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FORMULATION AND EVALUATION OF HYDROXYPROPYL METHYLCELLULOSE (HPMC) BASED MATRIX TABLET OF METOPROLOL TARTRATE

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ABSTRACT

Increased complications and costs of marketing of innovative drugs focused greater attention to the development of sustained release (SR) or controlled release (CR) drug delivery systems. Delivery systems extended release or controlled release rate can achieve predictable and reproducible, the extended duration of activity for the short time of life-drugs, reduced toxicity, and dose reduction request, the optimized therapy and better patient compliance. It is controlled primarily by the type and the proportion of the polymers used in the preparation. Metoprolol tartrate is a cardioselective β1-adrenergic blocking agent used for acute myocardial infarction (MI), heart failure, angina pectoris and mild to moderate hypertension. It may also be used for supraventricular and tachyarrhythmias and prophylaxis for migraine headaches. The objective of present work was to develop and evaluated oral sustained release matrix tablet of metoprolol tartrate prepared by the method of direct compression, using hydroxy propyl methyl cellulose (HPMC) and tragacanth polymer alone and in combination at various concentrations. Pre-compression parameters were evaluated. The tablets were evaluated for post-compression parameters such as thickness, hardness, average weight, friability and In vitro release studies. No interactions were observed between metoprolol tartrate and excipients from the Fourier transform infrared spectroscopy. The present research work was successful in improving the efficacy metoprolol tartrate oral therapy as the drug release was extended for 24 hours thus reducing dosing frequency thereby improving patient compliance. The study also revealed the applicability of HPMC K-15, tragacanth and PVP K25as rate-controlling polymers in matrix tablets. The hydrophilic matrix of HPMC alone cannot control the release metoprolol tartrate effective for 24 h while when combined with tragacanth, may slow down the release of the drug and therefore, can be successfully employed for the formulation of matrix tablets SR. It may be concluded from the study that, the optimized formulation F-1 was shown maximum drug release 99.78% in 24h of dissolution.

KEYWORDS: Metoprolol tartrate, Pre/post-compression parameters, Direct compression, HPMC, Tragacanth.

INTRODUCTION

The conventional dosage forms such as tablets and capsules are the major oral preparations and have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance in last two decades.[1] Sustained release dosage forms are the formulations which release the therapeutically active agents for longer period of time at expected rate after its single dose administration.[2] When highly water soluble drugs are prepared as oral sustained release dosage form cause problems like they may be released more rapidly and result in toxicity if not prepared in appropriate fashion.[3] Many methods are there to formulate oral sustained release dosage form among which matrix system is most appropriate due to consistency, validation, scale up and cost effective.[4] Microcrystalline cellulose and PVP were used as diluents and binder respectively. Oral CR systems present a variety of benefits above conventional dosage forms that include decrease in dosage rate, patient ease, minimum toxicity and improved patient compliance.[5] On the other hand, more constant level of drug in the blood constant flow with minimum peak-valley is reached, achieve greater efficacy. HPMC has been employed extensively as hydrophilic matrix former in oral controlled-release dosage forms for different drugs. Its popularity can be attributed to the polymer's non-toxic nature, small influence of processing variables on drug release, ease of compression, and its capability to accommodate high levels of drug loading, its ability to swell upon jellification once in contact with water.[6-8] Tragacanth is a naturally occurring dried gum obtained from

Astragalus gummifer Labillardiere and other species of Astragalus. The gum consists of a mixture of water-insoluble and water-soluble polysaccharides. Bassorin, which constitutes 60% to 70% of the gum, is the main water-insoluble portion, while the remainder of the gum consists of the water-soluble material, tragacanth. Tragacanth gum is used as an emulsifying and suspending agent in a variety of pharmaceutical formulations. It is used in creams, gels, and emulsions at various concentrations according to the application of the formulation and the grade of gum used.[9] Metoprolol is a cardioselective beta-blocker and it is used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, and heart failure. The half-life of the metoprolol is stated to be 3ñ4 h. Metoprolol tartrate, with its incomplete oral bioavailability (due to extensive first-pass metabolism), short half-life, and multiple daily dosing, is appropriate for a formulation in a once-a-day extended-release dosage form. Therefore, metoprolol tartrate is the ideal candidate for sustained release system because it is water-soluble and has a short half-life.[10] Hence, in the present study, an attempt has been made to develop sustained release matrix tablets of metoprolol tartrate using the synthetic polymers like HPMC K-15 and natural polymers like tragacanth and fixed to retard the drug release up to 24 h.

MATERIALS AND METHODS

Materials

Metoprolol tartrate were obtained as pure sample from Sun Pharmaceutical Industries Ltd. Dewas, as gift samples along with their analytical reports. HPMC K15M was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Tragacanth, Polyvinyl Pyrrolidone K 25, Lactose and Talc were purchased from SD Fine Chem. Limited, Mumbai. Magnesium stearate was purchased from Loba Chemie Pvt. Ltd, Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Methods

Preformulation studies

Organoleptic properties: It refers to the evaluation by sensory characters i.e. taste, odour, colour.

Solubility studies: The solubility of the drug is an important physicochemical property because it affects the bio availability of the drug, the rate of drug release into dissolution medium consequently the therapeutic efficiency of the pharmaceutical products. The solubility of the drug in various solvents is determined as a first step. This information is valuable in developing a formulation.

FT-IR spectroscopy: Infra-red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound. The region from 0.8 µ to 2.5 µ is called near Infra-red and that from 15 µ to 200µ is called far infra-red region.

Spectrophotometric analysis of metoprolol tartrate

First of all calibration of all glassware's was carried out. Accurately weighed 10 mg of drug and dissolved in 10 ml of water in a volumetric flask and suitable diluted to make it to a concentration of 1000 µg/ml, this is called stock solution. Then 1 ml of solution is pipette out from aliquot and added distilled water to make volume up to 10 ml. The concentration of drug in sub stock solution is 100µg/ml. Then make suitable dilutions of 5, 10, 15, 20, 25 µg/ml. The absorbance was taken on UV spectrophotometer using λ_{max} at 280 nm. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Pre compression evaluation

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, tapped density, carr's index, and hausner's ratio.

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation**.**

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

Where, h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index**.**

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula.[15,16]

Hausner's ratio = Tapped density/Bulk density.

FORMULATION DEVELOPMENT OF TABLETS

Direct compression method

The tablets were compressed by the direct compression method, in this method all the ingredients was weigh accurately and transferred into a mixer jar and mixed properly for 15 minutes. After proper mixing of powder sieve from 80 meshes, and after sieving tablets was compressed by using mini press-I tablet compression machine.

Table 1: Composition of metoprolol tartrate matrix tablet.

Ingredients	F1	F2	F3	F4
Metoprolol tartrate	100	100	100	100
HPMC E-15	280	-	140	150
Tragacanth	-	280	140	150
PVP K-25	20	20	20	-
Magnesium stearate	2.5	2.5	2.5	2.5
Talc	97.5	97.5	97.5	97.5
Total	500	500	500	500

Evaluation of metoprolol tartrate matrix tablets

Thickness test

The thickness of the tablet was measured by using digital venire caliper, ten tablets were randomly selected from each batch and thickness was measured.

Hardness test

The hardness of the tablets was measured using Monsanto tablet hardness tester, for each batch three tablets were tested.

Friability

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolution the tablets were dusted and weighed again. The observed value should not be more than 1%. The percentage friability was measured using the formula:

$$\% F = \{1-(Wt/W)\} \times 100$$

Where, % F = friability in percentage, W = Initial weight of tablets, Wt = weight of tablets after revolution

Weight variation test

Twenty tablets were randomly selected from each batch individually weigh, the average weight and standard deviation of 20 tablets was calculated.

Drug content uniformity

Five tablets were weighed individually, and the drug was extracted in water the solution was filtered through 0.45-µ membrane. The absorbance was measured at 280 nm after suitable dilution.

In-vitro dissolution study

The in vitro dissolution study of formulated metoprolol tartrate matrix tablets were carried out using USP apparatus Type-II in 500 ml of phosphate buffer solution (pH 6.8) at 37°C ± 0.5C at a rotational speed 50 rpm. At 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 24 h after starting the test, 10 ml sample of dissolution medium were withdrawn and analyzed spectrophotometrically at 280 nm by using Shimadzu-1800 UV/visible spectrophotometer. An equal volume of fresh dissolution medium, maintained at the same temperature, was added after withdrawing each sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally (r =0.9995).

RESULTS AND DISCUSSION

Solubility of metoprolol tartrate was freely soluble in water and methanol, slightly soluble in acetonitrile and ethanol, soluble after heating in ethyl acetate. The melting point of metoprolol tartrate was 121-123ºC and λ_{max} of metoprolol tartrate was found to be 280nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25 µg/ml Fig.1. Identification of metoprolol tartrate was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification Fig.2. Tablet powder blend was subjected to various pre-compression parameters Table 2. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.451 to 0.465 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.523 0.539 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 11.597 to 15.084 which show that the powder has good flow properties. All the formulations have shown the Hauser's ratio ranging between 1.131 to 1.178 indicating the powder has good flow properties. The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight. The hardness of the tablets ranged from 4.0 to 4.8kg/cm^2 and the friability values were less than 0.9% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 4.5 to 4.7mm. All the formulations satisfied the content of the drug as they contained 96 to 98 % of metoprolol tartrate and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control. The tablets were evaluated for in vitro dissolution studies in phosphate buffer solution (pH 6.8) for 24 hours. The results of in-vitro drug release revealed that the metoprolol tartrate was released in a controlled manner from all the formulations where formulation F1 showed maximum drug release i.e. 99.78% at the end of 24th hour. The results of release studies of formulations F1 to F4 are shown in Table 4 and Figure 3.

Table 2: Result of pre-compression properties of metoprolol tartrate matrix tablets.

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's index	Hauser's ratio
F1	0.458	0.523	12.428	1.142
F2	0.465	0.526	11.597	1.131
F3	0.458	0.539	15.028	1.177
F4	0.456	0.537	15.084	1.178

Table 3: Results of post compression properties of metoprolol tartrate matrix tablets.

Batch Code	Thickness (mm)	Deviation in weight variation test (%)	Drug content (%)	Hardness (kg/cm^2)	Friability (%)
F1	4.5	500±1.2	96.37±0.02	4.0±0.25	0.85±0.05
F2	4.5	500±0.08	98.55±0.12	4.6±0.15	0.71±0.04
F3	4.7	499±1.22	96.51±0.02	4.6±0.16	0.73±0.03
F4	4.5	500±1.21	97.50±0.03	4.8±0.23	0.68±0.11

Table 4: *In vitro* dissolution profile of metoprolol tartrate.

Time (hrs)	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
1	29.38	24.33	22.84	18.92
2	33.78	27.02	25.75	24.21
3	42.35	36.12	32.39	28.61
4	49.56	44.27	40.35	34.04
5	58.43	53.56	49.71	40.57
6	69.64	63.66	56.51	45.76
7	75.49	69.25	63.71	50.76
8	88.46	71.88	65.74	55.26
10	92.48	77.75	72.71	60.33
12	99.58	86.01	79.40	65.09
24	99.78	98.06	99.99	95.27

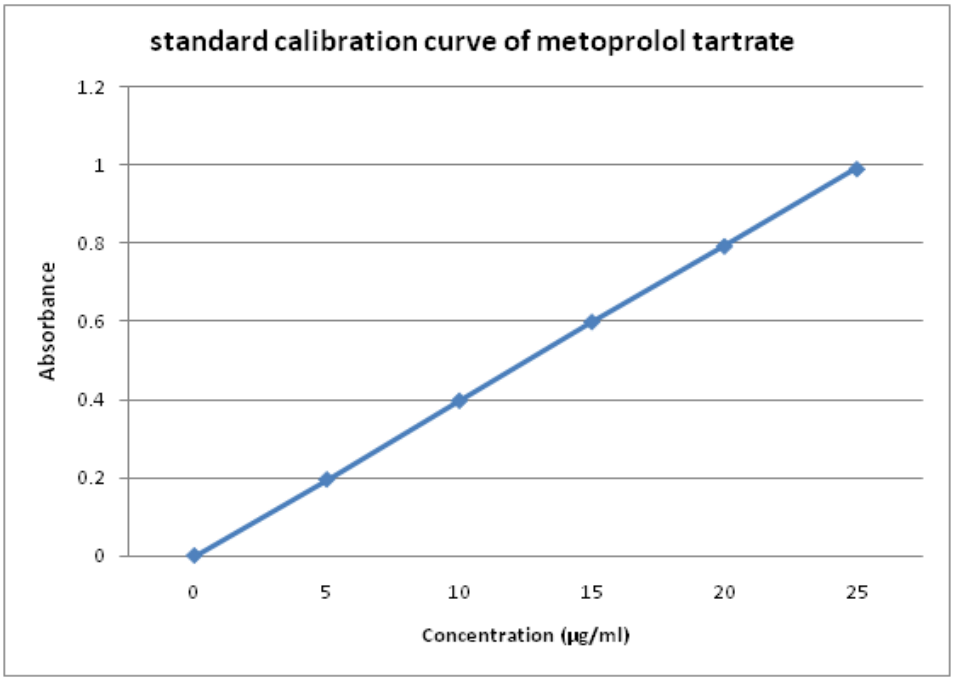

Fig. 1: Calibration curve of metoprolol tartrate at 280 nm.

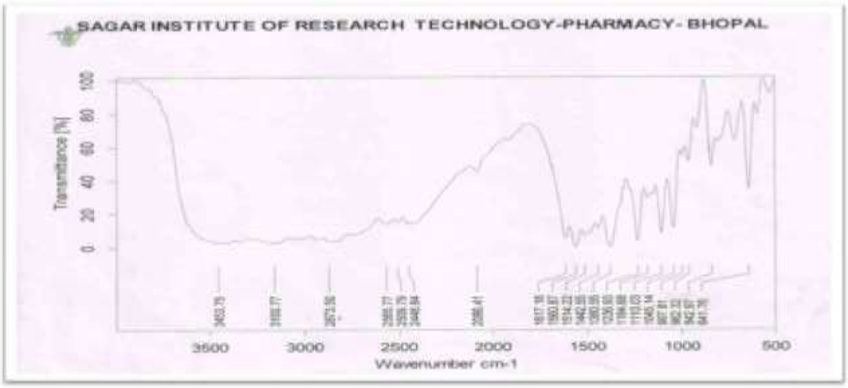

Fig. 2: FT-IR Spectrum of pure drug (metoprolol tartrate).

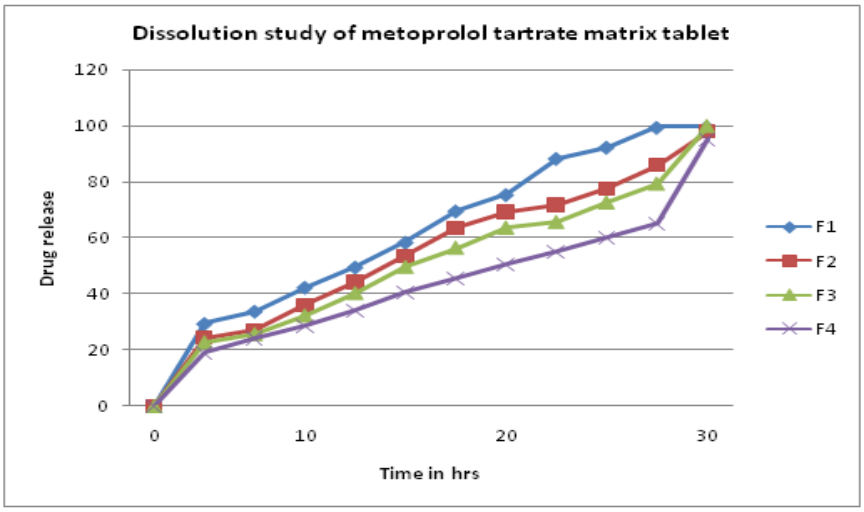

Fig. 3: *In-vitro* drug release study of matrix tablets.

CONCLUSION

In the current study indicate that the matrix tablet of metoprolol tartrate prepared using HPMC E-15, tragacanth and PVP K-25 can successfully formulated. We concluded that both hydrophilic and hydrophobic polymers plays a major role for the sustained release of metoprolol tartrate, both types of polymers are influence the release rate of drug. All the formulations showed diffusion dominated drug release. Above discussion concludes that matrix tablets are helpful to overcome the patient compliance and efficiency of dosage form in eliciting desired therapeutic response related problems associated with the conventional dosage forms. Cost effectiveness and once-daily dose are the plus points along with other benefits. Hence, sustained-release matrix tablets trends towards the optimization of the dosage form design. The controlled release drug delivery system aims to release the drug at the desired rate over extended period of time to maintain the therapeutic level in blood. Nowadays, the oral route of administration for controlled release drug delivery system has received more attention due to its more flexibility, reduced dosing frequency and better patient compliance. The design of oral controlled release drug delivery system depends on various factors like, physic chemical properties of drug, type of delivery system, disease being treated, patient condition, treatment duration, presence of food, gastrointestinal motility and co-administration of other drugs. From the above discussion, we can conclude that the controlled release drug delivery system is very helpful in increasing the efficiency of the dose as well as the patient compliance. Moreover; the reasonable cost of oral controlled release drug delivery system has lead ease of market penetration as replacement of oral conventional drug delivery system.

REFERENCES

1. Gujar, K.N., Nemmaniwar, S.B., Kulkarni, N.B. and Jamkar, P.M. Formulation and evaluation of gastroretentive nanoparticles of Repaglinide. *Int. J. Pharm. Sci. Nanotech*, 2014; **7**: 2363-2370.
2. Hoffman A. Pharmacodynamic aspects of sustained release preparations. Adv Drug Deliv Rev., 1998; 33(3): 185-99.
3. Reddy KR, Mutalik S, Reddy S. Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation. AAPS Pharm Sci Tech., 2003; 4(4): 480-8.
4. Sharma G, *et al*. Recent trends in pulsatile drug delivery systems-A review. International Journal of Drug Delivery, 2010; 2(3).
5. Augsburger LL, Zellhofer MJ. Tablet formulation. Encyclopedia of Pharmaceutical Technology, 2006; 3641-52.

6. Gil, E.C.; Colarte, A.I.; Bataille, B.; Pedraz, J.L.; Rodrigez, F.; Heinamaki, J. Development and optimization of a novel sustainedrelease dextran tablet formulation for propranolol hydrochloride. Int. J. Pharm., 2006; 317(1): 32-39.
7. Lopez, C.M.; Lobo, J.M.S.; Pinto, J.F.; Costa, P. Compressed minitablets as a biphasic delivery system. Int. J. Pharm., 2006; 323: 93-100.
8. Varshosaz, J.; Tavakoli, N.; Eram, S.A. Use of natural gums and cellulose derivatives in production of sustained release metoprolol tablets. Drug Del., 2006; 13(2): 113-119.
9. Reza M., Jalali M.B., Monajjemzadeh F., Ghaffari F., Azarmi S.: AAPS PharmSciTech., 2005; 6: 77.
10. Tomuta, I., Leucuta S.E.: Drug Dev. Ind. Pharm., 2007; 33: 1070.