



## FORMULATION AND EVALUATION OF SUSTAINED RELEASE LIQUISOLID TABLETS OF METOPROLOL SUCCINATE

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### ABSTRACT

Liquisolid technique is the novel concept of drug delivery via the oral route. This technique is applied to poorly water soluble, water insoluble or lipophilic drugs. According to the new formulation method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. The present research endeavor is directed towards the development of liquisolid compact for the production of sustained release tablet of water-soluble Metoprolol succinate. Liquisolid compacts were prepared by using Tween 80 as the liquid vehicle or non-volatile solvent, Avicel PH 102 as absorbing carrier and Aerosil 200 as adsorbing coating material. The prepared liquisolid systems were evaluated for their micromeretic properties and possible drug-excipients interactions. P-XRD analysis confirmed that no change in crystallinity of Metoprolol succinate Liquisolid compacts. The DSC and IR spectra analysis study ruled out no any significant interaction between the drug and excipients used in preparation of Metoprolol succinate Liquisolid compacts. The tableting properties were falling within acceptable limits. The in vitro dissolution study confirmed reduction in drug release from Liquisolid compacts compared to conventional matrix tablet, in-vivo study was carried out to check the plasma drug concentration. Tween 80 has plasticizer effect by which it can reduce the glass transition temperature of polymer and impart flexibility in sustaining the release of drug from liquisolid matrices. The results showed that wet granulation had a remarkable impact on the release rate of Metoprolol succinate from liquisolid compacts, reducing the release rate of drug from liquisolid compacts.

**Key words:** Metoprolol succinate, Liquisolid Tablets, Sustained Release, Avicel.

### INTRODUCTION

Metoprolol succinate is a  $\beta_1$  (Cardio selective) blockers i.e.  $\beta$ -receptor antagonist acting as a competitive inhibitor of the action of catecholamine's like noradrenalin at  $\beta$ -adrenergic receptor sites. It is widely used in therapeutics for its antihypertensive and antiarrhythmic properties. It is also called as sympathetic and Anti adrenergic drugs. It is a water soluble drug having a half life about 3-4 hrs, which makes it a suitable candidate to be delivered at a controlled rate. There are several techniques for preparation of sustained release formulations, among which control of drug dissolution is one of the best and most successful methods due to its simplicity and low cost (Jantzen and Robinson, 1996). To achieve this aim, several methods have been developed such as preparation of salt form of the drug, coating with special materials and incorporation of drugs into hydrophobic carriers. The term 'liquisolid systems' (LS) are a powdered form of liquid drug formulated by converting liquid Lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-volatile solvent systems, non adherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials.

The present work was focused on the formulation and evaluation of the sustained release liquisolid tablet of metoprolol succinate. Sustain release tablet was formulated by using non volatile solvent such as tween 80 in which drug having least solubility, matrix formulation done by using different polymers like Hydroxypropyl Methylcellulose (HPMC) and Avicel PH 102 as absorbing carrier and Aerosil 200 as adsorbing coating material and evaluated for different in- vitro and in- vivo parameters along with development of RP-HPLC method for estimation of Metoprolol succinate from plasma.

It is suggested here that the present research work has the potential to be optimized for the reduction of the drug dissolution rate and thereby the production of sustained release systems.

### MATERIALS AND METHODS

#### Materials

Metoprolol succinate was provided by Cipla Ltd. Patalganga, Raigad, Polyethylene glycol 400 (Research Lab, Mumbai), Propylene glycol, Acetonitrile (HPLC grade) and Methanol (HPLC grade) provided by Finar Chem. Ltd. Ahmadabad, HPMC (Colorcon, Goa), Liquid paraffin (Loba Chem. Mumbai), Aerosil (Degussa India Pvt. Ltd.) Lactose (Research Lab, Mumbai), Potassium dehydrogenate ortho phosphate (Loba Chem. Mumbai), Avicel PH 102 and 200 (Maple Biotech Pvt. Ltd. Pune), Tween 80 (Research Lab, Mumbai).

#### Preparation of metoprolol succinate conventional matrix tablets (MS-CMT)

Metoprolol succinate CMT was prepared by mixing of drug with Avicel-Silica mixture for a period of 10 min in a mortar. The mixture was compressed on a 13 mm punch. Sufficient compression pressure was applied in order to produce tablets with the hardness around 4 kg/cm<sup>2</sup>. Each tablet contains 25 mg metoprolol succinate, 425 mg Avicel PH 102 as a carrier material, 21 mg of nm-sized silica as coating material and 10% HPMC as a binder.

#### Preparation of metoprolol succinate Liquisolid tablets/compact (MS-LC) by wet granulation

Nine batches of sustained release tablets, each containing 25 mg Metoprolol succinate were prepared by wet granulation technique. The granules used for the preparation had good flow property and compressibility index. All the ingredients

were passed through sieve # 100. HPMC K15M 1% w/v was used as a binding agent. MS was dispersed in tween-80 to make 10-50% w/w solutions (denoted as LS-1 to LS-9). Then a binary mixture of carrier and coating material containing Avicel PH 102 as the carrier material and Aerosil-200 as the coating material at a ratio of 20:1 was prepared. The binary mixture was added to the liquid medication under continuous mixing in a mortar. After preparation of liquisolid systems, HPMC solution was added into the mixture to obtain wet mixture of powders. Then the mixture was granulated through sieve # 12 and kept at room temperature ( $25 \pm 1$  °C) for 24 hrs. After this period, the dried mixture was sieved using sieve # 20 to obtain uniform size granules. Then the final mixture was compressed with pressure 2 tons, to achieve tablet hardness around 4 kg/cm<sup>2</sup> with acceptable friability. Composition of the liquisolid formulations is shown in **Table 1**.

### Solubility studies of Metoprolol succinate

To select the best non volatile solvent for suspending of Metoprolol succinate in liquid medication, solubility studies of Metoprolol succinate were carried out in 4 different non-volatile solvents i.e. Water, PEG 400, Tween 80 and Propylene glycol (PG). Excess amount of metoprolol succinate was placed in the different study media (n = 3) and was shaken by orbital shaker (REMI RIS-24BL) for 48 h at 25 °C under constant vibration. After this period the saturated drug solutions were filtered, diluted with respective solvents (at least 1000 times) and then analyzed by a UV - spectrophotometer (Jasco v430, Japan) at a wavelength of 274 nm.

### Precompression study

#### a) Infrared spectra analysis (IR)

Infrared spectrum of Metoprolol succinate was determined on Fourier Transform Infrared Spectrophotometer (FTIR-4100s) using the KBr dispersion method. The base line correction was done using dried potassium bromide.

#### b) Differential Scanning Calorimetry (DSC)

Thermograms of the samples (Metoprolol succinate, excipients, and LS systems) were recorded on a DSC (SDT Q600 V20.9 Build 20). Thermal behavior of the samples was investigated under a scanning rate of 10°C/min, covering a temperature range of 30–300°C.

#### c) Powder-X Ray Diffraction (P-XRD)

X-ray diffractograms of Metoprolol succinate, excipients, physical mixture and Liquisolid formulations were performed by using Philips Analytical XRD (PW 3710). The cross section of samples was exposed to X-ray radiation (Cr) with wavelength of 2.28970 °Å. The scanning range was from 10-70 °2θ.

#### d) The flow properties of the Metoprolol succinate Liquisolid system

The flow properties of the Liquisolid systems were estimated by determining the angle of repose, Carr's Compressibility index (CCI), and Hausner's ratio (HR). Angle of repose was measured according to the fixed funnel and free standing cone method. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip 2 cm height, *H*, above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so

formed just reaches the tip of the funnel. The radius of the heap was calculated and tangent of the angle of repose was given by:

$$\theta = \tan^{-1}(H/R) \quad (1)$$

Where,  $\theta$  is the repose angle, *H* is the height of the pile and *R* is radius of the pile.

The Bulk density and Tap densities were determined for the calculation of Hausner's ratio (HR) and Carr's Compressibility Index. (CCI)

$$CCI = \frac{(TD - BD)}{TD} \times 100 \quad (2)$$

$$HR = \left( \frac{TD}{BD} \right) \quad (3)$$

Where, TD and BD are tapped density and bulk density respectively.

### In vitro evaluation

#### a) Weight variation test

The weight variation test was performed as per USP and results for all the batches of Metoprolol succinate Liquisolid compacts are shown in Table 4.

#### b) Hardness test

Hardness test was performed by using the Monsanto Hardness Tester. Results for all the batches of Metoprolol succinate Liquisolid compacts are shown in Table 4.

#### c) Diameter and thickness

Diameter and thickness were performed by using a digital vernier caliper.

#### d) Friability test

Friability of prepared compacts was performed using Roche Friabilator. For friability test first calculating the initial weight and weight after time *t'* resulting in percent weight loss of each formulation, thus giving its friability. The results are expressed in terms of the percentage of weight lost during the process.

$$\% \text{ Weight loss} = \frac{(W_0 - W_t)}{W_0} \times 100 \quad (4)$$

Where,  $W_0$  = Initial weight,  $W_t$  = Final weight

#### e) Pressure- Relative Density (Heckel plot)

The granules of Metoprolol succinate liquisolid system ( $593 \pm 5$  mg) were compressed by manual tablet punch machine using 13 mm flat faced punch and die set at pressures of 1, 2, 3, 4, 5, 6 and 7 tons for 1 minute of dwell time in triplicate. A 1% w/v dispersion of magnesium stearate in acetone was used to carry out the lubrication of die and punch. After 24 hours of relaxation period, the weight, diameter, and thickness of compacts was measured. The data obtained was subject to Heckel equation,

$$\ln \left( \frac{1}{1 - P_f} \right) = KyP + A \quad (5)$$

Where  $P_f$  is the packing fraction (relative density) of granules, *P* as applied pressure, *Ky* and *A* (*y* intercept) were the constants. *Ky* is equal to  $1/3\sigma_0$ . Where;  $\sigma_0$  is yield strength and  $3\sigma_0$  as mean yield pressure (MyP).

**f) Pressure - Tensile Strength Relationship**

The same compacts measured in Heckel pilot studies were used for Tensile strength (TS) determination in triplicate for all batches LS<sub>1</sub> to LS<sub>9</sub>.

After determination of the diameter (D) and thickness (t), the force (F) required to break the compacts (hardness) (Monsanto-type hardness tester) was used to determine the TS ( $\sigma_t$ ) using the following equation.

$$\sigma_t = \frac{2F}{\pi Dt} \quad (6)$$

Where, 'D' is diameter, 't' is the thickness of compacts; and 'F' is the force required to break the compacts.

**g) In vitro dissolution study**

The in vitro dissolution tests were performed on the USP dissolution apparatus II (paddle type), using 900ml dissolution medium (pH 1.2 or pH 6.8) with a rotation speed of 50 rpm. The dissolution tests for all tablets were run for 2 h in a simulated gastric fluid (HCl solution, pH 1.2 without pepsin) at 37±0.2 °C, and subsequently in a simulated intestinal fluid (phosphate buffer, pH 6.8 without pancreatin) at 37°C for 6 h. Samples were collected at suitable time intervals (e.g. 15, 30, 60, 90, 120, 180, 240, 300, 360, 420 and 480min). Five milliliters of sample were removed from each dissolution vessel and filtered through a whatman's filter paper (no.42). The same amount of fresh dissolution fluid was added to replace the amount withdrawn. The samples were then analyzed at 274 nm by UV spectrophotometer (Jasco V 430, Japan). All the release studies were conducted in triplicate and the mean values were plotted versus time with standard deviation less than three indicating reproducibility of results.

**In-vivo evaluation of liquisolid compact**

The protocol in prescribed proforma B for animal studies entitled "Estimation of pharma- cokinetic parameters of Metoprolol succinate compacts" was submitted on 10<sup>th</sup> September 2009 to IAEC of Bharati Vidyapeeth College of pharmacy, Kolhapur. The protocol was approved by the IAEC in the presence of the CPCSEA nominee with Approval no. BVC PK/ CPCSEA/ IAEC/33/2009 dated 26<sup>th</sup> September 2009 at Bharati Vidyapeeth College of pharmacy, Kolhapur.

**Estimation of Pharmacokinetic parameters**

A 20 µl of sample solution was injected into the chromatography system using the fixed volume loop injector. The pharmacokinetic parameters for MS following

oral administration were determined from plasma concentration-time data. The maximum plasma concentration ( $C_{max}$ ) and corresponding time ( $t_{max}$ ) were obtained directly from plasma concentration-time data. The Area under the concentration-time curve (AUC) was estimated according to trapezoidal rule. Elimination rate constant ( $K_{el}$ ) was determined by Reppas et al. method

**Statistical analysis**

Maximal plasma concentration ( $C_{max}$ , ng/ml) and time to reach the peak concentration ( $T_{max}$ , h) were obtained directly by the plasma concentration-time profile. The  $AUC_{0 \rightarrow t}$ ,  $AUC_{0 \rightarrow \infty}$  (ng h/ml) and  $t_{1/2}$  (h) were determined by non-compartmental analysis. The slope of the terminal log-linear portion of the concentration-time profile was determined by least-squares regression analysis and was used as an elimination rate constant ( $K_{el}$ , h<sup>-1</sup>). The elimination half-life was obtained from the formula,  $t_{1/2} = 0.693/ K_{el}$ . The  $AUC_{0 \rightarrow t}$  from time zero to the last quantifiable point ( $C_t$ ) was calculated using trapezoidal rule and the extrapolated AUC from  $C_t$  to infinity ( $AUC_{t \rightarrow \infty}$ ) was determined as  $C_t/K_{el}$ . The  $AUC_{0 \rightarrow \infty}$  was computed through the formula,  $AUC_{0 \rightarrow \infty} = AUC_{0 \rightarrow t} + AUC_{t \rightarrow \infty}$ . The pharmacokinetic characteristics of Metoprolol succinate following oral administration of directly compressed tablets and the prepared Liquisolid compacts were evaluated statistically using one-way analysis of variance (ANOVA). Differences between two related parameters were considered statistically significant for  $P > 0.05$ . All the pharmacokinetic parameters and statistical analysis were performed on logarithmically transformed data of  $C_{max}$ ,  $AUC_{0 \rightarrow t}$ , and  $AUC_{t \rightarrow \infty}$  using statistical software package SYSTAT (Ver. 12.00.08) and Graph pad (Ver. 3.00) graph pad software, San Diego, CA, USA.

**Determination of Flowable Liquid retention potential (Φ- value)**

The corresponding Φ-value calculated from equation 7,

$$\Phi\text{-value} = \text{weight of liquid} / \text{weight of solid} \quad (7)$$

The Φ -values were plotted graphically against the corresponding angles of slide θ. The Φ-value corresponding to an angle of slide of 33<sup>o</sup>, represented the flowable liquid retention potential (Φ-value) of powder excipients. From reported Φ -value the liquid load factor (Lf) and quantities of the carrier and coating materials were calculated by using the following formulae,

$$Lf = \Phi + \phi (1/R)$$

Φ - Flowable retention potential of carrier material

φ - Flowable retention potential of coating material

$$L_f = W/Q; Q_o = W/Lo; q_o = Q_o/R$$

Table 1: Formulation of MS Liquisolid compacts with different drug Concentration

Liquisolid System	Drug concentration in liquid medication (%)	Liquid medication (gm)	Carrier material (gm)	Coating material (gm)	Tablet wt (gm)
LS-1	10	0.250	1.06	0.053	1.363
LS-2	12.5	0.200	0.850	0.042	1.092
LS-3	15	0.167	0.710	0.035	0.912
LS-4	20	0.125	0.532	0.026	0.683
LS-5	25	0.100	0.425	0.021	0.546
LS-6	30	0.083	0.353	0.018	0.454
LS-7	35	0.071	0.302	0.015	0.388
LS-8	40	0.062	0.264	0.013	0.339
LS-9	50	0.050	0.213	0.010	0.273

All formulations containing, liquid load factor - 0.235, Liquid medication - Tween 80, carrier: coating material ratio - 20 and each formulation contains Metoprolol succinate 25 mg. (These excipients calculated according to equation no. 19 to 23)

**Table 2. Solubility of Metoprolol succinate in different solvent**

Solvent	Solubility (mg/ml)
Tween 80	12.8±0.745
Propylene glycol	103.7±0.325
Polyethylene glycol- 400	64.9±0.840
Water	161.7±0.423

**Table 3: Flow properties of MS Liquisolid system**

Liquisolid system	Angle of repose (θ)	Carr's compressibility index	Hausner's ratio
LS-1	34.76±1.30	16.67±1.48	1.18±1.50
LS-2	35.35±1.45	17.34±1.30	1.17±1.21
LS-3	34.37±1.12	19.87±1.61	1.23±1.32
LS-4	36.08±1.67	16.66±1.31	1.19±1.65
LS-5	32.56±1.96	9.09±1.74	1.10±1.72
LS-6	35.79±1.26	18.21± 1.27	1.24±1.24
LS-7	34.12±2.54	17.51±1.63	1.27±1.74
LS-8	38.01±2.33	14.28±1.30	1.17±1.44
LS-9	35.53±1.15	19.62±1.12	1.25±1.61

All readings are average ± SD (n=3)

**Table 4: Evaluation data for MS Wet Granulation Liquisolid compacts**

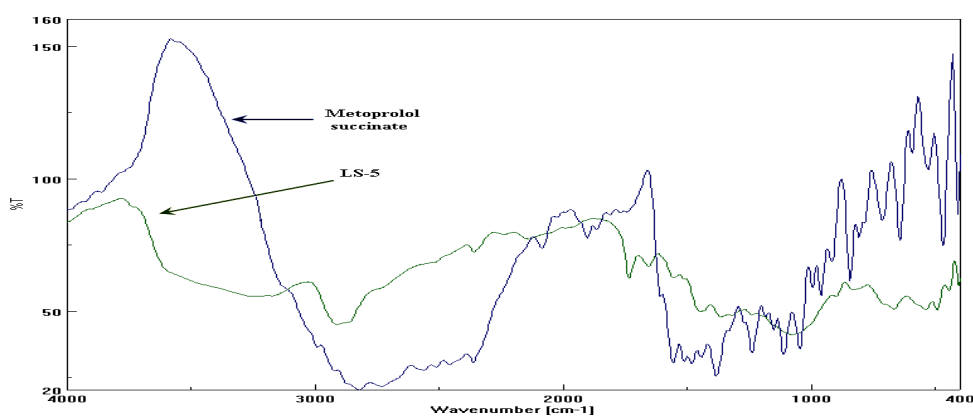
Formulation	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm <sup>2</sup> )	Wt. Variation (gm)	Friability (%)
LS-1	13.16± 0.123	5.04± 0.013	5	1.363±0.142	0.095 ± 0.007
LS-2	13.17± 0.152	4.92± 0.061	5	1.092±0.074	0.126 ± 0.003
LS-3	13.21± 0.333	4.84± 0.073	5	0.912±0.152	0.274 ± 0.002
LS-4	13.23± 0.264	4.21± 0.044	5	0.683±0.476	0.089± 0.006
LS-5	13.16± 0.177	3.65± 0.070	5	0.546±0.159	0.072± 0.008
LS-6	13.22± 0.149	3.31± 0.087	4	0.454±0.176	0.099± 0.002
LS-7	13.17± 0.153	2.95± 0.054	4	0.388±0.081	0.094± 0.003
LS-8	13.22± 0.123	2.42± 0.061	4	0.339±0.270	0.199 ± 0.006
LS-9	13.18± 0.173	2.19± 0.042	4	0.273±0.197	0.168± 0.002

All readings are average ± SD (n=3)

**Table 5: Pharmacokinetic data for MS Liquisolid compacts and conventional matrix tablet in plasma**

Sr. No.	Pharmacokinetic parameters	Liquisolid compacts <sup>a</sup>	Conventional matrix tablet <sup>a</sup>	P-value <sup>b</sup>
1	AUC <sub>0-24</sub> ng h ml <sup>-1</sup>	16710.4±685	14736.7±1241	0.0252(S)
2	AUC <sub>0-∞</sub> ng h ml <sup>-1</sup>	20728.5±1537	17631.3±1129	0.0363(S)
3	C <sub>max</sub> ng ml <sup>-1</sup>	1115.9±78	1022.2±29	0.0379(S)
4	T <sub>max</sub> h	12.52±0.6	12.11±0.5	0.2458(NS)
5	K <sub>el</sub> h <sup>-1</sup>	0.204±0.14	0.224±0.34	0.4352(NS)
6	t <sub>1/2</sub> H	3.40±0.12	3.12±0.65	0.2486(NS)

a Mean ± SD (n=3), b P- value of the variance., S- Significant; NS- Not significant



**Figure 1: Overlain IR spectrum of Metoprolol succinate and LS-5 formulation**

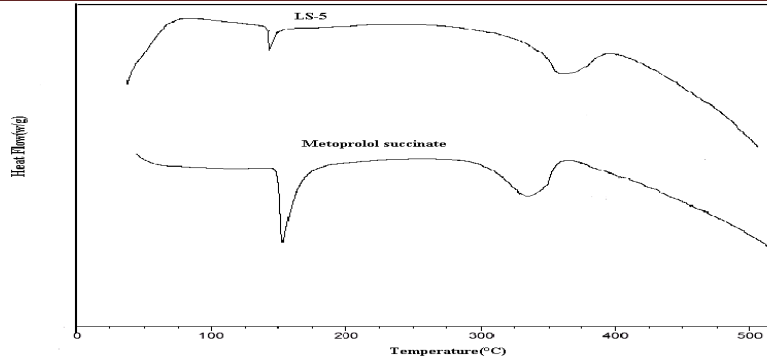


Figure 2: Differential scanning calorimeter plot of liquisolid formulation (LS-5) and pure Metoprolol succinate.

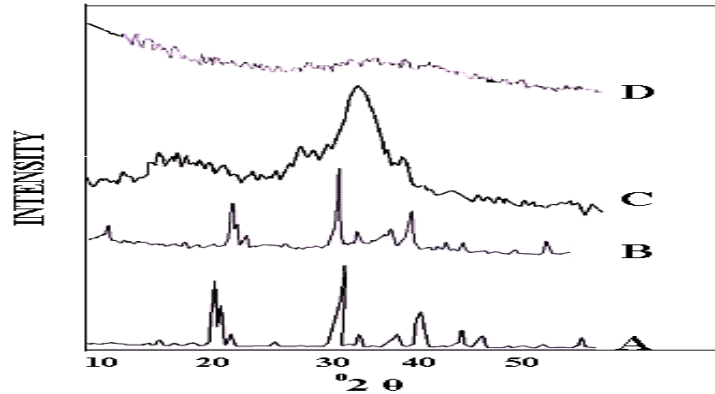


Figure 3: X-ray diffractograms of (A) Pure MS, (B) Physical Mixture (C) Liquisolid powder system (D) Avicel PH 102

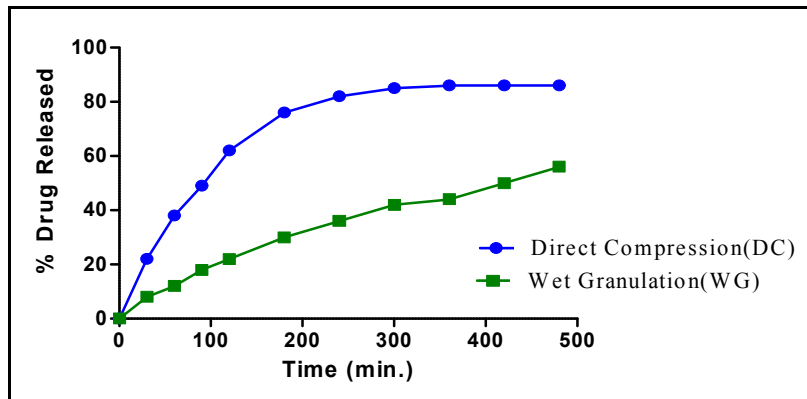


Figure 4. Effect on drug release retardation property by wet granulation method

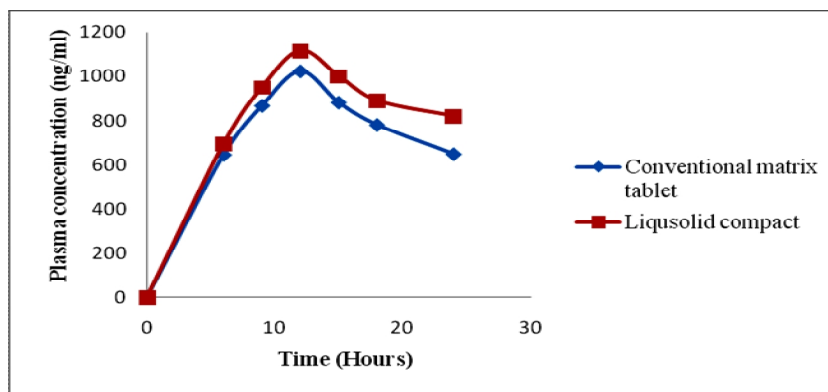


Figure 5. Mean metoprolol succinate plasma profiles following single-dose, A crossover bioavailability study comparing MS conventional Matrix and liquisolid tablets.

## RESULT AND DISCUSSION

Metoprolol was selected as the model drug for these studies since it is a water soluble drug and a suitable candidate for testing the potential of sustained release liquisolid compacts. All the standard curves of metoprolol succinate solutions obeyed Beer's law which was linear over the concentration range tested since 5-30 µg/ml. Their results are presented in **Table 2**.

The flow properties of the Liquisolid powder system are affected by physical, mechanical as well as environmental factors. Therefore different flow parameters were employed such as, the angle of repose ( $\theta$ ), Carr's compressibility index and Hausner's ratio and their results are presented in **Table 3**.

### IR spectrum of Metoprolol succinate (IR)

In which characteristic peaks of aromatic N-H stretching at 3399.89  $\text{cm}^{-1}$  and peak at 3734.48  $\text{cm}^{-1}$  indicating presence of O-H group, and peak at 1508.06  $\text{cm}^{-1}$  indicating aromatic C=C group. (**Figure 1**) shows overlain IR spectrum of formulation and drug shows no interaction between drug and excipients.

### Differential scanning calorimetry (DSC)

The possible interactions between a drug entity and excipients in Liquisolid compacts were determined by DSC. (**Figure 2**) reveals the thermal behaviors of the pure components together with the thermal behavior of the final Liquisolid system prepared. Metoprolol succinate peaks are clear, demonstrating a sharp characteristic endothermic peak at 146.03°C corresponding to its melting temperature ( $T_m$ ); such sharp endothermic peak signifies that Metoprolol succinate used was in a pure crystalline state. The liquisolid (LS-5) formulation showed the same peaks in this area, which indicates that there is no interaction between drug and excipients during the formulation process. From above finding it can be concluded that the delayed dissolution rate of Metoprolol succinate liquisolid compacts is not due to the formation of the complex between the drug and excipients or changes in crystallinity of the drug.

### Powder-X-Ray Diffraction (P-XRD)

Polymorphic changes of drugs are important factors which might affect the dissolution rate and in turn bioavailability. It is necessary to study polymorphic changes of MS in Liquisolid compacts. The pharmaceutical implication of the presence of meta stable crystalline forms in the excipients is well recognized. The crystal structure could also affect tablet porosity and density, the mechanism of aggregation and disintegration and the plastic and elastic properties of solid dosage forms (Bartolomei et al, 1999). (**Figure 3**) shows the P-XRD of pure MS, pure excipients, physical mixture and Liquisolid system. Metoprolol succinate shows (**Figure 3 A**) sharp peaks at 10.47, 20.97, 21.205, 30.035 and 36.355 $^{\circ}2\theta$ . Liquisolid powder system shows (**Figure 3 C**) sharp diffraction peak at 30.010 at  $^{\circ}2\theta$  and Avicel PH 102 shows (**Figure 3 D**) sharp diffraction peak at 34.29, which indicate Avicel PH 102, also maintained its crystalline state. As above **Figure 3**, liquisolid and physical mixture (**Figure 3 B**) formulations have relatively the same diffraction pattern with minor changes which some of them could be due to peak noises. A reduction in peak height and sharpness in peaks might be due to lower concentration of the drug in these formulations in comparison with pure drug powder. Comparing the some changes in peak ratio of pure drug and

liquisolid formulations might be changes in the polymorphic ratio of the drug in the formulations. It can be concluded that no significant interaction between drug and polymers occurred during the formulation process.

### Evaluation of MS Liquisolid compacts:

The results of Diameter, thickness, Hardness, weight variation and friability test for all the batches of wet granulation MS Liquisolid compacts are shown in **Table 4**. The evaluations were performed on LS-1 to LS-9 formulations, the lowest percent weight loss was found to be in LS-5 formulation. All the selected metoprolol succinate liquisolid tablets had acceptable friability as none of the tested formulae had a percentage loss in tablet weights that exceed 0.5%. Also no tablet was cracked, split or broken in all these formulations.

### In vitro dissolution studies

(**Figure 4.**) Shows the drug release retardation properties of LS-5 direct compression tablet and LS-5 wet granulation compacts of Metoprolol succinate. In this study wet granulation technique shows more retardation properties compare to direct compression technique. It was found that wet granulation had a remarkable impact on the release rate of metoprolol succinate from liquisolid compacts. It was reported that granulation of diclofenac sodium using HPMC can slow down the release of the drug in comparison with dry technique. This could be due to the coating of drug particles by HPMC during the granulation process which sequentially retard the penetration of water into the granules or reduce the direct contact of the drug with dissolution medium. Finally we could find that granulation process induced the slow release effect or that was the retarding effect of HPMC, physical dry mixture of liquisolid and HPMC was prepared and the results of dissolution tests were compared. The results showed that there was no significant difference between the drug release profile of physical dry mixture of liquisolid formulation and LS formulation with HPMC. On the other hand significant difference was observed between granulation liquisolid formulation and granulation LS formulation with HPMC. These results confirmed the effect of a granulation method on the sustained release behavior of liquisolid tablets.

### Estimation of pharmacokinetic parameters of MS liquisolid compact

(**Figure 5.**) Shows Plasma concentration verses time profile of MS Liquisolid compacts and conventional matrix tablet. Liquisolid compacts show higher concentrations of MS in plasma as compared to conventional matrix tablets. Liquisolid compacts demonstrate better bioavailability which can be confirmed from pharmacokinetic data expressed in **Table 5**.

### Statistical analysis

The mean plasma concentration–time profiles of Metoprolol succinate following the oral administration of the conventional matrix Metoprolol succinate tablets and the prepared liquisolid tablets (LS-5) are shown in **Figure 5** and the calculated pharmacokinetic parameters are presented in **Table 5**. Crossover and multiple dose study should be carried out to ensure the formulation of drug to consider for clinical trial.

**CONCLUSION**

The present work showed that liquisolid technique can be optimized for the production of sustained release matrices of water-soluble drugs. Tween 80 was used as the liquid vehicle the release of drug from these formulations followed zero-order release kinetics. This investigation provided evidence that polysorbate 80 (Tween 80) has an important role in sustaining the release of drug from liquisolid matrices. Heat treatment had no effect on the release profile of drug from liquisolid tablets. Hardness and dissolution profile of the drug were not affected by aging. No crystallinity change was observed during the process of liquisolid formulation. The proposed new technique can be used in the preparation of sustained release formulations of water-soluble drugs such as metoprolol succinate.

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