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Thermal Stability and Drug-Excipient Compatibility Studies of Peppermint and Caraway Oils for Formulation of Chewable Tablets

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Drug delivery is highly innovative in terms of materials to assist delivery, excipients and technology which allows release of drugs in a manner desired for improved therapeutic efficacy, safety and patient compliance. Among many other factors cost of non-compliance alone estimated to be *ca.* 13 % of total healthcare expenditure per year. Providing patients with simplified oral medications that will improve compliance and thus result more effective treatment has been one of the major drivers for innovation in the oral controlled drug delivery market. In this connection the oral chewable tablets were investigated as possible alternative formulations for the delivery essential oils known to be effective for the treatment of various ailments and have been administered traditionally as aromatic waters, elixirs, or more recently in the soft gelatin capsules. Now-a-days when people are increasingly taking several products as breath freshener, the present concept to formulate these essential oils in the form of chewable dosage forms so that these can be administered for such therapeutic uses and can provide simultaneously breath freshness to consumer in view of the urban lifestyle. This paper discuss the thermal stability and drug-excipient compatibility studies of peppermint and caraway oils for formulation of chewable tablets as alternative dosage form towards improved patient compliance and market viability.

Key Words: Essential oils, Chewable tablets, Thermal studies, Drug delivery.

INTRODUCTION

Drug delivery is one of the frontier areas of research in the field of science and technology[1]. Drug delivery systems [DDS] play a vital role in performance of therapeutic moiety *in vivo* and its commercial viability; moreover the type of drug delivery system that will be chosen to meet a given clinical need will depend on a number of factors[2]. These include the route of administration, time required for onset of action, stability and physico-chemical properties of the drug, amount of drug delivered to the site of action through a dosage form, potency, safety profile and biological half life of the drug, need for localizing the effect of drug administered to a particular organ or tissue, cost of goods and ability of medicament to get absorbed from site of administration[3]. The essential oils have been used for the treatment of various ailments externally and internally, described in the pharmacopoeia, traditional systems of medicine and reported in folk medicine[4]. The peppermint and caraway oils too are having vide therapeutic utility for the treatment of non-ulcer dyspepsia, flatulence, gastritis also have antispasmodic, carminative, analgesic, flavouring properties[5-8]. In India the two oils are used widely in different forms by common people for the relief of dyspepsia, gastric spasm and carminative purpose in the form of aromatic waters, soft gelatin capsules or as elixirs, moreover the people are taking several products as breath freshener. This approach of formulating these essential oils as chewable tablets enables the patient friendly administration of these oils for therapeutic purposes and provides simultaneously breath freshness to consumer in view of the urban lifestyle increasingly demanding the use of chewables as refreshing agents. This can be a tool for improved patient compliance which has been otherwise a critical problem in therapeutics. In a recent study New England Healthcare Institute reported[9], the cost of non-compliance in US alone was estimated to be as much as $290 billion or 13 % of total annual healthcare expenditure. Providing patients with simplified oral medications that will improve compliance and thus result more effective treatment has been one of the major driver for innovation in the oral controlled drug delivery market[10].

Chewable dosage forms have long been the part of pharmacist's armamentarium for administration of medicaments and delivery of essential oils through chewable tablets

offers better palatability, by-passing first pass metabolism, better bioavailability through enhancing dissolution steps, patience convenience for the no need of water for swallowing, rapid onset of action, improved patient acceptance (especially in pediatrics) through pleasant and product distinctiveness from a marketing perspective, improved entrapment stability and comparative low production cost[11]. To formulate any medicament into new dosage form, a series of preformulation investigations are required. Assessment of stability and drug-excipient compatibly studies constitute an important part of such preformulation investigations which are explored in comprised study for peppermint and caraway oils.

EXPERIMENTAL

Peppermint oil (Arora Pharmaceuticals), caraway oil (Siva Aromatics), mannitol (Getec Ltd), dicalcium phosphate (Enar Chemie Ltd), hydroxy propyl cellulose (Dow Chemicals), Syloid (W.R. Grace), cabosil (Cabot Sanmar Ltd), stearic acid (Mallinckdrot), magnesium stearate (S. Kant Healthcare), Fl Novamint Peppermint 5060 40T (Firmenich), Fl Taste Mask Powder 501482 T P0424 (Firmenich), ProSolv SMCC50 (Penwest), nutra sweet powder (NutraSweet), Carbopol 974 P NF (Noveon).

Planetary mixer (M/s Dito Sama, France), Tablet friability test apparatus (Arkey Labtromix, India), Monsanto tester (Aarkey Labtromix, India), Fluidized bed dryer (Retsch Gmbh & Co, Germany), USP - Tapped density apparatus (Electrolab, India), Rotatory tablet compression-machine (Rimek, India), Mechanical stirrer (Remi, India), Digimatic caliper (Mitutoyo, Japan), Humidity chamber (Thermolab, India), 784KFP Titrino (Metrohm), HPTL Chromatography (Camag, Switzerland), I.R. moisture balance (Guru Nanak Instrument, India), Clarus500 Gas Chromatograph (Perkin Elmer).

Identification and quantification of marker: Identification of the marker compound was carried out by high performance thin layer chromatography (HPTLC) and the identified markers *viz*., menthol and carvone were quantified further using HPTLC and gas chromatograhy as described by Sachan *et al*.[12].

Standard preparation: Accurately weighed 50 mg of carvone was 50 mg transferred into 10 mL volumetric flasks, respectively. Toluene was added in small portion to dissolve the sample and volume was made up. Menthol and carvone were further diluted to 300 mg/mL.

Chromatography condition: The GC experiments were performed on a clarus-500 gas chromatograph. The sample was run in the column DB-1 (30 m × 250 μm) with reference of the standard carvone and menthol. The flow rate was 0.8 mL/min; temperature was maintained at 90 ºC for 5 min, 150 ºC for 5 min and 230 ºC for 10 min, respectively. Injector and detectors were used at 250 and 280 ºC, respectively. In HPTLC, the samples were applied in the form of bands on a precoated silica gel GF_{254} aluminium plate (Camag, LinomatIV, Switzerland). The solvent system of toluene and ethyl acetate (95:5) was used for the development, compound were detected by spraying anisaldehyde solution after drying at 105 ºC for 5 min. The plate was visualized after spraying anisaldehyde sulfuric acid reagent. The scanning was done at λ_{max}-515 nm for carvone and λ_{max}-610 nm for menthol, using Camag TLC scanner 3.

Sample preparation: Ten tablets were taken and their average weight was calculated. The tablets were powdered and the quantity equivalent to 30 mg of peppermint caraway oil was taken in a 50 mL volumetric flask and dissolved with a small portion of toluene by sonication for 10 min. The solution was filtered through membrane filter (PALL Life Sciences #0.45 m). The volume was made up with toluene.

Drug stability studies: The drug (peppermint oil and caraway oil) was packed in sealed glass vials individually and the admixture of both the drug at the ratio 1:1 were kept at different storage conditions, 5 ºC, 25 ºC and 60 % relative humidity and 40 ºC and 75 % relative humidity for 1 month and evaluated after interval of 1 week[13]. After sample preparation as above, both the standard solution and sample were run in the column and analyzed. The peak areas were noted and the amount present in the formulation was calculated using the standard (Fig. 1).

Drug-excipients compatibility studies: Admixtures of the drug and excipients was mixed properly in proportions of 1:5, respectively and packed in glass vials, then compatibility studies3 was done by storing at different storage conditions 5 ºC, 25 ºC and 60 % relative humidity and 40 ºC and 75 % relative humidity for one month and evaluated after interval of one week[14-16].

RESULTS AND DISCUSSION

The quality of drug product should be maintained under the various conditions that pharmaceuticals encounter, during production, storage in warehouses, transportation and storage in hospital and community pharmacies, as well as in the home. Therefore, in view of the chemical degradation and physical degradation of drug substances may change their pharmacological effects, resulting in altered efficacy therapeutic as well as toxicological consequences; the pharmaceuticals should be stable and maintain their quality until the time of usage or until their expiration date[17]. In the present stability investigations carried out as per ICH guidelines, it revealed that there was no physically observable change found in peppermint and caraway oils (Table-1) and no significant loss of content of active drug occurred at storage condition/sampling intervals of 25 ºC and at 60 % relative humidity for a period of 2 months. However, significant changes in both these parameters occurred at storage conditions/sampling intervals at 40 ºC and at 75 % relative humidity for a period of 1 month (loss: 0.065 and 0.101 %, respectively) and two months (loss: 0.115 and 0.211 %, respectively) (Table-2). Moreover there was no any new peak or alteration of retention time observed for these samples when compared with zero time observations under similar conditions. Thus the two oils are sufficiently stable suitable for the formulation of chewable tablets (Fig. 2).

Further the safety and efficacy of medicines depends not only on the active principles and manufacturing process but this also depend upon performance of excipients[18]. The magnitude of this effect will depend on the characteristics of the drug and on the quantity and properties of the excipients. Chemical and physical stability of active ingredients in fixed combinations (FDC) dosage forms may become very complicated due to the presence of two or more active ingredients, or

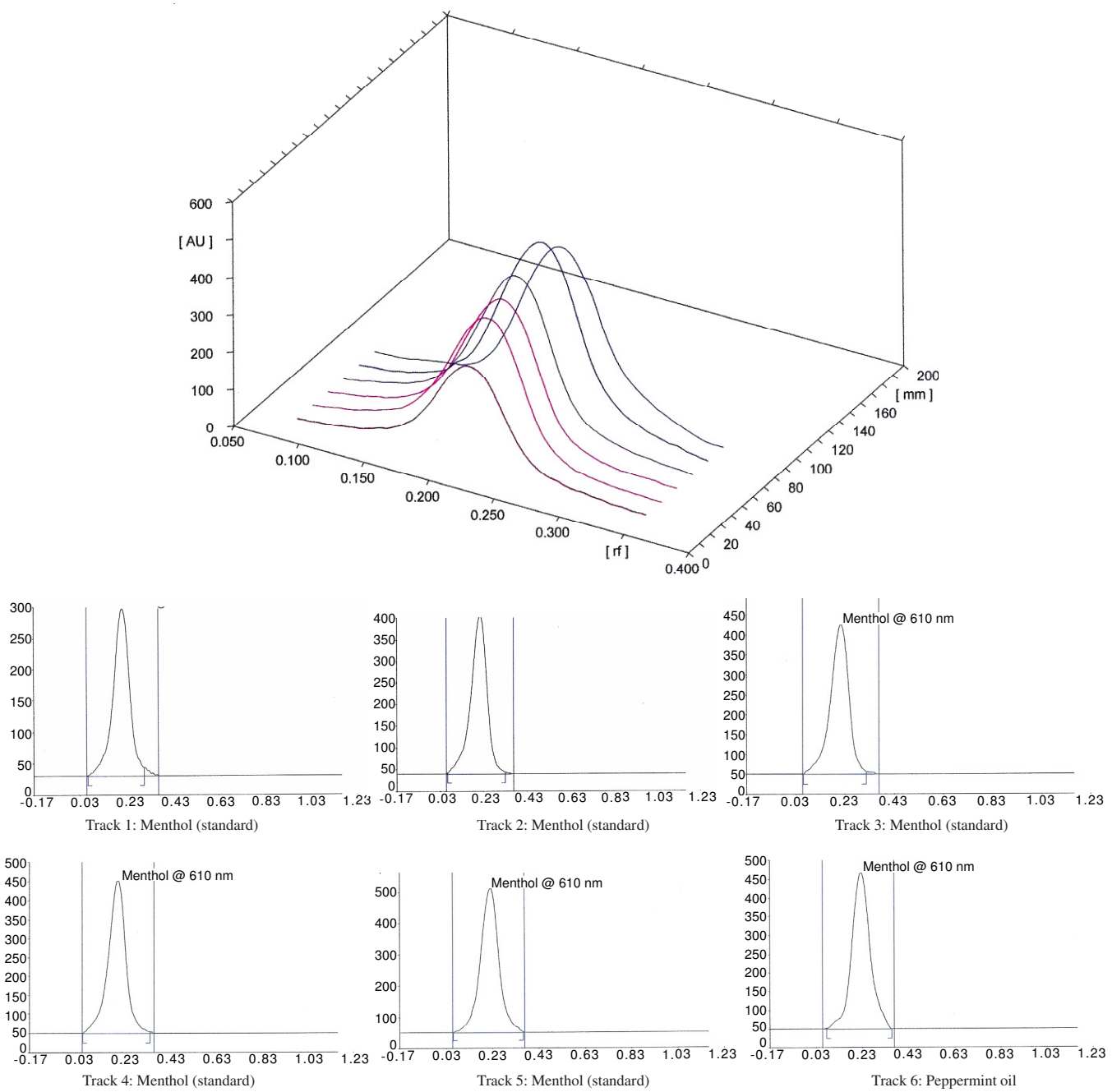

Fig. 1. (a) HPTLC chromatograms all tracks of standards (menthol) and sample at 610 nm

TABLE-1
STABILITY STUDY OF PEPPERMINT AND CARAWAY OILS

Storage conditions	Material (Time)											
	Peppermint Oil				Caraway Oil				Peppermint and Caraway oil (1:1)			
	Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4
05 ºC	No any physical changes was found in the samples packed in glass vials											
25 ºC and 60 % RH	No any physical changes was found in the samples packed in glass vials											
40 ºC and 75 % RH	No any physical changes was found in the samples packed in glass vials											

TABLE-2
MARKER CONCENTRATION IN ACCELERATED STABILITY DATA

Specification	Initial	40 ºC and 75 % RH/1M	Loss (%)	40 ºC and 75 % RH/2M	Loss (%)	25 ºC and 60 % RH/2M	Loss (%)
Menthol	0.775 %	0.71 %	0.065	0.66 %	0.115	0.75 %	0.025
Carvone	0.771 %	0.67 %	0.101	0.56 %	0.211	0.72 %	0.051

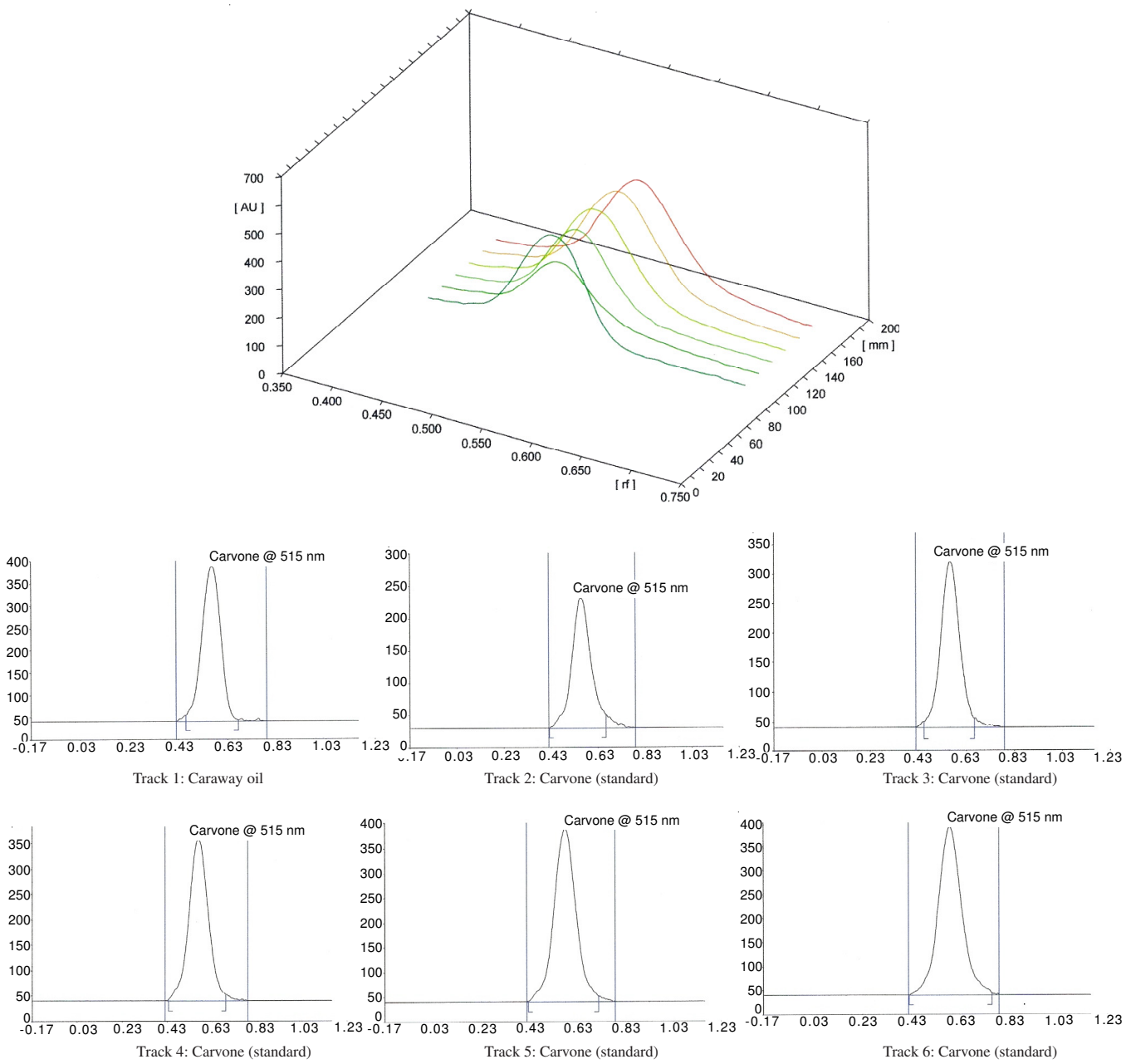

Fig. 1. (b) HPTLC chromatograms all tracks of standards (carvone) and sample at 515 nm

because potentially more or unique excipients are required to achieve the desired release rate for both actives[19]. Not only active ingredients may react each other to form degradants which may not seen in single dosage form, but also active ingredients may react with excipients which are otherwise compatible with one of single active ingredients[20]. These attributes create many new challenges for formulation development and pharmaceutical analysis of fixed combination products. Strategic design in drug-drug and drug-excipient compatibility studies and development of appropriate analytical method which is able to detect all potential impurities and degradants, are very important in successfully developing a stable fixed combination dosage form[21]. The drug-excipient compatibility studies showed that there is no change at accelerated storage condition for a month time period (Table-3).

TABLE-3
DRUG-EXCIPIENT COMPATIBILITY STUDIES

Storage time: Four weeks	Packing: Glass vials		
Composition of granules	Stress conditions		
	5 ºC	25 ºC with 60 % RH	40 ºC with 75 % RH
Lactose, Sucrose, Mannitol, CMC Sodium, Mg stearate, Light Mg carbonate, Di calcium Phosphate, Talc, Aerosil, Syloid, Starch, Microcrystalline Cellulose, Ethyl Cellulose, Hydroxypropyl- methyl cellulose, Stearic acid, Aspartame, ProSolv SMCC, Carbopol974P NF	No physical changes in samples and no new peak observed in GC.	No physical changes in samples and no new peak observed in GC.	No physical changes in samples and no new peak observed in GC.

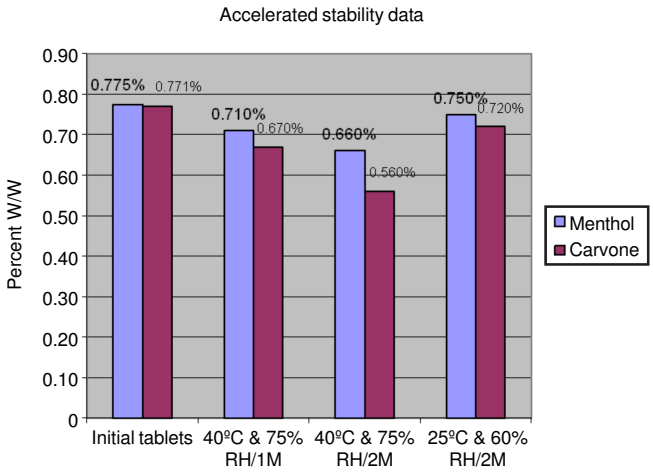

Fig. 2. Marker quantification in peppermint and caraway oils for accelerated stability testing

Conclusion

The present investigation revealed that the peppermint and caraway oils found sufficiently stable and without any marked chemical interaction with the tableting excipients for proposed chewable tablet formulation in view of their better patient acceptance/compliance through pleasant taste and product distinctiveness as well as through better palatability, fast onset of action over existing formulations additionally these formulations more commercially viable being capable faster and economic processing.

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