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FORMULATION AND DEVELOPMENT OF OSMOTIC CONTROLLED RELEASE TABLET BY PUSH PULL TECHNIQUE

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ABSTRACT

The aim of the current study was to design a bilayer-core osmotic tablet which does not require laser drilling or mechanical drilling to form the drug delivery orifice instead of it water soluble pore forming agents were used in the coating solution to form a micro porous membrane. The bilayer-core consisted of two layers: (a) drug layer and (b) push layer, and sodium chloride was used as osmogent and polyox N-80 as a suspending agent in the push layer. Cellulose acetate was employed as semi permeable membrane containing polyethylene glycol 400 as a pore forming agent and also as a plasticizer to improve the film properties. It has been observed that the drug release rate increased with the amount of osmogent because of increased water uptake, and hence increased driving force for drug release. The drug release was inversely proportional to amount of polymer used in drug layer and the membrane weight gain; however, directly related to the level of pore former, in the membrane. The optimized formulation was subjected to stability studies as per International Conference on Harmonisation (ICH) guidelines and formulations were stable after a 3 month study.

KEYWORDS: Osmotic tablet, Suspending agent, Plasticizer, Polymer, stability etc.

INTRODUCTION

Drug delivery research continues to identify the new therapies for the prevention and treatment of current and new diseases. It shows major role is played by drug delivery system by providing standardized products for existing drugs in terms of either enhanced or improved presentation of drug to the systemic circulation.[1]

The osmotic-controlled release oral delivery system (OROS) is an advanced controlled release oral drug delivery system in the form of a rigid tablet with a semi-permeable outer membrane. As the tablet passes through the body, water is absorbed through the semi permeable membrane via osmosis, and the resulting osmotic pressure is used to push the active drug through the opening(s) in the gastrointestinal tract.[2]

Osmotic drug-delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semi permeable membrane coating. This coating has one or more delivery ports through which a solution or suspension of the drug is released over time. The core consists of a drug formulation that contains an osmotic agent and a water swell able polymer. The rate at which the core absorbs water depends on the osmotic pressure generated by the core components and the permeability of the membrane coating. As the core absorbs water, it expands in volume, which pushes the drug solution or suspension out of the tablet through one or more delivery port.[3]

Push-pull osmotic drug delivery features a semi-permeable, rate-controlling membrane surrounding an osmotic core, which contains a push layer and a drug layer. The rate-controlling membrane consists of cellulose acetate with various hydrophilic-hydrophobic plasticizers. The push layer swells releasing the drug at a controlled rate. This method shows significant effect on patient by providing enhanced efficacy and reduced side effects and may also reduce the number of necessary daily doses compared to conventional therapies.[4]

MATERIAL AND METHODS

Materials: API USP/BP was obtained as a gift sample from Hetero Pvt Ltd. Hyderabad, Sodium Chloride USP/BP (Nacl) was used as osmogen and was obtained from Merck, Germany. Polyox WSR N-80 USP/BP were obtained as gift samples from DOW pharmaceuticals,

Spray dried lactose (DCl) USP/BP was obtained from DFE Pharma, Sodium lauryl sulphate USP/BP was obatained from BASF, Isopropyl alcohol was obtained from Merck, Talc USP/BP was obtained from union sportive, Magnesium Stearate USP/BP was obtained from Ferro, Iron Oxide yellow IH/USP/NF was obtained from Rockwood, Cellulose Acetate USP/BP was obtained from Eastman, Lutrol E400 USP/BP was obtained from DOW pharmaceuticals, Dichloromethane USP/BP was obtained from Merck. All the chemicals used were of analytical grade.

Formulation development

The formulation of bi-layer osmotic tablets involved following steps:

Step 1: Formulation of Drug layer: Wet granulation technique was used for the granulation. All ingredients were weighed accurately & passed through 40# sieve. Then all were mixed uniformly with API. IPA was used as granulating agent. It was added slowly during the granulation process to get proper granules. The granules were dried in Tray drier at 50ºC for 20-25 minutes. Then they were passed through 30# sieve to get uniform sized granules. At the end extra-granular components were uniformly mixed with the granules.[5]

Step 2: Formulation of Push layer: Wet granulation technique was used for the granulation. All ingredients were weighed accurately& passed through 40# sieve. Then all were mixed uniformly. IPA was used as granulating agent. It was added slowly during the granulation process to get proper granules. The granules were dried in Tray drier at 50ºC for 20-25 minutes. Then they were passed through 30# sieve to get uniform sized granules. At the end extra-granular components were uniformly mixed with the granules.

Step 3: Formulation of bi-layer tablets: 8 station rotary machine (Cadmac) was used for the formulation of bi-layer tablets. The tablets were made by using 5mm concave punches. Firstly the Drug layer was pre-compressed. Then the push layer granules were added in to the die cavity over the pre compressed drug layer and again it was compressed to get bi-layer tablet. The weight and hardness were adjusted.

Step 4: Coating of bi-layer tablets:

The tablets were coated by conventional Pan coating method.[6,7]

The coating parameters were as following:

Table 1: Coating parameters.

S. No	Requirement	specifications
1.	Pan specification	SS, 70mm diameter
2.	Pan rotating rate	40 - 60 rpm
3.	Spray rate	3 - 4 mL/min/gun
4.	Bed temperature	40 – 50^{0}C
5.	Inlet temperature	50 - 55 ^{0}C

Table 2: Formula for formulation F1-F8.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Model drug	100	100	100	100	100	100	100	100
Sodium chloride	20	20	20	30	35	30	35	30
Polyox N-80	35	35	35	25	20	15	10	10
DCL -21	55	55	55	55	50	55	55	60
SLS	10	10	10	10	15	20	20	20
Talc	4	4	4	4	4	4	4	4
Magnesium Stearate	3	3	3	3	3	3	3	3
PUSH LAYER								
Sodium chloride	50	50	60	60	60	60	60	60
Polyox N-80	50	50	45	50	50	50	40	50
DCL -21	65	65	60	55	55	55	65	55
Talc	4	4	4	4	4	4	4	4
Magnesium Stearate	3	3	3	3	3	3	3	3
Iron oxide yellow	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Total	400	400	400	400	400	400	400	400

Evaluation

Pre-compression Parameters

Drug was evaluated for following parameters: Flow property of Drug, Bulk Density, and Tapped Density, Carr's index and Hausner's Ratio, Solubility, UV Analysis of drug.

Evaluation of post Compressed Tablets

General appearance

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or

absence of odour, taste etc.

Size and shape
It can be dimensionally described & controlled. The thickness of a tablet is only a variable. Tablets thickness can be measured by Digital Vernier callipers. Tablet thickness should be controlled within a 7.5% variation of standard value.

Thickness: The thickness of tablets was determined using a thickness gauge (Vernier callipers). Ten tablets from each batch were used, and average values were calculated. Tablet thickness should be controlled within a ±5% w/w variation of a standard value.

Weight variation[8]
The weight of the tablet being made is routinely measured to help ensure that a tablet contains the proper amount of drug. Take 20 tablets and weigh individually. Calculate average weight and compare the individual tablet weight to the average. The tablet passes the USP test if no more than 2 tablets are outside the percentage limit and if no tablets differ by more than 2 times the percentage limit.

Hardness[9]
Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shake of handling in manufacture, packing and shipping. Hardness generally measures the tablets crushing strength. The hardness of all the formulations was checked using 8M hardness tester. The average hardness of 10 tablets of all the batches were measured and reported.

Friability[10]
Generally the test is run for once if any cracked or broken tablet present in the sample after tumbling the tablet fails the test

Content uniformity[11]
Place ten tablets in a 500-mL volumetric flask, and 150 mL of Methanol and acetonitrile (1:1), and stir for at least 4 hr or until dissolved. Dilute with *Diluent* to volume.

Mix thoroughly, centrifuge, and supernatant was analyze d spectrophotometrically at 239 nm.

Dissolution Study: As the system is independent of pH of dissolution medium, the release was carried out in 0.1N Hydrochloric acid. The drug content was estimated using a spectrophotometer (model UV-1700, Shimadzu, Japan) at the wavelength of 250 nm.[12]

Absorbance maxima (λ max)
Spectrophotometric determination of API was done by the UV spectrophotometer with 5 ppm solution of API by using methanol. Accurately weighed 10mg of API was transferred to a 100mL volumetric flask and made up of the volume up to 100mL. Pipette out 5mL of drug solution and transferred to a 100mL volumetric flask and made the volume up to 100mL with methanol. Examined the above solution in the range of 230 to 245nm, using methanol as a blank in double beam UV-Visible spectrophotometer.[13]

Calibration curve of API
100 mg of the pure drug was accurately weighed and dissolved in 75ml methanol and the volume was made up to 100ml with methanol to give a standard stock solution of 1000 µg/ml. Aliquots of standard stock solution were pipetted out and suitable dilutions were made with methanol to get standard solutions of concentration: 10,20,30,40 & 50 µg/ml. The absorbance of sample solution was measured by UV visible spectrophotometer at 239nm.

Compatibility studies
As mentioned in section 5.2 the compatibility studies were performed for the placebo with coating polymer, API+ excipients. This is the initial spectra before charging in to stability chamber at 60^0C for 30days.[14]

FTIR (Fourier transform infrared spectroscopy) Studies
The infrared spectrum matching approach was used for detection of any possible chemical interaction between the drug and the polymer. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 15 tons pressure. It was scanned from 4000 to 400 cm^{-1} in a Perkin Elmer FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peaks using FTIR peak matching method.[15]

***In Vitro* Release Kinetics[16]**
To study kinetices data obtained from *in vitro* release were plotted in various kinetic models.

Zero order Kinetics
This model represents an ideal release profile in order to achieve the pharmacological prolonged action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs.
%R = kt

First order Kinetics
This model is applicable to study hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.
Log% unreleased = kt / 2.303

Higuchi equation
This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.
$\%R=kt^{0.}$

RESULT AND DISCUSSION
The push-pull bilayered osmotic tablet was designed to have a tablet core consisting of drug along with osmagen, low viscosity hydrophilic polymer and other conventional excipients. The push compartment consists of swellable polymer and osmagen. The compressed bilayer tablet was surrounded by a membrane consisting of a semipermeable membrane-forming polymer and a plasticizer capable of improving the film-forming properties of the polymers. The semipermeable membrane-forming polymer was selected in regard to its permeability to aqueous fluids but substantially impermeable to the components of the core.

In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane. The drug is released through the holes present in the membrane. Cellulose acetate was used as water-insoluble polymer and Propylene glycol/Triethylcitrate were used as water-soluble and water-insoluble plasticizers, respectively. Formulation development involved trials using different ratios of types of polymers and osmotic agents in both layers.

Pre-compression Parameters
Table 3: Pre-compression evaluation.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Bulk density gm/ml	0.30	0.29	0.28	0.32	0.35	0.40	0.32	0.40
Tapped density gm/ml	0.42	0.43	0.424	0.43	0.40	0.45	0.43	0.45
Carr'sindex %	30.4	30.9	34.8	25.5	12.5	12.1	25.5	12.5
Hausner's ratio	1.42	1.44	1.53	1.34	1.14	1.12	1.34	1.14

Post-compression parameters
General appearance
The general appearance of prepared osmotic tablets was found Round, biconvex, 10mm white tablets.

Table 4: Post-compression evaluation.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Wt. variation (n=20)	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Thickness(mm) (n=10)	4.21±0.3	4.20±0.2	4.35±0.3	4.14±0.5	4.14±0.5	4.33±0.3	4.14±0.4	4.13±0.3
Hardness(Kp) (n=6)	5.4 kp	5.7 kp	5.9 kp	6.0kp	5.5kp	6.6 kp	6.4 kp	7.1 kp
Friability (%)	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Assay (%) (n=3)	99.8± 0.5	100.3± 0.2	100.3± 0.7	100.9± 0.5	99.1± 0.6	100± 0.4	101.3± 0.8	101.3± 0.8
Thickness of coat(µ) (n=10)	180± 20	170± 30	270± 20	160± 20	260± 30	260± 30	170± 20	180± 30

Dissolution Study
Table 5: *In vitro* drug release of various formulations.

Sr. No	Formulation	Time	1	2	3	4	5	6	8	12
1	F1	0	8.98	18.68	22.5	26.71	28.06	30.21	46.07	61.04
2	F2	0	10.51	21.39	26.02	31.32	33.5	42.5	50.08	64.06
3	F3	0	14.46	30.87	36.54	40.32	45.31	52.72	65.53	72.58
4	F4	0	12.63	25.08	29.72	38.44	42.26	45.52	65.46	83.76
5	F5	0	9.85	21.09	27.75	31.62	34.72	49.25	62.93	80.73
6	F6	0	12.03	26.31	30.52	42.74	48.78	52.23	67.32	84.66
7	F7	0	16.5	21.39	30.87	36.54	42.74	56.72	69.53	97.63
8	F8	0	14.69	36.37	42.35	51.79	55.74	60.1	64.2	88.25

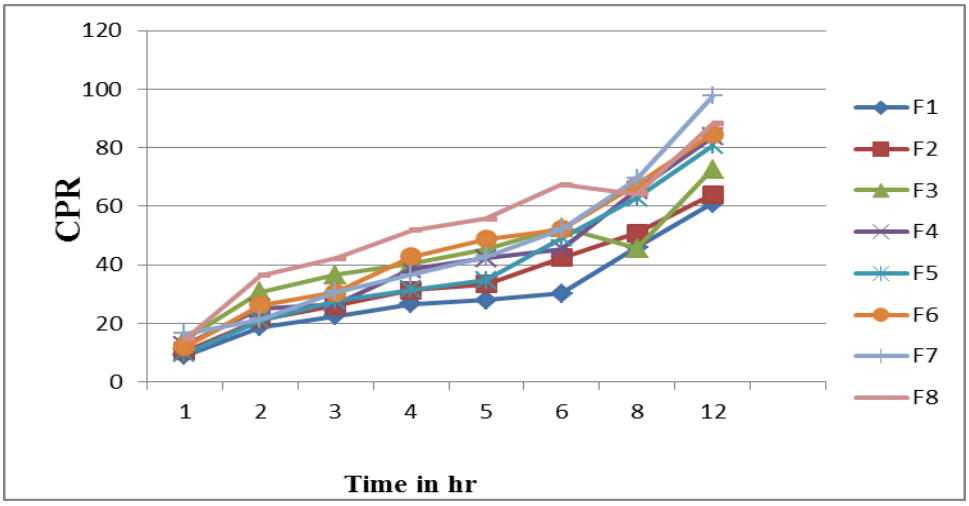

Fig. 1: *In vitro* drug release of various formulations.

Determination of Absorbance Maxima (λ max)

The procedure for determining λ max was given in section 6.6. The maximum absorbance was observed at wavelength **239 nm (**λ max), which was matched with reported wavelength.

Calibration curve

By following the procedure mentioned in section the linearity curve was plotted between concentration and absorbance.

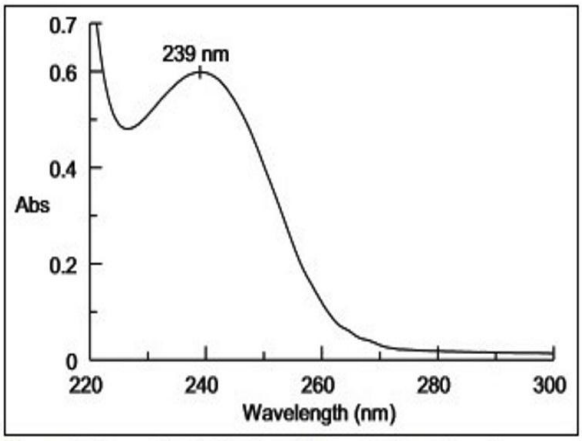

Fig. 2: UV Spectra of API at 5 ppm concentration.

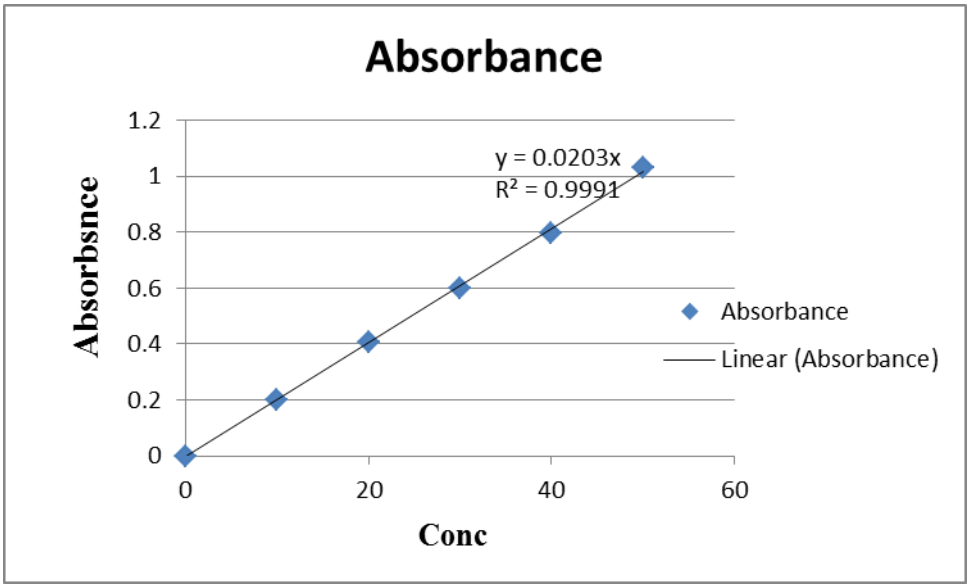

Fig. 3: Linearity curve was plotted between concentration and absorbance.

Compatibility studies

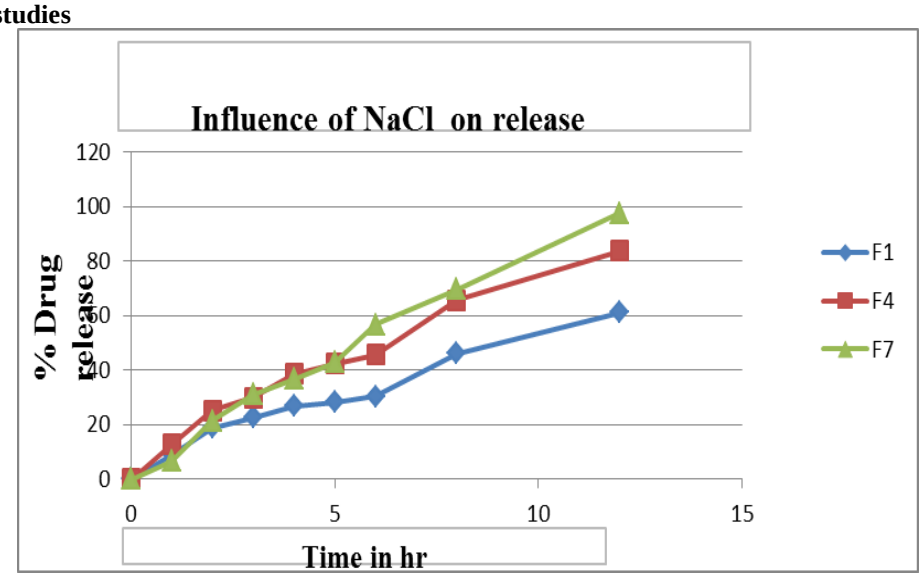

Fig. 4: Effect of sodium chloride on drug release of F7 formulation.

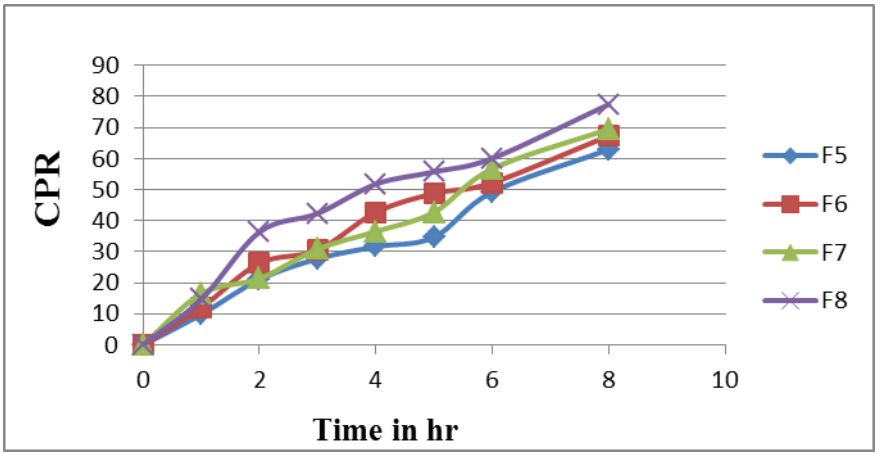

Fig. 5: Effect of PEO on drug release of F7 formulation.

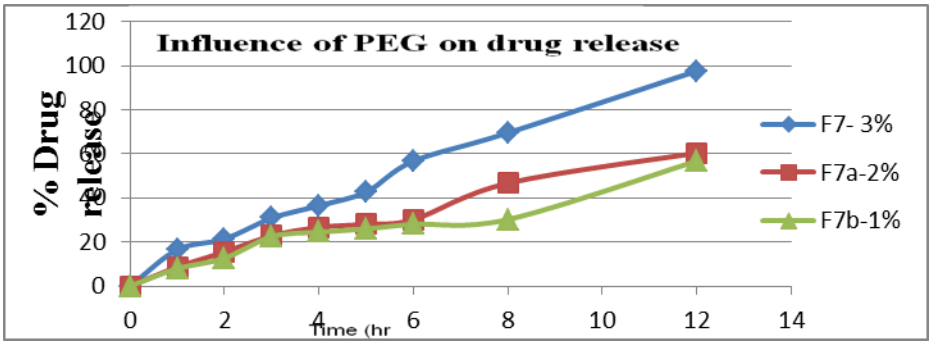

Fig. 6: Effect of PEG 400 on drug release of F7 formulation.

FTIR (Fourier transform infrared spectroscopy) Studies

Initial spectra: The compatibility studies were performed for the placebo with coating polymer, API+ excipients. This is the initial spectra before charging in to stability chamber at 60^0C for 30days. The initial mixing of API with various excipients used in the formulations. After charging the drug and excipients in a stability chamber at 60^0C for 15 days it was found that there was no shift in the functional groups of API when mixed along with various excipients. Hence, good API and excipient compatibility was found.

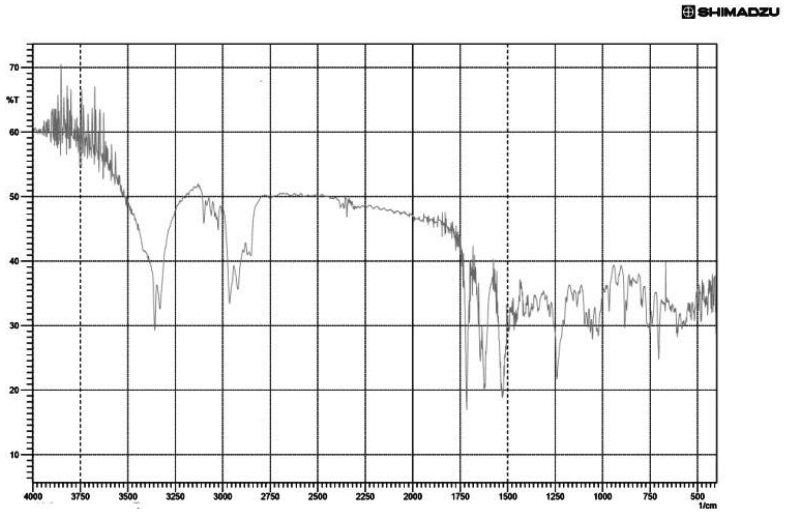

Fig. 7: FTIR spectra of API with NaCl.

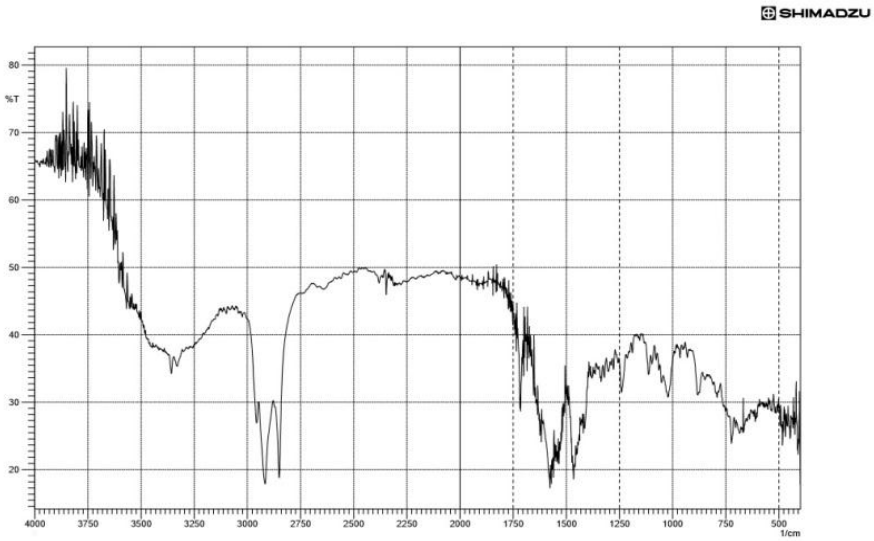

Fig. 8: FTIR spectra of API+PEO.

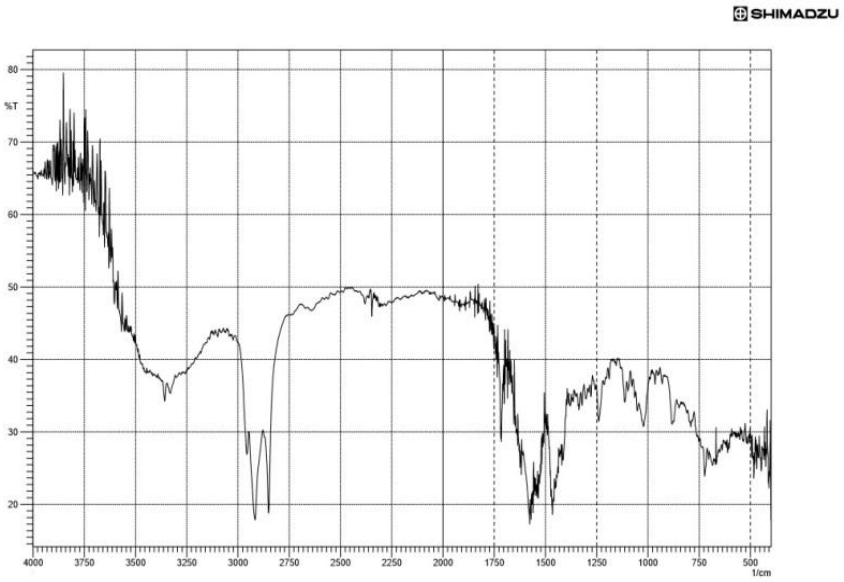

Fig. 9: IR spectra of API+spray dried lactose.

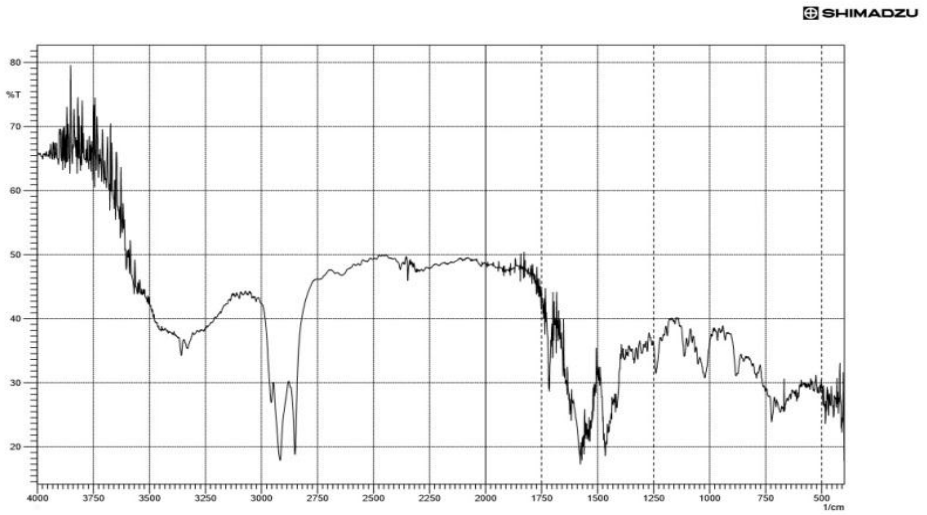

Fig. 10: IR spectra of API+Sodium lauryl sulphate.

IR Spectra after 30 days

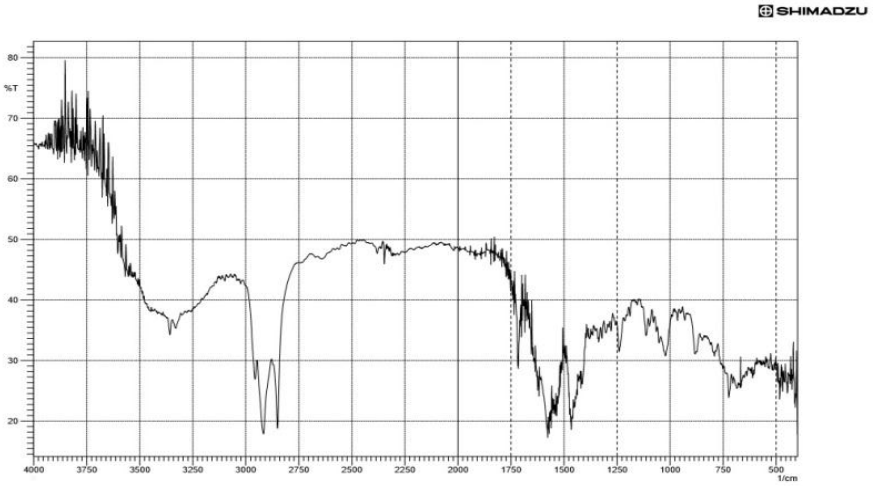

Fig. 11: FTIR spectra of API + talc.

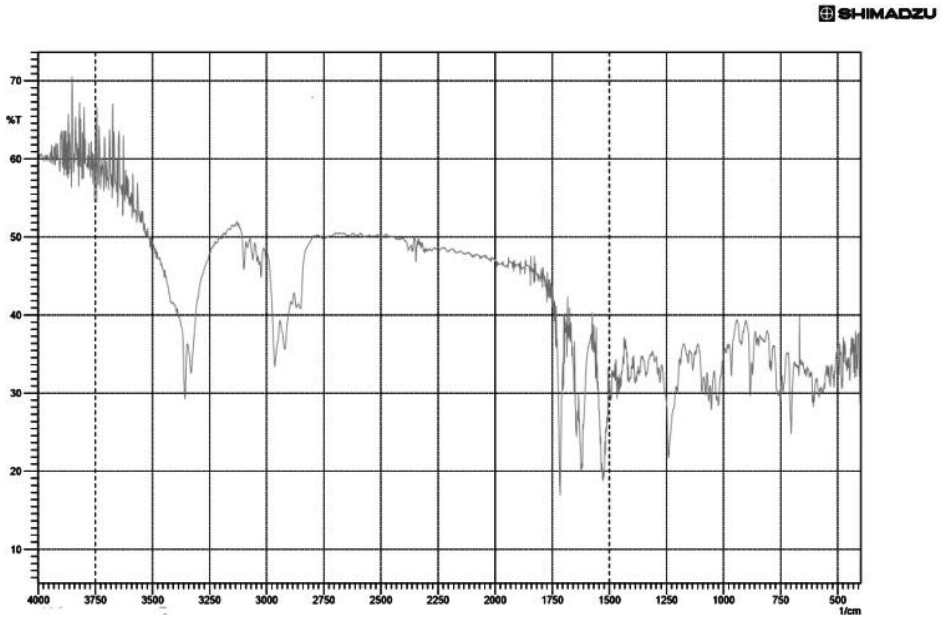

Fig. 12: ATR spectra of API+ Magnesium state.

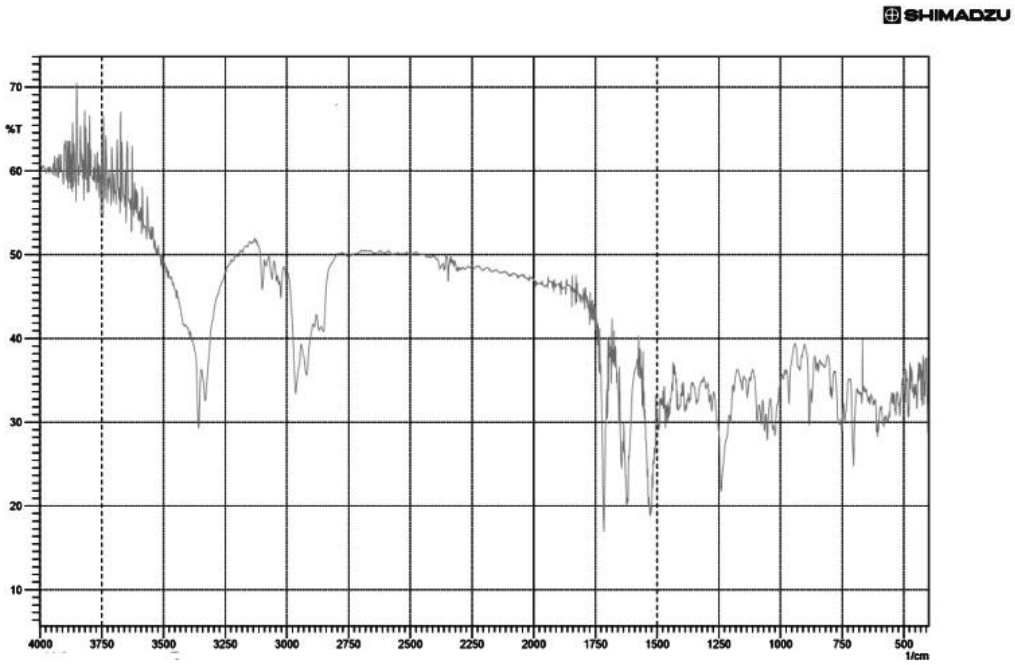

Fig. 13: FTIR spectra of API+ coating polymer.

***In vitro* release kinetics**

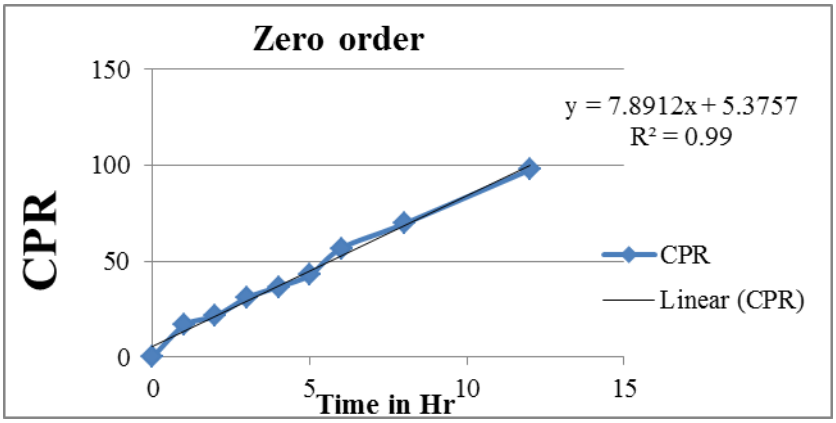

Fig. 14: Zero order kinetics for F7 formulation.

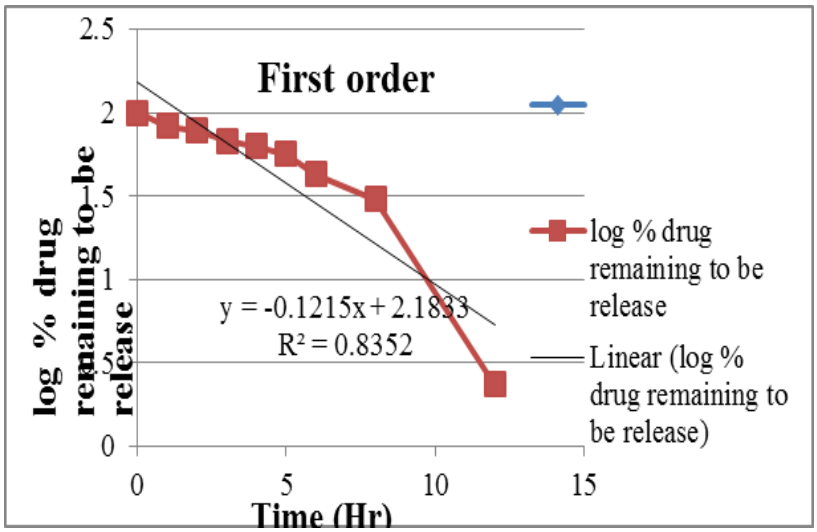

Fig. 15: First order kinetics for F7formulation.

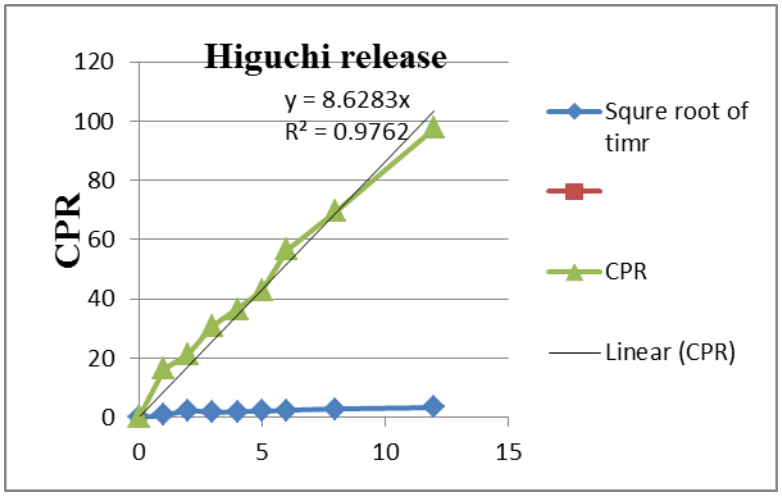

Fig. 16: In Higuchi release profile for F7.

Stability Studies

The optimized formulation F7 was subjected for temperature dependent stability studies as per ICH guidelines. The formulation was stored at 40±2°C/ 75±5% RH in stability chamber for a period of 3 months. The formulations were evaluated for appearance, hardness, drug content and *In-vitro* drug release. The formulations subjected to stability studies at each of the three temperature and humidity conditions were evaluated in terms of appearance, drug content and in vitro drug release. No significant changes were seen in the physicochemical parameters of the formulations over a period of 3 months.

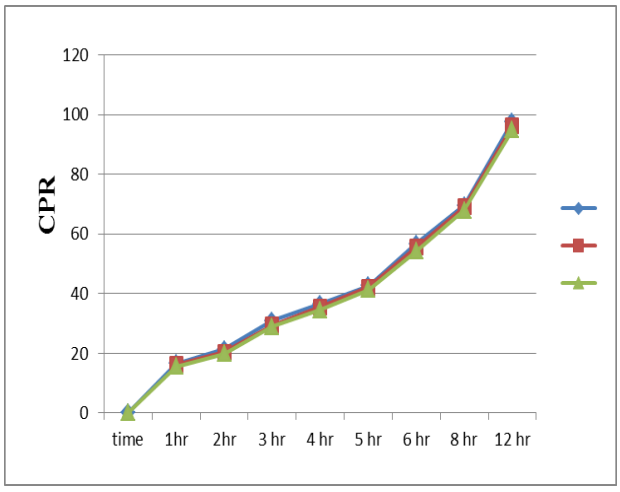

Fig. 17: Stability data for F7 formulation stored at 40^{0}C/75%RH.

CONCLUSION

The push pull osmotic tablets (PPOT) have been successfully prepared with the purpose of delivering water soluble drug. The drug release is controlled by a drug layer. The desired zero-order release profile was obtained by optimizing the concentrations of Osmogen and polymer in both the layers. From the results it was observed that the drug release increases with the amount of osmogen due to the increased water uptake and increased driving force for drug release. Sodium chloride amount in drug layer, PEO amount in drug layer, % PEG in coating membrane and % weight gain of coating membrane have profoundly positive influence on drug release. The drug release was further retarded using a proper concentration of PEO to achieve the desired zero-order release profile. Here, PEG is also used as plasticizer that improved the film properties of membrane. These prepared tablets were independent of release media. The drug release from these prepared osmotic tablets was 12 hr. As per literature survey there is no extended release formulation of antiviral drug. The system was easy to formulate and cost effective.

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