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Formulation and evaluation of sublingual tablets of raloxifene hydrochloride

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ABSTRACT

Raloxifene hydrochloride is recommended for treatment of osteoporosis. However, its oral bioavailability is 2 % due to extensive hepatic first pass metabolism and half-life is 27.7 hours. Also nil solubility of drug makes it difficult for bioavailability achievement. Hence, it was envisaged to solubilize drug and developed by sublingual drug delivery system. Drug and polymers were characterized by FT-IR spectroscopy which found no interaction. For solubilization of drug in water, inclusion complex of raloxifene hydrochloride and ß-cyclodextrin (1:2 and 1:4) were prepared and optimized by kneading method. Phase solubility studies revealed that, solubility of raloxifene hydrochloride was increased by complexation with ß-CD and by addition of co-solvent ethanol and increase in pH. Sublingual tablets were prepared by direct compression by using inclusion complex of raloxifene (1:4), MCC PH101, cros carmellose sodium, mannitol and magnesium stearate. Formulation batches were evaluated for physicochemical parameters and *in vitro* drug release. Studies revealed that, all physicochemical parameters were found within range as per Indian Pharmacopoeia. Batch S1 was considered to be best among other batches since it exhibited a good dissolution profile which (93.54±0.224 %)which was more than marketed formulation (Ralista), disintegration time (29.4±0.07 sec), wetting time (20.21±0.05 sec), water absorption ratio (93.80±0.07 %) and uniformity of drug content (97.89±0.83 %). Stability studies of sublingual tablets revealed no significant changes in hardness, friability, weight variation, drug content, *in vitro* dispersion time, wetting time, water absorption ratio and *in vitro* drug release when stored at room temperature and at 40 °C/75 %RH.

KEYWORDS: Osteoporosis, raloxifene hydrochloride, ß-cyclodextrin, inclusion complex.

INTRODUCTION

Osteoporosis exerts a significant burden on both individuals and community[1,2]. It becomes a serious health threat for aging postmenopausal women by predisposing them to an increased risk of fracture[3]. Raloxifene hydrochloride is very well recommended for treatment of osteoporosis. It is selective estrogen receptor modulator which exhibits estrogen agonist activity on bone and cardiovascular tissue. It decreases rate of bone reabsorption and preserves bone density[4]. It has biological half life of 27.7 hrs. It belongs to BCS class II drug i.e. low solubility in water and undergoes extensive hepatic first pass metabolism. Its oral bioavailability is 2%. A severe hepatic first pass metabolism and very low bioavailability pointing towards development of sublingual immediate release drug delivery system that avoids first pass metabolism and provides immediate drug delivery as well as quicker onset of action for better patient compliance[5]. In order to solubilize the poorly water soluble drug molecules, cyclodetrins are very well recommended in oral drug delivery.

Thus, the objective of present research work was to prepare inclusion complex of poorly water soluble drug raloxifene hydrochloride to enhance its aqueous solubility and to develop drug delivery system that lowers dissolution as well as disintegration time and act as immediate release dosage form to avoid hepatic first pass metabolism and formulate, optimize and evaluate sublingual tablets of raloxifene hydrochloride. Hence, it was envisaged to solubilize drug and developed by sublingual drug delivery system.

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MATERIALS AND METHODS

Materials

Raloxifene hydrochloride was obtained as gift sample from Alkem Laboratories Ltd., Mumbai (India). ß-cyclodextrin was obtained from Concept Pharmaceuticals Ltd., Aurangabad (India). All the other chemicals were of analytical grade.

Drug and polymer characterization by FT- IR spectroscopy[6,8]

Drug was triturated with potassium bromide in 1:5 ratio and compressed at pressure of 5 tons in a hydraulic press. Thirty scans were obtained at a resolution of 2 cm^{-1} from 4000 to 500 cm^{-1}.

UV spectroscopy studies[6,8,15]

A solution containing 50 (µg/mL) of raloxifene hydrochloride in 0.1 %w/v tween 80 solution in water was prepared. A series of dilutions

were made and scanned over range of 200 to 400 nm against blank solution.

Phase solubility studies[6, 7]

1. Saturation solubility studies of raloxifene hydrochloride

Phase solubility studies of raloxifene hydrochloride with ß-cyclodextrin (0-25 mM) were performed. Excess amount of raloxifene hydrochloride was added to 10 mL distilled water containing 0-25 mM ß-cyclodextrin in a series of 25 mL screw capped vials and mixture was shaken for 24 hours at room temperature on water bath shaker. After 24 hours of shaking, solutions were filtered through Whatman # 1 filter paper. Filtered samples were diluted suitably and assayed. Similar process was carried for phosphate buffer pH 6.8 and 7.4.

2. Saturation solubility studies in presence of co-solvent ethanol

Similarly, effect of co-solvent ethanol on saturation solubility was studied by using increasing concentration of co-solvent from 0-50 mL.

Preparation and characterization of inclusion complex[8,9,10]

Inclusion complex of raloxifene hydrochloride with ß-cyclodextrin in 1:2 and 1:4 ratios were prepared by kneading method and optimized spectrophotometrically at wavelength of 290.5 nm and characterized by FT-IR spectroscopy. To the slurry of ß-cyclodextrin (ß-CD: water 1:3) calculated quantity of raloxifene hydrochloride was added step wise with continuous triturating in same direction. Slurry was then dried at 40 °C for 24 hours in hot air oven and resulted complex was ground and passed through sieve # 150.

Formulation of sublingual tablets of raloxifene hydrochloride[10,11,12]

Sublingual tablets containing 60 mg raloxifene hydrochloride were prepared by direct compression method. Initially, inclusion complex of raloxifene hydrochloride and ß-cyclodextrin (1:4 ratio) was prepared. To it MCC PH 101, cros carmellose sodium and mannitol were mixed in geometrical order. Magnesium stearate was uniformly mixed with above mixture and then compressed 500 mg tablet in a single punch tablet compression machine with 10 mm flat punch. Composition of formulations is shown in table 1.

Evaluation of sublingual tablets[13,14]

All developed sublingual tablets of raloxifene hydrochloride were evaluated for following parameters.

i.Hardness

Hardness was measured by using Monsanto tablet hardness tester. For each formulation, three tablets were tested.

ii.Friability

Twenty tablets were weighed and placed in Roche friability test apparatus. After 100 revolutions, tablets were dedusted and weighed again. Percentage friability was determined by using following formula

$$\% F = \{1-(Wt/W)\} \times 100$$

Where, % F = Friability in percentage

W = Initial weight of tablet

Wt = Weight of tablets after revolution

iii.Thickness

Thickness of tablets was measured by digital vernier scale. Limit for this was average thickness ± 0.2mm.

iv.Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. Average weight and standard deviation of twenty tablets was calculated. Batch passes test for weight variation if not more than two of the individual tablet weight deviate from average weight by more than percentage shown in table 5 and none deviate by more than twice percentage shown.

v.Drug content

Twenty tablets were weighed accurately and powdered. Powder equivalent to 100 mg of raloxifene hydrochloride was accurately weighed and suitably extracted in 50 ml of 0.1 %w/v tween 80 solution in water. From above solution, 1mL was taken and diluted upto 50 mL of 0.1 %w/v tween 80 solution in water and analyzed specrophotometrically at 290.5 nm.

***vi.In vitro* disintegration time**

In vitro disintegration time of sublingual tablet was determined by USP disintegration test apparatus. The limit for disintegration was not more than 2 minutes at 37 °C.

Procedure: 6 tablets were placed individually in each tube of disintegration test apparatus and discs were placed. Water bath was maintained at 37±0.5 °C and time taken for all tablets to disintegrate completely was noted.

vii.Wetting time

Wetting time was determined by placing a piece of tissue paper twice in small petridish having internal diameter of 6.5 cm. 10 ml of water was added. A tablet was placed on paper and time for complete wetting of tablet was measured in seconds.

viii.Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6 mL of water. A tablet was put on tissue paper and allowed to wet completely. Wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

$$R = 100 \times Wa - Wb/Wa$$

Where, Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption

d. *In vitro* drug release studies[23,24]

Cumulative % drug release of sublingual tablets of raloxifene hydrochloride and marketed formulation of immediate release tablet of raloxifene hydrochloride (Ralista by Cipla) was determined and compared by using the USP type I dissolution test apparatus (Basket).

Dissolution test was performed using 900 mL 0.1 %w/v tween 80 in water at 37±2 ºC and rotational speed of 50 rpm. 10 mL aliquots were withdrawn at an interval of 5 minutes for 45 minutes. Samples were replaced by their equivalent volume of dissolution medium. Samples were suitably diluted and analyzed at 290.5 nm by UV spectrophotometer. Cumulative % drug release was calculated using calibration curve.

e. Stability studies[25,26,27]

Stability studies on optimized formulation batch was carried out to determine effect of presence of formulation additives on stability of drug and also to determine physical stability of formulations under accelerated storage conditions. Tablets were stored in an aluminium foil and placed in oven maintained at temperature and humidity condition of 40±2 ºC/ 75±5 % RH and at room temperature. Samples were withdrawn on 30th day and analyzed for physical evaluation, and *in vitro* drug release studies.

RESULTS AND DISCUSSIONS

FT-IR spectrum of drug, excipients and their mixture revealed that no interaction was observed between drug and polymers. Hence, it was good to formulate sublingual immediate release films as shown in figure 1 and 2. Calibration curve was obey Beer Lambert's law within concentration range of 0-24 (µg/ml) in 0.1 %w/v tween 80 in water with correlation coefficient (R^2) of 0.999. Phase solubility studies of raloxifene hydrochloride with ß-CD (0-25 mM) were performed. Per cent solubilization of drug into ß-CD was increased from 4.29 to 46.83 % as shown in table 2 and figure 3. This is due to more solubility of ß-CD in water. Effects of basic pH, pH 6.8, pH 7.4 and co-solvent ethanol on solubilization of raloxifene hydrochloride by ß-CD were studied. Results indicated that solubility of raloxifene hydrochloride was increased from distilled water to pH 7.4 as shown in table 3 and figure 4. So, it can be concluded that basic pH help in formation of inclusion complex between raloxifene hydrochloride and ß-CD. Result indicated that solubility of raloxifene hydrochloride was increased up to 2.049±0.082 mM in presence of ethanol but more solubility was found in presence of ß-CD, up to 3.093±0.038 mM as shown in table 4 and figure 5 which indicates synergistic effect of ethanol with ß-CD on solubalization of raloxifene hydrochloride was observed. Inclusion complex of raloxifefene hydrochloride and ß-CD were prepared in1:2 and 1:4 ratios by kneading method and optimized spectrometrically which concluded that inclusion complex 1:4 gives more prominent solubility than 1:2 in water as shown in figure 6. In order to characterize inclusion complex formation between drug and ß-CD (1:4) in solid state, FT-IR spectrum was recorded which showed that all characteristic peaks of raloxifene hydrochloride at 1464.02 and 1597.33 cm^{-1} were disappeared except peak for carbonyl group but it is shifted towards higher wave number as shown in figure 7. It shows complex has been formed between raloxifene hydrochloride and ß-CD. Sublingual tablets were prepared by direct compression by using inclusion complex of raloxifene (1:4), MCC PH101, cros carmellose sodium, mannitol and magnesium state. All formulation batches were evaluated

Table 1: Formulation composition of sublingual tablets

Sr. No.	Formulation Batches	Raloxifene Hydrochloride and ß-Cyclodextrin complex 1:4 ratio (mg)	MCC PH 101 (mg)	Cros carmellose sodium(mg)	Mannitol (mg)	Magnesium stearate (mg)
1	S1	300	85	100	10	5
2	S2	300	100	85	10	5

Table 2: Effect of ß-CD on saturation solubility of raloxifene hydrochloride in water

Sr. No.	ß-CD Concentration(mM)	Absorbance at 290.5 nm	Solubilization (%)
1	0	0.1116	4.29
2	5	0.3351	14.68
3	10	0.5419	26.05
4	15	0.7827	32.72
5	20	0.9876	40.59
6	25	1.1965	46.83

Table 3: Effect of pH on solubilization of raloxifene hydrochloride by ß-CD

Sr. No.	Concentration of ß-CD (mM)	Concentration of raloxifene hydrochloride (mM) Distilled water (Mean ± S. D)	Phosphate buffer pH 6.8 (Mean ± S. D)	Phosphate buffer pH 7.4 (Mean ± S. D)
1	0	0.1116 ± 0.0023	0.1350 ± 0.0031	0.1421 ± 0.0092
2	5	0.3231 ± 0.027	0.3962 ± 0.0073	0.4548 ± 0.015
3	10	0.5419 ± 0.017	0.6218 ± 0.011	0.6543 ± 0.011
4	15	0.7827 ± 0.014	0.8437 ± 0.021	0.8792 ± 0.021
5	20	0.9876 ± 0.021	0.9537 ± 0.018	0.9742 ± 0.012
6	25	1.1965 ± 0.019	1.3087 ± 0.013	1.4729 ± 0.016

Table 4: Effect of co-solvent ethanol on solubilization of raloxifene hydrochloride using ß-CD

Sr. No.	Concentration of ethanol (% v/v)	Concentration of raloxifene hydrochloride (mM) Drug	Drug + ß-cyclodextrin
1	0	0.058±0.0087	0.492±0.031
2	10	0.135±0.076	0.567±0.072
3	20	0.453±0.056	0.693±0.084
4	30	0.764±0.049	1.228±0.061
5	40	1.409±0.046	2.356±0.034
6	50	2.049±0.082	3.093±0.038

Table 5: Percentage deviation allowed under weight variation test

Percent deviation allowed under weight variation test Average weight of tablet (X mg)	Percent deviation
X ≤ 80 mg	10
80 < X < 250 mg	7.5
X ≥ 250 mg	5

Table 9: Cumulative % drug release of formulation batch S1 at room temperature and at 40 °C/75 %RH

Time (minutes)	Cumulative % drug released At room temperature 0 day	30 days	At 40 °C/75 %RH 30 days
0	0	0	0
5	51.09 ± 0.231	42.19±0.765	44.32±0.918
10	58.65 ± 0.421	49.23±0.036	47.49±0.276
15	66.53 ± 0.071	56.01±0.196	54.92±0.792
20	68.16 ± 0.219	62.79±0.754	63.75±0.572
25	75.17 ± 0.017	68.54±0.258	71.63±0.631
30	80.24 ± 0.528	72.35±0.369	76.67±0.910
35	85.60 ± 0.045	88.47±0.028	81.59±0.734
40	84.26 ± 0.416	81.15±0.731	85.92±0.330
45	93.54 ± 0.224	87.26±0.482	89.14±0.095

Table 6: Physicochemical parameters of formulation batches

Sr. No.	Formulation Batch	Hardness (Kg/cm²)	Friability (%)	Thickness (mm)	Weight Variation (%)	Drug Content (%)	*In vitro* Disintegration Time (sec)	Wetting time (sec)	Water absorption ratio (%)
1	S1	3.4±068	0.45±0.19	4.51±0.39	2.45±0.64	97.89±0.83	29.4±0.07	20.21±0.05	93.80±0.07
2	S2	3.5±0.54	0.66±0.05	4.42±0.71	3.76±0.09	95.07±0.03	32.7±0.03	23.87±0.09	88.34±0.34

Table 7: Cumulative % drug release of sublingual tablets of raloxifene hydrochloride compared with marketed formulation

Time (mins)	Cumulative % drug release (Sublingual tablets) S1	S2	Ralista (Cipla)
0	0	0	0
5	51.09 ± 0.231	48.87 ± 0.438	49.93 ± 0.119
10	58.65 ± 0.421	50.77 ± 0.365	51.39 ± 0.253
15	66.53 ± 0.071	61.15 ± 0.118	62.26 ± 0.082
20	68.16 ± 0.219	67.66 ± 0.162	66.53 ± 0.315
25	75.17 ± 0.017	74.48 ± 0.216	68.67 ± 0.324
30	80.24 ± 0.528	80.67 ± 0.372	56.19 ± 0.416
35	85.60 ± 0.045	83.64 ± 0.381	82.69 ± 0.026
40	84.26 ± 0.416	86.75 ± 0.08	87.46 ± 0.429
45	93.54 ± 0.224	91.61 ± 0.531	89.95 ± 0.517

Table 8: Study of physicochemical parameters of S1 at room temperature and at At 40 °C/75 %RH

Parameters	At room temperature 0 day	30 days	At 40 °C/75 %RH 30 days
Hardness (kg/cm²)	3.4±0.68	3.3±0.94	3.3±0.39
Friability (%)	0.45±0.19	0.48±0.33	0.53±0.58
Weight variation (mg)	2.45±0.64	2.89±0.20	3.02±0.31
Drug content (%)	97.89±0.83	94.38±0.14	95.52±0.27
In vitro disintegration time (sec)	29.4±0.07	38.92±0.61	38±0.32
Wetting time (sec)	20.21±0.05	27.45±0.32	32±0.74
Water absorption ratio (%)	93.80±0.07	90.34±0.02	91.08±0.12

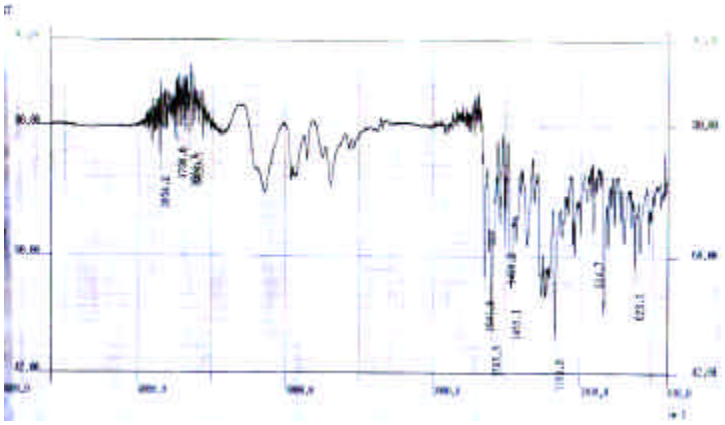

Figure 1: FT-IR spectrum of raloxifene HCI

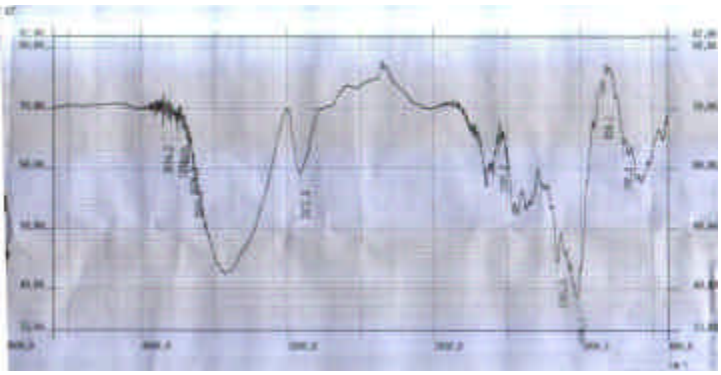

Figure 2: FT-IR spectrum of raloxifene HCI MCC PH 101, cros camellose sodium

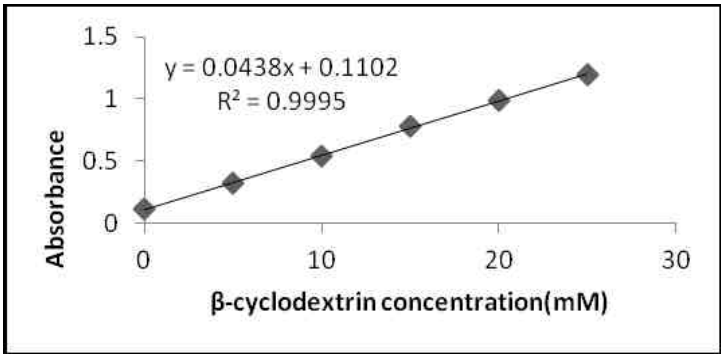

Figure 3: Phase solubility diagram of drug and ß-CD

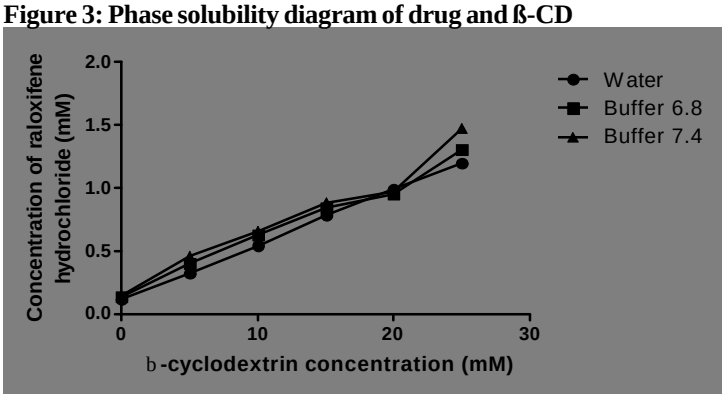

Figure 4: Effect of pH on solubilization of drug and ß-CD

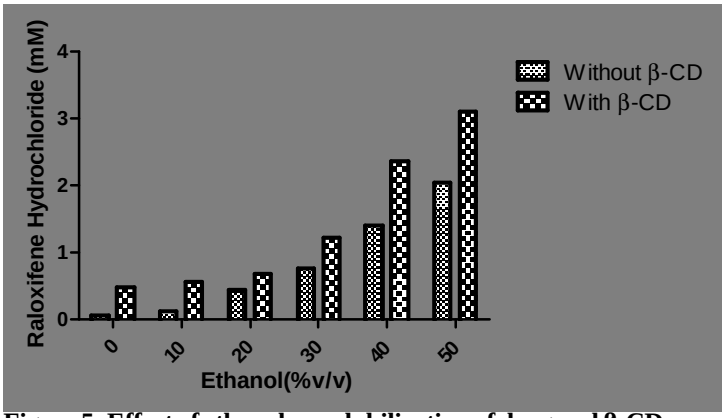

Figure 5: Effect of ethanol on solubilization of drug and ß-CD

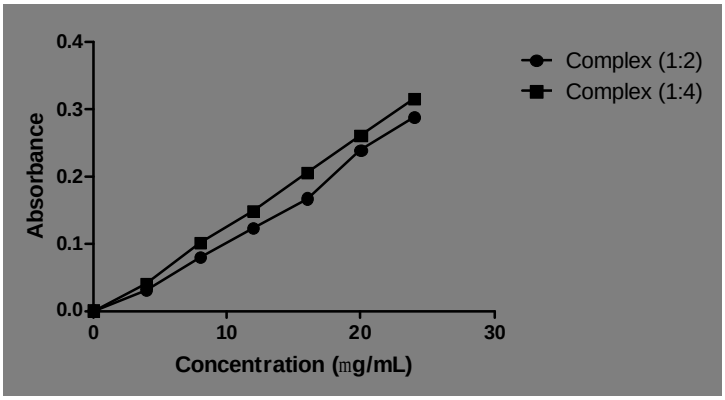

Figure 6: Ratio optimization of inclusion complex at 290.5 nm

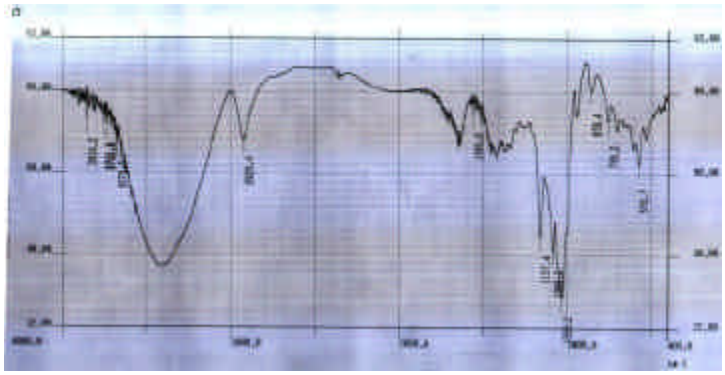

Figure 7: FT-IR spectrum of inclusion complex of drug and ß-CD

Figure 8: Wetting profile of sublingual tablets A-Initially, B-Started wetting, C-Completely wetted

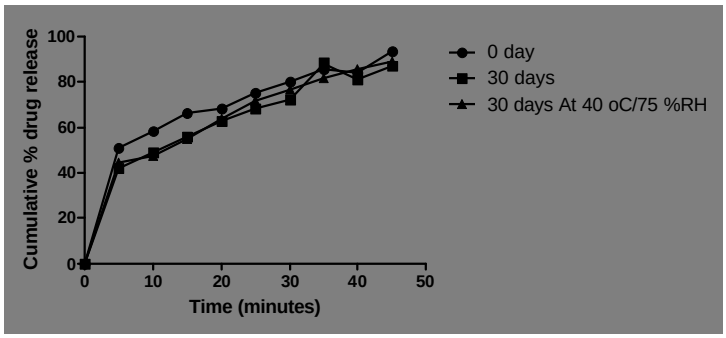

Figure 9: Cumulative % drug release profile of sublingual tablets of raloxifene hydrochloride compared with Ralista (marketed formulation)

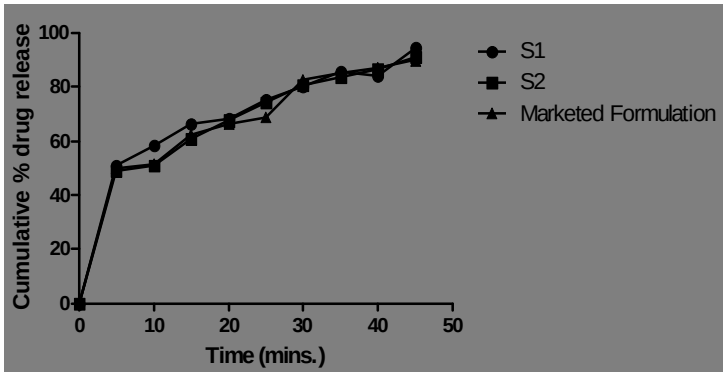

Figure 10: *In vitro* drug release profile of formulation batch S1 stored at room temperature(0 and 30 days) and at 40°C/75% RH (30 days)

for various physicochemical parameters such as hardness, thickness, weight variation, friability, drug content, *in vitro* disintegration time, wetting time and water absorption ratio as shown in table 6. All parameters are within the limit as given in Indian pharmacopoeia. Results were indicated that due to presence of superdisintegrant i.e. cros carmellose sodium and mannitol as diluents and sweetner, *in vitro* disintegration time was decreased i.e. 29.4±0.07 seconds in batch S1 whereas in batch S2, *in vitro* disintegration time was found to be more i.e. 32.7±0.03 seconds. Thus formulation S1 has less *in vitro* disintegration time than S2. The wetting time was decreased i.e 20.21±0.05 seconds in batch S1 whereas in batch S2 wetting time was found to be more i.e. 23.87±0.09 seconds. Thus formulation batch S1 has less wetting time than S2. Photographs of wetting time of sublingual tablets of raloxifene hydrochloride are shown in figure 8. Water absorption ratio was increased in batch S1 i.e. 93.80±0.07 percents whereas in batch S2, water absorption ratio was decreased i.e. 88.34±0.34 percents. Thus, formulation batch S1 has more water absorption ratio than S2. From these studies we found that, formulation batch S1 of sublingual tablet has shown good results of physicochemical properties as shown in table 6. Cumulative per cent drug release of sublingual tablets of raloxifene hydrochloride and marketed formulation of immediate release tablet of raloxifene hydrochloride (Ralista by Cipla) were performed using 0.1% w/v of tween 80 in water as dissolution medium for 45 minutes and drug concentrations were analyzed spectrophotometrically at 290.5 nm. Results indicated that both formulation batches S1 and S2 showed rapid dissolution rate and cumulative % drug release as compared to Ralista (marketed formulation). It was also observed that formulation batches S1 and S2 had been released more than 80 % of drug than that of Ralista (Marketed formulation). Formulation batch S1 has shown 93.54 ± 0.224 % drug release which was more than that of S2 as well as Ralista (marketed formulation) as shown in table 7 and figure 9. Thus, formulation batch S1 has been considered as optimized formulation of sublingual tablet of raloxifene hydrochloride. Stability studies was performed on optimized formulation batch of sublingual tablet S1 for hardness, friability, weight variation, drug content, *in vitro* disintegration time, wetting time, water absorption ratio and *in vitro* drug release studies. Stability studies of sublingual tablets revealed no significant changes in various parameters when stored at room temperature and at 40 °C/ 75 %RH as shown in table 8, 9 and figure 10.

CONCLUSION

From various phase solubility studies, it can be concluded that ß-cyclodextrin helps in enhancing solubility of raloxifene hydrochloride. Sublingual tablets were prepared and evaluated for various parameters showed promising results. Thus, it can be concluded that the concept of sublingual tablets of raloxifene hydrochloride offers suitable and practical approach in serving desired objective of management of osteoporosis.

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