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Development and Evaluation of Sandwiched Osmotic System Of Isoxsuprine Hydrochloride

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Abstract

The aim of present study was to design and evaluate sandwiched 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 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:- Sandwiched Osmotic System, Zero order, Isoxsuprine Hydrochloride, Controlled release, Semipermeable Membrane, Cellulose Acetate, Polyethylene Oxide

INTRODUCTION: -

Most of the drugs are given by oral route because it is most preferred and patient convenient route. The oral route can 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[3-6]

1] Elementary Osmotic Pumps (EPO)[7-8]
2] Push-pull Osmotic Pumps (PPOP)[9-17]
3] Controlled Porosity Osmotic Pumps (CPOP)[18]
4] Sandwiched Osmotic Tablet System (SOTS)[19-27]

Sandwiched Osmotic Tablet System is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment the middle push layer containing the swelling agents' swells and the drug is released from the two orifices situated on opposite sides of the tablet and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa [1,19-27]

Isoxsuprine is a 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. So it is advisable to prepare drug in control release formulation to improve the patient compliance[28-30].

EXPERIMENTAL

Materials and Methods

Isoxsuprine Hydrochloride was gifted by S.Kant Healthcare and Tablet India Ltd, Cellulose Acetate as a semipermeable membrane former was obtained from Central Drug House and Signet Chemicals Mumbai. Sodium Chloride and Triacetine was purchased from S.D.Fine Chemicals. Polyethylene Oxides (PEO) of Dow Chemicals of various grades was gifted by Colorcon India. Magnesium Stearate and Microcrystalline Cellulose was gifted by Vasa Pharmachem, Ahmedabad. Colloidal Silicon Dioxide was obtained from as gift sample from Glenmark Pharmaceutical, Nasik.

Preparation of core tablets

Core tablets of Isoxsuprine Hydrochloride were prepared by direct compression method. All the excipients were passed through the sieve 40#. All the excipients except lubricant (magnesium stearate) were manually blended homogeneously in a mortar and pestle through geometric dilution. The blend was mixed for 10-15 minutes. Then this blend was again passed through the sieve 40#. Magnesium Stearate as lubricant was added before the compression. The homogenous blend was then compressed into tablets having an average weight of 500 mg using single stroke 9 mm tablet punching machine. The formula for different batches of core formulation is shown in Table 1.

Coating of Core Tablet

The coating of core tablets was done in conventional coating pan. The composition of coating solution is given in Table 1. Cellulose acetate (7% w/v) as semipermeable membrane (SPM) former and Triacetin 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 2. Orifices of different diameters (0.5, 0.7, 0.9 & 1 .1 mm) were drilled manually on one side of the coated tablet by a mechanical drill in different batches.

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 and details are given in Table 2

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 and details are given in Table 2

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

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 and details are given in Table 2.

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

Hausners ratio = Tapped Density/Bulk Density

Evaluation of Core 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 2.

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 2.

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

Orifice diameter

The average orifice diameter of the osmotic pump tablets (n=20) was determined microscopically using optical microscope fitted with a pre-calibrated ocular scale.

Table 1 – Formulation of Core Tablet and Coated Tablet

Core Tablet									
Material	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Isoxsuprine Hydrochloride	40	40	40	40	40	40	40	40	40
Sodium Chloride	10	10	10	10	10	10	10	10	10
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Colloidal Silicon Dioxide	1	1	1	1	1	1	1	1	1
Microcrystalline Cellulose	75	75	75	75	75	75	75	75	75
Push Compartment									
PEO 100000	70	60	50	0	0	0	40	30	20
PEO 300000	0	0	0	70	60	50	30	40	50
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Colloidal Silicon Dioxide	3	3	3	3	3	3	3	3	3
Iorn Oxide Red	2	2	2	2	2	2	2	2	2
Microcrystalline Cellulose	173	183	193	173	183	193	173	173	173
Drug Compartment									
Isoxsuprine Hydrochloride	35	35	35	35	35	35	35	35	35
Sodium Chloride	10	10	10	10	10	10	10	10	10
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Colloidal Silicon Dioxide	1	1	1	1	1	1	1	1	1
Microcrystalline Cellulose	75	75	75	75	75	75	75	75	75
Coating									
Cellulose Acetate	35	35	35	35	35	35	35	35	35
Triacetin	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Acetone/IPA	350	350	350	350	350	350	350	350	350

Table 2 – Evaluation of Blend before compression

Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Bulk Density (gm/ml)	0.507	0.506	0.511	0.501	0.507	0.503	0.508	0.503	0.504	0.508	0.511	0.513
Tapped Density (gm/ml)	0.423	0.415	0.415	0.432	0.424	0.43	0.445	0.43	0.451	0.439	0.42	0.415
Hausners Ration	1.20	1.22	1.23	1.16	1.20	1.17	1.14	1.17	1.12	1.16	1.22	1.24
Carrs Index	16.57	17.98	18.79	13.77	16.37	14.51	12.4	14.51	10.52	13.58	17.81	19.1
Angle of Repose	31.7	32.9	33.7	34.8	35.6	31.7	33.6	36.4	33.9	36.6	34.3	35.1

Table 3 – Evaluation of Core and Coated Tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core Tablet Weight (mg)	501.3±0.46	503.3±0.57	504.25±0.46	503.7±0.75	510.0±0.21	506.89±0.28	501.27±0.51	504.23±0.43	504.33±0.93
Coated Tablet Weight (mg)	539.62±0.37	544.5±0.83	541.9±0.71	544.62±0.57	541.29±0.57	546.8±0.9	537.4±0.47	545.21±0.51	541.6±0.21
Hardness of Core Tablet (Kg/cm^{2})	5.21±0.58	5.332±0.41	5.65±0.21	5.21±0.67	5.51±0.27	5.36±0.65	5.51±0.62	5.47±0.13	6.10±0.58
Diameter of Core Tablet (mm)	9.05±0.09	9.04±0.3	9.06±0.4	9.09±0.1	9.08±0.7	9.04±0.2	9.06±0.2	9.08±0.4	9.09±0.1
Diameter of Coated Tablet	9.61±0.3	9.52±0.4	9.58±0.6	9.49±0.3	9.59±0.1	9.51±0.7	9.48±0.8	9.51±0.3	9.57±0.3
Thickness of core Tablet (mm)	5.7±0.3	5.2±0.5	5.4±0.3	5.9±0.4	5.6±0.9	5.4±0.8	5.2±0.1	5.2±0.7	5.6±0.5
Thickness of Coated Tablet	5.9±0.8	6.2±0.3	6.1±0.5	6.3±0.7	6.2±0.8	6.2±0.5	6.4±0.3	6.3±0.5	6.6±0.1

Method of Analysis

A simple, accurate, validated and reproducible UV-spectrophotometric method has been used to estimation of Isoxsuprine Hydrochloride in the formulations. Isoxsuprine Hydrochloride in tablet formulation were estimated at 274.2 nm. The Beer's law was obeyed by the concentration ranges of 2-20ug/ml. Mean recovery of 99.90% for respectively signifies the accuracy of the method.

Drug content uniformity

For determining the drug content, one accurately weighed tablet was crushed. The powdered sample was dissolved in 100 ml of ethanol. The solution was filtered through Whatmann filter paper and after sufficient dilution with the same solvent the samples were analyzed using double beam UV spectrophotometer (Systronic 2202) at 274.2 nm.

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 37± 0.5°C for 12 hrs at 50 rpm. The samples were withdrawn (5ml) at different time interval and replaced with an equivalent amount of fresh medium over 12 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 concentration, amount of drug released and the percentage drug release were calculated.

Influence of different process variables on in- vitro drug release

Influences of Osmogents

Different amount of osmogents (i.e. different grade of Polyethylene Oxide) 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 (F5) were performed in 0.1 N Hydrochloric Acid solution (pH 1.2), Phosphate Buffer (pH 6.8) and Distilled Water at 37± 2°C. The samples were taken out at predetermined intervals and analyzed after filtration by UV spectroscopic method at 274.2.

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.

Influence of orifice size and membrane thickness

The push pull osmotic 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.

RESULT AND DISSCUSSION

To study the influence of various tablet formulation variable, on drug release from tablet. Tablets were prepared as per the formula given in Table 1 with various compositions and coated as per the formula given in the Table 1. On drug release kinetics it was observed that the formulation F5 gives the zero order drug release so that was selected for further studies. Significant effect of PEO 300000 was observed. With increasing concentration of PEO drug release was increase due to increased osmotic pressure inside the tablet.

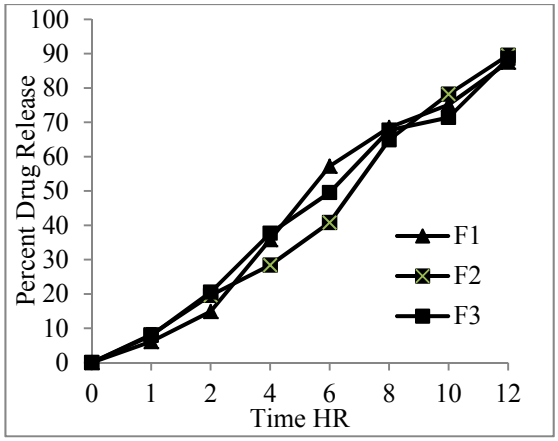

Fig 1 – Influence of PEO 100000

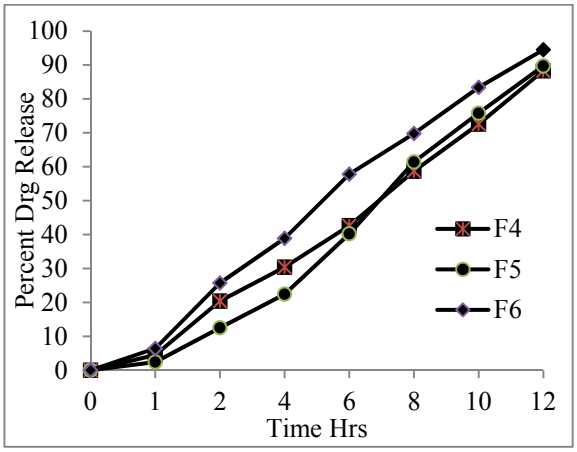

Fig 2 – Influence of PEO 300000

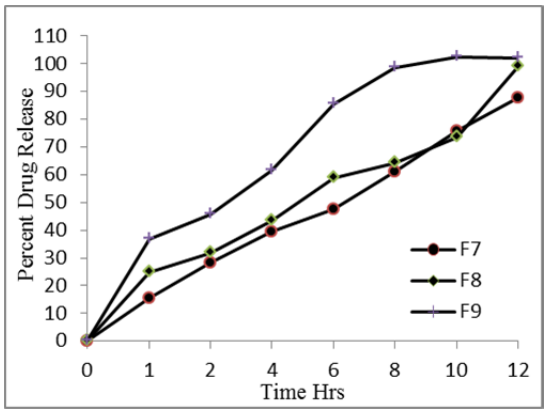

Fig 3 – Influence of combination of PEO 100000 and PEO 300000

The release rate at 50 rpm, 100 rpm and 150 rpm agitation intensity of dissolution were analyzed. And upon calculation of **f 2** factor (similarity factor) it was observed that release profile of at different rpm could be considered similar to theoretical profile of F5. So it could be predicted that there is no effect of gastrointestinal track motility on drug release from the elementary osmotic pump.

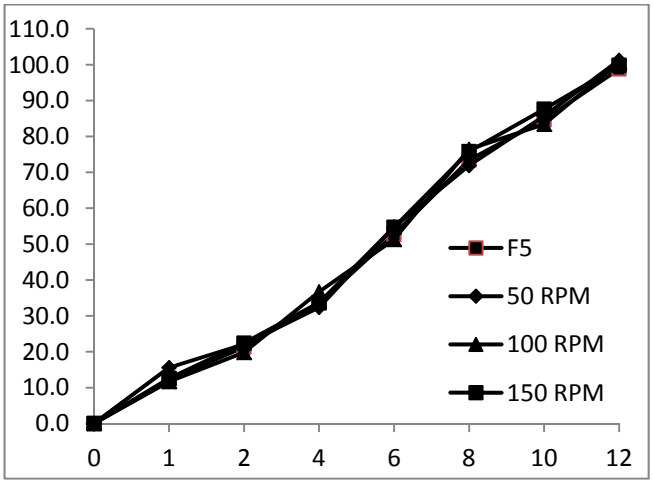

Fig 4- Influence of different agitation intensity

The optimal formulation F5 release pattern was studied in different dissolution media i.e. 0.1 N HCL, 6.8 pH Phosphate Buffer. It was observed release pattern in media is almost same. **f 2** value showed a release profile which could be considered similar to the target profile of F5. This can be explained as the cellulose acetate act as semipermeable membrane since ions are not readily exchanged through it. Therefor release of the drug from this system is independent of pH of the surrounding medium. (Fig 5)

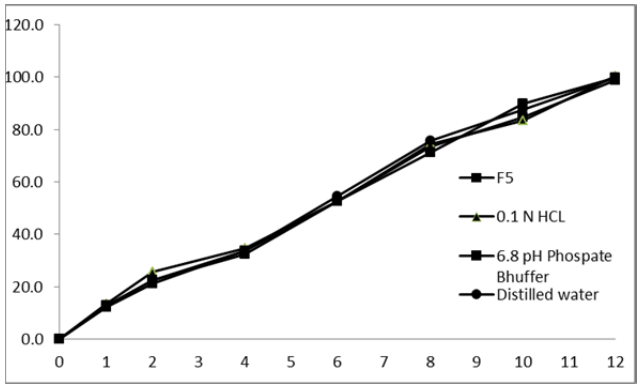

Fig 5 – Influence of dissolution media on drug release.

The formulation F5 was coated with the formula given in the Table I at different coating levels. For further studies 7% was adopted. No significant effect was observed on release pattern of drug in the tablet coated 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 similar to the theoretical target profile of F5 but it deviates for thickness of 6%.

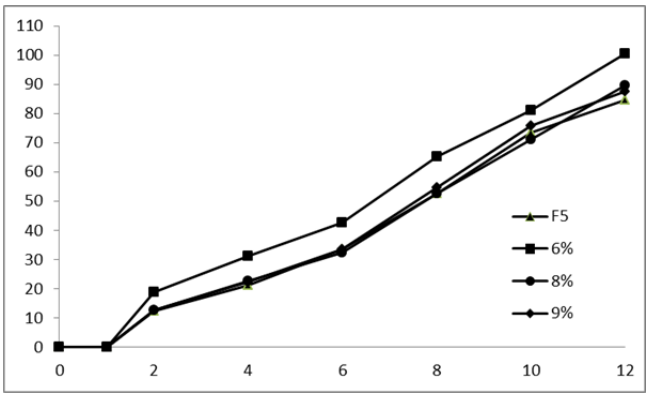

Fig 6- Influence of coating thickness on drug release.

The formulation F5 was coated with the formula given in the Table I and the drug release profile was recorded for drug for different orifice. For the further study 0.5 mm orifice size was selected. No significant difference in release profile of drug was observed in the table with orifice size of 0.7mm and 0.9 mm (Fig. 7). But it shows higher drug release through the larger diameter i.e. 1.1 mm. This may be because of diffusion of drug through the orifice. **f 2** value showed a release profile which could be considered similar to the theoretical target profile of F5 for orifice size 0.5 mm, 0.7mm and 0.9 mm. But it deviates for 1.1 mm.

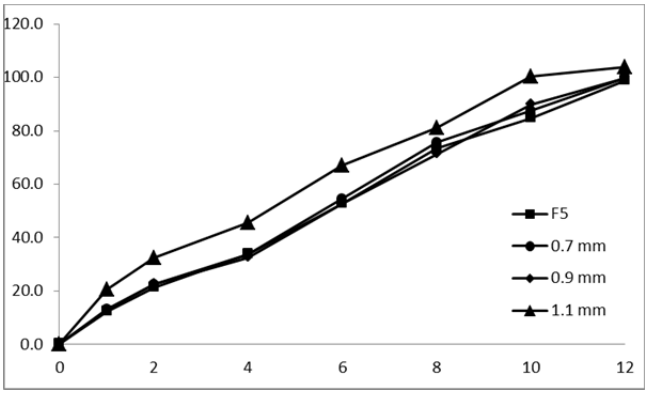

Fig 7 – Influence of Orifice Size on drug release.

CONCLUSION

So it may conclude that the formulation containing PEO 300000 shows the perfect zero order drug release. And the coated formulation does not have any effect of dissolution media and agitation speed which is compared by **f 2** value. But it shows the effects of smaller coating thickness and higher orifice size on drug release.

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