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PREPARATION AND CHARACTERIZATION OF GLIPIZIDE OSMOTIC TABLETS FOR COLON

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Abstract:

The aim of present study was to prepare and evaluate an osmotic drug delivery system for controlled release of glipizide for treatment of type II noninsulin dependent diabetes mellitus. In order to make bi-layer push-pull osmotic tablets, PEO was used as an expansion agent. Tablets were coated with Opadry CA and mechanically drilled. By changing the percentage of sodium chloride in the push layer, Preparations F10 and F11 were prepared to prevent the drug's initial delayed release. The drug release was accelerated by increasing the sodium chloride concentration, and the release profile resembled that of the innovator. Preparations F12, F13, and F14 were created by covering them with Opadry CA and achieving weight gains of 8%, 10%, and 12%, respectively, to test the impact of weight growth. When compared to the innovator, preparations F12 and F13 with 8% and 10% of release displayed quick release, while design F14 with 12% of release showed equivalent release. When related to the innovator, the relative release profiles of preparations with 12% and 14% exhibited a like release outline. To obtain the appropriate release profile, a coating of 131% semi-permeable membrane can be advised. However, 12% was decided upon as the optimized mass increase when linked to additional preparations, ultimate F14 as the improved preparation and conducting additional research to scale-up preparations. For three months, stability investigations were carried out at 40 ºC and 75% RH. The optimized preparation F14 was found to be stable and to comply with the Innovator product in terms of appearance, assay, and dissolving profile.

Keywords: *Glipizide, Osmotic drug delivery system, Poly ethylene glycol, Opadry CA, Stability.*

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INTRODUCTION:

Various technologies have been developed for controlled drug delivery. Majority of the oral dosage forms fall in the category of matrix, reservoir, or osmotic systems [1,2]. Osmotic devices, use technology that delivers the drug at a zero-order rate and minimizes the drug plasma concentration fluctuations, thus reducing the adverse reactions, and improving the patient compliance. Osmotic systems utilize the principles of osmotic pressure for controlled delivery of drugs. The osmotic system for oral administration has advantages such as- It delivers drugs at zero-order release kinetics, Constant delivery rate and thereby reduce risk of adverse reactions, Delivery of drugs takes place in solution from which it is ready for absorption, In - vivo delivery rate can be accurately predicted on the basis of in-vitro data, The delivery rate from osmotic devices is not influenced by gastric pH and hydrodynamic conditions. The phenomenon of osmotic pressure difference for delivery of active ingredients was first developed by Rose and Nelson in the 1950s [3,4].

The devices are made up of core and semi permeable membrane that coats the core, having an orifice to release the active material. The core contains an active material and an osmotic agent. When the system comes in contact with gastro-intestinal fluid, water enters into the preparation through semi permeable membrane and dissolves the active material in the core, due to generation of osmotic pressure inside the core; drug is released continuously in the form of solution at a slow rate [5]. These systems are suitable for delivery of drugs having high to moderate water solubility. However, by modulating solubility of these drugs within the core, effective release patterns may be obtained for the drug. Glipizide lowers glucose concentration by stimulating the release of insulin from pancreatic β-cells. Thus, the glipizide is more effective. Hence this study was aimed to develop controlled release of glipizide [6].

MATERIALS AND METHODS:

Materials

Glipizide was purchased from Sri Krishna Drugs Limited, Telangana. Poly ethylene oxide low molecular weight and low molecular weight was purchased from Colorcon®, Goa, India. Sodium Chloride was purchased from Sigma Aldrich.

Methods

Pre-Formulation Studies:

Solubility:

Both at the beginning and 24 hours afterwards, the drug's saturation solubility was tested using various dissolution media.

Melting Point:

Using a capillary tube, the melting point of the API sample was determined.

Hygroscopicity Studies:

It is founded on measuring the equilibrium moisture content of samples that have been adjusted to a specific relative humidity by means of saturated salt solutions in the desiccators' wells [7].

Each of the 4 previously tarred Petri dishes was filled with 2g of the drug powder, which was then incubated in desiccators using a saturated salt solution of ammonium chloride at 25°C and 80% RH. The samples were taken at various intervals of 2, 4, 8, and 24 hours, and the percentage of mass gain and LOD were recorded. Additionally highlighted was the sample's original LOD.

Sieve Analysis:

A vibrating sieve shaker was used to determine the average size of the APIs. A sieve shaker was loaded with 50g of API after being weighed. The test was run for 15 minutes at 50 amplitudes. Fines and percentage of each sieve's #20, #30, #40, #60, #80, and #100 retained material were calculated [8].

Moisture Content:

Using a Sartorius moisture analyzer with a 1 g of sample at 105°C for 5 min., the moisture content of API was determined. The values received were used to calculate the percentage loss during drying.

Bulk Density:

A dry, 100 ml measuring cylinder that was empty and graduated was precisely weighed. Using a funnel, 20 g of medication that had earlier been put through # 20 strainers was moved into the cylinder [9]. Without compacting, the powder was properly levelled to determine the unsettled apparent volume (V0). To determine the precise weight of powder (M) in the cylinder, the full cylinder was measured again. The difference between the initial and final weights was then determined.

$$\textit{Bulk density (BD) = Mass of powder (M) / Bulk volume } (V_0)$$

Tapped Density:

The sample container was raised and allowed to fall

under its own weight. After tapping the cylinder for 500 times, the tapped volume (V1) was restrained to the adjacent graduated units [10]. The cylinder was then tapped a second time for 750 times, and the second tapped volume (V2) was measured to the adjacent graded units.

Tapped Density (TD) = Mass of powder (M) / Tapped volume (V_2)

Compressibility Index:
The compressibility index of the powder mixture was calculated by evaluating a powder's BD, TD, and packing down speed requires only a few basic steps.

Carr's Index (%) = [(TD-BD) x100]/TD

Hausner's Ratio:
The Hausner's ratio is connected to the flowability of a powder or gritty solid.

Hausner's Ratio = TD / BD

Angle of Repose *(θ)*:
An aspect of inter-particulate friction, or the struggle to particle movement, is angle of repose. It is the pile of material prepared on a horizontal basis at a constant three-dimensional angle.

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

Formulation and Development of OCDDS:
DRUG / PULL LAYER:
To remove any agglomerates, API, MCC, PEO, and NaCl were first run over a 40# sieve. The dry-mixed powder was then processed for 10 minutes in a quick mixer granulator. Direct usage of hydro-alcoholic solution as a binder liquid was made [11]. No additional agent was used because polyethylene oxide had effective binding characteristics. As a binder liquid, solution up to 30% of the weight was utilized. It is accomplished by spewing the hydro-alcoholic solution for two minutes, followed by two minutes and thirty seconds of kneading. The wet bulk was then for 45 minutes using at temperature of 40ºC. Granules of dried material were put through a 20# filter. Magnesium stearate was applied to the aforementioned granules for 3 minutes while the blender was running at 10 rpm

PUSH LAYER:
To remove any agglomerates, all ingredients were first run through a 40# sieve. The dry-mixed powder was then processed for 10 minutes in a quick mixer granulator. The liquid used as the binding agent was ethanol. No further agent was added because polyethylene oxide possesses effective binding capabilities. The solution was utilised as the binding liquid up to 30% of the weight [12]. The ethanol solution is sprayed for two minutes, and then it is kneaded for two minutes and thirty seconds to complete the granulation process. The wet bulk was transferred to the drier, where it was dried for 45 minutes of temperature 40 ºC. Dry grains were approved over 20# mesh. Magnesium stearate was used to lubricate the aforementioned granules for 3 minutes while the blender was running at 10 rpm. A bi-layer rotary compression machine was used to compress the bi-layer tablet by means of the previously made blends 1 and 2. In a rotational compression machine, greased grains were squeezed by means of 9.5 mm typical concave punches that were plain on together edges.

Preparation of Coating Solution:
Opadry CA: Opadry CA was dissolved in acetone and water (9:1) to prepare the coating solution, which was then stirred for 45 minutes.

Opadry Pink: Opadry pink was dissolved in water (1:10) and used to make a colour coating solution. The mixture was stirred for 45 minutes.

Colour Coating:
By adjusting the following process parameter on the Sams India coater machine, colour coating was carried out using a prepared solution of Opadry pink. To obtain the needed % weight gain, the average pill weight was verified on a regular basis [13]. The coated tablet was placed in a pan and allowed to dry at 40 ºC with 3 rpm.

Drilling of Orifice:
Mechanical drill technology was used to drill an orifice on the push layer with a diameter of 0.5 mm.

***In-Vitro* Dissolution Study:**
The ready tablet was then put through an in-vitro analysis to decide which preparation would work best by comparing it to the innovator.

Preparation Development:
Two stages of trials were performed:

- Optimization of core tablet in push layer
- Optimization of Core Tablet

Optimization of PEO in Pull and Push layer:
By examining the viscosity of the reference product and using information from the literature to comprehend reverse technology, it was discovered that PEO with little and high molecular masses was utilized in the pull and push layers, respectively. Low

mol. wt. PEO (6 lakhs) was initially used for pull layer optimization at several concentrations from F1 to F3 trials, but because the outcomes were unacceptable for increasing medicine release, it was substituted by PEO (3 lakhs), and trials F4 to F6 were carried out [14]. Similar to the pull layer, trials F1–F6 employed high molecular weight polyethylene oxide (50 lakhs) in a variety of concentrations, however because the drug release was too sluggish, PEO (70 lakhs) was substituted, and trials F7–F9 were then conducted.

Optimization of Sodium Chloride in push layer:
F9 was optimized, and trials F10 and F11 were carried out by lowering and raising the concentration of NaCl in push layers, correspondingly, to shorten the first lag phase [15].

Optimization of Semi-Permeable Membrane:
Trials F12, F13, and F14 were selected for weight gains of 8%, 10%, and 12%, respectively, in order to further examine the impact of coating weight rise on drug release. The above-optimized experiment F11 was also chosen for this purpose [16].

Evaluation of Osmotic Tablets:
Assay:
By using a mortar and pestle, 20 tablets of the preparation were broken into a fine powder. 100 milligram of the powder was then balanced in 100 ml of volumetric solution and dilute with 7.5 phosphate buffer in a flask. The diluted solution was filtered after 15 minutes of ultrasonication. Using a UV spectrophotometer, the total amount of medication in each tablet was evaluated [17].

Weight Variance:
Twenty tablets of each preparation were separately balanced by means of a Sartorius electronic balance in order to evaluate weight variance. The test was carried out in accordance with the established guidelines.

Hardness:
After each lot, ten tablets were nominated at arbitrary and tested for hardness using a Varian hardness tester.

Thickness:
Using digimeter vernier callipers, ten tablets were arbitrarily selected from each lot and measured for thickness.

Friability:
Digimeter vernier callipers were used to measure the thickness of ten tablets at random from each batch.

***In-vitro* drug release studies:**
At a temperature of 37°± 2°C, an in-vitro release rate test was performed utilizing a (USP-II) paddle kind dissolution equipment with 900 ml of pH 7.5 phosphate buffer [18]. At intervals of 1, 2, 4, 8, and 16 hours, samples were taken out and analyzed spectrophotometrically.

Accelerated Stability Studies:
A medication must generally be assessed below storing circumstances and, if necessary, its susceptibility to moisture or possible for solvent loss [19].

Table-1: Stability study

Storage state	Period
40°C ± 2°C/75% RH ± 5% RH	3 months

RESULTS AND DISCUSSION:

Pre-Formulation studies:
Solubility
In Table 2, the drug candidate's saturation solubility is listed. Glipizide's solubility study revealed that it possesses pH-dependent solubility, becoming solvable at pH 7.5. Additionally, a review of the literature shows that the medication glipizide is quite permeable. Thus, it was determined that the model medication is a member of BCS class II because of its high permeability and low solubility

Table 2: Solubility

Media	mg softened per 100 ml
pH 5.5 Phosphatebuffer	0.346
pH 6.8 Phosphatebuffer	1.486
pH 7.5 Phosphatebuffer	4.469

Melting Point:
The melting point of glipizide exhibited 216 ℃
Hygroscopicity Studies:
The rate of weight gain was within acceptable limits and was 0.02% and 0.025% at RH 50% and 80% later 24 hours, correspondingly. As a result, glipizide was determined to be non-hygroscopic.

Table 3: Comments of the studies

Parameter	After 2nd hrs %	After 4th hrs %	After 8th hrs %	After 24th hrs %
Primary % LOD	0.58	0.58	0.58	0.58
RH 55% and 25°C				
% Weight increase	0.0	0.0	0.0	0.02
% LOD at 105°C for 5 min	0.58	0.60	0.61	0.61
RH 80 % and 25°C				
% Mass gain	0.0	0.0	0.01	0.024
% LOD at 105°C for 5 min	0.58	0.60	0.59	0.60

Sieve Analysis:
From the sieve examination outcome, it was found that mainstream units lie overhead mesh no #60 (250 µm).

Table 4: Particle dimensions dispersal of the API

Sieve no.	Retaining % w/w
# 20.0	1
# 30.0	3.1
# 40.0	18.3
# 60.0	52.9
# 80.0	8.7
# 100.0	2.5
Over 100	7.5

Moisture Content of API:
It was found to be 0.15% w/w.

The results of the Carr's index, Hausner ratio, and angle of repose demonstrated the extremely poor flow of the glipizide powder.

Table 5: Physical characteristics of the API

Parameter	Value
Bulk density	0.16gm/ml
Tapped density	0.27 gm/ml
Carr's index	38.25
Hausner ratio	1.55
Angle of repose	43.13º

Formulation Development:
Optimization of Core Tablet:

Table 6: Optimization of Polyethylene oxide in Pull and Push layers

Pull layer (drug layer)						
Constituents (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Drug	10	10	10	10	10	10
Polyethyleneoxide (6 lakhs MW)	145	160	175	---	---	---
Polyethyleneoxide (3 lakhs MW)	---	---	---	145	160	175
NaCl	10	10	10	10	10	10
MCC	45	30	15	45	30	15
MagnesiumStearate	1	1	1	1	1	1
Total	211	211	211	211	211	211
Push layer						
Polyethyleneoxide (50 lakhs MW)	85	85	85	85	85	85
NaCl	30	30	30	30	30	30
MCC	15	15	15	15	15	15
Fe_2O_3 Yellow	1	1	1	1	1	1
Mg. Stearate	1	1	1	1	1	1
Total	132	132	132	132	132	132
Coating of Semi-Permeable sheath (14% gain)						
Opadry CA	48	48	48	48	48	48
Total	391.06	391.06	391.06	391.06	391.06	391.06
Colour coat (3% mass increase)						
Opadry pink	11.7	11.7	11.7	11.7	11.7	11.7
Total	402.76	402.76	402.7	402.76	402.76	402.76

Table 7: Optimization PEO and NaCl in Pull and Push layers

Pull layer (drug layer)					
Ingredients (mg)	**F7**	**F8**	**F9**	**F10**	**F11**
Glipizide	10	10	10	10	10
PEO (3 lakhs MW)	174	174	174	174	174
NaCl	10	10	10	10	10
MCC	15	15	15	15	15
Mg. stearate	2	2	2	2	2
Total	211	211	211	211	211
Push layer					
PEO (70 lakhs MW)	80	85	90	90	90
NaCl	30	30	30	20	40
MCC	20	15	10	20	0
Fe_2O_3 Yellow	1	1	1	1	1
Mg. stearate	1	1	1	1	1
Total	132	132	132	132	132
Coating of Semi-Permeable membrane (14% increase)					
Opadry CA	48	48	48	48	48
Total	391.06	391.06	391.06	391.06	391.06
Colour coat (3% mass increase)					
Opadry pink	11.7	11.7	11.7	11.7	11.7
Total	402.76	402.76	402.76	402.76	402.76

Table 8: Optimization of semi-permeable membrane

Pull layer (drug layer)			
Constituents (mg)	**F12**	**F13**	**F14**
DRUG	10	10	10
PEO (3 lakhs MW)	174	174	174
NaCl	10	10	10
MCC	15	15	15
Mg. stearate	2	2	2
Total	211	211	211
Push Layer			
PEO (70 lakhs MW)	90	90	90
NaCl	40	40	40
MCC	0	0	0
Fe_2O_3 Yellow	1	1	1
Mg. stearate	1	1	1
Total	132	132	132
Coating of Semi-Permeable sheath			
	8%	10%	12%
Opadry CA	27.4	34.3	41.1
Whole	370.46	377.36	384.16
Color coat (3% mass increase)			
Opadry pink	11.1	11.3	11.5
Total	381.56	388.66	395.66

Assessment of Osmotic Tablets

It was clear from Table 9, the produced Tablets' thickness and hardness properties met internal standards. The orifice's diameter was determined to be between 0.53 and 0.56 mm.

Table 9: Compression constraints of trials F1-F14

BatchNo.	Assay (%)	Average Mass (mg)	Hardness (kp)	Thickness(mm)	Friability(%)	Weight variation
F1	98.06	341.3 ± 0.56	13	4.95	0.118	Complies
F2	102.3	343.8 ± 1.26	14	4.92	0.137	Complies
F3	99.1	344.8 ± 1.53	14.8	4.93	0.154	Complies
F4	103.2	343.4 ± 0.29	14	4.93	0.241	Complies
F5	101.0	341.6 ± 2.10	13	4.94	0.148	Complies
F6	98.7	342.6 ± 0.12	13.6	4.93	0.160	Complies
F7	102.07	342.8 ± 2.01	13.5	4.90	0.213	Complies
F8	98.6	344.8 ± 1.02	14.8	4.91	0.256	Complies
F9	99.8	341.2 ± 2.06	13	4.92	0.222	Complies
F10	96.7	345.4 ± 0.75	15	4.91	0.157	Complies
F11	100.8	341.5 ± 1.96	13	4.90	0.250	Complies
F12	98.6	342.2 ± 1.25	13.8	4.93	0.231	Complies
F13	101.2	343.6 ± 0.46	14	4.95	0.168	Complies
F14	99.05	341.3 ± 0.26	13	4.96	0.226	Complies

***In- Vitro* Dissolution**

When compared to F5, F6 displayed a larger cumulative release percentage, and it also displayed a release profile that was more similar to the innovator.

Table 10: % cumulative drug release data

Time(h)	Innovator	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
2	1	1	2	1	1	1	1
4	16	10	12	10	8	10	12
8	48	23	29	24	27	31	27
16	98	44	47	56	73	70	76
20	100	55	59	62	76	76	81
24	100	56	63	65	78	80	84

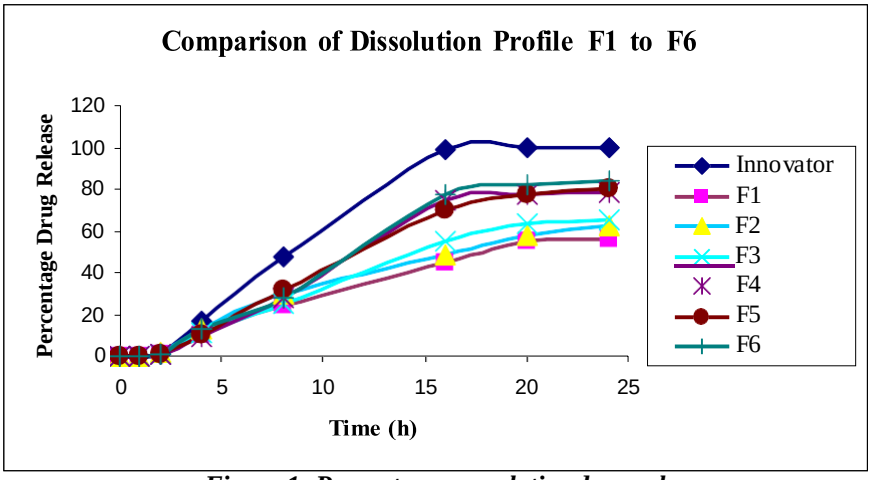

Figure 1: Percentage cumulative drug release

Optimization of PEO in Pull and Push Layer

According to the aforementioned tests, preparation F9 demonstrated good zero-order release kinetics, it was selected for further optimization.

Table 11: % cumulative drug release data

Time(h)	Innovator	F7	F8	F9
0	0	0	0	0
1	0	0	0	0
2	1	1	1	1
4	16	8	9	10
8	46	29	25	32
16	98	67	76	92
20	100	81	90	95
24	100	84	92	96

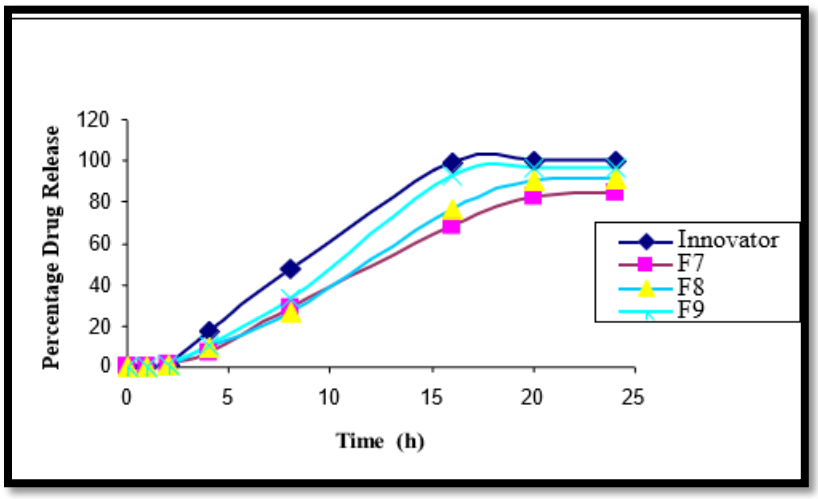

Figure 2: Percentage cumulative drug release

Optimization of NaCl in Push Layer

The dissolution profiles of formulations F10 and F11 visibly demonstrated that the initial drug release increased with an increase in sodium chloride in push layer concentration. Formulation F11 had a higher f2 value and a release rate that was closer to the innovator than F10 did. F11 preparation was chosen as the ultimate core because, among other formulations, the f2 and the dissolving profile exhibited promising indicators

Table 12: % cumulative drug release

Time (h)	Innovator	F10	F11
0	0	0	0
1	0	0	0
2	1	1	1
4	16	7	14
8	46	29	45
16	98	92	98
20	100	94	99
24	100	95	100

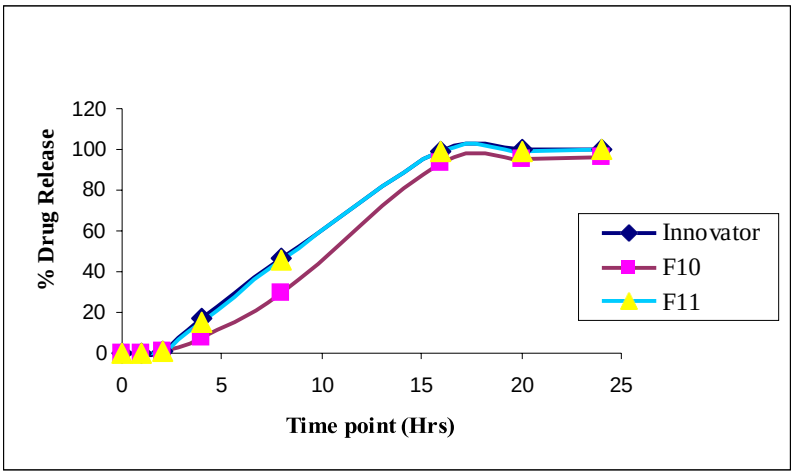

Figure 3: Percentage cumulative medicine release

Optimization of Semi-Permeable Coating

Three preparations of 8%, 10%, and 12% semi-permeable membrane were created and tested in order to better understand its function in the formulation. Figure 38's findings revealed that all formulations had good zero order release kinetics. In comparison to F14, F12 and F13 demonstrated a quicker percentage medicine release. However, when compared to the innovator, formulation F14 displayed a comparable release profile.

Table 13: % cumulative drug release data

Time (h)	Innovator	F12	F13	F14
0	0	0	0	0
1	0	5	3	0
2	1	8	5	2
4	16	31	23	18
8	46	63	57	50
16	98	100	100	99
20	100	100	100	100
24	100	100	100	100

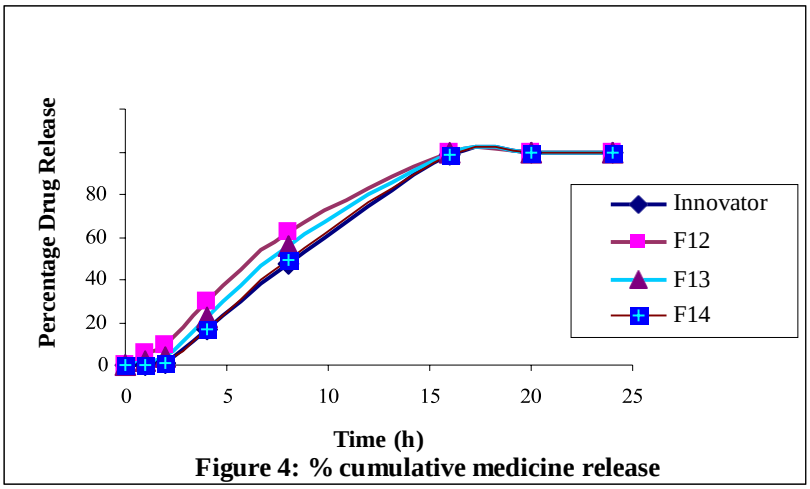

Figure 4: % cumulative medicine release

Comparison of Formulation F11 and Formulation F14:

Table 14: % cumulative medication release data

Time (h)	Innovator	F11	F14
Coating of Semi-permeablemembrane		**14%**	**12%**
0	0	0	0
1	0	0	0
2	1	1	1
4	17	15	17
8	47	46	49
16	99	99	99
20	100	99	100
24	100	100	100

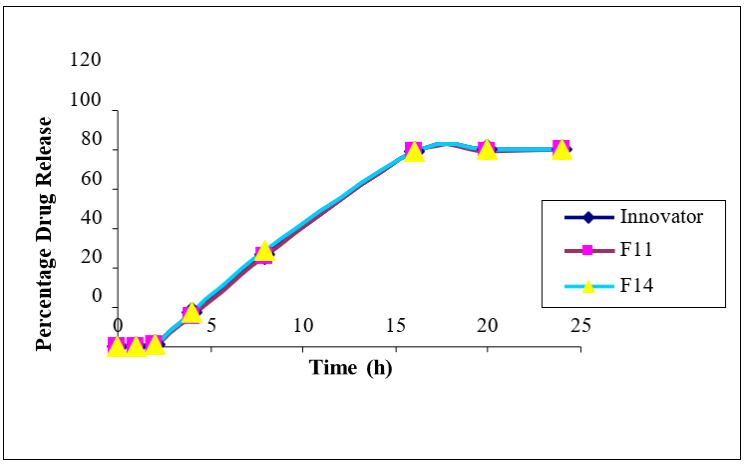

Figure 5: % cumulative drug release

When the innovator's release profile was compared to those of formulations F11 and F14, the release was determined to be comparable. The release profile may be further decreased by an upsurge in coating (i.e., >14%) in a semi-permeable membrane. Accordingly, a drop in coating (between 8 and 10 percent) demonstrated a faster profile than the innovator's (Formulation F12 and F13).

A coating of 131% will do to satisfy the needs of the study since Preparation F14 with 12% covering and F11 with 14% covering were nearer to the release outline of the reference preparation.

Physical Characteristics of Optimized Formulation.

The physical characteristics of the lubricated F14 blend are evaluated and listed. It was discovered that the push layer and pull layer mixes both have good flow characteristics.

Table 15: Physical features of F14

Parameters	**Pull layer**	**Push layer**
Bulk density (g/ml)	0.44	0.512
Tapped density (g/ml)	0.53	0.57
Carr's index (%)	13.1	11.2
Hausner's ratio	1.13	1.12
Angle of repose	25.73	24.5

Table 16: Particle size study

Mesh Number	**% Weight retained on mesh**	
	Pull layer	Push layer
20	0.0	0.3
30	5.5	2.0
40	7.8	3.1
60	20.1	33.5
80	21.3	21
100	10.8	8.1
Pan	32.7	31.5

Table No. 17: Physical features of F14

Limits	F14
Average mass	395.4+1.97
Friability (%)	0.18
Hardness (kp)	24 ± 1.0
Thickness (mm)	5.53 ± 0.05
Average diameter	9.0 ± 0.7

Figure 6: Optimized batch (F14) Osmotic tablets

The covered Tablets of the f14 preparation's average weight, friability, hardness, thickness, and typical width were examined, and they were judged to be acceptable.

Stability Data of Optimized Formulation:

For stability investigations, the optimal formulation was preserved and its assay, and dissolving profile were examined after 1 and 3 months. It was discovered that formulation F14 was stable with respect to our target criteria.

***Table 18: Stability data of F14 batch at* 40ºC/75% RH**

S. No	Test		Initial	1 month	3 months
I.	Assay (%)		99.04	99.46	100.10
II	Dissolution release profile (%)	2 hrs	1 ± 0.58	1 ± 0.58	2 ± 0.58
		8 hrs	49 ± 5.69	50 ± 4.04	48 ± 6.51
		16 hrs	99 ± 1.15	97 ± 3.06	98 ± 2.08

CONCLUSION:

The current study's objective remained to develop and assess a generic osmotic controlled distribution arrangement for an anti-diabetic medicine created by an inventor. In order to make bi-layer push-pull osmotic tablets, PEO was used as an expansion agent. Tablets were coated with Opadry CA and mechanically drilled.

When compared to the innovator, preparations F12 and F13 with 8% and 10% of release displayed quick release, while design F14 with 12% of release showed equivalent release. When related to the innovator, the relative release profiles of preparations with 12% and 14% exhibited a like release outline. To obtain the appropriate release profile, a coating of 131% semi-permeable membrane can be advised. However, 12% was decided upon as the optimized mass increase when linked to additional preparations, ultimate F14 as the improved preparation and conducting additional research to scale-up preparations.

For three months, stability investigations were carried out at 40 ºC and 75% RH. The optimized preparation F14 was found to be stable and to comply with the Innovator product in terms of appearance, assay, and dissolving profile.

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