Systematic Development and Characterization of Liquisolid Compacts of Atorvastatin-Glipizide Binary Mixture to Achieve Enhanced Dissolution and Stability Profile

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Abstract

Objective: The objective of present study is to evaluate the potential of liquisolid (LS) technology to enhance the dissolution characteristics of a combination of two poorly soluble drugs formulated as a single tablet. **Materials and Methods:** LS compacts have been prepared using compositions with varying ratios of propylene glycol (as water miscible non-volatile vehicle), lactose, and microcrystalline cellulose PH 102 (MCC PH 102) (as carriers), while Syloid® 244FP silica as a coating material. To evaluate the role of additives on various parameters such as loading factor, powder flow, disintegration, and dissolution profile of prepared LS formulations, number of additives such as Kollidon® 30, hydroxy propyl methyl cellulose-low viscosity, polyethylene glycol 4000, Kollidon® VA64, and low-substituted hydroxypropyl cellulose-LH-11 were added to the formulation. **Results and Discussion:** Among the tested carriers, MCC PH 102 was found to enhance drug release considerably. Addition of additives was found to further enhance powder flow and provide faster release of drugs from formulations. Among all the LS formulations prepared, LS - 18 demonstrated the fastest disintegration time (1.02 min) and fastest dissolution rate (84.6% in 10 min for glipizide and 44.6% for atorvastatin) with 100% drug release. **Conclusion:** The study demonstrated that LS technology can lead to suitable coformulation of two poorly soluble drugs for antidiabetic-antihyperlipidemic cotherapy of metabolic syndrome with enhanced dissolution.

Key words: Atorvastatin, glipizide, lactose, microcrystalline cellulose PH 102, Syloid® 244FP

INTRODUCTION

Advancement in the field of drug discovery, like combinatorial chemistry and high throughput screening have led to invention of a large number of active moieties with high therapeutic potential.[1] However, 40% of newly developed drugs are reported to be hydrophobic in nature.[2] Their low solubility becomes a major limiting factor in formulation development for their effective drug delivery. A number of approaches have, therefore, been explored to enhance the solubility of poorly soluble drugs. These approaches include increasing the surface area, formulation in a dissolved state,[3] particle size reduction,[4] cogrinding,[5] amorphization,[6] coamorphization,[7] liquisolid (LS) compacts,[8] preparation of inclusion complexes,[9] solid dispersions,[10] use of prodrugs,[11] generation of metastable polymorphs,[12] and lipid-based systems such as self - emulsifying drug delivery systems.[13] LS technique is a recent approach that has emerged as a promising strategy for enhancing the release of poorly soluble drugs.[14,15]

LS systems are composed of a non-volatile liquid vehicle having good solubility in water, drug, solid carrier, and coating materials.[14,15] The liquid portion in the formulation may be a liquid drug, or a drug suspension, or a drug solution in a suitable non-volatile liquid vehicle. The liquid vehicle is popularly called liquid medication. The liquid medication is adsorbed on the surface of a porous carrier (e.g., MCC, hydroxy propyl methyl cellulose [HPMC], Neusilin, etc.). Once the carrier gets completely saturated with the non-volatile liquid, addition of coating material turns it into a dry, free-flowing powder with good compressibility characteristics. The enhanced dissolution profile achieved by this technique can be attributed to increased surface area and favorable wettability of the drug particles in the non-volatile liquid.[16] The increased drug solubility, in turn, provides an improved drug absorption in the gastrointestinal tract thereby improving the bioavailability of the drug.[17] Several reports on stability studies of LS systems assure about the satisfactory stability profiles of formulations prepared by this technique, both in terms of drug release profile and hardness.[18] Hence, enhanced drug release, simple manufacturing process, cost-effectiveness, good stability, and amenability to scale up make it a promising approach to overcome the common problems associated with poor dissolution profile of a drug.[3]

However, the wide application of the LS technology is limited by certain essential prerequisites, i.e., high solubility of drug in small amount of non-volatile solvent, high specific surface area and absorption capability of carrier and coating material to adsorb non-volatile solvent.

Another limitation of the technique is squeezing out of liquid from the formulation at the time of compression, which generally results in inappropriate hardness. Moreover, drugs with higher doses (>100 mg) are difficult to be formulated as LS compacts because of high volumes of non-volatile liquid required to dissolve the high quantity of drug. This, in turn, requires larger amount of adsorbent to adsorb the liquid. This may result in increasing the total unit weight of tablet to an unrealistic value.[18]

The technology becomes still more complicated when two or more poorly soluble drugs need to be concomitantly formulated in a single unit. However, judicious choice of non-volatile liquid, carrier, and coating material can overcome the limitations of LS technology.[18]

Atorvastatin and glipizide are widely used together for the treatment of hyperlipidemia and hyperglycemia, two disorders which are known to be closely associated with each other. Long-term use of glipizide is reported to result in fat depositions in the vital organs of the body. A survey by the WHO reported that 40-60% of the diabetic patients are obese, in which diabetic dyslipidemia occurs due to increased triglycerides, low high-density lipoprotein cholesterol, and high low-density lipoprotein cholesterol.[19] Atorvastatin is one of the most commonly used drugs to treat hyperlipidemia

in diabetic patients.[20] Both glipizide and atorvastatin (ATV) belong to biopharmaceutical classification system Class II and exhibit poor solubility.[21] In the present study, these two drugs will be formulated in a single unit dosage form by the use of LS technology.

Therefore, formulation of LS compacts of binary mixture of these two drugs is expected to provide a rational combination therapy for the treatment of patients suffering from the commonly prevalent comorbidities, i.e., atherosclerosis and Type II diabetes mellitus.

To reach an optimum formulation, various components of the formulation were varied in their ratios so as to achieve the desirable values of essential process variables such as powder flow, powder compaction, and characteristics of final formulation like disintegration time and dissolution profile.

MATERIALS AND METHODS

Materials

Atorvastatin was a gifted by Rhydburg Pharmaceuticals, India; glipizide was procured from Jackson Laboratories, India. Boric acid, hydrochloric acid, polyethylene glycol 400 (PEG 400), PEG 4000, propylene glycol (PG), sodium hydroxide pellets, Span 20, 40, 60, and 80, sodium starch glycolate (SSG), and magnesium stearate were purchased from Loba Chemie, India. HPMC - low viscosity (HPMC E5LV) was procured from Colorcon Asia Ltd. Kollidon® VA64 (polyvinyl pyrrolidone [PVP] VA 64) and Kollidon® 30 (PVP K-30) were purchased from BASF, India. Low-substituted hydroxypropyl cellulose-LH-11 (L-HPC LH-11) and microcrystalline cellulose PH 102 (MCC PH 102) were gifts from Signet, India. Tween 20, 40, 60, and 80 were purchased from Molychem Ltd., India. Syloid® 244FP was a gift from Grace Material Technologies, Discovery Sciences, India. Aerosil® was a gift sample from Evonik Pharma, India.

Estimation of glipizide and ATV by reversed-phase high-performance liquid chromatography (RP-HPLC)

HPLC analysis of glipizide and ATV was carried out using Shimadzu LC20AD HPLC system (Shimadzu Corporation, Japan) with a diode array detector using LC solution software. A phenomenex RP C18 (250 mm × 4.6 mm) column was used as a stationary phase, whereas methanol: acetate buffer (pH 5.0) in the ratio of 50:50 v/v was used as mobile phase. The flow rate was maintained at 0.7 ml/min. Detection wavelength was 225 nm for glutathione peroxidase (GPZ) and 242 nm for ATV, respectively. The retention times (Rt) were found to be 3.22 min for ATV and 16.35 min for GPZ. The standard curves for both the drugs were found to be linear

in the concentration ranges of 5-25 µg/ml (r^2 was 0.9939 for GPZ and 0.9999 for ATV).

Solubility studies in non-volatile solvents

Solubility studies of glipizide and ATV were carried out in different non-volatile solvents to select the most appropriate solvent. Saturated solutions were prepared by adding known excess of drugs to the liquid vehicles. The saturated solutions were kept shaken at 50 rpm for 48 h at 25°C. The resulting solutions were filtered through a 0.45 µm Millipore filter. The filtrates were diluted with phosphate buffer (pH 7.5) and analyzed using HPLC. The solvents evaluated include Tween 20, 40, 60, and 80, PEG 200, 400, 600, 800, and PG.

Drug loading capacity of PG

From the solubility studies, glipizide and ATV were found to exhibit maximum solubility in PG (see results and discussions). It was, therefore, selected as liquid medication for both the drugs. To calculate the drug loading capacity of PG, ATV and glipizide were added together slowly in 1 ml of PG, till the sample showed saturation of both the drugs.

Evaluation of liquid adsorption capacity to select carrier and coating material

To select effective carrier and coating material, liquid adsorption capacity of MCC PH 102, lactose, Aerosil® and Syloid® 244FP silica was evaluated. Each of the carriers (2 g) was placed in a beaker and PG was added drop-wise using a burette. It was mixed thoroughly with the sample. Addition of PG was continued until a thick paste-like mass was formed without residual PG remaining. The volume of PG consumed was recorded, and the liquid adsorption capacity was calculated.

Formulation of LS powders

Formulation of LS compacts includes the evaluation of liquid loading factor, solidification of the liquid medication, and attaining free-flowing compressible powder.[14] To achieve this, 50 mg of both the drugs were loaded in 1 ml of PG. This mixture was stirred well and heated gently at 40°C for complete solubilization of drug mixture in the liquid. To this liquid medication, measured amount of carrier material (MCC PH 102/Lactose) was added (the amount of carrier used is given in Table 1), mixed thoroughly, and followed by addition of coating material (Syloid® 244FP) to get free-flowing powder. During the liquid (PG) adsorption experiment, Syloid® 244FP was found to exhibit the best liquid (PG) adsorption capacity and was, therefore, selected as coating material (see results and discussions). To evaluate the effect of additives on loading factor, 10% of different

additives (e.g., Kollidon® 30/HPMC E5LV/PEG 4000/ Kollidon® VA64/L-HPC LH-11) were added in the liquid medication. A total of 24 formulations were prepared, of which, 12 batches contained lactose as carrier, whereas 12 batches contained MCC PH 102 [Table 1]. The purpose of addition of additive was to evaluate their effect on liquid loading factor, powder flow, disintegration, and dissolution behavior.

Determination of drug content in LS powder samples

Percentage of drug in the dried samples was evaluated by dissolving 100 mg of the sample in 100 ml of phosphate buffer solution (pH 7.5) and stirring the solution using a magnetic stirrer (400 rpm) at room temperature for 24 h. The solutions were filtered and analyzed through HPLC for both the drugs. The study was carried out in triplicate, and mean data were recorded.

Evaluation of flow property of precompressed LS powders

The fixed funnel method was used to determine angle of repose (θ), as reported by Singh *et al*. (2012a).[8] The experiments were performed in triplicate, and mean data were recorded. Angle of repose was determined by following equation 1.

$$\text{Angle of repose}\,(\theta) = \frac{\tan^{-1} h}{r} \tag{1}$$

Preparation of LS compacts

24 LS formulations were prepared; out of which, 12 (LS-1 to LS-12) were prepared using lactose as carrier, whereas 12 (LS-13 to LS-24) were prepared using MCC PH 102 as carrier. For each formulation, glipizide (50 mg) and ATV (100 mg) were dissolved in PG (1 ml) to form liquid medication. The solution was stirred well and heated at 40°C to achieve clear liquid solution. Calculated amount of carrier was added to convert the liquid into solid. This was followed by addition of 10% additives (Kollidon® K30/HPMC E5LV/ PEG 4000/Kollidon® VA64). The mixture was stirred well and kept aside for 15 min for proper adsorption of liquid onto the carrier. A calculated amount of coating material (Syloid® 244FP) was added to this wet powder to provide free-flowing LS powder. To convert into tablet, 5 mg of the SSG as super disintegrant was added and compressed.

The formulations with L-HPC LH-11 were prepared with MCC PH 102/lactose to L-HPC LH-11 ratio of 9:1. In the formulation containing L-HPC LH-11, no super disintegrant was added because it itself is known to act as binder as well as super disintegrant.[22] The prepared powders were compressed to get

Table 1: Formulation of LS compacts and directly compressed tablets with lactose/MCC PH 102 as carrier

LS formulation	Lactose (carrier) (mg)	MCC PH 102 (carrier) (mg)	Amount of propylene glycol (mg)	Loading factor (L_f) without additive	Additives	Amount of additives (mg)	Loading factor (L_f) with additive	Amount of Syloid® 244FP (mg)	Carrier to coating ratio (R value)	Talc (mg)	Sodium starch glycolate (mg)	Unit dose (mg)
LS-1	600.00	-	102	0.17	-	-	-	40	15	8	5	755.00
LS-2	600.00	-	102	0.17	Kollidon® 30	76	0.15	45	15	8	5	836.00
LS-3	600.00	-	102	0.17	HPMC E5LV	76	0.15	45	15	8	5	836.00
LS-4	600.00	-	102	0.17	PEG 4000	76	0.15	45	15	8	5	836.00
LS-5	600.00	-	102	0.17	Kollidon® VA64	76	0.15	45	15	8	5	836.00
LS-6	600.00	-	102	0.17	L-HPC LH-11	67	0.15	44	15	8	-	821.00
LS-7	600.00	-	102	0.17	-	-	-	30	20	8	5	745.00
LS-8	600.00	-	102	0.17	Kollidon® 30	74	0.15	34	20	8	5	823.00
LS-9	600.00	-	102	0.17	HPMC E5LV	74	0.15	34	20	8	5	823.00
LS-10	600.00	-	102	0.17	PEG 4000	74	0.15	34	20	8	5	823.00
LS-11	600.00	-	102	0.17	Kollidon® VA64	74	0.15	34	20	8	5	823.00
LS-12	600.00	-	102	0.17	L-HPC LH-11	67	0.15	33	20	8	-	810.00
LS-13	-	480.00	102	0.21	-	-	-	32	15	8	5	627.00
LS-14	-	480.00	102	0.21	Kollidon® 30	63	0.19	36	15	8	5	681.00
LS-15	-	480.00	102	0.21	HPMC E5LV	63	0.19	36	15	8	5	690.00
LS-16	-	480.00	102	0.21	PEG 4000	63	0.19	36	15	8	5	690.00
LS-17	-	480.00	102	0.21	Kollidon® VA64	63	0.19	36	15	8	5	690.00
LS-18	-	480.00	102	0.21	L-HPC LH-11	53	0.19	29	15	8	-	672.00
LS-19	-	480.00	102	0.21	-	-	-	24	20	8	5	619.00
LS-20	-	480.00	102	0.21	Kollidon® 30	62	0.19	27	20	8	5	690.00
LS-21	-	480.00	102	0.21	HPMC E5LV	62	0.19	27	20	8	5	690.00
LS-22	-	480.00	102	0.21	PEG 4000	62	0.19	27	20	8	5	690.00
LS-23	-	480.00	102	0.21	Kollidon® VA64	62	0.19	27	20	8	5	690.00
LS-24	-	480.00	102	0.21	L-HPC LH-11	53	0.19	22	20	8	-	665.00
DCT-1	400	-	-	-	-	20	-	12	-	8	5	445.00
DCT-2	400	-	-	-	Kollidon® 30	20	-	12	-	8	5	465.00
DCT-3	400	-	-	-	HPMC E5 LV	20	-	12	-	8	5	465.00
DCT-4	400	-	-	-	PEG 4000	20	-	12	-	8	5	465.00
DCT-5	400	-	-	-	Kollidon® VA64	20	-	12	-	8	5	465.00

(Contd...)

Table 1: (Continued)

LS formulation	Lactose (carrier) (mg)	MCC PH 102 (carrier) (mg)	Amount of propylene glycol (mg)	Loading factor (L$_f$) without additive	Additives	Amount of additives (mg)	Loading factor (L$_f$) with additive	Amount of Syloid® 244FP (mg)	Carrier to coating ratio (R value)	Talc (mg)	Sodium starch glycolate (mg)	Unit dose (mg)
DCT-6	400	-	-	-	L-HPC LH-11	20	-	12	-	8	-	460.00
DCT-7	-	400	-	-	-	20	-	12	-	8	5	445.00
DCT-8	-	400	-	-	Kollidon® 30	20	-	12	-	8	5	465.00
DCT-9	-	400	-	-	HPMC E5LV	20	-	12	-	8	5	465.00
DCT-10	-	400	-	-	PEG 4000	20	-	12	-	8	5	465.00
DCT-11	-	400	-	-	Kollidon® VA64	20	-	12	-	8	5	465.00
DCT-12	-	400	-	-	L-HPC LH-11	20	-	12	-	8	-	460.00

In all the formulations, the concentration of glipizide was 5 mg and atorvastatin 10 mg. The concentration of additives (except L-HPC LH-11) was 10% of formulation and concentration of sodium starch glycolate as super disintegrant was 2% with respect to carrier (Lactose). The ratio of L-HPC LH-11 to carrier was 1:9. DCT: Directly compressed tablets, L-HPC LH-11: Low-substituted hydroxypropyl cellulose-LH-11, PEG 4000: Polyethylene glycol 4000, HPMC E5LV: Hydroxy propyl methyl cellulose low viscosity, MCC PH 102: Microcrystalline cellulose PH 102, LS: Liquisolid

LS compacts. The compacts were compressed by using tablet compression machine (Multi Punch, Trover Pharm, India).

Preparation of conventional direct compression tablets

Glipizide and ATV conventional tablets were prepared by mixing the drugs with MCC PH 102 and Syloid® 244 FP in different ratios. Further, the blend was mixed with additives for a period of 10 min in a cubic mixer. To this mixture, 5 mg SSG was added and triturated for 10 min. The mixture was compressed using 10 mm punch by tablet compression machine. Compressional force was adjusted to produce tablets with hardness values ranging from 55 to 70 N. Each tablet contained 5 mg of glipizide and 10 mg of ATV; 400 mg of MCC PH 102/lactose, 20 mg of Kollidon® K30/HPMC E5LV/PEG 4000/Kollidon® VA64/L-HPC LH-11*;* 12 mg of Syloid® 244FP; 5 mg SSG, and 8 mg talc. In the formulation containing L-HPC LH-11*,* no super disintegrant was added as it acts both as binder as well as super disintegrant.[22] The formula composition is given in Table 1.

Evaluation of prepared tablets

All the prepared formulations, i.e., LS tablets and direct compression tablets were evaluated for quality control parameters such as content uniformity, weight variation, hardness, friability, wettability, disintegration, and dissolution studies.

Content uniformity

10 tablets were crushed and an accurately weighed amount of powder equivalent to unit dose of a single tablet (5 mg for glipizide and 10 mg for ATV) was taken. This was dissolved in 100 ml phosphate buffer (pH 7.4), subjected to sonication and then filtered through a membrane filter (Millipore, 0.45 µm pore size). The drug content was determined by HPLC analysis. Each study was carried out in triplicate, and mean data were recorded.

Uniformity of weight

20 tablets from each formulation batch were individually weighed and the mean weight was calculated. Percentage weight variation was calculated for each batch.

Uniformity of tablet thickness and diameter

The diameter and thickness of 10 tablets were measured using a digital Vernier Caliper (Mitutoyo, Japan) at three different positions. Mean of three measurements was recorded.

Friability testing

10 preweighed tablets from each batch were placed in the drum of the friabilator (Friability Testing Apparatus FT 1020,

Lab India) and rotated at 25 rpm for a period of 4 min. Their final weight was measured. The percentage loss in weight was calculated and taken as a measure of friability. The experiment was carried out in triplicate and mean data were recorded.

Hardness

The average breaking strength of tablets was determined by tablet hardness tester (Monsanto, H. L. Scientific Industries, India). From each batch, 10 tablets were tested and the mean value of hardness was determined.

In vitro disintegration time

The test was carried out on six tablets using tablet disintegration tester (DT 1000, Lab India, India) in 900 ml phosphate buffer (pH 7.4) at $37 \pm 0.5°C$. The time taken for complete disintegration of tablets with no palpable mass remaining in the apparatus was measured.

In vitro dissolution studies

The dissolution studies of LS compacts of glipizide and ATV were performed using USP II apparatus (DS 8000, Lab India, India) in 900 ml 0.2 M phosphate buffer (pH 7.4) at $37 \pm 0.5°C$ at 50 rpm for 90 min. Samples were withdrawn at specific intervals and replaced with an equal volume of fresh medium. After filtration through a 0.45 µm membrane filters, samples were assayed for percentage drug release using HPLC.

Scanning electron microscopy (SEM)

The surface morphology of the pure drug and the prepared LS powder samples (selected batch) was studied by SEM. Double-sided conductive tape (diameter 12 mm, Oxon, Oxford Instruments, UK) was used to fix the sample onto the metallic stub. A Supra 35 VP (Oberkochen, Germany) SEM was used with an acceleration voltage of 1.00 kV and a secondary detector.

X-ray power diffraction analysis (XRPD)

The XRPD pattern of pure drug, their physical mixture, and selected batch of LS formulation were obtained using an X-ray diffractometer (Bruker axs, D8 Advance). A copper line was used as the source of radiation. The standard runs were carried out at a voltage of 40-kV and a current of 40-mA at a scanning rate of 0.013 min^{-1} over a 2 µm resolution range. Scanning was carried out in the range of 3°–45° 2θ.

Differential scanning calorimetry (DSC)

The thermal characteristics were determined for pure glipizide, pure ATV, glipizide and ATV physical mixture and their LS formulation (selected batch) as procedure reported by Renuka *et al*., 2014. The instrument, DSC (Mettler

Toledo 851E finished with mettle star. SW 9.00 software), was calibrated for heat flow. A temperature gradient of 20°C was used at a temperature range of 25-250°C with nitrogen purging (50 ml/min). About 1-3 mg of the samples were sealed in aluminum crimped cell and tapped to make uniform bed. An empty aluminum pan was used as reference.[12]

Accelerated stability studies

12 tablets from selected batch of LS compacts (LS-18) were stored at $40°C \pm 5°C$ and $75\% \pm 5\%$ relative humidity for 3 months. The hardness of the tablets was measured as described in section 2.11.5. The values obtained were compared to those of freshly prepared samples. The stored samples were also evaluated under the same dissolution conditions as that of fresh tablets as described in section 2.11.7. The dissolution profiles of aged LS compacts were compared to those of freshly prepared LS compacts.

Statistical analysis of data

The *in vitro* release profiles of fresh and accelerated stability samples (selected batch) were compared using similarity factor as defined by the equation 2:

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t) \right]^{-0.5} \times 100 \right\}$$

(2)

Here, n indicates the number of time points at which the determinations were made for the % drug dissolved, R_t is the % drug dissolved of formulation at a given time point, T_t indicates the % drug dissolved of the formulation being investigated, at the same time point.[23]

Furthermore, the data for dissolution studies were statistically analyzed by analysis of variance using InStat 1 software. Results are quoted as significant where $P < 0.05$.

RESULTS AND DISCUSSIONS

Solubility studies in different non-volatile solvents

Both the drugs were found to exhibit maximum solubility in PG [Figure 1]. The percentage solubility of glipizide and ATV was 62.10 (w/w%) and 92.87 (w/w%), respectively. Hence, PG was selected as liquid vehicle.

Drug loading capacity of PG

Loading capacity of PG was found to be 50 mg/ml of glipizide and 100 mg/ml of ATV when mixed together. It was observed that 50 mg glipizide and 100 mg ATV got dissolved in 1 ml of PG. Hence, in 1 ml of PG, the ratio of glipizide and
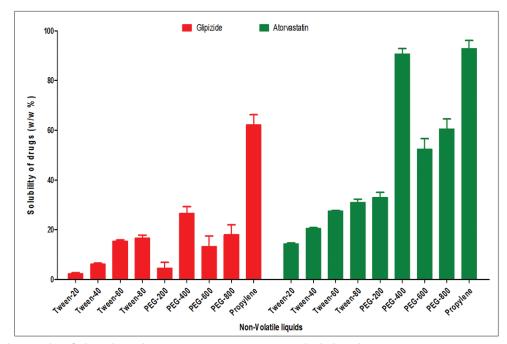
Figure 1: Solubility results of glipizide and atorvastatin in various non-volatile liquids

ATV was 1:2, which was much desirable as our purpose was to formulate a tablet that should contain 5 mg glipizide and 100 mg ATV.

Selection of carrier and coating material

The liquid (PG) adsorption capacity of MCC PH 102, lactose, Aerosil® and Syloid® 244FP silica was found to be 107, 78, 210, and 330 g/100g of PG, respectively. The maximum PG adsorption capacity was found with Syloid® 244FP, followed by Aerosil, MCC PH 102, and lactose respectively. Syloid® 244FP silica is mesoporous, amorphous, and micronized silica which possess very good adsorption capacity, porosity, particle size, and large surface area.[24] Although Syloid® 244FP and aerosil have provided comparatively better liquid adsorption capacity as compared to lactose and MCC PH 102, their highly amorphous nature and poorer binding properties were found to aggravate compaction problems as the formulations already contain liquid. Hence, lactose and MCC PH 102 were selected as carriers (fillers) and Syloid® 244FP silica as coating material.

Flow properties of LS powders

A total of 24 batches of LS powders were prepared in which LS-1, 7, 13, and 19 did not contain any additive [Table 1]. Batches LS-1 to 6 contained lactose as carrier and LS-13 to 18 contained MCC PH 102 as carrier, wherein the ratio of lactose/MCC PH 102 to Syloid® 244FP was 15. Batches LS-7 to 12 contained lactose as carrier and LS-19 to 24 contained MCC PH 102 as carrier, wherein the ratio of lactose/MCC PH 102 to Syloid® 244FP was 20. It was observed that the loading factor got decreased with the addition of additives.

In case of lactose, the loading factor decreased from 0.17 to 0.15 and in case of MCC PH 102 from 0.21 to 0.19. It has been reported that decreased loading factor is an indication of enhanced flow properties; hence, it can be assumed that addition of additives could increase the micromeritic properties of formulations.[18] This could be the reason that the formulations, which contained additives, have been shown to exhibit better flow properties as compared to those formulations in which additive was not added [Table 2].

Formulations containing lactose as carrier has shown comparatively poor flow properties than formulations containing MCC PH 102 which is not only more amorphous but also provides more surface area for liquids to get adsorbed onto itself as compared to lactose.[8] Hence, it was able to provide better liquid adsorption capacity than lactose. Among the formulations prepared using additives, LS-2, 8, 14, and 20, in which Kollidon® 30 was used, have shown the best results [Table 2], whereas formulations containing PEG 4000 as additives (LS-4, 10, 16, and 22) have shown comparatively higher values of angle of repose. High values of angle of repose indicate poor flow. The flow of LS formulations containing various additives decreased in the following order:

Kollidon® 30 >Kollidon® VA64 >L-HPC LH-11 >HPMC E5LV >PEG 4000.

As carrier to coating ratio (R) was increased from 15 to 20, the wettability of formulations increased and thereby flow of powders decreased. At a value of 15, the amount of Syloid® 244FP silica was higher as compared to the carriers used. As Syloid® 244FP silica has higher liquid adsorption capacity as compared to lactose and MCC PH 102, hence, the prepared

Formulations	Angle of repose (θ) (mean±SD) (*n*=3)	Percentage drugcontent (mean±SD) (*n*=3)	Weight variation (mg) (mean±SD) (*n*=3)	Hardness (kg lbs/cm²) (mean±SD) (*n*=3)	Percentage Friability (mean±SD) (*n*=3)	Disintegration time in min. (mean±SD) (*n*=3)
LS-2	26.5±0.39	98.02±0.55	836.0±0.18	3.5±0.98	0.95±0.19	7.03±0.65
LS-3	32.5±0.32	98.32±0.43	836.0±0.48	3.0±0.54	1.00±0.18	10.6±0.52
LS-4	38.8±0.19	99.01±0.65	836.0±0.73	4.5±0.47	0.92±0.93	4.53±0.28
LS-5	29.2±0.39	99.09±0.52	836.0±0.11	4.0±0.49	0.52±0.91	2.59±0.59
LS-6	31.3±0.18	98.21±0.56	821.0±0.82	3.5±0.36	0.82±0.43	1.81±0.93
LS-8	32.3±0.29	98.65±0.92	823.0±0.48	4.0±0.39	0.97±0.83	13.1±0.49
LS-9	36.8±0.21	99.04±0.91	823.0±0.48	4.5±0.46	0.62±0.94	14.3±0.58
LS-10	42.1±0.19	99.34±0.34	823.0±0.92	4.5±0.12	0.99±0.47	7.34±0.18
LS-11	31.1±0.12	98.91±0.32	823.0±0.31	5.1±0.36	0.03±0.84	5.09±0.51
LS-12	35.5±0.21	99.01±0.28	810.0±0.43	5.0±0.37	0.05±0.84	3.54±0.38
LS-14	21.5±0.91	98.02±0.48	681.0±0.05	6.5±0.43	0.04±0.93	4.43±0.49
LS-15	31.7±0.24	99.09±0.43	690.0±0.13	5.5±0.48	0.02±0.95	5.10±0.24
LS-16	33.3±1.09	98.12 ± 0.31	690.0±0.23	4.0±0.57	0.04±0.94	9.58± 0.53
LS-17	27.8±0.81	98.21±0.39	690.0±0.93	4.5±0.58	0.02±0.75	2.14±0.38
LS-18	29.4±0.92	98.09±0.59	672.0±0.68	4.5±0.48	0.05±0.46	1.02±0.55
LS-20	25.3±0.91	99.06±0.39	690.0±0.54	4.0±0.43	0.12±0.38	8.43±0.47
LS-21	33.5±1.01	97.79±0.57	690.0±0.54	4.5±0.69	0.23±0.95	10.2±0.52
LS-22	36.4±0.99	98.23±0.91	690.0±0.24	4.1±0.43	0.44±0.76	11.35±0.5
LS-23	29.2±0.87	99.18±0.03	690.0±0.45	4.0±0.59	0.35±0.54	4.12±0.54
LS-24	29.5±0.91	98.43±0.42	665.0±0.46	4.5±0.58	0.12±0.69	2.57±0.47
DCT-2	20.7±0.17	99.56±0.57	465.0±0.97	5.0±0.56	0.11±0.12	5.56±0.36
DCT-3	24.0±0.25	99.32±0.91	465.0±0.47	5.5±0.45	0.22±0.38	6.20±0.54
DCT-4	17.0±0.23	99.08±0.03	465.0±0.92	4.5±0.52	0.13±0.57	8.19±0.54
DCT-5	19.9±1.02	99.21±0.42	465.0±0.08	4.0±0.91	0.11±0.83	4.52±0.57
DCT-6	19.0±0.68	99.93±0.43	460.0±0.45	4.5±0.31	0.34±0.39	1.11±0.73
DCT-8	20.5±0.61	99.90±0.08	465.0±0.62	4.0±0.69	0.23±0.22	5.43±0.91
DCT-9	19.0±0.31	99.21±0.67	465.0±0.26	3.5±0.83	0.22±0.53	6.54±0.48
DCT-10	22.5±0.01	99.45±0.43	465.0±0.56	4.0±0.22	0.41±0.45	7.43±0.73
DCT-11	18.3±0.01	99.49±0.92	465.0±0.68	4.5±0.56	0.23±0.62	4.10±0.63
DCT-12	18.1±0.02	99.21±0.08	460.0±0.93	3.5±0.78	0.11±0.86	0.58±0.53

Table 2: Evaluation parameters of LS compacts and directly compressed tablets

DCT: Directly compressed tablets, SD: Standard deviation, LS: Liquisolid

LS formulations for which "R" value was 15, wherein the amount of Syloid® 244FP silica was more, provided complete coating of powder and thereby provided better flow properties.

The powder mixtures prepared for the formulation of all conventional directly compressed tablets (DCT-1 to 12) have shown very good flow [Table 2]. Because of poor flow properties, all the LS formulations which do not contain additives (LS-1, 7, 13, and 19), were not subjected to further evaluation. Moreover, their compositions in direct compression form (DCT-1 and 7) were also withdrawn from further evaluation.

Evaluation of prepared LS compacts and DCTs

The tablets were evaluated for quality control parameters, and the data are shown in Table 2. All the tablets were found to pass the tests for % drug content, weight variation, hardness, % friability as per USP 30 NF 25 limits. However, a drastic change was observed in the disintegration behavior of the prepared LS tablets. It was observed that the tablets containing L-HPC LH-11 (LS-6, 12, 18, and 24) showed very fast disintegration as compared to the formulations containing Kollidon® 30, HPMC E5LV, PEG 4000, and Kollidon® VA64. As the MCC PH 102 to Syloid® 244FP ratio (R) was increased from 15 to 20, the disintegration time of

formulations increased. Disintegration time for formulations containing MCC PH 102 was found to be shorter than formulations containing lactose. This shows that MCC PH 102 possesses better super disintegrant property as compared to that of lactose. Syloid® 244FP has a high surface area (200 m²/g) and is highly amorphous in nature. Hence, it provides comparatively less binding property as compared to lactose as well as MCC PH 102. This could be the reason behind the faster disintegration of formulations (LS-1 to 6 and LS-13 to 18), in which the amount of Syloid® 244FP was higher than those of carriers (lactose/MCC PH 102).

The disintegration time of LS formulations containing various additives decreased in the following order:

PEG 4000 >HPMC E5LV >Kollidon® 30 >Kollidon® VA64>L-HPC LH-11.

Among MCC PH 102/lactose ratios to Syloid® 244FP (R), the disintegration time of LS formulations decreased in the following order:

Syloid® 244FP to lactose (R = 20) >Syloid® 244FP to Lactose (R = 15) >Syloid® 244FP to MCC PH 102 (R = 20) >Syloid® 244FP to MCC PH 102 (R = 15).

In vitro dissolution studies

Figures 2a and 3a show the dissolution profiles of LS compacts of glipizide and ATV with different additives containing lactose as a carrier with lactose to Syloid® 244FP ratio 15. To further explore the potential of LS technology for dissolution rate enhancement, the dissolution profiles of pure drugs using

the same additives prepared by direct compression (DCT 2, 3, 4, 5, and 6 containing lactose and DCT 8, 9, 10, 11, and 12 containing MCC PH 102) were also compared.

From Figures 2a and 3a, it was observed that LS-6, containing L-HPC LH-11 shows faster drug release than LS-2, LS-3, LS-4, and LS-5. This showed that the L-HPC LH-11 has good super disintegrant as well as good wettability characteristics. The formulations containing Kollidon® 30 and Kollidon® VA64 as additive (LS-2 and LS-5) has provided a higher dissolution rate than conventional tablets prepared by DCT, containing HPMC E5LV (LS-3), and PEG 4000 (LS-4), respectively. The lowest dissolution rates were observed for LS tablets containing PEG 4000. This can be attributed to PEG 4000 being a wax-like material, wetting of tablet by dissolution media becomes difficult. In other words, PEG 4000 might have increased the viscosity of the stagnant diffusion layer and decreased dissolution rate of the drug. This could be the probable reason behind the lowest dissolution rate of LS-4 in comparison with LS-2, LS-3, LS-5, and LS-6 tablets. The lower dissolution rate of LS-3 in comparison with LS-6, LS-5, and LS-2 can be attributed to gel forming properties of HPMC LV 5 around the disintegrated particles. The high viscosity around drug particles may slow down the penetration of water into particles and this, in turn, could have reduced the dissolution rate of the drug from particles. It is important to note here that Kollidon® 30 and Kollidon® VA64 are the brand names of PVP. The main reason for the increased dissolution of the drug in the presence of PVP (LS-2 and LS-5) might be due to crystal growth inhibition. It has been shown that PVP may serve to inhibit precipitation of drug from the supersaturated solution.[8] Another reason for the increased dissolution of drug in the presence of PVP
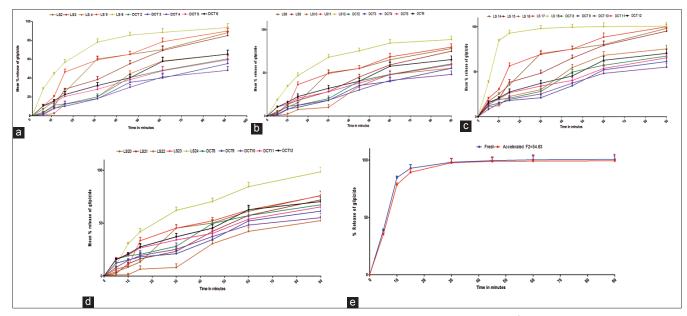

Figure 2: Dissolution profiles of liquisolid formulation containing glipizide, (a) lactose to Syloid® 244FP ratio is 15; (b) lactose to Syloid® 244FP ratio is 20; (c) microcrystalline cellulose PH 102 (MCC PH 102) to Syloid® 244FP ratio is 15; (d) MCC PH 102 to Syloid® 244FP ratio is 20. Dissolution profiles of liquisolid-18 formulation containing fresh and accelerated samples of glipizide (e)
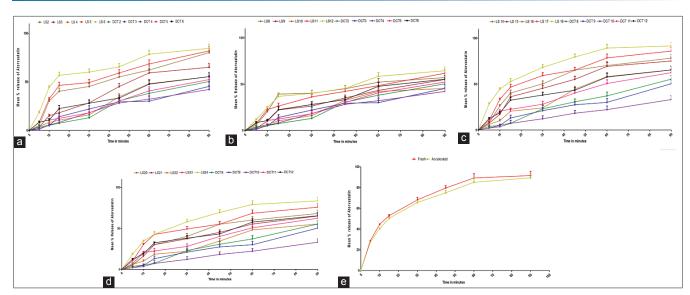
Figure 3: Dissolution profiles of liquisolid formulation containing atorvastatin, (a) lactose to Syloid® 244FP ratio is 15; (b) lactose to Syloid® 244FP ratio is 20; (c) microcrystalline cellulose PH 102 (MCC PH 102) to Syloid® 244FP ratio is 15; (d) MCC PH 102 to Syloid® 244FP ratio is 20. Dissolution profiles of liquisolid-18 formulation containing fresh and accelerated samples of atorvastatin (e)

could be the amorphous nature of PVP, which provided an increased surface area to the drug to get exposed to the dissolution medium.[8,18,25,26]

The dissolution rate of LS formulations containing various additives increased in the following order:

PEG 4000 <HPMC E5LV <Kollidon® 30 <Kollidon® VA64< L-HPC LH-11.

Similar results were observed for formulations containing lactose in which lactose to Syloid® 244FP ratio was 20. Figures 2b and 3b show the dissolution profiles of LS compacts of glipizide and ATV with different additives (Kollidon® 30/HPMC E5LV/PEG 4000/Kollidon® VA64/L-HPC LH-11) containing lactose as a carrier with lactose to Syloid® 244FP ratio 20. However, when the ratio of lactose to silica was changed from 15 to 20, the dissolution rate of formulations decreased. This was attributed to two factors - (a) Due to higher surface area of Syloid® 244FP silica (200 m²/g), higher amounts of drug in molecular state could be adsorbed on its surface leading to higher dissolution rate of drugs (as was seen for LS-2 to LS-6) and (b) Improved water permeation as evident by disintegration time results which showed lower disintegration at carrier to coating ratios of 15 compared with 20.[8] A decrease in the amount of Syloid® 244FP (From R = 15 to R = 20) decreased the amount of drug release (LS-8 to LS-12).

To evaluate the effect of type of carrier on dissolution profile, several formulations were prepared using MCC PH 102 as carrier and dissolution tests were performed. The results are shown in Figures 2c and 3c for formulations containing MCC PH 102 to Syloid® 244FP silica ratio 15 and Figures 2d and 3d for formulations containing MCC PH 102 to Syloid® 244FP ratio 20. The effect of different additives on dissolution profile

of ATV and glipizide has already been discussed earlier in the same section. A significant increase in the dissolution profile was observed when carrier was changed from lactose to MCC PH 102. This can be attributed to disintegrant property of MCC. Because of the presence of a non-volatile solvent in the LS formulation, delayed disintegration time is expected. However, in the LS tablets containing MCC, a fast disintegration of tablet was formed which can be attributed to the disintegrant property of MCC with the exception of the tablets containing PEG 4000 (9.58 and 11.35 min for LS-16 and LS-22, respectively).

Among all the LS formulations prepared, LS-18 has given faster disintegration time (1.02 min) and faster dissolution rate (84.6% in 10 min for glipizide and 44.6% for ATV) with 100% drug release. Thus, out of all developed formulations, LS-18 has been chosen as the best formulation for stability studies.

Accelerated stability studies

12 tablets from LS-18 series were kept at 40°C/75% relative humidity for 6 months. Hardness and dissolution rate were measured. The results showed that there was no significant difference between the hardness of fresh (61.3 ± 7 N) and aged (58.5 ± 7.7 N) LS tablets *(P > 0.05)*. This indicated that the hardness of LS compacts was not affected by aging.

Figures 2e and 3e show the dissolution profile of fresh and aged LS tablets. Although the aged LS tablets appear to have lower dissolution rate than fresh LS tablets in the graph, similarity factor of the two release profiles was 54.63 for glipizide [Figure 2e] and 53.11 [Figure 3e] for ATV indicated acceptably similar profiles.[23] This indicates that aging has no

significant effect on dissolution behavior of the glipizide and ATV LS compacts.

Figure 4: Scanning electron microphotograph of, (a) glipizide; (b) atorvastatin and, (c) liquisolid-18 formulation containing glipizide and atorvastatin

SEM

SEMs [Figure 4a and b] show crystals of pure glipizide and ATV with average diameters of 100 μm. LS dispersions of glipizide and ATV revealed as irregular matrices due to the porous nature of the carrier with the fine particles of the drug deposited on it (Figure 4c). In some parts of LS formulation, an unclear gel-like matrix surrounding the crystal can be observed. This shows complete wettability of drugs with the liquid medication. Reduced particle size, dispersion of drugs in the non-volatile hydrophilic liquid, and porous nature of coating material appear to be the contributing factors toward enhancement in dissolution of drug.

XRPD

The diffraction pattern of pure glipizide, pure ATV powder, and their physical mixture is shown in Figure 5. It revealed several sharp high-intensity peaks at diffraction angles
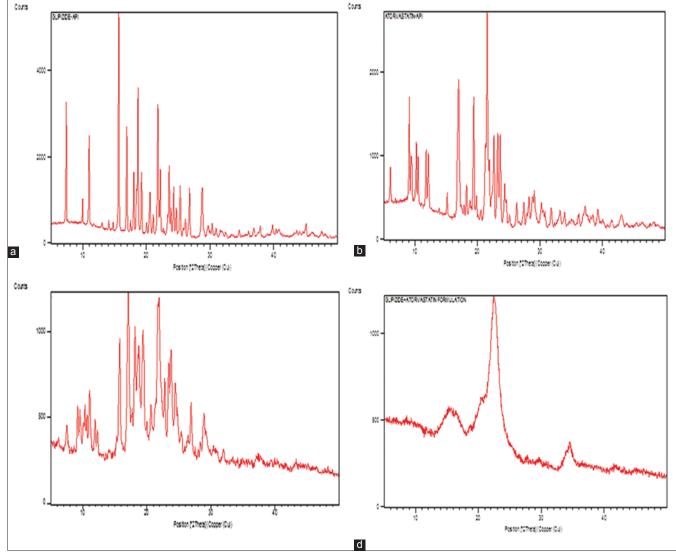

Figure 5: (a-d) Powder X-ray diffractograms of glipizide, atorvastatin, and liquisolid-18 formulations
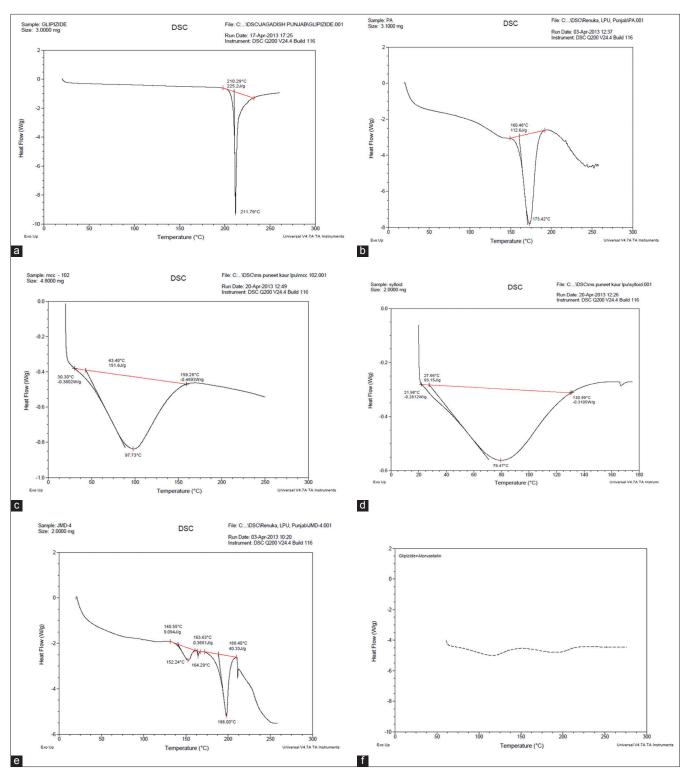
Figure 6: (a-f) Differential scanning calorimetry thermograms of pure glipizide, pure atorvastatin, microcrystalline cellulose PH 102, Syloid® 244FP, and liquisolid-18 formulation

(2θ) of 7.5°, 9.96°, 20.5°, 21°, 22°, 23.5°, 29°, 32°, and 33°, respectively, suggesting that both the drug existed as crystalline material before and after physically mixed. However, the LS formulation LS-18 shows a halo pattern with only two diffraction peaks at 22.53° and 34.40° indicating that the drug has got completely wetted by PG. This also reveals that the decrease in crystallinity of the formulation is

due to complete solubility of drugs in PG as no decrease in crystallinity was observed in case of physical mixtures.

DSC

The DSC thermograms of glipizide exhibited a sharp melting endotherm at 211.79°C and ATV exhibited a sharp

endotherm at 173.42°C [Figure 6]. The DSC of MCC PH 102 and Syloid® 244FP was also scanned. Melting peak of MCC PH 102 was found at 97.73°C and Syloid® 244FP melting point was found to be 79.47°C, respectively. It is clear from Figure 6 that there was no sharp melting endotherm observed with the prepared LS formulation. This states that both the drugs have got completely dissolved in PG. This has further supported the results of XRPD studies.

CONCLUSION

The present study deciphers successful coformulation of a pharmacologically relevant combination of two poorly soluble drugs in a single dosage form. Among the different non-volatile liquids used, PG was found to be the best option. Solid carriers and additives used in the study were able to convert the drug solution into free-flowing compressible mass. Carrier to coating ratio (R) was varied from 15 to 20 and its influence of powder flow, compaction, disintegration, and dissolution of drugs was investigated. A total of 24 formulations were prepared. It was observed that formulations containing "R" value 15 have shown better precompression properties as well as dissolution profiles as compared to formulations containing "R" value 20. Stability studies indicated that LS-18 formulation remained unaffected during the accelerated conditions.

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