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FORMULATION AND EVALUATION OF RAMIPRIL LIQUISOLID COMPACT USING NOVEL CARRIER

Vijendra Kumar Suryawanshi^{*}, Bina Gidwani, Astha Verma, Neha Dubey and Chanchal Deep Kaur

Shri Rawatpura Sarkar Institute of Pharmacy, Kumhari, Durg - 490042, Chhattisgarh, India.

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Correspondence to Author:

Vijendra Kumar Suryawanshi

Associate Professor,
Shri Rawatpura Sarkar Institute of
Pharmacy, Kumhari, Durg - 490042,
Chhattisgarh, India.

E-mail: khanna.vijendra@gmail.com

ABSTRACT: The aim of the present investigation was to enhance the dissolution of poorly water-soluble drug Ramipril (BCS - II) drug through Liquisolid compact. The liquisolid compacts were prepared with a varied quantity of liquid and powder ingredients using microcrystalline cellulose as a carrier, Aerosil 200 as a coating material, polyethylene glycol 400, propylene glycol and tween-80 as liquid vehicles, HPMC as additives to increase loading capacity. The required quantities of ingredients for the compressible admixture were calculated using various mathematical models. The *in-vitro* release characteristics of different dissolution conditions were performed. All formulated systems were assessed for precompression parameters like flow properties, FTIR analysis, X-ray diffraction (XRD), differential scanning calorimetry (DSC), and post-compression parameters like content uniformity, weight variation, hardness, friability, disintegration test, wetting time and *in-vitro* dissolution studies. As liquisolid compacts demonstrated significantly higher drug release rates, thereby indicating a promising strategy in improving the dissolution of poorly water-soluble drugs and formulating immediate release solid dosage forms.

INTRODUCTION: The poor dissolution of water-insoluble drugs is a foremost problem for the bioavailability of drug which decreases the therapeutic efficacy of drug^{1, 2}. Preparation of liquisolid systems (LSS) is a novel technique for improving solubility, dissolution, and bioavailability of such drugs. The fundamental of Liquisolid system preparation lies in the transformation of the drug in a liquid state into a dry powder by its absorption of these drug into suitable excipient such as microcrystalline cellulose, then coated with a material having high absorption capacity such as silicon dioxide commonly known as colloidal silica.

The advantages of liquisolid system are that cheap in comparison to soft capsules. The major benefit is the enhancement of bioavailability of poor water-soluble drug, by providing a large surface area available for absorption as explained by Spireas *et al.*³

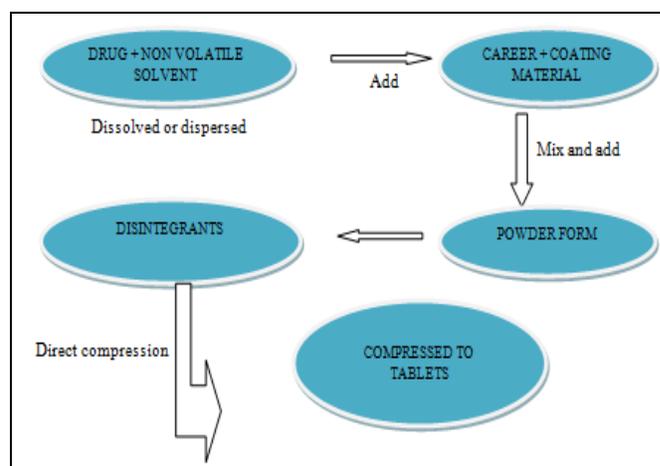


FIG. 1: A SCHEMATIC DIAGRAM OF METHOD OF LIQUISOLID PREPARATION

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Over the years, various formulation techniques like the formation of water-soluble molecular complexes, drug micronization, solid dispersion, coprecipitation, lyophilization, and micro-encapsulation are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs^{4, 5}. The liquisolid compacts are a new and promising addition towards such a novel aim. Using this new formulation technique, a liquid medication may be converted into a dry-looking, nonadherent, free-flowing, and readily compressible powder by a simple blending with selected powder excipients referred to as the carrier (cellulose, starch, lactose, etc.) and coating (silica) materials⁶. Research shows that soft gelatin capsules contain a solubilized liquid drug with a higher and more consistent bioavailability than the conventional oral dosage forms, due to the active ingredient present in the solution. Liquisolid system release drug component like soft gelatin capsule which contains liquid; where the specific solvent is used to dissolve the solid drug. Hence, the drug is present in the solution, even though it is in a tableted dosage form. As a result drug dissolution properties may be improved as demonstrated by Spireas S *et al.*, and Tiong N *et al.*^{7, 8}

To treat hypertension and congestive heart failure an angiotensin-converting enzyme (ACE) inhibitor Ramipril is used. Ramipril relaxing arterial muscles and enlarging the arteries by reducing the production of angiotensin II, as a result of the heart pump blood more easily, and increased blood flow due to enlarging the arteries⁶.

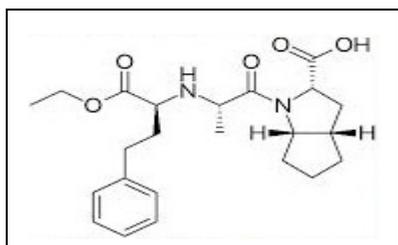


FIG. 2: STRUCTURE OF RAMIPRIL

Ramipril is a prodrug and is converted to the active metabolite ramiprilat by liver esterase enzymes. It is mainly used for hypertension⁹.

The oral absorption of Ramipril is slow, due to poor water soluble. Hence, it is necessary to

improve the dissolution rate of Ramipril to enhance the dissolution rate of Ramipril formulated liquisolid compacts of Ramipril.

The use of novel porous carriers such as microcrystalline cellulose as a carrier (Avicel PH 102) for an increased loading capacity of nonvolatile solvent along with the drug, so that liquisolid compact of high dose poorly water-insoluble drug Ramipril can be formulated. The prepared formulations were characterized and compared with the directly compressible tablet (DCT) of Ramipril¹⁰.

Theoretical Aspects: In the fundamental studies made by Spireas *et al.*,^{11, 12} flow and compression issue have been addressed with the use of the new mathematical model of liquisolid system which is based on the flowable (ϕ -value) and compressible (ψ -number) liquid retention potentials of the constituents powder. The smaller particle size and larger surface area provide better flow and compression properties of the liquisolid system.

Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used, the carrier (Q) and coating (q) powder materials can retain a specific amount of liquid while maintaining acceptable flow and compression properties.

$$R = Q / q \dots\dots Eq. 1$$

Where: R represents the ratio between the weights of the carrier (Q) and coating (q) materials present in the formulation.

Liquid Load Factor (L_f): The liquid load factor is the ratio of the weight of liquid medication (w) on the weight of the carrier material (Z) in the system; the preparation of compressible and free-flowing liquisolid system is based on the maximum liquid on the carrier material not exceeded beyond the limit of carrier material. Which should be possessed by an acceptably flowing and compressible liquisolid system^{13, 14} That is,

$$L_f = W / Z \dots\dots Eq. 2$$

By using liquid retention potentials (ϕ -value) of carrier and coating material, the liquid load factor and amount of carrier and coating material were calculate by formulations as follows:

$$L_f = \phi + \phi / R \dots\dots Eq. 3$$

As from equation (3), liquid retention potential of carrier material ϕ_{ca} and liquid retention potential of coating material ϕ_{co} are constants, so in order to determine the liquid load factor L_f , carrier and coating material ratio using lithe nier relationship between L_f versus $1/R$.

MATERIALS AND METHODS: Ramipril was obtained as a gift sample from Cadila Pharmaceuticals Ltd., Ahmadabad. Aerosil 200 was procured from Research Lab, Avicel PH 102 and Propylene Glycols were purchased from Loba Chemicals, Mumbai, Polyethylene Glycol 400, Tween 80, and Sodium Starch Glycolate was purchased from Merck. All chemicals and reagent used were of analytical grade.

Solubility Studies: Solubility study of Ramipril was done in various solvents like propylene glycol, polyethylene glycol 400, and Tween 80 by shake flask method. An excess amount of drug was transferred to each volumetric flask containing 1ml of solvent (PG, PEG 400 and Tween 80). The prepared solutions were placed on a rotary shaker for 48 h at room temperature. The drug concentration in each solution was analyzed by UV spectrophotometer at 210 nm.¹⁵

Preparation of Liquisolid Compacts: Ramipril liquisolid systems were prepared and compressed into tablets of 20 mg strength each, using a single punching machine with the aim of the desired hardness of 3-6 kg/cm². All liquisolid formulations contained microcrystalline cellulose as the carrier powder and silica as the coating material at a fixed powder excipient ratio (R) of 20. As a liquid vehicle Propylene Glycol was used to prepare the drug solution in different drug concentrations 10 to 20% w/w, included in the formulations F-1 to F-3.

On the other hand, PEG 400 was used as the liquid vehicle in the formulations F-4 to F-6, and similarly, Tween 80 was used as the liquid vehicle in the formulations F-7 to F-9 with similar drug concentration. Depending on the liquid vehicle and drug concentration in the liquid medication used, different liquid load factors (L_f) ranging from 0.133 to 0.294 (w/w) were employed in liquisolid preparations. Finally, 5% (w/w) Sodium Starch Glycolate was added as disintegrant into all prepared liquisolid system. In **Table 1** Concentration of formulations (F1-F9) of Ramipril liquisolid compacts is shown.

TABLE 1: FORMULATION OF PREPARED RAMIPRIL LIQUISOLID TABLETS

Liquisolid system	Liquid vehicle	Drug conc. (% w/w) in liquid medication (C_d)	Excipient ratio (R)	Avicel PH-102 (Q) mg	Aerosil 200 (q) mg	Liquid vehicle (mg)	Active ingredient Ramipril (mg)	Liquid load factor (L_f)	Molecular fraction (F_m)
F1	PEG-400	10	20	653.5	32.675	90	10	0.153	1.147
F2	PEG-400	15	20	425.8	21.29	56.7	10	0.157	1.147
F3	PEG-400	20	20	375.4	18.77	40	10	0.133	1.147
F4	PG	10	20	342.6	17.13	90	10	0.292	0.994
F5	PG	15	20	238.9	11.945	56.7	10	0.279	0.994
F6	PG	20	20	215.3	10.765	40	10	0.232	0.994
F7	Tween 80	10	20	340.7	17.035	90	10	0.294	0.612
F8	Tween 80	15	20	229.4	11.47	56.7	10	0.291	0.612
F9	Tween 80	20	20	180.6	9.03	40	10	0.277	0.612

W-weight of liquid medication (drug + liquid vehicle); L_f -liquid load factor; Q-weight of carrier material; q-weight of coating material; R-carrier: coating ratio; F1-F9: Formulations using Avicel. An appropriate amount of liquid medication containing 10 mg of drug was incorporated in each tablet. Excipient ration (R) equal to 20 in each formulation. Amount of carrier (Q) material. Amount of coating (q) material. Liquid load factor is defined as $L_f = W/q$. The fraction (F_M) of the molecularly dispersed drug was calculated by (7).

Application of Mathematical Model for Ramipril Liquisolid System for determining precompression properties:

Determination of the Angle of Slide for Aerosil 200: The angle of the slide is used as a measure of flow properties of powders. Two grams of Aerosil 200 were weighed accurately and placed at one end of an aluminum metal plate with a polished surface. This end was raised gradually until the plate made an angle θ with the horizontal at which the powder

was about to slide. This angle θ represented the angle of slide. The angle of slide corresponding to 33° considered as optimal flow properties¹⁶.

Determination of Flowable Liquid Retention Potential for Aerosil (ϕ -Value): An increasing amount of liquid vehicle (PG, PEG 400, and Tween 80) was added to the 10 g of Aerosil 200 power and mixed well. The aerosol adsorbed the liquid vehicle resulting into change in its flow properties. The

angle of the slide for aerosol was redetermined as stated earlier. The corresponding ϕ -value was calculated from the following equation:

$$\phi \text{-Value} = \text{Weight of liquid} / \text{Weight of solid} \dots \dots \text{Eq. 4}$$

The graph plotted against between ϕ -value and the corresponding angle of slide of material which represented the flowable liquid retention potential of Aerosil¹⁷.

According to Tayel *et al.*, in PEG 400, the ϕ -value is 0.137 for Avicel PH 102 and 2.76 for Aerosil 200. And for propylene glycol, the ϕ -value is 0.262 for Avicel PH 102 and 5.20 for Aerosil 200, thus showing no need to determine it practically. The liquid load factor for PG and PEG 400 liquisolid system was calculated from flowable liquid retention potential using R value (excipient ratio) of 20, which shown is as follows¹⁸.

Precompression Studies of Liquisolid System:

Flow Properties of Liquisolid System: The flow properties of liquisolid system were estimated by the angle of repose, Carr's index, and Hausner's ratio provide the information about flow properties of liquisolid system. Fixed funnel method was used to the measured angle of repose. The bulk density and tapped densities were determined for the calculation of Hausner's ratio and Carr's index^{19,20}.

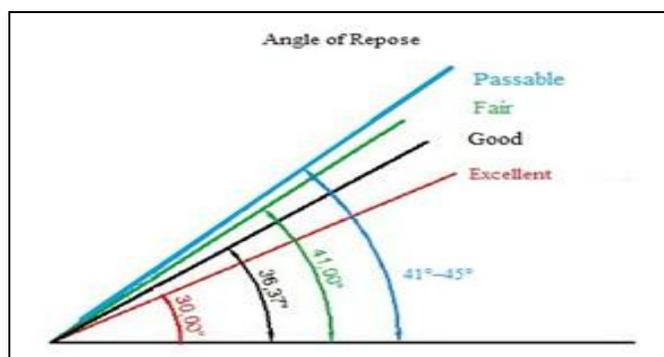


FIG. 3: ANGLE OF REPOSE AND FLOW PROPERTIES

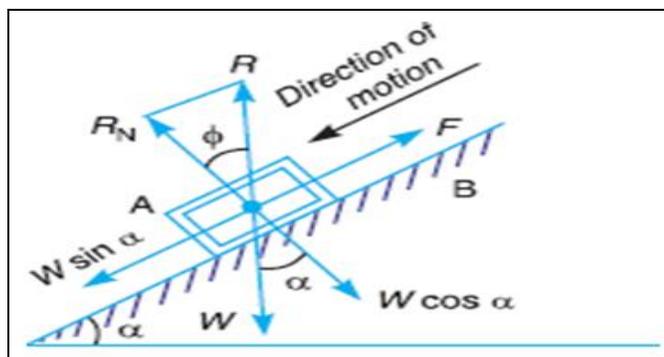


FIG. 4: ANGLE OF REPOSE

The angle or the critical angle of repose is a suitable measure to determine the angle of internal friction of less cohesive bulk materials and the size of particles is the same. It is the perpendicular angle of descent concerning the horizontal plane. The range of the angle is 0°-90°.

The classification of the angle of repose is based on some experimental variables as demonstrated by Mistry R *et al.*²¹

1. The height of the "funnel" by which the material pass may be permanent relative to the bottom.
2. The bottom on which the pile forms may be of a fixed diameter or the diameter of the powder cone may be allowed to vary as the pile forms.

Infrared Spectra Analysis: FTIR relies on the fact that most molecules absorb light in the infra-red region of the electromagnetic spectrum. This absorption corresponds specifically to the bonds present in the molecule. The frequency ranges are measured as wave numbers typically over the range 4000 - 600 cm^{-1} .^{22, 23}

Differential Scanning Calorimetry (DSC): Thermo-grams of the pure Ramipril and liquisolid system were recorded on a DSC. The thermal behavior of the samples was investigated at a scanning rate of 10°C/min, covering a temperature range of 40 - 2600 °C^{24, 25}.

Estimation of Fraction of Molecularly Dispersed Drug in Liquid Medication: The fraction (F_M) of the dissolved or molecularly dispersed drug in the liquid medication is the ratio of the drug's saturation solubility (C_L) in the liquid vehicle **Table 2** over the drug concentration (C_d) in the liquid medication²⁶.

$$F_M = C_L / C_d \dots \dots \text{Eq. 5}$$

Where $F_M = 1$ when $C_L / C_d > 1$

The value of the fraction of the molecularly dispersed drug F_M **Table 1** in any system cannot exceed unity.

Post-compression Parameters:

Content Uniformity: In uniformity of drug content 10 tablets from each batch were taken randomly to examine its content uniformity. Each tablet was weighed and crushed individually.

The crushed tablet powders were dissolved in methanol. The solution was filtered using Whatman filter paper. The drug content was measured using a UV spectrophotometer (UV-1800 Shimadzu) at 210 nm. According to the British Pharmacopoeia, the percentages drug content of the individual was calculated against the average drug content^{27, 20}.

Weight Variation: The weight variation test was performed on 20 tablets of liquisolid compacts as per British Pharmacopoeia^{28, 29}.

Hardness and Friability: Pfizer hardness tester is used to determine the hardness of prepared liquisolid tablets and mean hardness of three tablets was calculated. The Roche type apparatus was used for determination of friability, and the drum was rotated for 4 min at 25 rpm. The losses of the mass of 10 tablets were determined, and the % of friability was calculated³⁰ as follow:

$$\% \text{ Friability} = \text{Loss of Mass} \times 100 / \text{Initial Mass} \dots \dots \text{Eq. 5}$$

Disintegration Test: The disintegration test was performed at 37 ± 1 °C in distilled water for six tablets from each formulation using the tablet disintegration unit. The tablets were considered completely disintegrated as no residue remains on the screen. The desired hardness of tablet should be produced with low compression forces so that the compressed tablet allow rapid disintegration and drug dissolution at the same time³¹.

Wetting Time: The degree of wetting (wettability) is determined by a force balance between adhesive and cohesive forces. Wetting is an important step in the disintegration process to take place. A piece of tissue paper folded double was placed in a Petri dish containing 6 mL of water. The tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds³¹.

In-vitro Dissolution Studies: *In-vitro* dissolution profile from liquisolid compacts and directly compressed tablets were obtained using dissolution test apparatus USP-I. The dissolution studies were carried out in 900 ml, of 0.1 N HCl and distilled water as the dissolution medium at 37 °C \pm 1 °C and 50 rpm. Then, 5 ml samples were collected for up to 60 min at 5 min intervals up to 30 min and 15 min intervals from 30 to 60 min. The dissolution medium was replaced with 5 ml of fresh dissolution

fluid to maintain the sink condition. The withdrawn samples were filtered and analyzed spectrophotometrically at 210 nm^{32, 33}.

RESULT AND DISCUSSION:

Solubility Study: Beer's law was obeyed by all the standard curves of our Ramipril solution which were linear in the concentration range, that is, from 1 to 10 µg/ml. The solubility of Ramipril in propylene glycol, polyethylene glycol 400, and polysorbate-80 (Tween 80) determined in these studies are shown in **Table 2**.

TABLE 2: SOLUBILITY OF RAMIPRIL

Solvent	Solubility w/w
PEG 400	11.47
Propylene glycol	9.94
Polysorbate 80	6.12

Precompression Studies of the Liquisolid System: Flow Properties of the Ramipril Liquisolid System: The flow characteristics of the liquisolid powder system are affected by physicochemical and environmental factors. Therefore, different flow properties were employed. As the angle of repose (θ) is a characteristic of the internal friction or cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non cohesive. F-1 shows a good flow property with θ value of 28.61 and is considered as a liquisolid system with acceptable flowability. Carr's index up to 16 was considered acceptable as a flow property. Hausner's ratio was related to the inter-particle friction; powders with a low inter-particle friction had a ratio of approximately 1.25 indicating a good flow. On the basis of precompression studies of the formulation F-1 with Carr's index of 14.52 and Hausner's ratio of 1.17 was considered for further study and results of all batches of Ramipril liquisolid compacts are shown in **Table 3**.

IR Spectra Analysis: Samples of Aerosil 200, Avicel PH-102, pure Ramipril, and liquisolid system (F-1) were subjected to FT-IR spectroscopic analysis, and their spectra at 500 - 4000 cm^{-1} is shown in **Fig. 5**. Characteristics peaks of aromatic N-H stretching and C=O stretching at 3285.05 cm^{-1} and 1549.26 cm^{-1} appeared, respectively. A reduction in the intensity of the characteristics absorption bands of Ramipril was observed in the liquisolid formulation, which might be attributed to

the hydrogen bonding interaction between the carboxylic group of Ramipril and the hydroxyl group of the liquid vehicles; this resulted in drug dissolution enhancement. All the reference peaks which are observed in the IR spectrum of Ramipril were also observed in the IR spectrum of Ramipril

liquisolid compact formulation in **Fig. 5 & 6**. It was found that Ramipril was compatible with a solid carrier material (MCC) and coating material (Aerosil 200) used in the formulation and there were no extra peaks observed.

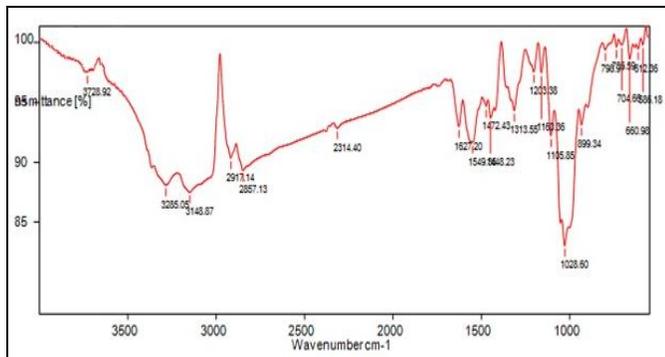


FIG. 5: FT-IR SPECTRA OF PURE RAMIPRIL

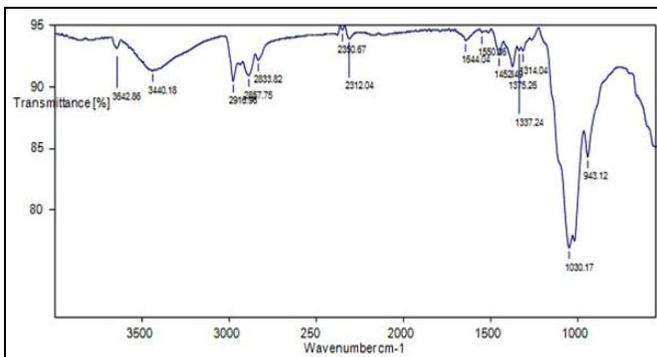


FIG. 6: FT-IR SPECTRA OF RAMIPRIL+MCC+AEROSIL 200

Differential Scanning Calorimetry (DSC):

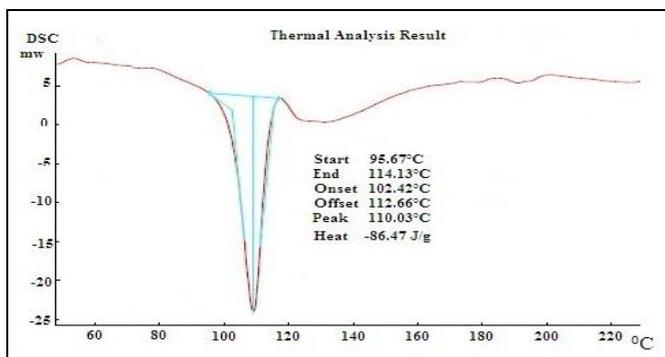


FIG. 7: DSC THERMOGRAMS OF PURE RAMIPRIL

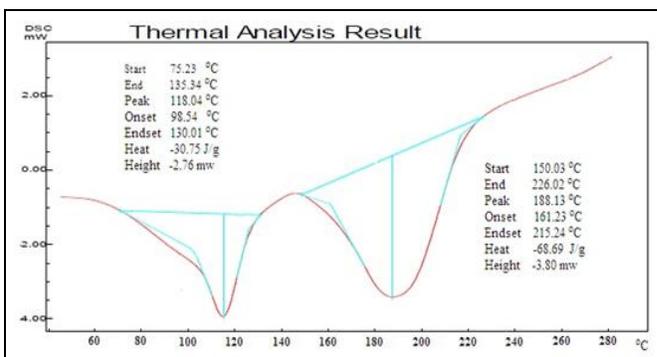


FIG. 8: DSC THERMOGRAM OF LIQUISOLID SYSTEM F-1

The possible interaction between a drug entity and excipient in liquisolid compact was determined by DSC. **Fig. 7** shows the thermal behavior of the pure component and the thermal behavior of the formulated liquisolid system. Pure Ramipril shows two characteristic peaks at 110.03 °C it is a primary indication for crystalline nature of the pure drug. Furthermore, the thermal behavior of liquisolid system (F-1) shows the shifting of the peak at 118.04 °C. It indicates that the crystalline nature of drug gets completely converted into amorphous form due to which there is a significant change in the endothermic peak of the formed liquisolid system.

Post Compression Studies of Liquisolid Compacts Tablet:

Content Uniformity: The weight uniformity test of all the prepared liquisolid compact of Ramipril and conventional tablets complied with the British

Pharmacopoeia (BP); and also, all the tablets had met content uniformity criteria, as per BP, in which drug content was found between 96.10% and 99.05% of the average content.

Friability, Weight Variation, and Fraction of Molecularly Dispersed Drug (F_M):

All the liquisolid compact of Ramipril reveals the satisfactory friability. The % of weight variation did not exceed 1% of the tablet weight, and no tablet was broken or collapsed. All the prepared formulation is expected to show adequate toughness and resist abrasion during handling. All the prepared batches had a hardness in the range 3.7-5.3 kg/cm². Generally, the ideal tablet hardness should be produced without applying excessive compression force where rapid tablet disintegration and drug dissolution are maintained at the same time²⁸.

Also, the batches passed the USP weight variation test. All the prepared batches had a disintegration time in range 1 to 5 min. The batches prepared with increasing drug concentration exhibited an increasing disintegration time. Determination of F_M value of each prepared liquisolid of Ramipril was calculated, the liquid vehicle is not used in the case

of directly compressed tablets which contain pure Ramipril powder. The result of friability, hardness, weight variation, disintegration time, and a fraction of molecularly dispersed drug (F_M) for all the formulation of liquisolid compacts of Ramipril are shown in **Table 4 & 1**.

TABLE 3: FLOW PROPERTIES OF RAMIPRIL LIQUISOLID SYSTEMS

Liquisolid system	Angle of repose*	Bulk density* (gm/cm ³)	Tapped density* (gm/cm ³)	Carr's index*	Hausner's ratio*
F1	28.61 ± 0.19	0.22 ± 0.01	0.26 ± 0.025	14.52 ± 0.27	1.17 ± 0.03
F2	29.46 ± 0.29	0.25 ± 0.02	0.31 ± 0.04	18.62 ± 0.19	1.24 ± 0.18
F3	31.71 ± 0.23	0.25 ± 0.01	0.30 ± 0.03	16.43 ± 0.11	1.19 ± 0.07
F4	31.49 ± 0.189	0.27 ± 0.01	0.32 ± 0.02	16.54 ± 0.28	1.19 ± 0.04
F5	30.42 ± 0.24	0.30 ± 0.01	0.36 ± 0.03	18.49 ± 0.14	1.20 ± 0.12
F6	33.43 ± 0.24	0.32 ± 0.02	0.36 ± 0.02	16.51 ± 0.30	1.17 ± 0.12
F7	35.62 ± 0.27	0.29 ± 0.02	0.34 ± 0.04	14.53 ± 0.30	1.18 ± 0.06
F8	34.30 ± 0.20	0.29 ± 0.015	0.35 ± 0.04	17.41 ± 0.15	1.22 ± 0.16
F9	36.60 ± 0.14	0.31 ± 0.01	0.36 ± 0.03	15.47 ± 0.22	1.17 ± 0.04

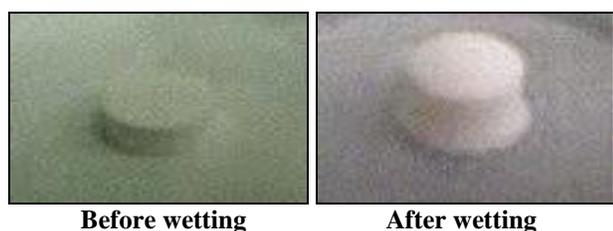
*mean ± S. D. n = 3

TABLE 4: PHYSICAL PARAMETER OF LIQUISOLID TABLET

Liquisolid System	Thickness* (mm)	weight variation* (mg)	Hardness* (kg/cm ²)	Friability* (%)	Disintegration time* (min)	Content uniformity* (%)
F1	5.51 ± 0.38	824.5 ± 1.01	4.55 ± 0.29	0.29 ± 0.15	1.36 ± 0.21	99.05 ± 0.16
F2	5.54 ± 0.24	538.9 ± 0.63	4.99 ± 0.17	0.42 ± 0.16	2.27 ± 0.14	98.22 ± 0.10
F3	3.44 ± 0.29	465.7 ± 0.58	5.27 ± 0.25	0.22 ± 0.11	2.23 ± 0.19	96.48 ± 0.24
F4	4.52 ± 0.34	481.6 ± 0.99	4.23 ± 0.10	0.36 ± 0.15	4.48 ± 0.47	98.02 ± 0.41
F5	5.66 ± 0.24	333.5 ± 1.29	3.77 ± 0.12	0.44 ± 0.20	3.29 ± 0.22	96.10 ± 0.66
F6	6.48 ± 0.34	288.8 ± 0.89	4.41 ± 0.37	0.30 ± 0.13	5.06 ± 0.43	96.26 ± 0.39
F7	4.56 ± 0.41	481.9 ± 1.31	4.57 ± 0.19	0.37 ± 0.18	3.33 ± 0.18	98.21 ± 0.28
F8	5.52 ± 0.30	322.6 ± 1.05	5.30 ± 0.17	0.56 ± 0.20	2.36 ± 0.23	97.98 ± 0.53
F9	5.64 ± 0.33	252.4 ± 0.79	5.07 ± 0.16	0.47 ± 0.10	3.27 ± 0.15	96.59 ± 0.39

*mean ± S. D. n = 3

Wetting Time: The internal structures are responsible for wetting behavior of the tablet as well as hydrophilicity of the powder excipient also affect the wetting time. A relationship between wetting time and disintegration time should be linear for liquisolid compacts. The wetting time of liquisolid system (F-1) was found to be 15-18 sec as compared to the conventional tablet which showed wetting time as 32-37 sec.



In-vitro Dissolution Studies: The liquisolid tablets demonstrated significantly improved drug dissolution properties. It seems that the drug

dissolution rate of liquisolid compacts is significantly faster than conventional tablets. According to the “diffusion layer model” dissolution theories, the dissolution rate of a drug is directly proportional to its concentration gradient ($\Delta C = C_s - C$) in the stagnant diffusion layer formed by the dissolving liquid around the drug particles. **Fig. 9** and **10** showed the dissolution profile of liquisolid compact of F-1 to F-9 with a directly compressible tablet (DCT) in 0.1 N HCl. Liquisolid compact F-1 produced a higher dissolution in 0.1 N HCl in comparison to a conventional tablet. The drug release from conventional Ramipril tablet as shown in **Fig. 7** was very poor. Only 39.29% dissolution enhancement of such poorly soluble drug was carried out by formulating liquisolid compacts. Among the ten formulations, F-1 has maximum dissolution rate.

It shows 42.34% percentage drug release in the first 15 min and 99.4% release in 90 min. From F-1 to F-3 (drug conc. 10, 15 & 20% w/w respectively), to F4 to F6 (drug conc. 10, 15 & 20% w/w respectively) and F7 to F9 (drug conc. 10, 15 & 20% w/w respectively) we can see that the dissolution rate gradually decreases. From the above results, it is clear that as we increase the amount of liquid vehicle as calculated from the mathematical model, there is an increase in the dissolution rate of the drug.

It is because of the increase in the surface area of the drug for dissolution, increased aqueous solubility, and increased wetting property of the drug. The data were processed for regression analysis using MS-EXCEL statistical functions. Evaluation of release kinetics and application of the best fit by correlation coefficient show that the drug release follows first order kinetics. This technology may be used industrially in future for conversion of solution or suspension of the poorly-water soluble drug into a more stable solid dosage form.

TABLE 5: IN-VITRO DISSOLUTION PROFILE OF LIQUISOLID COMPACT TABLETS OF RAMIPRIL (F1 TO F9) AND DCT

Medium	Time (min)	Cumulative % Ramipril Release									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	DCT
0.1 N Hydrochloric acid pH 1.2	5	5.78	6.41	7.63	4.19	4.23	4.22	8.81	7.81	5.78	6.87
	10	17.59	16.26	12.23	16.55	12.17	15.17	16.69	18.69	17.66	11.12
	15	42.34	42.47	46.52	42.18	41.78	38.47	43.34	30.34	30.38	16.54
	20	53.53	61.51	55.45	50.01	56.29	48.53	59.53	49.53	48.53	22.59
	30	72.31	71.18	68.57	66.64	64.22	63.42	72.28	58.28	57.28	38.64
	45	87.42	84.15	78.63	78.38	78.39	74.51	87.38	78.34	79.04	51.43
	60	91.55	87.23	85.73	82.53	86.73	81.62	91.55	81.55	81.78	59.94
	90	99.4	93.21	94.53	91.47	92.27	92.62	93.4	94.43	96.4	64.54

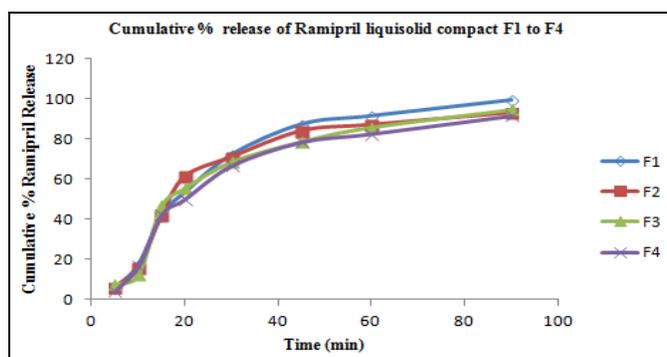


FIG. 9: DISSOLUTION PROFILE OF RAMIPRIL LIQUISOLID COMPACTS FORMULATION (F1 TO F4)

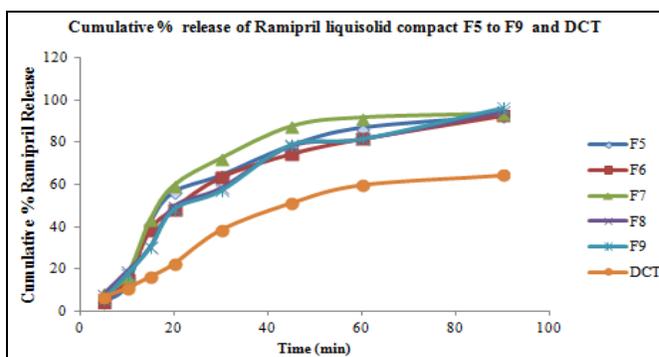


FIG. 10: DISSOLUTION PROFILE OF RAMIPRIL LIQUISOLID COMPACTS FORMULATION (F5 TO F9 AND DCT)

CONCLUSION: The overall objective of the present study was to enhance the dissolution of poorly water-soluble Ramipril by liquid solid compact technique. The liquid solid tablets formulated with the PEG-400 at drug concentrations of 10% w/w are the best formulation among all the batches of liquid solid tablets prepared, regarding faster disintegration time, superior dissolution profile, and acceptable tablet properties. PEG-400 was found to be a promising liquid vehicle in formulating liquid solid compacts of Ramipril. Furthermore, the interaction study done through DSC confirmed that there is no interaction between Drug and PEG-400. The liquid vehicle plays a contributing role in improving the dissolution profiles of a poorly water-soluble drug in the liquid solid compacts. The key step in

formulating a successful liquid solid tablet is the determination of the optimal flowable liquid retention potential (ϕ -value) utilizing various mathematical model. This technology may be used industrially for conversion of solution or suspension of poorly water soluble drug into more stable solid dosage form.

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CONFLICT OF INTEREST: Nil

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