ISSN: 0974-2115
www.jchps.com Journal of Chemical and Pharmaceutical Sciences

Solubility enhancement of poorly water soluble drug Simvastatin by solid dispersion technique using natural polymer Guar gum

Arun Salappa[1]*, E.Jaychandran[2], D. Srinivasa Rao [3], Sachin Kushare [4]
S.C.S. College of pharmacy Harpanhalli [1, 2]
K.C. Reddy institute of Pharmaceutical science, Medikonduru, Guntur[3]
School of pharmacy, S.R.T.M. University, Nanded[4]
Affiliation: [1] Ph. D. Research scholar, Acharya Nagarjun university,Nagarjuna Nagar, Guntur- 522 510
***Corresponding author: Email: arunsalappa@yahoo.com; Mobile: 09892279872**

ABSTRACT

The objective of this investigation was to improve solubility and dissolution rate of water insoluble drugs Simvastatin by Microwave Generated solid dispersion techniques. The solid dispersions prepared using natural polymer enhances solubility and dissolution rate of drug. Solid dispersions were characterized using DSC, SEM, XRD which indicates that crystalinity of Simvastatin has been reduced significantly. Solubility study result gave best ratio of drug and polymer. In vitro drug release from prepared immediate release tablet was compared with marketed formulation. In vivo study was performed in rats by measuring HMG Co-A reductase activity. A significant reduction in the HMG Co-A reductase activity was observed with Solid dispersions of Simvastatin as compared to plain drug. Accelerated stability study of optimized batch was performed at 40^0C/75% RH and the results suggested that the formulation was stable for three months. Therefore, the solid dispersions technique using natural polymer could be successful technique for enhancing the solubility of poorly water soluble Simvastatin.

Keywords: solid dispersions, modified guar gum, microwave energy, immediate release tablet

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion although for many drugs it can be problematic and inefficient for number of reasons. Limiting drug absorption resulting in poor bioavailability, Drug absorption form the gastrointestinal tract can be limited by a variety of factors with poor aqueous solubility and poor membrane permeability of the drug molecule. The rate-limiting step in the absorption process for poorly water-soluble drugs is dissolution rate of such drugs in the gastro intestinal fluids rather than the rapidity of their diffusion across the gut wall. Thus, it is important to improve the oral bioavailability of poorly water soluble drugs by improving their dissolution rate and solubility.

Depending on the classification of the drug, different strategies can be applied to increase or accelerate the absorption of a drug, either increasing the permeability of the absorbing membrane or increasing the amount of dissolved drug that is in contact with the absorbing membrane. Class- I drugs do not need a formulation strategy to increase the absorption. The strategy for class- II drugs, having dissolution limitations but no permeation limitations, is to increase the amount of dissolved drug molecules at the absorption site. This has proven to be effective in many studies. (Newa M.et al, 2007).

For class- III drugs, the permeation over the membrane is rate limiting. The strategy for class- III drugs is to increase the permeability of the absorbing membrane.

For a class- IV drug, both dissolution as well as permeability must be increased. However, increasing dissolution is more effective than increasing permeability. Therefore, the potential to increase the absorption by increasing the drug concentration is larger and it is more practical to increase the solubility even if permeability is further compromised.

The rate of dissolution can be further increased by using various techniques to increase the rate of solution and ultimately bioavailability of the drugs. This includes, salt formation, co- solvents, particle size reduction, surfactants etc. However, all these techniques have potential limitations. All poorly water soluble drugs are not suitable for improving their solubility by salt formation. Decreasing particle size increases solubility but there is poor wetting and flow. Use of co-solvents or surfactants to improve dissolution rate poses problems, such as patient compliance and commercialization. Solid dispersions can overcome these problems.

Hence the present work is aimed to explore the applicability of polymer of natural origin such as guar gum (GG) in the enhancement of dissolution rate and thereby oral bioavailability of poorly water soluble drug. The influence of microwave induced solid dispersions prepared using Guar gum (MWGG) as a hydrophilic carrier on solubility enhancement of poorly water soluble drug Simvastatin in comparison to that of plain drug was investigated.

MATERIALS AND METHODS

Simvastatin was obtained from Aritimis biotech Hyderabad, Guar gum was obtained from lucid colloids ltd, Mumbai. Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Sodium Starch Glycolate, Hydroxypropyl cellulose, Anhydrous dibasic calcium phosphate, Magnesium stearate, Talc, Colloidal silicon di oxide, Methanol, Hydrochloric acid (HCL), Sodium lauryl sulphate(SLS) Monobasic sodium phosphate Sodium hydroxide used were of analytical grade.

Swelling Index (SI: The swelling and water retention capacity of the GG, and MGG were estimated by a slightly modified method described by Gauthami and Bhat (1992).About 1.0 g of GG, and MGG powder were accurately weighed and transferred to a 100 ml stoppered measuring cylinder. The initial volume of the powder in the measuring cylinder was noted. The volume was made up to 100-ml mark with distilled water. The cylinder was stoppered and was shaken gently and set aside for 24 h. The volume occupied by the gum sediment was noted after 24h. Swelling capacity of GG, and MGG was expressed in terms of swelling index as follows. Swelling index (SI) was expressed as a percentage and calculated according to the following equation:

$$SI = \frac{[(Xt - X0)]}{X0} \times 100$$

Where, X0 is the initial height of the powder in graduated cylinder and Xt denotes the height occupied by swollen gum after 24 h.

Viscosity Measurement: The viscosity of a 1% aqueous GG, and MGG gums were measured according to USP specifications using a Brookfield DV-E viscometer

Modification of carriers: The natural gum GG was modified by microwave heating method powdered carriers were taken in a porcelain bowl and kept in microwave oven at different watt, temperature and time.

Preparation of sample:

Preparation of physical mixture: Physical mixture of drug (SIM) with carrier (GG, MWGG) were prepared respectively by simple blending of drug with polymer in1:1 to 1:9 ratio (drug: gum) for 10min. The physical mixture of drug with polymer were denoted as SIM (1-9), PGG_{SIM} (1-9), $MWGG_{SIM}$ (1-7)

Preparation of microwave induced solid dispersions: Solid dispersions were prepared using the microwave induced fusion method. The optimized ratio was found to be 1:6 w/w. First SIM and polymer (MWGG) were weighed in ratio 1:9w/w followed by homogeneous slurry. A fixed amount of mixture (5g) was subjected to microwave for different time 10 and 20 min at a constant power of 560W in a microwave instrument (Catalyst2R, Catalytic System). The temperature of the mixture at the end of treatment was noted with inbuilt temperature measurement probe. The samples were then grounded in glass motor and pass through sieve to get particle size from 80 to 250um. The SD's of drug with polymer were denoted as, $MWGG_{SIM}$.

Ratio optimization (drug: polymer) by solubility: Sample of solid dispersion equivalent to 30 mg of SIM were placed in 10mL solvent in Teflon coated screw capped vial and kept at equilibrium for period of 24 h on orbital shaking incubator (Remi Instrument .Ltd) at 37 ±0.5◦C and 50 rpm. The content of vial were filtered through 0.2 micron filter and analyzed using UV-Visible spectrophotometer (UV 1601, Shimadzu, Japan) at respective wavelength of the drug.

Solid mixture Characterization:

Melting point: Melting point of drug, carrier, SD was measured by capillary method. The samples were filled into a glass capillary tube, which was sealed at one end. The temperature was noted when it is completely melted.

Fourier transform infrared spectroscopy: Fourier transform infrared spectroscopy (FT-IR) spectra of pure drug, carrier (GG), and SD of Simvastatin with modified carriers (MWGG) prepared by microvave induced fusion method were obtained to study interaction if any between drug and gum in mixture using KBr disk method (1mg of sample in 100mg KBr).

Differential scanning calorimetry (DSC): DSC thermograms of pure drug, pure carrier(GG) and SD with individual modified carriers (MWGG) prepared by microwave induced fusion method were obtained using DSC-60, Shimadzu,Japan, at a heating rate of 10°C/min from 0 to 300 °C in nitrogen atmosphere.

X-Ray Diffraction study (XRD): XRD study of pure drug, carrier (GG) and SD with individual modified carriers (MWGG) prepared by microwave induced fusion method were obtained using Philips diffractometer (PW 1140) and Cu-kα radiation. The diffractograms were run at a scanning speed of 2°/mm and a chart speed of 2°/2 cm per 2Ø.

Scanning electron microscopy (SEM): SEM photomicrograph of pure drug, carriers(GG) and SD with individual modified carrier (MWGG) prepared by microwave induced fusion method were obtained using scanning electron microscopy (JSM 5610 LV, JEOL, Datum Ltd, Japan).

Solubility study: The solubility study of SIM, PGGSIM, and $MWGG_{SIM}$ were determined in PH 6.8 buffer. The solubility of drug, SD's were determined by taking an excess amount of drug (30 mg), SD's (equivalent to 30mg of drug) and added them in 10ml of pH 6.8 phosphate buffer, in Teflon facing screw capped vials. The samples were kept at equilibrium for a period of 48 h on orbital shaking incubator at 37±0.5°C and 50 rpm. The supernatant collected from vial was filtered through 0.2 micron filter and analyzed by UV-Visible spectroscopy (UV 1601, Shimadzu, Japan) at a λ max of SIM.

Drug content analysis: Drug content analysis was performed in order to study the amount of drug incorporated in SD's. Simvastatin was extracted from SD's by dissolving them in 25mL methanol. Simvastatin content in the methanolic extract was analyzed spectrophotometrically at λ max of SIM.

Powder dissolution test: The powder dissolution test of optimized ratio was carried out following the USP apparatus 2 in 900 ml of pH6.8 phosphate buffer at 37°C±0.5 with a paddle speed of 50rpm. 5 ml sample of dissolution medium was withdrawn at 5, 10, 15, 30 min. using cannula and syringe and replaced with fresh dissolution medium. Aliquots after filtration through Whatman filter paper were analyzed spectrophotometrically each sample were analyzed in triplicate

Preparation of immediate release tablets: The ratio of SD's which has shown best results in solubility and dissolution studies were selected for formulating the immediate release tablet. Tablets were prepared (F1 to F4 batch) using superdisintegrant for formulating tablet. The composition of tablet is given in table 1. All the components of tablet were sieved through sieve #40, mixed and compressed into tablet using 11mm punch on rotary tablet minipress (Rimek, Ahmadabad, India).

Table 1. Composition of immediate release tablets of $MWGG_{SIM}$

Ingredient Name	Quantity mg/tablet			
	F1	F2	F3	F4
Simvastatin solid dispersion ($MWGG_{SIM}$ 1:6)	35.0	35.0	35.0	35.0
Microcrystalline cellulose (Avicel PH102)	X	71.5	171.5	166.5
Pregelatinised starch(Starch 1500)	X	10.0	10.0	10.0
Lactose monohydrate (Supertab 30 GR)	189.0	100.0	X	X
Hydroxypropyl cellulose (L HPC LH-11)	10.0	10.0	10.0	10.0
Croscarmellose Sodium (Ac-Di-sol)	5.0	5.0	5.0	10.0
Ascorbic acid	X	5.0	5.0	5.0
Citric acid	X	2.0	2.0	2.0
Butylated hydroxyanisole	X	0.5	0.5	0.5
Colloidal silicon dioxide (Aerosil 200)	2.0	2.0	2.0	2.0
Talc	2.0	2.0	2.0	2.0
Mg Stearate	2.0	2.0	2.0	2.0
Opadry white	5.0	5.0	5.0	5.0

Evaluation of immediate release tablet:

Pre compression evaluation: Pre compression evaluation includes measurement of angle of repose and Hausner's ratio of optimized SD and various formulation mixtures. All the tests were performed as per the procedure given in USP 30 (2007).

Post compression evaluation: Post compression evaluation includes measurement of weight variation, hardness, friability, drug content and disintegration time (DT) of prepared formulation. All the tests were performed as per the procedure given in USP 30 (2007).

Drug-excipients interaction study: Powder mixture of formulation components were subjected to FT-IR and DSC studies to detect any interaction between various components of formulation.

Stability study: The accelerated stability study of tablets was checked for stability as per ICH guidelines at 40 º C/75%RH up to 3 months.the tablet were filled in cap vials and packed in aluminum stripes and stored for 3 months in stability chamber (CHM 10S, REMI instruments Ltd.India).Sample were removed and analyzed for in vitro drug release in time interval of 0, 30, 60and 90 days

***In Vivo* Study:** The high dietary cholesterol was concerned with the increasing concentrations of serum and hepatic total cholesterol (TC), especially the level of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) in serum, which is considered to be a primary risk factor of cardiovascular disease. Hypercholesterolemia rat model is represented for cardiovascular and cerebro vascular disease research, which can be established by feeding with 2% cholesterol-supplement diet for several weeks. Dietary 2% cholesterol can increase serum VLDL and LDL levels dramatically in rats. In this case, dietary cholesterol remarkably disturbed triglyceride (TG) metabolism.

Rats were divided into six groups (normal, control, MWGG SIM 200mg/kg, MWGG SIM 400mg/kg, Simvastatin 200mg/kg, Simvastatin 400mg/kg) each group consist of six animal. Animal in group I receives normal pallet diet, whereas group II, III, IV, V and VI receives high fat diet (HFD) containing 2% coconut oil, 1%sodium cholate,2%pure cholesterol for 30 days. Simvastatin were administered from 0 day up to 30 days by orally as suspension to respective group. Blood were collected initially before the administration of the diet i.e. on 0 day and after 24hrs of the 30th day blood samples were collected using micro capillaries by retro orbital puncture. Blood samples were centrifuged at 3000 rpm for 20 minutes. Serum was separated and used for biochemical estimation of lipid profile like total cholesterol (TC), Triglycerides (TG), low density lipoprotein (LDL), High density lipoprotein (HDL), total protein, total bilirubin, by using Auto-span diagnostic kits pvt. Ltd., India.

The study was approved and conducted as per the norms of the Institutional Animal Ethics Committee (Ref: HSK CP/IAEC, Clear/2010-11/1-12)

RESULTS AND DISCUSSION

As reported the GG having surfactant activity and also increases wetting by reducing the contact angle, thus enhance the solubilization and dissolution of drug particles. (Rowe et al., 2003) and this additional microwave treatment is very green, effective and advanced way for formation of SD.

Physical characterization of polymer: Result of swelling and viscosity of polymers are shown in table 2 from the result it can be concluded that the viscosity of MWGG is lower than GG and swelling index of and MWGG was not reduced significantly than GG. Because of no significant changes in swelling nature of modified carriers extensive surface increased during the dissolution and dissolution rate of drug is enhanced (Westerberg et al., 1986) and due to significant reduction in viscosity they are less prone to the formation of sturdy matrix which will assist rapid liberation of the Drug particles from SD.

Table.2.Characterization of polymer

Polymer	Viscosity (cp)	Swelling Index (%)
GG	352 ± 14.22	1655 ± 36.2
MWGG	123 ± 2.67	1585 ± 18.5

Solid mixture characterization:

Melting point: melting point of drug, carrier and modified carriers are given in table 3. From the melting point the conditions for modifications of carrier (GG) were set up.

Table.3.Melting point of drug and Carriers

Samples	Melting range
SIM	133 -139 ^{0} C
GG	210 – 225 ^{0} C
MWGG	205– 215 ^{0} C

Drug-carrier interaction study:

FT-IR studies: FTIR spectroscopy was used to study the possible interactions between SIM, pure carrier (GG), modified carriers (MWGG). All major peaks of SIM observed at wave numbers 3545 cm^{-1} (free O–H stretching vibrations); 2970 cm^{-1} (Methyl C-H asymmetric stretch); 2872 cm^{-1} (Methylene C-H symmetric stretch); and 1695 cm^{-1} (Ester C=O stretch); 1265cm^{-1} (Lactone -C -O-C stretch). The principle peak values of drug remain unchanged in the microwave treated SD's. Thus it can be concluded that there is no chemical interaction between the drug and gum.

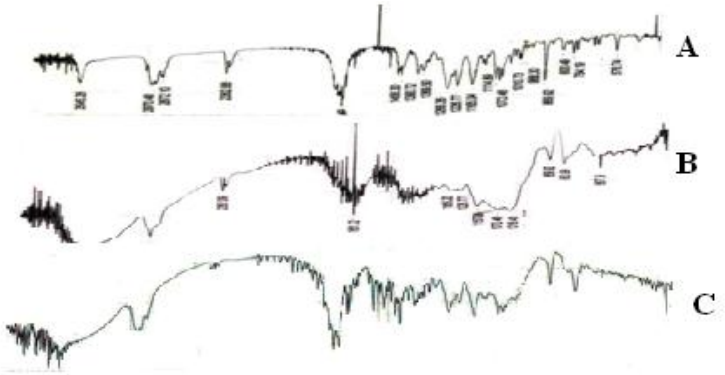

Figure.1.FT-IR Spectra of A) SIM, B) Microwave treated Guar Gum (MWGG) and C) Microwave Generated solid dispersion of SIM with GG Physical ($MWGG_{SIM}$)

DSC studies: DSC profile of drug, modified carrier (MWGG) and SD of SIM, with modified carriers (MWGG) is shown in the following figure 2. Crystalline nature of SIM can be easily recognized by the presence of sharp endothermic peak at around 165.33ºC. This endothermic peak is almost disappeared with broadened endotherm in DSC profile of indicating amorphous nature of SIM.

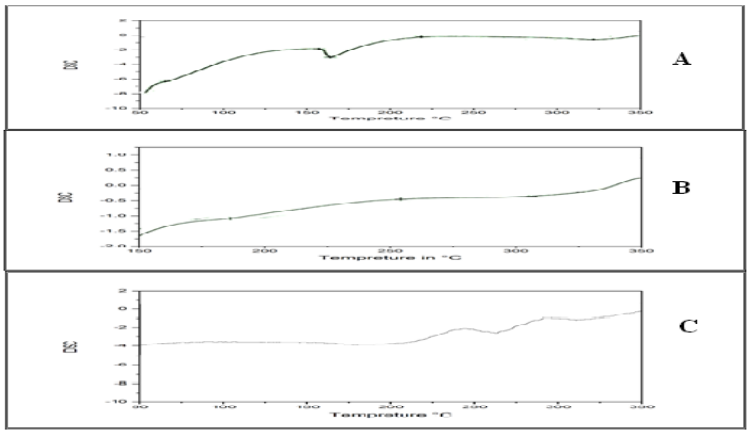

Figure.2.DSC thermograms of A) SIM, B) MWGG and C) $MWGG_{SIM}$

XRD studies: Powder X-ray Diffraction Studies of SIM, pure carrier (GG), modified carrier (MWGG) and SD of drug with modified carrier (MWGG) are shown in figure 3. The pure SIM exhibited intense crystalline peak between 4^0 and 45^0. Characteristic diffraction peaks at 5.84 ^{0}, 8.97 ^{0}, 12.73 ^{0}, 16.26 ^{0}, 17.34 ^{0}, 18.60 ^{0}, 22.33 ^{0}, 25.66 ^{0}, 26.23 ^{0} were observed with intense peak it indicating the crystalline nature of SIM. On the other hand, in $MWGG_{SIM}$ it is observed that peak intensity is reduced indicating conversion of Crystalline Drug to Amorphous form.

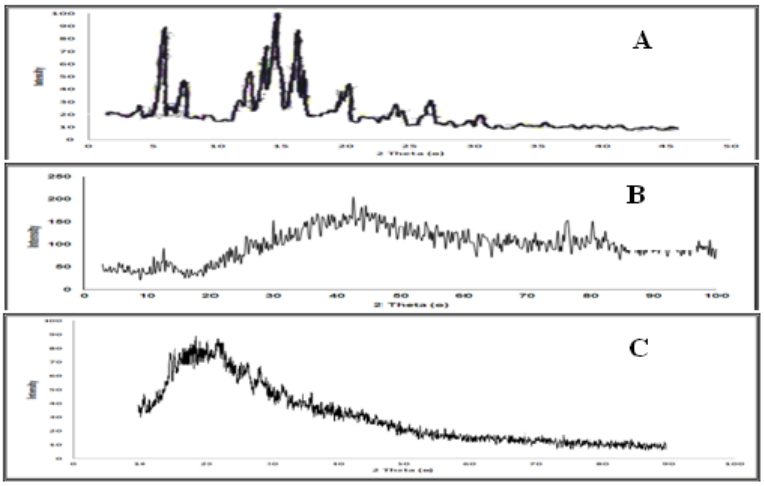

Figure.3.Powder X Ray Diffraction pattern of A) SIM, B)MWGG, C) $MWGG_{SIM}$

Scanning electron microscopy (SEM): The SEM studies are generally done to study surface morphology of drug particles. The morphology of pure drug, modified carries (MWGG) and SD of drug with modified carrier show in following figure 4. From the figure it can be concluded that SIM particles were plate shaped with smooth surface, while in case of MWGG it was observed that they were of irregular shape and size. Figure clearly shows that crystal shape of SIM was completely changed in MWGG showing embedded SIM crystals in the MWGG matrix.

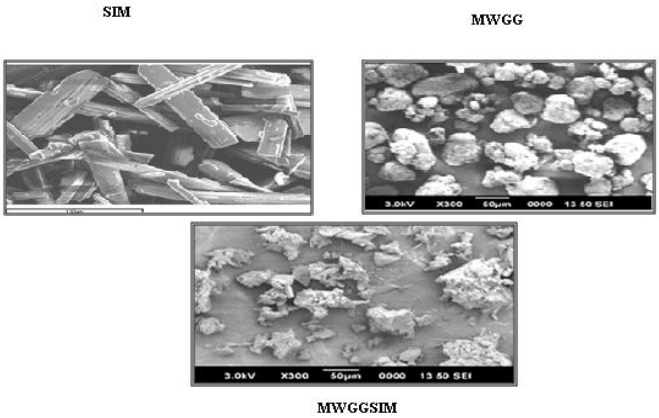

Figure 3: SEM photograph of A) SIM, B) MWGG and C) $MWGG_{SIM}$

Drug content analysis: Drug content analysis was performed in order to study the % amount of drug incorporated in SD formulations. After drug content analysis studies it was found that almost 97 to 99 % of drug was incorporated in the SD's which indicates uniform dispersion of drug.

Solubility Studies: Solubility studies gave the basis for selection of best ratio that is to be forwarded for formulation. Physical mixture of drug with polymer in various ratio as well as SD's of drug with modified polymer in various ratios was analyzed for solubility determination. The result of the same is shown in table 4. Solubility studies reveals modified carrier (MWGG) is having very good solubility enhancing property as they have good surfactant property and reduction of crystal size of the drug to amorphous form of SD's enhancing solubility. Solubility studies of physical mixtures and SD's clearly indicated that as the ratio of drug to polymer increases solubility also increases. It was also found that after certain ratio i.e. 1:6 solubility remains constant hence 1:6 ratio was optimized.

Table.4.Solubility studies and ratio optimization of Simvastatin solid dispersion

Ratio	Concentration (mg/ml)	
	PGG_{SIM}	$MWGG_{SIM}$
1:1	0.11±0.005	1.29±0.063
1:2	0.13±0.003	1.07±0.105
1:3	0.15±0.004	1.37±0.034
1:4	0.18±0.007	1.87±0.075
1:5	0.21±0.031	2.24±0.035
1:6	0.21±0.008	2.77±0.105
1:7	0.19±0.005	2.76±0.050
1:8	0.24±0.011	-
1:9	0.32±0.024	-

***In vitro* drug release study of prepared solid dispersions:** Optimized ratio from solubility studies were treated for solid dispersion dissolution study. From the dissolution profile of SD's of SIM (figure.5) was evident that a remarkable improvement of the dissolution rates of drug from SD's than the pure drug.

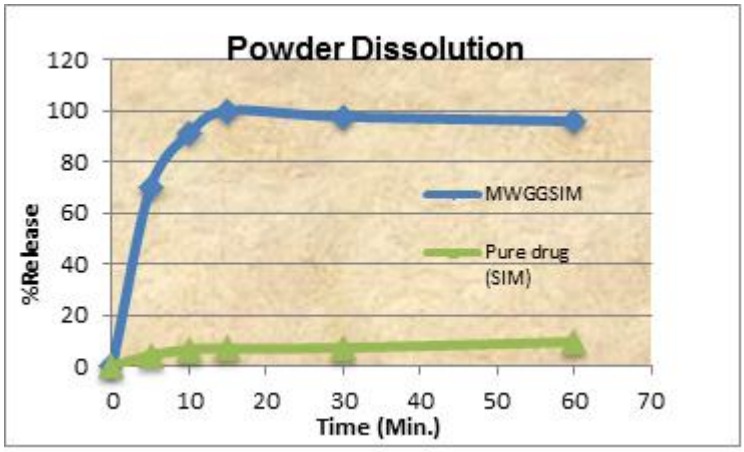

Figure.5.Dissolution profile of prepared solid dispersion

Pre compression evaluation:

Table 5: Pre compression parameters of lubricated blend of MWGG-Simvastatin Formulation

CODE	Angle of Repose (θ)	Hausner's Ratio
$MWGG_{SIM}$	26.83±2.40	1.61±0.0010
F_1	24.04±2.70	1.71±0.0005
F_2	26.90±0.38	1.80±0.0005
F_3	24.36±1.13	1.87±0.0004
F_4	21.76±0.36	1.76±0.0005

Post compression evaluation: Prepared formulations were subjected to various compendia tests for post compression evaluation n such as hardness, friability, content uniformity of prepared tablets, disintegration time (DT).results of post compression evaluation are shown in table .All the parameters are within the limits given in the USP 30 (2007).

Table 6: Physical parameters of MWGG-Simvastatin tablet

Batch $MWGG_{SIM}$	Weight Variation %	Hardness (Kg/cm^2)	Friability (%)	Drug Content Uniformity (%)	Disintegration time (sec)
F1	3.93	3.82±0.31	0.43	98.39	63±2.18
F2	3.55	3.55±0.09	0.23	101.18	41.5±2.11
F3	3.96	3.29±0.15	0.59	102.91	66.5±2.07
F4	3.02	3.21±0.13	0.39	100.58	32±2.28

***In vitro* drug release studies of IR tablets:** The optimized formulation ($MWGG_{SIM}$ -trial-F4) based on disintegration studies were subjected to in vitro drug release study. Percentage drug release of optimized formulation was compared with % drug release of MKT sample (figure).Formulation $MWGG_{SIM}$ trial-F4 showed 99.35±3.3.05% drug release, which is higher than that of MKT(97.77±2.51 %). This showed that drug release from prepared formulation and marketed formulation showed quite similarity but of drug release of optimized formulations is higher than the MKT sample.

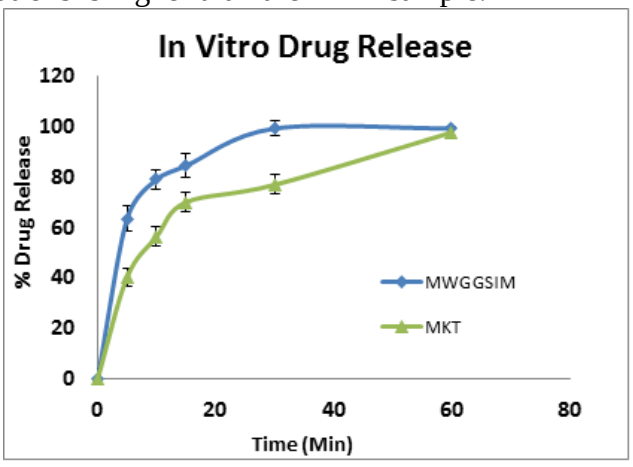

Figure.6.Dissolution profile of tablet samples $MWGG_{SIM}$ –trial-F4 and MKT sample in pH 6.8 buffer

In-vivo study and of Simvastatin solid dispersions in animal model: Hypolipidemic drug like Simvastatin (HMG-CoA reductase inhibitors) is known to reduce elevated total cholesterol and TG levels in blood, which promote the removal of cholesterol from peripheral cells and facilitate its delivery back to the liver (Jun et al., 2007). The SIM is the most marketed available drugs of Hypolipidemic category. But this drug is having poor aqueous solubility. Hence, in present study solid dispersion formulations of Simvastatin ($MWGG_{SIM}$) with enhanced solubility were prepared and their anti-cholesterol and anti-lipidimic activity were confirmed and compared with pure drug (API) of SIM. using indirect method for assessing variation in 3-hydroxy-3-methylglutaryl-coenzyme-A reductase (NADPH) activity in liver tissue. HMG CoA reductase inhibition activity was measured in terms of absorbance in all the seven groups the activity of enzyme which catalyzes the conversion of HMG CoA to mevalonate. One-way analysis of variance (ANOVA) followed by multiple comparisons Dunnet's test was used for comparison. All the results are shown as mean ± standard error. In the table it shows fall in serum lipid levels in 30 days Simvastatin showed a fall in serum cholesterol and protective HDL. The solid dispersion prepared by microwave induced fusion method as expected performed better than plain SIM.

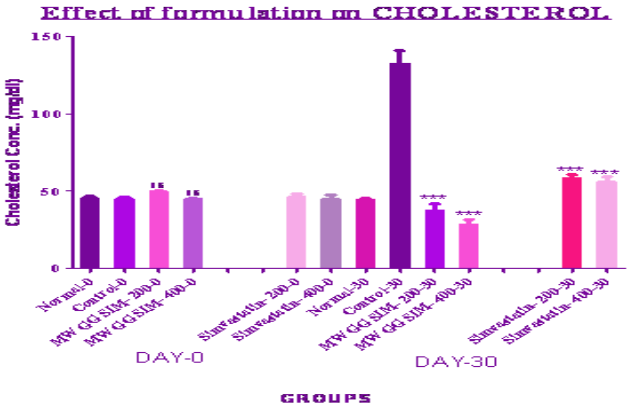

Figure.7.Anti-cholesterol effect of MWGG$_{SIM}$ formulations on serum total cholesterol.
ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

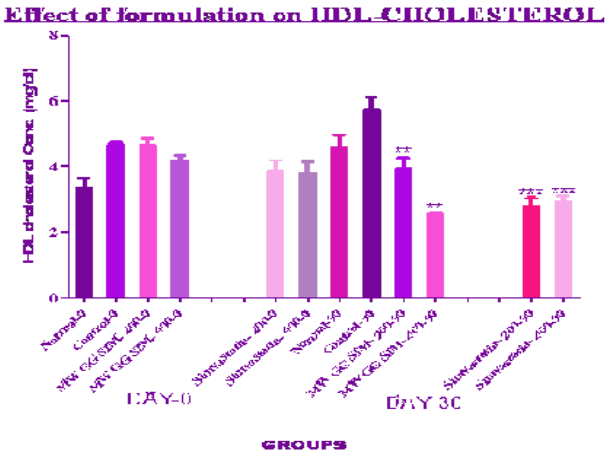

Figure.9.Anti-cholesterol effect of MWGG$_{SIM}$ formulations on serum HDL cholesterol
ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

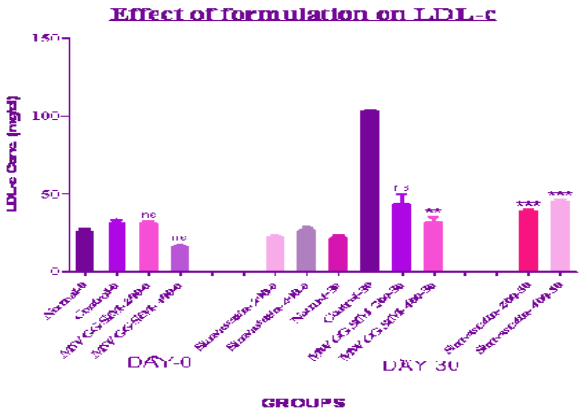

Figure.10.Anti-cholesterol effect of MWGG$_{SIM}$ formulations on serum LDL Cholesterol
ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

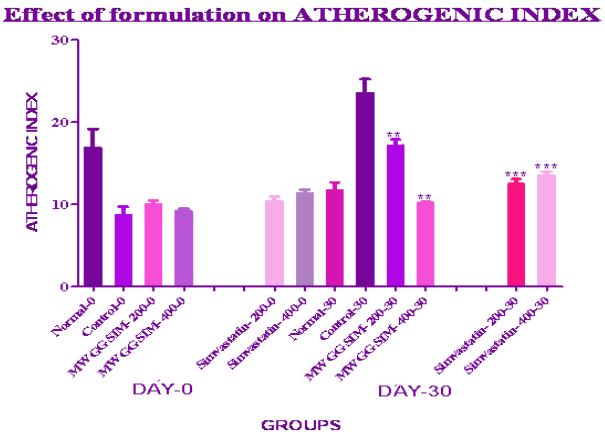

Fig.11. Anti-cholesterol effect of formulations MWGG$_{SIM}$ on Atherogenic index
ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

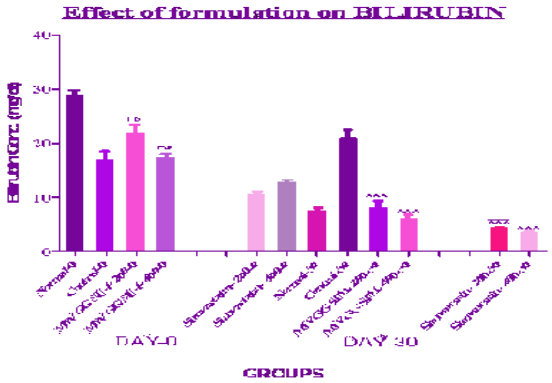

Figure.12.Anti-cholesterol effect of MWGG$_{SIM}$ formulations on serum Bilirubin
ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

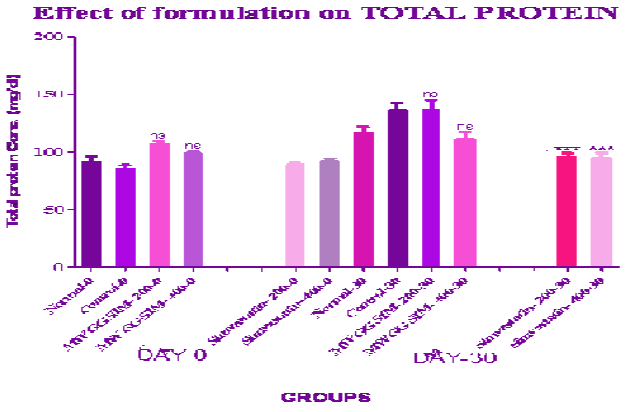

Figure.13.Anti-cholesterol effect of MWGG$_{SIM}$ formulations on serum Total protein
ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

Stability studies: Result of stability is shown in the table 7 Stability study showed there is no significant change in above mentioned parameters after elevated temperature and humidity condition during stability studies. Thus it can be proven from the stability studies that the prepared formulation is stable and not much affected by elevated humidity and temperature conditions.

Table.7.Stability studies of optimized $MWGG_{SIM}$ formulation (F4)

Time(days)	Disintegration time (sec)	Drug content (%)	In vitro drug release (%)
0	32±5.5	100.6±2.5	99.99±1.33
30	32±3.7	99.60±2.6	97.87±1.60
60	33±6.0	99.58±2.7	98.23±2.56
90	33±3.7	99.24±2.3	99.94±0.92

CONCLUSION

The natural polymers having surfactant activity that enhances the solubility and dissolution rate of drug, but due to high viscosity many of these polymers also having limitation as carriers for dissolution enhancement (Portero et al., 1998), this problem is overcome by reducing the viscosity of polymers. This natural polymers having advantage over other synthetic polymer as this polymers are biocompatible, biodegradable and having low cost (Sawayanqagi, 1983; Imasi, 1991; Acaturk, 1992; Portero, 1998). On heating of the natural polymers (GG) at particular time and temperature condition it reduces the viscosity and changes the surface property which is useful to polymers for use as drug carrier for dissolution enhancement. Modified natural polymer Guar gum have great potential for enhancement of solubility, dissolution rate and thereby bioavailability of poorly soluble Simvastatin. The SD's of Simvastatin with polymer enhances the solubility by converting it into amorphous form, reducing the particle size and increasing the wettability. The optimum ratio of drug to modified natural polymer was found to be 1:6 w/w. This shows higher dissolution as compared to marketed tablet. The selected SD's showed better anti-cholesterol and anti-lipidimic activity compared to plain drug.

REFERENCES

Ewa, M., Bhandari K.H., Li D. X., Kwon, T.H., Kim J.A., Yoo, B.K., Woo, J.S., Lyoo, W.S., Yong, C.S., Choi, H.G, Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with Poloxamer 188. Int. J. Pharm., 343, 2007, 228-237.

Gauthami, S., Bhat, V.R, A monograph on Gum Karaya. National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, 1992.

Chiou, W.L., Riegelman, S, Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci., 60(9), 1971, 1281–1285.

Leuner C, Dressman J, Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm., 50, 2000, 47-60.

Rowe, R.C., Sheskey, P.J., Weller, P.J, Hand book of pharmaceutical excipients, 4th ed. Pharmaceutical press, London, 123, 2003, 271.

Bergese P., Colombo I., Gervasoni D., Depero Le, Microwave generated nanocomposites for making insoluble drugs soluble. Mater. Sci. Eng C, 23, 2003, 791- 795.

Westerberg, M., Jonsson, B., Nystrom, C, Physicochemical aspects of drug release. IV. The effect of carrier particle properties on the dissolution rate from ordered mixtures, Int. J. Pharm., 28, 1986, 23–31.

Jun, S.W, Kim, M.S, Kim, J.S, And Hwang, S.J., Preparation and characterization of Simvastatin/hydroxypropyl- β -cyclodextrin inclusion complex using supercritical antisolvent (SAS) process, Eur. J. Pharm. Biopharm., 66, 2007, 413-421.

Portero, A., Remunan-Lopez, C., Vila-Jata, J.L, Effect of chitosan and glutamate enhancing the dissolution properties of the poorly water soluble drug nifedipine. Int. J. Pharm., 175, 1998, 75–84.

Sawayanqagi, Y., Nambu, N., And Nagai, T, Dissolution properties and bioavailability of phenytoin from ground mixtures with chitin or chitosan, Chem. Pharm. Bull., 31, 1983, 2064–2068.

Imasi, T., Shirasha, S., Saito, H., Otagiri, Interaction of indomethacin with low-molecular weight chitosan and improvement of some pharmaceutical properties of indomethacin by low-molecular weight chitosans. Int. J. Pharm., 67, 1991, 11–20.

Modi, A. And Tayade, P, Enhancement of dissolution profile by solid dispersion (kneading) technique. AAPS Pharm. Sci. Tech., 7(3), 2006, E1-E6.

Rane, Y., Mashru, R., Sankalia, M. And Sankalia, J, Effect of hydrophilic swellable polymers on dissolution enhancement of Carbamazepine solid dispersions studied using response surface methodology. AAPS PharmSciTech, 8, 2007, E1-E11.

Kim, E., Chun, M., Jang, J., Lee, I., Lee, K., Cho, H, Preparation of solid dispersions of felodipine using a solvent wetting method. Eur. J. Pharm. Biopharm., 64, 2006, 200-205

Chauhan, B., Shimpi, S., Paradkar, A, Preparation and evaluation of glibenclamide – polyglycolized glycerides solid dispersions with silicon dioxide by spray drying techniques, Eur. J. Pharm. Sci., 26, 2004, 281-286

Karanth, H., Subraya, V., Ramachandra Murthy, R, Industrially feasible alternative approaches in the manufacture of solid dispersions: Technical report. AAPS PharmSciTech., 7(4), 2007, 87

Mariarosa, M., Barbara, B., Pietro, B., Francesco, P., 2008. Microwave generated solid dispersions containing Ibuprofen. Int. J. Pharm., 361: 125–130.

Craig D, Q. M., 2002. The mechanism of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm, 234: 131-144

Vasconcelos, T., Bruno, S., Paulo, C, Solid dispersion as a strategy to improve oral bioavailability of poor water soluble drugs. Drug Discovery Today, 12, 2007, 23-24.

Acaturk, F., Kislal, O., Celebi, N, The effect of some natural polymers on the solubility and dissolution characteristics of nifidipine. Int. J. Pharm. 85, 1992, 1–6.

Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R, A theoretical base for a biopharmaceutic drug classification: the correlation of in-vitro drug product dissolution and in vivo bioavailability. Pharm. Res., 12, 1995, 413-420.

Bolhuis, G.K., Zuurman, K., Te Wierik, G.H, Improvement of dissolution of poorly soluble drugs by solid disintegrant II. The choice of super disintegrants and effect of granulation, Eur. J. Pharm. Sci., 5, 1997, 63–69.

Brian, R.R., 2001. Dissolution method development for poorly soluble compounds, Dissolution Tech, 1-5.

Goldberg, A.H., Gibaldi, M., Kanig, J, Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II. Experimental evaluation of eutectic mixtures urea: acetaminophen system. J. Pharm. Sci., 55, 1966, 482–487.

Hite, M., Turner, S., Federici, C, Part 1: Oral delivery of poorly soluble drugs, Pharmaceutical Manufacturing and Packing Sourcer Summer, 2003, 38-40.

Horter, D., Dressman, J.B, Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract, Advanced Drug Del. Rev., 25, 1997, 3-14.

Kawakami, K., Oda, N., Miyoshi, K., Funaki, T., Ida, Y, Solubilization behaviour of a poorly soluble drug under combined use of surfactants and cosolvents, Eur. J. Pharm., 28, 2006, 7–14.

Leuner, C., Dressman, J, Improving drug solubility for oral delivery using sold dispersions. Eur. J. Pharm. Biopharm., 50, 2000, 47–60.

Lipinski, C.A., Lombardo, F., Dominy, B.W., Freeney, P.J, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Advanced Drug Del. Rev., 23, 1997, 2-25.

Mitchell, S.A., Reynolds, T.D., Dasbach, T.P, A compaction process to enhance dissolution of poorly water soluble drugs using hydroxypropyal methylcellulose, Int. J. Pharm., 250, 2003, 3-11.

Murali Mohan Babu, G.V., Prasad, C.D.S., Ramana Murthy, K.V, Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water-soluble drug nimodipine, Int. J. Pharm., 234, 2002, 1-17.

Nadendla, R.R., Sudhakar, G., Srinath, N, Current status of dispersible dosage forms, Int. J. Pharma. Excip, 1, 2002, 25.

Patil, P., Patil, P., Paradkar, A., Formulation of a self-emulsifying system for oral delivery of simvastatin: In vitro and in vivo evaluation, Acta Pharm., 57, 2007, 111–122

Sundaram, V., Kharkar, M., Yarraguntla, S., Gudipati, S., Mandava, V, U. S. PATENT, 20060223882**,** amorphous simvastatin, 2005.