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EFFECT OF PROCESSING AND POLYMER VARIABLES ON INVITRO RELEASE OF METOPROLOL SUCCINATE EXTENDED RELEASE TABLETS

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ABSTRACT

The present study was aimed to develop an extended release tablet of Metoprolol Succinate for the treatment of hypertension. Four extended release formulations F1-F4 were developed using varying proportions of Hydroxyl propyl methyl cellulose K100M, Sodium carboxy methyl cellulose and Eudragit L30 D55 by wet granulation. Five extended release formulations F5-F9 containing HPMC K100M and HPMC 5cps in varying concentration were developed by direct compression. The physico-chemical and *in-vitro* release characteristics of all the formulations were investigated and compared. Two formulations, F7 and F8 have shown not more 25% drug release in 1st h, 20-40% drug release at 4th h, 40-60% drug release at 8th h and not less than 80% at 20th h and the release pattern conform with USP specification for 24 h extended release formulation. It can be conclusively stated that optimum concentration of HPMC K100M (58-65%) by direct compression method can yield an extended release of Metoprolol succinate for 24 hours.

INTRODUCTION: Conventional oral drug delivery systems are slowly fading away in the market owing to disadvantages. These delivery systems produce fluctuation of drug plasma level that either exist at safe therapeutic level or quickly falls below the minimum effective level. This effect is usually totally dependent on the particular agent's biological half life, frequency of administration and release rate. It is recognized that many patients can benefit from drugs intended for chronic administration by maintaining the plasma level within a safe effective range [1]. Extended oral drug delivery systems are highly recognized today for their benefits improving the disadvantages of conventional drug delivery systems. To be a successful extended-release product the drug must be released from the dosage from at a predetermined rate in gastrointestinal fluids, maintain sufficient gastrointestinal residence time and be absorbed at a rate that will replace the amount of drug being metabolized and excreted. Extended drug delivery systems are used in the treatment of chronic rather than the acute condition, and they process a good margin of safety [2].

Metoprolol succinate is a cardio selective β-blocker used in the treatment of hypertension, angina pectoris and heart failure. It is available commercially in 25 mg, 50 mg strength as immediate release tablets. Its half life is about 3 to 7 hours. Its bioavailability is 50% following oral administration. It has been reported that conventional dosage forms increase the plasma concentration of Metoprolol above that achieving the

maximum β_1 blockage (>300 nM). A therapeutic level of β blockage is achieved when plasma concentration are in the range of 80-300 nM.

Higher concentration produces more β2 blockage but little additional β1 blockage. "Lower concentration may result suboptimal β1 blockage". To meet the need for effective and well tolerated β1 blockage an extended release formulation of metoprolol succinate is beneficial to meet the objective of providing once daily dosing that maintains therapeutic plasma concentration and avoids the extreme peaks and troughs characteristics of metoprolol immediate release formulation [3].

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because they make it easier to achieve a desirable drug-release profile, they are cost-effective, and they have broad US Food and Drug Administration acceptance [4]. Among the hydrophilic polymers, cellulose derivatives such as methyl cellulose, hydroxyl propyl methyl cellulose, and sodium carboxy methyl cellulose are generally considered to be stable and safe as release retardant excipients in the development of oral extended release dosage forms. HPMC is widely used in oral and topical formulations. In oral product, HPMC is primarily used as a tablet binder, in film-coating, and as an extended-release tablet matrix.

Based on the above considerations, the present study was aimed to develop metoprolol succinate ER matrix tablets using HPMC in different viscosity, Eudragit L30 D55 (aqueous dispersion) and sodium carboxy methyl cellulose. The formulations were prepared by wet granulation as well as direct compression method and investigated for physicochemical and release characteristics.

MATERIALS AND METHODS:

Materials: Metoprolol succinate was obtained as a gift sample from Sun Pharma Ltd., Mumbai, India. HPMC K100M, HPMC 5cps and Povidone were purchased from Loba chemie Pvt. Ltd, Mumbai, India. Eudragit L30 D55 was obtained from Colorcon Ltd., Asia. Avicel 102 was obtained from Reliance Ltd., Mumbai, India. Sodium carboxyl methyl cellulose was purchased from Aurobindo pharma, Hyderabad, India. All other ingredients used were of analytical grade.

Methodology:

Preparation of Extended Release Tablets:

Wet granulation method: A Preliminary trial was conducted on the formulation of extended release tablets of metoprolol succinate. Four formulations (F1, F2, F3, and F4) were prepared by wet granulation techniques as shown in **Table 1**. The active ingredient metoprolol succinate, sodium carboxyl methyl cellulose, HPMC K100M and avicel 102 were passed through #40 mesh and mixing was done by using planetary mixer for 30 minutes.

Eudragit L30 D55 was dissolved in water and to that povidone solution was added with continuous stirring and this solution was added to the above mixture. Then the mixture was kept in a dryer at 60^{o}C until loss of drying (LOD) was not more than 1.8%. Then aerosil and avicel were passed through #40 mesh and lubricants such as talc and stearic acid, were passed through #60 mesh, added to the above granules in planetary mixer and mixed well. Then the granules were compressed into tablets using 16 stations rotary compressed machine with punch size 11.1mm.

Direct compression: Five formulations (F5, F6, F7, F8, and F9) were prepared by direct compression method based on preliminary trials on the formulation of Metoprolol succinate extended release tablets as shown in **Table 1**. Metoprolol succinate and HPMC K100M were accurately weighed, geometrically mixed and passed through #40 mesh and then, aerosil and avicel were accurately weighed and passed through #40 mesh.

Both mixtures were mixed in rapid mixer granulator for 5 minutes as a dry mixing. Then, the lubricant sodium steryl fumarate was passed through #60 mesh added to the mixture in the rapid mixer granulator and mixed for 2 minutes. Then the granules were compressed into tablets using 16 stations rotary compressed machine with punch size 11.1mm.

Coating of tablets: The compressed tablets obtained by wet granulation and direct compression method were coated by Tabcoat TC-white by pan coating.

Preparation of Coating Solution: 30 gm of Tabcoat TC readymade powder was weighed and dissolved in 500

ml of isopropylalcohol and methylene chloride (1:1). After complete dissolving, the solution was passed through #200 mesh and used for coating the tablets.

TABLE 1 FORMULATION OF METOPROLOL SUCCINATE EXTENDED RELEASE TABLET F1-F9

Ingredients	WET-GRANULATION				DIRECT COMPRESSION				
	F1	F2	F3	F4	F5	F6	F7	F8	F9
INTRA-GRANULATION									
Metoprolol Succinate	95	95	95	95	95	95	95	95	95
Avicel 102	95	80	50	30	15	18	62	92	108
Sodium CMC	-	23.5	23.5	23.5	-	-	-	-	-
Eudragit L30 D55	20	20	23.5	23.5	-	-	-	-	-
Povidone	11.5	11.5	11.5	11.5	-	-	-	-	-
Purified water	q.s.	q.s.	q.s.	q.s.	-	-	-	-	-
HPMC K100 M	188	190	221	254	367	344	320	290	274
HPMC 5 CPS	-	-	-	-	-	20	-	-	-
EXTRA-GRANULATION									
Avicel 102	43	34.5	30	17	-	-	-	-	-
Aerosil	10	10	10	10	5	5	5	5	5
Talc	7.5	7.5	7.5	7.5	-	-	-	-	-
Stearic acid	13	13	13	13	-	-	-	-	-
SSF	-	-	-	-	3	3	3	3	3
COATING SOLUTION (tabcoat tc white)	15	15	15	15	15	15	15	15	15
Average weight	500	500	500	500	500	500	500	500	500

Evaluation of Granules:

Flow Property Measurements: It is very important parameter to be measured since it affects the mass of uniformity of the dose. It is usually predicted from various parameters like Angle of repose, Bulk and Tapped density, compressibility index and Hausner's Ratio as shown in **Table 2**.

Angle of Repose: The angle of repose of granules was determined by the fixed funnel and freestanding cone method, where by accurately weighed granules (5gm were carefully poured through the funnel with its tip at 2 cm height (h) until the apex of the conical heap so formed just reached the tip of the funnel. The mean diameter (r1, of the base for the powder cone was measured and angle of repose (0) was calculated using the following equation.

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

Bulk Density and Tapped Density: A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

Compressibility index (Carr's index): Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible material is more flowable. A material having value of less than 18 % is defined as the free flowing material.

$$\text{FORMULA} = \text{T.D} - \text{B.D}/\text{T.D} \times 100$$

Hausner's Ratio: It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

$$\text{FORMULA} = \text{TD}/\text{BD}$$

Evaluation of tablets: All the prepared film coated tablets were evaluated for thickness, hardness, friability, weight variation and drug content uniformity as shown in Table 3 [5] (Banker et al., 1986).

Thickness: For each formulation the thickness of the tablets was determined by using a vernier caliper, mean and SD was calculated.

Hardness Test: For each formulation, the hardness of 5 tablets was determined using a Monsanto hardness tester, mean and SD were calculated

Friability Test: The friability of tablets was determined by "Roche" friabilator. 10 tablets were taken and weighed. After weighing the tablets were placed in the Roche friablator and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for 4 minutes, dropping the tablets from a distance of six inches with each revolution. After operation the tablets were dedusted and reweighed.

F = 100 (1-wo/wt)

Where, Wo = weight of tablets before friability test; Wt = weight of tablets after friability test

Weight Variation Test: The percentage weight variations for all formulations were determined. Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights should deviate from the average weight by more than the percentage deviation and none should deviate by more than twice the percentage USP official limits of percentage deviation of tablet.

TABLE 2 PRECOMPRESSION PROPERTIES OF METOPROLOL SUCCINATE GRANULES F1-F9

Batch no	Angle of repose	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility Index	Hausner's Ratio
F1	37°90′ ±0.40	0.401 ±0.001	0.476 ±0.01	19.13 ±0.12	1.19 ±0.002
F2	38°52′ ±1.07	0.454 ±0.002	0.531 ±0.002	17.20 ±0.16	1.16 ±0.003
F3	37°52′ ±1.65	0.435 ±0.007	0.492 ±0.002	18.13 ±0.50	1.17 ±0.003
F4	36°22′ ±1.16	0.391 ±0.003	0.447 ±0.008	17.07 ±0.69	1.17 ±0.003
F5	27°76′ ±1.02	0.403 ±0.008	0.423 ±0.004	11.63 ±0.38	1.14 ±0.012
F6	27°03′ ±0.36	0.447 ±0.008	0.476 ±0.006	8.82 ±0.13	1.12 ±0.002
F7	25°73′ ±0.58	0.408 ±0.003	0.451 ±0.003	8.64 ±0.31	1.12 ±0.006
F8	24°10′ ±0.51	0.417 ±0.004	0.431 ±0.015	7.55 ±0.32	1.07 ±0.04
F9	23º95′ ±0.44	0.412 ±0.005	0.437 ±0.005	7.52 ±0.28	1.04 ±0.012

Drug Content Uniformity:

Standard Solution: 0.0475gm of Metoprolol succinate was accurately weighed WRS into 100ml volumetric flask, 20ml of mobile phase was added, sonicated for 10 minutes and then made up to volume with mobile phase (pH 3.0 phosphate buffer and acetonitrile).

Test Solution: One tablet was transferred to 200ml volumetric flask, added 10ml of acetonitrile and allowed to disintegrate. Added 60ml of ethanol 95% and sonicated for 30 minutes. 40ml of 0.1M Hydrochloric acid was added into the volumetric flask and again sonicated for further 30 minutes. The solution was then cooled to room temperature and made up to volume with 0.1M Hydrochloric acid. 5ml was diluted to 25ml with mobile phase and filtered through 0.45micron membrane filter and the clear liquid was used.

Procedure: Equal volumes (about 40µl) of the standard solution and the test solution were injected separately into the chromatograph, the chromatograms recorded and the responses measured for the major peaks [6].

Dissolution Test: The release of metoprolol succinate from the extended release tablet was studied in 500 ml of pH6.8 phosphate buffer as dissolution medium using a USP type II dissolution paddle apparatus at 50 rpm and 37±0.5^{o}C. One tablet was placed in each bowl. The apparatus was run and withdrawn 10ml sample at 1, 4, 8 and 20th hour from each vessel, replacing the same amount every time with a fresh dissolution medium to maintain the sink condition. The solution was filtered through membrane filter and analyzed for percentage drug release by Liquid Chromatography Equipped with UV – Vis detector [6].

RESULTS AND DISCUSSION:

Tablet characteristics: The extended release tablets of Metoprolol succinate were prepared by wet granulation as well as direct compression method in order to assess the performance of preparation method on physicochemical and release characteristics. Precompression properties of granules reveal increased angle of repose ranging between 36° 22" to 37°90" in formulation F1 - F4 prepared by wet granulation method whereas those prepared by direct

compression F5 - F8 showed reduced angle of repose ranging between 23°95" to 27°76".

However, bulk densities, tapped density, compressibility index, Hausner's ratio of the granules were all within acceptable limits as per USP specification (Table 2). All the formulation F1 - F9 passed the USP specifications for diameter, hardness, thickness, friability, weight variation and drug content as shown in **Table 3**.

TABLE 3: PHYSICO-CHEMICAL PROPERTIES OF METOPROLOL SUCCINATE EXTENDED RELEASE FORMULATIONS (F1 – F9)

Batch No	Diameter (mm)	Hardness (Kg/cm2)	Thickness (mm)	Friability (%)	Weight Variation (mg)	Drug content (%)
F1	11.1	3.67 ±0.23	5.11 ±0.08	0.81 ±0.08	484.57 ±0.66	88.61 ±1.05
F2	11.1	5.30 ±0.32	5.24 ±0.04	0.70 ±0.02	484.03 ±1.20	90.61 ±0.42
F3	11.2	5.03 ±0.33	5.20 ±0.08	0.76 ±0.02	485.43 ±0.67	91.53 ±0.23
F4	11.1	5.63 ±0.33	5.20 ±0.08	0.52 ±0.06	485.87 ±0.60	91.39 ±0.26
F5	11.1	9.00 ±0.50	5.50 ±0.08	0.27 ±0.03	484.90 ±1.42	92.86 ±0.33
F6	11.1	7.40 ±0.21	5.37 ±0.04	0.27 ±0.02	486.17 ±1.04	97.31 ±0.10
F7	11.1	7.57 ±0.33	5.37 ±0.04	0.14 ±0.01	485.33 ±0.60	98.35 ±0.71
F8	11.1	6.60 ±0.29	5.30 ±0.08	0.13 ±0.13	484.70 ±0.77	98.79 ±0.81
F9	11.2	7.00 ±0.08	5.20 ±0.08	0.14 ±0.03	486.0 ±0.63	98.98 ±0.73
Acceptable limits as per USP	11.0 – 11.3 mm	4.0 – 8.0 Kg/cm^2	5.1 – 5.5 mm	Not more than 0.8% w/w	Not more than 5% deviation	80 – 110%

***In-vitro* Release Studies:** The release profile of Metoprolol succinate formulations F1 - F9 was observed at pH 6.8 buffer as per USP specification. Each experiment was done 3 times and the mean value was recorded as percentage release at 1st, 4th, 8thand 20th as per USP specification as shown in the **Figure 1**. All formulations showed burst release of the drug ranging between 10.57% to 34.1% in the first hour. The least release in 1st hour was observed in the formulation F5 (10.57%) and the maximum in formulation F1 (34.1%). Formulations F1 – F4 have showed higher percentage release (20.43% - 34.1%) as compared to formulations F5 – F9 (10.57% - 18.1%).

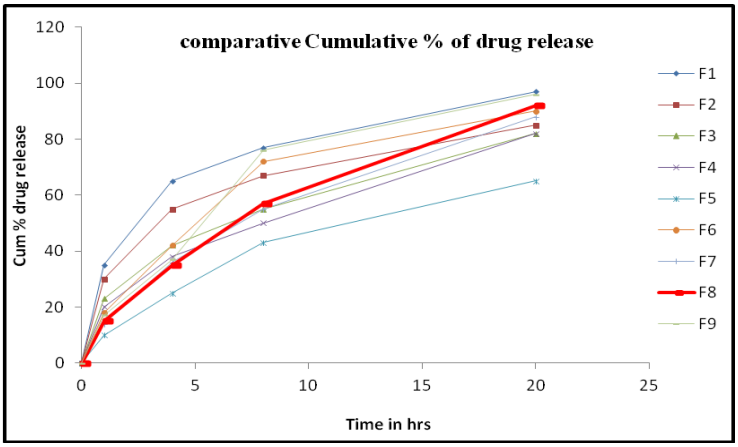

FIG. 1: COMPARATIVE CUMULATIVE % DRUG RELEASE OF METOPROLOL SUCCINATE EXTENDED RELEASE FORMULATIONS (F1 – F9)

Addition of HPMC K100M in increasing concentration has retarded the release rate from 29.87% to 20.43% in the 1st h (F2-F3-F4), (F2-F3 = P 0.01; F2-F4 = P<0.001). There was no significant deference in reduction release rate between F3 and F4 (P>0.05). These findings suggest that HPMC K100M in higher concentration slowed the drug release possibly due to viscosity of the gel structure. Comparison between F1 and F2 addition of CMC Na has further slowed down the release rate of drug indicating that CMC Na and HPMC K100M combination have better control on the drug release compared to HPMC K100M alone.

This result may be due to the additive effect of CMC Na to the viscosity of HPMC K100M. In formulations F1-F4 the addition of CMC Na and EudragitL30D55 to HPMC might have influenced the release behavior. In contrast, the addition of hydrophobic EudragitL30D55 polymer instead of retarding the release of the drug has in fact yielded faster release behavior. Where as in formulations F5-F9 percent release in 1st hour was less than that observed in formulations F1-F4. On comparison of release pattern between the formulations F5 – F9 in the 1st h (all formulations prepared by direct compression) it was shown that there was significant difference in the drug release between F5 and F6 (P<0.001), F5 and F8 (P<0.05), F5 and F9 (P<0.01).

These findings indicate that decreasing HPMC K100M concentration has increased significantly the release rate of the drug thus showing that concentration of HPMC K100M appears critical in controlling the release

rate of the drug. Similar release pattern was observed at 4th, 8th and 20thh of all formulations (F1 – F9). Further analysis of release characteristics at 4th, 8th and 20th hour indicates that the formulations F7–F8 are showing the release data as per USP specification for extended release formulation.

Accordingly, these formulations have shown not more than 25% release in 1st hour, between 20% and 40% release at 4th hour, between 40% and 60% release at 8th hour, and not less than 80% at 20th hour, conforming with the USP specification for extended release formulation. The concentration of HPMC K100M influences the drug release, as the concentration of HPMC K100M increases the drug release was proportionally slowed. Such a behavior was observed in the formulations F1-F9 where increasing the concentration of HPMC K100M slowed the drug release.

The optimum concentration required to produce extended release for 24 hours was found to be between 60-65% as seen in F7-F8 formulations. Beyond this concentration either at low level or higher level has resulted in unacceptable release profile of extended release formulation. HPMC K100M being hydrophilic in nature exhibits good water uptake which influence the swelling index and thus the release rates are well controlled.

When the concentration of HPMC is increased, the strength of the gel layer also increased, thus the drug release is controlled and extended due to the structural reorganization of the polymer [7]. The physical characteristics of all formulations were within acceptable limits and as such they did not show significant influence on the release pattern of the drug.

Kinetic Modeling of Drug Release: Fickian and non-Fickian (anomalous) behavior have been studied for determining the mechanism of drug release from extended release formulation. The kinetic of release was investigated using software version as shown in **Table 4**. Based on n value obtained from Korsmeyer's equation, the values of the exponent n for the formulations F1-F4 were between 0.34 and 0.43 indicating Fickian transport.

This suggests that the release is controlled by diffusion mechanism from these formulations. The values of exponent n for the formulations F5-F9 ranged between 0.55 to 0.63 indicating non-Fickian release suggesting that the transport from these formulations is controlled by diffusion and/or relaxation of the polymer. All the formulations F1-F9 showed first order release kinetics (R^2 = 0.945 to 0.998). Applying USP specification for percentage release for extended release pattern, formulations F7 and F8 appear fitting and these formulations were considered the best for 24 hours release characteristics.

Comparing between wet granulation and direct compression method it was observed that the formulations prepared by wet granulation (F1-F4) experienced manufacturing defects like capping, picking and sticking possibly due to the effect of binding agent povidone. Such defects were absent in formulations prepared by direct compression (F5-F9), where binding agent was not used.

TABLE 4 KINETIC DATA OF METOPROLOL SUCCINATE EXTENDED RELEASE FORMULATIONS (F1 –F9)

Formulation code	Zero-order	First-order	Higuchi	Korsmeyer's		Possible Drug Release mechanism
	Regression Coefficient (R^2)	Regression Coefficient (R^2)	Regression coefficient (R^2)	Slope (n)	Regression coefficient (R^2)	
F1	0.827	0.995	0.942	0.341	0.973	First order- Fickian
F2	0.845	0.973	0.954	0.349	0.98	First order- Fickian
F3	0.95	0.998	0.959	0.422	0.999	First order- Fickian
F4	0.962	0.994	0.994	0.433	0.995	First order- Fickian
F5	0.936	0.984	0.991	0.637	0.991	Diffusion- Non-Fickian
F6	0.837	0.974	0.942	0.558	0.942	First order- Non-Fickian
F7	0.961	0.992	0.998	0.612	0.997	Diffusion- Non-Fickian
F8	0.952	0.998	0.999	0.618	0.995	Diffusion- Non-Fickian
F9	0.852	0.945	0.959	0.607	0.964	Diffusion- Non-Fickian

DISCUSSION: Different approaches have been followed for development of extended released formulations. In pharmaceutical industries wet granulation, dry granulation and direct compression are the methods

commonly employed for the manufacture of extended release tablets. Hydrophilic polymers are the most widely employed in the preparation of extended release tablets because of their flexibility to obtain a desirable drug delivery profile, cost effectiveness and broad regulatory acceptance. HPMC is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery.

In this study, an extended release tablet formulation of Metoprolol succinate was developed. The effect of different polymers hydrophilic (HPMC K100M, CMC Na) as well as hydrophobic (Eudragit L30 D55) on the formulations was investigated. The influence of method of preparation viz. wet granulation or direct compression of the formulation was also studied. Results have indicated that all the formulations F1-F9 meet the requirement of physico-chemical characteristics.

The release profile of all formulations was studied. The results suggest that the polymers HPMC K100M, CMC Na, Eudragit L30 D55 have greater influence on the release pattern of the drug. It was observed that formulations developed with HPMC K100M by direct compression method, were found to provide extended release for 24 hours, as compared to those formulations developed with HPMC K100M, CMC Na, Eudragit L30 D55 by wet granulation method. The release data further indicate that HPMC K100M in an optimum concentration between 58-65% appear promising to achieve the desired extended release characteristic as evidenced in the formulations F7-F8.

The results of the present study conflict with earlier report [8], that drug release for extended duration, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted because of rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs with high water solubility, hydrophobic polymers are suitable, along with a hydrophilic matrix for developing sustained-release dosage forms.

CONCLUSION: The results of the study demonstrate that hydrophilic polymer HPMC K100M can effectively control the extended release of Metoprolol succinate for 24 hrs. Direct compression is feasible for development of once a day extended release tablet of Metoprolol succinate provided careful selection of optimum concentration of HPMC K100M is followed. It can be conclusively stated that development of extended release formulation of hydrophilic drugs does not necessitate the inclusion of the hydrophobic polymers to hydrophilic polymers and the desired extended release of hydrophilic drugs is also viable with hydrophilic polymer alone.

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