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Formulation and Evaluation of Controlled Release Tablets of Carvedilol using Hydrotropic Technique.

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Abstract: In case of oral administration, solubility is a key factor to demonstrate the pharmacological response in achieving the desired bioavailability of drugs. But most of the time, due to dissolution as the rate-limiting step intended for absorption of poorly aqueous soluble drugs (BCS Class-II and IV), it becomes challenging to formulate conventional dosage forms of such drugs. Different perspectives have been extensively inspected to improve the aqueous solubility and poor dissolution rate of BCS Class-II and Class-IV drugs such as micronisation, self-emulsification, pH-changing solubilization, salt formation, co-solvent, solid dispersion and hydrotropic use etc. Solubility and dissolution are the central principles of any physical or chemical science including biopharmaceutic and pharmacokinetic aspects in therapy with any medication. This analysis summarizes the use of hydrotropy, which is one of the promising practice for boosting solubility in several folds by adding surplus quantity of Hydrophilic solute to improve the aqueous solubility of the primary solute without any chemical alteration of the drug compound e.g. Urea, Niacinamide , Sodium salicylate, Sodium Citrate, etc. It has several advantages like it does not need organic solvent or establishment of the emulsion system.

Keywords: Controlled Release Tablets, Carvedilol, Hydrotropic Technique.

INTRODUCTION

Almost more than 90% drugs are orally administered. Drug absorption sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium. More than 90% of drugs approved since 1995 have poor solubility. It was estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble and not well absorbed after oral administration which can distract from the drugs inherent efficacy. Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in human are recognized today as one of the major challenges in oral delivery of new drug substances. Orally administered drugs on the model list of essential medicines of the World Health Organization (WHO) are assigned BCS classification on the basis of data available in the public domain .[1]

BCS (Biopharmaceutical classification system) based on drug solubility and permeability characteristics.

Class II Low solubility and high permeability	Class I High solubilit=y and high permeability
Class IV Low solubility and low Permeability	Class III High solubility and low permeability

Controlled released tablet:-

Oral drug delivery method is the most widely utilized routes for administration among all alternatives that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage forms. Popularity of the route may be ease of administration as well as traditional belief that by oral administration the drug is due to the well absorbed into the food stuff ingested daily. Controlled release (C.R) pharmaceutical products have gradually gained medical acceptance and popularity. Regulatory approval for marketing and their pharmaceutics superiority and clinical benefits over immediate release pharmaceutical products have been increasingly recognized. Modified release oral dosage forms have brought new lease of life into drugs that have lost market potential due to requirement of frequent dosing, dose related toxic effects and gastro intestinal disturbances. [2,3]

Materials and methods:

Preparation of pH 1.2 acidic buffer solution: 50 ml of 0.2 M potassium chloride solution in a 200 ml volumetric flask was taken added with 85.0 ml of 0.2 M hydrochloric acid solution shaken for complete admixture. The final was adjusted with distilled water.

Preparation of simulated gastric fluid (pH 1.2): Accurately weighed 2.0 gm of sodium chloride and 3.2 gm of purified pepsin were completely dissolved in 7.0 ml of hydrochloric acid and volume was made up to 1000 ml by distilled water and the pH (1.2) was adjusted.

Preparation of pH 5.8 Phosphate buffer solution: 50 ml of 0.2 M potassium Dihydrogen phosphate solution was poured in a 200 ml volumetric flask which was added with 3.6 ml of 0.2 M sodium hydroxide solution and shaken for complete mixture. The final volume was adjusted with distilled water.

Preparation of simulated intestinal fluid (pH 5.8): Accurately weighed 6.8 gm of monobasic potassium phosphate was dissolved in 250ml of distilled water, 77 ml of 0.2 M sodium hydroxide and 500 ml of distilled waterwere added. 10.0 gm of pancreatin was added, and dissolved finally diluted withdistilled water up to 1000 ml and pH 5.8 was adjusted.

Preparation of Carvedilol solution (stock) in the presence of solubilizing agent: Two samples each containing 1.0 mg of carvedilol was accurately weighed and transferred to 1000 ml volumetric flasks separately. 30ml of 10 % (methanol &ethanol) & 20% solution of solubilizer in distilled water were added and drug was dissolved in each flask. After complete dissolution of drug, sufficient distilled waterwas used to make up the volume.Similarly stock solutions of carvedilol were prepared incorporating different solubilizing agent's i.e urea, Nicotinamide, PEG 400, PEG 4000,Nicotinamide +Urea, Nicotinamide +PEG 400, Nicotinamide + PEG 4000, PEG 400+Urea, PEG4000 + PEG 400.The regression curves were obtained by plotting absorbances vs concentrations (in each case) using respective blanks employed in the processes concerned the concentration rang 0.5, 1.0, 1.5.2.0 and 2.5 mcg/ml of the drug.

Drug- excipient compatibility studies:

Compatibility study using FTIR Technique: Drug–excipient compatibility study was carried out by FTIR (Shimadzu Affinity-1)spectrophotometery. The mixture of drug and KBr (potassium bromide) was ground into fine powder using mortar pestle and then compressed into discs in a hydraulic press at a pressure of 75 kg/cm 2 . Each KBr discs was scanned 45 times at a resolution of 2 cm -1 . The characteristic peaks were recorded and compared with that obtained with individual formulation.

Equilibrium solubility determination:

Solubility of Carvedilol in distilled water and buffer system: The solubility of Carvedilol was carried out in distilled water, acidic buffer (pH 1.2) and phosphate buffers (pH 5.8 & pH 6.8). The excess drug was added gradually to 30ml of each solvent contained in 250 ml volumetric flask and shaken on mechanicalshaker at room temperature for 12 hrs so that equilibrium solubility can be achieved and solutions were allowed to equilibrate for 24 hrs. Then after the solutions weretransferred into centrifuge tubes and centrifuged at about 2000 rpm for 5 minutes and filtered through Whatman filter paper no. 5

Aliquots of the filtrate were suitably diluted. The diluted solutions were analyzed at 241 nm against the reagent blank.

Preparation of solid dispersion and Physical mixture:

For preparation of solid dispersion containing Carvedilol and PEG 4000, PEG 400 in the ratio of 1:2(w/w), 8.9 ml of PEG 400, 10 gm of Polyethylene glycol 4000 and 1 gm of Carvedilol were used. Minimum (possible) quantity of methanolic solution (10%) at 80-85 o C contained in a 250 ml beaker was used to dissolved PEG 400, Polyethylene glycol 4000. Then Carvedilol was added to the beaker and a Teflon coated magnetic bead was dropped in it. Stirring of magnetic bead in beaker was started using a hot plate magnetic stirrer. Carvedilol got completely solubilized. Stirring was continued till a semisolid was obtained in the beaker which was spread on watch glasses in thin layers forquick drying. The watch glasses were kept in oven maintained at 60-65 o C for drying.When mass became pulverizable, it was triturated with the help of pestle mortar andkept in oven for drying. After almost complete drying, the powder of solid dispersionwas passed through sieve # 100 and kept for 6 days in dessicator containing bluesilica gel. After this the solid dispersion powder was stored in air tight bottles Similarly solid dispersion of carvedilol and PEG 400, Polyethylene glycol 4000 [1:4,1:6 (w/w)].

Preparation of Physical Mixtures:

To prepare physical mixture containing carvedilol and PEG 4000 and PEG 400 in ratio of 1:2 (w/w), accurately weighed (1 gm) Carvedilol, 8.9 ml of PEG 400, 10 gm of Polyethylene glycol 4000 were triturated intensely for 10 min using glass pestle mortar. Then the powder mass was shifted through sieve # 100.Similarly physical mixtures of carvedilol and PEG 4000, PEG 400 in ratio of [, 1:4 & 1:6 (w/w)] were prepared.

Evaluation of solid dispersion and physical mixture:

Determination of drug content in prepared solid dispersion and physical mixture: Powdered solid dispersion /physical mixture containing Carvedilol equivalent to 10 mg was accurately weighed and transferred to 100 ml volumetric flask. About 900 ml distilled water was added and thecontent shaken to dissolved the formulation completely. Finally the volume was adjusted with distilled water and the absorbance of this solution was measured at 241 nm against respective reagent blank. The drug content was determined using regression equation.

In-vitro dissolution studies of physical mixtures and solid dispersion: In vitro dissolution study was performed using USP type II apparatus (paddle type) at50 rpm using distilled water as dissolution media maintained at temperature 37 ± 0.5 C. Aliquots of dissolution media were withdrawn at specific time

intervals replacing with fresh media and filtered. The amount of drug dissolved was determined by U.V. spectrophotometric analysis of withdrawn sample at 241 nm.

Selection of solid dispersion for further formulation development: Based on the data of drug content and the dissolution studies, a suitable solid dispersion was selected for further formulation development (tablet dosage form).

Pre compression parameters:

Bulk density (D b): It is the ratio of total mass to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It was expressed in gm/cc and given by:

$$D_b = M / V_o$$

Where M= Mass of powder

Vo= Bulk volume of the powder

Tapped density (Dt): It is the ratio of total mass of powder to its tapped volume. The tapped volume was measured by tapping the powder to certain volume it was expressed in gm/cc given by:

$$D_t = M/V_t$$

Where, M= Mass of powder

Vt= tapped volume of the powder.

Angle of repose: The frictional forces in a loose powder can be measured by the angle of repose (θ) as the maximum angle possible between the surface of a pile of powder and the horizontal plane

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

h= height in cm.

r= radius

Carr's index (i): It indicated the ease with which a material could be induced to flow and expressed in percentage as given by

$$I = Dt\text{-}Db/Dt \times 100$$

Where, Dt =tapped density of the powder.

Db=bulk density of the powder.

Formulation of tablet:

Direct compression method: The tablets were formulated employing direct compression method using single punch tablet punching machine. Tablets were compressed directly from mixtures of the drug and excipients without preliminary treatment like granulation.

Screening of excipients: Nine trial batches of formulations were designed for screening of different type of release modifier polymer (controlled released polymer).Based on the experiments designed to develop the formulations. The tablet consisted of solid dispersion (equivalent to 12.5 mg Carvedilol), The weight of tablets in each batch was kept constant. Effect of various types of release modifier polymers(individual) and in combination with other, on various tablet properties and in-vitro dissolution characteristic were studied and discussed. Tablets were formulated using Carvedilol from its solid dispersion with different excipients viz. Eudragit RS 100 & Ethyl cellulose (release modifier), mannitol as diluents and magnesium stearate.

Formulation of controlled release tablets of Carvedilol: Total nine batches are prepared using different release modifier (polymers) alone and in combinations.

Formulation chart of controlled release tablet of Carvedilol:

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Soliddispersion (mg)	266.66	266.66	266.66	266.66	266.66	266.66	266.66	266.66	266.66
Eudragit RS 100 (mg)	40	80	120	-	-	-	40	80	60
Ethylcellulose (mg)	-	-	--	40	80	120	80	40	60
Mannitol (mg)	89.36	49.30	9.30	89.30	49.30	9.30	9.30	9.30	9.30
Mg. stearate (mg)	4	4	4	4	4	4	4	4	4
Total weight (mg)	400	400	400	400	400	400	400	400	400

Post compression evaluation parameters:

Hardness: The hardness of the tablet was determined using a Monsanto hardness tester and expressed in Kg/cm 2.

Friability (F): The friability of the tablet was determined using Roche Friabilator and expressed in percentage (%). 10 tablets were initially weighted (W initial) and transferred into the fraibilator operated at 25 rpm for four min. The percentage friability was then calculated the formula:

F= W initial- W final/ W initial × 100

Weight variation: 20 tablets were selected at random and average weights were determined. Then individual tablet was weighed and was compared with the average weight values.

Thickness: The thickness of the tablets was measured by screw gauge and expressed in mm.

Uniformity of drug content: Ten tablets were weighed and powdered in a mortar. Accurately weighed powdered samples (equivalent to 42.275 mg of Carvedilol) was transferred to a 100 ml volumetric flask

and dissolved in 75ml methanol. Finally, the volume was made to 100 ml with methanol. This solution was suitably diluted with pH 1.2 acidic buffer and the absorbance was measured at 241nm. The concentration was estimated in triplicate.

In vitro dissolution studies: In vitro drug release was carried out for all batches by using USP (TDL-06L) type I dissolution test apparatus. The dissolution studies were carried out in pH 1.2 acidic buffer for 2 hrs. followed by pH 5.8 for 4 hrs. & pH 6.8 phosphate buffer up to 12 hrs. Similarly the parallel evaluation of dissolution parameter were conducted in simulated gastric (pH 1.2) accomparsied by simulated intestinal fluid (pH5.8 & ph 6.8) sequentially. The tablet was kept into the basket. The temperature and stirring rate were maintained at 37 ± 5 o C and 100 rpm respectively. 5 ml sample were withdrawn in each case, diluted suitably and analyzed for the drug content spectrophotometrically at λ max 241 nm using dissolution media (pH 1.2, pH5.8 & 6.8 phosphate buffer, simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 5.8 and pH 6.8) as blank.

Comparison of dissolution profile: Data obtained from the in vitro release of carvedilol matrix tablet formulation (F1-F9)were fitted to various kinetic equations i.e. as zero order, first order, Higuchi model and Korsmeyer-Pappas model.

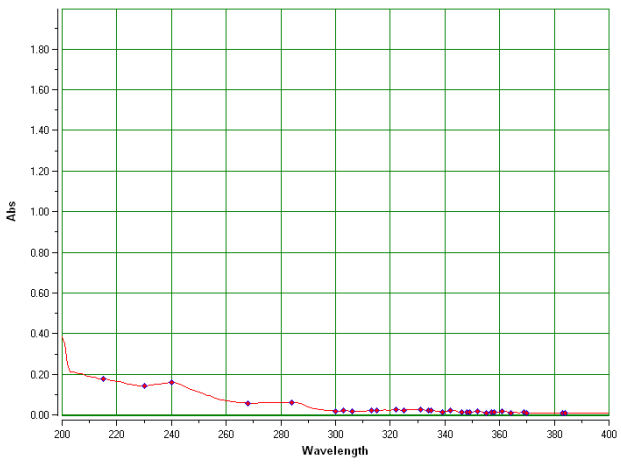
Stability study: The stability study of drug loaded matrix tablet was carried out for a period of 90 days at 40±2 o C temperature and relative humidity of 75±5% using stability chamber. Samples was collected after 90 days and evaluated for drug release.

RESULT AND DISCUSSION

Pre-formulation parameters for raw material: Pre-formulation parameter like foreign matter, moisture, water soluble extractive, alcohol soluble extractive, ash value, acid insoluble ash value was determined for herbs used in formulation.

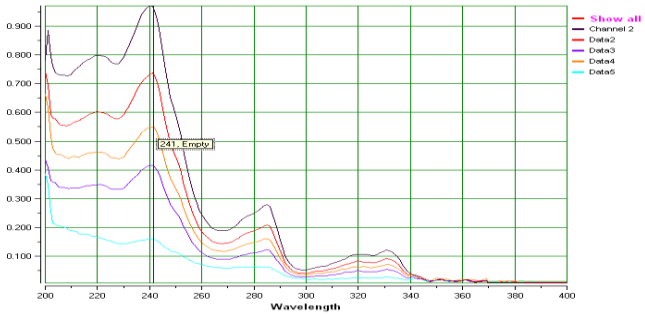
Determination of melting point: The melting point of Carvedilol was found to be 115 C.

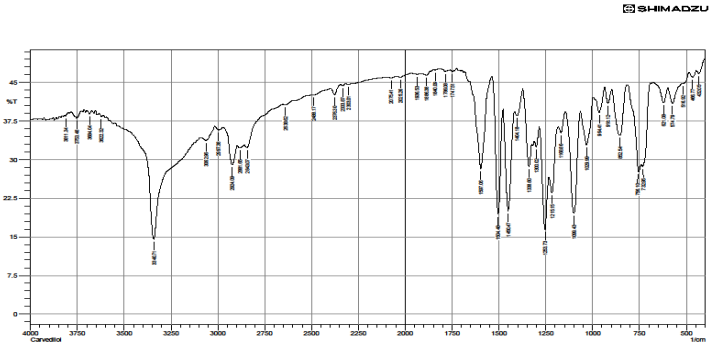
UV spectrophotometric scan of carvedilol: -



The stock solution of carvedilol was prepared using acidic buffer (pH 1.2). A randomly selected sample containing the drug (5µg/ml) was scanned between 200-400nm. The λ max was found to be 241nm.

Validation of λ max : -The samples containing different concentrations (5-25µg/ml) of the drug were run and overlain spectra describing the reproducibly of the λ max (earlier scanned) was obtained that confirmed and validated the process.





FTIR Analysis: IR absorption spectrum of Meloxicam was obtained by means of KBr pellet technique and peaks attained were compared with the reference as depicted in table 4.3, which demonstrate the distinct peaks of some functional groups. Similarly IR spectrum of drug and excipients i.e. Niacinamide, Anhydrous Sodium Citrate, Croscarmellose Sodium, Sodium Benzoate and Sodium Salicylate were obtained.

Pre-compression parameters for formulations of factorial designs: Pre compression parameters of diverse formulation blends (F1-F9) were calculated. Post-compression parameters of factorial designed formulations Post compression parameters i.e. Thickness, Hardness, Weight Variation, Friability and D.T for samples of diverse formulation (F1-F9), were calculated.

Post-compression parameters for formulations of factorial designs: The samples from each batch of tablet formulation were evaluated for post compression parameters such as thickness, weight variation, hardness, friability & disintegration time.

Post –compression parameter of tablets: Post compression parameter of formulation F 1 to F 9

	Thickness (mm)	Weight variation	Hardness (kg/cm 2)	Friability (%)	Drug content(%)
F1	2.48	Pass	5.30	0.975	94.00
F2	2.51	Pass	5.40	0.974	93.95
F3	2.51	Pass	5.90	0.974	92.11
F4	2.53	Pass	4.90	0.950	90.88
F5	2.51	Pass	5.08	0.875	90.26
F6	2.50	Pass	5.20	0.990	92.75
F7	2.51	Pass	6.00	0.977	95.58
F8	2.33	Pass	6.40	0.992	97.10
F9	2.42	pass	6.60	0.995	95.24

In-vitro dissolution rate studies of Formulation F 1 - F 9 in acidic buffer (pH1.2) and 5.8 pH & pH 6.8 phosphate buffer:

Sr. no	Time (minutes)	F1(%drug release)	F2(%drug release)	F3(%drug release)
1	0	0.000	0.00	0.00
2	30	12.960	13.680	9.900
3	60	35.412	27.676	22.255
4	120	43.577	41.074	26.584
5	180	57.509	49.695	29.731
6	240	62.653	52.676	46.699
7	300	65.748	59.359	51.259
8	360	76.565	64.196	56.018
9	420	80.131	69.578	61.638
10	480	90.382	78.450	67.921
11	540	94.165	82.036	75.788
12	600	94.249	92.729	84.042
13	660	94.503	92.789	86.930
14	720	94.504	92.789	88.967

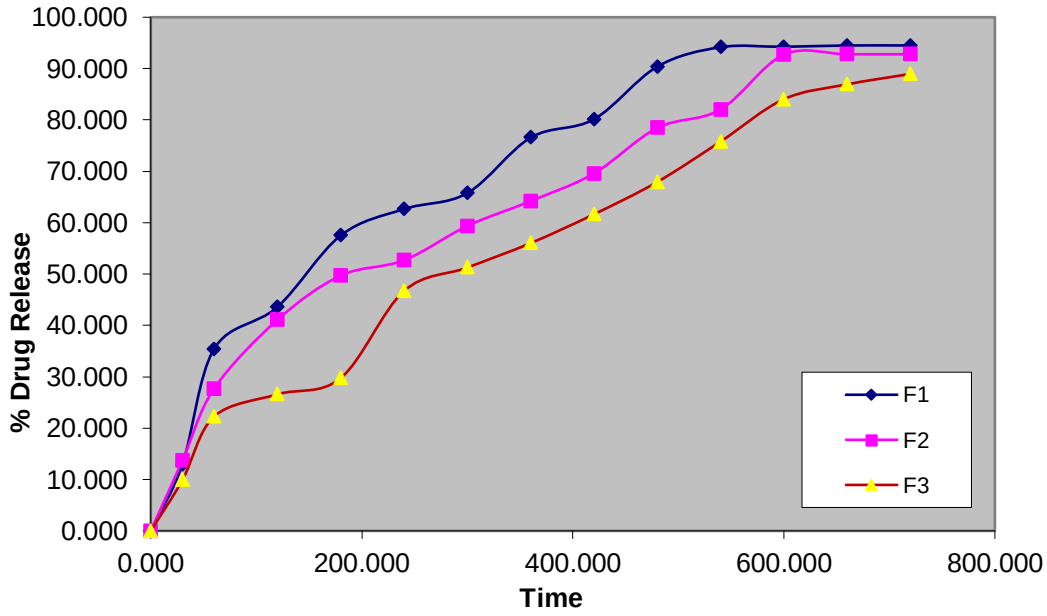


Fig: Zero order drug release of F 1, F 2 & F 3 batches in in acidic buffer (pH 1.2) and pH 5.8 and pH 6.8 phosphate buffer:

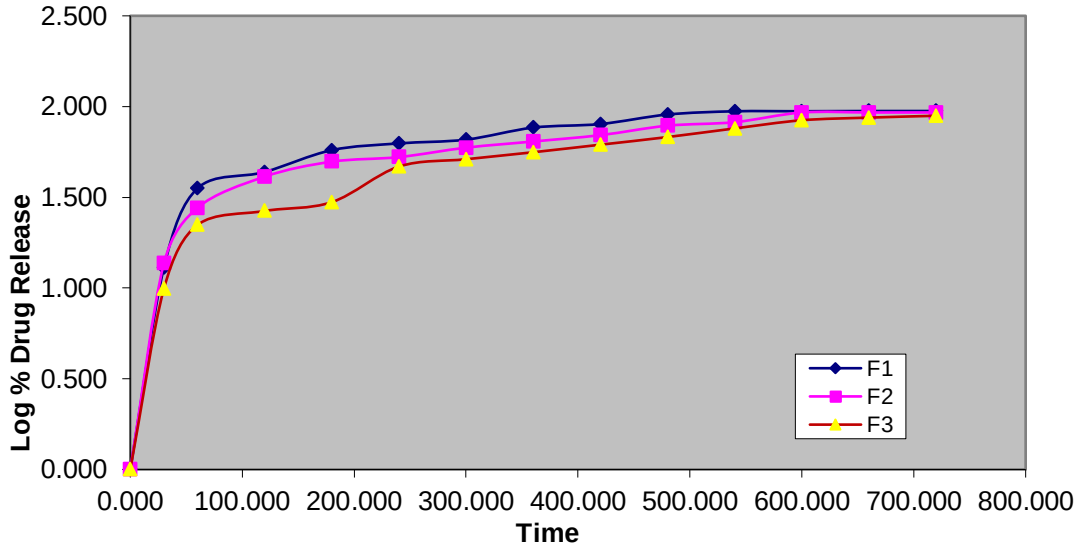


Fig: First order drug release of F 1, F 2 & F 3 batches in in acidic buffer (pH 1.2) and pH 5.8 and pH 6.8 phosphate buffer:

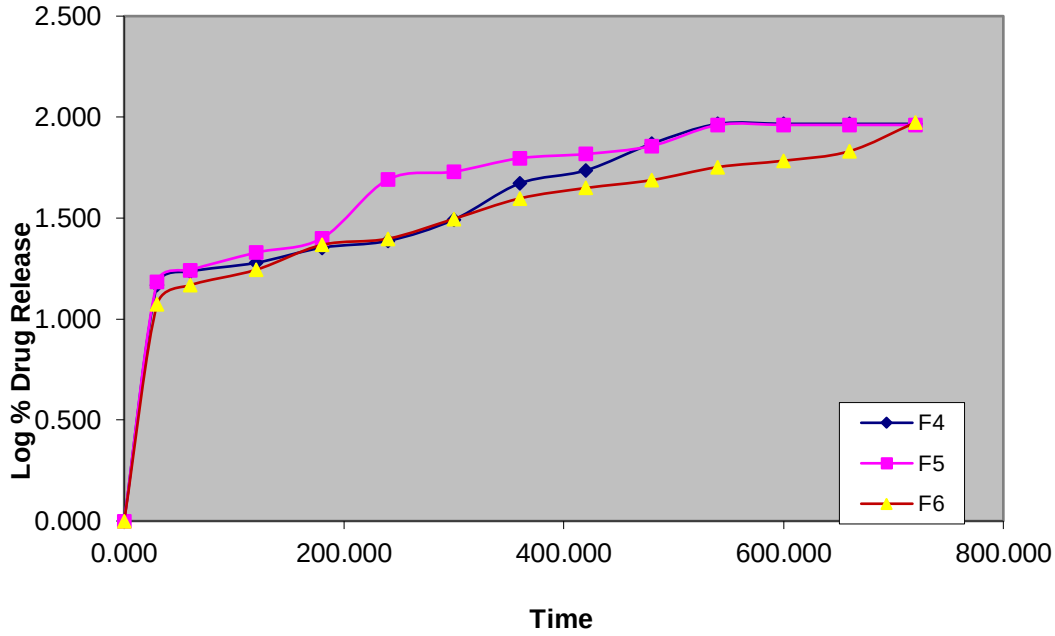


Fig: First order drug release of F 4, F 5 & F 6 batches in in acidic buffer (pH 1.2) and pH 5.8 and pH 6.8 phosphate buffer:

CONCLUSION:

So far the analysis was carried out on "Formulation and evaluation of controlled release tablets of carvedilol using hydrotropic technique" revealed following conclusions:

FTIR & uv spectrometric scan of carvedilol analysis were carried out. The characteristic peaks of the drug were compared in pure form with those obtained with drug-excipient combinations which remained almost the same of pure drug and that of drug-excipients combinations resulted approximately equivalent Rf values. Conclusively carvedilol was found to be compatible with excipients used tablet formulations.

Equilibrium solubility testing was carried out and its results concluded that the diluted solution were analyzed at 241nm against reagent blank relative to its aqueous solubility by using hydrotropy.

Among the trial batches of formulations, optimized results were attained with T3, which was further integrated into factorial design and developed as (F1-F9). other parameters of pre-compression calculated by the powdered blends were Bulk Density , Tapped Density , Angle of Repose , Carr's Index and Hausner,s Ratio . These formulations were exposed to different evaluation parameters for the analysis of post-compression parameters and the results were implicated:

Hardness , Thickness , Friability , Weight variation, Disintegration time and In-vitro drug release determination. The In-vitro release of drug was carried out by using USP(TDL-06L)TYPE 1 dissolution test apparatus. The stability test studies was conducted with optimized formulation in compliance with the ICH guidelines under officially defined conditions that showed that theformulations were stable and thus met the dose conformity criterion.

The present worker proposed that such a concept of formulation could be extended to drugs of various classifications lighting the way for prospective researchers to improve aqueous solubility and to devise more oral dosage forms with potential enhanced bioavailability.

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