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Original Article

STUDIES ON REFINED LIQUISOLID SYSTEM FOR SIMULTANEOUS IMPROVEMENT OF CONTENT UNIFORMITY AND DISSOLUTION PROFILE OF GLIMEPIRIDE

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ABSTRACT

Objective: To improve and compare dissolution contour of poorly soluble BCS Class II drug Glimepiride (GLD) by altering it to conventional solid dispersion (CSD), surface solid dispersion (SSD) and refined liquisolid system (RLS).

Methods: The three formulations of GLD namely CSD, SSD and RLS were fabricated using the conventional methods by employing the suitable polymer and solvent system. These formulations were optimized on the basis of powder flow properties, FTIR, DSC and XRD analysis. All the optimized formulations were compared to the marketed formulation for content uniformity and dissolution rate.

Results: The characteristic analysis of all the optimized formulations was obtained in the standard range. The average content uniformity (% age) of Marketed formulation, CSD, SSD and RLS found to be 88.28±0.721, 92.91±0.789, 95.98±0.478, 99.32±0.744 respectively. The *in vitro* dissolution rate (%age at 30 min time interval) fall in the range 59.78±0.036, 75.78±0.013, 93.11±0.019, 93.99±0.062 and 98.55±0.043 for pure drug, Marketed formulation, CSD, SSD and RLS respectively. All the analytical studies exhibited improved homogeneity/distribution of the drug in RLS.

Conclusion: The RLS formulation presented sheer expansion in the content uniformity and dissolution contour of GLD at a minimal cost.

Keywords: BCS, Glimepiride, Conventional solid dispersion, Surface solid dispersion, Content uniformity, Refined liquisolid system

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INTRODUCTION

Diabetes mellitus (DM) disorder is illustrated by hyperglycemia, glycosuria, hyperlipemia, negative nitrogen balance and sometimes ketonemia [1]. Sulphonylureas are generally prescribed to the category of diabetic patients. GLD is a potent second-generation sulfonyl derivative given to heal NIDDM (Non-Insulin-Dependent Diabetes Mellitus), which acts on sulfonylurea receptors (SUR1) on the pancreatic β cell membrane [2-4]. GLD is effective at low dose in diabetic patients and exhibits linear pharmacokinetic pattern [5-7]. The solubility of GLD can be improved by various techniques as reported in literature like microencapsulation [8], solid dispersion [9], liquisolid compact [10] and surface solid dispersion [11-14]. Solid Dispersion [15-17] is the term referred as the unit of solid products comprising of not less than two dissimilar components, usually a water-loving matrix and a water repellant drug. The kind of matrix can be either crystalline or amorphous [18]. CSD can be prepared by numerous techniques like melting/fusion [19, 20], solvent evaporation [21] or melting-solvent method [22, 23]. SSD is the dispersion system which encourages the dumping of the drug on the surface of an inactive carrier material resulting in variation in the dissolution performance of the drug [24-26]. SSD is prepared by dissolving the drug in the required solvent. Then the resulting solution is dumped on to the surface of the chosen carrier. Diverse techniques such as conventional co-evaporation, solvent evaporation using rota-evaporator can be employed to confiscate the solvent [27]. Liquisolid Compact (LS) is a novel encouraging loom which could alter the rate of dissolution by improving wetting properties as well as the surface area of the drug by translating it into non-adherent, unrestricted surge with ease of compression of the powder meld [28, 29]. LS compacts of poorly soluble drugs show a boost in the release of the drug because of the intensified surface area of the drug in soluble form in the non-volatile solvent will increase its aqueous solubility and reduction of contact angle for the drug particles [30-32]. *RLS* is the mutated form of LS in which the drug that has been distributed in the non-volatile solvent is transferred for adsorption on the surface of carrier matter such as aerosil. It is then blended well for getting a homogenous mixture. Unlike LS and SSD, RLS system does not require any addition of coating material thereby making RLS an easy and uncomplicated technique.

MATERIALS AND METHODS

Materials

GLD was supplied as a gift sample by Morepan Lab. Parwanoo, India. Aerosil 200, DMSO and ethanol (95%) AR grade were procured from CDH, India. All other AR grade excipients were utilized in the existing study.

Methods

Characterization of Aerosil 200

Aerosil 200 was characterized for its bulk density, true density, and liquid accommodating capacity. Bulk density and true density of Aerosil 200 were determined by using a conventional method using the graduated cylinder and liquid displacement method respectively. Liquid accommodating capacity of Aerosil 200 was determined by two methods i.e. AOR and AOS. The liquid (DMSO) was added in increasing amounts to the carrier till it stopped flowing. The flowing behavior was determined by using the data of the angle of repose and the angle of the slide.

Angle of Repose (AOR) is a feature concerned to resistance to flow among adjoining particles. It was determined by using the fixed funnel method. 10 g of Aerosil 200 was weighed and passed through the funnel from a height of 5 cm and the height and diameter of the heap were noted. The angle of repose enlisted in table 1 was ascertained using the equation tan α = h/R where h and R describe the height and radius of powder heap respectively [35, 36].

Angle of Slide (AOS) The angle of minimum slope is usually measured from the horizontal at which any loose solid material will flow. It was determined by designing an apparatus having a glass slab attached to full circle protector (360 °). The carrier was placed on the glass slab and the slab was rotated [35, 36]. The angle where the carrier started flowing was examined.

Preparation of conventional solid dispersion (CSD)

Conventional solid dispersion of Glimepiride (GLD) with PVP K 30 was prepared by solvent evaporation method using methanol as solvent. Accurately weighed quantity of GLD was dissolved in methanol and stirred to get a clear solution. A weighed amount of PVP K30 was

added to the drug solution and stirred to solubilize it in the drug solution. The CSD (CSD1, CSD2, CSD3, CSD4) were made in varying ratios 1:5, 1:10, 1:15 and 1:20 ratio. The final solution was placed on a water bath in a china dish at 45 °C and stirred until the solvent get evaporated completely. The product was then scrapped from the china dish, made to pass across sieve # 60 and placed in the desiccator [19].

Preparation of surface solid dispersion (SSD)

GLD and Aerosil 200 were taken in the respective ratio of 1:20 to prepare SSD. Aerosil 200 and methanol were utilized as carrier and volatile liquid respectively. The precise weighed proportion of GLD was solubilized in 10 ml of ethanol (95%, v/v). Aerosil 200 was diffused into it. Rota-evaporator (Heidolph, Germany) at 60 rpm and 40 °C temperature was exploited for removal of solvent. Further, the processed product was made to pass across sieve # 60 and placed in desiccator [37, 38].

Preparation of refined liquisolid system (RLS)

Aerosil 200 and DMSO were utilized to formulate RLS of GLD. The precise amount of GLD was distributed in DMSO for solubilization. This blend was further accumulated on the carrier i.e. Aerosil 200 and intermingled appropriately for the procurement of the finished product with 1:20 respective ratio of GLD and Aerosil 200. Finally, the processed product was made to pass across sieve # 60 and placed in a desiccator

Characterization

Evaluation of powder flow behavior

The flow characteristics of powder such as tapped density, bulk density, AOR and AOS were estimated for CSD, SSD and RLS.

Bulk density is the ratio of the weight of powder without tapping and volume of the powder without tapping. Voids between the particles are included. It is measured in units of g/ml. or g/cm^3. The weighed powder is placed in the measuring cylinder (100 ml) and the untapped volume is noted and the values obtained are placed in the following formula to calculate the bulk density [39].

Bulk density of sample = Weight of powder sample (w)/Bulk volume of powder sample (V_b).

Tapped density is determined by tapping the graduated measuring cylinder mechanically for 100 times. After that following formula applied to measure the tapped density. Tapped density is expressed in units similar to bulk density i.e. g/ml. or g/cm^3.

Tapped density of sample = Weight of powder sample (w)/Tapped volume of sample (V_t).

FTIR spectra

The FTIR Spectrum of GLD, PVP K 30, Aerosil 200, CSD, SSD and RLS were recorded on FTIR Spectrophotometer (IR Affinity-1 Shimadzu) by utilizing KBr disc assembly. All the processed pellets prepared by making use of KBr press further processed for scanning within 400-4000 cm^{-1}range [40].

DSC studies

Perkin Elmer DSC Model-4000 was employed for thermal analysis of GLD, PVP K30, Aerosil 200, CSD, SSD and RLS. Small amount (~5 mg) of each sample was positioned in the creased aluminium pan of DSC apparatus and heated at a probing speed of 100 °C/min up to 350 °C temperature starting from room temperature in presence of N_2 gas at 20 ml/min speed. For reference, an empty aluminium pan was employed [41].

Powder X-ray diffraction studies

GLD, PVP K 30, Aerosil 200, CSD, SSD, and RLS samples were examined through X-ray diffractometer (Philips). The functional settings used in X-ray diffractometer include Ni-filtered Cu-Kα radiations having (λ) α1=1.540560 °A and (λ) α2=1.544390 °A, current value of 20 mA, 40 kV generator tension,, intensity ratio 0.500, divergence slit 1ϕ and scanned at rate of 20/min within 2Θ range of 0 °-50 °[42].

Content uniformity studies

As per USP guidelines, the content homogeneity was estimated by taking precisely weighed ten samples from the procured products of CSD, SSD and RLS. All samples comprising 4 mg equivalent amount of GLD were made to dissolve in methanol and subjected to appropriate dilution. UV spectrophotometer at 250 nm wavelength was employed to estimate the content homogeneity of the samples [39].

Dissolution rate studies

USP Type II dissolution apparatus (LabIndia) was utilized to estimate the rate of dissolution of GLD using phosphate buffer (900 ml) of pH 7.8 upheld at 37±0.5 °C at a speed of 75 rpm. Amount of GLD corresponding to 4 mg in CSD, SSD and RLS was expended for the test. Samples of 5 ml were drawn at stated time periods and a similar amount of reservoir was added to the vessels containing media. All samples were filtered instantly and analyzed with HPLC. HPLC study of samples was carried using LC-2010 HT, Shimadzu using Luna 5u C18 (2) 100 A Phenomenex having dimensions 250 x 4.6 mm, with acetonitrile: phosphate buffer (pH 2.5) in 70:30 ratio as mobile phase, at 1 ml/min flow rate. 35 °C oven temperature and UV Spectrophotometer at wavelength 228 nm as detector utilized.

RESULTS AND DISCUSSION

Characterization of aerosil 200

Aerosil 200 is selected as a carrier for the formulation of SSD and RLS depending upon its flow properties and non-reactivity with GLD and solvent system. The flow properties like AOR, AOS, tapped density and bulk density determined and complied with the official limits [39, 40]. These are depicted below in table 1 and 2.

Table 1: Flow properties of Aerosil 200 (bulk density, tapped density, AOR, AOS and L_f)

S. No.	Sample	Bulk density (g/cm^3)	Tapped density (g/cm3)	AOR (in degrees)	AOS (in degrees)	L_f (Liquid load factor) (wt. of liquid/wt. of carrier)
1.	Aerosil 200	31.45±0.012	49.18±0.02	28.13±0.185	36±0.894	0.0932±0.001
2.	Aerosil 200+0.1 ml DMSO	37.71±0.032	57.63±0.011	27.65±0.029	34±0.548	0.1705±0.002
3.	Aerosil 200+0.2 ml DMSO	42.39±0.020	65.74±0.017	25.91±0.018	33±0.707	0.2345±0.002
4.	Aerosil 200+0.3 ml DMSO	52.6±0.035	79.91±0.015	25.46±0.033	32±0.548	0.2963±0.001
5.	Aerosil 200+0.4 ml DMSO	69.89±0.033	95.01±0.015	24.31±0.05	32±0.447	0.3376±0.003
6.	Aerosil 200+0.5 ml DMSO	73.33±0.018	105.92±0.017	24.11±0.04	31±0.548	0.3787±0.002
7.	Aerosil 200+0.6 ml DMSO	92.39±0.008	144.34±0.015	25.91±0.023	32±0.707	0.4178±0.001
8.	Aerosil 200+0.7 ml DMSO	121.89±0.027	213.40±0.026	26.12±0.058	31±0.837	0.4522±0.002
9.	Aerosil 200+0.8 ml DMSO	140.53±0.019	289.91±0.013	27.36±0.035	32±0.447	0.4841±0.004
10.	Aerosil 200+0.9 ml DMSO	178.34±0.024	344.21±0.01	28.44±0.025	32±0.447	0.5173±0.002
11.	Aerosil 200+1.0 ml DMSO	207.24±0.019	421.67±0.011	29.98±0.046	32±0.895	0.5701±0.001
12.	Aerosil 200+1.2 ml DMSO	276.81±0.012	481.21±0.013	30.93±0.028	33±0.447	0.6142±0.004
13.	Aerosil 200+1.4 ml DMSO	301.23±0.042	500.03±0.011	31.14±0.057	34±0.447	0.6439±0.001

(The data expressed as a mean±SD, n=3)

Evaluation of flow properties of CSD, SSD and RLS product

The formulation of CSD, SSD and RLS were subjected to different parameters of flow properties like bulk density, tapped density, Carr's index, Hausner's ratio, AOR and AOS. The values attained after applying the above formula enlisted in the table 2 which highlights the flow properties comparison between CSD SSD and RLS system.

Table 2: Flow properties of various products i.e. CSD, SSD and RLS (bulk density, tapped density, AOR, AOS)

S. No.	Product	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index	Hausner's ratio	Angle of repose (in degrees)	Angle of slide (in degrees)
1.	CSD (1:20)	0.637±0.008	0.723±0.05	0.119±0.017	1.135±0.04	26±0.128	32±0.488
2.	SSD (1:20)	0.1356±0.001	0.1775±0.004	0.236±0.003	1.309±0.002	25±0.006	31±0.378
3.	RLS (1:20)	0.229±0.010	0.315±0.019	0.273±0.002	1.376±0.015	25±0.066	32±0.577

(The data is expressed as a mean±SD, n=5)

FTIR spectra study

Fig. 2 (a,b,c,d,e,f) presents FTIR spectra of Aerosil 200, PVP K 30, GLD, CSD, SSD and RLS respectively. The FTIR spectrum of Aerosil 200 exhibited skeletal stretching vibrations at 3600-3300 cm^{-1} due to stretching bands (O-H) from Si-OH, 1650 cm^{-1} due to H_2O deformation, asymmetric stretching of Si-O and Si-O-Si at 1280 cm^{-1}, Si-O-asymmetric at 973 cm^{-1}, Si-O-symmetric at 820 cm^{-1}, O-Si-O deformation 479 $cm^{-1}$and vibrations for in-phase NH_2 observed at 3325 cm^{-1}. GLD FTIR spectrum exhibits characteristic peaks at 3300-3500 cm^{-1} due to functional group NH_2, O-H stretching vibration at 3300-2500 cm^{-1}; vibration for C-H stretching at 2850-3000 cm^{-1}; 1350-1550 cm^{-1} indicating N-O stretch vibrations; 1220-1020 cm^{-1} signifying C-N stretch vibrations; 1000-1300 cm^{-1} directing C=O bond stretch vibrations. The products (CSD, SSD and RLS) revealed specific peaks of GLD ensuring the presence of drug in said products. The shifts in the characteristic peaks of GLD were not observed confirming any specific interaction between the drug and the carrier [13].

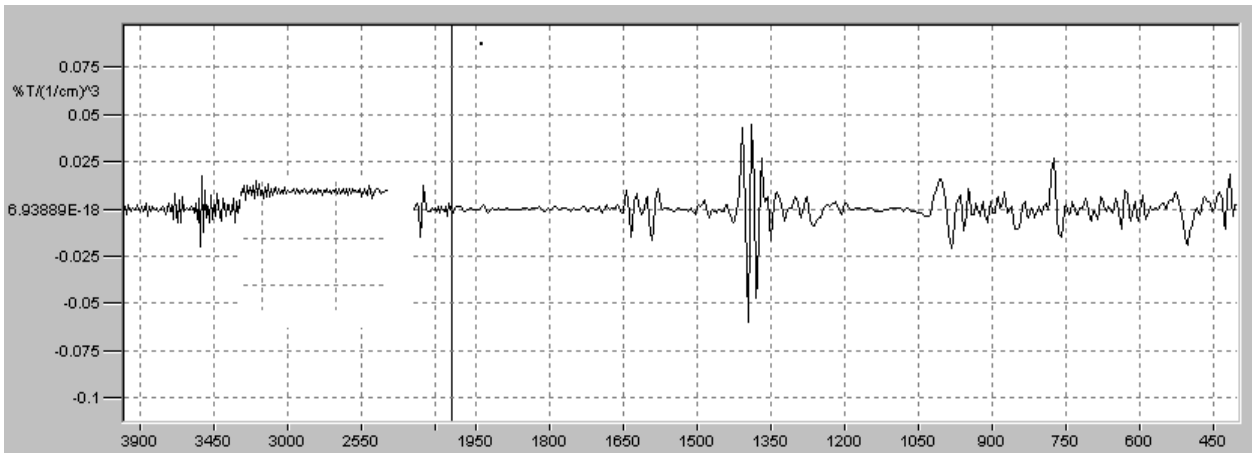

Fig. 1(a): FTIR spectra of Aerosil 200

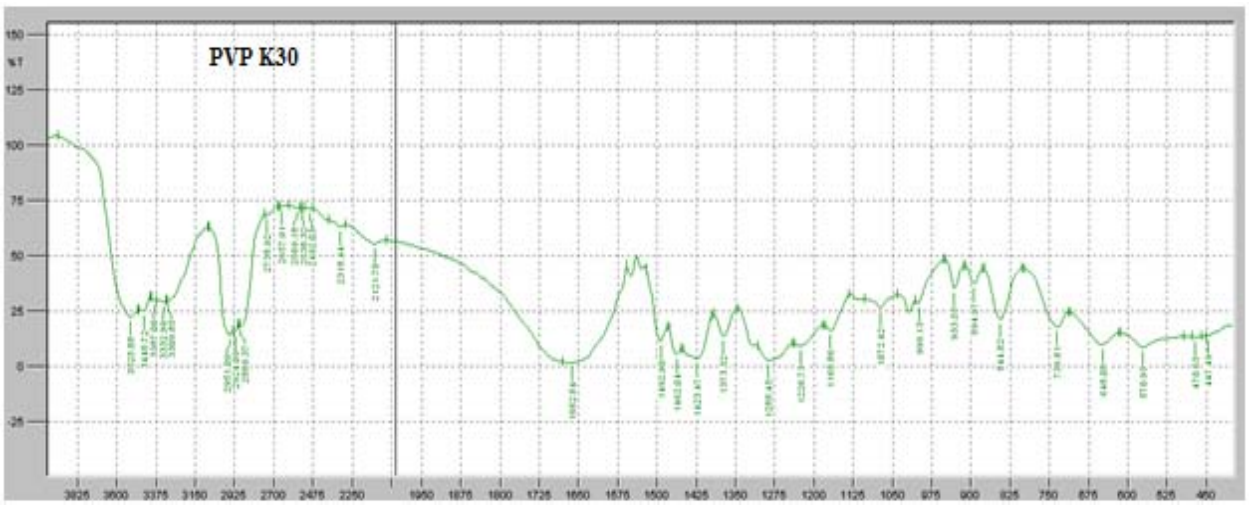

Fig. 1(b): FTIR spectra of PVP K30

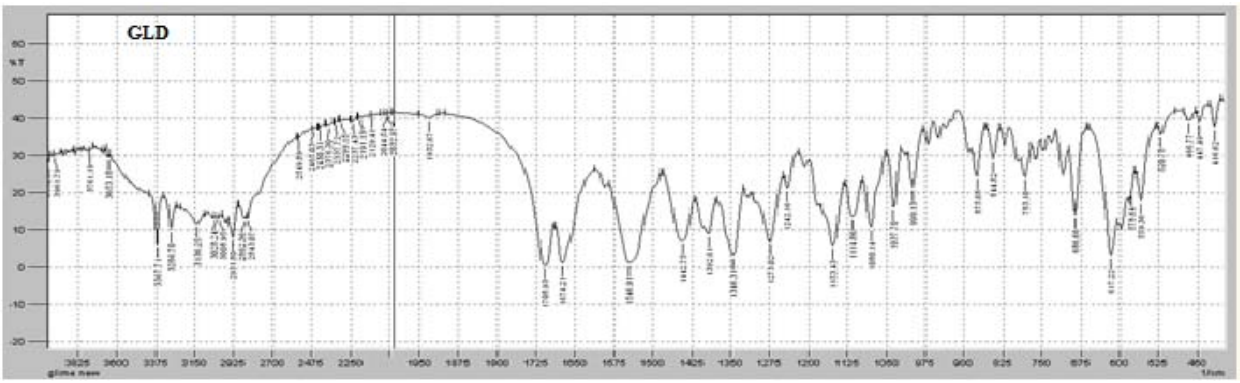

Fig. 1(c): FTIR spectra of glimepiride

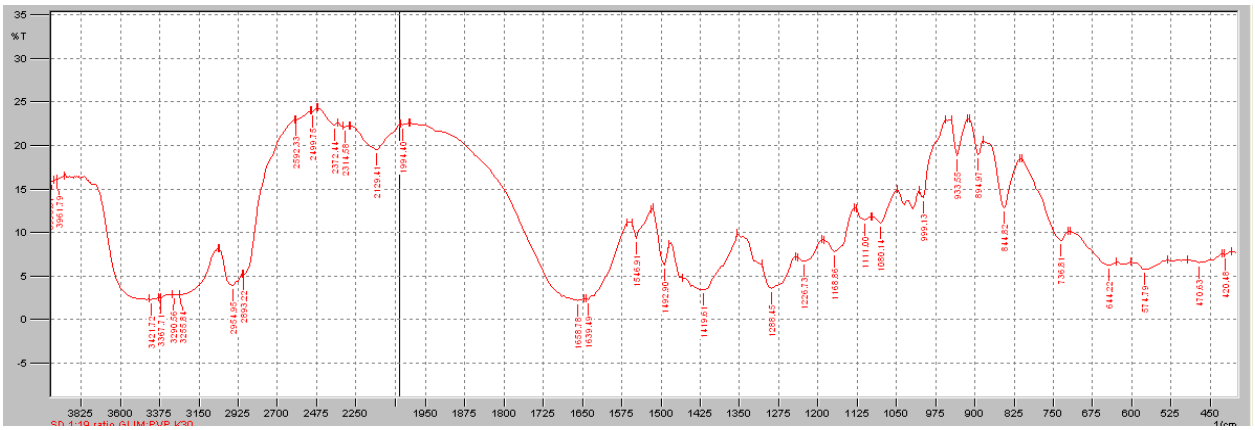

Fig. 1(d): FTIR spectra of CSD

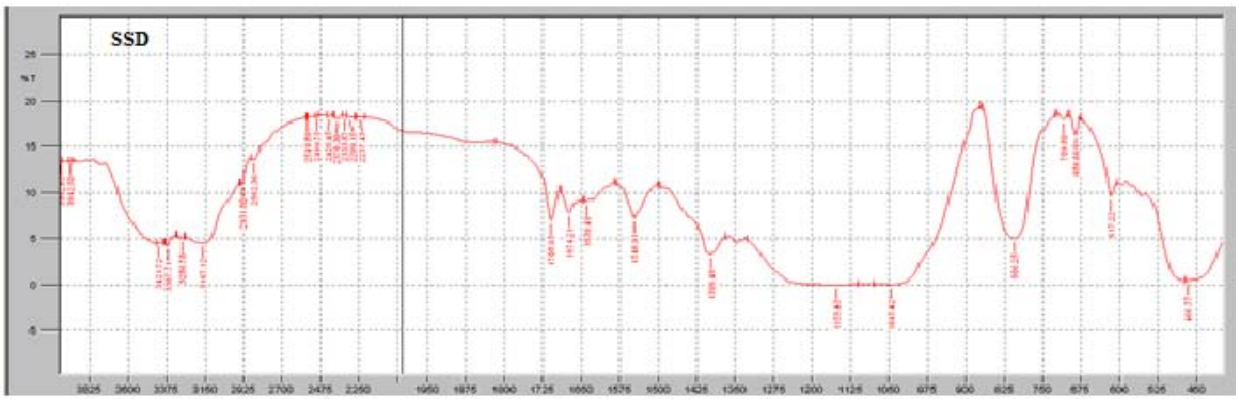

Fig. 1(e): FTIR spectra of SSD

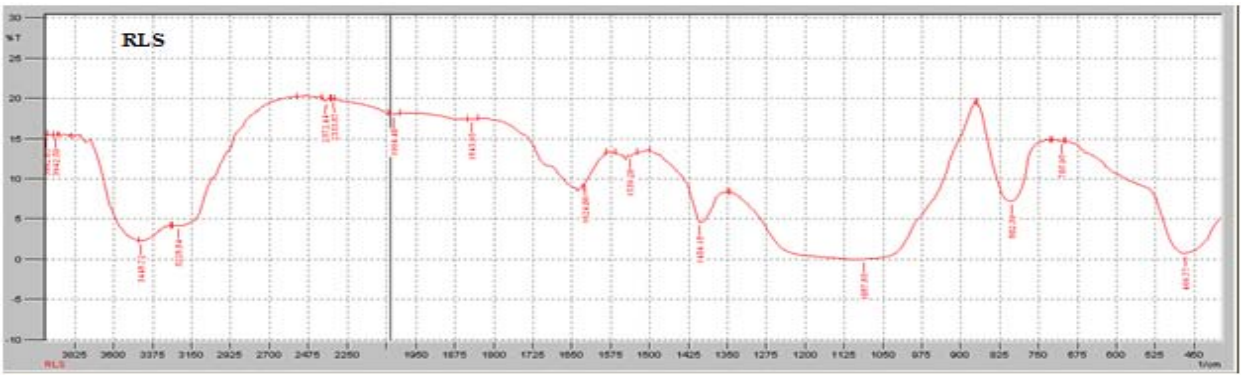

Fig. 1(f): FTIR spectra of RLS

DSC studies

Fig. 3 (a,b,c,d,e,f) depicted the thermograms of aerosil 200, PVP K 30,GLD, CSD, SSD and RLS respectively. GLD thermogram displayed the melting commencement at 213.87 °C and abrupt melting endothermic peak at 217.22 °C temperature corresponding to its melting point which indicated its crystalline nature. The thermograms of SSD and RLS did not exhibit any endothermic peak at 217.22 °C which signified that GLD is present at the molecular level and does not exhibit any crystal lattice of its own thereby confirming amorphous nature of GLD [41].

X-ray diffraction studies

Fig. 4(a,b,c,d,e,f) illustrated the powder X-ray diffractograms of, GLD, PVP K 30, Aerosil 200, CSD, SSD and RLS respectively. Comparison of a few characteristic peaks of diffractogram of the procured products was done with that of pure GLD. X-ray diffractogram of GLD illustrated the intense peak of 2θ (diffraction angle) at 13.41 °, 18.11 ° and 21.18 ° with 5667, 5431 and 8498 peak intensities respectively. Diffractogram of CSD, SSD and RLS showed no intense crystalline peak at 2θ values of GLD which indicated the amorphous nature of the GLD in the products [42, 43].

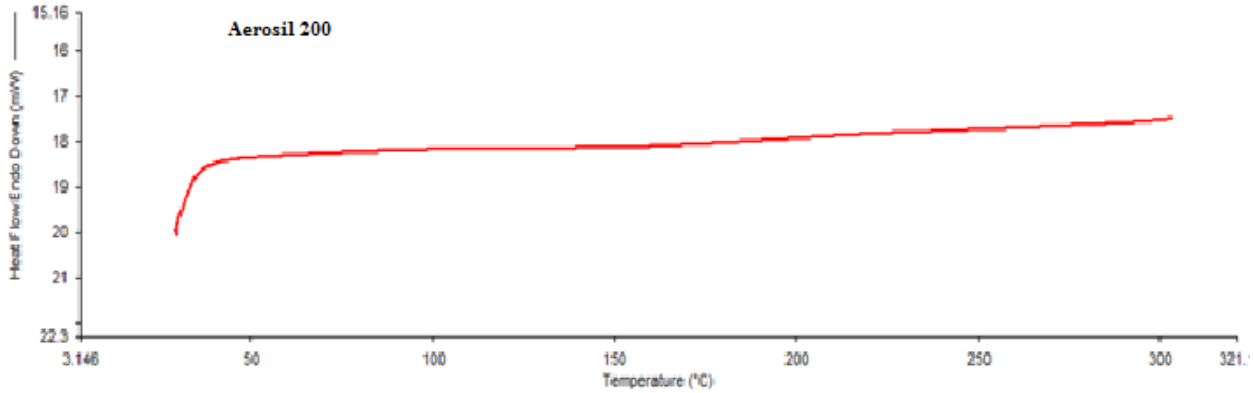

Fig. 2(a): DSC thermograms of Aerosil 200

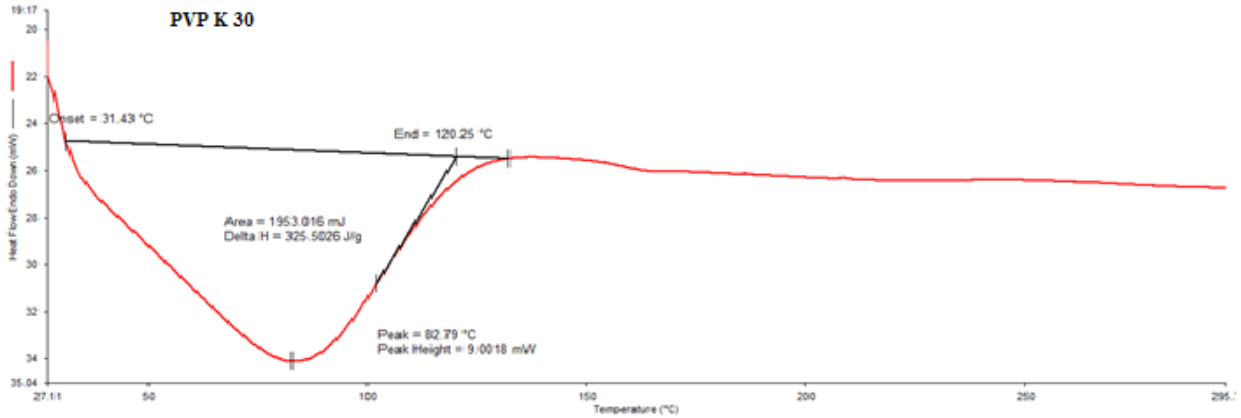

Fig. 2(b): DSC thermograms of PVP K30

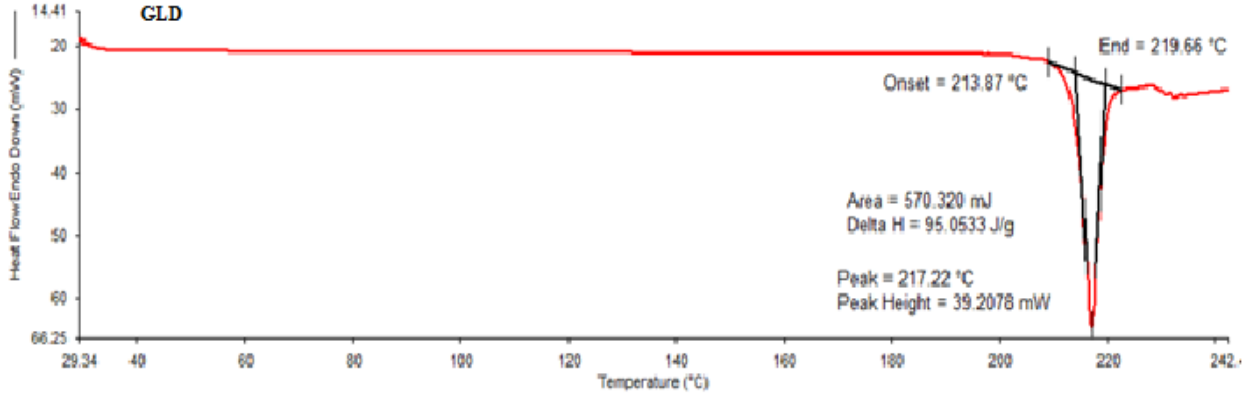

Fig. 2(c): DSC thermograms of GLD

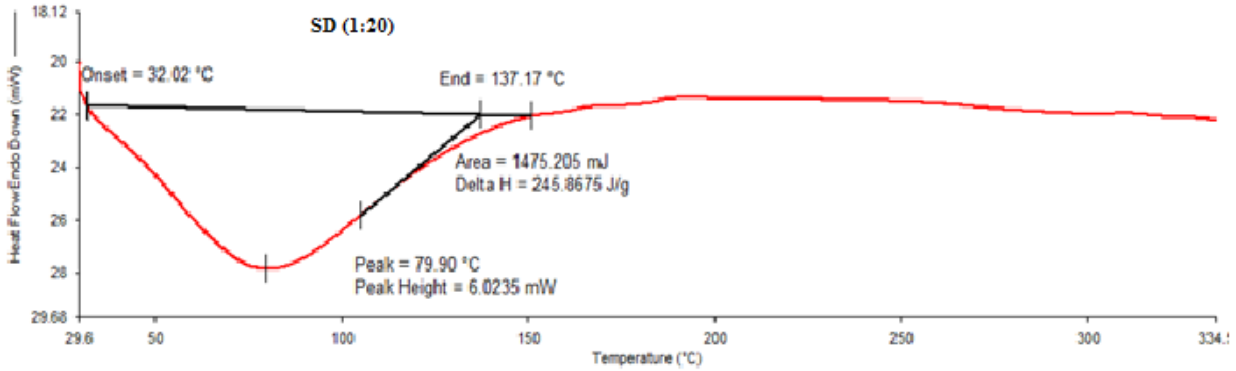

Fig. 2(d): DSC thermograms of CSD

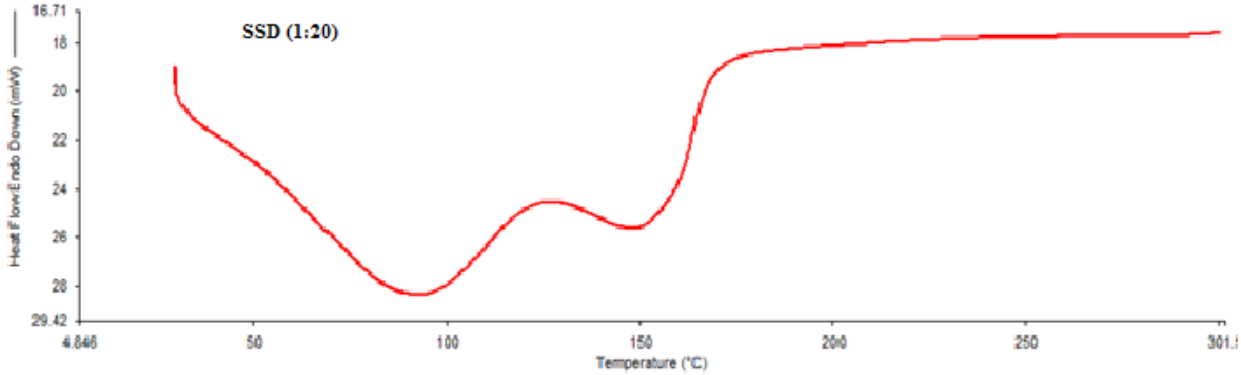

Fig. 2(e): DSC thermograms of SSD

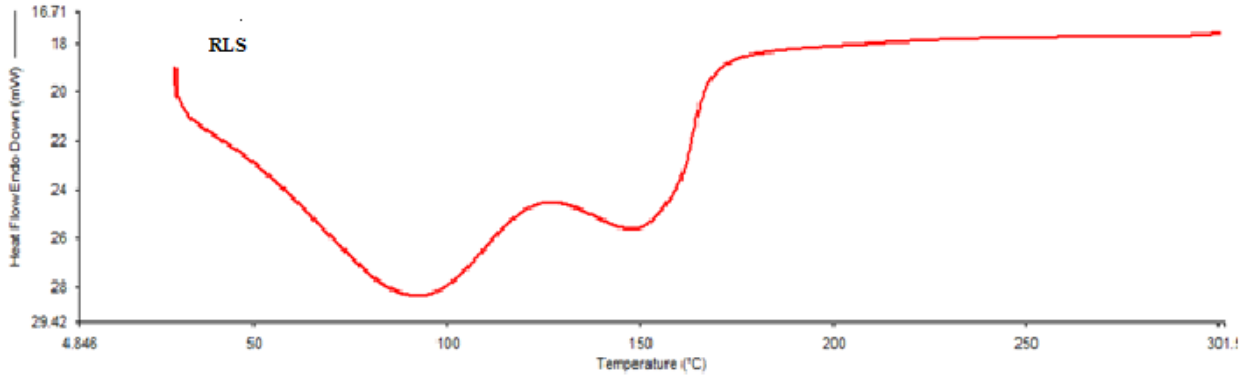

Fig. 2(f): DSC thermograms of RLS

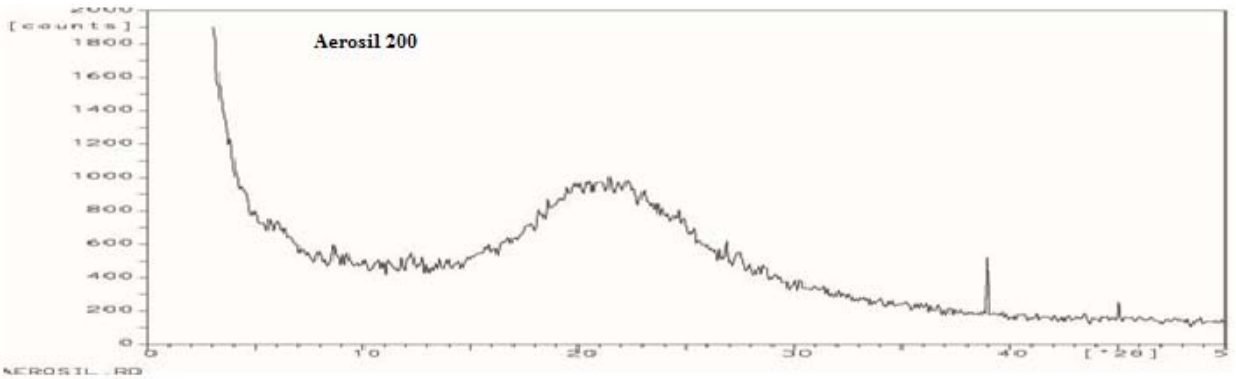

Fig. 3(a): Powder X-ray diffraction of aerosil 200

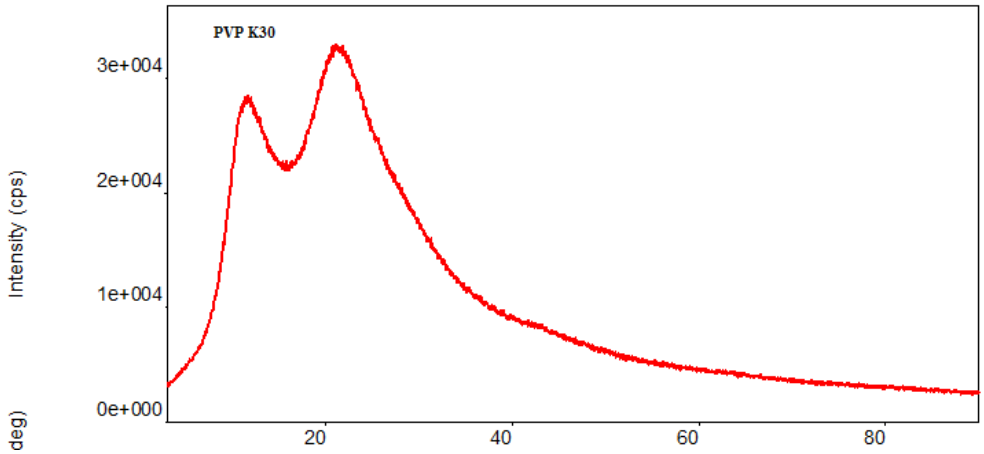

Fig. 3(b): Powder X-ray diffraction of PVP K30

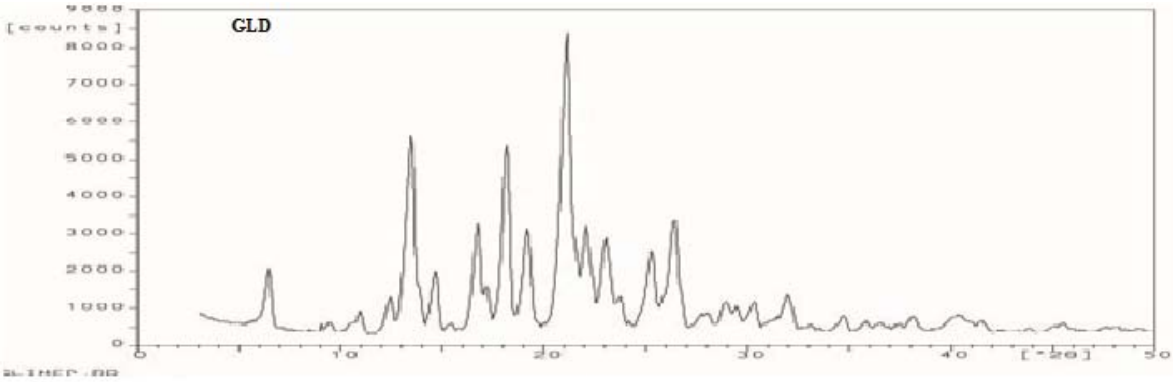

Fig. 3(c): Powder X-ray diffraction of GLD

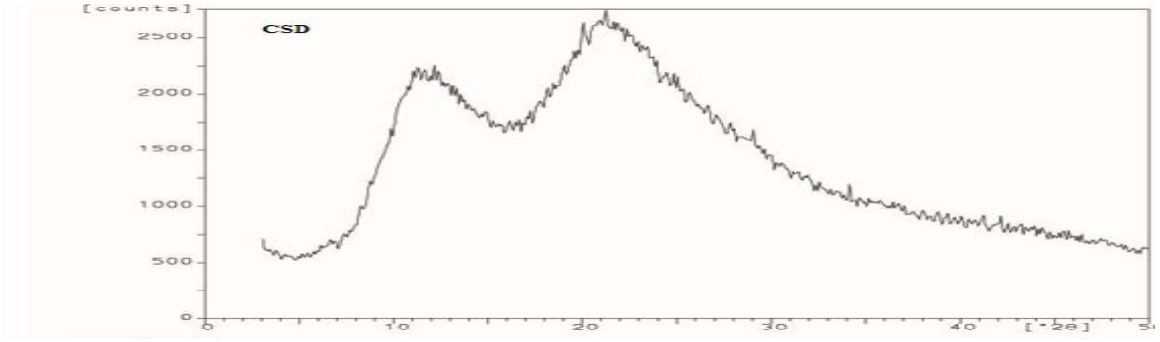

Fig. 3(d): Powder X-ray diffraction of CSD

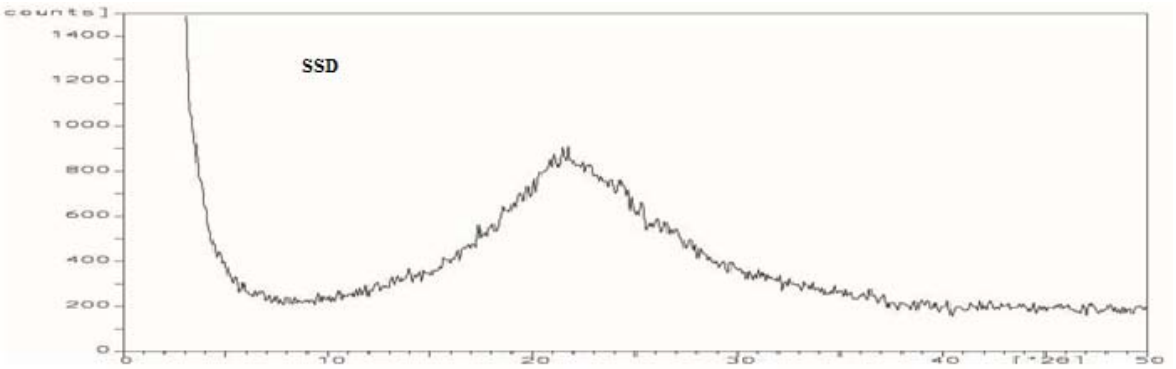

Fig. 3(e): Powder X-ray diffraction of SSD

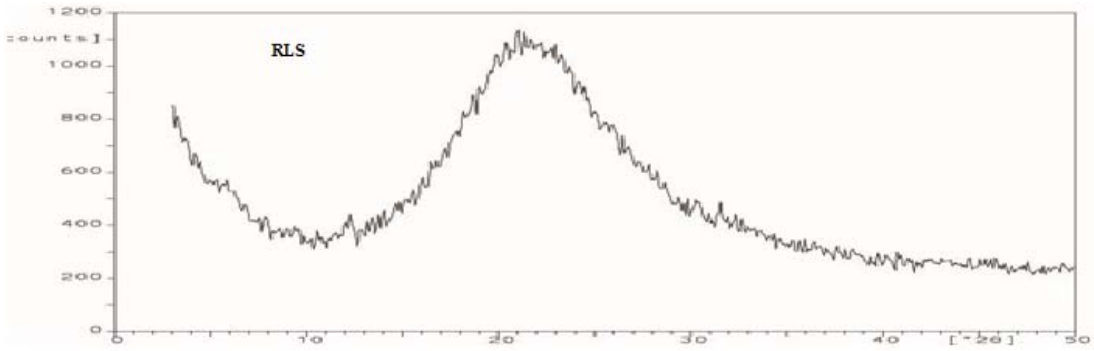

Fig. 3(f): Powder X-ray diffraction of RLS

Content uniformity studies

The test for the content homogeneity as recorded in USP monograph [39] carried out to certify consistency as well as the homogeneity of the potent drug. 85-115% drug of the label assert is the required criteria as per USP content uniformity test. If the formulation not succeeds to match the content uniformity test as per the official guidelines, it may lead to beneath or above the potent dose of drug. The content homogeneity evaluated for marketed tablet, CSD, SSD and RLS is depicted in table 3. From the content uniformity data, it is evident that the average content of drug in RLS is not significantly different. Thus RLS revealed exceptional content uniformity that can be utilized for progressive formulation of low dose drug.

Dissolution rate studies

Dissolution contours of pure GLD, marketed tablet, CSD, SSD and RLS are presented in table 4 and fig. 5. The proportion of dissolution illustrates fraction of drug being solubilized in the medium [13]. The degree of release of pure drug was observed to be relatively small while the data for dissolution of CSD, SSD and RLS revealed almost complete dissolution. In comparison to CSD and SSD, RLS shows steep increase in the rate of dissolution. In case of RLS the drug converts in its molecular form get homogenized with the carrier and remain adsorb on the surface without need of any coating material. The drug release from RLS was brisk and demonstrated sheer upsurge in rate of dissolution in contrast to pure drug GLD [44].

Table 3: Content uniformity data of products like marketed product, CSD, SSD and RLS

S. No.	Products of GLD	Average content uniformity (in %)
1.	Marketed Tablet (Blue Cross Laboratories Ltd.)	88.28±0.721
2.	CSD	92.91±0.789
3.	SSD	95.98±0.478
4.	RLS	99.32±0.744

(The results are expressed as a mean±SD, n=5)

Table 4: *In vitro* dissolution rate data of pure drug, marketed tablet, CSD, SSD and RLS

Time (min)	*In vitro* dissolution rate (in percentage)				
	Pure drug	Marketed tablet	CSD	SSD	RLS
0	0	0	0	0	0
5	15.67±0.031	26.98±0.027	39.87±0.026	43.33±0.028	45.66±0.085
10	24.35±0.022	39.73±0.009	58.13±0.022	61.55±0.022	64.77±0.031
15	28.78±0.018	55.12±0.011	69.78±0.015	73.45±0.022	79.66±0.013
20	37.31±0.027	67.51±0.045	78.98±0.045	82.11±0.028	88.38±0.041
25	48.04±0.045	71.29±0.013	88.65±0.042	91.55±0.018	94.45±0.045
30	59.78±0.036	75.78±0.013	93.11±0.019	93.99±0.062	98.55±0.043

(Result expressed as a mean±SD, n=5)

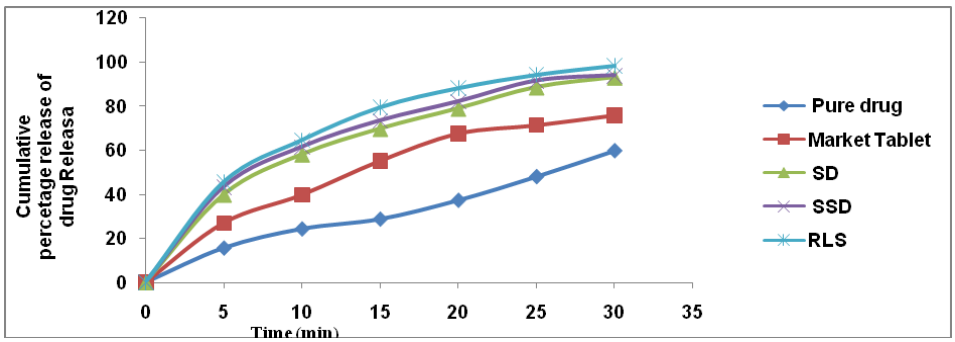

Fig. 4: Comparison of dissolution profile of pure drug GLD, CSD, SSD, RLS and marketed product (data information is expressed as a mean±SD, n=5)

CONCLUSION

In the existing research, GLD was successfully loaded on aerosil 200 in the form of RLS. The RLS formulation of GLD was confirmed by DSC, FTIR, and XRD studies. The RLS formulation of GLD was verified by FTIR, DSC and XRD analysis. Content uniformity revealed upgraded uniformity of content of GLD in RLS. *In vitro* dissolution studies depicted sheer upgrade in dissolution profile of GLD having poor aqueous solubility. RLS is a simple technique employing the carrier to incorporate the drug and there is no need of evaporating the solvent. RLS of GLD was non sticky, exhibited good flow properties and offers cosmic possibility for formulating the poorly soluble potent drugs as instant release dosage forms having enriched content homogeneity, dissolution contour at nominal expenditure.

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STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies with human and animal subjects performed by any of the authors.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICTS OF INTERESTS

The authors (Nishal S, Phaugat P and Dhall M) declare that they have no conflict of interest.

REFERENCES

1. Berner GM, Stevens CW. Pharmacology, drugs for diabetes mellitus. In: Saunders. 3rd ed. Philadelphia, Pennsylvania: Elsevier; 2010. p. 388-99.
2. Rosenkranz B, Profozic V, Metelko Z, Mrzljak V, Lange C, Malerczyk V. Pharmacokinetics and safety of glimepiride at clinically effective doses in diabetic patients with renal impairment. Diabetologia 1996;39:1617-24.
3. Ahmed I, Goldstein B. Diabetes mellitus. Clin Dermatol 2006;24:237-46.
4. Tripathi KD. Oral hypoglycaemic drugs. Essentials of medical pharmacology. 6th ed: New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2008. p. 266-8.
5. Draeger E. Clinical profile of glimepiride. Diabetes Res Clin Pract 1995;28:139-46.
6. Lestari M LAD, Indrayanto G. Glimepiride; profiles of drug substances, excipients and related. Methodology 2011;36:169-204.
7. Mascarello A, Frederico MJ, Castro AJ, Mendes CP, Dutra MF, Woehl VM, *et al.* Novel sulfonyl (thio) urea derivatives act efficiently both as insulin secretagogues and as insulinomimetic compounds. Eur J Med Chem 2014;86:491-501.
8. Bhandare PS, Gharge VG. Formulation and evaluation of microencapsulated Glimepiride produced by the emulsion-solvent evaporation method. Pharma Tutor 2018;6:2-30.
9. Rajpurohit VS, Rakha P, Goyal S, Dureja H, Arora G, Nagpal M. Formulation and characterization of solid dispersions of glimepiride through factorial design. Iran J Pharm Sci 2011;7:7-16.
10. Singh SK, Prakash D, Sirinivasan KK, Kuppusamy G. Liquisolid compacts of glimepiride: an approach to enhance the dissolution of poorly water-soluble drugs. J Pharm Res 2011;4:2263-8.
11. Kiran T, Shastri N, Sistla R, Sadanandam M. Surface solid dispersion of glimepiride for enhancement of dissolution rate. Int J Pharm Res 2009;1:822-31.
12. Rajpurohita VS, Rakha P, Goyal S, Dureja H, Arora G, Nagpal M. Formulation and characterization of solid dispersions of glimepiride through factorial design. Iran J Pharm Sci 2011;7:7-16.
13. Patil SK, Wagh KS, Parik VB, Akarte AM, Baviskar DT. Strategies for solubility enhancement of poorly soluble drugs. Int J Pharm Sci Rev Res 2011;8:75-80.
14. Choudhary A, Rana CA, Aggarwal G, Kumar V, Zakir F. Development and characterization of an atorvastatin solid dispersion formulation using skimmed milk for improved oral bioavailability. Acta Pharm Sinica B 2012;2:421-8.
15. Chau VLN, Chulhun P, Beom Jin L. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. Eur J Pharm Biopharm 2013;85:799-13.
16. Chiou WL, Riegelman S. Preparation and dissolution characteristics of several fast release solid dispersion of griseofulvin. J Pharm Sci 1969;58:1505-10.
17. Kurmi R, Mishra DK, Jain DK. Solid dispersion: a novel means of solubility enhancement. J Crit Rev 2016;3:1-8.
18. Arunachalam A, Karthikeyan M, Kishore K, Pottabathula PH, Sethuraman S. Solid dispersions: a review. Curr Pharma Res 2010;1:82-90.
19. Fazil, Shamsuddin M, Ansari HS, Ali J. Development and evaluation of solid dispersion of spironolactone using fusion method. Int J Pharm Investig 2016;6:63-8.
20. Huanga Y, Wei Guo D. Fundamental aspects of solid dispersion technology for poorly soluble drugs. Acta Pharm Sinica B 2014;4:18-25.
21. Kim KT, Lee JY, Lee MY, Song CK, Choi J, Kim D. Solid dispersions as a drug delivery system. J Pharm Invest 2011;41:125-42.
22. Marano S, Barker AS, Raimi Abraham TB, Missaghi S, Rajabi Siahboomi A, Craig DQM. Development of micro-fibrous solid dispersions of poorly water-soluble drugs in sucrose using temperature-controlled centrifugal spinning. Eur J Pharm Biopharm 2016;103:84-94.
23. Surampalli G, Kumar S, Nanjwade B, Patil PA. Amorphous solid dispersion method for improving oral bioavailability of poorly water-soluble drugs. J Pharm Res 2013;6:476–80.
24. Bary A Abd-El, Louis D, Sayed S. Olmesartan medoxomil surface solid dispersion-based orodispersible tablets: formulation and *in vitro* characterization. J Drug Delivery Sci Technol 2014; 24:665-72.
25. Bhagavanth GR, Madhusudhan A, Ramakrishna D. Development, evaluation and characterization of surface solid dispersion for solubility and dispersion enhancement of irbesartan. J Pharm Res 2013;7:472-47.
26. Fazil, Shamsuddin M, Ansari HS, Ali J. Development and evaluation of solid dispersion of spironolactone using fusion method. Int J Pharm Investig 2016;6:63-8.
27. Dixit RP, Nagarsenkar MS. *In vitro* and *in vivo* advantage of Celecoxib surface solid dispersion and dosage form development. Ind J Pharm Sci 2007;69:370-7.
28. Sisinthy SP, Selladurai S. Cinnarizine liquid solid compacts: preparation evaluation. Int J Appl Pharm 2019;11:150-7.
29. Rokade M, Khandagale P, Phadtare D. Liquisolid compact techniques: a review. Int J Curr Pharm Res 2018;10:1-5.
30. Vajir S. Enhancement of dissolution rate of poorly water soluble diclofenac sod. by liquisolid technique. Int J Pharm Chem Sci 2012;3:989-1008.
31. Hentzschel CM, Alnaief M, Smirnova I. Enhancement of griseofulvin release from liquisolid compacts. Eur J Pharm Biopharm 2012;80:130-5.
32. Sirisha VNL, Sruthi B, Namrata M, Harika IB, Kirankumar, Rao KK, *et al.* A review on liquid-solid compacts. Int J Pharm Phytopharmacol Res 2012;2:116-21.
33. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the world health organization model list of essential medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm 2004;58:265-78.
34. Nainar S, Rajiah K, Angamuthu S, Prabakaran D, Kasibhatta R. Biopharmaceutical classification system in *in vitro/in vivo* correlation: concept and development strategies in drug delivery. Trop J Pharm Res 2012;11:319-29.
35. Burkalow AV. Angle of repose and angle of sliding friction: an experimental study. GSA Bull 1945;56:669-707.
36. Denver Procedure for determining the angle of basic friction (static) uses a tilting table test. Materials Engineering and Research Laboratory, code 86-68180, Technical Service Center Designation USBR 6258-09; 1976.
37. Khatry S, Sood N, Arora S. Surface solid dispersion: a review. Int J Pharm Sci 2013;1:1915-24.

38. Rao M, Mandage Y, Thanki K, Bhise. Dissolution improvement of simvastatin by surface solid dispersion technology. Dissolution Technol 2010;6:27-34.
39. Anil A, Thomas L, Sudheer P. Liquisolid compacts: an innovative approach for dissolution enhancement. Int J Pharm Sci 2018;10:1-7.
40. Kapoor D, Lad C, Vyas R, Patel M. Formulation development, optimization and *in vitro* characterization of liquisolid compacts of oxicam derivative. J Drug Delivery Ther 2016;6:64-70.
41. Dias RJ, Mali KK, Ghorpade VS, Havaldar VD, Mohite VR. Formulation and evaluation of carbamazepine liquid-solid compact using novel carriers. Indian J Pharm Edu Res 2017;51(2S):69-77.
42. Bergum JS, Li H. Acceptance limits for the new ICH USP 29 content uniformity test. Pharm Tech 2007;31:91-6.
43. Mohanty SS, Biswal S, Biswal S, Sahoo J, Mahapatra AK, Murthy PN. Enhancement of dissolution rate of glimepiride using solid dispersions with polyvinylpyrrolidone k 90. Indian J Pharm Edu Res 2010;44:71-7.
44. Ibrahim EH, El-Faham TH, Mohammed FA, El-Eraky NS. Enhancement of solubility and dissolution rate of domperidone by utilizing different techniques. Bull Pharm Sci 2011; 34:105-20.