JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

IMPROVING SOLUBILITY AND DISSOLUTION PROPERTIES OF SPIRONOLACTONE USING NON-VOLATILE SOLVENT BY LIQUISOLID COMPACT TECHNIQUE

Lava S Gowda[1], Bharati Arali[1], Uma A Patil[2], Anitha M R[3]

Department of Pharmaceutics, East West College of Pharmacy, Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka, India.

Corresponding author mailing address

ANITHA M R

East West College of Pharmacy

Bharath nagar, Magadi main road

Bangalore, Karnataka, India-560091

Abstract: Spironolactone (SPL) is a commonly prescribed potassium-sparing diuretic that acts as an aldosterone antagonist and belongs to the BCS class II. It undergoes solubility testing in a non-volatile solvent and is formulated as a liquisolid. The liquisolid formulation's dissolving properties contrast with regular tablets and pure drugs. The liquisolid compacts were developed using three non-volatile solvents (including PEG400, propylene glycol, and glycerin), three carrier materials (lactose monohydrate, mannitol, and microcrystalline cellulose pH 102), and one coating material (aerosil 200) with an R-value of 15. FT-IR method was used to evaluate the compatibility of spironolactone with the liquisolid excipients. The findings showed that most liquisolid compacts satisfied the Indian Pharmacopeia's (IP) requirements.

By reaching 50 mg/ml, the solubility research showed enhanced solubility in PEG400. When spironolactone preparations were evaluated utilizing IP testing techniques, it was demonstrated that formulations using PEG400 as the non-volatile solvent, lactose monohydrate (carrier), and aerosil 200 (coating material) respectively, had a much higher dissolving rate. Only 18.32% of the pure drug and 74.81% of the traditional tablets were released in the same hour as 94.50% in this formulation. In conclusion, the use of non-volatile solvents in spironolactone liquisolid compacts enhances both the drug's solubility and its dissolution rate.

Keywords: Spironolactone, Liquisolid compact technique, PEG400, Propylene glycol, and Glycerine.

INTRODUCTION:

Oral, rectal, parenteral, nasal, topical, ophthalmic, and ear routes are among the various ways that drugs can be administered. It is crucial to thoroughly examine the relationship between the drug's properties and any clinical issues, including solubility and bioavailability. The most common and extensively utilized of these methods is the delivery of medications orally. Due in major part to its ease of use, it is preferred for its safety, low microbiological constraints associated with manufacture, and high patient compliance[1]. Due to their poor water solubility, which makes formulation difficult or even impossible, more than 70% of new chemical entities created by the pharmaceutical industry have not made it to market[2]. Approximately 35% to 45% of drugs suffer from

inadequate water solubility, which limits their absorption in the gastrointestinal system. This results in poor oral bioavailability, Excessive variability, the need for increased dosages, reduced therapeutic efficacy, and research failures[3].

Drugs with an aqueous solubility of less than 0.1 mg/ml pose unique challenges and are ideal candidates for advanced solubilization methods, such as the liquisolid compact approach[4].

To improve the solubility of medications that are not very soluble in water, liquisolid technology is utilized. There isn't a single liquid vehicle that can improve the dissolving of all hydrophobic medications, though, since several research have demonstrated that multiple liquid vehicles are required for this technique. The hydrophobic medication is dissolved and then almost molecularly dispersed in a water-miscible, non-volatile liquid medium. This promotes the drug's absorption via the gastrointestinal tract by improving its solubility[5-6].

Liquid vehicles are ideal for dissolving hydrophobic drugs, with high boiling points, chemical inertness, low viscosity, and water-miscibility. However, increasing moisture content can reduce powder flow properties. Coating materials like silica are used to maintain flowability.

Spironolactone, an aldosterone antagonist, is used for fluid management, high blood pressure, and feminizing hormone therapy. Despite its quick absorption, its effectiveness is hindered by low aqueous solubility due to extensive first-pass metabolism. Efforts are being made to improve dissolution characteristics using non-volatile liquid vehicles[7-10].

Materials and Methods

Hetero Labs Ltd. in Hyderabad sent Spironolactone as a complimentary sample. Methanol, Peg400, Propylene glycol, Glycerine, Lactose monohydrate, mannitol, Microcrystalline cellulose, Aerosil, Croscarmellose sodium, Sodium alginate, Magnesium stearate, Talc, Concentrated Hcl, Dicalcium phosphate and Distilled water were taken in analytical grade BP/IP/USP equivalent in EWCP laboratory.

Formulations of Spironolactone Liquisolid compacts:

Liquisolid formulation planning entails the following steps: To create a liquisolid drug, pure Spironolactone powder is first dissolved in non-volatile solvents such as glycerol, propylene glycol, and PEG-400. A dry and free-flowing powder admixture is then created by adding coating materials (Aerosil 200) and transporters (lactose monohydrate, mannitol, and microcrystalline cellulose pH 102) to the liquid medicine while continuously mixing with a mortar and pestle. For liquisolid formulations (F_1–F_9), 1.5% w/w lubricant (magnesium stearate) and 2% w/w glidant (talc) are added after croscarmellose sodium (4% w/w) and sodium alginate (10% w/w) are selected as disintegrants and diluents, respectively. A 10 mm punch is used to compress the resultant powder mixture to an average weight of 500 mg after it has been homogenized in the mortar until it is homogenous. To compare the dissolving characteristics of Spironolactone before and after utilizing non-volatile solvents, conventional Spironolactone tablets are also mad

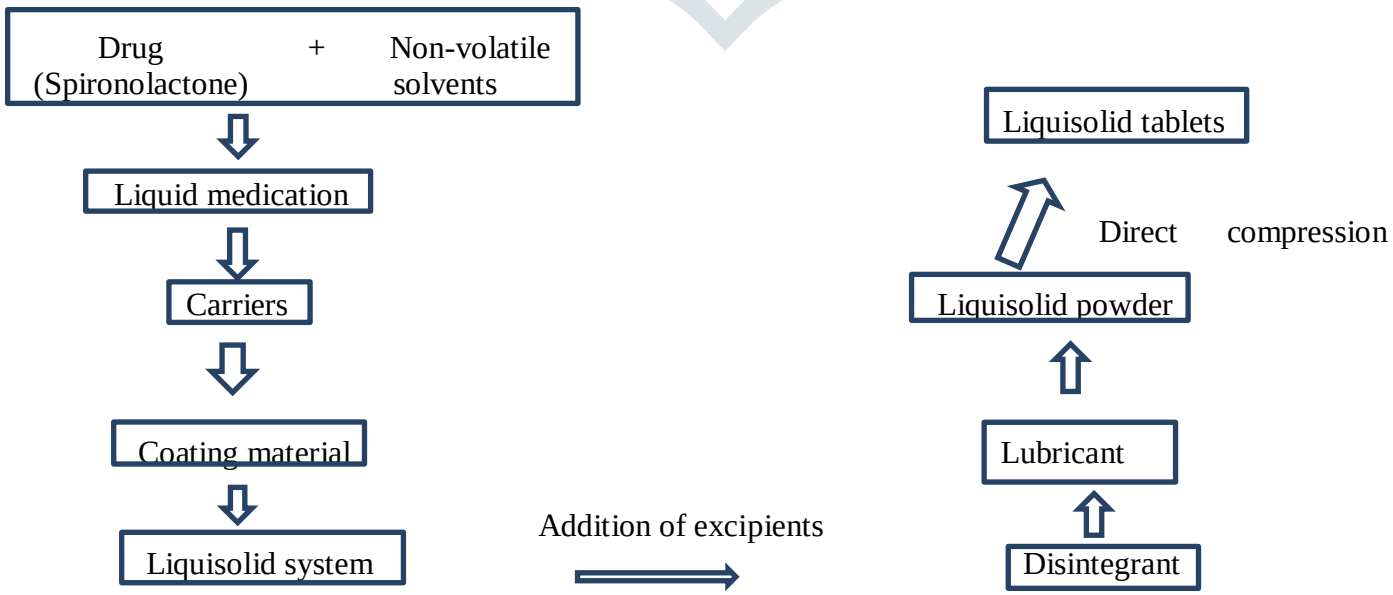

Chart-1: Flow chart representation of Liquisolid compact techniques.

Table 1: Composition of Spironolactone Liquisolid Compacts

Liquisolid compacts	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)	F_7 (mg)	F_8 (mg)	F_9 (mg)
Spironolactone	25	25	25	25	25	25	25	25	25
PEG-400	0.5	0.5	0.5	-	-	-	-	-	-
Propylene glycol	-	-	-	0.8	0.8	0.8	-	-	-
Glycerine	-	-	-	-	-	-	0.9	0.9	0.9
Lactose monohydrate	333.77	-	-	322.8	-	-	362.9	-	-
Mannitol	-	235.43	-	-	286.99	-	-	115.62	-
Microcrystalline cellulose 102	-	-	112.79	-	-	172.21	-	-	91.43
Aerosil 200	22.25	15.69	7.38	21.52	19.13	11.48	24.19	7.70	6.09
Croscarmellose sodium	20	20	20	20	20	20	20	20	20
SodiumAlginate	50	50	50	50	50	50	50	50	50
DCP	30.98	135.88	266.83	42.38	80.58	203.01	-	263.28	289.08
Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Talc	10	10	10	10	10	10	10	10	10
Total weight of each tablet	500	500	500	500	500	500	500.49	500	500

Evaluation of Prepared Spironolactone Liquisolid Mixtures and Compacts:

The drug mixtures and compacts were evaluated for pre and post compressional parameters as per IP standards.

***In vitro* drug release studies:**

Several Spironolactone liquisolid compacts were subjected to an *in vitro* dissolving investigation utilizing 0.1M HCl and a USP class II device. With 900ml of 0.1M HCl, the dissolving media was spun at 75 rpm while being kept at 37°C ± 0.5°C. To keep the sink condition, 1 ml samples were taken out and replaced with fresh 0.1M HCl at prearranged intervals. In a volumetric flask, the extracted materials were subsequently diluted to a level of 10 ml. A UV spectrophotometer set to 235 nm (the λ max of Spironolactone) was used to determine the drug concentration of these samples[11-12].

RESULTS AND DISCUSSION

FTIR Studies:

Infrared (IR) spectroscopy tests were utilized to verify the compatibility of the drugs and excipients employed in the creation of liquisolid compacts. Spironolactone, a pure drug, liquisolid mixtures, and excipients were used in the experiments. Analysis was done on spectra between 4000 cm-1 and 400 cm-1. The primary peaks for the pure drug were found at wave numbers 1766 cm-1 and 1765 cm-1 (-C(=O)-O- stretching of lactone ring) and 1690 cm-1 (-C=O stretching of thioacetyl carbonyl group). Furthermore, there was little to no band shift in the wavenumber of the characteristic peaks of liquisolid mixes (F_1-F_9) spectra, suggesting that the drugs and excipients in the liquisolid mixtures did not interact.

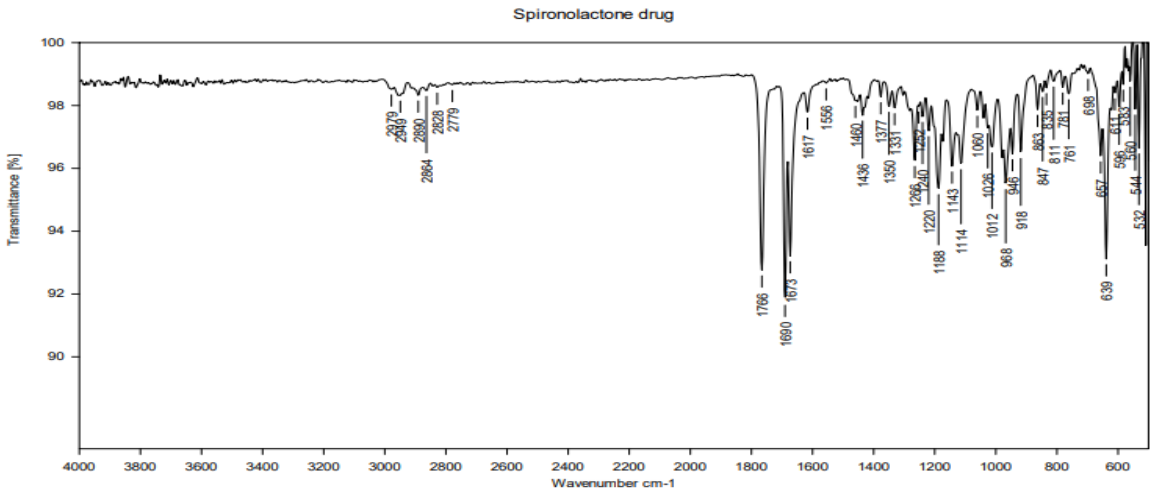

Figure1: FTIR studies of Spironolactone

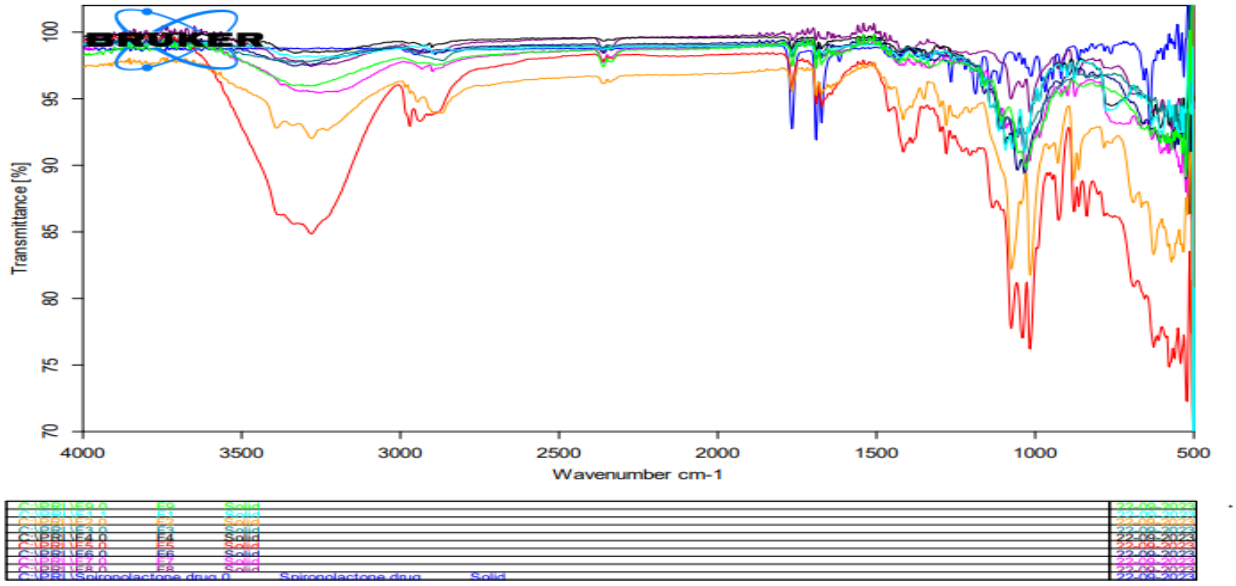

Figure 2: Comparative FTIR studies of spironolactone liquisolid compacts (F_1-F_9)

Evaluation of pre-compression parameters of Spironolactone liquisolid mixtures:

Another significant element that could affect the consistency of tablet weight is the flow of the liquisolid mixtures. The flow characteristics of the mixes were evaluated in order to calculate the required quantities of coating and carrier components to guarantee appropriate flow and compaction quality. Proving that the mixes have the necessary compression strength and flow properties in compliance with IP requirements.

Table 2: Data for pre-compression parameters of spironolactone liquisolid mixtures (F_1-F_9)

Formulations	Angle of repose (Ɵ)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index	Haunser's ratio
F_1	19.773±0.024	0.542±0.00346	0.651±0.009	16.743	1.201
F_2	30.113±0.429	0.445±0.0190	0.580±0.019	23.276	1.303
F_3	22.925±0.090	0.531±0.00664	0.688±0.006	20.833	1.263
F_4	20.690±0.002	0.554±0.0069	0.676±0.005	18.047	1.219
F_5	33.561±0.022	0.572±0.0085	0.738±0.011	22.493	1.290
F_6	33.853±0.213	0.549±0.0086	0.725±0.010	24.275	1.320
F_7	27.006±0.295	0.527±0.0046	0.684±0.004	22.953	1. 298
F_8	32.433±0.076	0.631±0.0092	0.851±0.008	25.852	1.348
F_9	34.832±0.360	0.513±0.0150	0.680±0.006	24. 559	1. 325

Compression of Spironolactone liquisolid mixtures:

Spironolactone liquisolid compacts with a hardness of 4-5 kg/cm^2 were created by direct compression using a 10mm punch. All the tablets were white and round, with a little rough surface.

Evaluation of post-compression parameters of Spironolactone liquisolid compacts:

All of the liquisolid compacts' post-compressional properties, when analyzed in various formulations, fell within reasonable ranges.

Table 3: Data for post-compression parameters of Spironolactone liquisolid compacts (F_1-F_9)

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration (sec)	Drug content (%)
F_1	499.82±0.434	4.1±0.00	4.50±0.070	0.0045	51.00±0.3	101.92
F_2	500.32±0.270	4.08±0.01	4.21±0.114	0.375	305.33±0.96	85.62
F_3	500.94±0.306	3.02±0.04	4.35±0.151	0.168	164.46±1.28	92.88
F_4	499.76±0.523	4.3±0.08	4.41±0.114	0.040	150.66±1.15	97.41
F_5	501.02±0.304	4.06±0.00	4.10±0.044	0.299	867.33±1.19	85.99
F_6	498.96±0.427	4.7±0.05	4.07±0.228	0.701	631.46±0.50	86.11
F_7	532.85±0.389	4.1±0.04	4.2±0.089	0.241	177.3±2.51	90.86
F_8	501.47±0.478	3.8±0.05	4.10±0.0547	0.685	511.16±2.51	86.31
F_9	501.51±0.506	4.5±0.09	4.10±0.0836	0.896	841.16±1.04	85.67

***In* vitro release studies:**

Formulation F1, which contained the medications together with PEG400, exhibited the fastest drug release, according to *in vitro* drug release experiments. The inclusion of these poorly water-soluble medications in the liquid carrier PEG400 is mostly to blame for the enhanced drug dissolution rate. Additionally, the medication is transported by powder particles (aerosil and lactose monohydrate) from the non-volatile solvent, which leads to a significantly quicker release because of the enhanced surface availability and wettability in the dissolving media. The liquisolid compacts F1 were formulated using lactose monohydrate as a carrier and aerosil as a coating ingredient. All liquisolid compact formulations were created at R-15 to investigate the impact of the carrier and coating material ratio (R-value) on medication dissolution. Overall results showed that the liquisolid compact formulation F_1 (drug: PEG400) with an R-value of 15 enhanced the drug's dissolving behavior (These formulations exhibited cumulative drug release percentages of 94.50%).

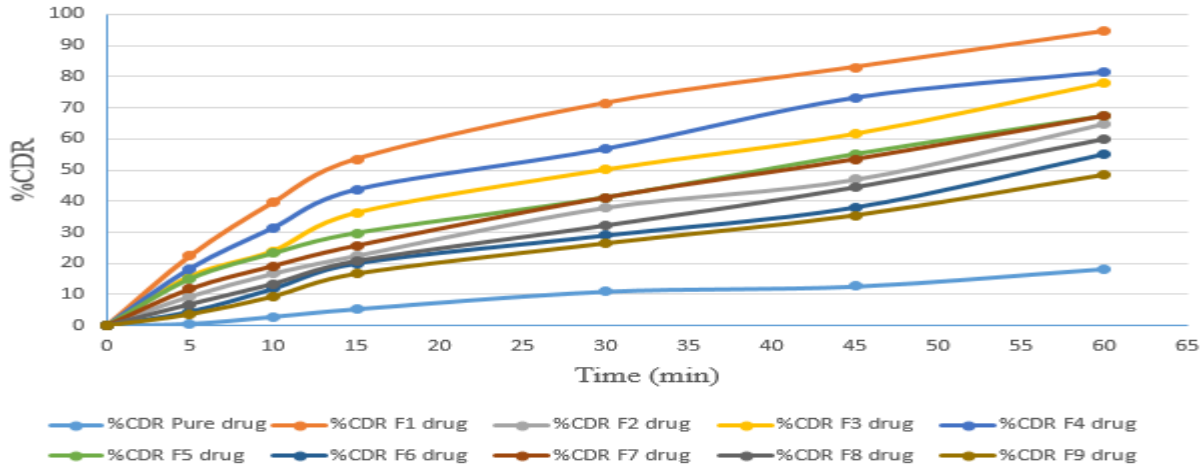

Figure 3: Relative *in vitro* dissolution profile of pure drug and liquisolid compacts (F_1-F_9)

F_1 was chosen above the other nine liquisolid compact formulations because of its considerable drug release rates of 71.47% at 30 minutes and 94.50% at 1 hour, as opposed to the traditional tablet, which had a drug release rate of 50.20% at 30 minutes and 74.81% at 1 hour. By encouraging drug release, this liquisolid compact technique may have improved oral bioavailability and gastrointestinal tract (GIT) absorption. Thus, formulation F_1 was found to be the optimal formulation out of the nine evaluated.

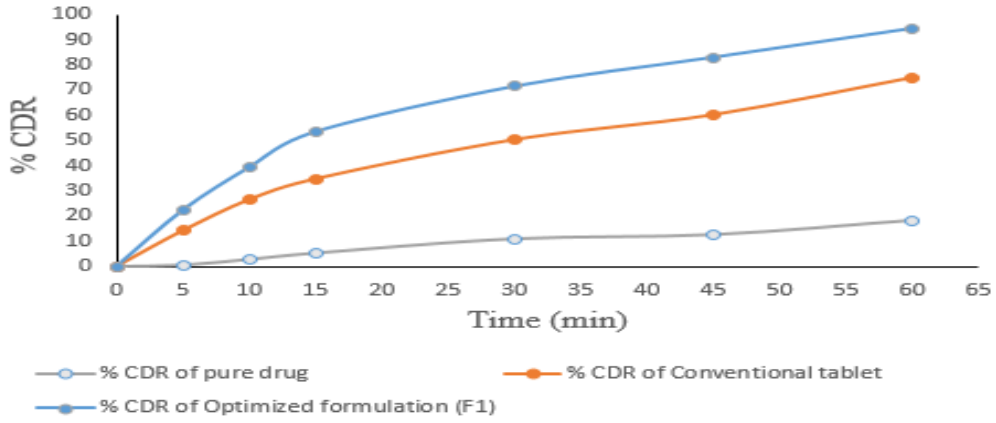

Figure 4: Comparative in vitro dissolving profiles of pure drugs, traditional tablets, and improved formulation (F_1).

Conclusion:

This study showed that spironolactone, a model hydrophobic drug with poor water solubility and low dissolving qualities, may be effectively dissolved using liquisolid compact technology. An appropriate non-volatile solvent is chosen for the procedure based on its viscosity and HLB (Hydrophilic-Lipophilic Balance) value. This study demonstrated the potential of PEG400, a novel non-volatile solvent, in the creation of liquisolid mixtures when paired with aerosil 200 as a coating material and lactose monohydrate as a carrier. Compared to previous liquisolid compacts, the spironolactone liquisolid compact made with lactose monohydrate, aerosil, and the non-volatile solvent PEG400 showed better dissolving qualities, attaining 94.50% dissolution in an hour. Furthermore, the tablet's disintegration, hardness, friability, and homogeneity of drug content all fell within acceptable bounds. Because of better wetting and a greater surface area accessible for breakdown, the increased dissolution rates seen in this investigation suggested a possible rise in oral bioavailability.

References:

1. Alderborn G. Tablet and compaction. In: Aulton's pharmaceuticals – The design and manufacture of medicines 2018:5;517-520.
2. Hite M, Turner S, Federici C. Oral delivery of poorly soluble drugs, part 2: formulation strategies for solid dosage forms and novel delivery systems for controlled release. Pharmaceutical Manufacturer Packing Sourcer 2003;1: 1-3.
3. Lipinski CA. Poor aqueous solubility—an industry wide problem in drug discovery. American Pharmaceutical Review 2002;5(3):82-85.
4. Patel M, Patel D. Fast dissolving valdecoxib tablets containing solid dispersion of valdecoxib. Indian Journal Of Pharmaceutical Sciences 2006;68(2):222-226.
5. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. International Scholarly Research Notices 2012;2012:1-10.
6. Elkordy AA, Xin NT, Ebtessam AE. European Journal of Pharmaceutics and Bio pharmaceutics 2013; 83: 203-223.
7. Pavani E, Noman SH, Syed IA. Liquisolid technique based sustained release tablet of trimetazidine dihydrochloride. Drug Invention Today 2013; 5: 302-310.
8. Searle. Aldactone (Spironolactone) tablets prescribing information. Chicago, IL; 2003.
9. Sica, Domenic A. Pharmacokinetics and Pharmacodynamics of Mineralocorticoid Blocking Agents and their Effects on Potassium Homeostasis. Heart Failure Reviews 2005; 10(1): 23–29.
10. Maron BA, Leopold JA. Mineralocorticoid receptor antagonists and endothelial function. Current Opinion Investigational Drugs 2008; 9(9): 963–969.
11. Vinod TW, Ritu MG and Rajendra DW. Solid Dispersion (kneading) Technique: A platform for Enhncement Dissolution Rate of Valsartan Poorly Water-soluble Drug. International Journal Pharmaceutical QA 2020;11(1):20-24.
12. Gao S, Bie C, Ji Q, Ling H, Li C, Fu Y *et.al.*, Preparation and characterization of cyanazine-hydroxypropyl-beta-cyclodextrin inclusion complex. Royal Society of Chemistry Advances. 2019;9(45):26109-26115.