FORMULATION AND EVALUATION OF LIQUISOLID TABLETS FOR POORLY SOLUBLE DRUGS CARBAMAZEPINE

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Abstract

Oral ingestion is the most suitable and convenient route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. Thus, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. Consequently, much effort is focused during drug discovery to identify orally active molecules that will provide reproducible and effective plasma concentrations in vivo. Unfortunately, about the 40% of new active candidates, including several powerful poorly water soluble drugs, are characterized by low aqueous solubility and the oral administration of these drugs are frequently associated with low bioavailability, and lack of proportional dose-therapeutic effect relationship. LS technique has been used successfully to produce a tablet dosage form of Carbamazepine with faster dissolution rate than the regular tablet. It showed significant increase in dissolution as compared DCT. It was found that there is a relationship between the carrier to coating material ratio (R value) and the in vitro release of Carbamazepine from LS tablets. The R value was directly proportional to the in vitro release of Carbamazepine from LS formulations. This study showed that the specific surface area of coating materials has an effect on the flow properties of LS powder blends and the particle size of coating materials affects the drug release from LS tablets. It was found that the liquid load factor (L_f) has an effect on the flow properties of LS powder blends but had no significant effect on the drug release from LS tablets. It was observed that aging had no significant effect on the hardness and dissolution profile of Carbamazepine LS compacts. In conclusion, this study showed that LS technique could be a promising strategy in improving dissolution of poorly water soluble drugs such as Carbamazepine and formulating immediate release dosage forms.

Keywords: Liquisolid Tablets, Carbamazepine, hydrophobic drug, powder blends,BCS.

INTRODUCTION

Oral ingestion is the most suitable and convenient route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. Thus, many of the generic drug companies are inclined more to produce bioequivalent oral drug products[1]. Consequently, much effort is focused during drug discovery to identify orally active molecules that will provide reproducible and effective plasma concentrations in vivo. Unfortunately, about the 40% of new active candidates, including several powerful poorly water soluble drugs, are characterized by low aqueous solubility and the oral administration of these drugs are frequently associated with low bioavailability, and lack of proportional dose-therapeutic effect relationship.[2] The Noyes-Whitney equation (Eq. 1) provides clear suggestion of parameters that can be modified enhance the dissolution rate of poorly soluble drugs:

$$dc/dt = AD (Cs – C) / h \quad (1)$$

Where dc/dt is the dissolution rate, A is the surface area exposed to dissolution medium, D is the diffusion coefficient of the drug in solution, Cs is the solubility of the drug, C is the drug concentration in the dissolution medium at time t, and h is the thickness of diffusion boundary layer. Several parameters in this equation can be adjusted to achieve the enhancement of the dissolution rate. For example, increasing either the surface area or diffusion coefficient can lead to a higher dissolution rate.[3] The absorption of an active pharmaceutical ingredient (API) released from the oral dosage form depends on two factors, the dissolution of the API in the gastrointestinal tract and its permeability through the mucosa.[4] Based on these two parameters, drugs have been divided in four categories, the so called Biopharmaceutical Classification System (BCS)

CLASS II Low solubility high permeability	**CLASS I** High solubility high permeability
CLASS IV Low solubility Low permeability	**CLASS III** High solubility Low permeability

Figure 1. BCS

Biopharmaceutical classification system.[5] The biopharmaceutical classification system (BCS) is the scientific framework for classifying drug substances based on their aqueous solubilit y and intestinal permeability. It is a drug development tool that allows estimation of the contributions of three major factors, dissolution, solubility and intestinal permeability that affect oral absorption of drugs.[6] BCS class II and IV drugs which have low solubility provide a number of challenges for formulation scientists working on oral delivery of drugs. The enhancement of drug solubility thereby its oral bioavailability remains one of the most challenging aspects of the drug development process especially for oral drug delivery system.[7] There are several methods available and reported in literature to enhance the solubility of lipophilic drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration , nature of excipients to be selected, and the nature of intended dosage form.[8] The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability, especially for class II (low solubility and high permeability) substances. According to the BCS, the bioavailability may be enhanced by increasing the solubility thereby increasing the dissolution rate of the drug in the gastrointestinal fluids.[9] As for BCS class II drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so improving the solubility in turn increases the bioavailability for BCS class II drugs.[10]

MATERIALS AND METHODS

Materials

Carbamazepine was provided by Rasino Drugs Pvt. Ltd. Propylene glycol, microcrystalline cellulose, colloidal silicon dioxide calcium silicate magnesium alumino metasilicate and sodium starch glycolate were obtain from central store MIP Belata. All other reagents were of analytical grade and used without further purification.

Methods

The formulation design of LS systems was done in accordance with a mathematical model. In this study, PG was used as a liquid vehicle, MCC was used as carrier material and three different coating materials were used. The concentration of the drug in solvent was kept constant in all formulations. According to this model, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flowability

and compressibility.

Firstly, the excipient ratio R of the powder is defined as,

$$R = Q / q$$

Where R is the ratio of the weight of carrier (Q) and coating (q) materials present in the formulation.

Secondly, the liquid load factor (L_f) is defined as the ratio of the weight of liquid medication (W) to the weight of the carrier material (Q) in the system. This ratio can be correlated with the flow and the compression properties of a given LS system. L_f is defined as,

$$L_f = W / Q$$

Preparation of LS powder blends and tablets of Carbamazepine

Calculated quantities of Carbamazepine and PG were accurately weighed and mixed together until a homogeneous drug solution was obtained. The resulting liquid medication was incorporated into calculated quantities of carrier and coating materials. The mixing process was carried out in three steps. In the first, the system was blended in a mortar using pestle at a mixing rate of one rotation per second for one minute in order to evenly distribute the liquid medication in the powder. In the second, the liquid/powder admixture was evenly spread as a uniform layer on the surface of a mortar and left standing for 5 min to allow the drug solution to be absorbed inside powder particles. In the third, the powder was scraped off the mortar surface using a spatula. The final mixture was compressed into tablets by using a manual hydraulic press (15 ton press, Specac, England) equipped with round flat-faced tooling (diameter 12.6 mm) using a compression force of 25 kN. Preliminary experiments were conducted to identify adequate LS composition (LS-1, Table) using common excipients. This system was composed of PG as a non-volatile liquid vehicle, MCC as a carrier, CSD as a coating material and SSG as a disintegrant. The robustness of this formulation to excipients modifications was evaluated.

Firstly, LS formulations of Carbamazepine (LS-1, LS-2 and LS-3, Table 2.1) with different R values (10.0, 20.9 and 30.2) were prepared to investigate the influence of the excipient ratio on the flow properties of LS powder blends and on the in vitro release of Carbamazepine from LS tablets.

Secondly, LS formulations of Carbamazepine (LS-1, LS-4 and LS-5, Table 2.1) were prepared to investigate the influence of the type of coating material on the flow properties of LS powder blends and on the in vitro release of Carbamazepine from LS tablets. The particle size and specific surface area of the coating materials may affect the flow properties and the

drug release.

Thirdly, LS formulations of Carbamazepine (LS-1, LS-6, LS-7 and LS-8, Table 2.1) with different (solid liquid element) L_f values (0.427, 0.382, 0.345 and 0.315) were prepared using PG as a non-volatile liquid vehicle to investigate the influence of the liquid load factor on the flow properties of LS powder blends and on the in vitro release of Carbamazepine from LS tablets. Each system (LS-1 to LS-8, Table 3) was containing 100 mg of Carbamazepine and 90 mg of PG. The detailed formulation characteristics of these systems are shown in Table.3

Preparation of conventional tablets of Carbamazepine

Conventional tablets of Carbamazepine were prepared for comparison purposes. These tablets were produced by direct compression using a manual hydraulic press (15 ton press, Specac, England) equipped with round flat-faced tooling (diameter 12.6 mm) using a compression force of 25 kN. Each tablet contained Carbamazepine (100 mg), MCC (405 mg), CSD (17 mg) and SSG (28 mg).

Table no. 3. Formulation design of Carbamazepine liquisolid tablets

System	Carbamazepine (mg)	PG (mg)	MCC (mg)	CSD (mg)	MAMS (mg)	CS (mg)	SSG (mg)	Total (mg)
LS-1	100.0	73.5	386.5	14			23.0	600
LS-2	100.0	83.5	368.0	14.5			24.0	600
LS-3	100.0	28.5	372.0	15			24.5	600
LS-4	100.0	54.0	380.5	-	18.5		25.0	600
LS-5	100.0	56.5	382.5	-		18.5	25.5	600
LS-6	100.0	57.0	385.0	15.5			26.0	600
LS-7	100.0	63.5	390.5	16.5			26.5	600
LS-8	100.0	65.0	391.0	17			27.0	600

Flow properties of LS systems

The tapping method was used to investigate the flow properties of prepared LS powder blends. Bulk density measurements were carried by placing fixed weight of powder in graduated cylinder and volume occupied was measured and initial bulk density was calculated. 20 grams of the prepared powder blends were placed in a 50 mL cylinder. The cylinder was then tapped 1000 times at a constant velocity. The

tapped density was determined on a tapped volume determination apparatus. Each analysis was carried out in triplicate.

Weight variation, hardness, friability and content uniformity tests

The prepared tablets were evaluated by carrying out tests for weight variation, hardness, friability and drug content uniformity. For estimating weight variation, 20 tablets were taken randomly from each tablet formulation and weighed individually. The average weight of all tablets and percentage deviation from the mean for each tablet were determined.

The hardness of formulated tablets was assessed using a hardness tester and the mean hardness of three tablets was determined. The friability was determined on ten tablets using a friability tester and the percentage loss in weight was calculated.

For drug content uniformity test, ten tablets were crushed individually and powder equivalent to 100 mg of Carbamazepine was dissolved in 100 mL of methanol. The solution was then passed through a 0.45 µm nylon filter and analyzed using UV spectrophotometer at 284 nm after sufficient dilution with pH 4.5 acetate buffer.

In vitro dissolution studies

The USP apparatus II (paddle method) (DTB 678 equipment with thermostatic bath and circulation pump was used for all the in vitro dissolution studies. In this method, acetate buffer having the pH of 4.5 was used as dissolution media. The rate of stirring was 50 rpm. The dosage forms were placed in 900 mL of pH 4.5 acetate buffer maintained at 37 ± 0.5 ºC. At appropriate intervals (5, 10, 15, 20, 30 and 45 min), 5 mL of the samples were taken. The dissolution media was then replaced by 5 mL of fresh dissolution fluid to maintain a constant volume. After proper dilution, the samples were analyzed at 284 nm spectrophotometrically. The mean of three determinations was used to calculate the drug release from each of the formulations.

Stability study

The effect of aging on the hardness and dissolution of LS tablets (LS-1) was determined by storing the tablets at 22 0C for up to 12 months. After that, the samples were tested for their dissolution profiles and hardnesses at the conditions that have been used with freshly prepared tablets. The results were compared with

the freshly tested tablets.

RESULTS AND DISCUSSION

Flow properties

Good flow properties are critical for larger scale production of tablet dosage forms. To evaluate the flow properties of the prepared LS powder blends, Carr's index was calculated from the bulk and tapped densities of the blends. According to the USP, powders are considered to have passable flow properties if they have a Carr's index value of less than 25% (USP36-NF31, 2013).

R value is an important formulation parameter for LS systems that may be optimized. The R values of LS-1, LS-2 and LS-3 were 20.9, 10.0 and 30.2 respectively. As shown in Table , LS-1 and LS-3 had fair flow properties because the formulations were containing high quantities of MCC and low quantities of colloidal silica. LS-2 exhibited passable flow properties because the formulation was containing high amounts of colloidal silica.

As shown in Table the LS-1 had fair and LS-4 had good flow properties according to the Carr's index, but LS-5 exhibited poor flow properties. CS with its petaloid crystal structure and large micropores exhibited the smallest specific surface area which is lower than that of CSD with its loose particle aggregates. MAMS which is prepared by spray drying resulting in spherically shaped, porous, ultralight granules showed an almost 1.5 fold larger specific surface area than CSD (Hentzschel, 2011). LS-5 powder system prepared using CS showed poor flow properties, because CS has the lowest specific surface area in comparison to CSD and MAMS. This study showed that the nature of the coating agent and most likely its specific surface area has an effect on the flow properties of LS powders.

As shown in Table, the LS-1 and LS-6 had fair and LS-7 and LS-8 had good flow properties according to the Carr's index. It was found that there is a relationship between L_f and the flow properties of LS powder blends. The LS systems with low L_f values have better flow properties. This can be explained by the fact that, the LS systems with high L_f values contain high amounts of liquid and low quantities of powder excipient. In contrast, the LS systems with low L_f values contain high amounts of carrier material (MCC) and low quantities of liquid.

Table no.4. Flow properties of powder blends

System	Carr's index (%)	Type of flow
LS-1	19.8 ± 0.3	Fair
LS-2	24.6 ± 0.3	Passable
LS-3	16.5 ± 0.7	Fair
LS-4	11.5 ± 0.4	Good
LS-5	30.0 ± 0.4	Poor
LS-6	17.6 ± 0.7	Fair
LS-7	15.2 ± 0.8	Good
LS-8	15.5 ± 0.5	Good

Weight variation, friability, hardness and content uniformity tests

The results of weight variation, friability, hardness and drug content are represented in Table. Average weight of LS tablets ranged from 598 ± 2 mg to 748 ± 2 mg. All the Carbamazepine LS tablets had acceptable friability as none of the tested formulae had percentage loss in tablet's weights that exceed 1%, a LS no tablet was cracked, split or broken in either formula. Since all prepared tablets met the standard friability criteria, they are expected to show acceptable durability and withstand abrasion in handling, packing and shipment.

In general, formulation should be directed at optimizing tablet hardness without applying excessive compression force, while at the same time assuring rapid tablet disintegration and drug dissolution. In other words, tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. The mean hardness of each LS tablet was determined and is presented in Table providing that all the LS tablets had acceptable hardness. All LS formulations have shown lower hardness compared with that of conventional formula (DCT). This was due to the presence of the liquid in the LS formulations that hinder the formation of the interparticle bonds (H-bonds in case of MCC) which are the main reason for the higher specific hardness obtained DCT. It was found that there is a relationship between R value and the hardness of the tablets. The R value was inversely proportional to the hardness of the tablets i.e., when the R value increases, the hardness of the tablet will decrease. This was obvious from the following results. LS-2 had R value equal to 10.0 and the mean hardness was 171 N. LS-3 had R value equal to 30.2 and the mean hardness was 104

N. This can be explained by that, increasing R value increases the amount of carrier powder (MCC) used which is a highly porous material and the amount of coating material (colloidal silica) will decrease and this subsequently leads to decreased hardness of the tablets. It was found that there is a relationship between L_f and the hardness of the tablets in the LS formulation having approximately the same R value. The L_f was inversely proportional to the hardness of the tablets i.e., when the L_f increases, the hardness of the tablets will decrease. This was obvious from the following results. LS-1, LS-6, LS-7 and LS-8 were having L_f 0.427, 0.382, 0.345 and 0.315 and the mean hardness of them was 120, 123, 167 and 194 N, respectively. This can be explained by that, increasing L_f of the formulation increases the amount of solvent used and decreases the amount of the powder excipient and this subsequently decreases the hardness of the tablets.

It was clear from Table that all the investigated Carbamazepine tablets complied with the pharmacopoeial requirements as regard their content uniformity which was found to lie within the range 90-110%.

Table no.5. Evaluation of Carbamazepine

LS system	Hardness (N)	Friability		Weight variation (mg)	Drug content (%)
		Fines (%)	No. of broken tablets		
LS-1	120 ± 2	0.25	None	599 ± 2	100 ± 2
LS-2	171 ± 5	0.12	None	598 ± 2	98 ± 3
LS-3	104 ± 8	0.34	None	600 ± 2	98 ± 5
LS-4	124 ± 4	0.23	None	599 ± 1	100 ± 4
LS-5	95 ± 7	0.14	None	599 ± 2	97 ± 5
LS-6	123 ± 7	0.28	None	649 ± 4	99 ± 3
LS-7	167 ± 8	0.18	None	699 ± 3	96 ± 5
LS-8	194 ± 10	0.45	None	748 ± 2	99 ± 3
DCT	216 ± 6	0.45	None	549 ± 2	101 ± 3

In vitro dissolution studies

The dissolution profiles of Carbamazepine LS tablets (LS-1) and directly compressed tablets (DCT) in pH 4.5 acetate buffer are shown in Figure 6. Dissolution rates of LS tablets were compared with DCT. LS formulation showed

greater release than DCT formulation. The percentages of drug released from LS-1 and DCT after 5 min were 99.6% and 32.5% respectively at pH 4.5 acetate buffer. This showed that the LS compacts produced faster dissolution rate in comparison with DCT. The enhanced dissolution rates of LS tablets compared to DCT may be attributed to the fact that, the drug is already in solution in PG, while at the same time, it is carried by the powder particles (MCC and CSD). When the drug within the LS system is completely dissolved in the liquid vehicle, it is located in the powder substrate still in a solubilized state. Therefore they show improved release rates.

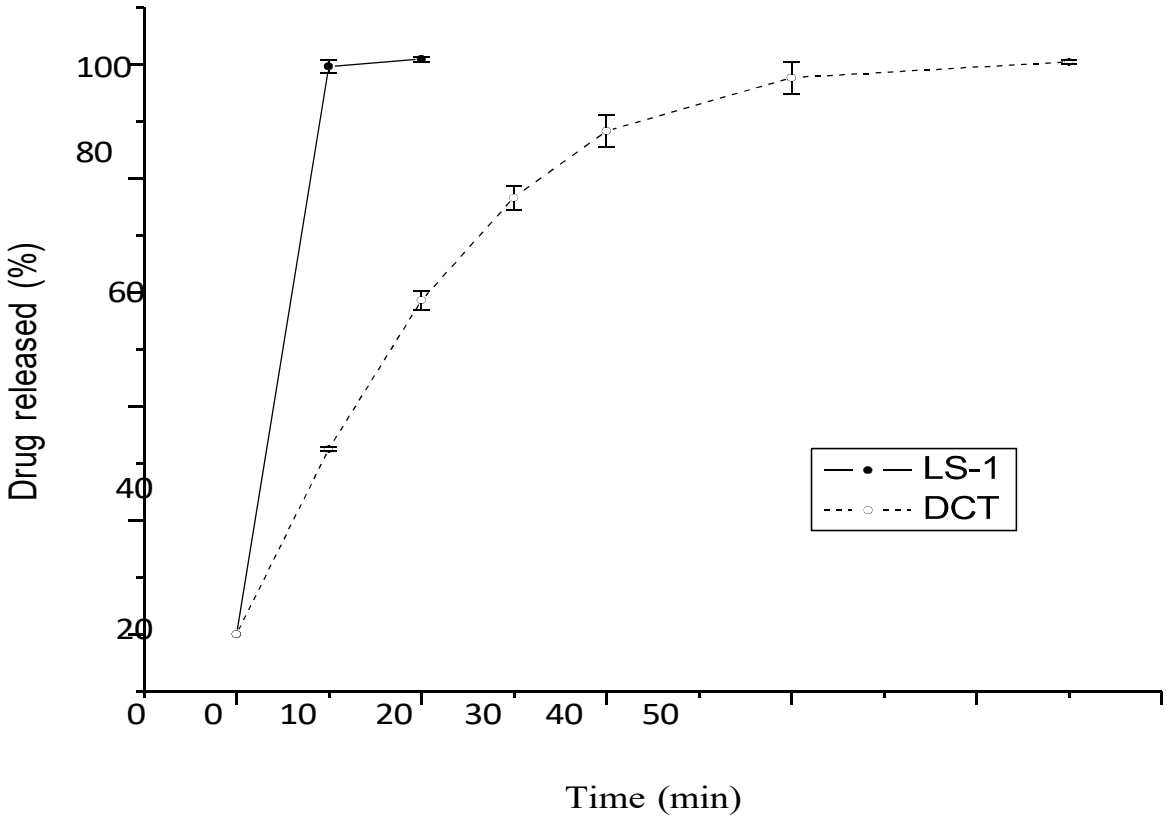

Figure no.6. Dissolution profiles of Carbamazepine directly compressed tablets (means ± SD; n=3)

The R value is an important parameter which is the ratio between the weights of the carrier and the coating material that may be optimized. An increase in the R value results in an enhanced release rate, if MCC and colloidal silica are used as carrier and coating material LS, respectively. LS compacts with high R values contain high amounts of MCC, low quantities of CSD and low liquid to powder ratios. This is associated with enhanced wicking, disintegration and thus, enhanced

drug release. In contrast, if high amounts of colloidal silica are used, which means that the R value is low, the LS compact is overloaded with liquid formulation due to a high L_f. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation or recrystallization of the drug and thus decreased release rates. As shown in Figure, the LS formulations that had R values of 20.9 (LS-1) and 30.2 (LS-3) exhibited similar drug release profiles with small variations while the LS formulation that had low R value of 10.0 (LS-2) showed lower drug release. This study confirmed that the R value is an important parameter for LS systems and must be minimum 20 to obtain enhanced drug release.

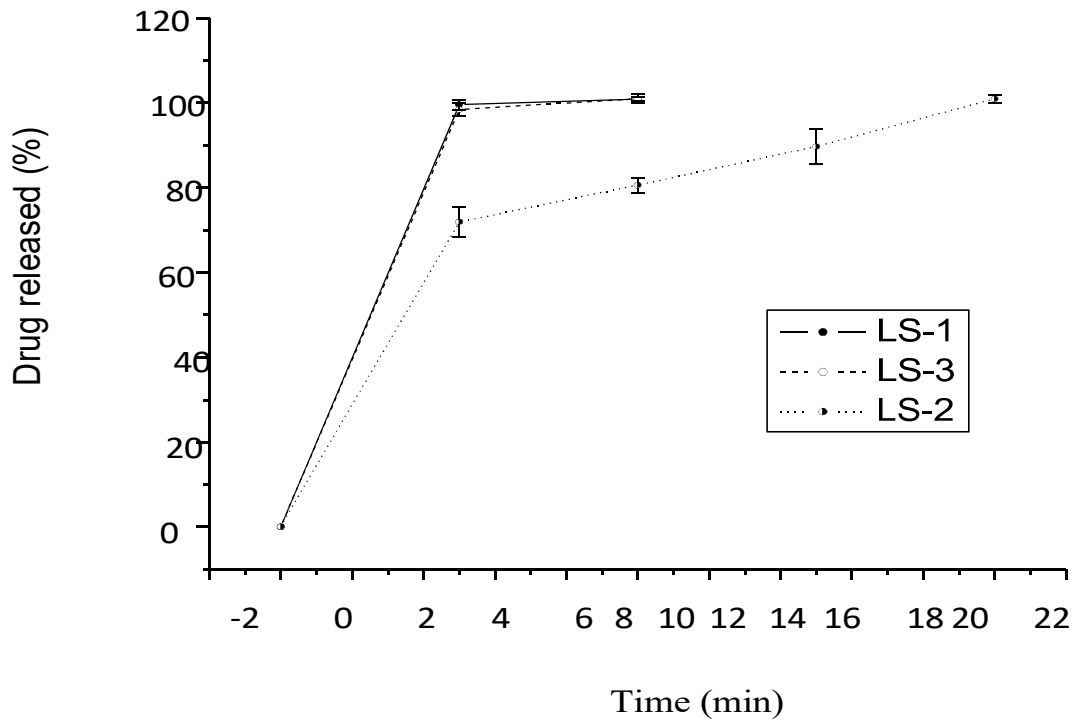

Figure no.7 Dissolution profiles of Carbamazepine had different R values (means ± SD; n=3)

The dissolution profiles of Carbamazepine from LS tablets containing different coating material LS in pH 4.5 acetate buffers are shown in Figure 2.3. The dissolution test results showed that LS-1 containing CSD had the highest drug release compared with LS-4 containing MAMS and LS-5 containing CS. The particle size of CS (74 μm) is smaller than that of MAMS (100 μm), but is much higher than that of CSD (12 μm). Therefore the drug release from LS-5 was higher

than that of LS-4, but was lower than that of LS-1 as expected. This study confirmed that the particle size of the coating material LS has an effect on the release of Carbamazepine from LS tablets and CSD is the best suitable coating material for preparing LS compacts of Carbamazepine.

Stability study

The effect of aging on the hardness and dissolution rate of LS tablets (LS-1) was determined by storing the tablets at 22^0C f or up to 12 months. The dissolution rate and hardness were measured for the LS tablets at the end of 3, 6 and 12 months. The results showed that storage at 22^0C neither had an effect on the hardness (Table) nor on the release profiles (Figure) of LS compacts. These results indicate that in the case of Carbamazepine the LS technology is a promising technique to enhance the release rate without having any stability issues.

Table no.5. Hardness results of Carbamazepine (fresh and aged)

LS system	Hardness (fresh)	Hardness (aged, 3 months)	Hardness (aged, 6 months)	Hardness (aged, 12 months)
LS-1	120 ± 2	110 ± 5	116 ± 6	114 ± 5

Differential Scanning Calorimetry (DSC)

It is used to determine the interactions between drug and excipients, which indicates the success of stability studies. The drug has a characteristic peak, absence of this peak in DSC thermogram indicates that the drug is in the form of solution in liquid formulation.

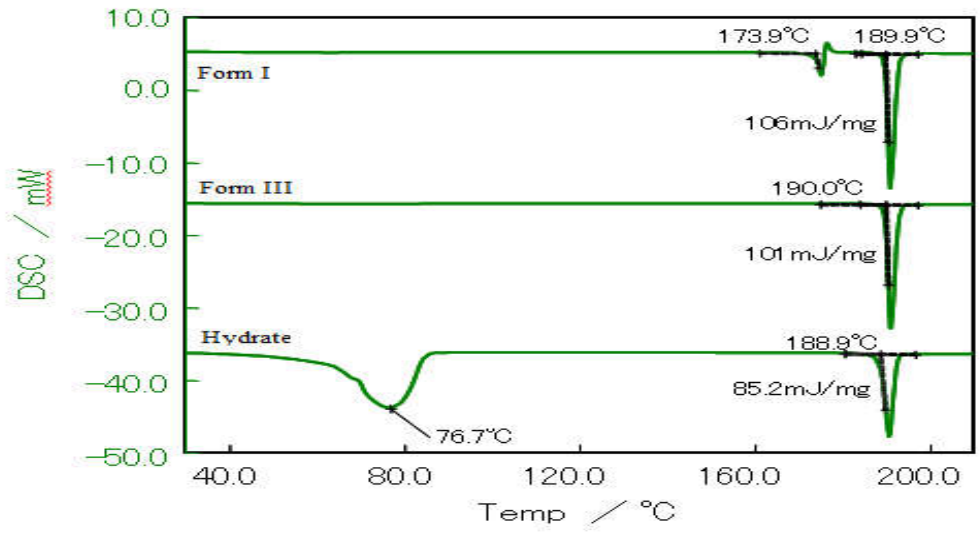

Figure no.8. DSC GRAPH OF CARBAMAZIPINE

Figure shows the DSC results for the three conditions of Carbamazepine. All samples showed a sharp endothermic peak at around 190 °C. From the Form III results, we can see that there was melting of the Form III crystals. The Form I sample showed an endothermic and an exothermic peak between 170 °C and 180 °C. The crystal structure of Form I crystals melts and then recrystallizes into the stable Form III. The hydrate sample showed an endothermic peak due to crystal water desorption at around 80 °C. This sample is likely crystal water adhered to Form III crystals. After dehydration, the Form III crystals showed no peaks before melting.

X-Ray Diffraction (XRD)

For characterization of the crystalline state, the XRD patterns are determined for drug, excipients used in formulation, physical mixture of drug and excipients, finally for the prepared LS system. Absence of constructive specific peaks of the drug in the LS X-ray diffractogram indicate that drug has almost entirely converted from crystalline to amorphous or solubilized form. Such lack of crystallinity in the LS system is understood to be as a result of drug solubilization in the liquid vehicle i.e., the drug has formed a solid solution.

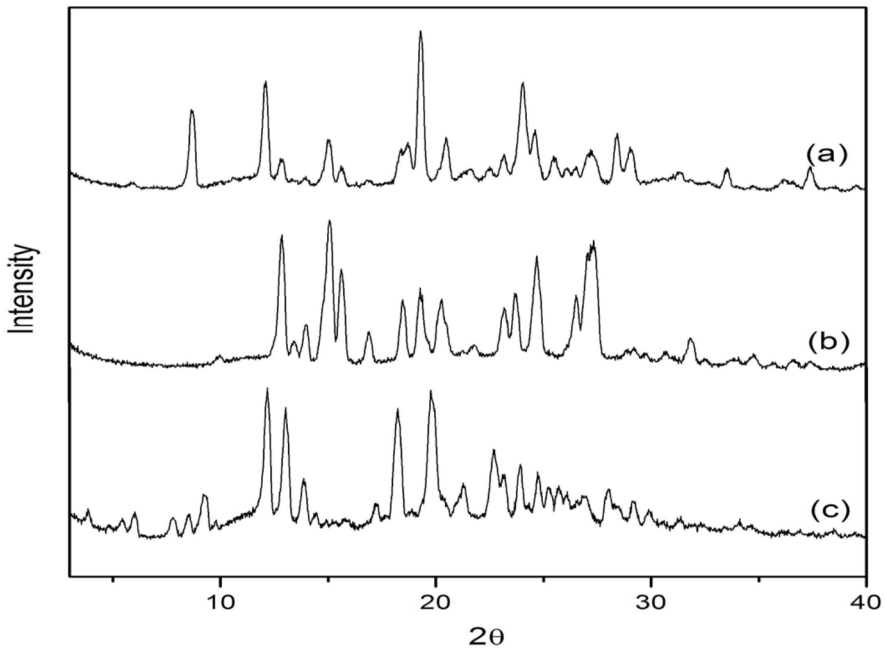

Figure no.9. X-Ray Difraction Carbamazipine

Fourier Transformed Infrared Spectroscopy (FTIR)

FTIR studies are performed to determine the chemical interaction between the drug and excipients used in the formulation. The presence of drug peaks in the formulation and absence of extra peaks suggest that there are no chemical interactions between the drug and the carrier when formed as LS system. the FTIR spectra obtained for the gases evolved during sample decomposition. The melting of CBZ at temperatures near 200 °C seems to indicate that Form I is most stable. Form I was formed preferentially by cooling, under the conditions used here; any subsequent conversion observed during the cooling-heating cycles occurred after Form I was obtained.

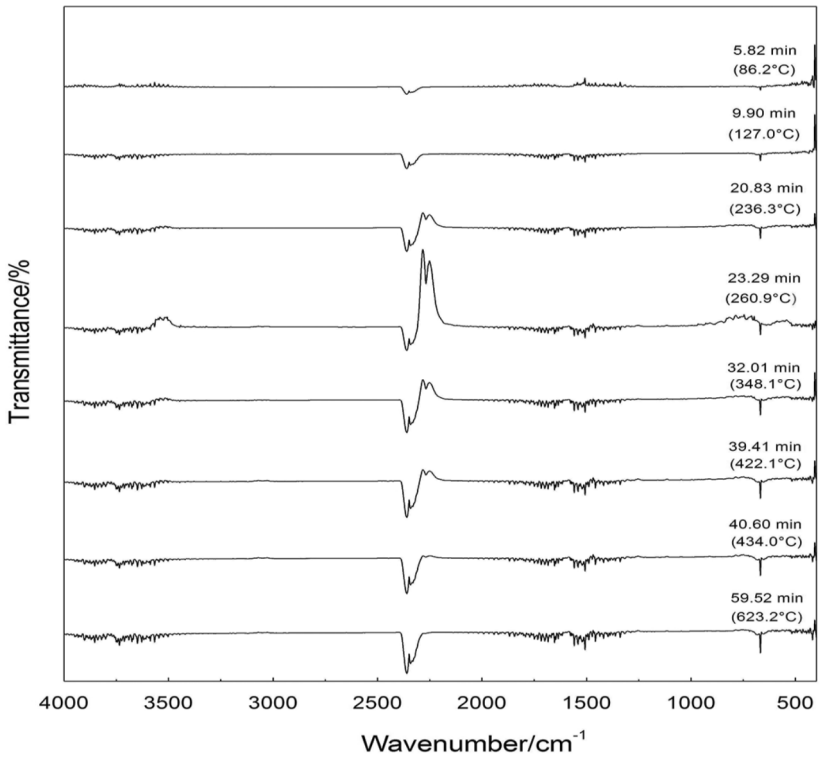

Figure no.10. FTIR Study of Carbamazipine

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