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DEVELOPMENT AND EVALUATION OF MEDICATED CHEWING GUM OF RALOXIFENE HYDROCHLORIDE

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ABSTRACT

In this study we formulate Raloxifene hydrochloride, edicated chewing gum to overcome first pass metabolism of it so bioavability increase of drug. We take polyvinyl acetate as chewing gum base. Aspartame, mannitol and sucrose as sweetener. Glycerin as a plasticizer. Beta-cyclodextrine as solubility enhancer and taste masking agent. First we evaluate the API by its melting point after we derived its calibration curve. After this we select proper ratio of Beta-cyclodextrine and API. After we study drug and excipients compatibility by using FTIR. XRD study perform for API and formulation. After we formulate our formulation and perform post-evaluation study like hardness, weight variation, % drug content and % drug release. From all formulation F5 formulation shows best % drug release and % drug content. After we perform stability study for our formulation and after study no major change show in formulation. And in last we perform buccal permeability study. On basis of all study results we can say that our formulation is successfully formed.

Keywords: Raloxifene hydrochloride, Medicated chewing gum, Buccal permeation, Osteoporosis.

Introduction

A BCS class II drug has lower solubility and higher permeability. In case of BCS class II drugs major problem is solubility. Many drugs are metabolized by first pass mechanism which is one of the major problem for oral formulations. Here we take Raloxifene hydrochloride which is BCS class II drug and having extensive first pass metabolism to the glucuronide conjugates. This drug also has unpleasant taste. This drug is use for the prevention of osteoporosis in post menopausal women which act as selective estrogen receptor modulator.

Raloxifene hydrochloride tablet is available in market which bioavability is approximately 60 %. In this study we formulate medicated chewing gum of this drug. Beneficial side of this project is drug is protect from first pass metabolism, use of sweetener we can improve formulations taste, solubility and dissolution enhance of drug and became more patients compliance. In this study we try to formulate and evaluate medicated chewing gum of Raloxifene hydrochloride.

Materials & Method

Chemicals and Instrumets

API Raloxifene hydrochloride is kindly gifted by Cadila Pharmaceuticles. Polyvinyl acetate use as a Chewing gum base, Sucrose use as a Sweetener, Peppermint is use as a flavoring

agent, Glycerine use as a plasticizers, Calcium Carbonate use as a Adjuvant and Fillers, Aspartame use as dipeptide based sweetener, and mannitol use as a Water soluble sweetening Agent. This all are gifted by Chemdyes Corporation. ß-cyclodextrin (ß-CD) is use as solubility enhancer and taste masking agent which gifted by Astron Chemicals. All chemicals are analytical grade. A digital weight balance use is C-100859 (Swisser Instruments,Gandhinagar), UV-Visible Spectroscopy (UV-1800, Shimadzu), Dissolution Test Apparatus (Fabricated instrument), FTIR (Spectrum GX, Sicart Research Lab), Electronic tongue (C - DAC,Kolkata) were used in study.

Methods

Preformulation studies

Melting Point

Melting point was evaluated by very popular capillary method.

UV-Visible Spectrophotometric method

Standard curve for Raloxifene hydrochloride

Standard curve of Raloxifene hydrochloride was taken in Simulated Saliva pH 6.8 buffer as medium. Standard drug solution of Raloxifene hydrochloride was prepared by dissolving (10 mg) Raloxifene hydrochloride in 100 ml of Simulated Saliva pH 6.8 buffer to obtain standard stock solution (100 µg/ml) concentration.

Determination of UV absorption maxima

For the determination of λmax, 10 µg/ml of Raloxifene hydrochloride solution was prepared from standard stock solution with Simulated Saliva pH 6.8 buffer. Spectrum was scanned between 200-400nm UV-spectrophotometer and the suitable absorption maximum was selected.

Preparation of Working Solution for standard curve of Raloxifene hydrochloride

From the prepared stock solution (100 µg/ml), accurately measured standard working sample solution of Raloxifene hydrochloride (1.0,1.2,1.4,1.6,1.8,2.0.2.2,2.4 ml) were taken in series and transfer to 10 ml of volumetric flask and diluted up to the mark with Simulated saliva pH 6.8 buffer to prepare the concentration of 10,12,14,16,18,20,22,24 µg/ml. Measure absorbance at 285nm at all solution using Simulated saliva pH 6.8 as blank and developed calibration curve.

Identification by FTIR (Fourier Transform Infra-Red Spectroscopy)

A Pellet of the drug & KBr was prepared using hydraulic pellet press at a pressure of 7-10 tones. FTIR was scanned from 400-4000 cm^{-1} of following:

Drug (Raloxifene hydrochloride), Drug + Polyvinyl acetate, Drug +Glycerine, Drug + Beta-Cyclodextrin, Drug + Polyvinyl acetate + Glycerine + Sucrose + Peppermint + Calcium carbonate + Aspartame + Mannitol + Beta-Cyclodextrin

Solubility Study

10 mg of Raloxifene hydrochloride was taken and solubility in distilled water, Simulated saliva pH buffer solution, methanol, Chloroform was carried out by analyzing in UV visible spectroscopy 285nm.

Method for increasing the solubility of raloxifene hydrochloride

Solubility of Raloxifene Hydrochloride is increased by preparing its inclusion complex using ß-cyclodextrin (ß-CD). The inclusion complex of drug with ß-CD was prepare by wetting the mixture of Raloxifene Hydrochloride : ß-CD in the different molar ratios 1:0.5,1:1,1:2 in mortar with a small volume of water –methanol (1:1 v/v) solution. The thick slurry that formed was kneaded for 45 min and then dried at 45 °C. The dried mass was sieved through sieve no. 60. And Store in a desiccators till further use.

Table 1: Different ratios of Drug- ß-CD for preparation of inclusion complex		
Inclusion complex composition	Drug and ß-CD ratio	Formulation code
Raloxifene HCl : ß-CD ratio	1:0.5	C1
	1:1	C2
	1:2	C3

Characterization of Raloxifene Hydrochloride: β-cyclodextrin inclusion complex

Solubility determination of Drug-β-cyclodextrin inclusion complex

10 mg sample was taken in 10ml of simulated saliva pH 6.8 buffer. Sample was filtered through 45 µm filter paper and diluted. Content is measured in UV spectroscopy at 285 nm

Drug Content

Prepare 10 µg/ml solution against Simulated saliva pH 6.8 buffer and measured at 285 nm. 20 mg of inclusion complex was assayed and it contain 10 mg of drug so for making the chewing gum, We have to take 120 mg of inclusion complex which contain 60 mg of Raloxifene hydrochloride

Method of preparation of taste masked inclusion complex by kneading method

Here the inclusion complex of drug and β-CD was prepared by wetting the physical mixture in a mortar with a minimum volume of methanol and water (1:1 by volume).Mixed and kneaded continuously with a pestle to obtain a paste, which was then dried under vacuum at room temperature, sieved through 60 no sieve and stored in desiccators until further Evaluation.

Optimization of concentration of β-cyclodextrine

β- cyclodextrine is used for masking the unpleasant taste of Raloxifene HCl. To mask the unpleasant taste of drug by using different concentration of β-cyclodextrine as given in Table 2. The taste masking effect was evaluated by E-tongue at CDAC research lab, Kolkata.

Table 2: Optimization of Concentration of β-cyclodextrine		
Batch Code	**Raloxifene HCL (mg)**	**β-cyclodextrine (mg)**
T0 (API)	60	00
T1 (1:0.5)	60	30
T2 (1:1)	60	60
T3 (1:2)	60	120

Method of preparartion of medicated chewing gum

- Weigh all the ingredients accurately.
- Melt the desired amount of Polyvinyl acetate at a temperature of 60-70℃.
- Add drug, plasticizer, and all the other remaining ingredients to the Polyvinyl acetate, allow them to get settled and form a fine mixture.
- Pour the above mixture into a Petri plate or desired molds to get a desired shape.

Table 3: Method of Preparation of Medicated Chewing gum

Step:1 Weight all ingredients accurately

Step: 2 Melt polyvinayl acetate at 60-70 °

Step:3 Add remaining ingridients in melt polyvinayl acetate and allow them to settled

Step: 4 Pour mixture into mould to get desired shape

Table 4: Formulations of the preliminary batches

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Inclusion complex	120	120	120	120	120	120	120	120	120
Polyvinyl acetate	200	200	200	235	235	235	270	270	270
Glycerin	10	15	20	10	15	20	10	15	20
Sucrose	200	200	200	200	200	200	200	200	200
Calcium carbonate	30	30	30	30	30	30	30	30	30
Aspartame	3	3	3	3	3	3	3	3	3
Mannitol	135	130	125	100	95	90	65	60	55
Peppermint flavour	2	2	2	2	2	2	2	2	2

Evaluation parameters

Drug content

Randomly selected MCG was crushed simulated saliva pH 6.8 buffer in mortar with pestle, solution was then withdrawn and absorbance was measured.

Drug release

Randomly selected MCG was kept in a modified disintegrating test apparatus, the apparatus was filled by the simulated saliva pH 6.8 buffer. Stroke speed of 60 strokes per minute was adjusted; 1ml of the sample was withdrawn every 10 minutes which was replaced by the fresh simulated saliva pH 6.8 buffer. Absorbance of the withdrawn buffer was

taken. %Cumulative index was calculated from it. This value gave the drug release rate.

%Cumulative index= (1-(absorbance (t)/absorbance (t0))*100)

Where, absorbance (t) = absorbance at initial time absorbance (t0) = absorbance at final time

Organoleptic properties

Such as color, odour, surface texture and appearance were checked out.

Stability studies

Drug decomposition or degradation happens during storage, due to chemical modification of the API or owing to product instability, lower the amount of the drug in the dosage form. The capacity of a scrupulous API or dosage form in a definite container to remain inside its physical, chemical, therapeutic, and toxicological specifications is known as Stability. The formulation is quite stable at different conditions of storage is known by stability study. Accelerated stability studies conceded at 40 °C ± 2 °C/75% RH ± 5% RH for 1 month.

Stickiness

The formulated medicated chewing gum base was placed on plain surface A mass of 250 gm was hammered on it up to 10 min. The frequency of hammering was about 30 min. None of the batch stuck to hammer or surface.

Weight variation

Chewing gum from each batch were individually weighed on analytical balance, the average weight and standard deviation were calculated which was found in acceptable limit.

Plasticity/hardness

Hardness of chewing gum was determined by Monsanto hardness tester and the average hardness and standard deviation were reported.

Percentage drug content

Percentage drug content % drug content of formulated chewing gum was determined by weighing 1000 mg chewing gum equivalent to 10 mg Raloxifene hydrochloride and transferring into volumetric flask. About 60 ml of artificial saliva was added, sonicated for 10 min, then shaken by mechanical means for 30 min and volume was adjusted to 100 ml with the same solvent. Again it was sonicated and filtered. Percentage drug content was determined spectrophotometrically at 285 nm. Same procedure was repeated for three times.

In vitro buccal permeation study for released drug

In an in vitro Franz diffusion Buccal permeation study, average proportion of Raloxifene hydrochloride which was released from optimized formulation after 30 min of chewing 60.56% were permeated which was placed in the donor compartment of diffusion cell containing phosphate buffer of salivary pH. It was allowed to permeate through buccal mucosa for 30min. After 30min (which is normal average chewing time), the sample was collected from the receiver compartment and analyzed by the UV-spectrophotometer at 285nm, to determine the total content of Raloxifene Hydrochloride permeated through buccal mucosa.

Results and Discussion

Preformulation Studies

Melting Point

Melting Point was observed 144-146°C (Standard value 144-147°C)

UV-Visible Spectrophotometric method

The λmax of Raloxifene HCl was determined by UV-spectrophotometer in the range of 200 - 400 nm and it was found to be 285 nm.

Preparation of calibration curve

The calibration curve of Raloxifene was drawn by plotting absorbance vs concentration. The λmax of Raloxifene hydrochloride in pH 6.8 simulated saliva buffer was determined to be 285 nm, So absorbance are taken at 285 nm. The absorbance value are reported in Table 5 Standard calibration curve of Raloxifene hydrochloride is shown in figure 2.

Table 5: Calibration curve of Raloxifene	
Concentration(mcg/ml)	**Absorbance**
0	0
10	0.34
12	0.42
14	0.49
16	0.54
18	0.62
20	0.71
22	0.81

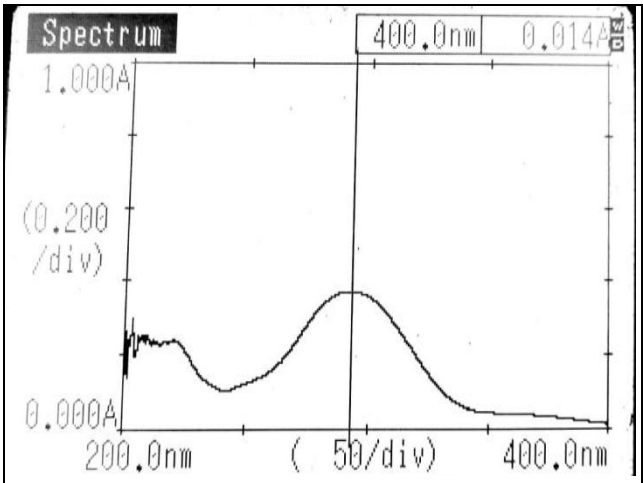


Figure 1: λmax of Raloxifene HCl

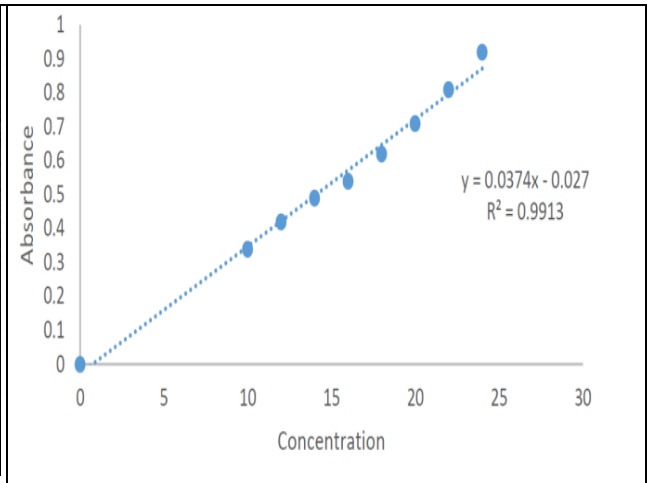


Figure 2: Calibration curve of Raloxifene

FTIR Spectra of Drug and Drug with Excipients

Compatibility study war performed using FT-IR Spectrophotometer. The IR spectra of physical mixture of drug and polymer was studied by making KBr pallet and it was compared with the pure drug spectra. The peaks obtained in the spectra of physical mixture correlates with spectra of pure drug, which indicates that the drug is compatible with the formulation component.

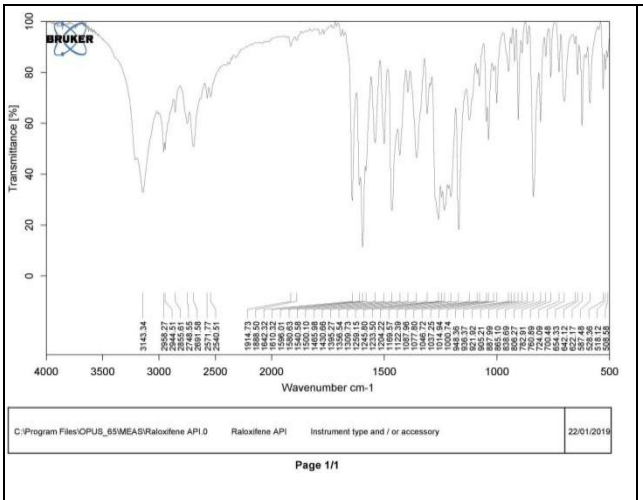


Figure 3: FTIR spectra of Raloxifene HCl

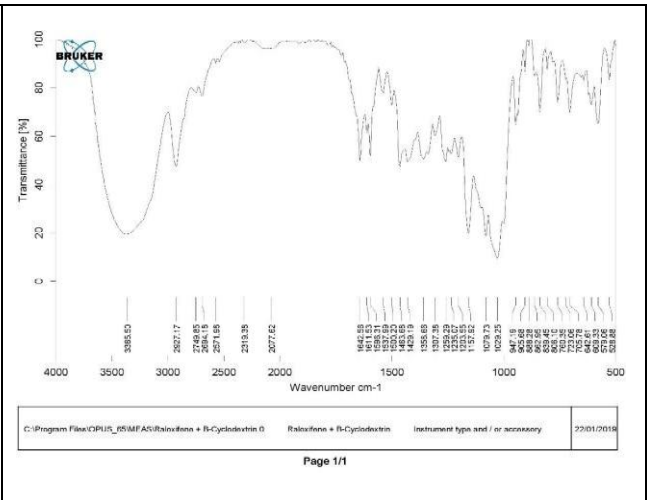


Figure 4: FTIR spectra of Raloxifene HCl + β-Cyclodextrine

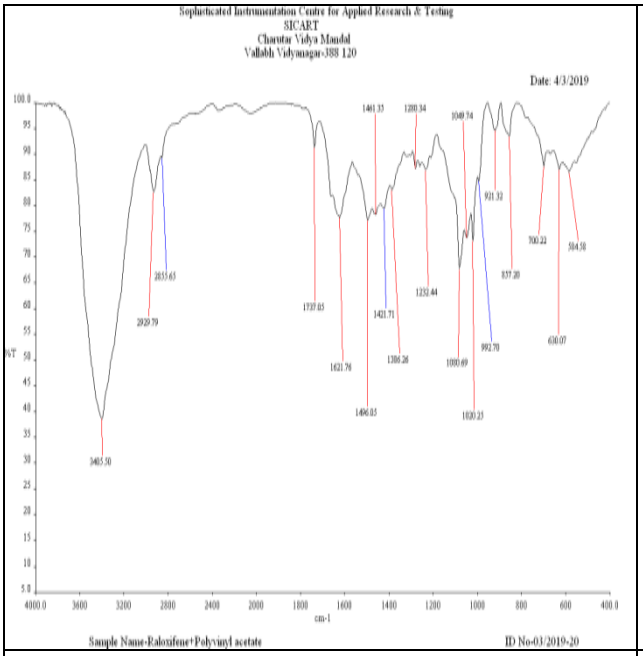


Figure 5: FTIR Spectra of Raloxifene HCl + Polyvinyl acetate

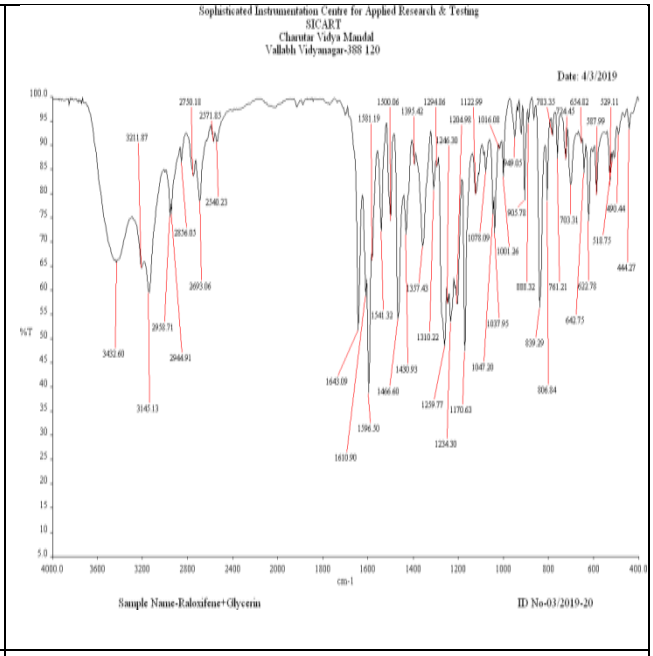


Figure 6: FTIR Spectra of Raloxifene HCl + Glycerine

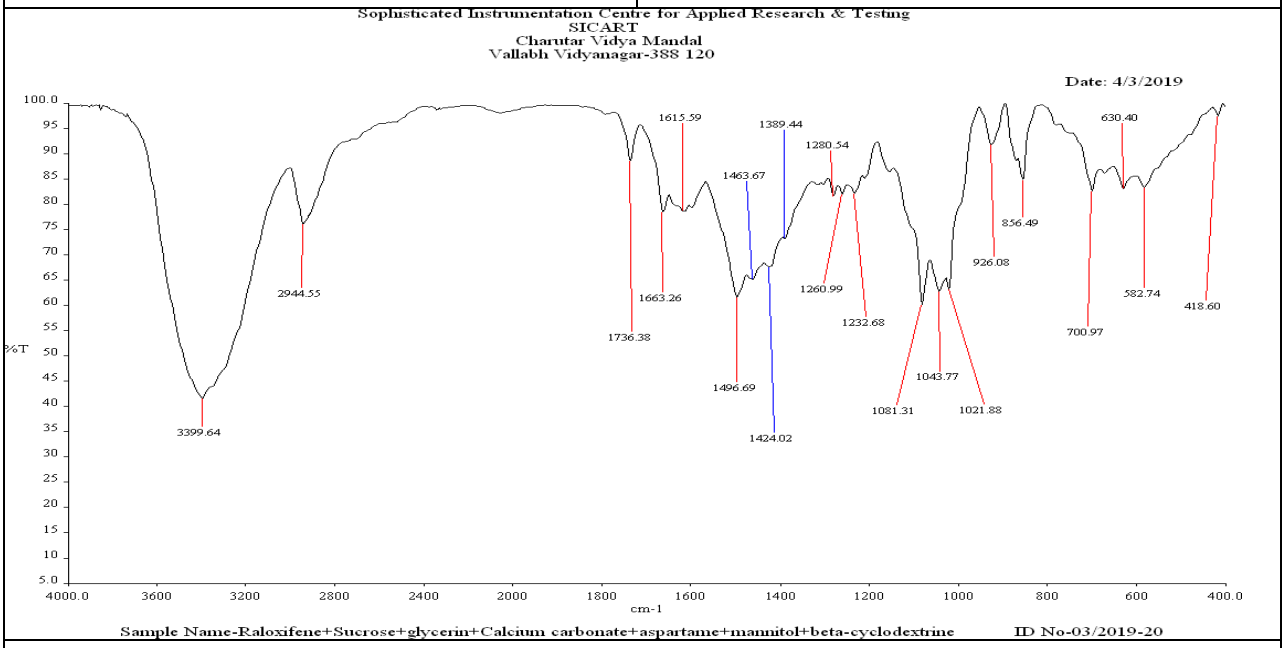


Figure 7: FTIR Spectra of Drug (Raloxifene hydrochloride) + Polyvinylacetate + Glycerine + Sucrose + Peppermint + Calcium Carbonate + Aspartame + Mannitol + Beta-Cyclodextrin

XRD Study

X-ray diffractogram of pure drug showing peaks appearing at 9.465, 10.632, 15.367, 19.599, 20.373, 22.637,27.084,29.712,32.847,37.441 at 2□ values supporting crystalline nature of drug while Shows X-ray Diffraction of Raloxifene hydrochloride agglomerates shows absence of characteristic peaks of Raloxifene hydrochloride which indication that the drug has almost converted from crystalline to amorphous state. Thus, these studies confirm that conversion of drug from its crystalline to amorphous state which results in solubility enhancement of drug. The strongly bound crystalline lattice structure was replaced by the nearly bound random structure of amorphous drug**.**

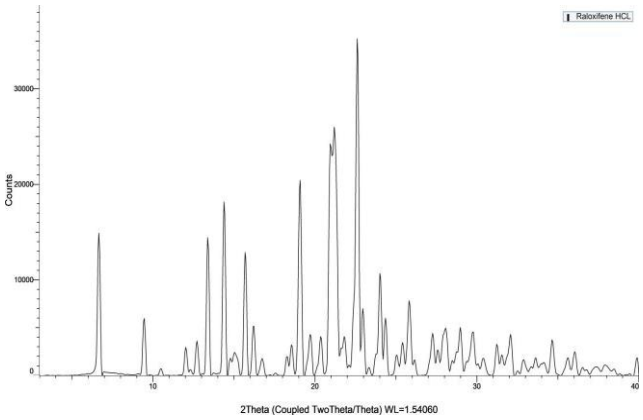


Figure 7. XRD of Pure Drug

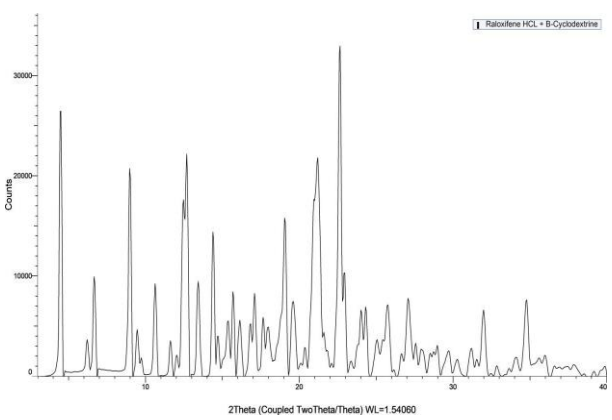


Figure 8. XRD of inclusion complex

Solubility study of drug

Table 6: Solubility study of drug

Sr no	Solvent	ml of solvent required	Solubility (µg/ml)
1	Distilled water	10 ml	33.3
2	Simulated saliva of pH 6.8 Buffer	10 ml	35.7
3	Methanol	10 ml	97.2
4	Chloroform	10 ml	100

Characterization of Raloxifene Hydrochloride : ß-cyclodextrin (ß-CD) inclusion Complex
Solubility of inclusion complex

Solubility of Raloxifene hydrochloride: ß-cyclodextrin inclusion complex was checked by taking 10mg inclusion complex in 10 ml of Simulated saliva pH 6.8 buffer it was agitated at 37^{O}C for 24 hours and after filtration content was measured in UV spectrophotometer at 285nm results are shown in table 7.

Table 7: Solubility of drug and inclusion complex

lation ratio β- cyclodextrin)	Solubility ((µg/ml)
Drug	36.88
PM 1:0.5	66.12
PM 1:1	82.51
PM 1:2	75.31
KM 1:0.5	77.86
KM 1:1	97.26
KM 1:2	82.51

KM - Kneading method and
PM - Physical mixture

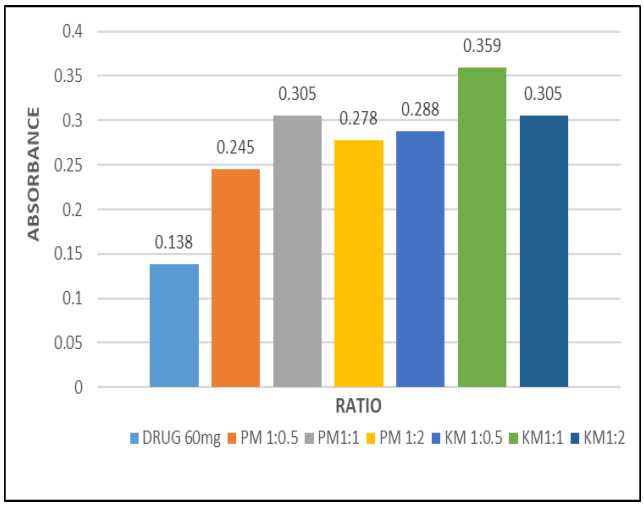


Figure 9: Solubility of Raloxifene hydrochloride inclusion complex

Table 8: Theoretical yield , Practical yield and Powder yield (%) of Raloxifene hydrochloride inclusion complex

Formulation	Theoretical yield (mg)	Practical yield(mg)	Powder yield (%)
1:0.5	900	693.75	92.50±0.20
1:1	1200	848.25	96.30±1.46
1:2	1800	1156.20	94.35±1.20

Optimization of concentration of β-cyclodextrin

The effect of a β-cyclodextrin, on masking Raloxifene hydrochloride taste was evaluated by e-Tongue was configured to determined the system discrimination power between the samples using data generated. Sample T1.1 contain 30 mg of β-cyclodextrin, Sample T2.1 contain 60 mg of β-cyclodextrin and sample T3.1 contain 120 mg of β-cyclodextrin. It shows that the electronic potential was decreases with the taste masking of the drug.

Table No.9 Optimization of concentration of β-cyclodextrin

Ingredients	API	T1.1	T2.1	T3.1
Raloxifene HCl (mg)	60	60	60	60
β – cyclodextrin (mg)	-	30	60	120
Potential Diffrence	29	8.45	5.15	2.95

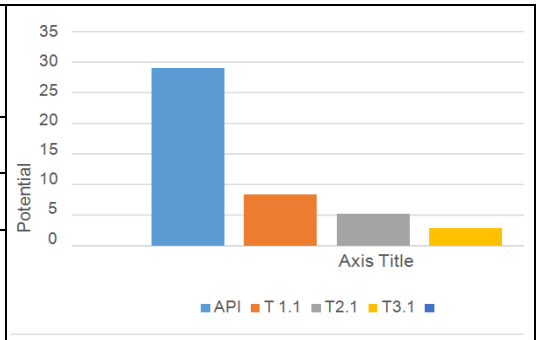


Figure 10: Response of electronic tongue to different concentrations of β-cyclodextrin

Table 10: Pre-evaluation parameters

Sr No	Batch	Stickiness	Colour	Appearance
1	F1	Non sticky	Off white-light yellow	Soft
2	F2	Non sticky	Off white-light yellow	Soft
3	F3	Non sticky	Off white-light yellow	Soft
4	F4	Non sticky	Off white-light yellow	Hard
5	F5	Non sticky	Off white-light yellow	Soft
6	F6	Non sticky	Off white-light yellow	Soft
7	F7	Non sticky	Off white-light yellow	Hard
8	F8	Non sticky	Off white-light yellow	Soft
9	F9	Non sticky	Off white-light yellow	Soft

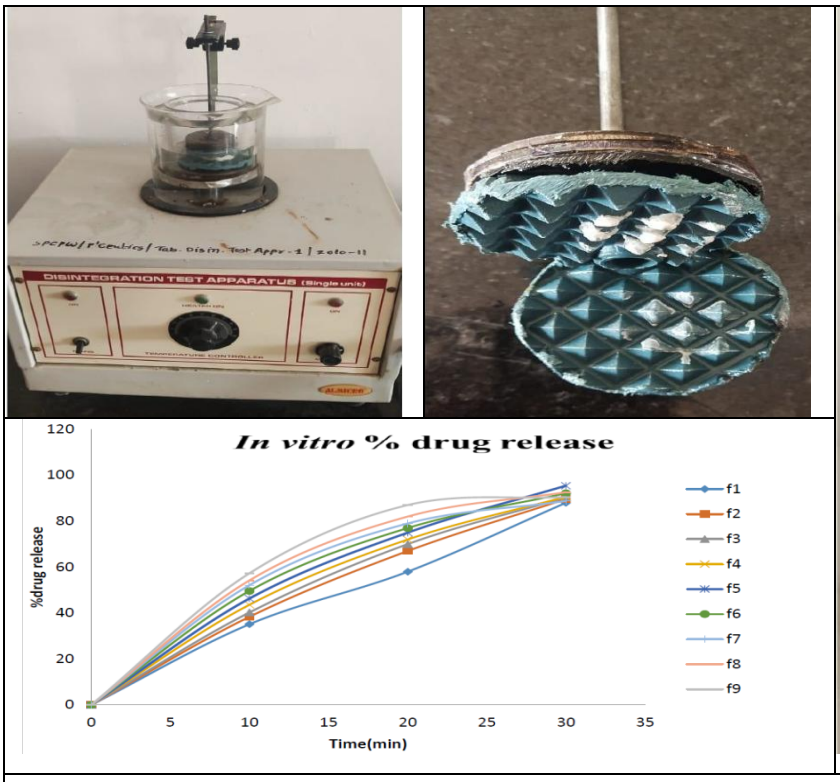
Figure 11. Batch F1-F9

Table 11: Post-evaluation parameters

Sr. No.	Batch	Weight variation (mg)	Hardness Kg/cm^2	% drug content	%drug release
1	F1	700.2 ± 0.21	2.5 ± 0.1	97.20 %	91.30 %
2	F2	700.5 ± 0.44	2.5 ± 0.1	98.76 %	95.10 %
3	F3	700.6 ± 0.31	2 ± 0.1	97.45 %	91.60 %
4	F4	700.4 ± 0.64	2.5 ± 0.1	98.80 %	95.36 %
5	F5	701.6 ± 0.14	2.5 ± 0.2	98.95 %	96.45 %

Table 12: In-Vitro % Drug Release study

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
0 min	0 %	0%	0%	0%	0%	0%	0%	0%	0%
10 min	35.13 ±0.12	38.36 ±0.28	40.25 ±0.39	43.62 ±0.28	46.32 ±0.90	49.63 ±0.20	52.13 ±0.30	54.21 ±0.45	57.31 ±0.80
20 min	58.12 ±0.12	67.23± 0.23	70.45 ±0.80	72.36 ±0.70	75.32 ±0.25	77.23 ±0.76	80 ± 0.47	82 ± 0.21	87 ± 0.31
30 min	91.30 ±0.32	95.10 ±0.87	91.60 ±0.78	95.36 ±0.45	96.45 ±0.12	91.45 ±0.45	91.55 ±0.45	90.63 ±0.24	91.20 ±0.45



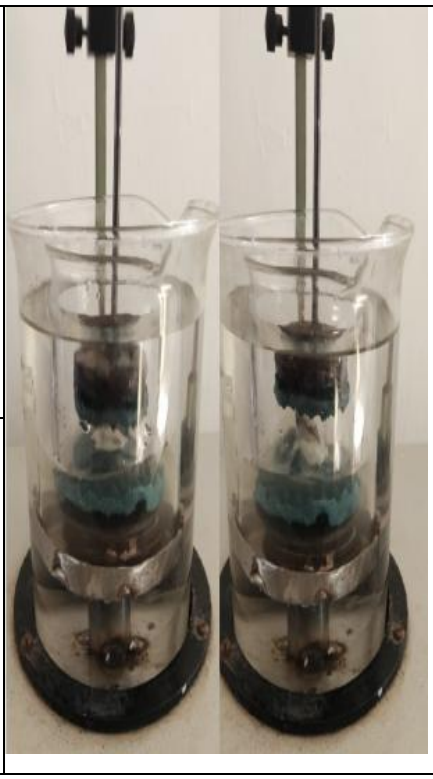


Figure 12: Dissolution apparatus and In-Vitro % Drug Release study (graphical)

Table 13: Stability study data

Parameter	Before test	After test
% Drug Content	98.95%	97.86 %
% Drug Release	96.45%	95.60%
Organoleptic Properties	Elegant	Elegant

Table 14: Comparison of % Drug release before and after stability Study

Time (min)	Before test (%)	After test (%)
0	0	0
10	46.32±0.90	45.75±0.80
20	75.32±0.25	74.12±0.53
30	96.45±0.45	94.40±0.25

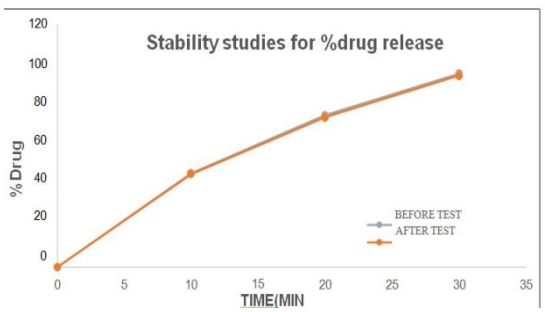


Figure 12. % drug release before and after stability study

Table No. 15 Result of Buccal permeation study

Time (min)	Observed% permeation(o)
0	00
10	46.30%
20	54.20%
30	60.56%

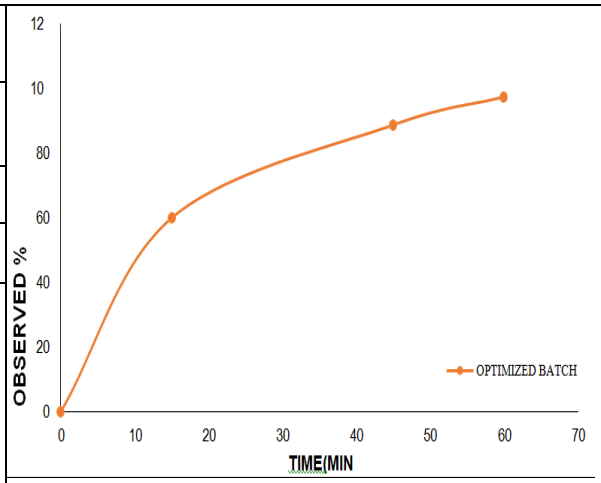


Figure 13. Buccal permeation study graph

Conclusion

The overall research suggests that medicated chewing gum of Raloxifene hydrochloride is a very good idea of formulation and basis of following results we can say that our formulation is successfully formulate and evaluate without any problem. Melting point study gives surety that API is pure. FTIR study proves that no interaction between drug and excipients. XRD study shows drug is converted crystalline form to amorphous form. Solubility study shows drug is more soluble in methanol and chloroform. From the study of inclusion complexes we take best ratio for formulation of drug and beta-cyclodextrine. Pre-evalution results are very good. Post-evaluation parameters shows formulation is successfully form and ready to further study. F5 formulation selected as best formulation basis on % drug release study. In stability study no major changes shows in formulation which indicate it's good shelf-life. In last we performed buccal permeability study which gives good results. So now our formulation is ready to help peoples which is suffer from osteoporosis.

References

1. Ferdous Hs, Afsana ,Qureshi Nk, Rouf Rsb. Osteoporosis: A review. Bridem medical journal. 2015;5(1):502-511.
2. Calik Basaran. An overview and management of Osteoporosis. Journal of Rheumatology 2017;4:46-56.
3. http:/www.iofbonehealth.org/fact-stastic
4. Nancy E. Epidemiology, etiology an diagnosis of osteoporosis. American Journal of Obstetrics and Gynecology. 2006;194,S3-S11.
5. Tarun Garg and Amit Goyel. Medicated Chewing Gum:Patient Compliance Oral Drug Delivery System. Bentham Sciences Publishers. 2014;72-78
6. Kinjal shah, Tejal. Medicated Chewing -A mobile Oral Drug Delivery System. International Journal of pharmatech Research. 2014; 35-78
7. Pramod Kumar and Anantkumar. An Updated Review on Medicated Chewing Gum. International Journal of advance in pharmacy, biology, chemistry. 2013;2(2): 351-359
8. Sharma Vijay and Himanshu chopra. Role Taste and Taste Masking of bitter drug in pharmaceutical industries -an overview. International Journal of pharmacy and Pharmaceutical Sciences. 2010;2: 14-18
9. Dumpala Rajesh, Patel Jignesh, Patadiya Nikunj, Patil Chirag. Solubility and Dissolution Enhancement of Erlotinib by Liquisolid Compact Technique. International Journal of PharmaO2. 2020; 2(4): 0271-0290
10. Mr. Nikunj Patadiya. Steroids : Classification, Nomenculture and Stereochemistry. International Jouranl of Universal Pharmacy and Bio Science. 2020; 9(5): 28-38.

11. Soni Dhruvi, Patadiya Nikunj. A Wonderful Harmone: Estrogen. International Journal of PharmaO2. 2020;2(5): 0362-0368
12. Nikunj Patadiya, Rajesh Dumpala. A high profile review on new oral clotting factor xa inhibitor : Betrixaban. European Journal of Pharmaceutical and Medical Research. 2021; 8(1): 239-247.
13. Tanuj Kolekar, Nikunj Patadiya. Dissolution Enhancement Technique : Self-Emulsifying Drug Delivery System (SEDDS). International Journal of Institutional Pharmacy and Life Science. 2020; 10(6) : 25-29
14. Mr. Tanuj Kolekar, Mr. Nikunj Patadiya. Self-Emulsifying Drug Delivery System (SEDDS) : A Novel Dissolution Enhancement Technique. 2020; 2(5): 10-20.
15. A Tripathi ,D Parmar , Dr. U Patel, G Patel,D Daslaniya, B Bhiman. Taste Masking: A Novel Approach for Bitter and Obnoxious Drugs. Jornal of pharmaceutical science and bioscientific research. 2011;1:136-142.
16. Neelam S, D Allawadi , S Singh and Sandeep Arora. Techniques for Bioavailability Enhancement of BCS class II Drug: A Review. International Journal OF pharmaceutical and Chemical Sciences. 2013;2(2):1092-1101.
17. E.M Martin del Valle. Cyclodextrin and their Uses : a review. Sciencesdirect. 2003 1031-1046.
18. Janisse Miranda, Tércio E, Fr Veiga, Humberto G F. Cyclodextrins and ternary complexes: technology to improve solubility of poorly soluble drugs. Brazilian Journal of Pharmaceutical Sciences. 2011;47:665-681.
19. https:/www.drugbank.ca/drug/DB00481.
20. http://www.wikipedia.org/wiki/Polyvinylacetate.
21. Raymond C Rowe, Paul J Sheskey and Marian E Quinn. Handbook of Pharmaceutical Excipients. 6th edition. pp:703-705
22. Helga Hansdóttir. Raloxifene for older women: a review of the literature'. Department of Geriatrics. Landspitali University Hospital, Landakoti.
23. Ravi v k. Optimization immediate release tablet of raloxifene hydrochloride wet granulation method. Indian journal pharmaceutical sciences and research. 2009;51-54 .
24. AM. Chanale, RP. Mishra. Formulation and Evaluation of Herbal Antimicrobial Chewing Gum Containing Neem Extract. 2016;5(1).
25. Pramod Kumar Biswal and Anantkumar. An Updated Review on Medicated Chewing gum. International Journal of Advances in Pharmacy Biology and Chemistry. 2014; 5(5):201-211.
26. Juber A Pathan, Manoj M Nitalikar. Formulation and Evaluation of Medicated Chewing Gum Containing Antibacterial Agent. Journal of Current Pharma Research. 2014;4(4):1291-1296.