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DEVELOPMENT AND EVALUATION OF MEDICATED CHEWING GUM OF *LACTO BACILLUS* SPOROGENES

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ABSTRACT

Dental plaque is a complex microbial community that develops on the tooth surface embedded in a matrix of polymers of bacterial and salivary origin. Then dental plaques were prevented/ cure by using the lactobacillus sporogenes microorganisms. The present work aimed to develop the medicated chewing gums using directly compressible Pharmagum-S and various polymers such as dibutyl phthalate, polyvinyl alcohol, paraffin wax and PVP K-30. Fourier transform infrared spectroscopy was confirmed the absence of any drug- polymers interactions. Twelve formulations (F1-F12) of medicated chewing gum tablets were prepared by using the various concentrations of polymers. Finally forms into tablets by using Cadmach 16 station compression machine by keeping hardness between 1-2 kg/cm$^{-2.}$ The prepared medicated chewing gum tablets were evaluated for thickens hardness, weight variation, friability, drug content uniformity, buccal absorption tests and *in-vitro* drug release studies.

Key Words:- Dental Plaque; Lactobacillus Sporogenes; Medicated Chewing Gum; *In vitro* drug release.

INTRODUCTION

The pharmacological active ingredients are formulated into varies dosage forms like tablets, capsules, inhalers etc. consider the physicochemical properties, pharmacokinetics and pharmacodynamic parameters and biopharmaceutical aspects of drug. An addition to MCG acts as confectionary role, chewing gum also has proven value as a delivers vehicle for pharmaceutical and nutraceutical ingredients, (Agarwal Ankit *et al*., 2012; Swamy N.G.N *et al*., 2012).

A medicated chewing gum is a solid, single dose preparation that is intended to be chewed to be in buccal cavity for a certain period of time, deliver the drug and which may contain one or more active pharmaceutical ingredients, (Vasudha Lakshmi S *et al*., 2014).

The use of medicated chewing gum is feasible in local treatment for different disease in oral cavity as well as treatment of systemic conditions. The most convenient and preferred route of administration to get raid onset of action in the intra oral route because of saliva, which delivers the drug to achieve local (or) systemic actions for a targeted tissues in the oral cavity. The intra-oral route of drug deliver avoids first-pass metabolism and ensure rapid systemic deliver with improved bioavailability of drug. Chewing gums can be retained in oral cavity for a prolong period of time and if the drug is readily absorbed across oral mucosa, chewing gum can provide a fast onset time for a systemic effect and the avoidance of gastrointestinal and hepatic first pass metabolisms of susceptible drugs, (Tanvee M. Deshpande *et al*., 2013).

Dental plaque is a complex microbial community that develops on the tooth surface, embedded in a matrix of polymers of bacterial and salivary origin. The dental plaque develops naturally on teeth, and forms part of the defense systems of the host by helping to prevent colonization of enamel by exogenous and microorganisms.

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The dental plaque is defined as the soft depositions that form the biofilm adhering to the tooth surface. The plaque is composed of organic, inorganic materials derived from saliva, gingival crevicular fluid, and bacterial production, (Introduction to dental plaque, 2014).

Lactobacillus sporogenes incorporated in medicated chewing gum, the Lactobacillus sporogenes is a gram positive, spore forming lactic acid producing bacillus. The organism requires a complexes mixture of organic substances for growth, including fermentation of carbohydrate and peptides. By the process of fermentation the bacteria break down sugar to create lactic acid. It also means that can germinate; creating spores that can provides vital health benefits. That why it is after use for in medicated chewing gum, for cavities and gingivitis, (Lactobacillus sporogenes Monograph, 2002).

Lactobacillus sporogenes may introduce into the granules of medicated chewing gum by direct compression method. There lactobacillus sporogenes containing medicated chewing gum was chewed in between the buccal cavity. It will release the drug in the presence of saliva it will enter into the gums to treat dental plaque, and various types of dental caries, gingivitis etc, (Lactobacillus Sporogenes Monograph, 2002).

Materials and methodology

Materials

Lactobacillus sporogenes was obtained as a gift sample from Macsur, pharma Pvt. Ltd. Puducherry. Pharmagum-S was purchased from thorab laboratories, Puducherry.

PVP K-30, magnesium striate, aerosil-200, sodium lauryl sulphate, aspartame, calcium carbonate (pharma grade) was purchased from drug India laboratories, Hyderabad.

Poly vinyl alcohol, dibutyl phthalate, paraffin wax-58-60°C (LR grade) was purchased from lab chemicals, Chennai.

Methods

Drug polymer compatibility studies

Compatibility of drug with excipients was determined by carrying out FTIR spectral analysis. FTIR spectrum of lactobacillus sporogenes, polyvinyl alcohol, Pharmagum-S, polyvinyl pyrrolidone K30 and physical mixture of drug and polymer were determined by using the shimadzu FTIR 8300 spectrophotometer using KBr dispersion method.

Preparation of medicated chewing gum

The medicated chewing gums containing lactobacillus sporogenes was prepared by directly compression method by excipients like PVP K30, PVA, Dibutyl phthalate, calcium carbonate, sodium lauryl sulphate, aspartame, magnesium stearate agents blends together with the help of suitable Pharmagum-S, it will form dry form (few drops of Dibutyl phthalate) added to the excipients. The dry mass passed through the sieve no 40 then obtains the uniform powder. The powder passed on the hopper with the help of upper and lower punches finally form a tablet of medicated chewing gum by using the 16 station punching machine by keeping the hardness 1-2kg/cm^{-2}.

Procedure for film forming coating of medicated chewing gums

The obtained lactobacillus sporogenes containing tablet was coated with the film former chemical. Weigh accurately 2% PVP K30, 0.05% dibutyl phthalate, 0.2% aspartame and 0.05% tween 80 taken in mortor triturated well and add few quantity of acetone, it will acts as a film former.

Thus tablets placed in the coating pan with the help of suitable sprayer, spray the film former solution onto get uniform distribution of film former medicated chewing gums.

Evaluation of medicated chewing gums

Pre-compression

Thickness: Ten chewing gum tablet of each batch were taken and its thickness was measured by individually by using vernier calipers.

Hardness: Five tablets were randomly picked from each formulation and mean and the standard deviation value were calculated. The hardness of medicated chewing gums containing 1-2kg/Cm^{-2}.

Weight variation: Ten medicated chewing gums were randomly selected and weighed and the mean weight was calculated.

Friability: The friability of the medicated chewing gum tablets was determined by using the Roche friabilator five tablets were weighed and put into the friabilator and set to rotate at 25 rounds per minute for about four minutes. The tablets were then removed and weighed again. The friability (F) is given by the formula.

$$F = 1 - \frac{W}{W0} \times 100$$

Content uniformity test: The drug content in each formulation was determined by triturated 20 MCG tablets

and powder equivalent to 1 gram of lactobacillus sporogenes sample was weighed in 250 ml volumetric flask containing 100 ml of saline and then make up to the volume. This was subjected to sonication for 10 minutes from this solution take one ml serially diluted with 9ml of saline upto get 10^6 dilutions.

The diluted 10^5 and 10^6 tubes were subjected to heat shock in water bath at 75°C for 30min. cool and to four plates (1ml each). Pour temporal GYEA media to the plates and incubate for 48 hrs at 37°C. Then the number of colonies was counted by using colony counter method.

Modified method for *In vitro* dissolution study for medicated chewing gum

In vitro dissolution study was performed by using USP-II basket disintegration test apparatus [lab Indian DT-100]. The equipment was in such a way to mimics the chewing action the bath temperature was maintained at 37°C±0.5°C, the prepared medicated chewing gums were soaked in 900ml of simulated salivary fluid in a beaker in which for 10 min. the chewing gum was swellon and became elastic in nature, then the gum was stressed the length of 10cm, one end was tied with glass plate which immersed into beaker the another end was tied with disintegration tube assembly. This mimics natural action, when disintegration tubes was moving up and down at a distance of 6cm. every 5min time interval the 5 ml of sample was withdrawn, it was replaced with fresh medium immediately.

The sample was further diluted in 10 ml and it is incubated at 40°C for 48 hrs in agar medium. The colonies formed were counted in calibrated for to dose.

RESULTS

Stability studies

The selected formulations were packed in their final containers and are tightly closed with the cap. They were stored at the stated conditions for three months. Samples were analyzed after 0, 15 and 30 days and they were evaluated for physical appearance, hardness, thickness, weight variation, friability, and *in-vitro* drug release rate.

Table 1. Formulation table of Lactobacillus sporogenes medicated chewing gum

Ingredient	All ingredients taken in milligrams(mg)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lactobacillus sporogenes	6	6	6	6	6	6	6	6	6	6	6	6
PVP K30	20	40	60	10	50	30	10	30	--	--	--	--
Polyvinyl alcohol	--	--	--	10	50	30	10	30	50	20	50	60
Paraffin wax	50	50	50	50	50	50	--	--	50	50	--	--
Calcium carbonate	100	100	100	100	100	100	100	100	100	100	100	100
Sodium lauryl sulphate	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	20	20	20	20	20	20	20	20	20	20	20	20
Aerosol	5	5	5	5	5	5	5	5	5	5	5	5
Aspartame	5	5	5	5	5	5	5	5		5	5	5
Pharmagum-S	To produce 1000mg of medicated chewing gum tablet											

*Dibutyl phthalate was used as quantity sufficient; Total weight of medicated chewing gum tablet is 1000mg.

Table 2. Evaluation parameters

F.Code	Evaluation parameters				
	Thickness (Mean±SD) (mm)	Hardness (Mean±SD)(Kg)	Friability% (Mean±SD) (%)	Average weight variation(mg)	%Drug content (Mean±SD)
F1	4.81±0.1	3.8±0.3	0.50±0.16	0.987±0.25	90±1.22
F2	4.74±0.3	3.7±0.4	0.47±0.32	0.992±0.22	92±1.12
F3	4.74±0.3	4.0±0.2	0.46±0.22	0.990±0.66	91±1.54
F4	4.82±0.3	4.0±0.3	0.49±0.19	0.996±0.70	95±1.16
F5	**4.73±0.2**	**3.7±0.3**	**0.40±0.22**	**0.996±0.83**	**99±1.76**
F6	4.80±0.4	3.7±0.1	0.36±0.19	1.010±0.70	93±1.62

F7	4.80±0.2	3.7±0.1	0.35±0.11	0.994±0.63	91±1.38
F8	4.80±0.2	3.9±0.4	0.29±0.14	0.996±0.69	97±1.58
F9	4.83±0.3	3.9±0.2	0.28±0.15	0.996±0.78	961.1.82
F10	4.83±0.5	3.9±0.5	0.25±0.17	0.995±0.72	98±1.43
F11	4.83±0.5	3.9±0.3	0.24±0.19	0.997±0.62	92±1.40
F12	4.83±0.3	4.0±0.3	0.24±0.18	1.015±0.30	91±1.33

Table 3. *In vitro* drug release

F.Code	Time (In minutes)					
	5	10	15	20	25	30
F1	8.99 ±1.42	13.78 ±1.31	21.98 ±1.61	30.96 ±1.56	41.81±1.75	49.76 ±1.23
F2	9.9 ±1.33	11.09 ±1.23	25.99 ±1.71	35.71 ±1.52	44.09 ±1.81	53.88 ±1.33
F3	10.98 ±1.22	19.33 ±1.42	26.01±1.32	38.02 ±1.87	43.99 ±1.67	56.01 ±1.43
F4	11.33 ±1.55	21.03±1.43	30.89±1.35	41.22±1.76	51.09±1.54	60.21±1.52
F5	14.88 ±1.56	26.26 ±1.43	37.82 ±1.23	46.23 ±1.24	57.98 ±1.88	69.88 ±1.23
F6	12.08 ±1.13	23.98 ±1.25	38.09 ±1.23	43.02 ±1.25	55.98 ±1.33	64.22 ±1.66
F7	10.02 ±1.27	24.08 ±1.25	34.03 ±1.37	45.09 ±1.66	54.33 ±1.52	65.33 ±1.54
F8	11.05 ±1.56	21.22 ±1.24	32.99 ±.55	43.22 ±1.45	54.99 ±1.87	63.01 ±1.23
F9	10.22 ±1.51	22.88 ±1.77	35.99 ±1.65	40.33 ±1.52	50.88 ±1.42	59.22 ±1.23
F10	12.55 ±1.66	25.02 ±1.25	30.22 ±1.44	44.99 ±1.24	52.98 ±1.65	63.22 ±1.26
F11	9.22 ±1.32	19.99 ±1.44	29.98 ±1.75	39.08 ±1.54	48.98 ±1.54	58.98±1.25
F12	11.98 ±1.51	23.11 ±1.24	30.98 ±1.54	40.78 ±1.52	50.98 ±1.42	60.98 ±1.43

Table 4. Physical appearance of optimized formulation after stability studies

Temperature and relative humidity	Days			Parameters
	0	15	30	
25±2°C/60%	No changes			Physical appearance
40±2°C/70%				

Table 5. Stability studies of medicated chewing gums best formulation F5

Number of days	Drug content (%)		Drug release (Number of colonies)	
	25±2°C/ 60%	40±2°C/ 70%	25±2°C/ 60%	40±2°C/ 70%
0	99.4	99.7	69.1	69.6
15	99.0	98.4	68.9	68.8
30	98.9	98.4	69.1	69.3

Figure 1. FTIR spectrum of lactobacillus sporogenes

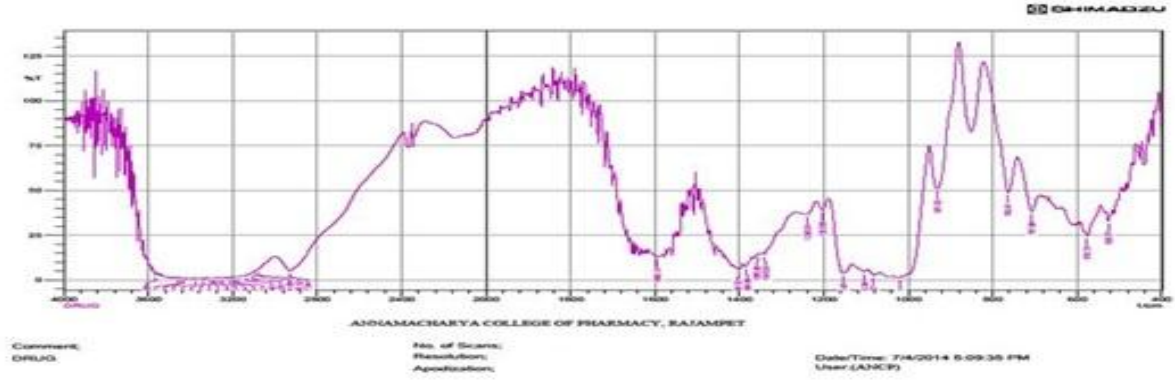


Figure 2. FTIR spectrums of lactobacillus sporogenes+ Pharmagum S

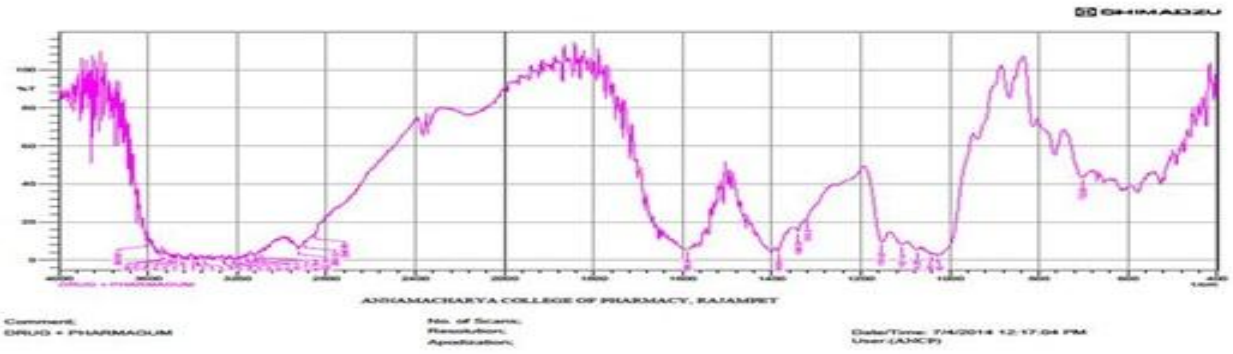


Figure 3. FTIR spectrum of lactobacillus sporogenes + PVA

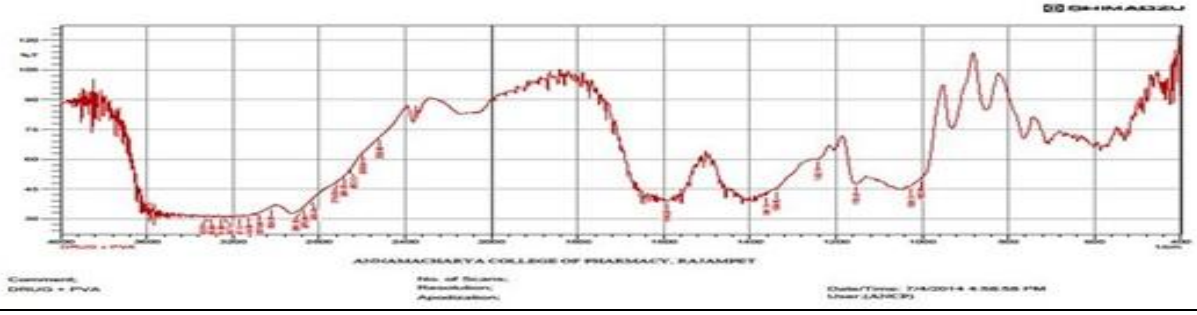


Figure 4. FTIR spectrums of lactobacillus sporogenes + PVP k30

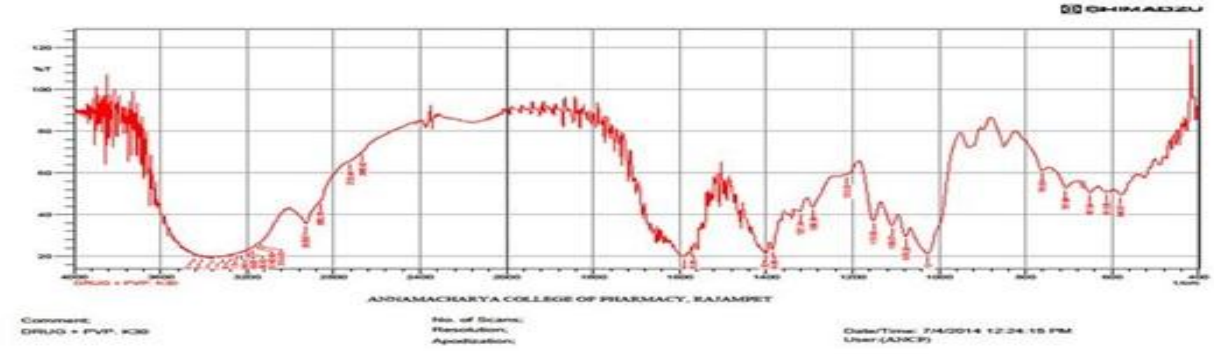
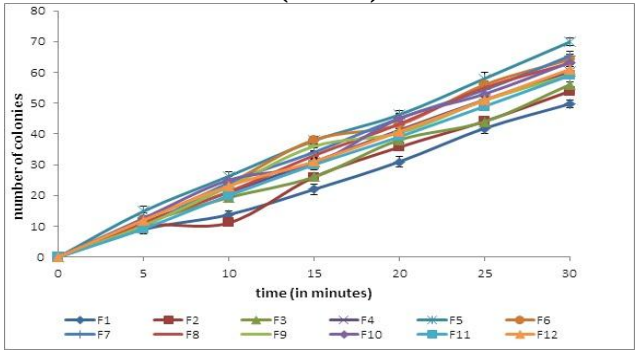


Figure 5. Modified method for in vitro dissolution study for medicated chewing gum

Figure 6. Comparison of cumulative drug release pattern (F1-F12)



DISCUSSION

Preformulation is an investigation of physicochemical properties of drug substance, individually as well as in combination with excipients. Before starting the formulation procedure, the selected drug polymers were evaluated for physical appearance, flow properties and derived properties. Satisfactory results were obtained in all the preformulation parameters.

Drug polymer compatibility studies were performed by FTIR method the spectra of lactobacillus sporogenes, Pharmagum-S, Polyvinyl alcohol, polyvinyl pyrrolidone K30 alone and prepared formulations of drug with above polymers were measure and interpretated. The IR spectra were depicted as figure 1-4. The IR spectra of drug and polymer alone and prepared formulations had shown no significant interactions between drug and polymer. An interpretation value indicates that there was no chemical interaction between drug and other excipients.

The physicochemical evaluation studies were performed by using the parameters such as thickness, hardness, friability, weight variation, drug content, for medicated chewing gum formulation. The values are given in table 2.

The thickness of MCG was in the range of 4.73 to 4.83mm. Hardness of MCG was maintained in the range of 3.7 to 4.0. Friability of MCG was maintained in the range of 0.24 to 0.49%. Weight variation of MCG was maintained in the range of 0.987 to 1.015 mg.

In vitro drug release study revealed that the medicate chewing gum of F5 has shown highest percentage of drug release (69.88±1.23) at end of 30 minutes this might be due to presence of adequate concentration of polymer such as Dibutyl Phthalate, Polyvinyl alcohol, polyvinyl pyrrolidone K30, paraffin wax 58-60°C, Pharmagum S.

Overall observations from different evaluation studies such as drug-polymer interaction, evaluation of powder, physicochemical parameters and in vitro drug release were carried out on all medicated chewing gum of lactobacillus sporogenes, the F5 has shown optimum results. Based on the obtained results the best formulation was subjected from further stability studies. The stability study was conducted as per ICH guidelines for the period of one month at various accelerated temperature and humidity conditions of 25°C/60%RH, 40°C/75%RH.

The formulations were evaluated for different parameters like physical appearance, hardness, friability, weight variation, thickness, drug content, percentage of drug release. The results are shown in the table 5.

The stability data showed that there no change in the appearance of the medicated chewing gum indicating that the formulation were stable at all the conditions to which they were exposed.

CONCLUSION

It was concluded that there was no interaction between the drug and polymer compatibility, which is analyzed by FTIR. The lactobacillus sporogenes incorporated into medicated chewing gum the microscopic technique and qualitative for lactic acid production it gives positive results. The physicochemical evaluation studies like thickness, hardness, weight variation, friability and drug content were performed. Among the 12 formulations the F5 formulation shows best results of *In vitro* drug release (14.88±1.56 to 69.88±1.23), the polymers like Pharma gum- S, Dibutyl phthalate, and polyvinyl alcohol and PVP k30 facilitated the release of drug from gum base.

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