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Design, evaluation and comparitive studies of oral thin films of alendronate

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ABSTRACT

The Aim of the present study is to design and evaluate fast dissolving Oral thin films (OTF) of Alendronate drug. The bisphosphonate called alendronate used for osteoporosis and several other bone diseases. Sixteen Formulations (F1–F16) of OTF were prepared by casting method using different concentrations of polymer increased tensile strength and folding endurance were improved with more dissolution time. 0.3% and above concentration of polymer showed good physical and rheological properties. Optimized formulation among OTF was an F4 with 1.5% Sodium alginate showing good folding endurance, tensile strength, disintegration time and 98.9% drug release with no casting problem and appearance.

Keywords: Fast dissolving Oral thin films, Alendronate, Solvent casting method.

INTRODUCTION

Oral route is the most preferred route by medical practitioners and manufacturer due to the highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc.) has the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance. Each pharmaceutical company wants to formulate the novel oral dosage form which has the highest bioavailability, quick action and most patient compliance. So they formulate the fast dissolving tablets by using super disintigrants and hydrophilic ingredients. Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for Pediatric and Geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms.

Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Dysphagia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reducing liquid intake/diets have difficulties in swallowing these dosage forms[1, 2].The main mechanism for the absorption of the drug into oral mucosa is via passive diffusion into the lipoidal membrane[3].

In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. The differences in permeability are generally based on the relative thickness, the blood supply, and degree of keratinization of these membranes. In addition to the differences in the permeability of the various mucous membranes, the extent of drug delivery is also affected by the physicochemical properties of the drug to be delivered[4].

Sublingual products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia) [5].

Oral Thin Films

Fast dissolving oral films (FDOFs) or Oral wafers or Oral strips (OS) or sublingual strips or oral thin films (OTF) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of APIs by dissolving within a minute in the oral cavity after the contact with saliva without chewing and no need of water for the administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin [9]. FDOFs are useful in patients such as pediatric, geriatric, bedridden, emetic patients, diarrhea, sudden episode of allergic attacks, or coughing for those who have an active lifestyle. It is also useful whether local action desired, such as a local anesthetic for toothaches, oral ulcers, cold sores or teething. OTFs also have an established shelf life of 2-3years, depending on the API but are extremely sensitive to environmental moisture[10].

The OTFs place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets / capsules. The oral thin-film technology is still in the beginning stages and has a bright future ahead because it fulfills all the need of patients. Eventually, film formulations having drug/s will be commercially launched using the OTF technology[11].

Oral thin films, a new drug delivery system for the oral delivery of the drugs, were developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue, or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oramucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. In contrast to other existing, rapid dissolving dosage forms, which consist of liophylisates, the rapid films can be produced by a manufacturing process that is competitive with the manufacturing costs of conventional tablets.

Application of Oral Strip in Drug Delivery

Oral mucosal delivery via Buccal, sublingual, and the mucosal route by use of OTFs could become a preferred delivery method for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders. Dissolvable oral thin films (OTFs) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products.

MATERIALS AND METHODS

Materials

Alendronate (Chandra labs), Guar gum, Xanthum gum, HPMC E6, PVP, Sodium Starch glycolate (coral Pharma), PEG 400, vanillin, sodium saccharine, water.

Method

Preparation of Oral thin film

The film was prepared by using specified polymer by solvent casting method. The specified amount of polymer was weighed and dissolved in a specified amount of water for overnight to get a uniform dispersion of 0.4 % to 2 % (w/v) solution respectively. Drug, sodium starch glycolate, vanilline and sodium saccharine were dissolved in specific amount of water in a beaker. The drug solution was added to the polymer solution and mixed using magnetic stirrer for 1 hour. The resulting solution was degaussed so as to remove any bubbles formed.

The bubble free solution was cast onto a petri dish of surface area 28.6 cm^2. It was dried for 24 hours at room temperature. The film was removed from the petri dish very carefully and observed for any imperfections. A film that was clear and bubble free was selected for further studies. Film of area 2.25 cm^2 (1.25 X 1.25) was cut and stored in a butter paper covered with aluminum foil and stored in a desiccator.

Formulation Development of oral thin films

Oral thin films containing Alendronate were prepared by casting method. The films of sodium alginate and xanthum gum were prepared with an objective to dissolve the film in the mouth. 1.5% sodium alginate and 0.7 % of xanthum gum films were exhibited desired mouth dissolving time and other film parameters, compared to other concentrations of films i.e. <1% sodium alginate have poor film forming capacity and >1% of xanthum takes lots of time for drying and which were difficult to remove and having low strength and exhibited unacceptable mouth dissolving time. Hence 1, 1.5, 2 w/v% of sodium alginate and 0.4, 0.7 w/v% concentrations of xanthum films were used for the study. Propylene glycol (5 % w/w of polymer) was used as plasticizer and to enhance the tensile strength of film.2 % sodium starch glycolate is used as disintegrant to dissolve the films rapidly when comes in contact with saliva. 1 % w/w Sodium saccharine was used as a sweetener and 1 % w/w of vanilin was used as flavoring agent.

Table: 1 formulation table by solvent casting method

S.no	Ingredients (mg/film)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
1	Alendronate	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
2	Guar gum*	0.4	0.7	1.0	2	-	-	-	-	-	-	-	-	-	-	-	-
3	Xantham gum*	-	-	-	-	0.4	0.7	1.0	2	-	-	-	-	-	-	-	-
4	HPMC E6*	-	-	-	-	-	-	-	-	0.4	0.7	1.0	2	-	-	-	-
5	PVA*	-	-	-	-	-	-	-	-	-	-	-	-	0.4	0.7	1.0	2
6	SSG	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
7	PEG 400**	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
8	Vanillin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
9	Sodium saccharine	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
10	Water	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	Qs	qs

Evaluation parameters of alendronate ODF

Estimation of alendronate

A UV Spectrophotometric method based on the measurement of absorbance at 239nm in methanol was used in the estimation of alendronate. The method obeyed Beer's law in the concentration range of 2-10µg/ml. Low RSD values ensured reproducibility of the method. Thus the method was found to be suitable for the estimation of ALENDRONATE content in various products and in vitro dissolution studies.

Evaluation of the prepared alendronate ODFs

Weight variation

This test ensures the uniformity of the formed film. Three small pieces were cut randomly, each of 1 cm^2 (1 × 1 cm) areas, and were weighed individually.

Thickness

The film thickness was measured using a micrometer screw gauge at five points (center and four corners) on the film to ensure the uniformity of the film thickness. The mean thickness was calculated from the five points. Samples with air bubbles, nicks or tears, and those having mean thickness variations greater than 5% were excluded from analysis.

Content uniformity

The content uniformity test was used to ensure that every film contains the intended amount of drug substance with little variation among films within a patch. Three pieces, each 1 cm^2 (1 ×1 cm), were cut from the whole patch, and assayed for drug content. [8]

Folding endurance

Folding endurance of the film was determined by repeatedly folding a small strip of film (2 × 2 cm) at the same place until it broke. The number of times that the film could be folded at the same place without breaking gives the value of folding endurance. [9],[10]

Thickness

The thickness of the film can be measured by micrometer screw gauge at different strategic locations (at least 5 locations). This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film.

Folding Endurance

Folding endurance is determined by repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking is noted as the folding endurance value.

Disintegration Time

Drug Content and Content Uniformity

This is determined by any standard assay method described in the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual film. Limit of content uniformity is 85-115%.

In vitro dissolution studies

In vitro disintegration

Two simple methods were used wherein; a small amount of disintegration medium was used. In the first method, one drop of water was dropped from a 10-ml pipette onto the tightly clamped film. The time taken for the water to make a hole through the film was measured as disintegration time (DT). In the second method, 2 ml of water was placed in a petri plate with a film on the surface of water; the time taken for the disintegration of the film was measured. This test was done in triplicates and the average value was taken as a DT. [18]

Invitro dissolution

According to previous studies, dissolution studies were performed using USP 23 apparatus 5, paddle over disc method. As the paddle over disc apparatus was not available, USP apparatus 1 (basket) (Electrolab TDT-08L) was used for this study. Nine hundred milliliters of phosphate buffer (pH 6.8), which is a prescribed media for LCTZ according to Indian pharmacopoeia, was used, and

was maintained at 37±5°C while the basket was set at 100 rpm. A film sample of 4 cm^2 (2×2 cm) was cut and taken into the basket. Five milliliters of samples were taken every 2 min, and the same amount was replaced with fresh buffer. The withdrawn samples were filtered and analyzed using a spectrophotometer at a wavelength of 230 nm. The percentage release was calculated from previously assayed values of the patch. The relationship between time and percentage release was plotted to determine when the maximum amount of drug is released. Dissolution studies were conducted for optimized formulations. [19],[20]

RESULTS AND DISCUSSION

Preformulation studies

API Characterization

Description

These tests were performed as per the procedure and the results were illustrated in the following table:

Table.2 description of drug

Test	Description
Colour	A white to off white colour powder
Odour	Odourless

Solubility

These tests were performed as per procedure and the results are illustrated in the following table.

Table.3 Solubility of Alendronate (API) in various solvents.

Solvents	Solubility
Water	Slightly soluble
pH6.8 Phosphate buffer	Soluble
Methanol	Freely soluble
Ethanol	Freely soluble
Propylene Glycol	Freely soluble

Discussion

Alendronate is slightly soluble in water, soluble in pH6.8 Phosphate buffer and freely soluble in alcohols like Methanol, Ethanol and Propylene glycol.

Melting Point

This test is performed as per procedure (8.1.3) and the result was illustrated in the following table.

Table.4 Melting point of API's

Material	Melting Point	Melting Point Range
Alendronate	150^0c	150-151^0c

Discussion

The Result was found to be within limits

Table.5 Standard calibration curve of alendronate in pH 7.4

Concentration in mcg	Absorbance at 242 nm ±SD, n=3
2	0.055±0.011

4	0.105±0.012
6	0.165±0.014
8	0.212±0.012
10	0.266±0.016

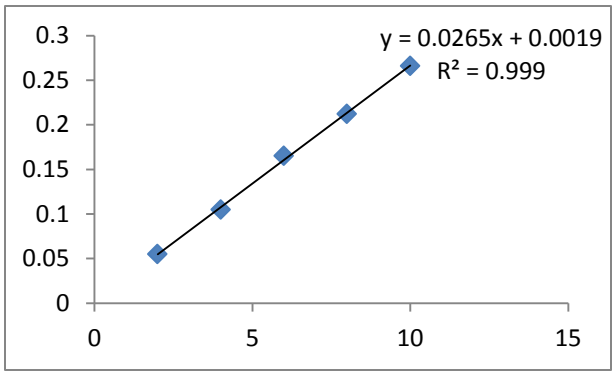

Figure-1 Calibration curve of Alendronate in PH 7.4

Discussion

Calibration curve was carried out as per the procedure. Standard graph of Alendronate in pH 7.4 Phosphate buffer saline shows linearity in the concentration range of 5 - 30 µg/ml with a correlation coefficient of 0.999 and the slope was found to be 0.0265.

Drug-Excipient Compatibility Studies

The drug – excipient compatibility studies were carried out by FTIR

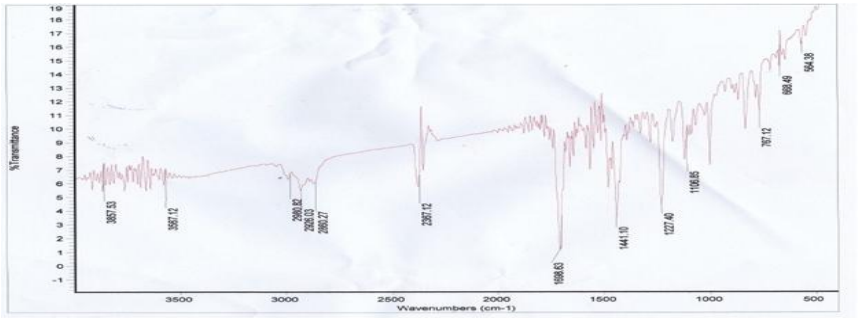

Figure-2 FTIR Spectra of Alendronate pure drug

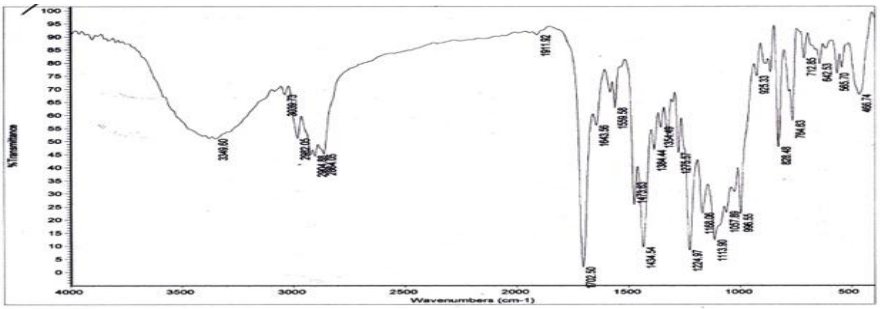

Figure-3 FTIR-3 Spectra of optimized formulation of Alendronate film

Discussion

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The Characteristic absorption peaks were obtained and as they were in official limits, the drug is compatible with excipients

Evaluation Parameters

Weight variation of the films

Discussion

Three Films each about 0.35 square inches were cut at three different places from cast films and weight variation was measured. Weight variation varies from 18.65 ± 0.016 to 25.21 ± 0.089. The results of weight variations are shown in the Table-13.

Table. 6 Comparative evaluation of Weight variation of oral thin film

S.NO	Formulation code	Average weight of the 2.25 square inch film in mg
1	F1	18.65±0.016
2	F2	22.31±0.011
3	F3	19.21±0.009
4	F4	22.54±0.011
5	F5	18.67±0.026
6	F6	23.31±0.061
7	F7	21.21±0.069
8	F8	24.74±0.031
9	F9	20.65±0.036
10	F10	20.31±0.061
11	F11	25.21±0.089
12	F12	24.54±0.021

***Standard deviation, n =3**

Thickness of the film

Discussion

The thickness of the film was measured using digital vernier calliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the film and averages were taken and SD was calculated. It was observed that as the polymer concentration increases the thickness of the film also increases.

Table.7 Comparative evaluation of Thickness of oral thin films

S.No	Formulation code	Average thickness in mm
1	F1	0.22 ± 0.025
2	F2	0.29 ± 0.01

3	F3	0.18 ± 0.00
4	F4	0.23 ± 0.01
5	F5	0.14 ± 0.02
6	F6	0.16 ± 0.01
7	F7	0.21 ± 0.01
8	F8	0.27 ± 0.01
9	F9	0.26 ± 0.01
10	F10	0.23 ± 0.01
11	F11	0.27 ± 0.01
12	F12	0.26 ± 0.01

***Standard deviation, n =3**

Folding endurance of the films

The folding endurance was measured manually. A strip of film 4squre cm was cut and subjected to the folding endurance studies until it broke in the same place.

Folding endurance increases with increase in polymer concentration. The no of times the film fold until it broke was reported.

Table.8 Comparative evaluation of folding endurance of oral thin films

S.No	Formulation code	Folding endurance (no of folds)
1	F1	20 ± 2.08
2	F2	26 ± 4.16
3	F3	28 ± 6.25
4	F4	32 ± 6.02
5	F5	40 ± 8.14
6	F6	18±11.01
7	F7	23 ± 2.15
8	F8	26 ± 3.60
9	F9	27±11.01
10	F10	30 ± 3.15
11	F11	26 ± 2.60
12	F12	29 ±1.01

***Standard deviation, n =3**

Discussion

All batches were showing good folding endurance, as polymer concentration increases folding endurance are also increased. Folding endurance is also a measurement of plasticizer concentration, but here all formulations have the same concentration of plasticizer, so the polymer concentration effect was easily studied in this research work.

Disintegration time

The disintegration time of the film was done by using the tablet disintegration test apparatus.

Table.9 Comparative evaluation of Disintegration time of oral thin films

S.No	Formulation code	Disintegration time in Sec
1	F1	46 ± 2
2	F2	54 ± 2
3	F3	63 ± 2
4	F4	69 ± 2
5	F5	42 ± 1
6	F6	45.33 ± 1.15
7	F7	42 ± 1
8	F8	45.33 ± 1.15
9	F9	33.33 ± 3.05
10	F10	46.33 ± 1.52
11	F11	33.33 ± 3.05
12	F12	46.33 ± 1.52
13	F13	49 ± 1
14	F14	57.33 ± 0.57
15	F15	33.33 ± 3.05
16	F16	46.33 ± 1.52

Discussion

Disintegration times of the films were found to be increased with an increase in the concentration of the polymer. The formulation F4 shows 18 Sec (disintegration time) as shown in the table 17. As the polymer concentration increases disintegration time was decreased in these formulations. F4 formulation showed good disintegration time along with good folding endurance property.

Mouth dissolving time

Table. 10 Comparative evaluation of Mouth dissolving time of oral thin films

S.NO	Formulation code	Mouth dissolving time in Sec
1	F1	53.6 ± 1.52
2	F2	64.66 ± 3.05
3	F3	53.6 ± 1.52
4	F4	64.66 ± 3.05
5	F5	47 ± 2
6	F6	55.33 ± 3.05
7	F7	47 ± 2
8	F8	55.33 ± 3.05

9	F9	40.66 ± 3.04
10	F10	52.66 ± 3.21
11	F11	40.66 ± 3.04
12	F12	52.66 ± 3.21
13	F13	59.66 ± 4.04
14	F14	65.55 ± 2.08
15	F15	40.66 ± 3.04
16	F16	52.66 ± 3.21

***Standard deviation, n =3**

Discussion

The mouth dissolving time was determined by using beaker containing 7.4-pH phosphate buffer. A size of 2.25 square inch film was subjected to this study. The mouth dissolving time of the film was reported in the Table-18. This mouth dissolving time is directly proportional to disintegration time. Here we can check the dissolution time, but specifically in saliva pH.

Drug content uniformity of films

Table. 11 drug content uniformity of oral film formulations

S.No	Formulation code	Drug content in mg
1	F1	99.40%
2	F2	98.20%
3	F3	99.40%
4	F4	98.20%
5	F5	95.60%
6	F6	95.80%
7	F7	95.60%
8	F8	95.80%
9	F9	97.20%
10	F10	96.80%
11	F11	97.20%
12	F12	96.80%
13	F13	94.40%
14	F14	96%
15	F15	97.20%
16	F16	96.80%

*Standard deviation, n =3

Each film contain 5 mg / 2.25 sq.cm

Discussion

The prepared film formulations were analyzed for drug content and it was observed that all the formulation found to contain an almost uniform quantity of drug as per content uniformity studies indicating reproducible technique.

In-vitro dissolution

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 500 ml of pH 7.4 phosphate buffer maintained at 37 ± 0.5^{0}C at 50 rpm. 5 ml aliquots of samples were taken at various time intervals which were replaced with the same volume of fresh pH 7.4 phosphate buffer maintained at 37 ± 0.5^{0}C. Alendronate in the samples was then determined spectrophotometrically at $\lambda_{max}$of 242 nm. The results were expressed in table no. 20

Table. 12 Comparative evaluation of *Invitro* dissolution studies of oral thin Films

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	15	19	21	25	31	23	28	33	33	42	17	22	28	31	40	35
2	23	28	36	32	46	30	39	49	40	54	23	36	37	42	49	49
3	28	37	43	41	58	36	47	56	51	68	32	41	46	51	58	64
4	37	47	57	50	69	46	58	65	69	79	42	49	55	63	70	78
5	48	55	68	63	81	50	67	70	81	94	48	62	62	78	83	99
6	57	67	73	80	100.1	63	75	79	93	99.9	62	72	73	85	98	
7	66	73	79	99		75	86	89	100.5		71	78	80	91		
8	72	79	96			81	90	101.2			79	85	99.7			
9	85	86	101.1			86	99.7				86	90				
10	90	90				92					95	100.6				
15	96	99.9				97					100.1					
20	101.2					100.1										

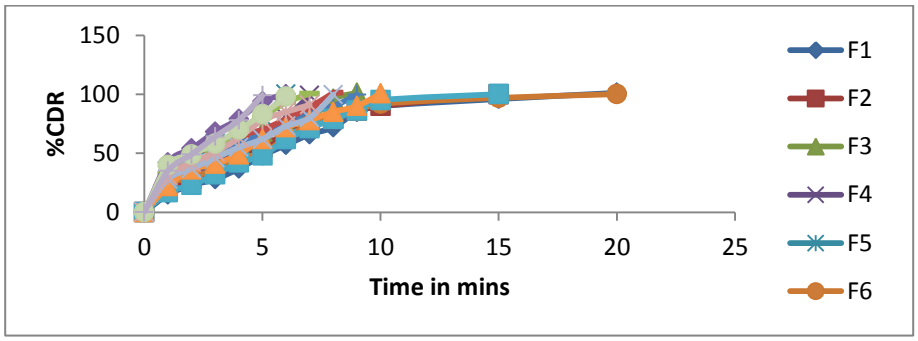

Figure-4 Drug release graphs of formulation F1 to F1

Discussion

Formulations F1 to F3 all showed 100% drug release within 10min but they are failing in folding endurance and tensile strength. Even formulations F1 to F3 have casting problems; they are not easy to remove from a petri dish as they are very thin so the yield is not good. As polymer concentration increases tensile strength and folding endurance were improved for a formulation, but dissolution takes much time, so optimization of formulation is based on the folding endurance, disintegration time and dissolution profile. Formulations F5 also showed good folding endurance, but the dissolution profile is better in F4 compared to F5 formulation. Formulations F7 to F10 showed good folding and

tensile properties. In these formulations F7 showed good dissolution profile compared to other formulations. F6 formulation is thin and problem in casting. Formulations F9 and F10 formulations have casting problems; they are thick and take much time for drying. Formulations F11 and F16 were prepared by using a combination of these two polymers (sodium alginate and xanthum gum) but these two formulations were not given the desired release pattern, tensile strength and appearance. From all these formulations it was concluded that F4 formulation with 1.5% sodium alginate showed good folding endurance, tensile strength, disintegration time and drug release profile with no casting problems and good appearance.

Stability studies

The stability studies of the optimized batch F4 were carried out at Room temperature and 8^0C. The films were found to be unacceptable at Room temperature. Films stored at Room temperature were unstable within a 1 week period by developing color change (slight yellow) and becoming sticky in appearance. Films stored at 8^0C were found to be stable for 3 weeks. The batch was found to be acceptable visually, mechanically, with slight change in in-vitro disintegration time. The above observations indicate that temperature and humidity play a critical role in the stability of the rapidly dissolving films containing Sodium alginate as the film forming polymer. Therefore, precautions would be required during packaging and selection of packaging container would play a crucial role for stability of the Oral thin films.

Table.13 Stability data of optimized formulation F4

S No	TIME	APPEARANCE		IN VITRO DISINTEGRATION TIME(sec)	
		0-8^{0}C	**Room temperature***	**0-8^{0}C**	**Room temperature***
1	1st week	Transparent and acceptable	Slightly yellow and acceptable	18	17
2	2nd week	Transparent and acceptable	Slightly yellow and sticky	19	16
3	3rd week	Transparent and acceptable	Slightly yellow and sticky	18	12

***Room temperature =**

In-Vivo bioavailability study

The efficacy of the edible gel in the improvement of oral bioavailability of ADR is evaluated after administering the dose to the rats. The plain drug suspension is prepared (ADR) and administered to the rats for comparative evaluation. The tested formulations (ODF) are dispersed in pH 7.4 phosphate buffer and administered orally. All the dosage forms are well tolerated and no obvious side effects are observed. After dosing, plasma samples are analyzed by HPLC for ADR levels and drug plasma concentrations as a function of time are shown in Fig. The plasma profiles are analyzed by non-compartmental analysis for extra-vasucular administration to determine the appropriate pharmacokinetic parameters of administered formulations and represented in Table 5. The ODF has shown increased Cmax value compared to ADR. The Cmax values of ODF and ADR are found to be increased. The enhancement in the Cmax from the ODF is 2.02 times higher compared to ADR. The AUC (0-inf) values are are also found increased in formulation ODF compared to ADR

Table.14 Mean Pharmacokinetic parameters for alendronate formulations in plasma after oral administrations to the rat

Parameter	ODF	ADR
Cmax (mcg/ml)	90.24	41.846
Tmax (hrs)	1.5	1.5
AUC (0-t) (mcg.hr/ml)	167.97	106.17

CONCLUSION

From this research it was concluded that F4 formulation of alendronate oral thin films were good in oral thin formulations.

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