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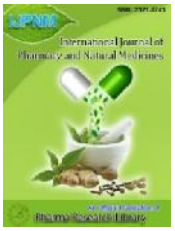

Research Article **Open Access**

Formulation and evaluation of Carvedilol Fast dissolving tablets by Liquisolid compacts

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A B S T R A C T

The main objective of the present study is the formulation of Fast dissolving tablets of Carvedilol by liquisolid compacts. In this method poorly water soluble drugs like Carvedilol are liquefied by using Solvents like PEG-400, polypropylene glycol and Tween 80 and different formulations were prepared in different ratios, and then mixed with a carrier particle like Microcrystalline cellulose-200, lactose anhydrous, Neusiline and coated by coating materials like Aerosil-200 in different ratios which forms a wet particles. The wet granules are dried uniformly dried and the flow properties of the granules like Carr's index, Hausner's ratio and Angle of repose were calculated and the granules were punched. The prepared Tablets was evaluated and weight variation, hardness, friability and Assay were and calculated and noted. The results suggest that the Formulation F12 shows better post and pre formulation properties and the drug release profiles of the optimized formulation and the Marketed Tablets were compared and concluded that the F12 Optimized formulation shows better bio-availability.

Keywords: Neusiline, Tween-80, Aerosil-200, Kyron T-314,Poly ethylene glycol-400, liquisolid compacts.

A R T I C L E I N F O

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1. Introduction

The therapeutic effectiveness of a drug depends upon the bioavailability, which is in turn dependent on the solubility of drug molecules. Solubility, is the important parameter to be achieved in order to obtain desired concentration of drug in systemic circulation for pharmacological response. The challenge for poorly water soluble drugs is to enhance the rate of dissolution, which results in subsequent improvement of absorption and bioavailability. Among

them liquisolid compacts is one of the most promising and new technique which promotes the dissolution rate of water insoluble drugs. The liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term '*liquid medication*' refers to liquid lipophilic (oily) drugs or water-insoluble solid drugs dissolved in suitable water-miscible non-volatile solvent systems termed as the liquid vehicle.

Liquisolid Compacts - A Novel Approach

The new Liquisolid technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water insoluble solid drugs carried in non-volatile liquid vehicles) into powders suitable for tableting or encapsulation. Simple blending of such liquid medications with calculated quantities of a powder substrate consisting of certain excipients referred to as the carrier and coating powder materials, can yield dry looking, non adherent, free flowing, and readily compressible powders.

Type of Liquisolid compacts based on the liquid medication

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered drug emulsions
4. Powdered liquid drug

The liquified portion, which may be either a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, which is introducwd or simply induced into the porous carrier material. The organic solvent systems should be inert, preferably water-miscible with high boiling point such as liquid polyethylene glycols, propylene glycol, or glycerine are most excellent fitting as liquid vehicles. The carrier material is saturated with the liquid, forms a layer on the particle surface which is instantly adsorbed by the fine coating particles

Mechanism for Liquisolid Compacts

Liquisolid system is a novel concept of drug delivery via the oral route. This technique is applied to water insoluble drugs and lipophilic drugs to sustain their release. Formulation and manufacture of the liquisolid tablet is quite simple method according to new mathematical model described by Spire's. The liquisolid tablet preparation method involves, first a mathematically calculated amount of pure drug weighed and dissolved in the suitable amount of solvent in a molecularly dispersed state. For attaining good flow properties trial and error methods were used i.e. changing the carrier: coating material ratio from 50:1 to 5:1 ratios according to new mathematical model expressions proposed. This liquid medication is poured on the suitable amount of carrier material. The liquid medication is absorbed into the carrier material internally and externally and then a suitable disintegrant was added to this material. Finally, coating material was added for dry looking, adherent to the carrier material for achieving good compression properties. As the drug is in the form of liquid medication it is either solubilised or molecularly dispersed state. Due to increased wetting and surface area for dissolution, liquisolid tablet of water insoluble drugs shows improved dissolution properties and in turn increased bioavailability. Liquid medication is incorporated into carrier medication which has a porous surface and closely matted fibers in its interior as cellulose .Both absorption and adsorption take place, i.e. the liquid absorbed into the interior of the particles is captured by its internal structure and after saturation of this process, adsorption of the liquid on to the internal and external surface of the porous carrier particles occurs .Excipients possessing fine and highly adsorptive particles such as various types of amorphous silicon dioxide (silica) are most suitable for this step. Before compression or encapsulation, various ingredients such as lubricants, disintegrants or Polymers, and binders, may be mixed with the finished liquisolid systems to produce liquisolid compacts in the dosage form of tablets or capsules.

Advantages of Liquisolid Compacts

1) Huge number of Bio-Pharmaceutical classification class II drugs with high permeability, slightly or very slightly water soluble and practically insoluble liquids and solid drugs can be formulated into liquisolid systems.
2) Improvement of bioavailability of an orally administered water insoluble drug is achieved.
3) This principle governs or administers the mechanism of drug delivery from liquisolid systems of powdered drug solutions and it is mainly responsible for the improved dissolution profiles exhibited by these preparations.
4) In this technique, production cost is low compared to soft gelatin capsules.
5) Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilised liquid state, which confers developed or improved drug wetting properties thereby improving drug dissolution profiles.

Disadvantages

1) Requirement of high solubility of drug in non-volatile liquid vehicles.
2) Low drug loading capacities.
3) Formulation of high dose lipophilic drugs the liquisolid tablet is one of the limitations of this technique.

Applications of Liquisolid Systems

- Solubility and dissolution enhancement.
- Used efficiently for water insoluble solid drugs or liquid lipophilic drugs.
- Rapid release rates.
- Designed for controlled release tablets.

Patented Technologies for Fast Dissolving Tablets

- Zydis technology
- Dura Solv technology
- OraSolv technology
- Flash dose technology

2. Materials and method

Materials

Microcrystalline Cellulose-200, Lactose anhydrous, Neusiline, Mannitol, Poly ethylene glycol-400, Propylene glycol, Tween-80, Aerosil-200 (Colloidal silicon di-oxide), Sodium starch glycolate, Cros Carmellose sodium, Kyron T-314, Magnesium stearate, Talc.

Methods

Fourier Transformation Infra-Red (FTIR) Analysis: Fourier-transform infrared (FTIR) spectra of the Drug and

polymer were obtained on Alpha Brooker FTIR (Tokyo, Japan). The spectra were scanned over the wave number range of 4200 to 500 cm^{-1}.

Procedure for Formulation:

A drug was initially dispersed in the non volatile solvent systems (Propylene glycol, PEG 400, Tween-80 and Cremophore-EL) termed as liquid vehicles with different drug : vehicle ratio. Then a mixture of carrier and coating materials were added to the above liquid by continuous mixing for a period of 10 to 20 minutes in a mortar. The amount of carrier and coating materials are enough to maintain acceptable flow and compression properties. To the above binary mixture disintegrant and other remaining additives are added according to their application and mixed in a mortar. The final mixture was compressed to achieve tablet hardness or encapsulated. Characterizes the final liquisolid granules for solubility, flowability, compressibility and dissolution.

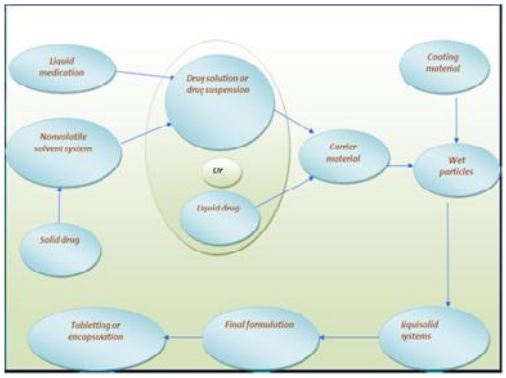

Figure 1

Evaluation of tablets:

The quantitative evaluation and assessment of tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

Physical Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Size & Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

Weight variation test:

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Content Uniformity:

The content uniformity test was used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes.

Method:

Randomly 30 tablets were selected. 10 of those assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If those conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Friability:

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It was usually measured by the use of the Roche friabilator.

Method:

A number of tablets were weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of the treatment or 100 revolutions, the tablets were weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test was considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\textbf{\% friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

Wetting time:

Five circular tissue papers of 10-cm diameter were placed in a petridish with a 10-cm diameter. 10 ml of water at $37^0C \pm 0.5^0C$ containing eosin, a water-soluble dye, was

added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted.

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio R, was determined using following equation

$$R = W_a - W_b / W_b \times 100$$

Where W_a = weight of tablet after absorption

W_b = weight of tablet before absorption

Disintegration time:

According to the European pharmacopoeia the fast disintegrating or Oro-dispersible tablets should disintegrate within 3minutes without leaving any residue on the screen.

Disintegration test:

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration.

The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.

Method:

The U.S.P. device to test disintegration uses 6 glass tubes that are long open at the top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet was placed in each tube and the basket rack was positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 20 C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. The basket containing the tablets was moved up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets.

Drug release

The drug release from the Carvedilol tablets was investigated in a USP-II (paddle) apparatus, 900 ml of Phosphate buffer pH6.8 (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analyzed with UV spectrophotometry at λmax=285nm.

Stability studies:

Selected Formulation was subjected to stability studies as per ICH guidelines.

- Following conditions were used for Stability Testing.
- 250C/60% RH analyzed every month for period of three months.
- 300C/75% RH analyzed every month for period of three months.
- 400C/75% RH analyzed every month for period of three months.

3. Results and Discussion

Fourier Transformation Infra-Red (FTIR) Analysis:

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).The instrument was calibrated by using polystyrene film.

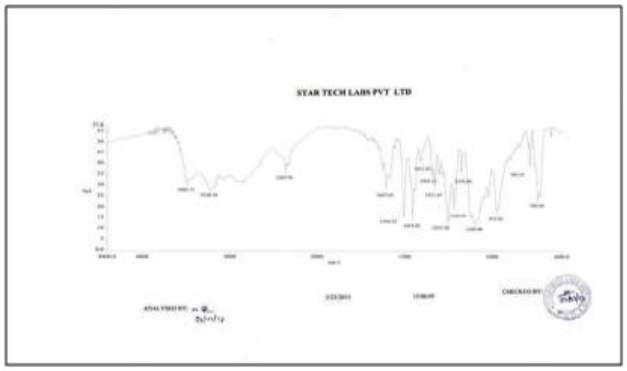

Figure 1: FT-IR of Carvedilol Drug

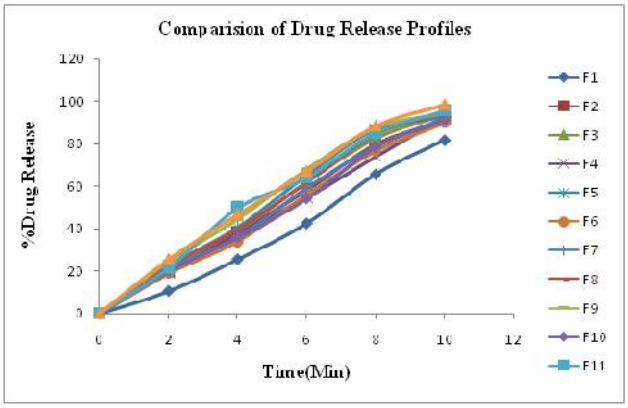

Figure 2: Dissolution profiles of prepared formulations

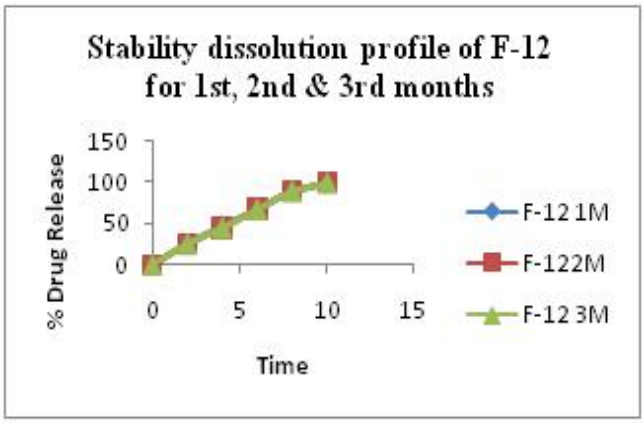

Figure 3: Stability dissolution profile of F-12 for 1st, 2nd & 3rd months

Stability Dissolution Profile of F-9 for 1st, 2nd & 3rd Months: The objective of the present study is to develop a Carvedilol Fast dissolving tablets by using liquisolid technique. In this present study an attempt was made to improve on set of action as well as to enhance bioavailability of drug. Systematic studies were conducted using different carriers in different concentrations for improving the solubility of Carvedilol then fabricated into Fast Dissolving tablet which can be approached by using different concentrations of Superdisintegrants. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies were conducted like micromeritic properties to assess flowability, compressibility properties and solubility studies. And all the formulations gave good results for above preformulation studies. Among the all formulations (F1-F12), it was observed that formulation-12 has shown better dissolution profile with sufficient wetting capability. So Formulation-12 was found to be the best formulation among others and the stability studies were carried out for period of 3 months as per ICH guidelines and was in acceptable limits.

Table 1: Composition of Carvedilol Tablets in Mg

Excipients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**Marketed**
Carvedilol	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
propylene glycol 400	12.5	---	---	---	12.5	---	---	---	12.5	---	---	---	---
PEG-400	---	12.5	---	---	---	12.5	---	---	---	12.5	---	---	---
Tween-80	---	---	12.5	---	---	---	12.5	---	---	---	12.5	---	---
Cremophore-EL	---	---	---	12.5	---	---	---	12.5	---	---	---	12.5	---
MCC-102	100	100	100	100	100	100	100	100	100	100	100	100	112.5
Aerosil-200	5	5	5	5	5	5	5	5	5	5	5	5	5
Mannitol	20	20	20	20	20	20	20	20	20	20	20	20	20
SSG	5	5	5	5	---	---	---	---	---	---	---	---	---
CCS	---	---	---	---	5	5	5	5	---	---	---	---	---
Kyron-T314	---	---	---	---	---	---	---	---	5	5	5	5	5
Mg.stearate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Talc	1	1	1	1	1	1	1	1	1	1	1	1	1
Total	152 (mg)	152 (mg)	152 (mg)	152 (mg)	152 (mg)	152 (mg)	152 (mg)	152 (mg)	152 (mg)	152 (mg)	152 (mg)	152 (mg)	152 (mg)

Limits for Tablet Weight variation test

Average weight of tablet (mg)	**% Difference allowed**
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

Pre Compression Parameters

Formulation	**Bulk density**	**Tapped density**	**Angle of repose**
F1	0.318	0.389	24.93
F2	0.331	0.399	24.25
F3	0.329	0.396	25.05
F4	0.345	0.409	56.40
F5	0.356	0.411	25.79
F6	0.39	0.444	27.56
F7	0.362	0.410	27.66
F8	0.338	0.378	28.67
F9	0.337	0.403	25.06
F10	0.350	0.414	26.71
F11	0.343	0.402	26.94
F12	0.367	0.422	27.10

Evaluation of Tablets

Formulation Code	**Weight Variation**	**Hardness Kg/Cm^2**	**Thickness (mm)**	**Friability (%)**	**Assay (%)**	**Wetting Time** (sec)
F1	Passes	5.1	2.34±0.038	0.12%	99.42	35
F2	Passes	5.3	2.35±0.033	0.15%	99.2	30

F3	Passes	5.8	2.35±0.03	0.12%	99.7	32
F4	Passes	5.4	2.55±0.048	0.14%	99.5	31
F5	Passes	5.5	2.53±0.040	0.15%	99.8	28
F6	Passes	5.2	2.55±0.17	0.14%	99.98	29
F7	Passes	5.4	2.52±0.054	0.16%	99.97	28
F8	Passes	5.5	2.58±0.11	0.15%	99.97	26
F9	Passes	5.2	2.35±0.04	0.13%	99.98	29
F10	Passes	5.2	2.51±0.040	0.17%	99.90	27
F11	Passes	5.4	2.53±0.17	0.14%	99.94	26
F12	Passes	5.3	2.54±0.054	0.12%	99.98	22
Marketed	Passes	4.9	2.35±0.05	0.15%	99.97	28

Dissolution Profile of Prepared Formulations

Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0	0	0	0	0	0	0
2	10.56	19.96	21.96	19.21	22.46	18.96	20.96	22.46	24.56	19.96	21.46	25.56
4	25.56	38.12	39.12	37.82	40.56	34.12	36.12	39.78	44.58	35.82	49.78	46.78
6	42.56	58.19	62.19	54.76	65.16	56.19	59.19	62.16	68.26	54.19	64.13	67.16
8	65.78	79.89	82.89	74.09	86.89	76.89	78.89	84.89	87.83	78.59	85.27	88.69
10	81.96	91.12	94.12	92.74	92.67	90.12	92.12	94.7	94.67	91.12	95.7	98.67

Stability Dissolution Profile of F-12 for 1st, 2nd & 3rd Months

S.No.	**TIME(Min)**	**F-12 1M**	**F-12 2M**	**F-12 3M**
1	0	0	0	0
2	2	25.56	25.54	25.53
3	4	46.78	44.73	44.69
4	6	67.16	67.11	67.1
5	8	88.69	88.69	88.71
6	10	98.66	98.64	98.63

4. Conclusion

All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies were conducted like micromeritic properties to assess flowability, compressibility properties and solubility studies. And all the formulations gave good results for above preformulation studies. Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, wetting time, content uniformity, all the formulations were found within the permissible range. Among the all formulations (F1-F12), it was observed that formulation-12 has shown better dissolution profile with sufficient wetting capability. So Formulation-12 was found to be the best formulation among others and the stability studies were carried out for period of 3 months as per ICH guidelines and was in acceptable limits.

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