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FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE CONTROLLED RELEASE TABLET BY MELT GRANULATION AND DIRECT COMPRESSION METHOD

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ABSTRACT

Controlled release products are designed to maintain constant therapeutic plasma concentration of the drug within the therapeutic range of the drug over prolonged period and offer minimum side effects. This can be achieved using a variety of delivery systems. These products are designed to reduce the frequency of dosing by modifying the rate of drug absorption. The frequency of administration or the dosing interval of any drug depends upon its half-life or mean residence time (MRT). Generally controlled release products administered by any route are design such that rate of drug absorption should be equal to rate of drug elimination. Controlled release tablet of metoprolol succinate was prepared by melt granulation and direct compression method using various hydrophilic polymers of natural and synthetic grades. The tablets from all formulations were evaluated for thickness, density, weight variation and friability. The drug release was influenced by the amount of polymer incorporation in the formulation.

KEYWORDS: Controlled release tablet, Oral drug delivery system, Metoprolol succinate

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INTRODUCTION

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively complete systemic drug absorption and onset of accompanying pharmacodyanmic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentration decline according to the drug's pharmacokinetic profile [(1)]. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage from that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. In recent years, various modified-release drug products have been developed to control the release rate of the drug and / (or) the time for drug release [(2)].

Metoprolol succinate is a beta1-selective (cardio selective) adrenoceptor blocking agent, for oral administration, available as extended-release tablets. Metoprolol succinate extended-release tablets has been formulated to provide a controlled and predictable release of metoprolol for once-daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 23.75, 47.5, 95 & 190 mg of metoprolol

succinate equivalent to 25, 50, 100 & 200mg of metoprolol tartrate USP respectively. This preferential effect is not absolute, however and at higher plasma concentrations, metoprolol also inhibits beta 2-adrenoreceptors, chiefly located in the bronchial & vascular musculature. Metoprolol has no intrinsic sympathomimetic activity & membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for betablockade.

Metoprolol succinate controlled-release tablets produced an improvement in left ventricular ejection fraction. It was also shown to delay the increase in left ventricular end-systolic & end-diastolic volumes after 6 months of treatment.

MATERIALS AND METHODS

Materials:

Metoprolol succinate drug was a gift sample from Unichem Laboratory, Uttar Pradesh, India. Sodium carboxyl methyl cellulose, HPMC K 4 M, HPMC K 15 M & HPMC K 100 M were obtained from Rubicon labs, Mumbai. Kondagogu gum, Eudragit L 100 and Carnauba wax were gifted from MSN Labs Ltd. Hyderabad. All other chemicals used were of analytical grade.

Methods:

The following Pre-compression parameters were conducted: Angle of repose [10], Carr's compressibility Index [11], Bulk Dentistry, Tapped Density [12], Hausner's Ratio. [13]

Formulation of Matrix Tablets of Metoprolol Succinate:

Manufacture of Tablets by Melt Granulation Method:

Melt granulation method is a process of size enlargement in which fine powder particles are agglomerated or brought together into larger, strong and relatively permanent structure called granules using a suitable non-toxic granulating fluid such as water, isopropanol or ethanol (or mixtures thereof).

The granulating fluid can be used alone or as a solvent containing binder or granulating agent. The choice of the granulating fluid depends greatly on the properties of the materials to be granulated. Powder mixing, in conjunction with the cohesive properties of the granulating agent, enables the formation of granules. The characteristics and performance of the final product, greatly depends on the extent to which the powder particles interact with each other to form aggregates (granules).

- **Step 1:** Weighing and mixing of formulation ingredients (excluding the lubricant).
- **Step 2:** Preparing the damp mass
- **Step 3:** Wet screening / Screening the dampened powder into pellets or granules
- **Step 4:** Drying of moist granules
- **Step 5:** Sizing the granulation by dry screening
- **Step 6:** Lubrication of granules
- **Step 7:** Compression of granules into tablets

Manufacture of Tablet of Metoprolol Succinate by Direct Compression Method:

Controlled release tablets of metoprolol succinate were prepared by direct compression method using microcrystalline cellulose as directly compressible vehicle. Bees wax, paraffin wax, Poly-6000, Poly-200 were used as retardant material for preparation of tablets. Other excipients were magnesium stearate as a lubricant and colloidal silicon dioxide as a glidant. For preparation of controlled release tablets of metoprolol succinate, drug and polymer were weighed accurately, all the ingredients were sieved through 40 mesh screen and mixed with other ingredients and the powder mixture was compressed using 16 station rotary tablet compression machine using 5 mm punches. Tablet compression weight was adjusted to 50 mg. The formula for various formulations attempted has been given in **Table 4**.

Evaluation tests of Controlled release tablets performed by Hardness, Friability [14], Weight variation, Drug content /Assay [15], Swelling & Erosion studies. [16]

In-Vitro Drug Release Studies using Phosphate Buffer pH 7.4:

Theoretically, an *in-vitro* test for drug availability should measure in reality the physical phenomenon controlling availability in-vivo. This is not feasible for orally administered dosage forms because G.I fluids are not constant in composition and the dosage form moves at some

unknown rate through the number of fluids. It is not possible to simulate a single test system which would incorporate reflection of all such variables as interaction between drugs and constituents, changes in volume, retention time, transit time and various other levels of agitation.

However, *in-vitro* test can be carried out which will indicate the effects of these variables on the mechanism and kinetics of drug release from a dosage form. This will give an idea of how the dosage form will behave when subjected to in-vivo studies.

Data Analysis (Curve Fitting Analysis):

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:

1. Cumulative percentage drug released Vs Time (In-Vitro drug release plots)
2. Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
3. Log cumulative percentage drug remaining Vs Time (First order plots)
4. Log percentage drug released Vs Log time (Peppas plots)

Stability Study:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. The International Conference on Harmonization (ICH) Guidelines titled "Stability Testing of New Drug substance and Products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions.

- ❖ Long-term Testing: 25 °C ± 2 °C / 60% RH ± 5% for 12 Months.
- ❖ Accelerated Testing: 40 °C ± 2 °C / 75% RH ± 5% for 6 Months.
- ❖ Stability studies were carried out at 25 °C / 60% RH and 40 °C / 75% RH for the selected formulation for the period of 3 months.

The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 25 °C / 60% RH and 40 °C / 75% RH for 3 months and evaluated for their physical appearance, drug content and drug excipients compatibility at specified intervals of time-intervals of time.

RESULTS AND DISCUSSION

Pre-compression Parameters:

All the powder mixture belonging to different formulations was tested for micrometrics studies in order to determine the flow properties. All the formulations MGF1 to MGF9 and DCF1 to DCF 9 showed good flow properties, the results are summarized in **Table 1** and **2**.

Formulation of Matrix Tablets of Metoprolol Succinate:

Metoprolol succinate tablets were manufactured by the melt granulation method and direct compression method.

Table 1: Precompression Parameter of Granules by Melt Granulation

Formulation Code	Angle of repose	Compressibility index	Hausner ratio	Drug content uniformity
MGF1	26°.23 ± 0.15	14.34 ± 0.14	1.176± 0.02	95.65 ± 0.45
MGF2	22°.27 ± 0.16	16.87 ± 0.12	1.167± 0.03	94.15 ± 0.44
MGF3	25°.87 ± 0.14	14.97 ± 0.13	1.320± 0.03	95.15 ± 0.43
MGF4	24°.56 ± 0.15	15.64 ± 0.12	1.132± 0.04	96.32 ± 0.45
MGF5	26°.34 ± 0.14	15.89 ± 0.14	1.240± 0.02	94.65 ± 0.42
MGF6	24°.21 ± 0.16	16.32 ± 0.12	1.162± 0.03	96.89 ± 0.45
MGF7	23°.32 ± 0.16	15.98 ± 0.12	1.231± 0.03	95.21 ± 0.45
MGF8	24°.90 ± 0.15	15.32 ± 0.13	1.176± 0.04	94.56 ± 0.46
MGF9	25°.67 ± 0.16	16.91 ± 0.13	1.145± 0.02	96.78 ± 0.43

Table 2: Precompression Parameter of Granules by Direct Compression

Formulation Code	Angle of repose	Compressibility index	Hausner ratio	Drug content uniformity
DCF1	25°.53 ± 0.16	15.23 ± 0.13	1.183 ± 0.02	96.15 ± 0.44
DCF2	23°.47 ± 0.13	15.56 ± 0.11	1.134 ± 0.03	95.89 ± 0.42

DCF3	23°.87 ± 0.13	14.32 ± 0.11	1.145 ± 0.03	96.45 ± 0.44
DCF4	25°.26 ± 0.14	16.24 ± 0.13	1.178 ± 0.04	96.45 ± 0.43
DCF5	26°.14 ± 0.16	15.19 ± 0.14	1.201 ± 0.02	95.89 ± 0.45
DCF6	26°.54 ± 0.13	16.23 ± 0.13	1.174 ± 0.02	96.99 ± 0.43
DCF7	24°.13 ± 0.15	14.19 ± 0.12	1.207 ± 0.04	97.01 ± 0.45
DCF8	25°.42 ± 0.14	16.12 ± 0.12	1.165 ± 0.02	95.16 ± 0.44
DCF9	25°.10 ± 0.16	16.32 ± 0.12	1.143 ± 0.03	95.72 ± 0.44

Table 3: Formulation of Batch MGF1 To MGF9 By Melt Granulation Method

Formulation code	Metoprolol succinate mg	PVG-2000	PVG-6000	Bees wax	M.C.C.	Mag. stearate	Total mg
MGF1	50	50	-	-	197	3	300
MGF2	50	100	-	-	147	3	300
MGF3	50	150	-	-	97	3	300
MGF4	50	-	50	-	197	3	300
MGF5	50	-	100	-	147	3	300
MGF6	50	-	150	-	97	3	300
MGF7	50	-	-	50	197	3	300
MGF8	50	-	-	100	147	3	300
MGF9	50	-	-	150	97	3	300

Table 4: Formulation of Batch DCF1 To DCF9 By Direct Compression Method

Formulation code	Metoprolol succinate mg	PVG-2000	PVG-6000	Bees wax	M.C.C.	Mag. stearate	Total mg
DCF 1	50	50	-	-	197	3	300
DCF 2	50	100	-	-	147	3	300
DCF 3	50	150	-	-	97	3	300
DCF 4	50	-	50	-	197	3	300
DCF 5	50	-	100	-	147	3	300
DCF 6	50	-	150	-	97	3	300
DCF 7	50	-	-	50	197	3	300
DCF 8	50	-	-	100	147	3	300
DCF 9	50	-	-	150	97	3	300

Table 5: Precompression Parameter of Granules by Melt Granulation

Formulation Code	Diameter (mm)	Thickness (mm)	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability %	Drug content %
MGF1	10.02 ± 0.011	4.45 ±0.12	301 ± 5	5.3 ± 0.12	0.187 ± 0.01	95.09 ± 0.15
MGF2	10.03 ± 0.010	4.37 ±0.14	302 ± 5	5.4 ± 0.13	0.191 ± 0.02	96.67 ± 0.18
MGF3	10.02 ± 0.011	4.41 ±0.12	303 ± 5	5.7 ± 0.14	0.168 ± 0.01	94.89 ± 0.16
MGF4	10.04 ± 0.012	4.33 ±0.14	304 ± 5	5.8 ± 0.11	0.176 ± 0.03	95.89 ± 0.14
MGF5	10.03 ± 0.010	4.39 ±0.15	302 ± 5	5.7 ± 0.14	0.191 ± 0.03	96.99 ± 0.16
MGF6	10.04 ± 0.012	4.40 ±0.16	304 ± 5	5.6 ± 0.12	0.201 ± 0.02	95.27 ± 0.14
MGF7	10.04 ± 0.010	4.38 ±0.13	305 ± 5	5.5 ± 0.13	0.167 ± 0.02	96.89 ± 0.15
MGF8	10.03 ± 0.012	4.37 ±0.13	302 ± 5	5.6 ± 0.14	0.194 ± 0.01	96.09 ± 0.16
MGF9	10.02 ± 0.010	4.35 ±0.12	303 ± 5	5.7 ± 0.15	0.189 ± 0.03	97.01 ± 0.17

Table 6: Precompression Parameter of Granules by Direct Compression

Formulation Code	Diameter (mm)	Thickness (mm)	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability %	Drug content %
DCF1	10.02 ± 0.011	4.36 ±0.11	304 ± 5	5.6 ± 0.14	0.191±0.01	94.99 ± 0.14
DCF2	10.03 ± 0.010	4.38 ±0.12	303 ± 5	5.3 ± 0.13	0.183±0.01	96.01 ± 0.15
DCF3	10.04 ± 0.012	4.33 ±0.15	305 ± 5	5.5 ± 0.12	0.179±0.02	95.26 ± 0.15
DCF4	10.03 ± 0.012	4.34 ±0.14	304 ± 5	5.8 ± 0.12	0.156±0.02	96.09 ± 0.16
DCF5	10.05 ± 0.011	4.37 ±0.13	305 ± 5	5.5 ± 0.12	0.168±0.01	96.59 ± 0.17
DCF6	10.02 ± 0.010	4.40 ±0.12	303 ± 5	5.5 ± 0.13	0.172±0.01	95.99 ± 0.15
DCF7	10.03 ± 0.011	4.39 ±0.15	302 ± 5	5.7 ± 0.12	0.159±0.02	96.89 ± 0.19
DCF8	10.03 ± 0.012	4.36 ±0.13	303 ± 5	5.9 ± 0.13	0.157±0.02	97.19 ± 0.15
DCF9	10.04 ± 0.013	4.37 ±0.12	305 ± 5	5.6 ± 0.13	0.190 ±0.01	96.59 ± 0.15

Swelling Index:

Swelling index of all formulations is shown in **Table 7** and **Table 8** as time increases the swelling index was increased, because weight gained by tablet was increased proportionally with the rate of hydration up to 3 hours, 4 hours for Polyethylene glycol 6000 and Bees wax respectively. Later on it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship

was observed between swelling index and polymer concentration, as polymer concentration increases, swelling index was increased. Comparison between Polyethylene glycol 6000 and Bee's wax. It has been observed that swelling index is more in Polyethylene glycol 6000 followed by Bee's wax. It was observed that cumulative % drug release decrease with increasing concentration of polymer and swelling index.

Table 7: Swelling Index Behavior Study of selected Formulations (DCF1-DCF9)

Time	DCF1	DCF2	DCF3	DCF4	DCF5	DCF6	DCF7	DCF8	DCF9
0	0	0	0	0	0	0	0	0	0
2	12.45	15.23	14.24	12.89	16.19	17.90	14.34	13.23	15.87
4	15.36	19.15	20.96	17.89	22.78	15.98	22.45	21.45	21.56
6	33.66	31.45	29.98	32.45	34.41	32.15	31.25	32.15	33.45
8	44.35	42.45	42.49	43.75	46.45	43.41	44.45	45.49	43.43
10	52.41	53.12	52.21	52.99	55.15	54.41	55.45	57.45	55.21
12	64.25	62.15	65.45	63.47	64.49	64.89	63.49	67.21	66.15

Table 8: Swelling Index Behavior Study of selected Formulations (MGF1-MGF9)

Time	MGF1	MGF2	MGF3	MGF4	MGF5	MGF6	MGF7	MGF8	MGF9
0	0	0	0	0	0	0	0	0	0
2	13.45	14.56	15.78	15.89	16.01	16.99	15.45	14.13	15.17
4	25.36	21.45	22.56	21.79	23.98	22.76	25.48	29.49	29.89
6	35.76	34.67	34.09	33.89	36.41	35.98	36.93	35.15	38.21
8	46.15	47.45	47.49	48.45	46.15	44.41	45.59	47.39	44.47
10	55.41	55.12	56.27	54.92	55.55	55.48	59.25	58.49	56.25
12	67.15	63.45	67.15	64.49	65.65	67.89	64.49	65.27	65.75

***In-Vitro* Drug Release:**

Effect of Type of Lipophilic binders:

The various polymers are considerable interest for the preparation of oral dosage form. Bee wax, Polyvinyl glycol 6000, PVG-2000 are used for the preparation-controlled release dosage form.

Among the liphophilic agents PVG-6000 was found to be specially effective for several reason, high melting point, avoids stocking to punches during tableting operations.

- PVG 6000 have M.P. = 64-66 °C
- PVG-2000 have M.P. = 58.63 °C
- Bee wax have M.P. = 62-64 °C

In the present study, effect of lipophilic binder on drug release property metoprolol succinate prepared by Melt granulation and direct compression method.

In both melt granulation and direct compression method show maximum retardation i.e. 90.48%, 80.29% respectively at the end of 8 hours and occur formulation shows 100% drug release.

Metoprolol succinate release occurs by different mechanism i.e. diffusion or erosion with depends on the lipophilic polymer is used.

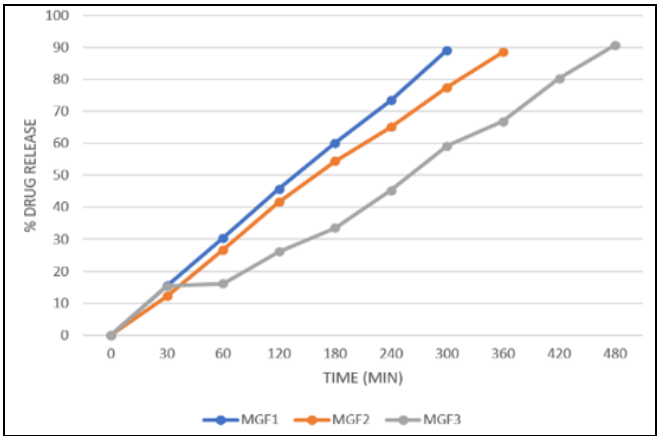

Figure 1: *In-vitro* drug release of formulation MGF1-MGF3

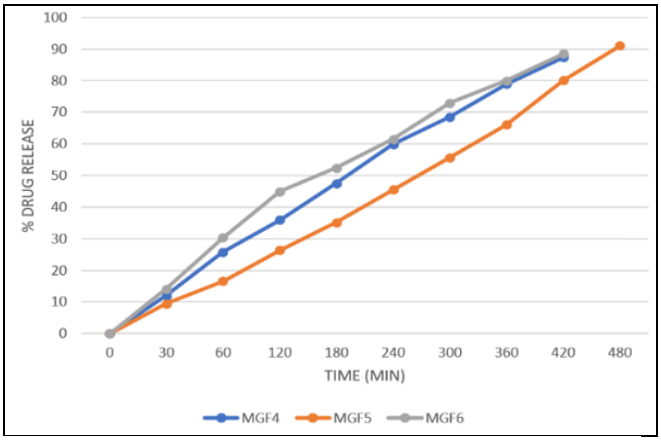

Figure 2: *In-vitro* drug release of formulation MGF4-MGF6

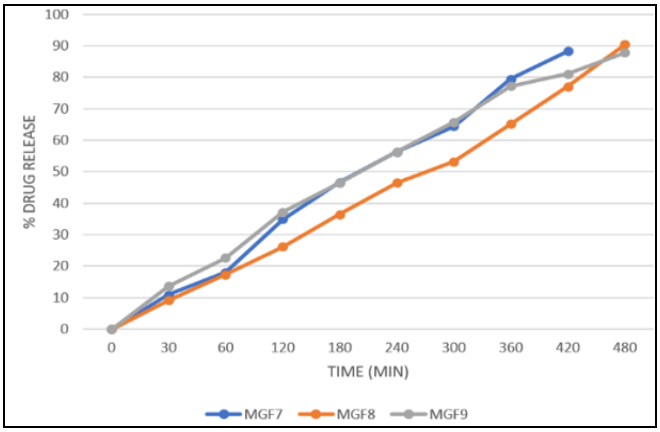

Figure 3: *In-vitro* Drug Release of Formulation MGF7-MGF9

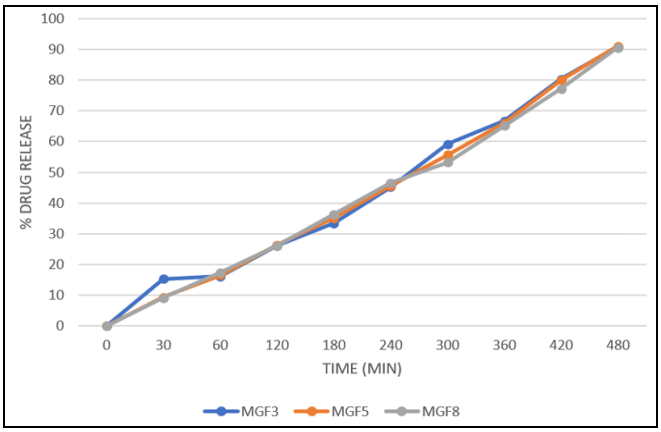

Figure 4: Comparative *In-vitro* Drug Release of Formulation MGF3, MGF5, MGF8

In the previous figure the MGF3 shows the maximum release and MGF1, MGF2 is less.

MGF3 > MGF2> MGF1

Meanwhile, MGF5 shows maximum release as compare with MGF4, MGF6.

MGF5 > MGF6> MGF4

In same series, the MGF8 shows maximum release and MGF7, MGF9 shows less drug release.

MGF8 > MGF9> MGF7

In same series, the MGF3, MGF5, MGF8 shows maximum release in which MGF5 is shows maximum drug release.

MGF5 > MGF3> MGF8

It shows MGF5 is shows the maximum drug release is 90.98%.

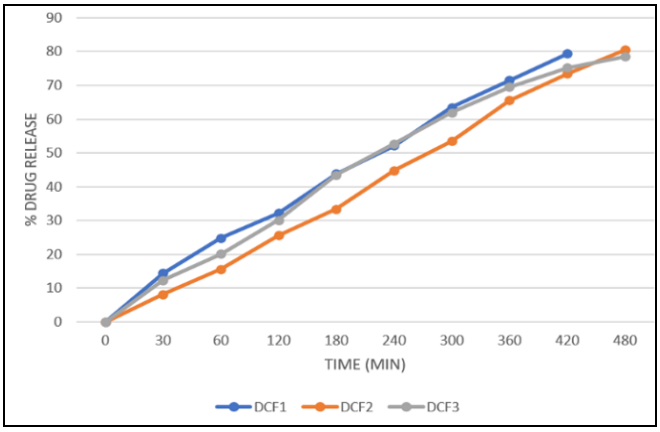

Figure 5: *In-vitro* Drug Release of Formulation DCF1-DCF3

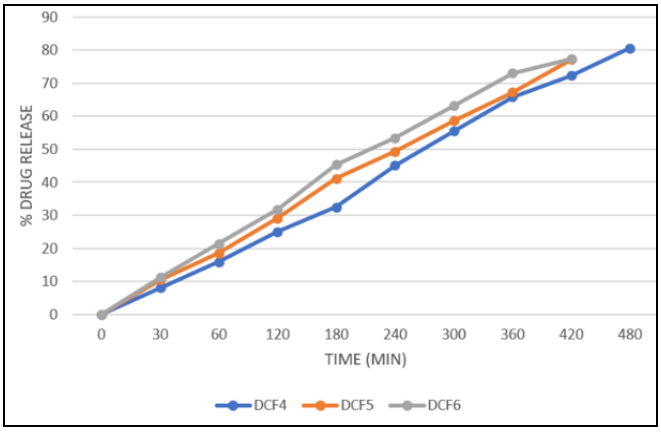

Figure 6: *In-vitro* Drug Release of Formulation DCF4-DCF6

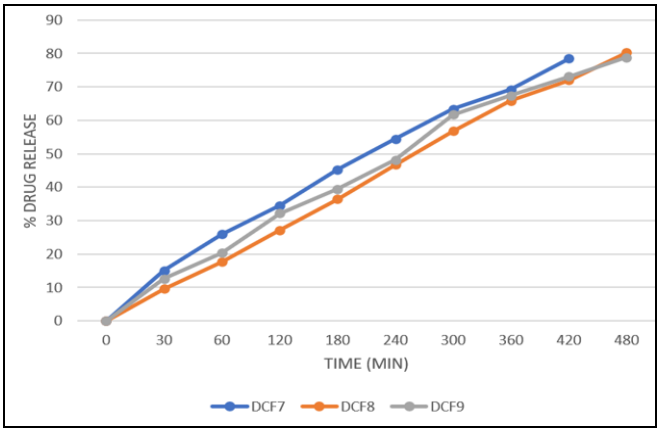

Figure 7: *In-vitro* Drug Release of Formulation DCF7-DCF9

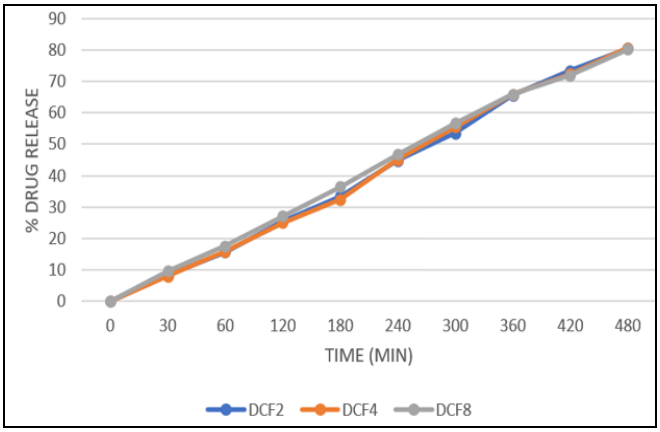

Figure 8: Comparative *In-vitro* Drug Release of Formulation DCF2, DCF4, DCF8

In this Figure DCF2 shows maximum drug release and DC1, DCF3 less release.

DCF2 > DCF3 > DCF1

DCF4 show maximum drug release and DCF5, DCF3 shows less release.

DCF4 > DCF6 > DCF5

And DCF8 shows maximum drug release and DCF7, DCF9 show less release.

DCF8 > DCF9 > DCF7

i.e. DCF2, DCF4, DCF8 are shows maximum drug release in which DCF4 shows the maximum drug release rate.

i.e. 80.69%

DCF4 > DCF2 > DCF8

The dissociation profiles of both the methods i.e. Melt granulation and direct compression shows that the formulation MGF5 and DCF4 maximum drug release i.e. 90.98% and 80.64% respectively.

Initially all formulation shows low drug release in both the methods, i.e. melt granulation and direct compression. For 30 min and at the end the DCF4 and MGF5 shows maximum release in 8 hours i.e. 80.69% and 90.98%.

Stability Studies:

The selected Formulation MGF5 & DCF8 were evaluated for stability studies which were stored at 40 °C at 75% RH tested for 3 months and were analyzed for their drug content at the monthly interval. The residual drug contents of formulations were found to be within the permissible limits and the results of 3 months duration are shown in the Table 9 & 10 which was estimated by seeing drug content uniformity.

Table 9: Stability data of MGF5 formulation

S. No.	Formulation MGF5 stored at 40^0C/ 75% RH	
	Physical appearance	% Drug content
1	+++	96.19
2	+++	95.32
3	++	94.04

+++ = Same as on zero day, ++ = Slight change in color

Table 10: Stability data of DCF8 formulation

S. No.	Formulation DCF8 stored at 40^0C/ 75% RH	
	Physical appearance	% Drug content
1	+++	96.76
2	+++	95.18
3	++	94.23

+++ = Same as on zero day, ++ = Slight change in color

CONCLUSION

The present works concludes with DCF8 and MGF5 as the best formulation for the controlled release of Metoprolol succinate following zero order kinetics with anomalous diffusion method. Furthermore *in-vivo* studies might confirm the formulation to substantiate the in-vitro results. It can be concluded that PVG-2000 combination and individual PVG-2000 respectively can be used as an effective matrix former to sustain the release of Metoprolol succinate for an extended period of 8 hrs.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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