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Research Article

FORMULATION AND EVALUATION OF ORAL CONTROLLED DRUG DELIVERY SYSTEM FOR A MODEL ANTI DIABETIC DRUG METFORMIN

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ABSTRACT

Metformin is poorly water soluble drug, so solubility is the main constraint for oral its bioavailability. An attempt has been made to increase the solubility of this model drug by formulating Matrix tablet Hydroxylpropyl methylcellulose (HPMC), Ethyl cellulose and PVP and Carbopol-934 polymer to control the release of drug with a view to develop Controlled release dosage form. Tablet formulations were prepared by direct compression technique and were evaluated for Precompression and post compression parameters. Among different formulations of direct compression containing drug is to polymer ratio 1:2 gives best dissolution profile and dissolution efficiency and among tablet formulations F1, F4, F11 Dissolution profiles compared with other formulations. Results showed that Hydroxylpropyl methylcellulose (HPMC) and Ethyl cellulose is promising polymer for enhancing the solubility of metformine. They are found to be with good physical integrity, free from any drug-polymer interaction and the results provided a method of achieving controlled drug action through uniform drug release.

Keywords: - Metformin HCl, HPMC E-5O, Carbopol -934, Ethyl cellulose and PVP Controlled release.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site of the body, to promptly achieve and then maintain the desired therapeutic drug concentration that elicits the desired pharmacological action and to minimize the incidence and the severity of unwanted adverse effects. To achieve this goal, it would be advantageous and more convenient to maintain a dosing frequency to once, or twice-daily regimen. An appropriately designed extended release dosage form can be a major advance in this direction compared to conventional immediate release dosage form. The development of improved method of drug delivery has received a lot of attention in the last two decades [1, 2].Among various technologies available, monolithic matrices-matrix tablets continue to be popular because of simple processing technologies required, reproducibility, and stability of the materials and dosage form as well as ease of scale-up operation.

In particular, the interest awakened by matrix type deliveries is completely justified in view of their biopharmaceutical and pharmacokinetics advantages over the conventional dosage forms. These are release systems for delay and controlled release of a drug that is dissolved or dispersed in a resistant support to disintegration. During the last two decades swelling polymers are being used as sustained or controlled release devices[3, 4]. Metformine is a third generation oral hypoglycemic drug used to treat type II diabetes mellitus. It has shown high anti-diabetic activity and is very effective in type II diabetes mellitus in addition to low toxicity. However, Metformine is practically insoluble in aqueous fluids, and as such its oral absorption is dissolution rate limited. Therefore, it displays poor solubility in GI fluids, which results in low and erratic oral bioavailability. It was selected as a model drug for dissolution enhancement studies in the present investigation. Attempts were made to enhance the dissolution of Metformine using a DC technique[5, 6, 7].

MATERIAL AND METHOD

Metformin hydrochloride was obtained from Strides Acro labs Ltd, Bangalore. , HPMC-E50, Ethyl cellulose, Povidone, Carbopol-934 were obtained S. D. Fine Chemicals Ltd.

Direct compression

The drug and excipients were passed through sieve no. 60 prior to the preparation of the dosage form. The entire ingredients were weighed separately and mixed thoroughly for 10 minutes to ensure uniform mixing in geometrical ratio. The tablets were prepared by direct compression technique using 10 mm punch in 10-station rotary machine; Rimek Machine.

Bulk density (D_b)

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduated measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by $\mathbf{D_b = M / V_0}$ Where, M is the mass of powder, V_0 is the bulk volume of the powder.

Tapped density (D_t)

Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by, $\mathbf{D_t = M / V_t}$ Where, M is the mass of powder. T_{Vs} is the tapped volume of the powder.

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height 'h, above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using following equation, $\mathbf{\theta = Tan^{-1} (h/r)}$ Where θ =Angle of repose, h=Height of pile, r=Radius of the base of the pile.

Carr's Consolidation Index (I)

Carr's index is an indication of the compressibility of a powder. It is expressed in percentage and is given by $\mathbf{I = D_t - D_b / D_t \times 100}$ Where Dt=Tapped density, D_b=Bulk density.

Thickness and diameter

Control of physical dimensions of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier Calipers. It is measured in mm.

Hardness

The Monsanto hardness tester was used to determine the tablet hardness .The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. It is expressed in kg/cm^2.

Friability (F)

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions in 4 min and were dedusted. The

percentage weight loss was calculated by reweighing the tablets. The % friability was then calculated by: -

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \times 100$$

Weight variation as per IP

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit. IP limit for weight variation in case of tablets weighting up to 120 mg is ± 10%, 120 mg to 300 mg is ± 7.5% and more than 300 mg is ± 5%.

$$\mathbf{PD = (W_{avg}) - (W_{initial}) / (W_{avg}) \times 100}$$

Where PD= Percentage deviation, W_{avg} =Average weight of tablet, $W_{initial}$ =Individual weight of tablet.

Drug content

Tablets equivalent to 100mg of drug were accurately weighed and transferred to 50ml volumetric flask. To this flask, sufficient amount of distilled water was added to dissolve the tablets completely. Then, the volume of flask was made up to the mark with same solvent. From this solution, 1ml of the sample was pipette out and transferred to 10 ml volumetric flask. The volume in the second flask was made up to the mark with distilled water. From this 0.6ml, 0.8ml, and 1ml sample was withdrawn and volume was made up to 10ml to maintain concentration within the beer's range. This final diluted solution was estimated UV spectrophotometrically at 232nm.

In vitro Release studies

In vitro dissolution studies for all the Matrix tablets were carried out using USP type II Dissolution apparatus in 500 ml of phosphate buffer (pH 6.8) as dissolution media, maintained at 37±0.5ºC at 50 rpm. 0.5 ml aliquots were withdrawn at every 1 hour and replaced by 0.5 ml of fresh dissolution media (37ºC). The collected samples were analyzed after suitable dilution (if required) at 232 nm using UV-visible spectrophotometer against phosphate buffer (pH 6.8) as the blank.

RESULTS AND DISCUSSION

The characterizations of different formulation were done for determination of mass-volume relationship parameters. The evaluated parameters are bulk density, tapped density, compressibility index, and angle of repose, Carr's index shown in table 1.

The bulk density of the powder for trial batch and also for optimized formulation of direct compression was in the range of 0.41-to 0.52gm/cc; the tapped density was in the range of 0.40 to 0.56gm/cc, which indicate powder was not bulky. The angle of repose of the drug powder was in the range of 17 ^{0} to 26 ^{0}, which indicate good flow of the powder, the Carr's index was found to be in the range of 3-6 indicating compressibility of the tablet blend is good.

Table 1: Pre-compression parameter for direct compression

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose (^{0})	Carr's index (%)
F-1	0.4274	0.4559	20.56	6.2513
F-2	0.4918	0.5152	18.57	4.5419
F-3	0.4612	0.4804	18.76	3.9966
F-4	0.4276	0.4090	17.87	4.3498
F-5	0.4108	0.4350	22.00	5.5686
F-6	0.4210	0.4432	21.06	5.0104
F-7	0.4373	0.4572	26.98	5.0246
F-8	0.4371	0.4644	25.70	5.8839
F-9	0.5263	0.5614	24.66	6.2522
F-10	0.4771	0.5070	23.54	5.9011
F-11	0.4713	0.5007	22.15	5.8905
F-12	0.4890	0.5195	25.65	5.8830
F-13	0.4236	0.4456	23.43	4.9371
F-14	0.4432	0.4701	24.23	5.7221

Table 2: Post-compression parameter for direct compression

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Avg. Weight Variation (mg)
F-1	10 ± 0.3	6.56 ± 0.04	0.300	350 ± 2.12
F-2	10 ± 0.2	6.55 ± 0.03	0.315	349 ± 3.01
F-3	9 ± 0.2	6.51 ± 0.01	0.322	347 ± 2.55
F-4	10 ± 0.1	6.52 ± 0.03	0.278	354 ± 3.11
F-5	8 ± 0.2	6.55 ± 0.01	0.290	351 ± 3.41
F-6	8 ± 0.3	6.55 ± 0.03	0.321	355 ± 1.21
F-7	10 ± 0.2	6.56 ± 0.03	0.285	350 ± 2.12
F-8	9 ± 0.3	6.54 ± 0.05	0.311	351 ± 2.31
F-9	9 ± 0.2	6.51 ± 0.05	0.319	350 ± 3.43
F-10	8 ± 0.4	6.54 ± 0.02	0.292	354 ± 1.22
F-11	10 ± 0.2	6.53 ± 0.02	0.298	354 ± 1.19
F-12	10 ± 0.1	6.54 ± 0.04	0.322	353 ± 3.03
F-13	10 ± 0.2	6.55 ± 0.01	0.329	350 ± 1.32
F-14	8 ± 0.3	6.53 ± 0.02	0.300	352 ± 2 07

The compressed tablets were tested for physical parameters like hardness, thickness, friability, weight variation evaluated for the drug content, *in- vitro* drug release profiles and stability studies.

Hardness, Thickness, Friability and Avg. weight variation of the tablet by direct compression were found to be 8-10 kg/cm^2 and 6.51-6.56 mm, 0.27-0.32% respectivey. Avg. weight variation of the tablet by direct compression was predicted that all the tablets exhibited uniform weight with low standard deviation values within the acceptable variation as per IP shown in table 2.

Drug release studies

In- vitro dissolution studies were performed for all the formulations using USP type II tablet dissolution tester employing basket type at 50 rpm using 500 ml of 0.1N HCl and 6.8 phosphate buffer dissolution medium. The samples withdrawn were analyzed by using UV spectrophotometer. In direct compression, F1, F4, F11 are shown good drug release shown in figure (1& 2), F3 is shown less drug release may be due to the presence of PVP.

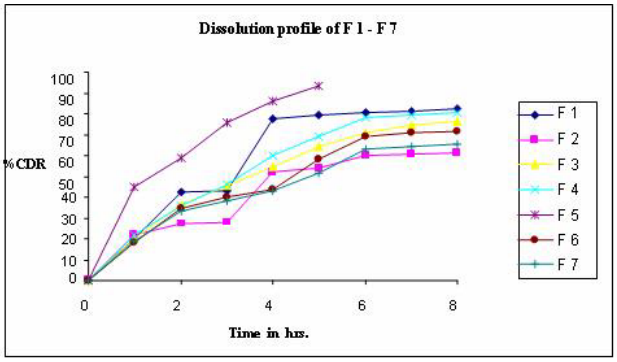

Fig. 1: Dissolution study for direct compression (F 1 – F 7)

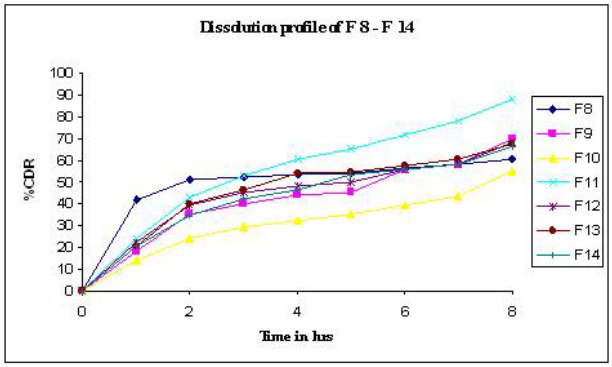

Fig. 2: Dissolution study for direct compression (F 8 – F 14)

CONCLUSION

Based on the Results and discussion, we can concluded that Controlled release tablets of Metformin HCl were prepared successfully by direct compression using the combination of different concentration of polymers like HPMC-E50, EC, PVP and carbopol-934 and other excipients such as magnesium stearate as lubricant, talc as glident and lactose as diluent were found to be good without chipping, capping and sticking.

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