AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Atorvastatin Calcium Solid Dispersion in Floating Tablets for Hypolipedmic Effect.

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ABSTRACT

The aim of this study was increasing the bioavailability of poorly water soluble, atorvastatin calcium (ATC) via preparation of solid dispersion then incorporating it in floating tablets for oral use. Physical mixtures of ATC were prepared by mixing the appropriate amounts of ATC and carriers (PVP k-2000, PEG 6000 and skimmed milk) in geometric proportions using a mortar and pestle, until a homogeneous mixture was obtained. Solid dispersions of ATC with all carriers were prepared at ratios of (1:1, 1:3, 1:5, 1:7 and 1:9 drug to carrier ratio w/w) by three methods, kneading method, solvent evaporation and melting method. Evaluation of solid dispersion was done by studying the phase solubility, *in-vitro* dissolution, FTIR spectroscopy, DSC and X-ray powder diffractometry. The selected solid dispersion formulation was incorporated in floating tablets which were prepared by melting granulation method. Evaluation of floating tablets was done by determination of tablet thickness, diameter, weight uniformity, content uniformity, hardness, friability, *in-vitro* dissolution, *in-vitro* buoyancy in addition to bioavailability studies. PEG 6000, PVP k-2000 and skimmed milk increased the solubility of ATC by 180, 290 and 1200 folds, respectively. Solid dispersion prepared using PEG 6000 (S2, 1:3 drug: polymer ratio) gave the highest % drug released than PVP k-2000 and skimmed milk. Floating tablet formulation (T1) showed the best drug dissolution rate which is 102.18% after 24 h. Bioavailability results showed that floating tablets containing ATC solid dispersion is effectively used for treatment of hyperlipedmia. Floating tablets contained PEG 6000 solid dispersion reduced the % of TC, TGS and LDL by 58.46, 32.00 and 91.21 %, respectively while the percent of HDL was raised by 11.11%.

Keywords: Atorvastatin calcium, PEG 6000, PVP, skimmed milk, floating tablets and cholesterol.

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Received 05 September 2016, Accepted 15 September 2016

Please cite this article as: Marwa AH *et al*., Atorvastatin Calcium Solid Dispersion in Floating Tablets for Hypolipedmic effect. American Journal of PharmTech Research 2016.

INTRODUCTION

Solid dispersions are prepared by blending one polymer or more with the drug as a mean of enhancement of drug release rate and increasing the drug bioavailability [1]. There are several methods used for solid dispersions preparation including melting method, solvent evaporation method, co-grinding method, melting-solvent method, kneading method, gel entrapment technique and electrospining method. Solid dispersions were classified, according to the used carrier, into three groups: first generation, second generation and third generation [2]. First generation solid dispersions are formed by using carriers with crystalline nature which is a drawback because the crystalline carrier gives slower drug release; examples of such carriers are sugar and urea. Second generation solid dispersions are formed using amorphous carriers as ethyl cellulose, poly ethylene glycol, polyvinyl pyrrolidone, hydroxypropyl methylcellulose and starch. Surfactants are used in third generation for more improvement in drug dissolution rate; examples of surfactants used are poloxamer and inulin [3]. There are several advantages of solid dispersions including decreasing the drug particle size, increasing solubility of poorly water soluble drugs, elimination of the drug's unfavorable taste and increasing the drug's wettability [4]. There are also several disadvantages related to their stability which is mainly affected by different dosage form manufacturing steps and storage, also the carriers used for solid dispersion preparation have high ability to absorb moisture which results in crystal growth phase separation and finally may lead to a decrease in solubility and dissolution rate [5]. Atorvastatin calcium (ATC), as a synthetic lipid-lowering agent, is an inhibitor of 3-hydroxy-3- methyl-glutaryl- coenzyme A (HMG - CoA) reductase which catalyzes the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Atorvastatin is currently used as calcium salt for the treatment of hypercholesterolemia [6].

The purpose of our study was to increase the bioavailability of ATC via preparation of solid dispersion in floating tablets for oral use.

MATERIALS AND METHOD

Materials:

Atorvastatin calcium (ATC), polyvinyl pyrrolidone k- 2000 (PVP), polyethylene glycol 6000 (PEG), white bees wax, hydroxypropyl methyl cellulose (HPMC), ethyl cellulose (EC), sodium bicarbonate, magnesium stearate and talc were obtained from Epico.co.10th of Ramadan city, Egypt. Methanol, ethanol, acetone and HCL all were in analytical grade and were obtained from El-Gomhoria Co. Cairo, Egypt. Skimmed milk was obtained from Arla foods amba, Denmark. Diagnostic kits were obtained from spin react, Spain.

Methods:

Preparation of solid dispersion:

Solid dispersion was prepared using three different polymers PEG 6000, PVP and skimmed milk. Kneading method and solvent evaporation method were used for preparation of solid dispersion from PVP, PEG 6000 and skimmed milk. PEG 6000 solid dispersion was prepared additionally by melting method. Solid dispersions of ATC with all carriers were prepared at ratios of (1:1, 1:3, 1:5, 1:7 and 1:9 drug to carrier ratio w/w).

Kneading method:

ATC was mixed with polymers and wetted with water, kneading was done in a mortar for 30 mins until paste formation then the paste was left to dry in a vacuum oven (Lab – line instruments, Inc, USA). Finally, the mixture was pulverized and sieved using a sieve No.60 [7].

Solvent evaporation:

ATC was mixed with polymers using different solvents (methanol, ethanol, and acetone). The mixture was then dried by solvent evaporation by keeping in a hot air oven for 24 h. Then the mixture was pulverized and sieved using a sieve No.60 [8].

Melting method:

Firstly PEG6000 was melted in a water bath then ATC was added to the melted PEG6000 in various drug to polymer ratios. The mixture was left to dry then was pulverized and sieved using a sieve No.60 [9].

Phase solubility study:

A Known excess amount of ATC was put in rubber sealed glass vials containing different concentrations of PEG 6000. The mixture was shaked for 24 h using a water bath shaker at 25^{o}C. Then the solution was filtered, diluted and the absorbance was measured at 246 nm using a Shimadzu UV- 160A spectrophotometer (Shimadzu Co, Japan) to get the drug concentration and hence the solubility of drug in polymer [10,11].

***In-vitro* dissolution studies:**

In- vitro dissolution studies were performed in triplicate with a Pharma test dissolution tester type II (SP6-400 Hamburg, Germany) in different mediums (500 ml distilled water or 500 ml 0.1 N HCL buffer) at 37 ± 0.2 °C, using a paddle rotating at 75 rpm. Solid dispersion containing 10 mg of drug and pure drug were subjected to dissolution testing. At fixed time, 5 ml samples were withdrawn and filtered using Whatman filter paper No. 41 and the samples were spectrophotometrically assayed for drug content at 246 nm. The initial volume was maintained by adding 5 ml of fresh dissolution medium.

The dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution over the same time.

Fourier transform infrared spectroscopy (FTIR):

FTIR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrophotometer using KBr disk method. The scanning range was 200–4000 cm^{-1} and the resolution was 1 cm^{-1}.

Differential scanning calorimetry (DSC):

DSC analysis was performed using a Model DT-60 DSC (Shimadzu). Samples weighing 2.65, 2.30, 2.63 and 2.60 mg of drug, polymer, physical mixture and solid dispersion respectively were heated in hermetically sealed aluminum pans over a temperature range of 10 – 200 °C at a constant rate of 10 °C min^{-1} under a nitrogen steam.

X-ray powder diffractometry (XRPD):

X-ray powder diffraction patterns were obtained D-5000 X-ray diffractometer with CuK α radiation over a 2θ range of 5 – 50° using a step size 0.01° at a scanning rate 0.55 with speed 0.02 s/step.

Formulation of floating solid dispersion tablets:

Floating tablets were prepared by melting granulation method. Amount of bees wax in a porcelain dish was melted on a water bath then the solid dispersion, HPMC, ethyl cellulose and sodium bicarbonate were added to the bees wax and mixed well, after complete melting the resulted paste was cooled. Magnesium stearate and talc were added and the mixture was sieved using sieve No.60 [12]. The granules were compressed were compressed using a single punch tablet machine (Korsch Frogerais, type AO, Berlin, Western Germany). Table (1) demonstrates the compositions of different tablet formulations.

Table 1: Formulations of floating tablets prepared from (1:3) PEG6000 solid dispersion.

Formulation code	White Bees wax (mg)	Solid dispersion (mg)	HPMC (mg)	Ethyl cellulose (mg)	Sodium bicarbonate (mg)	Magnesium stearate (mg)	Talc (mg)
T1	40	80	40	0	30	5	5
T2	40	80	30	10	30	5	5
T3	40	80	20	20	30	5	5
T4	40	80	10	30	30	5	5

Evaluation of floating tablets:

Physical properties and pharmacopoeial requirements [13]:

Tablets thickness and diameter:

The thickness and the diameter of 10 tablets were measured by means of a micrometer. The average thickness and diameter were determined and standard deviation was calculated.

Weight uniformity:

The test was carried out according to BP, 2006 where 20 tablets were individually weighed. The average weight was determined and the standard deviation was calculated.

Content uniformity:

A random sample of five tablets was selected according to BP, 2006 and the tablets were powdered in mortar. A weighed amount of powder equal to the mass of one tablet (200mg) was dissolved in 5 ml methanol by magnetic stirrer then volume was made up to 100 ml in a volumetric flask by 0.1N HCL buffer. The solution was filtered by a Whatman filter paper and analyzed by UV spectrophotometer at 246 nm.

Determination of the tablet crushing strength (hardness):

This test was intended to determine, under defined conditions, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing. Using Erweka hardness tester (Erweka-Apparatabeua, Frankfort, Western Germany), the measurement was carried out for 10 tablets and the mean value was calculated. For the measurement, the tablet was oriented in the same way with respect to the direction of application of the force (BP, 1998).

Determination of the tablet friability:

The test was carried out according to BP 2006 where 10 tablets were accurately weighed (W1) and placed in the drum of the friabilator which rotated at 25 rpm for a period of 4 mins after which tablets were reweighed (W2) and the loss in weight in terms of (%F) was taken as a measure of tablet friability according to the following formula:

$$\%F = [(W1 - W2)/W1]*100$$

***In-vitro* dissolution study of solid dispersion floating tablets:**

In-vitro dissolution studies were performed in triplicate with a Pharma test dissolution tester type II in 0.1 N HCL buffer (900 ml) at 37 ± 0.2 °C, using a paddle rotating at 75 rpm. The solid dispersion floating tablets, each containing 20 mg of ATC and 60 mg of PEG 6000 1:3 drug : polymer ratio, were subjected to dissolution testing. At fixed time, samples (5 ml) were withdrawn, filtered using Whatman filter paper No. 41, and spectrophotometrically assayed for drug content at 246 nm. The initial volume was maintained by adding 5 ml of fresh dissolution medium [14].

***In-vitro* buoyancy study:**

In-vitro buoyancy studies were performed for the four tablet formulations, randomly selected tablet was kept in a beaker containing 200 ml 0.1 N HCL buffer. The time interval between the

introduction of the tablet into the dissolution medium and its floating to the top of dissolution medium was the lag time [14]. The overall floating time was calculated.

Bioavailability of ATC solid dispersion floating tablets:

Bioavailability studies were done for 3 groups (n=3 per group) of male rabbits weighing (2± 0.25 kg) for each. Rabbits were purchased from the animal farm of faculty of agriculture, Zagazig University. Experimental design and animal handling were performed according to the guidelines of the Ethical Committee of the Faculty of Pharmacy, Zagazig University for animal use ‘’ECAHZU”. Hypercholesterolemia was induced in the three groups by oral feeding of high fat diet with composition of (60% normal food, 20% margarine and 20% sugar) per day for one week in addition to oral feeding of cholesterol suspended in 2ml of sesame oil for each rabbit daily for one week, their normal diet composition is (18% pure protein, 2.88% pure fats, and 10.5% pure fibers). Group A received ATC solid dispersion floating tablets in a dose of 20 mg/kg/day [15] for one week [16], group B received marketing tablets (ATOR®) in the dose of 20 mg/kg/day and group C (controlled group) received no treatment. Blood samples were collected from each rabbit in each group and total cholesterol (TC), triglycerides (TGS), HDL (high density lipoprotein) and LDL (low density lipoprotein) were measured for each rabbit. Values of TC, TGS, HDL and LDL pre-cholesterol administration, after cholesterol administration and after treatment of rabbits in each group were compared.

Statistical analysis:

All the means are presented with their standard deviation (mean± standard deviation, SD). Two way ANOVA test was used to analyze the results statistically. A p value <0.05 was considered significant.

RESULTS AND DISCUSSION

Solubility measurements:

Figure (1) shows the effect of different carriers on the solubility of ATC. Figure (1a) shows an increase in the solubility of ATC by 180 folds using 50 mg of PEG 6000. The enhancement of solubility caused by PEG6000 was due to its role in lowering the interfacial tension between ATC and the medium of dissolution [17]. While figure (1b) shows an increase in the solubility of ATC by 290 folds using 90 mg of PVP. This increase was due to the ability of PVP to form hydrogen bond with ATC [18]. Figure (1c) shows maximum increase in the solubility of ATC 1200 folds by addition of 90 mg of skimmed milk. Skimmed milk acts as a surfactant where its hydrophilic groups form micelle with ATC hydrophilic groups making it more water soluble [19].

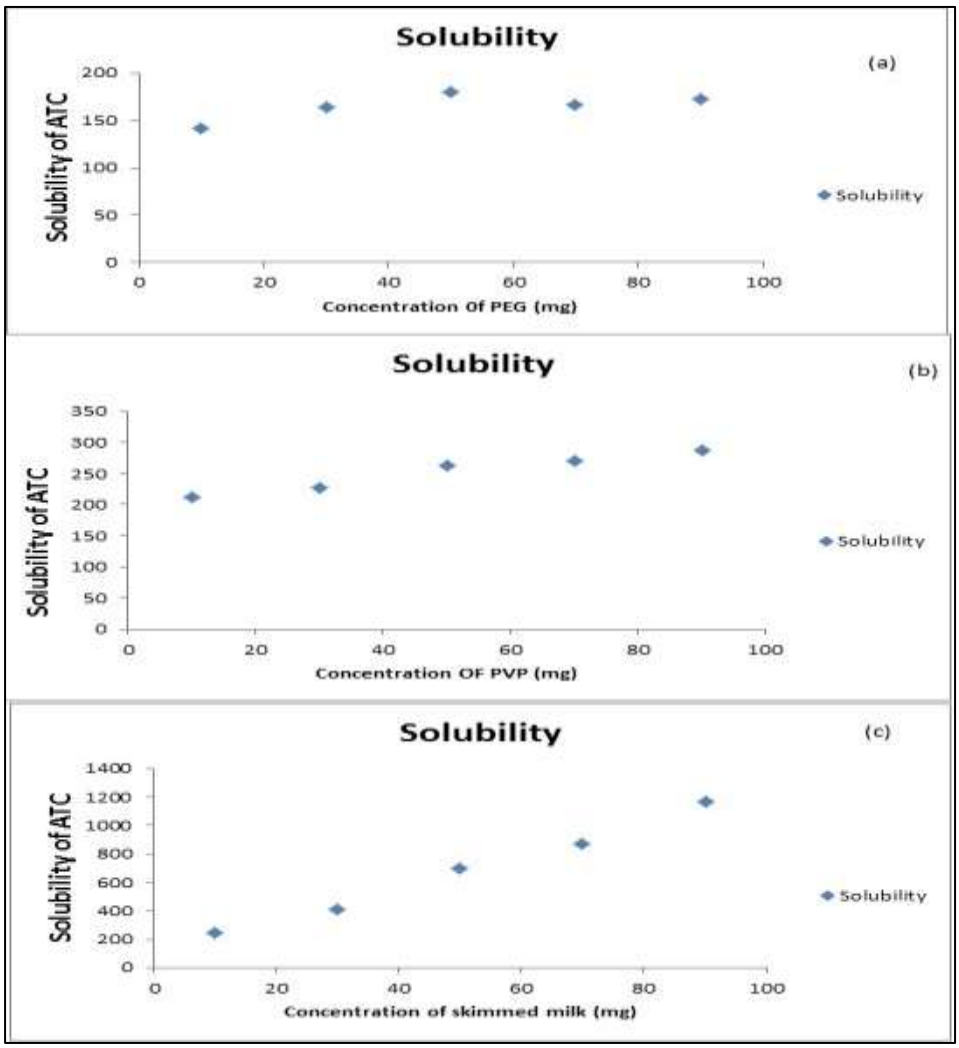

Figure 1: Phase solubility diagram of ATC in water at 25 ^{o}C in presence of (a) PEG 6000, (b) PVP and (c) Skimmed milk.

Dissolution studies of solid dispersion:

Table (2) demonstrates the cumulative % release of pure ATC, physical mixture and solid dispersion prepared by several methods using three polymers, PEG6000, PVP and skimmed milk after 60 mins in distilled water. It was found that, increasing the drug to polymer ratio from 1:1 to 1:3 the % drug released was increased significantly ($p<0.001$) then, further increase in the drug to polymer ratio showed a non significant increase in the % drug released ($p>0.05$). By comparing ratio 1:3 in all formulations from F1-F10 it was found that, the highest % drug released of PEG 6000 solid dispersion was from F2 prepared by kneading method, the highest % drug released of PVP solid dispersion was from F7 prepared by solvent evaporation method and the highest % drug released of skimmed milk was from F10 prepared by solvent evaporation method and the % drug released was decreased in the following order: F7>F2>F10.

Table 2: Cumulative % release of pure drug, physical mixtures and solid dispersions using PEG6000, PVP and skimmed milk in distilled water after 60 mins.

Drug: polymer ratio	Cumulative % release after 60 minutes in distilled water									
	Pure drug	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
	28.59±0.0.5										
1:1		64.18+3.30	85.00±1.10	71.43±1.52	80.99±1.99	56.79±2.23	96.83±1.26	84.84±0.04	49.85±0.88	67.37±1.52	77.69±0.63
1:3		68.57±0.50	92.20±0.20	89.00±2.10	91.47±1.30	70.85±0.05	96.33±0.06	98.86±0.84	34.62±0.75	74.36±0.66	85.66±1.31
1:5		70.34±0.10	91.54±0.04	99.88±3.20	96.28±2.20	74.69±0.22	95.00±1.60	98.67±0.51	49.00±2.10	70.58±1.24	77.71±2.20
1:7		71.32±0.32	99.00±1.99	99.42±1.40	91.17±1.70	72.82±2.50	93.77±1.11	98.49±2.31	50.28±1.23	72.32±1.45	89.11±1.85
1:9		70.75±0.52	89.53±0.80	96.87±1.38	95.82±1.35	78.13±1.80	96.16±0.68	98.00±1.71	51.20±2.10	70.22±0.32	88.10±0.78

Where, F1 is the physical mixture of ATC and PEG 6000, F2 is the solid dispersion of ATC and PEG 6000 prepared by kneading method, F3 is the solid dispersion of ATC and PEG 6000 prepared by solvent evaporation method, F4 is the solid dispersion of ATC and PEG 6000 prepared by melting method, F5 is the physical mixture of ATC and PVP, F6 is the solid dispersion of ATC and PVP prepared by kneading method, F7 is the solid dispersion of ATC and PVP prepared by solvent evaporation method, F8 is the physical mixture of ATC and skimmed milk, F9 is the solid dispersion of ATC and skimmed milk prepared by kneading method, F10 is the solid dispersion of ATC and skimmed milk prepared by solvent evaporation method.

Table (3) demonstrated the cumulative % release of pure ATC, physical mixture and solid dispersion prepared by several methods using PEG6000, PVP and skimmed milk after 60 mins in 0.1 N HCL. Comparing the five drug to polymer ratios 1:1,1:3,1:5,1:7 and 1:9 in all formulations from S1-S10 it was found that, increasing the drug to polymer ratio from 1:1 to 1:3 the % drug released is increased significantly ($p<0.001$) then, further increase in the drug to polymer ratio didn't cause a significant increase in the % drug released ($p>0.05$). Comparing ratio 1:3 in all formulations from S1-S10 it was found that, the highest % drug released of PEG6000 solid dispersion was S2, the highest % drug released of PVP solid dispersion was S7 and the highest % drug released of skimmed milk was S9 and the % drug released was descending in the following order: S9>S2>S7. From the previous results it was found that, the PEG6000 solid dispersion prepared by kneading method gave the highest % ATC released in 0.1 N HCL buffer, so it was used for preparation of floating tablets.

Table 3: Cumulative % release of pure drug, physical mixtures and solid dispersions using PEG6000, PVP and skimmed milk in 0.1 N HCL buffer after 60 mins.

Drug: polymer ratio	Cumulative % release after 60 minutes in 0.1 N HCL buffer									
	Pure drug	**S_1**	**S_2**	**S_3**	**S_4**	**S_5**	**S_6**	**S_7**	**S_8**	**S_9**	S_{10}
	31.05±0.05										
1:1		56.81±1.21	96.37±1.20	85.40±0.01	90.75±0.12	68.83±2.12	83.87±0.56	83.55±0.87	63.82±0.06	88.32±0.23	89.47±0.09
1:3		66.07±0.04	99.00±0.88	98.00±0.11	95.98±0.42	83.42±0.22	92.00±0.66	97.93±0.89	67.48±0.50	98.61±0.51	93.31±0.31
1:5		70.40±1.20	99.73±0.20	99.00±0.12	90.97±0.34	82.49±0.04	95.96±0.24	95.00±1.32	67.12±1.30	93.40±0.38	83.55±2.50
1:7		72.98±1.41	99.70±0.23	99.98±0.01	98.70±0.11	80.82±0.05	99.30±0.10	97.61±0.34	68.54±2.20	90.50±1.31	85.35±1.56
1:9		75.22±1.09	99.80±0.01	99.00±0.02	98.90±0.11	80.53±0.07	91.86±0.34	98.42±0.31	65.38±1.50	89.70±2.33	87.31±1.88

Where, S1 is the physical mixture of ATC and PEG 6000, S2 is the solid dispersion of ATC and PEG 6000 prepared by kneading method, S3 is the solid dispersion of ATC and PEG 6000 prepared by solvent evaporation method, S4 is the solid dispersion of ATC and PEG 6000 prepared by melting method, S5 is the physical mixture of ATC and PVP, S6 is the solid dispersion of ATC and PVP prepared by kneading method, S7 is the solid dispersion of ATC and PVP prepared by solvent evaporation method, S8 is the physical mixture of ATC and skimmed milk, S9 is the solid dispersion of ATC and skimmed milk prepared by kneading method, S10 is the solid dispersion of ATC and skimmed milk prepared by solvent evaporation method.

Fourier transform infrared spectroscopy (FTIR):

FTIR were performed to investigate the possible type of interaction between ATC and PEG 6000. Figure (2) shows that, the characteristic shoulders of ATC were traced at 3360 and 3365 cm^{-1} (N-H stretching), 3406 cm^{-1} (O-H), 3057 cm^{-1} (c=c),1315 and 1216 cm^{-1} (C-OH), 1433 cm^{-1} (C-C) ,1216 cm^{-1} (C-O), 1650 cm^{-1} (C=O), 3057 cm^{-1}(C-H Aromatic), 2923 and 2967 cm^{-1} (C-H Aliphatic) and 694 cm^{-1} (C-F).

In PEG 6000 PM, all the characteristic bands of drug and the polymer were the same except the hydroxyl group of PEG 6000 which was disappeared due to the intermolecular hydrogen bond. This reflected that there were interactions between the drug and the polymer. In case of PEG 6000 SD, it was noted the disappearance of O-H bands of the drug which may be due to the intermolecular hydrogen bond between the drug and polymer, which leads to formation of a network between them. C-O group of the drug was shifted from 1216 to 1240 cm^{-1} in solid dispersion.

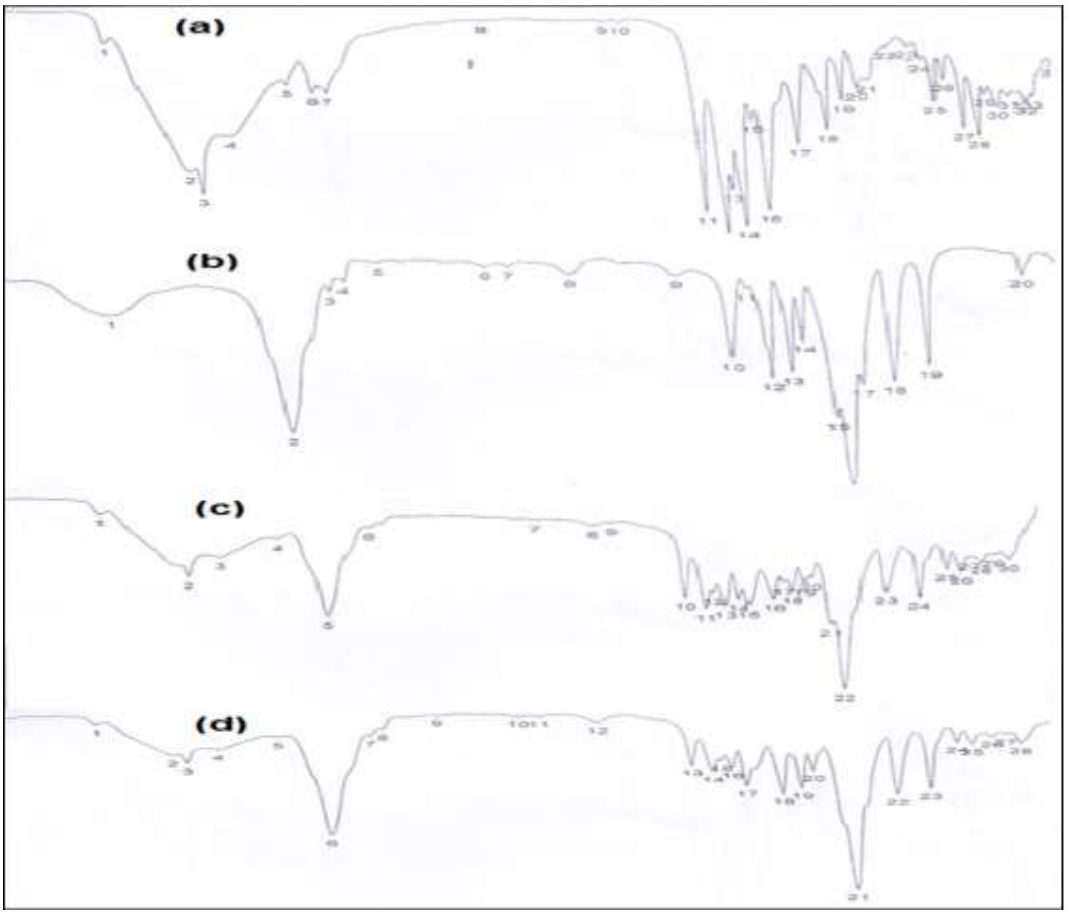

Figure 2: FTIR spectra of ATC-PEG6000 systems. (a) ATC alone, (b) Pure PEG 6000, (c) Physical mixture of ATC and PEG 6000 (1:3), (d) Solid dispersion of ATC and PEG 6000 (1:3).

Differential scanning calorimetry (DSC):

The DSC curve of ATC showed a sharp endotherm at 154.37°C indicating the melting point of ATC. DSC curve of PEG 6000 showed a characteristic peak at 58.12 °C. In the physical mixture, the endothermic peaks of ATC and PEG 6000 were observed at 57.91°C and 164.39°C. The characteristic peaks of ATC almost disappeared in the solid dispersion, which indicated ATC dissolution in PEG 6000 (Figure (3)).

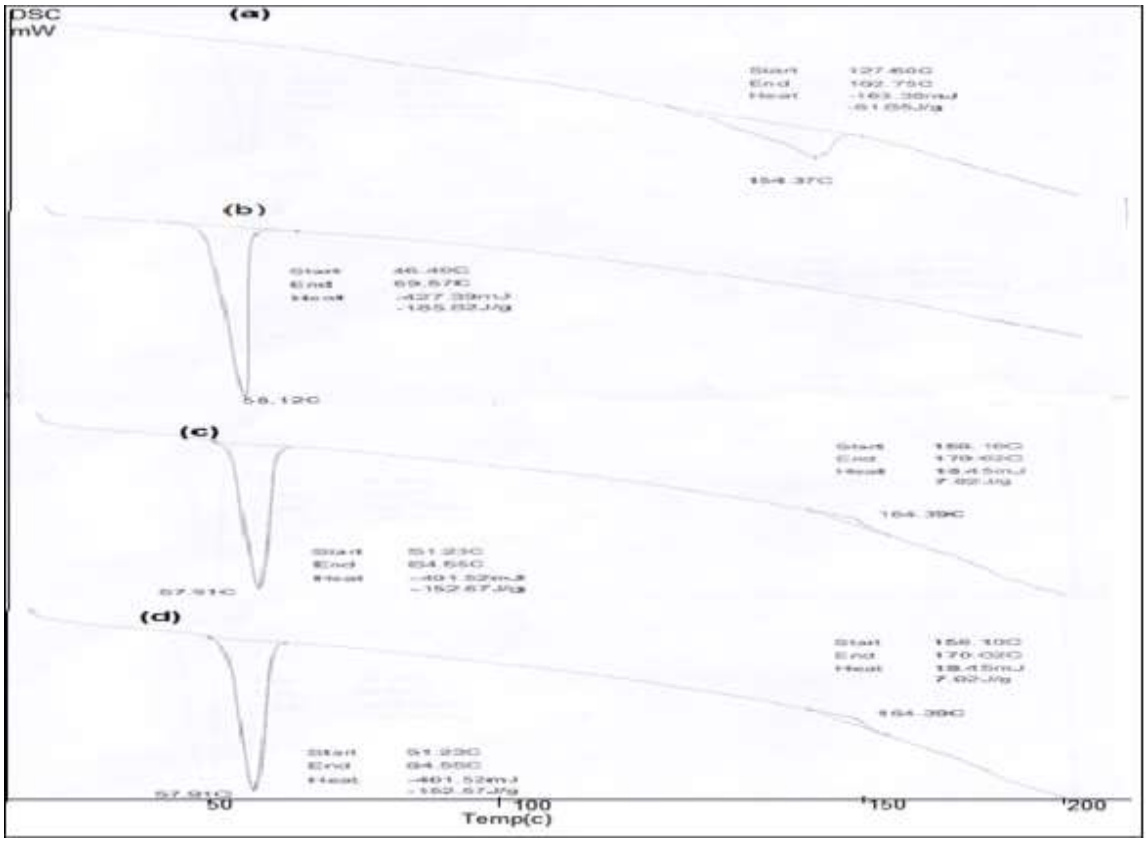

Figure 3: DSC spectra of ATC-PEG6000 systems.(a) ATC alone, (b) Pure PEG 6000, (c) Physical mixture of ATC and PEG 6000 (1:3), (d) Solid dispersion of ATC and PEG 6000 (1:3).

X-ray diffraction:

Figure (4) shows that, the x ray diffraction pattern of ATC gave special sharp peaks at 8.9, 9.26, 10.04, 10.34, 11.66, 11.96, 16.82, 19.22, 21.38, 22.46, 23.06 and 23.48, which illustrated that ATC was existing in the crystalline form which is also obvious in DSC. PEG 6000 gave two unique peaks at 19.22 and 23.36. ATC-PEG 6000 physical mixture gave the special peaks of ATC but less sharper, which certain the ATC crystalline nature. In contrast, the special peaks of ATC disappeared in ATC- PEG 6000 solid dispersion, which was close enough to PEG 6000. The x ray results as well as the DSC indicated formation of inclusion complex.

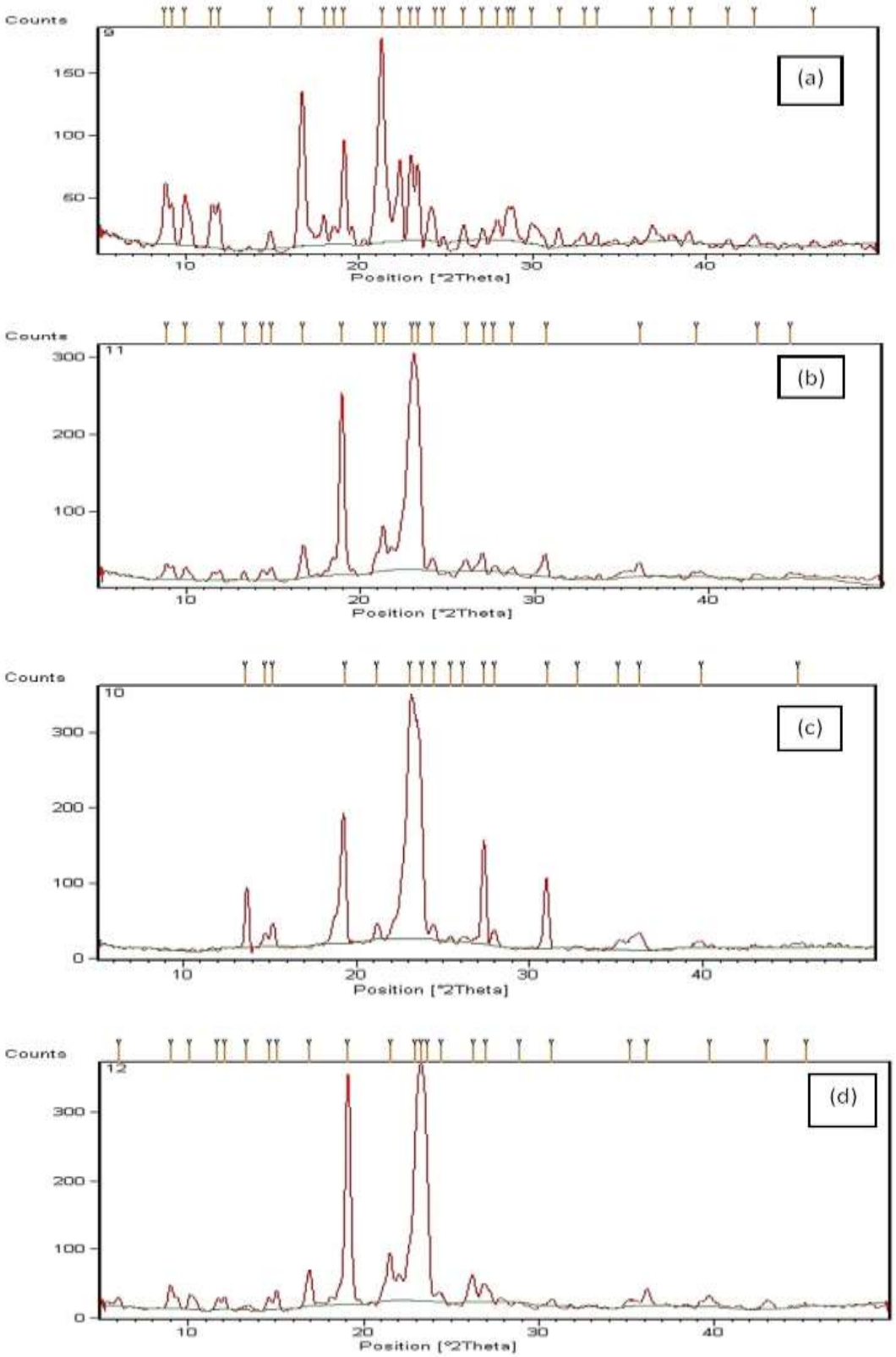

Figure 4: X ray spectra of ATC-PEG6000 systems. (a) ATC alone, (b) Pure PEG 6000, (c) Physical mixture of ATC-PEG6000, (d) Solid dispersion of ATC-PEG6000.

Physical properties and pharmacopoeial requirements of floating tablets:

Inspection of data in Table (4) shows that the average tablet thickness and diameter for the different formulations, ranged from 2.36 to 2.77 mm and 10.02 to 10.44 mm, respectively. The friability of the tested tablets ranged from 0.31% to 0.64%. All the formulations fulfilled the pharmacopoeial requirements for tablet friability test (BP 2006), where the weight loss of the prepared formulations did not exceed 1% of the weight of the tested tablets. As well, all the formulations fulfilled the pharmacopoeial requirements for both the weight variation and drug content uniformity (BP 2006) and none of the prepared tablets showed weight outside the stated limit (±5%). The amount of drug in each of the assayed tablets lied within the acceptable pharmacopoeial limits. Tablets crushing strengths between 3.6-3.9 kp were obtained using different polymers and polymer combinations.

***In- vitro* dissolution studies of floating solid dispersion tablets:**

From the *in-vitro* drug dissolution studies, Figure (5), Formulation having only HPMC showed more release when compared to other formulations where part of HPMC was replaced with ethyl cellulose (T1 against T2, T3 and T4). This is due to less permeability of water to ethyl cellulose. When the amount of ethyl cellulose was increased the drug release was found to be decreased which showed the sustained release effect of ethyl cellulose [12]. T1 was the formulation of the best drug dissolution rate which was 102.18% after 24 h, Formulations are arranged in the following descending order T1>T2>T3>T4.

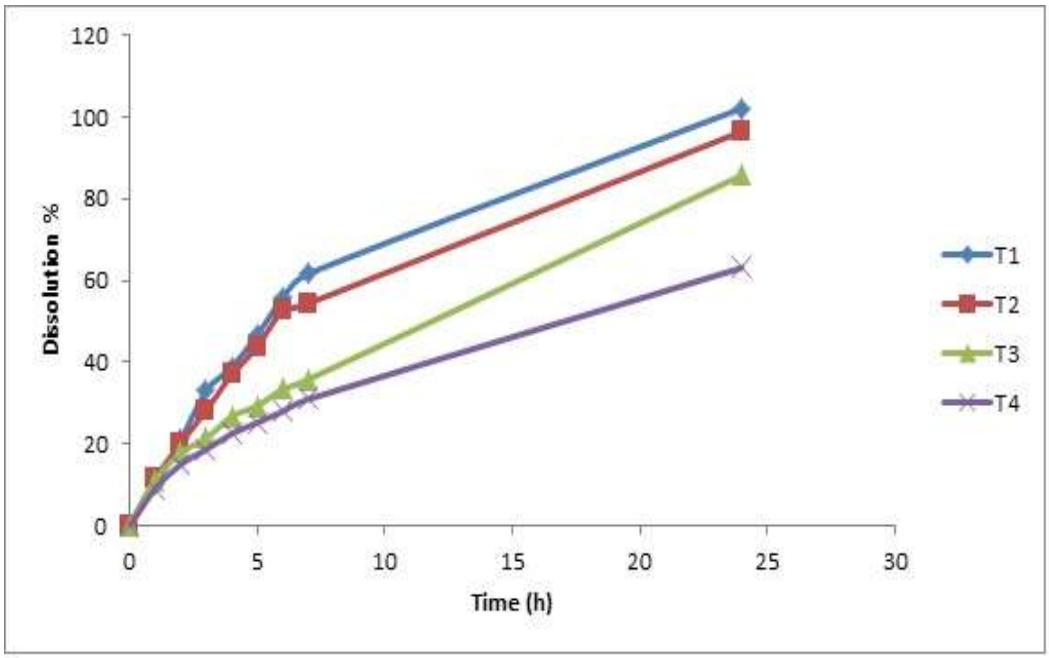

Figure 5: *In-vitro* dissolution studies of T1, T2, T3 and T4.

***In-vitro* buoyancy:**

In-vitro buoyancy studies of ATC solid dispersion floating tablets, illustrate the floating lag time and the duration of floating. The result shows that the total floating time for the formulations was more than 12 h and the floating lag time ranges from 48-77 seconds (Table 4).

Table 4: Physical properties and *in-vitro* buoyancy studies of ATC solid dispersion floating tablets.

Formula-tion Code	Weight (mg) ±SD	Thickness (mm) ± SD	Diameter (mm) ± SD	Hardness (kp) ± SD	Tablet Friability (%)	Drug Content (%)	Lag time (sec)	Floating time (h)
T1	200±1.10	2.77±0.01	10.44±0.02	3.80±0.05	0.31	99.30	64.00±0.01	>12
T2	199±0.30	2.36±0.02	10.03±0.02	3.90±0.01	0.31	99.60	77.00±0.10	>12
T3	200±1.30	2.39±0.03	10.02±0.02	3.60±0.01	0.64	99.70	48.00±0.02	>12
T4	201±1.50	2.45±0.01	10.20±0.18	3.80±0.10	0.34	98.90	50.19±0.10	>12

Bioavailability studies of floating ATC tablets:

The ability of solid dispersion floating tablets to decrease the blood total cholesterol level, the blood triglycerides level and the blood LDL level of rabbits was significantly higher than market drug ATOR ® at ($P<0.01$), figure (6 a-c). The ability of solid dispersion floating tablets to increase the blood HDL level of rabbits was significantly higher than market drug ATOR ® at ($P<0.001$), figure (6 d).

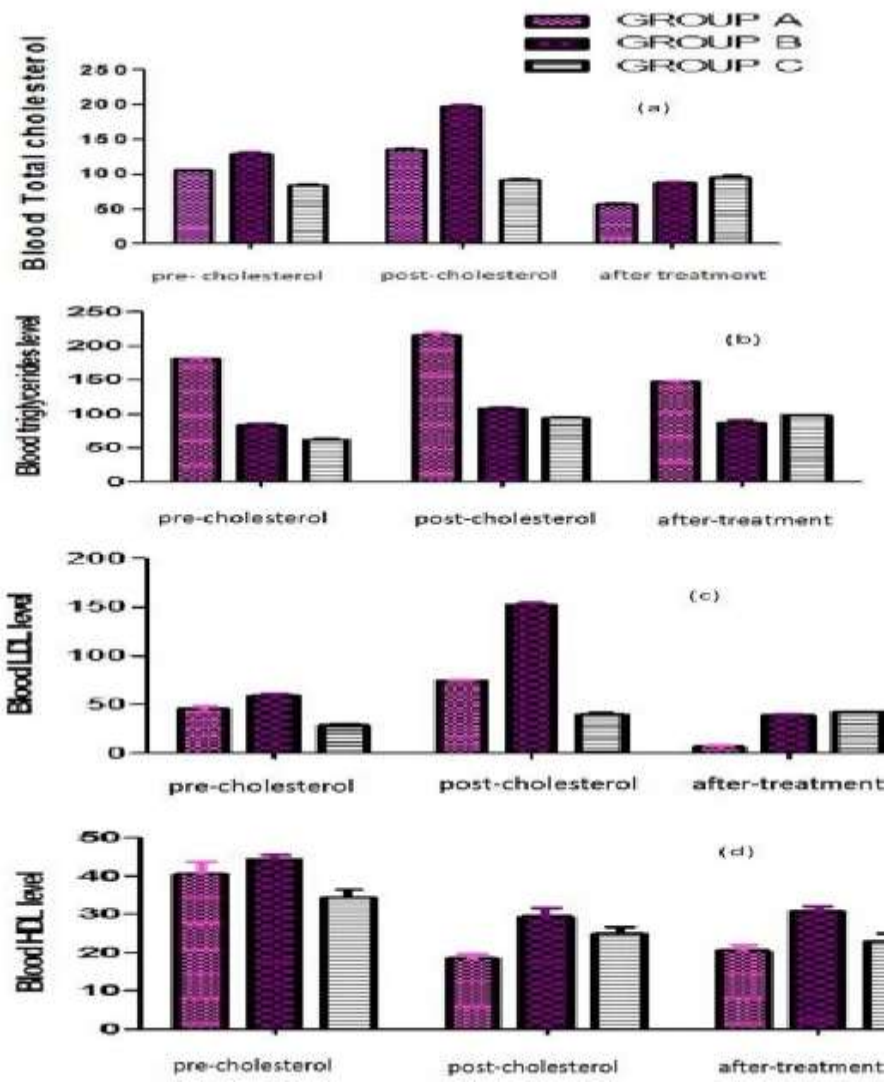

Figure 6: *In-vivo* bioavailability results.

CONCLUSION:

Skimmed milk gave the highest increase in ATC solubility in water which was 1200 folds. Solid dispersion of PEG6000 prepared by kneading method (S2) gave the highest % ATC released in 0.1 N HCL buffer which was 99%. The floating solid dispersion tablet formula (T1) gave the highest % ATC released which was 102.18%. The floating solid dispersion tablets decreased the rabbit's blood TC level, TGS and LDL by 58.46%, 32% and 91.21% respectively and increased the HDL by 11.11% which is more effectively than the market drug ATOR®.

REFERENCES:

1- Debjit B, Harish G, Duraivel S, Pragathi KB, Vinod R, Sampath K. Solid Dispersion – An approach to enhance the dissolution rate of poorly water soluble drugs. Pharm. Innov. J. 2012; 1(12): 24-38.

2- Sameer S, Raviraj SB, Lalit YA. Review on solid dispersion. Int. J. Pharm. Life. Sci. 2011; 2(9): 1078-1095.

3- Bhawana K, Ramandeep K, Sukhdeep K, Himani B, Sukhkaran K. Solid Dispersion: An evolutionary approach for solubility enhancement of poorly water soluble drugs. Int. J. Rec. Adv. Pharm. Res. 2012; 2(2): 1-16.

4- Argade PS, Magar DD, Saudagar RB. Solid Dispersion: Solubility enhancement technique for poorly water soluble drugs. J. Adv. Pharm. Edu. Res. 2013; 3(4): 427-239.

5- Ruchi T, Gaurav T, Birendra S, Awani KR. Solid Dispersions: An overview to modify bioavailability of bioavailability of poorly water soluble drugs. Int. J. Pharm. Tech. Res. 2009; 1(4): 1338-1349.

6- Colhoun HM, Betteridge DJ, Durrington PN. Primary prevention of cardiovascular disease with Atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes Study (CARDS): Multi center randomized placebo-controlled trial. Lancet. 2004; 364:685.

7- Aftab M, Pralhad T. Enhancement of dissolution profile by solid dispersion (kneading) technique. AAPS Pharm. Sci. Tech. 2006; 7(3): E1-E6.

8- Singh C, Kumar P. Solvent evaporation method for amorphous solid dispersions: predictive tools for improve the dissolution rate of pioglitazone hydrochloride. Int. J. Pharm. Chem. Bio. Sci. 2013; 3(2): 350-359.

9- Mogal SA, Gurjar PN, Yamgar DS, Kamod AC. Solid dispersion technique for improving solubility of some poorly soluble. Sci. Res. Lib. 2012; 4 (5): 1574-1586.

10- Pooja G, Gnanarajan AA, Preeti K. Floating drug delivery system: A Review. Int. J. Pharm. Res. Rev. 2015; 4(8): 37-44.

11- Shakti D, Vikash K. Floating drug delivery systems- A concept of gastro retention dosage form. Int. J. Res. Pharm. Bio. Sci. 2011; 2(4): 1413-1426.

12- Arunkumar N, Rani C, Mohanraj KP. Formulation and in vitro evaluation of oral floating tablets of atorvastatin calcium. Res. J .Pharm. Tech. 2008; 1(4): 492-495.

13- Ashok KD, Guru PM. Formulation and in vitro evaluation of famotidine floating tablets by lipid solid dispersion spray drying technique. Int. J. Res. Pharm. Chem. 2012; 2(4): 996-1000.

14- Amul M, Rinkesh KM, Deepak M, Harshvardhan S. Formulation and evaluation of gastroretentive tablet of ondansetron hydrochloride using 32 factorial design. Pharm. Chem. J. 2015; 2(1): 51-58.

15- Mohamed ME, Fatma RA, Sahar EE, Samih IE, Mohamed AS, Gehad M. E. Protective role of 10-dehydrogingerdione as modulator for CETP activity and HDL metabolism in cholesterol fed rabbits. Bio. Eng. Res. 2014; 3(2): 28-36.

16- Ratnakar P, Murthy RS. A rabbit model for studying hypocholestrolemic effect of drugs and hypocholestrolemic effects of extracts of garlic. Ind. J. Clin .Bio. 1998; 13(1):8- 11.

17- Bhatt S, Trivedi P. Development of Domperidone: Polyethylene glycol 6000 fast dissolving tablets from solid dispersions using effervescent method. J. Chem. Pharm. Res. 2011; 3(6): 889-898.

18- Liandong H, Deliang G, Qiaofeng H, Yanjing S, Na G. Investigation of solid dispersion of atorvastatin calcium in polyethylene glycol 6000 and polyvinylpyrrolidone,. Trop. J .Pharm. Res .2014; 13 (6): 835-842.

19- Ankush C, Avtar CR, Geeta A, Virender K, Foziyah Z. Development and characterization of an atorvastatin solid dispersion formulation using skimmed milk for improved oral bioavailability. Acta. Pharma. Sinica. B. 2012; 2(4): 421-428.