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FORMULATION AND EVALUATION OF ELEMENTARY OSMOTIC PUMP DOXOFYLLINE

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Abstract:
In the present study elementary osmotic pumps (EOP) of Doxofylline were formulated and evaluated. The target release profile was selected and different variables were optimized to achieve the same. Formulation variables like nature and concentration of plasticizer (0-20% w/w of polymer) osmogens comparission and role of osmogen concentration, aperture diameter and coat thickness were found to affect the drug release from the developed formulations. Doxofylline release was directly proportional to the level of plasticizer and osmotic pressure generated by an osmotic agent. Drug release from developed formulations was independent of pH and agitation intensities of release media. Burst strength of the exhausted shells increased with increase in coat thickness but decreased with increase in level of hydrophilic plasticizer.

Keywords: *Elementary osmotic pumps, Doxofylline, plasticizer.*

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INTRODUCTION:

Osmotic pumps are controlled drug delivery devices worked on the principle of osmosis. Wide range of osmotic devices are avaliable, out of them osmotic pumps are unique, dynamic and widely employed in clinical practice. Osmotic pumps shows many advantages like they (i) are easy to formulate and simple in operation, (ii) improve patient acceptence by decresing frequency of dosing (iii) shows good *in vitro in vivo* correlation. However wide variety of oral osmotic systems have been reported in literature, but most important osmotic drug delivery system is 'Theeuwes elementary osmotic pump' (EOP). Due to of its simple structure and high efficiency, EOPs are the most important osmotic devices and more than 540 patents have been devoted. Procardia XL® and Adalat CR® (nifedipine), Acutrium® (phenylpropanolamine), Minipress XL® (prazocine) and Volmax® (salbutamol) are examples of EOPs currently available in the market [1-3]. In this drug delivery system, the osmotic core is surrounded by a semipermeable membrane drilled with a drug delivery orifice. Once this system comes in contact with the gastrointestinal fluids, the osmotically driven water enters the system through the semipermeable membrane, dissolves the soluble agents, and exits through the delivery orifice. Because these systems use osmotic pressure for the controlled delivery of the active compound(s), delivery rates are expected to be independent of gastrointestinal condition [4].

The rate of drug release from osmotic pumps is dependent on the total solubility and the osmotic pressure of the core. The highly dihydrogenmonoxide (H2O) - soluble drugs may create considerable osmotic pressures and may release the active drug at desirable rates.

Asthma and COPD (Chronic Obstructive Pulmonary Disease) are the most common life threatening pulmonary disease that requires constant monitoring. Doxofylline, a methyl xanthine derivative that works by inhibition of phosphodiesterase IV activities, has recently drawn attention because of its better safety profile and similar efficacy over the most widely prescribed analogue, theophylline, indicated for asthma and chronic obstructive pulmonary disease due to decreased affinities towards adenosine A1 and A2 receptors. Doxofylline is chemically designated as 7-(1, 3 dioxolone-2-yl methyl) theophylline. Presence of a dioxolane group in position C-7 differentiates it from theophylline. Doxofylline is an anti-tussive and bronchodilator used for maintenance therapy in patients suffering with asthma and chronic obstructive pulmonary disease (COPD) and is extensively metabolized in the liver by demethylation and oxidation to an extent of 80-90% and 48% plasma protein bound. Elimination half life (t½) is around 6-7 h and<4% of an administered dose of Doxofylline is excreted unchanged in the urine. The daily dose is 200-400 mg two to three times in a day. Doxofylline is coming under class III of BCS classification and oral absorption is 62.2%. It is having solubility of 12 mg/ml in water and having PKa 9.87 [5].

The present study was aimed towards the development of EOP of Doxofylline. A theoretically designed zero-order delivery pattern was deigned to produce plasma level within the desired range. The manufacturing procedure was standardized.

MATERIALS AND METHODS:

Materials

Doxofylline(99.9% purity) was a gift sample from Smruthi Organics Pvt. Ltd., New Delhi, India. Hydroxypropyl methyl cellulose, ethyl cellulose and dibutylpthalate was gifted from Dr. Reddy's Labs Ltd., Hyderabad, India. cellulose acetate (39.8% acetylation), polyvinyl pyrrolidone (PVP K-30), microcrystalline cellulose (MCC pH 101), magnesium stearate, talc and sodium chloride from CDH Delhi, India. Acetone (HPLC grade), isopropyl alcohol, poly ethylene glycol-400, sodium hydroxide, hydrochloric acid, mannitol and potassium dihydrogen ortho-phosphate from S.D. Fine Chemicals, Mumbai, India.

Methods

Preparation of Core Tablets

Before starting formulation, compatibility of Doxofylline with different excipients were tested using the techniques of Differential scanning calorimetry (DSC) (METTLER, Toledo, UK) and Fourier transforms infrared spectroscopy (FT-IR) (PERKIN ELMER BX 1, USA). Excipients used in the final formulation were found to be compatible with Doxofylline.

Core tablets of Doxofylline were prepared by wet granulation method and batch size was kept as 50 tablets. Formulae of different core formulations of Doxofylline are listed in Table 1&2. Required amounts of Doxofylline and other excipients were weighed and passed through # 40 mesh. Osmotic agents Sodium chloride and mannitol were passed through #100 mesh. The blend was mixed for 10min and PVP K-30 was added. The mixture was granulated with water and the resulting wet mass passed through #18 mesh. The granules were dried at 70^0C. Then the dried granules were passed through #25 mesh. These granules were then blended with Magnesium stearate and Talc. Finally granules were compressed into tablets having an average weight of 700mg using 16 station rotary tablet compression machine (Riddhi, Ahmedabad, India) fitted with 12mm round standard concave punches. The

compression was adjusted to tablet with approximately 7-8 kg cm2 hardness. [6] The purity and drug content of the tablets was found to be within the limit of 98.24-99.65%.

Table 1: Formula for different batches of core formulation (manitol as osmogen)

Ingredients (mg/tablet)	Batch Number				
	F1	F2	F3	F4	F5
Doxofylline	400	400	400	400	400
Manitol	120	125	130	135	140
MCC	145	140	135	130	125
PVP-K30	25	25	25	25	25
Talc	5	5	5	5	5
Magnesium stearate	5	5	5	5	5
Total weight	700	700	700	700	700

Table 2: Formula for different batches of core formulation (sodium chloride as osmogen)

Ingredients (mg/tablet)	Batch Number				
	F6	F7	F8	F9	F10
Doxofylline	400	400	400	400	400
Sodium Chloride	120	125	130	135	140
MCC	145	140	135	130	125
PVP-K30	25	25	25	25	25
Talc	5	5	5	5	5
Magnesium stearate	5	5	5	5	5
Total weight	700	700	700	700	700

Coating and Drilling

Core tablets of Doxofylline containing different osmogens were coated in a conventional pan coater (VJ instruments, New Delhi, India) fitted with three baffles placed at angle of 120[7]. The composition of coating solutions used for coating of core tablets is given in Table 3. Cellulose acetate was dissolved in acetone and homogenized, plasticizer was added at various proportions and sprayed onto core tablets in pan coater. Ethyle cellulose was dissolved in isopropyl alcohol and quantities of plasticizers were added, mixed thoroughly and was used for coating. Pan speed was maintained at 23-27 rpm and hot air inlet temperature was kept at 50-550C. The manual coating procedure based on intermittent spraying and coating procedure was used with spray rate of 2-3 ml/min. Coat weight and thickness were controlled by the volume of coating solution consumed in coating process [8]. An appropriate size orifice (480-700 µm) is made on one side of all coated tablets using microdrill (Kamlesh Engineers, Udaipur, India). In all the cases active coated tablets were dried at room temperature for 24hrs before further evaluation. [9, 10].

Table 3: Composition of coating solutions

Ingredients	Coat code				
	A	B	C	D	E
Cellulose acetate (gm)	-	3	3	3	3
Ethyl cellulose (mg)	5	-	-	-	-
PEG-400 (gm)	-	0.3	0.6	-	-
DBP(gm)	0.6	-	-	0.3	0.6
HPMC(gm)	2	-	-	-	
Acetone(ml)		90	90	-	90
IPA(ml)	90			90	-

Evaluation of developed formulation

Evaluation of powder blend

The bulk and tap density of the powdered blend was determined using USP method I and Compressibility index and hausner ratio were calculated **[11]** .The results were presented in Table 4.

Evaluation of core and coated tablets

The core and coated tablets were evaluated for weight variation. Thickness and diameter of core and coated tablets were measured using digital screw gauze (Mitutoyo, Japan). Hardness of randomly selected tablets was tested using hardness tester (Pfizer hardness tester, Cadmach,Ahmedabad, India). Friability of core tablets was carried out on Roche friability tester (Roche, Mumbai, India) using 20 accurately weighed tablets.

Drug content uniformity

Accurately weighed 20 tablets (of all batches) were dissolved in 500 ml of distilled water. The samples were sonicated for 30 min. and filtered through 0.45µm nylon membrane filter. The filtered samples, after appropriate dilution with mobile phase, were analyzed at 274 nm using UV-Visible spectrophotometer (Elico, SD-159, India).

***In vitro* drug release study [12]**

The developed formulations (n=3) of Doxofylline were subjected to *in vitro* release studies using USP-II dissolution apparatus (Electro lab, India) at 50 rpm. 0.1N HCL dissolution media was used for 2hrs followed by pH 6.8 phosphate buffer (900ml) maintained at 37± 0.5 0C which was found to provide sink condition (solubility of Doxofylline was determined to be >1gm/ml) [12]. The samples (5 ml) were withdrawn at different time intervals and replaced with equivalent pre warmed (37± 0.5 0C)

volume of fresh medium. The withdrawn samples, after filtration through 0.45 µm nylon membrane filters, were analyzed using UV-Visible spectrophotometer (Elico, SD-159, India) at 274 nm.The cumulative percentage release and standard deviation were calculated. After analyzing the drug content in the dissolution samples, correction was made for the volume replacement and the graph of cumulative percent of drug release versus time was plotted.

Release kinetics

In order to understand the mechanism and kinetics of drug release, the results of the *in-vitro*
drug release study were fitted to various kinetics equations like zero order (% of cumulative drug
release vs. time), first order (log %cumulative drug remaining vs. time), Higuchi matrix (%
cumulative drug release vs. square root of time). In order to define a model which will represent a better fit for the formulation, drug release data were further analyzed by Peppas equation, $Mt/M\infty = ktn$, where Mt is the amount of drug released at time t and $M\infty$ is the amount released at ∞, $Mt/M\infty$ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent, a measure of the primary mechanism of drug release. R2 values were calculated for the linear curves obtained by regression analysis of the above plots.

RESULTS AND DISCUSSION:

The compatibility of the drugs and polymer was studied by FTIR. The IR spectra of drugs and polymer mixture shows the major characteristic absorption bands of the polymer PVP-K30 with negligible difference of absorption band values. So, FTIR spectra show there is no change in the nature and position of absorption bands which proves that there is no chemical reaction between Doxofylline and PVP-K30.

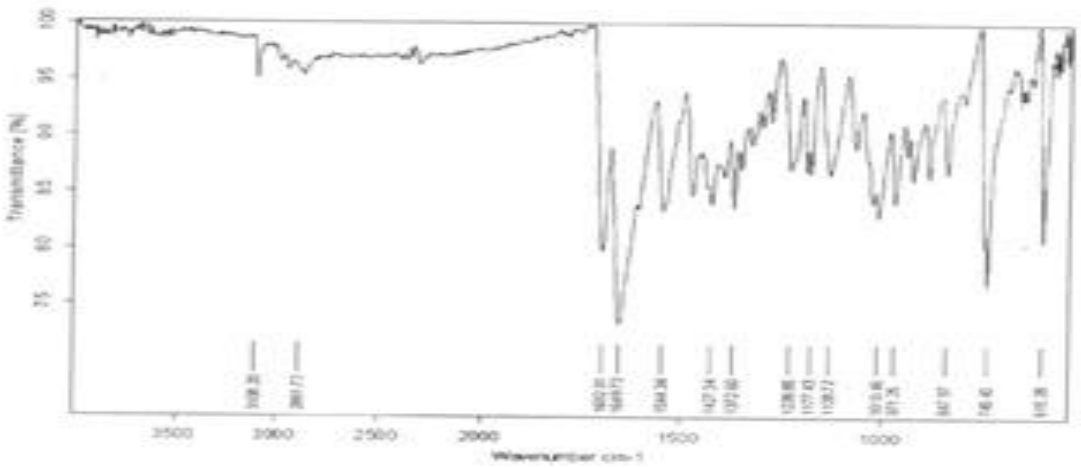

Fig 1: FT-IR spectra of Doxofylline

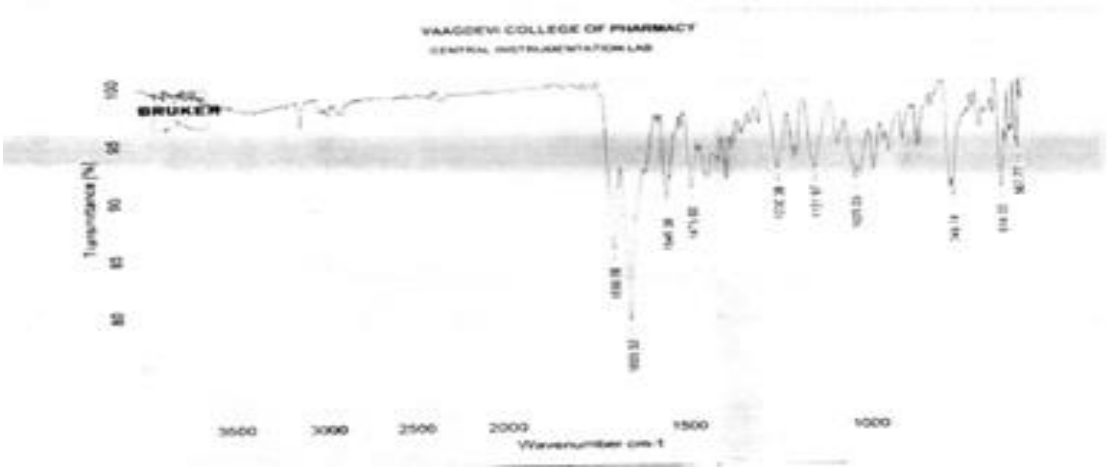

Fig 2: FT-IR spectra of Doxofylline +Manitol

Fig 3: FT-IR spectra of Doxofylline +NaCl

Table 4: Properties of the Powdered Blend, Core Tablets, and Final Coated Tablets of the Optimized Formulation (Batch-VE)

Parameters	Mean value± S.D
Bulk density[a] (mg/cm^3)	510
Tap density[a] (mg/cm^3)	560
Compressibility index[a] (%)	10.71
Hausnerratio[a]	0.90
Tablet weight (mg, n=10) Core tablet Coated tablet	 705.22±1.21 718.33±1.45
Thickness (mm, n=10) Core tablet Coated Tablet	 6.86±0.03 7.05±0.03
Hardness (Kg/cm^2) Core tablet Coated tablet	 8.20±0.5 12.50±0.5
Friability[b] (%)	0.096
Content uniformity[c] (%, n=5)	99.23±2

[a]properties of powder blend; [b] property of the core tablet; [c] property of final coated tablet

The results of the dissolution studies indicate that the influence of osmotic agent as well as the polymer shows the controlled release of drugs from the tablets. The results suggest that the ratio of drug to polymer has greater influence on the release pattern of Doxofylline. The drug release pattern showed a lag time of 1hour for all the formulations which is the basic character of the osmotic drug delivery systems.

It is observed that the all formulations are able to control the drug release up to 24 hours. The cumulative percentage drug release from the formulations met the standard criteria of drug release from extended release formulations as specified by the US-FDA which is around 20% within the first 4 hrs, 50 – 70 % at 12 hrs and > 85% after 24 hrs.

Table 5: Comparative *In- vitro* drug release data of formulations containing Manitol as osmogen (F1 to F5)

Time (Hrs)	Cumulative % drug release* F1 F2 F3 F4 F5				
	F1	F2	F3	F4	F5
0	0.00	0.00	0.00	0.00	0.00
1	0.6±0.173	0.83±0.115	0.46±0.208	0.53±0.230	1.16±0.251
2	2.96±0.152	4.73±0.642	3.36±0.450	3.66±0.450	5.06±0.556
3	11.36±0.152	11.16±0.251	10.2±0.400	11.03±0.351	12.73±0.503
4	16.01±0.300	17.03±0.251	15.93±0.251	15.36±0.305	19.86±0.305
5	22.03±0.251	22.8±0.600	21.33±0.351	21.9±0.458	26.33±0.472
6	38.09±0.500	29.63±0.493	26.66±0.750	27.83±0.404	31.93±0.251
7	34.13±0.404	36.0±0.655	34±0.360	35±0.300	40.02±0.558
8	38.93±0.416	41.63±0.750	40.33±0.351	41.09±0.264	47.96±0.378
9	45.06±0.305	47.0±0.721	44.66±0.709	49.25±0.503	55.03±0.650
10	52.16±0.667	55.43±0.832	51.63±0.702	55.06±0.251	62.03±0.321
12	59.86±0.378	60.04±0.818	57.04±0.360	61.93±0.321	70.76±0.602
14	67.46±0.832	67.01±0.700	64.04±0.321	70.8±0.400	78.56±0.288
16	72.56±0.611	76.23±0.450	71.16±0.971	76.09±0.458	83.86±0.493
20	82.08±1.153	82.96±0.611	76.66±0.776	81.73±0.589	89.04±0.360
24	87.03±0.458	91.05±0.700	82.63±0.665	90.03±0.793	96.06±0.360

***** Mean ± SD, n=3.

Table 6: Kinetic data of formulations containing Manitol as osmogen (F1 to F5)

F.Code	Zero order plot	First order plot	Higuchi's Plot	Korsemeyer-Peppa's plot		Mechanism of drug release
	R^2	R^2	R^2	n	R^2	
F1	0.976	0.989	0.982	0.987	0.947	Non-Fickian release
F2	0.980	0.976	0.903	0.977	0.948	Non-Fickian release
F3	0.968	0.986	0.977	0.966	0.934	Non-Fickian release
F4	0.990	0.981	0.987	0.996	0.964	Non-Fickian release
F5	0.980	0.961	0.972	0.914	0.957	Non-Fickian release

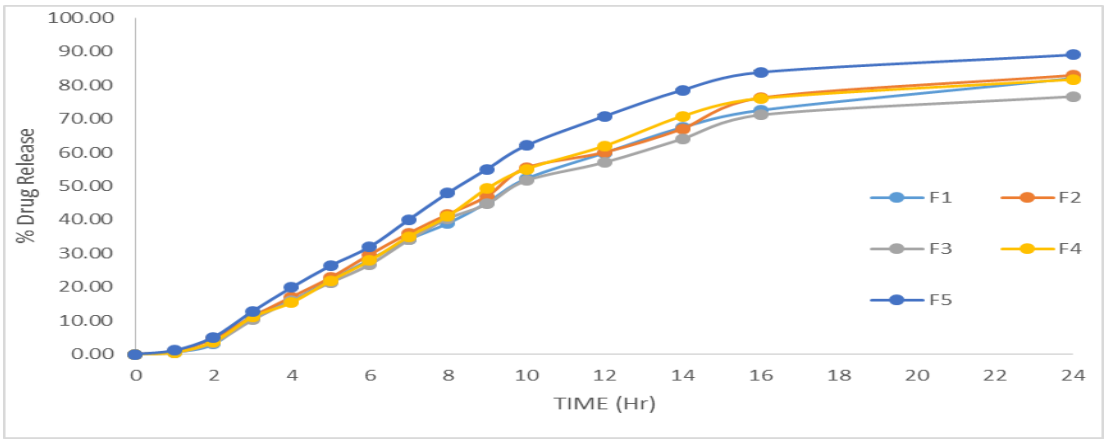

Fig 4: Comparative *In- vitro* drug release of formulations (F1-F5)

Effect of formulation variables on *in vitro* drug release [13, 14]

Effect of nature and type of semi-permeable membrane forming polymer

The choice of rate controlling membrane is an important aspect in the formulation development of oral osmotic systems. The delivery of drug from oral osmotic systems is controlled by the influx of solvent across the SPM, which in turn carries the agent to the outside environment. To study the effect of nature of semi-permeable membrane forming polymer on *in vitro* drug release, the core tablets were coated with cellulose acetate and ethyl cellulose and the dissolution data were compared.

A 5% ethyl cellulose (18-22 cps) dissolved in Isopropyl alcohol was used as a coating solution with dibutylphthlate (15% w/w of ethyl cellulose) as plasticizer. The results showed that coating with ethyl cellulose showed dose dumping after 4 hrs of dissolution because of the detachment of the coating. The reason may be attributed to the extreme hydrophobic surface of ethyl cellulose unable to attach to the smooth surface of Doxofylline core tablet. Thus, to increase the roughness of the surface and thus the adherence of ethyl cellulose, the core tablets of Doxofylline were coated with 3% aqueous solution of HPMC (15 cps) until 2% increase in weight of tablet was obtained. The coating remained for a period of 6 hrs, and then got detached resulting in dose dumping at the end of 6th hour. The bust strength of the ethyl cellulose coating was not sufficient to withstand the hydrodynamic pressure of the dissolution medium, due to formation of porous structure.

Cellulose acetate (CA) films are insoluble, yet semi-permeable to allow water to pass through the tablet coating. The water permeability of CA is relatively high and can be easily adjusted by varying the degree of acetylation. The permeability of CA film can be further increased by the addition of hydrophilic flux enhancer (necessary in case of poorly water soluble drugs). Incorporation of a plasticizer in CA coating formulation generally lowers the glass transition temperature, increases the polymer chain mobility, enhances the flexibility, and affects the permeability of the film. The semipermeable membrane formed from CA possesses sufficient wet strength and wet modulus so as to retain its dimensional integrity during the operation and the reflection coefficient, leakiness of the membrane (i.e., leakage of solute through the membrane) is near to 1 which is desired. The polymer is also biocompatible.

Cellulose acetate coating remained intact even after 24 hrs of dissolution. The 4% w/w of CA in acetone had excellent spray properties. CA coating improved the elegance of osmotic pump along with controlling the release of the drug from the core formulation.

Effect of nature and concentration of plasticizer

To study the effect of nature and concentration of plasticizer, hydrophilic plasticizer such as PEG-400 and hydrophobic plasticizer dibutylphthlate were included in the coating formulation at varying concentrations and their influence in controlling the drug release.

Core formulation of batch-F5 were coated with coating formulation B and C containing 10% and 20% w/w (of cellulose ace-tate) of PEG-400 respectively coded as batch VB and batch VC. It is clearly evident that level of plasticizer (PEG-400) has direct effect on the drug release. As the level of PEG-400 increases the membrane become more porous due to solubilization of water soluble PEG-400 in dissolution media resulting in higher drug release [15]. Another parameter affected by the level of plasticizer was burst strength of the exhausted shells. With the increase in level of PEG-400, the membrane became more porous after exposure to water, leading to a decrease in its strength.

In contrast core formulation of batch-F5 were coated with coating formulation D and E containing 10% and 20% w/w (of cellulose acetate) of Dibutylphthlate (DBP) respectively coded as batch VD and batch VE. As DBP is insoluble in water, it is difficult to leach. Because of its hydrophobic character, the residual DBP would resist water diffusion and, as a consequence the drug release was controlled. The more DBP incorporated into the membrane, the more difficult it was to leach, and in turn, the lower permeability of the membrane, the lower the drug release rate obtained. DBP in the concentration of 10% of cellulose acetate in the coating solution formed coating which was found to be brittle with low burst strength. DBP at a concentration of 20% w/w of the polymer was found to form a film with good flexibility, elegant appearance, controlling the imbibitions of water from the dissolution media and thus the drug release.

Effect of type and amount of osmogen

In osmotic drug delivery system osmotic pressure is the basic principle. To create osmotic pressure in dosage form, in formulation generally will use the osmogen.In the present study two osmogens(sodium chloride and manitol) were compared how the concentration of osmogen will effect the drug release from the dosage form.

Mannitol with an osmotic pressure of 38 (nearly ten times less than that of sodium chloride) was chosen as an osmogen. Formulations containing mannitol as osmogenat higher concentrations was found to release drug in zero-order for a period of 24hrs .

Effect of percentage increase in weight of coating

Formulations with percentage increase in weight from 1.9% to 8.05% were subjected to dissolution and the results are presented in the Table 7. It is evident from the results that the drug was released in less than 6hrs from formulations with % increase in weight from 1.90% to 4.86%. The reason may be attributed to non-uniform formation of coating with the resultant weak points at some places in coating through which drug might have leached. The coating with % increase in weight of 6.50% and 8.05% showed controlled release of drug over a period of 24 hrs. Among all the formulations, formulations with 6.50% increase in weight showed zero-order drug release.

Table 7: Effect of percentage increase in weight upon coating on *in vitro* drug release profile.

Time (hrs)	Percentage increase in weight upon coating					
	1.90 %	2.61 %	3.45 %	4.86 %	6.50 %	8.05 %
	Cumulative % release ± SD	Cumulative % release ± SD	Cumulative % release ± SD	Cumulative % release ± SD	Cumulative % release ± SD	Cumulative % release ± SD
1	30.85±2.71	41.75 ±2.85	17.24±1.71	19.56± 2.12	0.43±0.152	1.16±0.251
2	40.30±1.96	50.56±2.81	24.96±2.06	25.37±1.86	2.23±0.321	5.06±0.556
3	60.249±2.57	65.98±2.56	29.78±2.98	29.85±2.48	10.2±0.500	12.73±0.503
4	70.37±1.94	71.29±2.16	40.12±2.16	33.77±1.94	15.26±0.450	19.86±0.305
5	82.34±1.99	85.89±2.48	60.69±2.45	35.91±1.89	19.8±0.800	26.33±0.472
6	98.24±2.01	90.82±1.93	71.54±1.99	45.91±1.82	26.7±0.458	31.93±0.251
7	--	99.87±3.22	82.57±2.85	65.01±2.95	30.96±0.802	40.02±0.558
8	--	--	97.68±2.56	78.26±2.66	36.6±0.793	47.96±0.378
9	--	--	--	89.3±2.01	43.76±0.776	55.03±0.650
10	--	--	--	98.56±2.01	49.15±0.650	62.03±0.321
12	--	--	--	--	55.73±1.002	70.76±0.602
14	---	--	--	--	62.01±0.755	78.56±0.288
16	--	--	--	--	67.04±0.400	83.86±0.493
20	--	--	--	--	75.3±0.500	89.04±0.360
24	--	--	--	--	83.03±0.404	96.06±0.360

Values are expressed as mean cumulative percentage release ±SD = 3

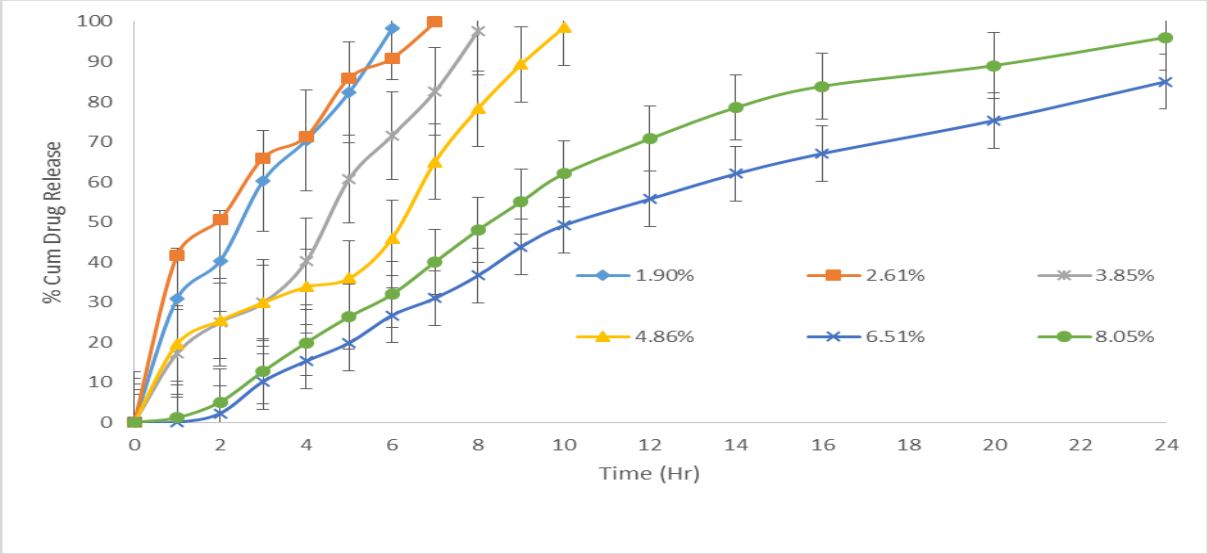

Fig 5: Effect of weight gain on release rate

Effect of pH

Formulation batch I was subjected to dissolution. The release media used were 900 ml of distilled water (pH = 7.0) and 900 ml of 0.1 N HCl (pH = 1.2) for the first 2hrs followed by 900 ml of phosphate buffer (pH 6.8) for the remaining time. The samples (5 ml) were withdrawn at predetermined intervals and analyzed using UV-visible spectrophotometer (Elico, India) at 274 nm. From the results it was evident that there was no significant difference in the cumulative percentage drug release form osmotic systems, proving that the osmotic systems release drug in zero-order which is independent of pH. The cumulative percentage of drug released in a dissolution medium of pH 7.0 and 0.1 N HCl ans pH 6.8 are 96.29% and 98.90%respectively. The reason could be attributed to the effective isolation of the core form the dissolution media by the semi-permeable membrane.

CONCLUSION:

The developed of elementary osmotic tablet shows a controlled drug release of Doxofylline. The results demonstrate that release profile is strongly dependent on the concentration of the polymer and osmogent. The results also indicate that the osmotic drug delivery system may be successfully utilized for the controlled delivery of Doxofylline up to 24hours. Drug release from the developed formulations was independent of pH and agitation intensity of the release media, assuring the release to be fairly independent of pH and hydrodynamic conditions of the absorption site. Doxofylline release from developed EOP was directly related to the level of plasticizer. Drug release data from Doxofylline formulations fitted well into zero-order kinetics. It can be conclusively stated that an elementary osmotic tablet of Doxofylline is a promising approach to alternate the conventional dosage forms**.**

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