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Formulation and Evaluation of Immediate-Release Solid Dosage Form Containing Niacin and Guggul as Antihyperlipidemic Agents

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ABSTRACT

Hyperlipidemia/dyslipidemia is associated with an abnormally high level of cholesterol and triglycerides in the blood. The National Commission on Macroeconomics and Health (NCMH) report suggest that there would be nearly 6.4 crore cases of Cardiovascular diseases (CVD) by 2015, with an incidence of 96% of Coronary heart diseases (CHD). The Coronary Drug Project report also indicated a decreased rate of cardiovascular events among patients with coronary heart disease who received immediate-release niacin formulations compared with those receiving placebo. Currently niacin is therapeutically employed for the treatment of dyslipidemia and significantly lowers the lipid profile. Conventional niacin therapy suffers from side-effect like flushing. Guggul (*Commiphora mukul*/ *Commiphora wightii*) also acts as an anti-hyper lipidemic agent and is known long back in Ayurvedic medicine. Pharmacological evaluation of niacin - guggul combinations in high fat induced rat model suggested that the Human equivalent dose (HED) of niacin can be reduced from 1000 mg/day to 350 mg/day when combined with guggul at a dose of 1000 mg/day. The incorporation of guggul helped to reduce the effective concentration of niacin and thus may reduce the dose related side effects of niacin. In future, the addition of guggul into niacin therapy may have additional benefits on the prevention and therapy of CVD. Niacin-Guggul immediate-release capsules of size '0' were successfully prepared and evaluated.

KEY WORDS: Niacin, Guggul, Hyperlipidemia, Immediate- release capsules.

1. INTRODUCTION

The increased risk of heart disease and stroke is associated with raised cholesterol levels. It is estimated that one third of ischemic heart disease globally is attributable to high cholesterol. It is estimated that high cholesterol causes 2.6 million deaths (4.5%) and 29.7 million disability adjusted life years (DALYS, 2.0%). A major cause of disease burden in both developed and developing countries is the elevated total cholesterol. A study in men aged 40 indicated that a 10% reduction in serum cholesterol will result in a 50% reduction in heart disease within 5 years; with a 20% reduction in heart disease occurrence for men aged 70 years. Anti-hyper lipidemic agents are used to modify blood lipid levels in the management of hyperlipidemia and for the reduction of cardiovascular risk. The major classes of lipid regulating drugs include statins, bile-acid binding resins, fibrates, omega-3-triglycerides and nicotinates.

For a very long time nicotinic acid (niacin) has been used for the treatment of hyperlipidemia and other cardiovascular complications. Niacin significantly modifies low-density lipoprotein [LDL], very low density lipoproteins [VLDL] and also increases high-density lipoprotein [HDL].Niacin is reported to inhibit hepatocyte diacylglycerolacyltransferase-2, a key enzyme for triglycerides (TG) synthesis. This results in accelerated intracellular hepatic apo B degradation which causes significant reduction in secretion of VLDL and LDL particles. Niacin also retards the hepatic catabolism of apo A-I which increases the HDL half-life and concentrations of lipoprotein A-I HDL sub fraction, which increases the reverse cholesterol transport. Niacin causes the flushing syndrome that results from the stimulation of prostaglandins D (2) and E (2) in subcutaneous Langerhans cells mediated via the G protein-coupled 109A niacin receptor.

Niacin is available in several generic forms, under several brand names, in many concentrations from 50 to 1000 mg each as either tablets or capsules. The intermediate release [IR] niacin must be taken several times daily to treat hyperlipidemia, which results in a high rate of cutaneous flushing. The recommended dosage of niacin is 1 to 6 grams daily, starting at low doses and increasing at weekly intervals based upon tolerance and effect. Sustained release [SR] formulations of niacin, taken once daily is less likely to result in flushing, but causes hepatotoxicity. Niacin in combination with other lipid lowering drugs such as lovastatin is also available. Common side effects of niacin include nausea, fatigue, pruritus and flushing; flushing being a major dose-limiting side effect.

Oleogum resin (known as guggul) obtained from guggul tree, *Commiphora mukul*, has been used in several clinical conditions including hyper-cholesterolemia, rheumatism, atherosclerosis and obesity over several thousands of years. The therapeutic effects of guggul are attributed to the presence of bioactive guggulsterones. It has been established that guggulsterone is an antagonist at farnesoid x receptor (FXR), a key transcriptional regulator for the maintenance of cholesterol and bile acid homeostasis. The FXR antagonism by guggulsterone has been proposed as the mechanism for its hypo lipidemic effect. A recent literature also suggested that guggulsterone up regulates the

bile salt export pump (BSEP), an efflux transporter responsible for removal of cholesterol metabolites, bile acids from the liver. This up regulation of BSEP expression accelerates cholesterol metabolism into bile acids, representing another possible mechanism for its anti-hyper lipidemic activity. Guggulsterone is also a potent inhibitor of a nuclear factor-kappaB (NF-kappaB) which is a critical regulator of inflammatory responses (Deng, 2007). Currently, the recommended daily dose of Guggul is 2-4 g.

The present work was aimed to prepare and evaluate effectiveness of immediate release solid dosage form (capsule) containing combination of gum guggul with niacin in the management of hyperlipidemia using the high fat diet induced hyper lipidemic model in rats compared to niacin alone. We presume that the addition of guggul may allow using lower doses of niacin necessary to achieve the full effect with increased patient compliance, the combination therapy being superior to niacin IR monotherapy and in the future, addition of guggul into niacin therapy may have additional advantages in CVD prevention and therapy.

2. MATERIALS AND METHODS

Materials: Guggul was obtained from the local market and was identified and evaluated as per the procedures mentioned in Ayurvedic Pharmacopeia. Niacin was purchased from Hi Media Laboratories Pvt. Ltd. Mumbai, India, and evaluated as per procedures mentioned in Indian Pharmacopoeia. Hard gelatin capsule shells were received as gift samples from ACG-Associated Capsules, Pune, India. The other materials used in the study were of analytical or pharmaceutical grade.

Analysis of active ingredients: Guggul was evaluated for foreign matter, total ash, acid insoluble ash, alcohol soluble extractive ash, water soluble extractive ash and volatile oil. To determine presence of active constituents, E- and Z-isomers of guggulsterones, HPTLC analysis was carried out and Rf values were noted (Musharraf, 2011). For evaluation of niacin, infrared spectroscopic studies and assay were carried out as per standard guidelines (Indian Pharmacopoeia, 2007).

Pharmacological evaluation of niacin-guggul combinations in high fat induced hyperlipidemic model in rats

Groups and treatment: All the experiments were performed according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India and approved by Institutional Animal Ethical Committee (IAEC), as per protocol Number 'DYPIPSR/IAEC/13-14/P-04'. Experiments were carried out on male wistar rats, Rattus norvegicus, age group 6-8 weeks, and weight 150-200 g. The animals were housed in a well-ventilated animal house in polypropylene cages bedded with sterilized rice husks with 12 h light: 12 h dark schedule at temperature of 25 ± 2° C and relative humidity of 45 to 55%. The animals were fed *ad libitum* with a high fat diet prepared in-house. The diet composed of cholesterol 20 % (Research Lab, Mumbai, India); coconut oil 10 %, sugar 10 % and vanspati ghee 10 % (local market) and animal pellet feed 50 % (Amrut feeds, Sangli, India). The animals had access to normal drinking water at all the times.

The animal equivalent doses were calculated as 37.1, 53, 79.5, 106 mg/kg/day for niacin and 106 mg/kg/day for guggul from the corresponding human equivalent doses (assuming averages human body weight of 60 kg) of 350, 500, 750, 1000 mg/day for Niacin and 1000 mg/day for Guggul.

The animals were randomly divided into seven groups (n = 6) as given below: Group I- Normal pellet diet fed rats (Control); Group II- High fat diet fed rats (Hyper lipidemic control); Group III- High fat diet fed rat treatment group with niacin 106 mg/kg/day orally for 8 weeks (Niacin standard); Group IV- High fat diet fed rat treatment group with guggul 106 mg/kg/day orally for 8 weeks (Guggul standard); Group V- High fat diet fed rats treatment group with niacin 37.1 mg/kg/day + guggul 106 mg/kg/day orally for 8 weeks (Treatment group 1); Group VI - High fat diet fed rat treatment group with niacin 53 mg/kg/day + guggul 106 mg/kg/day orally for 8 weeks (Treatment group 2) and Group VII - High fat diet fed rat treatment group with niacin 79.5 mg/kg/day + guggul 106 mg/kg/day orally for 8 weeks (Treatment group 3).

Estimation of blood lipid profiles : On completion of the treatment period, animals were anaesthetized, blood samples were withdrawn from all the seven groups of animals from retro-orbital plexus and total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) cholesterol and triglyceride (TG) levels in plasma were determined using commercially available kits (SPINREACT). Friedewald's formula was used for the determination of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) cholesterol, which states:

VLDL cholesterol = Triglyceride/5 and

LDL cholesterol = Total cholesterol - (VLDL + HDL cholesterol).

Statistical analysis: Values were expressed as mean ± S.E.M. The statistical significance was evaluated by one-way ANOVA using Bartlett's test (Kobayashi, 2012; Lawrence Hamilton, 2008). The statistical software used was Graph Pad Prism version 6.04. Value of $p < 0.05$ was considered statistically significant.

Preparation of immediate release capsule dosage form

Evaluation of capsule blend: The drug-drug compatibility studies of the prepared blends of niacin and guggul in ratio 1:2.8 (drug-to-drug ratio as in the final formulation) were taken in glass vials and placed in a stability chamber

at 50°C/75 % RH for 30 days and then analyzed by FT-IR spectroscopy (Chidambaram, 2014). The prepared blends were also evaluated for bulk density, tapped density, angle of repose and Hausner ratio (Lumay, 2012; Nyol, 2013).

Preparation and evaluation of immediate release capsule dosage form: Guggul and niacin were powdered and passed through mesh #44. Accurately weighed blends of the active agents consisting of 117 mg of niacin and 333 mg of guggul (Net content of capsule: 450mg) were filled in 'o el' hard gelatin capsule shell manually. The filled capsules were stored in air tight containers at temperature 22 ± 2°C and relative humidity NMT 55%.

The capsules prepared were inspected for denting, telescopic or cracking defects. The capsules were observed for appearance (orange body, red cap hard gelatin capsules of size '0 el'). Locking length was measured by vernier calipers. Uniformity of weight was determined as per standard procedures.

Assay of the capsule dosage form by UV visible spectrometric measurements: Stock solutions of niacin and guggul each, of concentration 100 µg/ml were prepared in methanol and suitably diluted with distilled water to obtain working standards (concentration range 10 -50 µg/ml). From the overlain UV spectra, 238.5 nm and 263 nm were selected for the simultaneous estimation of niacin and guggul respectively.

For both the drugs, the absorptivities (A1%, 1 cm) were determined at the selected wavelengths and simultaneous equations were constructed. For the estimation of drugs in the formulation, twenty capsule contents were weighed and average weight was calculated. The powder equivalent to 11.7 mg niacin and 33.3 mg of guggul was transferred to 100 ml volumetric flask containing 50 ml methanol and sonicated for 10 min, the volume was then made up to the mark with methanol, the resulting solution was filtered and appropriately diluted to obtain sample solution containing 11.7 µg/ml of niacin and 33.3 µg/ml of guggul. The concentration of guggul (C_x) and niacin (C_y) in the sample solutions were determined from the prepared simultaneous equations.

Validation of assay procedure: The developed assay procedure was validated as per ICH guidelines. Linearity of the method was established by measuring the response of standard solutions of niacin and guggul at the selected wavelengths. Calibration curves of absorbance versus concentration were constructed and the regression coefficients were determined.

The accuracy of the proposed methods were ascertained through recovery studies carried out by standard addition method at three different levels (80%, 100% & 120%, n=3 at each level). Method precision/repeatability was established by six replicate analysis of capsule formulation by the proposed method. Intermediate precision (Intra-day precision) was determined by analyzing capsule contents at different time intervals on same day in triplicate. Intermediate precision (Inter-day precision) was determined by analyzing capsule contents using different analysts, systems and on different days in the same laboratory.

Dissolution studies of capsule dosage form: For the dissolution study, the stock solutions and working standards were prepared as per the assay procedure. However, as 0.1 M HCl was employed as the dissolution media, calibration curves were plotted in the same solvent.

For the dissolution studies, the wavelengths of 260.5 nm and 276 nm were selected for niacin and guggul respectively for the formation of simultaneous equations. The dissolution of capsule dosage form containing guggul and niacin was carried out in 900 ml of 0.1 M HCl, maintained at 37ºC ± 0.5 ºC, in apparatus 2 (paddle apparatus) at 100 rpm for 60 min using sinker. Suitable aliquots (5 ml) were withdrawn at specific time intervals (5, 10, 15, 20, 30, 45 and 60 mins) of the study and replaced with an equal volume of the fresh medium to maintain sink condition. At end of each test time, sample aliquots were withdrawn, suitably filtered, diluted in dissolution medium and quantified using UV spectrometric measurements.

Validation of dissolution procedure: The dissolution procedure was also validated as per ICH guidelines. Specificity was examined by analyzing placebo solutions containing capsule shell components without drugs. The placebo samples were transferred to dissolution vessel containing 900 mL of medium at 37 ± 0.5 °C and stirred for 1 hr at 100 rpm using USP apparatus-Paddle with sinker. Aliquots of these solutions were filtered before recording the absorbance. % Interference was calculated using following equation-

$$= CS\ X\ 100\ X\ \frac{AP}{AS}\ X\ \frac{V}{L}$$

Where, AP- Absorbance of placebo, AS= Absorbance of standard, CS= Conc. of standard (mg/ml), V -Volume of medium (ml), L- Label claim (mg).

The linearity of measurements was evaluated by constructing calibration plots using working standard solutions of different concentrations.

In the accuracy study, performed by recovery study pure drugs - niacin and guggul were added to the dissolution vessel in known amounts at 80%, 100%, and 120% of test concentration. Accordingly 93.6 mg, 117 mg and 140.4 mg of niacin and 266.4 mg, 333 mg and 399.6 mg of guggul were added along with each 450 mg capsule containing 117 mg niacin and 333 mg guggul. The dissolution test was performed; suitable aliquots (5 ml) were filtered and analyzed UV spectrophotometrically using simultaneous equation method. Each concentration was analyzed in triplicate.

Method precision / repeatability were estimated by analyzing six dissolution samples of capsule formulation using the optimized dissolution procedure. Intermediate precision (Intra-day and interday precision) was determined similar to the assay procedure.

3. RESULTS

Analysis of active ingredients: The results of the evaluation of niacin and guggul are shown in Table 1 and Table 2 respectively. In the HPTLC densitogram of guggul, peak 9 at R_f value 0.54 (E-guggulsterones) and peak 10 at R_f value 0.62 (Z-guggulsterones) as shown in Figure1, confirmed the presence of the bioactive components of guggul said to be responsible for its hypo lipidemic effect.

Table.1. Evaluation of Guggul as per Ayurvedic pharmacopoeia

Test	Standard Values	Observed values	Inference
Description	Vernicular or stalactitic pieces of pale yellow or brown colored mass; odour, aromatic; taste, bitter & astringent	Vernicular pieces of pale brown colored mass; odour, aromatic; taste, bitter & astringent	Passes
Foreign matter	Not more than 4 %	1 %	Passes
Total ash	Not more than 5 %	4.3 %	Passes
Acid-insoluble ash	Not more than 1 %	0.6 %	Passes
Alcohol-soluble extractive	Not less than 27 %	29.16 %	Passes
Water-soluble extractive	Not less than 53 %	54.4 %	Passes
Volatile oil	Not less than 1 %, v/w	1.6 %	Passes

Table.2. Evaluation results of Niacin as per IP 2007

Test	Standard values	Observed values	Inference
Description	A white or creamy-white, crystalline powder	A white, crystalline powder	Passes
Identification	Infrared absorption spectrum shall be comparable with that obtained with nicotinic acid RS	Infrared absorption spectrum is comparable with that obtained with nicotinic acid RS	Passes
Assay	Must contain NLT 99.5% and NMT 100.5% of $C_6H_5NO_2$, calculated on the dried basis.	99.8 %	Passes

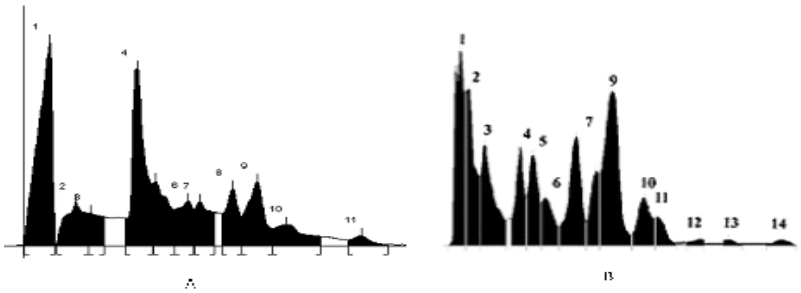

Figure.1. (A) HPTLC system able to differentiate many peaks in Guggul resin used in the formulation showing R_f value 0.54 (E-guggulsterone) and R_f value 0.62 (Z-guggulsterone), (B) A similar pattern as was reported by (Musharraf SG et al , 2011) showing R_f value 0.52 ± 0.01 (E-guggulsterone) and R_f value 0.67 ± 0.01 (Z-guggulsterone)

Pharmacological evaluation of niacin and guggul : Figure 2 shows the effects of drug treatment on serum total cholesterol, triglycerides, HDL, LDL, VLDL, LDLC/HDLC ratio, total cholesterol/HDLC ratio.

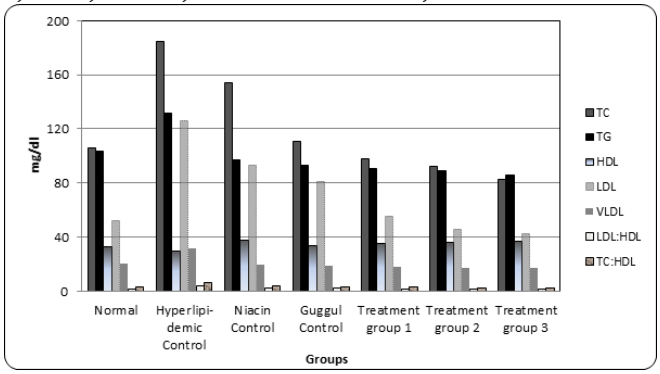

Figure.2. Effect of Niacin & Guggul administration on lipid profile in hyper lipidemic rats

Preparation of immediate release capsule dosage form : The results of the evaluation of capsule blend are shown in Table 3.The results of the physical tests, assay procedure and dissolution studies by UV spectrophotometric simultaneous equation method are presented in Table 4 and 5 respectively. The drug release verses time profile in the dissolution studies is shown in Figure 3.

Table.3. Evaluation of capsule blend

Test	Observed values	Inference
Bulk density	0.56 g/ml	-
Tapped density	0.66 g/ml	-
Angle of repose	35	Good flow property
Hausner ratio	1.17	Good flow property

Table.4. Evaluation of immediate release Capsule dosage form containing niacin and guggul

Test	Results
Visual Observations	Capsules are free from denting, telescopic and cracking defects
Appearance	Orange body, red cap hard gelatin capsules of size '0 el'
Locking length	23.10 ± 0.50 mm
Uniformity of weight	554 mg ± 7.5 %
Assay of Capsules*	Guggul: 99.56 %, Niacin: 99.79 %
Dissolution test*	Guggul: 94.82 % at 60 min, Niacin: 92.18 % at 60 min

Table.5. Summary of validation data for assay and dissolution method

Parameter		Assay method		Dissolution method	
		Niacin	**Guggul**	**Niacin**	**Guggul**
Linearity range (µg/ml)		10-80	10-80	05-80	05-80
Correlation coefficient (r^2)		0.995	0.996	0.996	0.998
Accuracy (% Recovery)*	**80 %**	99.86	99.23	98.72	99.98
	100 %	100.55	99.69	98.69	100.12
	120 %	99.73	98.95	98.17	99.67
Accuracy (% RSD)*	**80 %**	0.16	0.61	0.11	0.22
	100 %	0.25	0.64	0.15	0.31
	120 %	0.21	0.26	0.07	0.14
Repeatability **	**Mean %**	11.7	33.3	92.18 %	94.82 %
	(%RSD)	0.76	0.73	0.14	0.24
Intermediate precision	**Intraday Mean *****	11.66 µg/ml	33.27 µg/ml	92.17 %	94.78 %
	Intraday (%RSD) ***	1.70	1.40	0.11	0.23
	Inter day Mean**	11.70 µg/ml	33.01 µg/ml	92.25%	94.70%
	Inter day (%RSD)**	0.67	1.55	0.15	0.26

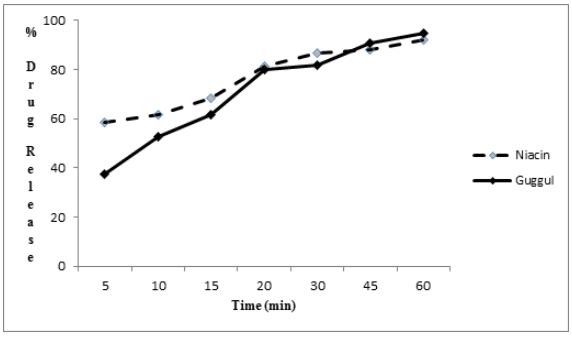

Figure.3. Percent drug release versus time of Niacin-Guggul capsule dosage form

DISCUSSION

Analysis of active ingredients: The IR spectrum of niacin shows a peak at 1707 cm^{-1} for the C=O stretching of carboxylic acid group which confirms the identity of niacin. The results of the assay as per IP 2007 confirm the % purity of niacin (99.8%, Table 1). In the IR spectrum of guggul, α, β-unsaturated ketone functionality was detected at 1620 cm^{-1}. The IR absorption bands at 1728 and 1878 cm^{-1} also confirmed presence of the two carbonyl functionalities, present in guggul.

Pharmacological evaluation of niacin and guggul: Wistar rats fed on a diet enriched with cholesterol for 8 weeks caused a significant elevation in serum total cholesterol, LDLC, VLDL levels, while a significant decrease in HDLC

was recorded. The rat treatment group with niacin and guggul showed significant improvement in the lipid profile as compared to normal group and hyper lipidemic control group (Figure 2).

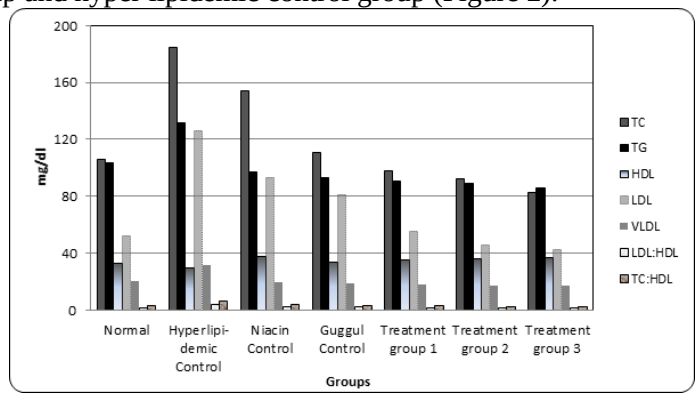

Figure.4. Effect of Niacin & Guggul administration on lipid profile in hyper lipidemic rats

'Niacin control group' receiving 106 mg/kg/day showed significant reduction in TC, TG, LDLC, VLDLC (17, 26, 27, 39 % respectively) with 26 % increase in HDLC. 'Guggul control group' receiving guggul 106 mg/kg/day showed reduction in TC, TG, LDLC, VLDLC (40, 29, 36, 40 % respectively)with 12 % increase in HDLC. As compared to the control group receiving niacin, guggul alone, the 'Treatment group 1' receiving niacin 37.1 mg/kg/day and guggul 106 mg/kg/day showed reduction in TC, TG, LDLC, VLDLC (47, 31,56,44 % respectively) with 17 % increase in HDLC. It was observed that combination of niacin and guggul was more effective in reducing the triglycerides significantly than control groups. 'Treatment group 2' receiving niacin 53 mg/kg/day and guggul 106 mg/kg/day and 'Treatment group 3' receiving niacin 79.5 mg/kg/day and guggul 106 mg/kg/day showed more significant decrease in TC, TG, LDLC, VLDLC with significant elevation of HDLC.

As per the results, niacin-guggul combination therapy showed a significant decrease in TC, LDL, VLDL and TG along with significant increase in HDLC. The dose combination of 'Treatment group 3' (niacin 79.5 mg/kg/day + guggul 106 mg/kg/day) showed most significant improvement in the lipid profile. However taking into consideration the formulation aspect, dose combination of 'Treatment group 1' (niacin 37.1 mg/kg/day + guggul 106 mg/kg/day) which was also comparatively effective in improving the overall lipid profile when compared to niacin mono-therapy, was used to prepare capsule solid dosage form.

Preparation of immediate release capsule dosage form: In the drug-drug compatibility studies, the physical evaluation of mixture revealed no discoloration or apparent sign of degradation. The IR spectrum of the drug mixtures showed characteristic absorption bands which were comparable with standard spectra indicating the chemical stability of the niacin-guggul combinations.

Immediate release hard gelatin capsules of size '0 el' were formulated containing niacin and guggul as active ingredients; the net content of the capsules was 450 mg which consisted of 117 mg of niacin and 333 mg of guggul. As the blend showed good flow properties, no additional excipients were incorporated for formulation of capsule dosage form.

In the UV spectrophotometric procedure for the assay of the prepared dosage form, the % content of guggul was found to be 99.56 % and niacin, 99.79 %. The results of the validation of the assay procedure are summarized in Table 5. In the linearity studies, the Beer- Lambert's concentration range was found to be 10-80 µg/ml for both guggul and niacin respectively with correlation co-efficient $r^2 > 0.99$ indicating the linearity of the method. The recovery studies results were well within standard limit (98-101%) which reflects the accuracy of the method. In the precision studies, the standard deviation and % RSD calculated was < 2 %, indicating high degree of precision of the proposed method.

The UV spectrophotometric Simultaneous Equation method was also developed for the dissolution studies. The % release of guggul was found to be 94.82 % and niacin as 92.18 % at 60 min of the study. The results of the validation of the dissolution test procedure are summarized in Table 5. The Beer- Lambert's concentration range was found to be 5-80µg/ml for both guggul and niacin respectively ($r^2 > 0.99$). In the specificity studies, the placebo (shell capsule) showed no interferences at the selected wavelengths 260.5 & 276 nm. In the accuracy of the method, as indicated by recovery studies, the mean % recovery was found to be 98.52 and 99.92% for niacin and guggul respectively. In the precision studies, as shown in Table 5, the standard deviation and % RSD calculated was low (< 2 %), indicating high degree of precision of the proposed method.

4. CONCLUSION

In the present study, attempts have been made to prepare multicomponent immediate release capsule dosage form containing guggul and niacin, for the effective treatment of hyperlipidemia. The niacin-guggul combination when studied on high fat diet induced hyper lipidemic rats, suggested that the human equivalent dose (HED) of niacin

can be reduced from 1000 mg/day to 350 mg/day when combined with guggul at a dose of 1000 mg/day. The combination of guggul helped to reduce the effective concentration of niacin and thus may reduce the dose related side effects of niacin. We thereby conclude that the addition of guggul may allow using lower doses of niacin necessary to achieve the full effect with probable increased patient compliance, the combination therapy being superior to Niacin IR monotherapy. In future, the addition of guggul into niacin therapy may have additional advantages in CVD prevention and therapy. However further studies are required to establish and elucidate the subsequent reduction of niacin-induced side effects like flushing.

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