International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 16, Issue 6, 2024

Original Article

FORMULATION AND CHARACTERISATION OF RISEDRONATE SODIUM SUBLINGUAL SPRAY

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Received: 20 Sep 2024, Revised and Accepted: 28 Oct 2024

ABSTRACT

Objective: To formulate a propellant-free sublingual spray of Risedronate sodium, addressing issues of gastrointestinal side effects associated with current oral formulations and improving patient compliance.

Methods: Initially, a fractional factorial design was used to screen variables, followed by a face-centered central composite design for optimization. Formulation batches were characterized by spray pattern, spray angle, leak test, prime test, drug delivery uniformity, drug content per spray, and ex-vivo permeation study.

Results: The optimized batch O1 exhibited an ovality ratio of 1.1, a spray angle of 640, and a drug permeation percentage of 4. *In vivo* absorption analysis revealed that the relative bioavailability of optimized batch O1 was 2.27 times higher than that of the plain drug solution. Compatibility of the product pack with excipients and the drug was confirmed through stability studies of batch O1.

Conclusion: The study concluded that Risedronate sodium sublingual spray presents a promising alternative to oral administration, potentially reducing gastrointestinal side effects and enhancing patient compliance.

Keywords: Risedronate sodium, Sublingual spray, *Ex-vivo* permeation study, Face centred composite design

DOI: https://dx.doi.org/10.22159/ijcpr.2024v16i6.6004 Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

INTRODUCTION

Risedronate sodium (RIS) is the preferred medicine for the treatment of osteoporosis and other osteopathy conditions [1]. It is a bisphosphonate molecule with the potential to treat early-stage osteoporosis. RIS is a BCS class 3 medication that has good solubility but low permeability, resulting in an extremely low oral bioavailability of 0.6% [2]. Currently, RIS is available in tablet and capsule oral dose forms in various strengths [3]. The potential stomach and oesophagus side effects caused by the oral dosage forms of RIS render patients noncompliant with therapy [4]. To reduce these undesirable effects, patients are often recommended to take the medicine with water and remain in an upright position for at least 30 min following administration [5].

Currently, there is a lot of interest in developing innovative formulation options for RIS in order to boost oral bioavailability and diminish its gastro-oesophageal adverse effects [6]. In order to reduce RIS-related gastric irritation, floating formulations were prepared using lipophilic Gelucire® 39/01 and Caprol PGE 860. The formulations offered sustained release and reduced contact to gastric mucosal tissues with enhanced bioavability of the drug [7]. RIS particulate adducts were prepared using titanium dioxide and evaluated for bioavability enhancement in rats. It was found that the adducts increased the bioavability of the RIS by twofold compared to plain drug solution [8]. In another study, chitosan-coated liposomes containing RIS were administered orally in rats. Chitosan-coated liposomes showed increased the cellular uptake of RIS compared to an untreated drug by 2.5 fold. Increased permeability was attributed to mucoadhesive property of chitosan [9]. Particulate adducts, floating formulation and liposomes often are associated with gastric emptying, high amount of fluid intake and manufacturing complexity, respectively [10].

Drugs having high solubility and permeability can be administered sublingually [11]. Sublingual tablets, films, lozenges, spray, drops etc., are applied underneath the tongue. High permeability of sublingual mucosa enables increased permeation of highly soluble and poorly permeable drug to reach systemic blood circulation after absorption [12]. One such study included thermo-sensitive Poloxamer 188 and non-poloxamer-based piroxicame sublingual formulations and investigated for permeability study. It was found that the poloxamer-based solution turned in gel structure and adhered to the mucosa. This enabled a longer stay in the applied region and resulted in higher permeation of drug compared to the non-poloxamer drug solution [13].

The sublingual route is more convenient for patients, has a relatively quick onset of action, and has a large contact surface, all of which contribute to rapid and extensive drug absorption [14]. In the context of the above information, this research focuses on formulating RIS as a sublingual spray. Research work included RIS formulation containing poloxamer 188 as a mucoadhesive polymer and permeability enhancer. The study included physiochemical characterization of spray device, *ex-vivo* permeability study and *in vivo* study in rats.

MATERIALS AND METHODS

Materials

A gift sample of RIS was obtained from Vaikunth Chemicals Pvt Ltd., Ankaleshwar. Devices for the sublingual spray pump were purchased from the local market. All other chemicals and reagent were of AR grade. The use of animal tissue in research was permitted by the IAEC and in compliance with proposal no. PhD/13-14/22.

Methods

Preparation of sublingual spray formulation

Formulation Batches were made as follows for the screening and optimization study. To produce the solution, a measured amount of propylene glycol, alcohol, and little amount of distilled water was poured into a clean beaker and stirred it thoroughly. The required amount of Poloxamer 188 and RIS were added to this solution and sonicated. Finally, volume was made using distilled water. The formulated solution was filled in a pump spray container for characterization. From the screening study, Concentration of Risedronate sodium (X_1) and Propylene glycol (X_2) and Poloxamer 188 (X_3) were selected as the causal factors for optimization study and their effects were seen on residence time (Y1), % drug released (Y2) and % drug permeated (Y3).

RIS sublingual spray characterization

RIS sublingual spray formulations were characterized for the spray pattern test and was determined by ovality ratio, which was calculated using the equation

$$\text{Ovality Ratio} = D_{max}/D_{min}$$

Where the maximum and minimum spray pattern diameters are denoted by Dmax and Dmin, respectively [15-17]. A priming test was performed to determine the number of actuations (priming actuations) that should be shot into the waste solution prior to using the product [17]. Drug content per spray was determined by taking shots of two sprays in a beaker containing 0.1N HCL. This solution was shaken for 5 min and the drug content was determined at 262 nm by the UV-spectroscopy [18]**.** Empty containers were weighed before filling and then reweighed after packed containers and the difference obtained was the net content [16]. Spray profiling (Delivered Dose Uniformity) test was used to determine the dose's reproducibility in accordance with USP. The average amount of active ingredient delivered through the actuator per spray was assayed. By running the test at the starting, intermediate and ending points, the uniformity of the content was evaluated [17]**.** Spray angle study was conducted using the spray impingement method on a sheet of paper. Patent blue V (10 mg) was dissolved in the formulation to aid in visualisation. The sprays were directed horizontally onto a white paper fixed at 1 cm from the nozzle. The radius of the circle drawn on the paper was measured for both minimum and maximum sizes. Spray angle (θ) was calculated by equation [16]**.**

$$\theta = \tan^{-}(h/r)$$

θ= angle in degree, h= height of the triangle and r radius of circle

***Ex-vivo* drug permeation study**

The ex-vivo permeation experiment was performed using the Franz diffusion cell. A magnetic stirring bar-equipped receiver chamber was filled with 20 millilitres of pH 7.4 phosphate buffer. The recipient and donor compartments were separated by treated goat sublingual mucosa, which was kept in ringer's solution at 2–8 °C in the refrigerator until it was required to maintain its viability [17]. The IAEC authorised the experiments in compliance with proposal number PhD/13-14/22.

The entire assembly was placed on a magnetic stirrer, and the temperature was gradually increased to 37 °C and maintained. Each Spray formulation containing RIS was applied in donor compartment and 2 ml samples from the receiver compartment were collected through a sample withdrawal tube and an equal volume of phosphate buffer was replaced at the interval of 10 min for one hour. Procedure was repeated for each spray formulation. Absorbance of Withdrawn samples was measured at 262 nm by UV spectroscopy [18].

Flux and apparent permeability determination

Flux and apparent permeability were calculated using following equation and

$$\text{Flux } (J_{ss}) = \Delta Q_t/\Delta t \times S$$

Where,

$\Delta Q_t/S$ is the cumulative drug permeation per unit of mucosal surface area (μg/cm^2), t is time expressed in h

$$\text{Apparent permeability } (P_{app}) = J_{ss}/C_d$$

Where,

$J_{ss}$is the Flux and C_d is the concentration of drug in donor compartment [19].

***In vivo* absorption study**

An *in vivo* absorption research was conducted on rats to determine the amount of drug absorbed from the optimised formulation compared to the simple drug solution and marketed formulation [20]. The 200–250 g male Wister rats were allowed free access to water during their overnight fast. RIS sublingual spray was applied sublingually, and RIS plain drug solution and RIS marketed formulation were given orally via an oral feeding cannula at a dose equal to 3.61 mg/kg of RIS. After being extracted from the retro-orbital plexus, the blood sample was collected in heparin-containing microcentrifuge tubes. Plasma was isolated from blood samples after they were centrifuged for 10 min at 4 °C at 10,000 RPM. Acetonitrile was used to extract the drug, which was then injected into an HPLC column and subjected to an analysis at 262 nm using a buffer: methanol (88:12) mobile phase [21].

Stability study of the optimized formulation

For an optimised batch, a short-term stability study was conducted for three months at 40 °C±2 °C/75±5% RH, in accordance with ICH recommendations Q1C [22]. The optimized formulation was maintained at ambient temperature and relative humidity. Measured responses at the conclusion of the trials were utilised to optimise the formulation.

RESULTS

Risedronate sublingual spray formulations were prepared and filled in spray container were labelled FF1 to FF16. Each formulation was tested for. Table 1 represents formulation composition and tested responses residence time, % drug release and % drug permeation angles that were suitable for applying to the sublingual mucosal surface [23].

Table 1: Test results of RIS spray formulation batches

Formulation	RIS conc. X1 mg	Propylene glycol X2 %	Poloxamer 188 X3 %	Residence time Y1 min	drug release Y2 %	Drug permeation Y3 %
FF1	3.0	10.0	7.50	53	90	54
FF2	3.0	15.0	5.0	49	90	63
FF3	1.0	10.0	10.0	58	87	50
FF4	1.0	15.0	7.5	53	87.9	51.5
FF5	1.0	20.0	10.0	58	92.3	51
FF6	5.0	20.0	10.0	59	92	67
FF7	3.0	15.0	7.5	52	88	62.5
FF8	5.0	15.0	7.5	53	89	56
FF9	3.0	15.0	7.5	53	88.8	63
FF10	3.0	15.0	10.0	55	87.5	62
FF11	5.0	20.0	5.0	46	93	66
FF12	1.0	20.0	5.0	45	90	51
FF13	3.0	20.0	7.50	52	89.5	63
FF14	5.0	10.0	10.0	57	87	57
FF15	5.0	10.0	5.0	45	91	57
FF16	1.0	10.0	5.0	44	90	52

Effect of selected variables on residence time Y1

In preliminary study the Poloxamer 188 was having 1 to 5% level. This level of the poloxamer 188 could not give the sufficient residence time for the absorption of the poorly absorbed drug RIS. In order to increase the residence time of the sprayed formulations over sublingual mucosal surface poloxamer level was increased from 5 to 10%. Table 1 and fig. 1 indicated that increase in poloxamer 188 concentration increased residence time of the sprayed droplets impressively. FF 16 showed 44 min of stay while maximum residence time was observed for FF6 formulations. All other formulations showed varied residence time according to their poloxamer contents.

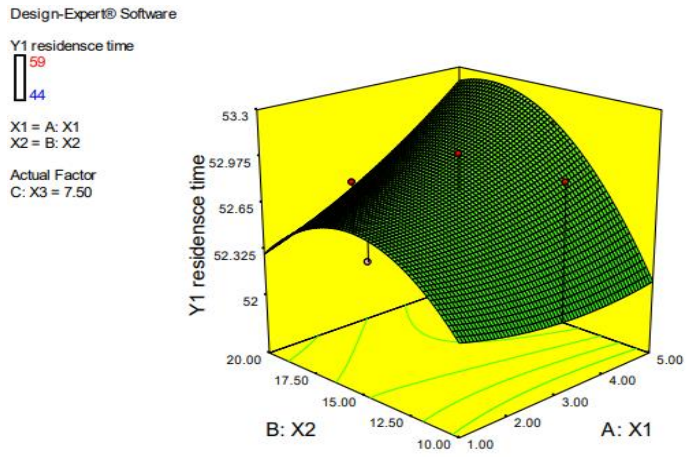

Fig. 1: Shows effect of RIS and propylene glycol concentration over residence time

Y1 residence time =+19.04655+1.09569*X_1+0.70655*X_2+5.11310*X_3-0.050000*X_1*X_2-0.20000*X_1*X_3-0.030000*X_2*X_3+0.021552*X_{12}-0.016552*X_{22}-0.14621*X_{32}+1.00000E-002 * X_1 * X_2 * X_3

From equation positive and bigger coefficient of X3 suggested that it had significant effect on response Y1. Other term X1 and X2 had little positive effect on Y1.

Effect of selected variables on % drug release Y2

A mucoadhesive gel-forming polymer called Poloxamer 188 was used to keep medications at the sublingual mucosa. Table 1 and fig. 2 illustrates higher poloxamer X3 concentrations resulted in the gel matrix's development, which might pause more drug release resistance than lower X3 concentrations, which could hinder drug release.

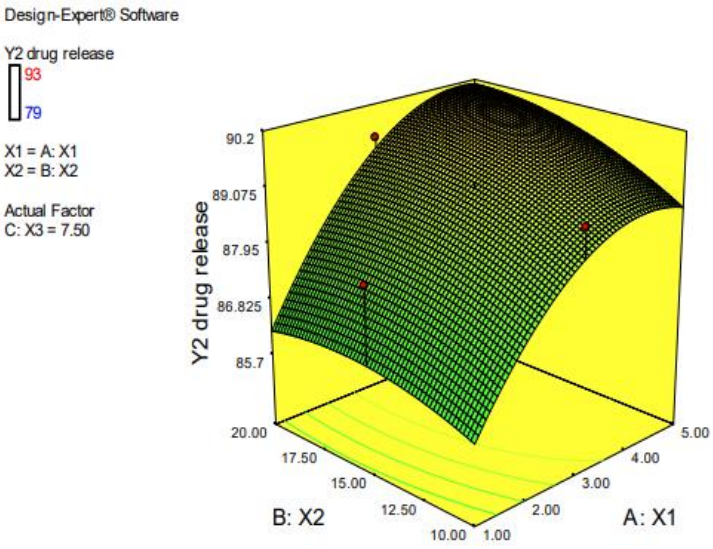

Fig. 2: Shows effect of RIS and propylene glycol concentration over drug release

Y_2 % drug release =+91.84750+0.42000 * X_1+0.21000 * X_2-0.47000 * X_3+0.100000 * X_1 * X_2+0.35000 *X_1 *X_3+0.030000 *X_2 * X_3-0.28750 * X_{12}-0.014000 * X_{22}-0.13600 * X_{32}-1.00000E-002 * X_1 * X_2 *X_3

Equation indicated that X3 had a significant impact on Y2, meaning that a higher X3 was associated with a lower Y2, but X1 and X2 were found to be correlated in a opposite way. Negative coefficient of quadratic term indicated rectilinear behaviour.

Effect of selected variables on % drug permeation Y3

Drug permeation is a rate limiting step for poorly absorbed drug. From the table 1 and fig. 3, Propylene glycol X2 and RIS concentration X1 were found to have a substantial impact on the percentage drug permeation Y3. Propylene glycol X2 being solvent also has permeation enhancement property particularly for the hydrophilic molecules. Propylene glycol could have acted by opening the water channels of the mucosal cell barrier there by increasing the passage of the drug.

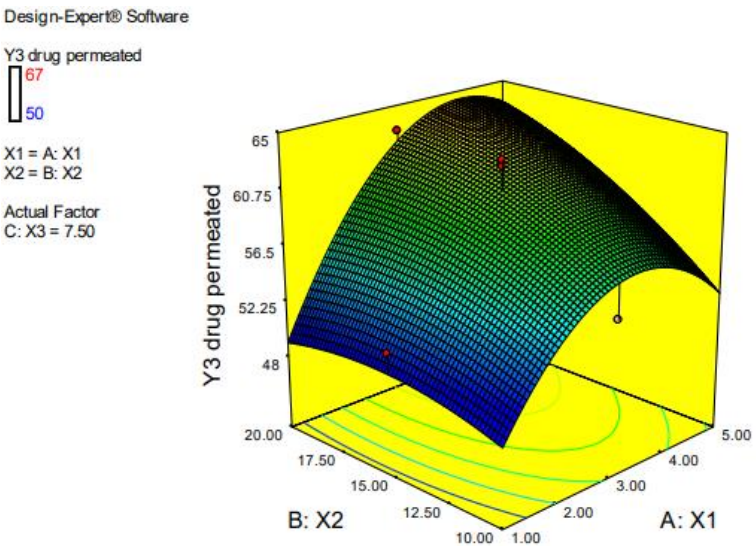

Fig. 3: Shows effect of RIS and propylene glycol concentration over drug permeated

% drug permeated (Y_3) =+36.51+11.28 * X_1+2.97 *X_2+1.49 * X_3+0.79 * X_1 *X_2+1.04 * X_1 * X_3-0.49 * X_2 * X_3-3.18* X_1^2+0.50* X_2^2+0.077* X_3^2

Equation suggested that X_1 and X_2 affected Y_3 strongly than X_3. Negative coefficient of the quadratic term X_1 and X_2 showed that there was interaction behaviour in higher order.

Table 2: Device performances

Formulation code	Spray pattern (Y1)	Leak test		Primes	Pump delivery	Drug content per spray (N=3)	Spray profiling for device performance (Drug content per spray)			Spray angle (Y2)
	D_{max} (mm)/D_{min} (mm)=Ovality Ratio	Wight of original container at o month	Wight of original container at 1 mo	No of press	Weight in gm	mg	Beginning	Mid	Tail off	θ
FF1	1.15	15	15	3	0.14	1.1±0.2	1.1	1.05	1.1	60.0
FF2	1.05	15. 8	15.6	3	0.16	1.0±0.1	0.95	1.0	1.0	60.0
FF3	1.09	15.3	15.0	3	0.14	1.2±0.2	1.1	1.2	1.0	69.0
FF4	1.19	15.2	15.1	3	0.16	4.9±0.05	1.0	0.95	1.0	61.1
FF5	1.19	15.1	15.0	3	0.14	4.85±0.02	0.95	1.0	1.0	61.0
FF6	1.19	15.3	15.0	3	0.15	3.15±0.1	1.10	1.10	1.10	60.0
FF7	1.19	15.4	15.1	3	0.15	0.43±0.1	1.0	1.10	1.10	69.0
FF8	1.19	15.2	15.0	3	0.15	2.95±.05	1.0	1.1	0.95	62.0
FF9	1.19	15.3	15.0	3	0.15	3.0±0.05	1.0	1.1	1.0	62.3
FF10	1.08	15.2	15.1	3	0.17	3.1±0.1	1.0	1.1	1.1	61.0
FF11	1.21	15.3	15.0	3	0.16	1.0±0.05	0.9	1.0	1.0	60.0
FF12	1.04	15.2	15.0	3	0.15	3.0±0.05	1.1	1.0	1.0	61.2
FF13	1.10	15.2	15.2	3	0.14	3.06±0.05	1.0	1.0	0.9	68.0
FF14	1.04	15.1	15.0	3	0.15	5.1±0.05	1.0	1.1	0.95	61.0
FF15	1.05	15.9	15.3	3	0.16	5.05±0.05	1.0	1.1	1.0	62.1
FF16	1.07	15.0	14.8	3	0.15	5.49±0.05	1.0	1.1	1.1	60.1

Every spray formulation was sprayed from the device used in the spray pattern test, and the spray pattern was noted on treated paper. The ovality ratio was calculated by measuring the spray portion's minimum and maximum diameters for every spray formulation [16]. As seen in fig. 4, the spray pattern that was observed was circular, meaning that the ovality ratio was close to 1. The priming test results were comparable to those of the preliminary tests; that is, formulations FF1–FF6, FF9–FF10, FF14–FF16, and those with higher amounts of poloxamer 188 X3 and propylene glycol X2 took three primes to emit, while formulations with lower amounts emittedat the conclusion of the two primes. RIS content per shot ranged from 88 to 102% in the test for material released in a single shot. Handling errors and variations in the amount of product emitted per shot could be the cause of this content disparity. Nonetheless, the outcomes demonstrated that every spray device operated as intended [17]. According to table 2, all of the formulations, F1 through F16, had acceptable spray profiling, indicating that the formulations were properly formulated and in a homogeneous solution state. The valve assembly's proper operation served as more evidence for this. During product usage, uniform spray shots at the beginning, midway and tail off states guaranteed accurate and repeatable dose emission. The spray angle for formulas FF1 through FF16 ranged from 50 to 69°θ. The variation in these recipes' uniformity as well as the components of the device caused this spray angle discrepancy. Nonetheless, all formulation devices yielded spray angles that were suitable for applying to the sublingual mucosal surface [15].

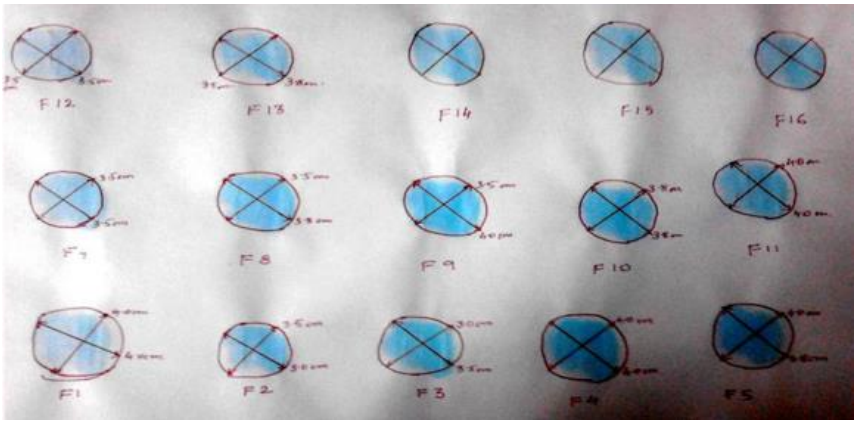

Fig. 4: Spray pattern for F1 to F16

***Ex-vivo* permeability test**

Goat sublingual mucosa, which was freshly obtained before the evolutions and stored in a deep freezer to prevent tissue degradation, was used for the ex vivo permeability test [24]. The purpose of the ex-vivo permeability test was to determine how the formulation's constituents affected the penetration of RIS. Any molecule's apparent permeability can be estimated using the penetrating molecule's permeability coefficient. The results presented in table 3 indicate that the formulation FF9 had a maximum permeability coefficient (P) of 5.5×10^{-5} (cm/s), while the formulation FF3 had a minimum P of 1.9×10^{-5}. The simple medication solution's permeability coefficient was determined to be 1.09×10^{-6}, confirming the low permeability of RIS.

Optimization and validation of model

An optimized formula was predicted using numerical method and prepared it as describe in the---. Optimized batch O1 was characterised and the predicted results were compared with experimented. Table 4 and 5 indicates the close relationship between the two and validate the model.

Table 3: *Ex-vivo* drug permeation study

Formulation code	Cumulative % drug permeated AT 60 min (Y3)	J_{SS} (µg. cm^{-2}. min^{-1})	K_P(cm^{-2}. min^{-1})
FF1	20.4	0.011	1.07×10^{-04}
FF2	25.2	0.014	1.42×10^{-04}
FF3	21.5	0.0087	1.93×10-[05]
FF4	46.8	0.018	7.90×10-[05]
FF5	38	0.0097	3.96×10-[05]
FF6	34.2	0.018	8.66×10-[05]
FF7	15.4	0.0034	3.67×10-[05]
FF8	36	0.012	6.1×10-[05]
FF9	37.1	0.012	9.9×10-[05]
FF10	41.4	0.0225	7.52×10-[05]
FF11	25.1	0.018	1.83×10-[04]
FF12	39	0.021	6.96×10-[05]
FF13	33.2	0.008	2.84×10-[05]
FF14	44.2	0.029	5.88×10-[05]
FF15	50.1	0.034	6.89×10-[05]
FF16	47	0.027	1.09 ×10-[06]

Table 4: Optimised formulation

Optimised formulation	Quantity (%)					
	RS	PG	P-188	EDTA	EtOH	DH2O
O1	5.00	20	1%	0.5%	30%	q. s. to 10 ml

Table 5: Response for optimised formulation

Optimised formulation	Spray pattern (Y1) valityrati	Spray angle (Y2) θ	% Drug permeated (Y3)
Predicted	1.0	64.46	46.89
Experimental	1.1	65	47.02

***In vivo* absorption study**

The goal of the *in vivo* absorption investigation was to ascertain the degree of absorption as well as the improvement in permeability of the stabilised and optimised RIS formulations O1 following oral administration in rats. Rats were divided in different three groups and blood samples were collected at regular interval for 8 h. Various pharmacokinetic parameters like C_{max}, T_{max} and AUC were found 920±0.045ng/ml, 5 h and 3710±0.18 ng. h/ml for sublingual formulations O1.

Table 6: Pharmacokinetic parameters of RIS administered in rats

Parameters	Drug solution	Conventional formulation	Sublingual spray formulation
C-max (ng/ml)	420±20	460±23	920±35
T-max (h)	6	6	5
AUC_{0-8} ng*h/ml	1630±8	1855±10	3710±18
F	-	1.13	2.27

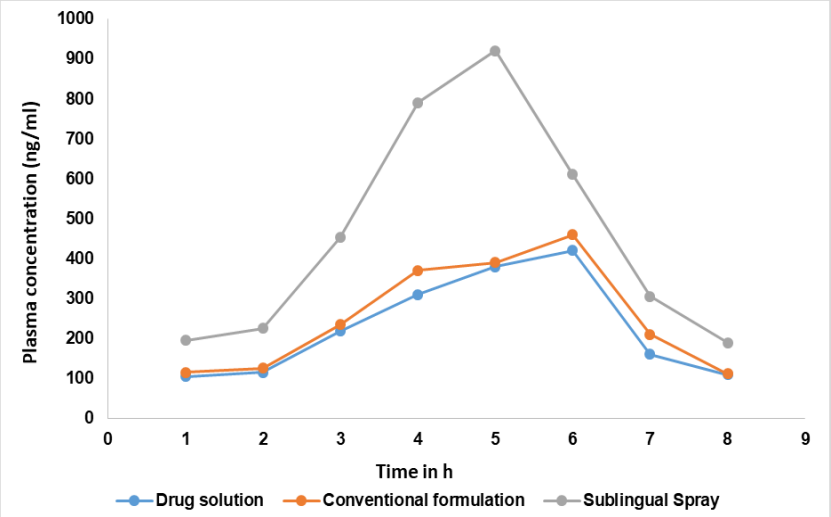

Fig. 5: Plasma concentrations versus time

Table 7: Stability data of O1 at room temp

Optimised formulation	Spray pattern (Ovality ratio)	Spray angle (Θ)	% Drug permeated	% Drug release	Residence time (min)	Content per spray (mg/ml)
0 days	1.1	64	66.44	86.39	55.21	1.48
30 days	1.08	66.98	65.14	85.76	56.09	1.49
60 days	1.05	63.54	63.94	87.47	57.25	1.48
90 days	1.1	65.26	61.14	86.31	55.21	1.48

Table 8: Stability data of O1 at accelerated condition

Optimised formulation	Spray pattern (Ovality ratio)	Spray angle (Θ)	% drug permeated	% drug release	Residence time (min)	Content per spray (mg/ml)
0 days	1.05	62.87	65.76	84.36	53.24	1.49
30 days	1.1	67.24	66.32	86.59	57.64	1.49
60 days	1.12	64.71	63.51	88.12	56.15	1.48
90 days	1.08	63.61	62.45	87.63	56.47	1.48

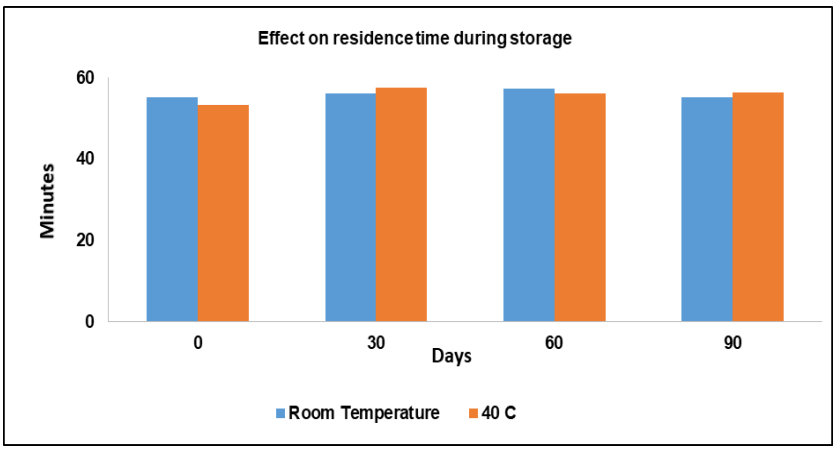

Fig. 6: Effect on residence time during storage

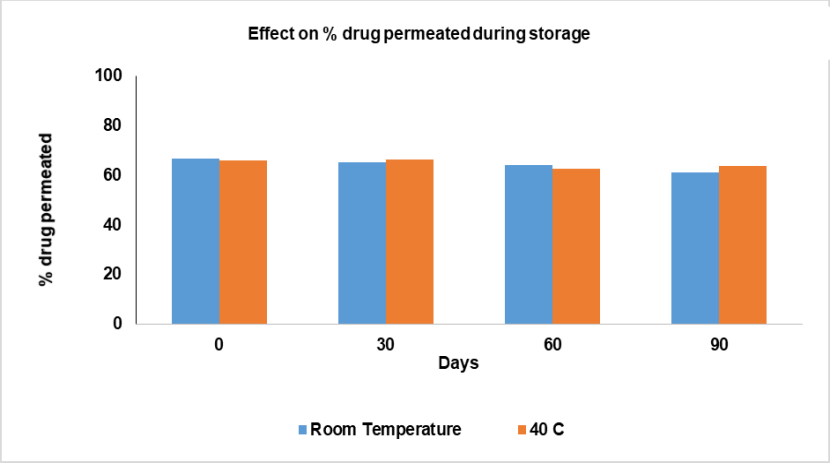

Fig. 7: Effect on % drug permeated during storage

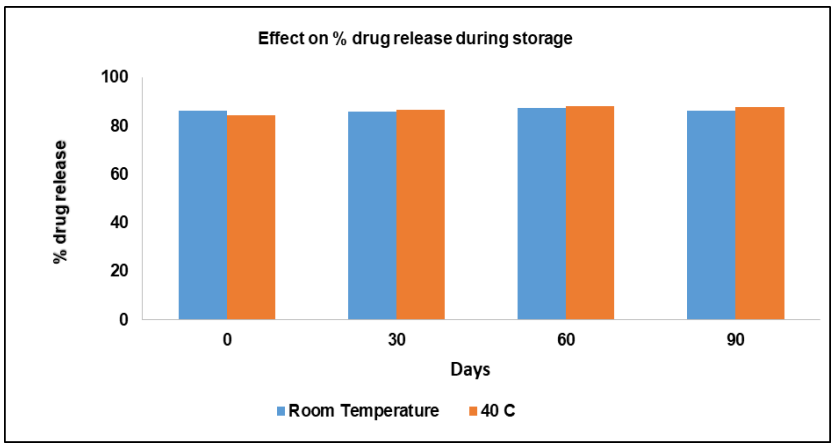

Fig. 8: Effect on % drug release during storage

Stability study revealed that the values of responses after storage period very close to those observed before.

DISCUSSION

Drugs having lipophilic nature can easily pass through sublingual mucosal barrier while drugs having poor permeability and hydrophilic nature finds difficult to cross the barrier in short time [25, 26]. In order to improve their absorption, this drug should stay longer time over sublingual mucosal surface thereby increasing absorption rate [26]. Due to slow and continual salivary secretion major portion of applied drug would drain to stomach [27]. This can be circumvented by prolonging the residence of the applied dosage to sublingual region by addition of mucoadhesive polymer and increasing viscosity. It was clear that the RIS sublingual spray solution without poloxamer 188 could not adhered to the sublingual mucosa and reside for 3 min. Poloxamer 188 shows reversible thermal responsiveness, causing mucosal adhesion when it reaches body temperature and is suitable for dermal and mucous application [28]. Formulations having higher amount of poloxamer 188 showed higher residence time in sublingual mucosa which could cause higher penetration of RIS.

Bioavailability of the drug might be influence by its release and absorption at the site of application. Sublingual site provides greater chances of absorption for poorly permeable drugs both because of high permeability of membrane and avoidance of food interaction. Absorption of the drug depends on the availability of drug in molecular form at site which in turn is related to drug release [13]. RIS sublingual spray formulation with high and low level of poloxamer 188 concentration showed drug release up to 93% and 87 % respectively. Propylene glycol was used as solvent and permeation enhancer for RIS. Propylene glycol act by opening the water channels of the mucosal cell barrier there by increasing the passage of hydrophilic drug [29]. From the table 1, it was evident that 50% and 67 % permeation was observed for low and high concentration of propylene glycol. The outcome of device performance test suggested that, the formulation components had no effect on the spray pattern of the emitted formulations. Prime test results suggested possible variation in the product's capacity to flow through the dip tube might be the cause of this prime number discrepancy. This also emphasise the importance of the priming before use[30]. In the spray angle test, F1 to F16 spray formulation showed acceptable device performance suggesting accuracy in the makeup of the devices. Ex-vivo permeability study was conducted to mark difference between the RIS spray formulation containing deferent proportion of propylene glycol. Propylene glycol and RIS concentrations were higher in the FF9, and they worked together to boost RIS penetration. Propylene glycol worked by opening water channels and increasing the drug's action, while RIS's concentration gradient across the sublingual mucosa led to preferential partition through the barrier and increased permeation. Since RIS is a hydrophilic molecule, it preferentially travels through these water channels and divides throughout the mucosa.

The total amount of drug in the plasma following oral administration of several drug formulations to rats was used to assess the impact of the formulation on the bioavailability of RIS [31]. As shown in table 6 and fig. 5, the sublingual formulation considerably ($P<0.05$) increased drug absorption in rats as compared to the conventional formulation (untreated drug) and plain drug solution. Specifically,

compared to the drug's plain solution and conventional formulation, the total amount of drug present in the plasma of rats given sublingual administration increased by 1.9 times. Increment in the AUC of RIS sublingual spray formulation O1 compared to plain drug solution and triturated marketed RIS tablet formulation, it could be said that thermo responsivepoloxamer 188 formed gel structure enabling adhesion to mucosal surface and released RIS slowly. Propylene glycol having penetration enhancer effect on hydrophilic molecules also played role in the absorption enhancement. In addition the avoidance of food interactions and the high permeability of sublingual mucosa enhanced the absorption of RIS applied sublingually.

Stability study of formulation O1 was conducted to observe the compatibility of the spray device with the formulation components and were found stable over the period of the time. After 90 days, formulation O1 and device performance was up to the mark and did not differentiated markedly to initial values.

CONCLUSION

Present research study resulted in successful formulation and characterization a sublingual spray formulation of the BCS Class III drug, Risedronate sodium, utilizing poloxamer 188 and propylene glycol as key components. The formulation strategy aimed to enhance the bioavailability and patient compliance of Risedronate sodium by leveraging the advantages of sublingual administration.

The inclusion of poloxamer 188 was found to impart mucoadhesion and improve the drug's avabilityover applied area when sprayed, while propylene glycol acted as an effective co-solvent, contributing to the optimal drug delivery characteristics. Evaluation of the sublingual spray demonstrated a uniform spray pattern, acceptable angle, and consistent drug content per spray, which are critical for achieving reliable dosing.

Pharmacokinetic studies indicated enhanced absorption and bioavailability of Risedronate sodium when administered via the sublingual route in rats compared to plain drug solution and marketed oral forms (triturated and suspended), aligning with the formulation's objectives. Stability testing confirmed that the spray maintained its quality and efficacy under recommended storage conditions.

In conclusion, the developed Risedronate sodium sublingual spray presents a promising alternative to conventional oral dosage forms, offering potential benefits in terms of enhanced drug absorption and patient compliance.

ACKNOWLEDGEMENT

We express our gratitude to Vaikunth Chemicals Pvt. Ltd., Ankaleshwar, Gujarat, for donating gift samples of Risedronate Sodium for this study. We are grateful to Faculty of Pharmacy, the Maharaja Sayajirao University of Baroda for providing the resources required to finish this research study.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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