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RESEARCH ARTICLE

DEVELOPMENT OF SANDWICHED OSMOTIC TABLET OF GLIPIZIDE

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ABSTRACT

The Sandwiched Osmotic Tablet System (SOTS), which is composed of sandwiched osmotic tablet core surrounded by a cellulose acetate membrane with two orifices on both side surfaces has been successfully prepared with the purpose of delivering Glipizide. In this a core composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. Influences of tablet formulation variables and membrane variables on Glipizide release of SOTS have been studied. NaCl was used as an osmogent and MCC 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 exhibited zero order kinetics with a drug release of 98.10 % in 24 hrs. The optimized formulation was also found to stable upon stability studies. The ideal formulation (F6) was stable when it was stored at 40±2 ^{0}c/ 75±5% RH as per ICH Guidelines for 6 months. It can be concluded that release of Glipizide was significantly controlled from sandwiched osmotic drug delivery systems.

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INTRODUCTION

Osmotically controlled Oral Drug Delivery Systems utilize osmotic pressure as the energy source for the controlled delivery of drugs. Drugs release from these systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system. The first device using osmotic principles to deliver active ingredients was reported in the 1950s by Rose and Nelson. The Elementary osmotic pump (EOP) was introduced in 1970s by Theeuwes and the coworkers. The EOP is very simple in preparation and can deliver water-soluble drugs at an approximate zero-order rate. However, EOP is unsuitable for delivering water-insoluble drugs. The two-layer push-pull osmotic tablet system appeared in 1980s. Push-pull osmotic tablet operates successfully in in delivering water-insoluble drugs, it has a disadvantage that the complicated laser drilling technology should be employed to drill the orifice next to the drug compartment. A monolithic osmotic tablet system is simple in preparation and can deliver water-insoluble drugs for up to 24 hrs. However, it has a shortcoming that its release profile deviates from the straight line. A Sandwiched Osmotic Tablet System (SOTS) was reported in the patent literature. The sandwiched tablet core consisted of a middle push layer and two attached drug layers. After coating, two orifices were simply drilled on both side surfaces, which avoided side identification before drilling of that of push pull osmotic tablet system. Also, as this system delivers drug from two opposite orifices differing from that of single orifice of the push-pull osmotic tablet system, it may decrease the potential local irritation of drug. Glipizide, an oral hypoglycemic agent is one of the most commonly used drugs for the treatment of patients with type II diabetes mellitus. It is practically water-insoluble, but the absolute bioavailability is equal to 1. Glipizide has a relatively short elimination half-life (2-4 hrs), thereby requiring twice daily dosing in large number of patients. Thus, there is a strong clinical need and market potential for a dosage form that will deliver Glipizide in a controlled manner to a patient needing this therapy, thereby resulting a better patient compliance. The present study was aimed towards the development of SOTS to deliver Glipizide and to study the influence of tablet core variables, including sodium chloride amount and microcrystalline cellulose (MCC) amount of both drug layer n push layer, drug loading and orifice size as well as membrane variables including nature and

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amount of plasticizer and thickness on drug release rate. And to study and evaluate the in vitro release rates of SOTS.

MATERIALS AND METHODS

Glipizide was obtained as gift sample from Mylan Pharmaceuticals, Sinnar, Microcrystalline cellulose (MCC) was gift sample, Sodium chloride, PVP K30, Lactose, cellulose acetate, polyethylene glycol 400 (PEG 400), acetone were purchased from Research-lab Fine Chem. Industry- Mumbai.

Preparation of Tablets

Core tablets of Glipizide were prepared by wet granulation method. The composition of core tablets is given in table no 16. Firstly granules of Drug layer and push layer were prepared. Glipizide was mixed with microcrystalline cellulose, lactose this powder blend was kneaded in the morter and pestle for 15-20 min. the blend was granulated using PVP K30 as a binder. And mixture of Sodium chloride, microcrystalline cellulose and magnesium stearate the blend was also kneaded in the morter pestle for 15-20 min, the blend was granulated using PVP K30 as a binder. And for both the layers wet mass was formed; resulting wet mass was passed through sieve #22. Granules were dried in oven at 50°C for 2 hrs. granules was evaluated for powder characteristics and flow properties like bulk density, tapped density, carr's index, angle of repose and Hausner's ratio. Then desired amount of blend was compressed into the tablet using Rimek tablet punch machine equipped with 8 mm punch, weight of the tablet was kept to 375 mg.

Coating of Glipizide core tablets

The coating solution was prepared by dissolving 5% w/v of cellulose acetate in acetone: alcohol (1:1). Add 1% v/v PEG 400 in the solution and solution was stirred for 20 min.

Coating method

The tablets were warmed to 40 ± 2^0C before applying coating solution. Dip coating technique was used for the coating of osmotic tablet. Tablet was dip into a coating solution and dried for 40^0C.

Drilling of Osmotic Tablets

The formulated coated tablets, a small orifice were drilled through both side of each coated tablet by standard mechanical drilling technique using 0.8mm needle.

Characterization

FTIR of Glipizide

The obtained sample was examined by infrared absorption spectral analysis and was compared with the reference standard IR of Glipizide. Infrared absorption spectrum of Glipizide was recorded with the wave number 2000 to 400 cm-1.

Evaluation of Granules

Flow properties of granules were evaluated by established methods. Angle of Repose was determined using funnel method. Bulk Density, Tapped Density, Compressibility index and Hausner's ratio were calculated.

Evaluation of Core Tablets

The formulated core tablets were evaluated for different parameters like hardness, thickness, weight Variation, friability and drug content uniformity of tablet.

Thickness

The uniformity of thickness was measured using digital vernier caliper. The average thickness of the tablet was calcutated.

Weight Variation Tests

20 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.

Hardness

The hardness of tablets was measured using Monsanto hardness tester. In this tablet was place between the plungers, and was tightened from one end, and pressure required to break tablet diametrically was measured.

Friability

In this test 20 tablet were weighed and placed in a roche friabilator test apparatus. 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.

Table 1. Composition of Sandwiched Osmotic tablet of Glipizide as per Factorial design

Ingredients	Formulation code								
Quantity(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug Layer (Two)									
Glipizide	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Microcrystalline cellulose	130	130	130	150	150	150	170	170	170
PVP K30	08	08	08	08	08	08	08	08	08
Lactose	61.5	56.5	51.5	41.5	36.5	31.5	21.5	16.5	11.5
Push Layer									
Sodium Chloride	5	10	15	5	10	15	5	10	15
Microcrystalline cellulose	150	150	150	150	150	150	150	150	150
Magnesium Stearate	10	10	10	10	10	10	10	10	10
PVP K30	08	08	08	08	08	08	08	08	08
Total	375	375	375	375	375	375	375	375	375

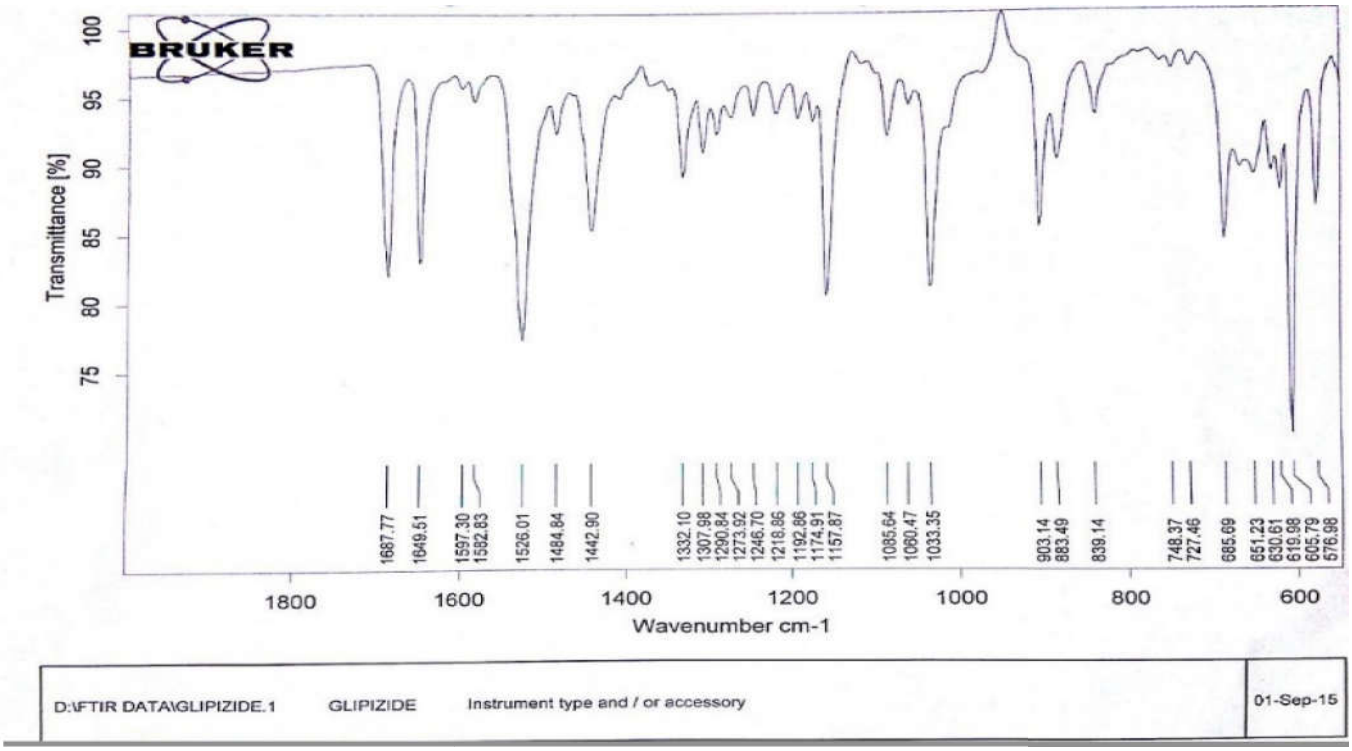

Fig. 1. FTIR Spectra of Glipizide

Table 2. Ranges of the functional groups present in I.R. of Glipizide

S. No.	Standard peaks at (cm^{-1})	Observed peaks at(cm^{-1})	Bond and Functional group
1	910-665	902	N-H (Amine)
2	910-665	685	C-H out of plane
3	1320-1000	1033	O=S=O
4	1700-1350	1444	C-H bending
5	1700-1400	1525	C=N (Aromatics)
6	1700-1400	1649	C=O(Aldehydes)

Table 1. Evaluation of Powder Bulk 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	26.89±0.67	0.3163±0.0041	0.3398±0.0052	12.97±0.1365	1.06±0.026
F2	27.11±0.8095	0.3206±0.0007	0.3567±0.0098	13.25±0.4986	1.13±0.015
F3	27.50±0.9060	0.3141±0.010	0.3501±0.0006	12.87±0.4181	1.121±0.071
F4	27.70±0.1627	0.3297±0.0007	0.3342±0.0044	12.39±0.4202	1.24±0.093
F5	26.43±0.3609	0.3402±0.0095	0.3516±0.0018	12.21±0.3274	1.20±0.017
F6	27.45±0.4365	0.3384±0.001	0.3425±0.0141	12.89±0.536	1.23±0.068
F7	28.00±0.1431	0.3470±0.010	0.3522±0.0011	13.56±0.3837	1.34±0.041
F8	26.82±0.3538	0.3513±0.0015	0.3609±0.0061	12.88±0.1301	1.35±0.065
F9	26.85±0.6950	0.3358±0.001	0.3445±0.0130	13.63±0.2369	1.25±0.045

Table 2. Precoating evaluation parameters of osmotic tablets

Formul-ation 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	373.4±0.5416	0.1450	4.59±0.4184	4.43±0.1628	0.88±0.0027	98.11±0.523
F2	372.1±0.7371	0.1980	4.20±0.4827	4.43±0.3068	0.61±0.0015	97.74±0.653
F3	371.9±0.6403	0.1721	4.55±0.1280	4.76±0.2736	0.64±0.0045	97.5±0.428
F4	369.9±0.9	0.2433	4.57±0.4278	4.76±0.3544	0.67±0.0024	96.82±0.734
F5	371.7±0.6674	0.1795	4.86±0.3550	4.58±0.4300	0.48±0.0038	97.29±0.652
F6	371.8±0.6960	0.1872	4.58±0.4081	4.31±0.568	0.72±0.0037	98.14±0.834
F7	371.9±0.4818	0.1295	4.23±0.6313	4.58±0.4365	0.67±0.0078	96.00±0.677
F8	369.7±0.6674	0.1805	5.15±0.6731	4.42±0.364	0.72±0.0046	96.21±0.568
F9	372.3±0.1500	0.1500	4.50±0.4512	4.71±0.3794	0.59±0.0061	96.57±0.498

Table 3. 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	383.9±0.4866	0.6546	5.37±0.1765	0.46±0.05
F2	384.2±0.6543	0.4365	5.51±0.2845	0.54±0.09
F3	382.5±0.6456	0.7834	5.57±0.1532	0.40±0.12
F4	379.7±0.2879	0.3466	5.71±0.3548	0.47±0.03
F5	381.1±0.4451	0.2287	5.62±0.1828	0.52±0.06
F6	380.8±0.5369	0.3409	5.41±0.27	0.55±0.04
F7	383.9±0.4777	0.4623	5.35±0.096	0.38±0.28
F8	384.5±0.5877	0.8009	5.23±0.48	0.40±0.20
F9	385.7±0.5809	1.4935	5.41±0.2977	0.35±0.14

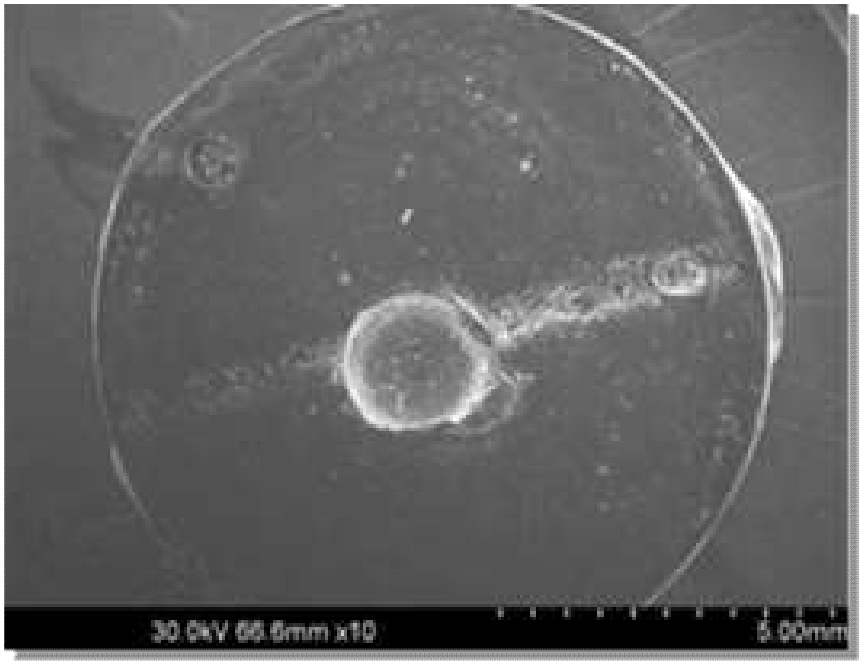

Fig. 2. Scanning Electron Microscopy (SEM) of Delivery orifice

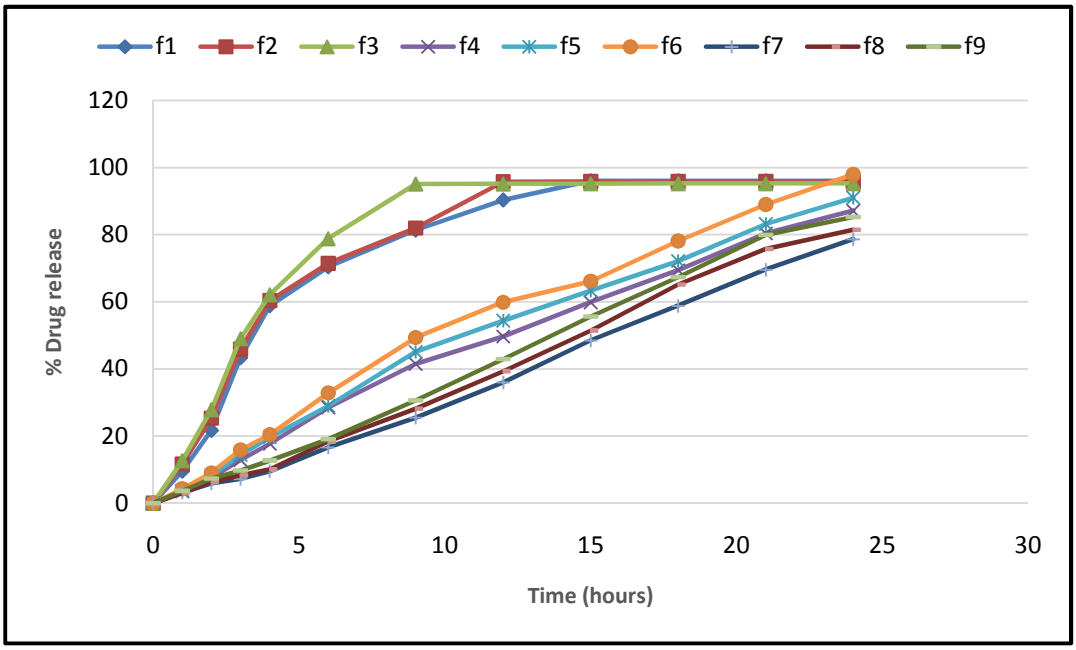

Fig. 2. Dissolution Profile of Formulation Batches (F1-F9)

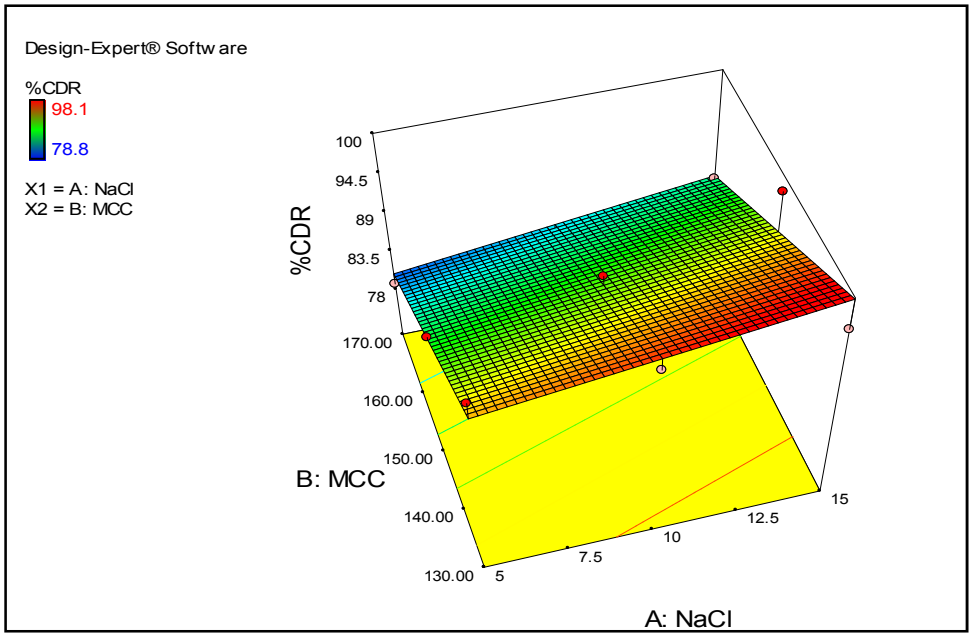

Fig. 3. Surface Response plot showing effect of Sodium chloride and microcrystalline cellulose on release

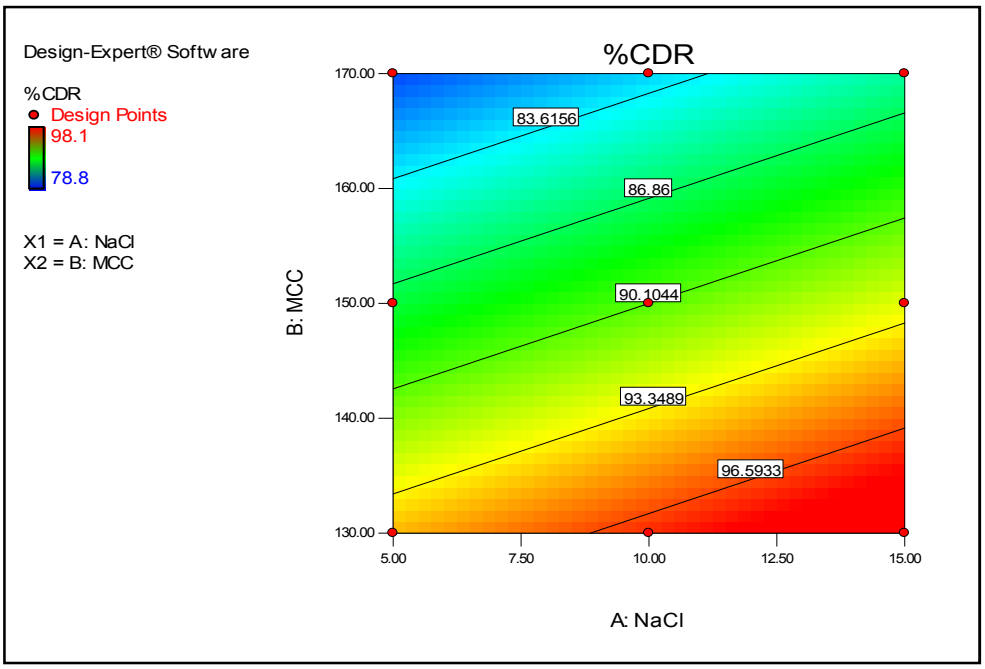

Fig. 4. Contour plot showing effect of Sodium chloride and microcrystalline cellulose on drug release

$$\% \text{ friability} = \frac{Initialweightoftablet - finalweightoftablet}{finalweightoftablet} \quad 100$$

Uniformity of Content

Twenty tablet weighed individually and powdered in mortar; 2.5 mg of drug dissolved in the 100 ml of phosphate buffer 6.8.

The solution was filtered and the content of Glipizide in the solution was determined by measuring absorbance on double beam uv spectrophotometer (Jasco V-630) at 276 nm.

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.

Thickness of film

Thickness of film was calculated by considering difference between coated tablet and uncoated tablet.

Thickness of coat =

$$\frac{t\ icknessofcoatedtablet \quad t\ icknessofuncoatedtablet}{2}$$

Weight Variation Tests

20 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.

Diameter of delivery orifice

The size of the delivery orifice was determined using scanning electron microscopy (SEM).Tablet before and after dissolution was taken and scanned.

In –vitro Release Studies

In vitro 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^{0}C. The dissolution medium (900ml) was 0.1N HCl for the first 2 hrs and phosphate buffer (pH 6.8) there after sample (5ml) were withdrawn at specific time intervals over a 24 hrs period and the medium was replenished with fresh dissolution fluid.

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 Glipizide formulation was assessed at 40±2 ^{0}c/ 75±5% RH as per ICH Guidelines. Tablets were packed in aluminium foil and stored for 6 months. Samples were analyzed after 6 months for physical appearance, drug content, and in vitro dissolution profile.

RESULTS AND DISCUSSION

The Infra-Red spectrum of Glipizide in (Figure 1).

The FTIR spectra of pure Glipizide showed the peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug.

Evaluation of Granules

The angles of repose of all formulations were with in the range of 26°-28° indicative of excellent and good flow ability. The bulk density of powder was found to be 0.31-0.35 gm/cm^3. The values indicates good packing capacity of granules. The tapped density of granules of factorial design batches were found in the range of 0.33-0.35 gm/cm^3. The compressibility index of the powder was found to be 12.21-13.63, indicating good compressibility of the granules.

Precoating evaluation

All formulated precoated osmotic tablet batches were evaluated for Weight variation, Hardness, thickness, friability and drug content. Weight variation, hardness, thickness, friability and drug content of uncoated tablets were found within the range.

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.

Diameter of delivery orifice

Evaluation of diameter size of delivery orifice was measured by Scanning Electron Microscope and was found to be 0.8 mm. SEM data given in (Figure 1).

In *Vitro* Dissolution study of Formulations (F1-F9)

The result shows that with increase in concentration of Sodium chloride (NaCl) and decreasing the concentration of microcrystalline cellulose (MCC) the release rates gradually increases. The results showed that the osmotic tablet has the ability to extend the release of Glipizide for the duration of about 24 hrs. On the basis of in–vitro drug release profile the optimum formulation f6 was selected. As it releases 98.10 % drug within 24 hrs.

Surface Response plot

Contour plot:

The contour plot showing effect of Sodium chloride and Microcrystalline cellulose on release is shown in (Figure 4).

Stability Study

Table 5. Characteristics of optimized formulation F6 after 3 months storage

Parameter	Initial sample of optimized formulation	After storage at 40±2°C / 75±5% RH, for 3 months
	F6	F6
Colour	White	White
Drug content	98.15%	98.03 %
% Drug Released (After 24 hrs.)	98.10%	98.05%

Conclusion

The sandwiched osmotic tablet system has been successfully prepared with the purpose of delivering Glipizide. The drug release of the SOTS is controlled by a drug and push layer. MCC amount of drug layer and NaCl amount of push layer have profoundly positive influence on Glipizide release. PEG increases Glipizide release rate of SOTS. Two orifices with diameter ranging from 0.50 to 1.41 mm are suitable for SOTS. A 3^2 full factorial design was performed, and the desired

release of Glipizide from the SOTS was achieved through careful monitoring of the selected formulation variables. The variables Osmogen (NaCl) and release retardant (MCC) evaluated in the study exhibited significant effect on drug release of formulation. In-vitro dissolution of osmotic tablet was performed for 24 hr and drug release was found 98.10% in 24 hr. Dissolution kinetics was studied for all formulations and optimized formulation F6 follows zero order dissolution kinetic model. The formulated formulation leads to the development of controlled release of Glipizide, can avoid dose dumping and extend the duration of action. Stability testing of optimized formulation was carried out for 6 months as per ICH guidelines and it was observed that optimized formulation was stable and there was no significant variation in the physical appearance, drug release and formulation. Overall, a controlled release SOT system for Glipizide has been successfully developed using the 3^2 full factorial designs.

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