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Design and evaluation of edible gels of alendronate

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ABSTRACT

The Aim of the present study is to Design and Evaluate Edible gel (EG) loaded with Alendronate drug. The Bisphosphonate called Alendronate used for osteoporosis and several other bone diseases. Ten Formulation (EG1-EG10) of EG was prepared by varying concentrations of Gellan Gum (0.1-0.5%), 0.3% and above the concentration of polymer showed good physical and Rheological properties. Optimized formulation among EG was EG8 with no syneresis showing 99% drug release with good consistency and viscosity increasing the mouth feel. Based on the stability of EG at room temperature and also due to its high patient compliance based on appearance and ease of administration, EG was preferred as better dosage form for geriatrics and paediatrics.

Keywords:- Alendronate, Edible Gels

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.) have 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 superdisintigrants 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 reduced liquid intake/diets have difficulties in swallowing these dosage forms[1, 2].

Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly into the blood stream through the ventral surface of the tongue and the floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and brachycephalic vein and then drained into systemic circulation.

The main mechanism for the absorption of the drug into oral mucosa is via passive diffusion into the lipoidal membrane[3]. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity.

Sublingual absorption is most rapid in action, but also short acting in duration. Nitroglycerine, for example, is an effective antianginal drug, but is extensively metabolized when taken orally (>90%). It is rapidly absorbed through the sublingual mucosa, and its peak plasma level is reached within 1-2 min. Because of its short biological half-life (3-5 min.), however the blood concentration of nitroglycerine declines rapidly to a level below the therapeutic concentration within 10-15 min.

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].

EDIBLE GEL

Oral administration is the most popular route due to ease of ingestion, pain avoidance, no requirement of sterile conditions, less expensive to manufacture and patient compliance. However, tablets, capsules, and liquids, which are used orally, are difficult to swallow in case of dysphagia patients[3,4]. Patients with advanced age cannot easily take tablets or capsules. The irritation or pain resulting from the contact of the solid preparation with the oral cavity or with the larynx and pharynx, or physical injury caused upon rubbing of the solid preparation against mucous membrane can give discomfort to a patient. However, certain modifications are undesirable, such as crushing of the enteric-coated or sustained-release tablet which can lead to adverse events. Crushed tablets are the most frequent cause of obstruction of feeding tubes, which results in increased morbidity, trauma to the patient besides the cost of replacing the tube (surgical).

Dysphagia is a clinical syndrome resulting from a biomechanical disorder defined as "an inability to swallow, or a sensation that solids or liquids do not pass easily from the mouth to the stomach". Swallowing disorders (dysphagia) occur in all age groups, preterm babies to the elderly. The problem with swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients.

Des loratidine available as tablets and syrups are found difficult for swallowing in dysphagic patients. Injections cause pain at the site of injection and also needs a trained person to administer.

Thickened liquids play a vital role in reducing risk of aspiration for dysphagia patients. Previous studies have indicated the importance of viscosity as a bolus variable during the swallowing process. Dietary professionals work closely with the speech-language pathologist (SLP) to determine the appropriate consistencies of fluid for each patient. A video fluoroscopy swallow study (VFSS) is carried out to look closely at the swallowing process. The VFSS will test your ability to drink safely and comfortably. If you have trouble swallowing, you may be at risk for aspiration.

Aspiration occurs when food or drink enters the windpipe, potentially going into the lungs. Aspiration may put you at risk for developing an infection of the lungs, called aspiration pneumonia. Even swallowing problems may also put you at risk for not getting enough liquids or food (dehydration or malnutrition). So based on information from the study, the SLP, and doctors will tell how thick liquids (consistency) should be for you to swallow safely.

In 2002, the American Dietetic Association established the National Dysphagia Diet (NDD) guidelines for thickened dietary supplements. This Task Force proposed viscosity ranges for thin, nectar-thick, and honey-thick and spoon thick liquids. To ensure safety during oral administration, patients with dysphagia require an appropriate oral dosage form or modification of the dosage form. The objective of this work is to prepare and evaluate eatable dosage form for the treatment in dysphagia patients using a polymer.

MATERIALS AND METHODS

Materials

Alendronate, Guar gum*, Xantham gum*, HPMC E6*, PVA*, SSG, PEG 400**.

Method

Preparation of Edible gels

➤ Gellan gum powder was dispersed in 50 ml of distilled water maintained at 95°C. The dispersion was stirred at 95°C for 20 min using a magnetic stirrer to facilitate hydration of gellan gum.

➤ The required amount of mannitol was added to the gellan gum solution with continuous stirring and the temperature was maintained above 80°C the drug was added with stirring.

➤ Then mannitol, citric acid and methylparaben were added with stirring.

➤ Finally, required amount of sodium citrate was dissolved in 10 ml of distilled water and added to the mixture.

➤ At last flavor was added.

➤ The weight of the gel was monitored continuously during manufacturing and finally it was adjusted to the 100 gm with distilled water.

Formulation development of edible gel

Alendronate edible gel formulations were prepared by varying concentrations of gellan gum from 0.1% to 0.5%, lower concentrations, i.e. 0.1 and 0.2% of gellan gum does not form a gel, and these two formulations were fluid in consistency. 0.3% and above concentrations of polymer showed good physical and rheological properties. As the polymer concentrations increased dissolution take more time due to the entrapment of drug in a polymer. So concentrations of polymer and cross linking agent are the main criteria in this formulation development.

S.No	Ingredients	EG-1	EG-2	EG-3	EG-4	EG-5	EG-6	EG-7	EG-8	EG-9	EG-10
1	Drug (mg)	100	100	100	100	100	100	100	100	100	100
2	Gellan gum (%)	0.1	0.1	0.2	0.2	0.3	0.3	0.4	0.4	0.5	0.5
3	PEG 400 (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
4	Citric acid (%)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
5	Mannitol (%)	30	30	30	30	30	30	30	30	30	30
6	Sucralose (%)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
7	Sodium citrate (%)	0.3	0.5	0.3	0.5	0.3	0.5	03	0.5	0.3	0.5
8	Methyl parabin (%)	0.2	0.2	0.2	0.2	0.2	02	02	0.2	0.2	0.2
9	Flavour (%)	2	2	2	2	2	2	2	2	2	2
10	Water (upto % w/w)	100	100	100	100	100	100	100	100	100	100

RESULT S AND DISCUSSION

Preformulation studies: API Characterisation

Description

Description of Alendronate (API)

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

Discussion

The results were found as per specifications.

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

Solubility

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

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.

Melting point of API's

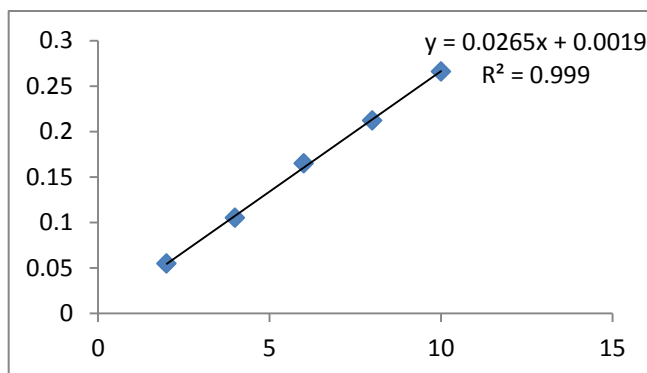| Material	Melting Point	Melting Point Range
Alendronate	$150^{0}c$	$150-151^{0}c$

Discussion

The Result was found to be within limits.

Calibration curve of Alendronate

Standard calibration curve of Alendronate in pH7.4

Concentration in mcg	Absorbance at 242nm ±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

$y = 0.0265x + 0.0019$
$R^2 = 0.999$

Standard graph of Alendronate

Discussion

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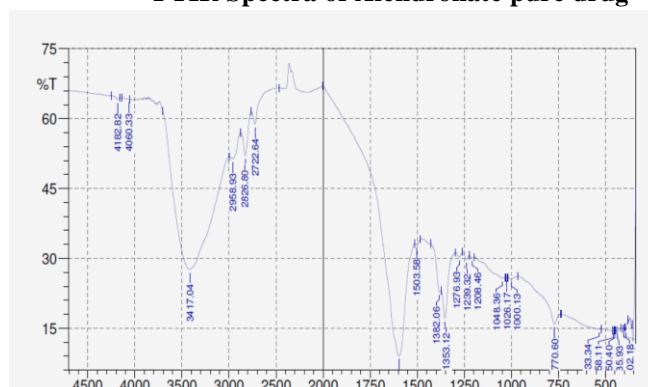 linearity in the concentration range of 5 - 30 µg/ml with a correlation coefficient of 0.999 and the slope was found to be 0.0265.

Drug-Excipient Compatibility Studies

The drug – excipient compatibility studies were carried out by FTIR.
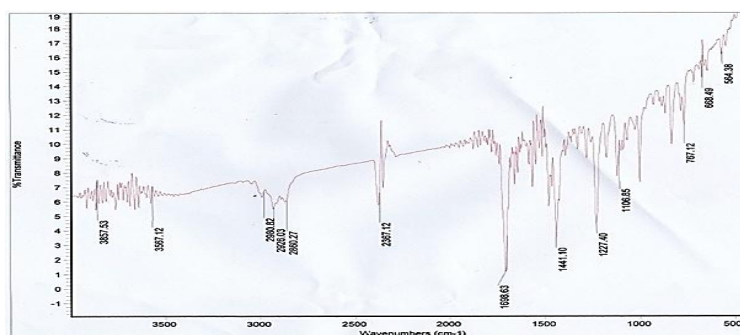
FTIR Spectra of Alendronate pure drug

FTIR of optimized formulation of alendronate edible gel

TABLE.1 Evaluative parameter of Edible Gel

S. No	Evaluation parametes	EG-1	EG-2	EG-3	EG-4	EG-5	EG-6	EG-7	EG-8	EG-9	EG-10
1	pH of gel	5.63	5.68	5.58	5.67	5.70	5.75	5.78	5.80	5.68	5.73
2	Appearance	NS,NG	NS,NG	NS,NG	NS,NG	NS,NG	NS,NG	SS,NG	SS,NG	S,SG	S,SG
3	Viscosity (cps)	512	837	1563	2089	3876	5026	5907	7023	8342	9681
4	Consisteny	---	---	--	--	-	+	++	++	+++	+++
5	Drug content	100	102	101	102	99	98	98	99	99	99

*NS- Non Sticky, NG- Non Gritty, SS- Slightly Sticky, S – Sticky, SG- Slightly Gritty
Indicates fluidity, +   indicates spoon thickness

Appearance

The results of the evaluation of Alendronate edible gel batches are shown in table no. 1. All the batches of edible gels were transparent in appearance. The gel of batches EG1, EG2, EG3, EG4, EG5 and EG6 were non-sticky and non-gritty while the gel of batches EG7 and EG8 were slightly sticky and non-gritty. EG9 and EG10 batches were sticky and slightly gritty. The non-gritty nature of the batches may be due to the suitable concentration of gellan gum and sodium citrate but EG10 was gritty due to higher concentration of gellan gum and sodium citrate.

Consistency

Gellan gum has a good gelling power, hence it can produce gels at low concentration. Table no.1 shows, batches EG1 to EG4 exhibited fluid like consistency while the gels of batches EG6 to EG10 were thick in consistency. As the consistency of gels depends on the concentration of the polymer, batches EG6, EG7 and EG8 had acceptable consistency. These visual inspection results are supported by the viscosity measurements.

Viscosity

Viscosity is the one important parameter which provides vital information during the optimization of the edible gel. The results of the evaluation of Alendronate gellan gum edible gel batches MG1-MG8 are shown in Table no.1.

Discussion

The viscosity of the batches EG1 to EG4 were low because of its fluid like consistency while the viscosity of the batches EG9 and EG10 were high because they were very thick in consistency. But, viscosity of batch EG6, EG7 and EG8 were near to in house specification and spoon thickness consistency. As batches EG9 and EG10 were thick in consistency, sticky and gritty, they failed to give a good mouth feel. The viscosity of the batches EG6, EG7 and EG8 were acceptable supported by their acceptable consistency. The consistency and viscosity of the edible gels are related to each other because both are dependent on the concentration of gellan gum, sodium citrate, and co-solute.

Effect of concentration of co-solute (mannitol and sucralose) on the viscosity and consistency of all the batches of the edible gel was same because it was constant in all the batches. It is clearly evident from the results that changes in the viscosity and consistency of soft gel are greatly because of change in concentration of gellan gum and slightly because of change in concentration of sodium citrate. Free carboxylate groups are present in the structure of gellan gum; therefore gellan gum is anionic in nature and thus it would undergo ionic gelation in the presence of both divalent and monovalent cations such as Ca^{++}, Mg^{++}, K^+, Na^+, and H^+ from acid. However, its affinity for divalent cations such as Ca^{2+} and Mg^{2+} is much stronger than monovalent such as Na^+ and K^+.

Therefore, gels of batch EG5 to EG10 were selected for further studies under drug content and in vitro dissolution studies.

pH

Discussion

The pH of the most stable Alendronate in the aqueous phase is in between 4 and 9. It is also reported that the apparent viscosity of gellan gum dispersion can be markedly increased by increase in both pH and cation concentration. Therefore, the pH of the formulated gels was adjusted and maintained in between 5 and 7 with the help of buffering agents such as citric acid and sodium citrate. The amount of citric acid was kept minimum, i.e., just to adjust the required pH. Sodium citrate was selected as a salt to contribute cation because it also act as sequestrant, buffering agent and helps in maintaining mechanical property of the gel. The pH of gels of batches EG1 to EG10 is shown in Table No.

Syneresis

Syneresis is one of the major problems associated with low acylated gellan gum gels. Syneresis means a contraction of gel upon standing and separation of water from the gel. Syneresis is more pronounced in the gels were lower concentrations of gelling agent is used. Syneresis was not noticed at room temperature probably due to binding of free water by co-solute. Batches EG6 to EG10 were not showing any syneresis but EG5 slightly showed syneresis.

Drug Content

The drug content of all batches of edible gel was within the acceptable limit.

Invitro Dissolution studies

Table. Drug release profiles of edible gel formulations

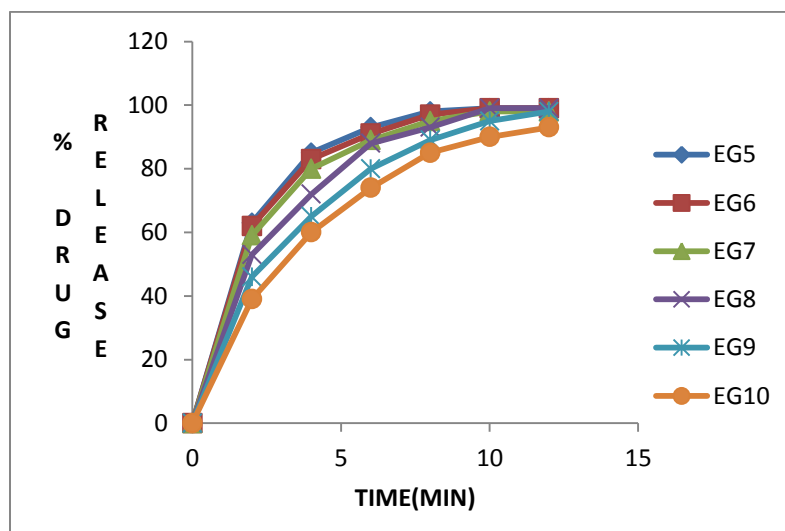| TIME (min)	EG-5	EG-6	EG-7	EG-8	EG-9	EG-10
2	63	62	59	53	46	39
4	85	83	80	72	65	60
6	93	91	89	88	80	74
8	98	97	95	93	89	85
10	99	99	98	99	95	90
12	99	99	98	99	98	93

FIGURE-1 Invitro drug release profile of edible gel formulations

Discussions

The results shown in table no. reveal that gels of the batches EG5 to EG10 were exhibited acceptable consistency and viscosity. Thus, they were subjected to dissolution study to draw any conclusion and their percentage drug release at different time intervals has been shown Results show that EG5 and EG6 had a good drug release, but the consistency is not good. EG7and EG8 showed good drug release and also good consistency in these two batches EG8 showed very good consistency and spoon thickness viscosity over EG7 batch and very similar drug release compared with EG7. There was no significant difference between release profiles of the EG7 and EG8, but the release profile of batch EG7 does not meet the spoon thickness consistency. Also, the viscosity of the batch EG8 batch showed good spoon thickness consistency compared to EG7 which may increase the mouth feel, thus batch EG8 was chosen as the optimized batch.

Stability studies

The results of short-term stability studies, shown in Table no., indicated insignificant changes in pH, viscosity, and appearance in the optimized formulation with time. Precipitation of alendronate in the soft gels was not observed in any of the gels. Also, synergesis was not observed in any of the samples at both temperatures. Therefore, it is recommended that edible gel should be stored at about 25°C.

Table. Stability data of optimized formulation EG8

	1st week		2nd week		3rd week	
At temperature(0-8⁰)	5.80pH	7023cps	5.76pH	7029cps	5.71pH	7031cps
At Room temperature*	5.78pH	7028cps	5.73pH	7032cps	5.70pH	7035cps

*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 (EDG) 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 4.3.

The EDG has shown increased Cmax value compared to ADR. The Cmax values of EDG and ADR are found to be increased. The enhancement in the Cmax from the EDG is 2.02 times higher compared to ADR. The AUC (0-inf) values are are also found increased in formulation EDG compared to ADR.

Table Mean Pharmacokinetic parameters for alendronate formulations in plasma after oral administrations to the rats

Parameter	EDG	ADR
Cmax (mcg/ml)	82.39	41.846
Tmax (hrs)	1.5	1.5
AUC (0-t) (mcg.hr/ml)	133.52	106.17

CONCLUSION

From this research it was concluded that EG8 formulation of alendronate edible gel was best in edible gel formulations.

In these edible gel preparations EG8 formulation of edible gel is very good due to its patient's compliance, yield, stability-storage requirements and along with these good properties edible gel shows the drug release profile.

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