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Formulation And Evaluation Of Osmotically Controlled Oral Drug Delivery System Of Salbutamol Sulphate

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ABSTRACT

Osmotically Controlled Release Tablets (OCRT) of Salbutamol Sulphate (SS) that achieve zero-order drug release, independent of gastrointestinal physiological factors were formulated and evaluated in this study. SS is a highly water-soluble drug, leading to rapid release and absorption when administered orally. To mitigate this, the study aimed to control the drug's release rate using an osmotic pump system and to arrive at an optimal formulation by assessing the effect of varying concentration & type of osmogen and the size of orifice on the release rate of the drug. Core tablets containing Salbutamol sulphate and varying concentrations of different types of osmogens (Sodium Chloride (NaCl), Potassium Chloride (KCl) and Sodium Chloride – Potassium Chloride (1:1) mixture) were prepared and covered by a semipermeable coating membrane composed of cellulose acetate and Poly Ethylene Glycol (PEG) 400. Delivery orifices of different sizes (0.2mm, 0.4mm and 0.6mm) were created on the coating one side of the tablets forming an Elementary Osmotic Pump System. The 30 OCRT formulations were evaluated for physicochemical properties and In vitro drug release, which was then compared to a marketed controlled-release product. Scanning Electron Microscopy (SEM) was used to examine the membrane morphology and orifice size. Short-term stability studies were also conducted under extreme condition for 60 days. The study revealed that the OCRT of SS with higher concentration (75%w/w) of NaCl and a 0.4mm Orifice exhibited optimal controlled release properties. SEM analysis confirmed the consistency and integrity of the membrane and orifice. Stability studies indicated that the optimized formulation remained stable under extreme conditions for 60 days. The study demonstrates that the type and concentration of osmogen, along with the orifice diameter, are critical factors in controlling the release rate of Salbutamol Sulphate in OCRT formulations. The optimized formulation achieved a zero-order release profile, offering a potential improvement over existing controlled-release products.

Keywords: *Salbutamol Sulphate, Osmotically Controlled Released Tablets, Osmogen, Elementary Osmotic Pump System, Delivery Orifice, Zero Order Release Pattern.*

1. INTRODUCTION

Osmotically Controlled Drug Delivery Systems (OCDDS) are advanced oral formulations designed to deliver medications at a controlled and predetermined zero-order rate for prolonged periods.[1,2] These systems utilize osmotic pressure as the driving force for drug release, ensuring consistent plasma drug concentrations and improved therapeutic outcomes.[3] Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semipermeable membrane. Osmotic pumps (OP) are standard dosage forms for a constant-rate drug delivery.[4] The three basic components of Osmotic pumps are the Drug, Osmogen, Semipermeable membrane (SPM).[1] Osmotic pump has an orifice in order to release the active material. When the system happens to be inside the gastrointestinal tract, the fluid

enters the core through the membrane and dissolves the active material.[5,6] The osmotic pressure generated in the core induces release of the drug in solution at a slow but constant rate particularly beneficial for drugs requiring controlled plasma levels, such as those used in the management of chronic conditions like hypertension, asthma and diabetes.

Salbutamol sulphate is a directly acting sympathomimetic agent with predominant β-adrenergic activity exhibiting selective action on β_2-receptors. It is primarily utilized in the treatment of bronchial asthma and other forms of diffuse airways obstruction.[7-9] Physico chemically, Salbutamol sulphate appears as a white crystalline powder, odourless, freely soluble in water and Pharmacokinetically, it has elimination half-life (t½) of 2.5-5 hrs makes it a suitable drug candidate for Osmotically Controlled Drug Delivery System, providing sustained therapeutic levels, particularly beneficial in managing nocturnal asthmatic attacks.[10-12]

2. MATERIALS AND METHODS

Materials

Salbutamol Sulphate was obtained as a gift sample from Tablets India (P) Ltd.,Chennai. NaCl and KCl (Paxmi Chemicals) were used as osmogens. Cellulose Acetate IP (Loba chemicals) and PEG 400 IP (S.D. Fine Chemicals) were used as SPM and Plasticiser respectively. Magnesium Stearate IP and Talc IP (Loba Chemicals) were used as lubricants, Lactose IP (S.D. Fine Chemicals) as diluent and Povidone IP (S.D. Fine Chemicals) as a binder. The other chemicals used were of analytical grade.

Methods

Solubility Studies

Preparation of calibration curve of Salbutamol Sulphate

Primary stock solution was prepared by dissolving 100mg Salbutamol Sulphate in 100ml of 0.1 M HCl and suitable dilutions were made to get concentration range of 1 – 10 mcg/ml and the absorbance was measured at 276nm using UV – Visible spectrophotometer.[10] The above procedure was repeated using buffer pH 1.2, pH 6.8 and distilled water (Figure 1 - 4).

Procedure

Solubility studies were performed for Salbutamol Sulphate in water and in saturated solution of osmogens viz., NaCl, KCl and NaCl – KCl mixture (1:1). An excess quantity of drug (Salbutamol Sulphate) was suspended in 10 ml of water and 10 ml of clear saturated solution of osmogen(s) and equilibrated by intermittent shaking for 72 hrs maintained at room temperature and then filtered. 1ml of the filtered solution was taken, diluted suitably and the drug concentration was analysed spectrophotometrically at 276nm (Table 2).[13]

Preparation of Osmotically Controlled Release Tablet (OCRT) Formulations

Preparation of Core tablets [14]

Ten formulations of SSCT were prepared. Out of which nine formulations were developed by using two different osmogens separately and in combination and with varying proportions of other ingredients shown in Table 1. The tenth formulation was developed as reference (without osmogen).

Table 1: Composition of different batches of Salbutamol sulphate core tablet

INGREDIENTS	QUANTITY/TABLET (mg)									
	A (Control)	**B (25% w/w NaCl)**	**C (50% w/w NaCl)**	**D (75% w/w NaCl)**	**E (25% w/w KCl)**	**F (50% w/w KCl)**	**G (75% w/w KCl)**	**H (25% w/w NaCl-KCl (1:1))**	**I (50% w/w NaCl-KCl(1:1))**	**J (75% w/w NaCl-KCl (1:1))**
Salbutamol sulphate eq. to 8mg salbutamol I.P	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6
Lactose I.P	368.4	366	363.6	361.2	366	363.6	361.2	366	363.6	361.2
PVP K30 I.P	10	10	10	10	10	10	10	10	10	10
Isopropyl Alcohol I.P	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Talc I.P	8	8	8	8	8	8	8	8	8	8
Magnesium Stearate I.P	4	4	4	4	4	4	4	4	4	4
Sodium Chloride I.P	-	2.4	4.8	7.2	-	-	-	1.2	2.4	3.6
Potassium Chloride I.P	-	-	-	-	2.4	4.8	7.2	1.2	2.4	3.6

Wet granulation technique was employed to form the granules. Salbutamol Sulphate (Sieve No.100) and Lactose (Sieve No. 60) were mixed well by geometric dilution. 2.5% w/w paste of Polyvinyl Pyrrolidone K30 (PVP K30) in Isopropyl alcohol (IPA) was prepared. PVP K30 paste was added to the drug mixture to form a coherent mass and was dried at 60°C in a tray drier for 2 hours and then the dried granules were passed through standard sieve No.18. Sodium chloride and potassium chloride sized through sieve No.18 were added to the granules and then lubricated with 2% Talc and 1% w/w Magnesium stearate for 15 min. Then the granules were evaluated for its various physicochemical parameters as per standard procedures.[15]

Evaluation of Granules

a. **Assessment of flow properties**: The flow property was assessed by determining the angle of repose (θ) which was measured by allowing the granules to fall over a paper placed on a horizontal surface through a funnel kept at a height of about 6 cm from the paper using the formula, $\theta = \tan^{-1} h/r$, where h and r represents the height and radius of the heap respectively (Table 4).[16]

b. **Bulk Density**: It was measured by pouring granules into a cylinder and dividing the mass of the granules by the volume they occupy (Table 4).[17]

c. **Moisture Content**: It was assessed by estimating the loss on drying using the Moisture content analyser (Advance) at temperature 100°C and the values were tabulated (Table 4). The evaluated granules were compressed into tablets by Direct Compression method using 9.6mm round concave punch using Single Punch tablet machine (Cadmach). The average thickness, weight and hardness were set to 4.8mm ± 5%, 400mg ± 5% and 7-8kg/cm^2 respectively and were evaluated as per standard methods and the results were tabulated (Table 5-7).

Evaluation of Uncoated Tablets

a. Appearance: The tablets prepared were white, circular, slightly biconvex, with beveled edges.

b. Thickness: Tablet thickness was measured using Vernier caliper (Mitutoyo) and the results were tabulated in Table 5.

c. Weight Variation: Twenty tablets from each formulation were selected randomly and weighed individually. The average weight was then determined (Table 6).

d. Hardness: The hardness of the tablets was determined using Monsanto Hardness tester and the results were tabulated (Table 7)

e. Friability: 15 tablets were weighed and placed in the friability apparatus and were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After a given number of rotations the tablets were weighed and the loss in weight was calculated and tabulated (Table 7)

f. Drug Content Analysis: Ten tablets were taken from each formulation and powdered. From the powder an accurately weighed amount equivalent to 30 mcg of Salbutamol Sulphate was taken and dissolved in 0.1M HCl. The filtered solution was then assayed for drug content by measuring the absorbance at 276nm using UV-Visible spectrophotometer[10]. The data is presented in Table 8.

Preparation of Coated tablets: The tablets were coated to a target thickness of about 0.2mm using 5%w/w of Cellulose Acetate (Polymer) and 1.5%w/w of PEG 400 (Plasticizer) dissolved in Dichloromethane and Methanol in a 4:1 ratio using a Pan coating machine (Cadmach) with a 30 cm stainless steel pan rotating at 25 rpm.[20] The coating solution was applied via an atomizer spray gun at 5 mL/min to achieve a film thickness of approximately 0.2 mm. Coating uniformity was evaluated through SEM analysis. (Figure 16).

Evaluation of Coated tablets: The parameters like appearance, thickness, weight variation, hardness, friability and drug content were evaluated using the same procedure as that of uncoated tablets and the results were tabulated.[18] (Table 5-8).

Drilling of Coated Tablets

The drug delivery orifice of 3 different diameters (0.2mm, 0.4mm and 0.6mm) were made with stainless steel drill pins (Addison) by using Microdrill ("WEBO" west Deutsche Bohrmachinen) on the surface of one side of the tablets. Jig plate

was used to mount 15 tablets at a time and the drilled tablets were observed using Reflecting Optical Microscope (Leica) to measure the delivery orifice diameter.[19] The tablet formulations with 0.2mm,0.4mm, 0.6mm orifice diameter were given a number suffix '1','2' and '3' respectively. As a result, 30 different OCRT formulations were arrived and then labeled as given in Table 2.

Table 2: Formulation of different batches of Osmotically controlled Release Tablet (A1 to J3)

S.No	Osmogen (%)	Orifice Diameter		
		0.2mm	0.4mm	0.6mm
1	Control	A1	A2	A3
2	25% NaCl	B1	B2	B3
3	50% NaCl	C1	C2	C3
4	75% NaCl	D1	D2	D3
5	25% KCl	E1	E2	E3
6	50% KCl	F1	F2	F3
7	75% KCl	G1	G2	G3
8	25% NaCl : KCl (1:1)	H1	H2	H3
9	50% NaCl : KCl (1:1)	I1	I2	I3
10	75% NaCl : KCl (1:1)	J1	J2	J3

In vitro Drug Release Studies[22]

In vitro release study of OCRT (A1 to J3) were carried out using USP XX1 type II (Paddle) Dissolution Apparatus at 37° ± 1°C at 100 rpm in 250ml of dissolution medium for about 8 hours. The dissolution medium was Simulated Gastric Fluid (SGF pH 1.2 buffer) for first two hours followed by transfer into another flask containing Simulated Intestinal Fluid (SIF pH 6.8 phosphate buffer) for subsequent 6 hours.[23] Aliquot samples of 10 ml were withdrawn at 1 hour time interval and same volume of medium was replaced to maintain the sink condition. The amount of drug released was estimated by measuring the absorbance at 276nm using UV-Visible spectrophotometer (Figure 5-14).[20]

Comparison of drug release profile of selective OCRT with Marketed formulation

The *invitro* release study of the marketed product (DURA CR) was carried out using USP XXI type I (basket) dissolution apparatus. The amount of drug released was estimated and compared with the selected formulation (OCRT – D2, G2 and J2) as represented in Figure 15.

Scanning Electron Microscopy (SEM)

The selected formulations were subjected to SEM analysis to reveal the uniformity of coating and orifice characteristics.[21] Samples for SEM analysis were mounted on the specimen stubs using an adhesive. Samples were coated with gold to a thickness of 100Å using Hitachi vacuum evaporator, Model HUS 5 GB. Coated samples were analysed in Hitachi Scanning Electron Microscope model S-450 operated at 15 KV, and photographed (Figure 16).

Short Term Stability Studies

Stability studies were conducted on the optimized formulation exhibiting satisfactory invitro drug release. Samples were stored in amber-colored containers at three different temperatures: refrigerated (4 ± 2°C), room temperature (27 ± 4°C), and elevated temperature (50 ± 2°C) for a duration of two months. Assessments of drug content and dissolution profiles were performed on the 30th, 45th, and 60th days to evaluate the stability of the formulations under these conditions (Table 9 & 10).

3. RESULTS AND DISCUSSION

In the present study, the osmotically controlled release dosage form was designed on the basis of pharmacokinetic data of Salbutamol Sulphate (SS). With a maintenance dose of 8mg, the release of active drug at a controlled rate for 12 hours was found to be ideal. The drug showed high aqueous solubility (270mg/ml) and the solubility was decreased and the release was controlled in the presence of NaCl and KCl. Initially, the effect of osmogens on the aqueous solubility of SS was observed. Then the OCRT containing osmogens of different type (NaCl, KCl, NaCl-KCl mixture (1:1)) and

concentration (25%,50% and 75%) were formulated and coated with cellulose acetate and three different orifice sizes (0.2mm, 0.4mm & 0.6mm) were made on one side of the tablet. The formulations (OCRT: A1–J3) were evaluated for various physicochemical parameters, content uniformity, and morphology of membrane and size of orifice by SEM analysis. The *invitro* dissolution rate was done in sequenced SGF and SIF media to find out the effect of osmogen and orifice size on the release kinetics of SS. The release of selected OCRT - D2, G2 and J2 were compared with the release performance of marketed formulation of SS statistically. From the results of release studies of all the formulations, the best formulation was selected and subjected to short-term stability studies at different temperatures.

Calibration Curve of Salbutamol Sulphate

Calibration curve of Salbutamol Sulphate in the concentration range of 10 – 100 mcg/ml in four different medium showed that it obeys Beers law (Figure 1-4) and it was used to find the aqueous solubility of the drug, drug content in formulations and cumulative percentage drug release from OCRT.

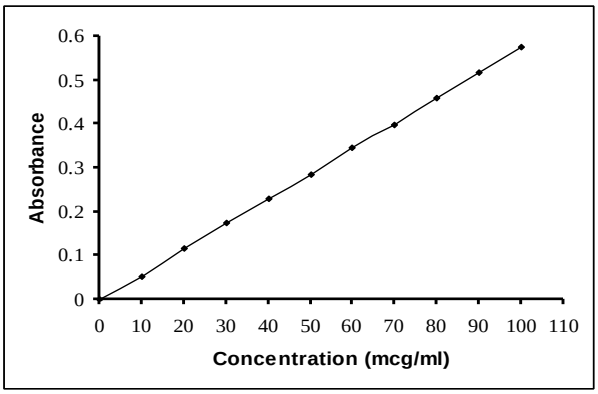

Figure 2: 0.1M HCl

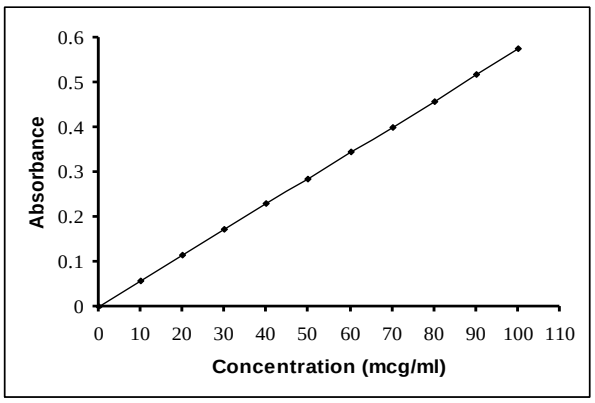

Figure 1: Distilled Water

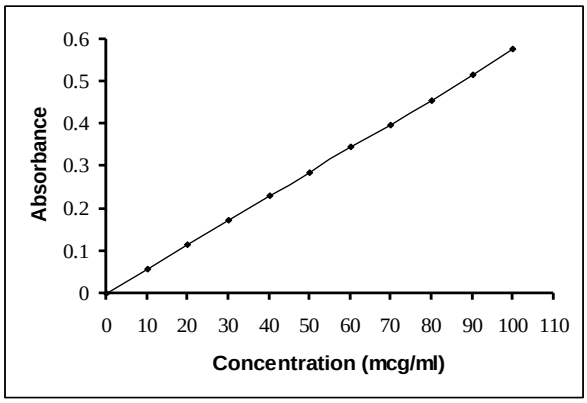

Figure 3: pH 1.2 Buffer

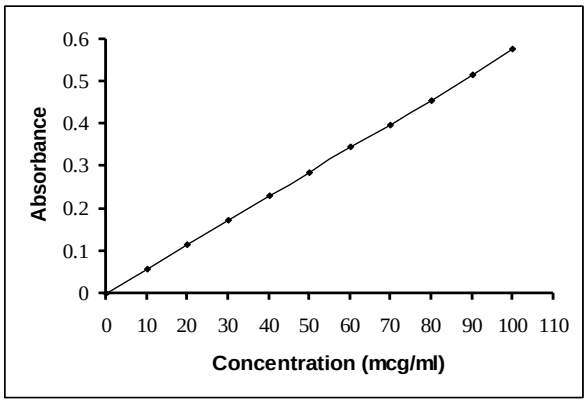

Figure 4: pH 6.8 Buffer

Calibration Curve of Salbutamol Sulphate in 4 different medium at 276nm.

Solubility Studies

The solubility of SS was least in saturated solution of NaCl when compared to the saturated solution of KCl and NaCl - KCl mixture (1:1). Magruder *et al* reported that the solubility of the drug depends upon the greater interaction between the osmogen and solvent. This lesser solubility of the drug in osmogen solutions is desirable in controlling the release rate of the drug from OCRT formulations (Table 3).[22]

Table 3: Effect of Osmogens on Solubility of Salbutamol sulphate

S.No	SOLVENT	SOLUBILITY (mg/ml) ± SEM*
1	Distilled Water	270 ± 0.23
2	Saturated solution of NaCl	12 ± 0.14

3	Saturated solution of KCl	35 ± 0.09
4	Saturated solution of NaCl-KCl Mixture (1:1)	23 ± 0.17

Physicochemical Evaluation of Granules and Tablets

Evaluation of Granules

The values of angle of repose (around 25º-30º) indicated that the granules of all the formulations had good flow properties. The result of bulk density and moisture content of the granules were within the generally acceptable limits and was favorable for easy compression (Table 4).

Evaluation of Tablets

a. General Appearance: The prepared tablets were white, circular, slightly biconvex, beveled edge coated tablets with an orifice on the surface of one side of the tablet.

b. Thickness: The thickness of the coated tablets was ranging between 5.00 and 5.09mm whereas the thickness of uncoated tablets was between 4.80 and 4.87mm. The thickness of coating membrane was limited to approximately 0.2mm which was found to be desirable in considering its influence on the release of the drug from the coated tablets (Table 5).

Table 4: Evaluation of Granules

S.No.	Formulation	Angle of Repose	Bulk Density	Moisture Content (%)
1	A	28°21”	0.5001	0.8
2	B	28°24”	0.5173	1.0
3	C	27°25”	0.5000	1.2
4	D	26°22”	0.4839	1.0
5	E	28°41”	0.5358	1.0
6	F	27°31”	0.5170	1.2
7	G	27°13”	0.5557	1.0
8	H	28°25”	0.5173	1.0
9	I	27°21”	0.4837	1.2
10	J	28°21”	0.5357	1.0

Limit: Angle of repose within $25^0 – 30^0$ indicates free flowing property of the material.

Table 5: Thickness

Formulation	Thickness (mm)		
	Uncoated	Coated	Coating Membrane
A	4.84	5.08	0.24
B	4.87	5.09	0.22
C	4.83	5.06	0.23
D	4.86	5.07	0.21
E	4.85	5.06	0.21
F	4.80	5.00	0.20
G	4.84	5.07	0.23

H	4.83	5.05	0.22
I	4.80	5.02	0.21
J	4.81	5.03	0.22

Limit : Thickness should not vary beyond ± 5 % of the standard value.

Weight Variation and Percentage weight increase: The average weight of the coated tablets was ranging from 415.0 – 447.0 mg as compared to uncoated tablets whose average weight was ranging from 393.0 – 429.0 mg (Table-6). All the batches were found to pass the test for uniformity of weight. The percentage weight increase after coating was found to be between 4.79 % and 5.97 % which may be desirable to withstand the hydrostatic pressure created by the osmogens (Table 6).

Table 6: Weight Variation

Formulation	Weight Variation (mg)		% Wt. increase
	Uncoated	Coated	
A	393-410	420-423	5.14
B	396-412	420-424	4.99
C	391-407	415-419	5.40
D	403-421	428-433	4.86
E	404-421	431-434	4.80
F	398-421	427-428	4.90
G	411-427	437-438	4.79
H	420-429	445-447	5.69
I	410-420	440-442	5.97
J	408-416	432-435	4.99

Limit : Average weight 250mg or more : ± 5 %

d. Hardness and Friability: The hardness of the coated tablets ranged from 8.1 – 8.5 kg/cm^2 when compared to uncoated tablets for which hardness ranged from 7.0 – 7.6 kg/cm^2. This was within the generally acceptable limits. The increase in the hardness is due to the presence of intact coating membrane. The friability of formulated tablets was between 0.03 % and 0.09 %. It was found to be within the limits which showed good adhesion of the tablet ingredients (Table 7).

Table 7: Hardness and Friability

Formulation	Hardness (Kg/cm^2)		Friability (%)
	Uncoated	Coated	Uncoated
A	7.2	8.5	0.09
B	7.2	8.4	0.05
C	7.5	8.3	0.07
D	7.2	8.2	0.05
E	7.3	8.3	0.06

F	7.6	8.5	0.04
G	7.5	8.4	0.09
H	7.1	8.2	0.03
I	7.0	8.2	0.06
J	7.0	8.1	0.04

Limit: The Hardness of about 7-8 kg/cm^2 is considered to be effective for OCRT. Weight loss should not be more than 1 %.

Drug Content: The drug content in the coated as well as uncoated tablets was found to be within the prescribed limits (± 10% w/w of Salbutamol) and the results were presented in Table 8.

Table 8: Drug Content Analysis

Formulation	**Drug Content**			
	Uncoated		**Coated**	
	Amount (mg)	**Percentage (%) ± SEM ***	**Amount (mg)**	**Percentage (%) ± SEM ***
A	9.45	98.33 ± 0.33	9.49	98.79 ± 0.19
B	9.50	98.92 ± 0.33	9.53	99.17 ± 0.30
C	9.44	98.23 ± 0.33	9.43	98.20 ± 0.27
D	9.41	97.95 ± 0.36	9.41	97.99 ± 0.34
E	9.28	96.60 ± 0.29	9.27	96.53 ± 0.23
F	9.32	97.05 ± 0.37	9.33	97.09 ± 0.23
G	9.23	96.11 ± 0.23	9.25	96.32 ± 0.25
H	9.49	98.82 ± 0.37	9.51	99.03 ± 0.36
I	9.26	96.39 ± 0.07	9.26	96.43 ± 0.27
J	9.48	98.72 ± 0.25	9.48	98.68 ± 0.45

*Average value of three readings.

Limit: The drug content should not be less than 90% and not more than 110%w/w.

***In-vitro* Drug Release studies of the OCRT Formulations:**

Drug release profile of OCRT (A1 –A3) without osmogen: The cumulative percentage drug release from OCRT – A1, A2 & A3 without osmogen having delivery orifice of the size 0.2mm, 0.4mm and 0.6mm was found to be 90.16%, 91.24% and 93.76%, respectively after 8 hrs (Figure 5). It was observed that approximately 80% of the drug released within 5hrs for A1, 4hrs for A2 and 3hrs for A3. Therefore, the formulations showed higher release of SS in the absence of osmogens and the release rate were in ascending order on increasing the orifice diameter.

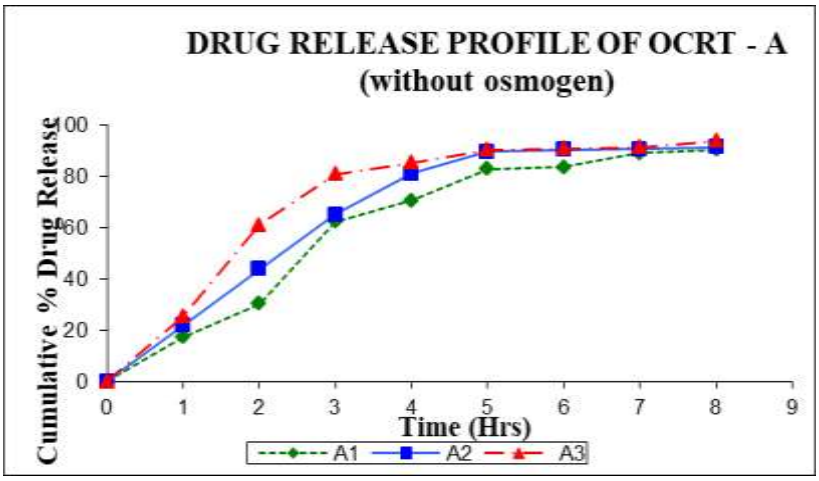

Figure 5: Drug release profile of OCRT (A1-A3)

b. Effect of osmogens in drug release profile of OCRT (B1 –B3)

The release studies showed that the cumulative percentage release of OCRT – B1, B2 and B3 containing 25% of NaCl were found to be 78.20%, 82.89% and 89.51% respectively (Figure 6), OCRT C1, C2 and C3 containing 50% of NaCl was found to be 57.82%, 64.09% and 72.25% respectively (Figure 7) and OCRT D1, D2 and D3 containing 75% of NaCl was found to be 43.17%, 50.64% and 58.79% respectively (Figure 8) after 8 hrs.

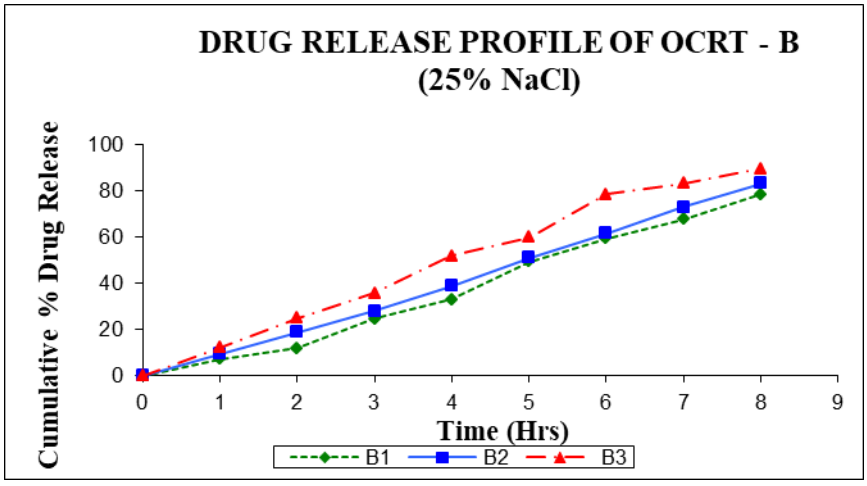

Figure 6: Drug release profile of OCRT (B1 –B3)

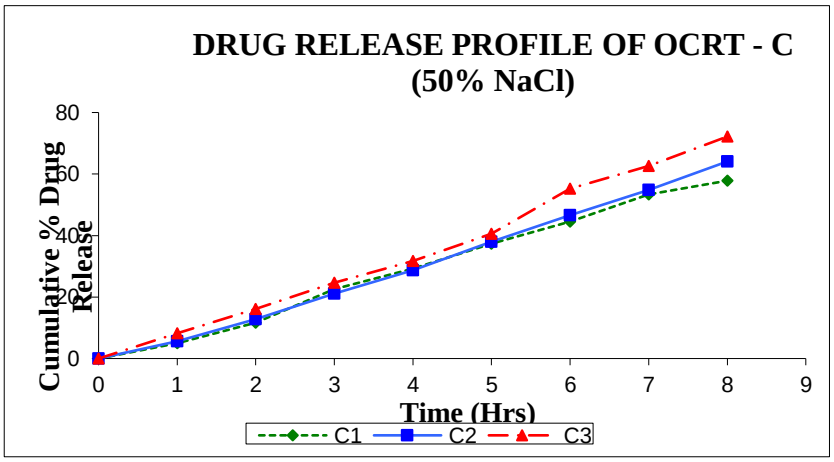

Figure 7: Drug release profile of OCRT (C1 –C3)

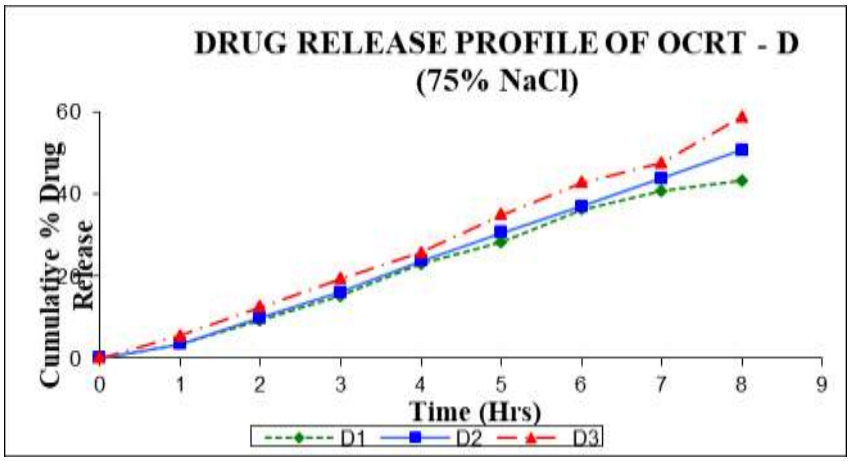

Figure 8: Drug release profile of OCRT (D1 –D3)

When compared the release of OCRT –B (25% NaCl) and C (50% NaCl) with OCRT – D (75% NaCl), the former two showed graded increase in the release rate of SS than the latter. From the results it was confirmed that the increase in concentration of NaCl had a negative effect upon the release of SS.[23]

Similarly, the cumulative percentage drug release from OCRT – E, F and G containing KCl as osmogen were studied. The release studies showed that the cumulative percentage release of OCRT – E1, E2 and E3 containing 25% of KCl were found to be 84.84%, 89.31% and 92.17% respectively (Figure 9), OCRT F1,F2 and F3 containing 50% of KCl were found to be 79.22%, 84.96% and 89.64% respectively (Figure 10) and OCRT G1, G2 and G3 containing 75% of KCl were found to be 73.07%, 77.27% and 85.44% respectively (Figure 11) after 8 hrs.

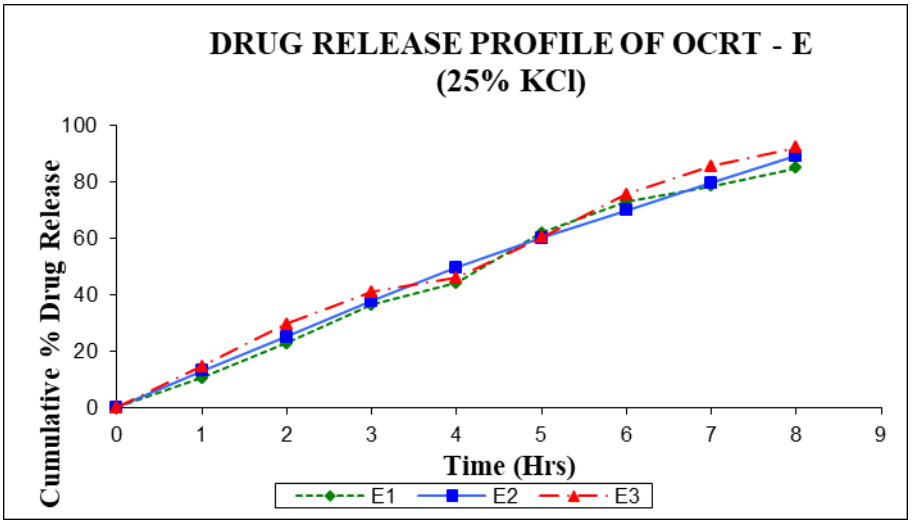

Figure 9: Drug release profile of OCRT (E1 –E3)

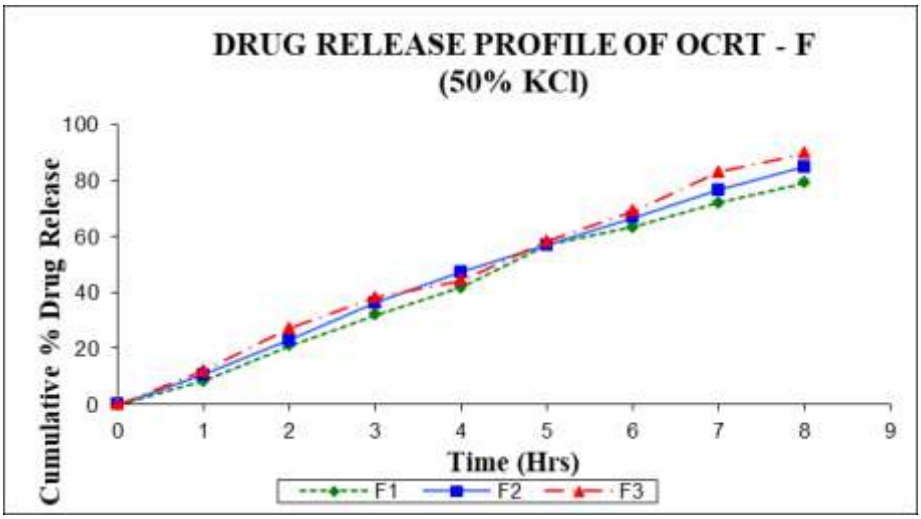

Figure 10: Drug release profile of OCRT (F1 –F3)

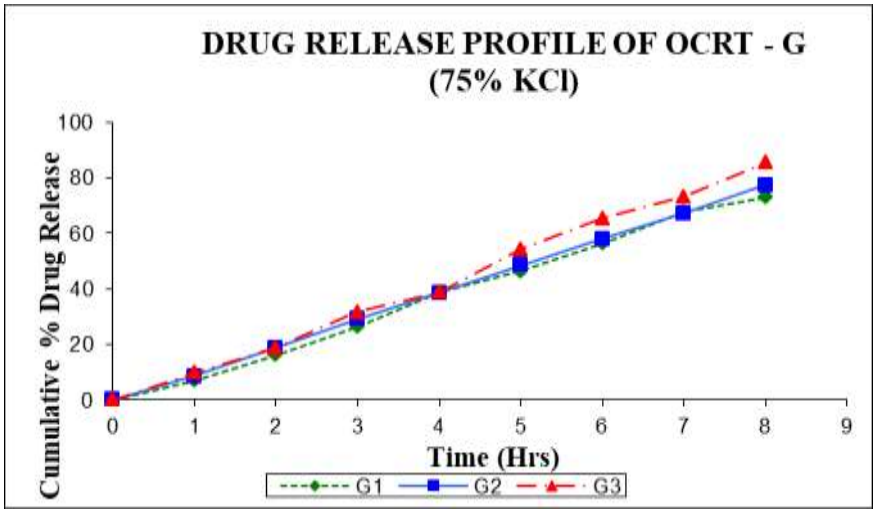

Figure 11: Drug release profile of OCRT (G1 –G3)

When comparing the release of SS from OCRT – E (25% KCl) and F (50% KCl) with OCRT - G (75% KCl), the former showed more release than OCRT–G. Further, the increase in concentration of KCl also has some negative effect upon the release of SS.

Then the cumulative percentage drug release profiles of OCRT – H, I and J were studied. The release of drug from OCRT – H1, H2 and H3 containing 25% of NaCl – KCl (1:1) were found to be 83.00%, 87.66% and 93.19% respectively after 8 hrs (Figure 12), OCRT – I1, I2 and I3 containing 50% of NaCl – KCl (1:1) were found to be 71.35%, 75.32% and 85.78% respectively after 8 hrs (Figure 13) and OCRT - J1, J2 and J3 containing 75% of NaCl – KCl (1:1) were found to be 56.95%, 60.72% and 67.73% respectively after 8 hrs (Figure 14). Here also, it can be observed that increase in the concentration of osmogen mixture indicated decrease in the release of SS.

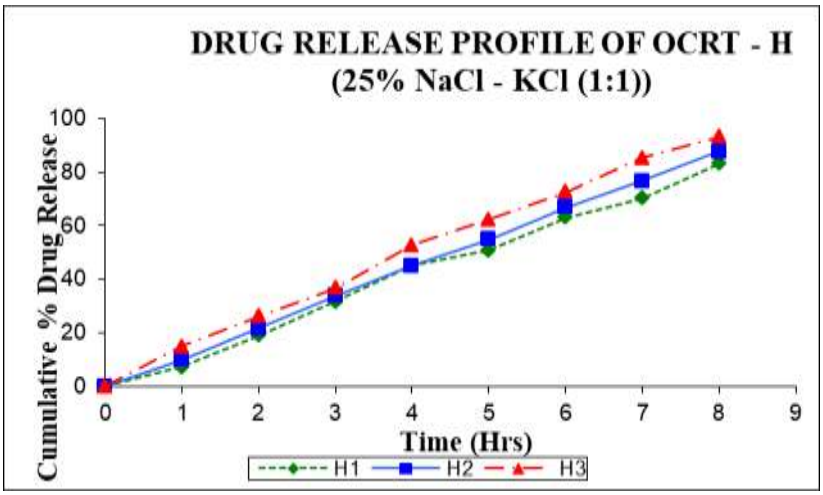

Figure 12: Drug release profile of OCRT (H1 –H3)

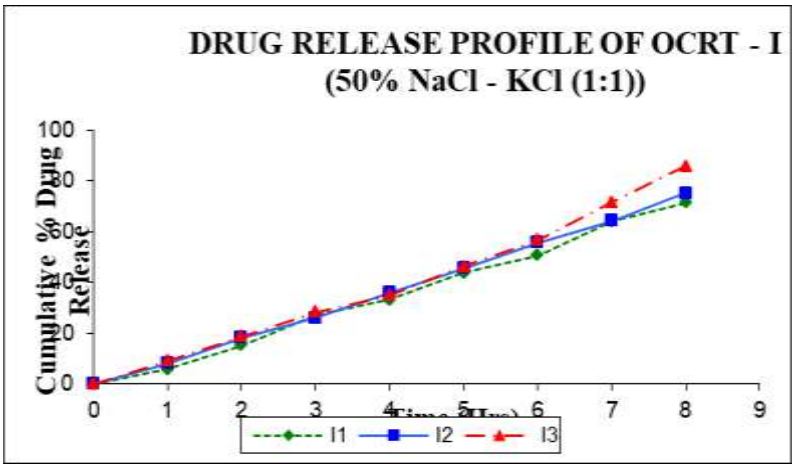

Figure 13: Drug release profile of OCRT (I1 –I3)

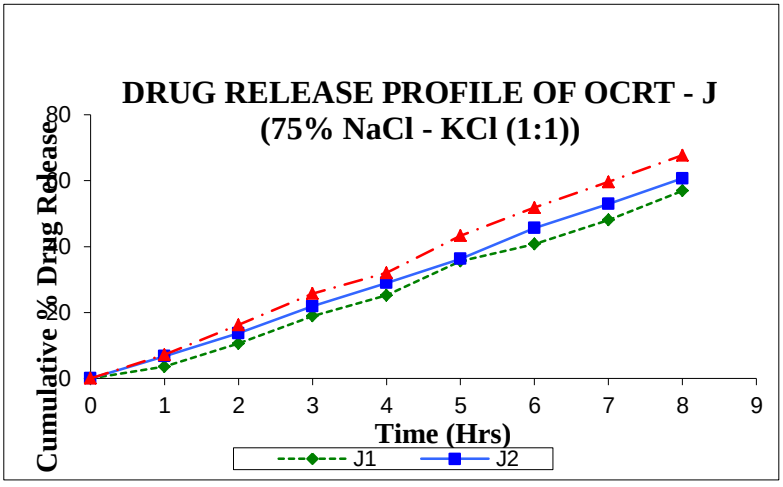

Figure 14: Drug release profile of OCRT (J1 –J3)

In short, the increase in concentration of osmogen showed decrease in the release of SS. It has been observed from all the results that presence of osmogen in the formulations controlled the release of SS when compared to OCRT without osmogen (Figures 5-14).

In the above release studies, it has been further observed that the formulation containing NaCl as osmogen (OCRT – B, C and D) has higher retardant effect on the release of SS than the formulations containing KCl as osmogen (OCRT – E, F and G). But the formulation containing NaCl – KCl mixture (1:1) showed retardant effect in-between.

Further it has been observed that OCRT – D, G and J, containing high concentration of osmogen (75%) showed slow release of SS and hence this concentration may be selected as an optimum concentration in controlling the release of SS from the OCRT. Among all the formulations OCRT – D containing 75% of NaCl showed better controlled release than the other OCRT – G and J containing 75% of KCl and 75% of NaCl – KCl (1:1) respectively.

Effect of orifice size in *in-vitro* drug release profile of OCRT

In the present study three different orifice diameters have been drilled to find its effect on the controlled release of SS and they are 0.2mm, 0.4mm and 0.6mm. From the above results, it has been observed that increase in orifice size resulted in an increase in release rate of drug. This could be attributed mainly to the increase of water influx through the delivery orifice (Figure 16).[24]

The study revealed that orifice diameter was an important factor in controlling the release of drug from the OCRT. From the Figure 5 - 4, it has been found that the OCRT having orifice diameter 0.4mm showed uniform release whereas the other two orifice diameters showed fluctuations in the release rate.

Further, irrespective of different nature and concentration of osmogen the OCRT with the orifice diameter 0.4mm showed uniform release throughout the studies. And hence the orifice diameter 0.4mm may be selected along with the high concentration of osmogen to get better control in release of drug and to minimise the gradient of hydrostatic pressure inside and outside the tablets.[25]

Hence, the formulations having diameter 0.4mm with high concentration of osmogen i.e., OCRT – D2 (75% NaCl), G2 (75% KCl) and J2 (75% NaCl – KCl (1:1)) possessed the above qualities and may be selected for comparison with marketed controlled release product.

Comparison of selected OCRT with Marketed Controlled release formulation (DURA-CR)

The *invitro* release profile of marketed controlled release formulation (DURA-CR) was compared with formulation having 0.4mm orifice diameter and high concentration of osmogens i.e., OCRT – D2 (75% NaCl), G2 (75% KCl) and J2 (75% NaCl–KCl (1:1)).

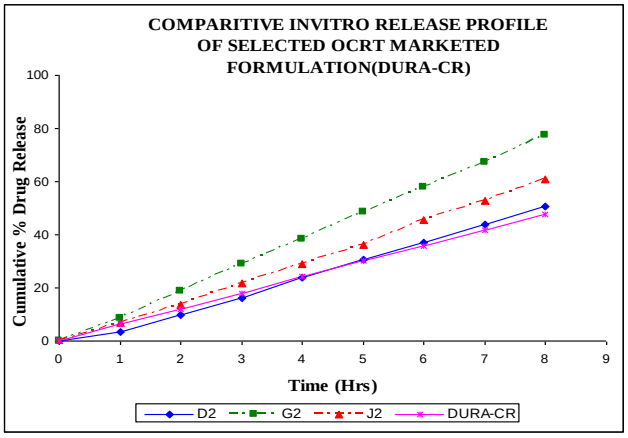

Figure 15: Drug release profile of OCRT Marketed Formulation

From the Figure 15, it was observed that marketed sample and OCRT-D2 showed 47.67% and 50.64% respectively after 8 hrs and these formulations showed similar release pattern. But the other formulations showed higher release rate. An initial lag time was observed with OCRT – D2, which may be due to the presence of intact membrane barrier to imbibe aqueous media.

SEM Analysis

The OCRT subjected to SEM analysis revealed that coating was uniform and smooth and the orifice diameter measures 0.2mm, 0.4mm and 0.6mm for OCRT D1, D2 and D3, on completion of the dissolution studies (Figure 16).

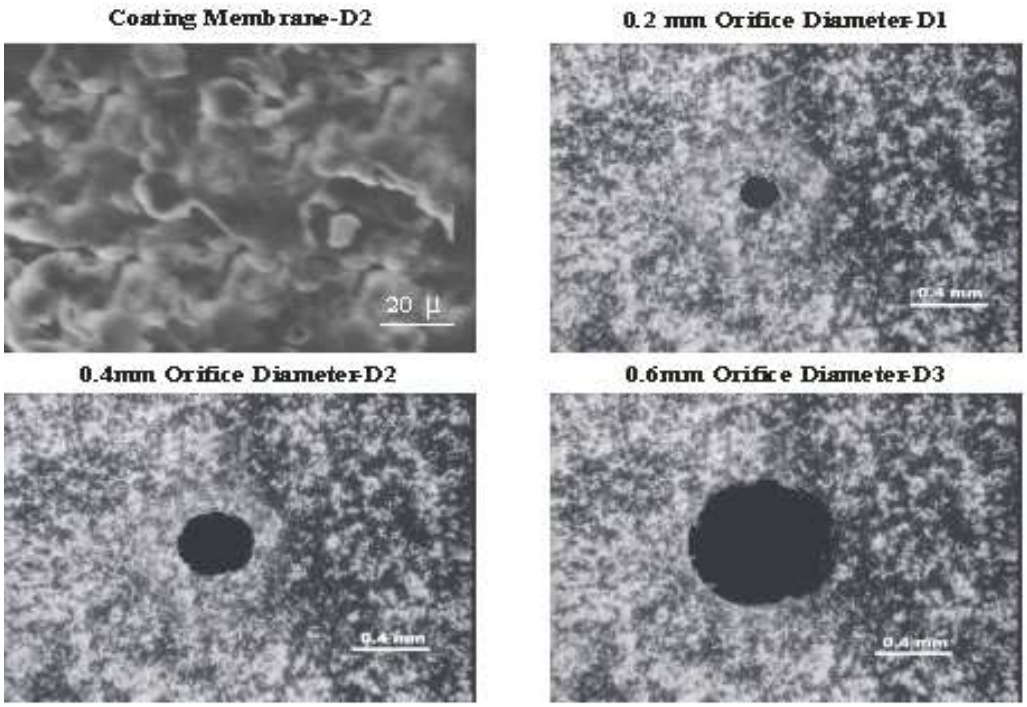

Figure 16: SEM Analysis of OCRT (D1-D3)

Stability studies

The stability studies were carried out for selected formulation OCRT – D2 by storing the samples at extreme temperatures for 60 days. The formulation did not show any colour change for 60 days. The samples were analysed for drug content at various intervals of 30th, 45th and 60th day. The results showed that percentage of SS was between 97.29 % and 98.20% for all the samples stored at different temperatures for 60 days (Table 9). It revealed that there was no degradation of SS in OCRT – D2 formulation.

Table 9: Stability Studies – Drug Content Analysis

Temperature	Formulation	Percentage of Drug Content ± SEM*			
		0th day	30th day	45th day	60th day
$4^0 \pm 2^0$C	D2	98.15 ± 0.25	97.98 ± 0.10	97.55 ± 0.42	97.29 ± 0.46
$27^0 \pm 4^0$C	D2	98.20 ± 0.27	98.11 ± 0.24	97.29 ± 0.26	97.94 ± 0.59
$50^0 \pm 2^0$C	D2	98.07 ± 0.34	97.76 ± 0.20	97.34 ± 0.59	97.45 ± 0.63

*Average value of three readings

Dissolution studies carried out at 30th, 45th and 60th day revealed that there was no significant change in the release rate of SS from OCRT – D2 when compared to release rate of formulation on 0th day. These results indicated the stability of formulation proposing the absence of interaction between the drug, excipients and osmogens (Table 10).

Table 10: Invitro Release Profile of OCRT -D2 at 4° ± 2°C, 27° ± 4°C and 50° ± 2°C

Temperature		**Cumulative Percentage Drug Release***							
		Time (Hours)							
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	0th day	3.51±0.29	9.15±0.43	15.88±0.44	22.71±0.69	29.66±0.40	36.64±0.33	44.50±0.58	**50.76±0.19**

4⁰±2⁰C	**30th day**	4.09±0.04	9.92±0.29	15.92±0.60	23.35±0.75	31.13±0.62	36.53v0.87	44.48±1.20	**51.08±0.24**
	45th day	4.06±0.05	10.25±0.12	16.46±0.48	23.72±0.30	32.02±0.95	37.28±0.54	44.07±0.99	**50.94±0.50**
	60th day	4.44±0.33	9.81±0.24	15.45±0.15	23.90±0.11	32.05±0.36	37.07±1.27	44.97±1.20	**50.16±0.38**
RT (27⁰±4⁰C)	**0th day**	3.67±0.11	9.34±0.59	16.30±0.21	24.91±3.39	29.52±0.48	36.58±0.28	44.60±0.63	**50.62±0.10**
	30th day	4.10±0.05	9.79±0.45	15.53±0.18	23.27±0.70	31.42±0.60	36.96±0.36	45.00±0.59	**51.17±0.16**
	45th day	3.76±0.39	10.03±0.36	16.22±0.77	23.53±0.54	31.68±0.59	37.05±0.27	43.92±0.85	**51.08±0.32**
	60th day	3.77±0.35	9.68±0.14	15.78±0.43	23.82±0.02	31.49±0.46	37.70±0.60	45.51±0.54	**50.17±0.39**
50⁰±2⁰C	**0th day**	3.71±0.12	9.49±0.64	16.40±0.09	25.38±3.14	29.96±1.02	36.72±0.39	44.99±0.97	**50.88±0.17**
	30th day	4.09±0.04	10.05±0.12	15.81±0.47	23.27±0.70	31.82±0.86	37.20±0.16	45.51±0.24	**50.82±0.52**
	45th day	3.94±0.52	10.25±0.50	15.74±0.70	23.13±0.58	31.89±0.68	37.25±0.36	43.88±0.84	**51.03±0.65**
	60th day	3.77±0.35	9.68±0.14	15.78±0.43	23.82±0.02	31.49±0.46	37.70±0.60	45.51±0.54	**50.17±0.39**

4. CONCLUSION

The study aimed to develop an Osmotic controlled release tablet (OCRT) of Salbutamol Sulphate (SS) for asthma treatment. Various formulations using NaCl, KCl, and NaCl–KCl (1:1) as osmogens (at 25%, 50%, 75%) were prepared and tested with different orifice sizes (0.2mm, 0.4mm, 0.6mm). NaCl at 75% with a 0.4mm orifice (formulation D2) showed the best controlled drug release, matching the marketed product (DURA-CR). The tablets passed physicochemical and stability tests, and SEM confirmed uniform coating. Hence, it is concluded that Osmogen type, concentration, and orifice size were key factors in controlling the drug release. Further research is recommended for clinical application.

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