



Formulation and evaluation of amlodipine besylate elementary osmotic tablets

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Received: 19-02-2016 / Revised: 11-03-2016 / Accepted: 18-03-2016 / Published: 27-03-2016

ABSTRACT

The present work was aimed to formulate and evaluate osmotic pump delivery system of Amlodipine Besylate using two osmogens (NaCl and KCl) by wet granulation method. The osmogens used in this study did not alter the physicochemical properties of drug, as tested by FTIR. Prior to compression, the prepared granules were evaluated for flow and compression characteristics. After compression, the tablets were evaluated for thickness, hardness, weight variation, friability, percentage of weight gain, drug content, and *in vitro* release studies. The tablets were further coated and evaluation of coated tablets were performed and compared with uncoated tablets. The coated tablets after drying were drilled on the surface using Microdrill to get delivery orifices of different diameters (0.5mm, 1.0mm & 1.5mm). The percentage of weight gain after coating was found to be between 5.57-7.11%. A slow drug release was observed in coated tablets compared to uncoated formulations. The optimized formulation, F3 (1.5mm diameter pore size) showed maximum drug release 88.2% at the end of 24th hours. The optimized formulation F3 (1.5mm diameter) was found to be stable even after subjected to stability study maintained at 25±2°C/60±5%RH and 40±2°C/ 75±5% RH for two months. In conclusion, Amlodipine Besylate may be successfully formulated as elementary osmotic pump tablets to provide a control release of drug upto 24 hours.

Keywords: Amlodipine Besylate, Coated tablets, Elementary osmotic pump, Microdrill, Stability study.



INTRODUCTION

The basic rationale of controlled drug delivery system is to optimize the biopharmaceutical, pharmacokinetics and pharmacodynamic properties of drug in such a way that its therapeutic utility is maximized [1]. Oral controlled release drug delivery provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit. Among Oral controlled drug delivery systems, Osmotically Controlled Release Systems plays a major role. Osmotic pressure has been used extensively in the fabrication of these drug delivery systems. Osmotic drug delivery system differs from diffusion based systems in the delivery of the active agents in driven by an osmotic gradient rather than the concentration of drug in the device [2]. In osmotic drug delivery system, it is possible to achieve and sustain a drug plasma concentration within the therapeutic window of drugs, which reduces the side effects and frequency of administration [3,4]. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to

modulate the release characteristic by optimizing the properties of drug and system [5]. Osmotic Pump Tablet (OPT) generally consist of a core including the drug, an osmotic agent, other excipients and semi permeable membrane coat [6]. Amlodipine Besylate is selected as a model drug in the preparation of osmotic pump tablets. Amlodipine is an antihypertensive agent [7]. It also act as a vasodilator agent, calcium channel blockers, and anti- anginal agents. The conventional marketed product of Amlodipine Besylate tablet released more than 80% of the drug within 90minutes. So a controlled delivery system is necessary to deliver the drug for a prolonged time. Hence the present work was aimed to design, develop and evaluate an oral osmotic delivery system of Amlodipine Besylate using two osmogens (NaCl and KCl) in order to achieve constant and controlled release of the drug to obtain the desired therapeutic effect.

MATERIALS AND METHODS

Materials: Amlodipine Besylate was obtained from Sun Pharmaceuticals, Chennai. Ethyl cellulose, Magnesium stearate and Talc were

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procured from Loba Chemie Pvt. Ltd, Mumbai. Sodium chloride was purchased from Molychem, Mumbai. Potassium chloride was procured from Reachem Laboratory Chemicals Pvt. Ltd, Chennai. Polyethylene glycol 400 from Paxmy Speciality Chemicals, Chennai, Polyvinyl pyrrolidone from Yarrow Chem. Products, Mumbai, Isopropyl Alcohol from S.D. Fine Chem. Pvt. Ltd, Mumbai and Dicalcium phosphate was procured from Finar Chemicals Ltd, Ahmedabad. All other chemicals and reagents used were of analytical grade.

Methods

PREFORMULATION STUDIES

Compatibility Studies: To detect any interactions of drug with other excipients, the IR spectroscopic analysis was carried out. The potassium bromide disc was used for preparing sample. Pure drug and physical mixture of drug and excipients was prepared to record the spectrum in the range of 400 cm^{-1} to 4000 cm^{-1} by using FTIR Spectrophotometer. If there was no change in peaks of mixtures when compared to pure drug, it indicates the absence of interactions^[8].

EVALUATION OF GRANULES

Micromeritic Properties: The Micromeritic properties of prepared granules were studied by determining various parameters like the bulk density, tapped density, angle of repose and Carr's index. The angle of repose was determined by the fixed-base cone method. Bulk and tapped density were determined using digital bulk density apparatus^[9].

Preparation of osmotic pump tablets: The preparation of osmotic pump tablet of Amlodipine Besylate involves two steps.

1. Preparation of osmotic pump core tablets.
2. Coating of tablets.

Preparation of amlodipine besylate osmotic pump core tablet^[10]: Four formulations of Amlodipine Besylate core tablets (F1, F2, F3 and F4) were prepared by using sodium chloride and potassium chloride as osmogens by wet granulation method. Out of which two formulations were developed by using two different osmogens separately, one formulation was in combination with two osmogens and one formulation was without osmogens (control).

Preparation of core tablets: Granules of Amlodipine Besylate were prepared by wet granulation method. All the ingredients except PVP K30, magnesium stearate and talc were accurately weighed and mixed in a mortar with a pestle for 10 minutes to get uniform mixture. The dry blend was granulated with sufficient quantity of PVP K30,

which was dissolved in isopropyl alcohol. The coherent mass was kept at room temperature for air drying (until IPA smell ceases/ evaporated) and the passed through sieve No: 10. The granules were dried at 50°C in hot air oven for two hrs. The dried granules were again passed through sieve No: 20 and once again dried in hot air oven at 50°C for 30 minutes. The dried granules were mixed with magnesium stearate and talc and compressed into tablets using Minipress tablet punching machine. The compression was adjusted to give tablets with approximately 5-6 kg/cm^2 hardness and checked with Monsanto tablet hardness tester (Table-1).

COATING OF THE CORE TABLETS

Preparation of Coating Solution: As per the method described by Sakthikumar et al coating solution was prepared by mixing 5% Ethyl cellulose coating agent /semi permeable membrane and 15% PEG 400 (pore former and plasticizer) with respect to ethyl cellulose were dissolved in acetone: methanol solvent(40:10) mixture and stirred to get homogeneous solution.

Dip Coating Method^[11]: In the present study, dip coating method was used to coat the tablets. The weighed core tablets were dipped into the coating solutions by holding with forceps and after dipping the coated tablets were placed on a glass plate for drying in air for 15 minutes at room temperature. The tablets were then dried at 60°C in an oven for 30 minutes and then weighed. After drying, delivery orifices of different diameters (0.5mm, 1.0mm & 1.5mm) were drilled on the surface of the coated tablets using Microdrill^[12].

Evaluation of osmotic pump tablets of amlodipine besylate: After compression, Amlodipine besylate osmotic tablets both uncoated and coated were evaluated for thickness, hardness, uniformity of weight, percentage weight gain and drug content. The friability of uncoated osmotic tablets was also determined. The thickness was measured using vernier-caliper. Hardness of the tablets was determined by Monsanto hardness tester. In the weight variation test, twenty tablets were selected at random and average weight was calculated. Then individual tablets were compared with the average weight. In percentage weight gain study twenty tablets (before and after coating) from each formulation were selected randomly, weighed individually and average weight was calculated. The average weight increase due to coating was determined from the difference in weight of coated and uncoated tablets. In the drug content analysis three tablets were taken and powdered. From the powder, accurately weighed amount equivalent to 100mg of Amlodipine besylate was weighed and dissolved in pH 1.2 buffer solution. The solution

was suitably diluted (10µg/ml) and assayed for the drug content by measuring the absorbance at 237nm using UV-Visible spectrophotometer. Friability test for uncoated tablets was done by Roche friabilator [13-16].

In Vitro Drug Release Studies [16]: In vitro drug release of the formulations was carried out in a USP dissolution apparatus (paddle type) at a rotating speed of 50 rpm and temperature of 37⁰±2°C. The dissolution medium was 900 ml of pH 1.2 buffer solution. Samples of 5ml were withdrawn at specified time intervals over 10-hour period and finally at 24 hour and the medium was replenished with fresh 5 ml dissolution fluid so that the volume of dissolution medium was maintained at 900ml. The withdrawn sample was transferred to 10ml standard flask, the volume was adjusted to 10ml with pH 1.2 buffer solution and analyzed spectrophotometrically at 237nm, and the drug release was calculated.

Curve Fitting Analysis/ Kinetic Studies [17]: The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:

Log cumulative percent drug release versus time (zero order kinetic model).

Log cumulative percent drug remaining versus time (first order kinetic model).

Cumulative percent drug release versus square root of time (Higuchi model).

Log cumulative percent drug release versus log time (Korsmeyer's Peppas model).

Accelerated Stability Study [18]: The optimized formulation of Amlodipine besylate was packed in airtight container and stored in ICH certified stability chamber maintained at 25±2°C/60±5%RH and 40±2°C/ 75±5% RH for two months. The samples were withdrawn on 31st, 46th, and 61th days and evaluated for the appearance, drug content and in-vitro drug release studies.

RESULTS AND DISCUSSION

In the present study, the osmotic pump delivery system was designed by wet granulation technique and evaluated for various pre compression and post compression parameters. The major functional groups of Amlodipine Besylate in FT-IR spectrum are amino group (at 3298.28), aromatic CH group (at 3030.25), aliphatic CH group (at 2985.52), ketone group (at 1685.79), carbonyl group (at 1612.49), methane group (at 1205.51) appeared in the above peaks and wave number. Osmogens such as sodium chloride, potassium chloride are transparent to infrared radiation. Therefore, no signals appeared for sodium chloride and potassium chloride. The

same functional groups are also present in the peaks and patterns of Amlodipine Besylate with other excipients. The result proved that there were no significant interactions between the drug and other excipients used in the formulations.

Evaluation of granules: The physical characters of granules of all formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner ratio. The result showed that the angle of repose of all the formulation was between 27.69⁰ and 33.20⁰. The bulk density and tapped density were found in the range of 0.53-0.63g/mL and 0.62-0.77 gm/mL which are within the acceptable limits. The compressibility index of the powder exist in the range between 11.87 -13.52 and Hausner ratio lies between 1.12- 1.18. The result indicates good flow property of the granules.

Evaluation of osmotic pump tablets of amlodipine besylate: The thickness of the coated tablets was ranging between 2.16 and 2.22 mm whereas the thickness of uncoated tablets was ranged between 0.40 and 0.44mm. The thickness of coating was 1.76-1.78mm. The hardness of the coated tablets was 6.2-6.5kg/cm² when compared to uncoated tablets whose hardness ranges from 5.4-5.6kg/ cm². The increase in the hardness may be due to increased coating thickness. The friability of uncoated tablets was ranging between 0.33 and 0.98%. The weight of one tablet was 300mg. The acceptable deviation is ±10%. The result of weight variation test showed that the weight of all formulated uncoated tablets was within the range of 293.49-299.54 mg and the coated tablet was 311.38-318.28mg. The percentage of weight gain after coating was found to be between 5.94-7.11%. This may be desirable to withstand the hydrostatic pressure created by the osmogens. The drug content in the coated as well as uncoated tablets was found to be within the prescribed limits (±10% w/w of Amlodipine Besylate). The drug content of the coated tablet was 95.82-98.24% and uncoated tablet was 95.94 to 98.13%.

In vitro dissolution rate studies: The dissolution studies of all the formulations (coated and uncoated) of Amlodipine Besylate were performed and the drug release was compared with conventional marketed Amlodipine Besylate tablet. The percentage of drug release from the marketed product of Amlodipine Besylate tablets was 89.8% whereas the drug release from the uncoated Amlodipine Besylate tablets (with osmogen) was 72.0%(F1), 68.8%(F2), 97.8%(F3) and 64.8%(F4-without osmogen) respectively in 90 minutes. Core tablets were coated with Ethyl cellulose coating solutions. The cumulative percentage of drug

release from coated formulations F1, F2, F3, and F4 (control- without osmogen) were found to 92.6%, 87.5%, 82.4% and 89.5% respectively in 24 hours. The slow drug release compared to uncoated formulations may be due to increase in coating thickness.

The coated tablets after drying were drilled on the surface using Microdrill to produce delivery orifices of different diameters (0.5mm, 1.0mm & 1.5mm). The formulations F1, F2, F3, and F4 (control- without osmogen) were subjected to drilling to produce different orifice diameter (0.5mm, 1.0mm & 1.5mm). The formulations are subjected to drug release studies which showed that the release profiles of different formulations varied according to the orifice diameter and the nature of osmogens with different osmotic pressure.

Effect of Orifice Diameter on Drug release: The cumulative percentage of drug release from formulations F1, F2, F3, and F4 (control- without osmogen) with 0.5mm orifice diameter was 76.2%, 68.4%, 81.3% and 65.2% respectively in 24 hours. The cumulative percentage of drug release with orifice diameter 1.0mm from formulations F1, F2, F3 and F4 was 81.1%, 72.3%, 84.7% and 69.4% respectively in 24 hours. The orifice diameter 1.5mm showed percentage of drug release of 85.6(F1), 80.4(F2), 88.2(F3) and 72.4(F4) in 24 hours. The drug release profiles of formulation F1, F2, F3, and F4 (control- without osmogen) from all the three pore size with orifice diameter 0.5mm, 1.0mm and 1.5mm are shown in Figure 1-4.

The result showed that the drug release from the diameter of the orifice 0.5mm was lower than that of the orifice diameter 1mm and 1.5mm from all the formulations. This may be due to the drug may occlude in the coating membrane and so the release may be somewhat slower from such a small orifice diameter 0.5mm. The formulations with orifice diameter 1.0mm, the drug release was less than 1.5mm and more than 0.5mm diameter. The drug release was maximum from all the formulations with orifice diameter 1.5mm. This may be attributed to the fact that there may be more diffusion from the bigger orifice diameter 1.0mm.

The drug release from the formulations F4 (control- without osmogen) was 65.2%, 69.4% and 72.4% with orifice diameter 0.5mm, 1.0mm and 1.5mm respectively. This less drug release may be due to low number of pores through which less amount of drug may be leach out from the formulations F4.

Effect of Coating Thickness on Drug release: The percentage of drug release from the coated formulation F2 (from 0.5mm, 1.0mm and 1.5mm

pore size) was found to be 68.4%, 72.3% and 80.4% respectively in 24 hours and the drug release was slightly lower than F1 and F3 (from 0.5mm, 1.0mm and 1.5mm pore size). This decreased drug release may be due to increased in coating thickness in formulation F2.

Effect of osmotic pressure on Drug release: An increased percentage of drug release was observed in formulation F3 81.3% (0.5mm), 84.7% (1.0mm) and 88.2% (1.5mm) in 24 hours when compared to F1 and F2 from all the three pore size. The increased drug release from F3 may be due high osmotic pressure exerted by the combinations of sodium chloride and potassium chloride used as osmogens. From these results it was concluded that the drug release was maximum in formulation F3 from 1.5mm pore size in 24 hours. Hence F3 may be the optimized formulation and the optimum orifice diameter may be 1.5mm size.

Kinetic Study: In order to understand the mechanism of drug release from all the formulations, percentage of drug release data were treated to various kinetic models like zero order, first order, Higuchi's model and korsmeyers equation. The result showed that all the formulations were fitted to zero order kinetics which is evident from highest regression coefficient values (R^2). This confirms that the drug release from all the formulations was found to be zero order.

Stability Study: The stability study of the optimized formulation F3 (with orifice diameter 1.5mm) was carried out by storing at $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$ and $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$ for 60 days. After 60 days of storage, the formulation was observed physically. There was no physical change observed. The samples were analyzed for drug content at intervals of 31st, 46th and 61th days. The result showed that percentage of Amlodipine Besylate was between 97.11% and 98.87% (Table -2). It revealed that there was no degradation of Amlodipine besylate osmotic pump tablet (formulation F3). Dissolution studies were also carried out and the percentage of drug release after 24 hrs was presented in Table-3. From the results it was observed that there was no significant change in the release rate of Amlodipine Besylate osmotic pump tablet F3 after 60 days. These results proved that the formulation F3 was stable.

CONCLUSION

Amlodipine Besylate is a potent Anti-hypertensive drug and therefore a constant and controlled release of this drug is essential in curing hypertension. Amlodipine Besylate was successfully formulated

as elementary osmotic pump tablets using sodium chloride and potassium chloride as osmogens by wet granulation method. Formulation F₃ with orifice diameter of 1.5mm size was found to be the optimized formulation. The optimized formulation provide a control release of drug upto 24 hours and

was stable when stored at 25±2°C/60±5%RH and 40±2°C/75±5%RH for 60 days. Hence it can be concluded that formulation like an osmotic tablets on this drug may be considered as a suitable alternative to currently available formulations of Amlodipine Besylate.

TABLE 1-FORMULATION OF AMLODIPINE BESYLATE OSMOTIC PUMP TABLETS

S.NO	Ingredients(mg)	Formulations			
		F1	F2	F3	F4
1.	Amlodipine Besylate	5	5	5	5
2.	Sodium Chloride	50	-	50	-
3.	Potassium Chloride	-	50	50	-
4.	Polyvinyl Pyrrolidone K ₃₀	20	20	20	20
5.	Isopropyl Alcohol	q.s	q.s	q.s	q.s
6.	Dicalcium Phosphate	209	209	159	259
7.	Magnesium Stearate	6	6	6	6
8.	Talc	10	10	10	10

Weight of each tablet= 300 mg

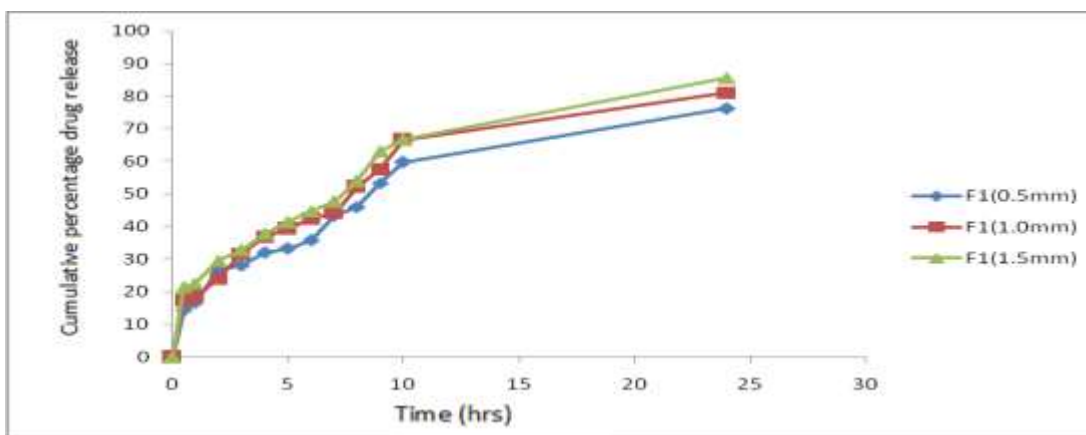


Figure-1: Drug Release Profile of Formulation F1 from 0.5mm,1.0mm & 1.5mm Delivery orifice

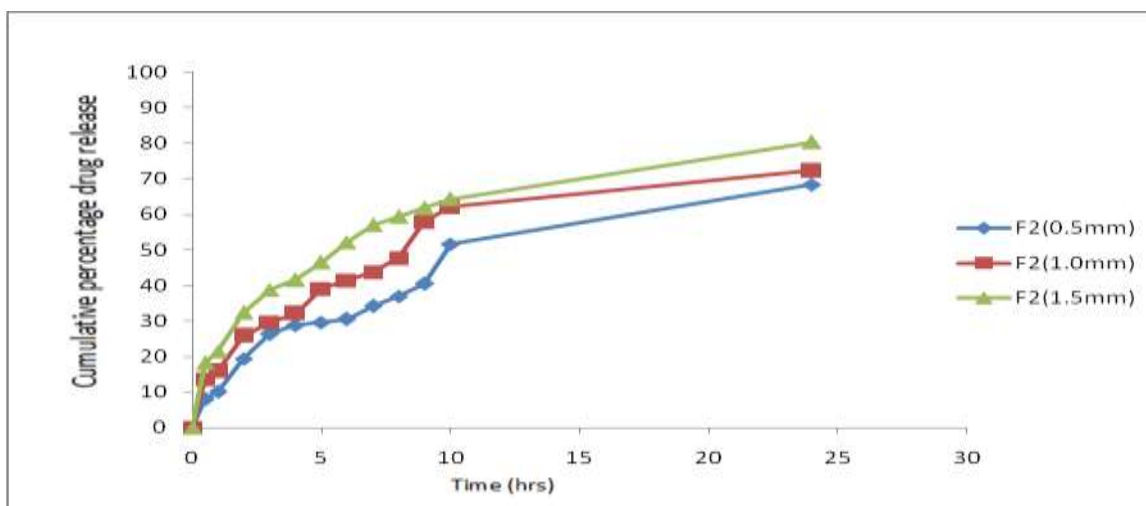


Figure-2: Drug Release Profile of Formulation F2 from 0.5mm,1.0mm & 1.5mm Delivery orifice

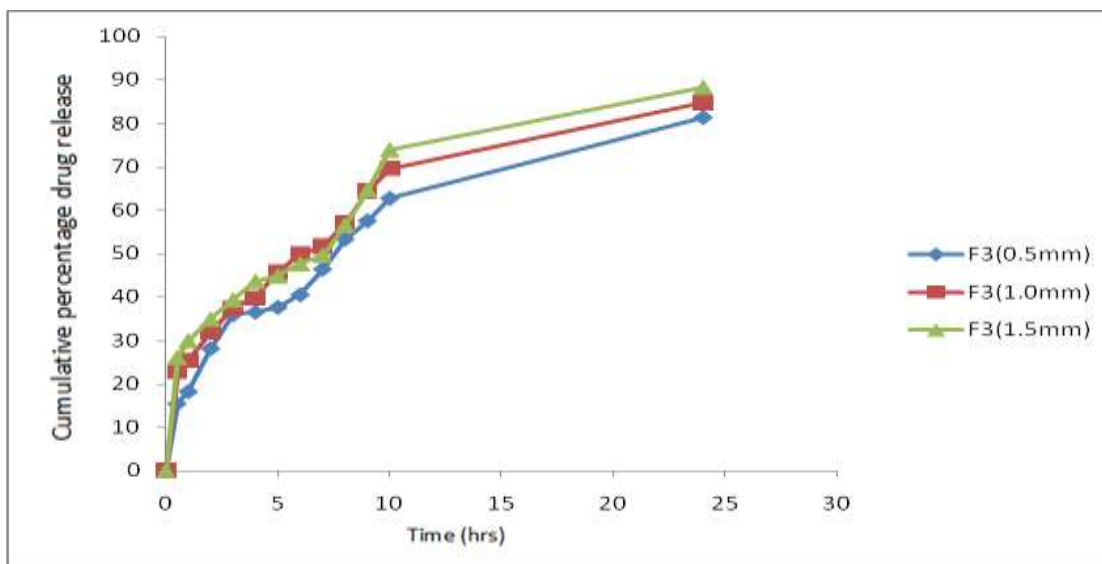


Figure-3: Drug Release Profile of Formulation F3 from 0.5mm,1.0mm & 1.5mm Delivery orifice

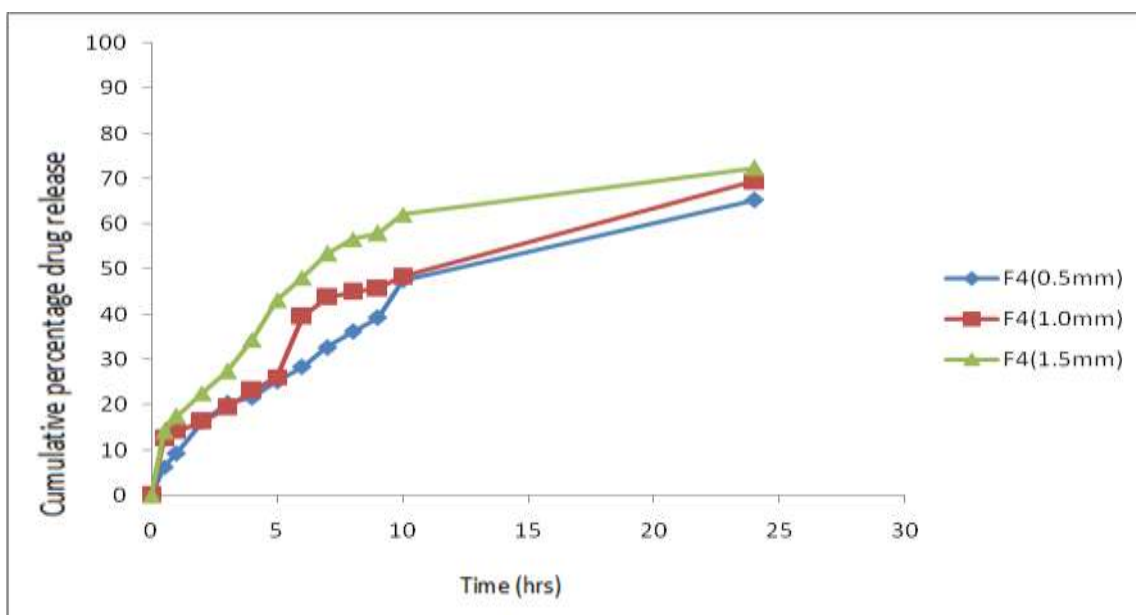


Figure-4: Drug Release Profile of Formulation F4 from 0.5mm,1.0mm & 1.5mm Delivery orifice

TABLE 2- STABILITY STUDY OF OSMOTIC PUMP TABLET F3 (1.5MM ORIFICE DIAMETER)

Description	TEMPERATURE					
	25±2°C/60±5%RH			40±2°C/ 75±5% RH		
	31 st day	46 th day	61 th day	31 st day	46 th day	61 th day
Drug content (%)	98.87±0.54	98.42±0.52	97.38±0.47	97.14±0.21	97.32±0.19	97.51±0.54
Percentage Drug Release at the end of 24 hr (%)	88.75±0.40	88.28±0.84	88.17±0.65	88.56±0.59	88.42±0.36	87.73±0.98

*All values are expressed as mean ± standard deviation, n=3

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