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Preparation and Evaluation of Sustained Release Matrix Tablets of Penbutolol Sulfate

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ABSTRACT

The purpose of the present study was to prepare and characterize twice-daily sustained-release matrix tablets of Penbutolol Sulfate (PS) using different concentrations of hydrophilic, hydrophobic, and plastic polymers. The effect of the nature of the diluents and the method of preparation was also studied. Preparations were evaluated for the release of PS for 12 hours using the United States Pharmacopoeia (USP) type-II dissolution apparatus. Along with physical properties, the dynamics of water uptake and erosion degree of tablets were also studied. The *in-vitro* drug release study revealed that the most successful formulation of the study F23 (with a drug to polymer ratio 1:2) which includes both HPMC K100M and EC (1:1), extended the drug release up to 12 hours, exhibited satisfactory drug release in the initial hours, and the total release pattern was close to the theoretical release profile with similarity factor (f_2) above 50. The drug release from optimized formulation (F23) followed first-order kinetics via non-Fickian (anomalous) diffusion. FTIR studies revealed that there was no interaction between the drug and excipients. Microcrystalline cellulose (water-insoluble) was found to be better diluent compared to lactose (water-soluble) in the formulation of sustained-release tablets of water-soluble drugs like PS. Compared to direct compression, wet granulation was found to be the method of choice for the preparation of these matrix tablets. In conclusion, the results indicated that the prepared sustained-release tablets of PS could perform therapeutically better than conventional tablets with improved efficacy and better patient compliance.

1. INTRODUCTION:

High patient compliance and flexibility in designing dosage forms attracted the oral drug delivery systems to be the most convenient mode of drug administration when compared to other dosage forms. Of these, matrix systems have gained widespread importance in controlled drug delivery due to cost-effective manufacturing technology. The swellable matrices for oral administration are commonly prepared as tablets by compression of hydrophilic micro particulate polymers.[1].

Many natural polysaccharides like chitosan, alginate, and gums/mucilage like Xanthan, gaur gum more sustain the release of drug from matrix system than widely used synthetic materials like methylcellulose, hydroxypropyl methylcellulose, and sodium carboxymethyl cellulose. These natural or synthetic polysaccharides form a hydrogel in aqueous media. Over the past few decades, advances in hydrogel technologies have spurred development in many biomedical applications including controlled drug delivery [2-7].

Hydrogels are very versatile materials and have attracted significant attention recently as a drug delivery system. The hydrogels are entangled polymer networks that trap a large amount of water without dissolving. Hydrogels are comprised of cross-linked polymer networks that have a high number of hydrophilic groups or domains. These networks have a high affinity for water but are prevented from dissolving due to the chemical or physical bonds formed between the polymer chains and water penetrates these networks causing swelling, giving the hydrogel its form. The development of hydrogels from a variety of synthetic and natural materials has provided a great deal of flexibility in fabricating modified release systems [8].

Penbutolol Sulfate (PS) is rapidly and completely absorbed. Peak plasma concentrations of penbutolol occur between 2 and 3 hours after oral administration and are proportional to single and multiple doses between 10 and 40 mg once a day. The average plasma elimination half-life of penbutolol is approximately 5 hours in normal subjects. There is no significant difference in the plasma half-life of penbutolol in healthy elderly persons or patients on renal dialysis. Twelve to 24 hours after oral administration of doses up to 120 mg, plasma concentrations of parent drug are 0% to 10% of the peak level. No accumulation of penbutolol is observed in hypertensive

patients after 8 days of therapy at doses of 40 mg daily or 20 mg twice a day. Penbutolol is approximately 80% to 98% bound to plasma proteins.

The metabolism of penbutolol in humans involves conjugation and oxidation. The metabolites are excreted principally in the urine. When radiolabeled penbutolol was administered to humans, approximately 90% of the radioactivity was excreted in the urine. Approximately 1/6 of the dose of penbutolol was recovered as penbutolol conjugate while the remaining fraction was not identified. Conjugated penbutolol has a plasma elimination half-life of approximately 20 hours in healthy persons, 25 hours in healthy elderly persons, and 100 hours in patients on renal dialysis. Thus, accumulation of penbutolol conjugate may be expected upon multiple-dosing in renal insufficiency. An oxidative metabolite of penbutolol, 4-hydroxy penbutolol, has been identified in small quantities in plasma and urine. It is 1/8 to 1/15 times as active as the parent compound in blocking isoproterenol-induced ß-adrenergic receptor responses in the isolated guinea-pig trachea and is 1/8 to 1 time as potent in anesthetized dogs.

In this present study, an attempt has been made to develop the sustained-release matrix tablets of Penbutolol sulfate using hydrophilic HPMC K100M CR in combination with hydrophobic ethylcellulose, and the sustained pattern of Penbutolol sulfate was evaluated by in-vitro drug release for 12 hours. The drug release data were plotted using various kinetic equations (zero-order, first-order, Higuchi's kinetics, Korsmeyer's equation, and Hixson-Crowell cube root law) to evaluate the drug release mechanism and kinetics. In-vivo drug release, biopharmaceutical evaluation, and *in-vitro*/*in-vivo* correlations were beyond the scope of this study and will be considered in future work.

2. MATERIALS AND METHODS:

Construction of Standard Graph of Penbutolol sulfate

An accurately weighed amount of 100 mg Penbutolol Sulfate was transferred into a 100 ml volumetric flask. 20 mL of 0.1N hydrochloric acid (HCl) was added to dissolve the drug and volume was made up to 100 mL with the same HCl. The resulted solution had a concentration of 1mg/ml which was labeled as 'stock'. From this stock solution, 10 ml was taken and diluted to 100 mL with 0.1N HCl which has given the solution having the concentration of 100 mcg/mL.

Necessary dilutions were made by using this second solution to give the different concentrations of Penbutolol Sulfate (5 to 50 mcg/mL) solutions.

The absorbances of the above solutions were recorded at λ_{max} (271 nm) of the drug using a double beam UV-Visible spectrophotometer. A standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis). Similarly, a standard graph was plotted with a 6.8 pH phosphate buffer.

Preparation of 0.1 N HCl: Accurately measured 8.5 mL of concentrated hydrochloric acid was added to 1000 mL of distilled water.

Preparation of pH 6.8 phosphate buffer: Accurately measured 50 mL of 0.2 M potassium dihydrogen orthophosphate was transferred to a 200 mL volumetric flask and 22.4 mL of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 mL with distilled water, mixed and pH was adjusted to 6.8 with 0.2 M sodium hydroxide or 0.2 M orthophosphoric acid.

Preparation of 0.2 M potassium dihydrogen phosphate solution: Accurately weighed 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

Calculation of Sustained-Release Dose & Theoretical Release Profile of Penbutolol sulfate

The total dose of Penbutolol sulfate for twice-daily SR formulation was calculated by Robinson Eriksen (Robinson and Eriksen, 1966) equation using available pharmacokinetic data.

The zero-order drug release rate constant (k_0) was calculated using the following equation

$$k_0 = DI \times k_e$$

Where DI is the initial dose (i.e., conventional dose = 10 mg) and k_e is the first-order rate constant for overall elimination.

$$k_e = 0.693 / t_{1/2}$$

where $t_{1/2}$ = Biological half-life of timolol maleate = 4 h

Therefore $k_e = 0.693 / 4$

$= 0.1732$ mg/h.

Availability rate $R = k_e \times DI$

$= 0.1732 \times 10$

$= 1.732$ mg/h.

Loading dose = $D_L = DI - R \times t_{max}$

where $t_{max} = 2$ h

Therefore $D_L = 10-(1.732 \times 2)$

$= 6.54$ mg.

Maintenance dose = $D_M = R \times H$

where H = Number of hours for which sustained action is desired after the initial release.

Therefore $D_M = 1.732 \times 11$

$= 19.05$ mg.

Total dose required = $D_T = D_L + D_M$

$= 6.54+19.05$

$= 25.59$ mg

$\cong 25$ mg

Hence an oral controlled release formulation of timolol maleate should contain a total dose of 25 mg and should release 6.54 mg in the first 1 hour like conventional tablets, and 1.73 mg/h up to 12 hours thereafter.

Preparation of Penbutolol sulfate Matrix Tablets

All the matrix tablets, each containing 25 mg of timolol maleate, were prepared by wet granulation method and some of the formulations were prepared by direct compression method also to study the effect of method of manufacture on the drug release.

Wet granulation: Drug and the diluent (MCC or Lactose) were sifted through sieve No. 40 manually and mixed well to ensure the uniformity of the premix blend. Several drug-diluent premixes were then mixed with the selected ratio of polymer(s), previously sifted through sieve No. 40, for 5 minutes. Premix blend was wet granulated with 5% w/v solution of PVP K-90 in a mortar. The wet mass was passed through the No. 18 sieves. The wet granules were dried at 55°C ± 5°C for 1 hour in a hot-air oven and the dried granules were sieved through a No. 22 sieves.

These granules were blended with lubrication mixture (1% w/w magnesium stearate and 2% w/w talc) and compressed using 16 stations rotary tableting machine, equipped with flat-faced, round punches of 6-mm diameter.

Direct compression: Accurately weighed amounts of drug, polymer, and diluent were mixed geometrically in a mortar. This mixture was passed through the No. 40 sieves and thoroughly mixed in a polythene bag for 15 minutes. The powder blend was then lubricated with magnesium stearate and talc for 2 minutes and compressed into tablets on a 16 station rotary tableting machine using 6 mm round, flat-faced punches.

The drug-polymer ratio was developed to adjust drug release as per the theoretical release profile and to keep the total weight of the tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 120 mg with different drug-polymer ratios like 1:0.5, 1:1, 1:1.5, 1:2. The various polymers used were HPMC K15M, Polyethylene oxide, Kollidon-SR, HPMC K100M CR, and Ethylcellulose. Diluents like MCC (water-insoluble) or lactose (water-soluble) were used for the preparation of matrix tablets.

Table. No. 1: List of Different Formulations

Formulae	Polymer (s)	Diluent	Method
F1 to F4	HPMC K15M	MCC	Wet granulation
F5 to F8	Polyethylene oxide	MCC	Wet granulation
F9 to F12	HPMC K 100M	MCC	Wet granulation
F13 to F16	Ethylcellulose	MCC	Wet granulation
F17 to F20	Kollidon-SR	MCC	Direct compression
F21 to F25	HPMC K100M & EC	MCC	Wet granulation
F26 to F30	HPMC K 100M &HPMC K 15M	MCC	Wet granulation
F31 to F35	HPMC K100M & EC	Lactose	Wet granulation
F36 to F40	HPMC K100M & EC	MCC	Direct compression

Formulations

In the formulations prepared, the release retardants included were hydroxypropylmethylcellulose (HPMC K15M, HPMC K100M CR), polyethylene oxide (PEO), ethylcellulose (EC), and Kollidon-SR. Microcrystalline cellulose (MCC), lactose were used as diluents. Magnesium stearate (MS) 1% and talc 2 % were used as lubricants. 5 % w/v solution of polyvinylpyrrolidone (PVP-K90) in isopropyl alcohol (IPA) was used as a binder. Compositions of different formulations were given in the following Tables (Table No. 2 to Table No. 10).

Table No. 2: Composition of Matrix Tablets Containing HPMC K15M*

F.Code	TM (mg)	HPMC K15M (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F1	25	12.5	72.9	6	qs	1.2	2.4	120
F2	25	25	60.4	6	qs	1.2	2.4	120
F3	25	37.5	47.9	6	qs	1.2	2.4	120
F4	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F1, F2, F3, and F4 respectively.

Table No. 3: Composition of Matrix Tablets Containing Polyethylene Oxide

F.Code	TM (mg)	PEO (mg)	MCC (mg)	PVP-K90 (mg)	IPA (ml)	MS (mg)	Talc (mg)	Total (mg)
F5	25	12.5	72.9	6	qs	1.2	2.4	120
F6	25	25	60.4	6	qs	1.2	2.4	120
F7	25	37.5	47.9	6	qs	1.2	2.4	120
F8	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F5, F6, F7, and F8 respectively.

Table No. 4: Composition of Matrix Tablets Containing HPMC K100M CR*

F.Code	TM (mg)	HPMC K 100M (mg)	MCC (mg)	PVP-K90 (mg)	IPA (ml)	MS (mg)	Talc (mg)	Total (mg)
F9	25	12.5	72.9	6	qs	1.2	2.4	120
F10	25	25	60.4	6	qs	1.2	2.4	120
F11	25	37.5	47.9	6	qs	1.2	2.4	120
F12	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F9, F10, F11, and F12 respectively.

Table No. 5: Composition of Matrix Tablets Containing Ethylcellulose*

F.Code	TM (mg)	EC (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F13	25	12.5	72.9	6	qs	1.2	2.4	120
F14	25	25	60.4	6	qs	1.2	2.4	120
F15	25	37.5	47.9	6	qs	1.2	2.4	120
F16	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F13, F14, F15, and F16 respectively.

Table No. 6: Composition of Matrix Tablets Containing Kolliodon-SR*

F.code	TM (mg)	Kollidon-SR (mg)	MCC (mg)	PVP-K90 (mg)	MS (mg)	Talc (mg)	Total (mg)
F17	25	12.5	72.9	6	1.2	2.4	120
F18	25	25	60.4	6	1.2	2.4	120
F19	25	37.5	47.9	6	1.2	2.4	120
F20	25	50	35.4	6	1.2	2.4	120

* Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F17, F18, F19, and F20 respectively.

Table No. 7: Composition of Matrix Tablets Containing Combination of HPMC K100M and EC*

F.Code	TM (mg)	HPMC K100M (mg)	EC (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F21	25	40	10	35.4	6	qs	1.2	2.4	120
F22	25	30	20	35.4	6	qs	1.2	2.4	120
F23	25	25	25	35.4	6	qs	1.2	2.4	120
F24	25	20	30	35.4	6	qs	1.2	2.4	120
F25	25	10	40	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:2; HPMC to EC ratio is 4:1, 3:2, 1:1, 2:3, and 1:4 for F21, F22, F23, F24, and F25 respectively.

Table No. 8: Composition of Matrix Tablets Containing Combination of HPMC K100M and HPMC K15M*

F.Code	TM (mg)	HPMC K100M (mg)	HPMC K15M (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F26	25	40	10	35.4	6	qs	1.2	2.4	120
F27	25	30	20	35.4	6	qs	1.2	2.4	120
F28	25	25	25	35.4	6	qs	1.2	2.4	120
F29	25	20	30	35.4	6	qs	1.2	2.4	120
F30	25	10	40	35.4	6	qs	1.2	2.4	120

*qs = quantity sufficient; Drug to Polymer ratio is 1:2; HPMC K100M to HPMC K15M ratio is 4:1, 3:2,1:1, 2:3, and 1:4 for F26, F27, F28, F29, and F30 respectively.

Table No. 9: Composition of Matrix Tablets Containing Combination of HPMC K100M and EC (Lactose as a diluent)

F.Code	TM (mg)	HPMC K100M (mg)	EC (mg)	Lactose (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F31	25	40	10	35.4	6	qs	1.2	2.4	120
F32	25	30	20	35.4	6	qs	1.2	2.4	120
F33	25	25	25	35.4	6	qs	1.2	2.4	120
F34	25	20	30	35.4	6	qs	1.2	2.4	120
F35	25	10	40	35.4	6	qs	1.2	2.4	120

qs = quantity sufficient; Drug to Polymer ratio is 1:2; HPMC to EC ratio is 4:1, 3:2, 1:1, 2:3, and 1:4 for F31, F32, F33, F34, and F35 respectively.

Table No. 10: Composition of Matrix Tablets Containing Combination of HPMC K100M and EC (Direct Compression Method)

F.Code	TM (mg)	HPMC K100M (mg)	EC (mg)	MCC (mg)	PVP-K90 (mg)	MS (mg)	Talc (mg)	Total (mg)
F36	25	40	10	35.4	6	1.2	2.4	120
F37	25	30	20	35.4	6	1.2	2.4	120
F38	25	25	25	35.4	6	1.2	2.4	120
F39	25	20	30	35.4	6	1.2	2.4	120
F40	25	10	40	35.4	6	1.2	2.4	120

Drug to Polymer ratio is 1:2; HPMC to EC ratio is 4:1, 3:2, 1:1, 2:3, and 1:4 for F31, F32, F33, F34, and F35 respectively.

Evaluation of powder blends for recompression parameters (Angle of repose, Carr's index, Hausner's ratio): The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in

such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and the angle of repose was calculated using the following equation. tan θ = h/r Where, h, and r are the height and radius of the powder cone, θ is the angle of repose. The angle of repose values more than 40 indicates excellent, good poor flow properties. An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V0) was measured. Then the graduated cylinder was closed with a lid and set into the tap density tester (USP model). The density apparatus was set for 100 tabs and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formula. Bulk density = W/V0 Tapped density = W/Vf Where, W = weight of the powder; V0 = initial volume; Vf = final volume Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. CI = (TD - BD) x 100/ TD Where TD is the tapped density and BD is the bulk density. Hausner's ratio is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and as such could be used to predict powder flow properties. Generally, a value less than 1.25 indicates good flow properties, which is equivalent to 20 % of Carr's index.

Evaluation of tablets for a post-compression parameter (Hardness, Thickness, and weight variation): Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in the manufacture, packaging, and shipping. The hardness of the tablets was determined using the Monsanto Hardness tester. It is expressed in Kg/cm^2.

Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated. The thickness of three randomly selected tablets from each formulation was determined in mm using a Screw gauge. The weight variation test was performed as per the procedure of IP. The weight (mg) of each of the 20 individual tablets, selected randomly from each formulation was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation.

Drug content 13: The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 90 % to 110 % of the standard amount. Three tablets were weighed and taken into a mortar and crushed into a fine powder. An accurately weighed portion of the powder equivalent to about 25 mg of TM was transferred to a 50 ml volumetric flask containing 20 ml of 0.1N HCl. It was shaken by mechanical means for 1 h. Then it was filtered through a Whatman filter paper (No.1) and diluted to 50 ml with 0.1N HCl. From this resulted solution 1 ml was taken, diluted to 100 ml with 0.1N HCl, and absorbance was measured against blank at 271nm.

***In-vitro* Swelling study:** The swelling index of the matrix tablet was evaluated in 0.1 N HCL for the first 2 h and then in phosphate buffer pH 6.8 for 3 to 12 h. The initial weight of the tablet was determined and then the tablet was placed in 20 ml 0.1 N HCL in a Petri dish and then from hour 3 in phosphate buffer, 6.8 pH was incubated at 37^{o}C. The tablet was removed at different time intervals (1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0 and 12.0 h) blotted with filter paper and reweighed (W2). The swelling index is calculated by the formula: Swelling index = 100 (W2-W1) / W1 Where, W1 = Initial weight of the tablet, W2 = Final weight of the tablet.

Scanning Electron Microscopy: Electron micrographs of timolol maleate matrix tablets were obtained using a scanning electron microscope (model JSM T200, Joel Ltd., Tokyo, Japan). The specimens were coated under vacuum with gold in an argon atmosphere before observation. The scanning electron microscope was operated at an acceleration voltage of 20 kV.

***In-vitro* Drug Release Study:** The study was carried out in USP XXIII tablet dissolution test apparatus-II (Electrolab TDT-06), employing basket stirrer at 50 rpm and 900 ml of 0.1N HCL for first 2 h and then dissolution medium was changed with fresh phosphate buffer pH 6.8 as dissolution medium for 3 to12 h maintained at 37□0.5oC. At different time intervals, 5 ml of sample was withdrawn and replaced with fresh medium. The samples were filtered through 0.25 µm membrane filter paper and analyzed for timolol maleate after appropriate dilution at 295 nm using Shimadzu-1700 UV-Visible spectrophotometer.

Similarity Factor Analysis (*f2*): To determine the similarity factor, the *in-vitro* release profile of all the batches of tablets was compared with the theoretical release profile, which was

calculated earlier. If f2 > 50, it is considered that two products share similar drug release behaviors. The data were analyzed by the following formula15. *f2* = 50 log {*1+ (1/N) Σ (Ri – Ti) 2]-0.5 x 100} Where, N = number of time points, Ri and Ti = dissolution of reference and test products at time i. **Data analysis** 16: The ANOVA (Analysis of variance) was performed for all the variables like the concentration of guar gum, xanthan gum, sodium alginate; concentration of secondary polymers like EC (ethylcellulose) and HEC (hydroxyl ethyl cellulose) on different evaluation parameters like swelling behavior and *in-vitro* drug release. The regressional analysis was performed by using INSTAT software on the *in-vitro* release data to best fit into various kinetic models like zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell model according to the regression coefficient 'r2' values.

3. RESULTS AND DISCUSSION:

Standard Graph of Penbutolol Sulfate (PS)

The standard graph of Penbutolol Sulfate (PS) (Table No. 11) has shown good linearity with R^2 values 0.9955 and 0.9966 in 0.1 N HCl (Figure No. 1) and pH 6.8 buffer (Figure No. 2) respectively, which suggests that it obeys the "Beer-Lambert's law".

Table No. 11: Standard Graph of Penbutolol Sulfate (PS)

Conc. (mcg/mL)	Absorbance	
	0.1N HCl	6.8 pH Buffer
5	0.158	0.134
10	0.208	0.248
15	0.318	0.352
20	0.428	0.433
25	0.512	0.535
30	0.605	0.671
35	0.718	0.759
40	0.860	0.858
45	0.932	0.934
50	1.009	1.011
R^2	0.9956	0.9968

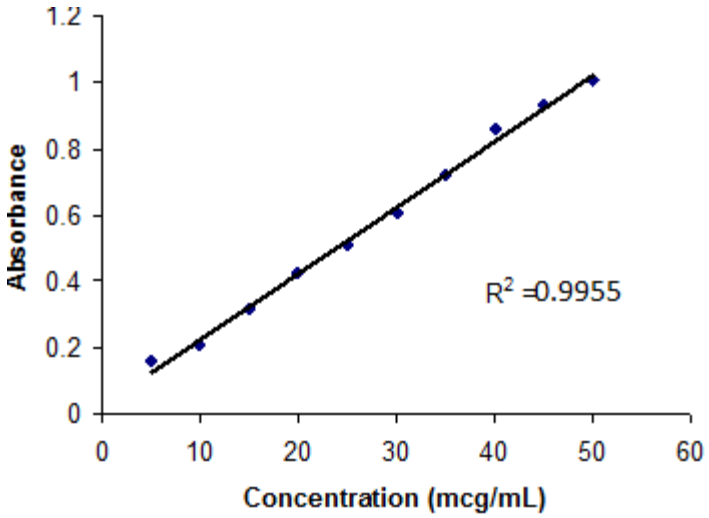

Figure No. 1: Standard graph of Penbutolol Sulfate (PS) in 0.1 N HCl

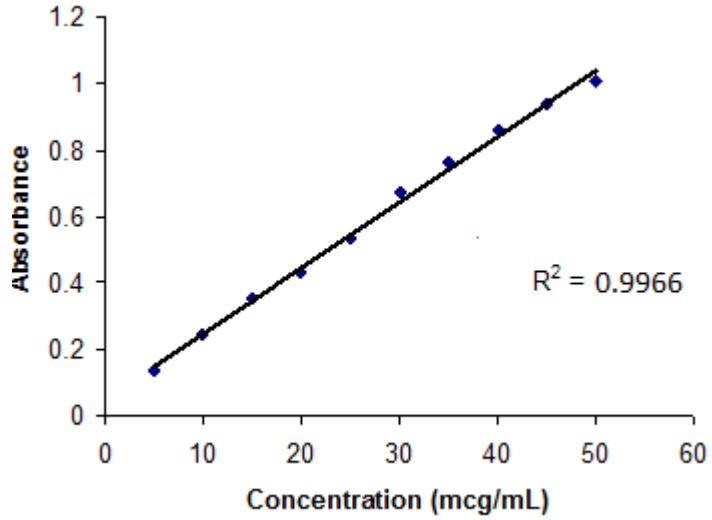

Figure No. 2: Standard graph of Penbutolol Sulfate (PS) in 6.8 pH buffer

Dose Calculations and Theoretical Release Profile

As calculated before, the total dose required for twice-daily SR formulation of Penbutolol Sulfate (PS) was found to be 25 mg and its theoretical release profile is given in Table No. 12.

Table No. 12: Theoretical Release Profile of Penbutolol Sulfate (PS) from SR tablets

Time (hours)	Cumulative % Release
1	26.16
2	33.08
3	40
4	46.92
6	60.76
8	74.6
10	88.44
12	> 90

Characterization of Granules

The granules for matrix tablets were characterized for the angle of repose, bulk density, tapped density, Carr's index, and drug content (Table No. 13). The angle of repose was less than 35° and Carr's index values were less than 21 for the granules of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties. The drug content was more than 90 % for all the granules of different formulations.

Table No. 13: Physical Properties of Precompression Blend

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	25.48	0.221	0.242	14.64	1.12
F2	26.33	0.308	0.361	15.22	1.16
F3	29.22	0.251	0.331	14.16	1.24
F4	26.45	0.332	0.371	12.23	1.26
F5	29.01	0.318	0.352	13.71	1.28
F6	32.32	0.338	0.342	19.28	1.19
F7	33.71	0.510	0.631	17.13	1.18
F8	33.29	0.529	0.618	17.16	1.13
F9	26.41	0.418	0.526	16.45	1.09
F10	28.44	0.471	0.552	15.89	1.28

F11	27.18	0.463	0.545	16.09	1.14
F12	25.18	0.518	0.581	12.28	1.81
F13	26.51	0.451	0.461	14.63	1.19
F14	24.32	0.471	0.564	9.14	1.16
F15	26.41	0.429	0.518	15.66	1.13
F16	28.16	0.552	0.641	13.93	1.15
F17	29.56	0.329	0.391	15.73	1.15
F18	28.71	0.364	0.423	15.41	1.16
F19	30.42	0.383	0.471	18.33	1.24
F20	26.41	0.373	0.443	15.13	1.13
F21	19.21	0.431	0.493	12.63	1.15
F22	21.24	0.518	0.571	10.52	1.38
F23	26.23	0.485	0.563	13.16	1.13
F24	25.41	0.493	0.564	12.71	1.15
F25	27.83	0.541	0.640	15.32	1.16
F26	27.31	0.511	0.593	13.71	1.14
F27	28.74	0.534	0.615	13.62	1.19
F28	28.42	0.497	0.581	14.41	1.14
F29	32.50	0.536	0.651	17.34	1.26
F30	33.18	0.485	0.583	18.12	1.29
F31	28.41	0.395	0.463	14.71	1.18
F32	22.28	0.441	0.581	9.17	1.09
F33	26.66	0.478	0.553	13.16	1.17
F34	32.41	0.521	0.623	16.51	1.18
F35	34.28	0.538	0.628	16.33	1.26
F36	30.39	0.452	0.543	17.53	1.18
F37	26.22	0.429	0.518	13.58	1.19
F38	29.44	0.481	0.518	14.18	1.13
F39	30.78	0.461	0.564	16.71	1.18
F40	31.66	0.514	0.632	18.25	1.24

Physical Evaluation of matrix tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 20. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 118.4 and 122.3 mg. The hardness of the tablets ranged from 5.08 to 6.16 kg/cm^2 and the friability values were less than 0.8 % indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 2.88 to 3.40 mm. All the formulations satisfied the content of the drug as they contained 90 to 103 % of timolol maleate and good uniformity in drug content was observed.

Thus, all the physical attributes of the prepared tablets were found to be practically within control.

In-Vitro Drug Release Studies

Drug Release from HPMC K15M Matrices

The results of release studies of formulations F1 to F4 are shown in Table No. 14 and Figure No. 3. The release of the drug depends not only on the nature of the matrix but also upon the drug-polymer ratio. As the percentage of polymer increased, the kinetics of release decreased. Formulation F1 composed of a drug-polymer ratio of 1:0.5 failed to sustain release beyond 6 h. This formulation underwent erosion before complete swelling could take place. Formulations with drug-polymer ratios 1:1 (F2), 1:1.5 (F3) have extended the drug release for 8 h. Further increasing the ratio to 1:2 (F4), the release was sustained for 10 h. All these formulations have shown more than 30 % release in the first 1 hour indicating burst release. This phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet before gel layer formation around the tablet core [9]. It is reported in the literature that more than 30 % release of drug in the first hour of dissolution indicates the chance of dose dumping [10].

Table No. 14: *In-vitro* Release Data of Penbutolol Sulfate (PS) from HPMC K15M Matrices*

TIME (HOURS)	F1	F2	F3	F4
1	41.66±0.53	39.54±0.62	37.33±1.51	36.44±1.81
2	53.54±0.31	50.11±0.51	50.18±0.45	48.32±1.61
3	74.43±1.75	67.23±0.18	63.11±0.76	62.53±0.33
4	82.23±1.19	80.44±1.90	77.54±0.32	75.23±0.45
6	94.55±1.16	89.58±1.54	86.71±1.18	83.61±0.52
8	-	97.32±0.43	93.51±0.61	91.33±0.51
10	-	-	-	98.53±0.93
12	-	-	-	-

*All **v**alues represent mean cumulative percent drug released ± SD (n=3).

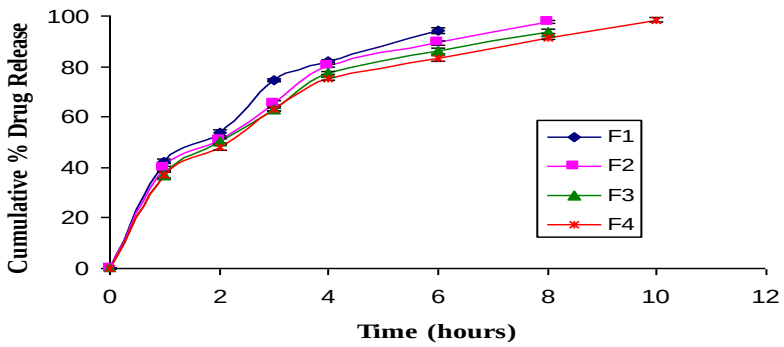

Figure No. 3: Release Profiles of Penbutolol Sulfate (PS) from HPMC K15M Matrices

Drug Release from Polyethylene Oxide Matrices

High molecular weight polyethylene oxides have recently been proposed as an alternative to HPMC in controlled release matrix tablets. As shown in Table No. 15 and Figure No. 4, the drug release was extended up to 6 h with initial burst release for the formulation F5. Further increase in the concentration of polymer the drug release was decreased slightly (97.19 %, 92.57 %, and 90.77 % at 8 hours for F6, F7, and F8, respectively). No burst release was observed during the first hour for the formulations F6, F7, and F8 with the release of 28.81 %, 25.56 %, and 22.38 % respectively. PEO matrices have shown faster drug release compared to HPMC-containing formulations.

Table No. 15: *In-vitro* Drug Release Data of Penbutolol Sulfate (PS) from Polyethylene Oxide Matrices*

TIME (HOURS)	F5	F6	F7	F8
1	32.34±1.21	28.82±0.71	25.51±0.42	22.32±0.92
2	44.12±0.52	40.32±0.41	37.31±1.63	35.21±0.82
3	58.21±0.93	55.41±0.72	54.42±1.54	51.62±0.93
4	73.72±1.11	69.33±0.93	66.52±1.44	63.41±0.63
6	92.31±0.54	84.63±0.51	82.41±1.21	79.52±0.81
8	-	97.11±1.42	92.51±1.32	90.71±0.62
10	-	-	-	-
12	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3).

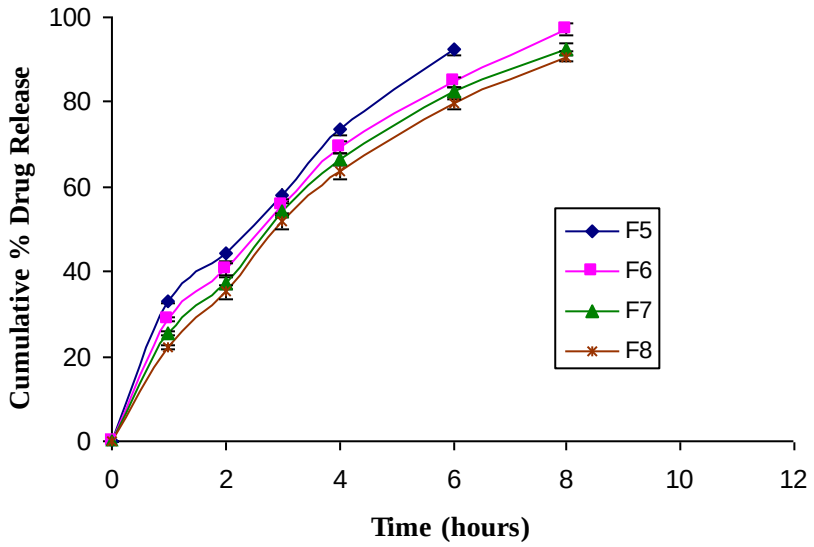

Figure No. 4: Release Profiles of Penbutolol Sulfate (PS) from Polyethylene Oxide Matrices

Drug Release from HPMC K100M CR Matrices

Low molecular weight HPMC is used predominantly for tablet film coating, while high molecular weight HPMC is used as a rate-controlling polymer to retard the release of drugs from a matrix at levels of 10 % to 80 % w/w in tablets and capsules. Results for the drug release from HPMC K100M matrices are shown in Table No. 16 and Figure No. 5. Formulations containing HPMC K100M (F9 to F12) have shown initial burst release and extended the release for 8 to 12 h. As the drug-polymer ratio increased to 1:2 (F12), the kinetics of release decreased (98.97 % at 12 h). The drug release was slower from matrices containing HPMC K100M compared to HPMC K15M. This may be due to the structural reorganization of HPMC. An increase in concentration and viscosity of HPMC may increase the tortuosity or gel strength of the polymer. When HPMC is exposed to an aqueous medium, it undergoes rapid hydration and chain relaxation to form a viscous gelatinous layer (gel layer). Failure to generate a uniform and coherent gel may cause rapid drug release.[11].

Similar findings were reported by few studies, they revealed that 30-40 % HPMC K100M was able to extend the release of water-soluble drugs for more than 8 h.[12].

Table No. 16: *In -vitro* Release Data of Penbutolol Sulfate (PS) from HPMC K100M Matrices*

Time (hours)	F9	F10	F11	F12
1	37.21±0.92	35.32±1.43	35.11±1.34	34.94±0.53
2	51.71±1.62	50.45±0.81	50.04±1.24	49.81±0.91
3	71.52±0.83	69.11±0.62	67.51±0.91	66.91±0.72
4	80.70±0.51	78.31±0.81	77.71±1.52	76.81±0.39
6	89.41±1.62	86.83±0.41	83.81±0.53	81.84±0.94
8	97.11±0.51	94.54±0.72	90.83±1.70	89.81±0.71
10	-	98.17±1.34	96.23±1.16	93.18±0.17
12	-	-	-	98.16±0.14

*All **v**alues represent mean cumulative percent drug released ± SD (n=3).

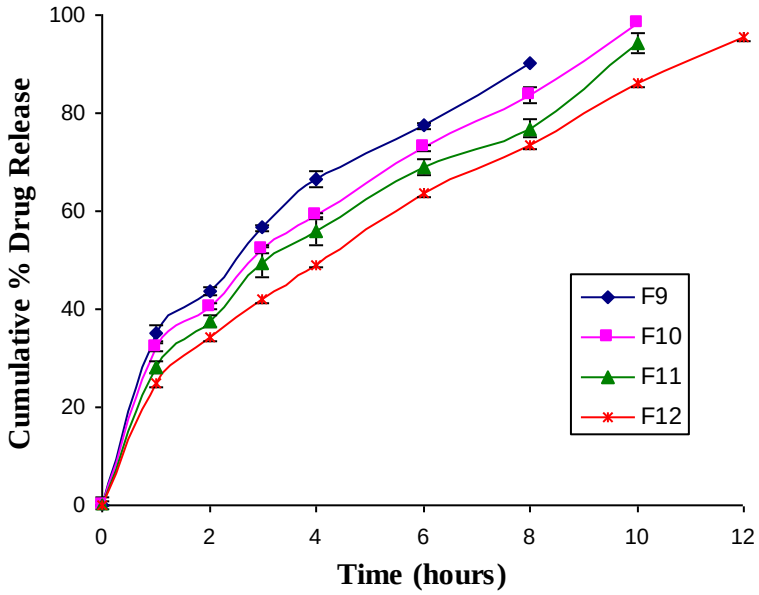

Figure No. 5: Release Profiles of Penbutolol Sulfate (PS) from HPMC K100M Matrices

Drug Release from Ethylcellulose Matrices

Hydrophobic ethylcellulose can be used as a matrix former for the formulation of sustained-release dosage forms. Batches containing ethylcellulose (F13 to F16) as release retardant, extended the release up to 8 -10 hours with initial burst release. As the drug-polymer ratio increased, the release rate was decreased. During dissolution, erosion was observed. The results were shown in Table No. 17 and Figure No. 6.

Table No. 17: *In-vitro* Release Data of Penbutolol Sulfate (PS) from Ethylcellulose Matrices*

Time (hours)	F13	F14	F15	F16
1	42.33±0.24	38.14±0.66	35.44±0.24	32.33±0.51
2	52.28±0.41	47.25±0.55	46.29±0.41	42.65±0.44
3	64.38±0.51	59.61±0.61	56.81±0.31	54.55±0.41
4	77.19±0.65	74.23±0.25	72.18±0.61	68.17±1.42
6	86.44±0.51	81.31±0.82	79.51±0.18	76.44±0.16
8	98.17±0.58	96.66±0.61	94.51±0.78	85.18±0.92
10	-	-	-	97.33±0.52
12	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3).

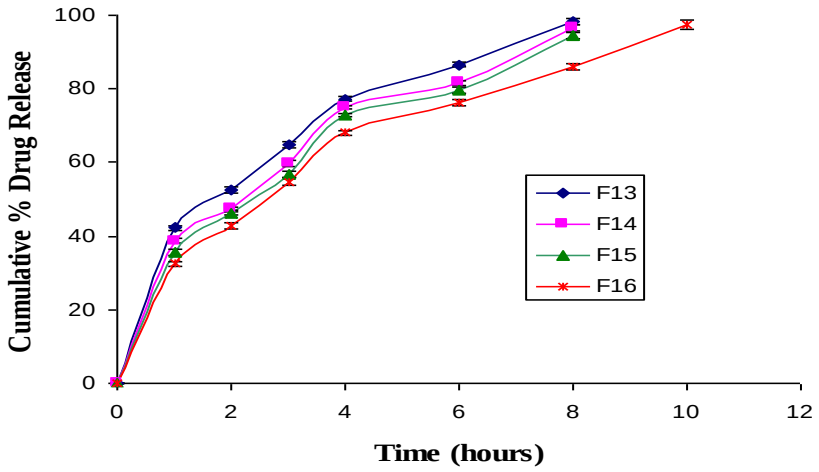

Figure No. 6: Release Profiles of Penbutolol Sulfate (PS) from Ethylcellulose Matrices

Drug Release from Kollidon-SR Matrices

Kollidon-SR based formulations (F17 to F20) have shown initial burst release with sustaining the release up to 8-10 hours. The results of release studies were given in Table No. 18 and Figure No. 7.

Table No. 18: *In-vitro* Release Data of Penbutolol Sulfate (PS) from Kollidon-SR Matrices*

Time (hours)	F17	F18	F19	F20
1	44.46±0.81	41.05±0.71	39.71±0.82	34.83±1.34
2	55.71±0.75	52.73±0.81	48.46±0.43	42.33±0.92
3	67.21±1.81	64.82±0.64	60.91±0.63	54.94±0.75
4	77.33±0.18	75.18±1.45	72.52±0.22	67.16±0.22
6	89.34±0.23	84.35±0.37	81.44±0.36	78.22±0.43
8	97.11±0.19	94.38±0.44	92.17±0.61	89.22±0.49
10	-	-	-	97.55±0.36
12	-	-	-	-

*All **v**alues represent mean cumulative percent drug released ± SD (n=3).

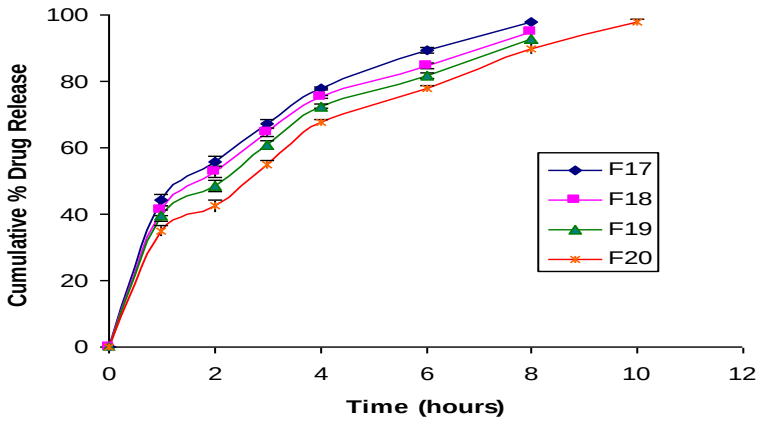

Figure No. 7: Release Profiles of Penbutolol Sulfate (PS) from Kollidon-SR Matrices

Drug Release from Combination of HPMC K100M and EC Matrices

Batches containing a combination of HPMC K100M and ethylcellulose (F21 to F25) have shown better release profiles (Table No. 19 and Figure No. 8). There was no burst release observed with formulations F21 to F23, and release was extended up to 10 to 12 hours. As the ethylcellulose concentration increases the drug release was decreased further in formulations F24 and F25. They prolonged the release for 8 hours only. Batch F23 was found to be optimum, as it showed a similar release pattern as that of the theoretical release profile.

Table No. 19: *In -vitro* Release Data of Penbutolol Sulfate (PS) from Tablets Containing HPMC K100M CR and Ethylcellulose*

Time (hours)	F21	F22	F23	F24	F25
1	27.33±0.22	28.16±0.27	25.18±1.38	31.38±1.28	32.19±1.71
2	40.55±0.28	42.19±0.28	35.41±1.41	44.28±1.21	47.51±1.66
3	54.19±1.81	55.91±1.28	51.19±1.61	59.61±1.55	64.19±1.41
4	66.33±1.19	66.44±1.41	62.81±1.68	70.19±1.09	75.18±1.04
6	80.22±1.15	83.19±1.09	73.16±2.33	87.18±1.17	89.11±1.38
8	88.16±1.28	90.71±1.18	81.18±2.02	94.33±1.28	98.18±0.28
10	95.51±2.39	98.29±2.18	87.18±2.73	-	-
12	-	-	97.31±2.71	-	-

*All values represent mean cumulative percent drug released ± SD (n=3).

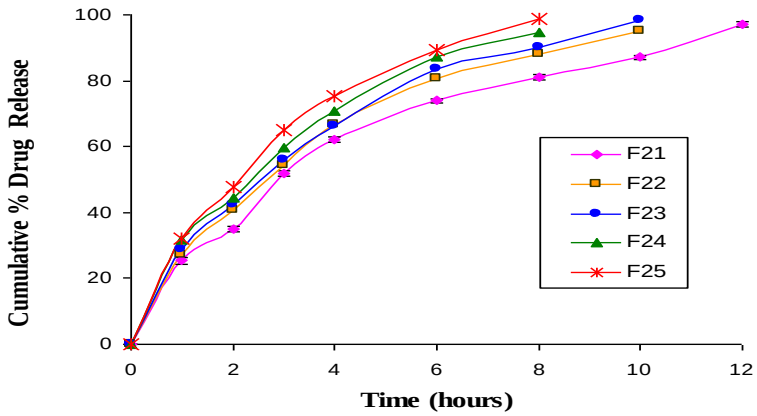

Fig. No. 8: Release Profiles of Penbutolol Sulfate (PS) from Tablets Containing HPMC K100M CR and Ethylcellulose

Drug Release from Combination of HPMC K100M and HPMC K15M

Matrices

A combination of HPMC K100M and HPMC K15M was extended the release for 10 hours. No significant change in the drug release was observed with changing the ratio of polymers. All the batches (F26 to F30) have shown burst release also. Data is given in Table No. 20 and Figure No.9.

Table No. 20: *In-vitro* Release Data of Penbutolol Sulfate (PS) from Tablets Containing HPMCK100M and HPMC K15M*

Time (hours)	F26	F27	F28	F29	F30
1	31.33±0.19	32.24±0.88	32.89±0.51	33.61±0.44	34.19±0.16
2	38.19±0.45	42.81±0.76	44.61±0.29	45.81±0.52	47.47±0.19
3	53.61±0.44	56.41±0.33	57.61±0.21	59.41±0.44	61.55±0.48
4	66.51±0.31	67.99±0.51	69.61±0.62	71.33±0.55	74.81±0.69
6	74.31±0.44	76.19±0.81	76.72±0.09	79.14±0.33	81.22±0.25
8	83.54±0.31	85.12±0.34	86.16±0.65	88.16±0.55	89.72±0.50
10	90.44±0.52	93.19±0.33	95.17±0.37	96.16±0.72	97.37±0.16
12	-	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3).

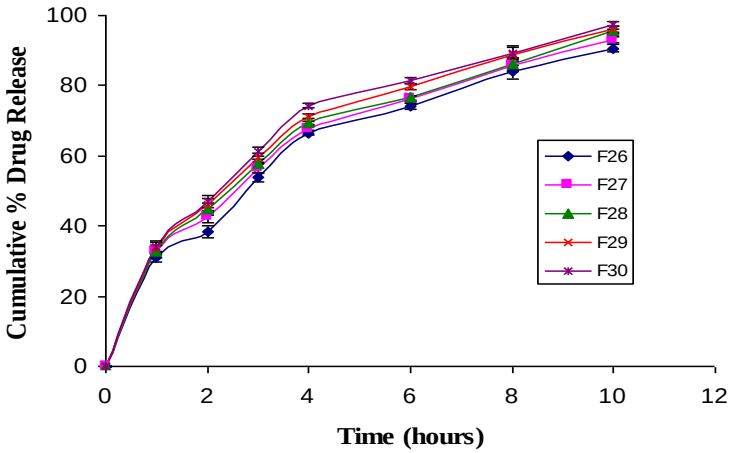

Figure No. 9: Release Profiles of Penbutolol Sulfate (PS) from Tablets Containing HPMCK 100M and HPMC K15M

Drug Release from Combination of HPMC K100M and EC Matrices (Lactose as a Diluent)

Lactose-containing batches (F31 to F35) have increased the rate of drug release as compared to MCC-containing formulations. This is due to the water-soluble nature of lactose and drug. Release data are given in Table No. 21 and Figure No. 10. Even though the total concentration of polymers was 40 %, more than 90 % drug release was observed within 6 hours only.

Table No. 21: *In -vitro* Release Data of Penbutolol Sulfate (PS) from Tablets with HPMC K100M and Ethylcellulose (Lactose as a diluent) *

Time (hours)	F31	F32	F33	F34	F35
1	31.22±0.16	33.17±0.31	33.22±0.71	35.26±0.41	37.18±0.44
2	42.33±0.23	44.16±0.18	44.33±0.19	48.16±0.38	52.44±0.23
3	53.17±0.33	56.52±0.41	59.31±0.14	62.16±0.33	67.22±0.51
4	65.44±0.26	68.31±0.48	68.19±0.33	71.15±0.19	77.25±0.22
16	77.18±0.72	80.44±0.52	81.18±0.49	92.66±0.59	94.48±0.18
8	91.22±0.38	96.51±0.61	98.38±0.61	-	-
10	-	-	-	-	-
12	-	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3).

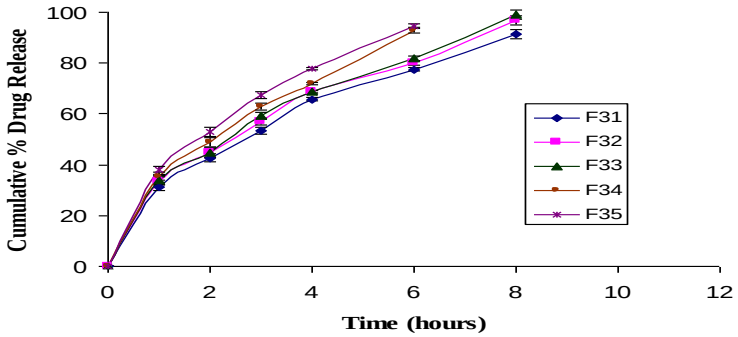

Figure No. 10: Release Profiles of Penbutolol Sulfate (PS) from Tablets with HPMC K100M and Ethylcellulose (Lactose as a diluent)

Drug Release from Combination of HPMC K100M and HPMC K15M Matrices

Compared to the wet granulation method, formulations prepared by direct compression (F36 to F40) have shown an increased rate of drug release (Figure No. 11 and Table No. 22). In the direct compression, the release was extended up to 8-10 hours with initial burst release, whereas with the wet granulation method release was extended up to 10 -12 hours without burst release.

Table No. 22: *In-vitro* Release Data of Penbutolol Sulfate (PS) from Tablets with HPMC K100M and Ethylcellulose (direct compression) *

Time (hours)	F36	F37	F38	F39	F40
1	32.84±0.82	35.21±0.84	37.11±0.63	39.81±0.52	41.20±0.79
2	40.41±0.30	45.54±0.75	48.81±0.56	51.53±0.61	53.51±0.71
3	53.79±0.24	56.61±0.41	59.18±0.36	63.81±0.41	65.96±0.53
4	65.08±0.41	69.24±0.75	73.31±0.46	76.84±0.62	77.71±0.52
6	77.24±0.81	82.74±0.64	85.94±0.75	89.51±0.64	89.81±0.63
8	88.53±0.61	92.84±0.53	95.41±0.62	98.73±0.56	97.34±0.51
10	97.94±0.81	-	-	-	-
12	-	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3)

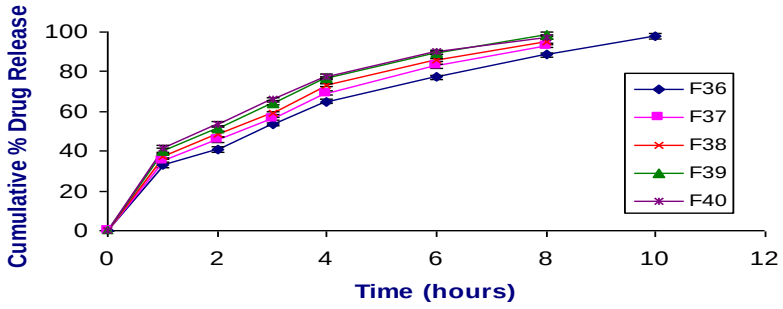

Figure No. 11: Release Profiles of Penbutolol Sulfate (PS) from Tablets with HPMC K100M and Ethylcellulose (direct compression)

Out of a total of 40 batches, the drug release was extended up to 12 hours for the formulations F12 and F23. So, these two formulations were selected for further studies like kinetic data analysis and similarity factor analysis.

Kinetic analysis of dissolution data

The release rate kinetic data for the F12 and F23 are shown in Table No. 23 and Table No. 24 respectively. As shown in Figures No. 12-14, drug release data were best explained by the first-order equation, as the plots showed the highest linearity (r^2 = 0.9955), followed by Hixson-Crowell (r^2 = 0.9800) and Higuchi's equation (r^2 = 0.9661). As the drug release was best fitted in first-order kinetics, indicating that the rate of drug release is concentration dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases. The applicability of the formulation to the Hixson –Crowell cube root law indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time.

Mechanism of drug release

As shown in Figure No. 12, the corresponding plot (log cumulative percent drug release vs time) for the Korsemeyer-Peppas equation indicated good linearity (r^2 = 0.9741). The diffusion exponent n was 0.66, which appears to indicate coupling of the diffusion and erosion mechanism

(Anomalous diffusion) and may indicate that the drug release was controlled by more than one process.

Table No. 23: Drug Release Kinetics of Batch (F12) Matrix Tablets*

Zero-order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
r^2	$K_0\,(h^{-1})$	r^2	$K_1\,(h^{-1})$	r^2	$K_H\,(h^{-1/2})$	r^2	$K_{HC}\,(h^{-1/3})$	r^2	n	$K_{KP}\,(h^{-n})$
.8455	5.199	0.8688	0.1845	0.9324	24.856	0.9699	0.2478	0.9944	0.61	0.4238

* r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.

Table No. 24: Drug Release Kinetics of Optimized (F23) Matrix Tablets*

Zero-order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
r^2	$K_0\,(h^{-1})$	r^2	$K_1\,(h^{-1})$	r^2	$K_H\,(h^{-1/2})$	r^2	$K_{HC}\,(h^{-1/3})$	r^2	n	$K_{KP}\,(h^{-n})$
0.8990	5.872	0.9966	0.2019	0.9672	27.844	0.9866	0.1991	0.9751	0.88	0.3269

* r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.

Similarity factor analysis

Similarity factor results for the batches F12 and F23 are given in Table No. 25. Similarity factor analysis between F23 tablets and theoretical release has shown an f_2 factor greater than 50 at each time point with an average value of f_2 factor 80.18. In the case of F12 tablets, an average value of the f_2 factor was greater than 50, but at the 3rd and 4th hours, the f_2 factor was less than 50.

The *in-vitro* release behavior of F12, F23 batches of tablets were compared with the theoretical release profile. A close relationship was observed between F23 formulation and theoretical release patterns, compared to a relationship between F12 and theoretical release patterns (Figure No. 19). So, F23 was considered as an optimized formulation, as these tablets did not show any

burst release and extended the release for 12 hours with a similar release pattern to that of the theoretical release profile.

Table No. 25: Similarity Factor Analysis

Time (hrs)	Theoretical release	*Average % Drug Release*		*f2 factor*	
		F12	**F23**	**F12**	**F23***
1	26.19	34.94	25.39	73.04	99.06
2	33.09	49.84	35.06	59.61	95.04
3	40.22	66.96	51.44	49.62	66.99
4	46.81	76.62	62.91	47.24	61.11
6	60.44	81.51	73.66	64.51	64.69
8	74.64	89.81	81.07	54.79	78.83
10	88.41	93.04	87.02	61.53	97.32
12	99.01	98.04	97.31	66.76	77.95

* Average value of *f2* factor = 80.44

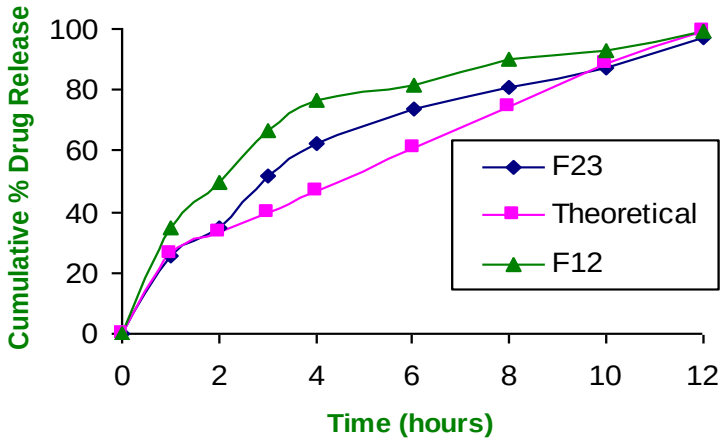

Figure No. 12: Comparative *In-vitro* Drug Release Profile

Swelling and erosion behavior, FTIR studies, and stability studies were performed on the optimized formulation (F23).

Determination of swelling and eroding behavior

Since the rate of swelling and erosion is related and may affect the mechanism and kinetics of drug release, the penetration of the dissolution medium and the erosion of the hydrated tablets

were determined. Simultaneously with the swelling study, the percentage erosion of polymer was determined. The percentage swelling and erosion of the optimized tablet was shown in Figure No.13, and data was given in Table No. 26. Maximum swelling was observed in the first 2 hours and gradually it was decreased with simultaneous erosion of the polymer.

Table No. 26: Swelling and Erosion Study of Optimized Formulation (F23)

Time (hours)	% Swelling	% Erosion
1	76.41	18.79
2	128.22	24.32
3	84.51	28.17
4	71.16	42.51
6	60.71	56.44
8	49.25	64.63
10	36.11	72.18
12	24.71	93.94

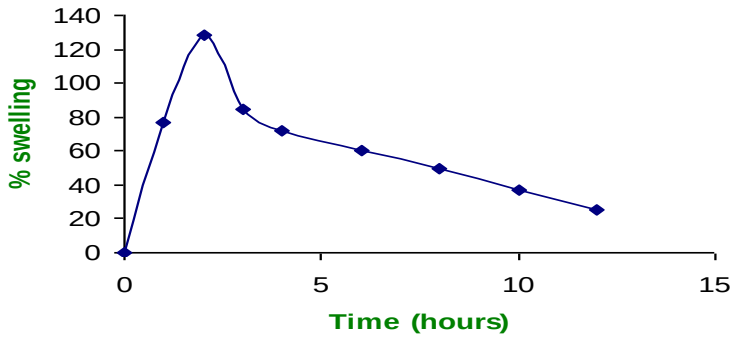

Figure No. 13: Swelling Study of Optimized Formulation (F23)

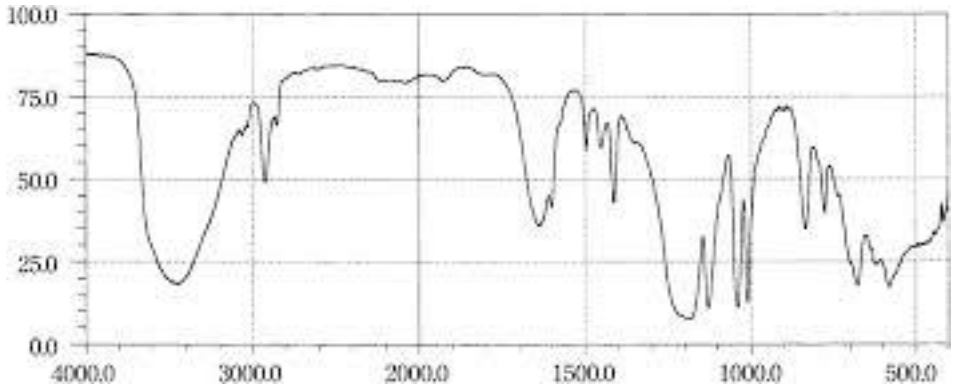

Figure No. 14: FTIR of Penbutolol

Stability studies

Stability studies of the optimized formulation did not reveal any degradation of the drug and there was no significant change in the physical properties, drug content, and in vitro release profiles of the optimized formulation after storage for 3 months.

4. CONCLUSION:

Hence, the matrix tablets of Penbutolol Sulfate (PS) can be prepared with hydrogel-forming polysaccharides like sodium alginate, xanthan gum, guar gum alone and in combination with HEC to prolonged the release of Penbutolol Sulfate (PS) up to 12 h which showed similar theoretical release profiles may be helpful for the better management of hypertension.

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