WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 5, 1285-1297. Research Article ISSN 2277– 7105

# DEVELOPMENT AND EVALUATION OF ELEMENTARY OSMOTIC PUMP OF ISOXSUPRINE HYDROCHLORIDE

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Article Received on
12 March 2016,
Revised on 03 April 2016,
Accepted on 24 April 2016
DOI: 10.20959/wjpr20165-6203

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## ABSTRACT

The aim of present study was to design and evaluate an elementary osmotic pump-based drug delivery system for controlled release of Isoxsuprine hydrochloride for peripheral and cerebral vasodilation. Core tablets were prepared by direct Compression method. Effects of different variables like amount of osmogen, orifice size, coating thickness and dissolution media were studied on release profile. It observed that the combination of PEO 100000 and PEO 300000 give the desired drug release. On increasing the amount of osmogen, the release of drug was found to be increased. On comparison of ***f2*** value no significant effect of pH of dissolution medium, agitation rate was observed but it was observed that the coating thickness decrease it shows the faster drug release and increase in orifice size also increases the drug release. It was concluded that the osmotic pump tablets could provide more prolonged and controlled release that may result in an improved therapeutic efficacy and patient compliance.

**KEYWORDS:** Elementary osmotic pump, Zero order, Isoxsuprine Hydrochloride, Controlled release.

## INTRODUCTION

Most of the drugs are given by oral route because it is most preferred and patient convenient route. The oral route cans also effectively achieving both local and systemic effects. The tablet is the most favorable dosage form for oral route. The tablet having many advantages over other dosage form such as the tablet dose is most precise, least content variability, lightest, compact, transportation is easy and cheap.[1] However, the conventional tablet dosage form have many disadvantages like dosing frequency; no control over release of drug, for maintaining the effective concentration at target site periodic administration of excessive

drug, is essential the plasma concentration is changing and unpredictable. Controlled release (CR) is the most ideal oral drug delivery because it provides the desired concentration of drug at absorption site, maintaining plasma concentration within the therapeutic range and reducing dosing frequency. CR is most effectively used in chronic condition, reduced side effect and the dosing frequency so greater patient convenience. CR mechanism can be achieved generally by three methods a) matrix system b) reservoir system and c) osmotic system.

In matrix system, the drug is embedded in polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded \ coated by the rate controlling membrane. However factor like pH, presence of food and other physiological factor may affect drug release from conventional controlled release systems. Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system.

Osmotic drug delivery systems mechanism is mainly depends on the osmosis. The osmosis is the process of moment of solvent from lower concentration to higher concentration and for this the pressure is required, and this pressure is created in the tablet by the osmogent present in the tablet.[2] When an osmotic system is exposed to water or any other fluid, the drug core osmotically drives water at a constant and controlled rate, determined by the membrane water permeability and the osmotic pressure of the core formulation. This causes an increased internal osmotic pressure. Then the drug is comes out from the tablet through the orifice that is created by laser or mechanical drill. The rate of drug delivery is constant as long as drug is present, but thereafter it declines parabolically to zero. As the drug is exhausted, concentration of solute falls below saturation levels and the osmotic pressure gradient across the membrane vanishes. There are four methods of osmotic drug delivery system are as follows.[2-25]

1] Elementary Osmotic Pumps (EPO)

2] Push-pull Osmotic Pumps (PPOP)

3] Controlled Porosity Osmotic Pumps (CPOP)

4] Sandwiched Osmotic Tablet System (SOTS)

Elementary osmotic pumps are systems that deliver the drug in form of solution, at a controlled rate. 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.

Isoxsuprine is an α-receptor antagonist with β-receptor agonist action. It causes peripheral and cerebral vasodilatation by directly acting on vascular smooth muscle. It also causes cardiac and uterine relaxation.[26-28]

## MATERIALS AND METHODS

Isoxsuprine Hydrochloride was gifted by S.Kant Healthcare, Cellulose acetate as membrane former obtained from Central Drug House, New Delhi, India and Signet Chemical Mumbai. Sodium Chloride and Triacetin was purchased from S.D. Fine Chemical. Various grades of Polyethylene Oxide (PEO) of Dow Chemical was gifted Colorcon India. Magnesium Stearate and Microcrystalline Cellulose was gifted by Vasa Pharmachem, Ahmedabad. Colloidal Silicon Dioxide (HDK N20 Pharma) was Gifted by Wacker Chemie.

### Preparation of Core Tablet

The tablet was prepared by direct compression method. The weighed quantity of Isoxsuprine Hydrochloride, Sodium Chloride and Polyethylene Oxide, Microcrystalline Cellulose and Colloidal Silicon Dioxide were passed through the sieve 40#. Material was blended homogeneously in mortar and pestle in geometric proportion. Blend was again shifted through the sieve 40#. The above shifted material was lubricated by magnesium stearate just before the compression. These blended materials were ready for compression. Different formula was given in Table 1.

### Evaluation of Tablet Blend

**Bulk Density:** An accurately weighed quantity of powder, which was previously passed through sieve # 40 [USP] and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The

volume measure was called as the bulk volume and the bulk density is calculated by following formula; **Bulk density = Weight of powder / Bulk volume.**

**Tapped Density**

After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (Va) and again tapped for 750 times and volume was noted as (Vb). If the difference between Va and Vb not greater than 2% then Vb is consider as final tapped volume. The tapped density is calculated by the following formula.

**Tapped density = Weight of powder / Tapped volume**

**Carr's Index [Compressibility Index] and Hausner's Ratio**

Carr's index and Hausner's ratio measure the propensity of powder to be compressed and the flowability of powder. Carr's index and Hausner's ratio can be calculated from the bulk and tapped density.

$$\text{Carr's index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped Density}} \times 100$$

**Hausner's ratio = Tapped density / Bulk density**

**Coating of core tablets:** The coating of core tablets was done in coating pan. The composition of coating solution is given in Table ll. Cellulose acetate (7% w/V) as semipermeable membrane (SPM) former and PEG 400 as plasticizer were used in coating solution. The core tablets were placed in coating pan which was initially rotated at low speed (2-8 rpm) and heated air was passed on the tablet bed. Later on speed was kept at 15-20 rpm and coating solution was manually sprayed over the surface of the tumbling tablets with a spray gun. The inlet air temperature was kept at 50-55°C and this manual coating procedure was based on intermittent spraying and drying. After coating, the tablets were dried overnight at 60°C to remove residual solvent. The coating composition of tablets is shown in Table ll. Orifices of different diameters (0.5, 0.7, & 0.9 mm) were drilled manually on one side of the coated tablet by a mechanical drill in different batches.

**Evaluation of Coated Tablet**

**Weight variation:** The weight variation test was carried out for 20 randomly selected tablets (core and coated) from each batch and weighed them individually. The average weight was

calculated and compared with the individual tablet weights with the average tablet weight. Details are given in Table 3.

**Hardness of core tablets:** Tablet hardness is defined as the load required crushing or fracturing a tablet placed on its edge. It is also termed as tablet crushing strength. In this study Pfizer hardness tester was used. The diametrical crushing strength test was observed for 10 tablets from each formulation. The results are shown in Table 3.

**Thickness of core and coated tablets**

Thickness of 20 core and coated tablets from every batch of formulation was measured using a screw gauge and standard deviation was calculated. The results are shown in Table 3.

**Diameter of core and coated tablets:** Diameter of 20 core and coated tablets from each batch was measured using screw gauge and standard deviation was also calculated. The results are shown in Table 3.

**Table 1 – Formula of core tablet and coated tablet**

| Core Tablet | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Material** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| **Isoxsuprine Hydrochloride** | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 |
| **Sodium Chloride** | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| **PEO 100000** | 70 | 60 | 50 | 0 | 0 | 0 | 40 | 30 | 20 |
| **PEO 300000** | 0 | 0 | 0 | 70 | 60 | 50 | 30 | 40 | 50 |
| **Magnesium Stearate** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Colloidal Silicon Dioxide** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Microcrystalline Cellulose** | 325 | 335 | 345 | 325 | 335 | 345 | 325 | 325 | 325 |
| | | | | | | | | | |
| **Coating** | | | | | | | | | |
| **Cellulose Acetate** | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |
| **PEG 400** | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| **Acetone/IPA** | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |

**Table 2 – Evaluation of Blend before compression**

| **Parameters** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** | **F10** | **F11** | **F12** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Tapped Density (gm/ml)** | 0.506 | 0.506 | 0.498 | 0.487 | 0.499 | 0.502 | 0.501 | 0.499 | 0.503 | 0.501 | 0.509 | 0.51 |
| **Bulk Density (gm/ml)** | 0.437 | 0.431 | 0.421 | 0.414 | 0.434 | 0.436 | 0.431 | 0.428 | 0.425 | 0.432 | 0.431 | 0.436 |
| **Hausners Ration** | 1.16 | 1.17 | 1.18 | 1.18 | 1.15 | 1.15 | 1.16 | 1.17 | 1.18 | 1.16 | 1.18 | 1.17 |
| **Carrs Index** | 13.64 | 14.82 | 15.46 | 14.99 | 13.03 | 13.15 | 13.97 | 14.23 | 15.51 | 13.77 | 15.32 | 14.51 |
| **Angle of Repose** | 32.5 | 33 | 34.7 | 33.9 | 33.5 | 35.2 | 34.8 | 33 | 33.9 | 35.6 | 34.3 | 35.1 |

**Table 3 – Evaluation of Core and Coated Tablet**

| Parameter | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Core Tablet Weight (mg) | 501.3±0.75 | 502.3±0.56 | 501.25±0.65 | 499.87±0.59 | 503.5±0.24 | 507.57±0.76 | 501.73±0.67 | 508.53±0.39 | 502.77±0.57 |
| Coated Tablet Weight (mg) | 537.25±0.27 | 534.8±0.57 | 539.56±0.81 | 535.62±0.32 | 538.64±0.93 | 540.20±68 | 538.38±0.47 | 540.64±0.68 | 535.27±0.19 |
| Hardness of Core Tablet ($Kg/cm^{2)}$ | 4.89±0.65 | 5.15±0.69 | 5.34±0.10 | 5.2±0.30 | 5.22±0.17 | 5.12±0.28 | 5.42±0.40 | 5.30±0.50 | 5.10±0.20 |
| Diameter of Core Tablet (mm) | 9.01±0.1 | 9.08±0.4 | 9.03±0.3 | 9.02±0.2 | 9.01±0.5 | 9.07±0.1 | 9.03±0.2 | 9.04±0.7 | 9.02±0.2 |
| Diameter of Coated Tablet | 9.45±0.9 | 9.54±0.8 | 9.48±0.5 | 9.46±0.7 | 9.53±0.2 | 9.51±0.5 | 9.47±0.4 | 9.48±0.6 | 9.46±0.7 |
| Thickness of core Tablet (mm) | 5.6±0.1 | 5.5±0.2 | 5.6±0.2 | 5.5±0.3 | 5.5±0.1 | 5.6±0.2 | 5.7±0.2 | 5.6±0.4 | 5.0±0.1 |
| Thickness of Coated Tablet | 6.1±0.2 | 6.0±0.1 | 6.1±0.7 | 5.9±0.2 | 6.1±0.3 | 6.0±0.2 | 5.9±0.2 | 6.0±0.2 | 6.1±.3 |

**Table 4: Kinetics of in-vitro drug release from different batched of monolayer osmotic pump**

| Formula | Zero Order | First Order | Higuchi | Peppas |
|---|---|---|---|---|
| F1 | 0.9726 | 0.8125 | 0.992 | 0.963 |
| F2 | 0.9852 | 0.9032 | 0.9507 | 0.9837 |
| F3 | 0.983 | 0.8269 | 0.99 | 0.9516 |
| F4 | 0.9939 | 0.8269 | 0.9744 | 0.9312 |
| F5 | 0.9927 | 0.8208 | 0.9657 | 0.9619 |
| F6 | 0.9819 | 0.9792 | 0.9949 | 0.9309 |
| F7 | 0.9785 | 0.9129 | 0.9742 | 0.9886 |
| F8 | 0.9946 | 0.9945 | 0.9755 | 0.9895 |
| F9 | 0.8672 | 0.8713 | 0.9583 | 0.9748 |

**In-vitro dissolution study:** All the developed formulations of Isoxsuprine hydrochloride were subjected to in-vitro release studies using USP-1 basket type dissolution apparatus. The formulated tablet was added to 900 ml of phosphate buffer pH 6.8 at 371 0.5°C for 12hrs at 50 rpm. The samples were withdrawn (5ml) at different time interval and replaced with an equivalent amount of fresh medium over 18 hrs. The dissolution samples were filtered to remove particulate matter, after filtration samples were analyzed using UV spectrophotometer (Systronic 2202) at 274.2 nm. The absorbance of all samples at different time interval was measured. The concentration, amount of drug released and the percentage drug release were calculated.

**Influence of different process variables on in-vitro drug release**

**Influences of osmagents:** Different amount of osmagents (i.e.sodium chloride, PEO 100000 and PEO 300000) and PVP K-30 was taken in core tablets. The effect of their presence on release pattern was studied.

**Influences of dissolution media on drugs release**

To study the effect of dissolution media on drug release and to assure a reliable in-vitro performance, release studies tests of the optimal formulation(OPT-3) were performed in 0.1 N hydrochloric acid solution (pH 1.2), phosphate buffer (pH 6.8) and phosphate buffer (pH 7.4) at 371 2°C. The samples were taken out at predetermined intervals and analyzed after filtration by UV spectroscopic method at 274.2 nm for isoxsuprine hydrochloride.

**Influences of agitation intensity on drug release**

Drug release from osmotic pumps to a large extent is independent of agitation intensity of the release media. To study this parameter, release studies of the optimized formulation was performed at different agitation intensity 50, 100 and 150 rev/min. in USP-1 basket type dissolution apparatus. All samples were withdrawn at predetermined intervals and analyzed after filtration by double beam UV Spectrophotometer (Systronic 2202) at 274.2 nm for isoxsuprine hydrochloride.

**Influence of orifice size and membrane thickness**

The elementary osmotic pump (EOP) systems contain at least one delivery orifice in the membrane for drug release. It was suggested that the size of delivery orifice must be in appropriate range; this must be smaller, than the maximum limit to minimize the diffusion of drug and also must be larger than the minimum size to minimize hydrostatic pressure inside the system. Similarly EOP systems must also have optimum thickness of for better release of drug.

**Kinetics of drugs release**

Dissolution data of the prepared formulations of isoxsuprine hydrochloride osmotic pump tablet was fitted to various mathematical models (zero-order, first order, Higuchi and Hixson-crowell) in order to describe the kinetics of drug release.

## RESULT AND DISCUSSION

To study the influence of tablets formulation variables on drug release, tablets with various compositions were prepared, subsequently coated with composition given in table 1. The data revealed that formulation F9 containing combination of Polyethylene Oxide 100000 (PEO 100000) and Polyethylene Oxide 300000 (PEO 300000) have higher drug release rate than formulation F8 having lesser amount of PEO 100000 and PEO 300000. The higher release rate from F 9 may be due the presence of PEO 100000 and PEO 300000 which acts as

osmagent and hence increases the osmotic pressure and results more drug release from the core. Formulation F 8 was selected for further studies because it gives the desired drug release. A significant influence of combination PEO 100000 and PEO 300000 of was observed. With an increasing amount of PEO, the release rates were increased, because the increasing osmotic pressure made more drugs release.

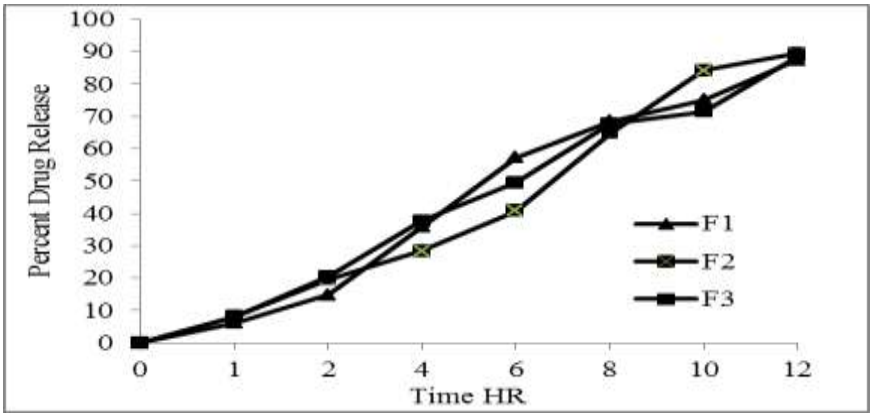


**Fig 1 Influence of PEO 100000 on drug release**

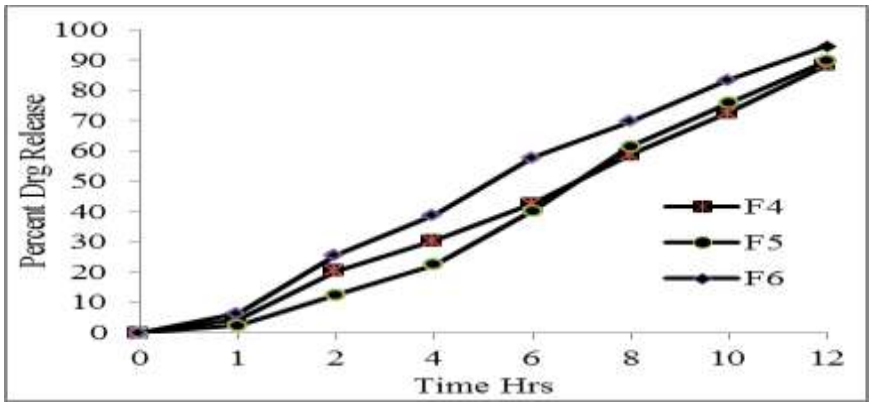


**Fig 2 Influence of PEO 300000 on drug release**

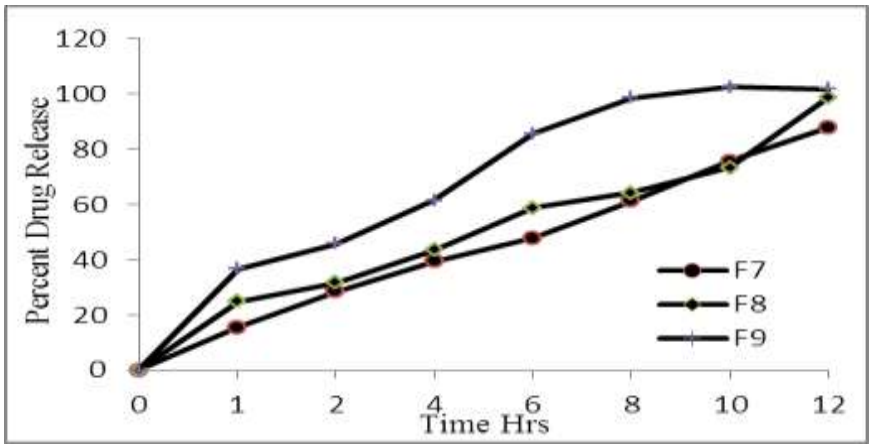


**Fig 3 Influence of combination of PEO 100000 and PEO 300000 on drug release**

The release rate at 50 rpm, 100 rpm, and 150 rpm were analyzed. Also ***f*2** factor (similarity factor) was analyzed. ***f*2** value showed a release profile which could be considered similar to the theoretical target profile i.e. F8Thus it could be predicted that the mobility of gastrointestinal tract may not affect the drug release of the osmotic pump tablets F8.

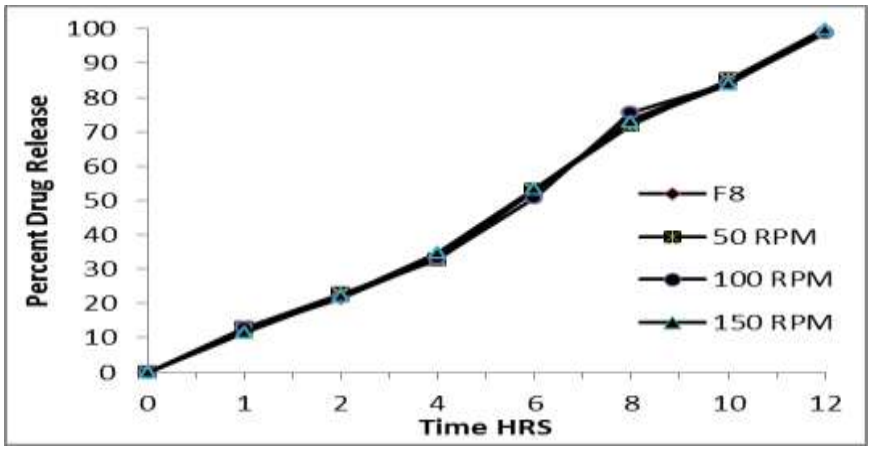


**Fig 4 Influence of agitation on drug release**

F8 in different dissolution media were recorded. Release pattern in all media was found almost to be similar. ***f*2** value showed a release profile which could be considered similar to the theoretical target profile i.e. F8. This can be explained as the CA act as semipermeable membrane since, ions are not readily exchanged through it. Therefore the release of the drug from these systems is independent of pH of the surrounding medium. (Fig.5).

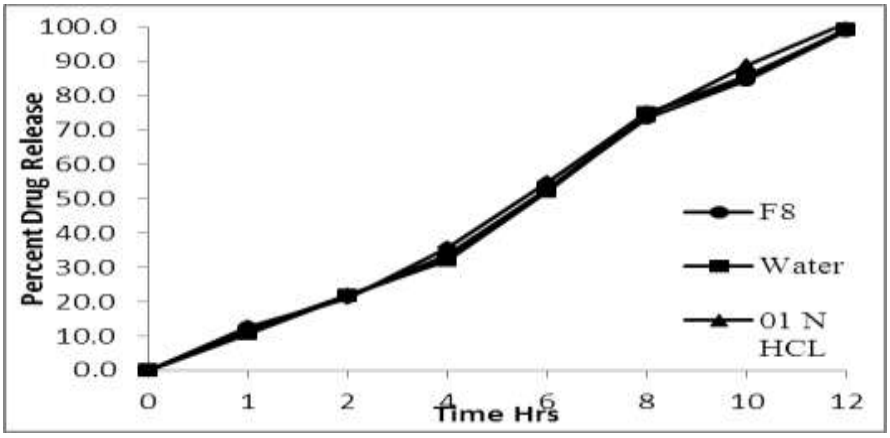


**Fig 5 Influence of dissolution media on drug release**

The formulation F8 was coated with coating solution as per formula in Tabe1 for the different coating levels. For further study 7% was adopted. No significant difference in release of drug was observed in the tablets with membrane thickness of 8% and 9%. (Fig. 6). But it shows higher drug release at 6%. ***f*2** value showed a release profile which could be considered

similar to the theoretical target profile of F8 for 8% and 9%. But it deviates for thickness of 8%.

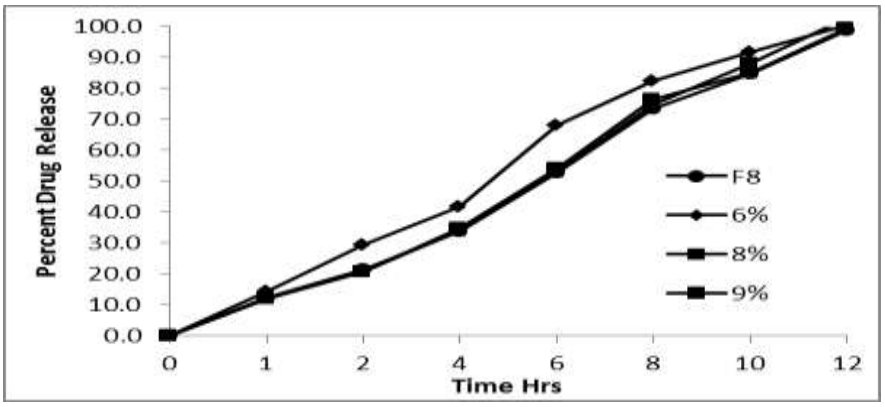


**Fig 6 Influence of coating thickness on drug release**

The formulation F8 was coated with coating solution as per formula in Tabe1 and the drug release profile was recorded for drug from the larger orifice. For further study 0.5 mm orifice diameter was adopted. Further it was also observed that the tablet with the orifice size of 0.5 mm showed the maximum and rapid drug release. No significant difference in release of drug was observed in the tablets with orifice size of O.7mm and 0.9 mm. (Fig. 7). But it shows higher drug release through the large diameter i.e. 1.1. This may be because of diffusion of drug through the orifice. ***f2*** value showed a release profile which could be considered similar to the theoretical target profile of F8 for orifice size 0.5 mm, 0.7 mm and 0.9 mm. But it deviates for 1.1 mm orifice size.

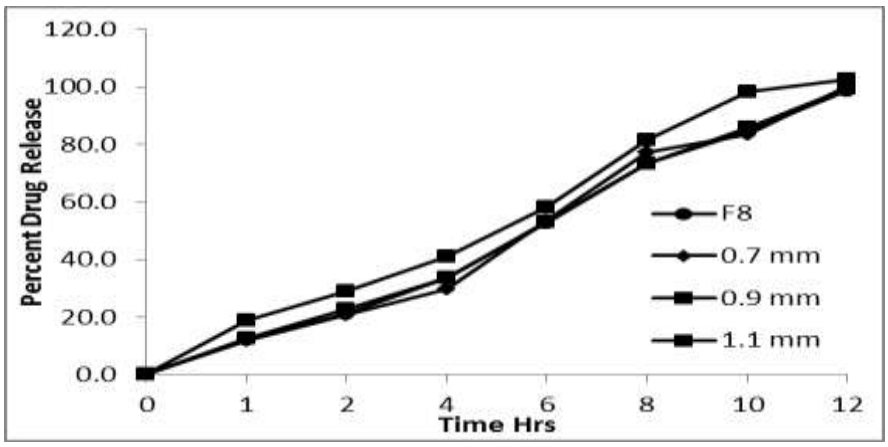


**Fig 7 Influence of orifice size on drug release**

## CONCLUSION

So it may conclude that the formulation containing the combination of PEO 100000 and PEO 300000 shows the zero order drug release. And the coated formulation show no effect of

dissolution medium and agitation speed which is compared by ***f2*** value. But it shows the significance effect of coating thickness and orifice size.

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