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FORMULATION AND CHARACTERIZATION OF OSMOTIC TABLETS FOR COLON-SPECIFIC DRUG DELIVERY SYSTEM

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Abstract:

The present study aimed to prepare and evaluate an osmotic drug delivery system for the controlled release of glipizide for the treatment of type II noninsulin-dependent diabetes mellitus. 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. 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. 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, Polyethylene glycol, Opadry CA, Stability.*

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INTRODUCTION:

The colonic region of the gastrointestinal tract is one area that would benefit from the development and use of modified-release technologies. The colon is vulnerable to several disorders including ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS) and carcinomas. Targeted drug delivery to the colon would therefore ensure direct treatment at the disease site, lower the dosing rate and reduce systemic side effects [1]. IBS is a mild intestinal chronic disorder highly associated with abdominal pain, altered bowel motility resulting in either diarrhea or obstipation and an increase in visceral hypersensitivity and visceral pain [2]. Although IBS is not a life-threatening illness [3], the subjective nature of IBS diagnosis presents special challenges for both clinicians and researchers [4]. Regarding specific IBS symptoms, women with IBS are more likely to report problems with constipation, while men more commonly report diarrhea. Epidemiological studies have demonstrated that women with IBS are at higher risk of abdominal surgery including hysterectomy [5].

There is currently no universally effective therapy for IBS. Standard therapy generally involves a symptom-directed approach: anti-diarrheal agent for bowel frequency, soluble fiber or laxative for constipation, and smooth muscle relaxants and anti-spasmodic for pain [6]. Anti-spasmodic drugs have traditionally formed the basis of treating IBS. Dicyclomine hydrochloride, an anti-cholinergic drug, has direct smooth muscle relaxant action, in addition being weak anti-cholinergic, and exerts anti-spasmodic action [7].

Drug delivery systems for treating colonic disorders such as IBS are failing as the drugs do not reach the site of action in the appropriate concentration. Thus, there is a need to develop effective and safe therapy for the treatment of these colonic disorders, using a site-specific drug delivery approach [8]. However, the development of such a system is a challenging task for pharmaceutical technologists. The available conventional dosage forms are not very effective in the treatment of these colonic diseases as dosing frequency is quite high which leads to many adverse effects. This work aimed to design and characterize an osmotic tablet for colon-specific delivery, which can reach intact the site of action and could deliver the drug at a constant rate for 24 h. Such a system was expected to help reduce the dosing frequency and side effects, thus increasing patient compliance.

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 500 times, the tapped volume (V1) was restrained to the adjacent graduated units. 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) /

MATERIALS AND METHODS:

Materials:

Glipizide was purchased from Sri Krishna Drugs Limited,Telangana. Polyethylene oxide was obtained from Colorcon®, Goa, India. Microcrystalline cellulose, Sodium Chloride, and Magnesium Stearate were attained from Sigma Aldrich.

Methods:

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 [9].

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. 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 [10]. The difference between the initial and final weights was then determined.

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 [11].

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

Formulation and Development of OCDDS:

Procedure

DRUG / PULL LAYER:

Dry Mixing:

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 [12].

Binder Solution:

Direct usage of hydro-alcoholic solution as a binder liquid was made. No additional agent was used because polyethylene oxide had effective binding characteristics. As a binder liquid, a solution up to 30% of the weight was utilized [13].

Granulation:

It is accomplished by spewing the hydro-alcoholic solution for two minutes, followed by two minutes and thirty seconds of kneading.

Drying:

The wet bulk was then for 45 minutes using at a temperature of 40ºC

Sizing:

Granules of dried material were put through a 20# filter.

Lubrication:

Magnesium stearate was applied to the aforementioned granules for 3 minutes while the blender was running at 10 rpm

PUSH LAYER:

Dry Mixing:

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 [14].

Binder Solution:

The liquid used as the binding agent was ethanol. No further agent was added because polyethylene oxide possesses effective binding capabilities. The solution was utilized as the binding liquid up to 30% of the weight.

Granulation:

The ethanol solution is sprayed for two minutes, and then it is kneaded for two minutes and thirty seconds to complete the granulation process.

Drying:

The wet bulk was transferred to the drier, where it was dried for 45 mins of temperature 40 ºC

Sizing:

Dry grains were approved over 20# mesh.

Lubrication:

Magnesium stearate was used to lubricate the aforementioned granules for 3 minutes while the blender was running at 10 rpm.

Compression:

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 using 9.5 mm typical concave punches that were plain on together edges [15].

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 color coating solution. The mixture was stirred for 45 minutes.

Coating Process

The following process parameters were set when the coating was done using a Sams India coater and a prepared solution of Opadry CA.

To achieve the needed % weight gain, the average pill weight was verified regularly. The coated tablet was permissible to dry in a pan at 40 ºC for three revolutions.

Color Coating:

By adjusting the following process parameters on the Sams India coater machine, color coating was carried out using a prepared solution of Opadry pink.

To obtain the needed % weight gain, the average pill weight was verified regularly. The coated tablet was placed in a pan and allowed to dry at 40 ºC at 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 [16].

Preparation Development:

Two stages of trials were performed:

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

Optimization of PEO in the 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 [17].

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.

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 was then conducted.

Optimization of Sodium Chloride in the 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 [18].

Optimization of Semi-Permeable Membrane:

Trials F12, F13, and F14 were selected for weight gains of 8%, 10%, and 12%, respectively, to further examine the impact of coating weight rise on drug release. The above-optimized experiment F11 was also chosen for this purpose.

Evaluation of Osmotic Tablets:

Assay:

By using a mortar and pestle, 20 tablets of the preparation were broken into a fine powder. 100 milligrams of the powder was then balanced in 100 ml of volumetric solution and diluted 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.

Weight Disparity:

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 by the established guidelines.

Hardness:

After each lot, ten tablets were nominated arbitrarily and tested for hardness using a Varian hardness tester.

Thickness:

Using diameter vernier calipers, ten tablets were arbitrarily selected from each lot and measured for thickness.

Friability:

Digimeter vernier calipers were used to measure the thickness of ten tablets at random from each batch [19].

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. At intervals of 1, 2, 4, 8, and 16 hours, samples were taken out and analyzed spectrophotometrically [20].

Accelerated Stability Studies:

A medication must generally be assessed below storing circumstances and, if necessary, its susceptibility to moisture or possible solvent loss.

Table- 2: Stability study

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

RESULTS AND DISCUSSION:

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 3: 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 4: Optimization of Polyethylene oxide in Pull and Push layers

	Pull layer (drug layer)					
Constituents (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Medicine	10	10	10	10	10	10
Polyethyleneoxide (6 lakhs MW)	145	160	175	---	---	---
Polyethylene oxide (3 lakhs MW)	---	---	---	145	160	175
NaCl	10	10	10	10	10	10
MCC	45	30	15	45	30	15
Magnesium Stearate	1	1	1	1	1	1
Whole	**211**	**211**	**211**	**211**	**211**	**211**
	Push layer					
Polyethylene oxide (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
Whole	**132**	**132**	**132**	**132**	**132**	**132**
	Covering 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 5: Optimization PEO and NaCl in Pull and Push layers

	Pull layer (medicine 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**
	Covering 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 6: 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
Entire	**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
Entire	**132**	**132**	**132**
Covering 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
Entire	**381.56**	**388.66**	**395.66**

Figure 1: Upper and side view of coated osmotic tablet by drilling

Assessment of Osmotic Tablets:

It was clear from Table 7, 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 7: 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.

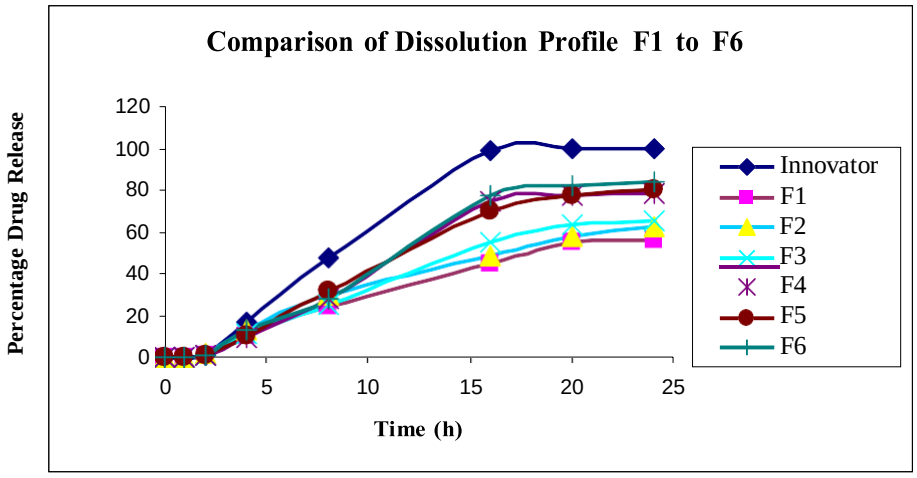

Figure 2: Percentage cumulative drug release

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.

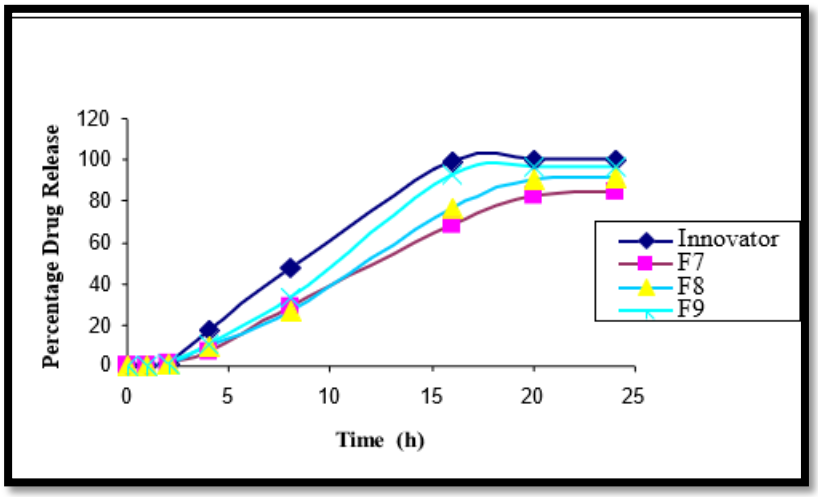

Figure 3: Percentage cumulative drug release

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.

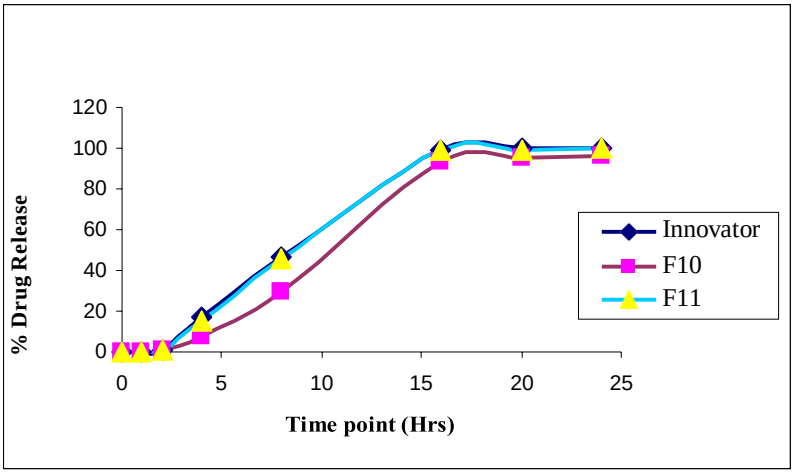

Figure 4: Percentage cumulative medicine release

Optimization of Semi-Permeable Casing:

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.

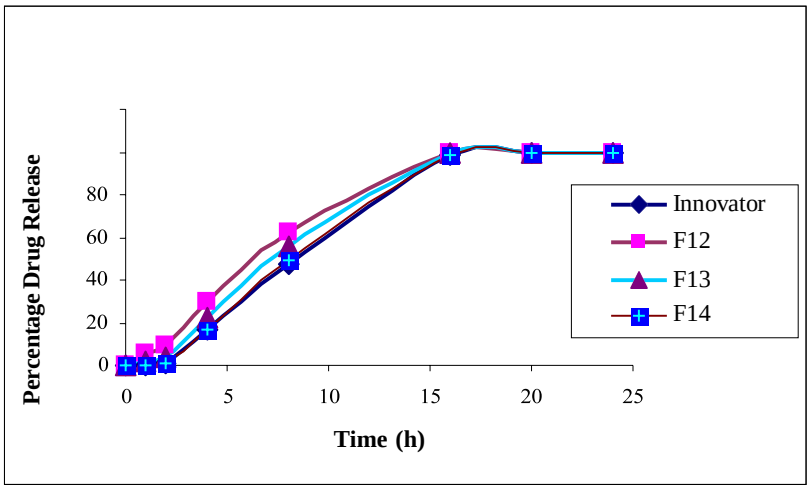

Figure 5: % collective medicine release

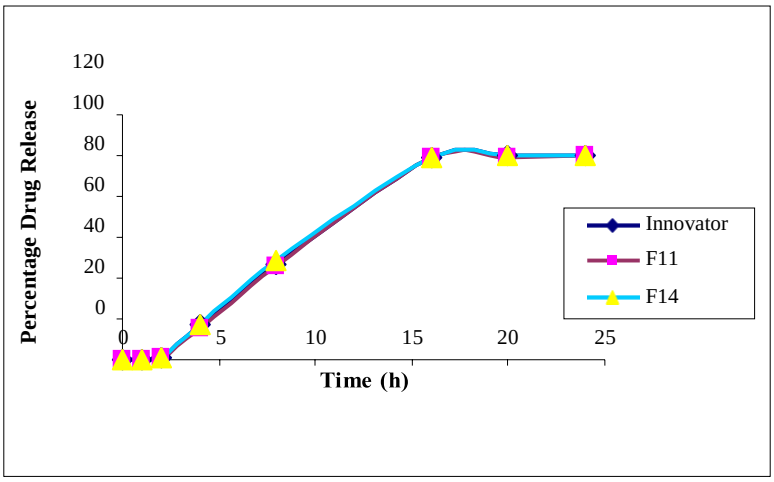

Figure 6: % cumulative medicine release

When the innovator's release profile was compared to those of formulations F11 and F14, the release was determined to be comparable (Table 27). 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 8: 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 9: Particle size study

Mesh Number	**% mass 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 10: Physical features of the coated tablets of F14

Constraints	**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 7: 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 11: 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

SUMMARY AND 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. To make bi-layer push-pull osmotic tablets, PEO was used as an expansion agent. Tablets were coated with Opadry CA and mechanically drilled. 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.

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