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In vitro and *In vivo* Assessment of the Effect of Okra Gum Solid Dispersion in Atorvastatin Solubility

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Abstract

***Background*:** Atorvastatin is BCS class II drug; it is lipid-lowering medication. Okra gum (OKG), from the pods of *Abelmoschus esculentus*, is natural product contain polymers having advantages over synthetic ones as it is safe, chemically inert, nonirritant, biodegradable, and does not require toxicological studies. ***Aim*:** This study aimed to assess the effect of okra gum solid dispersion in atorvastatin solubility. ***Method*:** The gum was extracted by hot water extraction and the dry extract was evaluated for percentage practical yield, flow properties, pH values and FTIR spectroscopy. Then solid dispersions with different drug to polymer ratios were prepared from OKG, and hydroxy propyl methyl cellulose (HPMC) by solvent evaporation method. Saturation solubility was tested for the solid dispersions prepared, the physical mixtures and atorvastatin. Tablets were prepared from solid dispersions with the highest saturation solubility, then tablets were tested and evaluated. Finally, *in vivo* test was done using Swiss albino mice and data were analyzed using one way Anova test followed by T test. ***Results**:* The content percent of atorvastatin in the solid dispersion prepared were 99,9- 100.1%, the tablets showed satisfactory physicochemical properties as 1.29% RSD in tablet weight variation, 24 min disintegration time, 5.24±0.457 Hardness and OKGSD tablets showed sustained release manner and 87% of drug released in 6 hrs. Lipid profile results showed significant decrease in total cholesterol level with marked decrease in LDL when using OKGSD tablets. ***Conclusion*:** It was concluded that OKG is promising excipient that can be used in dosage forms formulation to enhance solubility of low soluble drugs.

Keywords: Atorvastatin. Okra gum, triton WR1339, solid dispersion, solubility.

INTRODUCTION

Atorvastatin: Is(3R,5R)-7-[2-(4-fluorophenyl) -3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid [1]. It is lipid-lowering medication used in the primary and secondary prevention of coronary heart disease. By preventing the conversion of HMG-CoA to mevalonate, Atorvastatin decreases cholesterol production in the liver. It also increases the number of LDL receptors on the surface of hepatic cells [2].

Atorvastatin is rapidly absorbed after oral administration with a peak plasma concentration at 1 to 2 hours, its bioavailability is low ≈ 14%. It is highly bounded to plasma protein (over 98%). The half-life of atorvastatin is about 14 hours, while its active metabolites have a half-life of about 20 to 30 hours [3].

Solid dispersion as a solubility enhancement technique: Solubility is defined as the maximum quantity of solute that can be dissolved in a certain quantity of solvent or quantity of solution at a specified temperature. Various techniques are available to improve the solubility of poorly soluble drugs [4]. Solid dispersion is one of solubility enhancement techniques in which poorly water-soluble drugs dispersed in an inert hydrophilic carrier at solid state provided by different methods. The solid dispersion provides the possibility of

reducing the particle size of drug to nearly a molecular level, to transform the drug from the crystalline to the amorphous state, hence increases its saturation solubility. So, solid dispersion may enhance the bioavailability of water insoluble drugs by increasing their saturation solubility in the gastrointestinal fluids [5].

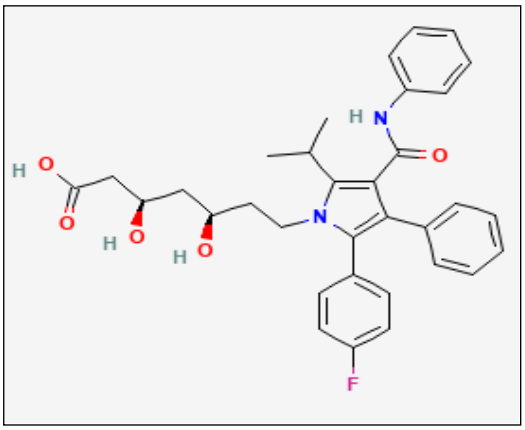

Figure 1: Atorvastatin chemical structure

Development History of Solid Dispersion:

First generation solid dispersions: Urea and sugars were the first crystalline carriers to be used in dispersion. Solid dispersion systems were developed by using molecular dispersions instead of using eutectic mixtures with mannitol as carrier by Levy and Kanig [6]. These improvements were due to faster carrier dissolution, releasing particles of drug. These dispersions prepared using crystalline carriers were described as first generation of solid dispersions. The formulation of eutectic mixtures improved the rate of drug release which in turn increases the bioavailability of poorly water soluble drugs. The major drawback of first generation solid dispersion is that they form crystalline solid dispersions, which -being thermodynamically more stable- did not release the drug as quickly as amorphous ones.

Second generation solid dispersions: Due to thermodynamic stability, the solid dispersions with drug in the crystalline state are not as effective as amorphous one. Therefore, second generations of solid dispersions were introduced having amorphous carriers instead of crystalline. Formerly, the drugs were molecularly dispersed in amorphous carriers which are usually polymers in random pattern.

Third generation solid dispersions: The third generation solid dispersions contain surfactant carriers or a mixture of amorphous polymers and a surfactant as carrier. The third generation solid dispersions stabilize the solid dispersions, increase the bioavailability of the poorly soluble drugs and reduce re-crystallization of drug. The use of surfactants such as poloxamer 407 as carriers resulted in high polymorphic purity and improved *in vivo* bioavailability [7].

Okra gum(OKG): The gum from the pods of *Abelmoschus esculentus* (family: *Malvaceae*) is one of the advantageous polysaccharides that is currently being studied in the pharmaceutical industry as a hydrophilic polymer in pharmaceutical dosage forms. Okra plant grows very fast, it grows in all soil types, and is among the most heat and drought-tolerant vegetables [8]. It has been investigated as a binding agent for tablets and has also been shown to produce tablets with good hardness, friability, and drug release profiles [9]. It has advantage over most commercial synthetic polymers as it is safe, chemically inert, nonirritant, biodegradable, biocompatible, and eco-friendly. Since it is widely harvested and does not require toxicology studies, it is therefore considered to be economical. Okra gum contains random coil polysaccharides consisting of galactose, rhamnose, and galacturonic acid. The repeating units of the gum were found to be (1-2)-rhamnose and (1-4)-galacturonic acid residues with disaccharide side chains and a degree of acetylation (DA = 58) [10]. When extracted in water, these polysaccharides can produce highly viscous solution with a slimy appearance. Gums are carbohydrate biomolecules that have the potential to bind water and form gels. Gums have several forms, such as mucilage gums, seed gums, and exudate gums. Plant gums are one of the most important gums because of their bioavailability. Plant-derived gums have been used by humans since ancient times for numerous applications. The main features that make them appropriate for use in different applications are high stabilization, viscosity, adhesive property, emulsification action, and surface-active activity. In many pharmaceutical formulations, plant-based gums and mucilages are the key ingredients due to their bioavailability, widespread accessibility, non-toxicity, and reasonable prices. These compete with many polymeric materials for use as different pharmaceuticals in today's time and have created a significant achievement from being an excipient to innovative drug carriers. In particular, scientists and pharmacy industries around the world have been drawn to uncover the secret potential of plant-based gums and mucilage through a deeper understanding of their physicochemical characteristics and the development of safety profile information. This innovative unique class of drug products, useful in advanced drug delivery applications, gene therapy, and biosynthesis, has been developed by modification of plant-based gums and mucilage.

Hydroxy propyl methyl cellulose (HPMC):

HPMC is a semi-synthetic polymer, it is one of the most extensively explored cellulosic polymers as a precipitation inhibitor and has proven to be effective in stabilizing solid dispersion formulations of many drugs. HPMC is a very versatile polymer and its extensive use can be attributed to the lack of drug specificity [11].

Triton WR 1339:

Triton WR1339 also named Tyloxapol (formaldehyde; oxirane;4-(2,4,4-trimethylpentan-2-yl) phenol) [12]. It is a nonionic liquid polymer of the alkyl aryl polyether alcohol type. It is used as a surfactant to aid liquefaction and removal of mucopurulent bronchopulmonary secretions administered by inhalation through a nebulizer or with a stream of oxygen. With intraperitoneal injection, Tyloxapol also blocks plasma lipolytic activity, and thus the breakdown of triglyceride-rich lipoproteins. This mechanism is used to induce experimental hyperlipidemia in animals [13].

Intravenous injection of non-ionic detergents such as Triton WR 1339 in experimental animals results in a progressive increase in the concentration of lipids in the blood. The action is believed to be due, at least in part, to the capacity of the detergents to associate with triglycerides in the plasma in such a way as to reduce their rate of hydrolysis by the enzyme, clearing factor lipase or lipoprotein lipase, and so to interfere with their uptake from the circulation by the extra-hepatic tissues.

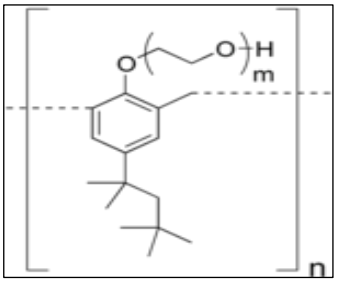

Fig 2: Triton WR1339 (Tyloxapol) chemical structure [14]

Materials:

- Atorvastatin working standard powder (ATVS) and Atorvastatin calcium powder (ATV) were kindly gifted from Azal pharmaceutical industries Co.Ltd, Khartoum north.
- Hydroxy-propyl methyl cellulose (HPMC) was obtained as gift sample from Blue Nile pharmaceutical factory, Khartoum north
- Okra pods were purchased from local market.

All reagents used were of analytical grade.

Plant materials were taxonomically authenticated at herbarium of Medicinal and Aromatic Plants and Traditional Medicines Research Institute, Khartoum, Sudan.

Methods:

Preparation of atorvastatin solid dispersions with HPMC: Accurately weighed quantities of Atorvastatin and HPMC (1:2, 1:4 and 1:6 drug to polymer ratio) were mixed with sufficient amount of water to get a solution then the solvent evaporated using freeze dryer (Beijing Boyikang Experimental instrument co. China) until dry, crushed, sieved then stored with silica gel [15].

Okra Gum (OKG):

Extraction of okra gum: The gum (OKG) was extracted using method described by Kaur et al [16]. Crushed Okra fruits were allowed to swell in water for 8–12 hrs., then filtered through muslin cloth and finally precipitated with absolute ethanol. The precipitate was then dried using freeze dryer, crushed, sieved and stored with silica gel till further use.

Preparation of Atorvastatin solid dispersion with OKG (OKGSD): Accurately weighed quantities of Atorvastatin and OKG (1:2, 1:4 and 1:6 drug to polymer ratio) were mixed and dissolved in a suitable amount of water, the solvent was evaporated using freeze dryer, crushed, sieved and finally stored with silica gel till further use [15].

Evaluation of gum and solid dispersion:

Percentage yield determination: The gum was extracted and isolated from 100 g of raw material, then dried well and percentage yield was calculated by following formula:

$$\%\ Yield = \frac{Practical\ Yield}{Amount\ of\ raw\ material} X\ 100$$

Determination of flow properties: Bulk density, tapped density, Carr's Index (CI), Hausner's ratio and Angle of repose for gum powder were tested and calculated.

Fourier Transform Infrared (FTIR) Spectroscopy test: Atorvastatin and OKGSD were characterized using FTIR spectroscopy. KBr discs were prepared by mixing the sample with potassium bromide powder in the ratio 1:9 sample to KBr, then compressed into thin disk by using hydrostatic press model HP15, which then tested in IR Affinity 1(Shimadzu, Japan) instrument. Data was recorded over the spectral range 500- 4000cm^{-1} and resolution 4 cm^{-1}.

Saturation solubility determination: Saturation solubility studies were done according to the method described by Higuchi and Connors [17]. Excess of drug, physical mixtures and each of the three ratios of the solid dispersions prepared were added to 6 ml water in test tubes. The tubes were set for 24 hours in a sonicator, the saturated solutions were centrifuged to separate the precipitate, 1 ml of the supernatant was suitably diluted and analyzed using spectrophotometer (PG Instrument T80 UV/VIS spectrophotometer, China) at λ max 240 nm, each test was performed three times (n= 3). The concentration of the resultant solutions was calculated using the equation from calibration curve.

Drug content determination: Solid dispersions equivalent to 20 mg atorvastatin were weighed accurately, dissolved in 100 ml of phosphate buffer, filtered, diluted, drug content was analyzed at λ max 240 nm against blank using UV spectrophotometer. Actual drug contents were calculated using the equation:

Percent Drug content = $\frac{Actual\ amount\ of\ drug\ in\ SD}{Theoretical\ amount\ of\ drug\ in\ SD}$ X 100%

Preparation of atorvastatin tablet from solid dispersion: Atorvastatin tablets were prepared by wet granulation method, as specified in the table of formulation (Table 3). Accurately weighed quantities of solid dispersion, lactose, sodium starch glycolate (primogel) and MCC were mixed, sifted and wetted with the least amount of water to form wet mass, then forced manually through a mesh screen No 8 to form large granules, which then dried at 60°C for 30 min in the oven, crushed and passed through mesh No 12. Mg stearate and talc powder were mixed with dry granules and finally compressed on an 8 mm punch and die using single punch tableting machine (Shakti, India).

Tablet evaluation: Weight variation, hardness, friability, and disintegration tests were carried out for the prepared tablets and the results were recorded in table (4).

***In vitro* dissolution study:** The dissolution rate of the tablet prepared was studied in 900 ml phosphate buffer pH 6.8 using USP type II dissolution test apparatus (RC806D Dissolution Tester, China) with a paddle stirrer at 75 rpm and temperature 37±0.5°C were maintained throughout the study. Each sample was tested in 6 flasks and the mean absorbance was recorded. Samples from dissolution media (5ml) were withdrawn through syringe filters (0.45µ) at different time intervals (5, 10, 30, 45, 60,120, 180, 240, 300, 360, 480, 600 and 720 min) and directly assayed at λ 240 nm. The samples withdrawn at each time were replaced with fresh buffer fluid [18]. The concentration of each sample and the amount of drug in each sample were calculated. Finally, the percentages of drug released were calculated and plotted against time in dissolution profile, Figure (7).

***In vivo* study in mice:** Swiss albino mice were used in this study, the animals were kept in air conditioned room (24–25 °C) with constant humidity and allowed to eat and drink freely before they were distributed into experimental groups. They were divided into five groups (normal group, triton only group, pure Atorvastatin group, marketed drug group and OKGSD group) each group consists of six animals. Animals in group 1 were injected with normal saline whereas the other 5 groups were injected intraperitoneally with 400 mg/ kg triton WR1339 (Tyloxapol). After six hours, animals in group 3 were given pure Atorvastatin powder, group 4 were given marketed atorvastatin tablet and group 5 were given OKGSD in the dose of 20 mg/kg. The animals were fed the drugs in suspension form using intra-gastric tube. After 24 hours, blood samples were collected by decapitation method [19]. Serum was separated and used for biochemical estimation of lipid profile, i.e. total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL), percentage decrease in lipid concentration was calculated and results were plotted in figures [8-11].

Data Analysis

The comparison among the lipid profiles of all tested groups was carried out by one-way analysis of variance test (ANOVA) followed by T test (n = 6). $P < 0.05$ was considered as significant.

RESULTS

Table 1: Percentage yield determination and flow properties of okra gum

Property	Yield%	Bulk density	Tapped density	Carr's Index	Hausner's ratio	Angle of repose	pH value
Value	18	0.135	0.18	25	1.33	16	6.1

Fourier Transform Infrared (FTIR) Spectroscopy results:

FTIR spectra of Atorvastatin, OKG, FSM, OKGSD and FSMSD showed similar peaks without much shifting in the spectra of the drug and carriers which can be observed in Figures (3-5).

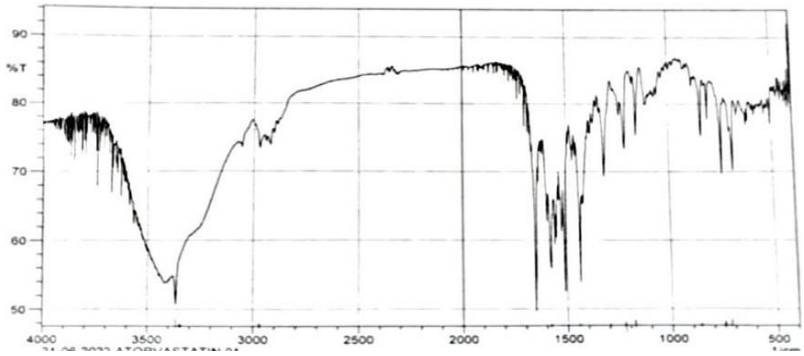

Figure 3: FTIR spectrum of pure Atorvastatin

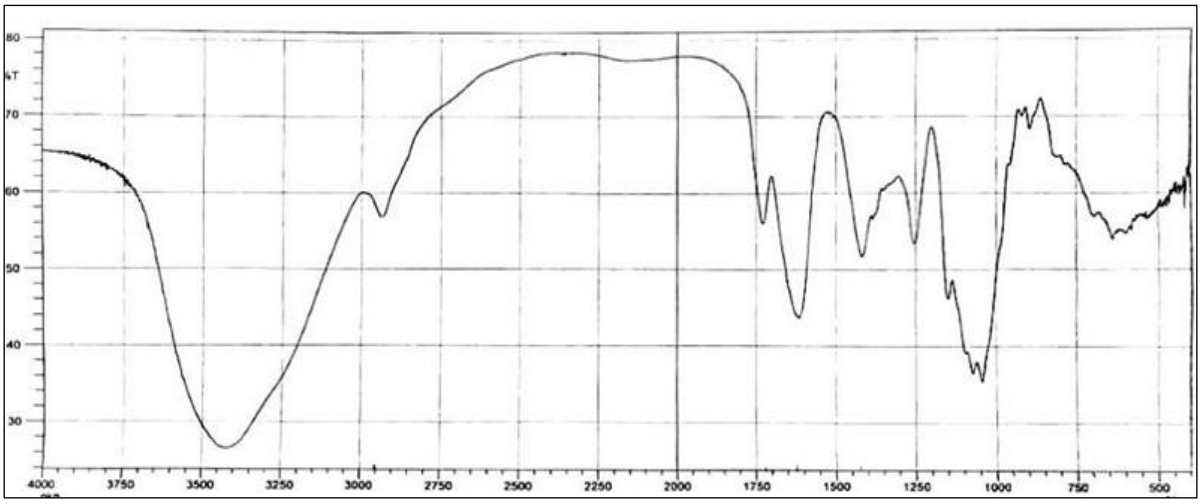

Figure 4: FTIR spectrum of OKG

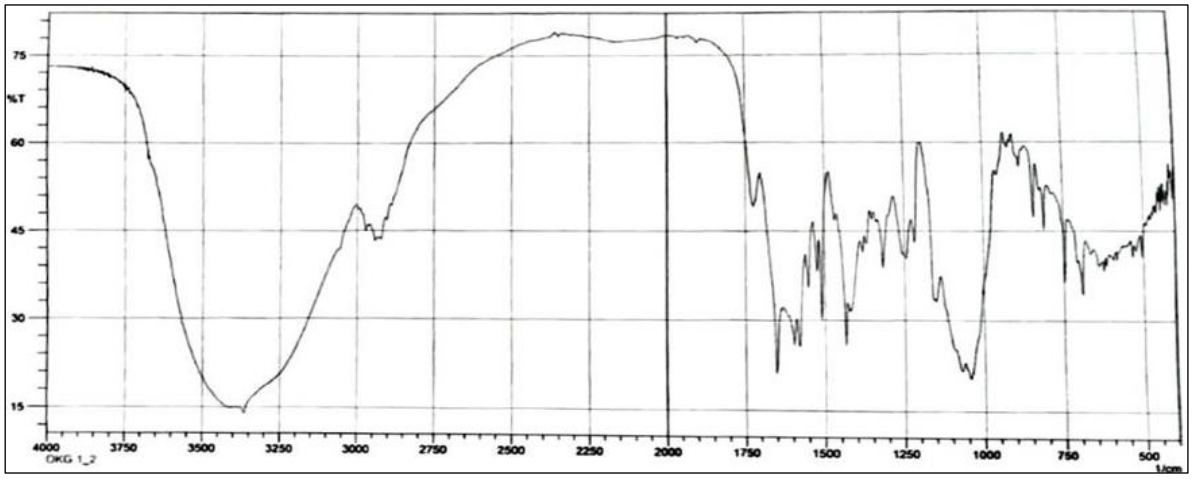

Figure 5: FTIR spectrum of OKGSD

Saturation solubility results:

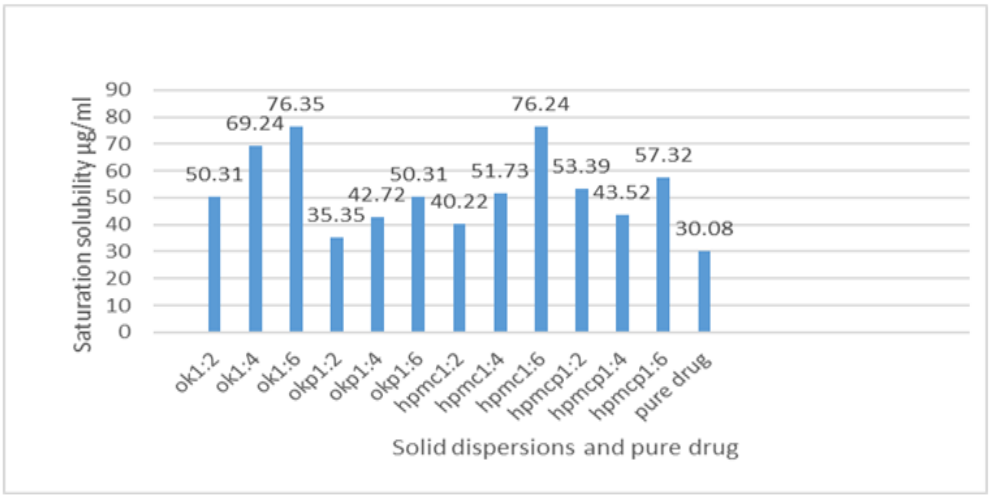

Figure 6: Saturation solubility of pure drug and solid dispersions

Where:

- ok: okra gum and atorvastatin solid dispersion
- okp: okra gum and atorvastatin physical mixture
- hpmc: hydroy propyl methyl cellulose and atorvastatin solid dispersion
- hpmcp: hydroy propyl methyl cellulose and atorvastatin physical mixture

Drug content determination results:

Table 2: Content percent of atorvastatin in the solid dispersions prepared

Polymer	Ratio	Absorbance	Weight(mg)	Content %
OKGSD	1:2	0.892	19.98	99.9
	1:4	0.886	19.84	99.2
	1:6	0.894	20.02	100.1
HPMC	1:2	0.890	19.95	99.8
	1:4	0.889	19.93	99.7
	1:6	0.890	19.90	99.5

Table 3: Tablet formulation:

Ingredient	Quantity/ tablet (mg)	%
Solid dispersion	140	40
Lactose	110	31
Mcc	80	23
Primogel	13	4
Talc	3.5	1
Mg stearate	3.5	1
Distilled water	Qs	-

Table 4: Physicochemical properties of the tablets prepared:

Average weight (mg ±SD)	Disintegration time(min)	Hardness test (Kg/cm^2)	Friability %	% Dissolved In 45 min
352 ± 6.23	24	5.24 ±0.457	0.001	89

I*n vitro* dissolution study results:

Tablets showed sustained release profile, and 87% of the drug released after 6 hours.

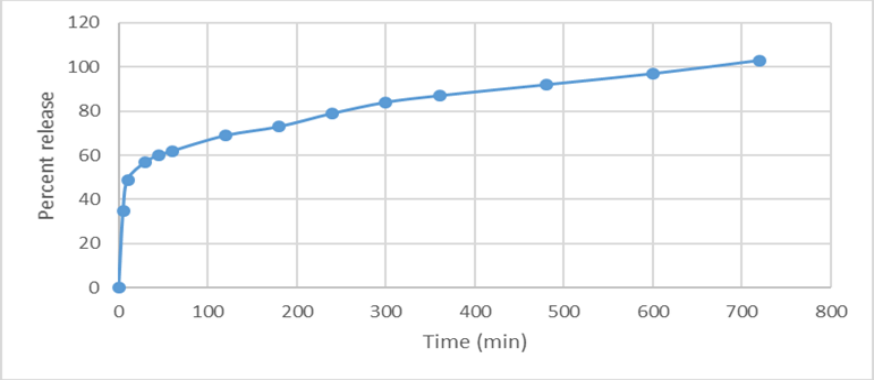

Figure 7: Dissolution profile of OKGSD tablet

***In vivo* test results:** The serum lipid profiles of all the experimental groups after a 24-h interval are presented in Table 5. along with the corresponding % decreases in lipid profiles of the four tested drugs compared to triton group.

Table 5: Lipid-Lowering Profile for *In vivo* Study in mice

Parameter / Group	TC (mg/dL)	Decrease %	TRI (mg/dL)	Decrease %	HDL (mg/dL)	Decrease %	LDL (mg/dL)	Decrease %
Normal	155±3.2	-	232±4.3	-	91±2.4	-	18±3.3	-
Triton	244±2.5	-	336±5.5	-	144±4.6	-	32±3.0	-
OKGSD	133±2.9	45	140±3.5	58	84±3.9	41	21±2.9	34
Marketed	153±3.4	37	120±3.0	64	100±2.7	31	28±3.7	13
Standard	169±3.2	28	176±4.0	47	105±2.6	27	29±3.6	9

Where:

- TC = Total cholesterol
- TRI = triglycerides,

- HDL = high density lipoprotein
- LDL = low density lipoprotein
- FSMSD = fenugreek seed mucilage solid dispersion
- OKGSD = okra gum solid dispersion.

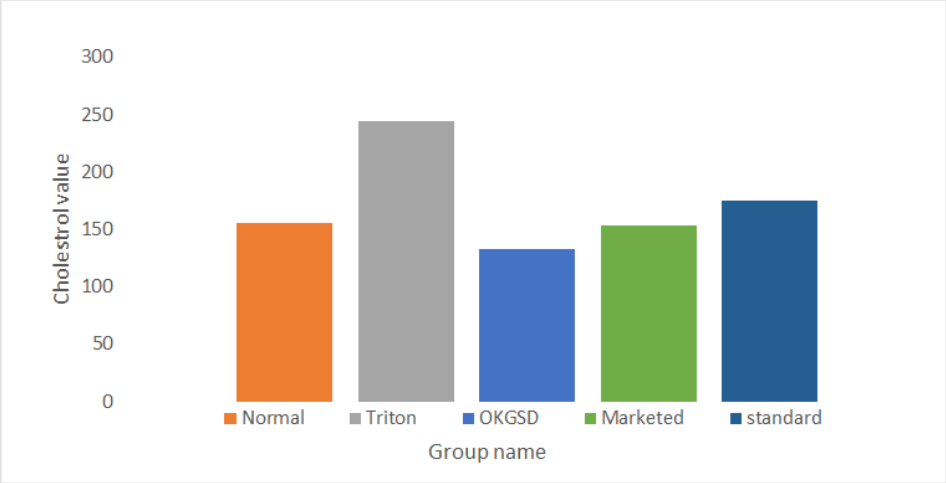

Figure 8: Total Cholesterol concentration in the different tested groups

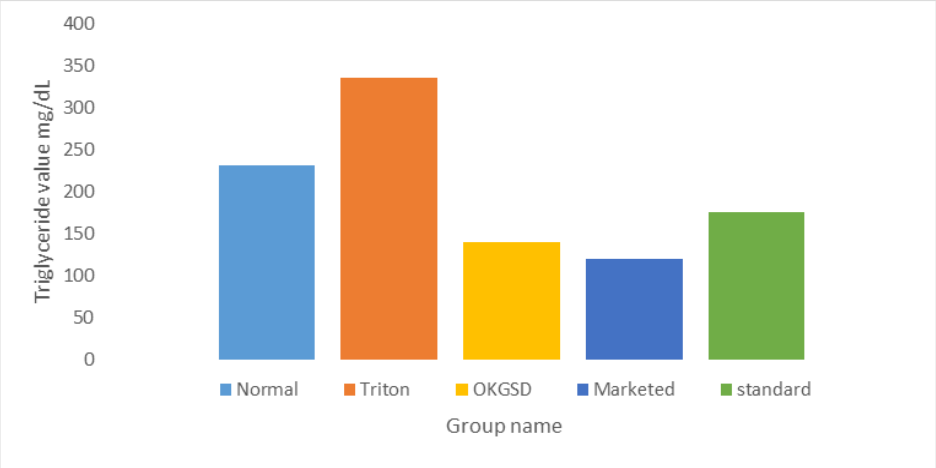

Figure 9: Triglycerides concentration in the different tested groups

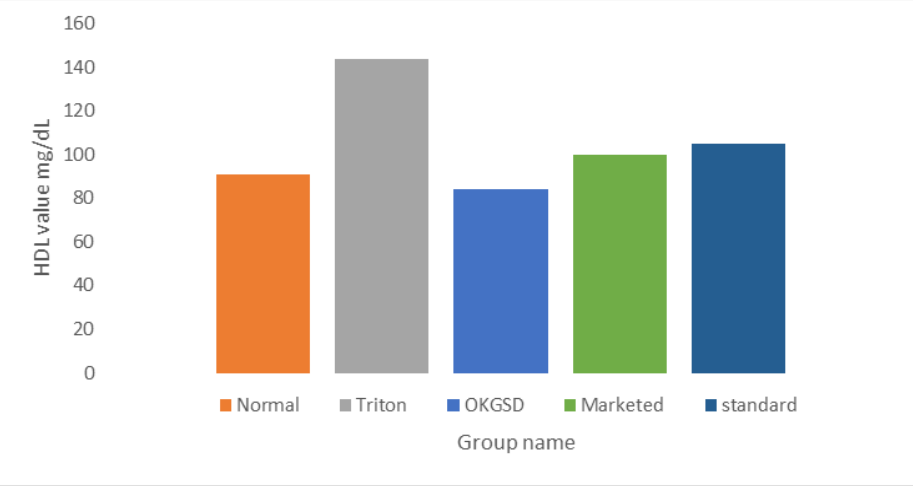

Figure 10: HDL concentration in the different tested groups

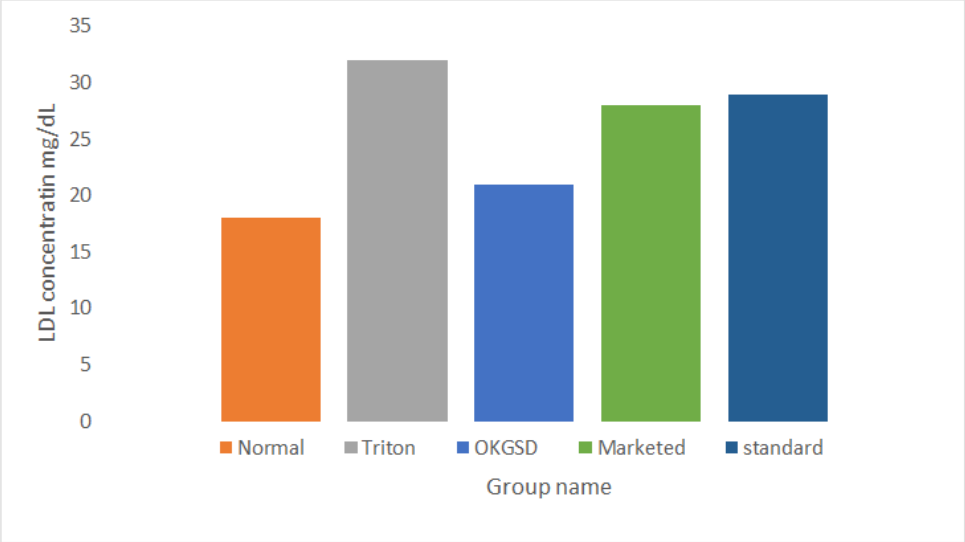

Figure 11: LDL concentration in the different tested groups

DISCUSSION

The aim of the present study was to assess the effect of okra gum solid dispersion in atorvastatin solubility (BCS class II drug has low solubility and high permeability). Enhancing the solubility of atorvastatin increases its oral bioavailability which is very low ≈ 14%. Okra gum is a natural product containing hydrophilic polymers, which are biocompatible, biodegradable, has low toxicity and relatively low production cost from abundant natural sources. These polymers degrade into biologically accepted molecules that are metabolized and removed from the body through normal metabolic pathways [20]. Okra gum was used by researchers as pharmaceutical excipients in drug formulation [21].

OKG was extracted by hot water extraction method, followed by precipitation by absolute ethanol then dried using freeze dryer. The yield was 18% w/w gum. This percentage was moderately low, which may increase the cost of the final product. So other methods must be developed to increase the yield.

In the study, HPMC was used as a synthetic polymer that previously used to enhance the solubility of poor water soluble drugs using solid dispersion technique [22]. Solid dispersions with different ratios of drug to gum were prepared and compared to HPMC.

pH value obtained was 6.1, which indicates that the extracts were not irritant to the gastrointestinal tract and can be used safely in oral dosage forms preparation.

The prepared gum had good flow properties and poor compressibility, which necessitate the use of wet granulation method in tablet preparation.

FTIR spectroscopy test was carried out for the investigation of possible interaction between the drug and the polymers used in the test. The principle IR absorption peaks of the solid dispersions prepared were observed and found having similar peaks of the spectra of the pure drug without much shifting in the main peaks. Thus, from the spectra it understood that there was no interaction between atorvastatin and the polymers used in the preparation of solid dispersions, these outputs confirm the possibility of using these polymers in drug formulation safely.

When testing saturation solubility of the solid dispersions prepared, it found that different drug to polymer ratios had different saturation solubility. It was noticed that, there was marked increase in saturation solubility with increasing the polymer ratio. With 1:6 drug to polymer ratio, there was about two folds' increase in saturation solubility. In physical mixtures there was moderate increase in saturation solubility values compared to solid dispersions (one fold). The use of high gum ratio markedly increases saturation solubility, but it takes large amount of the gum at expense of the other tablet excipients which may limit its use in tablet formulation. OKG solid dispersion had higher values of saturation solubility compared to pure drug and HPMC.

The results of content percent test of drug in solid dispersions, was in the range 99.2 -100.1%, which comply with the pharmacopeia.

The dissolution test for the different ratios of the solid dispersions prepared showed wide differences in release profiles. The release of atorvastatin from OKGSD powder was faster than HPMC.

For tablet preparation the solid dispersion used was 1:6 drug to polymer ratio, which had the highest saturation solubility compared to the other prepared ratios, so the concentration of the polymer is moderately high. According to the previous tests, OKG showed good

flowability and bad compressibility, which necessitate the use of wet granulation method in tablet preparation. The physicochemical properties of OKGSD tablets were found satisfactory as per official guideline, the mean tablet weight was 352.9± 6.23 mg, the hardness of the tablets was moderate and in the range specified by the pharmacopeia (5.2 kg cm^2), the tablets had good friability results [23]. In spite of the use of primogel as super disintegrant, OKGSD tablets took 24 min to disintegrate, which indicates the high binding effect of OKGM.

When conducting dissolution test, OKGSD tablet exhibited sustained released profile,60%,87% and 97% of the drug released into dissolution medium in 45 min, 6 hrs and 12 hours respectively, while OKGSD powder showed immediate release profile which may be due to enhancement of the binding effect of OKG by granulation and compression of the tablets.

Swiss albino mice were used in this study to test the changes that occur in lipid profile when using OKGSD tablet compared to marketed tablets and pure atorvastatin powder. As expected, after 24 hours of treatment with Triton (WR1339), the control group (triton group) showed a significant increase in total cholesterol, Tri, LDL and HDL. With OKGSD tablets, lipid levels were decreased markedly; 45,58, 41, 43% decrease for TC, TRI, HDL and LDL respectively. In case of Marketed drug and standard powder, there was high percentage of decrease in TC, TRI and HDL, while LDL had 13 and 9% decrease respectively. When comparing each part of the lipid profile individually, we found that total cholesterol was decreased significantly in all tested groups compared to control group, i.e. 153 and 175 for marketed drug, and standard drug with maximum decrease in OKGSD group (p value = 0.0 for all groups). For triglycerides, it was noticed that, the maximum percent decrease with the marketed drug, with significant decrease in triglycerides level in all tested groups. When observing HDL levels, it was shown that there was significant decrease in its levels (p value =0.0) for all groups, with the highest percent decrease in OKGSD group. LDL group showed insignificant decrease in its level in MD and STD group. Compared to atorvastatin standard powder, it can be noticed that the two other tested groups had higher percent decrease in lipid levels.

A comparison among groups was carried out by one-way analysis of variance (ANOVA) followed by T test (n = 6). $P < 0.05$ was considered as significant. All the groups had significant decrease in lipid level compared to triton group.

Thus, OKGSD tablets performed better than MD and standard atorvastatin powder in reducing total cholesterol, TG, HDL and LDL levels, which could be attributed to the improved solubility and dissolution associated with amorphization of the drug and wetting effect of OKG.

CONCLUTION

From the previously discussed results, it can be concluded that:

- Content percent of the drug in the solid dispersions prepared was found in the range accepted by the pharmacopeia (from 99.9 to 100.1 %).
- FTIR spectroscopy showed no evidence of interaction between the drug and the gum used.
- Compared to pure drug, the saturation solubility of atorvastatin was doubled in value (from 30 µg /ml for pure powder to 76 µg /ml) for OKGSD with 1:6 drug to polymer ratio.
- Tablets prepared showed satisfactory physicochemical properties.
- Drug release from the tablet after 6 hrs was 87% for OKGSD.
- OKGSD tablets exhibited long disintegrating time and sustained release profile.
- *In vivo* studies in mice showed a higher percentage decrease in cholesterol and triglyceride levels in mice than those achieved with pure drug. This may be due to improved bioavailability in mice and elevated extent of drug release when drug was administered in solid dispersion form.

RECOMMENDATIONS

- Extraction method other than that used in this research should be developed to increase the yield percent and decrease production cost.
- Additional research required to study the effect of OKG in drug release and developing sustained release dosage form.
- Further Studies should be done to estimate the pharmacokinetic parameters for OKGSD tablets.

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