Development And Evaluation of a Novel Herbal Chewable Tablet for Tobacco and Smoking Cessation

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Abstract*— Tobacco addiction is one of the leading causes of disabilities and mortality. Addicts struggle with nicotine addiction and withdrawal symptoms. This study aimed to develop and test herbal chewable tablets, taking into account their pharmacological properties as an herbal treatment for reducing nicotine dependence using Areca Nut and Cinnamon, and their identification was done by Thin Layer Chromatography (TLC) and in the case of Areca Nut Total, Phenolic Content was also carried out. Flow property of powder was found to be fair and poor compressibility of powder leads to the selection of the Wet Granulation method of Tablet preparation with Non-sugar sweetening agent Stevia and peppermint oil as flavoring agents. Initially, the fair flow property was enhanced in this study by comparing various granulation processes via different batches of Wet granulation using Lactose Monohydrate, Dry granulation using Pregelatinized Starch (Starch 1500), in Direct Compression using Microcrystalline cellulose powder (MCCP) and Polyvinylpyrrolidone (PVP) K30. The optimized formulation, i.e. batch with Lactose Monohydrate and PVP K30, was incorporated with varying concentrations of binders and the batch with 17% binder concentration showed the best results. Various post-compression parameters were evaluated for the prepared tablets. Tablets have been evaluated for weight variation test in which optimized batch showed results within pharmacopoeial limits, with 0.25% friability, with 2.25 kg/m2 hardness; the time required for complete chewing was found to be an acceptable limit. This preparation is a stable, solid dosage form, and it revealed that the composition ratio of ingredients of herbal tablets does not affect the stability parameters. This formulation was also compared with the other marketed chewable tablet formulation and showed all the required results necessary for chewable tablet formulation.

Indexed Terms-- Chewable tablet, Herbal formulation, Nicotine dependency, Tobacco and Smoking Cessation.

I. INTRODUCTION

Tobacco is the leading reason for preventable cancers. United Nations agency calculable around 1.27 billion tobacco users worldwide. Tobacco consumption alone accounts for nearly 5.4 million deaths per annum, and one billion folks could die during this century if global tobacco consumption remained at the present levels [1]. Nicotine is an alkaloid present in plants that mainly acts on the cholinergic receptor, which causes dependency syndromes and makes a person addicted [2]-[3]. Marketed nicotine products are cigarettes, nicotine gum, smoking patches, and e-cigarettes [4]. Nicotine causes real addiction, indicating users are habitual to craving the substance, and psychological, indicating users consciously desire nicotine's impacts. It can cause various acute and chronic diseases like lung cancer, chronic bronchitis, emphysema, etc.[5]. NRT is the most common medication to assist in quit attempts [6]. The use of herbal plants has been indicated for the treatment of nicotine. Ghani et al. showed the effect of betel quid chewing behaviour in Malaysian adults and discovered gender and history of smoking as the factors that influence the development and cessation of this habit. [7] Areca nuts are alternative to nicotine chewing Winstock et al.

have reported a dependence syndrome associated with areca nut chewing. [8] By consuming betel nuts and cinnamon, a person refrains himself from chewing tobacco and smoking, which improves social life. According to Paulino et al., Chamorro, Palauan, and Yapese chewers of betel quid are proud of their practice since it promotes social ties. It also aims to pass on the habit to future generations. [9] Cinnamon zeylanicum has been reported to make the taste of tobacco unpalatable thus reducing its craving. [10] There are numerous synthetically marketed formulations for preventing nicotine addiction. It includes nicotine gums, transdermal patches, nasal spray, etc. however they have some limitations; likewise, radio metabolism in the liver, skin irritation action and accurate dose ejectment is not achieved. Tablets are solid preparations containing a single dose of one or more active substances and are usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole after being chewed, some are dissolved or dispersed in water before being administered, and some are retained in the mouth where the active substance is liberated.[11] Because of their ease of self-administration, compactness, and ease of manufacture, tablets are the most extensively used dosage form. However, it may be difficult for juvenile and geriatric people to ingest it. To overcome this problem, in recent years, increasing attention has been focused on formulating chewable tablets that are intended to dissolve or disintegrate rapidly in the mouth. Tablet disintegration has been considered the rate-limiting step in faster drug release.[12] Recent breakthroughs in Novel Drug Delivery System (NDDS) attempt to improve drug molecule safety and efficacy by producing a convenient dosage form for administration and improving patient compliance. Tablets are the most widely utilized oral dose format. A novel tablet concept that offers ease of oral administration and increased patient compliance is the chewable tablets disintegrating from the mouth itself.[13] The main benefit is that the absorption and start of therapeutic effects are faster. This formulation has the extra benefit of a speedier onset of action than a regular compressed tablet. [14] The properties of the chewable tablet, such as porosity, hardness, and ability to chew after being swallowed, are necessary to investigate during manufacturing which decides the product performance. As defined in USP, chewable tablets must be chewed or crushed before swallowing to avoid choking and ensure the release of the active ingredients. Jyoti Dahiya et al. have told that the core is composed of an insoluble gum base like fillers, waxes, antioxidants, sweeteners, and flavouring agents. A flavouring agent is included to make it more palatable.[15] Designing the chewable tablets has helped reduce nicotine dependence as it has better bioavailability, improved patient acceptance, no need for water for swallowing, and can be used as a substitute for liquid dosage forms where the rapid onset of action is needed, absorption of the drug is faster, the large size of the dosage form is difficult to swallow.

II. MATERIALS AND METHODS

Material:

Seeds of *Areca catechu* Linn and the inner bark of the coppiced shoots of *Cinnamomum zeylanicum* powders were prepared using a mixer grinder and were obtained from Yucca Enterprise. Lactose, PVP K30, Talc, Magnesium, and Stevia were obtained from Rankem.

Identification of Herbal Drug (API) by Thin-layer Chromatography (TLC)

Areca Nut TLC: was done by densitometry estimation of epicatechin using pre-coated plates of silica gel 60 Fast (E. Merck) of uniform thickness of 0.2 mm and Solvent system Toluene: Ethyl acetate: Methanol: Acetic acid (2.7: 6.0: 1.0: 0.3) was taken. Identification was made by spraying the plate with anisaldehyde - sulphuric acid reagent followed by heating at 100 till the colored bands appeared, and scanning was done at 455 nm after derivatization. The test solution was prepared by macerating 1.0 g of powdered drug in methanol (2 x 10 ml) for 24 h and then filtering the solution, and filtered extracts were evaporated to dryness and then dissolved the residue in 10 ml methanol. The standard solution was prepared by dissolving 25 mg of standard (-) - epicatechin in 25 ml of methanol in a volumetric flask, and from this stock solution, standard solutions of 100 to 500 µg/ ml concentrations were prepared by taking aliquots (10 to 5.0 ml) of stock solution to 10 ml volumetric flasks and adjusting the volume to 10 ml with methanol. [16] Cinnamon TLC was carried out by extraction of essential oil from the dried inner stem bark by taking

100 g dried inner stem bark in a 21 round-bottomed flask by adding 11 glasses of water into it and was subjected to hydro distillation in a Clevenger's apparatus for 4 h and the volume of the oil collected was noted and using this oil for the GLC (Gas Liquid Chromatography) analysis, and quantitative estimation of cinnamaldehyde was done. Upon applying five microliters of the test solution and five microliters of standard solution on a precoated silica gel, 60 F254 TLC plate (E. Merck) of uniform thickness (0.2 mm) was developed, and the plate in the solvent system to a distance of 8 cm and Solvent system Toluene: Ethyl acetate (19.5: 0.5) was used. Plates were observed after spraying with anisaldehyde- sulphuric acid reagent and heating the plate at 105 ° C for 5 min. The standard solution was prepared by dissolving one microliter of cinnamaldehyde in 1 ml of chloroform. [17] The test solution was prepared by taking 2 g of powdered drag in a 100 ml stoppered conical flask and 20 ml of n-hexane: chloroform (1:1) mixture was added into it and upon shaking the mixture at regular intervals of 1h for 6 h and keeping overnight extract was removed keeping solvent under reduced pressure and then dissolving the residue in 2 ml of chloroform to make the test solution.

Determination of total phenolic content

The Areca nut is a tannin-containing compound, so the Total Phenolic Content was carried out. The reaction mixture consisting of 1ml of extract (Areca nut) and 5ml of distilled water was taken in a volumetric flask. 0.5 ml of the *Folin–Ciocalteu* reagent was treated with the mixture and shaken well. After five minutes, 1.5 ml of 20% Na_2CO_3 solution was treated with the mixture. The volume was made up to 10ml with distilled water. A set of standard solutions of Gallic acid (10, 20, 30, 40, and 50 µg/ml) were prepared in the same manner described above. The mixture was incubated for 2hrs at room temperature, and the absorbance was taken at 750nm by UV spectroscopy (UV-1800-Shimadzu). [18]

FT – IR spectra of Pure API and Final Formulation

To identify the API in the finished formulation, the FT-IR spectra [INFRA 3000 series-Shimadzu] were carried out, the various peaks were observed and matched, and the different functional groups were identified and matched with the standard peak. Corresponding to the standard, functional groups like alcohols, aldehydes, esters, phenols, hydrocarbons, etc., have been identified.

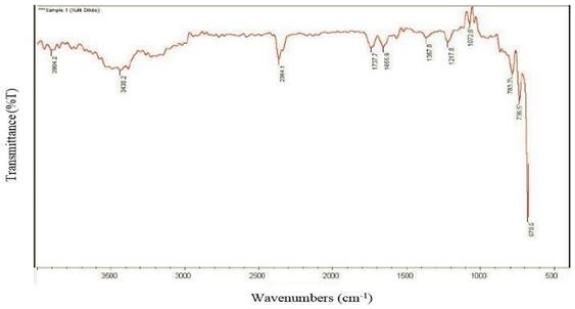

Fig. 1: Spectra of Pure Areca Nut[19]

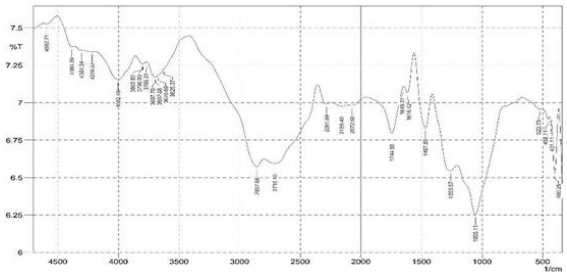

Fig. 2: Spectra of Formulation

Table 1: Functional Group for FTIR spectra of Formulated Tablet

Functional Group	Standard Wave no (cm^{-1})	Sample Wave no (cm^{-1})
C=C (Aromatic)	1600 and 1475	1616.42 and 1467
-OH (Alcohol)	3650-3600	3625.37
C-0 (Alcohol)	1300-1000	1259.57
N-H (Bending)	1640-1690	1649.21
COOR (Ester)	1750-1730	1744.69
O-H (Acid)	2400-3400	2710.1
CHO (Aldehyde)	1740-1720	1744.69
CH_3 (Alkanes)	3000-2850	2857.66 (Starching)
CH_2 (Bending)	1465	1467.89
O-H (Phenol)	3610-3640	3625.37

Pre-compression Parameters of Pure drug and granules blend [20][21][22][23][24]

Angle of repose: Determined by using the funnel method. In a funnel, accurately weighed granules were placed, and the funnel's height was adjusted so that the funnel's tip just touched the heap's top. The granules were allowed to flow out of the funnel onto the surface freely. The diameter of the powder cone was measured.

Loose bulk density (LBD): A weighed quantity of grains is poured into a graduated cylinder, and the volume and weight are measured.

Tapped bulk density (TBD): A graduated cylinder containing a known mass of granules is used to determine this. At two-second intervals, the cylinder was permitted to fall under its own weight onto a hard surface from a height of 10 cm. The tapping kept going until there was no more change in volume.

Hausner's ratio: It is the measurement of the drug's frictional resistance. The optimal range is between 1.2 and 1.5.

Compressibility index: The Compressibility index of the blends was determined by Carr's compressibility index.

Loss on drying: 1 g of granules was placed in a small weighing bottle with a dry glass stopper. The contents were uniformly distributed throughout the drying chamber. To attain a constant weight, the stopper was removed from the bottle, and the contents were dried for a given duration.

III. DEVELOPMENT OF FORMULATION

As the powder was poorly compressible, selecting the method for tablet preparations and seeing the convenience for small-scale preparations, the wet granulation method was selected for table preparations. Drugs and excipients were accurately weighed and mixed properly. Fillers & binder added before granulation into drug-excipient powder mixture. Then binder solution of PVP in Isopropyl alcohol was added to the drug excipient mixture and mixed it properly, and made into granules by passing through a 10# sieve. Then granules were allowed to dry in the oven. Dry granules were then sieved through a 40/60 # sieve. Then granules were mixed with lubricant and glidant. Then granule mixture is punched into the tablet with an 11.5 mm punch using a rotary tablet machine (Rimek Mini Tablet press punching machine). [25]

Preparation of Herbal Chewable Tablet

Tablet granules were prepared using isopropyl alcohol with different compositions of herbal drugs, using Polyvinylpyrrolidone (PVP) K30 as the binder, Lactose monohydrate as filler, Talc as a lubricant, magnesium stearate as a glidant, and stevia as a sweetener and peppermint as a flavoring agent. The formulations were coded as F1, F2, F3, F4, F5, and F6. (Table 2)

Table 2: Formulation of Herbal Chewable Tablet

Dry Powder (mg)	F1	F2	F3	F4	F5	F6
Areca Nut	200	195	190	200	190	200
Cinnamon	100	95	90	100	95	90
Lactose	95	105	105	90	115	100
PVP K_{30}	80	80	90	85	75	85
Magnesium Stearate	5	5	5	5	5	5
Talc	10	10	10	10	10	10
Stevia	10	10	10	10	10	10
Peppermint Oil	2-4 Drops	2-4 Drops	2-4 Drops	2-4 Drops	2-4 Drops	2-4 Drops

Power blends were compressed to 500 mg tablet on hand rotating single punch tablet presses using 11 X 8 mm punch set with appropriate compression pressure. The granules were mixed with talc and magnesium stearate before punching, the die cavity was adjusted for required weight, and the granules were punched into tablets. Even after this, there was a hardness issue with the tablet, and tablet defects were observed, so

due to these, it became friable, and so three different concentrations of the binders were taken, i.e., 80, 85, and 90 mg in 500 mg of tablet respectively and the blend was prepared, and tablet was formed. The best results were obtained in the batch having 85mg of the binder, i.e.17% of the total weight of the formulation. This batch had the proper hardness and even least friable, so this batch was optimized, i.e., the F4 batch was selected as the final optimized batch.

Post Compression Evaluation Parameters [26][27]
Thickness: Thickness was determined using a Vernier calliper. Ten tablets from each batch were used, and the average value was calculated.

Hardness: Hardness was measured with the Monsanto tablet hardness tester. The hardness (crushing strength) of three tablets per batch was determined, and the mean value was calculated.

Weight Variation: The average weight was obtained when twenty tablets were randomly chosen. The average weight of each tablet was compared.

Friability: Friability of the tablets was determined using the Roche friabilator (Erection and Instrumentation Engineers). 20 tablets were utilized to measure friability. The device was operated at 25 rpm for 4 minutes. Tablet weight was measured before and after the friability test.

Stability: The stability of a chewable tablet formulation is important mainly for the safety of the consumer and maintenance of quality over its shelf-life. It is also important to avoid economic losses to the manufacturer and comply with regulatory requirements. The result of stability testing guides the establishment of storage conditions and shelf-life of the product. Stability studies were carried out as per ICH guidelines for the long-term, intermediate and accelerated studies. [28]

IV. RESULT AND DISCUSSION

Thin Layer Chromatography was performed to estimate the active constituents present in the API. So separately, the TLC has been performed for both Areca Nut having epicatechin as marker and Cinnamon having cinnamaldehyde as marker were identified, and the Rf value for Areca Nut was found to be 0.55 having the brown color corresponding to the standard peak of Areca Nut, and that of Cinnamon was found to be 0.71 having a violet color corresponding to the standard peak of Cinnamon.

Table 3: TLC of Standard Solution of Areca catechu and Cinnamon [15]

Rf Value	Color of the Band of Areca Catechu	Rf Value	Color of the Band of Cinnamon
0.08	Brown	0.16	Pink
0.13	Brown	0.26	Light Pink
0.24	Brown	0.44	Greyish Black
0.29	Brown	0.82	Pink
0.53	Brown {(-) Epicatechin}	0.85	Violet

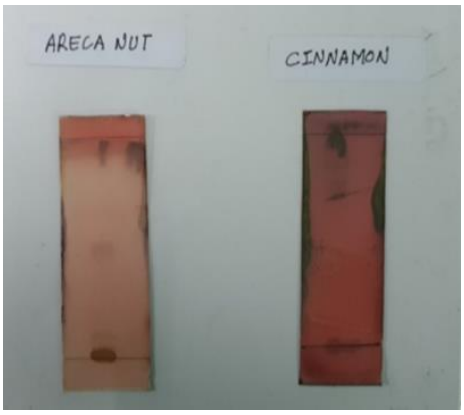

Fig. 3: TLC of Areca Nut and Cinnamon Test Solution

Initially, Standard Gallic acid was taken, and in Shimadzu UV spectrophotometer, its calibration curve was taken as shown in fig.4, and then the extract of the Areca nut was taken. At different concentrations, the spectra were taken and based on their reading, as shown in Table 4, the calibration curve was plotted, and the total phenolic content of areca nut extract was 75.5 mg tannic acid equivalent/g.

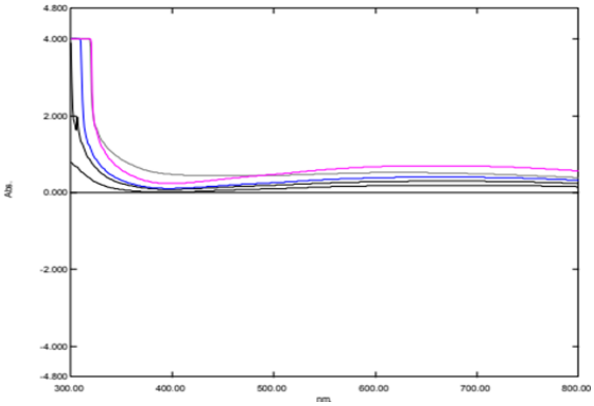

Fig. 4: Gallic Acid UV Spectra [17]

Table 4: Total Phenolic Content

Concentration (mcg/ml)	Absorbance	Volume of Galic acid in (ml) For test	Concentration (mcg/ml)
1	0.229	1	0.03
2	0.404	5	0.15
3	0.585	10	0.3
4	0.771	100	3.0
5	0.998	200	6.0

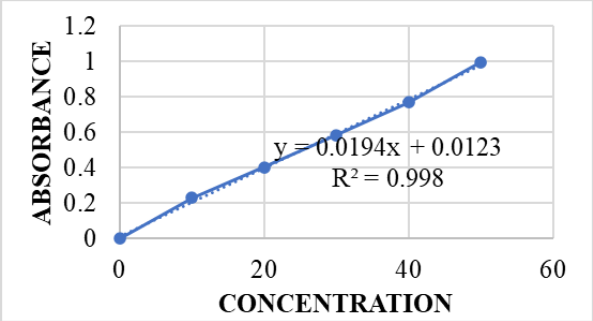

Fig. 5: Calibration Curve for Total Phenolic Content

Table 5: Flow property of Pure API Powder

Material	Angle of repose (In degrees) (n=3)	Bulk density, (g/cm^3) (n=3)	Tapped density (g/cm^3) (n=3)	Hausner's ratio (n=3)	Carr's index (%) (n=3)
Areca Nut	37	0.65 ± 0.02	0.71 ± 0.152	1.10 ± 0.004	9.47%
Cinnamon	31	0.45 ± 0.02	0.51 ± 0.152	1.15 ± 0.005	12.94%

Table 6: Flow Properties of Granules

Parameters	F1	F2	F3	F4	F5	F6
Angle of repose (In degrees) (n=3)	36	35	34	37	34	36
Bulk density (g/cm^3) (n=3)	0.66 ± 0.029	0.67 ± 0.015	0.66 ± 0.025	0.68 ± 0.02	0.65 ± 0.028	0.64 ± 0.02
Tapped bulk density (g/cm^3) (n=3)	0.71 ± 0.152	0.71 ± 0.152	0.71 ± 0.152	0.71 ± 0.152	0.71 ± 0.152	0.71 ± 0.152
Hausner's ratio (n=3)	1.07 ± 0.015	1.09 ± 0.019	1.11 ± 0.004	1.10 ± 0.029	1.09 ± 0.015	1.08 ± 0.020
Carr's index (%) (n=3)	9.46±1.19	9.50±1.24	9.43±1.07	9.47±1.1.02	9.52±1.08	9.50±1.14
Loss on Drying (%) (n=3)	0.96 ± 0.007	0.99 ± 0.012	0.980 ± 0.002	0.95 ± 0.019	0.95 ± 0.009	0.96 ± 0.012

The angle of repose for the physical mixture of Areca nut was 37° and was compared with IP standards which indicate fair flow property. The bulk density for the physical mixture of Areca Nut was found in the range of 0.65 ± 0.02 g/ml. The tapped density for the physical mixture of Areca Nut was found in the range of 0.71 ± 0.152 g/ml. Hausner's ratio for the physical mixture of Areca Nut was found in the range of 1.10 ± 0.004, and Carr's index for the physical mixture of Areca Nut was 9.4%. So as the flow was fair and compressibility was poor so various batches with different excipients and different methods of Tablet preparation were done and based on the feasibility and improving the flow property of granules Wet Granulation Method was selected for Tablet preparation. As the flow property was improved the blend was compressed to form tablets and its various batches were prepared with varying concentrations of binders based upon the required hardness of the formulation the batch which satisfied the criteria was optimized. While formulating, the different concentrations of the binders were taken ranging from 75mg to 90 mg as shown in table 2 and it was found that the tablet containing 85 mg of the binder i.e. 17% of the total formulation gave the required tensile strength and hardness to the tablet. After which various post-compression parameters were carried out.

Table 7: Post Compression data of different batches

Batch	Thickness(cm) n=3	Weight Variation(g)n=3	Hardness (kg/m^2) n=3	Friability (%) n=3
F1	0.49 ± 0.05	0.48 ± 0.0289	2.00	0.46± 0.007
F2	0.47 ± 0.03	0.49 ± 0.0289	2.50	0.47 ± 0.007
F3	0.44 ± 0.04	0.46 ± 0.0404	2.20	0.38 ± 0.013
F4	0.48 ± 0.03	0.50 ± 0.0289	2.25	0.26 ± 0.002
F5	0.42 ± 0.03	0.49 ± 0.0058	2.40	0.45 ± 0.003
F6	0.50 ± 0.03	0.48 ± 0.0289	2.45	0.47 ± 0.002

From the above evaluation parameters and based upon the tensile strength of tablet, the F4 batch gave the desired and necessary results, and hence out of the given six batches, the F4 batch was optimized and was selected as the final batch for the formulation, and its stability testing was done as per ICH guidelines. The taste of the Chewable Tablet was checked, and it tastes sweet. It had a characteristic odor and produced a lingering cool effect on the tongue, and the color is coffee.

Table 8: Stability Studies as per ICH guidelines

Study	Storage	Color	Odor	Texture	Weight Variation (g)	Hardness (kg/m^2)
Long Term	25±2°C and RH 60% ±5	NC	NC	NC	0.48	2.1
Intermediate	30±2°C and RH 65% ±5	NC	NC	NC	0.46	2.0
Accelerated	40±2°C and RH75% ±5	NC	NC	NC	0.45	1.98

No marked changes in color, odor, texture, average weight, and hardness were observed in optimized the Batch, i.e., F4.

CONCLUSION

The present studies deal with the preparation of the herbal chewable tablet dosage form. Identification of API was carried out by TLC and total phenolic content. Granules were prepared via wet granulation and evaluated for pre-compression parameters like angle of repose, Carr's Index, and Hausner's ratio, and it was found good flowability as well as the compressibility. All tablet formulations were subjected to various evaluation parameters like Weight variation, hardness, and friability and the results obtained were within the Pharmacopoeia limit. Finally, a stability study of the formulation was carried out as per ICH guidelines and no marked change was observed in the general appearance of the tablets like color, texture, average weight, hardness, and friability in all the formulations. FT-IR spectra have been taken out for the formulation and the pure API, and it identifies the various functional groups like alcohol, carbonyl, hydrocarbons, esters, and acidic functional groups. By consuming these tablets, slowly and steadily, the person refrains himself from chewing tobacco and smoking. This study concluded that using traditional knowledge and the recent technologies and medicinal plants have application in the preparation of cost-effective tablet formulations to improve stability, consumer compliance, and acceptability.

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