Absorbance spectra by UV:

Spectra in pH 6.8 phosphate buffer with 3% tween 80

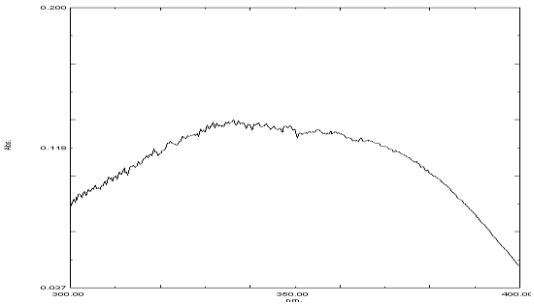

Fig: 01 Absorbance spectra by UV

Calibration Curve:

Table: 05 Calibration Curve

Concentration (ppm)	Absorbance
0	0
5	0.067
10	0.147
15	0.215
20	0.294
25	0.333
30	0.402

Drug Excipient Compatibility

Table: 06 After 4 Weeks of study physical appearance of these compositions were made and compared with the initial observation.

S.No:	Combinations	Ratio	Initial	Room temperature	1month 40°C/75%RH (open)	1month 40°C/75%RH (closed)
1	Drug		Yellow fine powder	yellow fine powder	yellow fine powder	yellow fine powder
2	Drug + Poly ethylene oxide WSR coagulant	1:1.5	yellow powder	yellow powder	yellow powder	yellow powder
3	Drug + sodium chloride	1:1	yellow powder	yellow powder	yellow powder	yellow powder
4	Drug +iron oxide	10:1	yellow brown powder	yellow brown powder	yellow brown powder	yellow brown powder
5	Drug +hydroxy propyl cellulose	3:1	yellow powder with loose cake	yellow powder with loose cake	yellow powder with loose cake	yellow powder with loose cake
6	Drug +Poly ethylene oxide WSR N 80	1:4	yellow powder with loose cake	yellow powder with loose cake	yellow powder with loose cake	yellow powder with loose cake
7	Drug +cellulose acetate	1:1	yellow powder	yellow powder	yellow powder	yellow powder
8	Drug +Poly ethylene glycol 4000	10:1	yellow powder	yellow powder	yellow powder	yellow powder

Differential scanning calorimetry

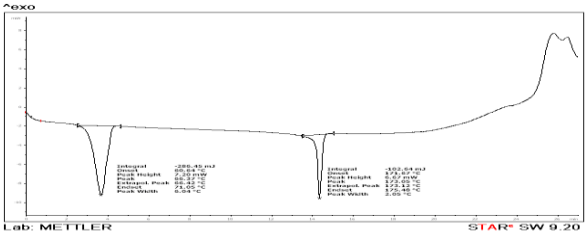

Fig: 02 Differential scanning calorimetry Differential scanning calorimetry (DSC) thermograms for physical mixture of Drug

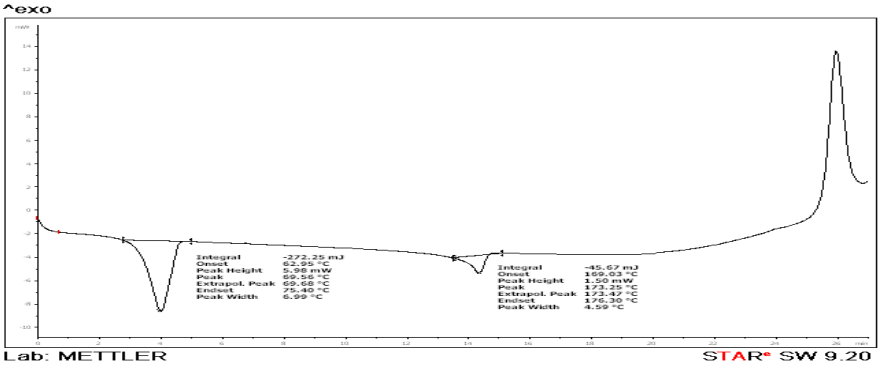

Fig: 03 Differential scanning calorimetry (DSC) thermograms for physical mixture of Drug and excipients

Report of DSC

Table: 07 Report of DSC

Sample	Peak onset	Peak	Peak end set
Drug	171.48ºC	172.28ºC	174.50ºC
Drug + Poly ethylene oxide WSR coagulant	169.03ºC	173.25ºC	173.47ºC
Drug + sodium chloride	172.43ºC	173.83ºC	176.09ºC
Drug +iron oxide	171.69ºC	173.0ºC	175.64ºC
Drug +hydroxy propyl cellulose	171.83ºC	173.14ºC	175.93ºC
Drug +Poly ethylene oxide WSR N 80	171.67ºC	173.05ºC	175.48ºC
Drug +cellulose acetate	171.21ºC	172.97ºC	177.24ºC
Drug +Poly ethylene glycol 4000	167.36ºC	171.07ºC	172.79ºC

Characterization of Drug and Push Layer Blends

Drug layer

Table: 08 Characterization of drug layer blend

Parameter	Observation
Bulk density	0.42g/ml
Tapped density	0.5g/ml
Compressibility index	16.67%
Hausner's ratio	1.2
Loss on drying	0.63%w/w

Table: 09 Particle size distribution of drug layer blend

Sieve Mesh Number	Sieve Size Opening(µm)	Mass of Sample Retained On Each Sieve(g)	Percentage of Sample Retained on Each Sieve (%)	Cumulative Percentage Of Sample Retained on Each Sieve (%)	Cumulative Percentage of Sample Passing through Each Sieve (%)
20	841	0.01	0.01	0.1	99.9
30	600	0.532	5.32	5.42	94.58
40	425	1.831	18.31	23.73	76.27
60	250	2.656	26.56	50.29	49.71
80	180	1.357	13.57	63.86	36.14
100	150	0.437	4.37	68.23	31.77
120	125	0.461	4.61	72.84	27.16
Pan	-	2.716	27.16	100	0

Comment: Most of the drug layer blend has particles in the range of 250-425µm.

Push layer

Table: 10 Characterization of push Layer blend

Parameter	Observation
Bulk density	0.48g/ml
Tapped density	0.63g/ml
Compressibility index	23.81%
Hausner's ratio	1.31
Loss on drying	0.61%w/w

Table: 11 Particle size distribution

Sieve Mesh Number	Sieve Size Opening(µm)	Mass of Sample Retained On Each Sieve (g)	Percentage of Sample Retained on Each Sieve (%)	Cumulative Percentage Of Sample Retained on Each Sieve (%)	Cumulative Percentage of Sample Passing through Each Sieve (%)
20	841	0.01	0.1	0.1	99.9
30	600	0.54	5.4	5.5	94.5
40	425	2.379	23.79	29.29	70.71
60	250	2.995	29.95	59.24	40.76
80	180	1.029	10.29	69.53	30.47
100	150	0.332	3.32	72.85	27.15
120	125	0.452	4.52	77.37	22.63
Pan	-	2.263	22.63	100	0

Comment: Most of the push layer blend has particles in the range of 250-425µ

Table: 12 Compression parameters

Parameter	Observation
weight of Tablet(mg)	166.6-168.5
Thickness (mm)	4.3-4.7
Hardness (kp)	7.5-8.2
Friability (%)	0.105
% Drug content	99.28

Scanning Electron Microscopy Analysis

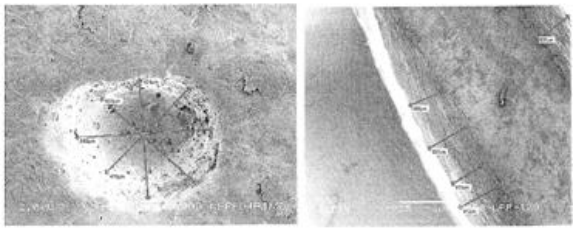

Fig: 04 SEM analysis of tablet

The scanning electron microscopy picture indicates that the orifice diameter is 500µm and the thickness of the coating membrane is 600 µm.

Invitro Drug Release

Effect of functional coating weight build up

Table: 12 F1 (100:0 ratio of cellulose acetate and poly ethylene glycol) % drug release

TIME	12% wt. gain	14% wt. gain	16% wt. gain	18% wt. gain	20% wt. gain	22% wt. gain
0	0	0	0	0	0	0
1	2	2	1	0	0	0
2	3	2	2	1	1	1
5	31	24	19	17	15	13
8	51	47	36	32	30	29
12	79	73	63	53	42	41
18	92	90	86	76	66	61

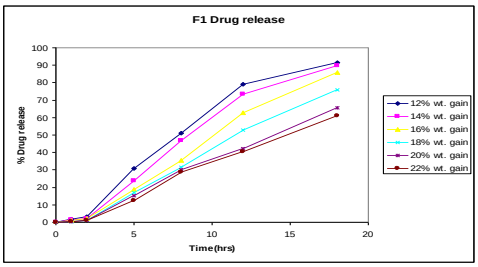

Fig: 05 Percent drug release of F1 graph

Table: 13 F2 (97.5:2.5 ratio of cellulose acetate and poly ethylene glycol) % drug release

TIME	12% wt. gain	14% wt. gain	16% wt. gain	18% wt. gain	20% wt. gain	22% wt. gain
0	0	0	0	0	0	0
1	4	3	2	0	0	0
2	6	5	4	1	1	1
5	34	27	20	18	17	13
8	66	55	38	33	31	30
12	95	75	63	58	50	43
18	100	94	92	75	67	64

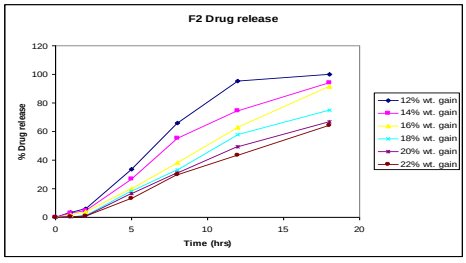

Fig: 06 Percent drug release of F2 graph

Table: 14 F3 (97.25:4.75) ratio of cellulose acetate and poly ethylene glycol) % release

TIME	12% wt. gain	14% wt. gain	16% wt. gain	18% wt. gain	20% wt. gain	22% wt. gain
0	0	0	0	0	0	0
1	4	4	2	0	0	0
2	7	5	4	1	1	1
5	34	33	22	20	17	16
8	71	62	47	36	33	33
12	100	96	63	59	52	47
18	100	100	92	81	73	68

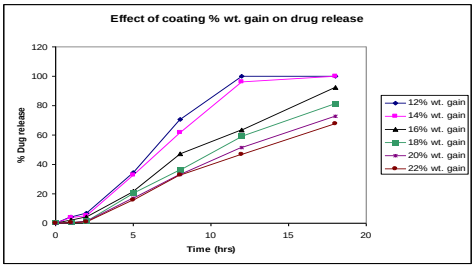

Fig: 07 Percent drug release of F3 graph

Table: 15 F4 (90:10 ratio of cellulose acetate and poly ethylene glycol) % drug release

TIME	14% wt. gain	16% wt. gain	18% wt. gain
0	0	0	0
1	43	34	23
2	63	49	40
5	79	70	63
8	88	80	74
12	100	98	93
18	100	100	100

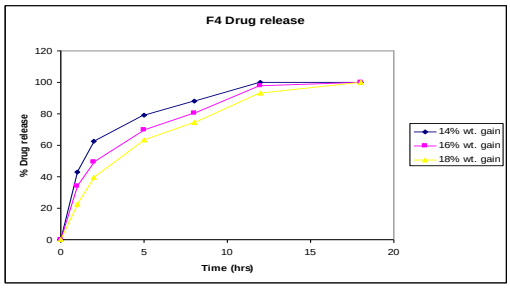

Fig: 08 Percent drug release of F4 graph

Table: 16 Comparison of dissolution profiles with innovator product

Time Interval	Innovator	F3 18% wt.gain
0	0	0
1	4	0
2	6	1
5	16	20
8	32	36
12	57	59
18	87	81

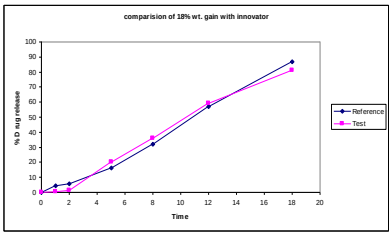

Fig: 09 f_2= 69.7 Comparison of dissolution profiles graph

Comment: From the above data it is clear that the similarity factor f2 is 69.7 which is greater than 50 infers that the formulation has same release profile as that with innovator.

Table: 17 Rate kinetics

	R^2 values of Innovator	R^2 values of F3 18% wt. gain
zero order	0.9903	0.9913
first order	0.9345	0.9231

Comment: The drug release of formulation was compared with the innovator. Nature of release of the drug from the designed coated tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. Optimized formulation showed zero order drug release kinetics with R^2value of 0.9848.

Effect of Dissolution Media on release profile of model drug

The osmotic tablets of optimized formulation were evaluated for effect of different pH media on the drug release from the osmotic extended release formulations. The dissolution media was pH 0.1HCL, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer and 4.5 acetate buffer with 3% tween 80.

Table: 18 Rate kinetics Percent drug release at different pH

TIME	1.2pH	4.5pH	6.8pH	7.5pH
0	0	0	0	0
1	0	0	0	0
2	0	1	1	0
5	17	15	20	14
8	31	30	36	29
12	53	50	59	49
18	76	75	81	73

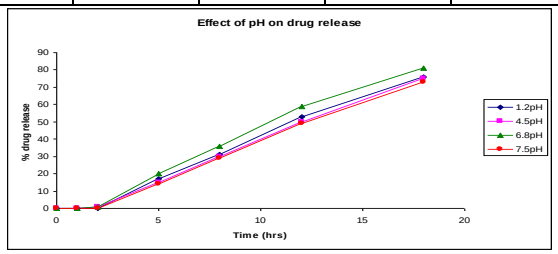

Fig: 10 Effect of Dissolution Media on drug release graph

Inference: pH of the dissolution media does not have much effect on drug release profile. Thus the fluid in different parts of the gastro intestinal tract will less affect drug release from the osmotic system.

Effect of agitation speed

Table: 19 Percent drug release at different speeds

TIME	50 rpm	100 rpm
0	0	0
1	0	1
2	1	2
5	20	22
8	36	39
12	59	62
18	81	85

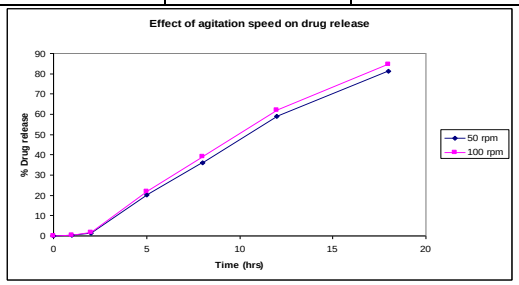

Fig: 11 Effect of agitation speed graph

Table: 20 Effect of pore forming agent

TIME	4.75% PEG	10% PEG
0	0	0
1	0	23
2	1	40
5	20	63
8	36	74
12	59	93
18	81	100

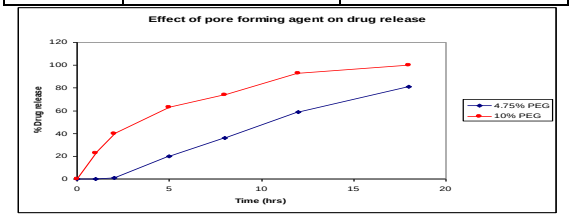

Fig: 12 Effect of pore forming agent graph

Comment: From the above dissolution profile it is clearly evident that the concentration of poly ethylene glycol had a direct effect on drug release. As poly ethylene glycol was a hydrophilic plasticizer, it could be leached easily and left behind porous structure, which enhanced the membrane permeability and drug release rate.

Effect of orifice size

The osmotic tablets of optimized formulation were evaluated for the effect orifice size on drug release.

Table: 21 Percent drug release of different orifice sizes

Time	0.5mm	1mm
0	0	0
1	0	2
2	1	4
5	20	25
8	36	42
12	59	65
18	81	84

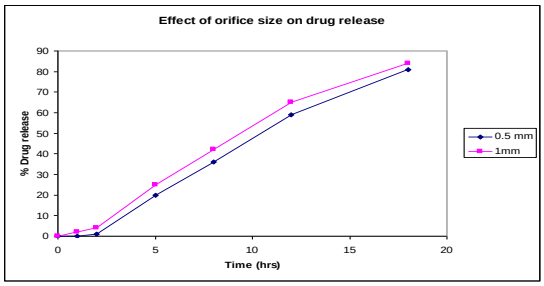

Fig: 13 Effect of orifice size graph

it is known that as the orifice size increases there is no significant difference in drug release profile indicating that the drug release depends on osmotic pressure.

Effect of number of orifices

The osmotic tablets of optimized formulation were evaluated for the effect of number of orifices on drug release.

Table: 22 Perfect drug release of different orifice no's

TIME	2 orifice	3 orifice
1	1	2
2	8	9
5	34	39
8	50	53
12	75	80
18	97	98

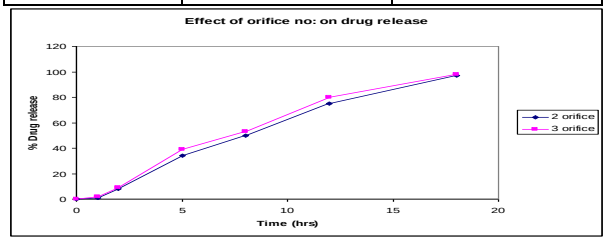

Fig: 14 Effect of number of orifices graph

Comment: From the above data it is known that as the number of orifices increases there is no significant difference in drug release profile indicating that the drug release depends on osmotic pressure generated in the system.

Conclusion

The aim of the present work is to formulate and evaluate the extended release tablets of nifedipine. A dose of 20mg is selected for the extended release osmotic drug delivery. *In-vitro* drug release studies are performed to confirm the extended zero order release. In the present dissertation nifedipine was formulated into a push pull osmotic system using poly ethylene oxide, hydroxyl propyl cellulose, sodium chloride and iron oxide into a bilayer tablet. Cellulose acetate and poly ethylene glycol are used as semipermiable membrane coating of the core bilayer tablet. The work resulted in the development of a novel osmotically controlled drug delivery system of nifedipine. The best formulation developed (F3 with 18% weight gain) has the following composition:

Formula of drug layer

Table: 23 Formula of drug layer

S.No	Ingredients	mg/tablet
1	Model Drug	22
2	Poly ethylene oxide WSR N 80	82.2
3	Hydroxy propyl cellulose	6.66
4	Purified water	6
5	Isopropyl alcohol	54
6	Magnesium stearate	0.466

Table: 24 Formula for push layer

S.No	Ingredients	mg/tablet
1	Hydroxy propyl cellulose	3.2
2	Purified water	2.66
3	Isopropyl alcohol	24
4	Poly ethylene oxide WSR coagulant	36.33
5	Sodium chloride	15.33
6	Iron oxide	0.266
7	Magnesium stearate	0.023

Table: 25 Formula for coating layer

S.No	Ingredients	Mg/tablet
1	Cellulose acetate	47.626
2	Poly ethylene glycol 4000	2.374
3	Acetone	912
4	Water	38

This formulation (F3 with 18% weight gain) provided slow and controlled release of nifedipine over 24hrs and comparable to innovator product.

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Conflicts of Interests
There are no conflicts of interest.

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Nil

Authors Contributions
All the authors have contributed equally.

Ethical Considerations
Not Applicable

References
1. Rajan k. verma et al., Osmotic Pumps in Drug Delivery of critical reviews in therapeutic drug delivery systems Year 2004, Volume 21 / Issue 6.
2. 2. Longer M.A., Robinson J.R. "Sustained release drug delivery system" chapter 91 in "Remington's pharmaceutical sciences" 18th edition, Mack Publishing Company 1990: 1675-1684pp.
3. Lordi N.G. "Sustained release dosage form" chapter 14 in "Theory and practice of Industrial Pharmacy" edited by Lachman et al., 3rd edition, Varghese Publishing House, 1991: 430-431pp.
4. Welling P.G., Dobrinska M.R. "Dosing considerations and bioavailability assessment of controlled drug delivery systems" chapter 6 in "Controlled drug delivery; fundamentals and applications" edited by Robinson J.R., Vincent Lee, 2nd edition, Marcel Dekker Inc., Volume 29, 1978: 254-289pp.
5. Kumar S., Sharma, "Controlled Release Dosage Forms" The Eastern Pharmacist, 2001: Sept.: 17-21pp.
6. Hui ho-wah, "Design and fabrication of oral controlled release drug delivery systems" chapter 9 in "Controlled drug delivery; fundamentals and applications", edited by Robinson J.R., Vincent Lee, 2nd edition, Marcel Dekker Inc., Volume 29, 1978: 391-420pp.
7. Verma,R.K., Garg,S.,Pharm.Technol.,2001, 25, 1.
8. Theuwes, F., Swanson, D. R., Guitttard, G., Ayer, A., Br. J.Clin. Pharmacology, (1985), 19, 69-76.
9. Santus, G., Baker, R.W., J. Control. Release, 1995, 35, 1-21.
10. Verma, R.K., Garg, S., J. Control. Release, 2002, 79, 7-27.
11. Verma,R.K., Mishra, B., Drug Dev. Ind .Pharm. 2001, 22.
12. Santus, G., Baker, R.W., J.Control.Release, 1995, 35, 2.
13. Pfefer,W.E.P.Osmotishe Umtersuchen, Leipzig,1877.
14. Ramakrishna., Mishra B. Pharmazie 2001; 56: 958.
15. Bhatt P Padmanabh. Osmotic drug delivery system for poorly soluble drug, Pharma venture ltd. (2004).