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Pharmaceutics

Formulation and Evaluation of Extended/Immediate Release Bilayered Tablet

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Abstract **Original Research Article**

Extended release formulations are better over conventional multidose delivery system, particularly for long- term therapeutic effect and for the treatment of chronic disease. Two-layer tablets may be designed for one layer for immediate release of the drug and the second layer for extended release thus maintaining prolonged blood level The tablets had satisfactory physical properties i.e. hardness, friability etc. The objective of present study was to formulate a bilayered tablet, which produce immediate/ extended release of drug having short biological half-life for longer period of time and to evaluate release profile of drug from this formulation. The bilayered tablet is innovation drug delivery system. This type of dosage form for oral administration in which one layer contains immediate releasing drug and another layer contains immediate releasing drug. The result shows that bilayered oral concomitant E.R. formulation of Metoprolol succinate by matrix tablet using hydrophilic polymers in optimum concentration in one layer and second layer of Ramipril with immediate release. The matrix system is most frequently applied among the innumerable methods used in controlled release of drugs from a pharmaceutical dosage form.

Keywords: Multilayer tablet, extended release tablet, Metoprolol succinate, Ramipril.

INTRODUCTION

Tablet is a solid pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compressed form a powder into a solid dose.

Bilayer tablet concept has been investigated to develop combination of sustained and immediate released tablet 1. Many terms used to describe extended-release products including modified-release, Prolonged-release, controlled release, controlled-delivery, slow-release and sustained-release. These preparations have a reduced rate of release of active substance. Delayed-release product are modified-release they involve the release of discreate amount of drug sometime after drug administration. Extended release is a designed to slowly release a drug in the body over an extended period of time specially to reduce dosing frequency.

The development of pharmaceutical product for oral delivery, irrespective of it's physical form involves varying extent of optimization of dosage form characteristics within the inherent constraints of GI physiology. Therefore, the fundamental understanding of various disciplines including GI physiology, pharmacokinetic, pharmacodynamic, and formulation design are essential to achieve a systematic approach to the successful development of an oral pharmaceutical dosage form.

The pharmaceutical companies are currently developing bilayered tablets, for a variety of reasons: patent extension, therapeutic, marketing to a few. To reduce capital investment, quit often existing but modified tablet presses are used to develop and produce such tablets. Multilayer tablet are bilayer, trilayer and four layer tablets. Mainly bilayer tablet is the new era for the successful development of controlled release formulation. Bilayer tablet is single dosage form with combination of two or more Active Pharmaceutical Ingredients (API) which promoting patient convenience compliance. Bilayer tablet are the great example of avoiding chemical incompatibilities between the APIS, and providing different drug release profile (immediate release with extended release). In Bilayer tablet, amongst the two layers first layer act for loading dose purpose and second will for maintenance purpose. Multilayer tablets made by compressing several different granulations fed into a die in succession, one on top of another in layers. Each layer comes from a separate feed frame with

individual weight control. Rotary tablet presses can be set up for two or three layers. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes.

The bilayered tablet is innovative drug delivery system. This is a type dosage form for oral administration in which one layer contains extended-release drug and another layers contains immediate releasing drug. Certain medical condition like hypertension, diabetes, arthritis, etc. Drug having short biologically half-life is required to give 2-3 times a day for maintaining constant plasma concentration.

Advantages of Multilayer tablets

Incompatible substances can be separated by formulating them in separate layers as s two layer tablet or separating the two layers by a third layer.

Two layer tablets may be designed for sustained release- one layer for immediate release of the drug and the second layer for extended release thus containing a prolonged drug-blood concentration.

Layers may be colored differently to identify the product

Allow the effective drug loading

Formulation cost reduction

Improves patient compliance

Metoprolol is $_{1}$- selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, Metoprolol also inhibits beta$_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic parasympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for – blockade. Animal and human experiments indicate that Metoprolol slows sinius rate and decreases AV nodal conduction. Ramipril inhibits ACE and inhibits formation of Angiotensin II. The plasma half-life of it's active metabolite ramiprilat is 8-18 hr, but terminal t- half is longer due to slow release of tissue bound drug.

MATERIAL AND METHOD

Metoprolol part-
Procedure:

Metoprolol, microcrystalline cellulose, hyroxypropylmethyl cellulose and carbomer-71G were sifted through #40.

The above materials were loaded into the RMG and mixed at slow speed impeller for 15 minutes.

The PVPK-30 binder solution was added slowly into the RMG at slow speed impeller and chopper off.

The mixing was continued at fast speed impeller and with chopper for 2 minutes until end point is reached.

The wet mass passed through 10mm screen.

The wet mass loaded in Fluidized Bed Dryer and then dried at 55-60°C until LOD was not more than 2%.

The dried material was sifted through # 20 using vibratory sifter.

At last lubrication was done with magnesium stearate.

PROTOYPE FORMULATION

Metoprolol Succinate

Table-1: Prototype formulation of Metoprolol Succinate

Sr. No.	Name of ingredients	Category
1.	Metoprolol succinate USP	Beta blocker
2.	Microcrystalline cellulose IP	Diluent
3.	Hydroxy Propyl Methyl Cellulose (Methocel K 15 M) USP	Rate Controlling polymer for sustained release
4.	Carbomer (Carbopol 71 G) USPNF	Release-modifying agent
5.	Povidine (P.V.P.K 30) IP	Tablet binder
6.	Isopropyl alcohol IP	Solvent for the binder preparation
7.	Magnesium stearate IP	Lubricant

Table-2: Development trials of Metoprolol Succinate

	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Trial 8	Trial 9	Repro batch
Metoprolol Succinate	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5
Lactose	108	-	-	-	-	-	-	-	-	-
MCC	-	108	96	55	49	22.5	0	7.25	20.5	20.5
HPMC	62/25 %	62/25 %	62/25 %	98/40 %	98/40 %	122.5/50 %	147/58 %	135.75/55 %	122.5/50 %	122.5/50 %
Carbopol	-	-	12/5%	12/5%	18/7%	18/7%	22/9%	22/9%	22/9%	22/9%
PVPK-30	25	25	25	30	30	30	30	30	30	30
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Ramipril part-

Procedure –

Ramipril was sifted through # 60and sodium bi carbonate was sifted through # 40 sieve and both were mixed geometrically

Cross carmellose sodium was sifted through # 40 sieves and was mixed with above mixture.

Then directly compressible lactose, pregelatinised starch were sifted through # 40 sieves.

Then color yellow iron oxide was passed through # 100 sieves, mixed with above ingredients.

The above blend was loaded into RMG and mixed for approximately 15 minutes.

At lubrication was done with sodium stearyl fumarate.

PROTOTYPE FORMULATION

Ramipril

Table-3: Protype formulation of Ramipril

Sr.No	Name of ingredients	Category
1	Ramipril IP	ACE inhibitor
2	Sodium bi carbonate IP	Buffering agent
3	Directly compressible lactose DCL 21(PHARMATOSE) IP	Diluent
4	Cross carmellose sodium USPNF	Super disintegrant
5	Pregelatinised starch BP	Binder
6	Sodium stearyl fumarate BP	Lubricant
7	Yellow oxide of iron IH	Coloring agent

Table-4: Development Trials of Ramipril

	Trial 1	Trial 2	Trial 3	Trial 4	Repro batch
Ramipril	5	5	5	5	5
Sodium bi-carbonate	10	10	10	10	10
DCL-21	-	101.5	94	94	94
Micro-crystalline cellulose	101.5	-	-	-	-
Cross carmellose sodium	-	-	5	5	5
Pregelatinised starch	30	30	30	30	30
Sodium stearyl fumarate	2.5	2.5	5	5	5
Yellow oxide of iron	1	1	1	1	1

EVALUATION OF BLEND

The ready for compression was evaluated for flow properties as follows 1 Bulk density. Apparent bulk density (p_b) was determined by pouring blend into a graduated cyclinder. The bulk volume (V_b) and weight of the powder (M) was determined.

The bulk density was calculated using the formula.

$$p_b = \frac{M}{Vb}$$

Tapped densities

It was determined by placing a graduated cyclinder, containing a known mass of drug excipients blend, which was tapped for a fixed time until the powder bed volume has reached a minimum. The minimum volume (V_t) occupied in the cyclinder and

the weight (M) of the blend was measured. The tapped density (p_t) was calculated using the following formula.

$$p_t = \frac{m}{(Vt)}$$

3% Compressibility

The simplest way for measurement of free flow of powder is compressibility. An indication of the case with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows

$$I = \frac{pt-pb}{pt} \chi\ 100$$

Where p_b is tapped density and p_b is the bulk density

Table-5: Compressibility Index

Sr. No	Compressibility Index	Flowability
01	05-12	Excellent
02	12-16	Good
03	18-21	Fair-possible
04	23-35	Poor
05	33-38	Very poor
06	>40	Very very poor

4Angle of Repose

It is the maximum angle that can be obtained between the freestanding surface of the granule heap and the horizontal

Tan Θ =2h/d

If the angle of repose is less than 30° then granules are considered to be free flowing. Angle of repose is greater than 40° indicate poor flow.

Evaluation of physical parameter of tablet

Description

Yellow colored biconvex, uncoated bilayered tablet of which one layer is white to off-white and other layeris light yellow to yellow colored.

Average weight

Weigh twenty tablets taken randomly on an electronic balance and determines the average weight. It should be within the specified limits.

Physical Appearance

Physical appearance of the tablet, its visual identifies and overall elegance is essential for consumer acceptance, for control of lot to lot and from tablet to tablet uniformity. Tablet thickness is the only dimensional variable related to compression. Also the diameter of tablet should be maintained with specification

The tablet thickness is measured using a slide calipers. This is a rapid method of measurement. The thickness should be controlled with ± 5% variation of standard value. The size and shape of the tablets, the density of the materials used and their proportion determines the weight of tablet.

4Uniformity of weight

Weight individually twenty tablets taken at random and determine the variation from average weight. It should be within the specified limits.

Hardness

Mansanto hardness tester was used to test the hardness of the tablets. Tablet was kept diagonally between the two plungers and a pressure was applied to it until the tablet down to two parts completely and the reading on the scale was noted down. Ten tablets were tested for hardness.

Friability

Twenty tablets were weighed and placed in the USP friability tester. After 100 revolution at 25rpm tablet were dedusted and weighed.

The percentage friability was measured using the formula:

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

Where,

%F = Friability in percentage,

W_o = initial weight of tablet,

W = weight of tablet after revolution.

RESULT AND CONCULSION

Precompression Study

Metoprolol Succinate

Table-6: Physical parameter of blend of Metoprolol Succinate

Trial No / Parameters	1	2	3	4	5	6	7	8	9
Bulk Density, p_b (gm/cm^3)	0.33	0.31	0.33	0.32	0.31	0.30	0.28	0.31	0.33
Tapped Density, p_t, (gm / cm^3)	0.38	0.37	0.41	0.38	0.37	0.37	0.34	0.37	.38
Angle of repose, (Tan Θ)	24	26	30	25	25	27	26	24	26

Ramipril

Table-7: Physical Parameter of Blend of Ramipril

Trial No / Parameters	1	2	3	4	Repro Batch
Bulk Density, p_b (gm/cm^3)	0.48	0.50	0.50	0.53	0.50
Tapped Density, p_t (gm/cm^3)	0.56	0.59	0.56	0.62	0.62
Angle of Repose, (Tan Θ)	28	24	23	24	28
% Compressibility *I*	14.3	15.2	10.7	14.5	19.35

Post Compression Study

Evaluation is a necessary step, since it enables the development scientist to know whether his product possesses the projected qualities or not following tests had been done on the tablets, which are reported in Table

Table-8: Physical Parameter of Tablet

Specification	Trial No.								
	1	2	3	4	5	6	7	8	9
Thickness(mm)	3.92	3.86	3.94	3.90	3.80	3.85	3.90	3.93	3.97
Hardness (kg/cm^2)	8	8.5	8	9	8.5	8	8	8.5	8.5
Friability %	0.12	0.14	0.22	0.20	0.11	0.15	0.16	0.21	0.20
Uniformity of Weight (mg)	340	343	340	345	344	342	344	342	346

Trial 1:

In first trial25% HPMC of total tablet was taken using lactose as diluent, but release of drug was not prolonged and show large variation in release of drug.

Table-9: Cumulative % Drug release in Trial 1

Time (hr)	(MP)	Trial 1 Cumulative % Release
0	0	0
1	18.7	41.36
4	35.46	77.09
8	54.29	94.41
20	83	100

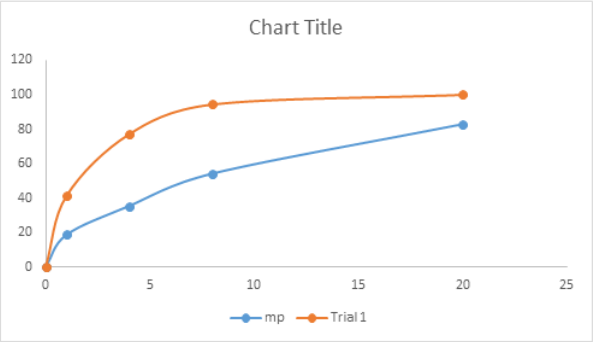

Fig-1: Comparative in vitro Release Profile of market product and Trial 1

Trial 2

Second trial was taken by replacing lactose with MCC and keeping concentration of HPMC same as in previous trial to study as there is any effect of diluent on release. As lactose is water soluble it may not help to keep the integrity of matrix.

Table-10: Cumulative % Drug Release in Trial 2

Time	(MP)	Trial 2 Cumulative % release
0	0	0
1	18.7	38.86
4	35.46	71.56
8	54.29	92.81
20	83	100

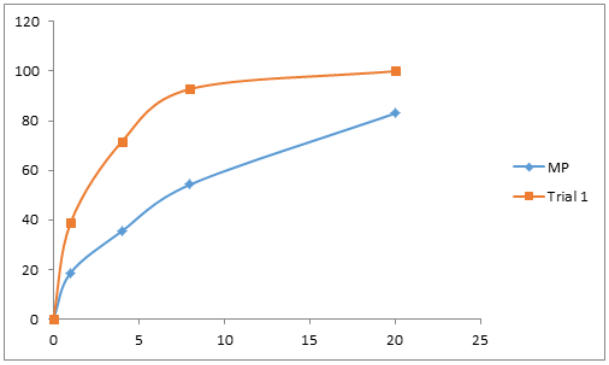

Fig-2: Comparative in Vitro Release Profile of Market Product and Trial 2

Trial 3

In third trial Carbopol 71G, 5% as a release rate retardant, and concentration of HPMC 25%, but as such no release was retarded.

Table-11: Cumulative % Drug Release in Trial 3

Time (hr)	(MP)	Trial Cumulative % release
0	0	0
1	18.7	36.12
4	5.46	60
8	54.29	80.16
20	83	96.31

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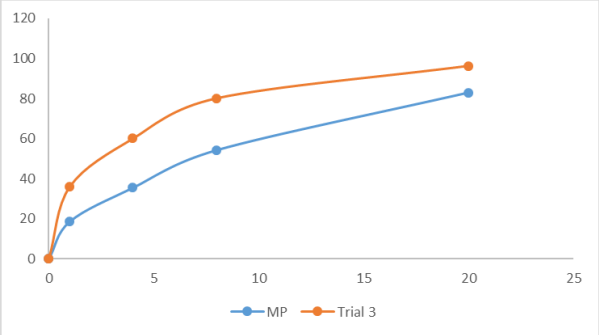

Fig-3: Comparative in Vitro Release Profile of Market Product and Trial 3

Trial 4

In fourth trial concentration of PVPK-30 and 40% HPMC was increased, keeping same concentration of Carbopol.

Table-12: Cumulative % Drug Release in Trial 4

Time (hr)	(MP)	Trial 4 Cumulative % release
0	0	0
1	18.7	29.67
4	35.46	47.31
8	54.29	67.43
20	83	94

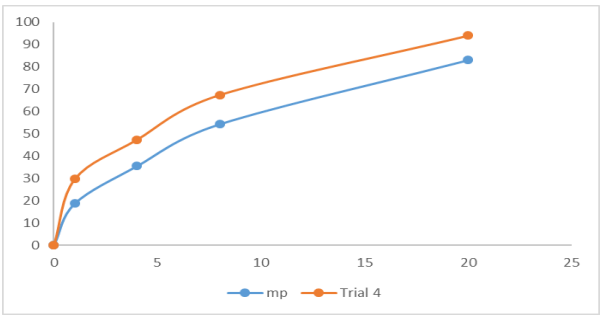

Fig-4: Comparative in Vitro Release Profile of Marketed Product and Trial 4

Trial 5

Fifth trial batch was taken with same concentration of HPMC, but Concentration of Carbopol was increased by 2% i.e. 7%.

Table-13: Cumulative % Drug release in Trial 5

Time (hr.)	MP	Trial 5 Cumulative % Release
0	0	0
1	18.7	25.63
4	35.46	36.54
8	54.29	61.92
20	83	86.62

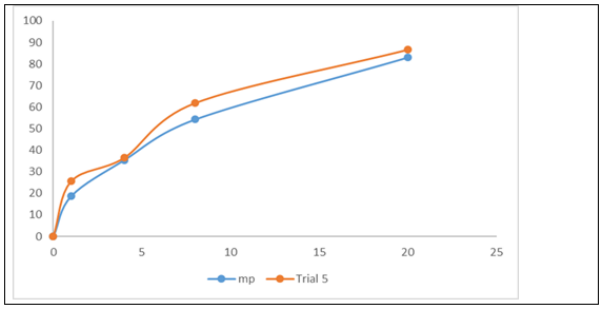

Fig-5: Comparative in Vitro Release Profile of Market Product and Trial 5

Trial 6

In this trial batch HPMC K-15 was taken 50%, and carbopol 71G%

Table-14: Cumulative % Drug Release in Trial 6

Time	(MP)	Trial 6 Cumulative % release
0	0	0
1	18.7	18.31
4	5.46	44.17
8	4.29	53.61
20	83	81.14

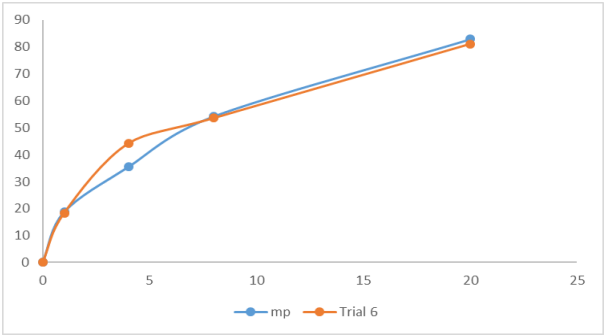

Fig-6: Comparative in Vitro Release Profile of Market Product and Trial 6

Trial 7

In this trial concentration of HPMC was taken 58%, and quantity of Carbopol 71G was increased by 2% i.e.9% was taken.

Table-15: Cumulative % Drug Release in Trial 7

Time	(MP)	Trial 7 Cumulative % release
0	0	0
1	18.7	14.69
4	35.46	34
8	54.29	49.89
20	83	74.18

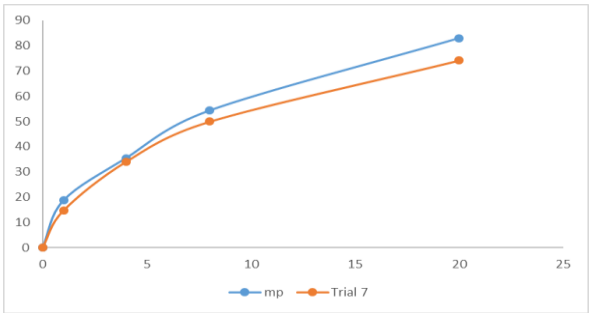

Fig-7: Comparative In vitro Release Profile of Market Product and Trial 7

Trial 8

Table-16: This trial was carried out by taking 55% of HPMC and 9% of Carbopol 71G

Time	(MP)	Trial 8 Cumulative % release
0	0	0
1	18.7	16.39
4	35.46	35.13
8	54.29	58.79
20	83	78.12

Table no: Cumulative % drug release in Trial 8

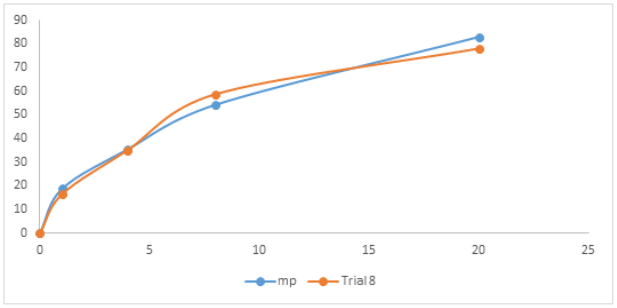

Fig-7: Comparative in Vitro Release Profile of Market Product and Trial 8

Trial 9:

This trial was carried out by taking 50% of HPMC and 90% of Carbopol 71G.

Table-17: Cumulative % Drug Release in Trial 9

Time (hr.)	(MP)	Trial 9 Cumulative % release
0	0	0
1	18.7	15.19
4	35.46	37
8	54.29	56
20	83	85.09

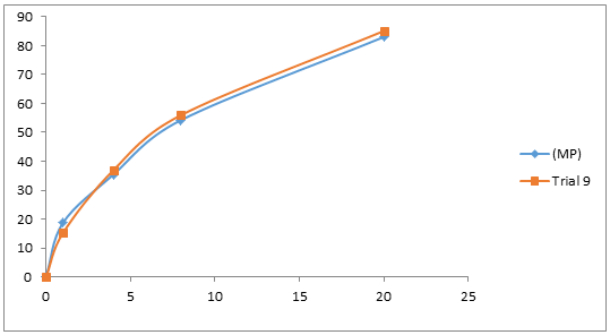

Fig-9: Comparative In vitro Release Profile of Market Product and Trial 9

Reproducible Batch
Trial 9

Table-17: This trial was carried out by keeping same concentration HPMC and Carbopol 71G as in

Time (hr.)	(MP)	Repro-batch cumulative % release
0	0	0
1	18.7	15
4	35.46	34.20
8	54.29	54.40
20	83	88.88

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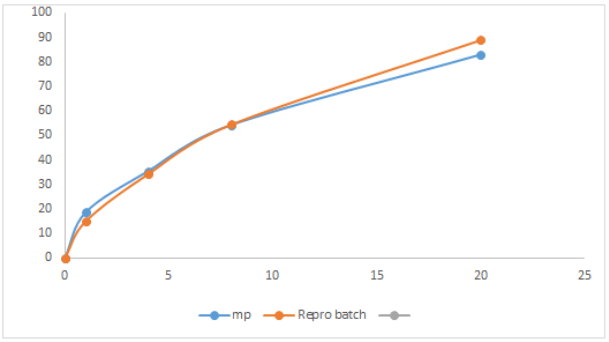

Fig-10: Comparative In Vitro Release Profile of market Product and Reproducible batch

CONCLUSIONS

In the investigation, an attempt has been made to develop Bilayered oral administration E.R. formulation of metoprolol succinate by matrix tablet using hydrophilic polymers in optimum concentration in one layer and second layer of Ramipril with immediate release.

From our study was observed that best retardation for E.R. formulation of metoprolol succinate 50mg was containing 50% HPMC k-15 (15000 cps) may be due to its swelling effect. Betterment in retardation was found with 9% Carbopol 71G due to its high viscosity (90,000-1, 00,000 cps) which will retard the diffusion of drug through matrix. The above formulation gave good release for Metoprolol succinate and release was extended up to 20 hours. This study concludes that viscosity is major factor affecting the release of metoprolol succinate.

In that study found that HPMC viscosity, the presence of Carbopol and their interaction has significant impact on the release of the delivery system. The decrease in the release rate was observed with an increase in the viscosity of the polymeric system. The % Drug release of oral Metoprolol succinate extended release tablet was also studied in PH 1.2 buffer for 2 hours to see the effect of dissolution medium. Ramipril was immediate release layer. In this layer to reduce the disintegration time cross-carmellose sodium was added, disintegration time was reduced from 10 minute to 6 minute and to avoid sticking concentration sodium stearyl fumarate was increased from 2% to 4%

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